UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

School of Chemistry

THE SYNTHESIS OF 1,2,4-TRIAZINE-3,6-DIONES AND THE STRUCTURE-BASED DESIGN AND SYNTHESIS OF HIV-1 PROTEASE INHIBITORS

by

Sally Katherine Radford

Thesis for the degree of Doctor of Philosophy

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The research work described in this thesis was carried out by myself, under the supervision of Dr. A. Ganesan at the University of Southampton between October 2003 and November 2006. No part of this thesis has been submitted in any previous application for a higher degree.

Sally Katherine Radford August 2007

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ABSTRACT

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The heterocyclic structure 1,2,4-triazine-3,6-dione is chosen as a peptidomimetic analogue of cyclic dipeptides (diketopiperazines), and its potential as a novel scaffold for drug discovery is assessed.

A two-step synthesis towards 1,2,4-triazine-3,6-diones, producing a range of 20 novel 1,2,4-triazine-3,6-diones is described. Boc protected hydrazines and amino acid methyl esters are reacted with triphosgene in a one-pot reaction to give a range of over 30 novel semicarbazides. The cyclisation of these semicarbazides under thermal and microwave conditions is explored. Two novel 3-aminohydantoins are also isolated and the assignment of the two heterocyclic structures according to their spectral data is discussed. The 1,2,4-triazine-3,6-diones are tested for biological activity against breast cancer cells and their improved activity compared to the cyclic dipeptide cyclo(Phe-Pro) is discussed.

Mechanistic investigations into the reaction of α-hydroxy esters with Mitsunobu reagents are described. It is shown that the α-hydroxy esters are oxidised to α-keto esters following the proposed literature mechanism. In addition this work has provided a novel synthesis of 1,2,3-oxadiazole-2,3-dicarboxylic esters from α-keto esters and 1,2-diketones.

Chapter two describes the structure-based design of the HIV-1 protease inhibitor core Phe-Pro diol and the synthesis towards this structure. The coupling of the two amino acid derived fragments is explored using Julia, modified Julia and Hoppe coupling procedures. The advantages and sensitivities of these three methods are compared and discussed.

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Most of all I would like to thank Dave not only for his excellent proof-reading but for all of his endless love, support, encouragement and cups of tea. I could never have done it without you and I can't thank you enough.

ABBREVIATIONS

Ac – Acetyl

ADME – Absorption, Distribution, Metabolism, Excretion

AIDS – Acquired immunodeficiency syndrome

Ar – Aryl

ARV – Antiretroviral

Asp – Aspartic acid

BEMP resin – 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine polymer bound

Bn – Benzyl

Boc – *tert*-Butyloxycarbonyl

br – Broad (NMR)

Bu – Butyl

^{t}Bu – *tert*-butyl

Bz – Benzoyl

°C – Degrees centigrade

Cby – 2,2,4,4-Tetramethyl-oxazolidine

Cbz – Carboxybenzyl

CNS – Central nervous system

cm^{-1} – Wave numbers

d – Doublet (NMR)

DBAD – Di-tert-butyl azodicarboxylate

DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC – *N,N*-dicyclohexylcarbodiimide

DEAD – Diethyl azodicarboxylate

DEPT – Distortionless Enhancement through Polarisation Transfer

DIAD – Diisopropyl azodicarboxylate

DIBAL – Diisobutylaluminum hydride

DIC – Diisopropyl carbodimide

DMAP – *N,N*-4-Dimethylaminopyridine

DME – 1,2-Dimethyoxyethane

DMF – *N,N*-Dimethylformamide

DMSO – Dimethyl sulfoxide

DNA – Deoxyribonucleic acid

EDC – 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Hydrochloride

Et – Ethyl

FDA – Food and Drug Administration

g – Grams

Gly – Glycine

h – Hour

^{1}H – Proton

HAART – Highly Active Antiretroviral Therapy

His – Histidine

HIV – Human immunodeficiency

HMDS – Hexamethyldisilazide

HoBt – 1-Hydroxybenzotriazole

Hz – Hertz

Ile – Isoleucine

IR – Infrared

J – Coupling constant

Leu – Leucine

LRMS – Low-resolution mass spectra

m – Multiplet (NMR)

M – molar

***m*-CPBA** – *meta*-Chloroperoxybenzoic acid

Me – Methyl

mg – Milligrams

MHz – Megahertz

Min – Minute

mL – Millilitres

mmol – Millimoles

Mp – Melting point

Ms – Methanesulphonyl (mesyl)

MW – Molecular weight

m/z – Mass to charge ratio

NMO – *N*-Methylmorpholine-*N*-oxide

NMM – *N*-Methylmorpholine

NMR – Nuclear magnetic resonance

NOE – Nuclear Overhauser effect

P – Partition coefficient

PCC – Pyridinium chlorochromate

Ph – Phenyl

Phe – Phenylalanine

ppm – Parts per million

Pr – Propyl

***i*Pr** – isopropyl

Pro – Proline

Py – Pyridine

py-BOP – Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate

py-BrOP – Bromo-tris-pyrrolidino phosphonium hexafluorophosphate

q – quartet

QSAR – Quantitative structure-activity relationship

RNA – Ribonucleic acid

r.t – Room temperature

s – Singlet (NMR) or strong (IR)

Sept – Septet (NMR)

t – Triplet (NMR)

TFA – Trifluroacetic acid

THF – Tetrahydrofuran

TLC – Thin layer chromatography

TMEDA – N,N,N',N'-tetramethyl-1,2-ethylenediamine

TPAP – Tetra-N-propylammonium perruthenate

TPP – Triphenylphosphine

Tf – Trifluromethanesulfonyl (Triflyl)

Ts – *p*-Toluenesulphonyl (Tosyl)

Tyr – Tyrosine

UV – Ultraviolet

Val – Valine

W – Watt

δ – Chemical shift

3D – Three dimensional

Chapter One

The Synthesis Of 1,2,4-Triazine-3,6-Diones

1.1.0 INTRODUCTION

1.1.1 Drug Discovery

A drug can be defined as any species that either prevents disease in a healthy individual or assists in the recovery or comfort of a diseased patient. As such, the discovery or design of new drugs is fundamental to the success of modern medicine. The science involved in the discovery or in more recent years the design, of new drugs, known as medicinal chemistry, draws on many different scientific disciplines and can be considered to be both a complex and relatively adolescent science.[1]

At the end of the 19th century Ehrlich and Langley proposed the concept of the receptor, giving the first understanding as to why only certain molecules produce a therapeutic response.[2] Since this time, the vast complexities of the human body's many receptors have been increasingly appreciated and studied. In addition to the resulting intricacies involved in achieving the required potency and selectivity for the targeted receptor, the toxicological, pharmacokinetic and pharmacodynamic properties of the molecule must also be suitable if the compound is to become a successful drug. Moreover, if the pharmaceutical company is to recover any of its investment then commercial factors will also have to be considered. It is therefore perhaps not surprising that the process of drug discovery, from first idea to market, typically takes between 8 – 12 years and that for the drugs that reach market several million compounds would have been rejected.[1]

i) The drug discovery process [1, 3]

The drug discovery process will pass through a number of stages before a drug molecule reaches the market. The first stage is to identify a disease target and decide on a likely method of drug action that has either not been previously explored or for which therapy is not available. Once a suitable screen has been devised the search for a lead compound can begin. This is generally a compound that has a good level of affinity for the target receptor in initial screening, has a drug-like structure that is free from toxic moieties and shows activity in later more in-depth biological screens. Lead compounds are therefore the starting point of

drug discovery and from these structures the active part of the molecule, or pharmacophore, can be identified. Optimisation of the lead compound will then follow and will have to take into account not only the various effects the drug will have on the body but also how the drug molecule will be affected by the body itself. The absorption, distribution, metabolism and excretion of the molecule must be considered if a drug, however active, is to have the desired action. Molecules with improved potency, selectivity and fewer side-effects or other problems will be progressively discovered. From this work a candidate drug would be selected and detailed biological work would be carried out to test the utility and safety of this molecule. Following large-scale synthesis and formulation studies, clinical trials could then begin. Since compounds can, and frequently will, fail to meet required standards at any stage in this process, alternative compounds from earlier stages will have to be returned to and brought forward. The process, therefore, is not linear but a continual spiral towards the desired end.[4]

ii) What kind of molecules become drugs?

As mentioned above, if a compound is to be a useful drug it must not only have an affinity for the targeted receptor but must first reach the receptor, intact and in a suitable quantity. For obvious reasons the preferred means of administration for most drugs is oral. It is therefore useful to know what properties will likely make a molecule sufficiently 'drug-like' for oral dosing. By looking at the properties of known orally effective drugs, Lipinski and co-workers at Pfizer were able to establish that the majority of these drugs obey a number of rules, now known as Lipinski's Rule of Five.[5] These rules state that for a compound to have a greater likelihood of good absorption and permeability it should fit four criteria. These are:

- Molecular weight < 500
- Fewer than or equal to 5 hydrogen-bond donating groups
- Fewer than or equal to10 hydrogen-bond accepting groups
- Calculated log *P* (*c* Log *P*) between -1 and +5

Although these rules can only be considered a useful guide and many biologically active compounds that do fit these criteria do not become drugs, few compounds that do become orally active drugs fall outside of these limits. Incorporating these rules into the drug-seeking program from a very early stage, therefore, increases

the probability that when an active lead compound is found, optimising it to drug candidate status will be possible.

iii) Where do lead molecules come from?

Although as explained above, there is definite advantage in screening mainly small drug-like structures in the search for a lead molecule, it is estimated that the total number of possible small organic molecular structures is approximately $10^{63.6}$ This leaves the question; where do the molecules for initial screening come from?

The oldest source of drug lead compounds is natural products. Long before drug discovery existed as a science, plant extracts were used for medicinal purposes. Some drugs that have their origins in medical folklore, for example morphine (Opium poppy used in Ancient Egypt) and aspirin (willow bark used in medieval England), are still used in modern medicine. Equally, a large number of isolated natural plant products have gone on to become important drugs, a well known example being the anti-cancer agent Taxol. Animal products are also a useful source of lead compounds; snake venom, for example, led to the discovery of angiotensin converting enzyme inhibitors. Fermentation products from soil micro-organisms have produced many important medicinal compounds, the earliest being powerful antibiotics, e.g. penicillin, produced for the organisms' own safety. Natural products from the world's seas have not been extensively explored, but some promising anti-cancer agents have been and continue to be discovered from marine sources. It has been estimated that approximately 52% of all new chemical entities for therapeutic use discovered in the period 1981 to 2006 were natural products, derived from natural products, or could be considered to be mimics of an active natural product.[7] In some disease areas this figure can be much higher; anti-cancer agents originating from a natural product accounted for 78% of all the new anti-cancer drugs discovered in this time period. Conversely, in some disease areas, e.g. hypnotics, the drugs are purely synthetic with no input from natural products.[7]

Natural products have been an extremely important source of new drugs; of particular value is nature's ability to produce compounds of vast complexity and structural diversity that might not otherwise be created by the synthetic chemist. Natural products do, however, have some drawbacks as a source of lead compounds. Despite the huge range of diversity, finding activity for a specific

biological target can be extremely challenging. This is perhaps less surprising when we consider that there is no known advantage for plants or other non-mammals to produce chemicals with biological affinity for human receptors and any activity that we do discover is purely fortuitous.

Another useful source of lead compounds for drug discovery is the large reserve of organic molecules that have already been synthesised by the organic chemist. This can include molecules not originally synthesised for drug discovery, an example being the red dye prontosil that was discovered to be effective against streptococcal infections in 1935 and led to a new class of antibacterial drugs called the sulphonamides.[3] Compounds that have been synthesised in previous drug discovery projects can also be useful sources of lead compounds. A competitor's drug can be improved upon by reducing side effects or improving dosing, a strategy known as 'Me-too' drugs that can prove difficult to patent. Alternatively a known compound might have an interesting side-effect that could be enhanced to give a drug with a totally different biological affinity compared to that sought in the original project, the drug Viagra being infamous for its discovery in this manner!

Of most relevance, however, are the large compound archives that most pharmaceutical companies have built up over many years of synthesis. It is estimated that the average size of these archives could be 200 000 compounds although with the modern use of combinatorial chemistry, the larger companies could easily have several million individual compounds to hand (currently Pfizer's collection is estimated at 6 million compounds).[8] With the automated screening technologies currently available thousands of these compounds could be screened every day and this is frequently the approach taken by many pharmaceutical companies in the search for a lead compound. There are, however, several disadvantages to using these archives. Firstly, the importance of the purity and stability of these stored compounds has not always been appreciated and 'false positives' can result from mixtures that were thought to be one compound. More important is the fact that the structural diversity of these archives is quite limited, being biased by the kind of structures synthesised in previous projects. It is interesting to reflect on whether the frequent occurrence of certain core structural classes in new lead compounds, sometimes known as privileged templates or scaffolds e.g. benzodiazepines, dihydropyridines or β-lactams (Figure 1.1), is a result of the disproportionate number of these structures in pharmaceutical

archives rather than any biological superiority over other less well known structural types.

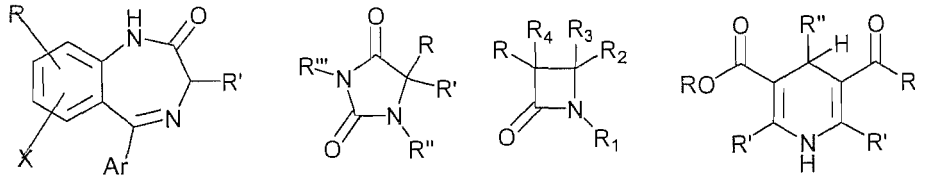


Figure 1.1: Examples of several 'privileged' or commonly occurring scaffolds in drug discovery.

Lead compounds are occasionally discovered when compounds are synthesised purely on a speculative basis. The benzodiazepines were first synthesised because they were almost completely unexplored in the literature and yet looked like suitably drug-like structures.[9] It was only after any initial interest in these compounds had waned that their excellent biological properties as tranquilisers and sedatives came to light, resulting in much study of this structural class and ultimately to a number of successful drugs.

Although this speculative approach to finding lead compounds has not always been a popular choice, it is relevant when we consider the lack of diversity seen in some pharmaceutical archives. Combinatorial chemistry was seen by many as an opportunity to discover thousands of new biologically active structures very rapidly when it first became main-stream in the pharmaceutical industry. This proved to be wildly optimistic and the resulting disillusion seems to have done the industry no favours. Lead discovery from combinatorial libraries is, however, an important source. Good quality libraries will contain a large number of a diverse range of drug-like structures suitable for automated biological screening for a novel lead compound. In fact, some companies specialise in producing such diverse libraries to sell on to large pharmaceutical companies for this very purpose.

iv) Heterocycles in drug discovery[10, 11]

A large proportion of known and marketed drug molecules are heterocyclic in structure. Although when contemplating common drug structures this seems evident it is much harder to rationalise why this is the case. Approaching from a different angle and considering the range of heterocycles that are known to the modern chemist we can observe that many known heterocycles are found in nature and it is perhaps nature's propensity to create heterocyclic structures and

the extensive use of natural products as lead structures that has led to a proliferation of heterocycles in our day to day medicines (table 1.1).

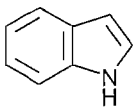
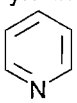
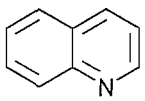
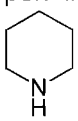
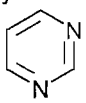
Heterocycle	Examples of natural product	Examples of medicinal drugs
Furan 	Found in natural products with intense odour e.g. coffee and rose furan.	Nitrofural – antibiotic used for treatment of infectious diseases.
Tetrahydrofuran 	Many natural products including class known as 'furanoses'. Also muscarine from toadstool fly agaric.	Polyether antibiotics contain THF rings, e.g. monensin.
Pyrrole 	Some important natural products incl. the antibiotic pyrrolnitrin. Also tetrapyrroles - cyclic tetrapyrroles e.g. heamin and chlorophyll and linear tetrapyrroles e.g. bilirubinoids.	Analgesic and antifungal drug zomepirac.
Indole 	Amino acid tryptophan. Natural product serotonin - acts as vasoconstrictor and neurotransmitter. Also indole alkaloids, a very large class of important natural products.	Anti-inflammatory drug indomethacin and antidepressant drug iprindole.
Pyrrolidine 	Amino acid proline. Also the alkaloid hygrin from the coca plant and the alkaloid nicotine.	Antihypertensive drug captopril.
Pyridine 	Nicotinic acid otherwise known as vitamin B_5 and pyridoxol (vitamin B_6). Pyridine alkaloids e.g. nicotine.	Nicotinic acid derivatives used as vasodilators and anticoagulants. Nifedipin and other 1,4-dihydropyridines used as antihypertensive agents.
Quinoline 	Alkaloids from the cinchona bark e.g. camptothecin which is highly toxic.	8-Hydroxyquinoline and halogenated derivatives are used as antiseptics. Chloroquine is an antimalarial. *N*-Alkyl-4-quinolone-3-carboxylic acid and derivatives are used as antibacterials.
Piperidine 	(*S*)-Pipecolic acid is widely distributed in higher plants, microorganisms and animals. Piperine is the active ingredient in black pepper. Also tropane alkaloids which occur abundantly in nature e.g. cocaine.	Most common heterocycle in pharmaceutical agents e.g. antihistamine bamipine, local anaesthetic bupivacine, antidiarrhoeal diphenoxylate.
Pyrimidine 	Many natural products incl. the 'pyrimidine bases' thymine, cytosine and uracil, which are important building blocks for nucleic acids.	Present in many drugs e.g. chemotherapeutics trimethoprim and sulfadiazine. Also zidovudin (AZT) used in HIV treatment.

Table 1.1: Structures of a few common heterocycles and examples of their occurrence in known natural products and in medicinal drugs.[10]

Heterocycles are also particularly useful as scaffolds when designing lead-seeking libraries. Ideally a scaffold should be 'spider-like' with substituents dispersed around it to give as much information about the 3D biological space of the targeted receptor as possible. The substituents should be such that they can be varied independently of each other during synthesis and should have a diverse range of functional groups to probe the binding site for possible interactions. Heterocyclic

scaffolds with small molecular weights that can be synthesised in this manner are therefore much used for this purpose, particularly the previously mentioned privileged scaffolds (figure 1.1).

v) Peptides in drug discovery [1, 12]

Peptides are defined as consisting of between two and fifty amino acids linked through amide bonds (proteins are more than fifty amino acids long). In the body they mainly act as neurotransmitters, neuromodulators and hormones and are therefore the tools by which cells can carry out their normal inter- and intra-cellular processes. For this reason, peptides are involved in a wide range of physiological processes including metabolism, immune defence, digestion, respiration, sensitivity to pain, reproduction and behaviour. A large number of these important endogenous human peptides have been isolated and their function in the body characterised. It is, therefore, understandable that peptide creation, breakdown and peptide-receptor interaction in various disease states are seen as potential biological targets for drug discovery.

Peptides themselves, however, are rarely used as drugs. In a healthy patient they are usually biosynthesised and stored near to their site of action in order to be specific to that receptor. When administered as a drug the peptide must survive a much longer journey through the digestive system and various cell membranes before it can reach its site of action. This journey presents several fundamental problems for the peptide resulting in their being poor orally administered drugs. In short, peptide drugs have the following drawbacks:

- low oral bioavailability
- rapid degradation by endogenous peptidases
- rapid excretion due to their high polarity
- side effects due to lack of selectivity for one receptor

Designing analogues of active peptides that incorporate more drug-like properties is therefore the focus of much drug discovery research, and these structures are generally known as peptidomimetics. A set of rules known as Farmer's Rules are a guide to the process of designing a peptidomimetic from the original peptide. The process is however quite complex, especially since peptides are extremely flexible and can form a large number of different conformations or secondary structures

such as α-helices, β-sheets and turns. Cyclic peptides, therefore, have some advantages over their linear counterparts; their inherent conformational rigidity can often confer better resistance to degradation and stronger selectivity for one receptor than an equally active linear peptide.[13]

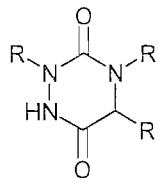
1.1.2 1,2,4-Triazine-3,6-diones as Novel Scaffolds for Drug Discovery

The aim of this project is to design and synthesise novel scaffolds to form part of a diverse library suitable for lead-seeking biological screening. It is hoped that in synthesising heterocyclic structures that have not previously been tested for any biological activity, which have only been sparsely reported in the literature and are sufficiently drug-like there is the potential to discover new drugs that would not otherwise be found. In designing our novel scaffold there are some crucial factors to consider. Firstly, the final compounds must fit with Lipinski's rule of five in order to have a strong chance of being orally active, secondly, the scaffold should have a 'spider-like' structure and be suitable for combinatorial synthesis as mentioned previously, and finally, the structure must be as novel as possible.

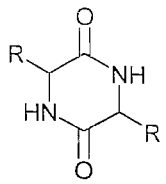
With these criteria in mind we have given ourselves the following specifications for our novel scaffold:

- The scaffold must be a 5 or 6 membered ring with a low molecular weight and three R groups to give a spider-like structure
- As the R groups are likely to be hydrophobic, the core must have at least 5 heteroatoms to counter this
- To allow at least one hydrogen bond acceptor/donor in each R group the number in the scaffold must be low
- For combinatorial synthesis the starting materials must be simple and readily available
- No more than 20 examples of the scaffold reported in the literature

In addition to these rules we wish to maximise any chances of biological activity by mimicking an active natural product structural type. We have therefore chosen to synthesise 1,2,4-triazine-3,6-diones as novel scaffolds and analogues of 2,5-diketopiperazines, since the 1,2,4-triazine-3,6-dione structure fits our requirements and the naturally occurring cyclic dipeptide is known to have a diverse range of biological activities (figure 1.2).



1,2,4-Triazine-3,6-dione



2,5-Diketopiperazine
or cyclic dipeptide

Figure 1.2: Structures of novel 1,2,4-Triazine-3,6-dione scaffold and naturally occurring 2,5-diketopiperazine scaffold.

i) 2,5-Diketopiperazines or cyclic dipeptides

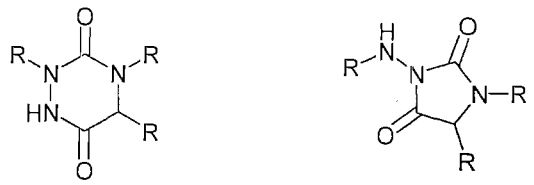
Cyclic dipeptides or 2,5-diketopiperazines are among the simplest peptides found in nature and as such they are also one of the most common peptide derivatives. Most of these cyclic dipeptides have been discovered as a by-product of fermentation or food processing, including processed cocoa, cheese and beer. In these cases it was thought that they were the result of non-enzymatic cyclisation of dipeptides during storage or thermal manipulations during processing. Cyclic dipeptides have, however, been found to be endogenous to some mammals, plants and marine sponges both in their own right and as part of more complex molecules. Some of these cyclic dipeptides have been shown to be enzymatically synthesised in protist and plant species, for example cyclo(Pro-Leu), cyclo(Pro-Val) and cyclo(Pro-Phe) in the *Rosellinia necatrix* fungus.[13, 14]

Although these cyclic dipeptides have been known about since the early 1900's it is only fairly recently that the large range of their biological activities has been discovered. Cyclo(His-Pro) has been proven to be endogenous to the mammalian brain and it has also been shown to modify a range of CNS biological activities, thereby eliciting various behavioural effects including reducing the sedative effects of ethanol. There is also some evidence that this cyclic peptide may play a role in the eating disorders anorexia nervosa and bulimia.[14] Cyclo(Leu-Gly) and cyclo(Pro-Phe) have been proved to reduce physical addiction to morphine and cyclo(Pro-Phe) has also been reported to show antifungal activity.[13, 14] The cyclic peptide cyclo(Asp-Pro) has been shown to reduce calorie intake and has been particularly associated with a selective decrease in dietary fat intake.[14] In a study of the biological activities of the two cyclic dipeptides cyclo(His-Phe) and cyclo(His-Tyr); cyclo(His-Tyr) was seen to slow blood clotting and exhibited excellent antibacterial and antifungal activity, while cyclo(His-Phe) reduced heart rate and coronary flow rate in rats as well as having excellent anti-tumour and antifungal activity.[15] There have also been several additional studies into the

anticancer properties of various cyclic dipeptides. These have resulted in the discovery that cyclo(Phe-Pro) and cyclo(Tyr-Pro) can induce differentiation in colon cancer cells and that cyclo(Phe-Pro) inhibits the growth of human colon, cervical and breast cancer cells in addition to inducing apoptosis in colon cancer cells.[13, 16]

ii) Previous syntheses of 1,2,4-triazine-3,6-diones

The 1,2,4-triazine-3,6-dione structure is quite rare in the literature, a Scifinder search of the structure in figure 1.3, with a hydrogen atom at N-1 gives only 16 known examples. There are in fact fewer than this, since earlier papers mistakenly reported aminohydantoins as 1,2,4-triazine-3,6-diones (figure 1.3).



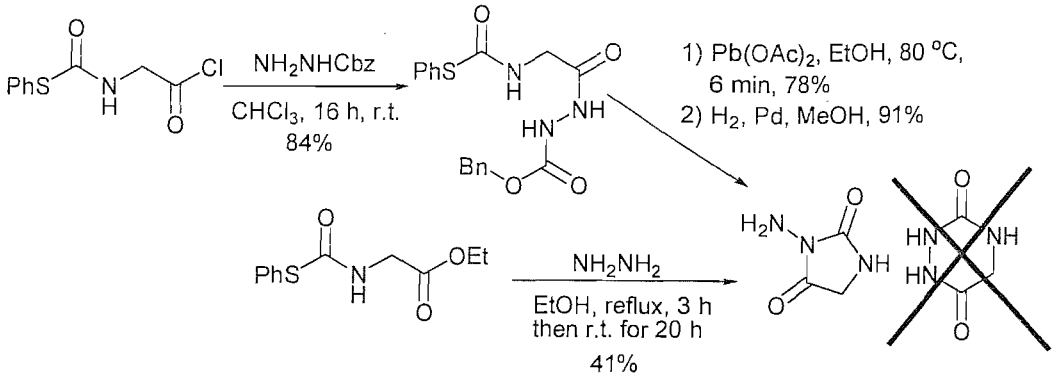
1,2,4-Triazine-3,6-dione

3-Amino-imidazolidine-2,4-dione
or aminohydantoin

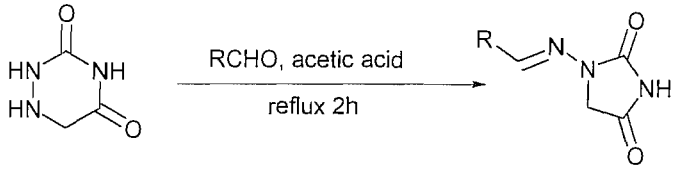
Figure 1.3: Structure of 1,2,4-triazine-3,6-dione and that of its isomer 3-amino-imidazolidine-2,4-dione or aminohydantoin.

The earliest paper describing the synthesis of 1,2,4-triazine-3,6-diones was published in 1952 where Lindenmann *et al.* reacted hydrazine hydrate with phenylthiocarbonylglycine ethyl ester (scheme 1.1).[17] The actual structure of the product from this reaction was, however, later proved by Schwan in 1983 to be 3-amino-2,4-imidazolidinedione or aminohydantoin.[18] Milne *et al.* reported the same reaction in 1960 again reporting the aminohydantoin as the 1,2,4-triazine-3,6-dione, they also reported the infrared spectrum of the product that further confirmed that this was indeed the aminohydantoin when compared to data in later papers.[19]

A paper published in 1967 by Gut *et al.* although not reporting the synthesis of 1,2,4-triazine-3,6-diones specifically, discussed both the spectral differences between aminohydantoins and six-membered hydrazides and the ring-contraction of triazinediones to aminohydantoins.[20] Gut *et al.* concluded that there are significant infrared spectral differences between the two isomers, and that six-membered hydrazides can react with aldehydes to give five-membered N-amino compounds (scheme 1.2).[20]

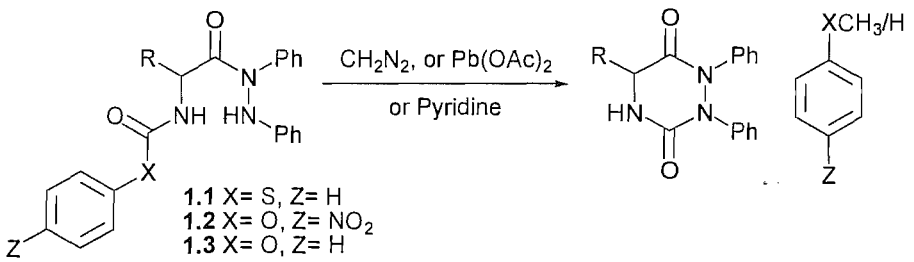


Scheme 1.1: Lindemann *et al.*'s synthesis of aminohydantoins that was originally reported as the synthesis of 1,2,4-triazine-3,6-diones.[17]



Scheme 1.2: Gut *et al.*'s ring-contraction of 1,2,4-triazine-3,5-diones to aminohydantoins.

A French group expanded on the earlier reported cyclisations with lead acetate to form 1,2,4-triazine-3,6-diones and in addition reported cyclisations in the presence of diazomethane or pyridine (scheme 1.3).[21]

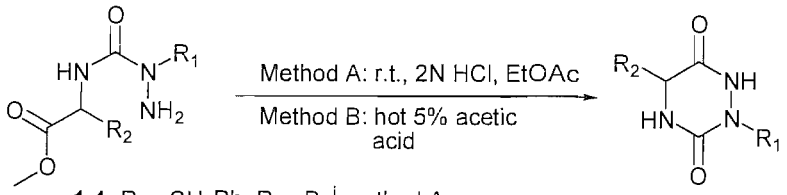


Scheme 1.3: Cyclisations to 1,2,4-triazine-3,6-diones reported by Baudet *et al.*[21]

These cyclisations were, however, solvent and leaving group dependent. The cyclisation of **1.3** in the presence of diazomethane was only successful in solvents with a high dielectric constant (e.g. nitromethane) whereas the reaction of **1.1** and **1.2** proceeded smoothly in ethanol. Cyclisation using lead acetate did not work for **1.3** and the cyclisation in the presence of pyridine was only successful for **1.2**.

Dutta and Morley briefly mentioned the synthesis of 1,2,4-triazine-3,6-diones in a paper on aza-peptides.[22] The cyclisation of these α-aza-dipeptides was seen to be influenced by steric factors; for example aza-dipeptide **1.4** cyclised when stored at room temperature for long periods whereas the aza-dipeptides **1.5** and **1.6** were

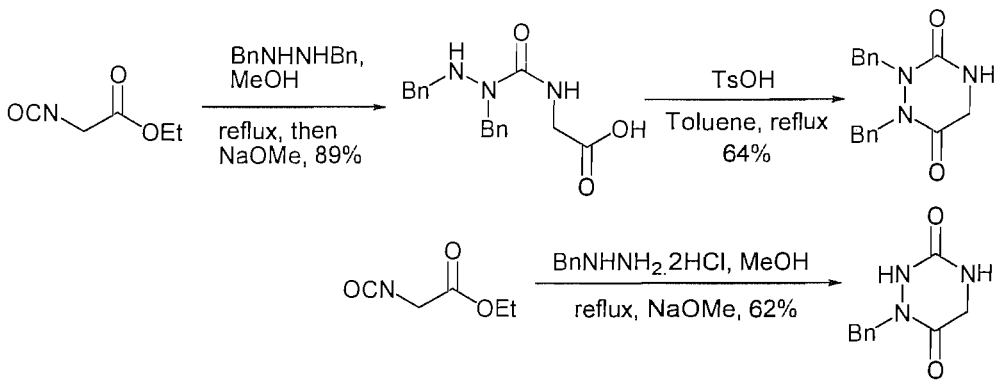
stable at elevated temperatures and only cyclised in the presence of 5% acetic acid.



1.4: R_1= CH_2Ph, R_2= Bu^i method A
1.5: R_1= R_2= Bu^i method B
1.6: R_1= Pr^i R_2= Bu^i method B

Scheme 1.4: Cyclisation of α-aza-dipeptides to 1,2,4-triazine-3,6-diones.[22]

In addition to his discussion on the structures in the Lindenmann paper, Schwan reports several syntheses of the 1,2,4-triazine-3,6-dione heterocycle (scheme 1.5).[18] He also reports the ring contraction of 1,2,4-triazine-3,6-diones to aminohydantoins when treated with benzaldehyde in acetic acid (*c.f.* Gut *et al.*) and when refluxed with methanolic HCl followed by treatment with base.[18]



Scheme 1.5: Schwan's syntheses of 1,2,4-triazine-3,6-diones.[18]

Following on from the previously published discussions on the structure assignment of the 1,2,4-triazine-3,6-diones and 3-aminohydantoins, Lalezari synthesised aminohydantoins from α-amino acids and reports a probable mechanism for the formation of the five-membered over that of the six-membered ring (figure 1.4).[23]

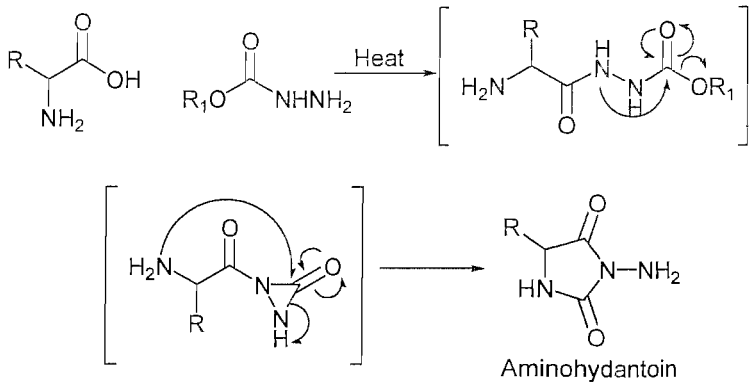
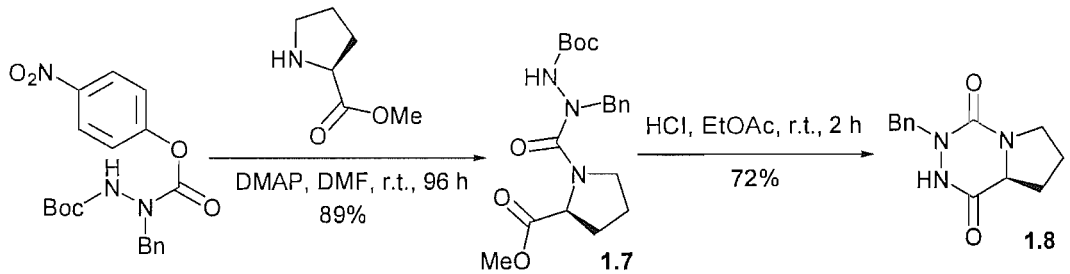


Figure 1.4: Mechanism proposed by Lalezari for the formation of the 5-membered aminohydantoin.[23]

Pinnen *et al.* synthesised a 1,2,4-triazine-3,6-dione heterocycle as an aza-analogue of cyclo(Phe-Pro) in their research towards pseudopeptidic ergopeptines.[24, 25] Deprotection of the Boc-protected semicarbazide **1.7** gave the 1,2,4-triazine-3,6-dione **1.8** at room temperature in 72% yield (scheme 1.6). Cyclisation of **1.7** to give the Boc-protected heterocycle was also reported, the methyl ester being hydrolysed and the crude product being coupled with *p*-nitrophenol using DCC to give the ester that cyclised spontaneously to give the Boc-protected triazinedione in 95% yield from **1.7**.



Scheme 1.6: Pinnen *et al.*'s synthesis of the 1,2,4-triazine-3,6-dione cyclo(-azaPhe-Pro) **1.8**.

The confusion of structural assignment between the two isomers has continued however, with Hoffman *et al.* mistakenly reporting the synthesis of aminohydantoins in 1995 as 1,2,4-triazine-3,6-diones.[26] They later realised their error and published a second paper where they explored how to control the cyclisation to give either the 5 or 6 membered ring as required .[27] They concluded that cyclisation to the 5-membered ring would always be favoured unless the first nitrogen atom was blocked with an R group. Monosubstituted hydrazines with bulky or conjugating groups reacted at the terminal nitrogen thereby giving the aminohydantoin heterocycle and simple monoalkylhydrazines reacted at the internal nitrogen to give the 1,2,4-triazine-3,6-dione (figure 1.5). They also

confirmed that structural assignments could be made based on the infrared spectrum of the compound, reporting that 1,2,4-triazine-3,6-diones have IR bands corresponding to the carbonyl group near 1680 cm^{-1} whereas *N*-aminohydantoins have a carbonyl band near 1780 cm^{-1} and a stronger carbonyl band at about 1730 cm^{-1}.[27]

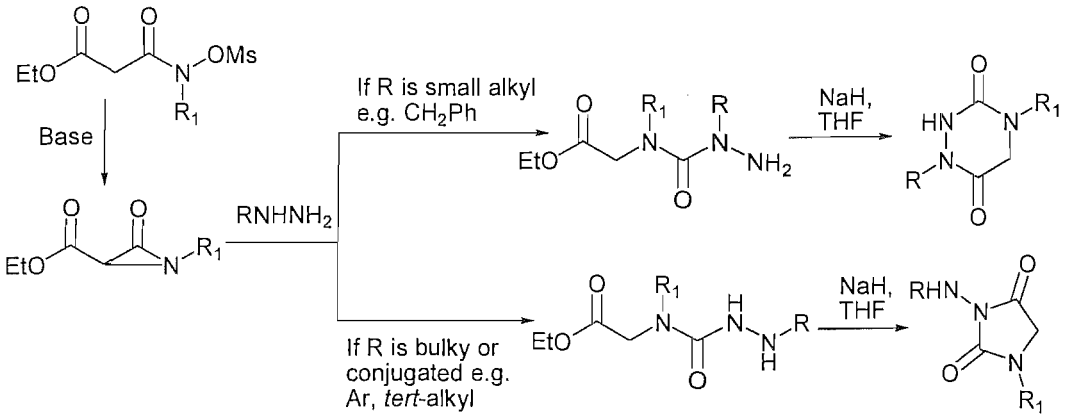


Figure 1.5: Hoffman *et al.*'s controlled synthesis of 1,2,4-triazine-3,6-diones and 3-aminohydantoins.[27]

A paper published in 1999 on the solid-phase synthesis of urea peptidomimetics also examines how the cyclisation to the 1,2,4-triazine-3,6-dione or the aminohydantoin depends on the regioselective addition of the hydrazine.[28] In this study, Hamuro *et al.* discovered that all the monosubstituted hydrazines they used, apart from methylhydrazine, reacted at the unsubstituted nitrogen giving the aminohydantoin on cyclisation (figure 1.6). In their structure assignment they compared the chemical shifts of the amide carbonyls in the ^{13}C spectra, hypothesizing that compounds with an amide carbonyl chemical shift of 170 ppm or above is an aminohydantoin, while the 1,2,4-triazine-3,6-dione products have a lower carbonyl chemical shift. X-ray crystal structures of each of the two isomers were also reported and they further confirmed the aminohydantoin structures by examining the splitting pattern of the hydrazine-NH peaks in the ^{1}H NMR spectra (figure 1.6). They also altered their synthesis to provide 1,2,4-triazine-3,6-diones exclusively (figure 1.6).

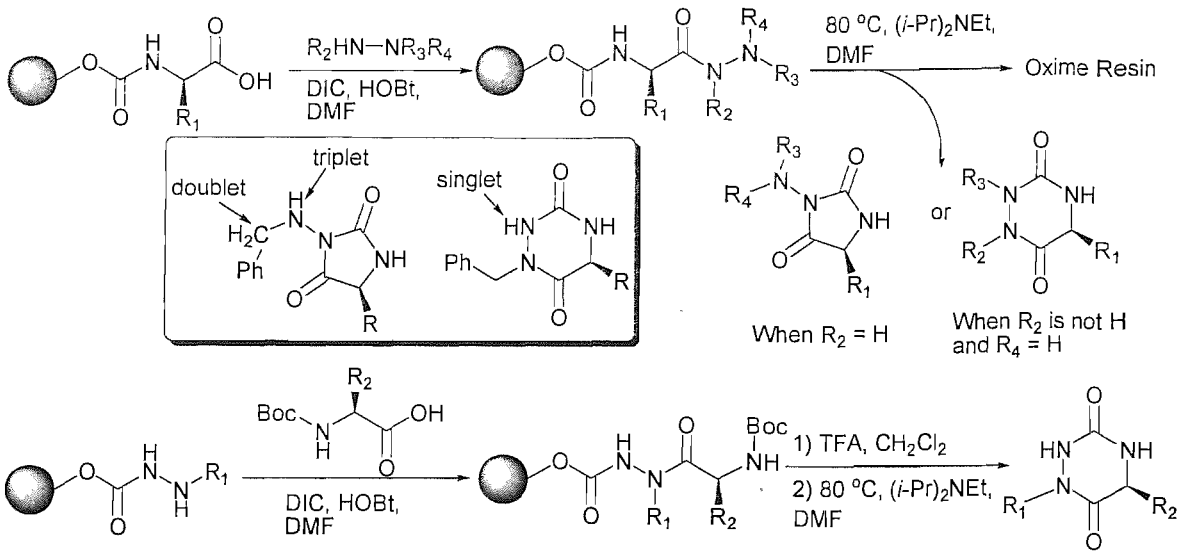
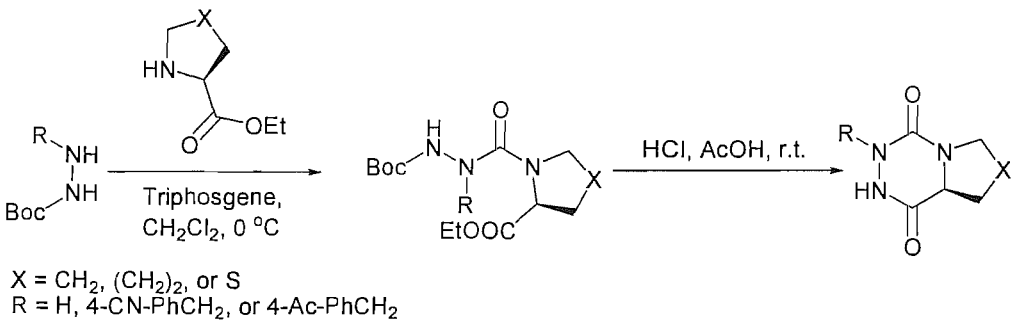


Figure 1.6: Hamuro *et al.*'s solid-phase synthesis of aminohydantoins and 1,2,4-triazinediones and the ^{1}H NMR coupling between the CH_2 and NH in the aminohydantoin structure.[28]

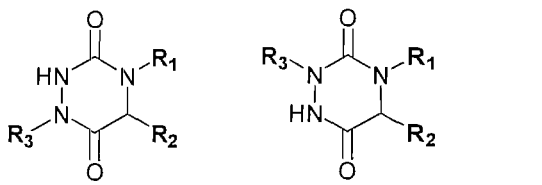
The final literature example of 1,2,4-triazine-3,6-diones was published in 2003 by Obreza *et al.* and describes the two step synthesis of seven triazinediones from Boc-protected hydrazines and proline ester type compounds (scheme 1.7).[29]



Scheme 1.7: Obreza *et al.*'s two step synthesis of 1,2,4-triazine-3,6-diones.[29]

iii) Proposed retrosynthesis of 1,2,4-triazine-3,6-dione scaffold

In our aim of synthesising 1,2,4-triazine-3,6-diones as novel scaffolds we wish to include three variable R groups and have chosen two substitution patterns for investigation (figure 1.7).



1,4,5-Trisubstituted -1,2,4-triazine-3,6-dione

2,4,5-Trisubstituted -1,2,4-triazine-3,6-dione

Figure 1.7: The two triazinedione structures with three R groups to be synthesised.

In designing our retrosynthesis towards these two triazinediones we must take into account the propensity of any intermediates to form the aminohydantoin structure over that of the triazinedione. We therefore propose the following two retrosyntheses (figure 1.8) to starting materials with a broad range of different R groups.

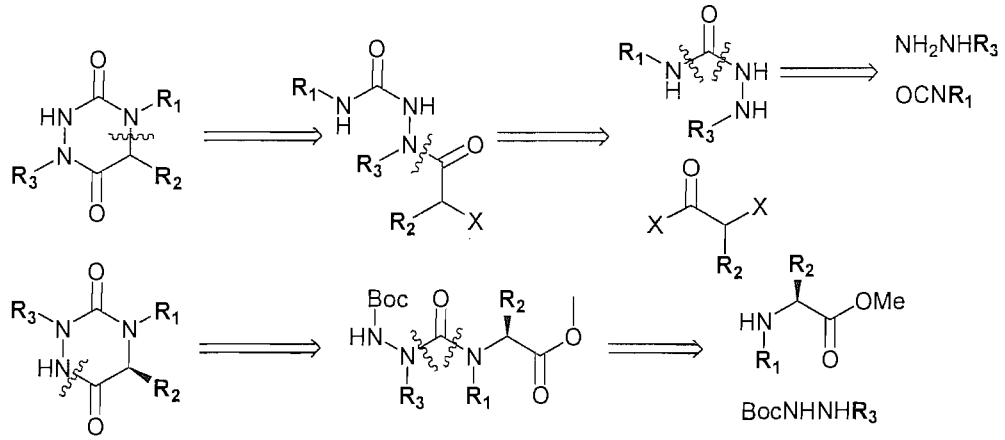


Figure 1.8: Retrosynthesis of the two 1,2,4-triazine-3,6-dione structures.

1.1.3 Conclusion

As the present understanding of many disease states and the receptors involved is not sufficient for design of molecules that will elicit the required biological response, the pharmaceutical industry often relies on finding compounds that give the desired biological response through screening of their compound collections.

These libraries consist mainly of compounds that have been synthesised for previous drug campaigns and although the collections are often very large, they can lack diversity. The natural world can often supply structurally unique, biologically active compounds that form the lead in a new drug discovery campaign, but natural products are usually first isolated and then found to have important biological activity rather than the other way round.

This being the present nature of drug discovery, the potential of small novel heterocyclic drug-like compounds to add diversity to the lead seeking libraries of new drug campaigns is extremely important. Without this diversity, new drugs that are sufficiently different in structure to give any choice or improvement in the treatment of old and new disease types are unlikely to be discovered. It is for this reason that this project aims to design and synthesise novel heterocyclic scaffolds suitable for lead-seeking biological screening.

We have chosen to synthesise the 1,2,4-triazine-3,6-dione scaffold as a heterocyclic structure with good orally administered drug potential and as an aza-peptidomimetic of the cyclic dipeptide structure it has a likelihood of having useful biological activity in a range of therapeutic areas.

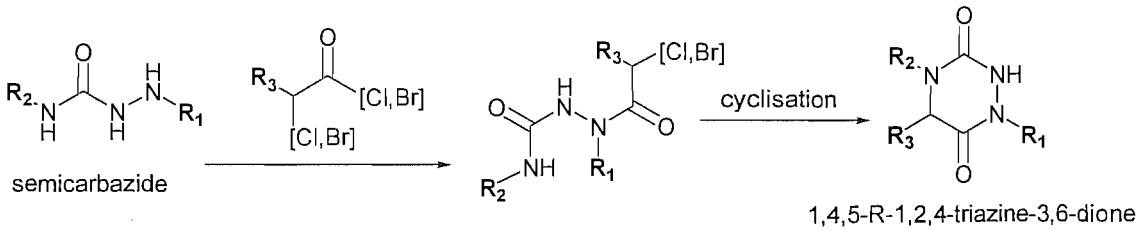
The past literature syntheses and attempted syntheses of this structure have allowed us to propose two retrosyntheses to the triazinedione heterocyclic with alternative substitution patterns as well as giving us important insights into the structural assignment of the triazinedione and aminohydantoin structures.

1.2.0 RESULTS AND DISCUSSION

1.2.1 Synthesis of 1,4,5-Trisubsitituted 1,2,4-Triazine-3,6-diones

i) Synthesis of semicarbazides

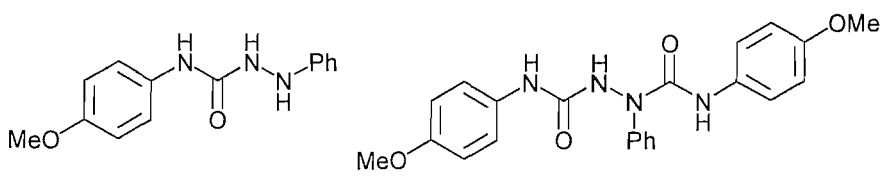
As discussed previously we intend to synthesise the triazinedione structures with two substitution arrangements (figure 1.7), the first being the 1,4,5-trisubsitituted 1,2,4-triazine-3,6-dione. The proposed retrosynthesis for this scaffold (figure 1.8) gave three starting materials; a hydrazine, an isocyanate and an α-bromo acid bromide or α-chloro acid chloride biselectrophile, and the proposed forward synthesis (scheme 1.8).



Scheme 1.8: Proposed synthesis of the 1,4,5-subsitituted 1,2,4-triazine-3,6-dione scaffold.

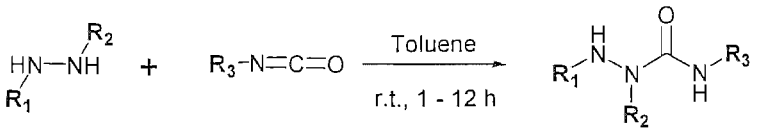
As it is known from the literature that acyl isocyanates react selectively with arylhydrazines to give 1-aryl-4-acyl semicarbazides, it was felt that this reaction could be extended to give the required semicarbazides for the above synthesis.[30, 31]

Once the appropriate conditions were established for this reaction, a range of semicarbazides were synthesised from commercially available hydrazines and isocyanates (table 1.2). Semicarbazides **1.8** to **1.12** were synthesised by reacting one equivalent of isocyanate with 1.5 equivalents of hydrazine, stirring in toluene at room temperature. These reactions were generally both facile and easily scalable to give gram quantities of recrystallised product. It was realised early on that an excess of the hydrazine was required to avoid contamination of the desired product with the disubstituted product (figure 1.9).



1.8 **1.8a**

Figure 1.9: 1-Phenyl-4-(4-methoxyphenyl) semicarbazide **1.8** & disubstituted product **1.8a**.



Product	R_1	R_2	R_3	Yield [a]
1.8	Ph	H	*p*-C_6H_4OMe	87
1.9	H	Me	*p*-C_6H_4OMe	47
1.10	Ph	Ph	CH_2Ph	58
1.11	H	Me	CH_2Ph	99
1.12	H	CH_2Ph	CH_2Ph	55
1.13	Ts	H	CH_2Ph	98
1.14	Ts	Me	CH_2Ph	91

[a] Percentage yield of isolated product

Table 1.2: Range of semicarbazides synthesised.

In synthesising these semicarbazides we discovered, as Hoffman *et al.*[27] and Hamuro *et al.*[28] had done, that the monosubstituted hydrazines reacted regioselectively depending on whether the substituted group was aryl or alkyl (table 1.2). The ^{1}H NMR spectra of the aryl and alkyl products, for example **1.8** and **1.9**, provide evidence for the different regioselectivities of the starting hydrazines. The principal differences are the **NH** signals; in the ^{1}H NMR spectra for **1.8** there are three separate **NH** signals at 8.54 ppm, 8.08 ppm and 7.72 ppm each integrating to one proton, whereas in the ^{1}H NMR spectra for **1.9** there are two signals, one at 8.82 ppm integrating to one proton and the other at 4.73 ppm corresponding to two protons (figure 1.10).

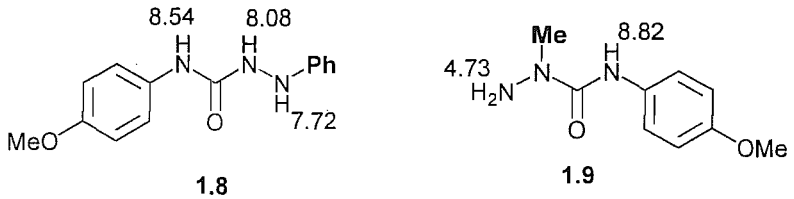


Figure 1.10: ^{1}H shifts (ppm) for **NH** protons of **1.8** & **1.9**.

This evidence, in addition to literature reports on this type of hydrazine reaction,[27, 28, 32] means we can confidently assign the semicarbazide structures (table 1.2 and figure 1.10). The regioselectivity of the monosubstituted hydrazines can probably be explained by the positive inductive effect of the alkyl group versus the steric bulk and mesomeric electron-withdrawing effect of the aryl group. Since

Hamuro *et al.* did not see attack of the substituted nitrogen when reacting benzylhydrazine with their polymer supported reactant we must therefore assume that steric factors are more important when the reaction is carried out on solid-phase.[28]

Semicarbazides **1.13** and **1.14** were synthesised at a much later date than **1.8** – **1.12** and their purpose is to be discussed later (Results and Discussion, section 1.2.1, part ***iii***). However their facile synthesis and excellent yields compare well with those of the earlier semicarbazides. The synthesis of **1.13** and **1.14** varies only slightly from the synthesis of **1.8** – **1.12**; since *p*-toluene-sulphonyl hydrazine **1.15** is not commercially available it was first synthesised according to a literature procedure[33] and then reacted with benzyl isocyanate to give **1.13** in excellent yield (98%, figure 1.11). 2-Methyl-4-(4-methoxyphenyl) semicarbazide **1.11** was reacted with tosyl chloride to give **1.14** again in excellent yield (91%, figure 1.11).

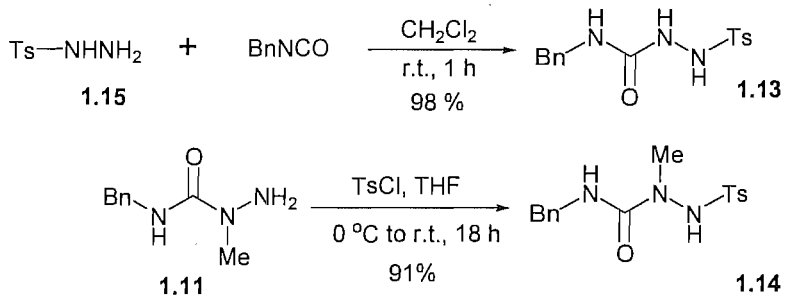


Figure 1.11: Synthesis of semicarbazides **1.13** and **1.14** by different pathways

ii) Reaction of semicarbazides and cyclisation to 1,4,5-trisubsitituted 1,2,4-triazine-3,6-diones

In the proposed synthesis of the 1,4,5-trisubstituted 1,2,4-triazine-3,6-dione scaffold (figure 1.10) the semicarbazide is reacted with either chloroacetyl chloride or bromoacetyl bromide to give a straight-chain intermediate, followed by cyclisation to the desired heterocycle. With a range of semicarbazides produced, the reaction of **1.8** – **1.12** with the halogenated reagents was explored.

In a series of test reactions, 1-phenyl-4-(4-methoxyphenyl) semicarbazide **1.8** was reacted with chloroacetyl chloride and bromoacetyl bromide to give the products 1-chloroacetyl-1-phenyl-4-(4-methoxyphenyl) semicarbazide **1.16** in a fair yield (55%) and 1-bromoacetyl–1-phenyl-4-(4-methoxyphenyl) semicarbazide **1.17** in a good yield (78%, scheme 1.9).

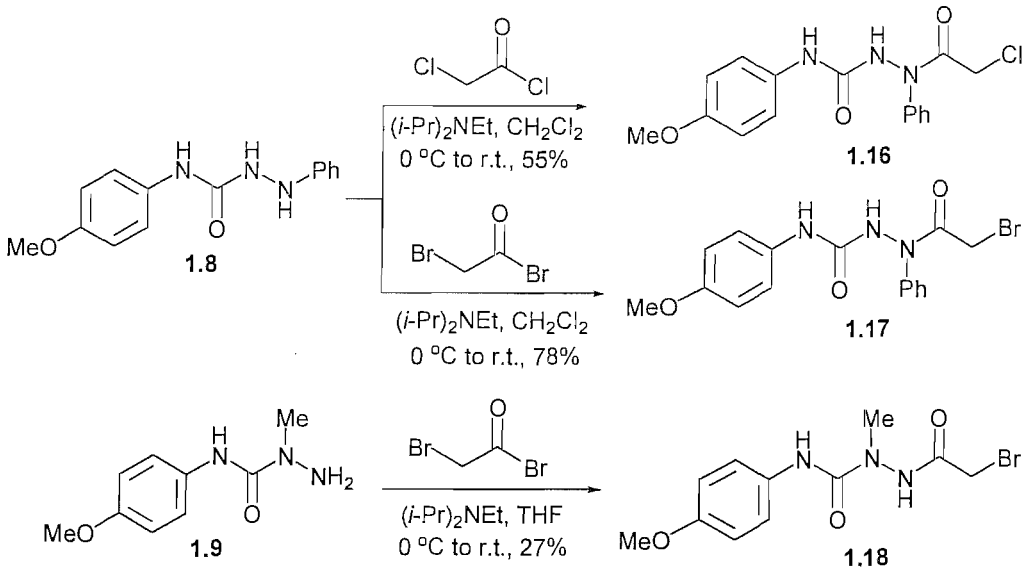


Figure 1.9: Reaction of semicarbazide **1.8** with chloroacetyl chloride and bromoacetyl bromide to give intermediates **1.16** and **1.17**, and reaction of semicarbazide **1.9** with bromoacetyl bromide to give intermediate **1.18**.

Although reaction of bromoacetyl bromide with semicarbazide **1.9** was successful, if low yielding, (27%, figure 1.9), the reactions of semicarbazides **1.10 – 1.12** with both bromoacetyl bromide and chloroacetyl chloride have consistently failed, with neither starting material recovered in any of these reactions. Since these failed reactions all started from a semicarbazide with a benzyl group in the R_3 position, it may well be that the 4-methoxyphenyl group gives the products **1.16**, **1.17** and 1-bromoacetyl-2-methyl-4-(4-methoxyphenyl) semicarbazide **1.18** some vital stability. In all of these unsuccessful reactions a thick black oil that could not be purified was observed. It is thought that, in these reactions the desired product may well be formed but continues to react with other molecules of product or starting material forming a complex mixture of polar dimers and chains; this would explain the absence of the starting materials and the black tar that was seen as a baseline streak on TLC.

The three intermediates **1.16**, **1.17** and **1.18**, due to the different substitution patterns in their semicarbazide starting materials, will on cyclisation produce different substitution arrangements in the final triazinedione scaffold. The differences between the 1,4-substituted intermediates **1.16** and **1.17** and the 2,4-substituted intermediate **1.18** should therefore be considered. For example, the ^{1}H NMR spectra of the intermediate **1.17** contains two extremely broad doublets corresponding to the CO**C**$\underline{\mathbf{H}}_2$Br protons. Variable temperature NMR experiments showed that the two broad doublet peaks coalesced to one singlet at about 90 °C.

From this evidence it would seem that the intermediates **1.16** and **1.17** exist as two rotamers at lower temperatures (figure 1.10). The ^{1}H NMR spectrum of **1.18**, however, shows the CO$\underline{CH_2}$Br signal as a singlet, indicating that the intermediate **1.18** does not exist as conformationally constrained rotamers at room temperature.

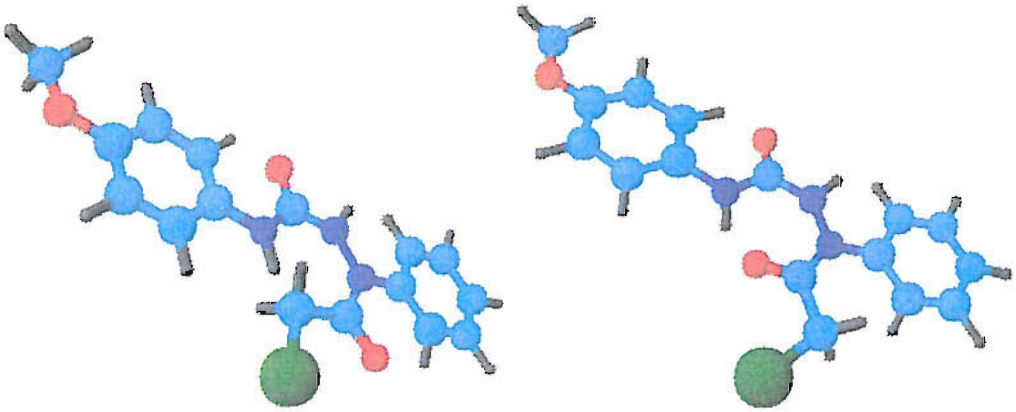
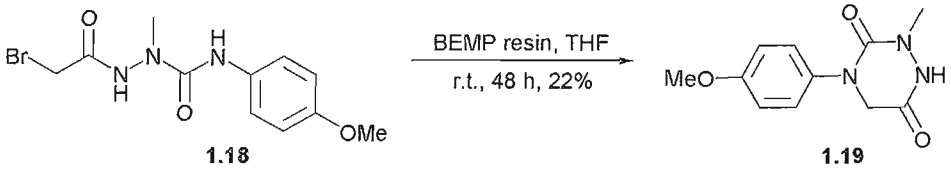


Figure 1.10: 3D diagram of two rotamer conformations of the intermediate **1.17**.

Since in order to achieve the most favourable conformation for cyclisation the intermediates **1.16** and **1.17** must overcome this rotational restriction in the amide bond, it is likely that elevated temperatures would be needed to achieve cyclisation for these intermediates. Unfortunately, although **1.17** was stable in the variable temperature NMR experiments, even gentle heating of a solution of **1.17** or **1.16** in dioxane in the presence of Hünig's base led to the rapid breakdown of the semicarbazide. Potassium *tert*-butoxide was observed to cause the complete breakdown of **1.17** in THF at room temperature in less than 2 h.

The intermediate **1.18**, however, proved to be much more stable than **1.16** or **1.17**. In a small test reaction, **1.18** was stirred with potassium *tert*-butoxide in THF at room temperature. The intermediate did not break down; instead nucleophilic attack of the butoxide group took place, replacing the bromine atom with O^{t}Bu. From this experiment it was clear to us that a strong but non-nucleophilic base was required for the cyclisation. Following on from this thought, the intermediate **1.18** was dissolved in THF and stirred slowly with a large excess of the very basic BEMP resin. After 2 days the reaction was complete by TLC and the resin was filtered to give the desired product; 2-methyl-4-(4-methoxyphenyl)-1,2,4-triazine-3,6-dione **1.19** in a low yield (22%, scheme 1.9). The ^{1}H NMR spectrum of this heterocycle shows it to exist as two distinct conformers and the infra red spectrum

was shown to be consistent with those bands reported in the literature as characteristic of the 1,2,4-triazine-3,6-diones.[27]



1.18 **1.19**

Scheme 1.9: Cyclisation of semicarbazide **1.18** to heterocycle **1.19**.

The problems encountered in this synthetic route to the 1,4,5-trisubstituted 1,2,4-triazine-3,6-dione scaffold seem to be inherent to the structure of the intermediates, indeed the triazinedione that was successfully synthesised was in fact substituted at the 2 and 4 positions. We therefore looked at alternative routes to the triazinedione scaffolds.

iii) Reaction of α-hydroxy esters with hydrazines and semicarbazides

While considering the difficulties experienced in synthesising the 1,4,5-trisubstituted 1,2,4-triazine-3,6-dione scaffold, we read a paper by Hoffman *et al.*[34] describing the reaction of Boc hydrazine with α-hydroxy esters to produce 2-hydrazinyl ester derivatives. It occurred to us that this reaction could be used to synthesise 1,2,4-triazine-3,5-diones and their aminohydantoin isomers (figure 1.11). Although this was not in the original project's aims, we felt that both these heterocycles would be of interest as they are scarcely reported in the literature and meet the five specifications outlined previously (Introduction, section 1.1.2). We therefore set about exploring the reaction of α-hydroxy esters with hydrazines and semicarbazides.

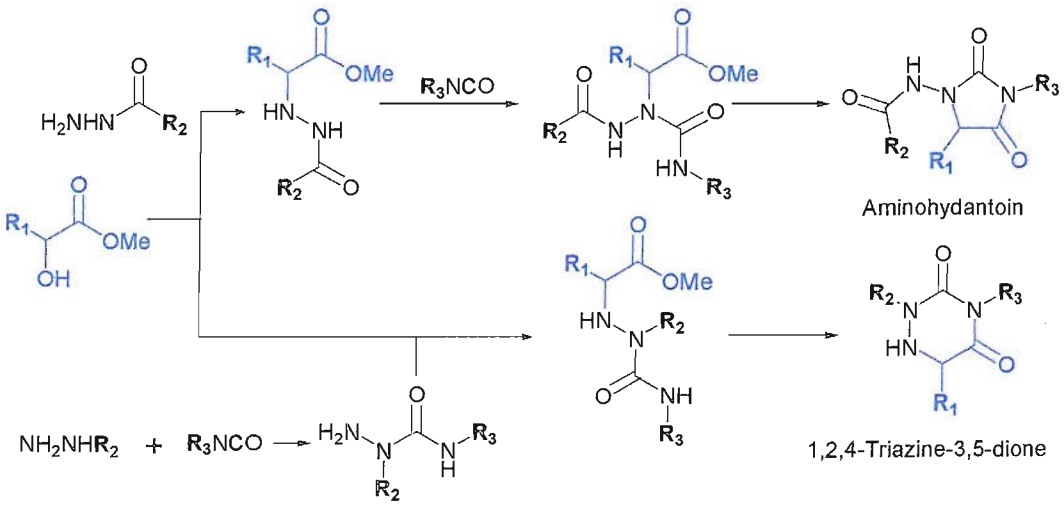
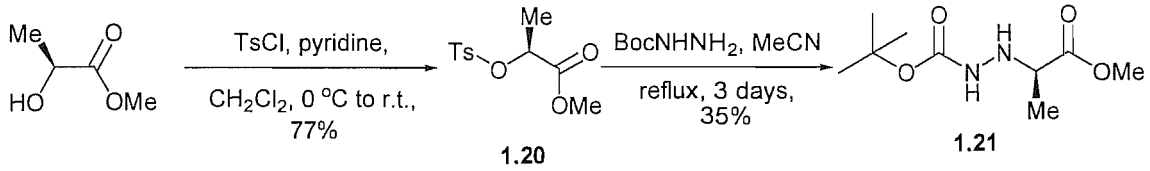


Figure 1.11: Proposed synthesis of 1,2,4-triazine-3,5-diones and their aminohydantoin isomers.

In the paper by Hoffman *et al.*, α-hydroxyl esters were converted to 2-triflyloxy esters and then reacted with Boc protected hydrazine in a one-pot procedure.[34] Our attempts to reproduce these one-pot reactions with either Boc-hydrazine or the previously prepared, 2-methyl-4-benzyl semicarbazide **1.11**, have been consistently unsuccessful. Again it would seem that the starting materials and product continue to react, producing complex mixtures from which the desired product could not be separated. Hoffman *et al.*, however, also reported that 2-nosyloxy esters reacted with Boc-hydrazine to produce the desired hydrazino esters in good yields in refluxing acetonitrile. With this methodology in mind, 2-(toluene-4-sulfonyloxy)-propionic acid methyl ester **1.20** was synthesised from (*S*)-methyl lactate in good yield (77%, scheme 1.10). Ester **1.20** was then reacted with Boc-hydrazine in refluxing acetonitrile to give 2-(*N*-*tert*-butoxycarbonyl-hydrazino)-propionic acid methyl ester **1.21** in moderate yield (35%, scheme 1.10).



Scheme 1.10: Reaction of (*S*)-methyl lactate with tosyl chloride to give ester **1.20** and reaction of Boc-hydrazine with ester **1.20** to give methyl ester **1.21**.

As the low yield and slow reaction time of the above reaction was not ideal we wished to discover if the α-hydroxy esters could be reacted directly with the hydrazines under Mitsunobu conditions. Since this would reduce the synthesis by one step, in addition to avoiding the slow step, this would obviously be a preferred route.

Consulting the literature we found a paper reporting that *p*-toluene-sulphonyl hydrazines undergo Mitsunobu reactions with a range of alcohols.[35] Following this work we reacted the previously synthesised tosyl hydrazine **1.15** (figure 1.11) with (*S*)-methyl lactate under typical Mitsunobu conditions (figure 1.12). Although triphenylphosphine oxide was clearly seen by TLC and isolated after column chromatography, no other compounds could be cleanly separated from the crude mixture and there seemed little evidence that the desired product was present. Further reading of the literature, however, suggested that the desired product is unlikely to be particularly stable, with loss of dinitrogen and disintegration to the deoxygenated product (figure 1.13).[36, 37]

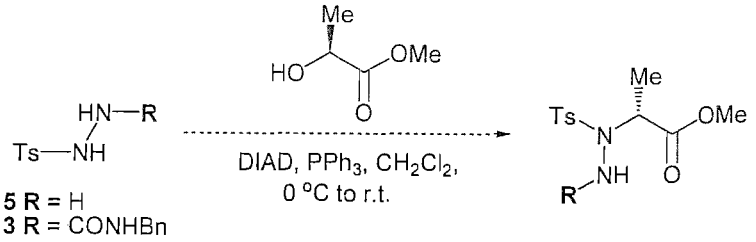


Figure 1.12: Attempted reactions of tosyl hydrazine **1.15** and semicarbazide **1.13** with (*S*)-methyl lactate under Mitsunobu conditions.

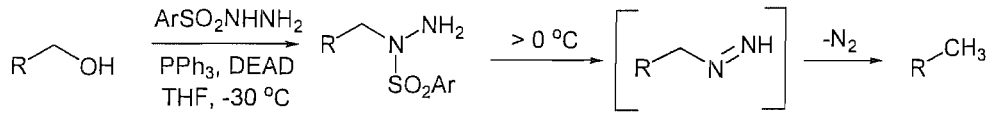


Figure 1.13: Example of Mitsunobu reaction with tosyl hydrazine where the product disintegrates to give the deoxygenated product and toluenesulfonic acid with loss of nitrogen gas.[36, 37]

It was realised that if the tosyl hydrazine was functionalised on the β-nitrogen, the loss of dinitrogen would then not be possible. It was for this reason that the two novel semicarbazides *p*-toluenesulphonyl-4-benzyl semicarbazide **1.13** and *p*-toluenesulphonyl-2-methyl-4-benzyl semicarbazide **1.14** were synthesised (table 1.2, in Results and Discussion, section **1.2.1**, part ***i)***). The semicarbazide **1.13** was then reacted with (*S*)-methyl lactate under standard Mitsunobu conditions (figure 1.12). Again, triphenylphosphine oxide was seen by TLC and isolated after column chromatography. This time, however, the majority of the starting material **1.13** was also isolated (88%). The yield of triphenylphoshine oxide (84%) was more than would be expected if the remaining percentage of semicarbazide **1.13** were the only nucleophile in this reaction. This intriguing result suggested that it was perhaps the hydrazine formed from the Mitsunobu azo compound that was acting as the nucleophile instead of the desired hydrazine.

A paper published in 1996 by Di Grandi *et al.*[38] added further support to this theory as it describes how the authors hoped that by stirring an α-hydroxy ester under Mitsunobu conditions the hydrazine formed from the azo compound would act as the nucleophile and give them their desired α-hydrazino esters (figure 1.14). Although Di Grandi *et al.* were expecting the α-hydroxy esters to react under Mitsunobu conditions to give α-hydrazino esters what they actually observed was dihydrohydrazino ester products.

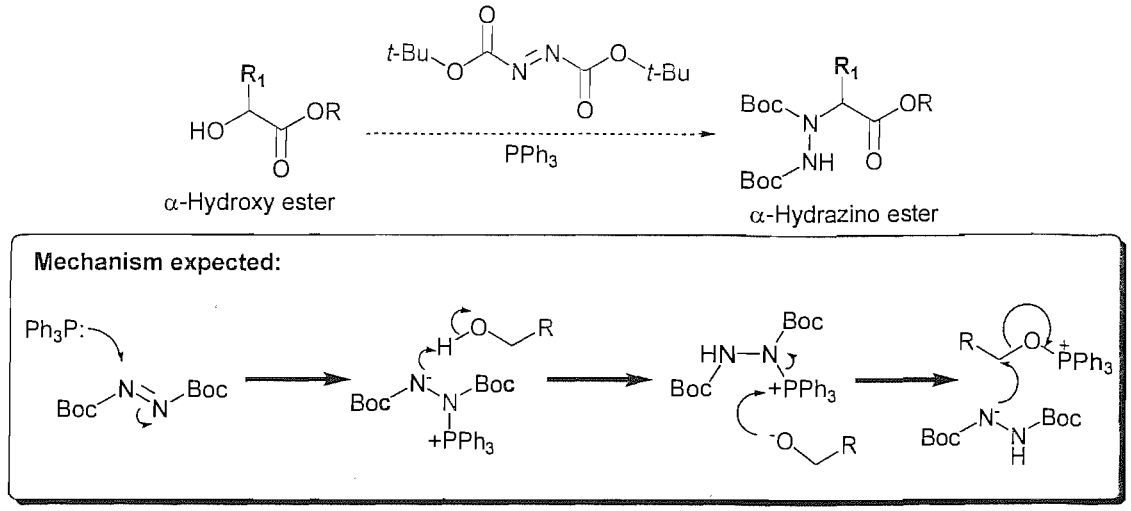


Figure 1.14: Reaction type attempted by Di Grandi *et al.* and the mechanism they hoped would give them their desired product.[38]

An older paper published by Kolasa and Miller[39] also reports the reaction of α-hydroxy esters under Mitsunobu conditions to give dihydrohydrazino esters and a recent paper by Liu *et al.*[40] describes the synthesis of vinyl hydrazines from ketones via Mitsunobu chemistry. All three sets of authors propose the same or a very similar mechanism for this reaction type (figure 1.15).[38-40]

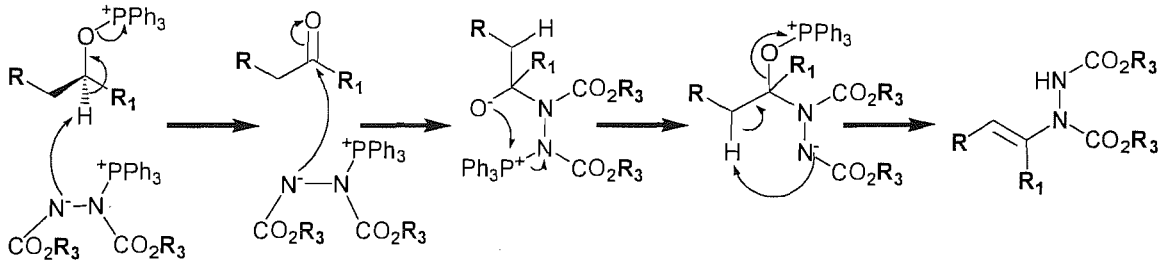


Figure 1.15: Mechanism proposed for the synthesis of dihydrohydrazino esters from α-hydroxy esters and the synthesis of vinyl hydrazines from ketones.[39]

Kolasa and Miller also reported observing a second product, an oxadiazole heterocycle in addition to the dihydrohydrazino esters in their reaction of α-hydroxy esters under Mitsunobu conditions.[38-40]

The observations from our own reactions with α-hydroxy esters combined with these three separate literature reports suggested to us that that these compounds are incompatible with the Mitsunobu reaction for our purposes. Indeed, the whole deviation from the original aim of synthesising 1,2,4-triazine-3,6-diones by investigating the synthesis of 1,2,4-triazine-3,5-diones was proving less fruitful than had been hoped and was therefore not pursued further.

1.2.2 Mitsunobu reactions with carbonyl compounds.

We were sufficiently interested in the reaction of the α-hydroxy esters with the Mitsunobu reagents and the mechanism proposed for this reaction that we wished to establish for ourselves if this was indeed the mechanism for this unusual reaction. The mechanism proposed by Kolasa *et al.* and Di Grandi *et al.* starts with the α-hydroxy ester being first oxidised to an α-keto ester (figure 1.15). We therefore wondered if α-keto esters would react with the Mitsunobu reagents to give the same products as the α-hydroxy esters.

Following this line of enquiry, methyl pyruvate **1.22** was reacted with diisopropyl azodicarboxylate and triphenylphosphine to give triphenylphosphine oxide and the known compound 5-methoxy-4-methyl-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester **1.23** in excellent yield (98%, table 1.3). Although Kolasa and Miller[39] had reported oxadiazole products in addition to the dihydrohydrazino ester products, the fact that we only saw the formation of the oxadiazole product and in such excellent yield was unexpected. This result does however suggest that the mechanism proposed by Di Grandi *et al.*[38] and Kolasa and Miller[39] is viable and allows us to suggest the following mechanism for the formation of the oxadiazole heterocycles (figure 1.16).

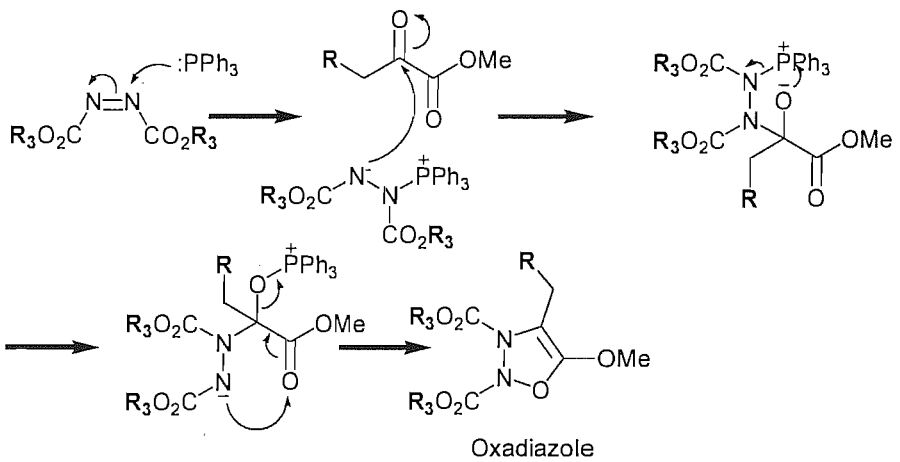
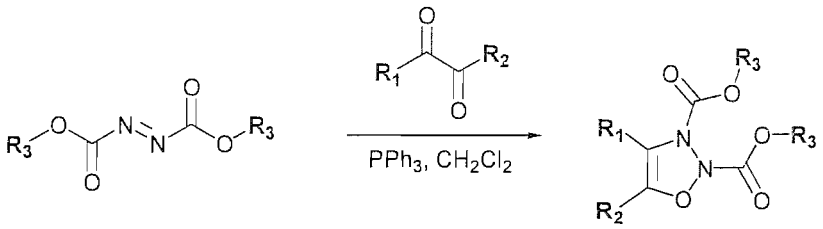


Figure 1.16: Mechanism for formation of oxadiazole heterocycle.

Since we did not know if this result was a single anomaly or a general reaction for α-keto esters, three known α-keto esters (**1.24** – **1.26**) were synthesised for reaction with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP) in order to investigate this reaction more fully (figure 1.17).



Product	R_1	R_2	R_3	Yield [a]
1.23	Me	OMe	^{i}Pr	98
1.28	^{i}Pr	OMe	^{i}Pr	71
1.29	^{n}Bu	OEt	^{i}Pr	80
1.30	$PhCH_2$	OMe	^{i}Pr	27
1.31	Ph	OMe	^{i}Pr	61
1.32	Ph	Ph	^{i}Pr	83
1.33	Ph	Me	^{i}Pr	31
1.34	Me	OMe	^{t}Bu	97
1.35	$PhCH_2$	OMe	^{t}Bu	81

[a]Percentage yield of isolated product.

Table 1.3: [1,2,3]Oxadiazole-2,3-dicarboxylic acid esters synthesised from α-keto esters under Mitsunobu conditions.

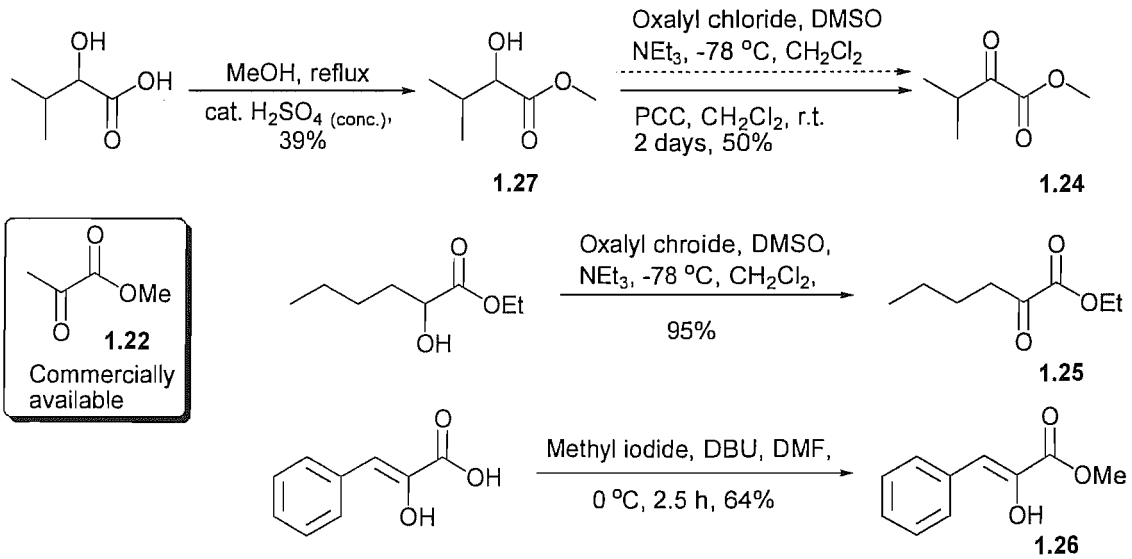


Figure 1.17: Synthesis of the α-keto ester starting materials used in reaction with Mitsunobu reagents.

Methyl 2-hydroxy-3-methylbutanoate **1.27** was synthesised according to a literature procedure.[41] Subsequent Swern oxidation of this ester, however, consistently failed and oxidation using pyridinium chlorochromate was found to be the best method of oxidation for this alcohol, giving a 1:1 inseparable mixture of

starting material and methyl 3-methyl-2-oxobutanoate **1.24** (figure 1.17). Swern oxidation of ethyl 2-hydroxyhexanoate gave α-keto ester **1.25** in excellent yield (95%, figure 1.17) following a literature procedure[42] and esterification of phenyl pyruvic acid gave α-keto ester **1.26** in good yield (64%, figure 1.17) also following a literature procedure.[43]

The 1:1 inseparable mixture of alcohol **1.27** and α-keto ester **1.24** was reacted with DIAD and TPP to give the oxadiazole **1.28** in good yield (71%, table 1.3); again no dihydrohydrazino ester products were observed and the remaining alcohol **1.27** could be separated cleanly. Reaction of **1.25** with DIAD and TPP gave the product oxadiazole **1.29** in excellent yield (80%, table 1.3). The reaction of **1.26** with DIAD and TPP, however, gave the product oxadiazole **1.30** in a much lower yield (27%, table 1.3), the reduced azo product hydrazine **1.36** was also isolated from this reaction in a good yield, (60%, figure 1.18) suggesting that the triphenylphosphine might have preferentially attacked the DIAD instead of the α-keto ester **1.26** (figures 1.16 and 1.18). This may be due to the fact that α-keto ester **1.26** exists mainly in the enol form unlike the other α-keto esters used thus far (figure 1.17).

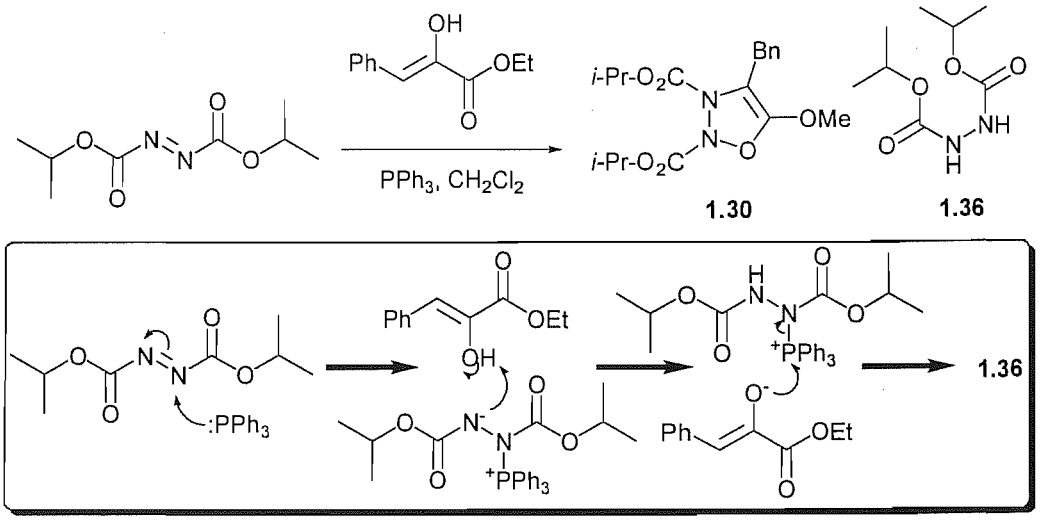


Figure 1.18: Reaction of α-keto ester **1.26** with DIAD and TPP to form oxadiazole **1.30** and mechanism of DIAD reduction to hydrazine **1.36**.

The commercially available oxo-phenyl-acetic acid ester was reacted with DIAD and TPP to give the expected heterocycle **1.31**. Although this product is very unstable and deteriorated rapidly at room temperature it was initially isolated in good yield (61%, table 1.3).

Since the proposed mechanism for this reaction (figure 1.16) would allow 1,2-diketones as well as α-keto esters to form oxadiazoles heterocycles, two 1,2-diketones were also reacted with the Mitsunobu reagents (table 1.3). Benzil reacted with DIAD and TPP to give the known oxadiazole **1.32** in excellent yield (83%, table 1.3) whereas 1-phenyl-propane-1,2-dione gave a mixture of products; oxadiazole **1.33** and dihydrohydrazino ketone product **1.33a** (figure 1.19). This result further suggesting that the α-hydroxy esters, α-keto esters and the 1,2-diketones all proceed through the same reaction mechanism when reacted with triphenylphosphine and azodicarboxylates.

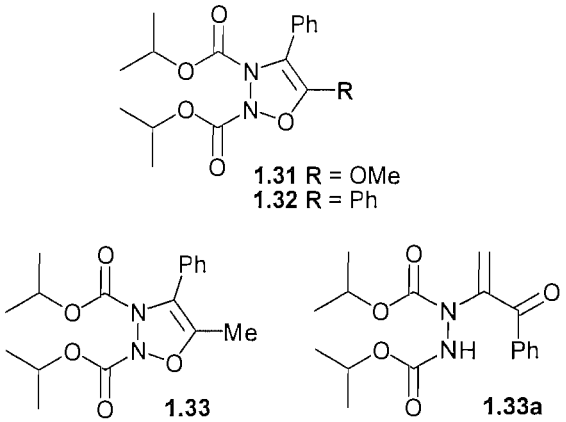


Figure 1.19: Structures of oxadiazoles **1.31** to **1.33** and dihydrohydrazino ketone **1.33a.**

Finally, methyl pyruvate **1.22** and methyl phenyl pyruvate **1.26** were reacted with di-*tert*-butyl azodicarboxylate (DBAD) and triphenylphosphine to give the oxadiazoles **1.34** and **1.35** respectively in excellent yields (97% and 81%, table 1.3). Interestingly, while the α-keto ester **1.26** did not react well with DIAD the yield with DBAD was considerably better (27% *c.f.* 81%). The increased steric bulk of the *tert*-butyl group on the azodicarboxylate must hinder the triphenylphosphine enough that it favours attack of the α-keto ester in this case.

Since α-keto esters and 1,2-diketones both react well under these Mitsunobu conditions to give the oxadiazole heterocycles we decided to try to extend the reaction to α-keto amides. Two α-keto amides were synthesised, the first, α-keto amide **1.37** was synthesised from the carboxylic acid in good yield (68%, figure 1.20) following a literature procedure.[44] The second, α-keto amide **1.38**, was synthesised from the coupling of methyl pyruvate and pyrrolidine with diisopropylcarbodimide (DIC) (figure 1.20).[45] Neither reaction of **1.37** or **1.38** with DIAD and TPP produced either the oxadiazole heterocycle or the

dihydrohydrazino amide; in both cases only the hydrazine **1.36** was isolated. We believe that the amide rotamers mean that the C-C double bond between the two carbonyl carbon atoms cannot form thereby stopping the mechanism altogether (figure 1.20).

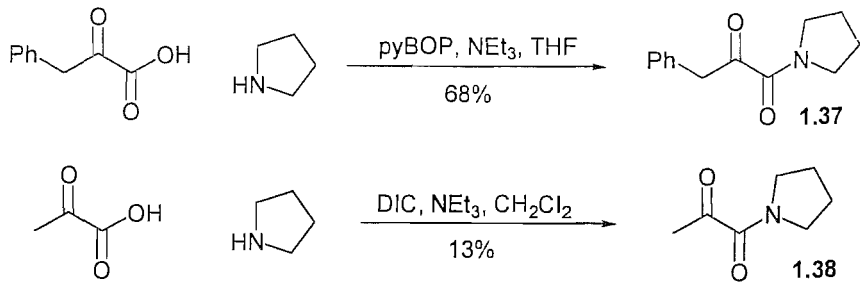


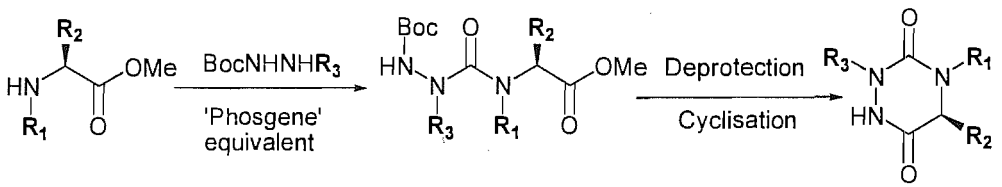
Figure 1.20: Synthesis of α-keto amides **1.37** and **1.38** from their carboxylic acids.

In synthesising a range of novel and known oxadiazoles from α-keto esters and 1,2-diketones under Mitsunobu conditions, we have shown that the α-hydroxy esters are oxidised to α-keto esters by the Mitsunobu reagents thereby supporting the mechanism proposed in the literature, as well as demonstrating a simple and novel synthesis of these unusual heterocycles.

1.2.3 Synthesis of 2,4,5-Trisubsitituted 1,2,4-Triazine-3,6-diones

i) Reductive alkylations of Boc Hydrazine

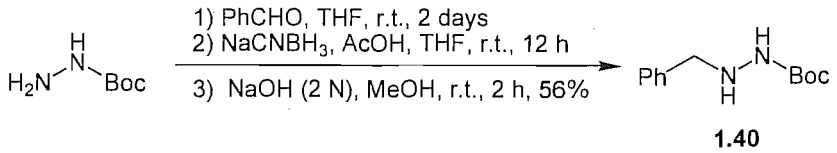
The second of the two triazinedione structures initially proposed for synthesis was the 2,4,5-trisubstituted 1,2,4-triazine-3,6-dione (figure 1.7). The retrosynthesis for this heterocycle was based on the literature report of Obreza *et al.*,[29] and involves the following forward synthesis (scheme 1.11).



Scheme 1.11: Proposed forward synthesis of 2,4,5-trisubstituted 1,2,4-triazine-3,6-dione.

One of the important features of this synthesis over triazinedione syntheses previously reported in the literature, is the fact that the hydrazine is protected on one nitrogen and substituted on the other, meaning that there can be no confusion or choice in which nitrogen attacks in the ring closing step; only the six membered ring can form.

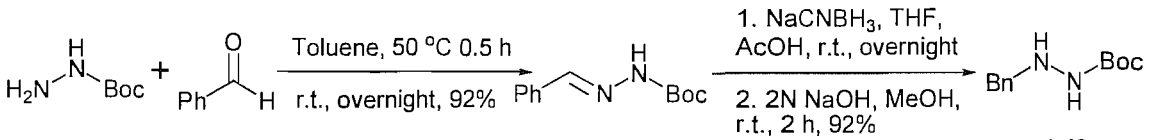
The first step in this route is to synthesise the two starting materials: the alkylated amino acid methyl esters; and the Boc protected alkylated hydrazines. We started by reductively alkylating the commercially available Boc hydrazine. Boc hydrazine was reacted with benzaldehyde in THF at room temperature. When the starting material had completely disappeared by TLC, the resulting hydrazone **1.39** was reduced without isolation and the final product was worked up with sodium hydroxide in methanol to give the known hydrazine **1.40** in a slightly disappointing yield (56%, scheme 1.12).[46, 47]



1.40

Scheme 1.12: Reductive alkylation of Boc hydrazine to give *N'*-benzyl *N*-Boc hydrazine **1.40**.

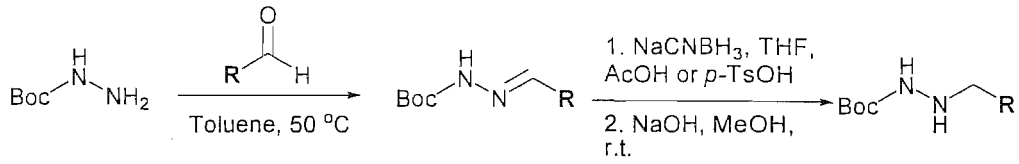
We subsequently found that if the Boc hydrazine and benzaldehyde were stirred in toluene at 50 °C the hydrazone **1.39** formed far more rapidly. Allowing the cooled reaction mixture to stand at room temperature overnight meant the hydrazone precipitated out of solution and could be easily isolated and recrystallised before reduction. This two step approach meant that the overall yield of hydrazine **1.40** was greatly improved (85% for two steps, scheme 1.13 and table 1.4).



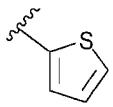
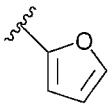
1.39 **1.40**

Scheme 1.13: Improved reductive alkylation of Boc hydrazine to give product hydrazine **1.40**.

Following this improved route, a total of fifteen hydrazines were synthesised in this manner (table 1.4). Hydrazines **1.40** to **1.50** were synthesised soon after we developed the improved synthesis of **1.39** using six commercially available aldehydes including benzaldehyde. A carousel system of reaction vessels was used in order to carry out these reactions simultaneously on a two to three gram scale. The hydrazone products could then be filtered, washed with cold toluene and recrystallised to give the pure crystalline products in good to excellent yields (73 – 95%, table 1.4). Hydrazone **1.49** did not precipitate out of solution on cooling however, and the solvent was therefore removed *in vacuo* and the crude residue was triturated with *n*-hexane to give the hydrazine **1.50** before recrystallisation.



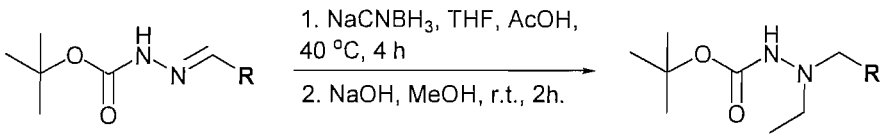
Hydrazone **Hydrazine**

	R	M. Pt. [a]	Yield [b]		M. Pt. [c]	Yield [d]	Yield [f]
1.39	Ph	185-186	92	**1.40**	-	92	85
1.41	4-$MeOC_6H_4$	133-134	95	**1.42**	-	77	73
1.43	4-$Me_2NC_6H_4$	156-157	73	**1.44**	-	87	64
1.45	4-$NO_2C_6H_4$	165-166	84	**1.46**	89-90	87 [e]	73
1.47	3,4,5-$(MeO)_3C_6H_4$	167	87	**1.48**	62-64	79 [e]	69
1.49	$CH_3(CH_2)_3$	54-56	84	**1.50**	-	83	70
1.51	2-BrC_6H_4	179	82	**1.52**	70	91	75
1.53	3-BrC_6H_4	131	75	**1.54**	68	95	71
1.55	4-BrC_6H_4	155	82	**1.56**	74	79	65
1.57		194-195	90	**1.58**	31-32	75	68
1.59		161-162	69	**1.60**	44-45	82	57
1.61	2-$MeOC_6H_4$	135-136	74	**1.62**	60-61	69	51
1.63	3-$MeOC_6H_4$	121-122	87	**1.64**	-	65	57
1.65	3,5-$(MeO)_2C_6H_4$	161	77	**1.66**	45-46	79	61
1.67	2,4,6-$(MeO)_3C_6H_4$	172	95	**1.68**	-	47	45

[a] Melting point of hydrazone in degrees Celsius, [b] Percentage yield of isolated hydrazone, [c] Melting point of hydrazine in degrees Celsius [d] Percentage yield of isolated hydrazine, [e] *p*-TsOH used instead of AcOH, [f] Percentage yield of isolated hydrazine over two steps.

Table 1.4: The melting points and yields of the hydrazones and hydrazines synthesised from Boc hydrazine.

The six hydrazones **1.39** to **1.49** were reduced in parallel using the conditions previously established for the reduction of **1.39**. Two of the reactions (reduction of **1.45** and **1.47**), however, did not appear to change by TLC whereas the other four proceeded as expected. The two unchanging reactions were stirred for a further 12 h with an additional equivalent of $NaCNBH_3$ at room temperature. Again no change was seen by TLC and the reactions were warmed to 40 °C; after 4 h at this temperature a second spot was seen by TLC and the reactions were worked up as before. The purified products, however, were discovered to be the unexpected hydrazines **1.69** and **1.70**; neither of the desired products were isolated (scheme 1.14).



1.45 R = 4-NO_2Ph
1.47 R = 3,4,5-$(MeO)_3$Ph

1.69 R = 4-NO_2Ph, 54%
1.70 R = 3,4,5-$(MeO)_3$Ph, 24%

Scheme 1.14: The formation of unwanted hydrazines **1.69** and **1.70**.

It is thought that the hydrazones are reduced on heating to the desired hydrazines but these then react rapidly with the acetic acid before being further reduced to give the additional ethyl groups seen in the NMR spectra. The literature reported some hydrazone to hydrazine reductions using *p*-toluene sulphonic acid and sodium cyanoborohydride. [46] We, therefore, decided to try using identical reaction conditions but with *p*-toluene sulphonic acid in place of acetic acid.

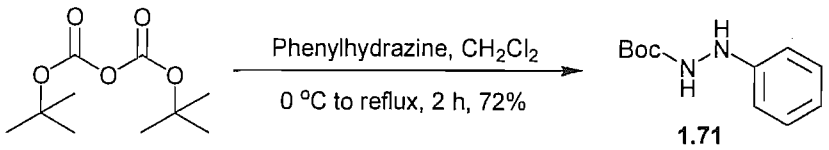
After stirring at room temperature overnight no change was seen by TLC and it was only when these two reactions were heated to reflux did we see conversion to the hydrazines. Four hours refluxing under these conditions gave complete conversion of hydrazone **1.47** to the desired hydrazine **1.48**, whereas the hydrazone **1.45** had not been completely reduced after four hours and the mixture of hydrazine **1.46** and **1.45** was separated by column chromatography - the recovered hydrazone being recycled at a later date. Alternatively, the reduction of **1.45** could be left over 2 days to give complete conversion and an improved yield of hydrazine **1.46** (87%, table 1.4).

The three hydrazones **1.51**, **1.53** and **1.55** were synthesised in excellent yield (75-82%, table 1.4) following the same reaction conditions as used previously. These

were then reduced using sodium cyanoborohydride, acetic acid and the conditions established earlier to give the hydrazines **1.52**, **1.54** and **1.56** again in excellent yield (79-95%, table 1.4). Hydrazones **1.57** and **1.59** were synthesised following our standard procedure, however they took longer to precipitate out of solution and the lower yield of **1.59** is probably due to a more difficult recrystallisation rather than a poor reaction (**1.59** yield 69%, **1.57** yield 90%, table 1.4). Reduction to the hydrazines **1.58** and **1.60** using the sodium cyanoborohydride and acetic acid method again proceeded in excellent yield (75-82%, table 1.4).

The final four hydrazones **1.61**, **1.63**, **1.65** and **1.67** were synthesised following the same procedure as for the others and were isolated in good to excellent yields (74-95%, table 1.4). The reduction to the hydrazines **1.62**, **1.64**, **1.66** and **1.68**, however gave poorer yields than the previous experiments (47-79% *c.f.* 75-95%, table 1.4). This may have been because these four reactions were allowed to stir with NaOH in methanol for longer than the standard two hours. As a result the products were not clean after work-up and had to be purified by column chromatography. The resulting poorer yields most likely indicate that the hydrazines were not stable in the strongly basic solution for the extended period. Despite this, enough of the final four hydrazines were isolated for further reaction that the reactions were not needed to be repeated and these lower yields therefore cannot be seen as truly representative of this reaction.

The method used above for the synthesis of alkylated Boc-protected hydrazines cannot, obviously, be used to synthesise aryl hydrazines. We wished to use at least one aryl hydrazine in our synthesis and so we synthesised *N*-Boc *N'*-phenylhydrazine **1.71** from commercially available phenylhydrazine. Phenyl hydrazine and di-*tert*-butyl dicarbonate were heated to reflux in dichloromethane for 2 h to give the product **1.71** in good yield (72%, scheme 1.14).



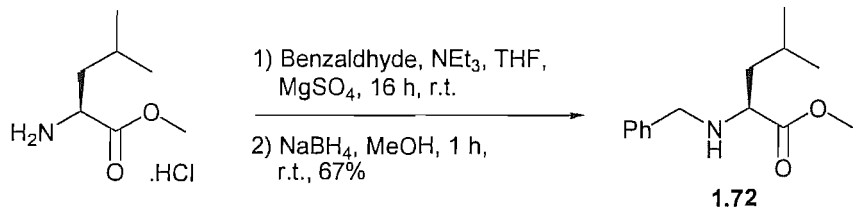
1.71

Scheme 1.14: Synthesis of *N*-Boc *N'*-phenylhydrazine **1.71** from phenylhydrazine.

ii) Reductive alkylations of amino acid methyl esters

In addition to using the commercially available amino acid methyl ester HCl salts, we wished to be able to vary the second R group to produce a more diverse range of final 1,2,4-triazine-3,6-diones. It also seemed likely that varying this R group was likely to affect the reactions later in the synthesis and so it was important to have alkylated amino acid esters in order to fully explore the scope of the later reactions.

The first of these amino acid esters to be alkylated was L-leucine methyl ester HCl. Following a literature procedure, L-leucine methyl ester HCl was reacted with benzaldehyde to give the imine before being reduced with sodium borohydride to the secondary amine **1.72** in good yield (67%, scheme 1.15).[48]

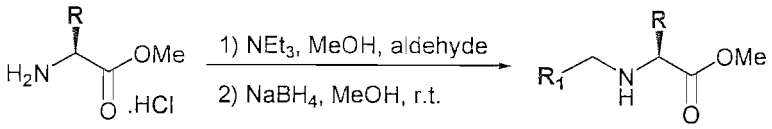


1.72

Scheme 1.15: Reductive alkylation of L-leucine to give the *N*-benzyl leucine product **1.72**.

Again following a literature procedure, the benzylated L-serine product **1.73** was synthesised in excellent yield (95%, table 1.5).[49] Although this synthesis was similar to that used for L-leucine, there were a few differences; methanol was used from the start of the reaction, the reaction time was shorter (a total of 2.6 h) and there was no use of any drying agent. These differences made the reaction easier and faster to carry out, potentially making parallel and larger scale reactions using this method more practical.

The product **1.74** was synthesised from L-tryptophan in an acceptable yield using the same method as that used for product **1.73** (65%, table 1.5). Attempts to synthesise **1.75** in this way or further quantities of **1.72**, however, resulted in unacceptably poor yields (~15%). Addition of dry magnesium sulphate to the methanol in the first stage of the reaction gave good yields for the remaining three products **1.75**, **1.76** and **1.77** (72-79%, table 1.5).



Product	Amino Acid	R_1	Yield [a]
1.72	L-Leucine	CH_2Ph	67
1.73	L-Serine	CH_2Ph	95
1.74	L-Tryptophan	CH_2Ph	65
1.75	L-Phenylalanine	CH_2Ph	74
1.76	L-Leucine	$CH_2C_6H_4$-4-NO_2	79
1.77	L-Leucine	$CH_2C_6H_4$-4-OMe	72

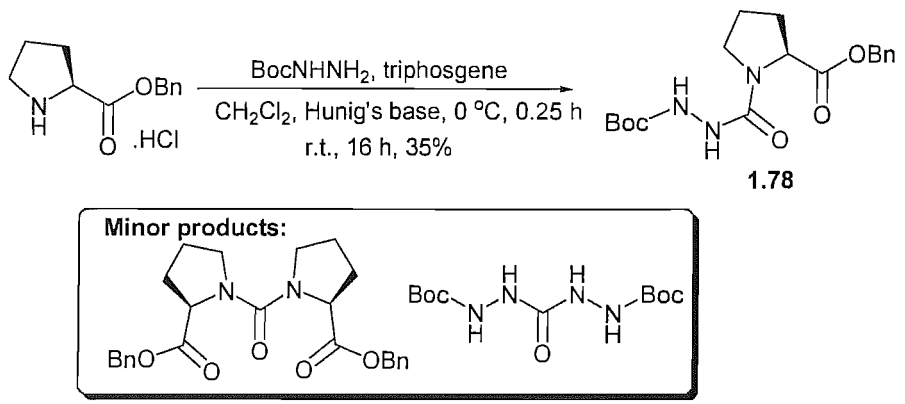
[a] Percentage yield of isolated product.

Table 1.5: Alkylated amino acid starting materials synthesised from commercially available amino acids.

iii) One-pot reaction with triphosgene to give semicarbazides

With a range of the two starting materials synthesised (the Boc protected substituted hydrazines and the amino acid esters with two R groups) we could then examine the reaction of these starting materials with a phosgene equivalent to give the semicarbazides as outlined in our proposed synthesis (scheme 1.11, section **1.2.3**, part ***i)***).

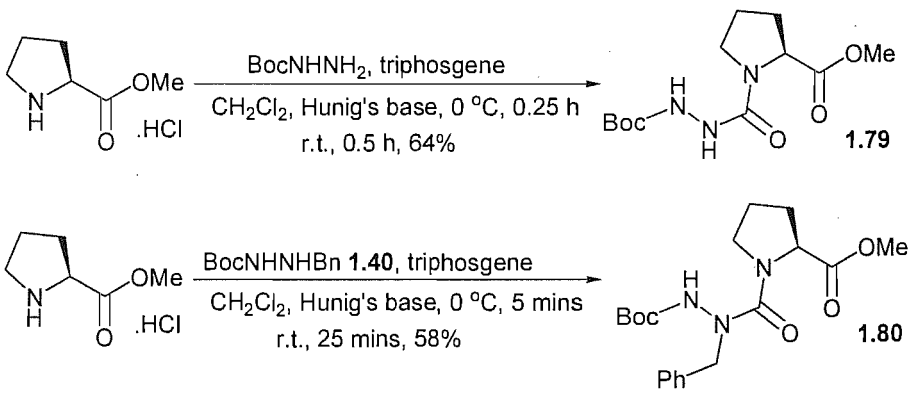
In order to establish the best conditions for this reaction, we first tried the reaction with L-proline benzyl ester and Boc hydrazine. We discovered that although none of the desired product was isolated if either carbonyldiimidazole or diphosgene were used, reaction with triphosgene in dichloromethane gave the correct product in low yield (35%); small quantities of both possible dimers were also isolated (scheme 1.16).



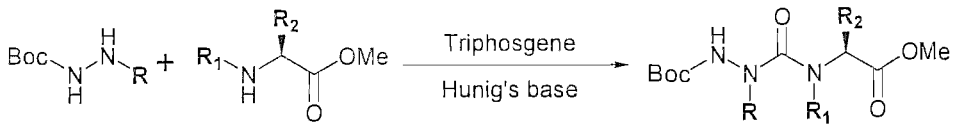
Scheme 1.16: First synthesis of semicarbazide using triphosgene, hydrazine and amino acid ester.

The success of this reaction was dependent on several factors: firstly the order of addition had to be a dilute solution of the hydrazine and Hünig's base added dropwise to a dilute solution of the triphosgene; then after a few minutes stirring, addition of a solution of the benzyl ester and Hünig's base. Changing this order of addition resulted in none of the desired semicarbazide being formed. The quantity of base was also vital, with a total of five equivalents of Hünig's base for every one equivalent of triphosgene used, 2.5 equivalents of Hünig's base being premixed with 2.25 equivalents each of the two starting materials. This premixing and quantity of base was successful for the reactions with the commercial ester hydrochloride salts and the alkylated amino acid esters. The most important factor for the success of this reaction, however, was discovered to be the timing of addition and how long the reaction mixture was allowed to stir.

The reaction between L-proline methyl ester and Boc hydrazine was shown to give a much better yield than the reaction with the benzyl ester (64% *c.f.* 35%, scheme 1.17). Monitoring the disappearance of the ester starting material by TLC was not always easy for these reactions and we found that when the reaction was concentrated after a total of 45 minutes an improved yield was seen; allowing the reaction to continue stirring for a further hour resulted in complete breakdown of the semicarbazide product to the starting materials. This was also seen in the reaction of *N*-benzyl *N'*-Boc hydrazine **1.40** with L-proline methyl ester and triphosgene (58%, scheme 1.17 and table 1.6). A total reaction time of 0.5 h gave semicarbazide **1.80** in a yield of 58% compared to a reduced yield of 50% when the reaction was left for a further 15 minutes.



Scheme 1.17: Synthesis of semicarbazides **1.79** and **1.80** from triphosgene, L-proline methyl ester HCl and Boc hydrazines.



Product	R	R_1	R_2	Yield *a*	Yield *b*
1.80	$PhCH_2$	$-CH_2CH_2CH_2-$		58	–
1.81	$PhCH_2$	CH_2Ph	$CH_2CH(CH_2)_2$	66	–
1.82	$PhCH_2$	H	CH_2Ph	59	–
1.83	Ph	CH_2Ph	$CH_2CH(CH_3)_2$	0	48
1.84	4-$MeOC_6H_4CH_2$	CH_2Ph	$CH_2CH(CH_3)_2$	90	–
1.85	$PhCH_2$	H	CH_2OH	0	79
1.86	3,4,5-$(MeO)_3C_6H_4CH_2$	H	CH_2-2-indole	66	–
1.87	4-$NO_2C_6H_4CH_2$	H	$CH_2CH(CH_3)_2$	44	86
1.88	$CH_3(CH_2)_4$	H	CH_2OH	20	90
1.89	4-$Me_2NC_6H_4CH_2$	H	CH_2Ph	0	25
1.90	4-$Me_2NC_6H_4CH_2$	H	$CH_2CH(CH_3)_2$	29	–
1.91	3,4,5-$(MeO)_3C_6H_4CH_2$	$-CH_2CH_2CH_2-$		73	–
1.92	$PhCH_2$	CH_2Ph	CH_2OH	0	81
1.93	3,4,5-$(MeO)_3C_6H_4CH_2$	CH_2Ph	CH_2-2-indole	0	55
1.94	Ph	H	$CH_2CH(CH_3)_2$	–	60
1.95	$CH_3(CH_2)_4$	CH_2Ph	CH_2Ph	–	88
1.96	4-$Me_2NC_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	89
1.97	$CH_3(CH_2)_4$	H	CH_2Ph	–	27
1.98	4-$NO_2C_6H_4CH_2$	CH_2Ph	CH_2Ph	–	82
1.99	3-$BrC_6H_4CH_2$	H	$CH_2CH(CH_3)_2$	–	52
1.100	4-$MeOC_6H_4CH_2$	$CH_2C_6H_4$-4-NO_2	$CH_2CH(CH_2)_2$	–	76
1.101	2-furanCH_2	$-CH_2CH_2CH_2-$		–	62
1.102	2-thiopheneCH_2	$-CH_2CH_2CH_2-$		–	73
1.103	2-$MeOC_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	68
1.104	3-$MeOC_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	64
1.105	3,5-$(MeO)_2C_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	86
1.106	2,4,6-$(MeO)_3C_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	56
1.107	3,4,5-$(MeO)_3C_6H_4CH_2$	–(*R*)-$CH_2CHOHCH_2-$		–	92
1.108	$PhCH_2$	–(*R*)-$CH_2CHOHCH_2-$		–	93

[a] Percentage yield of isolated product when CH_2Cl_2 is used as solvent, [b] Percentage yield of isolated product when THF is used as solvent.

Table 1.6: Semicarbazides synthesised from hydrazines, amino acid esters and triphosgene.

With our new understanding of this reaction, we then wished to discover if the reaction could be extended to other amino acid esters, especially since Obreza *et al.*[29] had only reported using cyclic amino esters.

Benzyl L-leucine methyl ester **1.72** was reacted with hydrazine **1.40** and triphosgene using the same conditions as used previously. A total reaction time of 40 minutes resulted in no isolated product, whereas a total of 20 minutes before removal of solvent gave the desired semicarbazide **1.81** in good yield (66%, table 1.6).

In carrying out this reaction, we discovered two spots seen on the TLC plate that were extremely close but just separable by careful column chromatography; both looked like they could be the semicarbazide **1.81** structure by ^{1}H NMR spectroscopy. The continuous decomposition of these products during and after purification, however, meant that these two oils could not be fully characterised. Instead, they were both immediately reacted on in separate cyclisation reactions (details reported later), both products cyclised successfully to the same 1,2,4-triazine-3,6-dione heterocycle that could then be fully characterised. The two oils were, therefore, both retrospectively identified as the semicarbazide **1.81**, isolated in a total yield of 66%.

It is thought that the rotation of the amide bonds in the semicarbazide are so restricted due to the steric hindrance of the bulky groups on each of the semicarbazide nitrogen atoms, that two of the conformers may exist independent of each other for long enough to be separated by column chromatography. Since both cyclise to the 1,2,4-triazine-3,6-dione it is likely that removal of the Boc group reduces the steric hindrance sufficiently to allow the amide bonds to rotate more easily. Since first synthesising semicarbazide **1.81** we have occasionally observed other semicarbazides showing a 'figure of eight' on TLC plates, although in the interests of yield we have not attempted to separate them and have been able to characterise these products as pure semicarbazides after rapid purification.

From this point forward we realised that the stability of the semicarbazide products was dependent on how long they were in solvent. We found that as a general rule the reaction mixture should not be allowed to stir for more than 15 minutes before the solvent is removed. Column chromatography and collection of NMR spectra

and other non destructive characterisation data should also be as rapid as possible. Once pure and free of all solvents, the semicarbazides could be stored as oils or solids for a few days at room temperature or indefinitely at low temperatures. Some decomposition has been seen in some of these semicarbazides after a few months storage in a fridge but they could be rapidly purified again by column chromatography if required.

Returning to the semicarbazides reported in table 1.6; hydrazine **1.40** was reacted with L-phenylalanine and triphosgene to give the semicarbazide **1.82** in an acceptable yield (59%, table 1.6). Phenylhydrazine **1.71** and benzyl L-leucine methyl ester **1.72**, however, did not give any of the desired semicarbazide **1.83** using our conditions for this reaction.

A range of previously synthesised hydrazines (**1.40**, **1.42**, **1.44**, **1.46**, **1.48** and **1.50**) were then reacted with the commercially available amino acid methyl esters (L-leucine, L-serine, L-tryptophan, L-phenylalanine and L-proline) or the benzyl alkylated amino acid methyl esters (**1.72** to **1.74**) and triphosgene, following the conditions that had proved successful for our earlier experiments (products **1.84** to **1.93**, table 1.6). The results of these ten experiments were varied; several of the semicarbazides were isolated in good to excellent yield (**1.86**, **1.91** and **1.84**, 66-90%, table 1.6), others were only isolated in poor yield (**1.88**, **1.90** and **1.87**, 20-44% yield, table 1.6) or not at all (**1.85**, **1.89**, **1.92** and **1.93**, table 1.6).

In carrying out these reactions we noticed that the some of the starting materials were difficult to dissolve in dichloromethane and the reaction mixture became cloudy on addition of the ester, this was particularly noticeable for the experiments where the yield of product was low or nonexistent. Repeating these unsuccessful reactions with THF as the solvent and warming the starting solutions gently to 30 °C gave the desired semicarbazides in all cases (**1.83**, **1.85**, **1.89**, **1.92** and **1.93**, table 1.6). Two of the lower yielding reactions carried out in dichloromethane were also found to give improved yields when carried out in THF (**1.87**: 44% improved to 86% and **1.88**: 20% improved to 90%, table 1.6).

Even with this improvement to the synthetic method, a few of these semicarbazides were still only isolated in quite low yield (**1.83**: 48%, **1.89**: 25% and **1.90**: 29%). It is thought that these three semicarbazides are less stable than

others due to increased steric clashes between the R group on the hydrazine part of the semicarbazide and the R group or groups on the amino acid part. This is corroborated by the fact that the phenylhydrazine **1.71** reacted with L-leucine methyl ester and triphosgene to give the semicarbazide **1.94** in a much higher yield (60%, table 1.6) than the semicarbazide **1.83** (48%, table 1.6). 4-Dimethylaminobenzyl hydrazine **1.44** also reacted with L-proline and triphosgene in a much higher yield (**1.96**: 89%, table 1.6) than with L-phenylalanine or L-leucine (**1.89**: 25%, **1.90**: 29%, table 1.6). This was probably because although the cyclic proline is a secondary amino acid, the R groups are 'tied-back' and therefore do not clash with the bulky 4-dimethylaminobenzyl group as much as the benzyl or *iso*-butyl groups (figure 1.21). Although semicarbazide **1.96** was isolated in a better yield, it started to deteriorate quite rapidly and while it could be assigned from its ^{1}H NMR and mass spectrum full characterisation was not possible.

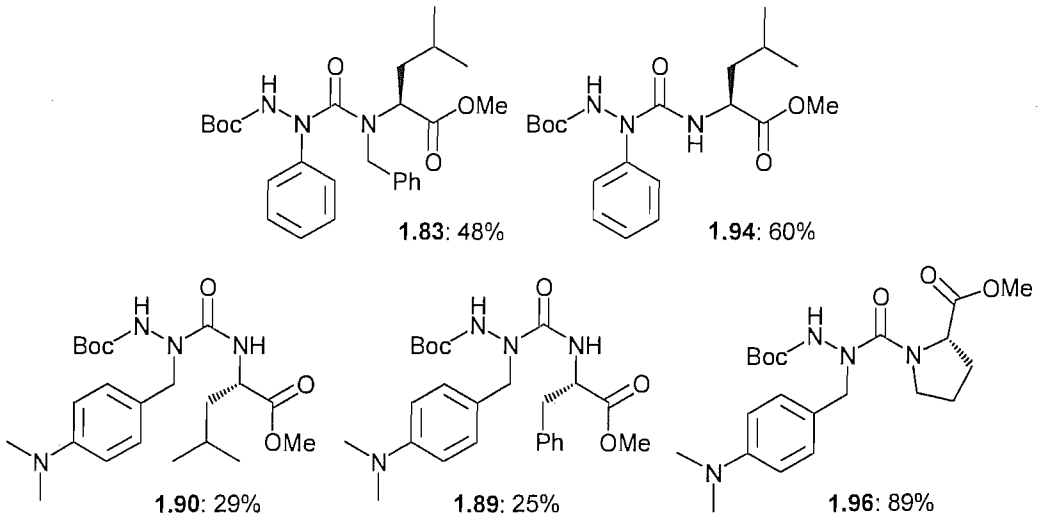
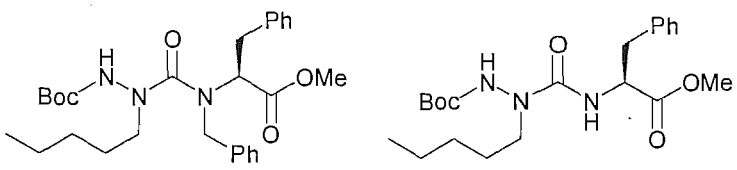


Figure 1.21: Structures and yields of semicarbazides, **1.83**, **1.94**, **1.90**, **1.89** and **1.96**.

The remaining fifteen semicarbazides (**1.94** to **1.108**) were synthesised using THF as the solvent and the reaction conditions described earlier. These products were, with a few exceptions, isolated in good to excellent yield (60-93%, table 1.6). Semicarbazides **1.99** and **1.106** were two of the exceptions, (**1.99**: 52%, **1.106**: 56%, table 1.6). These two reactions were probably low yielding because of steric clashing between the bulky benzyl groups on the hydrazines and the leucine or proline groups. The semicarbazide **1.97** was also isolated in a poor yield (27%, table 1.6). This was especially unexpected as the semicarbazide **1.95** was isolated in a very good yield (88%, table 1.6, figure 1.22).

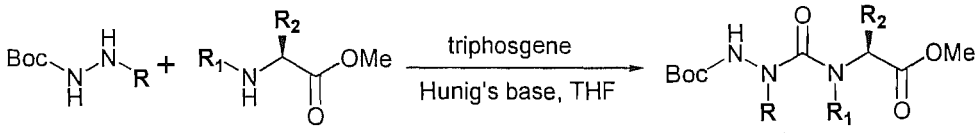
It was noted at the time that the hydrazine **1.50** had solidified to a hard clear glass-like solid on storage making dissolving the hydrazine more difficult than normal; it is though that this was probably the contributory factor in the low yield for this reaction. The dimer product formed from reaction of two molecules of L-phenylalanine methyl ester with phosgene was also seen as a product of this reaction. Reaction of hydrazine **1.50** and benzyl L-serine methyl ester **1.73** with triphosgene in THF, carried out at the same time as the reaction with L-phenylalanine methyl ester did not give any of the desired product at all, most probably for the same reason as for the low yield for the L-phenylalanine reaction.



1.95: 70% **1.97**: 27%

Figure 1.22: Structures and yields of semicarbazides **1.97** and **1.95**.

During this time, a third year undergraduate student working in our research group began to synthesise some semicarbazides under the author's direct supervision. The student (Mark Cobb) synthesised six semicarbazides (**1.109** to **1.114**, table 1.7) in good to excellent yields (50-98%, table 1.7) following the same triphosgene in THF methodology used to synthesise the previous semicarbazides.[50] Semicarbazide **1.114** was particularly unstable and only ^{1}H NMR spectra was obtained before the compound decomposed completely.



Product	R	R_1	R_2	Yield [a]
1.109	2-$BrC_6H_4CH_2$	$-CH_2CH_2CH_2-$		98
1.110	3-$BrC_6H_4CH_2$	$-CH_2CH_2CH_2-$		90
1.111	4-$BrC_6H_4CH_2$	$-CH_2CH_2CH_2-$		52
1.112	4-$NO_2C_6H_4CH_2$	$-CH_2CH_2CH_2-$		94
1.113	4-$MeOC_6H_4CH_2$	$-CH_2CH_2CH_2-$		98
1.114	4-$BrC_6H_4CH_2$	4-$MeOC_6H_4CH_2$	$CH_2CH(CH_3)_2$	50

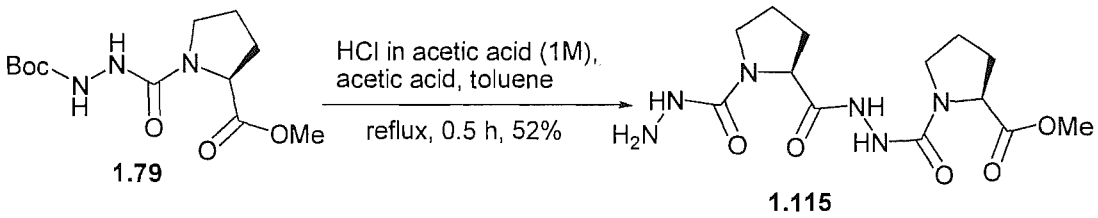
[a] Percentage yield of isolated product

Table 1.7: Semicarbazides synthesised from hydrazines, amino acid esters and triphosgene.[50]

iv) Cyclisation of semicarbazides to 1,2,4-triazine-3,6-diones

The cyclisation conditions for the semicarbazides described in Obreza *et al.*[29] were a simple deprotection using hydrochloric acid in acetic acid at room temperature (scheme 1.7, Introduction, section **1.1.2**, part *ii)*).

We submitted our first synthesised semicarbazide **1.79** to these reaction conditions; although Obreza *et al.*[29] suggested that this semicarbazide should cyclise to the 6-membered ring, we reserved judgement, at first expecting the deprotected semicarbazide to cyclise to the 5-membered ring if at all. Removal of the acetic acid from the crude product, however, was difficult and excess toluene was added and removed *in vacuo* in order to azeotrope off the remaining acetic acid. The final product was identified as the product of two deprotected molecules of semicarbazide reacting together; dimer **1.115** (scheme 1.18).

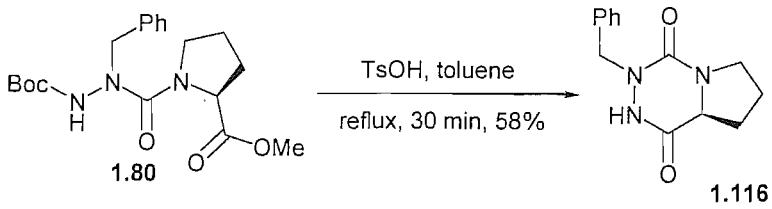


Scheme 1.18: Deprotection of semicarbazide **1.79** and resulting reaction to dimer **1.115**.

We suspect that semicarbazide **1.79** was deprotected at room temperature and it was during the period of reduced pressure and increased temperature needed to remove the remaining solvent that the deprotected semicarbazide reacted to form product **1.115**. Since Obreza *et al.*[29] stated in their experimental section that their acetic acid was distilled off before the bicyclic products were isolated we suspect that the cyclisation of their compounds occurs during this distillation. From this experience we decided that we required elevated temperatures for cyclisation of the deprotected semicarbazides, and we also wanted an acid for the deprotection that would be easier to remove than the acetic acid had been.

We chose *p*-toluenesulfonic acid since it is strong enough to deprotect the semicarbazide, but we hoped would be easier to remove from the reaction; it was also used by Schwan *et al.*[18] in his cyclisation to triazinediones (scheme 1.5, Introduction, section **1.1.2**, part *ii)*). Heating semicarbazide **1.80** to reflux in toluene with 2 equivalents of *p*-toluenesulfonic acid for half an hour gave the 1,2,4-triazine-3,6-dione **1.116** in 58% yield (scheme 1.19, table 1.8). Although the

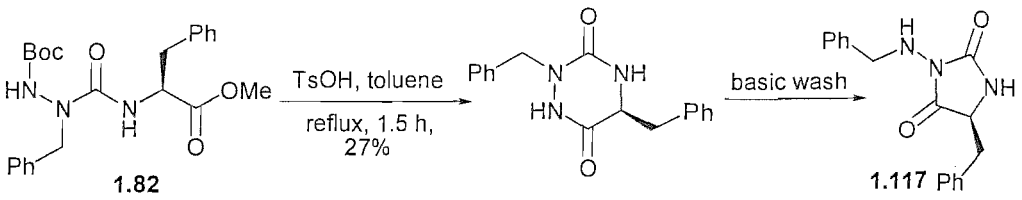
cyclised product precipitated out of solution as a green solid on cooling, purification was difficult and it was only after column chromatography that the product was isolated as a pearly white crystalline solid.



Scheme 1.19: Cyclisation of semicarbazide **1.80** to 1,2,4-triazine-3,6-dione **1.116**.

The spectral data of the 1,2,4-triazine-3,6-dione **1.116** was noted to correspond to the 1,2,4-triazine-3,6-dione structure as described in the literature. The carbonyl peak in the IR spectrum for **1.116** was 1685 cm^{-1}. Both Schwan[18] and Hoffman *et al.* [27] reported IR bands near 1680 cm^{-1} as indicative of the 1,2,4-triazine-3,6-dione structure. The chemical shift of the carbonyl in the ^{13}C NMR spectra for **1.116** was 165.7 ppm. Hamuro *et al.* reported a chemical shift for the amide carbonyl in the ^{13}C NMR lower than 170 ppm as characteristic of the 1,2,4-triazine-3,6-dione structure.[28] The NH peak in the ^{1}H NMR spectra at 10.40 ppm was a broad singlet, again an indication of the triazinedione structure. Finally, since the 1,2,4-triazine-3,6-dione **1.116** is a known compound, the ^{1}H and ^{13}C NMR spectra were compared to the data in the literature for this compound and were found to compare well.[24]

The next semicarbazide to be cyclised was **1.82**; a small scale reaction using *p*-toluenesulfonic acid in refluxing toluene gave a very small amount of the cyclised crude product. A larger cyclisation reaction of **1.82** was carried out and after 1.5 h refluxing, TLC monitoring suggested that the cyclised product had been formed. Since the crude product was difficult to purify, we redissolved the crude product in dichloromethane and washed the organic layer with saturated sodium hydrogen carbonate solution in an effort to remove the remaining acid. This workup removed baseline impurities on TLC and made column chromatography purification of the cyclised product more facile. The cyclised product **1.117** was isolated as a white solid in quite low yield (27%, scheme 1.20).



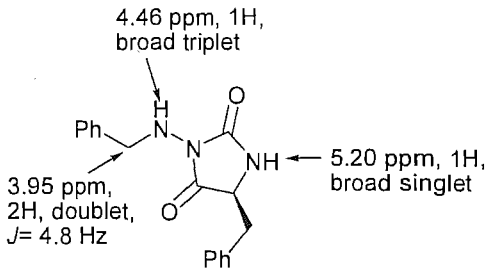
Scheme 1.20: The cyclisation of semicarbazide **1.82** to the 1,2,4-triazine-3,6-dione that rearranged to the isolated 3-aminohydantoin **1.117**.

The spectral data of the product **1.117** looked like the cyclised 1,2,4-triazine-3,6-dione at first glance. The Boc group and methyl group were missing in the NMR spectra and the mass spectrum was correct for the desired product. However, the infrared spectrum had a band at 1759 cm^{-1} and none near 1680 cm^{-1}. The ^{13}C NMR spectrum showed the carbonyl peak at 170.6 ppm, just over the 170 ppm mark. Both these factors concerned us, either the 1,2,4-triazine-3,6-dione had rearranged spontaneously to the 3-aminohydantoin during the basic wash, something that the observations of Schwan[18] would confirm as possible or the structural assignment rules set out by Schwan[18], Hoffman *et al.* [27] and Hamuro *et al.*[28] which were only based on a few synthesised compounds each are not as rigid as they reported.

Since synthesising the rest of the 1,2,4-triazine-3,6-diones in table 1.8, we have had a greater number and range of triazinedione spectra to compare to that of product **1.117**. The majority of the triazinediones synthesised have had IR spectra with a band near 1680 cm^{-1} and none near 1730 cm^{-1}. All but one other (see discussion later) had a ^{13}C NMR spectrum with the carbonyl peak below 170 ppm. Also noticeable was the chemical shift for the NH proton in the ^{1}H NMR, in all the cases that the NH peak was visible in the ^{1}H NMR spectrum the peak was 7.72 ppm or higher. The only two exceptions to this pattern were product **1.117** and the only other cyclised product with a carbonyl peak above 170 ppm in the ^{13}C NMR which we will discuss later in this report.

The most convincing piece of evidence for the structural assignment of product **1.117** as the aminohydantoin was again from the NH peaks in the ^{1}H NMR. From the spectra of the other triazinediones with two NH protons in their structure and the semicarbazides where the NCONH proton is likely to have a similar shift to the NCOCH proton in the cyclised product, we could estimate that the NCONH proton in **1.117** should be about 5.00 – 6.50 ppm in the ^{1}H NMR spectrum. This would fit

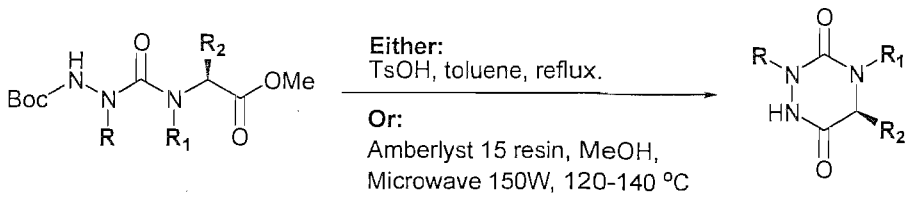
with the NH peak at 5.20 ppm in **1.117**'s spectrum, seen as a broad singlet. The other NH peak is at 4.46 ppm and closer inspection reveals that it is in fact a broad triplet. From the splitting patterns of the other peaks in the spectrum we can assign the $PhCH_2N$ protons as a doublet at 3.95 ppm. These splitting patterns would be completely impossible if product **1.117** was the 1,2,4-triazine-3,6-dione. Heterocycle **1.117** is therefore assigned as the 3-aminohydantoin structure (figure 1.23).



1.117

Figure 1.23: Structure of product **1.117** and the ^1H NMR splitting patterns that allowed assignment as the 3-aminohydantoin.

The next cyclisation was on the semicarbazide **1.81**. As discussed previously the semicarbazide **1.81** was isolated as two oils that were both unstable. Both oils were dissolved in toluene with *p*-toluenesulfonic acid and heated to reflux. The first of the two oils (the least polar of the two) was heated to reflux for 2 h, after which time there appeared to be no remaining starting material by TLC. The reaction mixture was concentrated and the crude product was purified by column chromatography to give the 1,2,4-triazine-3,6-dione **1.118** in 26% yield. The second, more polar, oil was refluxed in toluene with *p*-toluenesulfonic acid for 2.5 h to give the 1,2,4-triazine-3,6-dione **1.118** in an improved yield (48%, table 1.8). The longer reaction time for the second oil was due to the persistence of the starting material in the reaction mixture seen by TLC monitoring, suggesting that of the different rotamers in the two oils, the first oil contained rotamers that were deprotected more rapidly than those in the second oil.



Product	R	R_1	R_2	Yield [a]	Yield [b]
1.116	$PhCH_2$	$-CH_2CH_2CH_2-$		58	55
1.118	$PhCH_2$	CH_2Ph	$CH_2CH(CH_3)_2$	48	–
1.119	$4\text{-}MeOC_6H_4CH_2$	CH_2Ph	$CH_2CH(CH_3)_2$	43	–
1.120	$4\text{-}NO_2C_6H_4CH_2$	H	$CH_2CH(CH_3)_2$	19	38
1.121	$3,4,5\text{-}(MeO)_3C_6H_4CH_2$	$-CH_2CH_2CH_2-$		28	–
1.122	$3,4,5\text{-}(MeO)_3C_6H_4CH_2$	CH_2Ph	CH_2-2-indole	40	–
1.124	$CH_3(CH_2)_4$	CH_2Ph	CH_2Ph	–	59
1.125	$CH_3(CH_2)_4$	H	CH_2Ph	–	68
1.126	$PhCH_2$	CH_2Ph	CH_2OH	–	72
1.127	$3\text{-}BrC_6H_4CH_2$	H	$CH_2CH(CH_3)_2$	–	4
1.128	$4\text{-}NO_2C_6H_4CH_2$	CH_2Ph	CH_2Ph	–	38
1.129	$4\text{-}MeOC_6H_4CH_2$	$CH_2C_6H_4\text{-}4\text{-}NO_2$	$CH_2CH(CH_3)_2$	–	66
1.130	$2\text{-}MeOC_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	20
1.131	$3\text{-}MeOC_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	50
1.132	$3,5\text{-}(MeO)_2C_6H_4CH_2$	$-CH_2CH_2CH_2-$		–	66
1.133	$3,4,5\text{-}(MeO)_3C_6H_4CH_2$	$-(R)\text{-}CH_2CHOHCH_2-$		–	63
1.134	$PhCH_2$	$-(R)\text{-}CH_2CHOHCH_2-$		–	44

[a] Percentage yield of isolated product using refluxing toluene and *p*-TsOH, [b] Percentage yield of isolated product using methanol and Amberlyst 15 resin under microwave irradiation.

Table 1.8: 1,2,4-Triazine-3,6-diones synthesised using two methods and yields of products isolated from each method.

1,2,4-Triazine-3,6-diones **1.119** to **1.122** were synthesised from the semicarbazides **1.84**, **1.87**, **1.91** and **1.93** in refluxing toluene with *p*-TsOH; after the solvent was removed *in vacuo* the crude products were purified by column chromatography (table 1.8). 1,2,4-Triazine-3,6-dione **1.120** was isolated in a lower yield (19%, table 1.8) than the other heterocycles. This is probably because as the only example with two R groups it is comparatively more polar and was noticeably more difficult to purify. Although the yields of these triazinediones seem quite poor, five other semicarbazides **1.85**, **1.86** and **1.88** to **1.90** failed to cyclise at all under these conditions. In all cases although the semicarbazides were thought to Boc

deprotect on addition of the acid (single very polar spot observed on TLC plates), no cyclisation to the desired heterocycles was seen and the deprotected semicarbazides broke down during the reaction.

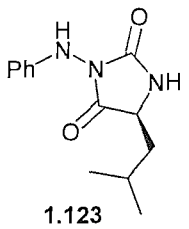
From this it seemed to us that we required not only an easier method of purifying our heterocycles once they had formed (which would not allow them to rearrange to the 3-aminohydantoin structure) but also a way of heating the reactions quickly to reduce the chances of the fragile semicarbazides breaking down. We hoped we could achieve this with solid-phase polymer supported acid that could be easily filtered from the reaction and heating the reaction in a microwave.

To test this idea we dissolved a small mass of semicarbazide **1.80** in toluene with 1.5 equivalents of TsOH and heated the mixture for three minutes at 140 °C (150 W) in a focused microwave instrument. The semicarbazide **1.80** Boc deprotected but did not cyclise, since toluene is not an ideal solvent to be heated in a microwave we tried the reaction again with methanol. This time we achieved a 42% yield of the triazinedione **1.116** and a 17% yield of the deprotected semicarbazide. Repeating the reaction again with an excess of Amberlyst 15 resin beads (polymer supported *p*-toluenesulfonic acid) stirred with **1.80** in methanol at 140 °C for up to 15 minutes in a microwave gave only the deprotected product. However, 20 minutes at 140 °C with Amberlyst 15 in methanol gave the 1,2,4-triazin-3,6-dione **1.116** in a comparable yield to that obtained when *p*-toluenesulfonic acid in refluxing toluene was used (55% *c.f.* 58%, table 1.8).

A solution of semicarbazide **1.87** in methanol was then heated for 30 minutes at 120 °C in a microwave with an excess of Amberlyst 15 resin. The reaction mixture was much easier to purify than the previous cyclisation reaction of **1.87** and gave an improved yield of 1,2,4-triazine-3,6-dione **1.114** (38%, table 1.8).

Semicarbazide **1.94** was cyclised by both methods to give the heterocyclic product **1.123**. Refluxing in toluene with *p*-toluenesulfonic acid for 30 minutes gave **1.123** in 27% yield whereas 30 minutes at 120 °C in a microwave with Amberlyst 15 resin beads gave **1.123** in 48% yield. The analytical data on the product **1.123** suggests that the product isolated from both reactions is in fact the aminohydantoin structure. The infrared spectrum shows a peak at 1723 cm^{-1} and no peaks near 1680 cm^{-1}. The carbonyl peak in the ^{13}C NMR spectrum is 172.5

ppm and the NH proton peaks in the ^{1}H NMR spectrum are 6.38 ppm and 6.19 ppm (both broad singlets). Unfortunately product **1.123** was isolated as an oil and could not be crystallised in order to get an x-ray crystal structure. Our experience with the assignment of 3-aminohydantoin **1.117** allowed us to assign the product **1.123** as the 3-aminohydantoin with confidence, based on the above spectral evidence (figure 1.24).



1.123

^{1}H NMR: 6.38 ppm, 1H, broad singlet and 6.19 ppm, 1H, broad singlet corr. to the two NH protons.
IR: 1723 cm^{-1} carbonyl peak.
^{13}C NMR: 172.5 ppm carbonyl peak.

Figure 1.24: Structure of 3-aminohydantoin product **1.123** and the spectral evidence for the aminohydantoin assignment.

It is thought that the 1,2,4-triazine-3,6-dione heterocycle from the cyclisation of semicarbazide **1.94** must have formed and then spontaneously rearranged to the aminohydantoin **1.123**. The fact that no base was required for this to happen suggests that the 6 membered ring with the phenyl R group must have been particularly unstable. The semicarbazide **1.83,** also with a phenyl R group, did not cyclise at all under either microwave or thermal heating conditions and only deprotected semicarbazide was detected. The microwave conditions for the cyclisation of **1.94** did produce a better yield of aminohydantoin **1.123** than the refluxing toluene method. Since the yield of **1.123** must be proportional to the yield of the short-lived 1,2,4-triazine-3,6-dione the microwave conditions are therefore the more productive method. In addition, when the cyclisation reaction of **1.94** was first removed from the microwave reactor, a second spot very close to that of **1.123** was seen on TLC plates; this spot had disappeared by the time the solvent had been removed and the crude purified by column chromatography. It is possible that this spot was the triazinedione heterocycle.

The improved yields, easier purification and the chance that the unstable compounds might survive for longer, made the microwave conditions preferable to refluxing in toluene. Semicarbazides **1.92**, **1.95** and **1.97** to **1.99** were stirred at 120 °C in methanol with Amberlyst 15 in a microwave for 30 minutes and cyclised successfully to the 1.2.4-triazine-3,6-diones **1.124** to **1.128** (table 1.8).

Semicarbazide **1.96** did not cyclise using this method and the deprotected semicarbazide was destroyed under the microwave conditions.

Semicarbazide **1.100** was heated at 120 °C for 30 minutes with Amberlyst 15 in the microwave, as the other reactions had been. However, TLC analysis at this point showed that there was still plenty of unprotected semicarbazide present. The reaction was put back in the microwave for a further 10 minutes to try to improve the yield of cyclised product. The 1,2,4-triazine-3,6-dione **1.129** was isolated in 26% yield in this reaction. An identical reaction was stirred at 120 °C for a further 20 minutes giving a reduced yield of 18% (total time 30+10+20 minutes). If this reaction was heated at 120 °C for 1 hour without stopping and cooling in order to TLC the mixture, an improved yield of **1.129** was achieved (66%, table 1.8). This reaction was repeated and found to give a comparable yield of **1.129** (64%).

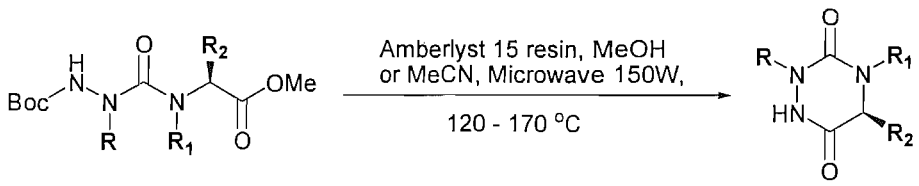
We wondered how long we could heat these reactions for before the yield started to drop. Would deprotected semicarbazides cyclise or decompose if the reaction times were longer? TLC monitoring of the cyclisation reaction of **1.103** showed that both product and deprotected semicarbazide were present after 1h and 1.5h reacting. After a total of 3 h at 120 °C, however, the TLC showed that the deprotected semicarbazide had been broken down to the hydrazine and proline starting materials, the final yield of 1,2,4-triazine-3,6-dione **1.130** being poor (20%, table 1.8).

The semicarbazides **1.104** to **1.108** were then heated at 120 °C in the microwave for 1.5 hours to give the triazinediones **1.130** to **1.134** in fairly good yield for these reactions (44-66%, table 1.8). Semicarbazide **1.106** broke down completely and semicarbazides **1.101** and **1.102** broke down after only 30 minutes heating under the microwave conditions.

The semicarbazides **1.109** to **1.113**, synthesised previously by an undergraduate student (Mark Cobb), were then cyclised by the student under the author's supervision using the following microwave conditions (table 1.9).[50] Semicarbazide **1.109** was heated with Amberlyst 15 resin beads in methanol for 35 minutes at 120 °C in the microwave reactor. The triazinedione **1.135** was isolated in good yield and repeating the reaction at 140 °C for a total of 55 minutes gave a comparable yield (120 °C: 65%, 140 °C: 63%, table 1.9). Semicarbazide **1.110**

was stirred with the Amberlyst 15 resin at 140 °C in methanol to give the triazinedione **1.136** in good yield for these cyclisations (50%, table 1.9). These two semicarbazides are similar in structure to semicarbazides **1.103** and **1.104** and as the yields of the cyclisations of **1.110** and **1.104** are identical we can assume that the yield of triazinedione **1.130** would be comparable to that of **1.135** had the reaction been stopped after 35 or 55 minutes.

Although it is now clear that extended reaction times give poorer yields in these cyclisation reactions due to breakdown of the deprotected semicarbazide, we were not yet sure if increased temperatures for shorter time periods would have the same effect or increase the yields of cyclised triazinediones. Since 140 °C was about the upper safe temperature for methanol in our microwave reactor we tested the cyclisation of semicarbazide **1.109** in acetonitrile at 170 °C. The semicarbazide was heated for 45 minutes with Amberlyst 15 resin as before to give the triazinedione **1.135** in a comparable yield to previous reactions (60% *c.f.* 63-65%. table 1.9).



Product	R	R_1	R_2	Yield [a]
1.135	2-$BrC_6H_4CH_2$	$-CH_2CH_2CH_2-$		65
1.136	3-$BrC_6H_4CH_2$	$-CH_2CH_2CH_2-$		50
1.137	4-$BrC_6H_4CH_2$	$-CH_2CH_2CH_2-$		19
1.138	4-$NO_2C_6H_4CH_2$	$-CH_2CH_2CH_2-$		21

[a] Percentage yield of isolated product

Table 1.9: 1,2,4-Triazine-3,6-diones synthesised using microwave reactor and yields of products isolated. Reactions carried out by M. Cobb under supervision of S. Radford.[50]

Semicarbazide **1.111** did not cyclise when stirred at 120 °C in methanol for 30 minutes with Amberlyst 15. Only the deprotected semicarbazide was observed. Heating to 140 °C in methanol with Amberlyst 15 for 50 minutes however, only resulted in the deprotected semicarbazide decomposing. We now knew that stirring in acetonitrile at elevated temperatures did not cause increased levels of semicarbazide decomposition from the cyclisation reactions of **1.109**. With this in mind we then heated semicarbazide **1.111** with Amberlyst 15 in acetonitrile at 160

°C for 30 minutes. This reaction gave the desired triazinedione **1.137** in an acceptable yield for these cyclisation reactions (19%, table 1.9).

Semicarbazide **1.112** did not cyclise when stirred at 140 °C in methanol for 40 minutes under the microwave conditions. As was observed with the reaction of **1.111** only the deprotected semicarbazide was seen. Semicarbazide **1.112** was then reacted with Amberlyst 15 in acetonitrile at 170 °C for 30 minutes to give the desired triazinedione **1.138** (21%, table 1.9). Repeating the reaction in acetonitrile at 170 °C for 55 minutes gave a reduced yield of triazinedione **1.138** (9%). Semicarbazide **1.113** was heated to 160 °C in acetonitrile for 30 minutes in the microwave. No cyclisation to the desired triazinedione **1.139** was observed in this reaction as the deprotected semicarbazide decomposed.

In order to confirm that the products we assigned as triazinediones were the 6-membered ring structures, we wanted to get X-ray diffraction analysis on at least one of our 1,2,4-triazine-3,6-dione products. Very few of our triazinediones were crystalline, however, and the only two products that formed crystals suitable for analysis were the very similar 1,2,4-triazine-3,6-diones **1.131** and **1.136** (figure 1.24). The analysis was carried out by the Departmental Single Crystal X-Ray Diffraction Service (run by Dr Mark Light at the University of Southampton) and confirmed that the structure of both of the compounds was the six-membered triazinedione in a twisted boat-like conformation (figure 1.25).

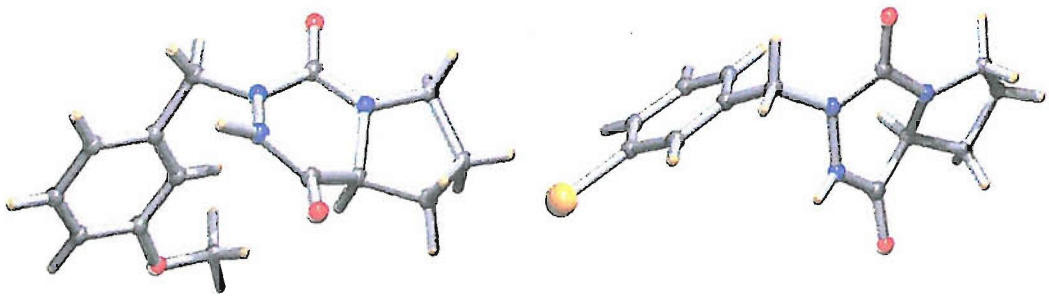
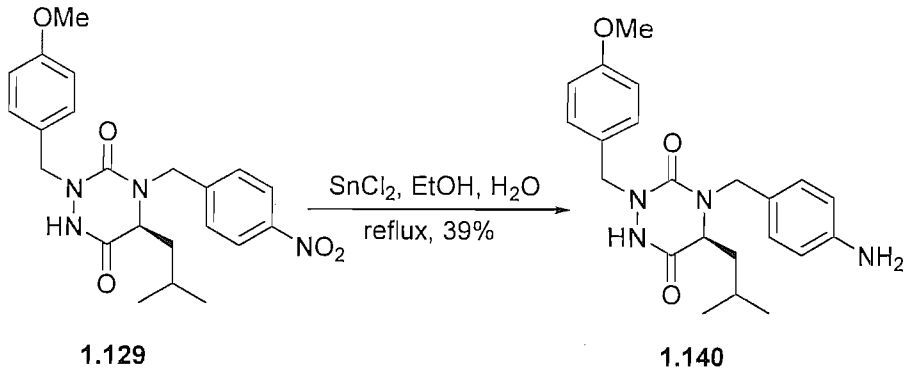


Figure 1.25: X-ray crystal structure of 1,2,4-triazine-3,6-diones **1.131** and **1.136**.

v) Reactions of the 1,2,4-triazine-3,6-diones

Having successfully synthesised over twenty 1,2,4-triazine-3,6-diones we wished to explore if they could be functionalised further, allowing this synthesis to be a route to an even greater range of structural diversity.

1,2,4-Triazine-3,6-dione **1.129**, which had been synthesised in a much better yield than the only other triazinedione containing a nitro group **1.120** (66% *c.f.* 38%, table 1.8), was reduced using tin (II) chloride in refluxing ethanol to the triazinedione **1.140** following a literature procedure (yield 39%, scheme 1.21).[51]

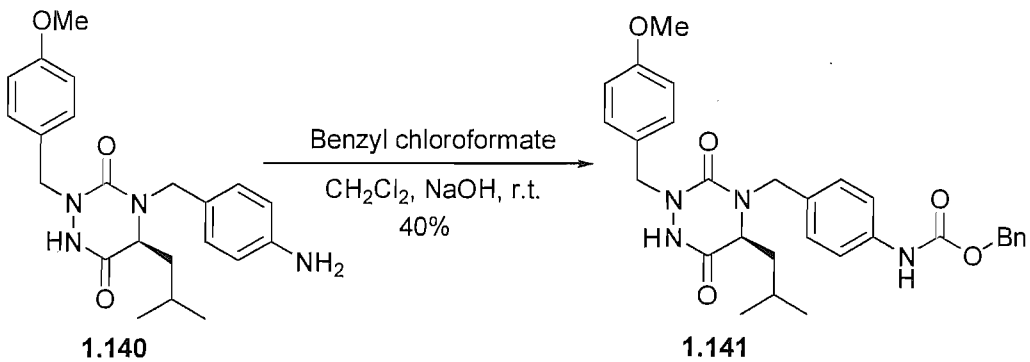


1.129 **1.140**

Scheme 1.21: Reduction of nitro group in 1,2,4-triazine-3,6-dione **1.129** to the amine group in 1,2,4-triazine-3,6-dione **1.140**.[51]

Although the yield for this reaction was disappointingly low, the triazinedione was remarkably stable to these reaction conditions, with no break down of the starting heterocycle and no formation seen of any other products. It is especially worth noting that the 1,2,4-triazine-3,6-dione did not rearrange to the 3-aminohydantoin and the product triazinedione **1.140**'s spectra was correct for the 6 membered structure. The low yield was probably due to an aqueous work-up being used to remove the tin chloride and the product being slightly soluble in water.

The 1,2,4-triazine-3,6-dione **1.140** was then alkylated using benzyl chloroformate and sodium hydroxide with stirring at room temperature for 3 hours (40%, scheme 1.22). The spectra of the product **1.141** was also correct for the 1,2,4-triazine-3,6-dione structure proving that the 1,2,4-triazine-3,6-dione structure can have some level of stability in the presence of strong bases.



1.140 **1.141**

Scheme 1.22: Alkylation of the 1,2,4-triazine-3,6-dione **1.140** to give the product **1.141**.

The low yield of the triazinedione **1.141** is mainly due to the desired product continuing to react with the excess of benzylchloroformate to give a second product with a mass equivalent to that of **1.141** + CO_2Bn – H. The ^1H NMR showed that what was thought to be one product was in fact mainly one compound, but with a minor impurity. This impurity showed many of the same peaks as the main compound but shifted slightly (ratio of product to impurity 5:1). Despite repeated and careful chromatography the mixture could not be separated.

It was not clear from the data collected on the second product what the exact structure is. Conceivably, either of the two amide NHs could have reacted with the second molecule of benzylchloroformate. This could give us three possible structures for the main component of this product mixture (figure 1.24). NOE NMR experiments suggest that the NH proton is near to the aromatic protons on the 4-*N* benzyl group, this means that the first possible structure **1.142a** can be dismissed as unlikely. The second and third structures are much harder to distinguish between; although the compound has an IR spectra showing peaks at 1765, 1731 and 1653 cm^{-1}, these could be from the two urethane-like carbonyls rather than the aminohydantoin carbonyls in **1.142c**. The ^{13}C NMR spectrum shows all carbonyl peaks below 170 ppm, but since the product cannot be completely purified we cannot be sure that any of this data is truly representative of the pure compound. It is thought that the inseparable mixture is most probably a mixture of **1.142b** and **1.142c** (figure 1.26).

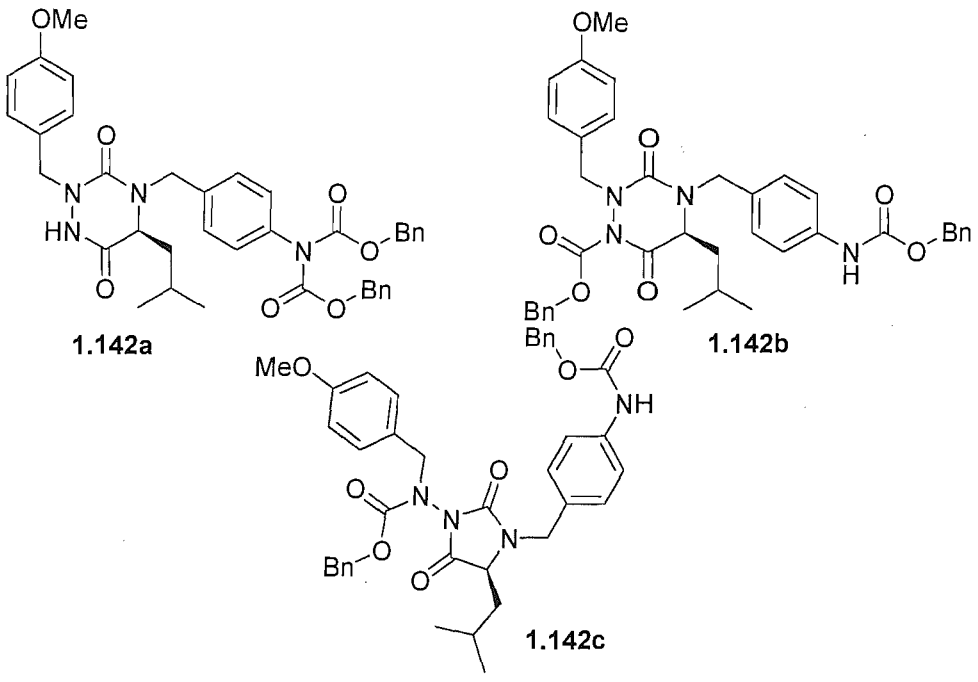
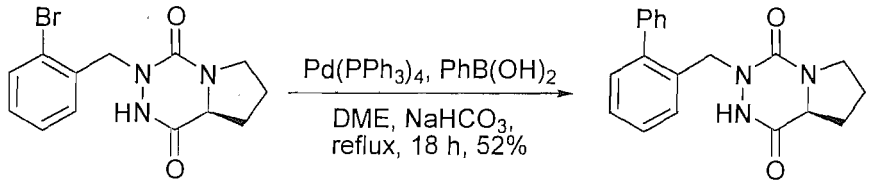


Figure 1.26: Three possible structures of product of reaction of **1.141** with benzylchloroformate.

The 1,2,4-triazin-3,6-dione **1.135** previously synthesised by an undergraduate project student (M. Cobb) was then further functionalised by the student using a Suzuki cross-coupling reaction under the supervision of the author (S. Radford). The reaction was carried out following a literature procedure using commercially available palladium tetrakis triphenylphosphine, phenyl boronic acid and base in DME.[52] The reaction gave the desired product **1.143** in acceptable yield (52%, scheme 1.23).



1.135 **1.143**

Scheme 1.23: Suzuki cross-coupling of triazinedione **1.135** with phenyl boronic acid to give triazinedione **1.143**.

vi) Biological testing of the 1,2,4-triazine-3,6-diones

As discussed in the introduction to this chapter, the cyclic dipeptide cyclo(Phe-Pro) has been shown to inhibit the growth of breast cancer cells.[13, 16] To our knowledge none of the triazinediones previously described in the literature have been tested for any biological activity. Since the 1,2,4-triazine-3,6-diones can be considered aza-analogues of cyclic dipeptides we wished to discover if any of the 1,2,4-triazine-3,6-diones we had synthesised had any anticancer activity against breast cancer cells.

The research group of Prof. Graham Packham based at the School of Medicine, University of Southampton, generously carried out the biological testing on our compounds. The experiments were first carried out on 24 of our triazinediones and semicarbazides (figure 1.27). For each experiment, 1000 breast cancer cells were treated with 50 μM of the compound and the number of cells remaining was measured after 6 days. The percentage of cells left after the treatment with each compound compared to untreated cells was calculated and the average value for each compound from three separate experiments carried out in duplicate was reported in the bar graph shown below (figure 1.26).

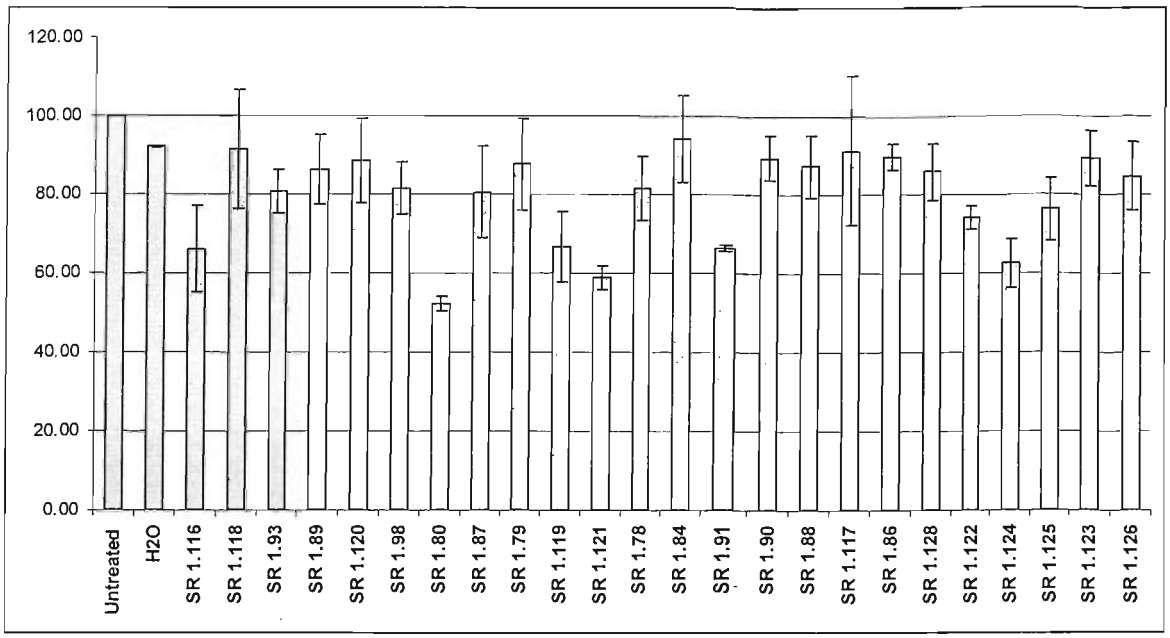
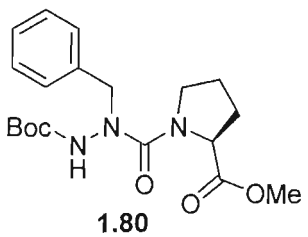
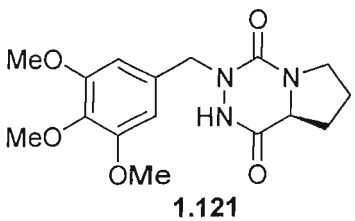


Figure 1.27: Bar graph showing the percentage of cells remaining after 6 days (y-axis) when treated with our compounds (x-axis) compared to untreated cells averaged from three experiments.

From the data we received the two most active compounds were found to be semicarbazide **1.80** and triazinedione **1.121** (figure 1.28). Compared to the results reported for the dipeptide cyclo(Phe-Pro) at this concentration these two compounds are significantly more active. Cyclo(Phe-Pro) was reported to reduce the number of breast cancer cells to less than 20% of the controls number of cells at a concentration of 10 mM.[13] From a dose response experiment reported in the same paper, it is clear that at 50 μM (the concentration our compounds were tested at) cyclo(Phe-Pro) has no effect on breast cancer cells. From this we can estimate that our most active 1,2,4-triazine-3,6-dione **1.121** is approximately 100 times more active than the cyclic dipeptide Phe-Pro in the inhibition of breast cancer cell growth.



1.80



1.121

Figure 1.28: Structures of semicarbazide **1.80** and 1,2,4-triazine-3,6-dione **1.121**. .

The triazinedione **1.121** has three methoxy groups and we synthesised the triazinediones **1.130** to **1.132** hoping that their biological activity would give us some idea as to whether all three groups are necessary for the activity of **1.121**.

None of the subsequently synthesised compounds **1.129** to **1.142** were more active than **1.121** (figure 1.29). The most active of the later synthesised compounds was **1.129**, which was slightly more active than the very similar compound **1.119** (figures 1.29 and 1.27).

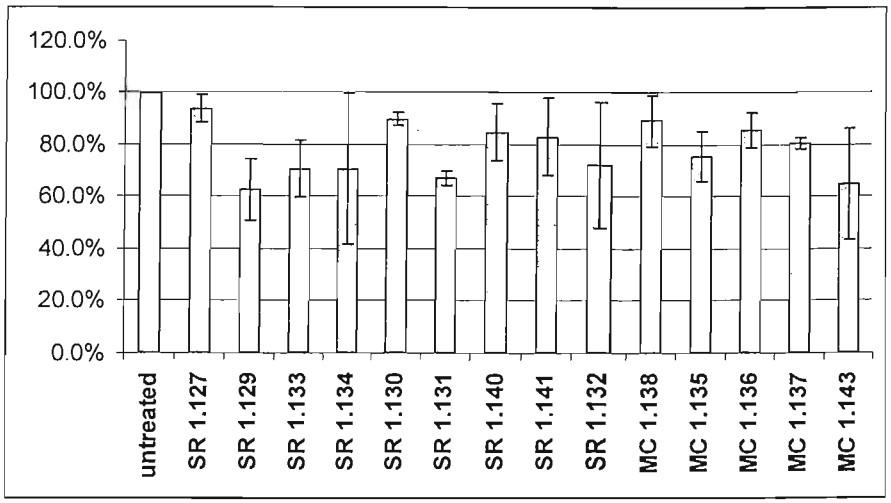
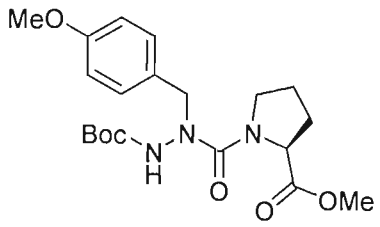
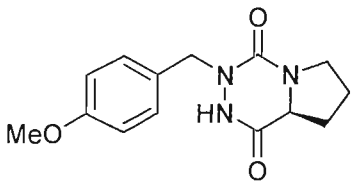


Figure 1.29: Bar graph showing the percentage of cells remaining after 6 days (y-axis) when treated with our compounds (x-axis) compared to untreated cells averaged from two experiments.

From this work it would seem that the most biologically interesting 1,2,4-triazine-3,6-dione is one containing both the proline group and a benzyl group with a methoxy moiety in the *para* position. It was for this reason semicarbazide **1.113** was synthesised although it has not yet been possible to cyclise it to the triazinedione product **1.139** for biological testing (figure 1.30).



1.113



1.139

Figure 1.30: Previously synthesised semicarbazide **1.113** and its cyclised product: 1,2,4-triazine-3,6-dione **1.139** to be synthesised and tested in the future.

1.3.0 CONCLUSION

The aim of this project was to synthesise novel heterocyclic scaffolds. As discussed in the introduction we focused on the synthesis of 1,2,4-triazine-3,6-diones as analogues of cyclic dipeptides with two alternative arrangements of the three R groups (figure 1.7).

The first of our two synthetic routes proposed in the introduction afforded us a range of seven semicarbazides **1.8** – **1.14** synthesised from isocyanates and hydrazines. The monosubstituted hydrazines reacted regioselectively depending on the substituted group, meaning that the R groups were not necessarily in the desired arrangement. Reaction of the semicarbazides with bromoacetyl bromide or chloroacetyl chloride proved difficult to control with only three of the desired intermediates **1.16** – **1.18** being successfully synthesised. The intermediate **1.18** was successfully cyclised to the novel 1,2,4-triazine-3,6-dione using BEMP resin although in a disappointing yield (22%, scheme 1.9).

Since the synthesis of triazinediones with an aryl group has not been possible with our second synthetic method, it might be interesting to explore this route to these triazinediones further in the future. Biological testing of the triazinedione **1.19** for comparison with the later triazinediones would also be worth investigating.

The potential of the reaction of α-hydroxy esters under Mitsunobu conditions for the synthesis of triazinediones and their isomeric aminohydantoins, led us to investigate the mechanism of the reaction between the α-hydroxy esters and the Mitsunobu reagents. From our work, reacting various carbonyl compounds with DIAD or DBAD and TPP, we were able to conclude that the α-hydroxy esters are oxidised to α-keto esters thereby supporting the proposed literature mechanism. In addition to improving the understanding of this mechanism, this work provided a simple and novel synthesis to the unusual heterocycle structure, [1,2,3]oxadiazole-2,3-dicarboxylic acid ester (compounds **1.23** to **1.35**).

The second of our two synthetic routes to 1,2,4-triazine-3,6-diones gave us a large range of semicarbazides (**1.79** – **1.114**) synthesised from our Boc protected monosubstituted hydrazines (**1.40** – **1.71**) and amino acid methyl esters (**1.72** – **1.77**). These semicarbazides were found to be, to varying degrees, unstable in solution. From our results we can conclude that the greater the steric hindrance

between the R groups on the semicarbazide the greater the likely instability of that semicarbazide.

These semicarbazides were then cyclised to the desired 1,2,4-triazine-3,6-dione heterocycles, at first by heating in toluene and later by using an improved microwave methodology. There was found to be a fine balance between the length of time and elevated temperature required for the cyclisation to take place versus the decomposition of the unstable semicarbazides. Equally the steric hindrance between the R groups on the semicarbazides although making the compound unstable seemed to encourage the likelihood of cyclisation. In addition to the synthesis of these 20 novel 1,2,4-triazine-3,6-diones (**1.116 – 1.138**) we have also isolated two aminohydantoins. Comparison of our spectral data has allowed us to conclude that to correctly assign these structural isomers the ^{1}H, ^{13}C NMR and IR spectra should all be considered.

We have also shown that, although the 1,2,4-triazin-3,6-dione structure can rearrange to the aminohydantoin under basic conditions or when the product is particularly hindered the 1,2,4-triazin-3,6-diones can be successfully further functionalised. This is obviously desirable in a heterocyclic scaffold.

Finally the 1,2,4-triazine-3,6-diones were tested for activity against breast cancer cells. The most active of our compounds was shown to be considerably more active against breast cancer cells than the cyclic dipeptide Phe-Pro, suggesting that these heterocycles have the potential to be biologically interesting scaffolds for drug discovery.

1.4.0 EXPERIMENTAL

1.4.1 General Experimental Methods

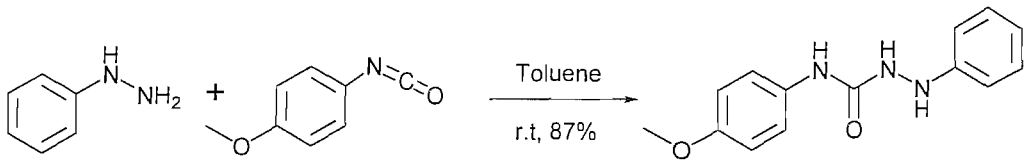
Chemicals and general reagents were purchased from commercial suppliers, and unless stated otherwise were initially used without further purification. Anhydrous dichloromethane was freshly distilled from calcium hydride, THF was distilled from sodium wire with benzophenone as an indicator and toluene was distilled over molten sodium metal. Where necessary, all other solvents and reagents were purified according to standard methods.[53] Unusual purification methods of reagents are described where used.

All air and/or moisture sensitive reactions were carried out under an inert atmosphere of argon gas, in oven-dried glassware. Reactions were monitored by TLC using pre-coated aluminium or plastic plates coated with 0.14 mm of silica gel 60 containing a fluorescence indicator active at 254 nm. Visualisation was carried out under UV light (254 nm) and by staining with, most commonly, 20% phosphomolybdic acid in ethanol, cerium sulphate/ammonium molybdate in 2M H_2SO_4 (aq) or 10% aqueous $KMnO_4$. Flash column chromatography was performed with 40-63 μm silica gel. 'Brine' refers to a saturated aqueous solution of sodium chloride. The term *in vacuo* refers to the removal of solvents by the means of evaporation at reduced pressure, using a Buchi rotary evaporator.

Melting points were obtained in open capillary tubes on a hot stage apparatus and are uncorrected. Polarimetry was recorded on a POLAAR 2001, and corrected for solvent use; solvent used was chloroform unless stated otherwise. Infrared spectra were recorded either on a Bio-Rad FTS 135 instrument using a Golden Gate adapter or a Perkin Elmer spectrometer with a Golden Gate adapter. Absorptions were recorded in wave numbers (cm^{-1}) and are described as strong (s), medium (m) or weak (w). ^1H NMR and ^{13}C NMR were recorded on Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers (300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C). Characteristic splitting patterns due to spin spin coupling are expressed as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts are given in ppm and coupling constants are measured in Hertz. Low-resolution mass spectra were obtained on a Micromass platform single quadrupole mass spectrometer with an electospray ion source using acetonitrile or methanol as the delivery eluent. The microwave reactor was a CEM Discover and conditions used were as stated.

1.4.2 Experimental Details for Chapter One

1-Phenyl-4-(4-methoxyphenyl) semicarbazide (1.8)



4-Methoxyphenyl isocyanate (1.00 g, 6.1 mmol) was added dropwise to a stirring solution of phenylhydrazine (0.98 g, 9.1 mmol) in toluene (25 mL) at room temperature. A white solid precipitated immediately and was filtered under vacuum. The white solid, **1.8** was recrystallised from (50% CH_2Cl_2/ethanol) to give fine needle-like crystals (1.44 g, 87%).

Mp 172 – 173 °C (dichloromethane/ethanol), literature value 169 – 170 °C.[54, 55]

IR: 3361 (m), 3285 (m), 3256 (m), 1659 (s), 1596 (m), 1536 (s), 1512 (s), 1492 (s) cm^{-1}.

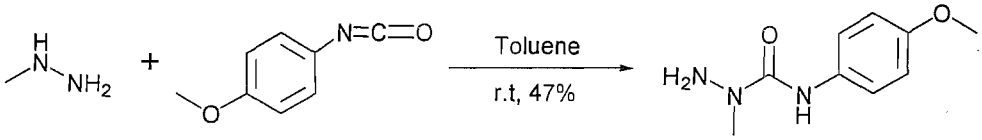
^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (1H, s, **NH**); 8.08 (1H, s, **NH**); 7.72 (1H, s, **NH**); 7.44 (2H, m, **CH_3OArHNH**); 7.18 (2H, m, **CH_3OArHNH**); 6.82 – 6.72 (5H, m, **ArH**); 3.71 (3H, s, **CH_3O**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6): δ 157.8 (**CO**), 155.3 (**C**), 150.4 (**C**), 133.8 (**C**), 129.7 (**CH**), 121.5(**CH**), 119.9 (**CH**), 114.6 (**CH**), 113.5 (**CH**), 56.1 (**OCH_3**) ppm.

LRMS (ES^+): *m/z* 772 ([3M + H^+], 10%), 515 ([2M + H^+], 90%), 258 ([M + H^+], 100%).

Melting point corresponds to literature values, no other reported data available for this known compound.[54, 55]

2-Methyl-4-(4-methoxyphenyl) semicarbazide (1.9)



4-Methoxyphenyl isocyanate (1.00 g, 6.1 mmol) was added dropwise to a stirring solution of methylhydrazine (0.42 g, 9.1 mmol) in toluene (25 mL) at room temperature. A white solid precipitated immediately and was filtered under

vacuum. The white solid, **1.9** was recrystallised from (50% CH_2Cl_2/ethanol) to give a crystalline solid (0.60 g, 47%).

Mp 107 – 108 °C (dichloromethane/ethanol)

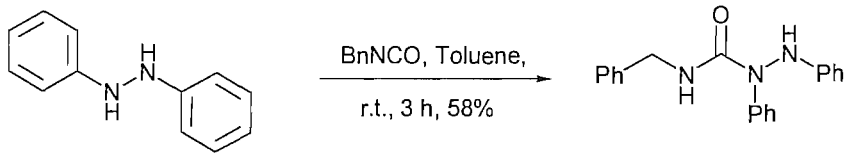
IR: 3376 (m), 3310 (m), 1643 (s), 1604 (sh), 1510 (s), 1459 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82 (1H, br s, **NH**); 7.43 (2H, d, *J*= 9.0 Hz, **ArH**); 6.80 (2H, d, *J*= 9.0 Hz, **ArH**); 4.73 (2H, s, **NH**); 3.69 (3H, s, **OCH_3**); 3.03 (3H, s, **NCH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 157.5 (**CO**), 155.0 (**C**), 134.2 (**C**), 120.8 (**CH**), 114.6 (**CH**), 56.0 (**OCH_3**), 38.2 (**NCH_3**) ppm.

LRMS (ES^+): *m/z* 608 ([3M + Na^+], 20%), 413 ([2M + Na^+], 100%), 391 ([2M + H^+], 20%), 297 (40), 196 ([M + H^+], 30%).

1,2-Diphenyl-4-benzyl semicarbazide (1.10)



Benzyl isocyanate (0.66 g, 4.9 mmol) was added dropwise to a stirring solution of 1,2-diphenylhydrazine (1.1 equiv., 1.00 g, 5.43 mmol) in toluene (25 mL). The bright orange reaction mixture was stirred for 3 h at room temperature. The solvent was removed *in vacuo* and the residues redissolved in CH_2Cl_2 (10 mL). The organics were then washed with water (2 x 10 mL), brine (10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (25 – 100% ethyl acetate/hexane). The appropriate fractions were combined and solvent removed *in vacuo* to give **1.10** as a white solid (0.90 g, 58%).

Mp 177 – 179 °C (isopropanol).

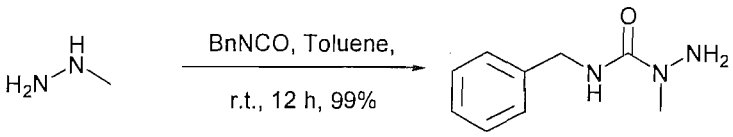
IR: 3404 (m), 3221 (m), 3026 (m), 1650 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 8.80 (1H, s, **NH**); 7.97 (1H, t, *J*= 5.7 Hz, **CH_2NH**); 7.55 – 7.52 (2H, m, **ArH**); 7.30 – 7.13 (9H, m, **ArH**); 7.02 – 6.97 (1H, m, **ArH**); 6.77 – 6.75 (3H, m, **ArH**); 4.32 (2H, d, *J*= 5.7 Hz, **CH_2**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 156.9 (**C**O), 146.8 (**C**), 142.0 (**C**), 140.8 (**C**), 129.1 (**C**H), 128.2 (**C**H), 128.1 (**C**H), 127.1 (**C**H), 126.6 (**C**H), 123.6 (**C**H), 122.2 (**C**H), 119.5 (**C**H), 112.9 (**C**H), 42.2 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 657 ([2M + Na^+], 10%), 635 ([2M + H^+], 10%), 318 ([M + H^+], 10%), 190 (100), 169 (70).

2-Methyl-4-benzyl semicarbazide (1.11)



Benzyl isocyanate (1.00 g, 7.5 mmol) was added dropwise to a stirring solution of methylhydrazine (1.5 equiv., 0.52 g, 11.3 mmol) in toluene (25 mL) at room temperature. The reaction mixture was allowed to stir overnight, the solvent was then removed *in vacuo* and the residues redissolved in CH_2Cl_2 (10 mL). The organics were washed with water (2 x 10 mL), brine (10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. This yielded the product, **1.11** as a white crystalline solid (1.32 g, 99%).

Mp 82 – 83 °C (hexane/isopropanol), literature value 83 – 84 °C[56]

IR: 3391 (m), 3308 (m), 1621 (s), 1524 (s) cm^{-1}.

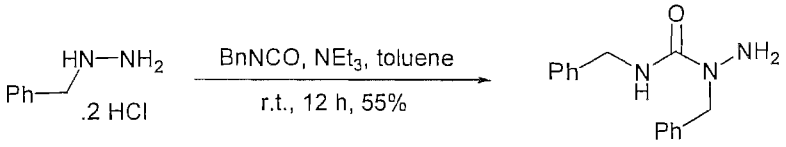
^{1}H NMR (300 MHz, DMSO-d_6): δ 7.29 – 7.21 (6H, m, **Ar**H & **N**H); 4.50 (2H, s, **N**H_2); 4.22 (2H, d, *J*= 6.3 Hz, **C**H_2); 2.97 (3H, s, **NC**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 160.2 (**C**), 142.2 (**C**), 129.1 (**C**H), 128.0 (**C**H), 127.4 (**C**H), 44.0 (**C**H_3), 38.8 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 381([2M + Na^+], 10%), 359 ([2M + H^+], 10%), 317 (15), 297 (30), 243 ([M + MeCN + Na^+], 15%), 202 ([M + Na^+], 5%), 180 ([M + H^+], 100%).

Melting point corresponds to the literature value for this known compound.[56]

2,4-Dibenzyl semicarbazide (1.12)



Benzyl isocyanate (0.62 g, 4.7 mmol) was added dropwise to a stirring solution of benzylhydrazine dihydrochloride (1.1 equiv., 1.00 g, 5.1 mmol) and triethylamine (3 equiv., 1.43 g, 14.1 mmol) in toluene (25 mL). After stirring overnight at room temperature, the reaction mixture was filtered and the precipitate washed with excess toluene. The filtrate was concentrated *in vacuo* and the residues redissolved in CH_2Cl_2 (10 mL). The organics were washed with water (3 x 10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (50 – 100% ethyl acetate/hexane). The appropriate fractions were combined and solvent removed *in vacuo* to give **1.12** as a white solid (0.66 g, 55%).

Mp 82 – 84 °C (isopropanol).

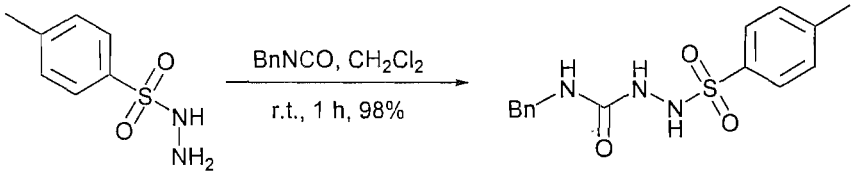
IR: 3380 (m), 3301 (m), 1619 (s), 1515 (s) cm^{-1}.

^{1}**H NMR** (400 MHz, DMSO-d_6): δ 7.43 – 7.22 (10H, m, **ArH**); 6.79 (1H, br s, **NH**); 4.73 (2H, s, **CH_2N**); 4.46 (2H, d, *J*= 5.8 Hz, **CH_2NH**); 3.37 (2H, s, **NH_2**) ppm.

^{13}**C NMR + DEPT** (100 MHz, DMSO-d_6): δ 159.6 (**CO**), 140.3 (**C**), 137.0 (**C**), 129.2 (**CH**), 129.0 (**CH**), 128.9 (**CH**), 128.2 (**CH**), 128.0 (**CH**), 127.5 (**CH**), 54.0 (**CH_2N**), 44.8 (**CH_2NH**) ppm.

LRMS (ES^+): *m/z* 788 ([3M + Na^+], 5%), 533 ([2M + Na^+], 65%), 319 ([M + MeCN + Na^+], 15%), 278 ([M + Na^+], 10%), 256 ([M + H^+], 100%).

p-Toluenesulphonyl-4-benzyl semicarbazide (1.13)



Benzyl isocyanate (0.13 g, 0.98 mmol) was added dropwise to a stirring solution of tosylhydrazine (1.1 equiv., 0.20 g, 1.08 mmol) in dichloromethane (20 mL). After 1 h stirring at room temperature a white precipitate formed. The reaction mixture

was filtered and washed with dichloromethane to give the pure product **1.13** as a fluffy white solid (0.31 g, 98%).

Mp 208 – 209 °C (dichloromethane/isopropanol).

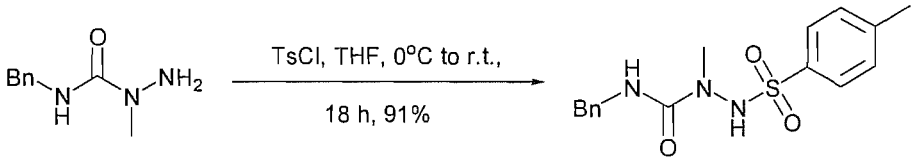
IR: 3410 (m), 3107 (m), 2973 (m), 1650 (s), 1553 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.44 (1H, s, **NH**); 8.05 (1H, s, **NH**); 7.71 (2H, d, *J*= 8.4 Hz, **C_6H_4**); 7.38 (2H, d, *J*= 8.4 Hz, **C_6H_4**); 7.30 – 7.14 (5H, m, **C_6H_5**); 6.90 (1H, t, *J*= 6.2 Hz, **$NHCH_2$**); 4.16 (2H, d, *J*= 6.2 Hz, **CH_2**); 2.40 (3H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 157.5 (**C**O), 143.3 (**C**CH_3), 140.3 (**C**CH_2), 135.3 (**C**SO_2), 129.4 (**C**H), 128.0 (**C**H), 127.8 (**C**H), 126.8 (**C**H), 126.4 (**C**H), 42.5 (**C**H_2), 21.0 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 980 ([3M + Na^+], 30%), 661 ([2M + Na^+], 50%), 639 ([2M + H^+], 50%), 383 ([M + MeCN + Na^+], 35%), 361 ([M + MeCN + H^+], 20%), 320 ([M + H^+], 100%).

p-Toluenesulphonyl-2-methyl-4-benzyl semicarbazide (1.14)



2-Methyl-4-benzyl semicarbazide (2.2 equiv., 0.20 g, 1.21 mmol) dissolved in THF (1.0 mL) was added dropwise to a stirring solution of *p*-toluenesulphonyl chloride (0.11 g, 0.55 mmol) in THF (1.0 mL) at –78 °C. The reaction mixture was warmed gradually to room temperature and stirred at this temperature overnight. The organics were washed with water (2 x 10 mL) and brine (10 mL), the aqueous phase was extracted with THF (3 x 10 mL), dried over $MgSO_4$, filtered through Celite and concentrated *in vacuo* to give a yellow oil. The oil was redissolved in the minimum volume of CH_2Cl_2 and hexane added until the excess starting material precipitated out of solution. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (0 – 100% ethyl acetate/hexane, followed by 10% MeOH/CH_2Cl_2). The appropriate fractions were combined and solvent removed *in vacuo* to give the product **1.14** as an off-white solid (167 mg, 91%).

Mp 129 – 130 °C (isopropanol)

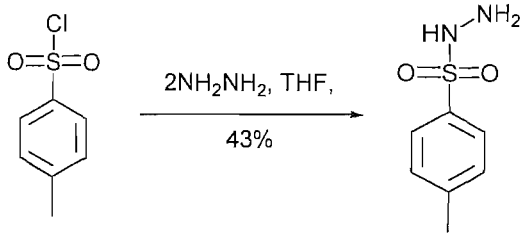
IR: 3440 (m), 3254 (m), 1691 (s), 1525 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.70 (1H, s, **NH**); 7.79 (2H, d, *J*= 8.3 Hz, **C$_6$H$_4$**); 7.42 (2H, d, *J*= 8.3 Hz, **C$_6$H$_4$**); 7.26 – 7.12 (6H, m, **C$_6$H$_5$** & **NH**); 4.16 (2H, d, *J*= 6.0 Hz, **CH$_2$**); 2.62 (3H, s, **OCH$_3$**); 2.40 (3H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 158.3 (**C**O), 144.1 (**C**), 140.2 (**C**), 135.8 (**C**), 129.8 (**C**H), 127.9 (**C**H), 127.8 (**C**H), 126.7 (**C**H), 126.3 (**C**H), 43.2 (**C**H$_2$), 35.9 (**C**H$_3$), 21.1 (**C**H$_3$) ppm.

LRMS (ES$^+$): *m/z* 689 ([2M + Na$^+$], 20%), 684 ([2M + NH$^+$], 20%), 397 ([M + MeCN + Na$^+$], 20%), 356 ([M + Na$^+$], 65%), 334 ([M + H$^+$], 100%).

p-Toluenesulfonyl hydrazine (1.15)



Synthesised according to literature procedure.[33]

p-Toluenesulfonyl chloride (1.00 equiv., 0.20 g, 1.05 mmol) was dissolved in THF (35 mL) and stirred at 10 °C for 10 minutes. Hydrazine hydrate (2.20 equiv., 0.07 g, 0.13 mL) was then added and the reaction mixture was stirred for a further 20 minutes at 10 °C. The reaction mixture was allowed to warm to room temperature and stir for 3 days. The reaction mixture was then washed with brine (2 x 20 mL). The organic layer was dried over $MgSO_4$ and filtered through Celite. The Celite was washed with excess THF and the combined organics were concentrated to give the crude product. The residues were recrystallised to give pure product **1.15** (0.08 g, 43%).

Mp 108 – 110 °C (tetrahydrofuran/diethyl ether), literature value 109 °C.[33]

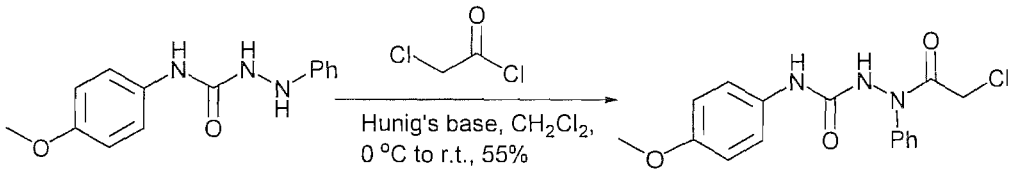
IR: 3385 (m), 3252 (m), 1598 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (2H, d, *J*= 8.2 Hz, **ArH**); 7.37 (2H, d, *J*= 8.2 Hz, **ArH**); 5.76 (1H, br s, **NH**); 3.57 (2H, br s, **NH$_2$**); 2.46 (3H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 144.7 (**C**), 133.3 (**C**), 130.0 (**C**H), 128.3 (**C**H), 21.7 (**C**H$_3$) ppm.

The data acquired corresponds to the literature values for this known compound.[33]

1-Chloroacetyl-1-phenyl-4-(4-methoxyphenyl) semicarbazide (1.16)



To a stirred suspension of **1.8** (100 mg, 0.39 mmol) and diisopropylethylamine (1.1 equiv., 0.43 mmol, 55 mg) in dichloromethane (5 mL) at 0 °C was added dropwise chloroacetyl chloride (1.1 equiv., 0.43 mmol, 48 mg). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The organics were washed with water (3 x 15 mL) and the aqueous phase extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid. The white solid was recrystallised from ethanol to give a white crystalline solid, **1.16** (71 mg, 55%).

Mp 214 – 216 ° C (ethanol).

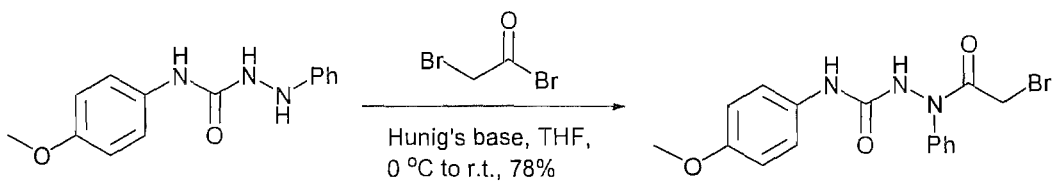
IR: 3358 (m), 3238 (m), 1680 (s), 1534 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.20 (1H, br s, **NH**); 9.05 (1H, br s, **NH**); 7.52 – 7.24 (7H, m, **ArH**); 6.84 (2H, d, *J*= 9.0 Hz, **ArH**); 4.76 (1H, br d, *J*= 14.6 Hz, **CH_2**); 4.48 (1H, br d, *J*= 14.6 Hz, **CH_2**); 3.70 (3H, s, **OCH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6): δ 168.7 (**C**O), 155.9 (**C**O), 155.1 (**C**), 142.6 (**C**), 132.8 (**C**), 129.6 (**CH**), 127.2 (**CH**), 124.1 (**CH**), 121.7 (**CH**), 114.8 (**CH**), 56.1 (**CH_3**), 45.2 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 686 and 684 ([2M + NH_4^+], 10%, 3:1 ratio), 353 and 351 ([M + NH_4^+], 35%, 3:1 ratio), 336 and 334 ([M + H^+], 10%, 3:1 ratio), 130 (100).

1-Bromoacetyl-1-phenyl-4-(4-methoxyphenyl) semicarbazide (1.17)



To a stirred solution of **1.8** (250 mg, 0.97 mmol) and diisopropylethylamine (2.0 equiv., 1.94 mmol, 251 mg) in tetrahydrofuran (25 mL) at 0 °C was added dropwise bromoacetyl bromide (1.1 equiv., 1.07 mmol, 216 mg). The reaction mixture was allowed to warm to room temperature and stirred for 2h. The solvent was removed *in vacuo* and the residue redissolved in CH_2Cl_2 (10 mL). The

organics were then washed with water (3 x 10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residues were then repeatedly triturated with CH_2Cl_2 to give **1.17** as a white solid. This was then recrystallised from diethyl ether: CH_2Cl_2: ethanol (1:1:0.25) to yield **1.17** as a white crystalline solid (285 mg, 78%).

Mp 200 – 202 °C (diethyl ether/CH_2Cl_2/ethanol)

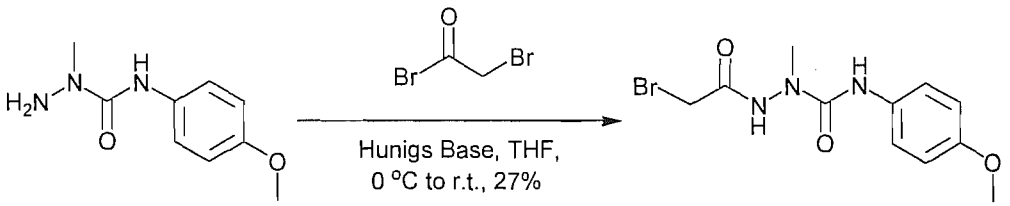
IR: 3355 (m), 3240 (m), 1676 (s), 1598 (m), 1531 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.28 (1H, br s, **NH**); 9.01 (1H, br s, **NH**); 7.48 – 7.25 (5H, m, **ArH**); 7.33 (2H, d, *J*= 10.0 Hz, **ArH**); 6.84 (2H, d, *J*= 10.0 Hz, **ArH**); 4.54 (1H, br d, **CH$_2$**); 4.30 (1H, br d, **CH$_2$**); 3.70 (3H, s, **OCH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 168.8 (**C**O), 155.9 (**C**O), 155.1 (**C**), 142.6 (**C**), 132.9 (**C**), 129.9 (**C**H), 127.2 (**C**H), 124.3 (**C**H), 121.7 (**C**H), 114.8 (**C**H), 56.1 (**C**H$_3$), 31.8 (**C**H$_2$) ppm.

LRMS (ES$^+$): *m/z* 776 and 774 ([2M + NH_4^+], 30%, 1:1 ratio), 397 and 395 ([M + NH_4^+], 60%, 1:1 ratio), 380 and 378 ([M + H^+], 40%, 1:1 ratio), 130 (100).

1-Bromoacetyl-2-methyl-4-(4-methoxyphenyl) semicarbazide (1.18)



To a stirred solution of 2-methyl-4-(4-methoxyphenyl) semicarbazide, **1.9** (200 mg, 1.02 mmol) and diisopropylethylamine (2.0 equiv., 2.05 mmol, 265 mg) in tetrahydrofuran (20 mL) at 0 °C was added dropwise bromoacetyl bromide (1.1 equiv., 1.13 mmol, 227 mg). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was filtered and the white precipitate washed with excess tetrahydrofuran. The filtrate was concentrated *in vacuo* and the residue redissolved in CH_2Cl_2 (10 mL). The organics were then washed with water (2 x 10 mL), brine (10 mL) and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (0 – 80% ethyl acetate/hexane). The appropriate fractions were

combined and solvent removed *in vacuo* to give a yellow oil. The oil was repeatedly triturated with hexane to give **1.18** as a white solid (86 mg, 27%).

Mp 87 – 89 °C (hexane/dichloromethane).

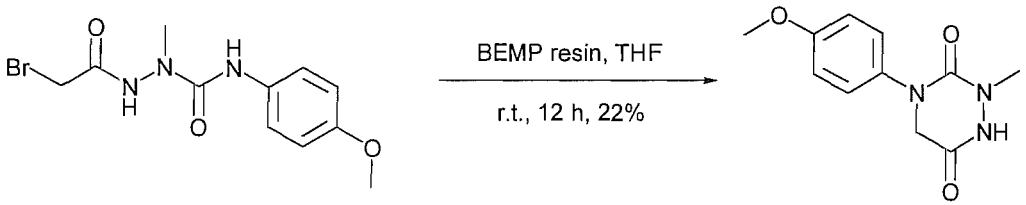
IR: 3354 (m), 3256 (m), 1666 (m), 1542 (s) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 9.52 (1H, s, **NH**); 7.43 (1H, s, **NH**); 7.17 (2H, d, *J*= 8.9 Hz, **ArH**); 6.74 (2H, d, *J*= 8.9 Hz, **ArH**); 3.67 (5H, br s, **CH_3O** & **CH_2**); 3.00 (3H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 166.9 (**CO**), 156.5 (**CO**), 130.7 (**C**), 128.4 (**C**), 123.1 (**CH**), 114.2 (**CH**), 55.5 (**CH_3**), 35.7 (**CH_3**), 26.2 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 657, 655 and 653 ([2M + Na^+], 5%, 1:2:1 ratio), 652, 650 and 648 ([2M + NH_4^+], 20%, 1:2:1 ratio), 635, 633 and 631 ([2M + H^+], 15%, 1:2:1 ratio), 417 and 415 ([M + NH_4^+ + 2MeCN], 5%, 1:1 ratio), 381 and 379 ([M + NH_4^+ + MeCN], 10%, 1:1 ratio), ([M + NH_4^+], 10%, 1:1 ratio), ([M + H^+], 85%, 1:1 ratio), 130 (100).

2-Methyl-4-(4-methoxyphenyl)-1,2,4-triazine-3,6-dione (1.19)



BEMP resin (1.0 equiv., 2.7 mmol, 1.24 g) was added to a solution of 1-bromoacetyl-2-methyl-4-(4-methoxyphenyl) semicarbazide, **1.18** (86 mg, 2.7 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 2 days, followed by filtration. The resin was washed with large volumes of THF and methanol. The organics were concentrated *in vacuo* to give **1.19** as a white solid. The crude product was then purified by column chromatography (10% (NEt_3/methanol)/ dichloromethane). This yielded **1.19** as a white crystalline solid (14 mg, 22%) after being recrystallised from methanol.

Mp 276 – 279 °C (methanol).

IR: 3464 (w), 3366 (w), 1667 (s) cm^{-1}.

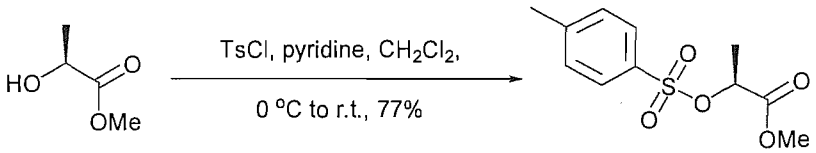
^{1}H NMR (400 MHz, DMSO-d_6) **(Major form)**: δ 8.82 (1H, br s, **NH**); 7.38 (2H, d, *J*= 8.6 Hz, **ArH**); 7.02 – 6.98 (2H, m, **ArH**); 4.51 (1H, d, *J*= 16.1 Hz, **CH_2**); 4.25 (1H, d, *J*= 16.1 Hz, **CH_2**); 3.84 (3H, s, **OCH_3**); 3.18 (3H, s, **NCH_3**) ppm.

^{1}H NMR (400 MHz, DMSO-d_6) **(Minor form)**: δ 8.73 (1H, br s, **NH**); 7.48 (2H, d, *J*= 8.5 Hz, **ArH**); 7.02 – 6.98 (2H, m, **ArH**); 4.59 (1H, d, *J*= 16.1 Hz, **CH_2**); 4.28 (1H, d, *J*= 16.1 Hz, **CH_2**); 3.84 (3H, s, **OCH_3**); 3.15 (3H, s, **NCH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6) **(Major & Minor form)**: δ 164.8 (**C**), 163.7 (**C**), 156.4 (**C**), 156.2 (**C**), 155.6 (**C**), 155.1 (**C**), 132.8 (**CH**), 132.6 (**CH**), 124.6 (**CH**), 123.3 (**CH**), 114.6 (**CH**), 114.5 (**CH**), 56.1 (**CH_2**), 56.0 (**CH_2**), 51.5 (**CH_3**), 33.1 (**CH_3**) ppm.

LRMS (ES$^+$): *m/z* 963 ([4M + Na^+], 10%), 958 ([4M + NH_4^+], 50%), 941 ([4M + H^+], 10%), 493 ([2M + Na^+], 2%), 471 ([2M + H^+], 100).

(*S*)-2-(Toluene-4-sulfonyloxy)-propionic acid methyl ester (1.20)



1.20

A solution of *p*-toluenesulfonyl chloride (2.0 equiv., 19.2 mmol, 3.66 g) in dichloromethane (10 mL) was added portion-wise to a stirred ice-cold solution of (*S*)-methyl lactate (9.6 mmol, 1.00 g) and pyridine (3.0 equiv., 58.8 mmol, 4.65 g) in dichloromethane (10 mL). The reaction was stirred at room temperature for 12 hours. Diethyl ether (10 mL) and water (10 mL) was then added to the reaction mixture, the organics were washed with $HCl_{(aq)}$ (2 N, 10 mL), saturated $NaHCO_{3\,(aq)}$ (10 mL), and water (10 mL). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the product **1.20** as a pale yellow oil (1.90 g, 77%).

IR ($CDCl_3$): 1761 (s), 1368 (s), 1178 (s) cm^{-1}.

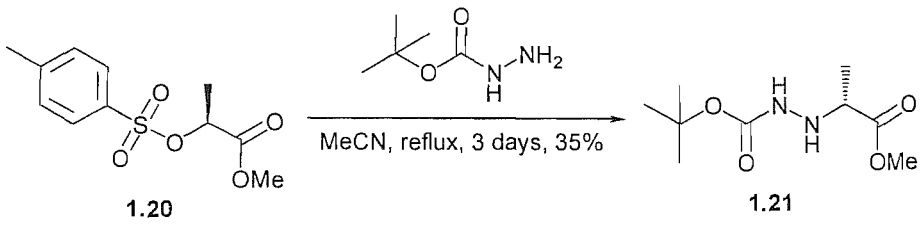
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, *J*= 6.9 Hz, **ArH**); 7.35 (2H, d, *J*= 6.9 Hz, **ArH**); 4.95 (1H, q, *J*= 6.2 Hz, CH_3**CH**); 3.67 (3H, s, **CH_3**); 2.45 (3H, s, **CH_3**); 1.51 (3H, d, *J*= 6.2 Hz, **CH_3**CH) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 170.1 (C), 145.7 (C), 134.1 (C), 130.4 (CH), 128.6 (CH), 74.7 (CH_3), 53.2 (CH), 22.3 (CH_3), 19.0 (CH_3) ppm.

LRMS (EI): *m/z* 258 ([M^+], 19 %), 199 (91), 155 (100), 139 (51), 91 (94).

The data acquired corresponds to the literature values for this known compound.[57]

(*R*)-2-(*N*-*tert*-Butoxycarbonyl-hydrazino)-propionic acid methyl ester (1.21)



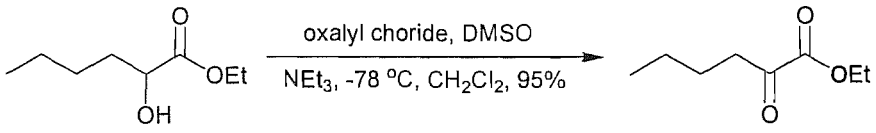
1.20 1.21

Hydrazinecarboxylic acid *tert*-butyl ester (1.5 equiv., 1.45 mmol, 0.19 g) was added dropwise to a stirring solution of 2-(toluene-4-sulfonyloxy)-propionic acid methyl ester **1.20** (0.25 g, 0.97 mmol) in acetonitrile (30 mL). After 3 days refluxing, the reaction mixture was an orange solution with a white precipitate. The reaction mixture was filtered and the precipitate washed with excess acetonitrile. The filtrate was concentrated *in vacuo* to give an orange oil. The crude product was then purified by column chromatography (50–100% ethyl acetate/hexane). The appropriate fractions were combined and solvent removed *in vacuo* to give **1.21** as a colourless oil (0.074 g, 35%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (1H, br s, **NH**); 3.82 (1H, br s, **NH**); 3.67 (4H, m, **CH_3CH** and **OCH_3**); 1.38 (9H, s, **3 x CH_3**); 1.25 (3H, d, J=7.1, **CH_3CH**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.8 (**CO**), 156.0 (**CO**), 80.2 (**C**), 58.1 (**CH**), 51.7 (**OCH_3**), 27.9 (**CH_3**), 15.6 (**CHCH_3**) ppm.
LRMS (ES^+): *m/z* 459 ([2M + Na^+], 100 %), 437 ([2M + H^+], 30 %), 282 ([M + MeCN + Na^+], 70 %), 241 ([M + Na^+], 50 %), 219 ([M + H^+], 50 %).

The data acquired corresponds to the literature values for this known compound.[58]

Ethyl-2-oxohexanoate (1.25)



Synthesised according to literature procedure.[42]

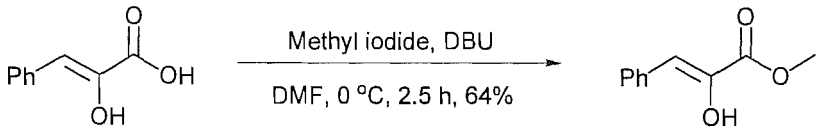
A solution of dimethyl sulfoxide (4.00 equiv., 50.00 mmol, 3.55 mL) in dichloromethane (10 mL) was added over 5 minutes to a solution of oxalyl chloride

(2.00 equiv., 25.00 mmol, 2.21 mL) in dichloromethane (25 mL) stirring at - 78 °C. After 10 minutes stirring a solution of ethyl-2-hydroxyhexanoate (1.00 equiv., 12.50 mmol, 2.07 mL) in dichloromethane (10 mL) was added to the reaction mixture over 5 minutes. The reaction mixture was allowed to warm to – 60 °C and to stir for 15 minutes. Triethylamine (8.00 equiv., 100.00 mmol, 13.94 mL) was added and the reaction mixture was then allowed to warm to room temperature. The reaction mixture appeared to be a thick white foam at this point, water (50 mL) was added and the two layers separated on stirring. The organic layer was washed with aqueous HCl (2N, 50 mL), water (50 mL) and then aqueous $NaHCO_3$ (saturated, 50 mL). The organic layer was then dried over $MgSO_4$, filtered and solvent removed *in vacuo* to give the product **1.25** as a clear colourless oil (1.88 g, 95%).

IR (Neat): 2961 (w), 2936 (w), 1726 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.24 (2H, q, *J*= 7.2 Hz, **OC$\underline{H}_2$CH$_3$**); 2.75 (3H, t, *J*= 7.2 Hz, **OCH$_2$C$\underline{H}_3$**); 1.59 – 1.49 (2H, m, **C$\underline{H}_2$**); 1.33 – 1.25 (4H, m, 2 x **C$\underline{H}_2$**); 0.85 (3H, t, *J*= 7.3 Hz, **CH$_2$C$\underline{H}_3$**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 194.7 (**C$\underline{O}$**), 161.3 (**C$\underline{O}$**), 62.2 (**OC$\underline{H}_2$**), 38.9 (**C$\underline{H}_2$**), 26.1 (**C$\underline{H}_2$**), 22.0 (**C$\underline{H}_2$**), 13.9 (**C$\underline{H}_3$**), 13.8 (**C$\underline{H}_3$**) ppm.
LRMS (EI): *m/z* 158 ([M + H$^+$], 21 %), 85 (100), 57 (49).

The data acquired corresponds to the literature values for this known compound.[42]

2-Hydroxy-3-phenyl-2-propenoic acid methyl ester (1.26)



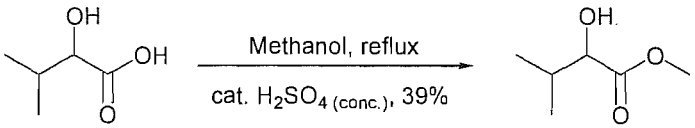
Methyl iodide (5.0 equiv., 20 mmol, 1.24 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.0 equiv., 4.02 mmol, 0.60 mL) were added to a stirring solution of phenyl pyruvic acid (4.02 mmol, 0.66 g) in DMF at 0 °C. The reaction was stirred at 0 °C for 2.5 h before being poured onto a mixture of $HCl_{(aq)}$ (1 M, 10 mL) and diethyl ether (10 mL). The organics were washed with water (2 x 15 mL) and brine (15 mL). The aqueous layer was extracted with ether (2 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the

product as a pale yellow solid (0.46 g, 64%). [The product was reacted on without further purification.]

IR: 3474 (m), 1741 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (2H, d, *J*= 7.1 Hz, **ArH**); 7.42 – 7.37 (3H, m, **ArH**); 6.55 (1H, s, **CH**); 6.43 (1H, br s, **OH**); 3.94 (3H, s, **OCH_3**) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.7 (**CO**), 139.0 (**C**), 134.0 (**C**), 129.9 (**CH**), 128.5 (**CH**), 128.0 (**CH**), 111.2 (**CHCOH**), 53.3 (**OCH_3**) ppm.
LRMS (ES^+): *m/z* 469 ([$2M^+$ + MeOH + MeCN + K^+], 80%), 452 ([2M + MeOH + MeCN + Na^+], 100%), 411 ([2M + MeOH + Na^+], 95%).

The data acquired corresponds to the literature values for this known compound.[43]

2-Hydroxy-3-methylbutyric acid methyl ester (1.27)

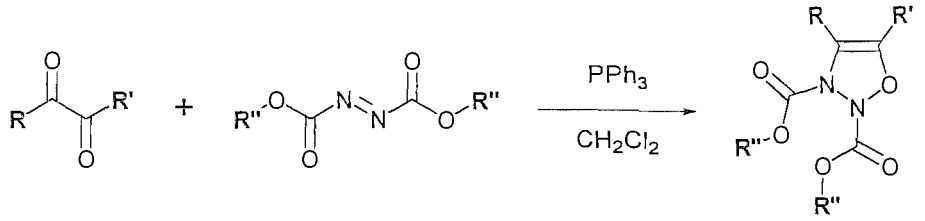


Synthesised according to literature procedure.[41]

A solution of 2-hydroxy-3-methylbutyric acid (1.00 equiv., 2.00 g, 16.93 mmol) and conc. H_2SO_4 (0.4 mL) in methanol (20 mL) was refluxed for 36 h. The reaction was allowed to cool and the solvent removed *in vacuo*. The crude residues were dissolved in diethyl ether (50 mL). The reaction mixture was washed with an aqueous solution of $NaHCO_3$ (50 mL) and then brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the clean product **1.27** (0.96 g, 43%). The product was used without further purification.

IR (Neat): 3504 (m), 2963 (m), 2877 (w), 1731 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.98 (1H, d, *J*= 3.5 Hz, **CH**); 3.72 (3H, s, **OCH_3**); 2.01 (1H, d sept, *J*= 3.5 Hz, J= 6.9 Hz, **$(CH_3)CHCH$**); 0.95 (3H, d, *J*= 6.9 Hz, **CH_3**); 0.80 (3H, d, *J*= 6.9 Hz, **CH_3**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 175.4 (**CO**), 75.1 (**OCH_3**), 52.3 (**CH**), 32.2 (**CH**), 18.7 (**CH_3**), 16.0 (**CH_3**) ppm.
LRMS (EI): *m/z* 133 ([M + H^+], 9 %), 90 (96), 73 (100), 55 (80).

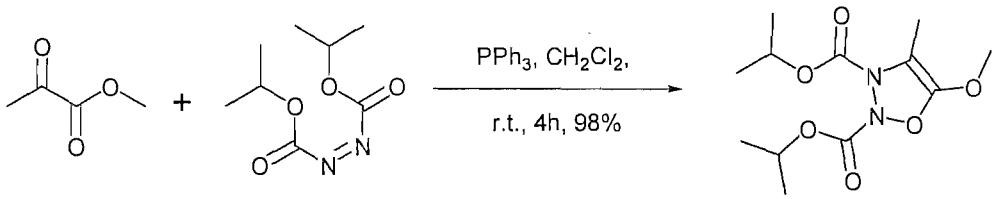
Oxadiazole-2,3-dicarboxylic acid esters (1.23 and 1.28 to 1.35)



General Experimental:

Diisopropyl azodicarboxylate (1.0 equiv.) was added dropwise to a stirred solution of the α-keto ester (1.0 equiv.) and triphenylphosphine (1.0 equiv.) in dichloromethane. The reaction mixture was stirred for several hours (2.5 – 12 h) at room temperature. The reaction was concentrated *in vacuo* and the crude product purified by column chromatography (10 – 100% ethyl acetate/hexane followed by 10% methanol/ethyl acetate). The appropriate fractions were combined and solvent removed *in vacuo* to give the pure oxadiazole and triphenylphosphine oxide (yields 98 – 27%).

5-Methoxy-4-methyl-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.23)



Product was a clear yellow oil (0.63 g, 98%).

IR: 2983 (m), 1732 (m) (C=O), 1674 (m) (C=C) cm^{-1}.

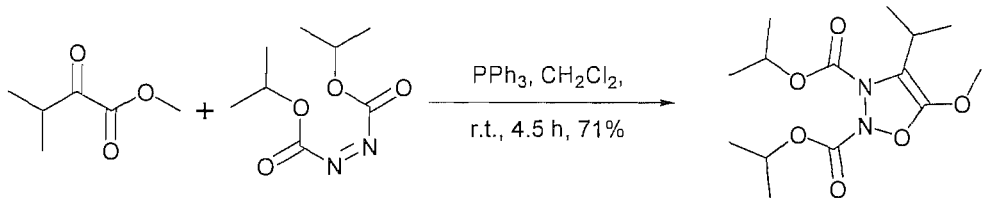
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.91 (1H, sept, *J*= 6.2 Hz, **CH_3CHCH_3**); 4.88 (1H, sept, *J*= 6.2 Hz, **CH_3CHCH_3**); 3.73 (3H, s, **OCH_3**); 1.81 (3H, s, **CH_3**); 1.31 (6H, d, *J*= 6.2 Hz, **$CHCH_3$**); 1.25 – 1.16 (6H, m, **$CHCH_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.3 (**$COCH_3$**), 156.5 (**CO**), 150.9 (**CO**), 95.6 (**CCH_3**), 76.8 (**CH**), 69.5 (**CH**), 52.7 (**OCH_3**), 21.5 (**CH_3**), 21.4 (**CH_3**), 21.2 (**CH_3**) ppm.

LRMS (CI): *m/z* 289 ([M + H^+], 100 %), 203 (40), 188 (98), 116 (64).

The data acquired corresponds to all the given literature values for this known compound.[39]

4-Isopropyl -5-methoxy-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.28)



Product was a clear colourless oil (0.69 g, 71%).

IR: 2981 (m), 1756 (s), 1670 (s) cm^{-1}.

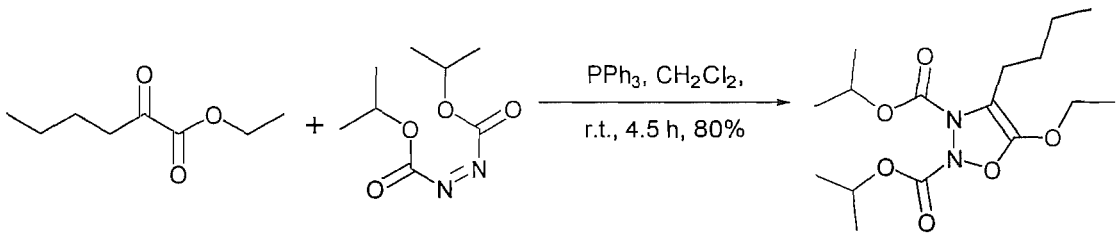
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92 (1H, sept, *J*= 6.2 Hz, **C**H); 4.89 (1H, sept, *J*= 6.2 Hz, **C**H); 3.72 (3H, s, **OC**H_3); 2.81 (1H, sept, *J*= 6.8 Hz, **C**H); 1.33 (3H, d, *J*= 6.2 Hz, **C**H_3); 1.32 (3H, d, *J*= 6.2 Hz, **C**H_3); 1.22 – 1.17 (6H, m, **C**H_3); 1.02 (3H, d, *J*= 6.8 Hz, **C**H_3); 0.93 (3H, d, *J*= 6.8 Hz, **C**H_3)ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.3 (**C**O**C**H_3), 157.5 (**C**O), 151.1 (**C**O), 100.3 (**C**), 77.1 (**C**H), 70.0 (**C**H), 52.8 (**C**H), 31.5 (O**C**H_3), 21.9 (**C**H_3), 21.8 (**C**H_3), 21.6 (**C**H_3), 21.5 (**C**H_3), 16.3(**C**H_3), 15.6 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 655 ([2M + Na^+], 100%).

The data acquired corresponds to the literature values for this known compound.[39]

4-Butyl-5-ethoxy-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.29)



Product was a clear colourless oil (0.35 g, 80%).

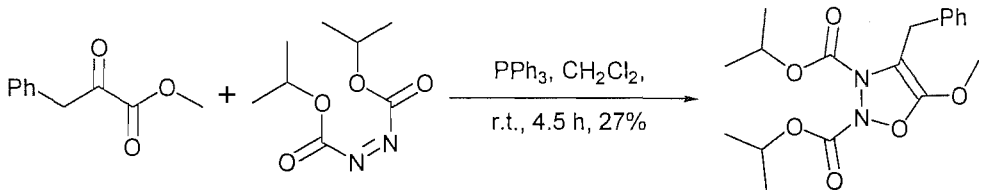
IR: 2982 (m), 1753 (s), 1668 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.92 (1H, sept, *J*= 6.2 Hz, **C**H); 4.88 (1H, sept, *J*= 6.2 Hz, **C**H); 4.18 (2H, q, *J*= 7.1 Hz, **OC**H_2**C**H_3); 2.27 – 2.11 (2H, m, **C**H_2); 1.32 – 1.20 (19H, m, **C**H_2 and **C**H_3); 0.85 (3H, t, *J*= 7.1 Hz, **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.3 (**C**O**C**H_2**C**H_3), 157.2 (**C**O), 151.1 (**C**O), 98.3 (**C**), 77.1 (**C**H), 69.9 (**C**H), 62.3 (O**C**H_2), 32.6 (**C**H_2), 23.8 (**C**H_2), 22.3 (**C**H_2), 21.9 (**CH**CH_3), 21.6 (**CH**CH_3), 14.0 (**C**H_3), 13.9 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 712 and 711 ([2M + Na^+], 100%, 0.35: 1 ratio).

4-Benzyl-5-methoxy-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.30)



Product was a white solid (0.14 g, 27%).

Mp 78 – 79 °C (ethyl acetate/hexane), literature value 76 – 80 °C.

IR: 2980 (m), 1759 (sh), 1737 (s), 1669 (s) cm^{-1}.

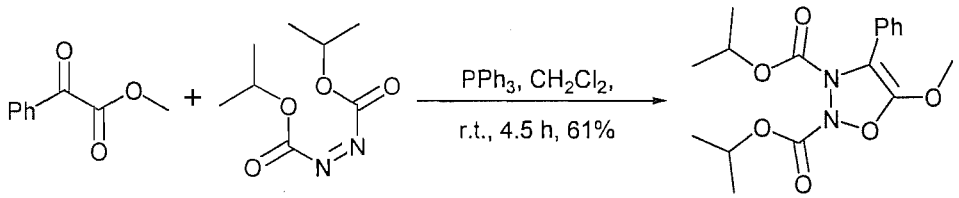
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 – 7.11 (5H, m, **ArH**); 4.98 (1H, sept, *J*= 6.2 Hz, **CH**); 4.55 (1H, sept, *J*= 6.2 Hz, **CH**); 3.76 (3H, s, **OCH_3**); 3.51 (1H, br d, *J*= 14.8 Hz, **CH_2**); 3.36 (1H, br d, *J*= 14.8 Hz, **CH_2**); 1.27 – 1.15 (9H, m, **CH_3**); 0.90 (3H, d, *J*= 6.2 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.5 (**C**OCH_3), 156.8 (**C**O), 150.9 (**C**O), 132.8 (**C**), 130.7 (**C**H), 128.2 (**C**H), 127.3 (**C**H), 96.9 (**C**CH_2), 77.4 (**C**H), 70.0 (**C**H), 52.0 (O**C**H_3), 38.6 (**C**H_2), 21.9 (**C**H_3), 21.7 (**C**H_3), 21.5 (**C**H_3), 21.1 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 752 and 751 ([2M + Na^+], 100%, 0.40: 1 ratio).

The data acquired corresponds to the literature values for this known compound.[39]

4-Phenyl-5-methoxy-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.31)



Product was a white solid (0.26 g, 61%).

Mp 84 - 86 °C (ethyl acetate/hexane).

IR: 2983 (m), 1763 (s), 1701 (s), 1669 (s) cm^{-1}.

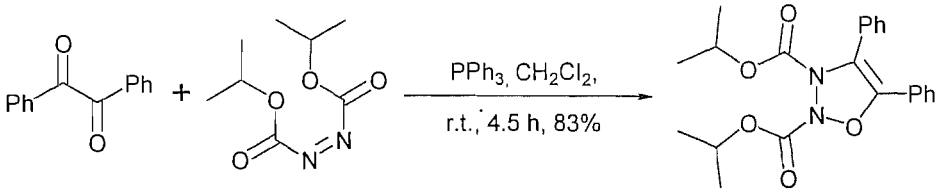
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 – 7.41 (5H, m, **ArH**); 5.03 (1H, sept, *J*= 6.2 Hz, **CH**); 5.00 (1H, sept, *J*= 6.2 Hz, **CH**); 3.87 (3H, s, **OCH_3**); 1.43 (3H, d, *J*= 6.2 Hz,

C$\underline{H}_3$); 1.39 (3H, d, *J*= 6.2 Hz, **C**$\underline{H}_3$); 1.26 (3H, d, *J*= 6.2 Hz, **C**$\underline{H}_3$); 1.22 (3H, d, *J*= 6.2 Hz, **C**$\underline{H}_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.4 (**C**$\underline{O}$**OCH**$_3$), 157.0 (**C**$\underline{O}$), 150.2 (**C**$\underline{O}$), 134.7 (**C**$\underline{H}$), 129.7 (**C**$\underline{H}$), 128.0 (**C**$\underline{H}$), 127.2 (**C**$\underline{H}$), 97.3 (**C**$\underline{H}$), 77.6 (**C**$\underline{H}$), 70.4 (**C**$\underline{H}$), 53.5 (**OC**$\underline{H}_3$), 21.9 (**C**$\underline{H}_3$), 21.8 (**C**$\underline{H}_3$), 21.7 (**C**$\underline{H}_3$), 21.6 (**C**$\underline{H}_3$) ppm.

LRMS (ES^+): *m/z* 723 ([2M + Na^+], 100%,), 432 ([M + 2MeOH + NH_4^+], 5%), 414 ([M + MeCN + Na^+], 15%), 373 ([M + Na^+], 20%).

4,5-Diphenyl-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.32)



Product was a white crystalline solid (0.20 g, 83%).

Mp 84 - 86 °C (diethyl ether/hexane), literature value °C.

IR: 2988 (m), 1777 (s), 1675 (s) cm^{-1}.

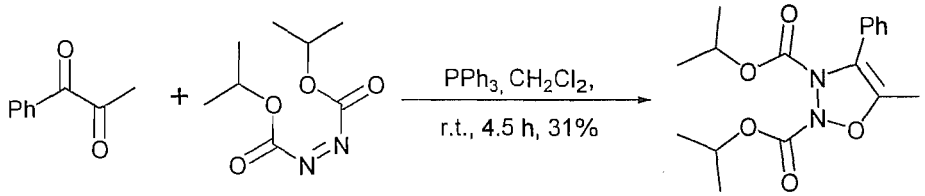
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 – 7.81 (2H, m, **Ar**$\underline{H}$); 7.76 – 7.72 (2H, m, **Ar**$\underline{H}$); 7.52 – 7.44 (2H, m, **Ar**$\underline{H}$); 7.39 – 7.33 (4H, m, **Ar**$\underline{H}$); 4.88 (2H, sept, *J*= 6.2 Hz, 2 x **C**$\underline{H}$); 1.17 (12H, d, *J*= 6.2 Hz, **C**$\underline{H}_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 193.5 (**C**$\underline{O}$), 174.8 (**C**$\underline{O}$), 150.7 (**C**$\underline{O}$ & **C**$\underline{O}$), 134.8 (**C**$\underline{H}$), 134.0 (**C**$\underline{O}$), 132.5 (**C**$\underline{H}$), 132.0 (**C**$\underline{O}$), 129.5 (**C**$\underline{H}$), 129.0 (**C**$\underline{H}$), 128.8 (**C**$\underline{H}$), 128.3 (**C**$\underline{H}$), 60.4 (**C**$\underline{H}$), 21.6 (**C**$\underline{H}_3$**CHC**$\underline{H}_3$) ppm.

LRMS (ES^+): *m/z* 817, 816 and 815 ([2M + Na^+], 100%, 0.23: 0.48: 1 ratio).

The data acquired corresponds to the literature values for this known compound.[39]

4-Phenyl-5-methyl-[1,2,3]oxadiazole-2,3-dicarboxylic acid diisopropyl ester (1.33)



Product was a yellow oil (0.14 g, 31%).

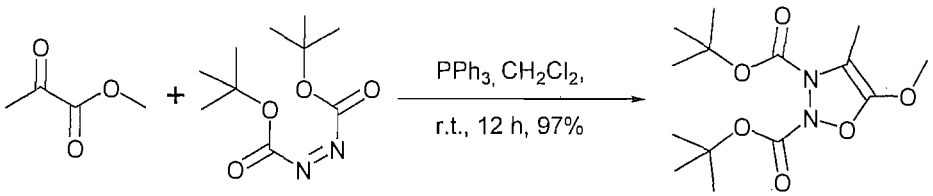
IR: 2983 (m), 1788 (sh), 1750 (s), 1673 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (2H, d, *J*= 7.4 Hz, **Ar**H); 7.56 (1H, t, *J*= 7.4 Hz, **Ar**H); 7.40 (2H, t, *J*= 7.4 Hz, **Ar**H); 5.04 (2H, sept, *J*= 6.2 Hz, 2 x **C**H); 2.09 (3H, s, **CC**H_3); 1.28 (12H, d, *J*= 6.2 Hz, **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 191.4 (**C**), 173.4 (**CO**), 150.0 (**C** & **CO**), 134.5 (**C**), 134.0 (**CH**), 131.0 (**CH**), 128.4 (**CH**), 72.0 (**CH**), 21.6 (**C**H_3**CHC**H_3), 15.9 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 692 and 691 ([2M + Na^+], 100%, 0.37: 1 ratio).

5-Methoxy-4-methyl-[1,2,3]oxadiazole-2,3-dicarboxylic acid di-*tert*-butyl ester (1.34)



Product was a yellow-white solid (0.60 g, 97%).

Mp 108 – 109 °C (ethyl acetate/hexane).

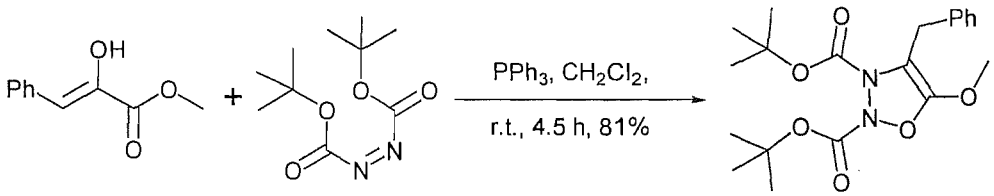
IR: 3205 (m), 1799 (s), 1758 (s), 1708 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (3H, s, **OC**H_3); 1.94 (3H, s, **C**H_3); 1.50 (18H, s, 6 x **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 161.2 (**C**), 147.7 (**C**), 146.6 (**C**), 88.5 (**C**), 79.3 (**C**), 48.1 (**C**H_3), 22.7 (**C**H_3), 16.9 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 215 ([M – $CO_2{}^tBu$]$^+$, 100%).

5- Benzyl-4-methyl-[1,2,3]oxadiazole-2,3-dicarboxylic acid di-*tert*-butyl ester (1.35)



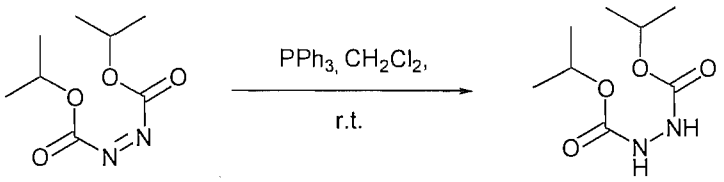
Product was a yellow oil (0.36 g, 81%).

IR: 2980 (m), 1803 (sh), 1759 (s), 1708 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 – 7.14 (5H, m, **Ar**H); 3.80 (3H, s, **C**H$_3$); 3.48 – 3.35 (2H, m, **C**H$_2$); 1.38 (18H, s, 6 x **C**H$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.3 (**C**), 152.7 (**C**O), 151.3 (**C**O), 132.3 (**C**), 130.1 (**C**H), 129.2 (**C**H), 128.1 (**C**H), 94.7 (**C**), 84.5 (**C**), 53.5 (**C**H$_3$), 39.4 (**C**H$_2$), 28.1 (**C**H$_3$) ppm.

N,N'-Dicarboxylic acid diisopropyl ester hydrazine (1.36)



Isolated as a side product in Mitsunobu reactions.

Mp 104 – 105 °C (ethyl acetate/hexane), literature value 107 – 108 °C.[37]

IR (golden gate): 3279 (m), 3245 (m), 3033 (w), 2981 (w), 1734 (s), 1686 (s), 1525 (s) cm^{-1}.

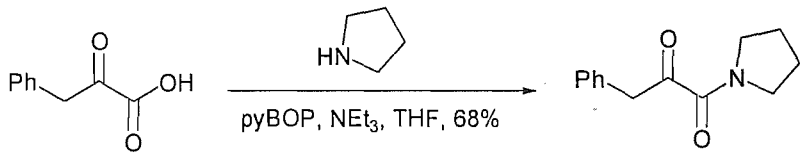
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (2H, s, 2 x **NH**); 4.91 (2H, sept, *J*= 6.2 Hz, 2 x **C**H); 1.20 (12H, d, *J*= 6.2 Hz, 4 x **C**H$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 156.5 (**C**O), 70.2 (**C**H), 22.1 (**C**H$_3$) ppm.

LRMS (ES^+): *m/z* 509 (100), 487 ([2M + MeCN + K^+], 60%), 450 ([2M + MeCN + H^+], 15%), 431 ([2M + Na^+], 20%), 409 ([2M + H^+], 10%), 268 ([M + MeCN + Na^+], 20%), 205 ([M + H^+], 12%).

The data acquired corresponds to the literature values for this known compound.[59]

3-Phenyl-1-pyrrolidin-1-yl-propane-1,2-dione (1.37)



Synthesised according to literature procedure.[44]

Triethylamine (2.00 equiv., 3.10 mmol, 0.43 mL) was added to a pale yellow solution of phenylpyruvic acid (1.00 equiv., 0.25 g, 1.54 mmol) and pyrrolidine (1.00 equiv., 1.54 mmol, 0.13 mL) in THF (20 mL) stirring at room temperature. A solution of pyBOP (1.10 equiv., 0.88 g, 1.69 mmol) in THF (10 mL) was then added to the reaction mixture. The reaction mixture was stirred at room

temperature for 2.5 h. The solvent was removed *in vacuo* and the residues redissolved in dichloromethane. The organics were washed with brine (50 mL) and water (2 x 50 mL). The organics were then dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography (50% ethyl acetate/ hexane) to give **1.37** as a yellow oil (0.23 g, 68%).

IR: 1716 (s), 1631 (s) cm^{-1}.

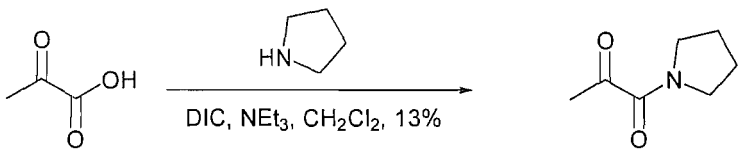
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.25 (5H, m, **ArH**); 4.15 (2H, s, **CH_2**); 3.49 (2H, t, *J*= 6.8 Hz, **NCH_2CH_2**); 3.42 (2H, t, *J*= 6.8 Hz, **NCH_2CH_2**); 1.84 – 1.80 (4H, m, **$CH_2CH_2CH_2CH_2$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 197.4 (**CO**), 162.8 (**CO**), 132.4 (**C**), 129.9 (**CH**), 128.7 (**CH**), 127.3 (**CH**), 47.2 (**CH_2**), 46.2 (**CH_2**), 46.1 (**CH_2**), 26.2 (**CH_2**), 23.6 (**CH_2**) ppm.

LRMS (EI): *m/z* 217 ([M + H^+], 22 %), 98 (100).

The data acquired corresponds to the literature values for this known compound.[44]

1-Pyrrolidin-1-yl-propane-1,2,dione (1.38)



Triethylamine (2.0 equiv., 4.54 mmol, 0.46 g) and diisopropyl carbodimide (1.5 equiv., 3.41 mmol, 0.43 g) were added to a stirring solution of pyruvic acid (0.20 g, 2.27 mmol) and pyrrolidine (2.27 mmol, 0.16 g) in dichloromethane (20 mL). After 2 h stirring at room temperature the reaction mixture was a bright orange solution. The organics were washed with water (2 x 50 mL), then brine (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (50 mL). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified by column chromatography (25 – 100% ethyl acetate/hexane). The appropriate fractions were combined and solvent removed *in vacuo* to give **1.38** as a yellow oil (0.043 g, 13%).

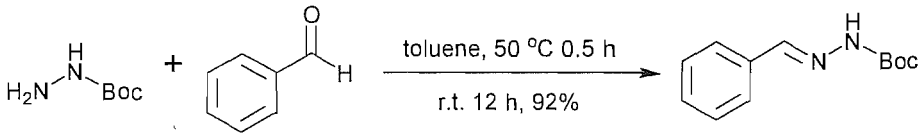
IR: 1715 (w), 1637 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (2H, t, *J*= 6.7 Hz, **NC$\underline{H}_2$CH$_2$**); 3.45 (2H, t, *J*= 6.7 Hz, **NCH$_2$C$\underline{H}_2$**); 2.38 (3H, s, **COC$\underline{H}_3$**); 1.92 – 1.76 (4H, m, **CH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 197.3 (**$\underline{C}$O**), 161.4 (**$\underline{C}$O**), 46.3 (**$\underline{C}$H$_2$**), 45.4 (**$\underline{C}$H$_2$**), 26.0 (**$\underline{C}$H$_3$**), 25.3 (**$\underline{C}$H$_2$**), 22.5(**$\underline{C}$H$_2$**) ppm.

LRMS (EI): *m/z* 142 ([M + H$^+$], 71 %), 98 (77), 55, (100).

N'-Benzylidene-hydrazinecarboxylic acid *tert*-butyl ester (1.39)



tert-Butylcarbazate (1.00 g, 1.00 equiv., 7.57 mmol) and benzaldehyde (1.10 equiv., 8.32 mmol, 0.846 mL) were stirred at 50 °C in toluene (10 mL) for 30 minutes. The reaction mixture was allowed to cool to room temperature overnight and the crude product crystallised out of solution. The product **1.39** was filtered and dried *in vacuo* (1.53 g, 92%). The crude product was used without further purification.

Mp 185 – 186 °C (toluene), literature value 187 – 189 °C.[60]

IR: 3246 (m), 1690 (s), 1524 (s) cm^{-1}.

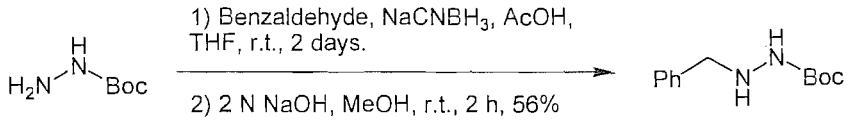
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (1H, br s, **C$\underline{H}$**); 7.84 (1H, br s, **N$\underline{H}$**); 7.69 – 7.66 (2H, m, **Ar$\underline{H}$**); 7.37 – 7.35 (3H, m, **Ar$\underline{H}$**); 1.54 (9H, s, **C$\underline{H}_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 152.6 (**$\underline{C}$**), 143.8 (**$\underline{C}$H**), 134.1 (**$\underline{C}$**), 129.9 (**$\underline{C}$H Ar**), 128.6 (**$\underline{C}$H Ar**), 127.3 (**$\underline{C}$H Ar**), 81.5 (**$\underline{C}$CH$_3$**), 28.4 (**$\underline{C}$H$_3$**) ppm.

LRMS (ES$^+$): *m/z* 463 ([2M + Na$^+$], 95%), 284 ([M + MeCN + Na$^+$], 50%), 243 ([M + Na$^+$], 20%), 221 ([M + H$^+$], 30%).

The melting point and ^{1}H NMR fit the data given in the literature for this known compound.[60]

N'-Benzyl-hydrazinecarboxylic acid *tert*-butyl ester (1.40)



Hydrazinecarboxylic acid *tert*-butyl ester (1.0 equiv., 0.20 g) and benzaldehyde (1.0 equiv., 0.15 mL) were dissolved in tetrahydrofuran (5 mL) and the reaction mixture was stirred for 2 days. Sodium cyanoborohydride (2.5 equiv., 3.78 mmol, 0.24 g) and acetic acid (0.85 mL) were added and the reaction mixture was stirred overnight. Ethyl acetate (20 mL) and water (20 mL) were added to the reaction mixture, followed by solid $NaHCO_3$ until basic. The layers were separated and the organics were washed with brine (20 mL), saturated $NaHCO_{3\,(aq)}$ (20 mL), and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give a clear oil. The oil was re-dissolved in methanol (10 mL) and $NaOH_{(aq)}$ (2N, 10 mL) and stirred for 2 h. The solvent was removed *in vacuo* and the residues re-dissolved in ethyl acetate (50 mL). The organics were washed with brine (2 x 20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude product as a yellow oil. The crude product was then purified by column chromatography (75 % ethyl acetate/hexane). The appropriate fractions were combined and solvent removed *in vacuo* to give **1.40** as a clear oil (0.186g, 56%).

Experimental procedure adapted from the literature.[46, 47, 61]

IR: 1704 (s), 1453 (s) cm^{-1}.

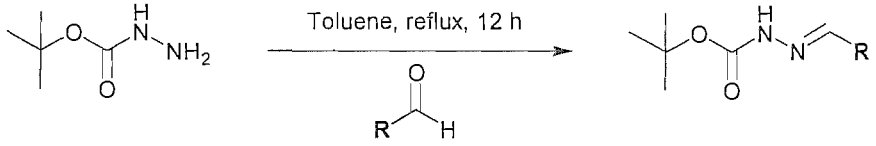
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.31 (5H, m, **ArH**); 6.10 (1H, br s, **NH**); 4.20 (1H, br s, **NH**); 4.01 (2H, s, **CH_2**); 1.47 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 156.7 (**C**), 137.7 (**C**), 129.1 (**CH**), 128.6 (**CH**), 127.6 (**CH**), 80.7 (**C**), 55.9 (**CH_2**), 28.5 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 535 ([2M + MeCN + MeOH + NH_4^+], 35%), 445 ([2M + H^+], 25%), 286 ([M + MeCN + Na^+], 15%), 264 ([M + MeCN + H^+], 40%), 245 ([M + Na^+], 10%), 223 ([M + H^+], 95%), 129 (100%).

The data acquired corresponds to the correct structure for this known compound.[46, 47]

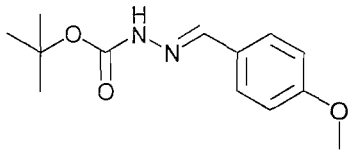
N'-Hydrazone-carboxylic acid *tert*-butyl esters (1.41 to 1.67).



General Experimental:

tert-Butylcarbazate (1.00 equiv.) and the aldehydes (1.10 equiv.) were stirred at 50 °C in toluene (10 mL) for 40 minutes. The reaction mixture was allowed to cool to room temperature overnight and the crude products crystallised out of solution. The products were filtered, washed with excess cold toluene and dried *in vacuo* (where the product did not crystallise out of solution the solvent was removed *in vacuo* to give the crude product). The crude products were then recrystallised.

N'-(4-Methoxy-benzylidene)-hydrazine carboxylic acid *tert*-butyl ester (1.41)



Product was a crystalline white solid (3.61 g, 95%).

Mp 133 – 134 °C (Ethyl acetate/hexane), literature value 137 – 138 °C.[62]

IR: 3207 (m), 2964 (w), 1685 (s) cm^{-1}.

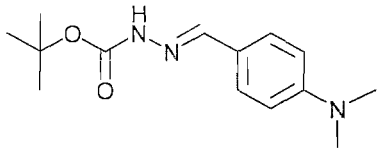
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 and 7.78 (2H, 2 x br s, **CHN** and **NH**); 7.62 (2H, d, *J*=8.8 Hz, **ArH**); 6.89 (2H, d, *J*= 8.8 Hz, **ArH**); 3.82 (3H, s, **OCH_3**); 1.53 (9H, s, **CCH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 161.0 (**C**O), 152.9 (**C**), 143.8 (**NC**H), 128.8 (**C**H), 126.9 (**C**), 114.1 (**C**H), 81.3 (**C**), 55.4 (**O**CH_3), 28.4 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 523 ([2M + Na^+], 20%), 273 ([M + Na^+], 20%), 251 ([M + H^+], 10%), 195 (100%).

The data acquired corresponds to all the given literature values for this known compound.[62]

N'-(4-Dimethylamino-benzylidene)-hydrazine carboxylic acid *tert*-butyl ester (1.43)

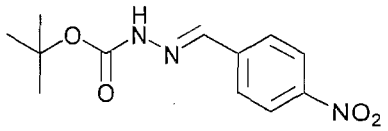


Product was a crystalline white solid (2.92 g, 73%).

Mp 156 – 157 °C (Ethyl acetate/hexane), literature value 156 – 157 °C.[29]
IR: 3248 (m), 2972 (w), 2796 (w), 1684 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (1H, s, **NH**); 7.65 (1H, s, **CHN**); 7.55 (2H, d, *J*= 8.8 Hz, **ArH**); 6.67 (2H, d, *J*= 8.8 Hz, **ArH**); 3.00 (6H, s, 2 x **NCH_3**); 1.53 (9H, s, **CCH_3**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 158.4 (**C**), 151.6 (**C**), 144.7 (**NCH**), 128.7 (**CH**), 121.9 (**C**), 111.9 (**CH**), 81.0 (**C**), 40.3 (**NCH_3**), 28.5 (**CH_3**) ppm.
LRMS (ES^+): *m/z* 549 ([2M + Na^+], 20%), 286 ([M + Na^+], 10%), 264 ([M + H^+], 80%), 208 (100%).

The data acquired corresponds to all the given literature values for this known compound.[63]

N'-(4-Nitro-benzylidene)-hydrazine carboxylic acid *tert*-butyl ester (1.45)

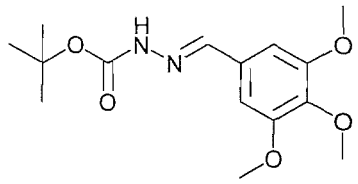


Product was a crystalline yellow solid (3.36 g, 84%).

Mp 165 – 166 °C (Ethyl acetate/hexane), literature value 169 – 171 °C.[63]
IR: 3276 (m), 2984 (w), 1701 (s), 1513 (s) (N=O), 1342 (s) (N=O) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (2H, d, *J*= 8.8 Hz, **ArH**); 8.10 (1H, br s); 7.96 (1H, br s); 7.83 (2H, d, *J*= 8.8 Hz, **ArH**); 1.55 (9H, s, **CCH_3**) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 152.2 (**C**), 148.3 (**C**), 140.8 (**CH**), 140.3 (**C**), 127.7 (**CH**), 124.1 (**CH**), 82.4 (**C**), 28.3 (**CH_3**) ppm.
LRMS (ES^+): *m/z* 553 ([2M + Na^+], 10%), 329 ([M + MeCN +Na^+], 75%), 288 ([M + Na^+], 60%), 210 (100%).

The data acquired corresponds to all the given literature values for this known compound.[63]

_N'_-(3,4,5-Trimethoxy-benzylidene)-hydrazine carboxylic acid _tert_-butyl ester (1.47)

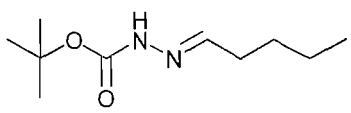


Product was a crystalline white solid (4.10 g, 87%).

Mp 167 °C (Ethyl acetate/hexane).
IR: 3190 (m), 2969 (m), 2832 (m) (OC–H), 1705 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 and 7.77 (2H, 2 x br s, **C<u>H</u>N** and **N<u>H</u>**); 6.91 (2H, s, **Ar<u>H</u>**); 3.88 (9H, s, 3 x **OC<u>H</u>$_3$**); 1.54 (9H, s, **CC<u>H</u>$_3$**) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 153.5 (**<u>C</u>**), 143.7 (**<u>C</u>H**), 139.6 (**<u>C</u>**), 129.6 (**<u>C</u>**), 129.1 (**<u>C</u>**), 104.3 (**<u>C</u>H**), 81.5 (**<u>C</u>**), 60.9 (**O<u>C</u>H$_3$**), 56.2 (**O<u>C</u>H$_3$** & **O<u>C</u>H$_3$**), 28.4 (**<u>C</u>H$_3$**) ppm.
LRMS (ES^+): *m/z* 643 ([2M + Na^+], 60%), 374 ([M + MeCN + Na^+], 40%), 333 ([M + Na^+], 65%), 311 ([M + H^+], 10%), 255 (100%).

The data acquired corresponds to the structure for this commercially available compound, no literature data is available.

_N'_-Pentylidene-hydrazine carboxylic acid _tert_-butyl ester (1.49)



Product did not crystallise from toluene, the solvent was removed *in vacuo* and the residue triturated with hexane to give the product as a fine white crystalline solid (1.27 g, 84%).

Mp 54 – 56 °C (Ethyl acetate/hexane).
IR: 3287 (m), 2931 (m), 1702 (s) cm^{-1}.

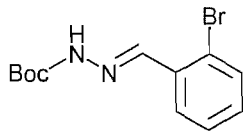
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (1H, br s, **NH**); 7.14 (1H, t, *J*= 5.7 Hz, **CHN**); 2.29 (2H, dt, *J*= 5.7 Hz, *J*= 7.9 Hz, **CH_2CH**); 1.50 (9H, s, **CCH_3**); 1.53 – 1.44 (2H, m, **CH_2**); 1.41 – 1.29 (2H, m, **CH_2**); 0.91 (3H, t, *J*= 7.4 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 152.7 (**C**), 147.7 (**CH**), 80.9 (**C**), 32.0 (**CH_2**), 28.9 (**CH_2**), 28.4 (**CH_3**), 22.5 (**CH_2**), 13.9 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 423 ([2M + Na^+], 100%), 201 ([M + H^+], 5%).

The data acquired corresponds to all the given literature values for this known compound.[64]

N'-(2-Bromo-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.51)



Title compound isolated as a crystalline white solid (2.05 g, 82%).

Mp 179 °C (Toluene).

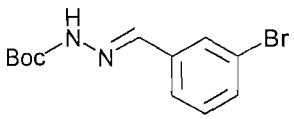
IR: 3235 (m), 2983 (w), 2970 (w), 1705 (s), 1533 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (1H, br s); 8.22 (1H, br s); 8.07 (1H, d, *J*= 7.8 Hz, **ArH**); 7.52 (1H, d, *J*= 7.8 Hz, **ArH**); 7.31 – 7.26 (1H, m, **ArH**); 7.21 – 7.16 (1H, m, **ArH**); 1.54 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 152.4 (**C**), 142.4 (**CH**), 133.0 (**CH**), 131.0 (**CH**), 129.2 (**C**), 128.1 (**CH**), 127.7 (**CH**), 123.8 (**C**), 81.8 (**C**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 623, 621, 619 ([2M + Na^+], 1:2:1 ratio, 40%), 332, 330 (1:1 ratio, 100%).

N'-(3-Bromo-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.53)



Title compound isolated as a crystalline white solid (1.86 g, 75%).

Mp 131 °C (Toluene).

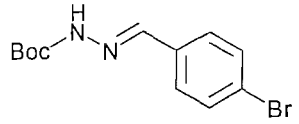
IR: 3190 (m), 2991 (w), 2975 (w), 1709 (s), 1686 (s), 1557 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, br s); 7.85 (1H, br s); 7.80 (1H, br s); 7.57 (1H, d, *J*= 8.0 Hz, **ArH**); 7.47 (1H, ddd, *J*= 8.0, 2.0, 1.0 Hz, **ArH**); 7.36 – 7.22 (1H, m, **ArH**); 1.54 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 150.0 (**C**), 142.2 (**CH**), 136.2 (**C**), 132.8 (**CH**), 130.2 (**CH**), 129.9 (**CH**), 125.9 (**CH**), 123.0 (**C**), 81.9 (**C**), 28.4 ($\underline{C}H_3$) ppm.

LRMS (ES^+): *m/z* 623, 621, 619 ([2M + Na^+], 1:2:1 ratio, 100%), 332, 330 (1:1 ratio, 35%).

N'-(4-Bromo-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.55)



Title compound isolated as a crystalline white solid (2.04 g, 82%).

Mp 155 °C (Toluene).

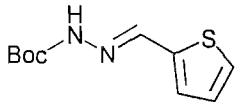
IR: 3191 (m), 3052 (w), 2981 (w), 1717 (s), 1694 (s), 1542 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, br s); 7.81 (1H, br s); 7.54 (2H, d, *J*= 8.5 Hz, **ArH**); 7.49 (2H, d, *J*= 8.5 Hz, **ArH**); 1.54 (9H, s, **C**$\underline{H}_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 152.7 (**C**), 142.5 (**CH**), 133.1 (**C**), 132.0 (**CH**), 128.7 (**CH**), 124.1 (**C**), 81.8 (**C**), 28.4 ($\underline{C}H_3$) ppm.

LRMS (ES^+): *m/z* 623, 621, 619 ([2M + Na^+], 1:2:1 ratio, 100%), 332, 330 (1:1 ratio, 90%).

N'-Thiophen-2-ylmethylene-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.57)



Title compound isolated as a white crystalline solid (1.55 g, 90%).

Mp 194 – 195 °C (Toluene).

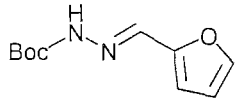
IR: 3244 (m), 2983 (w), 2965 (w), 1694 (s), 1536 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (1H, br s); 7.77 (1H, br s); 7.35 – 7.33 (1H, m, **ArH**); 7.20 (1H, dd, *J*= 3.7, 0.9 Hz, **ArH**); 7.02 (1H, dd, *J*= 5.1, 3.7 Hz, **ArH**); 1.53 (9H, s, **C**$\underline{H}_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 152.0 (**C**), 139.1 (**C**), 129.0 (**CH**), 127.9 (**CH** x 2), 127.2 (**CH**), 81.5 (**C**), 28.3 ($\underline{C}H_3$) ppm.

LRMS (ES^+): *m/z* 701 ([3M + Na^+], 10%), 491 ([2M + K^+], 10%), 475 ([2M + Na^+], 100%), 453 ([2M + H^+], 5%), 290 ([M + MeCN + Na^+], 25%).

***N'*-Furan-2-ylmethylene-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.59)**



Title compound isolated as a white crystalline solid (1.10 g, 69%).

Mp 161 – 162 °C (Toluene/hexane).

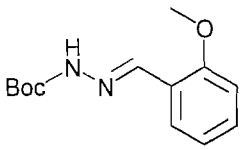
IR (golden gate): 3236 (m), 2983 (w), 2971 (w), 1693 (s), 1520 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (1H, br s); 7.90 (1H, br s); 7.46 (1H, dd, *J*= 1.8, 0.7 Hz, **ArH**); 6.71 (1H, d, *J*= 3.3 Hz, **ArH**); 6.45 (1H, dd, *J*= 3.3, 1.8 Hz **ArH**); 1.53 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 152.5 (**C**), 149.6 (**C**), 143.9 (**CH**), 134.3 (**CH**), 111.7 (**CH** x 2), 81.5 (**C**), 28.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 653 ([3M + Na^+], 10%), 459 ([2M + K^+], 10%), 443 ([2M + Na^+], 100%), 438 ([2M + NH_4^+], 10%).

***N'*-(2-Methoxy-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.61)**



Title compound isolated as a crystalline white solid (1.41 g, 74%).

Mp 135 – 136 °C (Toluene).

IR: 3248 (m), 2979 (w), 2935 (w), 1705 (s), 1267 (s), 1054 (s) cm^{-1}.

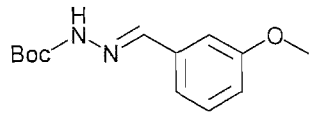
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (1H, br s); 8.00 (1H, dd, *J* = 7.7, 1.6 Hz, **ArH**); 7.90 (1H, br s); 7.31 (1H, ddd, *J* = 8.4, 7.3, 1.6 Hz, **ArH**); 6.98 – 6.93 (1H, m, **ArH**); 6.87 (1H, dd, *J* = 8.4, 0.7 Hz, **ArH**); 3.83 (3H, s, **OCH_3**); 1.53 (9H, s, **$C(CH_3)_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 157.8 (**C**), 139.6 (**C**), 135.5 (**CH**), 131.1 (**CH**), 126.8 (**CH**), 122.6 (**C**), 121.0 (**CH**), 111.0 (**CH**), 81.3 (**C**), 55.6 (**CH_3**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 523 ([2M + Na^+], 30%), 273 ([M + Na^+], 50%), 251 ([M + H^+], 25%), 195 (100).

***N'*-(3-Methoxy-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester**

(1.63)



Title compound isolated as a crystalline white solid (1.65 g, 87%).

Mp 121 – 122 °C (Toluene).

IR: 3187 (m), 2975 (w), 2936 (w), 1705 (s), 1683 (s), 1267 (s), 1057 (s) cm^{-1}.

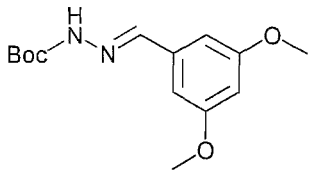
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (1H, br s); 7.81 (1H, br s); 7.31 – 7.29 (1H, m, **ArH**); 7.28 – 7.24 (1H, m, **ArH**); 7.18 – 7.15 (1H, m, **ArH**); 6.91 (1H, ddd, *J* = 8.2, 2.7, 1.1 Hz, **ArH**); 3.83 (3H, s, **OCH_3**); 1.54 (9H, s, **$C(CH_3)_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 159.9 (**C**), 152.8 (**C**), 143.9 (**CH**), 135.5 (**C**), 129.5 (**CH**), 120.6 (**CH**), 116.7 (**CH**), 110.7 (**CH**), 81.4 (**C**), 55.3 (**CH_3**), 28.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 523 ([2M + Na^+], 30%), 314 ([M + MeCN + Na^+], 10%), 273 ([M + Na^+], 30%), 195 (100).

***N'*-(3,5-Dimethoxy-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester**

(1.65)



Title compound isolated as a crystalline white solid (0.90 g, 77%).

Mp 161 °C (Toluene), literature 161 – 163 °C.[5]

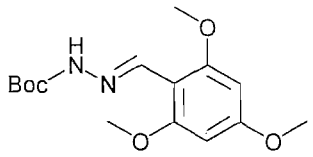
IR: 3296 (m), 3220 (m), 2970 (w), 2940 (w), 1705 (s), 1249 (s), 1061 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (1H, br s); 7.76 (1H, br s); 6.83 – 6.82 (2H, m, **ArH**); 6.47 – 6.45 (1H, m, **ArH**); 3.80 (6H, s, **OCH_3**); 1.54 (9H, s, **$C(CH_3)_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 160.9 (**C**), 152.8 (**C**), 143.9 (**CH**), 136.1 (**C**), 105.0 (**CH**), 102.8 (**CH**), 81.4 (**C**), 55.5 (**CH_3**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 583 ([2M + Na^+], 40%), 561 ([2M + H^+], 10%), 344 ([M + MeCN + Na^+], 10%), 303 ([M + Na^+], 20%), 225 (100).

N'-(2,4,6-Trimethoxy-benzylidene)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.67)



Title compound isolated as a crystalline white solid (2.22 g, 95%).

Mp 172 °C (Toluene).

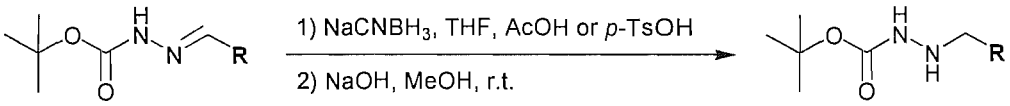
IR: 3203 (m), 2976 (w), 2934 (w), 1691 (s), 1250 (s), 1052 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 8.15 (1H, br s); 7.69 (1H, br s); 6.11 (2H, s, **ArH**); 3.85 (9H, s, **OCH$_3$**); 1.53 (9H, s, **C(CH$_3$)$_3$**) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 162.3 (**C**), 160.4 (**C**), 152.6 (**C**), 139.7 (**CH**), 104.5 (**C**), 90.7 (**CH**), 80.6 (**C**), 56.0 (**CH$_3$**), 55.3 (**CH$_3$**), 28.3 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 643 ([2M + Na^+], 100%), 333 ([M + Na^+], 40%), 311 ([M + H^+], 40%).

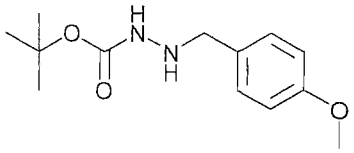
***N'*-Alkyl-hydrazinecarboxylic acid *tert*-butyl esters (1.42 to 1.68).**



General Experimental:

N'-Hydrazone-carboxylic acid *tert*-butyl esters (1.0 equiv.) and sodium cyanoborohydride (2.5 equiv.) were suspended in tetrahydrofuran (10 mL). Acetic acid (2 mL) was added and the reaction mixtures stirred at room temperature overnight. In two specific cases, **1.46** and **1.48**, *p*-toluene-sulphonic acid was used instead of acetic acid and the reaction mixtures were refluxed for 4 hours. All reactions were then concentrated *in vacuo*, ethyl acetate (20 mL) and water (20 mL) were added to the reaction mixture, followed by solid $NaHCO_3$ until basic. The layers were separated and the organics were washed with brine (20 mL), saturated $NaHCO_{3\,(aq)}$ (20 mL), and brine (20 mL). The organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residues were re-dissolved in methanol (10 mL) and $NaOH_{(aq)}$ (2N, 10 mL) and stirred for 2 h. The solvent was removed *in vacuo* and the residues re-dissolved in ethyl acetate (50 mL). The organics were washed with brine (2 x 20 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the crude products.

N'-(4-Methoxy-benzylidene)-hydrazine carboxylic acid *tert*-butyl ester (1.42)



Product was a yellow oil (0.39 g, 77%).

IR: 3330 (m), 2971 (m), 1704 (s) cm^{-1}.

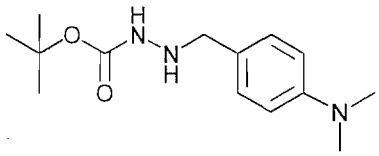
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (2H, d, *J*= 8.8 Hz, **ArH**); 6.87 (2H, d, *J*= 8.8 Hz, **ArH**); 6.04 (1H, br s, **NH**); 3.91 (2H, s, **CH_2**); 3.80 (3H, s, **OCH_3**); 1.46 (9H, s, **CCH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 159.3 (**CO**), 156.8 (**C**), 130.4 (**CH**), 129.6 (**C**), 114.1 (**CH**), 80.8 (**C**), 55.3 (**OCH_3**), 55.3 (**CH_2**), 28.5 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 527 ([2M + Na^+], 100%), 316 ([M + MeCN + Na^+], 75%), 275 ([M + Na^+], 60%).

The data acquired corresponds to all the given literature values for this known compound.[46]

N'-(4-Dimethylamino-benzyl)-hydrazine carboxylic acid *tert*-butyl ester (1.44)



Product was a yellow oil (2.19 g, 87%).

IR: 3290 (m), 2973 (m), 2927 (m), 2927 (m), 2799 (m), 1707 (s) cm^{-1}.

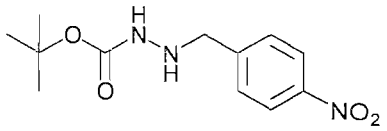
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (2H, d, *J*= 8.8 Hz, **ArH**); 6.71 (2H, d, *J*= 8.8 Hz, **ArH**); 3.88 (2H, s, **CH_2**); 2.94 (3H, s, **OCH_3**); 1.47 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 157.0 (**CO**), 150.3 (**C**), 130.1 (**CH**), 125.0 (**C**), 112.8 (**CH**), 80.7 (**C**), 55.5 (**CH_2**), 40.7 (**CH_3**), 28.5 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 553 ([2M + Na^+], 100%), 329 ([M + MeCN + Na^+], 15%), 288 ([M + Na^+], 25%).

The data acquired corresponds to all the given literature values for this known compound.[46]

N'-(4-Nitro-benzyl)-hydrazine carboxylic acid *tert*-butyl ester (1.46)



Product was a crystalline yellow solid (2.06 g, 68%).

Mp 89 – 90 °C (Ethyl acetate), literature value 97 – 98 °C.

IR: 3288 (m), 2980 (m), 1696 (s), 1508 (s) (N=O), 1341 (s) (N=O) cm^{-1}.

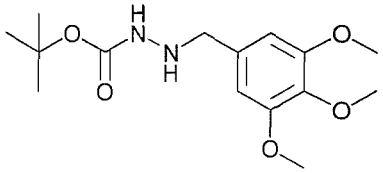
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (2H, d, *J*= 9.0 Hz, **ArH**); 7.53 (2H, d, *J*= 9.0 Hz, **ArH**); 6.00 (1H, br s, **NH**); 4.32 (1H, br s, **NH**); 4.11 (2H, d, *J*= 3.8 Hz, **CH_2**); 1.46 (9H, s, **CCH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 147.5 (**C**), 145.7 (**C**), 136.6 (**C**), 129.6 (**CH**), 123.8 (**CH**), 81.1 (**C**), 55.1 (**CH_2**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 824 ([3M + Na^+], 12%), 802 ([3M + H^+], 8%), 557 ([2M + Na^+], 12%), 535 ([2M + H^+], 10%), 253 (85), 212 (100).

The data acquired corresponds to all the given literature values for this known compound.[46]

N'-(3,4,5-Trimethoxy-benzyl)-hydrazine carboxylic acid *tert*-butyl ester (1.48)



Product was a crystalline white solid (2.38 g, 79%).

Mp 62 – 64 °C (isopropanol).

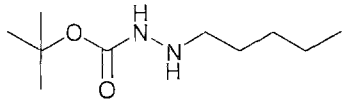
IR: 3330 (m), 2968 (m), 1730 (s), 1708 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (2H, s, **ArH**); 6.04 (1H, br s, **NH**); 3.94 (2H, s, **CH_2**); 3.86 (9H, s, 3 x **OCH_3**); 1.47 (9H, s, **CCH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.5 (**CO**), 153.5 (**C**), 137.7 (**C**), 131.4 (**C**), 106.3 (**CH**), 82.1 (**C**), 60.9 (**CH_3**), 56.3 (**CH_2**), 56.2 (**CH_3**), 28.2 (**CH_3**), 20.8 (**CH_3**) ppm.

Anal. Calcd for $C_{15}H_{24}N_2$: C, 56.94; H, 7.17; N, 14.22. Found: C, 56.89; H, 7.20; N, 14.20.

N'-Pentyl-hydrazine carboxylic acid *tert*-butyl ester (1.50)

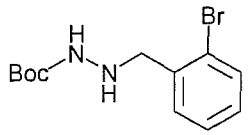


Product was a colourless oil (0.16 g, 81%).

IR: 3299 (m), 2928 (m), 1693 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (1H, br s, **NH**); 2.82 (2H, t, *J*= 7.1 Hz, **CH_2NH**); 1.49 (9H, s, **CH_3**); 1.33 – 1.30 (4H, m, 2 x **CH_2**); 0.92 – 0.87 (5H, m, **CH_2CH_3**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 157.1 (**CO**), 80.7 (**C**), 52.4 (**CH_2**), 29.4 (**CH_2**), 28.5 (**CH_3**), 27.6 (**CH_2**), 22.7 (**CH_2**), 14.1 (**CH_3**) ppm.

The data acquired corresponds to all the given literature values for this known compound.[64]

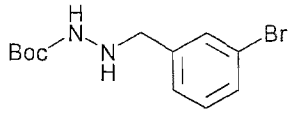
***N'*-(2-Bromo-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.52)**



Title compound isolated as a white crystalline solid (1.59 g, 91%).

Mp 70 °C (ethyl acetate/hexane).
IR: 3326 (m), 3246 (m), 2978 (w), 2962 (w), 1699 (s), 1514 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (1H, dd, *J*= 7.7, 1.3 Hz, **ArH**); 7.40 (1H, dd, *J*= 7.7, 1.8 Hz, **ArH**); 7.28 (1H, td, *J*= 7.7, 1.3 Hz, **ArH**); 7.14 (1H, td, *J*= 7.7, 1.8 Hz, **ArH**); 6.04 (1H, br s, **NH**); 4.33 (1H, br s, **NH**); 4.10 (2H, s, **CH_2**); 1.45 (9H, s, **CH_3**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 156.6 (**C**), 137.1 (**C**), 133.0 (**CH**), 131.1 (**CH**), 129.2 (**CH**), 127.5 (**CH**), 124.8 (**C**), 80.7 (**C**), 55.9 (**CH_2**), 28.5 (**CH_3**) ppm.
LRMS (ES^+): *m/z* 627, 625, 623 ([2M + Na^+], 1:2:1 ratio, 20%), 366, 364 ([M + MeCN + Na^+], 1:1 ratio, 100%), 325, 323 ([M + Na^+], 30%), 303, 301 ([M + H^+], 25%).

N'-(3-Bromo-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.54)



Title compound isolated as a white crystalline solid (1.38 g, 79%).

Mp 68 °C (ethyl acetate/hexane).

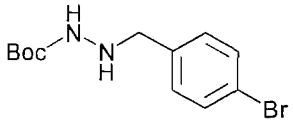
IR: 3312 (m), 3261 (m), 2983 (w), 2947 (w), 1698 (s), 1536 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.51 (1H, br s, **ArH**); 7.42 – 7.38 (1H, m, **ArH**); 7.27 – 7.25 (1H, m, **ArH**); 7.20 (1H, t, *J*= 7.7 Hz, **ArH**); 6.14 (1H, br s, **NH**); 4.23 (1H, br s, **NH**); 3.99 (2H, s, $\mathbf{CH_2}$); 1.46 (9H, s, $\mathbf{CH_3}$) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 156.8 (**C**), 140.3 (**C**), 132.0 (**CH**), 130.7 (**CH**), 130.1 (**CH**), 127.6 (**CH**), 122.6 (**C**), 80.8 (**C**), 55.2 ($\mathbf{CH_2}$), 28.5 ($\mathbf{CH_3}$) ppm.

LRMS (ES^+): *m/z* 627, 625, 623 ([2M + Na^+], 1:2:1 ratio, 20%), 605, 603, 601 ([2M + H^+], 1:2:1 ratio, 60%), 366, 364 ([M + MeCN + Na^+], 1:1 ratio, 10%), 325, 323 ([M + Na^+], 1:1 ratio, 15%), 288, 286 ([M – ^{t}Bu + MeCN + H^+], 1:1 ratio, 25%), 247, 245 ([M – ^{t}Bu + H^+], 1:1 ratio, 100%).

N'-(4-Bromo-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.56)



Title compound isolated as a white crystalline solid (1.67 g, 95%).

Mp 74 °C (ethyl acetate/hexane).

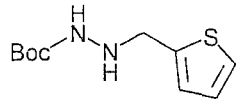
IR: 3292 (m), 2974 (w), 2931 (w), 1708 (s), 1507 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.45 (2H, d, *J*= 7.4 Hz, **ArH**); 7.24 (1H, d, *J*= 7.4 Hz, **ArH**); 7.21 (1H, d, *J*= 7.4 Hz, **ArH**); 6.02 (1H, br s, **NH**); 4.20 (1H, br s, **NH**); 3.94 (2H, s, $\mathbf{CH_2}$); 1.46 (9H, s, $\mathbf{CH_3}$) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 156.8 (**C**), 136.9 (**C**), 131.7 (**CH** x 2), 130.8 (**CH** x 2), 121.5 (**C**), 80.8 (**C**), 55.3 ($\mathbf{CH_2}$), 28.5 ($\mathbf{CH_3}$) ppm.

LRMS (ES^+): *m/z* 366, 364 ([M + MeCN + Na^+], 1:1 ratio, 40%), 286, 288 (1:1 ratio, 100%).

N'-Thiophen-2-ylmethyl-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.58)



Title compound isolated as a crystalline white solid (0.82 g, 75%).

Mp 31 – 32 °C (ethyl acetate/hexane).

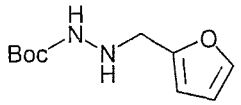
IR: 3379 (m), 3285 (m), 2974 (w), 1689 (s), 1486 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 – 7.22 (1H, m, **ArH**); 7.0 – 6.95 (2H, m, **ArH**); 6.22 (1H, br s, **NH**); 4.28 (1H, br s, **NH**); 4.19 (2H, s, **CH_2**); 1.46 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 156.7 (**C**), 140.8 (**C**), 126.9 (**CH**), 126.4 (**CH**), 125.3 (**CH**), 80.8 (**C**), 50.4 (**CH_2**), 28.5 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 457 ([2M + H^+], 100%), 292 ([M + MeCN + Na^+], 98%), 251 ([M + Na^+], 55%), 229 ([M + H^+], 30%).

N'-Furan-2ylmethyl-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.60)



Title compound isolated as a crystalline white solid (0.82 g, 82%).

Mp 44 – 45 °C (ethyl acetate/hexane).

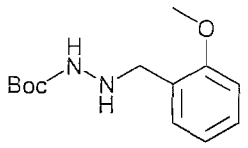
IR: 3332 (m), 3244 (m), 2976 (w), 2929 (w), 1704 (s), 1549 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (1H, m, **ArH**); 6.32 – 6.31 (1H, m, **ArH**); 6.24 – 6.23 (2H, m, **NH** & **ArH**); 4.22 (1H, br s, **NH**); 3.99 (2H, s, **CH_2**); 1.46 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 156.6 (**C**), 151.7 (**C**), 142.4 (**CH**), 110.3 (**CH**), 108.5 (**CH**), 80.7 (**C**), 48.5 (**CH_2**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 447 ([2M + Na^+], 70%), 425 ([2M + H^+], 15%), 276 ([M + MeCN + Na^+], 100%), 235 ([M + Na^+], 55%).

N'-(2-Methoxy-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.62)



Title compound isolated as a crystalline white solid (0.90 g, 69%).

Mp 60-61 °C (Ethyl acetate/Hexane).

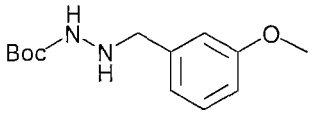
IR: 3311 (m), 2975 (w), 2933 (w), 1702 (s), 1242 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.27 – 7.24 (2H, m, **ArH**); 6.95 – 6.86 (2H, m, **ArH**); 5.93 (1H, br s, **NH**); 4.01 (2H, s, **CH_2**); 3.85 (3H, s, **OCH_3**); 1.46 (9H, s, **CH_3**) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 158.1 (**C**), 156.6 (**C**), 130.8 (**CH**), 129.0 (**CH**), 125.9 (**C**), 120.5 (**CH**), 110.5 (**CH**), 80.3 (**C**), 55.5 (**CH_3**), 51.5 (**CH_2**), 28.5 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 527 ([2M + Na^+], 60%), 505 ([2M + H^+], 100%), 354 ([M + 2MeCN + Na^+], 65%), 253 ([M + H^+], 5%).

***N'*-(3-Methoxy-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.64)**



Title compound isolated as a clear colourless oil (0.99 g, 65%).

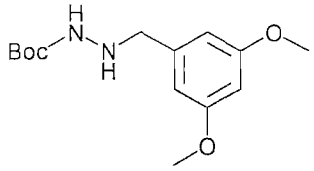
IR: 3308 (m), 2977 (w), 2935 (w), 1702 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.27 – 7.21 (1H, m, **ArH**); 6.94 – 6.91 (2H, m, **ArH**); 6.84 – 6.80 (1H, m, **ArH**); 6.06 (1H, br s, **NH**); 4.20 (1H, br s, **NH**); 3.97 (2H, s, **CH_2**); 3.80 (3H, s, **OCH_3**); 1.46 (9H, s, **CH_3**) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 159.8 (**C**), 156.8 (**C**), 139.4 (**C**), 129.5 (**CH**), 121.3 (**CH**), 114.3 (**CH**), 113.2 (**CH**), 80.5 (**C**), 55.8 (**CH_2**), 55.3 (**CH_3**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 527 ([2M + Na^+], 95%), 505 ([2M + H^+], 100%), 316 ([M + MeCN + Na^+], 20%).

N'-(3,5-Dimethoxy-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.66)



Title compound isolated as a crystalline white solid (0.55 g, 79%).

Mp 45-46 °C (chloroform).

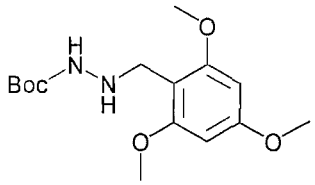
IR: 3311 (m), 2976 (w), 2936 (w), 1705 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 – 6.51 (2H, d, *J*= 2.2 Hz, **ArH**); 6.38 (2H, t, *J*= 2.2 Hz, **ArH**); 6.01 (1H, br s, **NH**); 4.20 (1H, br s, **NH**); 3.94 (2H, s, **CH_2**); 3.79 (6H, s, **CH_3**); 1.46 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 161.0 (**C**), 156.7 (**C**), 140.2 (**C**), 106.7 (**CH**), 99.7 (**CH**), 80.5 (**C**), 55.9 (**CH_2**), 55.4 (**CH_3**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 587 ([2M + Na^+], 100%), 565 ([2M + H^+], 45%), 346 ([M + MeCN + Na^+], 10%).

N'-(2,4,6-Trimethoxy-benzyl)-hydrazine-*N*-carboxylic acid *tert*-butyl ester (1.68)



Title compound isolated as a clear colourless oil (0.98 g, 47%).

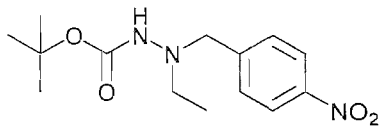
IR: 3308 (m), 2976 (w), 2938 (w), 1705 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.12 (2H, s, **ArH**); 5.91 (1H, br s, **NH**); 4.01 (2H, s, **CH_2**); 3.81 (9H, s, **OCH_3**); 1.46 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 160.9 (**C**), 159.9 (**C**), 156.5 (**C**), 106.5 (**C**), 90.5 (**CH**), 79.8 (**C**), 55.8 (**CH_3**), 55.3 (**CH_3**), 43.9 (**CH_2**), 28.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 647 ([2M + Na^+], 60%), 625 ([2M + H^+], 100%).

N'-Ethyl-*N*'-(4-Nitro-benzyl)-hydrazine carboxylic acid *tert*-butyl ester (1.69)



Product was isolated as a crystalline yellow solid (0.30 g, 54%).

Mp 112 – 113 °C (Ethyl acetate/hexane).

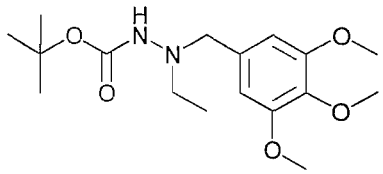
IR: 3289 (m), 2979 (m), 1696 (s), 1508 (s), 1341 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (2H, d, *J*= 8.8 Hz, **ArH**); 7.49 (2H, d, *J*= 8.8 Hz, **ArH**); 5.43 (1H, br s, **NH**); 3.97 (2H, s, **CH_2**); 2.81 (2H, q, *J*= 6.9 Hz, **CH_2CH_3**); 1.32 (9H, s, **CH_3**); 1.06 (3H, t, *J*= 6.9 Hz, **CH_2CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 147.4 (**C**), 145.5 (**C** x 2), 129.8 (**CH**), 123.5 (**CH**), 80.3 (**C**), 60.8 (**CH_2**), 51.4 (**CH_2**), 28.4 (**CH_3**), 12.4 (**CH_3**) ppm.

Anal. Calcd for $C_{14}H_{21}N_3O_4$: C, 56.94; H, 7.17; N, 14.22. Found: C, 56.89; H, 7.20; N, 14.20.

_N_'-Ethyl-_N_'-(3,4,5-trimethoxy-benzyl)-hydrazine carboxylic acid _tert_-butyl ester (1.70)



Product was isolated as a crystalline white solid (0.13 g, 24%).

Mp 78 – 79 °C (Ethyl acetate/hexane).

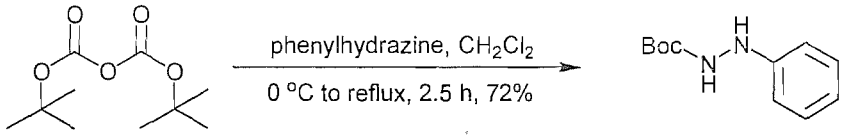
IR: 3332 (m), 2968 (m), 1725 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (2H, s, **ArH**); 5.35 (1H, br s, **NH**); 3.86 (9H, s, **OCH_3**); 3.74 (2H, s, **CH_2**), 2.83 (2H, m, **CH_2**); 1.40 (9H, s, **CH_3**); 1.13 (3H, t, *J*= 7.3 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 155.5 (**C**), 153.5 (**C** x 2), 137.4 (**C**), 133.1 (**C**), 106.0 (**CH**), 80.1 (**C**), 61.7 (**CH_2**), 60.9 (**CH_3**), 56.2 (**CH_3**), 51.3 (**CH_2**), 28.5 (**CH_3**), 12.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 703 ([2M + Na^+], 20%), 404 ([M + MeCN + Na^+], 50%), 363 ([M + Na^+], 40%), 341 ([M + H^+], 100%).

N'-Phenyl-hydrazinecarboxylic acid *tert*-butyl ester (1.71)

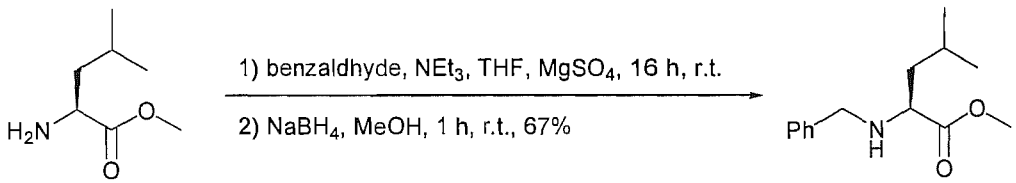


A solution of di-*tert*-butyl dicarbonate (1.0 equiv., 2.25 mmol, 2.02 g) in dichloromethane (10 mL) was added to a stirred ice-cold solution of phenyl hydrazine (1.00 g, 9.25 mmol) in dichloromethane (10mL). The reaction was heated to reflux for 2.5 h; the solvent was then removed *in vacuo*. The crude product was then purified by column chromatography (50% ethyl acetate/hexane) to give the title compound as a crystalline white solid (1.39 g, 72%).

Mp 86 – 87 °C (isopropanol).
IR: 3348 (m), 3277 (m), 2974 (w), 1695 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 – 7.21 (2H, m, **ArH**); 6.90 – 6.81 (3H, m, **ArH**); 6.34 (1H, br s, **NH**); 5.71 (1H, br s, **NH**); 1.46 (9H, s, **CH_3**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 154.6 (**C**), 146.8 (**C**), 129.3 (**CH**) 121.0 (**CH**), 113.2 (**CH**), 81.4 (**C**), 28.4 (**CH_3**) ppm.
LRMS (ES^+): *m/z* 439 ([2M + Na^+], 100%), 272 ([M + MeCN + Na^+], 32%).

The data acquired corresponds to all the given literature values for this known compound.[65]

(*S*)-2-Benzylamino-4-methyl-pentanoic acid methyl ester (1.72)



Synthesised according to literature procedure.[48]

A solution of the L-Leucine methyl ester HCl salt (1.0 equiv., 1.00 g, 5.50 mmol) and triethylamine (2.0 equiv., 11.0 mmol, 0.1.53 mL) in THF (25 mL) was stirred for approximately 10 minutes at room temperature. Benzaldehyde (2.0 equiv., 11.0 mmol, 1.12 mL) and $MgSO_4$ (1.00 g) was added and the reaction stirred at room temperature overnight. The reaction mixture was filtered, concentrated *in vacuo* and the residue redissolved in methanol (5 mL). Sodium borohydride (2.0 equiv.)

was added portion-wise and the reaction mixture was allowed to stir for a further 1 h. Aqueous NaOH (1N, 20 mL) was added and the product was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (3 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Column chromatography (50% Ethyl acetate/ hexane) gave the pure product **1.72** as a clear colourless oil (0.86 g, 67%).

IR: 2953 (s), 1732 (s) cm^{-1}.

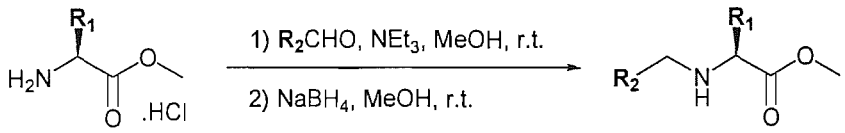
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.23 (5H, m, **ArH**); 3.80 (1H, d, *J*= 12.8 Hz, **CH_2Ph**); 3.71 (3H, s, **OCH_3**); 3.60 (1H, d, *J*= 12.8 Hz, **CH_2Ph**); 3.30 (1H, t, *J*= 7.3 Hz, **CH**); 1.85 – 1.71 (2H, m); 1.50 – 1.43 (2H, m, **CH_2**); 0.91 (3H, d, *J*= 6.6 Hz, **CH_3**); 0.84 (3H, d, *J*= 6.6 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 176.6 (**CO**), 140.1 (**C**), 128.4 (**CH**), 128.3 (**CH**), 127.1 (**CH**), 59.4 (**CH**), 52.3 (**CH_2**), 51.7 (**CH_3**), 43.0 (**CH_2**), 25.0 (**CH**), 22.9 (**CH_3**), 22.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 258 ([M + Na^+], 30%), 236 ([M + H^+], 100%).

The data acquired corresponds to all the given literature values for this known compound.[66]

(*S*)-2-Alkylamino acid methyl esters (1.73 to 1.74)

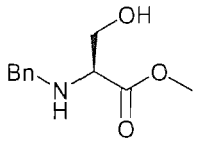


General Experimental:

A solution of the amino acid methyl ester HCl salt (1.0 equiv., 1.00 g) and triethylamine (1.0 equiv.) in MeOH (10 mL) was stirred for approximately 10 minutes at room temperature. The aldehyde (1.0 equiv.) was added and the reaction mixture was stirred at room temperature overnight. Sodium borohydride (2.0 equiv.) was added portion-wise and the reaction mixture was allowed to stir for a further 0.5 h. Diethyl ether (30 mL) and $HCl_{(Aq.)}$ (2 N, 30 mL) were added to the reaction, the organic layer was then washed with $HCl_{(Aq.)}$ (2 N, 2 x 25 mL) and discarded. The aqueous layer was neutralised with solid $NaHCO_3$ and then extracted with diethyl ether (3 x 20 mL). The combined organics were washed with

brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the clean title compounds.

(*S*)-2-Benzylamino-3-hydroxy-propionic acid methyl ester (1.73)

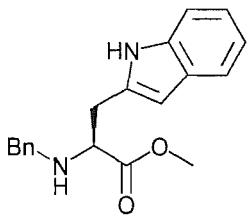


Title compound isolated as a clear colourless oil (1.28 g, 95%).

[α]$_D$ – 44.9 (*c* 0.5, $CHCl_3$, 26 °C).
IR: 3150 (m), 2951 (m), 2929 (m), 2870 (m), 2842 (m), 1725 (s) cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.37 – 7.26 (5H, m, **ArH**); 3.88 (1H, d, *J*= 12.8 Hz, **CH**$_2$); 3.80 – 3.76 (2H, m, **CH** & **CH**$_2$); 3.74 (3H, s, **CH**$_3$); 3.61 (1H, dd, *J*= 10.7, 6.0 Hz, **CH**$_2$); 3.43 (1H, dd, *J*= 6.0, 4.5 Hz, **CH**$_2$) ppm.
^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 173.6 (**C**), 139.4 (**C**), 128.7 (**CH**), 128.4 (**CH**), 127.5 (**CH**), 62.6 (**CH**$_2$), 62.0 (**CH**$_3$), 52.30 (**CH**), 52.25 (**CH**$_2$) ppm.
LRMS (ES^+): *m/z* 210 ([M + H^+], 100%).

The data acquired corresponds to all the given literature values for this known compound.[49]

(*S*)-2-Benzylamino-3-(1*H*-indol-2-yl)-propionic acid methyl ester (1.74)



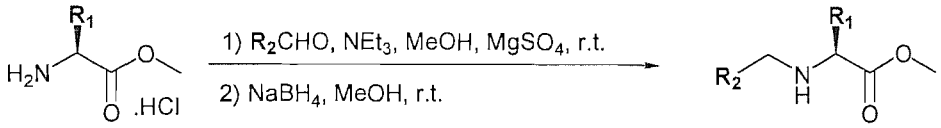
Title compound isolated as a clear colourless oil (0.79 g, 65%).

[α]$_D$ – 7.8 (*c* 0.5, $CHCl_3$, 26 °C).
IR: 3287 (m), 2924 (m), 2863 (m), 2955 (w), 1740 (s) cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 8.03 (1H, br s, **NH**); 7.57 (1H, d, *J*= 8.1 Hz, **NH**); 7.37 – 7.00 (9H, m, **ArH**); 3.82 (1H, d, *J*= 13.2 Hz, **CH**$_2$); 3.71 – 3.64 (2H, m, **CH** & **CH**$_2$); 3.62 (3H, s, **CH**$_3$); 3.16 (2H, m, **CH**$_2$) ppm.
^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 175.5 (**C**), 139.9 (**C**), 136.3 (**C**), 128.5 (**CH**), 128.3 (**CH**), 128.1 (**C**), 127.5 (**CH**), 122.7 (**CH**), 122.1 (**CH**), 119.4 (**CH**), 118.8 (**CH**), 111.4 (**C**), 111.1 (**CH**), 61.3 (**CH**$_3$), 52.1 (**CH**$_2$), 51.7 (**CH**), 29.3 (**CH**$_2$) ppm.

LRMS (ES^+): *m/z* 331 ([M + Na^+], 10%), 309 ([M + H^+], 100%).

The data acquired corresponds to all the given literature values for this known compound.[67]

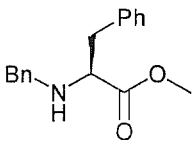
(*S*)-2-Alkylamino acid methyl esters (1.75 to 1.77)



General Experimental:

A solution of the amino acid methyl ester HCl salt (1.0 equiv., 1.00 g), triethylamine (1.0 equiv.) and dried magnesium sulfate (1.00 g) in MeOH (10 mL) was stirred for approximately 10 minutes at room temperature. The aldehyde (1.0 equiv.) was added and the reaction mixture stirred at room temperature overnight, it was then filtered to remove the $MgSO_4$. Sodium borohydride (2.0 equiv.) was added portion-wise and the reaction mixture was allowed to stir for a further 1 h. $NaOH_{(Aq.)}$ (1 N, 20 mL) was added to the reaction mixture, and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude products were purified by flash chromatography (10 - 50% ethyl acetate/hexane) to give the pure title compounds.

(*S*)-2-Benzylamino-3-phenyl-propionic acid methyl ester (1.75)



Title compound isolated as a clear colourless oil (0.24 g, 74%).

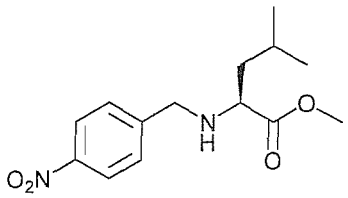
IR: 3028 (m), 2949 (m), 2843 (m) 1732 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.15 (10H, m, **ArH**); 3.83 – 3.64 (2H, m, **CH_2**); 3.65 (3H, s, **CH_3**); 3.54 (1H, t, *J*= 6.8 Hz, **CH**); 2.96 (2H, d, *J*= 6.8 Hz, **CH_2**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 175.6 (**C**), 140.2 (**C**), 137.9 (**C**), 129.8 (**CH**), 128.9 (**C**), 128.8 (**CH**), 128.7 (**CH**), 127.6 (**CH**), 127.2 (**CH**), 62.6 (**CH_3**), 52.6 (**CH_2**), 52.2 (**CH**), 40.3 (**CH_2**) ppm.

The data acquired corresponds to all the given literature values for this known compound.[68]

(*S*)-2-(4-Nitro-benzylamino)- 4-methyl-pentanoic acid methyl ester (1.76)



Title compound isolated as a crystalline white solid (1.21 g, 79%).

Mp 167 °C (Ethyl acetate/hexane).

[α]$_D$ – 1.54 (*c* 0.7, MeOH, 26 °C).

IR: 3011 (m), 2958 (m), 2868 (m), 1742 (s), 1521 (s), 1344 (s) cm^{-1}.

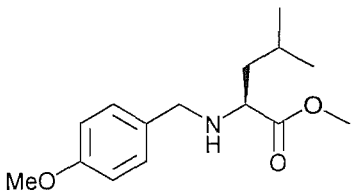
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 8.25 (2H, d, *J*= 8.4 Hz, **ArH**); 7.90 (2H, d, *J*= 8.4 Hz, **ArH**); 4.33 (1H, *J*= 13.9 Hz, **CH$_2$**); 4.27 (1H, d, *J*= 13.9 Hz, **CH$_2$**); 3.80 (3H, s, **CH$_3$**); 3.60 (1H, t, *J*= 6.8 Hz, **CH**); 1.99 – 1.79 (3H, m, **CH** & **CH$_2$**); 0.89 (3H, d, *J*= 6.6 Hz, **CH$_3$**); 0.88 (3H, d, *J*= 6.6 Hz, **CH$_3$**) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 176.2 (**C**), 147.8 (**C**), 130.5 (**C**), 128.7 (**CH**), 123.6 (**CH**), 59.3 (**CH**), 51.7 (**CH$_3$**), 51.3 (**CH$_2$**), 42.8 (**CH$_2$**), 24.9 (**CH**), 22.8 (**CH$_3$**), 22.0 (**CH$_3$**) ppm.

LRMS (ES$^+$): *m/z* 281 ([M + H$^+$], 100%).

The data acquired corresponds to all the given literature values for this known compound.[69]

(*S*)-2-(4-Methoxy-benzylamino)-4-methyl-pentanoic acid methyl ester (1.77)



Title compound isolated as a clear colourless oil (1.76 g, 72%).

[α]$_D$ – 31.17 (*c* 1.5, $CDCl_3$, 27 °C).

IR: 3327 (w), 2953 (w), 2867 (w), 1732 (s), 1511 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.24 (2H, d, *J*= 8.6 Hz, **ArH**); 6.85 (2H, d, *J*= 8.6 Hz, **ArH**); 3.79 (3H, s, **CH$_3$**); 3.78 (1H, d, *J*= 11.7 Hz, **CH$_2$**); 3.72 (3H, s, **CH$_3$**); 3.55

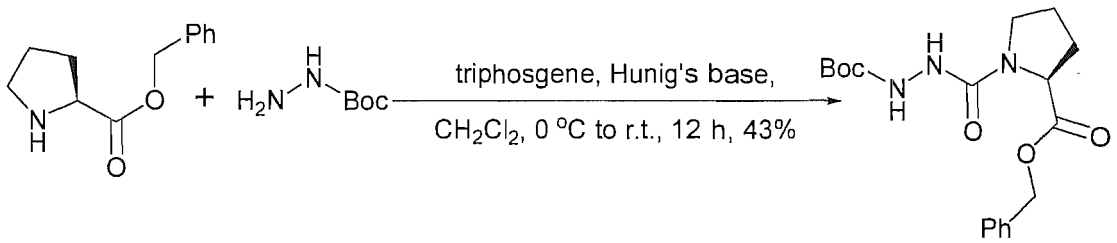
(1H, d, *J*= 11.7 Hz, C<u>H</u>$_2$); 3.29 (1H, t, *J*= 7.3 Hz, C<u>H</u>); 1.76 (1H, sept, *J*= 7.0 Hz, C<u>H</u>); 1.46 (2H, t, *J*= 7.3 Hz, C<u>H</u>$_2$); 0.91 (3H, d, *J*= 6.6 Hz, C<u>H</u>$_3$); 0.85 (3H, d, *J*= 6.6 Hz, C<u>H</u>$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 176.7 (<u>C</u>), 158.8 (<u>C</u>), 132.2 (<u>C</u>), 129.6 (<u>C</u>H), 113.9 (<u>C</u>H), 59.3 (<u>C</u>H), 55.4 (<u>C</u>H$_3$), 51.7 (<u>C</u>H$_2$), 51.6 (<u>C</u>H$_3$), 42.9 (<u>C</u>H$_2$), 25.0 (<u>C</u>H), 22.9 (<u>C</u>H$_3$), 22.3 (<u>C</u>H$_3$) ppm.

LRMS (ES^+): *m/z* 266 ([M + H^+], 100%).

The data acquired corresponds to the correct structure, no literature data available for this known compound.[70]

1-(*N'-tert*-Butoxycarbonyl-hydrazino carbonyl)-pyrrolidine-2-carboxylic acid phenyl ester (1.78)



A solution of *tert*-butylcarbazate (2.25 equiv., 0.76 mmol, 0.100 g) and Hünig's base (2.50 equiv., 0.85 mmol, 0.148 mL) in dichloromethane (5 mL) was added drop-wise to a stirred ice-cold solution of triphosgene (1.00 equiv., 0.34 mmol, 0.101 g) in dichloromethane (5 mL). After 15 min the reaction mixture was allowed to warm to room temperature and a solution of proline benzyl ester HCl (2.25 equiv., 0.183 g) and Hünig's base (0.148 mL) in dichloromethane (10 mL) was added to the reaction in one-portion. After stirring over night the solvent was removed *in vacuo*. The crude product was purified by column chromatography (50 – 100% ethyl acetate/hexane) to give **1.78** as a white crystalline solid (0.107 g, 43%).

Mp 81 – 83 °C (methanol/ethyl acetate).

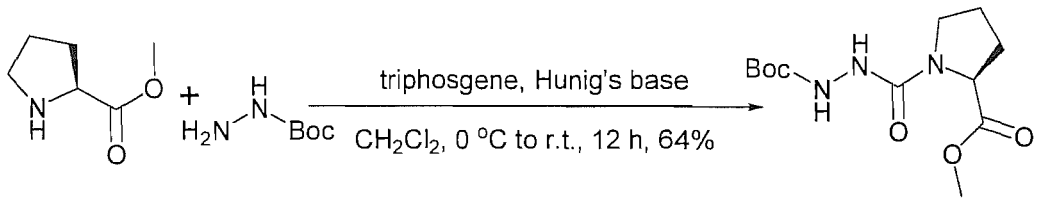
IR: 3282 (m), 2978 (m), 1727 (s), 1658 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.27 (5H, m, **Ar**<u>H</u>); 6.75 (1H, br s, **N**<u>H</u>); 6.59 (1H, br s, **N**<u>H</u>); 5.16 (2H, d, *J*= 6.2 Hz, C<u>H</u>$_2$); 4.55 – 4.52 (1H, m, C<u>H</u>); 3.54 – 3.45 (2H, m, 2 x C<u>H</u>$_2$); 2.16 – 2.00 (4H, m, 2 x C<u>H</u>$_2$); 1.46 (9H, s, 3 x C<u>H</u>$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.8 (**C**O), 156.7 (**C**O), 156.6 (**C**O), 135.7 (**C**), 128.7 (**C**H), 128.4 (**C**H), 128.2 (**C**H), 81.3 (**C**CH_3), 67.1 (**C**H_2), 59.5 (**C**H), 45.8 (**C**H_2), 29.6 (**C**H_2), 28.3 (**C**H_3), 24.6 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 386 ([M + Na^+], 100%), 364 ([M + H^+], 10%).

1-(*N'-tert*-Butoxycarbonyl-hydrazino carbonyl)-pyrrolidine-2-carboxylic acid methyl ester (1.79)



A solution of *tert*-butylcarbazate (2.25 equiv., 1.51 mmol, 0.200 g) and Hünig's base (2.50 equiv., 1.68 mmol, 0.292 mL) in dichloromethane (5 mL) was added drop-wise to a stirred ice-cold solution of triphosgene (1.00 equiv., 0.67 mmol, 0.199 g) in dichloromethane (5 mL). After 15 min the reaction mixture was allowed to warm to room temperature and a solution of proline methyl ester HCl. (2.25 equiv., 0.251 g) and Hünig's base (0.292 mL) in dichloromethane (10 mL) was added to the reaction in one portion. After stirring overnight the solvent was removed *in vacuo*. The crude product was purified by column chromatography (50 – 100% ethyl acetate/hexane) to give **1.79** as a white crystalline solid (0.277 g, 64%).

Mp 107 – 109 °C (methanol).

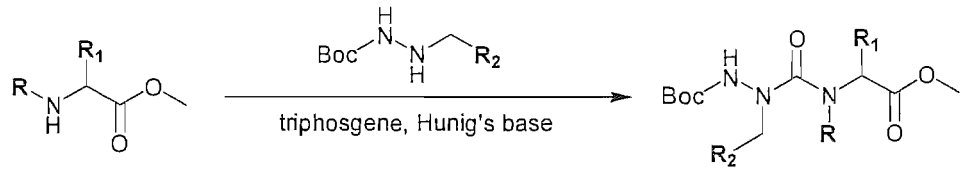
IR: 3262 (m), 2970 (m), 1717 (s), 1738 (s), 1651(s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (1H, br s, **NH**); 6.71 (1H, br s, **NH**); 4.42 (1H, dd, *J*= 3.1 Hz, *J*= 8.2 Hz, **CH**); 3.65 (3H, s, **OC**H_3); 3.52 – 3.37 (2H, m, **C**H_2); 2.14 – 1.93 (4H, m, 2 x **C**H_2); 1.38 (9H, s, 3 x **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.6 (**C**O), 156.7 (**C**O), 156.6 (**C**O), 81.0 (**C**CH_3), 59.3 (**C**H), 52.3 (**OC**H_3), 45.7 (**C**H_2), 29.5 (**C**H_2), 28.2 (**C**H_3), 24.6 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 597 ([2M + Na^+], 100%), 575 ([2M + H^+], 30%), 351 ([M + MeCN + Na^+], 15%), 310 ([M + H^+], 75%).

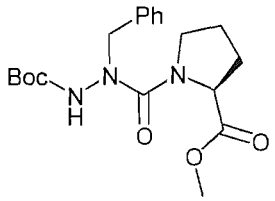
N-α-Amino-methyl esters-*N'*-alkyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazides (1.80 to 1.108).



General Experimental:

A solution of the alkyl hydrazine carboxylic acid *tert*-butyl ester (2.25 equiv.) and diisopropyl ethylamine (2.50 equiv.) in tetrahydrofuran or dichloromethane (5 mL) was added dropwise to a stirred solution of triphosgene (1.0 equiv.) in dry tetrahydrofuran or dichloromethane (5 mL). After stirring for 5 minutes a solution of amino acid methyl ester (2.25 equiv.) and diisopropyl ethylamine (2.50 equiv.) in tetrahydrofuran or dichloromethane (5 mL) was added in one-portion. The reaction mixture was stirred at room temperature for a further 10 minutes before the solvent was removed *in vacuo*. The crude products were rapidly purified by column chromatography (10 – 100% ethyl acetate/hexane) to give the title semicarbazides as a mixture of rotamers.

1-(*N*-Benzyl-*N'*-*tert*-butoxycarbonyl-hydrazinocarbonyl)-pyrrolidine-2-carboxylic acid methyl ester (1.80)



Title compound isolated as a clear colourless oil (0.43 g, 50%).

IR: 3266 (m), 1725 (s), 1632 (s) cm^{-1}.

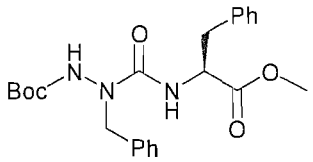
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 – 7.16 (5H, m, **ArH**); 6.3 (1H, br s, **NH**); 4.55 – 4.36 (3H, m, **CH_2** & **CH**); 3.61 (3H, s, **OCH_3**); 3.53 – 3.49 (2H, m, **CH_2**); 2.15 – 1.72 (4H, m, 2 x **CH_2**); 1.35 (9H, m, 3 x **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.5 (**CO**), 159.1 (**CO**), 154.4 (**CO**), 136.1 (**C**), 129.2 (**CH**), 128.4 (**CH**), 127.5 (**CH**), 81.3 (**CCH_3**), 60.6 (**CH**), 52.8 (**CH_2**), 51.8 (**CH_3**), 48.4 (**CH_2**), 29.7 (**CH_2**), 28.0 (**CH_3**), 24.4 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 778 and 777 ([2M + Na^+], 100%, 0.42: 1 ratio).

The data acquired corresponds to all the given literature values for this known compound.[24]

_N_-[2-(3-Phenyl-propionic acid methyl ester)]-_N'_-benzyl-_N''_-carboxylic acid _tert_-butyl ester semicarbazide (1.82)



Title compound isolated as a clear colourless oil (0.11 g, 59%).

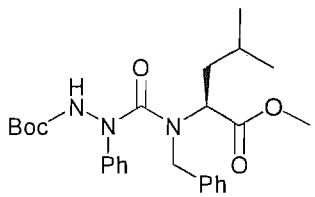
IR: 2961 (m), 1732 (s), 1649 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 – 7.13 (8H, m, **ArH**); 7.04 (2H, d, *J*= 6.0 Hz, **ArH**); 5.88 (1H, br s, **NH**); 5.80 (1H, br d, *J*= 8.0 Hz, **NH**); 4.75 (1H, dt, *J*= 8.0 Hz, *J*= 5.5 Hz, **CH**); 3.63 (3H, s, **OCH$_3$**); 3.06 (2H, d, *J*= 3.5 Hz, **CH$_2$**); 1.35 (11H, br s, **CH$_2$** and 3 x **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 170.6 (**C**), 154.9 (**C**), 152.3 (**C**), 134.2 (**C** x 2), 127.5 (**CH**), 127.0 (**CH**), 126.9 (**CH**), 126.6 (**CH**), 126.0 (**CH**), 125.1 (**CH**), 80.4 (**C**), 52.4 (**CH**), 50.3 (**OCH$_3$**), 36.6 (**CH$_2$** x 2), 26.2 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 877 ([2M + Na^+], 65%), 450 ([M + Na^+], 100%), 428 ([M + H^+], 25%).

(_S_)-_N_-Benzyl-_N_-[2-(4-Methyl-pentanoic acid methyl ester)]-_N'_-phenyl-_N''_-carboxylic acid _tert_-butyl ester semicarbazide (1.83)



Title compound isolated as clear oil (0.22 g, 48%).

[α]$_D$ -24.0 (*c* 0.5, $CHCl_3$, 24 °C).

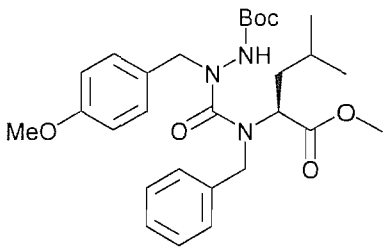
IR: 2954 (w), 2928 (w), 2869 (w), 1793 (s), 1735 (s), 1649 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 – 7.71 (2H, m, **ArH**); 7.36 – 7.10 (8H, m, **ArH**); 3.73 (1H, d, *J*= 12.8 Hz, **CH$_2$**); 3.64 (3H, s, **CH$_3$**); 3.54 (1H, d, *J*= 12.8 Hz, **CH$_2$**); 3.23 (1H, t, **CH**); 1.81 – 1.64 (1H, m, **CH**); 1.56 (9H, s, **CH$_3$**); 1.43 – 1.38 (2H, m, **CH$_2$**); 0.85 (3H, d, *J*= 6.6 Hz, **CH$_3$**); 0.77 (3H, d, *J*= 6.6 Hz, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 176.6 (**C**), 153.4 (**C**), 140.1 (**C**), 136.5 (**C**), 129.2 (**CH**), 128.5 (**CH**), 128.4 (**CH**), 127.1 (**CH**), 126.6 (**C**), 125.5 (**CH**), 118.0 (**CH**), 88.2 (**C**), 59.4 (**CH_3**), 52.3 (**CH_2**), 51.7 (**CH**), 43.0 (**CH_2**), 27.9 (C**CH_3**), 25.0 (**CH**), 22.9 (**CH_3**), 22.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 235 ($[M + 2H^+]^{2+}$, 100%).

(*S*)-*N*-Benzyl-*N*-[2-(4-Methyl-pentanoic acid methyl ester)]-*N'*-(4-methoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.84)



Title compound isolated as a clear colourless oil (0.18 g, 90%).

$[\alpha]_D$ + 1.3 (*c* 0.5, MeOH, 26 °C).

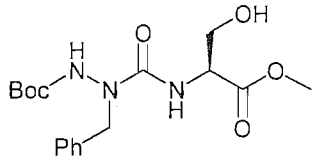
IR: 3304 (m), 2957 (w), 2932 (w), 1739 (s), 1514 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.31 (1H, br s, **NH**); 7.56 (2H, d, *J*= 6.5 Hz, **ArH**); 7.38 – 7.05 (5H, m, **ArH**); 6.96 – 6.58 (2H, m, **ArH**); 4.69 – 4.58 (2H, m, **CH_2**); 4.12 (2H, s, **CH_2**); 3.79 – 3.63 (6H, m, **CH_3**); 3.56 – 3.46 (1H, m, **CH**); 2.03 – 1.49 (3H, m, **CH_2CH**); 1.44 – 1.15 (9H, m, **CH_3**); 0.88 – 0.60 (6H, m, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$, rotamers): δ 173.0 (**C**), 168.7 (**C**), 162.0 (**C**), 159.1 (**C**), 153.6 (**C**), 138.1 (**C**), 130.9 (**CH**), 130.4 (**CH**), 129.6 (**CH**), 129.0 (**CH**), 128.3 (**CH**), 127.4 (**CH**), 127.0 (**CH**), 114.1 (**CH**), 113.9 (**CH**), 82.2 (**C**), 58.9 (**CH**), 56.5 (**CH_3**), 55.2 (**CH_3**), 52.8 (**CH_3**), 51.9 (**CH_3**), 49.5 (**CH_2**), 38.5 (**CH_2**), 34.4 (**CH_2**), 28.0 (**CH_3**), 24.7 (**CH**), 22.6 (**CH_3**), 21.4 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 1049 ($[2M + Na^+]$, 20%), 536 ($[M + Na^+]$, 100%), 514 ($[M + H^+]$, 40%).

(*S*)-*N*-(2[3-hydroxy-propionic acid methyl ester])-*N*'- benzyl -*N*''-carboxylic acid *tert*-butyl ester semicarbazide (1.85)



Title compound isolated as a clear colourless oil (0.33 g, 79%).

[α]$_D$ 4.7 (*c* 0.6, $CHCl_3$, 23 °C).

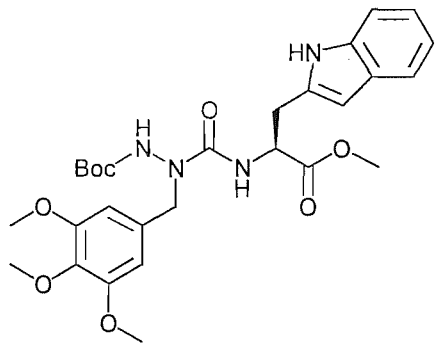
IR: 3307 (m), 2980 (w), 2954 (w), 1732 (s), 1651 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ 7.32 – 7.25 (5H, m, **ArH**); 6.89 and 6.74 (1H, 2 x br s, **NH**); 6.38 and 6.00 (1H, 2 x br d, *J*= 7.3 Hz, **NH**); 4.55 – 4.37 (3H, m, **CH_2** & **CH**); 3.90 (2H, m, **CH_2**); 3.76 and 3.73 (3H, 2 x s, **CH_3**); 2.62 (1H, br s, **OH**); 1.41 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 171.6 and 170.8 (**C**), 159.2 and 157.7 (**C**), 154.5 (**C**), 136.1 (**C**), 129.0 (**CH**), 128.6 (**CH**), 127 (**CH**), 82.3 (**C**), 66.8 (**CH_2**), 63.1 and 62.8 (**CH_2**), 56.1 and 53.8 (**CH**), 53.0 and 52.5 (**CH_3**), 28.1 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 1124 ([3M + Na^+], 5%), 757 ([2M + Na^+], 35%), 752 ([2M + H^+], 10%), 390 ([M + Na^+], 100%), 368 ([M + H^+], 50%).

_N_-{2-[3-(1H-indol-2-yl)-propionic acid methyl ester]}-_N_'-(3,4,5-trimethoxy-benzyl)-_N_''-carboxylic acid *tert*-butyl ester semicarbazide (1.86)



Title compound isolated as a white foam (0.292 g, 66%).

Mp 88 – 90 °C (ethyl acetate/hexane).

IR: 3281 (m), 2933 (w), 1725 (s), 1647 (s) cm^{-1}.

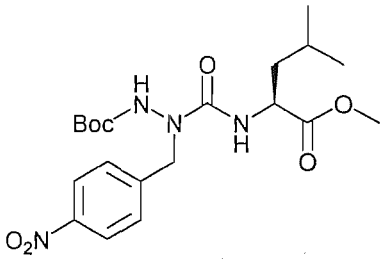
^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ 8.75 and 8.63 (1H, 2 x br s, **NH**); 7.50 – 7.43 (1H, m, **ArH**); 7.31 – 7.23 (1H, m, **ArH**); 7.14 – 7.09 (1H, m, **ArH**); 7.04 –

6.99 (1H, m, **ArH**); 6.92 and 6.80 (1H, 2 x d, *J*= 2.2 Hz, **ArHCNH**); 6.45 (2H, s, 2 x **ArHCOCH$_3$**); 6.22 (1H, br s, **NHBoc**); 6.02 and 5.85 (1H, 2 x d, *J*= 7.9 Hz, **NHCO**); 4.82 – 4.76 (1H, m, **CHN**); 3.82 and 3.75 (9H, 2 x s, 3 x **OCH$_3$**); 3.59 (3H, s, **COOCH$_3$**); 3.45 (2H, s, **CH$_2$**); 3.28 and 3.12 (2H, 2 x d, *J*= 5.5 Hz, **CH$_2$**); 1.38 (9H, s, **CCH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 173.8 and 173.0 (**C**), 157.3 and 157.1 (**C**), 154.4 (**C**), 153.4 (**C**), 137.6 (**C**), 136.2 and 136.1 (**C**), 131.7 (**C**), 127.6 and 127.5 (**C**), 123.6 (**CH**), 123.1 (**CH**), 121.9 and 121.7 (**CH**), 119.4 and 119.2 (**CH**), 118.5 and 118.3 (**CH**), 111.4 and 111.3 (**CH**), 109.7 and 109.4 (**C**), 106.0 (**CH**), 82.1 (**C**), 60.8 and 60.4 (**CH$_3$**), 56.1 (**CH$_3$**), 54.2 (**CH**), 52.2 (**CH$_3$**), 51.0 (**CH$_2$**), 28.0 (**CH$_3$**), 27.8 (**CH$_2$**) ppm.

LRMS (ES^+): *m/z* 1130 ([2M + NH_4^+], 50%), 579 ([M + Na^+], 100%).

N-[2-(4-Methyl-pentanoic acid methyl ester)]-*N'*-(4-nitro-benzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.87)



Title compound isolated as a colourless oil (0.182 g, 44%).

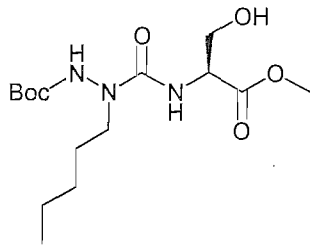
IR: 3268 (m), 2954 (w), 1730 (s), 1649 (s), 1515 (s), 1341(s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (2H, d, *J*= 8.8 Hz, **ArH**); 7.46 (2H, d, *J*= 8.8 Hz, **ArH**); 6.33 (1H, br s, **NH**); 5.82 (1H, br d, *J*= 8.7 Hz, **NH**); 4.54 (1H, dt, *J*= 8.7 Hz, *J*= 4.6 Hz, **CH**); 3.74 (3H, s, **CH$_3$**); 1.72 – 1.51 (5H, m, 2 x **CH$_2$** and **CH**); 1.49 (9H, s, 3 x **CH$_3$**); 0.96 (6H, t, *J*= 6.2 Hz, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.3 (**C**), 157.3 (**C** x 2), 147.7 (**C**) 144.2 (**C**), 129.5 (**CH**), 124.0 (**CH**), 82.9 (**C**), 52.4 (**NCH**), 52.2 (**OCH$_3$**), 51.2 (**CH$_2$**), 42.0 (**CH$_2$**), 28.0 (**CH$_3$**), 25.0 (**CH**), 23.0 (**CH$_3$**), 22.0 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 899 ([2M + Na^+], 60%), 502 ([M + MeCN + Na^+], 40%), 461 ([M + Na^+], 100%), 439 ([M + H^+], 55%).

(*S*)-*N*-(2[3-hydroxy-propionic acid methyl ester])-*N'*-pentyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.88)



Title compound isolated as a clear colourless oil (0.39 g, 90%).

[α]$_D$ 7.7 (*c* 1.3, $CHCl_3$, 27 °C).

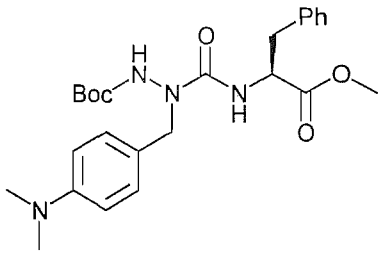
IR: 3271 (m), 2956 (w), 2931 (w), 1736 (s), 1647 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, rotamers): δ 7.16 and 6.64 (1H, 2 x br s, **NH**); 6.23 (1H, br s, **NH**); 4.64 – 4.55 (1H, m, **CH$_2$**); 4.53 – 4.42 (2H, m, **CH$_2$** & **CH**); 3.92 (2H, m, **CH$_2$**); 3.82 and 3.76 (3H, 2 x s, **OCH$_3$**); 1.56 – 1.51 (2H, m, **CH$_2$**); 1.49 (9H, s, **CCH$_3$**); 1.37 – 1.23 (4H, m, 2 x **CH$_2$**); 0.89 (3H, t, *J*= 7.0 Hz, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 171.9 and 170.9 (**C**), 159.4 and 157.8 (**C**), 155.2 and 155.1 (**C**), 82.2 (**C**), 66.8 (**CH$_2$**), 63.1 and 62.9 (**CH$_2$**), 55.9 and 53.8 (**CH**), 53.0 and 52.5 (**CH$_3$**), 28.8 (**CH$_2$**), 28.1 (**CH$_3$**), 26.8 (**CH$_2$**), 22.4 (**CH$_2$**), 13.9 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 717 ([2M + Na^+], 50%), 411 ([M + MeCN + Na^+], 20%), 370 ([M + Na^+], 90%), 348 ([M + H^+], 35%).

(*S*)-*N*-[2-(3-Phenyl-propionic acid methyl ester)]-*N'*-(4-dimethylamino-benzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.89)



Title compound isolated as a clear colourless oil (0.16 g, 25%).

[α]$_D$ 38.7 (*c* 1.1, $CHCl_3$, 24 °C).

IR: 3341 (m), 2978 (w), 2928 (w), 1734 (s), 1651 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.18 (4H, m, **ArH**); 7.12 – 7.07 (3H, m, **ArH**); 6.67 (2H, d, *J*= 8.8 Hz, **ArH**); 6.01 (1H, br s, **NH**); 5.87 and 5.44 (1H, 2 x d, *J*= 8.4 Hz, **NH**); 4.84 – 4.72 (1H, m, **CH**); 3.67 (3H, s, **OCH$_3$**); 3.63 (2H, s, **CH$_2$**); 3.12 (1H,

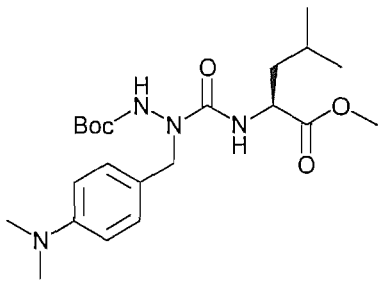
d, *J*= 5.9 Hz, **C**H$_2$); 3.01 (1H, d, *J*= 5.9 Hz, **C**H$_2$); 2.92 (6H, s, **NC**H$_3$); 1.43 (9H, s, **CC**H$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 173.1 and 172.6 (**C**), 157.0 and 156.4 (**C**), 154.4 (**C**), 150.4 (**C**), 136.3 and 136.2 (**C**), 130.1 (**C**H), 129.4 (**C**H), 128.5 (**C**H), 126.9 (**C**H), 123.4 (**C**), 112.8 and 112.7 (**C**H), 82.0 (**C**), 54.3 and 54.1 (**C**H), 52.2 (**C**H$_3$), 49.8 (**C**H$_2$), 40.6 (**C**H$_3$ x 2), 38.6 and 38.5 (**C**H$_2$), 28.1 (**C**H$_3$) ppm.

LRMS (ES^+): *m/z* 941 ([2M + Na^+], 100%).

Anal. Calcd for $C_{25}H_{34}N_4$: C, 63.81; H, 7.28; N, 11.90. Found: C, 63.57; H, 7.15; N, 11.51.

(*S*)-*N*-[2-(4-Methyl-pentanoic acid methyl ester)]-*N'*-(4-dimethylamino-benzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.90)



Title compound isolated as a clear pale yellow oil (0.12 g, 29%).

[α]$_D$ – 6.1 (*c* 1.0, $CHCl_3$, 26 °C).

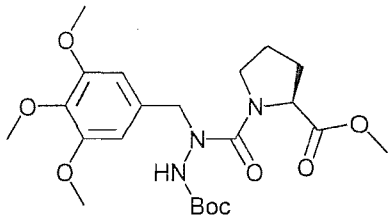
IR: 3335 (m), 2955 (w), 1732 (s), 1648 (s), 1615 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (2H, d, *J*= 8.6 Hz, **Ar**H); 6.67 (2H, d, *J*= 8.6 Hz, **Ar**H); 6.14 (1H, br s, **N**H); 5.77 (1H, d, *J*= 8.4 Hz, **N**H); 4.60 – 4.50 (1H, m, **NC**H); 3.72 (5H, br s, **C**H$_2$ & **OC**H$_3$); 2.93 (6H, s, 2x **NC**H$_3$); 1.75 – 1.52 (3H, m, **CHC**H$_2$); 1.45 (9H, s, **CC**H$_3$); 0.96 (3H, d, *J*= 6.2 Hz, **C**H$_3$); 0.93 (3H, d, *J*= 6.6 Hz, **C**H$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.3 (**C**), 157.3 (**C**), 154.6 (**C**), 150.4 (**C**), 130.2 (**C**H), 123.5 (**C**), 112.8 (**C**H), 82.1 (**C**), 52.2 (**C**H$_3$), 51.9 (**C**H), 50.1 (**C**H$_2$), 42.0 (**C**H$_2$), 40.6 (**NC**H$_3$ x 2), 28.1 (**C**H$_3$), 24.8 (**C**H), 23.0 (**C**H$_3$), 22.0 (**C**H$_3$) ppm.

LRMS (ES^+): *m/z* 873 ([2M + H^+], 100%), 436 ([M + H^+], 45%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(3,4,5-trimethoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.91)



Title compound isolated as a white foam (0.41 g, 55%).

[α]$_D$ – 16.5 (*c* 0.89, $CHCl_3$, 27 °C).

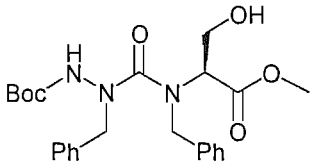
IR: 2977 (w), 2951 (w), 1732 (s), 1634 (s), 1593 (s) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 6.56 (2H, s, **ArH**); 6.16 (1H, br s, **NH**); 4.46 (1H, m, **CH**); 3.85 (11H, br s, **ArOCH$_3$** & **CH$_2$**); 3.71 (3H, s, **OCH$_3$**); 3.59 – 3.58 (2H, m, **NCH$_2$**); 2.21 – 2.17 (1H, m, **CH$_2$**); 1.95 – 1.88 (3H, m, **CH$_2$**); 1.46 (9H, s, **CCH$_3$**) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 173.7 (**C**), 159.3 (**C**), 154.6 (**C**), 153.4 (**C**), 137.6 (**C**), 131.7 (**C**), 106.3 (**CH**), 81.5 (**C**), 60.8 (**CH** & **CH$_3$**), 56.2 (**CH$_3$** x 2), 53.2 (**CH$_2$**), 52.1 (**CH$_3$**), 48.7 (**CH$_2$**), 29.9 (**CH$_2$**), 28.2 (**CH$_3$**), 24.8 (**CH$_2$**) ppm.

LRMS (ES^+): *m/z* 957 ([2M + Na^+], 100%), 952 ([M + NH_4^+], 60%), 934 ([M + H^+], 20%).

(*S*)-*N*-Benzyl-*N*-(2[3-hydroxy-propionic acid methyl ester])-*N'*-benzyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.92)



Title compound isolated as a clear colourless oil (0.25 g, 81%).

[α]$_D$ -16.6 (*c* 1.0, $CHCl_3$, 27 °C).

IR: 3473 (m), 3314 (m), 2978 (w), 2950 (w), 1732 (s), 1654 (s) cm^{-1}.

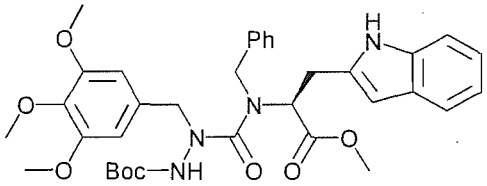
^{1}**H NMR** (400 MHz, $CDCl_3$, rotamers): δ 7.28 – 7.18 (10H, m, **ArH**); 4.82 (1H, d, *J*= 14.6 Hz, **CH$_2$**); 4.55 (2H, s, **CH$_2$**); 4.33 (1H, dd, *J*= 9.5, 9.0 Hz, **CH$_2$**); 4.27 (1H, dd, *J*= 9.0, 5.0 Hz, **CH$_2$**); 4.17 (1H, d, *J*= 14.6 Hz, **CH$_2$**); 4.03 (1H, dd, *J*= 9.5, 5.0 Hz, **CH**); 3.70 and 3.67 (3H, 2 x s, **CH$_3$**); 1.36 and 1.24 (9H, 2 x s, **CH$_3$**) ppm.

^{13}**C NMR + DEPT** (100 MHz, $CDCl_3$, rotamers): δ 171.2 and 170.0 (**C**), 157.7 (**C**), 137.3 (**C**), 135.2 (**C** x 2), 129.3 (**CH**), 128.9 (**CH**), 128.8 (**CH**), 128.6 (**CH**), 128.4

(CH), 127.0 (CH), 127.4 (CH), 127.0 (CH), 82.4 (C), 64.4 (CH_2), 56.0 (CH), 52.9 (CH_2), 52.4 and 53.3 (CH_3), 47.5 (CH_2), 28.2 (CH_3) ppm.

LRMS (ES^+): *m/z* 937 ([2M + Na^+], 45%), 521 ([M + MeCN + Na^+], 30%), 480 ([M + Na^+], 100%), 458 ([M + H^+], 80%).

(*S*)-*N*-Benzyl-*N*-[2-(3-{1*H*-indol-2-yl}-propionic acid methyl ester)]-*N'*-(3,4,5-trimethoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.93)



Title compound isolated as clear oil (0.28 g, 55%).

$[\alpha]_D$ - 10.5 (*c* 1.3, $CHCl_3$, 27 °C).

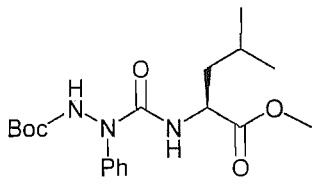
IR: 3340 (m), 2962 (w), 2931 (w), 1728 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (1H, br s, NH); 8.24 (1H, br s, NH); 7.56 (1H, d, *J*= 7.5 Hz, ArH); 7.33 – 6.99 (9H, m, ArH); 6.85 (1H, br s, ArH); 6.60 (1H, br s, ArH); 4.43 (1H, m, CH); 3.85 – 3.80 (2H, m, CH_2); 3.80 (9H, s, CH_3); 3.70 – 3.67 (2H, m, CH_2); 3.61 (3H, s, CH_3); 3.20 (1H, dd, *J*= 14.6, 5.8 Hz, CH_2); 3.14 (1H, dd, *J*= 14.6, 7.0 Hz, CH_2); 1.19 (9H, s, CH_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.7 (C), 171.5 (C), 161.6 (C), 153.4 (C), 152.7 (C), 139.0 (C), 137.0 (C), 136.6 (C), 135.5 (C), 130.8 (C), 127.6 (CH), 126.4 (CH), 122.3 (CH), 121.3 (CH), 118.6 (CH), 118.1 (CH), 117.7 (CH), 110.5 (CH), 106.1 (CH), 80.5 (C), 60.6 (CH_3), 60.2 (CH_2), 55.5 (CH_3 x 3), 52.1 (CH), 51.4 (CH_2), 28.7 (CH_2), 27.3 (CH_3) ppm.

LRMS (ES^+): *m/z* 669 ([M + Na^+], 15%), 647 ([M + H^+], 5%), 390 (100%).

(*S*)-*N*-[2-(4-Methyl-pentanoic acid methyl ester)]-*N'*-phenyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.94)



Title compound isolated as a clear colourless oil (0.11 g, 60%).

$[\alpha]_D$ 1.3 (*c* 0.7, $CHCl_3$, 23 °C).

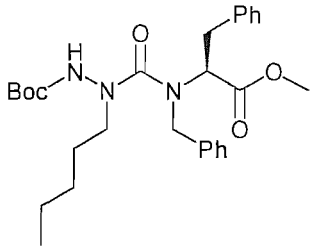
IR: 2954 (w), 2871 (w), 1735 (s), 1661 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): 7.43 – 7.21 (5H, m, **Ar**H); 6.91 (1H, br s, **N**H); 4.60 – 4.54 (1H, m, **C**H); 3.73 (3H, s, **C**H_3); 1.70 – 1.51 (3H, m, **C**H_2 & **C**H); 1.45 (9H, s, **C**H_3); 0.96 – 0.91 (6H, m, **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 174.9 and 174.5 (**C**), 157.2 (**C**), 155.9 (**C**), 141.7 (**C**), 128.9 (**C**H), 126.4 (**C**H), 124.5 (**C**H), 82.2 (**C**), 52.3 (**C**H_3), 51.7 (**C**H), 42.1 and 41.5 (**C**H_2), 28.1 (**CC**H_3), 24.9 and 24.8 (**C**H), 23.0 and 22.8 (**C**H_3), 22.1 and 21.9 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 781 ([2M + Na^+], 100%).

(*S*)-*N*-Benzyl-*N*-[2-(3-Phenyl-propionic acid methyl ester)]-*N'*-pentyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.95)



Title compound isolated as a clear colourless oil (0.16 g, 88%).

[α]$_D$ -38.3 (*c* 0.8, $CHCl_3$, 27 °C).

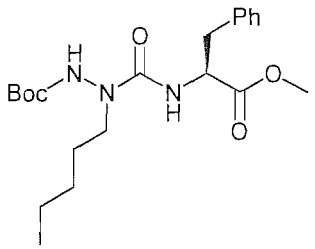
IR: 2950 (w), 2930 (w), 2864 (w), 1733 (s), 1655 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.01 (10H, m, **Ar**H); 6.24 (1H, br s, **N**H); 4.42 (1H, d, *J*= 16.9 Hz, **C**H_2); 4.29 (1H, d, *J*= 16.9 Hz, **C**H_2); 4.00 (1H, br m, **C**H); 3.69 (3H, s, **OC**H_3); 3.40 (1H, dd, *J*= 14.1, 6.5 Hz, **CHC**H_2); 3.38 – 3.27 (3H, m, **CHC**H_2 & **C**H_2); 1.55 – 1.51 (2H, m, **C**H_2); 1.31 (9H, s, **C**H_3); 1.30 – 1.16 (4H, m, **C**H_2); 0.87 (3H, t, *J*= 7.0 Hz, **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 171.9 (**C**), 154.6 (**C**), 151.6 (**C**), 138.6 (**C**), 137.3 (**C**), 129.7 (**C**H), 129.3 (**C**H), 128.6 (**C**H), 128.5 (**C**H), 128.4 (**C**H), 128.3 (**C**H), 127.3 (**C**H), 127.1 (**C**H), 126.8 (**C**H), 126.7 (**C**H), 80.7 (**C**), 62.6 and 62.2 (**C**H), 53.3 (**C**H_2), 52.2 and 52.1 (**C**H_3), 51.7 (**C**H_2), 36.0 (**C**H_2), 29.0 (**C**H_2), 28.2 (**C**H_3), 26.4 (**C**H_2), 22.6 (**C**H_2), 14.1 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 1017 ([2M + Na^+], 5%), 561 ([M + MeCN + Na^+], 5%), 520 ([M + Na^+], 80%), 498 ([M + H^+], 10%), 270 ([M + MeCN + $2H^+$]$^{2+}$, 100%).

(*S*)-*N*-[2-(3-Phenyl-propionic acid methyl ester)]-*N'*-pentyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.97)



Title compound isolated as a clear colourless oil (0.13 g, 27%).

$[\alpha]_D$ 38.9 (*c* 0.6, $CHCl_3$, 20 °C).

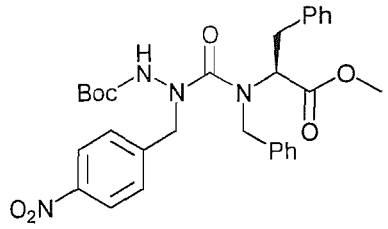
IR: 3268 (m), 2956 (w), 2932 (w), 1732 (s), 1650 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.21 (3H, m, **ArH**); 7.12 – 7.10 (2H, m, **ArH**); 6.26 (1H, br s, **NH**); 5.75 (1H, br d, *J*= 8.0 Hz, **NH**); 4.77 (1H, dt, *J*= 8.0, 5.7 Hz, **CH**); 3.72 – 3.66 (2H, m, **NCH_2**); 3.69 (3H, s, **OCH_3**); 3.10 (2H, d, *J*= 5.7 Hz, **$CHCH_2$**); 1.52 – 1.48 (2H, m, **CH_2**); 1.46 (9H, s, **CH_3**); 1.36 – 1.24 (4H, m, **CH_2**); 0.89 (3H, t, *J*= 7.0 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 172.8 (**C**), 157.0 (**C**), 136.3 (**C**), 135.9 (**C**), 129.4 (**CH**), 128.7 and 128.6 (**CH**), 127.3 and 127.1 (**CH**), 82.3 (**C**), 54.3 (**CH**), 52.4 and 52.2 (**CH_3**), 47.9 (**CH_2**), 38.6 and 38.4 (**CH_2**), 29.0 (**CH_2**), 28.2 (**CH_3**), 26.9 (**CH_2**), 22.5 (**CH_2**), 14.1 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 837 ([2M + Na^+], 30%), 430 ([M + Na^+], 100%), 408 ([M + H^+], 75%).

(*S*)-*N*-Benzyl-*N*-[2-(3-Phenyl-propionic acid methyl ester)]-*N'*-(4-nitrobenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.98)



Title compound isolated as a clear colourless oil (0.17 g, 82%).

$[\alpha]_D$ – 32.8 (*c* 0.5, $CHCl_3$, 25 °C).

IR: 3317 (m), 2980 (w), 2950 (w), 1793 (s), 1736 (s), 1638 (s) cm^{-1}.

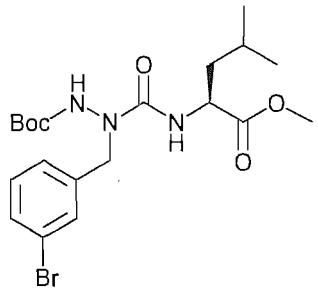
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 – 8.07 (2H, m, **ArH**); 7.44 – 7.41 (2H, m, **ArH**); 7.28 – 7.07 (10H, m, **ArH**); 4.79 (2H, s, **CH_2**); 3.86 (1H, d, *J*= 13.5 Hz, **CH_2**); 3.77

(1H, d, *J*= 13.5 Hz, C**H**$_2$); 3.61 – 3.57 (1H, m, C**H**); 3.54 (3H, s, C**H**$_3$); 3.12 (1H, dd, *J*= 13.5, 6.2 Hz, C**H**$_2$); 3.03 (1H, dd, *J*= 13.5, 7.7 Hz, C**H**$_2$); 1.44 (9H, s, C**H**$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 172.5 and 171.6 (**C**), 153.5 and 151.6 (**C**), 147.9 and 147.6 (**C**), 144.0 (**C**), 142.3 (**C**), 137.0 (**C**), 136.2 and 135.9 (**C**), 129.8 (**C**H), 129.5 (**C**H), 129.3 (**C**H), 126.2 (**C**H), 128.9 (**C**H), 128.7 (**C**H), 128.6 (**C**H), 128.5 (**C**H), 128.1 (**C**H), 127.1 (**C**H), 126.8 (**C**H), 124.1 (**C**H), 124.0 (**C**H), 123.7 (**C**H), 88.1 (**C**), 61.3 and 60.5 (**C**H), 52.3 and 52.1 (**C**H$_3$), 51.4 (**C**H$_2$), 48.5 (**C**H$_2$), 38.4 (**C**H$_2$), 28.1 (**C**H$_3$) ppm.

LRMS (ES^+): *m/z* 626 ([M + MeCN + Na^+], 70%), 585 ([M + Na^+], 100%), 563 ([M + H^+], 10%).

(*S*)-*N*-[2-(4-Methyl-pentanoic acid methyl ester)]-*N'*-(3-bromobenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.99)



Title compound isolated as a clear colourless oil (0.16 g, 52%).

[α]$_D$ – 7.3 (*c* 0.5, $CHCl_3$, 27 °C).

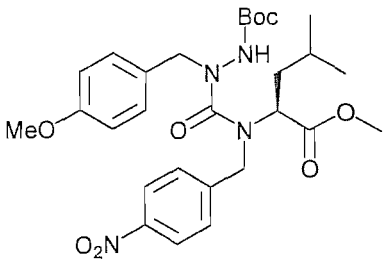
IR: 3338 (m), 2955 (w), 2929 (w), 1732 (s), 1651 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 – 7.41 (2H, m, **Ar**H); 7.20 – 7.19 (2H, m, **Ar**H); 6.38 (1H, br s, **N**H); 5.83 (1H, br d, *J*= 8.5 Hz, **N**H); 4.55 (1H, m, C**H**); 3.73 (3H, s, C**H**$_3$); 3.71 (2H, s, C**H**$_2$); 1.72 – 1.51 (3H, m, C**H**$_2$ & C**H**); 1.45 (9H, s, C**H**$_3$); 0.97-0.91 (6H, m, C**H**$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.9 (**C**), 157.3 (**C**), 157.0 (**C**), 138.8 (**C**), 132.0 (**C**H), 131.1 (**C**H), 130.4 (**C**H), 127.6 (**C**H), 122.9 (**C**), 82.7 (**C**), 52.3 (**C**H), 52.1 (**C**H$_3$), 51.7 (**C**H$_2$), 42.3 (**C**H$_2$), 28.2 (**C**H$_3$), 24.9 (**C**H), 23.0 (**C**H$_3$), 22.2 (**C**H$_3$) ppm.

LRMS (ES^+): *m/z* 969, 967 and 965 ([2M + Na^+], 30%, 1:2:1 ratio), 537 and 535 ([M + MeCN + Na^+], 10%, 1:1 ratio), 496 and 494 ([M + Na^+], 100%, 1:1 ratio).

(*S*)-*N*-(4-nitrobenzyl)-*N*-[2-(4-Methyl-pentanoic acid methyl ester)]-*N'*-(4-methoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.100)



Title compound isolated as a clear colourless oil (0.66 g, 76%).

[α]$_D$ – 11.7 (*c* 0.5, $CHCl_3$, 27 °C).

IR: 3309 (m), 2955 (w), 2933 (w), 1733 (s), 1653 (s), 1514 (s) cm^{-1}.

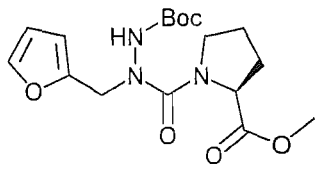
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 8.14 (2H, d, *J*= 8.8 Hz, **Ar**H); 7.58 (2H, d, *J*= 8.8 Hz, **Ar**H); 7.02 (2H, d, *J*= 8.8 Hz, **Ar**H); 6.79 (2H, d, *J*= 8.8 Hz, **Ar**H); 5.85 (1H, br s, **N**H); 4.59 (2H, s, **C**H_2); 4.39 – 4.33 (3H, m, **C**H & **C**H_2); 3.79 (3H, s, **C**H_3); 3.71 (3H, s, **C**H_3); 1.84 – 1.61 (3H, m, **C**H_2 & **C**H); 1.39 (9H, s, **C**H_3); 0.92 (3H, d, *J*= 6.6 Hz, **C**H_3); 0.87 (3H, d, *J*= 6.6 Hz, **C**H_3) ppm.

^{13}**C NMR + DEPT** (100 MHz, $CDCl_3$): δ 173.4 (**C**), 163.4 (**C**), 159.8 (**C**), 154.6 (**C**), 147.4 (**C**), 146.9 (**C**), 143.0 (**C**), 131.0 (**C**H), 128.8 (**C**H), 123.8 (**C**H), 114.5 (**C**H), 82.0 (**C**), 59.8 (**C**H), 55.7 (**C**H_3), 52.8 (**C**H_2), 52.5 (**C**H_3), 50.0 (**C**H_2), 39.9 (**C**H_2), 28.5 (**C**H_3), 25.6 (**C**H), 23.2 (**C**H_3), 22.3 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 1139 ([2M + Na^+], 50%), 622 ([M + MeCN + Na^+], 20%), 581 ([M + Na^+], 100%), 559 ([M + H^+], 30%).

Anal. Calcd for $C_{28}H_{38}N_4$: C, 60.20; H, 6.81; N, 10.02. Found: C, 59.85; H, 6.56; N, 9.62.

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-furan-2-ylmethyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.101)



Title compound isolated as a clear colourless oil (0.21 g, 62%).

[α]$_D$ – 26.1 (*c* 0.7, $CDCl_3$, 26 °C).

IR: 3271 (m), 2977 (w), 2888 (w), 1728 (s), 1635 (s) cm^{-1}.

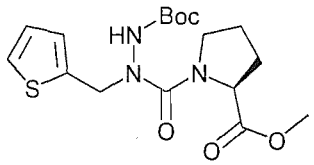
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.38 (1H, m, **Ar**H); 6.35 – 6.31 (1H, m, **Ar**H); 6.29 (1H, d, *J*= 2.9 Hz, **Ar**H); 4.60 (2H, br s, **ArC**H_2); 4.43 (1H, m, **C**H); 3.71 (3H, s,

$OC\underline{H}_3$); 3.59 (2H, t, *J*= 6.4 Hz, $NC\underline{H}_2$); 2.26 – 2.07 (1H, m, $C\underline{H}_2$); 2.01 – 1.79 (3H, m, $C\underline{H}_2$); 1.46 (9H, s, $C\underline{H}_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.6 (<u>C</u>), 158.8 (<u>C</u>), 154.4 (<u>C</u>), 150.1 (<u>C</u>), 142.5 (<u>C</u>H), 110.4 (<u>C</u>H), 109.7 (<u>C</u>H), 80.6 (<u>C</u>), 60.7 (<u>C</u>H), 52.0 ($\underline{C}H_3$), 48.5 ($\underline{C}H_2$), 45.8 ($\underline{C}H_2$), 29.9 ($\underline{C}H_2$), 28.1 ($\underline{C}H_3$), 24.4 ($\underline{C}H_2$) ppm.

LRMS (ES^+): *m/z* 757 ([2M + Na^+], 100%), 752 ([2M + NH_4^+], 20%), 390 ([M + Na^+], 50%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-thiophen-2-ylmethyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.102)



Title compound isolated as a clear colourless oil (0.15 g, 73%).

$[\alpha]_D$ – 26.9 (*c* 0.3, $CDCl_3$, 24 °C).

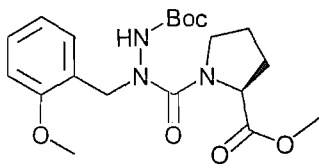
IR: 3268 (m), 2978 (w), 2891 (w), 1729 (s), 1635 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 (1H, d, *J*= 5.0 Hz, **Ar**<u>H</u>); 6.80 – 6.93 (2H, m, **Ar**<u>H</u>); 6.26 (1H, br s, **N**<u>H</u>); 4.75 (2H, br s, **ArC**$\underline{H}_2$); 4.36 – 4.35 (1H, m, **C**<u>H</u>); 3.62 (3H, s, **OC**$\underline{H}_3$); 3.50 (2H, t, *J*= 6.5 Hz, **NC**$\underline{H}_2$); 2.16 – 1.96 (1H, m, **C**$\underline{H}_2$); 1.92 – 1.70 (3H, m, **C**$\underline{H}_2$); 1.38 (9H, s, **C**$\underline{H}_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.6 (<u>C</u>), 157.8 (<u>C</u>), 153.4 (<u>C</u>), 137.0 (<u>C</u>), 127.2 (<u>C</u>H), 125.7 (<u>C</u>H), 125.3 (<u>C</u>H), 80.7 (<u>C</u>), 59.7 (<u>C</u>H), 51.1 ($\underline{C}H_3$), 47.5 ($\underline{C}H_2$), 46.4 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 27.2 ($\underline{C}H_3$), 22.5 ($\underline{C}H_2$) ppm.

LRMS (ES^+): *m/z* 789 ([2M + Na^+], 50%), 406 ([M + Na^+], 100%), 384 ([M + H^+], 10%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(2-methoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.103)



Title compound isolated as a clear colourless oil (0.33 g, 68%).

$[\alpha]_D$ – 20.4 (*c* 1.0, $CDCl_3$, 24 °C).

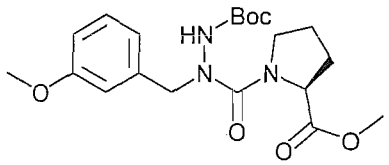
IR: 3269 (m), 2976 (w), 2951 (w), 1732 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.15 (2H, m, **Ar**H); 6.82 – 6.77 (2H, m, **Ar**H); 6.32 (1H, br s, **N**H); 4.57 (2H, br s, **ArC**H_2); 4.35 (1H, m, **C**H); 3.71 (3H, s, **OC**H_3); 3.59 (3H, s, **OC**H_3); 3.49 (2H, m, **NC**H_2); 2.13 – 1.95 (1H, m, **C**H_2); 1.92 – 1.61 (3H, m, **C**H_2); 1.34 (9H, s, **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.6 (**C**), 159.2 (**C**), 157.9 (**C**), 154.8 (**C**), 131.3 (**C**H), 128.8 (**C**H), 124.2 (**C**), 120.5 (**C**H), 110.3 (**C**H), 81.2 (**C**), 60.5 (**C**H), 55.2 (**C**H_3), 51.8 (**C**H_3), 48.4 (**C**H_2), 48.1 (**C**H_2), 29.9 (**C**H_2), 28.0 (**C**H_3), 24.3 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 837 ([2M + Na^+], 30%), 490 ([M + 2MeCN + H^+], 60%), 430 ([M + Na^+], 100%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(3-methoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.104)



Title compound isolated as a clear colourless oil (0.31 g, 64%).

[α]$_D$ – 23.6 (*c* 0.7, MeOH, 23 °C).

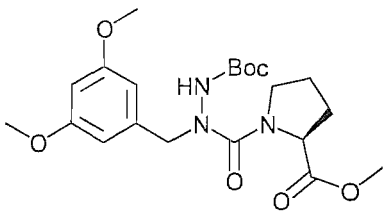
IR: 3279 (m), 2979 (w), 2950 (w), 1732 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (1H, t, *J* = 8.0 Hz, **Ar**H); 6.91 – 6.79 (3H, m, **Ar**H); 6.24 (1H, br s, **N**H); 4.64 (2H, br s, **ArC**H_2); 4.46 (1H, m, **C**H); 3.79 (3H, s, **OC**H_3); 3.70 (3H, s, **OC**H_3); 3.60 (2H, t, *J* = 6.3 Hz, **NC**H_2); 2.22 – 2.13 (1H, m, **C**H_2); 2.02 – 1.80 (3H, m, **C**H_2); 1.45 (9H, s, **C**H_3) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 173.5 (**C**), 159.7 (**C**), 159.1 (**C**), 154.4 (**C**), 137.6 (**C**), 129.4 (**C**H), 121.3 (**C**H), 114.3 (**C**H), 113.4 (**C**H), 81.4 (**C**), 60.6 (**C**H), 55.1 (**C**H_3), 52.8 (**C**H_2), 51.9 (**C**H_3), 48.5 (**C**H_2), 29.8 (**C**H_2), 28.0 (**C**H_3), 24.4 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 837 ([2M + Na^+], 30%), 832 ([M + NH_4^+], 20%), 490 ([M + MeCN + H^+], 20%), 430 ([M + Na^+], 100%), 408 ([M + H^+], 30%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(3,5-dimethoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.105)



Title compound isolated as a clear colourless oil (0.40 g, 86%).

[α]$_D$ – 28.7 (*c* 0.9, MeOH, 23 °C).

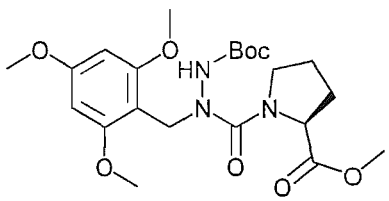
IR: 3276 (m), 2978 (w), 2954 (w), 1733 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.45 (2H, br s, **ArH**); 6.36 (1H, t, *J* = 2.0 Hz, **ArH**); 6.21 (1H, br s, **NH**); 4.66 (2H, br s, **ArCH$_2$**); 4.45 (1H, m, **CH**); 3.76 (6H, s, **OCH$_3$**); 3.69 (3H, s, **OCH$_3$**); 3.59 (2H, t, *J* = 6.0 Hz, **NCH$_2$**); 2.26 – 2.08 (1H, m, **CH$_2$**); 1.95 – 1.75 (3H, m, **CH$_2$**); 1.44 (9H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 173.6 (**C**), 160.9 (**C**), 159.2 (**C**), 154.4 (**C**), 138.4 (**C**), 106.8 (**CH**), 99.7 (**CH**), 81.4 (**C**), 60.7 (**CH**), 55.3 (**CH$_3$**), 52.8 (**CH$_2$**), 52.0 (**CH$_3$**), 48.6 (**CH$_2$**), 29.8 (**CH$_2$**), 28.1 (**CH$_3$**), 24.6 (**CH$_2$**) ppm.

LRMS (ES$^+$): *m/z* 897 ([2M + Na$^+$], 25%), 460 ([M + Na$^+$], 100%), 455 ([M + NH$_4^+$], 80%), 438 ([M + H$^+$], 20%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(2,4,6-trimethoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.106)



Title compound isolated as a clear colourless oil (0.42 g, 56%).

[α]$_D$ – 18.5 (*c* 1.7, MeOH, 23 °C).

IR: 3336 (m), 2974 (w), 2950 (w), 1739 (s) cm^{-1}.

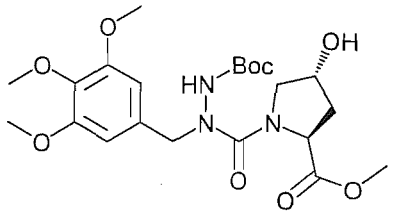
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (2H, s, **ArH**); 5.68 (1H, br s, **NH**); 4.84 – 4.13 (3H, m, **ArCH$_2$** & **CH**); 3.78 (9H, s, **OCH$_3$**); 3.74 – 3.42 (5H, m, **CH$_2$** & **CH$_3$**); 2.26 – 2.07 (1H, m, **CH$_2$**); 2.01 – 1.66 (3H, m, **CH$_2$**); 1.49 – 1.20 (9H, m, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$, rotamers): δ 173.8 (**C**), 161.1 (**C**), 160.1 (**C**), 159.8 (**C**), 155.2 (**C**), 154.9 (**C**), 103.8 (**C**), 90.3 (**CH**), 90.2 (**CH**), 80.8 (**C**), 80.0 (**C**), 60.1 (**CH**), 60.9 (**CH**), 55.6 (**CH$_3$**), 55.4 (**CH$_3$**), 55.1 (**CH$_3$**), 51.6 (**CH**), 48.8

(CH_2), 47.7 (CH_2), 41.5 (CH_2), 40.9 (CH_2), 29.9 (CH_2), 27.8 (CH_3), 24.3 (CH_2), 23.7 (CH_2) ppm.

LRMS (ES$^+$): *m/z* 957 ([2M + Na$^+$], 20%), 490 ([M + Na$^+$], 100%), 468 ([M + H$^+$], 50%).

(2*R*, 4*S*)-*N*-(Pyrrolidine-4-hydroxy-2-carboxylic acid methyl ester)-*N'*-(3,4,5-trimethoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.107)



Title compound isolated as a clear colourless oil (0.25 g, 94%).

[α]$_D$ 10.5 (*c* 0.7, MeOH, 25 °C).

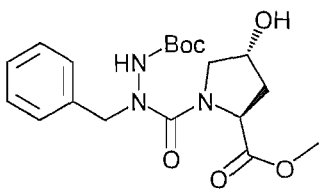
IR: 3383 (m), 2962 (w), 2938 (w), 1721 (s), 1627 (s) cm^{-1}.

^{1}H NMR (400 MHz, MeOD): δ 6.54 (2H, s, **ArH**); 4.50 (1H, t, *J*= 8.3 Hz, **CH**); 4.30 (1H, m, **CH**); 3.74 (6H, s, **CH$_3$**); 3.64 – 3.62 (7H, m, **CH$_3$** & **CH$_2$**); 3.43 – 3.30 (1H, m, **CH$_2$**); 3.22 – 3.19 (2H, m, **CH$_2$**); 2.20 – 1.98 (1H, m, **CH$_2$**); 1.91 – 1.74 (1H, m, **CH$_2$**); 1.34 (9H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-*d*$_6$): δ 173.4 (**C**), 154.8 (**C**), 153.1 (**C** x 3), 136.8 (**C**), 133.0 (**C**), 105.9 (**CH**), 80.1 (**C**), 69.2 (**CH**), 60.4 (**CH**), 56.2 (**CH$_3$**), 53.6 (**CH$_2$**), 52.1 (**CH$_3$**), 51.1 (**CH$_2$**), 37.3 (**CH$_2$**), 28.5 (**CH$_3$**) ppm.

LRMS (ES$^+$): *m/z* 989 ([2M + Na$^+$], 30%), 506 ([M + H$^+$], 100%), 504 ([M + NH$_4^+$], 20%).

(2*R*, 4*S*)-*N*-(Pyrrolidine-4-hydroxy-2-carboxylic acid methyl ester)-*N'*-benzyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.108)



Title compound isolated as a clear colourless oil (0.29 g, 93%).

[α]$_D$ + 1.6 (*c* 0.7, $CDCl_3$, 25 °C).

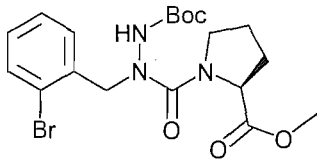
IR: 3394 (m), 2980 (w), 2953 (w), 1728 (s), 1633 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 – 7.08 (5H, m, **ArH**); 6.78 (1H, br s); 4.73 – 4.41 (2H, m, **ArCH_2** & **NCH**); 4.37 – 4.19 (1H, m, **OCH**); 3.71 – 3.52 (5H, m, **CH_3** & **ArCH_2** & **NCH_2**); 3.50 – 3.31 (1H, m, **NCH_2**); 2.24 – 1.97 (1H, m, **CH_2**); 1.91 – 1.65 (1H, m, **CH_2**); 1.34 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.8 (**C**), 159.7 (**C**), 154.4 (**C**), 136.0 (**C**), 129.1 (**CH**), 128.4 (**CH**), 127.5 (**CH**), 81.3 (**C**), 69.9 (**CH**), 59.2 (**CH**), 56.9 (**CH_2**), 53.1 (**CH_2**), 52.1 (**CH_3**), 37.2 (**CH_2**), 28.1 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 888 ([2M + NEt_3 + H^+], 10%), 495 ([M + NEt_3 + H^+], 100%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(2-bromobenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.109)



Title compound isolated as a clear colourless oil (0.15 g, 98%).

[α]$_D$ – 20.3 (*c* 0.5, $CDCl_3$, 26 °C).

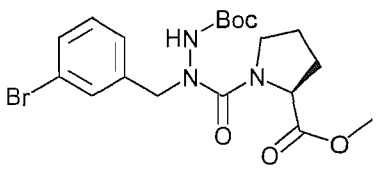
IR: 3258 (m), 1726 (s), 1630 (s), 1416 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (1H, dd, *J*= 7.7, 1.0 Hz, **CHCBr**); 7.31 – 7.26 (2H, m, **ArH**); 7.14 (1H, ddd, *J*= 7.7, 7.7, 1.0 Hz, **CHCHCBr**); 6.25 (1H, br s, **NH**); 4.80 (2H, s, **ArCH_2**); 4.46 (1H, t, *J*= 6.2 Hz, **CH**); 3.75 (3H, s, **OCH_3**); 3.59 (2H, t, *J*= 6.2 Hz, **CH_2**); 2.19 – 1.85 (4H, m, 2 x **CH_2**); 1.44 (9H, br s, 3 x **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 189.7 (**C**), 173.2 (**C**), 154.8 (**C**), 136.2 (**C**), 133.3 (**CH**), 131.9 (**CH**), 129.6 (**CH**), 128.1 (**CH**), 108.1 (**C**), 81.0 (**C**), 77.6 (**CH**), 68.4 (**CH_2**), 52.5 (**CH_3**), 49.0 (**CH_2**), 30.3 (**CH_2**), 28.6 (**CH_3**), 26.0 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 937, 935, 933 ([2M + Na^+], 1:2:1 ratio, 100%), 480, 478 ([M + Na^+], 1:1 ratio, 50%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(3-bromobenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.110)



Title compound isolated as a clear colourless oil (0.15 g, 90%).

[α]$_D$ – 12.0 (*c* 0.5, $CDCl_3$, 24 °C).

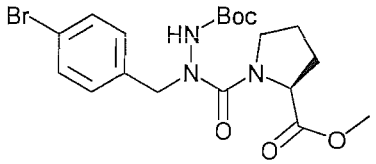
IR: 3263 (m), 1728 (s), 1631 (s), 1366 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 – 7.41 (2H, m, **Ar**H); 7.28 – 7.18 (2H, m, **Ar**H); 6.25 (1H, br s, **N**H); 4.48 (2H, br s, **ArC**H_2); 4.46 – 4.45 (1H, m, **C**H); 3.73 (3H, s, **OC**H_3); 3.59 (2H, t, *J*= 6.2 Hz, **C**H_2); 2.19 – 1.86 (4H, m, 2 x **C**H_2); 1.45 (9H, br s, 3 x **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.6 (**C**), 158.0 (**C**), 153.3 (**C**), 137.7 (**C**), 131.2 (**C**H), 129.8 (**C**H), 129.2 (**C**H), 126.9 (**C**H), 121.6 (**C**), 80.7 (**C**), 59.8 (**C**H), 51.2 (**C**H_2), 51.1 (**C**H_3), 47.6 (**C**H_2), 28.9 (**C**H_2), 27.2 (**C**H_3), 23.6 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 937, 935, 933 ([2M + Na^+], 1:2:1 ratio, 100%), 480, 478 ([M + Na^+], 1:1 ratio, 80%), 458, 456 ([M + H^+], 1:1 ratio, 50%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N*'-(4-bromobenzyl)-*N*''-carboxylic acid *tert*-butyl ester semicarbazide (1.111)



Title compound isolated as a clear yellow oil (0.054 g, 52%).

[α]$_D$ – 10.0 (*c* 0.5, $CDCl_3$, 25 °C).

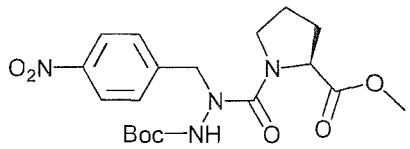
IR: 3280 (m), 1727 (s), 1631 (s), 1433 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (2H, d, *J*= 8.2 Hz, **Ar**H); 7.23 (2H, d, *J*= 8.2 Hz, **Ar**H); 6.25 (1H, br s, **N**H); 4.44 (2H, br s, **ArC**H_2); 4.45 (1H, t, *J*= 6.2 Hz, **C**H); 3.65 (3H, s, **OC**H_3); 3.60 (2H, t, *J*= 6.2 Hz, **C**H_2); 2.04 – 1.65 (4H, m, 2 x **C**H_2); 1.45 (9H, br s, 3 x **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.6 (**C**), 170.1 (**C**), 153.4 (**C**), 134.3 (**C**), 130.7 (**C**H), 130.1 (**C**H), 120.7 (**C**), 80.2 (**C**), 59.7 (**C**H_2), 59.4 (**C**H), 51.2 (**C**H_3), 47.6 (**C**H_2), 28.9 (**C**H_2), 27.0 (**C**H_3), 23.6 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 937, 935, 933 ([2M + Na^+], 1:2:1 ratio, 100%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(4-nitrobenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.112)



Title compound isolated as a clear yellow oil (0.22 g, 94%).

[α]$_D$ – 46.5 (*c* 0.5, $CDCl_3$, 24 °C).

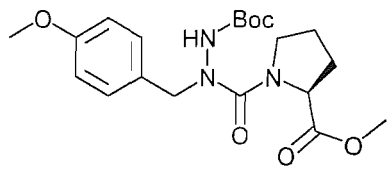
IR: 3281 (m), 1729 (s), 1632 (s), 1518 (s), 1433 (s), 1340 (s), 1152 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (2H, d, *J*= 8.6 Hz, **ArH**); 7.54 (2H, d, *J*= 8.6 Hz, **ArH**); 6.37 (1H, br s, **NH**); 4.69 (2H, br s, **ArCH$_2$**); 4.46 (1H, dd, *J*= 7.7, 5.1 Hz, **CH**); 3.72 (3H, s, **OCH$_3$**); 3.59 (2H, t, *J*= 6.2 Hz, **CH$_2$**); 2.21 – 1.81 (4H, m, 2 x **CH$_2$**); 1.45 (9H, br s, 3 x **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 173.2 (**C**), 159.0 (**C**), 154.2 (**C**), 147.5 (**C**), 144.1 (**C**), 129.7 (**CH**), 123.7 (**CH**), 80.3 (**C**), 60.7 (**CH**), 53.7 (**CH$_2$**), 52.1 (**CH$_3$**), 48.5 (**CH$_2$**), 29.8 (**CH$_2$**), 28.1 (**CH$_3$**), 24.7 (**CH$_2$**) ppm.

LRMS (ES^+): *m/z* 867 ([2M + Na^+], 20%), 445 ([M + Na^+], 100%).

(*S*)-*N*-(Pyrrolidine-2-carboxylic acid methyl ester)-*N'*-(4-methoxybenzyl)-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (1.113)



Title compound isolated as a white foam (0.15 g, 98%).

[α]$_D$ – 4.7 (*c* 0.5, $CDCl_3$, 24 °C).

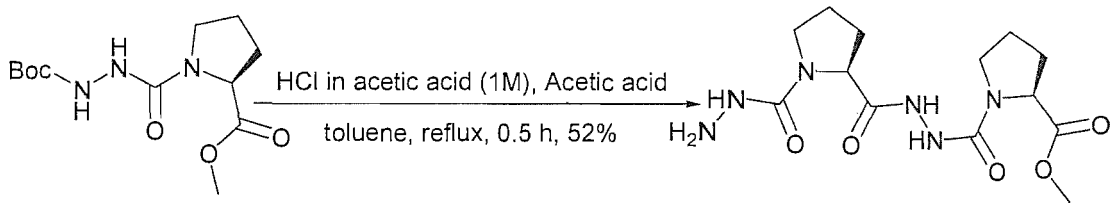
IR: 3282 (m), 1729 (s), 1631 (s), 1511 (s), 1433 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (2H, d, *J*= 8.4 Hz, **ArH**); 6.86 (2H, d, *J*= 8.4 Hz, **ArH**); 6.06 (1H, br s, **NH**); 4.60 (2H, br s, **ArCH$_2$**); 4.46 (1H, t, *J*= 7.7 Hz, **CH**); 3.79 (3H, s, **OCH$_3$**); 3.71 (3H, s, **OCH$_3$**); 3.59 (2H, t, *J*= 5.5 Hz, **CH$_2$**); 2.17 – 1.82 (4H, m, 2 x **CH$_2$**); 1.45 (9H, s, 3 x **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 173.7 (**C**), 159.3 (**C**), 154.5 (**C**), 145.7 (**C**), 130.7 (**CH**), 128.0 (**C**), 114.0 (**CH**), 81.5 (**C**), 60.7 (**CH**), 55.3 (**CH$_3$**), 52.1 (**CH$_3$**), 48.6 (**CH$_2$**), 38.5 (**CH$_2$**), 29.9 (**CH$_2$**), 28.2 (**CH$_3$**), 24.5 (**CH$_2$**) ppm.

LRMS (ES^+): *m/z* 837 ([2M + Na^+], 100%).

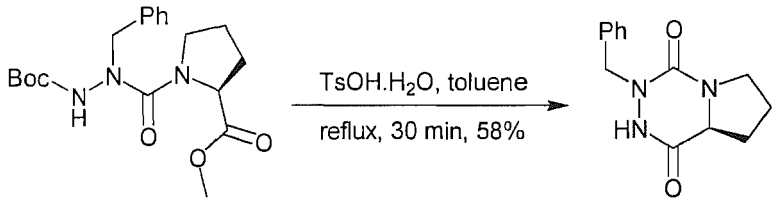
1[*N*'-(1-Hydrazinocarbonyl-pyrrolidine-2-carbonyl)-hydrazinocarbonyl]-pyrrolidine-2-carboxylic acid methyl ester (1.115)



Hydrochloric acid in acetic acid (1.0 M, 5 mL) was added to a stirred solution of 1-(*N*'-tert-butoxycarbonyl-hydrazinocarbonyl)-pyrrolidine-2-carboxylic acid methyl ester (0.10 g, 1.0 equiv.) in acetic acid (5 mL). The reaction was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*, toluene (20 mL) was added and the solvent removed *in vacuo*. This was repeated three more times to remove remaining acetic acid. After column chromatography (100% ethyl acetate to 1:9:90 NEt_3/methanol/ethyl acetate) the product was isolated as a yellow oil (0.031 g, 52%).

IR: 3319 (w), 3266 (w), 3200 (w), 2957 (w), 2891 (w), 1776 (m), 1698 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.54 – 4.35 (1H, m, **C**H); 4.06 – 4.00 (1H, m, **C**H); 3.67 (3H, s, **C**H_3); 3.59 – 3.56 (1H, m, **C**H_2); 3.43 – 3.36 (1H, m, **C**H_2); 3.32 – 3.18 (2H, m, **C**H_2); 2.25 – 2.17 (1H, m, **C**H_2); 2.10 – 1.95 (6H, m, **C**H_2); 1.74 – 1.61 (1H, m, **C**H_2) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 173.5 (**C**O), 172.1 (**C**O), 159.7 (**C**O), 159.1 (**C**O), 62.0 (**C**H), 59.1 (**C**H), 52.3 (O**C**H_3), 45.7 (**C**H_2), 45.5 (**C**H_2), 29.6 (**C**H_2), 27.5 (**C**H_2), 26.8 (**C**H_2), 24.5 (**C**H_2) ppm.
LRMS (ES^+): *m/z* 343 ([M + H^+], 100%).

(*S*)-3-Benzyl-hexahydro-pyrrolo[1,2-d][1,2,4]triazine-1,4-dione (1.116)



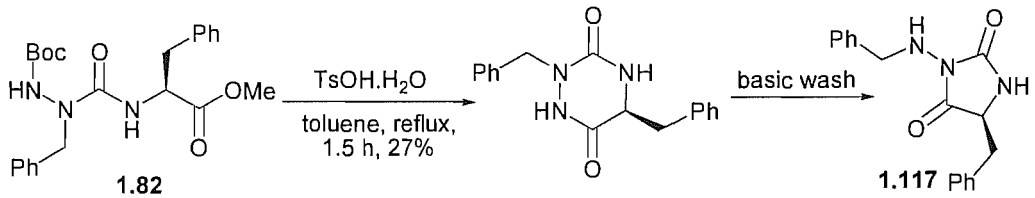
1-(*N*-Benzyl-*N*'-tert-butoxycarbonyl-hydrazinocarbonyl)-pyrrolidine-2-carboxylic acid methyl ester (0.050 g, 0.13 mmol, 1.00 equiv.) and *p*-toluene sulfonic acid .H_2O (2.00 equiv., 0.27 mmol, 0.050 g) were dissolved in toluene (3 mL) and refluxed for 30 min. On reaching reflux the colourless solution turned a clear blue-

green and a precipitate crystallised out of solution. On cooling the solid was filtered and purified by column chromatography (100% ethyl acetate to 1:9:90 NEt_3/methanol/ethyl acetate) to give **1.116** as a white crystalline solid (0.019 g, 58%).

Mp 222 – 223 °C (ethyl acetate), literature 217 – 218 °C.
IR: 1685 (s), 1643 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 10.40 (1H, br s, **NH**); 7.35 – 7.28 (5H, m, **ArH**); 4.95 (1H, d, *J*= 15.9 Hz, **CH_2**); 4.24 (1H, d, *J*= 15.9 Hz, **CH_2**); 3.90 (1H, t, *J*= 7.7 Hz, **CH**); 3.40 – 3.32 (2H, m, **CH_2**); 2.08 – 1.83 (4H, m, 2 x **CH_2**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 165.7 (**CO**), 153.7 (**CO**), 137.1 (**C**), 128.4 (**CH**), 127.5 (**CH**), 127.3 (**CH**), 57.0 (**CH**), 49.7 (**CH_2Ph**), 44.7 (**CH_2**), 26.6 (**CH_2**), 22.6 (**CH_2**) ppm.
LRMS (ES^+): *m/z* 758 ([3M + Na^+], 5%), 513 ([2M + Na^+], 10%), 246 ([M + H^+], 5%), 172 (100%).

The ^{1}H NMR and ^{13}C NMR acquired fit the data given in the literature for this known compound.[24]

(*S*)-5-Benzyl-3-(benzyl-amino)hydantoin (1.117)



N-[2-(3-Phenyl-propionic acid methyl ester)]-*N'*-benzyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (0.184 g, 0.43 mmol) and *p*-toluene sulphonic acid .H_2O (1.50 equiv., 0.65 mmol, 0.123 g) were dissolved in toluene (10 mL). The reaction mixture was heated to reflux and after stirring for 1.5 h was allowed to cool to room temperature. The solvent was removed *in vacuo* and the crude residues were dissolved in dichloromethane (10 mL) and washed with saturated $NaHCO_{3\,(Aq.)}$ (20 mL) and brine (20 mL). The organics were dried over $MgSO_4$, solvent removed *in vacuo* and the crude product was purified by column chromatography (50 – 100% ethyl acetate/hexane) to give the title compound as a white solid (0.034 g, 27%).

Mp 163 – 165 °C (Methanol/ethyl acetate).

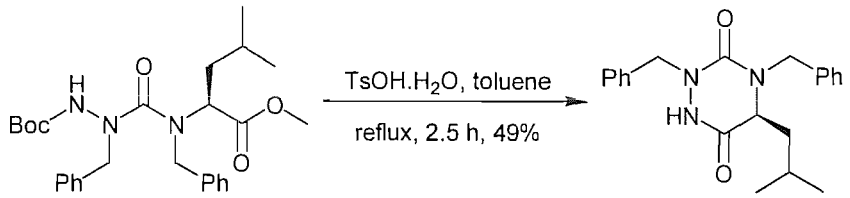
IR: 3269 (m), 2959 (w), 1759 (m), 1710 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 – 7.08 (10H, m, **ArH**); 5.20 (1H, br s, **NH**); 4.46 (1H, br t, *J*= 4.8 Hz, **NH**); 4.08 (1H, ddd, *J*= 8.8, 3.7, 1.3 Hz, **CH**); 3.95 (2H, d, *J*= 4.8 Hz, **CH_2**); 3.15 (1H, dd, *J*= 13.9, 3.7 Hz, **CH_2**); 2.62 (1H, dd, *J*= 13.9, 8.8 Hz, **CH_2**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 170.6 (**C**), 155.4 (**C**), 135.8 (**C**) 135.1 (**C**), 129.5 (**CH**), 129.4 (**CH**), 129.2 (**CH**), 128.7 (**CH**), 128.3 (**CH**), 127.8 (**CH**), 57.0 (**NCH**), 54.7 (**CH_2**), 38.1 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 613 ([2M + H^+], 20%), 296 ([M + H^+], 10%), 129 (100).

(*S*)-2,4-Dibenzyl-5-isobutyl-[1,2,4]triazinane-3,6-dione (1.118)



N-Benzyl-*N*-[2-(4-methyl-pentanoic acid methyl ester)]-*N'*-benzyl-*N''*-carboxylic acid *tert*-butyl ester semicarbazide (0.100 g, 0.21 mmol) and *p*-toluene sulphonic acid .H_2O (1.50 equiv., 0.31 mmol, 0.059 g) were dissolved in toluene (9 mL). The reaction mixture was heated to reflux and after stirring for 2.5 h was cooled to room temperature. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (10 – 50% ethyl acetate/hexane) to give the title compound as a white solid (0.035 g, 49%).

Mp 114 – 116 °C (ethyl acetate).

IR: 3118 (m), 2957 (w), 1738 (s), 1693 (s), 1624 (s) cm^{-1}.

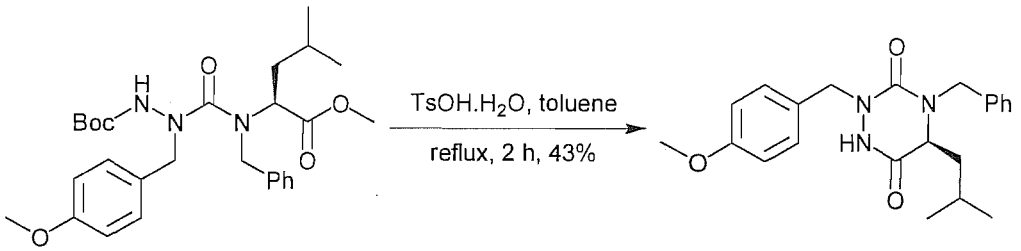
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.26 (10H, m, **ArH**); 5.02 (1H, d, *J*= 15.0 Hz, **CH_2**); 4.87 (1H, d, *J*= 15.0 Hz, **CH_2**); 4.55 (1H, d, *J*= 15.0 Hz, **CH_2**); 4.05 (1H, d, *J*= 15.0 Hz, **CH_2**); 3.62 (1H, td, *J*= 7.5 Hz, 2.6 Hz, **NCH**); 1.58 – 1.51 (1H, m, **CH**); 1.29 – 1.21 (2H, m, **CH_2**); 0.81 (3H, d, *J*= 6.2 Hz, **CH_3**); 0.77 (3H, d, *J*= 6.2 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.2 (**CO**), 154.3 (**CO**), 136.6 (**C**) 135.2 (**C**), 129.0 (**CH**), 128.9 (**CH** x 2), 128.6 (**CH**), 128.3 (**CH**), 128.1 (**CH**), 57.5 (**NCH**), 51.4 (**NCH_2**), 49.5 (**NCH_2**), 38.9 (**CH_2**), 24.6 (**CH**), 23.2 (**CH_3**), 21.9 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 725 ([2M + Na^+], 10%), 352 ([M + H^+], 25%), 129 (100).

Anal. Calcd for $C_{21}H_{25}N_3$: C, 71.77; H, 7.17; N, 11.95. Found: C, 71.38; H, 7.18; N, 12.04.

(*S*)-2-(4-Methoxy-benzyl)-4-benzyl-5-isobutyl-[1,2,4]triazinane-3,6-dione (1.119)



N-Benzyl-*N*-[2-(4-methyl-pentanoic acid methyl ester)]-*N*'-(4-methoxy-benzyl)-*N*''-carboxylic acid *tert*-butyl ester semicarbazide (0.100 g, 0.20 mmol) and *p*-toluene sulphonic acid .H_2O (1.50 equiv., 0.29 mmol, 0.056 g) were dissolved in toluene (10 mL). The reaction mixture was heated to reflux and after stirring for 2 h was cooled to room temperature. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (50% ethyl acetate/hexane) to give the title compound as a colourless oil (0.031 g, 43%).

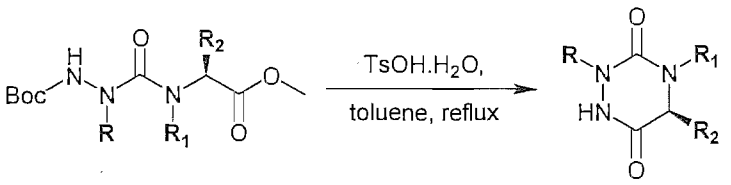
IR: 3153 (m), 2953 (w), 1642 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (1H, br s, **NH**); 7.34 – 7.27 (7H, m, **ArH**); 6.87 – 6.85 (2H, m, **ArH**); 5.02 (1H, d, *J*= 15.0 Hz, **CH$_2$**); 4.72 (1H, d, *J*= 15.0 Hz, **CH$_2$**); 4.59 (1H, d, *J*= 15.0 Hz, **CH$_2$**); 4.05 (1H, d, *J*= 15.0 Hz, **CH$_2$**); 3.80 (3H, s, **OCH$_3$**); 3.62 (1H, m, **CH**); 1.61 – 1.24 (3H, m, **CH$_2$CH**); 0.82 (3H, d, *J*= 6.6 Hz, **CH$_3$**); 0.78 (3H, d, *J*= 6.6 Hz, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.1 (**CO**), 159.9 (**CO**), 154.5 (**C**), 136.6 (**C**), 130.4 (**CH**), 129.0 (**CH**), 128.3 (**CH**),128.1 (**CH**), 127.0 (**C**), 114.5 (**CH**), 57.6 (**NCH**), 55.4 (**OCH$_3$**), 51.1 (**NCH$_2$**), 49.5 (**NCH$_2$**), 38.9 (**CH$_2$**), 24.6 (**CH**), 23.2 (**CH$_3$**), 21.9 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 785 ([2M + Na^+], 30%), 763 ([2M + H^+], 10%), 382 ([M + H^+], 10%), 129 (100).

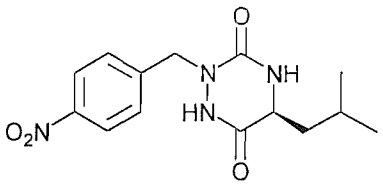
1,2,4-Triazine-3,6-diones (1.120 to 1.122) and 3-amino hydantoin (1.123).



General Experimental:

Semicarbazide (0.100 g) and *p*-toluene sulphonic acid .H_2O (1.50 equiv.) were dissolved in toluene (10 mL). The reaction mixture was heated to reflux and after stirring for 30 – 40 minutes was allowed to cool to room temperature. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (50 – 100% ethyl acetate/hexane) to give the title 1,2,4-triazine-3,6-dione.

(*S*)-5-Isobutyl-2-(4-nitro-benzyl)-[1,2,4]triazinane-3,6-dione (1.120)



Method: Refluxed for 40 minutes.

Title compound isolated as a clear colourless oil (0.03 g, 19%).

$[\alpha]_D$ – 12.0 (*c* 0.2, 1:1 MeOH/CH_3CN, 25 °C).

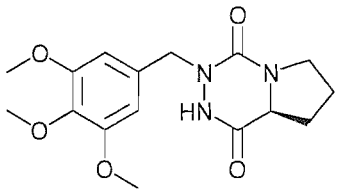
IR: 3194 (m), 3076 (m), 2955 (w), 1678 (s), 1673 (s), 1666 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.67 (1H, br s, **NH**); 8.35 (2H, d, *J*= 8.2 Hz, **ArH**); 7.66 (2H, d, *J*= 8.2 Hz, **ArH**); 7.48 (1H, d, *J*= 2.5 Hz, **NH**); 4.93 (1H, d, *J*= 16.1 Hz, **CH_2**); 4.68 (1H, d, *J*= 16.1 Hz, **CH_2**); 3.74 (1H, m, **CH**); 1.84 – 1.77 (1H, m, **CHCH$_2$**); 1.40 – 1.25 (2H, m, **CHCH$_2$**); 0.95 (3H, d, *J*= 6.8 Hz, **CH_3**); 0.90 (3H, d, *J*= 6.8 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (75 MHz, DMSO-d_6): δ 145.1 (**C**), 127.3 (**CH**), 121.8 (**CH**), 53.0 (**CH**), 49.3 (**CH_2**), 41.1 (**CH_2**), 23.9 (**CH**), 23.1 (**CH_3**), 22.3 (**CH_3**) ppm. (Quaternary carbons not showing with the maximum available extended scans.)

LRMS (ES^+): *m/z* 380 ([M + MeCN + MeOH + H^+], 100%), 306 ([M + H^+], 15%).

(*S*)-3-(3,4,5-Trimethoxy-benzyl)-hexahydro-pyrrolo[1,2-d][1,2,4]triazinane-3,6-dione (1.121)



Method: Refluxed for 30 minutes.

Title compound isolated as crystalline green solid (0.05 g, 28%).

Mp 270 °C (propan-2-ol/diethyl ether).

[α]$_D$ – 56.8 (*c* 0.5, $CHCl_3$, 25 °C).

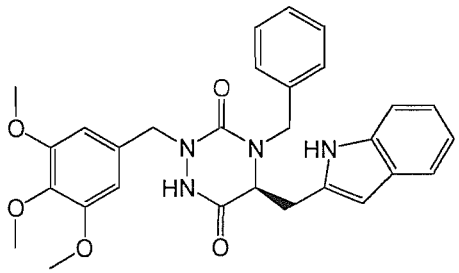
IR: 3143 (w), 2838 (w), 2957 (w), 1686 (s), 1633 (s), 1595 (s) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.72 (1H, br s, **NH**); 6.60 (2H, s, **ArH**); 4.77 (1H, d, *J*= 14.8 Hz, **CH$_2$**); 4.46 (1H, d, *J*= 14.8 Hz, **CH$_2$**); 3.92 (1H, t, *J*= 7.9 Hz, **CH**); 3.85 (9H, s, **OCH$_3$**); 3.58 – 3.53 (2H, m, **CH$_2$**); 2.25 – 2.16 (2H, m, **CH$_2$**); 2.03 – 2.94 (2H, m, **CH$_2$**) ppm.

^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 166.6 (**C**), 154.5 (**C**), 153.8 (**C** x 2), 130.6 (**C**), 106.1 (**CH**), 60.8 (**CH**), 57.9 (**CH$_3$**), 56.4 (**CH$_3$**), 51.1 (**CH$_2$**), 45.4 (**CH$_2$**), 26.9 (**CH$_2$**), 23.5 (**CH$_2$**) ppm.

LRMS (ES^+): *m/z* 1028 ([3M + Na^+], 30%), 693 ([2M + Na^+], 100%), 671 ([2M + H^+], 30%), 399 ([M + MeCN +Na^+], 25%), 336 ([M + H^+], 20%).

(*S*)-5-(1H-indol-2-ylmethyl)-2-(3,4,5-trimethoxy-benzyl)- 4-Benzyl-1,2,4-triazinane-3,6-dione (1.122)



Method: Refluxed for 30 minutes.

Title compound isolated as a crystalline white solid (60 mg, 40%).

Mp 82 – 84 °C (Ethyl acetate/hexane).

[α]$_D$ 34.4 (*c* 0.9, MeOH, 26 °C).

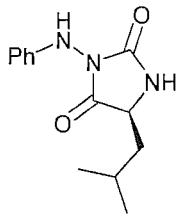
IR: 2929 (w), 1683 (s), 1644 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (1H, br s, **NH**); 7.54 (1H, d, *J*= 6.0 Hz, **ArH**); 7.36 – 6.99 (9H, m, **ArH**); 5.97 (2H, s, **ArH(OMe)$_3$**); 5.11 (1H, d, *J*= 14.6 Hz, **CH$_2$Ph**); 4.45 (1H, d, *J*= 14.1 Hz, **CH$_2$Ar(OMe)$_3$**); 4.00 – 3.95 (2H, m, **CH** & **CH$_2$Ph**); 3.70 and 3.67 (9H, 2 x s, **OCH$_3$**); 3.23 (1H, dd, *J*= 15.0, 4.0 Hz, **CHCH$_2$**); 3.09 (1H, dd, *J*= 15.0, 5.0 Hz, **CHCH$_2$**); 2.18 (1H, d, *J*= 14.1 Hz, **CH$_2$Ar(OMe)$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 174.1 (**C**), 165.2 (**C**), 153.7 (**C**), 136.3 (**C**), 136.1 (**C**), 129.3 (**CH**), 129.1 (**CH**), 128.5 (**CH**), 128.2 (**C**), 124.5 (**CH**), 122.5 (**CH**), 120.1 (**CH**), 119.4 (**CH**), 111.5 (**CH**), 109.0 (**C**), 106.0 (**CH**), 60.9 (**CH$_3$**), 59.3 (**CH**), 56.3 (**CH$_3$**), 52.8 (**CH$_2$**), 49.2 (**CH$_2$**), 25.9 (**CH$_2$**) ppm.

LRMS (ES$^+$): *m/z* 1051 ([2M + Na$^+$], 10%), 1029 ([2M + H$^+$], 5%), 578 ([M + MeCN + Na$^+$], 10%), 537 ([M + Na$^+$], 60%), 515 ([M + H$^+$], 10%), 150 (100).

(*S*)-5-Isobutyl-3-(phenyl-amino)hydantoin (1.123)



Method: Refluxed for 30 minutes, 1,2,4-triazine-3,6-dione product rearranges to 3-aminohydantoin (see Results and Discussion).

Title compound isolated as a clear colourless oil (7 mg, 48%).

[α]$_D$ – 41.3 (*c* 0.4, $CHCl_3$, 27 °C).

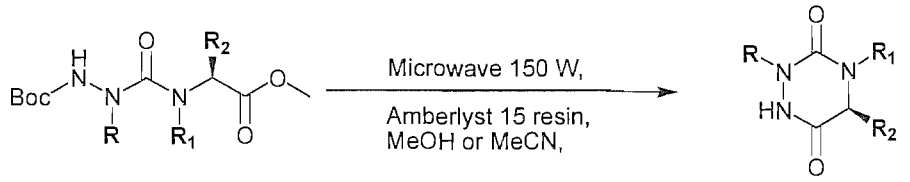
IR: 3307 (w), 2956 (w), 1723 (s), 1602 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 – 7.23 (2H, m, **ArH**); 6.97 (1H, t, *J*= 7.5 Hz, **ArH**); 6.79 – 6.77 (2H, m, **ArH**); 6.38 (1H, br s, **NH**); 6.19 (1H, br s, **NH**); 4.15 – 4.12 (1H, m, **CH**); 1.88 – 1.57 (3H, m, **CH$_2$CH**); 0.98 (3H, d, *J*= 6.3 Hz, **CH$_3$**); 0.96 (3H, d, *J*= 6.3 Hz, **CH$_3$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 172.5 (**C**), 156.0 (**C**), 145.5 (**C**), 129.5 (**CH**), 122.6 (**CH**), 114.2 (**CH**), 54.8 (**CH**), 41.2 (**CH$_2$**), 25.1 (**CH**), 23.2 (**CH$_3$**), 21.7 (**CH$_3$**) ppm.

LRMS (ES$^+$): *m/z* 517 ([2M + Na$^+$], 50%), 311 ([M + MeCN + Na$^+$], 20%), 129 (100).

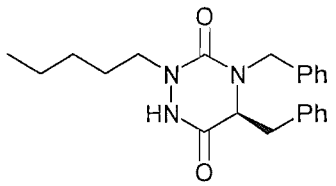
1,2,4-Triazine-3,6-diones (1.124 to 1.138).



General Experimental:

A solution of the semicarbazide (1.00 equiv.) in methanol or acetonitrile (3 mL) and Amberlyst 15 resin beads (5.00 equiv.) were stirred in a microwave reactor. The reaction mixture was heated to temperature (120 – 170 °C) and after the desired length of time (0.5 – 3 h) was allowed to cool to room temperature. The Amberlyst resin beads were removed by filtration and washed with an excess of methanol or acetonitrile solvent. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (50 – 100% ethyl acetate/hexane) to give the title 1,2,4-triazine-3,6-dione. Alternatively, if the product crystallised out of the solvent on cooling it was filtered and recrystallised to give the title 1,2,4-triazine-3,6-dione.

(*S*)-4,5-Dibenzyl-2-pentyl-1,2,4-triazine-3,6-dione (1.124)



Method: 120 °C, methanol, 30 minutes.

Title compound isolated as a clear colourless oil (22 mg, 59%).

$[\alpha]_D$ 15.5 (*c* 0.2, $CHCl_3$, 27 °C).

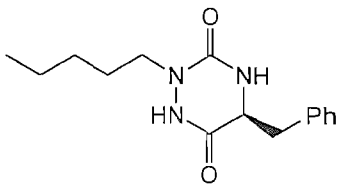
IR: 2924 (w), 1736 (s), 1639 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.19 (6H, m, **ArH**); 7.10 – 7.08 (4H, m, **ArH**); 4.97 (1H, d, *J*= 15.1 Hz, **NCH_2Ph**); 3.90 (1H, dd, *J*= 6.5, 5.5 Hz, **CH**); 3.60 (1H, d, *J*= 15.1 Hz, **NCH_2Ph**); 3.15 – 3.10 (2H, m, **NCH_2**); 2.96 (1H, dd, *J*= 14.1, 5.5 Hz, **CH_2CH**); 2.87 (1H, dd, *J*= 14.1, 6.5 Hz, **CH_2CH**); 1.46 – 1.31 (2H, m, **CH_2**); 1.25 – 1.15 (4H, m, **CH_2**); 0.82 (3H, t, *J*= 7.3 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.0 (**C**), 153.5 (**C**), 136.4 (**C**), 135.6 (**C**), 129.8 (**CH**), 129.0 (**CH**), 128.9 (**CH**), 128.3 (**CH**), 128.1 (**CH**), 127.5 (**CH**), 60.2 (**CH**), 49.4 (**CH_2**), 47.9 (**CH_2**), 35.8 (**CH_2**), 28.8 (**CH_2**), 26.9 (**CH_2**), 22.4 (**CH_2**), 14.1 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 753 ([2M + Na^+], 100%), 731 ([2M + H^+], 70%), 429 ([M + MeCN + Na^+], 30%), 388 ([M + Na^+], 20%), 366 ([M + H^+], 50%).

(*S*)-5-Benzyl-2-pentyl-1,2,4-triazine-3,6-dione (1.125)



Method: 120 °C, methanol, 30 minutes.

Title compound isolated as a clear colourless oil (23 mg, 68%).

$[\alpha]_D$ – 3.8 (*c* 2, MeOH, 26 °C).

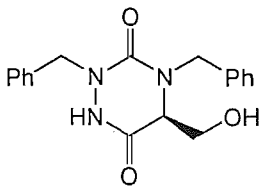
IR: 3207 (w), 2954 (w), 2355 (w), 1655 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (1H, br s, **NH**); 7.28 – 7.16 (5H, m, **ArH**); 5.22 (1H, br s, **NH**); 4.08 – 4.01 (1H, m, **CH**); 4.00 – 3.28 (2H, m, **CH_2**); 3.16 (1H, dd, *J*= 14.1, 4.0 Hz, **CH_2**); 2.82 (1H, dd, *J*= 14.1, 9.0 Hz, **CH_2**); 1.53 – 1.45 (2H, m, **CH_2**); 1.26 – 1.17 (4H, m, **CH_2**); 0.83 (3H, t, *J*= 7.0 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.4 (**C**), 153.6 (**C**), 135.5 (**C**), 129.6 (**CH**), 129.2 (**CH**), 127.6 (**CH**), 55.9 (**CH**), 47.1 (**CH_2**), 38.0 (**CH_2**), 28.7 (**CH_2**), 26.7 (**CH_2**), 22.4 (**CH_2**), 14.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 573 ([2M + Na^+], 20%), 551 ([2M + H^+], 70%), 276 ([M + H^+], 100%).

(*S*)-2,4-Dibenzyl-5-(hydroxymethyl)-1,2,4-triazine-3,6-dione (1.126)



Method: 120 °C, methanol, 30 minutes.

Title compound isolated as clear colourless oil (13 mg, 72%).

$[\alpha]_D$ 14.2 (*c* 0.3, MeOH, 27 °C).

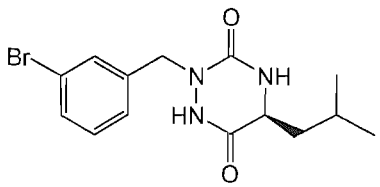
IR: 3380 (w), 2921 (w), 2850 (w), 1632 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.26 (10H, m, **ArH**); 5.08 (1H, d, *J*= 15.1 Hz, **CH_2**); 4.91 (1H, d, *J*= 15.1 Hz, **CH_2**); 4.52 (1H, d, *J*= 15.1 Hz, **CH_2**); 4.20 (1H, d, *J*= 15.1 Hz, **CH_2**); 3.76 – 3.70 (3H, m, **$CHCH_2$**); 2.56 (1H, br s, **OH**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 164.2 (C), 154.8 (C), 136.3 (C), 134.8 (C), 129.1 (CH x 2), 128.8 (CH x 2), 128.3 (CH), 128.2 (CH), 60.5 (CH), 60.1 (CH_2), 53.3 (CH_2), 49.2 (CH_2) ppm.

LRMS (ES^+): *m/z* 348 ([M + Na^+], 50%), 326 ([M + H^+], 100%).

(*S*)-2-(3-Bromobenzyl)-5-isobutyl-1,2,4-triazine-3,6-dione (1.127)



Method: 120 °C, methanol, 30 minutes.

Title compound isolated as a white solid (2 mg, 4%).

$[\alpha]_D$ – 23.5 (*c* 0.2, MeOH, 26 °C).

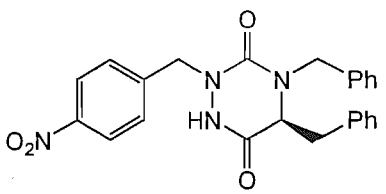
IR: 3200 (w), 2956 (w), 2926 (w), 1652 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (1H, br s, NH); 7.51 – 7.45 (1H, m, ArH); 7.29 – 7.21 (3H, m, ArH); 5.47 (1H, br s, NH); 4.75 (1H, d, *J*= 15.1 Hz, CH_2); 4.61 (1H, d, *J*= 15.1 Hz, CH_2); 3.86 – 3.82 (1H, m, CH); 1.76 – 1.42 (3H, m, CH_2CH); 0.97 (3H, d, *J*= 6.5 Hz, CH_3); 0.91 (3H, d, *J*= 6.5 Hz, CH_3) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.6 (C), 154.4 (C), 138.5 (C), 131.8 (CH), 131.7 (CH), 130.6 (CH), 127.3 (CH), 123.1 (C), 53.2 (CH), 50.2 (CH_2), 40.5 (CH_2), 24.3 (CH), 23.1 (CH_3), 21.6 (CH_3) ppm.

LRMS (ES^+): *m/z* 364 and 362 ([M + Na^+], 1:1 ratio, 30%), 352 (100%), 342 and 340 ([M + H^+], 1:1 ratio, 90%).

(*S*)-2-(4-Nitrobenzyl)-4,5-dibenzyl-1,2,4-triazine-3,6-dione (1.128)



Method: 120 °C, methanol, 30 minutes.

Title compound isolated as a clear colourless oil (13 mg, 38%).

$[\alpha]_D$ – 105.6 (*c* 0.7, MeOH, 23 °C).

IR: 3129 (w), 2996 (w), 2943 (w), 1687 (s), 1617 (s) cm^{-1}.

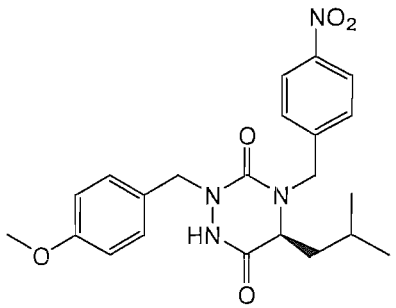
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (1H, br s, NH); 8.13 – 8.10 (2H, m, ArH); 7.36 – 7.07 (12H, m, ArH); 5.11 (1H, d, *J*= 15.4 Hz, CH_2); 4.52 (1H, d, *J*= 15.4 Hz, CH_2);

3.97 – 3.86 (3H, m, **CH** & **CH$_2$**); 2.96 (1H, dd, *J*= 13.9, 5.1 Hz, **CH$_2$**); 2.85 (1H, dd, *J*= 13.9, 5.5 Hz, **CH$_2$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 164.7 (**C**), 153.4 (**C**), 148.7 (**C**), 142.8 (**C**), 135.9 (**C**), 135.1 (**C**), 129.9 (**CH**), 129.3 (**CH**), 129.1 (**CH**), 129.0 (**CH**), 128.4 (**CH** x 2), 127.7 (**CH**), 124.0 (**CH**), 60.0 (**CH**), 51.2 (**CH$_2$**), 49.4 (**CH$_2$**), 35.9 (**CH$_2$**) ppm.

LRMS (ES^+): *m/z* 883 ([2M + Na^+], 10%), 431 ([M + H^+], 100%).

(*S*)-2-(4-Methoxybenzyl)-4-(4-nitrobenzyl)-5-isobutyl-1,2,4-triazine-3,6-dione (1.129)



Method: 120 °C, methanol, 1 hour.

Title compound isolated as a white crystalline solid (71 mg, 66%).

Mp 128 °C (Ethyl acetate/hexane).

[α]$_D$ 10.4 (*c* 0.4, $CDCl_3$, 26 °C).

IR: 3241 (w), 2956 (w), 2930 (w), 1697 (s), 1657 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 – 8.20 (2H, m, **ArH**); 7.47 – 7.45 (2H, m, **ArH**); 7.28 – 7.26 (2H, m, **ArH**); 6.89 – 6.87 (2H, m, **ArH**); 5.09 (1H, d, *J*= 15.6 Hz, **CH$_2$**); 4.70 (1H, d, *J*= 15.1 Hz, **CH$_2$**); 4.64 (1H, d, *J*= 15.1 Hz, **CH$_2$**); 4.14 (1H, d, *J*= 15.6 Hz, **CH$_2$**); 3.81 (3H, s, **OCH$_3$**); 3.63 (1H, dd, *J*= 9.5, 5.5 Hz, **CH**); 1.39 – 1.24 (3H, m, **CH$_2$CH**); 0.86 (3H, d, *J*= 6.5 Hz, **CH$_3$**); 0.81 (3H, d, *J*= 6.5 Hz, **CH$_3$**) ppm.

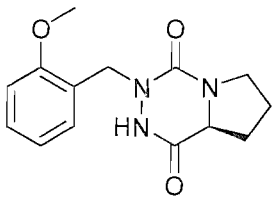
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.6 (**C**), 160.1 (**C**), 154.3 (**C**), 147.8 (**C**), 144.4 (**C**), 130.4 (**CH**), 128.7 (**CH**), 126.6 (**C**), 124.3 (**CH**), 114.6 (**CH**), 58.9 (**CH**), 55.5 (**CH$_3$**), 51.1 (**CH$_2$**), 49.3 (**CH$_2$**), 39.1 (**CH$_2$**), 24.7 (**CH**), 23.1 (**CH$_3$**), 22.0 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 875 ([2M + Na^+], 40%), 490 ([M + MeCN + Na^+], 20%), 449 ([M + Na^+], 100%).

Anal. Calcd for $C_{22}H_{26}N_4$: C, 61.97; H, 6.10; N, 13.14. Found: C, 61.66; H, 6.06; N, 12.99.

(*S*)-2-(2-Methoxybenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione

(1.130)



Method: 120 °C, methanol, 3 hours.

Title compound isolated as a clear colourless oil (20 mg, 20%).

$[\alpha]_D$ + 14.0 (*c* 0.5, MeOH, 27 °C).

IR: 3478 (w), 3355 (w), 2961 (w), 2895 (w), 1713 (s), 1644 (s) cm^{-1}.

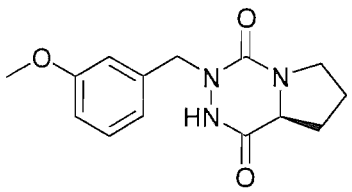
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (1H, br s, **NH**); 7.25 (1H, dd, *J*= 7.5, 1.5 Hz, **ArH**); 7.25 (1H, ddd, *J*= 8.0, 7.5, 2.0 Hz, **ArH**); 6.97 – 6.80 (2H, m, **ArH**); 4.66 (1H, d, *J*= 15.0 Hz, **CH_2**); 4.59 (1H, d, *J*= 15.0 Hz, **CH_2**); 3.90 – 3.75 (4H, m, **CH** & **OCH_3**); 3.46 – 3.41 (2H, m, **CH_2**); 2.28 – 1.99 (2H, m, **CH_2**); 1.94 – 1.75 (2H, m, **CH_2**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 164.4 (**C**), 156.2 (**C**), 153.2 (**C**), 131.4 (**CH**), 129.0 (**CH**), 122.7 (**C**), 120.6 (**CH**), 109.7 (**CH**), 56.7 (**CH**), 54.8 (**CH_3**), 44.3 (**CH_2**), 44.2 (**CH_2**), 26.0 (**CH_2**), 22.3 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 848 ([3M + Na^+], 25%), 573 ([2M + Na^+], 60%), 551 ([2M + H^+], 30%), 276 ([M + H^+], 60%), 130 (100%).

(*S*)-2-(3-Methoxybenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione

(1.131)



Method: 120 °C, methanol, 1.5 hours.

Title compound isolated as a white crystalline solid (50 mg, 50%).

Mp 170 – 171 °C (Ethyl acetate/hexane).

$[\alpha]_D$ – 25.4 (*c* 0.5, $CDCl_3$, 27 °C).

IR: 2988 (w), 2914 (w), 1684 (s), 1631 (s) cm^{-1}.

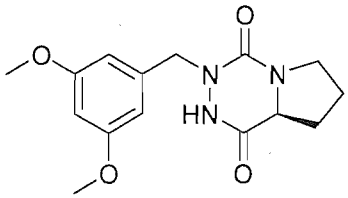
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (1H, br s, **NH**); 7.28 – 7.23 (1H, m, **ArH**); 6.93 – 6.83 (3H, m, **ArH**); 4.66 (2H, s, **CH_2**); 3.89 (1H, t, *J*= 8.0 Hz, **CH**); 3.79 (3H, s,

OC<u>H</u>$_3$); 3.54 (2H, t, *J*= 7.0 Hz, **C<u>H</u>$_2$**); 2.27 – 2.10 (2H, m, **C<u>H</u>$_2$**); 2.05 – 1.85 (2H, m, **C<u>H</u>$_2$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.4 (**<u>C</u>**), 160.1 (**<u>C</u>**), 154.3 (**<u>C</u>**), 136.7 (**<u>C</u>**), 129.9 (**<u>C</u>H**), 120.8 (**<u>C</u>**), 114.2 (**<u>C</u>H**), 113.8 (**<u>C</u>H**), 57.7 (**<u>C</u>H**), 55.3 (**<u>C</u>H$_3$**), 50.6 (**<u>C</u>H$_2$**), 45.3 (**<u>C</u>H$_2$**), 26.8 (**<u>C</u>H$_2$**), 23.4 (**<u>C</u>H$_2$**) ppm.

LRMS (ES^+): *m/z* 192 ([M + 2MeOH + $2Na^+$], 100%).

(*S*)-2-(3,5-Dimethoxybenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.132)



Method: 120 °C, methanol, 1.5 hours.

Title compound isolated as a clear colourless oil (69 mg, 66%).

[α]$_D$ – 9.22 (*c* 1.6, MeOH, 27 °C).

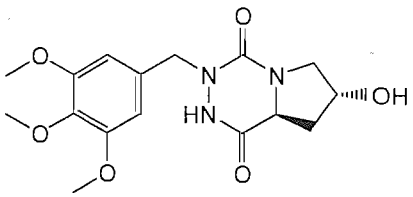
IR: 2949 (w), 2837 (w), 1646 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (1H, br s, **N<u>H</u>**); 6.50 (2H, d, *J*= 2.1 Hz, **Ar<u>H</u>**); 6.39 (1H, t, *J*= 2.1 Hz, **Ar<u>H</u>**); 4.64 (1H, d, *J*= 15.4 Hz, **C<u>H</u>$_2$**); 4.59 (1H, d, *J*= 15.4 Hz, **C<u>H</u>$_2$**); 3.91 (1H, t, *J*= 8.0 Hz, **C<u>H</u>**); 3.77 (6H, s, **OC<u>H</u>$_3$**); 3.54 (2H, t, *J*= 7.0 Hz, **C<u>H</u>$_2$**); 2.28 – 2.09 (2H, m, **C<u>H</u>$_2$**); 2.04 – 1.85 (2H, m, **C<u>H</u>$_2$**) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.3 (**<u>C</u>**), 161.2 (**<u>C</u>**), 154.2 (**<u>C</u>**), 136.6 (**<u>C</u>**), 106.5 (**<u>C</u>H**), 100.0 (**<u>C</u>H**), 57.7 (**<u>C</u>H**), 55.3 (**<u>C</u>H$_3$**), 50.6 (**<u>C</u>H$_2$**), 45.2 (**<u>C</u>H$_2$**), 26.8 (**<u>C</u>H$_2$**), 23.3 (**<u>C</u>H$_2$**) ppm.

LRMS (ES^+): *m/z* 633 ([2M + Na^+], 20%), 611 ([2M + H^+], 30%), 306 ([M + H^+], 100%).

(6*R*, 8*S*)-2-(3,4,5-Trimethoxybenzyl)-hexahydro-6-hydroxypyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.133)



Method: 120 °C, methanol, 1.5 hours.

Title compound isolated as clear colourless oil (46 mg, 63%).

$[\alpha]_D$ – 87.5 (*c* 0.1, $CDCl_3$, 23 °C).

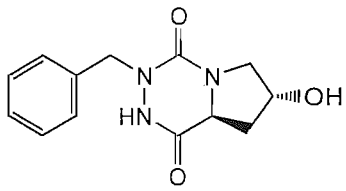
IR: 3403 (w), 2942 (w), 2836 (w), 1651 (s), 1593 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (2H, s, **Ar**<u>**H**</u>); 4.81 (1H, d, *J*= 15.1 Hz, **C**<u>**H**</u>$_2$); 4.59 (1H, t, *J*= 4.5 Hz, **C**<u>**H**</u>); 4.43 (1H, d, *J*= 15.1 Hz, **C**<u>**H**</u>$_2$); 4.30 – 4.26 (1H, m, **C**<u>**H**</u>); 3.85 (9H, s, **C**<u>**H**</u>$_3$); 3.72 – 3.71 (1H, m, **C**<u>**H**</u>$_2$); 3.63 – 3.60 (1H, m, **C**<u>**H**</u>$_2$); 2.35 – 2.23 (1H, m, **C**<u>**H**</u>$_2$); 2.23 – 2.11 (1H, m, **C**<u>**H**</u>$_2$); 1.25 (1H, s, **O**<u>**H**</u>) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.6 (<u>**C**</u>), 153.7 (<u>**C**</u>), 138.2 (<u>**C**</u>), 130.4 (<u>**C**</u>), 115.1 (<u>**C**</u>), 105.9 (<u>**C**</u>**H**), 69.4 (<u>**C**</u>**H**), 60.8 (<u>**C**</u>**H**$_3$), 56.8 (<u>**C**</u>**H**), 56.2 (<u>**C**</u>**H**$_3$), 54.0 (<u>**C**</u>**H**$_2$), 51.2 (<u>**C**</u>**H**$_2$), 36.5 (<u>**C**</u>**H**$_2$) ppm.

LRMS (ES^+): *m/z* 725 ([2M + Na^+], 30%), 703 ([2M + H^+], 20%), 374 ([M + Na^+], 90%), 352 ([M + H^+], 100%).

(6*R*, 8*S*)-2-Benzyl-hexahydro-6-hydroxypyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.134)



Method: 120 °C, methanol, 1.5 hours.

Title compound isolated as a colourless crystalline solid (39 mg, 44%).

Mp 126 – 128 °C (Ethyl acetate/hexane).

$[\alpha]_D$ – 48.8 (*c* 0.4, $CDCl_3$, 28 °C).

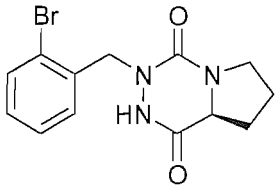
IR: 3375 (w), 3135 (w), 2924 (w), 1640 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 – 7.27 (5H, m, **Ar**<u>**H**</u>); 4.83 (1H, d, *J*= 15.0 Hz, **C**<u>**H**</u>$_2$); 4.65 – 4.51 (1H, m, **C**<u>**H**</u> & **C**<u>**H**</u>$_2$); 4.27 (1H, dd, *J*= 10.6, 7.0 Hz, **C**<u>**H**</u>); 3.72 (1H, dd, *J*= 12.1, 4.4 Hz, **C**<u>**H**</u>$_2$); 3.62 (1H, dd, *J*= 12.1, 2.9 Hz, **C**<u>**H**</u>$_2$); 2.36 – 2.06 (2H, m, **C**<u>**H**</u>$_2$); 1.88 (1H, br s) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.6 (**C**), 154.2 (**C**), 134.9 (**C**), 129.0 (**C**H), 128.5 (**C**H x 2), 69.4 (**C**H), 56.4 (**C**H), 54.1 (**C**H_2), 50.7 (**C**H_2), 36.5 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 604 ([2M + 2MeOH + NH_4^+], 30%), 316 ([M + MeOH + Na^+], 70%), 262 ([M + H^+], 20%), 170 (100%).

(*S*)-2-(2-Bromobenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.135)



Method: 120 °C, methanol, 35 minutes.

Title compound isolated as a white solid (16 mg, 65%).

[α]$_D$ – 33.2 (*c* 0.5, $CDCl_3$, 26 °C).

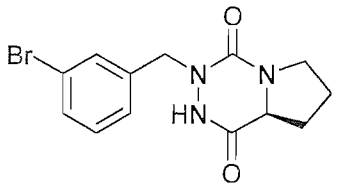
IR: 3160 (m), 1640 (s), 1433 (s), 1342 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (1H, br s, **NH**); 7.59 (1H, dd, *J*= 7.6, 1.0 Hz, **ArH**); 7.39 (1H, dd, *J*= 7.6, 1.6 Hz, **ArH**); 7.20 (1H, td, *J*= 7.6, 1.0, **ArH**); 7.10 (1H, td, *J*= 7.6, 1.6 Hz, **ArH**); 5.01 (1H, d, *J*= 15.7 Hz, **C**H_2); 4.69 (1H, d, *J*= 15.7 Hz, **C**H_2); 3.97 (1H, t, *J*= 7.7 Hz, **C**H); 3.56 (2H, t, *J*= 6.2 Hz, **C**H_2); 2.17 – 2.10 (2H, m, **C**H_2); 2.10 – 1.86 (2H, m, **C**H_2) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 166.4 (**C**), 154.2 (**C**), 134.8 (**C**), 133.2 (**C**H), 130.3 (**C**H), 129.8 (**C**H), 127.9 (**C**H), 123.9 (**C**), 57.7 (**C**H), 50.4 (**C**H_2), 45.3 (**C**H_2), 26.7 (**C**H_2), 23.4 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 673, 671, 669 ([2M + Na^+], 1:2:1 ratio, 25%), 389, 387 ([M + MeCN + Na^+], 1:1 ratio, 35%), 348, 346 ([M + Na^+], 1:1 ratio, 100%).

(*S*)-2-(3-Bromobenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.136)



Method: 140 °C, methanol, 40 minutes.

Title compound isolated as a white crystalline solid (50 mg, 50%).

Mp 236 – 236 °C (Methanol).

[α]$_D$ – 6.0 (*c* 0.5, DMSO, 26 °C).

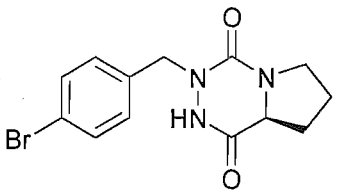
IR: 3109 (m), 1690 (s), 1626 (s), 1415 (s) cm^{-1}.

^{1}**H NMR** (400 MHz, DMSO-d_6): δ 10.75 (1H, br s, **NH**); 7.80 (2H, m, **ArH**); 7.64 (2H, m, **ArH**); 5.19 (1H, d, *J*= 16.6 Hz, **CH$_2$**); 4.61 (1H, d, *J*= 16.6 Hz, **CH$_2$**); 4.38 (2H, m, **CH$_2$**); 4.28 (1H, t, *J*= 7.8 Hz, **CH**); 2.44 – 2.14 (4H, m, **CH$_2$**) ppm.

^{13}**C NMR + DEPT** (100 MHz, DMSO-d_6): δ 203.8 (**C**), 181.2 (**C**), 137.8 (**C**), 134.2 (**CH**), 130.8 (**CH**), 130.6 (**CH**), 126.9 (**CH**), 121.6 (**C**), 59.8 (**CH**), 48.8 (**CH$_2$**), 44.9 (**CH$_2$**), 28.9 (**CH$_2$**), 22.9 (**CH$_2$**) ppm.

LRMS (ES$^+$): *m/z* 673, 671, 669 ([2M + Na$^+$], 1:2:1 ratio, 5%), 466 (system impurity, 100%), 348, 346 ([M + Na$^+$], 1:1 ratio, 10%).

(*S*)-2-(4-Bromobenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.137)



Method: 160 °C, acetonitrile, 30 minutes.

Title compound isolated as a white solid (14 mg, 19%).

[α]$_D$ 50.5 (*c* 0.5, DMSO, 26 °C).

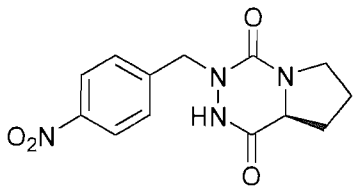
IR: 3398 (m), 1645 (s), 1435 (s), 1345 (s) cm^{-1}.

^{1}**H NMR** (400 MHz, DMSO-d_6): δ 10.43 (1H, br s, **NH**); 7.53 (2H, d, *J*= 8.4 Hz, **ArH**); 7.23 (2H, d, *J*= 8.4 Hz, **ArH**); 4.86 (1H, d, *J*= 15.3 Hz, **CH$_2$**); 4.23 (1H, d, *J*= 15.3 Hz, **CH$_2$**); 3.93 (1H, t, *J*= 7.9 Hz, **CH**); 3.39 – 3.34 (2H, m, **CH$_2$**); 2.07 – 1.86 (4H, m, 2 x **CH$_2$**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6): δ 166.2 (**C**), 154.7 (**C**), 147.3 (**C**), 145.8 (**C**), 129.1 (**CH**), 123.9 (**CH**), 57.6 (**CH**), 49.0 (**CH_2**), 45.2 (**CH_2**), 27.2 (**CH_2**), 23.2 (**CH_2**) ppm.

LRMS (ES^-): *m/z* 324, 322 ([M + H^+], 1:1 ratio, 100%).

(*S*)-2-(4-Nitrobenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.138)



Method: 170 °C, acetonitrile, 30 minutes.

Title compound isolated as a white crystalline solid (14 mg, 21%).

Mp 200 °C (MeCN).

[α]$_D$ – 6.0 (*c* 0.5, DMSO, 26 °C).

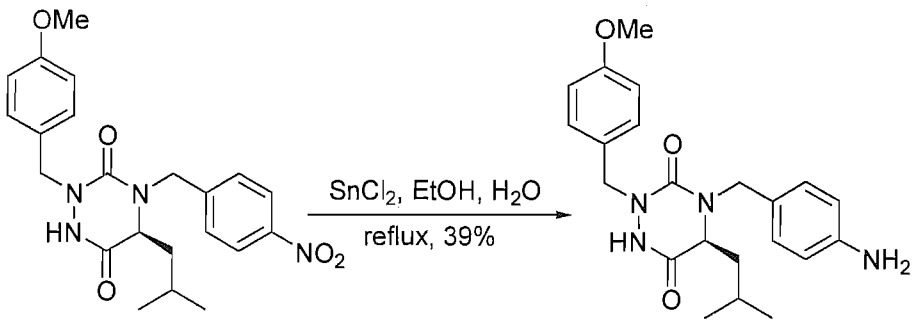
IR: 3097 (m), 1688 (s), 1629 (s), 1515 (s), 1403 (s) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (1H, br s, **NH**); 8.21 (2H, d, *J*= 8.8 Hz, **ArH**); 7.57 (2H, d, *J*= 8.8 Hz, **ArH**); 5.01 (1H, d, *J*= 16.5 Hz, **CH_2**); 4.44 (1H, d, *J*= 16.5 Hz, **CH_2**); 4.03 (1H, t, *J*= 7.3 Hz, **CH**); 3.40 – 3.36 (2H, m, **CH_2**); 2.11 – 1.85 (4H, m, 2 x **CH_2**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6): δ 170.6 (**C**), 162.1 (**C**), 157.9 (**C**), 152.1 (**C**), 134.0 (**CH**), 128.8 (**CH**), 54.3 (**CH**), 53.9 (**CH_2**), 50.1 (**CH_2**), 31.9 (**CH_2**), 28.0 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 291 ([M + H^+], 10%), 130 (100%).

(*S*)-4-(4-Aminobenzyl)-5-isobutyl-2-(4-methoxybenzyl)-1,2,4-triazine-3,6-dione (1.140)



Triazinedione **1.129** (1.0 equiv., 0.12 mmol, 0.05 g) was added to 5 mL of ethanol and the stirring mixture was warmed until the solid dissolved. Tin (II) chloride (5.0

equiv., 0.59 mmol, 0.11 g) was added to the reaction mixture with 2 drops of water. The reaction mixture was then refluxed for 80 minutes. The clear yellow solution was allowed to cool to room temperature and the solvent removed *in vacuo*. Ethyl acetate (10 mL) and water (10 mL) were added to the residue. The aqueous was then extracted with ethyl acetate (3 x 10 mL), the combined organics were washed with 2N $NaOH_{(Aq.)}$ (10 mL) and brine (10 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated to give the crude product. The product was purified by column chromatography (100% ethyl acetate to 1:9:90 NEt_3/methanol/ethyl acetate) to give **1.140** as a clear colourless oil (18 mg, 39%).

[α]$_D$ 4.6 (*c* 1.3, $CHCl_3$, 26 °C).

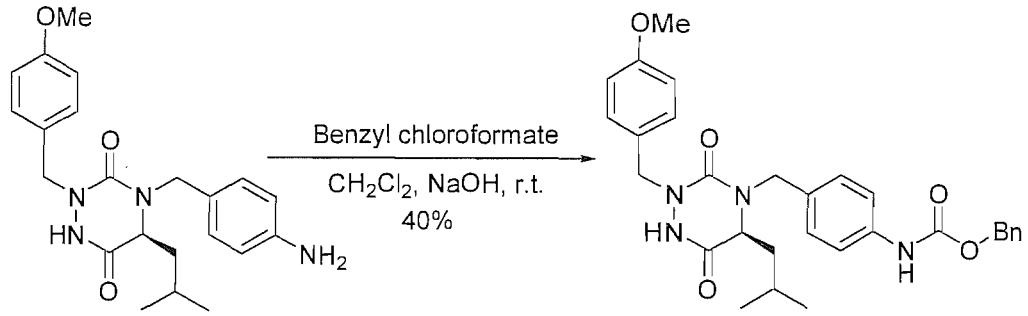
IR: 3445 (m), 3354 (m), 3223 (m), 2956 (w), 1683 (m), 1628 (s), 1611 (s), 1512 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (2H, d, *J*= 8.5 Hz, **ArH**); 7.05 (2H, d, *J*= 8.5 Hz, **ArH**); 6.84 (2H, d, *J*= 8.5 Hz, **ArH**); 6.63 (2H, d, *J*= 8.5 Hz, **ArH**); 4.88 (1H, d, *J*= 14.6 Hz, **CH$_2$**); 4.81 (1H, dd, *J*= 14.9, 2.8 Hz, **CH$_2$**); 4.45 (1H, dd, *J*= 14.9, 2.8 Hz, **CH$_2$**); 3.93 (1H, d, *J*= 14.6 Hz, **CH$_2$**); 3.79 (3H, s, **OCH$_3$**); 3.60 (1H, t, *J*= 7.5 Hz, **CH**); 1.54 (1H, m, **CH**); 1.26 – 1.18 (2H, m, **CH$_2$**); 0.81 (3H, d, *J*= 6.5 Hz, **CH$_3$**); 0.76 (3H, d, *J*= 6.5 Hz, **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.3 (**C**), 159.9 (**C**), 154.4 (**C**) 146.3 (**C**), 130.4 (**CH**), 129.8 (**CH**), 127.3 (**C**), 126.1 (**C**), 115.5 (**CH**), 114.4 (**CH**), 56.9 (**CH**), 55.4 (**CH$_3$**), 51.0 (**CH$_2$**), 49.0 (**CH$_2$**), 38.9 (**CH$_2$**), 24.6 (**CH**), 23.2 (**CH$_3$**), 22.0 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 815 ([2M + Na^+], 100%), 793 ([2M + H^+], 20%), 479 ([M + 2MeCN + H^+], 40%), 419 ([M + Na^+], 25%).

Benzyl 4-(((*S*)-2-(4-methoxybenzyl)-5-isobutyl-3,6-dioxo-1,2,4-triazin-4-yl)methyl)phenylcarbamate (1.141)



1.140 **1.141**

Benzyl chloroformate (1.0 equiv., 0.09 mmol, 13 µL) was added to a mixture of triazinedione **1.140** in dichloromethane (2 mL) and 2N NaOH (2 mL). The reaction mixture was stirred at room temperature for 3 h. The aqueous layer was then separated and extracted with dichloromethane (2 x 5 mL), the combined organics were washed with brine (10 mL), dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The crude product was purified by column chromatography (50% ethyl acetate/hexane to 100% ethyl acetate) to give **1.141** as a clear colourless oil (19 mg, 40%).

[α]$_D$ – 18.0 (*c* 0.2, MeOH, 2 °C).

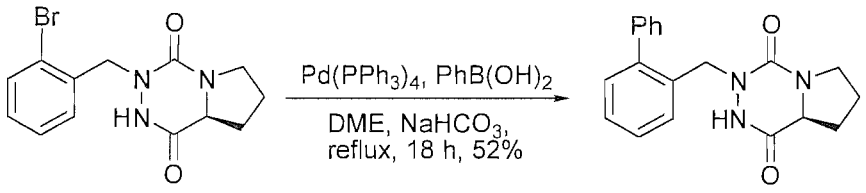
IR: 3271 (m), 2957 (m), 2923 (m), 1683 (m), 1645 (s), 1613 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (1H, br s, **NH**); 7.51 – 7.04 (10H, m, **ArH**); 6.95 – 6.63 (3H, m, **ArH**); 5.20 (2H, s, **CH_2**); 4.94 (1H, d, *J*= 15.1 Hz, **CH_2**); 4.68 (1H, d, *J*= 14.8 Hz, **CH_2**); 4.63 (1H, d, *J*= 14.8 Hz, **CH_2**); 4.01 (1H, d, *J*= 15.1 Hz, **CH_2**); 3.80 (3H, s, **OCH_3**); 3.61 (1H, dd, *J*= 9.5, 6.0 Hz, **CH**); 1.66 – 1.48 (1H, m, **CH**); 1.37 – 1.15 (2H, m, **CH_2**); 0.83 (3H, d, *J*= 6.5 Hz, **CH_3**); 0.79 (3H, d, *J*= 6.5 Hz, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 165.8 (**C**), 159.9 (**C**), 154.4 (**C**) 137.6 (**C**), 136.0 (**C**), 131.5 (**C**), 130.3 (**CH**), 129.0 (**CH**), 128.7 (**CH**), 128.4 (**CH**), 128.3 (**CH**), 126.7 (**C**), 124.0 (**C**), 119.4 (**CH**), 114.4 (**CH**), 67.1 (**CH_2**), 57.5 (**CH**), 55.3 (**CH_3**), 51.0 (**CH_2**), 49.0 (**CH_2**), 38.8 (**CH_2**), 24.6 (**CH**), 23.0 (**CH_3**), 21.9 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 553 ([M + Na^+], 100%), 531 ([M + H^+], 30%).

(*S*)-2-(2-Phenylbenzyl)-hexahydropyrrolo[1,2-*d*]-1,2,4-triazine-3,6-dione (1.143)



1.135 **1.143**

A solution of triphenylphosphine palladium (0) (10.0 mg, 8.70 µmol, 0.03 equiv.,) in DME (2 mL) was added to a solution of 1,2,4-triazine-3,6-dione **1.135** (97.5 mg, 0.302 mmol, 1.00 equiv.) in DME (1 mL). The solution became a dark red colour on addition. A solution of phenyl boronic acid (58.0 mg, 0.475 mmol, 1.50 equiv.) dissolved in the minimum volume of ethanol was added to the reaction mixture, followed by an aqueous solution of sodium hydrogen carbonate (2 M, 0.3 mL). The red reaction mixture became a yellow solution with a white precipitation, this was then heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature and filtered. The filtrate was concentrated *in vacuo* and the residue was redissolved in dichloromethane (10 mL). The organic layer was washed with water (2 x 20 mL) and then brine (20 mL). The organic layer was then dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* The crude product was purified by column chromatography (10 – 100% ethyl acetate/ hexane). The product **1.143** was isolated as a white foam (50.1 mg, 52%).

$[\alpha]_D$ – 33.6 (*c* 0.5, $CDCl_3$, 24 °C).

IR: 3073 (m), 1644 (s), 1513 (s), 1414 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.07 (1H, br s, **NH**); 7.55 – 7.14 (9H, m, **ArH**); 5.07 (1H, d, *J*= 16.4 Hz, **CH_2**); 4.53 (1H, d, *J*= 16.4 Hz, **CH_2**); 3.92 (1H, t, *J*= 7.7 Hz, **CH**); 3.53 (2H, t, *J*= 7.7 Hz, **CH_2**); 2.08 – 2.22 (2H, m, **CH_2**); 2.01 – 1.87 (2H, m, **CH_2**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 166.4 (**C**), 154.1 (**C**), 134.8 (**C**), 133.1 (**CH**), 132.2 (**CH**), 132.0 (**C**), 130.0 (**CH**), 129.5 (**CH**), 128.6 (**CH**), 128.4 (**CH**), 127.7 (**CH**), 123.7 (**C**), 57.7 (**CH**), 50.3 (**CH_2**), 45.3 (**CH_2**), 26.7 (**CH_2**), 23.4 (**CH_2**) ppm.

1.5.0 REFERENCES

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Chapter Two

Structure-Based Design and Synthesis of HIV-1 Protease Inhibitors

2.1.0 INTRODUCTION

2.1.1 AIDS/HIV

In 2006, according to the World Health Organisation, 39.5 million people were living with HIV. This number is approximately 1% of the total adult world population, and is 2.6 million more than in 2004. This increase is most striking in Eastern Europe and Central Asia where infection rates have increased by more than 50% in the last two years. Of those infected with HIV the vast majority will progress to AIDS within 8-13 years of first infection. AIDS is, at present, universally fatal causing 3 million deaths in 2006 alone.[1]

In the response to the HIV/AIDS epidemic the use of antiretroviral treatment is of vital importance. Antiretroviral (ARV) drugs can greatly improve the patient's long-term prognosis; the increase of ARV therapy from 7 to 24% between 2003 and 2006 in low and middle income countries is estimated to have gained 2 million life years for HIV patients.[1] This not only reduces unnecessary suffering, but also allows HIV infected people to continue to work, support their families and reduces discrimination against HIV infected people. Treatment strategies have been shown to greatly improve the success of prevention and education programs.[2] ARV therapy also reduces the number of people with HIV related diseases; of particular importance is the build up of drug-resistant strains of tuberculosis in untreated AIDS patients causing serious disease in those unaffected by HIV.[3]

i) What are AIDS and HIV?

AIDS, or acquired immunodeficiency syndrome, is the end-stage disease manifestation of infection with the human immunodeficiency virus or HIV.[3] The virus attacks both the immune system and the central nervous system (CNS); AIDS is the consequence of the resulting damage. The HIV virus infects two cell types in the immune system; the T-helper or CD4 lymphocytes, which are destroyed in large numbers by HIV; and the monocytes and macrophages in which the HIV virus replicates in great numbers. The loss of the CD4 lymphocytes results in severe immunosuppression with two consequences: the direct effects are

profound weight loss, chronic diarrhoea and pyrexia (elevated body temperature); the indirect effects are due to opportunistic infection from micro-organisms and growth of malignant tumours, and these effects are usually the cause of death.[3] Viral damage to the CNS causes destruction of neurones in the brain and spinal cord resulting in dementia and paralysis.[3]

The HIV virus is one of a family of RNA viruses known as the retroviruses. These viruses have the unique enzyme reverse transcriptase, responsible for DNA replication from the viral RNA. Surrounding the two strands of RNA and reverse transcriptase is the inner core or capsid of the virus, the viral envelope encases this core and has two viral proteins studding the outside of this outer layer that initially attaches the virus to its host cell. The genome of HIV-1 consists of three main genes that code for a) the inner proteins – the *gag* gene, b) the virus enzymes – the *pol* gene and c) the envelope proteins – the *env* gene. In addition HIV-1 has a number of regulatory genes.[3, 4]

There are several stages in the HIV-1 virus's replication cycle where antiretroviral drugs can halt the process and thereby reduce the viral load.[3, 4] The first stage of the virus replication is the attachment of the proteins on the outside of the viral envelope to the CD4 receptor site, the envelope then fuses to the cell membrane, a process that can be inhibited by fusion inhibitors. After this, the capsid enters the host cell and uncoats to release the viral RNA and reverse transcriptase. The viral RNA must then be reverse transcribed into proviral DNA before being integrated into the host's DNA. The enzyme that carries out the DNA polymerisation can be inhibited either directly, using non-nucleoside RT inhibitors, or by halting the polymerisation using a drug that mimics a natural nucleoside and thereby gets incorporated into the DNA strand. In the next stage, proviral DNA is transcribed to give viral and messenger RNA. This messenger RNA then directs the manufacture of proteins using the host cells ribosomes. These proteins are broken down into the required viral proteins by a viral protease enzyme, which can also be inhibited using antiviral drugs. After some minor additional processes the viral proteins are functional and the new viral particle is released from the host cell by budding through the cell membrane.

ii) Current drugs used in the treatment of HIV/AIDS

Currently there are twenty six antiretroviral drugs for the treatment of HIV infected patients approved by the FDA (Food and Drug Administration).[5] These fall into three main classes:

- Reverse transcriptase (RT) inhibitors
  a) Nucleoside/nucleotide RT inhibitors *12 FDA approved drugs*
  b) Non-nucleoside RT inhibitors *3 FDA approved drugs*
- Protease Inhibitors *10 FDA approved drugs*
- Fusion inhibitors *1 FDA approved drug*

None of these drugs are a 'cure' for HIV; used correctly, however, they can effectively suppress the virus and reduce the rate of opportunistic infections.

The recommended drug regime for HIV infected patients is a combination from at least two different classes of the above drugs taken every day for the remainder of the patient's life.[3, 5] This cocktail of medication (known as Highly Active Antiretroviral Therapy or HAART) has been shown to reduce co-infection from other micro-organisms, such as hepatitis C virus a common co-infection that can lead to liver cancer.[3] Since drug-resistant strains of HIV-1 are seen to rapidly emerge when only one drug is used, HAART is also an effective way of reducing drug resistance.[3, 5, 6]

Unfortunately, this complex drug regimen often has low adherence among HIV patients as the different drugs often require repeated dosing, fasting and cause unpleasant side-effects such as vomiting and diarrhoea. In addition, these drugs can have much more serious side effects including metabolic change, bone loss, build up of acid in the blood, allergic reaction and fatal organ damage.[3, 5]

The first FDA approved protease inhibitor of HIV-1 was Saquinavir, approved in 1996.[6, 7] Saquinavir has a low bioavailability due to poor absorption and first pass metabolism by cytochrome P450.[6] This degradation of Saquinavir and other protease inhibitors is usually countered by administering the drug in combination with Ritonavir an inhibitor of cytochrome P450 as well as a potent HIV-1 protease inhibitor in its own right. Since 1996 various protease inhibitors with improved bioavailability have been marketed.[5, 6] Amprenavir, for example, is a water-soluble

inhibitor with excellent bioavailability; in addition its long half-life means reduced side-effects and less frequent dosing. Viral resistance to these protease inhibitors, however, is commonly seen in both the clinic and laboratory. This resistance is usually due to amino acid substitutions in the protease, either in the active site or at residues important for binding the inhibitor. Since instances of viral resistance are reduced when more than one protease inhibitor is used, new HIV-1 protease inhibitors with different resistance-profiles are needed for continuously effective treatment. [3, 6, 7]

2.1.2 Protease Inhibitors[6]

There are four main classes of protease enzymes: aspartic, serine, cysteine and metallo, each of which selectively catalyses the hydrolysis of peptide bonds. Their resultant role in protein function and synthesis is vital in many physiological processes and in disease propagation. Inhibitors of protease enzymes are therefore important drug targets for treatment of diseases as diverse as cancer, viral infection, inflammatory and respiratory disease.[6]

For protease inhibitors to have therapeutic use they must not only be extremely potent but highly selective in binding to the targeted protease. In designing protease inhibitors information can be gained from looking at the structures of the peptides to which the proteases bind. Peptides, however, generally do not have good drug-like qualities, often having low bioavailability, poor pharmacological profiles and lacking stability. Traditionally, protease inhibitors have been developed from a natural product lead compound, reducing peptide nature and increasing potency through progressive structural changes. The availability of three-dimensional structural information for proteases in recent years, however, has improved drug-design through receptor based design.[6]

i) Aspartic Protease Inhibitors

Aspartic proteases generally bind between six to ten amino acid regions of their substrates, catalysing the hydrolysis of the substrate through two aspartic acid residues in the active site. This hydrolysis catalysed by the aspartic proteases is thought to go through the acid-base mechanism shown in figure 2.1.[8]

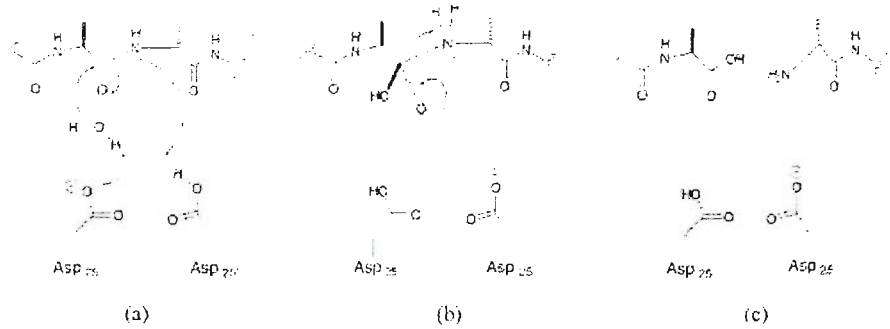


Figure 2.1: Catalytic mechanism for substrate hydrolysis by aspartic proteases. (a) Nucleophillic attack of an activated water molecule on the scissile bond and protonation of the amide nitrogen (b) give the zwitterionic intermediate (c) which collapses to the cleaved products.[8]

The ability of the aspartic proteases to bind this number of amino acid regions is important in designing inhibitors with high selectivity for the desired protease. Most aspartic protease inhibitors bind their target enzyme through non-covalent interactions. The greater the number of designed interactions between the inhibitor and the substrate binding groove, the greater the likely success of the inhibitor. Figure 2.2 shows the hydrogen-bonding between the HIV-1 aspartic protease and a selective inhibitor identified from its X-ray crystal structure.[6, 9, 10]

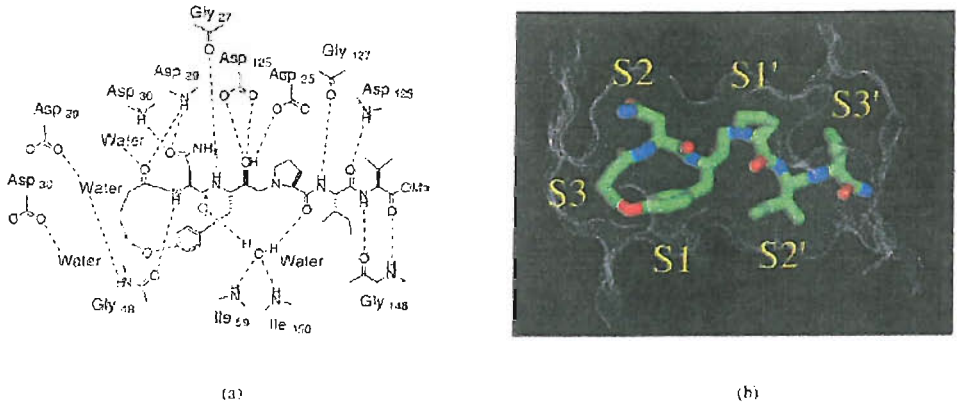


Figure 2.2: (a) Hydrogen-bonding interactions between an inhibitor and HIV-1 protease.[9] The hydroxyl of the hydroxyethylamine transition state isostere hydrogen-bonds with both catalytic aspartates. The water molecule that binds between the inhibitor and enzyme (Ile50 and Ile150) is thought to position the substrate in the active site and stretch the peptide bond, thereby activating it for hydrolysis.[6] (b) X-ray structure of the inhibitor bound in the HIV-1 protease. This view is from above, the hydroxyl that hydrogen-bonds with the aspartates points into the page.[10]

For an inhibitor to work well in vivo it must bind to the enzyme with a much higher affinity than the enzyme's natural substrate. Since the substrate is thought to be most strongly bound to the enzyme in its transition state, most designed protease inhibitors mimic this state. Defined as a functional group that mimics the

tetrahedral transition-state of amide bond hydrolysis but cannot itself be hydrolysed by the protease, these structures are known as transition-state isosteres.[6] There is a small range of commonly used structures for transition-state isosteres in the development of aspartic protease inhibitors.

2.1.3 Design and Synthesis of Inhibitors of HIV-1 Aspartic Protease

The protease of HIV-1 is an attractive target for drug design due to its vital role in the later stages of the virus's replication.[3, 6] The use of receptor based design has been important in this area, the drug Saquinavir was the first structure based designed protease inhibitor to be approved for human use.[6] Several protease inhibitors commonly used in treatment of HIV are shown in figure 2.3.[6, 11] The majority of the inhibitors developed to date are transition-state isosteres; three common core structural types for these isosteres can be seen in the six drugs shown in figure 2.3.

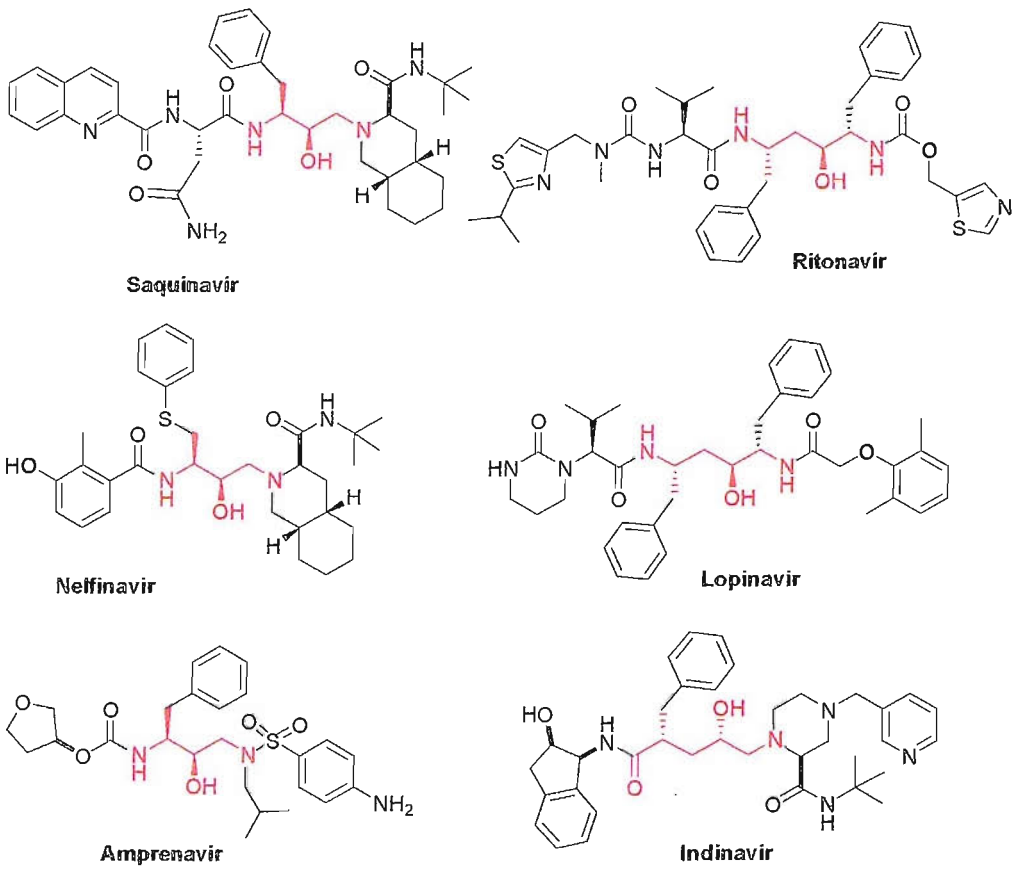


Figure 2.3: Six HIV-1 protease inhibitors used in treatment of HIV/AIDS. The highlighted red sections represent structures of common transition-state isosteres.[6, 11]

Recently, an Italian research group designed a series of peptidomimetic inhibitors of HIV-1 aspartic protease using structure based design methods.[12] Over a hundred compounds were modelled in the protease active site to give the most promising residues to go on either end of the transition-state isostere. Compounds with a dihydroxyethylene transition-state isostere core flanked by these residues were then analysed using a QSAR model to give an estimate of their potencies. The ADME properties of these compounds were also estimated and the compounds were ranked according to how effective an inhibitor they are likely to be in comparison to clinically used HIV-PR inhibitors. The most interesting inhibitor candidates have the general structure shown in figure 2.4.

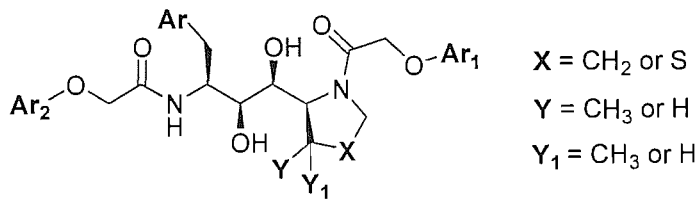
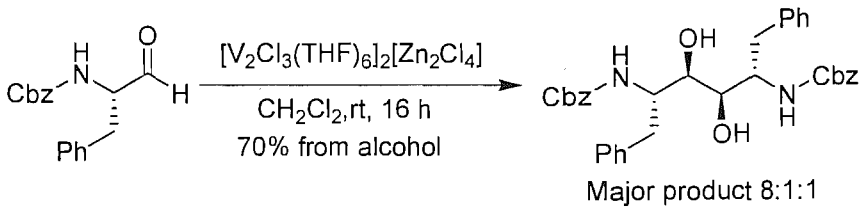


Figure 2.4: General structures of the ten most interesting designed inhibitors according to estimated potencies and ADME properties compared to FDA approved HIV-1 protease inhibitors.

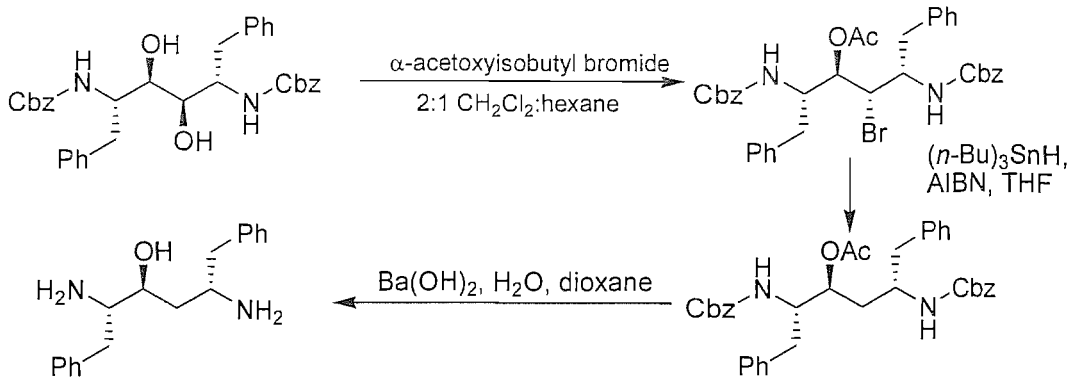
i) Previous Syntheses of Diaminodiol Dipeptide Isosteres

Several different approaches to the synthesis of C_2-symmetrical diaminodiol isosteres have been published. Earlier routes involved the pinacol-type coupling of α-aminoalkanals (Scheme 2.1).[13, 14]



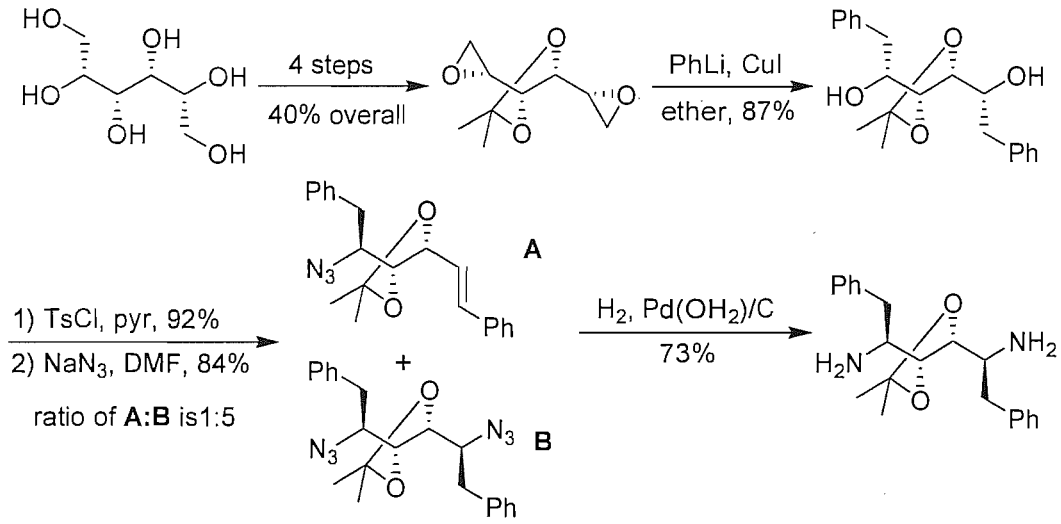
Scheme 2.1: Homocoupling of Cbz-L-phenylalaninal to give mixture; (3*S*,4*S*)-diol being the major product.[13]

This route to diaminodiols was used by Kempf *et al.* in the first synthesis of Ritonavir - the (3*S*,4*S*)-diol shown above was reacted with α-acetoxyisobutyryl bromide followed by radical displacement of the bromide and deprotection to give the core structure of Ritonavir (Scheme 2.2). [15]



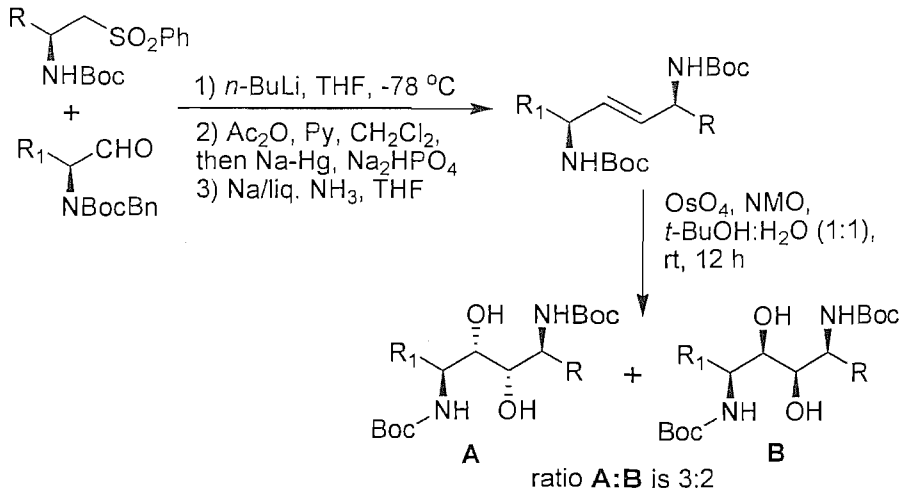
Scheme 2.2: First published synthesis of the HIV-1 protease inhibitor Ritonavir.[15]

Other syntheses of diaminodiols have made use of starting materials from the 'chiral pool' such as D-mannitol[16, 17] (Scheme 2.3) or D-tartrate.[18]



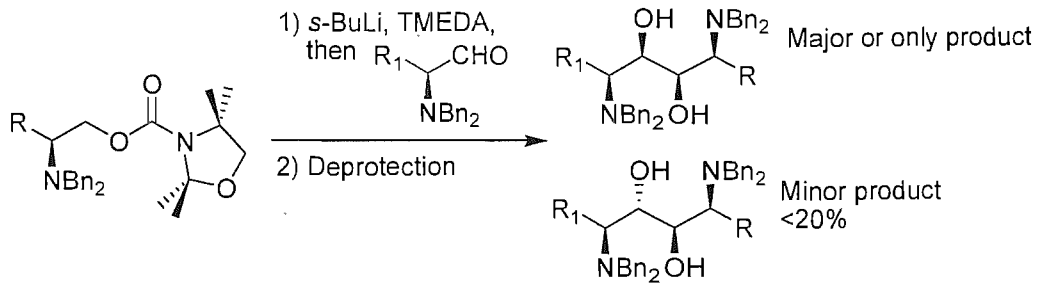
Scheme 2.3: General synthesis of diaminodiol core from D-mannitol.[17]

The nature of these syntheses means, however, that the diaminodiol core is completely symmetrical with both alkyl groups in this case being benzyl. More recently, published routes to the diaminodiol isostere allow the inclusion of non-identical alkyl groups. Work in this area published by Gurjar *et al.* makes use of Julia olefination as the key step (Scheme 2.4).[19]



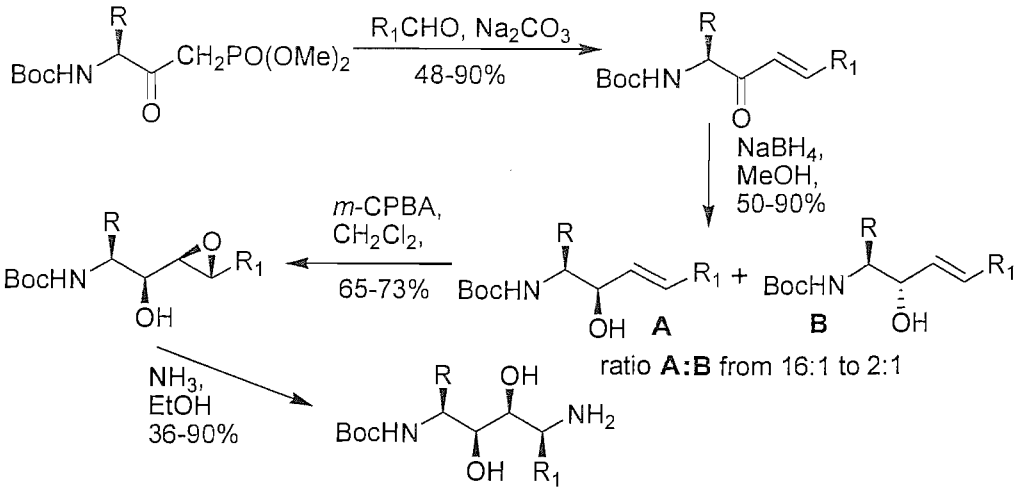
Scheme 2.4: Synthesis of diamiondiol core using Julia olefination followed by osmylation.[19]

Only two different R groups are described in this paper and although the stereoselectivity is poor, the two isomers are reported to be easily separated. A highly stereoselective synthesis of the diaminodiol core that also has a key coupling step was published by Hoppe *et al.* in 1999.[20] This method involves the deprotonation of carbamates derived from aminoalcohols with good diasteroselectivities before reaction with aminoaldehydes (Scheme 2.5).



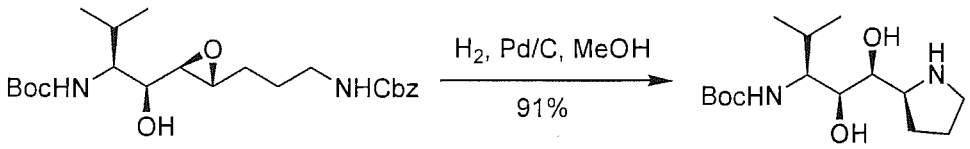
Scheme 2.5: Hoppe methodology to produce diaminodiol isostere.[20]

Although a small and diverse library of compounds were synthesised using this method, none of the alkyl groups were cyclic. An alternative synthesis that is much more linear in its design was published in 1997 (Scheme 2.6).[21, 22]



Scheme 2.6: Linear synthesis to diaminodiol dipeptide isostere published by Benedetti *et al.*[22]

More recently, this linear synthesis has been extended to allow the synthesis of proline-containing diaminodiol dipeptide isosteres.[7, 23] Reaction of the phosphonate with aldehyde methyl 4-formylbutanoate, followed by conversion of the ester group to a protected amine, allows a 5-exo ring opening of the epoxide to give the proline like ring (Scheme 2.7).



Scheme 2.7: Example of Val-Pro dipeptide isostere synthesis.[23]

ii) Proposed Retrosynthesis of Diaminodiol Dipeptide Isosteres

The aim of this project is to synthesise the protease inhibitor candidates proposed by the computer modelling work discussed above. Ideally we would like to make a small library of these compounds using combinatorial methods in order to compare actual biological activity with the predicted values. With this in mind, we required a convergent route with a key coupling step between the two main components to give the diol isostere (Figure 2.5).

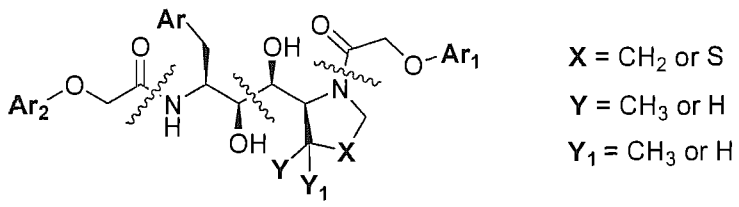
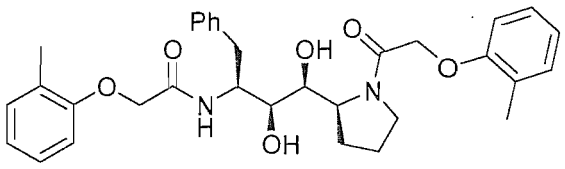


Figure 2.5: Proposed disconnections for the synthesis of the general target structure for proposed HIV-1 protease inhibitors.

We therefore propose to explore the scope of both the Julia olefination route (Scheme 2.4) and Hoppe's methodology (Scheme 2.5) for our own synthesis starting with the simplest of the diol isosteres shown in figure 2.6.



Target Molecule

Figure 2.6: Target molecule for establishing the most suitable convergent synthesis towards diamino diol isostere.

2.1.4 Conclusion

AIDS and HIV have unquestionably caused, and still cause, a huge amount of death and suffering across the globe. The end symptoms of this disease, combined with the fact that the infected can transmit the infection for the duration of their lifetime, have led to one of the greatest threats to mankind.

Although HIV/AIDS has been extensively studied since its discovery, there remains a continuing need for new therapies and a better understanding of the virus and its consequences. The emergence of drug-resistant strains of the virus along with the unpleasant side-effects and considerable expense of current drug therapies mean that there is a real need for new antiretroviral drugs. The use of HAART, particularly in the first world has made a huge improvement to the quality of life of infected patients. Protease inhibitors are an important part of this therapy and there is still a real need for new protease inhibitors to combat the drug-resistant strains of HIV. The amount that is known about the HIV-1 binding site for aspartic proteases and the various protease inhibitors already in use gives us considerable guidance when designing new potential inhibitors.

The proposed synthesis of the designed diol isosteres, illustrated in figure 2.4 is a new project in the search for new antiretroviral drugs. The use of a convergent synthetic route with a key coupling step could potentially provide a flexible combinatorial route to a small library of structurally significant inhibitor analogues.

2.2.0 Results and Discussion

2.2.1 Synthesis towards diol isostere utilising the Julia coupling reaction

i) The One-pot or Modified Julia reaction as the key coupling step[24, 25]

As discussed in the introduction, we wished to use Julia olefination as the key coupling step in the synthesis of our target molecule (shown in figure 2.6). With this in mind, the following retrosynthesis was proposed (figure 2.7).

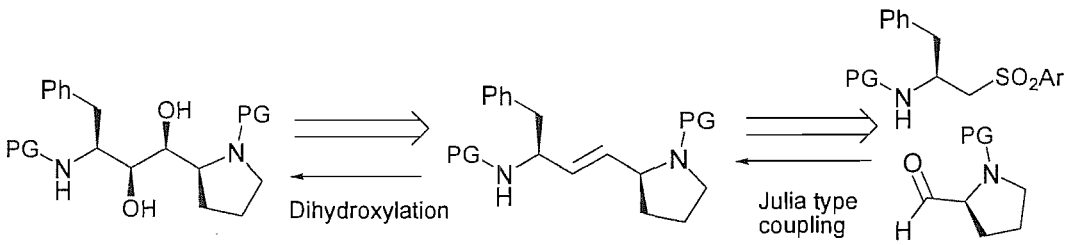
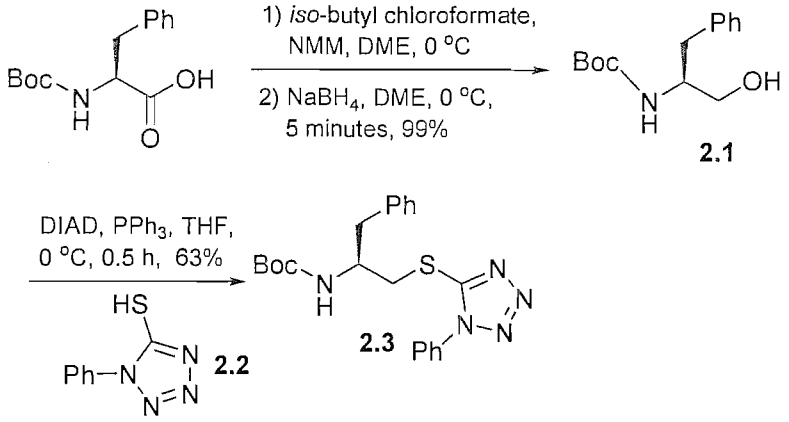


Figure 2.7: Proposed retrosynthesis using a Julia type coupling between two fragments followed by dihydroxylation.

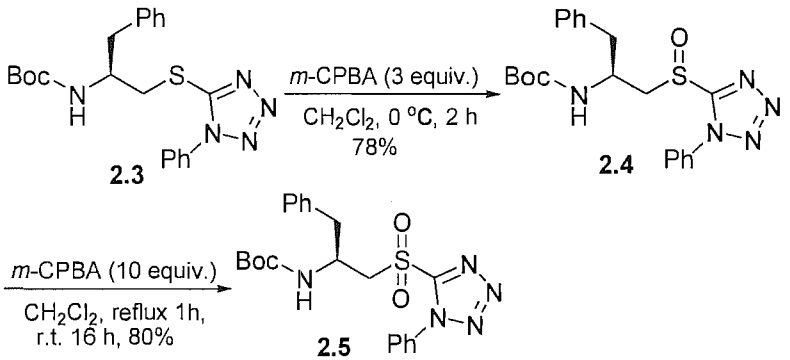
The classic Julia reaction is generally strongly stereoselective and favours formation of the *trans* alkene.[24] It is, however, experimentally quite cumbersome with four synthetic operations taking place. A more recent alternative is the modified or one-pot Julia olefination.[24] In the modified Julia reaction the phenylsulfone of the classical Julia is replaced with a heteroarylsulfone. There are four heteroarylsulfones typically used, all with an electrophilic imine-like group. This is responsible for changing the mechanistic pathway resulting in an unstable β-alkoxysulfone that undergoes a rearrangement, followed by the elimination of sulphur dioxide and the formation of the alkene in one experimental step.[24] Work published by Kocieński *et al.* suggested that 1-phenyl-1*H*-terazol-5-yl as the heteroarylsulfone in our synthesis would give the best yield, with a high level of *trans* selectivity.[25]

Boc protected phenylalanine was used as the starting material in the synthesis of the first fragment. After reaction with *iso*-butyl chloroformate the resulting mixed anhydride was reduced with sodium borohydride to give the alcohol **2.1** in excellent yield (99%). The alcohol was then transformed to the novel sulfide **2.3** under Mitsunobu conditions in good yield (63%), following an adapted procedure from the literature (scheme 2.8).[26]



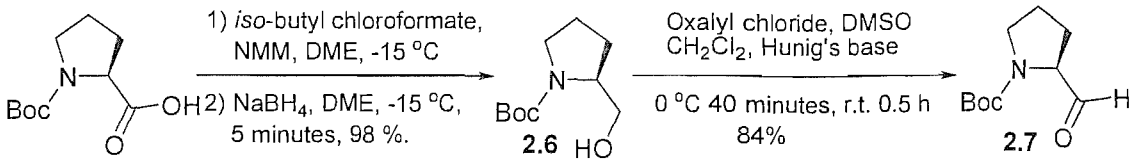
Scheme 2.8: Reduction of phenylalanine to alcohol followed by Mitsunobu reaction.[26]

Oxidation of sulfide **2.3** with 3 equivalents of *m*-CPBA at room temperature gave the sulfoxide **2.4** as the two diastereoisomers in excellent yield (78%). Long reaction times with a large excess of *m*-CPBA or potassium peroxymonosulfate (Oxone) failed to produce the desired sulfone. It was discovered that 10 equiv. of *m*-CPBA and a short period of heating followed by stirring at room temperature gave the sulfone **2.5** in good yield over the two steps (62%, scheme 2.9).



Scheme 2.9: Oxidation of the sulfide **3** to the required sulfone **2.5** with *m*-CPBA.

The second fragment was synthesised from Boc protected proline. The conditions for reduction of the acid to the alcohol that were used previously gave L-prolinol **2.6** in excellent yield (98%). Swern oxidation following a literature procedure gave the desired aldehyde **2.7** in very good yield (84%, scheme 2.10).[27] This aldehyde was stable enough to be purified by flash chromatography and could be stored in a freezer for several weeks without degradation.



Scheme 2.10: Reduction of Boc-protected proline to the primary alcohol followed by Swern oxidation to the aldehyde.

With the two fragments for the modified Julia reaction prepared, the coupling reaction was attempted (figure 2.8). Following the experimental conditions outlined in the literature the sulfone **2.5** was dissolved in DME and cooled to – 55 °C.[25] The sulfone was deprotonated with 2.2 equiv. of sodium hexamethyldisilazide seen by a colour change from colourless to yellow-orange. After 1 h the aldehyde **2.7** was added and the reaction was stirred for a further hour before warming to room temperature and stirring overnight. Unfortunately, the reaction did not work as anticipated and after workup only the aldehyde **2.7** was isolated. Repeated attempts with a test aldehyde **2.8** also failed, again with only the aldehyde being isolated after workup. Reducing the reaction temperature to – 78 °C for the deprotonation was not seen to help the reaction.

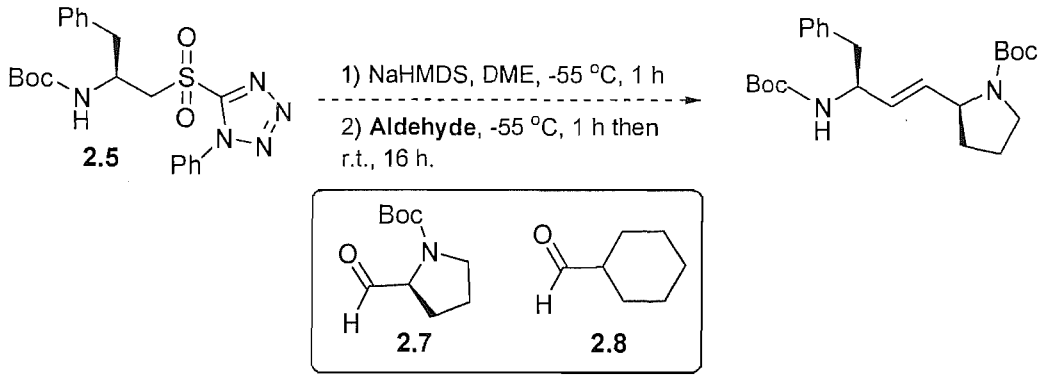
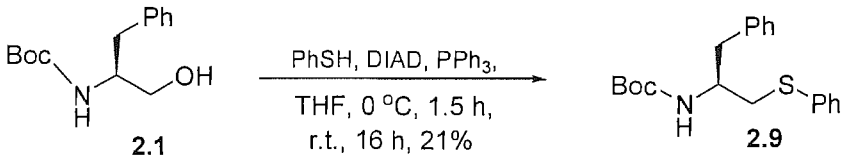


Figure 2.8: Kocieński modified Julia reaction with aldehydes **2.7** and **2.8** to form trans-alkene.

Since none of these attempts led to the isolation of the starting sulfone **2.5** after workup, it would seem that the lithiated sulfone is unstable even at low temperatures. This problem has been reported for some lithiated benzothiazolyl sulfones when used in the modified Julia reaction.[25] It was therefore decided that the traditional Julia coupling reaction might be more appropriate for this synthesis.

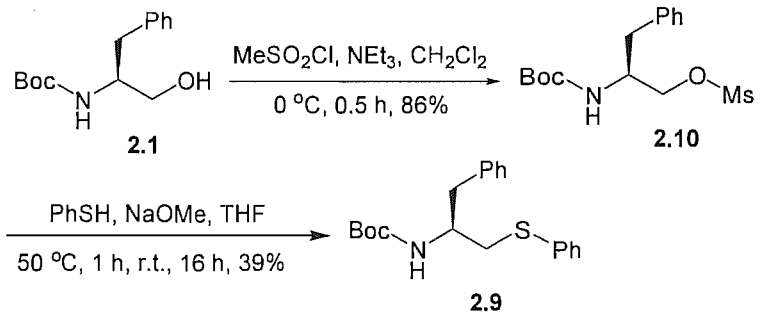
ii) The traditional Julia reaction in the synthesis of the diol isostere

The synthesis of the fragment needed for the Julia coupling reaction started from the primary alcohol **2.1** as before. The Mitsunobu conditions that were used to synthesise the sulfide **2.3** so successfully (scheme 2.8) did not, however, work well with thiophenol. In addition to the reaction being very slow, the product was difficult to separate from the hydrazine side-product, resulting in a poor yield (21%, scheme 2.11).



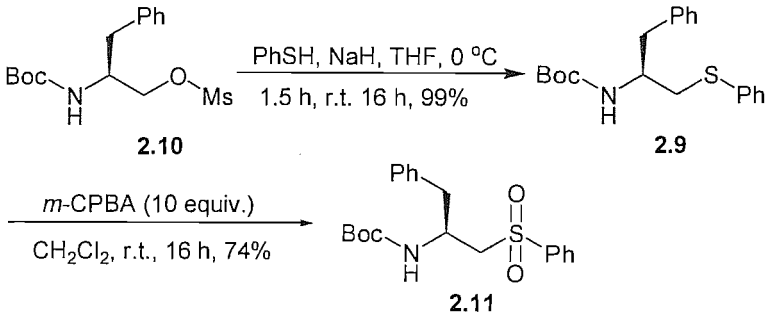
Scheme 2.11: Mitsunobu reaction with thiophenol to produce sulfide **2.9**.

An alternative two step synthesis to the sulfide **2.9**, reported in the literature was then tried (scheme 2.12).[28] Although this only gave a slightly improved yield over the two steps (34%), the first of the two steps proceeded in excellent yield (86%) with a poor yield for the second step (39%). The alcohol **2.1** was reacted with methanesulfonyl chloride and triethylamine to give the methanesulfonate **2.10**. The mesyloxy group was then substituted by the anion of thiophenol. The solid **2.10** was added to a premixed solution of sodium methoxide and thiophenol in tetrahydrofuran and heated to 50 °C. Although the base NaOMe was used in a large excess (3.3 equiv.) it would seem that it was not sufficient to deprotonate the thiophenol completely since each time this reaction was carried out, the starting material **2.10** was recovered (91% of unreacted **2.10**) in addition to the product **2.9**.



Scheme 2.12: Conversion of primary alcohol **2.1** to methanesulfonate **2.10** followed by reaction with thiophenol to give sulfide **2.9**.

Deciding that a different base might improve the yield of this reaction, sodium hydride was used instead of NaOMe at 0 °C in tetrahydrofuran (scheme 2.13). As reported in a later paper these conditions gave the sulfide **2.9** in an excellent yield over the two steps (85%).[29] Oxidation to the sulfone was carried out using 10 equivalents of *m*-CPBA as before, to produce the final sulfone in a good yield (74%, scheme 2.13).



Scheme 2.13: Improved substitution of methanesulfonate ester group with thiophenol to give sulfide **2.9** followed by oxidation to sulfone **2.11**.

Following the experimental described by Gurjar *et al.* for the Julia coupling reaction, the sulfone **2.11** was refluxed in dry THF until the sulfone was completely dissolved and then cooled to -78 °C.[30] On addition of one equivalent of *n*-BuLi the solution remained colourless; a second equivalent of base gave the bright yellow colour reported in the literature as characteristic of the dianion of sulfone **2.11**. Several papers, including that by Gurjar *et al.*,[30-33] write of the importance of activating the aldehyde before addition to the dianion of sulfone **2.11**. This is done by addition of DIBAL methoxide, (prepared by the addition of MeOH and THF to DIBAL at -78 °C) to the aldehyde at -78 °C followed by transfer of the aluminium complex via cannula to the solution of the sulfone dianion. Despite monitoring of the reaction temperature at all times and adherence to the precise experimental conditions described by Luthman *et al.*[31] in their discussion of the Julia reaction with the sulfone **2.11**, no reaction was seen with the aldehyde **2.7** (figure 2.9).

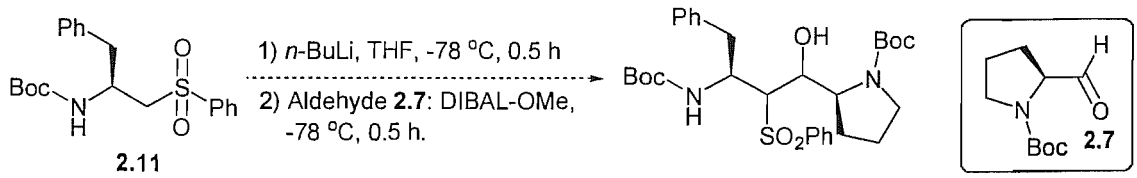
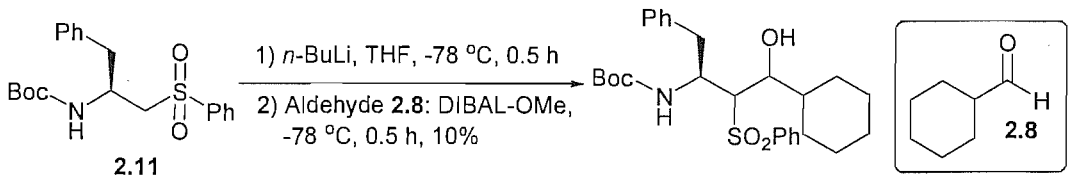


Figure 2.9: Failed Julia reaction of sulfone **2.11** with aldehyde **2.7** DIBAL methoxide complex.

Unlike the attempts at the modified Julia reaction, however, the starting sulfone **2.11** was recovered after work up (94%). On several occasions, after addition of the aldehyde aluminium complex to the dianion, small white crystals of the sulfone **2.11** were seen to precipitate out of solution as the yellow colour of the dianion faded. Although often the starting aldehyde was seen by TLC in the crude mixture, it was difficult to recover cleanly and could not be reused.

Using the same experimental conditions for a reaction between **2.11** and a commercially available aldehyde **2.8** had little success. Despite several careful attempts, minimal amounts of product were isolated (10%) - too little for full characterisation (scheme 2.14).



Scheme 2.14: Very low yielding Julia coupling between sulfone **2.11** and aldehyde **2.8**.

Although Julia coupling has been described in the literature using the above sulfone **2.11** with a small range of aldehydes, yields have always been quite poor (37% for Gurjar *et al.*,[30] 40% for Spaltenstein *et al.*[33] and 42-66% for Lutherman *et al.*[31, 32]). In addition to this, no reports of the aldehyde **2.7** being used in any Julia reactions have been found in the literature. It would seem that the problems with this reaction lie both with the sulfone **2.11** dianion being too readily quenched and the aldehyde **2.7** not being reactive enough.

Since at this point the Julia coupling reaction was very unlikely to provide the reliable coupling reaction we required to produce our desired range of diol isosteres, we turned our attention to the methodology of Hoppe *et al.* [20, 34]

2.2.2 Synthesis towards diol isostere using Hoppe methodology[20, 34]

i) Synthesis of starting materials

In the Hoppe methodology, shown in scheme 2.5 (Introduction, part 2.1.3), an aldehyde is reacted with the anion of the carbamate **2.12**, derived from (*S*)-2-(*N*,*N*-dibenzylamino)alkanols, to give the desired diol isostere directly (figure 2.10).

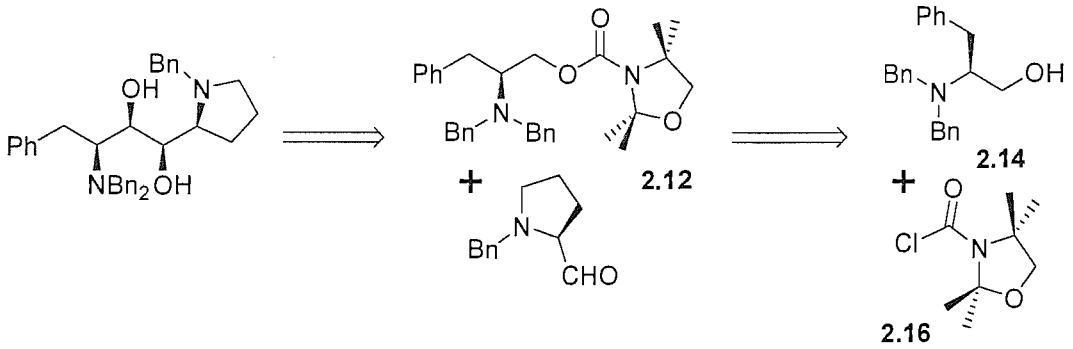
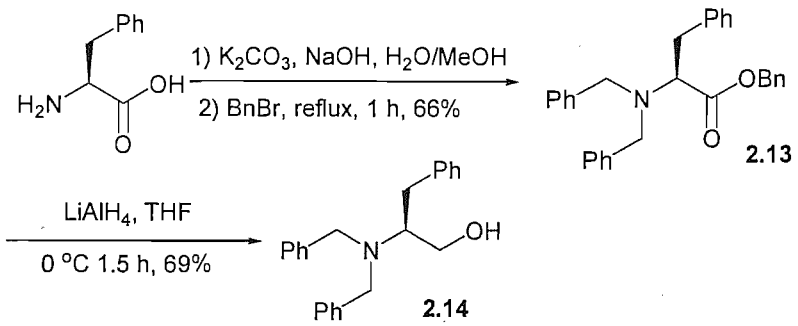


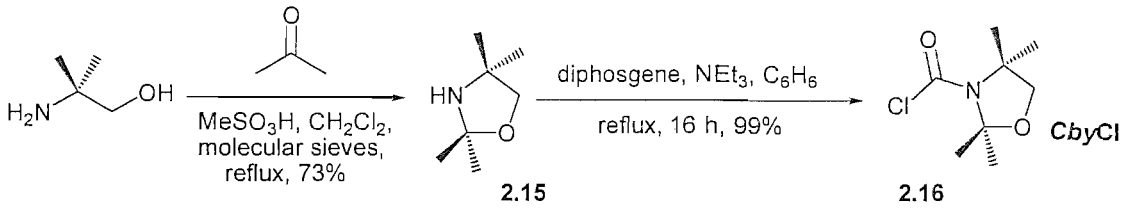
Figure 2.10: Retrosynthetic analysis of the Hoppe methodology to the diaminodiol isostere.

Two starting materials are needed in the synthesis of carbamate **2.12**: the dibenzyl protected alcohol **2.14** and the heterocycle **2.16** (referred to in Hoppe's work as ***Cby*Cl**).[20, 34] The known alcohol **2.14** was synthesised from L-phenylalanine in good overall yield over two steps (46%, scheme 2.15).[35] The amino acid was first reacted with 3 equiv. of benzyl bromide to give the benzyl ester, before being reduced with $LiAlH_4$ to give the desired alcohol **2.14**.



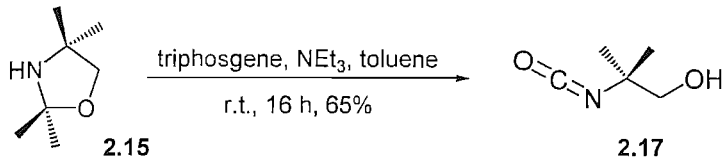
Scheme 2.15: Benzylation of L-phenylalanine followed by reduction with $LiAlH_4$ to give alcohol **2.14**.[35]

Hoppe *et al.*[36] describe using a 'water trap' in the synthesis of the heterocycle **2.15**, the precursor to **2.16** (scheme 2.16). We found that pre-dried 3 Å molecular sieves rapidly stirring in the reaction mixture worked efficiently, giving **2.15** in an excellent yield (73% *c.f.* Hoppe's yield 68%). Following Hoppe's experimental for the synthesis of **2.16**, the heterocycle **2.15** and triethylamine were added to a solution of diphosgene and refluxed in benzene overnight (scheme 2.16).[36]



Scheme 2.16: Synthesis of heterocycle **2.16** following slight improvements on Hoppe's experimental procedure.[36]

Although Hoppe reported a yield of 72% we experienced much better yields when following this procedure (99%).[36] Any attempts to use a solvent less toxic than benzene (toluene, dichloromethane or THF) resulted in much poorer yields (41–66%) and contamination with a side product. This by-product was thought to be the isocyanate **2.17** (scheme 2.17), the result of the breakdown of the desired product **2.16**.



Scheme 2.17: Formation of isocyanate **2.17** from the breakdown of heterocycle **2.16**.

In order to fully characterise this by-product the reaction was carried out with triphosgene in toluene and refluxed as before. When the reaction was seen to be complete by TLC a neutral aqueous work-up was carried out (instead of 2N $HCl_{(Aq.)}$), giving the previously seen by-product as the sole product in good yield (65%). Full characterisation confirmed this by-product as the isocyanate **2.17**. The mechanism for the formation of **2.17** is, therefore, thought to be due to attack of a water molecule on the heterocycle **2.16** causing elimination of acetone to give the stable crystalline isocyanate **2.17** (figure 2.11).

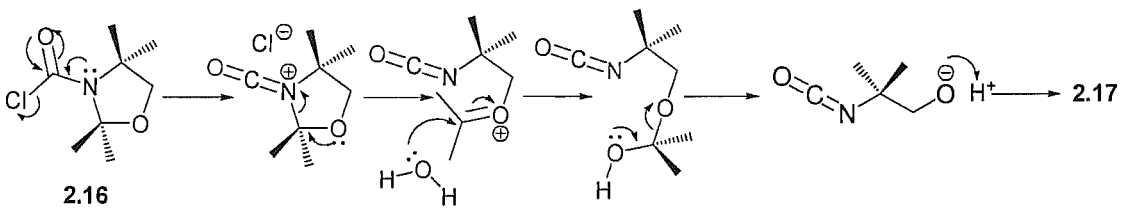
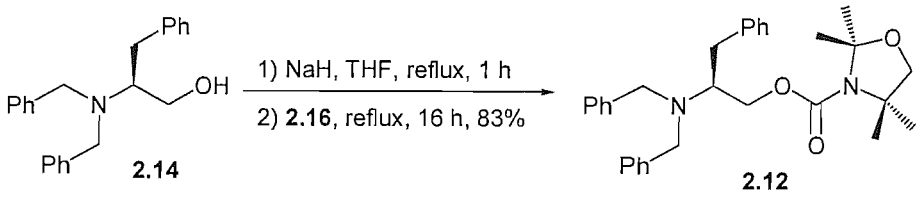


Figure 2.11: Proposed mechanism for breakdown of heterocycle **2.16** to isocyanate **2.17** via attack of water.

With the two starting materials, alcohol **2.14** and heterocycle **2.16** now prepared, we were able to synthesise the carbamate **2.12**. The alcohol **2.14** was refluxed with sodium hydride in THF for an hour before addition of the heterocycle **2.16** and refluxing the mixture for a further 16 hours, as described by Hoppe *et al.*[34] with a comparable yield of 83% to their yield of 81% (scheme 2.18).[34] Attempts to synthesise **2.16** in-situ and add immediately to the deprotonated **2.14**, although avoiding the use of benzene, consistently had lower yields (57%).



Scheme 2.18: Synthesis of carbamate **2.12** from alcohol **2.14** and heterocycle **2.16** according to Hoppe's procedure

ii) Deprotonation of carbamate and reaction with aldehyde to form diol

Hoppe's methodology (figure 2.10) hinges on the deprotonation of the carbamate **2.12** (or analogous carbamates) with *sec*-butyllithium and TMEDA to form two epimeric lithium complexes with good diastereoselectivities.[20, 34] The aldehyde then reacts with these lithium compounds to give two diols in corresponding diastereoselectivities (figure 2.12).

Following Hoppe *et al.*'s experimental,[20] carbamate **2.12** was dissolved in dry diethyl ether under argon and freshly distilled TMEDA was added. The reaction was cooled to -78 °C, recently titrated *sec*-BuLi was added and the reaction stirred for 6 hours. Initially we tried the reaction with the previously prepared aldehyde **2.7** (scheme 2.10). This was not successful however with both starting materials being recovered after work-up. Since all of Hoppe *et al.*'s examples[20, 34] had benzyl protecting groups on both reactants we decided to synthesise our aldehyde with a benzyl protecting group.

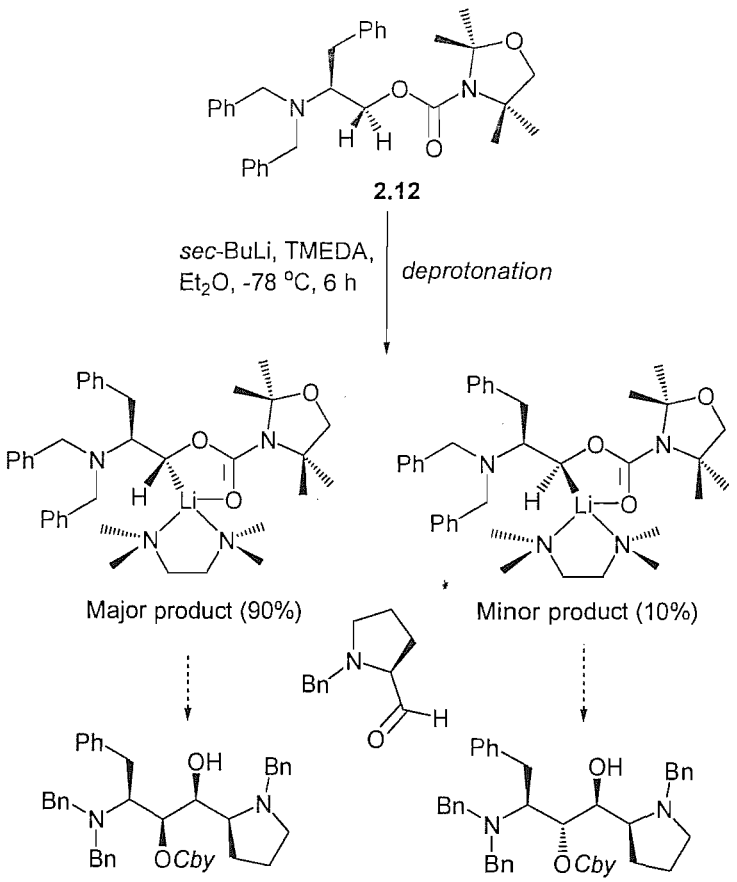
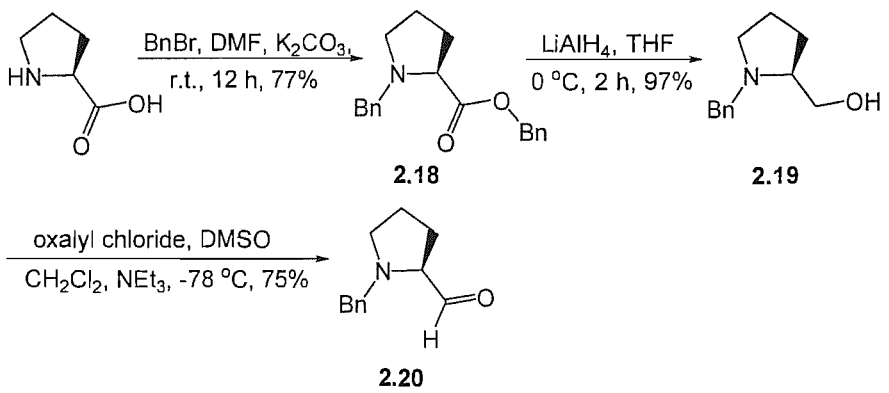


Figure 2.12: Deprotonation of carbamate **2.12** to give the two lithium compounds with major product giving desired diol isostere.[20]

The method used to benzylate L-phenylalanine (scheme 2.15; amino acid, K_2CO_3 and NaOH in water/methanol, reflux with BnBr for 1 hour) when used to benzylate L-proline produced a mixture of mono and di-benzylated L-proline. Using DMF, base and BnBr at room temperature, as reported in the literature, gave only the benzyl ester **2.18** in good yield (77%, scheme 2.18).[37] The benzyl ester was then reduced as before (scheme 2.15), to give the alcohol **2.19** in excellent yield (97%, scheme 2.19).



Scheme 2.19: Synthesis of benzyl-protected aldehyde **2.20**, following reduction of benzyl ester **2.18** and oxidation of resulting alcohol **2.19**

Oxidation to the aldehyde using Swern conditions, as were used for the oxidation to the Boc protected aldehyde **2.7**, gave the crude aldehyde in generally good yield (75%, scheme 2.19). Aldehyde **2.7** was stable for several weeks if stored cold and was purified by flash chromatography. By comparison, aldehyde **2.20** was quite unstable; attempts to purify the compound by flash chromatography or distillation saw the complete breakdown of the aldehyde. As a result, aldehyde **2.20** was used immediately after work-up of the Swern reaction.[38-40] Since the crude aldehyde was not completely clean by ^{1}H NMR spectroscopy and decomposed rapidly even when cold, full characterisation of **2.20** was not possible.

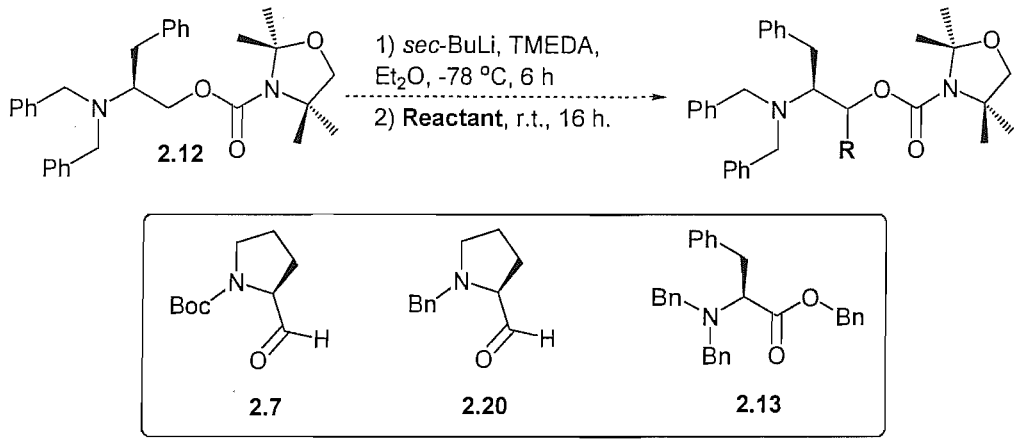
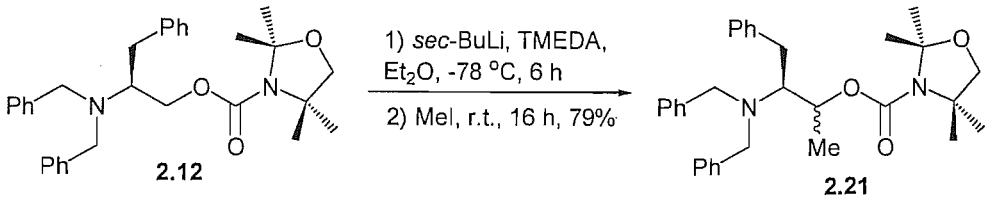


Figure 2.13: Experiments following Hoppe's procedure, reacting carbamate **2.12** with aldehydes **2.7**, **2.18**, ester **2.13** and MeI.

Again the carbamate **2.12** was deprotonated according to Hoppe *et al.*'s procedure and after 6 hours stirring the aldehyde **2.20** was added.[20] This reaction was also unsuccessful, with only the starting carbamate being recovered after work-up (60%). Since this key coupling step had now failed with both aldehyde **2.7** and **2.20** (figure 2.13) we needed to establish if we could repeat Hoppe *et al.*'s work using identical reactants to those they reported. As well as using aldehydes Hoppe *et al.* reported reactions of various electrophiles with the carbamate **2.12**, including benzyl ester **2.13** (scheme 2.15) and methyl iodide.[20] Reactions with both of these electrophiles were tried with no more success than seen with the two aldehydes.

Having followed Hoppe *et al.*'s experimental details so closely and having checked the quality of all our reagents we contacted Prof. Hoppe for advice on these reactions. It was suggested that any 'cloudiness' in the *sec*-butyl lithium solution

could upset the reaction and stop the lithium complexes forming properly. Although our *sec*-BuLi was newly purchased we did observe some small level of cloudiness. In order to remove this precipitate we needed to filter the *sec*-BuLi through a plug of celite under an argon atmosphere. After some work we established a reliable and safe method to filter the flammable *sec*-BuLi after which the clear solution was titrated and used immediately. The solution became cloudy again after 1 day's storage in a sealed Schlenk tube under argon.

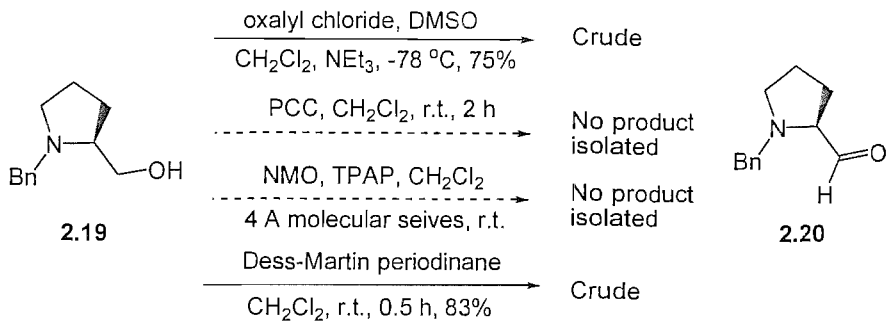


Scheme 2.20: Deprotonation of carbamate **2.12** with freshly filtered *sec*-BuLi followed by reaction with methyl iodide[20]

Repeating the reaction with freshly filtered *sec*-BuLi and adding methyl iodide to the resulting lithium compounds gave the desired product **2.21** in good yield (79% diastereoisomers not separated, scheme 2.20). With the methodology now working we tried the reaction with the two aldehydes **2.7** and **2.20**. Unfortunately, as before, both of these reactions failed to produce any of the desired diols.

iii) Synthesis of aldehyde and alternative reactants for reaction with carbamate

As it was now established that the carbamate could be successfully deprotonated and reacted with an electrophile the continuing problems with the aldehydes **2.7** and **2.20** must stem from the aldehydes themselves. With aldehyde **2.20** having to be used crude, it seemed likely that the impurities from the Swern oxidation were causing problems in this very sensitive reaction. Although **2.20** is known in the literature, it is only described as being used crude from the Swern reaction with purification generally carried out after the next reaction.[38-40] We hoped, however, to find a method of synthesising **2.20** that would give the crude product in a more pure form than that isolated from the Swern oxidation.



Scheme 2.21: Various oxidation methods for the oxidation of alcohol **2.19** to aldehyde **2.20**.

Several methods to oxidise the previously prepared alcohol **2.19** (scheme 2.19) to a more pure crude **2.20** were tried (scheme 2.21). Pyridinium chlorochromate was dissolved in dichloromethane with the alcohol **2.19** and stirred at room temperature. Although by TLC all starting material was reacted after 2 hours, no product was isolated after work-up, instead it seemed that the unstable product had broken down. Oxidation with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine-*N*-oxide (NMO) was equally unsuccessful. Following the work of Ley *et al.*,[41] TPAP was added to a mixture of **2.19**, NMO and finely ground 4 Å molecular sieves in dichloromethane. However, even after 16 hours stirring the starting alcohol **2.19** was still present by TLC; again after work-up no product was isolated although the starting material could be recovered in an impure form. Dess-Martin conditions[42] did produce the aldehyde in an excellent yield (~83% *c.f.* 75% for Swern) it was, however, less successful in the sense that the crude aldehyde had more impurities by ^{1}H NMR than the relatively clean aldehyde produced by the Swern oxidation.

The unstable nature of this aldehyde and its resulting rapid decomposition is a considerable problem that seems, at present, to be unanswerable when combined with the extreme sensitivity of the Hoppe methodology. In order to be able to carry out the necessary coupling reaction, the stability of the proline-derived reactant must be improved. We thought that we might be able to do this in one of two ways: either replace the aldehyde moiety with an ester or other reactive group, then reduce to the diol after the coupling reaction (figure 2.14), or altering the benzyl protecting group to increase the stability of the aldehyde.

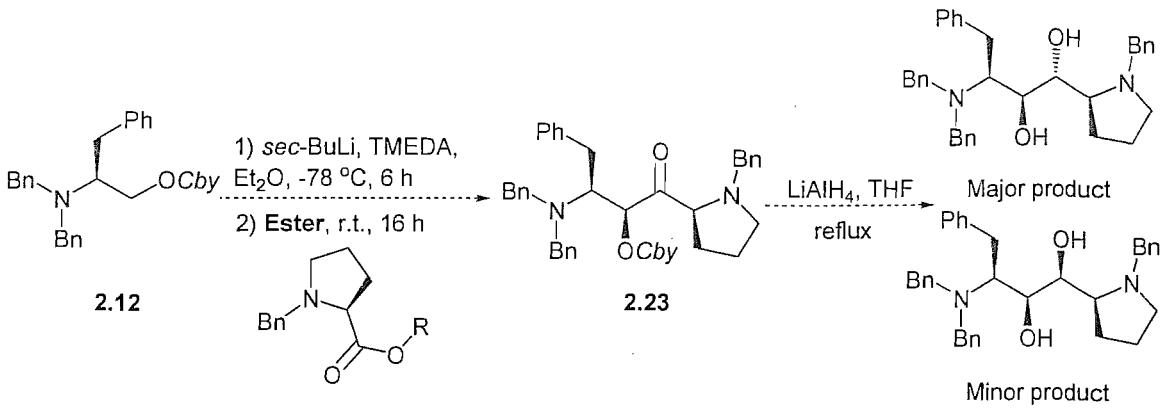
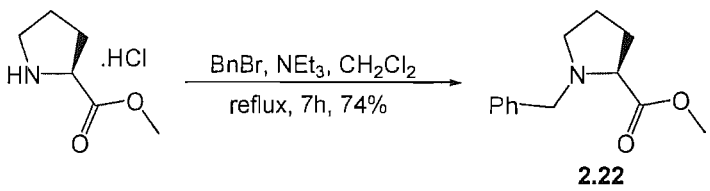


Figure 2.14: Reaction of the deprotonated carbamate with an ester followed by reduction to the diol.

We have already observed that Hoppe *et al.* reported reactions between the deprotonated carbamates and benzyl esters (e.g. benzyl ester **2.13**).[20] Although this route would seem to add an additional step, Hoppe *et al.* found that the ***Cby*** group could be removed at the same time as the reduction to give the unprotected diol (figure 2.14).[20] Unfortunately, lithium aluminium hydride reduction gives the major product as the unwanted diol according to Hoppe *et al* (figure 2.14).[20] From Hoppe *et al.*'s comments we were confident that with some experimentation to find the best solvent and reducing agent it would be possible to change this ratio to our advantage.[20]



Scheme 2.22: Synthesis of known methyl ester **2.22** from proline methyl ester HCl.[43, 44]

We started by synthesising the known methyl ester **2.22** from the proline methyl ester salt in good yield (74%, scheme 2.22).[43, 44] Reaction of this ester **2.22** with carbamate **2.12** under Hoppe *et al.*'s experimental conditions with the filtered *sec*-BuLi did not, however, yield the expected product **2.23** (figure 2.14); both starting materials were recovered from this reaction unchanged (~100% for both). Although Hoppe *et al.* did experience success with the benzyl esters in this reaction, they commented on the poor yields (26-59%) being due to the relatively low reactivity of these esters.[20] With the methyl ester **2.22** seeming not to be reactive enough, we went about synthesising some esters with better leaving groups. Following a literature procedure, benzyl protected proline **2.24** was

synthesised from proline in excellent yield (79%, figure 2.15).[43] Conversion of the carboxylic acid **2.24** to the acid chloride **2.25** was unsuccessful due the instability of **2.25**.

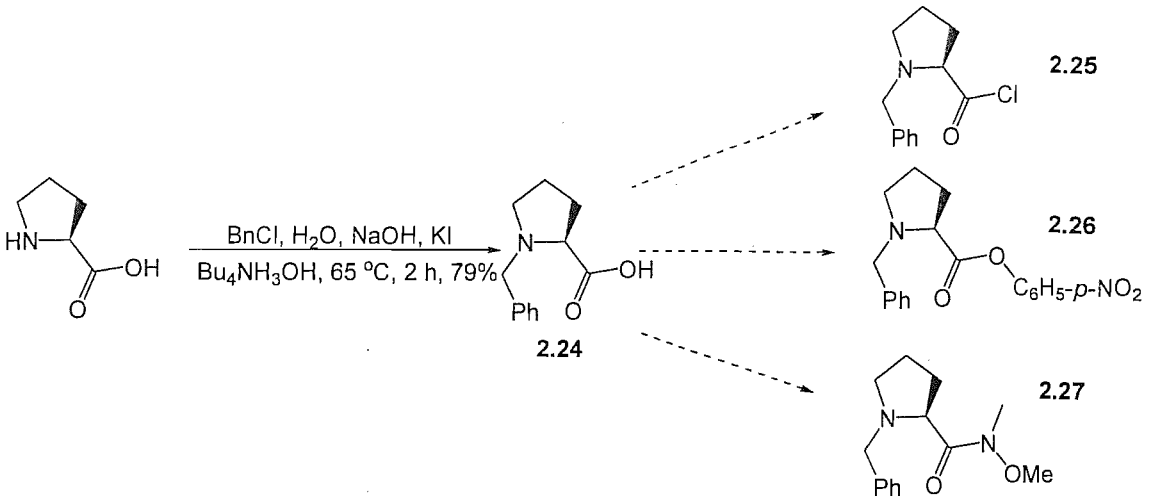
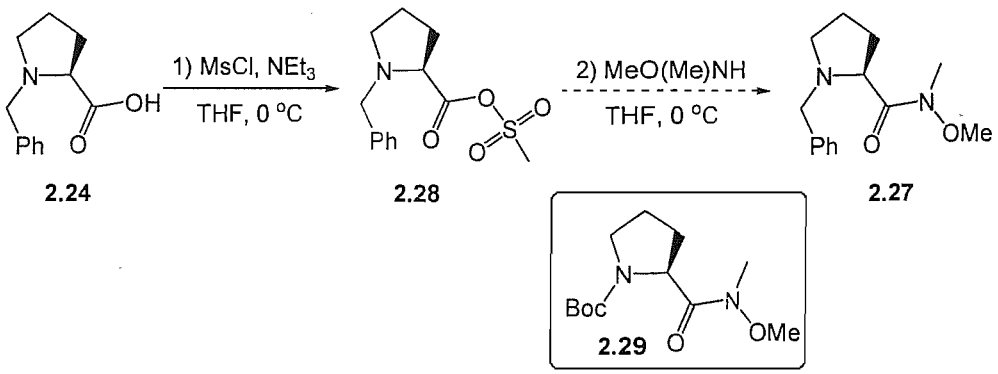


Figure 2.15: Synthesis of benzyl protected proline **2.24** as a starting material for various reactants

Coupling the acid **2.24** to *p*-nitrophenol with DCC or EDC and HoBt gave the crude ester **2.26**. Unfortunately, any form of aqueous work-up or column chromatography resulted in the breakdown of the ester to starting materials. The synthesis of the Weinreb amide **2.27** was attempted through several routes. A literature method used in our laboratory for the synthesis of similar Weinreb amides was initially tried.[45] The carboxylic acid **2.24** and triethylamine were dissolved in THF and methanesulfonyl chloride was added slowly, after which *N,O*-dimethylhydroxylamine was added and the reaction stirred for 1 hour. Although this method has given the proline Weinreb amide **2.29** (scheme 2.23) in excellent yield (88%) for a different project,[45] the benzyl protected proline **2.24** failed to give the correct product. On further investigation it became clear that the methanesulfonate **2.28** broke down rapidly in the reaction.



Scheme 2.23: Attempted synthesis of Weinreb amide **2.27** from methanesulfonate **2.28**, Weinreb amide **2.29** was successfully synthesised by this method

Attempts to couple the acid **2.24** directly with *N,O*-dimethylhydroxylamine using DCC or pyBrop also failed, with neither product isolated or starting material recovered.

Since many of the compounds synthesised with a benzyl protecting group are unstable, where the corresponding compound with a Boc group is stable and easy to handle, it would seem that our best chances of success would be to change the protecting group to improve stability. We know that the aldehyde **2.7** cannot be used in the Hoppe reaction with carbamate **2.12**; we also know that Hoppe *et al.* only used benzyl protected aldehydes. Hoppe *et al.* commented[34] that the benzyl protecting group is important although they do not explain what it is about the benzyl group that is so vital. Comparing the two aldehydes **2.7** and **2.20** (figure 2.16) there seem to be two differences that may be interfering with the lithium carbamate complexes (figure 2.12); either the additional oxygen atoms in the Boc group complexes the lithium, or the very different shape of the Boc group blocks the coupling reaction.

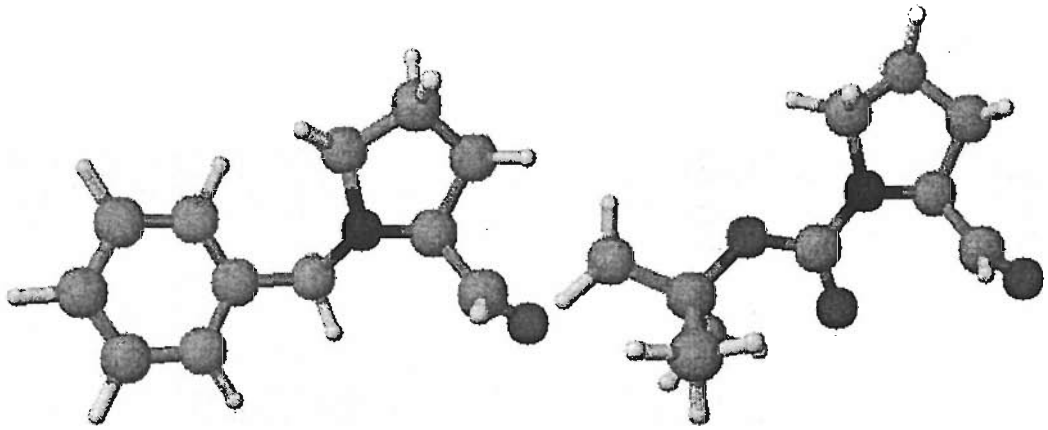


Figure 2.16: Three dimensional structures of aldehydes **2.20** (left) and **2.7** (right). Red atoms are oxygen, dark blue are nitrogen, light blue are carbon and white are hydrogen atoms.

To distinguish between these two potential problems we aimed to synthesise a protecting group that had a three dimensional shape as close to the benzyl group as possible but with the amide moiety that we hoped would give the resulting aldehyde greater stability. We also needed to consider that should our reaction be successful we would need to remove our new protecting group easily. The aldehyde **2.30** was proposed as an investigative structure since it could be easily removed by reduction by $LiAlH_4$ (a step that would remove the *Cby* group at the same time)[20, 34] followed by hydrogenation of the resulting benzyl group (figure 2.17).

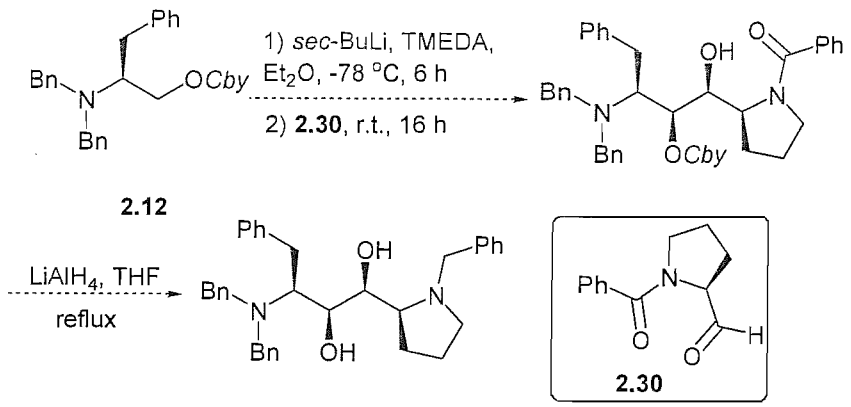
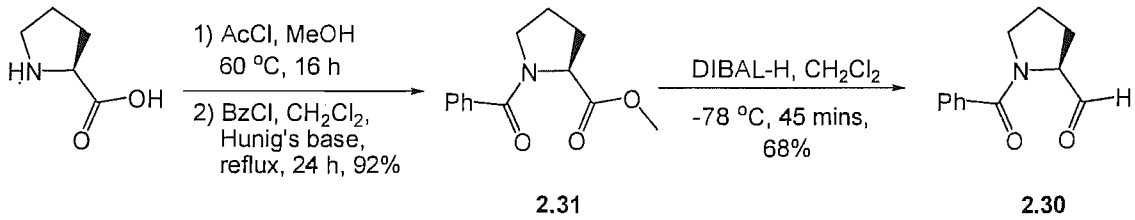


Figure 2.17: Structure of aldehyde **2.30** and proposed reaction and deprotection with $LiAlH_4$

We synthesised the methyl ester **2.31** in excellent yield (92%) in two steps from L-proline (scheme 2.23) following a literature procedure.[46] The ester **2.31** was then reduced using DIBAL-H, the aldehyde was isolated after an aqueous work-up with a solution of Rochelle's salt in good yield (68%, scheme 2.24), and was stable enough to be purified by column chromatography.



2.31 **2.30**

Scheme 2.24: Synthesis of the aldehyde **2.30** from L-proline

The reaction of aldehyde **2.30** with deprotonated carbamate **2.12** under Hoppe *et al.*'s conditions[20] did not give the desired product and both starting materials were recovered unchanged. It would seem that the additional oxygen atom in aldehyde **2.30** provides the necessary stability but interferes with the lithium complexes sufficiently to prevent the desired coupling reaction. At present we cannot see a way of inducing the required stability in the proline derived aldehyde without unfavourably affecting the coupling reaction.

2.3.0 CONCLUSION

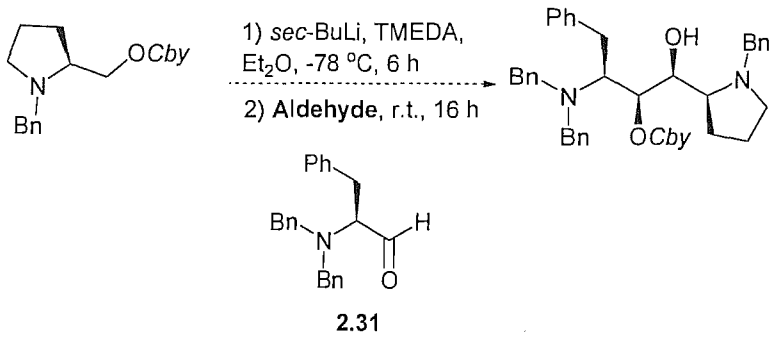
The aims for this project, as outlined in the introduction, were to synthesise the candidate protease inhibitors using Julia olefination or Hoppe *et al.*'s methodology for the key coupling step. Both routes have encountered difficulties in the synthesis of the target diol isostere (figure 2.6).

Synthesis of the novel sulfone **2.5** (4 steps, 39%) and the stable aldehyde **2.7** (2 steps, 82%) for the modified Julia reaction proceeded smoothly. Reaction of sulfone **2.5** with either aldehyde **2.7** or cyclohexanecarbaldhyde **2.8** under the modified Julia conditions consistently failed; this is thought to be due to the instability of the lithiated sulfone. The traditional Julia coupling reaction also had serious limitations for this synthesis. An improved route for the synthesis of the starting material gave sulfone **2.11** in good yield (4 steps, 62%), however, reaction with **2.7** was not successful and reaction with cyclohexane carbaldehyde **2.8** gave a very poor yield (10%). It seemed that, not only was the aldehyde **2.7** unsuitable for this coupling reaction but that the sulfone **2.11** was also a poor reactant in this type of reaction.

The starting materials for Hoppe *et al.*'s synthesis were synthesised as described in the literature and after initial failure we were able to successfully react carbamate **2.12** with methyl iodide when using pre-filtered *sec*-butyl lithium under Hoppe *et al.*'s experimental conditions. Reaction of **2.12** with benzyl protected aldehyde **2.20** or aldehyde **2.7** under these improved conditions was not successful. Attempts to synthesise the unstable aldehyde **2.20** cleanly by a number of different synthetic methods were prevented by the compound's instability. Synthesis of alternative structures for the proline derived reactant (**2.25**, **2.26**, **2.27** and **2.28**) was equally difficult due to their inherent instability. Changing the benzyl protecting group to improve stability gave the stable, clean aldehyde **2.30**. Reaction of **2.30** with the carbamate **2.12** under Hoppe *et al.*'s conditions, however, was unsuccessful.

Our experiences demonstrate the extremely sensitive nature of the Hoppe coupling reaction, both it seems to low levels of impurities and to any compounds that can complex lithium and thereby disrupt the carbamate-lithium complexes (figure 2.12).

The majority of the problems that we have encountered in our work have been due to the structure of the target molecule, particularly the cyclic or proline derived section. This may in part explain why this diol proline-like motif is so rarely seen in published examples of HIV-1 protease inhibitors. The only example we have found is where Benedetti *et al.* cyclised the proline like section as the final step in their synthesis to the diol isostere core.[23] This may be an approach that would work for our project in the future; however, an alternative would be to 'swap' the two fragments in our coupling step. For example in Hoppe *et al.*'s coupling reaction we could use the known phenylalanine derived aldehyde **2.31** and synthesise the required carbamate from the stable alcohol **2.6** (figure 2.18).



2.31

Figure 2.18: Proposed future work where fragments are 'swapped' for Hoppe methodology.

Our recently gained insights into this coupling reaction and the handling of similar compounds do lead us to believe that both the aldehyde **2.31** and the carbamate would be possible to synthesise and relatively stable. Similar alterations could be made to the Julia or modified Julia coupling routes, although the Hoppe reaction might be preferable since it gives the diol in one step.

Although the stated aim of synthesising the candidate protease inhibitors has not been achieved, we are satisfied that we have explored the scope of the Julia and Hoppe coupling reactions for the purposes of this synthesis and gained a detailed understanding of these reactions in this synthesis. We hope that this will be invaluable for the successful completion of this project at a later date.

2.4.0 EXPERIMENTAL

2.4.1 General Experimental Methods

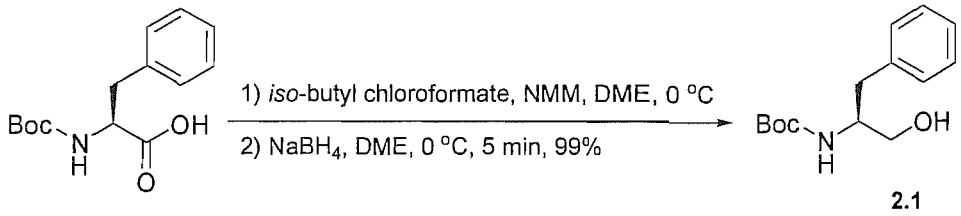
Chemicals and general reagents were purchased from commercial suppliers, and unless stated otherwise were initially used without further purification. Anhydrous dichloromethane was freshly distilled from calcium hydride, THF was distilled from sodium wire with benzophenone as an indicator and toluene was distilled over molten sodium metal. Where necessary, all other solvents and reagents were purified according to standard methods.[47] Unusual purification methods of reagents are described where used.

All air and/or moisture sensitive reactions were carried out under an inert atmosphere of argon gas, in oven-dried glassware. Reactions were monitored by TLC using pre-coated aluminium or plastic plates coated with 0.14 mm of silica gel 60 containing a fluorescence indicator active at 254 nm. Visualisation was carried out under UV light (254 nm) and by staining with, most commonly, 20% phosphomolybdic acid in ethanol, cerium sulphate/ammonium molybdate in 2M H_2SO_4 (aq) or 10% aqueous $KMnO_4$. Flash column chromatography was performed with 40-63 μm silica gel. 'Brine' refers to a saturated aqueous solution of sodium chloride. The term *in vacuo* refers to the removal of solvents by the means of evaporation at reduced pressure, using a Buchi rotary evaporator.

Melting points were obtained in open capillary tubes on a hot stage apparatus and are uncorrected. Polarimetry was recorded on a POLAAR 2001, and corrected for solvent use; solvent used was chloroform unless stated otherwise. Infrared spectra were recorded either on a Bio-Rad FTS 135 instrument using a Golden Gate adapter or a Perkin Elmer spectrometer with a Golden Gate adapter. Absorptions were recorded in wave numbers (cm^{-1}) and are described as strong (s), medium (m) or weak (w). ^1H NMR and ^{13}C NMR were recorded on Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers (300 or 400 MHz for ^1H and 75 or 100 MHz for ^{13}C). Characteristic splitting patterns due to spin spin coupling are expressed as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chemical shifts are given in ppm and coupling constants are measured in Hertz. Low-resolution mass spectra were obtained on a Micromass platform single quadrupole mass spectrometer with an electospray ion source using acetonitrile or methanol as the delivery eluent. The microwave reactor was a CEM Discover and conditions used were as stated.

2.4.2 Experimental Detail for Chapter Two

(*S*)-(1-Benzyl-2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (2.1)



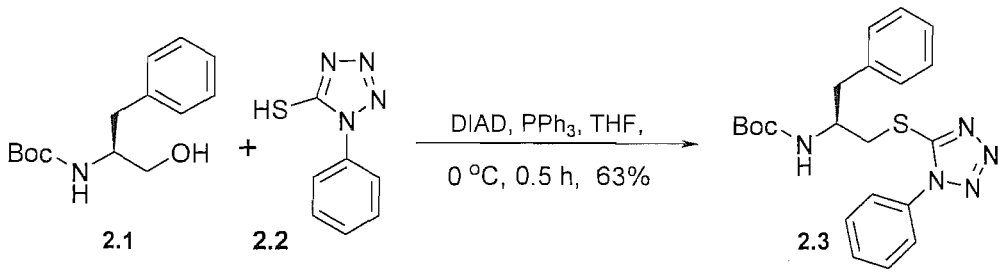
2.1

iso-Butyl chloroformate (1.0 equiv., 18.9 mmol, 2.45 mL) was added slowly to an ice-cold solution of Boc-L-phenylalanine (1.0 equiv., 18.9 mmol, 5.00 g) and *N*-methylmorpholine (1.0 equiv., 18.9 mmol, 2.08 mL) in DME (50 mL). A white precipitate was seen to form and after 2 minutes stirring, the reaction mixture was filtered and the precipitate was washed with excess DME. The clear colourless filtrate was cooled in an ice-bath and sodium borohydride (1.5 equiv., 28.4 mmol, 1.07 g) was added portionwise to the reaction. After the final addition, the reaction was stirred for a further 5 minutes before quenching of the excess $NaBH_4$ with water (150 mL). The organics were separated and the aqueous layer was extracted with CH_2Cl (3 x 150 mL). The combined organic layers were washed with brine (200 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was triturated with *n*-hexane to give the pure product as a white crystalline solid (4.70 g, 99%).

Mp 92 – 93 °C (ethyl acetate/hexane), literature values 93 – 95 °C.[48]
[α]$_D$ – 27.9 (*c* 1.1, $CHCl_3$, 24 °C), literature values – 19.15 (*c* 1.07, $CHCl_3$, 26 °C).[48]
IR: 3352 (s), 2983 (w), 2963 (w), 1685 (s), 1526 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.20 (5H, m, **ArH**); 4.72 (1H, br s, **NH**); 3.86 (1H, m, **CH**); 3.68 – 3.65 (1H, m, **CH_2**); 3.58 – 3.53 (1H, m, **CH_2**); 2.84 (2H, d, *J*= 7.5 Hz, **CH_2**); 2.31 (1H, br s, **OH**); 1.41 (9H, s, **CH_3**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 156.2 (**C**), 137.9 (**C**), 129.3 (**CH**) 128.5 (**CH**), 126.5 (**CH**), 79.7 (**C**), 64.2 (**CH_2**), 53.8 (**CH**), 37.5 (**CH_2**), 28.3 (**CH_3**) ppm.
LRMS (ES^+): *m/z* 551 (100), 525 ([2M + Na^+], 50%), 315 ([M + MeCN + Na^+], 70%), 274 ([M + Na^+], 90%).

The data acquired corresponds to the literature values for this known compound.[48]

(*S*)-[1-Benzyl-2-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)-ethyl]-carbamic acid *tert*-butyl ester (2.3)



This procedure was adapted from an analogous example in the literature.[26]

A premixed solution of 1-phenyl-1*H*-tetrazole-5-thiol **2.2** (1.6 equiv., 6.4 mmol, 1.14 g) and diisopropyl azodicarboxylate (1.6 equiv., 6.4 mmol, 1.29 g) in THF (30 mL) was added to an ice-cold stirred solution of alcohol **2.1** (1.0 equiv., 4.0 mmol, 1.00 g) and triphenylphosphine (1.6 equiv., 6.4 mmol, 1.29 g) in THF (20 mL). The reaction mixture was stirred at room temperature for 0.5 h after which the solvent was removed *in vacuo*. The residue was redissolved in ethyl acetate (20 mL) and water (20 mL) added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water (2 x 20 mL) then brine (20 mL) and dried over $MgSO_4$. The drying agent was filtered and the solvent removed *in vacuo* to give the crude product. Flash chromatography (0 – 100% ethyl acetate/hexane) gave the pure product **2.3** as a crystalline white solid (1.08 g, 63%).

Mp 117 °C (ethyl acetate/hexane).

[α]$_D$ 15.5 (*c* 0.6, $CHCl_3$, 24 °C).

IR: 3367 (s), 2991 (w), 2971 (w), 1687 (s), 1520 (s) cm^{-1}.

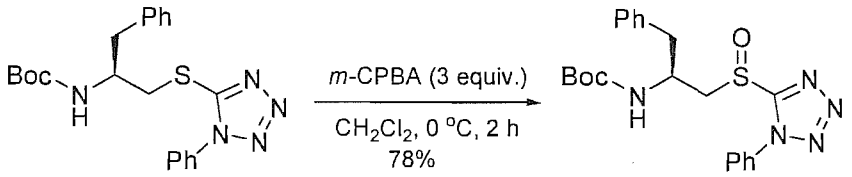
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.55 (5H, m, **ArH**); 7.26 – 7.20 (5H, m, **ArH**); 4.86 (1H, br s, **NH**); 4.24 – 4.17 (1H, m, **CH**); 3.63 (1H, dd, *J*= 13.6, 4.0 Hz, **CH$_2$**); 3.48 – 3.43 (1H, m, **CH$_2$**); 3.01 (1H, m, **CH$_2$**); 2.91 (1H, dd, *J*= 13.6, 7.0 Hz, **CH$_2$**); 1.35 (9H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 155.4 (**C**), 154.5 (**C**), 137.1 (**C**) 133.8 (**C**), 130.3 (**CH**), 129.9 (**CH**), 129.5 (**CH**), 128.8 (**CH**), 127.0 (**CH**), 124.1 (**CH**), 79.8 (**C**), 52.1 (**CH**), 40.6 (**CH$_2$**), 37.5 (**CH$_2$**), 28.4 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 845 ([2M + Na^+], 100%), 475 ([M + MeCN + Na^+], 30%), 434 ([M + Na^+], 95%).

Anal. Calcd for $C_{21}H_{25}N_5$: C, 61.13; H, 6.08; N, 17.03. Found: C, 61.04; H, 5.97; N, 16.67.

tert-Butyl (*S*)-1-(1-phenyl-1*H*-tetrazol-5-ylsulfinyl)-3-phenylpropan-2-ylcarbamate (2.4)



2.3 **2.4**

This procedure was adapted from the literature.[26]

A stirred ice-cold solution of sulphide **2.3** (1.0 equiv., 2.4 mmol, 1.00 g) in CH_2Cl_2 (30 mL) was treated with *m*-CPBA (3.0 equiv., 7.3 mmol, 1.26 g). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was treated with 10% sodium sulphite solution (80 mL) and diluted with CH_2Cl_2 (100 mL). The organics were washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10 – 50% ethyl acetate/hexane) gave the two diastereoisomers as white crystalline solids (Diasteroisomer A: 0.24 g, 23%, Diasteroisomer B: 0.30 g, 29%, total combined product including mixed fractions 0.81 g, 78%).

Diastereoisomer A

Mp 167 – 168 °C (ethyl acetate/hexane).

[α]$_D$ – 38.6 (*c* 1.1, $CHCl_3$, 26 °C).

IR: 3347 (s), 2982 (w), 2922 (w), 1687 (s), 1521 (s), 1047 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.58 (5H, m, **ArH**); 7.32 – 7.18 (5H, m, **ArH**); 4.95 (1H, br s, **NH**); 4.30 (1H, m, **CH**); 3.86 (2H, br s, **CH$_2$**); 3.13 – 3.11 (1H, m, **CH$_2$**); 3.00 -2.95 (1H, dd, *J*= 6.5, 7.0 Hz, **CH$_2$**); 1.33 (9H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 156.7 (**C**), 155.2 (**C**), 136.5 (**C**) 133.0 (**C**), 131.2 (**CH**), 129.9 (**CH**), 129.4 (**CH**), 129.0 (**CH**), 127.2 (**CH**), 125.1 (**CH**), 80.2 (**C**), 57.2 (**CH$_2$**), 48.1 (**CH**), 40.3 (**CH$_2$**), 28.3 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 1304 ([3M + Na^+], 10%), 877 ([2M + Na^+], 95%), 491 ([M + MeCN + Na^+], 55%), 450 ([M + Na^+], 100%).

Diastereoisomer B

Mp 138 – 139 °C (ethyl acetate/hexane).

[α]$_D$ 88.4 (*c* 1.1, $CHCl_3$, 26 °C).

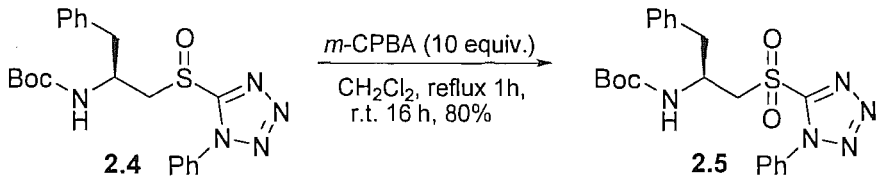
IR: 3367 (s), 2991 (w), 2971 (w), 1687 (s), 1520 (s), 1057 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 – 7.57 (2H, m, **ArH**); 7.56 – 7.55 (3H, m, **ArH**); 7.33 -7.17 (5H, m, **ArH**); 4.92 (1H, br d, *J*= 8.0 Hz, **NH**); 4.35 (1H, br d, *J*= 11.9 Hz, **CH$_2$**); 4.11 – 4.07 (1H, m, **CH**); 3.46 (1H, br t, *J*= 11.9 Hz, **CH$_2$**); 2.97 (2H, d, *J*= 6.5 Hz, **CH$_2$**); 1.17 (9H, s, **CH$_3$**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 156.4 (**C**), 155.5 (**C**), 135.8 (**C**) 133.2 (**C**), 130.9 (**CH**), 129.9 (**CH**), 129.3 (**CH**), 128.8 (**CH**), 127.1 (**CH**), 125.0 (**CH**), 80.1 (**C**), 59.8 (**CH$_2$**), 47.5 (**CH**), 40.2 (**CH$_2$**), 28.0 (**CH$_3$**) ppm.

LRMS (ES^+): *m/z* 877 ([2M + Na^+], 65%), 491 ([M + MeCN + Na^+], 55%), 450 ([M + Na^+], 95%), 372 (100).

tert-Butyl (*S*)-1-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)-3-phenylpropan-2-ylcarbamate (2.5)



A stirred ice-cold solution of **2.4** (1.0 equiv., 1.8 mmol, 0.75 g) in CH_2Cl_2 (20 mL) was treated with *m*-CPBA (10.0 equiv., 17.6 mmol, 3.04 g). The reaction mixture was allowed to warm to room temperature and then refluxed for 1 h. The reaction mixture was then allowed to stir at room temperature overnight. The reaction mixture was treated with 10% sodium sulphite solution (50 mL) and diluted with CH_2Cl_2 (60 mL). The organics were washed with saturated aqueous $NaHCO_3$ (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10 – 30% ethyl acetate/hexane) gave the product **2.5** as a white crystalline solid (0.62 g, 80%).

[α]$_D$ – 6.78 (*c* 0.6, MeOH, 26 °C).

IR: 3358 (m), 3006 (w), 2908 (w), 1767 (s), 1682 (s), 1349 (s), 1158 (s) cm^{-1}.

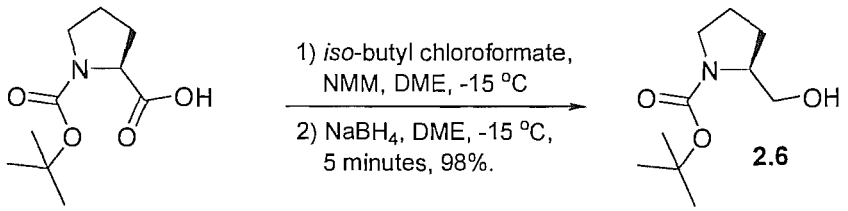
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.47 (5H, m, **ArH**); 7.24 – 7.07 (5H, m, **ArH**); 4.70 (1H, br s, **NH**); 4.23 – 4.38 (1H, m, **CH**); 3.97 (1H, dd, *J* = 15.1, 8.1 Hz, **CH$_2$**);

3.79 (1H, dd, J = 15.1, 4.5 Hz, C<u>H</u>$_2$); 2.99 – 3.08 (1H, m, C<u>H</u>$_2$); 2.94 (1H, dd, J = 13.6, 7.1 Hz, C<u>H</u>$_2$); 1.28 (9H, s, C<u>H</u>$_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 153.6 (<u>C</u>), 152.9 (<u>C</u>), 135.0 (<u>C</u>) 132.0 (<u>C</u>), 130.5 (<u>CH</u>), 128.6 (<u>CH</u>), 128.3 (<u>CH</u>), 127.9 (<u>CH</u>), 126.2 (<u>CH</u>), 124.4 (<u>CH</u>), 79.5 (<u>C</u>), 57.4 (<u>CH</u>$_2$), 47.1 (<u>CH</u>), 39.0 (<u>CH</u>$_2$), 27.2 (<u>CH</u>$_3$) ppm.

LRMS (ES^+): *m/z* 909 ([2M + Na^+], 40%), 507 ([M + MeCN + Na^+], 100%), 466 ([M + Na^+], 50%), 444 ([M + H^+], 30%).

(*S*)-*tert*-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (2.6)



iso-Butyl chloroformate (1.0 equiv., 6.1 mmol, 0.78 mL) was added slowly to an ice-cold solution of Boc-proline (1.0 equiv., 6.1 mmol, 1.30 g) and *N*-methylmorpholine (1.0 equiv., 6.1 mmol, 0.67 mL) in DME (15 mL). A white precipitate was seen to form and after 2 minutes stirring, the reaction mixture was filtered and the precipitate was washed with excess DME. The clear colourless filtrate was cooled in an ice-bath and sodium borohydride (1.5 equiv., 9.1 mmol, 0.34 g) was added portionwise to the reaction. After the final addition, the reaction was stirred for a further 5 minutes before quenching of the excess $NaBH_4$ with water (50 mL). The organics were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (60 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The white solid was used without further purification (1.19 g, 98%).

[α]$_D$ – 46.8 (*c* 1.0, MeOH, 27 °C), literature values – 52.48 (*c* 1.61, MeOH, 25 °C).[49]

IR: 3428 (m), 2979 (w), 2932 (w), 2872 (w), 1656 (s), 1365 (s), 1254 (s), 1054 (s) cm^{-1}.

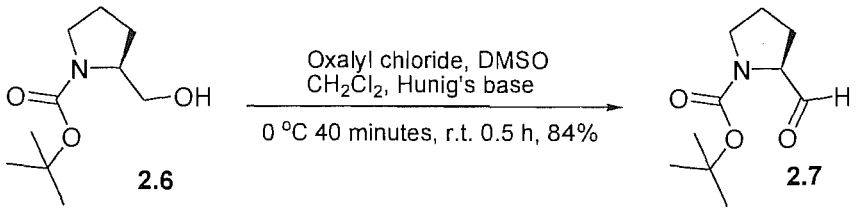
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (1H, m, <u>OH</u>); 3.92 (1H, m, <u>CH</u>); 3.63 – 3.51 (2H, m, C<u>H</u>$_2$); 3.47 – 3.35 (1H, m, C<u>H</u>$_2$); 3.35 – 3.21 (1H, m, C<u>H</u>$_2$); 2.05 – 1.90 (1H, m, C<u>H</u>$_2$); 1.86 – 1.68 (3H, m, C<u>H</u>$_2$); 1.44 (9H, s, C<u>H</u>$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 157.0 (**C**), 80.1 (**C**), 67.4 (**C**H_2) 60.1 (**C**H), 47.5 (**C**H_2), 28.7 (**C**H_2), 28.4 (**C**H_3), 24.0 (**C**H_2) ppm.

LRMS (ES^+): *m/z* 420 ([2M + NH_4^+], 100%), 265 ([M + MeCN + Na^+], 30%).

The data acquired corresponds to the literature values for this known compound.[27, 50]

(*S*)-*tert*-Butyl 2-formylpyrrolidine-1-carboxylate (2.7)



Synthesised according to literature procedure.[27]

A solution of dimethyl sulfoxide (2.2 equiv., 11.0 mmol, 1.68 mL) in CH_2Cl_2 (5 mL) was added dropwise to a solution of oxalyl chloride (1.2 equiv., 6.0 mmol, 0.51 mL) in CH_2Cl_2 (25 mL) stirred at – 78 °C. After 10 minutes stirring, a solution of alcohol **2.6** (1.0 equiv., 5.0 mmol, 1.00 g) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at – 78 °C for 0.5 h, Hünig's base (4.0 equiv., 20.0 mmol, 3.47 mL) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then washed with $HCl_{(Aq.)}$ (2.0 M, 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give the crude aldehyde. The crude product was purified by flash chromatography (10 – 50% ethyl acetate/hexane) to give the aldehyde **2.7** as a yellow oil (0.83 g, 84%) that was stored in a freezer.

[α]$_D$ – 109.29 (*c* 0.6, $CHCl_3$, 25 °C), literature values – 99.5 (*c* 0.61, $CHCl_3$, 25 °C).[49]

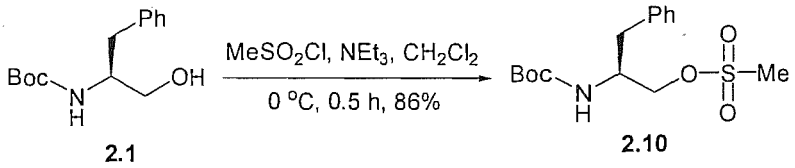
IR: 2975 (m), 2933 (w), 2878 (w), 1735 (s), 1687 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.51 and 9.43 (1H, 2 x br s, **CH**); 4.15 – 3.99 (1H, m, **CH**); 3.51 – 3.40 (2H, m, **C**H_2); 2.10 – 1.81 (4H, m, **C**H_2); 1.43 and 1.39 (9H, 2 x s, **C**H_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 200.4 and 200.1 (**C**H), 154.8 and 153.9 (**C**), 80.5 and 80.1 (**C**) 65.0 (**C**H), 46.6 (**C**H_2), 28.2 (**C**H_3), 27.9 (**C**H_2), 23.8 (**C**H_2) ppm.
LRMS (ES^+): *m/z* 838 ([4M + MeCN + H^+], 20%), 639 ([3M + MeCN + H^+], 80%), 440 ([2M + MeCN + H^+], 100%), 399 ([2M + H^+], 10%).

The data acquired corresponds to the literature values for this known compound.[27]

(*S*)-Methanesulfonic acid 2-*tert*-butoxycarbonylamino-3-phenyl-propyl ester (2.10)



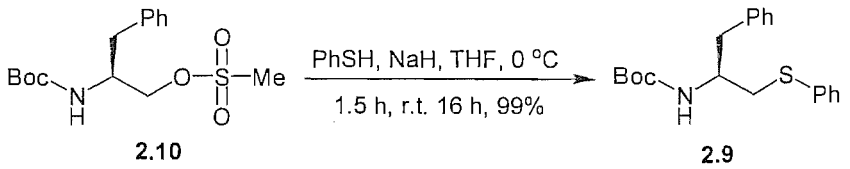
2.1 **2.10**

Methanesulfonyl chloride (2.5 equiv., 5.0 mmol, 0.39 mL) was added slowly to an ice-cold solution of alcohol **2.1** (1.0 equiv., 2.0 mmol, 0.50 g) and triethylamine (3.0 equiv., 6.0 mmol, 0.83 mL) in CH_2Cl_2 (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for 0.5 h. Water (20 mL) was added to the reaction and the two layers separated. The organics were washed with water (20 mL) and brine (20 mL) then dried over $MgSO_4$, filtered and concentrated. The crude product was recrystallised from ethyl acetate and *n*-hexane to give white needle-like crystals (0.54 g, 86%).

Mp 113 – 114 °C (ethyl acetate/hexane), literature 116 – 117 °C.[29]
[α]$_D$ – 21.1 (*c* 0.6, MeOH, 27 °C), literature values – 17.4 (*c* 1.0, $CHCl_3$).[51]
IR: 3354 (m), 2975 (w), 2936 (w), 1692 (s), 1526 (s), 1343 (s), 1162 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.12 (5H, m, **ArH**); 4.72 (1H, br s, **NH**); 4.32 – 4.18 (1H, m, **CH**); 4.17 – 4.01 (2H, m, **C**H_2); 3.01 (3H, s, **C**H_3); 2.95 – 2.77 (2H, m, **C**H_2); 1.42 (9H, s, **C**H_3) ppm.
LRMS (ES^+): *m/z* 681 ([2M + MeOH + Na^+], 100%), 393 ([M + MeCN + K^+], 70%), 352 ([M + K^+], 55%).

The data acquired corresponds to the literature values for this known compound.[51-53]

tert-Butyl (*S*)-3-phenyl-1-(phenylthio)propan-2-ylcarbamate (2.9)



2.10 **2.9**

Synthesised according to literature procedure.[29]

Thiophenol (1.1 equiv., 13.0 mmol, 1.37 mL) was added dropwise to a stirred ice-cold solution of NaH (60% in mineral oil, 1.1 equiv., 13.0 mmol, 0.52 g) in THF (50 mL). The reaction mixture was stirred for 0.5 h before a solution of **2.10** (1.0 equiv., 12.0 mmol, 4.00 g) in THF (50 mL) was added to the reaction mixture over 0.5 h. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with water (50 mL) and the solvent removed *in vacuo*. The remaining aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), the combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give the crude product. The product was purified by flash chromatography (10 – 50% ethyl acetate/hexane) to give **2.9** as white needle-like crystals (4.06 g, 99%).

Mp 80 - 83 °C (ethyl acetate/hexane).

[α]$_D$ 26.1 (*c* 0.6, MeOH, 27 °C).

IR: 3368 (m), 2974 (w), 2922 (w), 1692 (s), 1523 (s), 1263 (s), 1022 (s) cm^{-1}.

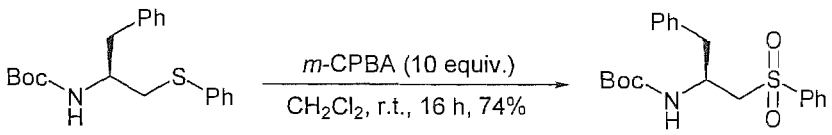
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 – 7.06 (10H, m, **ArH**); 4.65 (1H, br s, **NH**); 4.05 (1H, m, **CH**); 3.03 (2H, d, *J* = 5.9 Hz, **CH_2**); 2.91 (2H, d, *J* = 7.0 Hz, **CH_2**); 1.39 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 155.1 (**C**), 137.5 (**C**), 135.2 (**C**) 129.7 (**CH**), 129.4 (**CH**), 129.0 (**CH**), 128.5 (**CH**), 126.6 (**CH**), 126.3 (**CH**), 81.3 (**C**), 51.3 (**CH**), 39.5 (**CH_2**), 37.8 (**CH_2**), 28.3 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 709 ([2M + Na^+], 10%), 687 ([2M + H^+], 30%), 366 ([M + Na^+], 30%), 344 ([M + H^+], 50%), 288 ([M – ^{t}Bu + H^+], 100%), 244 ([M – Boc + H^+], 50%).

No literature data reported for this known compound.[29, 54]

tert-Butyl (*S*)-3-phenyl-1-(phenylsulfonyl)propan-2-ylcarbamate (2.11)



2.9 **2.11**

A stirred ice-cold solution of sulphide **2.9** (1.0 equiv., 9.2 mmol, 3.17 g) in CH_2Cl_2 (150 mL) was treated with *m*-CPBA (10.0 equiv., 92.3 mmol, 15.93 g). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was treated with 10% sodium sulphite solution (250 mL) and diluted with CH_2Cl_2 (250 mL). The organics were washed with saturated aqueous $NaHCO_3$ (2 x 250 mL), brine (250 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was triturated with *n*-hexane and the white solid was then recrystallised from methanol giving the pure sulfone **2.11** as a white crystalline solid (2.57 g, 74%).

Mp 206 – 208 °C (methanol), literature 207 – 209 °C (methanol).[55]

$[\alpha]_D$ – 37.9 (*c* 0.5, MeOH/CH_3CN 1/1, 27 °C), literature values – 32.7 (*c* 0.5, DMSO, 20 °C).[28]

IR: 3380 (m), 2976 (w), 2920 (w), 1692 (s), 1520 (s), 1267 (s), 1046 (s) cm^{-1}.

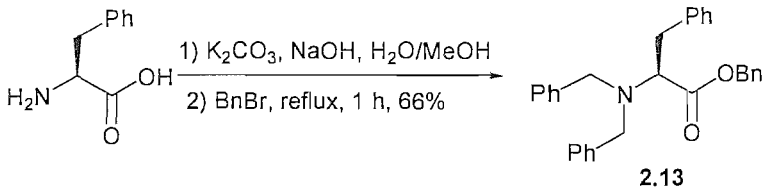
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.07 – 7.58 (5H, m, **ArH**); 7.42 – 7.11 (4H, m, **ArH**); 6.84 (1H, d, **ArH**); 4.10 (1H, br s, **NH**); 3.64 (1H, dd, *J* = 14.6, 8.5 Hz, **CH**); 3.43 (2H, dd, *J* = 14.6, 3.5 Hz, **CH_2**); 2.95 – 2.74 (2H, m, **CH_2**); 1.35 (9H, s, **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6): δ 154.2 (**C**), 139.5 (**C**), 137.6 (**C**) 133.6 (**CH**), 129.2 (**CH**), 129.1 (**CH**), 128.1 (**CH**), 127.7 (**CH**), 126.2 (**CH**), 77.6 (**C**), 58.2 (**CH_2**), 47.5 (**CH**), 40.7 (**CH_2**), 28.1 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 773 ([2M + Na^+], 100%), 751 ([2M + H^+], 10%), 398 ([M + Na^+], 40%).

The data acquired corresponds to the literature values for this known compound.[28]

(*S*)-2-Dibenzylamino-3-phenyl-propionic acid benzyl ester (2.13)



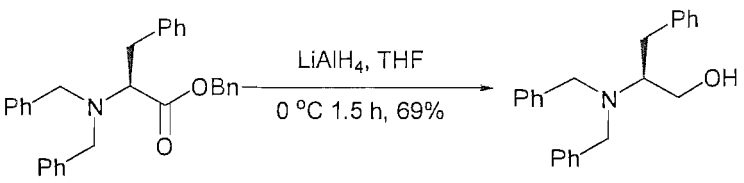
2.13

A suspension of (*S*)-phenylalanine (1.0 equiv., 50.0 mmol, 8.25 g) in a 1:1 mixture of methanol and water (120 mL) was refluxed. On reaching reflux, solid K_2CO_3 (1.7 equiv., 84.0 mmol, 11.61 g) and NaOH (1.7 equiv., 84.0 mmol, 3.36 g) was added to the reaction mixture. The refluxing suspension slowly became a clear colourless solution; the solution was refluxed for a further 10 minutes. Benzyl bromide (3.0 equiv., 150.0 mmol, 17.84 mL) was then added to the reaction which became instantaneously white and cloudy. The reaction was refluxed for another 1 h, over which time the reaction again became a clear colourless solution. The reaction mixture was allowed to cool to room temperature and extracted with diethyl ether (3 x 120 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give a viscous clear oil. Flash chromatography (10 – 100% ethyl acetate/hexane) gave the pure product **2.13** as a viscous clear colourless oil (14.3 g, 66%).

[α]$_D$ – 78.5 (*c* 0.9, $CHCl_3$, 26 °C), literature values – 72.9 (*c* 1.8, $CHCl_3$, 20 °C).[35]
IR: 3027 (m), 2928 (w), 2845 (w), 1728 (s) cm^{-1}.
^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.39 – 7.21 (5H, m, **ArH**); 7.19 – 7.11 (13H, m, **ArH**); 7.01 – 6.98 (2H, m, **ArH**); 5.23 (1H, d, *J* = 12.1 Hz, **CH$_2$**); 5.12 (1H, d, *J* = 12.1 Hz, **CH$_2$**); 3.92 (2H, d, *J* = 13.9 Hz, **CH$_2$**); 3.71 (1H, dd, *J* = 8.1, 7.3 Hz, **CH**); 3.54 (2H, d, *J* = 13.9 Hz, **CH$_2$**); 3.14 (1H, dd, *J* = 13.9, 7.3 Hz, **CH$_2$**); 2.99 (1H, dd, *J* = 13.9, 8.1 Hz, **CH$_2$**) ppm.
^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$): δ 172.3 (**C**), 139.4 (**C**), 138.2 (**C**), 136.1 (**C**), 129.6 (**CH**) 128.9 (**CH**), 128.7 (**CH**), 128.6 (**CH**), 128.5 (**CH**), 128.3 (**CH**), 128.2 (**CH**), 127.0 (**CH**), 126.4 (**CH**), 66.2 (**CH$_2$**), 62.6 (**CH**), 54.6 (**CH$_2$**), 35.8 (**CH$_2$**) ppm.
LRMS (ES^+): *m/z* 436 ([M + H^+], 100%).

The data acquired corresponds to the literature values for this known compound.[35]

(*S*)-2-Benzylamino-3-phenyl-propanol (2.14)



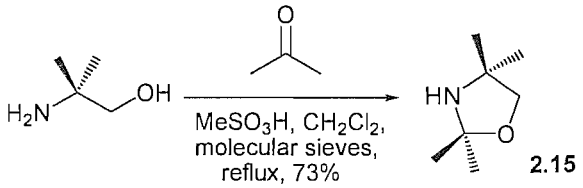
2.13 **2.14**

A solution of benzyl ester **2.13** (1.0 equiv., 20.2 mmol, 8.80 g) in THF (50 mL) was added slowly to a stirring ice-cold solution of lithium aluminium hydride (2.1 equiv., 42.5 mmol, 1.61 g) in THF (200 mL). The reaction was stirred for 1.5 h at 0 °C before warming to room temperature. Water (1.61 mL), 2M aqueous NaOH (1.61 mL) and water (4.84 mL) was added to the reaction in that order. The reaction was stirred for 10 minutes and then filtered. The granular solid was washed with excess THF and the filtrate concentrated. The residue was redissolved in CH_2Cl_2 (150 mL) and washed with water (2 x 150 mL) and brine (150 mL). The organics were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (50% ethyl acetate/hexane) gave the product **2.14** as a white crystalline solid (4.60 g, 69%).

Mp 65 – 67 °C (diethyl ether/hexane), literature 69 – 71 °C.[35]
[α]$_D$ 42.3 (*c* 0.7, $CHCl_3$, 26 °C), literature values 38.4 (*c* 1.5, $CHCl_3$, 20 °C).[35]
IR: 3384 (s), 3025 (w), 2924 (w), 695 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.09 (15H, m, **ArH**); 3.93 (2H, d, *J* = 13.1 Hz, **CH$_2$**); 3.54 – 3.48 (3H, m); 3.38 – 3.33 (1H, m); 3.14 – 3.04 (2H, m); 2.96 (1H, br s, **OH**); 2.47 – 2.41 (1H, m) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 139.6 (**C**), 139.5 (**C**), 129.4 (**CH**) 129.0 (**CH**), 128.8 (**CH**), 128.0 (**CH**), 127.7 (**CH**), 126.7 (**CH**), 61.4 (**CH**), 60.8 (**CH$_2$**), 53.7 (**CH$_2$**), 32.2 (**CH$_2$**) ppm.
LRMS (ES^+): *m/z* 346 ([M + H^+], 100%).

The data acquired corresponds to the literature values for this known compound.[35]

2,2,4,4-Tetramethyl-oxazolidine (2.15)



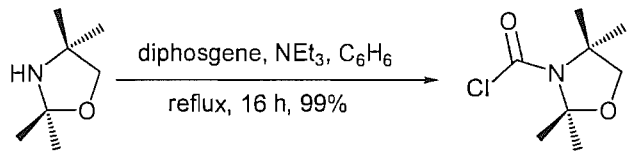
2.15

Pre-dried molecular sieves (4 Å, 3.0 g) were added to 30 mL of CH_2Cl_2 under argon and stirred at room temperature for 10 minutes. 2-Amino-2-methylpropanol (1.0 equiv., 50.0 mmol, 4.82 mL), acetone (1.4 equiv., 70.7 mmol, 4.11 g) and 0.5 mL of $MeSO_3H$ were added to the reaction mixture in that order. The reaction mixture was refluxed for 48 h under argon, allowed to cool to room temperature and the molecular sieves were filtered. The solution was dried over $MgSO_4$, filtered and concentrated. The resulting yellow oil was carefully distilled (b.pt. 132 – 134 °C, literature b.pt. 132 – 134 °C[36]) to give the product **2.15** as a clear colourless oil (4.71 g, 73%).

IR: 3318 (s), 2969 (s), 2925 (w), 1052 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (2H, s, **C<u>H</u>$_2$**); 1.71 (1H, br s, **N<u>H</u>**); 1.39 (6H, s, **C<u>H</u>$_3$**); 1.26 (6H, s, **C<u>H</u>$_3$**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 95.1 (**<u>C</u>**), 77.0 (**<u>C</u>H$_2$**), 59.4 (**<u>C</u>**), 28.6 (**<u>C</u>H$_3$**) 28.1 (**<u>C</u>H$_3$**) ppm.
LRMS (ES^+): *m/z* 171 ([M + MeCN +H^+], 15%), 130 ([M + H^+], 100%).

The data acquired corresponds to the literature values for this known compound.[36]

2,2,4,4-Tetramethyloxazolidine-3-carbonyl chloride (2.16)



2.15 2.16

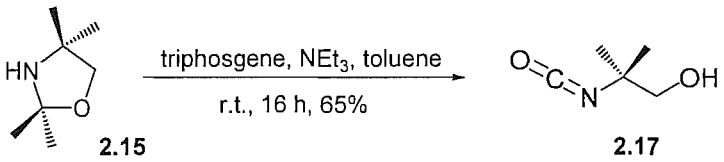
A solution of oxazolidine **2.15** (1.7 equiv., 38.8 mmol, 5.00 g) and triethylamine (1.5 equiv., 33.0 mmol, 4.60 mL) in benzene (25 mL) was added slowly to a solution of diphosgene (1.0 equiv., 22.0 mmol, 2.70 mL) in benzene (75 mL). A white precipitate formed and white fumes were seen, the reaction mixture was

then refluxed overnight. The resulting brown slurry was poured onto 2N aqueous HCl (100 mL) and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organics were washed with aqueous saturated $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and concentrated. Residual solvent was removed under vacuum to give the pure product **2.16** as a pale yellow oil (4.16 g, 99%).

^{1}H NMR (300 MHz, $CDCl_3$, two rotamers seen): δ 3.75 (1H, s, C**H**$_2$); 3.69 (1H, s, C**H**$_2$); 1.64 (3H, s, C**H**$_3$); 1.52 (3H, s, C**H**$_3$); 1.47 (3H, s, C**H**$_3$); 1.38 (3H, s, C**H**$_3$) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$, two rotamers seen): δ 142.6 (**C**), 141.4 (**C**), 98.0 (**C**), 96.3 (**C**), 76.5 (**C**H_2), 75.0 (**C**H_2), 63.8 (**C**), 61.2 (**C**), 25.7 (**C**H_3), 24.3 (**C**H_3), 23.4 (**C**H_3), 22.4 (**C**H_3) ppm.
LRMS (ES^+): *m/z* 192 ([M + H^+], 20%), 130 ([M – COCl + H^+], 100%).

The data acquired corresponds to the literature values for this known compound.[36]

2-Isocyanato-2-methylpropan-1-ol (2.17)



2.15 **2.17**

A solution of oxazolidine **2.15** (2.6 equiv., 5.2 mmol, 0.70 g) and triethylamine (2.6 equiv., 5.4 mmol, 0.76 mL) in toluene (5 mL) was added slowly to an ice-cold solution of triphosgene (1.0 equiv., 2.1 mmol, 0.63 g) in toluene (20 mL). The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was filtered and the solid washed with toluene. Water (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with water (60 mL), aqueous $NaHCO_3$ (60 mL), brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The crude yellow oil was purified by flash chromatography (50% ethyl acetate/hexane) to give **2.17** as a pale yellow crystalline solid (0.40 g, 65%).

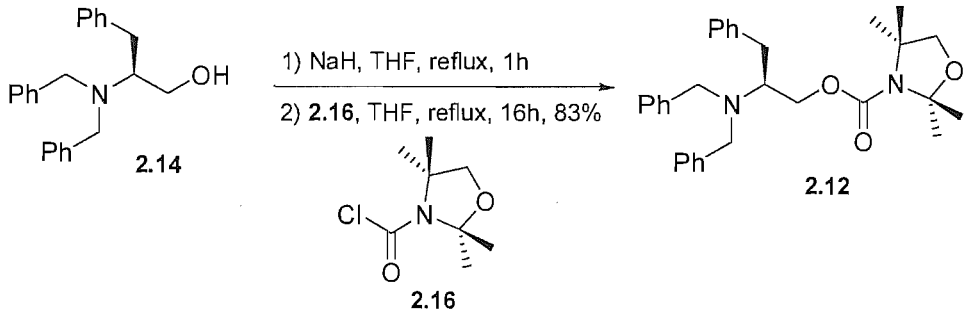
Mp 43 – 45 °C (ethyl acetate/hexane).
IR: 3213 (s), 2973 (s), 1727 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (1H, br s, O**H**); 4.08 (2H, s, C**H**$_2$); 1.36 (6H, s, C**H**$_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 159.5 (**C**), 76.9 (**C**H_2), 55.2 (**C**), 27.3 (**C**H_3) ppm.

LRMS (ES^+): *m/z* 368 ([3M + Na^+], 30%), 253 ([2M + Na^+], 10%), 179 ([M + MeCN + Na^+], 30%), 157 ([M + MeCN + H^+], 5%).

(*S*)-2-(Dibenzylamino)-3-phenylpropyl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (2.12)



Synthesised according to literature procedure.[34]

A solution of **2.14** (1.0 equiv., 20.0 mmol, 6.62 g) in THF (20 mL) was added dropwise to an ice-cold suspension of NaH (60% in mineral oil, 1.25 equiv., 25.0 mmol, 1.00 g) in THF (200 mL). The reaction mixture was refluxed for 1 h, a solution of **2.16** (1.1 equiv., 22.0 mmol, 4.20 g) in THF (20 mL) was added and the reaction mixture was refluxed overnight. On cooling, water (100 mL) and diethyl ether (100 mL) was added to the reaction mixture. The aqueous layer was extracted with diethyl ether (3 x 100 mL), the combined organics were then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (10 – 15% ethyl acetate/hexane) to give product **2.12** as a clear colourless oil (8.08 g, 83%).

[α]$_D$ – 4.0 (*c* 0.6, $CHCl_3$, 24 °C), literature values – 6.4 (*c* 1.0, $CHCl_3$, 20 °C).[34]

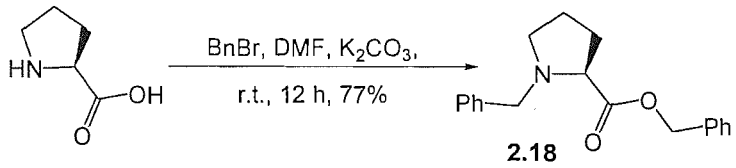
IR: 2981 (w), 2934 (w), 2866 (w), 1691 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.18 (13H, m, **Ar**H); 7.07 – 7.05 (2H, m, **Ar**H); 4.36 (1H, dd, *J*= 6.0, 11.3 Hz, C**H**$_2$); 4.21 – 4.17 (1H, m, C**H**$_2$); 3.79 – 3.67 (6H, m, 2x C**H**$_2$); 3.25 – 3.23 (1H, m, C**H**); 3.01 (1H, dd, *J*= 13.9, 7.7 Hz, C**H**$_2$); 2.98 – 2.73 (1H, m, C**H**$_2$); 1.59 – 1.53 (6H, m, 2x C**H**$_3$); 1.44 – 1.28 (6H, m, 2x C**H**$_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 153.2 (**C**), 155.2 (**C**), 140.0 (**C**) 129.7 (**CH**), 129.2 (**CH**), 128.7 (**CH**), 128.5 (**CH**), 127.2 (**CH**), 126.5 (**CH**), 96.5 (**C**), 95.2 (**C**), 76.9 and 76.5 ($\underline{C}H_2$), 63.9 ($\underline{C}H_2$), 61.2 (**C**), 60.0 (**C**), 59.0 (**CH**), 54.3 ($\underline{C}H_2$), 35.3 and 35.1 ($\underline{C}H_2$), 27.2 and 27.0 ($\underline{C}H_3$), 25.9 and 25.8 ($\underline{C}H_3$), 24.6 and 24.5 ($\underline{C}H_3$) ppm.

LRMS (ES^+): *m/z* 487 ([M + H^+], 100%).

(*S*)-Benzyl 1-benzylpyrrolidine-2-carboxylate (2.18)



2.18

To a suspension of L-proline (1.0 equiv., 50.0 mmol, 5.76 g) in DMF (125 mL) was added anhydrous K_2CO_3 (2.5 equiv., 125.0 mmol, 17.28 g) and benzyl bromide (2.0 equiv., 100.0 mmol, 11.89 mL). The reaction mixture was stirred rapidly for 12 h, after which the resulting slurry was diluted with diethyl ether (125 mL) and filtered. The organic filtrate was washed with water (4 x 1 L), dried over $MgSO_4$, filtered and concentrated to give a thick oil. Flash chromatography (10 – 100% ethyl acetate/hexane) gave the pure product **2.18** as a viscous clear colourless oil (11.4 g, 77%).

[α]$_D$ – 56.2 (*c* 0.7, $CDCl_3$, 27 °C), literature values – 55.1 (*c* 1.0, $CDCl_3$, 20 °C).[37]

IR: 3028 (w), 2954 (w), 2800 (w), 1729 (s) cm^{-1}.

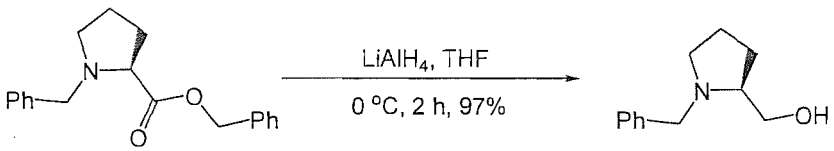
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.14 (10H, m, **ArH**); 5.13 (1H, d, *J* = 12.6 Hz, $\underline{C}H_2$); 5.09 (1H, d, *J* = 12.6 Hz, $\underline{C}H_2$); 3.92 (1H, d, *J* = 13.1 Hz, $\underline{C}H_2$); 3.56 (1H, d, *J* = 13.1 Hz, $\underline{C}H_2$); 3.31 (1H, dd, *J* = 8.5, 6.0 Hz, **CH**); 2.94 – 3.09 (1H, m, $\underline{C}H_2$); 2.44 – 2.38 (1H, m, $\underline{C}H_2$); 2.18 – 2.06 (1H, m, $\underline{C}H_2$); 2.01 – 1.82 (2H, m, $\underline{C}H_2$); 1.82 – 1.71 (1H, m, $\underline{C}H_2$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 173.9 (**C**), 138.5 (**C**), 136.0 (**C**), 129.1 (**CH**), 128.5 (**CH**), 128.2 (**CH**), 128.1 (**CH**), 127.5 (**CH**), 127.0 (**CH**), 66.2 ($\underline{C}H_2$), 65.2 (**CH**), 58.5 ($\underline{C}H_2$), 53.1 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 23.1 ($\underline{C}H_2$) ppm.

LRMS (ES^+): *m/z* 296 ([M + H^+], 100%).

The data acquired corresponds to the literature values for this known compound.[37]

((*S*)-1-Benzylpyrrolidin-2-yl)-methanol (2.19)



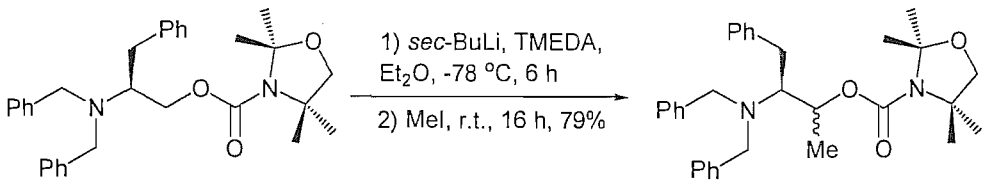
2.18 **2.19**

A solution of benzyl ester **2.18** (1.0 equiv., 16.9 mmol, 5.00 g) in THF (25 mL) was added slowly to a stirring ice-cold solution of lithium aluminium hydride (2.1 equiv., 35.6 mmol, 1.35 g) in THF (100 mL). The reaction was stirred for 2 h at 0 °C before warming to room temperature. Water (1.35 mL), 2M aqueous NaOH (1.35 mL) and water (4.05 mL) were added to the reaction in that order. The reaction was stirred for 20 minutes and then filtered. The granular solid was washed with excess THF and the filtrate concentrated. The residue was redissolved in CH_2Cl_2 (150 mL) and washed with water (2 x 150 mL) and brine (150 mL). The organics were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (50% ethyl acetate/hexane) gave the product **2.19** as a clear yellow oil (3.12 g, 97%).

[α]$_D$ – 65.7 (*c* 0.8, $CDCl_3$, 27 °C).
IR: 3366 (m), 2945 (m), 2872 (m), 2798 (m), 734 (s), 697 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.17 (5H, m, **ArH**); 3.96 (1H, d, *J* = 13.0 Hz, **CH$_2$**); 3.65 (1H, dd, *J* = 10.8, 3.7 Hz, **CH$_2$**); 3.42 (1H, dd, *J* = 10.8, 2.2 Hz, **CH$_2$**); 3.36 (1H, d, *J* = 13.0 Hz, **CH$_2$**); 3.05 – 2.89 (1H, m, **CH**); 2.80 – 2.67 (1H, m, **CH$_2$**); 2.59 (1H, br s, **OH**); 2.37 – 2.22 (1H, m, **CH$_2$**); 2.01 – 1.76 (2H, m, **CH$_2$**); 1.76 – 1.60 (2H, m, **CH$_2$**) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$): δ 139.3 (**C**), 128.7 (**CH**), 128.3 (**CH**), 127.0 (**CH**), 64.3 (**CH**), 61.8 (**CH$_2$**), 58.6 (**CH$_2$**), 54.4 (**CH$_2$**), 27.8 (**CH$_2$**), 23.4 (**CH$_2$**) ppm.
LRMS (ES^+): *m/z* 192 ([M + H^+], 100%).

The data acquired corresponds to the available literature values for this known compound.[39]

(*S*)-3-(Dibenzylamino)-4-phenylbutan-2-yl 2,2,4,4-tetramethyloxazolidine-3-carboxylate (2.21)



2.12 **2.21**

sec-Butyl lithium was filtered through a pad of celite under argon and washed through with excess dry diethyl ether. The clear *sec*-BuLi was titrated and used immediately. The starting material **2.12** (1.0 equiv., 0.2 mmol, 0.10 g) was dried under high vacuum for 0.5 h prior to use and was then dissolved in dry diethyl ether (10 mL) and cooled to – 78 °C. Freshly distilled TMEDA (2.0 equiv., 0.4 mmol, 0.06 mL) and the filtered *sec*-BuLi (2.0 equiv., 0.87 M, 0.47 mL) were added. The reaction mixture was stirred at – 78 °C for 6 hours and slowly changed from colourless to bright orange. Methyl iodide (3.0 equiv., 0.6 mmol, 0.04 mL) was added to the reaction mixture upon which it turned a pale cloudy yellow colour. The reaction mixture was then allowed to warm to room temperature and to stir overnight. Water (25 mL) was added to the reaction mixture and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (5 – 33% ethyl acetate/hexane) gave the pure product **2.21** as a clear colourless oil (0.08 g, 79%).

IR: 2977 (w), 2931 (w), 2867 (w), 1688 (s) cm^{-1}.

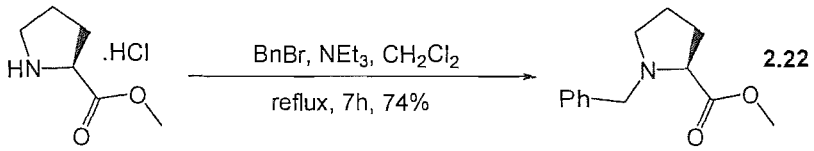
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 6.86 (15H, m, **ArH**); 5.55 – 5.35 (1H, m, **OCH**); 3.76 – 3.44 (6H, m, **NCH_2** & **OCH_2**); 2.99 – 2.79 (3H, m, **$PhCH_2$** & **NCH**); 1.59 – 1.10 (15H, m, 5 x **CH_3**) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 152.2 (**C**), 151.5 (**C**), 140.6 (**C**), 139.7 (**C**), 129.4 (**CH**), 128.6 (**CH**), 128.1 (**CH**), 128.0 (**CH**), 126.7 (**CH**), 125.9 (**CH**), 96.1 (**C**), 94.6 (**C**), 76.3 (**CH**), 76.0 (**CH_2**), 69.6 (**CH**), 69.5 (**CH**), 62.8 (**CH**), 53.7 (**CH_2**), 33.0 (**CH_2**), 32.9 (**CH_2**), 26.7 (**CH_3**), 26.3 (**CH_3**), 25.8 (**CH_3**), 25.7 (**CH_3**), 25.3 (**CH_3**), 25.0 (**CH_3**), 24.3 (**CH_3**), 24.2 (**CH_3**), 19.7 (**CH_3**), 19.6 (**CH_3**) ppm.

LRMS (ES^+): *m/z* 523 ([M + Na^+], 10%), 501 ([M + H^+], 100%).

The data acquired corresponds to the literature values for this known compound.[34]

(*S*)-Methyl 1-benzylpyrrolidine-2-carboxylate (2.22)



2.22

Triethylamine (2.0 equiv., 12.0 mmol, 1.67 mL) was added to a solution of (*S*)-methyl pyrrolidine-2-carboxylate hydrochloride (1.0 equiv., 6.0 mmol, 1.00 g) in CH_2Cl_2 (20 mL). A cloudy white precipitate was seen to form. Benzyl bromide (2.0 equiv., 12.0 mmol, 1.43 mL) was then added and the reaction mixture was heated to reflux. The reaction mixture was refluxed for 7 hours after which the reaction was allowed to cool to room temperature. The pink solution was diluted with $CHCl_3$ (20 mL) and 2N aqueous NaOH (20 mL). The organics were separated and washed with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (1 – 25% ethyl acetate/ hexane) gave the pure product **2.22** as a clear yellow oil (0.98 g, 74%).

$[\alpha]_D$ – 79.1 (*c* 0.7, MeOH, 25 °C), literature value for *R*-enatiomer 73.8 (*c* 2.2, $CHCl_3$, 24 °C).[43]

IR: 2949 (w), 2795 (w), 1731 (s) cm^{-1}.

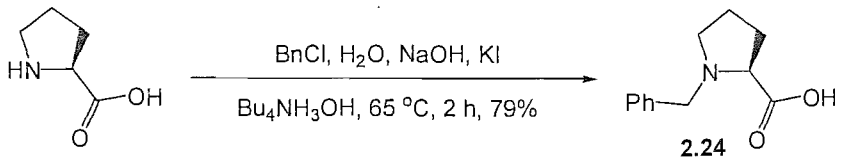
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.26 (5H, m, **ArH**); 3.90 (1H, d, *J* = 12.8 Hz, **CH_2**); 3.65 (3H, s, **CH_3**); 3.59 (1H, d, *J* = 12.8 Hz, **CH_2**); 3.28 – 3.23 (1H, m); 3.08 – 3.01 (1H, m); 2.41 – 1.79 (5H, m) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 174.6 (**C**), 138.3 (**C**), 129.2 (**CH**) 128.2 (**CH**), 127.1 (**CH**), 65.3 (**CH**), 58.7 (**CH_2**), 53.3 (**CH_2**), 51.8 (**CH_3**), 29.4 (**CH_2**), 23.0 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 242 ([M + Na^+], 20%), 220 ([M + H^+], 100%).

The data acquired corresponds to the literature values for the *R* -enantiomer of this compound.[43]

(*S*)-1-Benzylpyrrolidine-2-carboxylic acid (2.24)



2.24

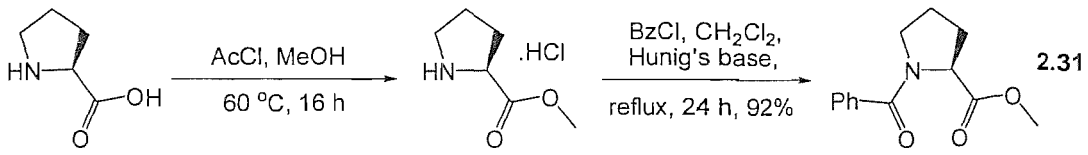
Synthesised according to literature procedure.[43]

L-Proline (1.0 equiv., 87 mmol, 10.0 g), KI (0.02 equiv., 1.7 mmol, 289 mg) and tetrabutylammonium hydroxide (40% in H_2O, 0.01 equiv., 0.87 mmol, 0.56 mL) were dissolved in water (65 mL) and 2M NaOH (45 mL) and stirred at room temperature. Benzyl chloride (1.26 equiv., 110 mmol, 12.5 mL) was added to the reaction mixture which turned white and cloudy. The reaction mixture was heated to 65 °C for 2 h. The cooled reaction mixture was then neutralised with 2M $HCl_{(Aq.)}$ (approx. 12 mL). Partial concentration *in vacuo* and addition of EtOH (100 mL) produced a white precipitate that was filtered off. Concentration of the filtrate produced a very sticky solid, washing with acetone allowed the filtering of the remaining white solid. The combined white solid was recrystallised from hot acetone to give the product **2.24** as a crystalline white solid (14.03 g, 79%).

Mp 170 – 171 °C (acetone), literature 177 – 179 °C.[56]
[α]$_D$ – 31.0 (*c* 0.6, MeOH, 25 °C), literature values – 29.1 (*c* 1.0, MeOH, 20 °C).[57]
IR: 3373 - 2874 (m), 1633 (s) cm^{-1}.
^{1}H NMR (400 MHz, MeOH): δ 7.37 – 7.63 (5H, m, **ArH**); 4.87 (1H, br s, **OH**); 4.53 (1H, d, *J* = 12.8 Hz, **CH$_2$**); 4.33(1H, d, *J* = 12.8 Hz, **CH$_2$**); 4.15 (1H, dd, *J* = 9.3, 7.3 Hz, **CH**); 3.61 – 3.48 (1H, m); 3.39 – 3.23 (1H, m); 2.59 – 2.46 (1H, m); 2.24 – 2.08 (2H, m); 2.04 – 1.87 (1H, m) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 174.5 (**C**), 132.2 (**C**), 132.1 (**CH**) 131.5 (**CH**), 130.7 (**CH**), 69.2 (**CH**), 60.0 (**CH$_2$**), 55.9 (**CH$_2$**), 30.0 (**CH$_2$**), 24.1 (**CH$_2$**) ppm.

The data acquired corresponds to the available literature values for this known compound.[56]

(*S*)-Methyl-1-benzoyl-pyrrolidine-2-carboxylate (2.31)



Synthesised according to literature procedure.[46]

A solution of acetyl chloride (3.0 equiv., 78 mmol, 5.55 mL) in dry methanol (100 mL) was stirred at 0 °C for 10 minutes. L-Proline (1.0 equiv., 26 mmol, 3.00 g) was added and the reaction mixture was heated to 60 °C overnight. The reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo*. Diethyl ether (100 mL) was added and the reaction was concentrated. This repeated a further six times to give the pure methyl ester as a clear colourless oil (characterised by ^{1}H NMR – corresponds to literature values). The methyl ester was dissolved in CH_2Cl_2 (250 mL), Benzoyl chloride (2.0 equiv., 52 mmol, 6.04 mL) and Hünig's base (3.0 equiv., 78 mmol, 9.51 mL) were added and the resultant mixture was heated to reflux for 24h. The solvent was removed *in vacuo* to give a yellow solid. This was redissolved in CH_2Cl_2 (100 mL) and washed with saturated aqueous $NaHCO_3$ (2 x 150 mL) followed by brine (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give a yellow oil. The crude product was purified by flash chromatography (10 – 75% ethyl acetate/hexane) to give **2.31** as a clear pale yellow oil that slowly crystallised (5.56 g, 92%).

Mp 81 – 82 °C (diethyl ether/hexane).

[α]$_D$ – 92.9 (*c* 0.7, MeOH, 23 °C).

IR: 2951 (w), 2878 (w), 1739 (s), 1621 (s) cm^{-1}.

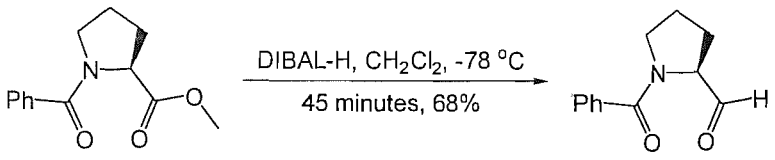
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 – 7.31 (5H, m, **ArH**); 4.68 (1H, dd, *J* = 8.4, 5.1 Hz, **CH**); 3.78 (3H, s, **CH_3**); 3.70 – 3.59 (1H, m); 3.59 – 3.46 (1H, m); 2.42 – 2.20 (1H, m); 2.09 – 1.84 (3H, m) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 172.7 (**C**), 169.6 (**C**), 136.2 (**C**), 130.1 (**CH**) 128.2 (**CH**), 127.2 (**CH**), 59.1 (**CH_3**), 52.2 (**CH**), 49.8 (**CH_2**), 29.3 (**CH_2**), 25.3 (**CH_2**) ppm.

LRMS (ES^+): *m/z* 722 ([3M + Na^+], 30%), 717 ([3M + NH_4^+], 10%), 530 ([2M + MeCN + Na^+], 10%), 489 ([2M + H^+], 100%), 484 ([2M + NH_4^+], 30%), 467 ([2M + H^+], 20%), 297 ([2M + MeCN + Na^+], 40%), 234 ([M + H^+], 40%).

The data acquired corresponds to the available literature values for this known compound.[46]

(*S*)-1-Benzoyl-pyrrolidine-2-carbaldehyde (2.30)



2.31 **2.30**

DIBAL (2.5 equiv., 1.0 M, 16.10 mL) was added slowly to a solution of ester **2.31** (1.0 equiv., 6.44 mmol, 1.50 g) in CH_2Cl_2 (75 mL) at -78 °C. The colourless solution turned a bright yellow and was stirred at -78 °C for 45 minutes. The reaction was then quenched with MeOH (12 mL) and a solution of Rochelle's salt (100 mL) was added. The mixture was stirred at room temperature for 1 h. The aqueous layer was extracted with ethyl acetate (3 x 80 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (1 – 50% ethyl acetate/hexane) gave the product **2.30** as a pale brown oil (0.89 g, 68%).

IR: 2978 (w), 2878 (w), 2717 (w), 1729 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68 and 9.31 (1H, 2 x br s, **C<u>H</u>**); 7.64 – 7.09 (5H, m, **Ar<u>H</u>**); 4.65 (1H, t, *J* = 6.8 Hz, **C<u>H</u>**); 3.73 – 3.40 (2H, m); 2.26 – 2.12 (1H, m); 2.10 – 1.79 (3H, m) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$): δ 199.2 (**<u>C</u>H**), 170.1 (**<u>C</u>**), 135.7 (**<u>C</u>**), 130.4 (**<u>C</u>H**), 128.3 (**<u>C</u>H**) 127.2 (**<u>C</u>H**), 65.1 (**<u>C</u>H**), 50.1 (**<u>C</u>H$_2$**), 26.2 (**<u>C</u>H$_2$**), 25.4 (**<u>C</u>H$_2$**) ppm.
LRMS (ES^+): *m/z* 429 ([2M + Na^+], 10%), 204 ([M + H^+], 100%).

2.5.0 REFERENCES

2.5.1 References for Chapter Two

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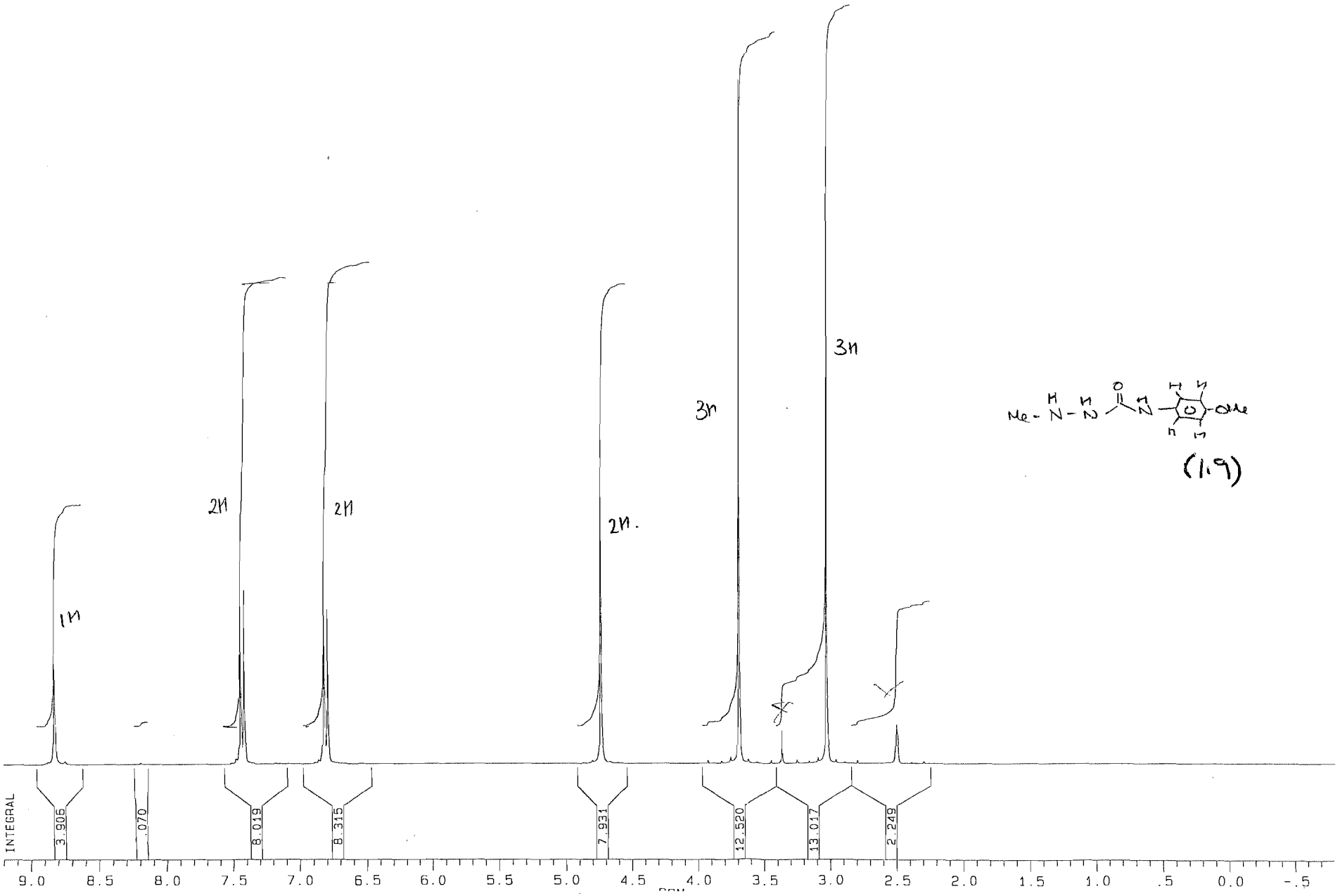
APPENDIX

SR3876-22



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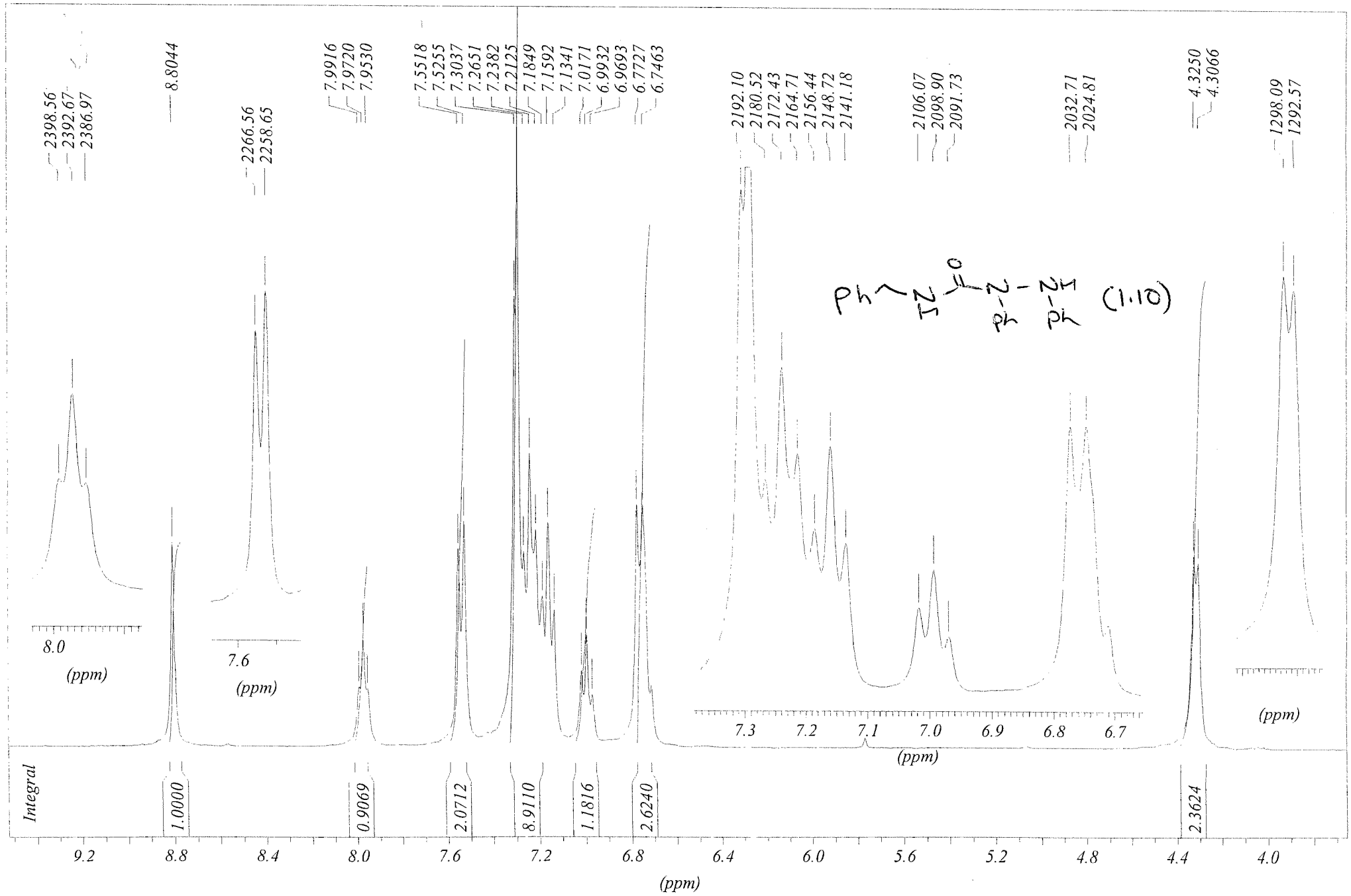
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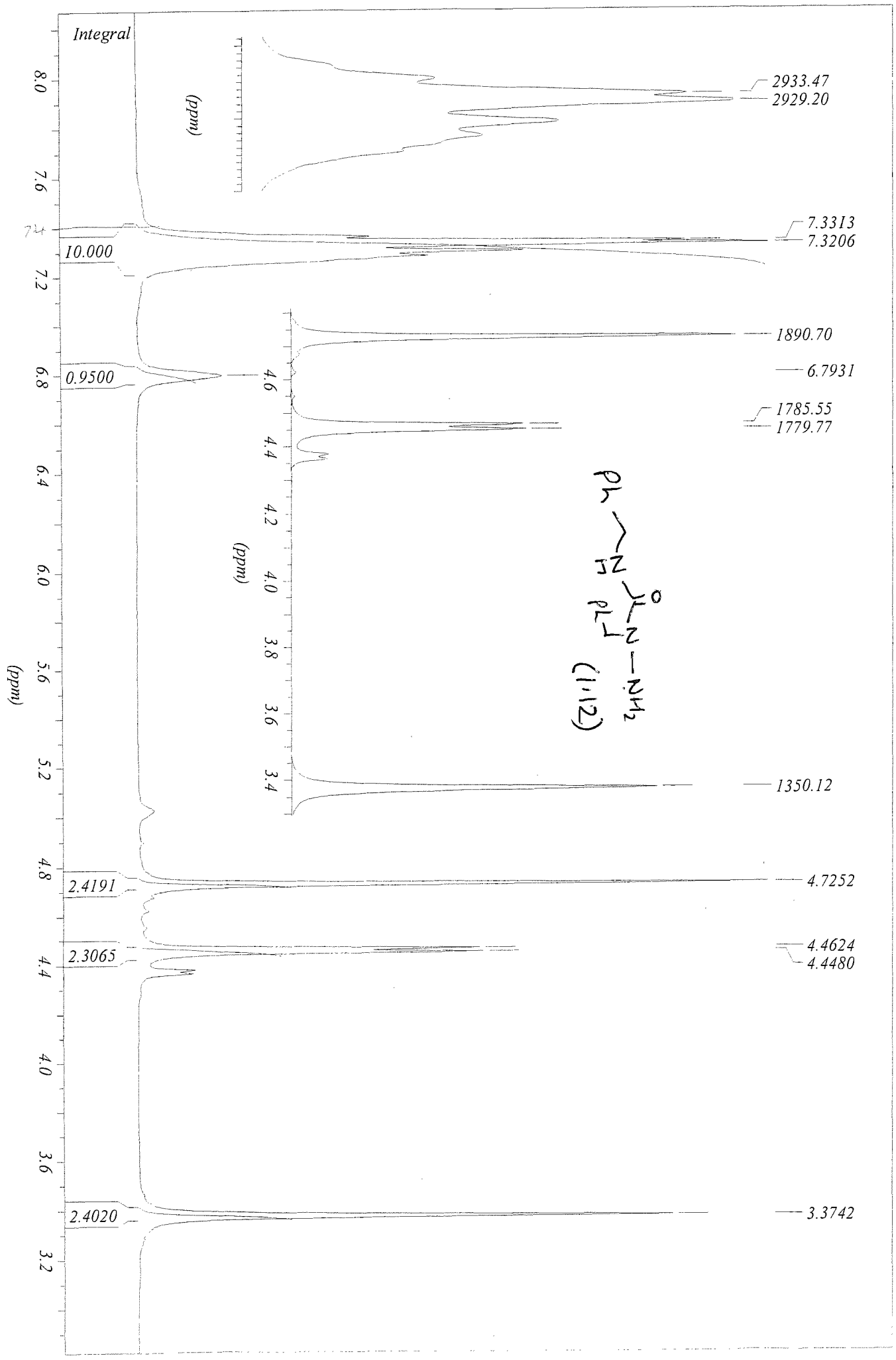
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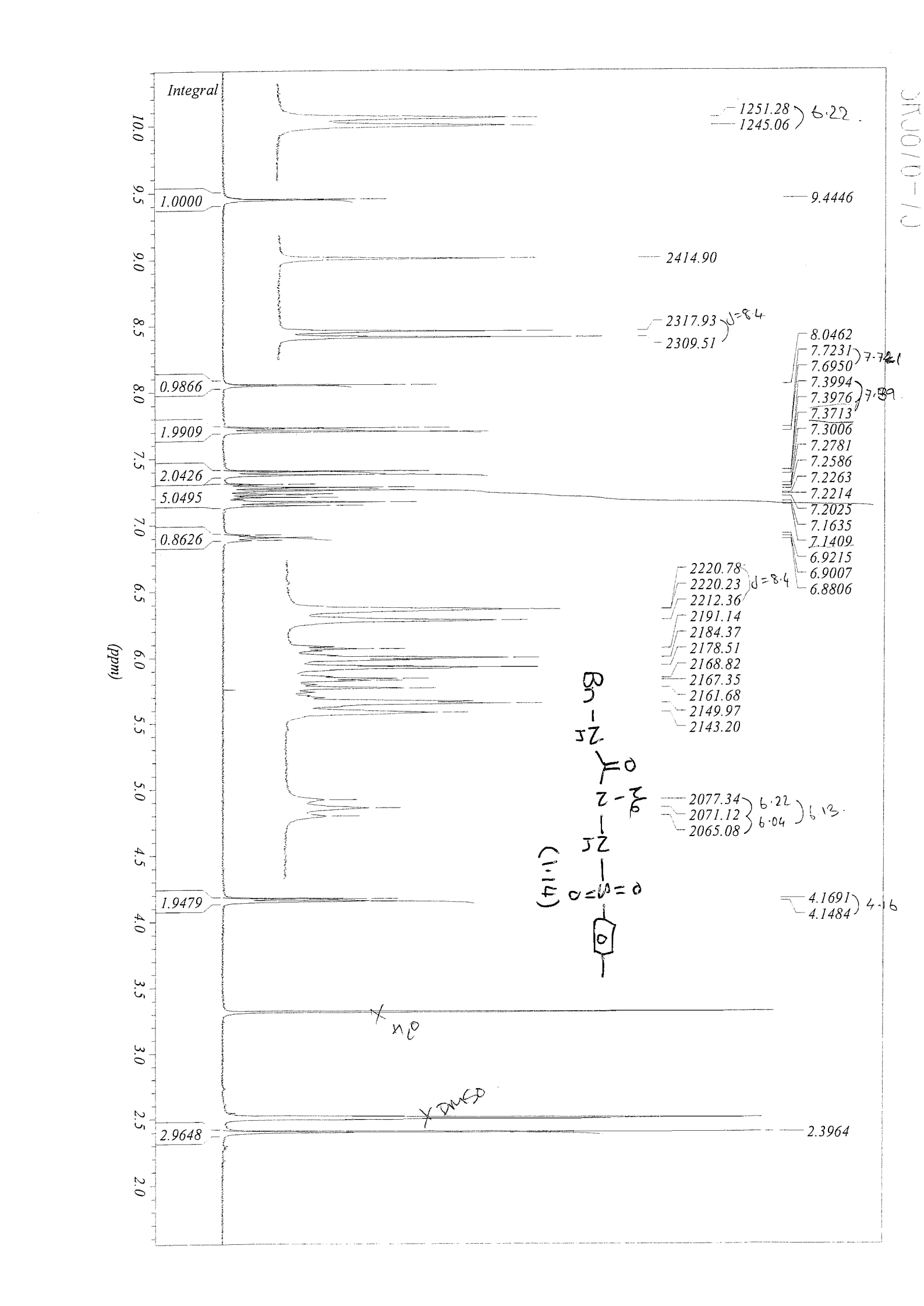
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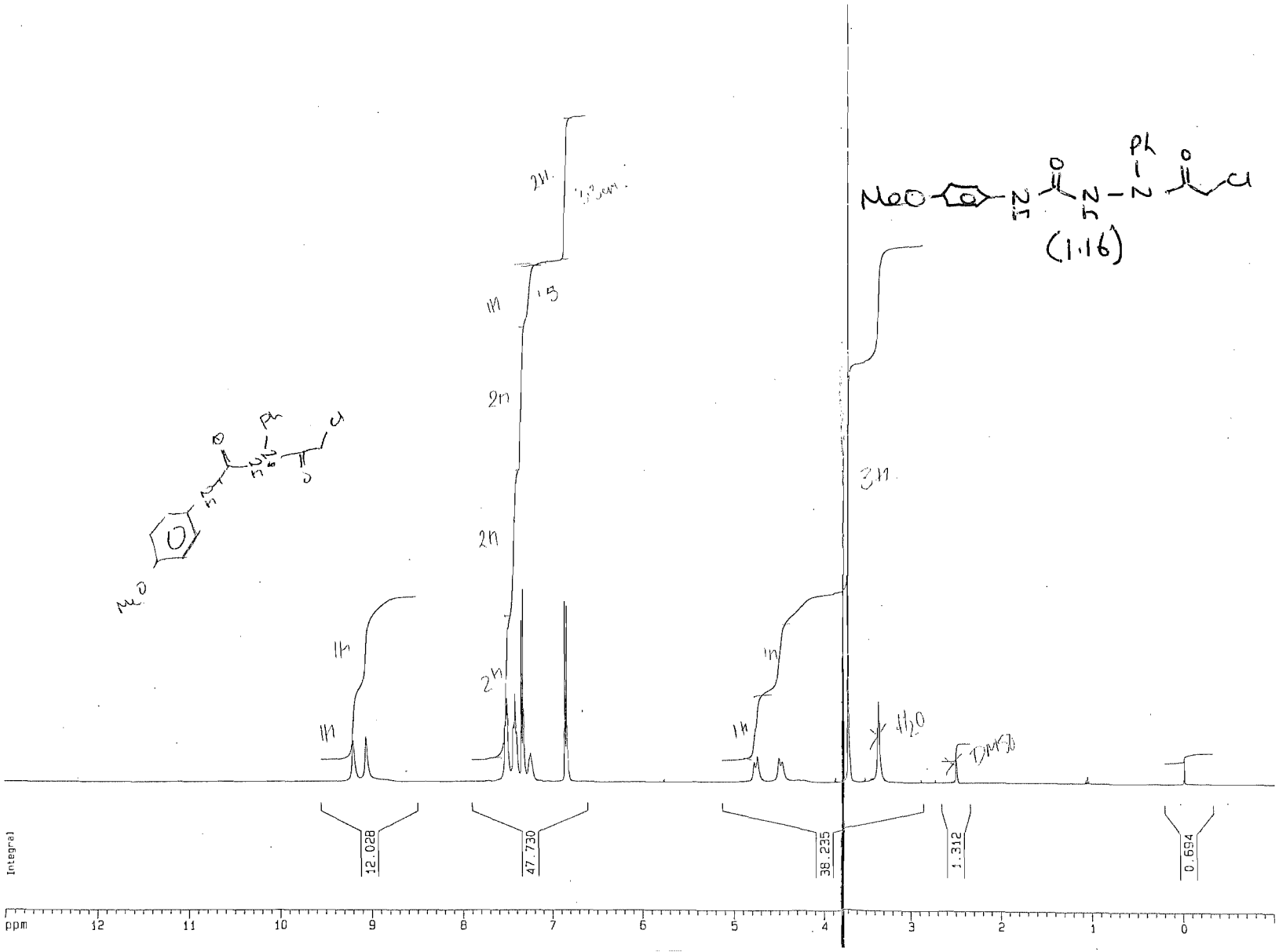


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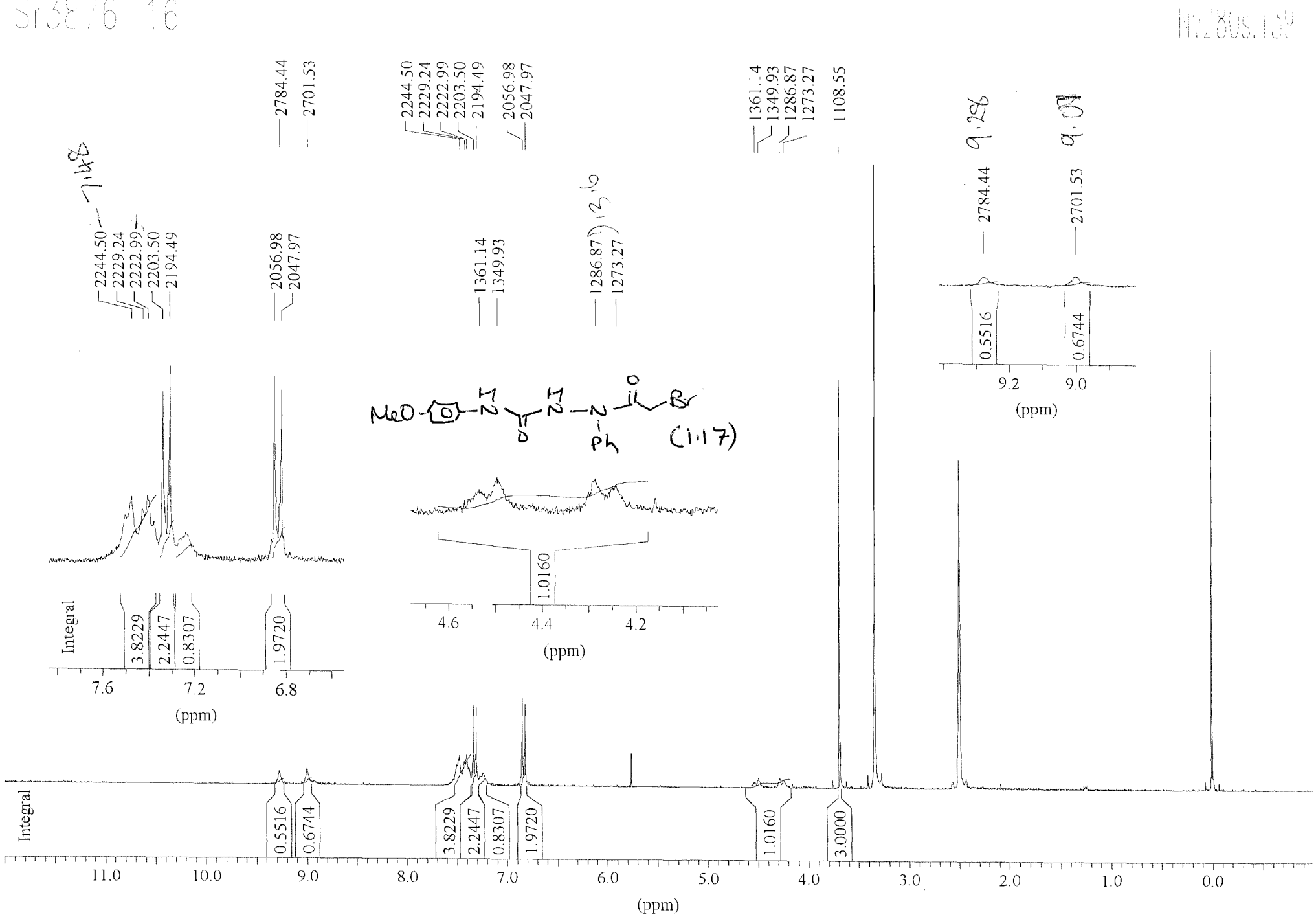
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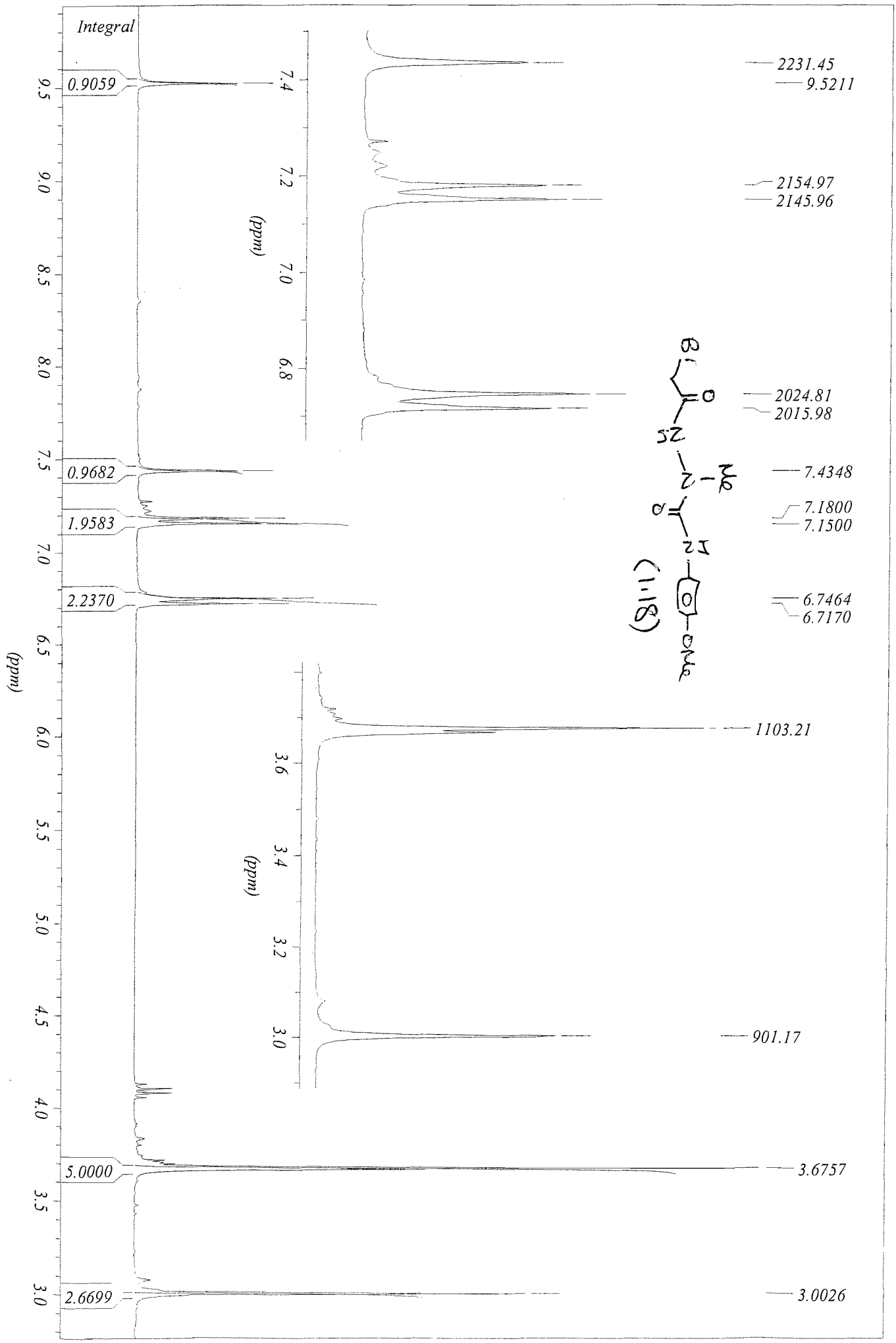
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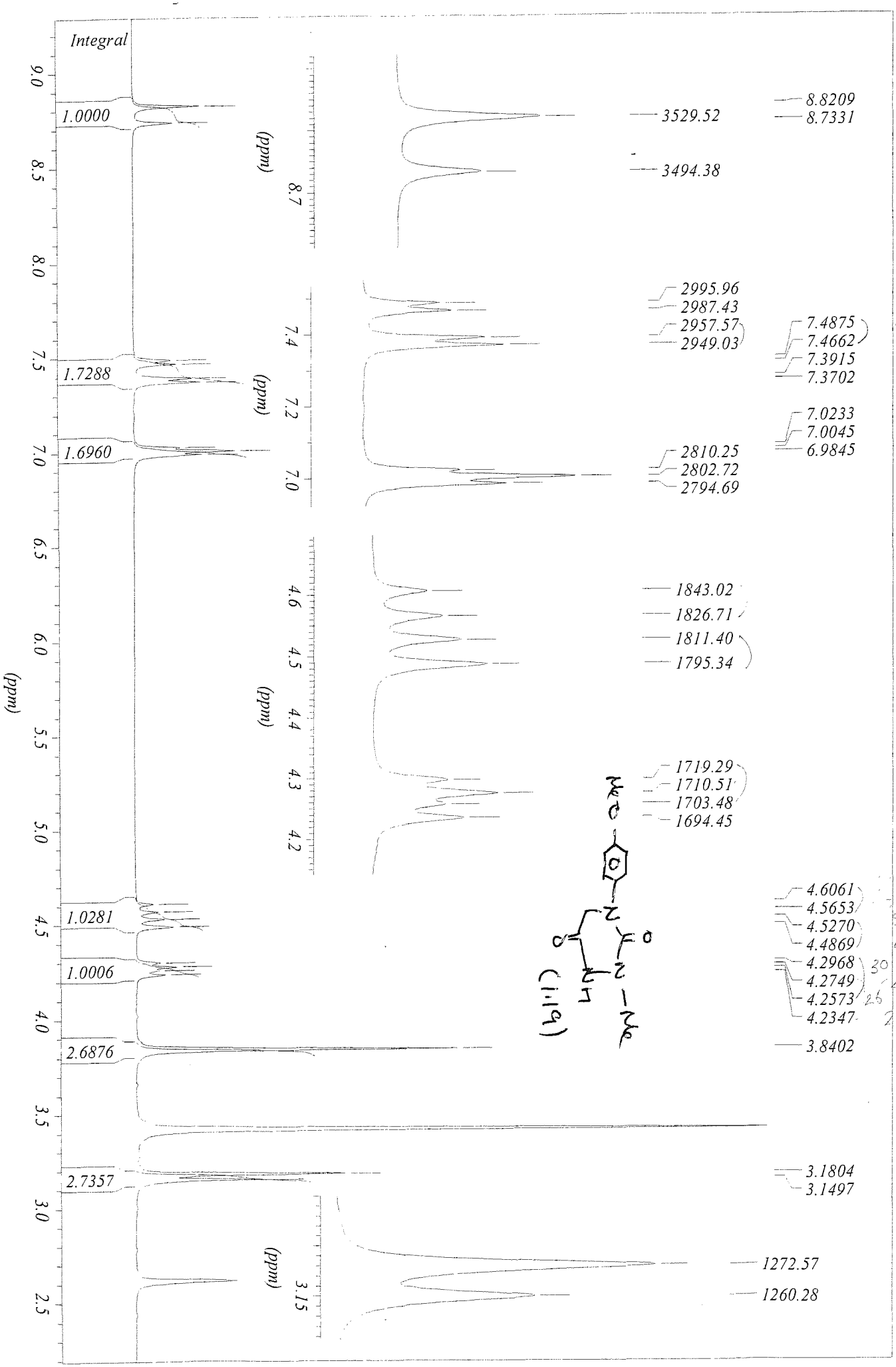
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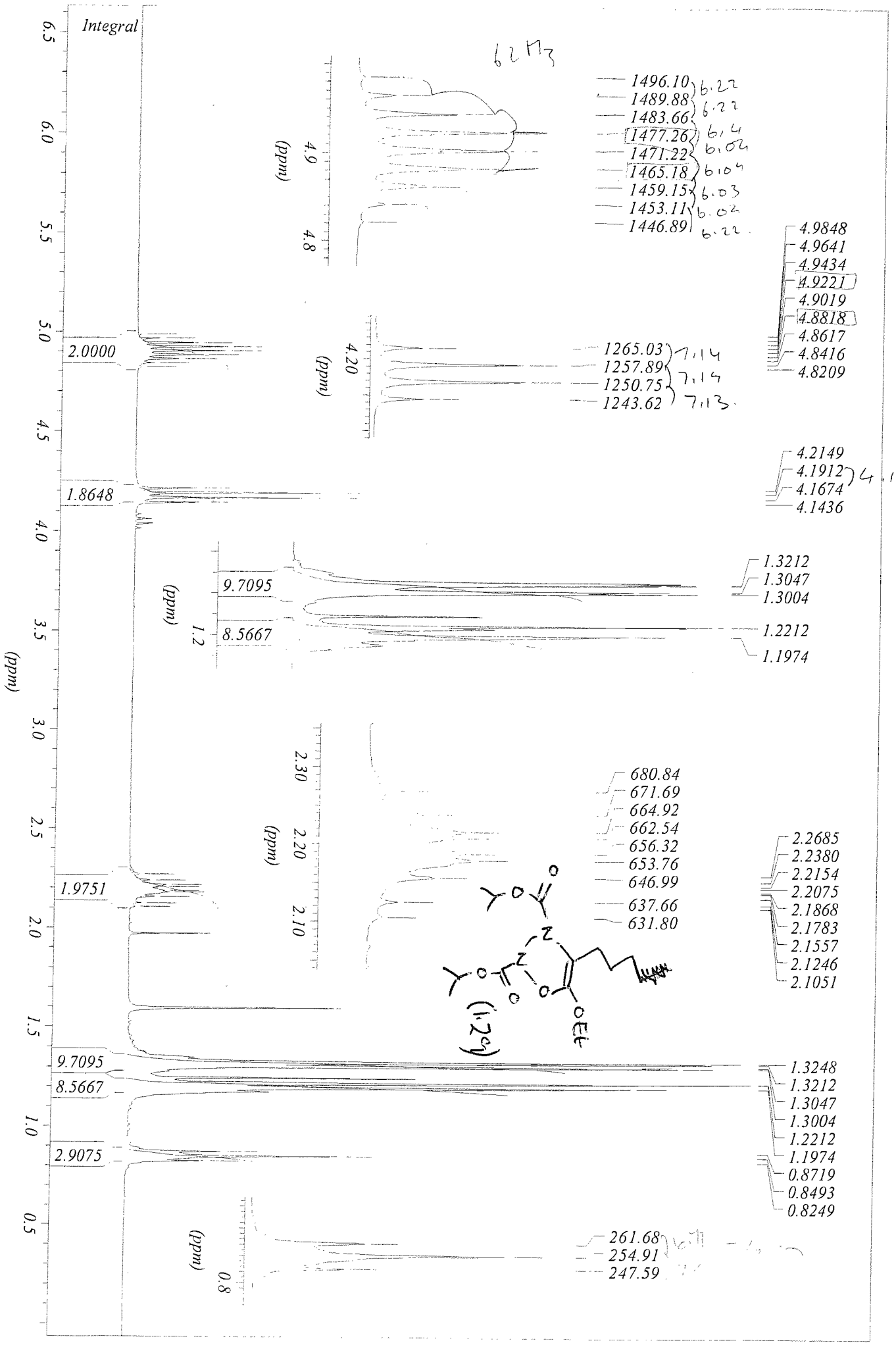
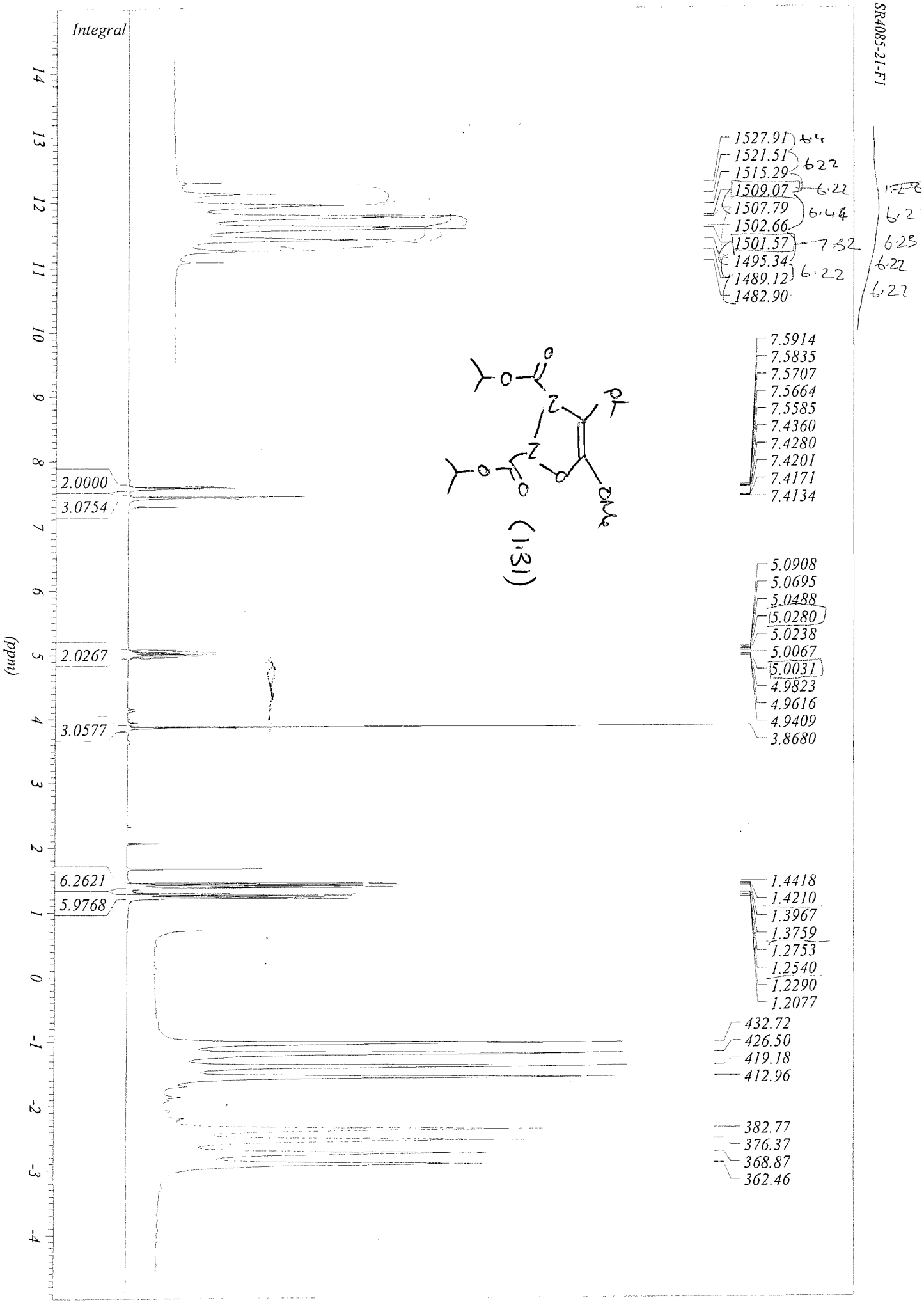
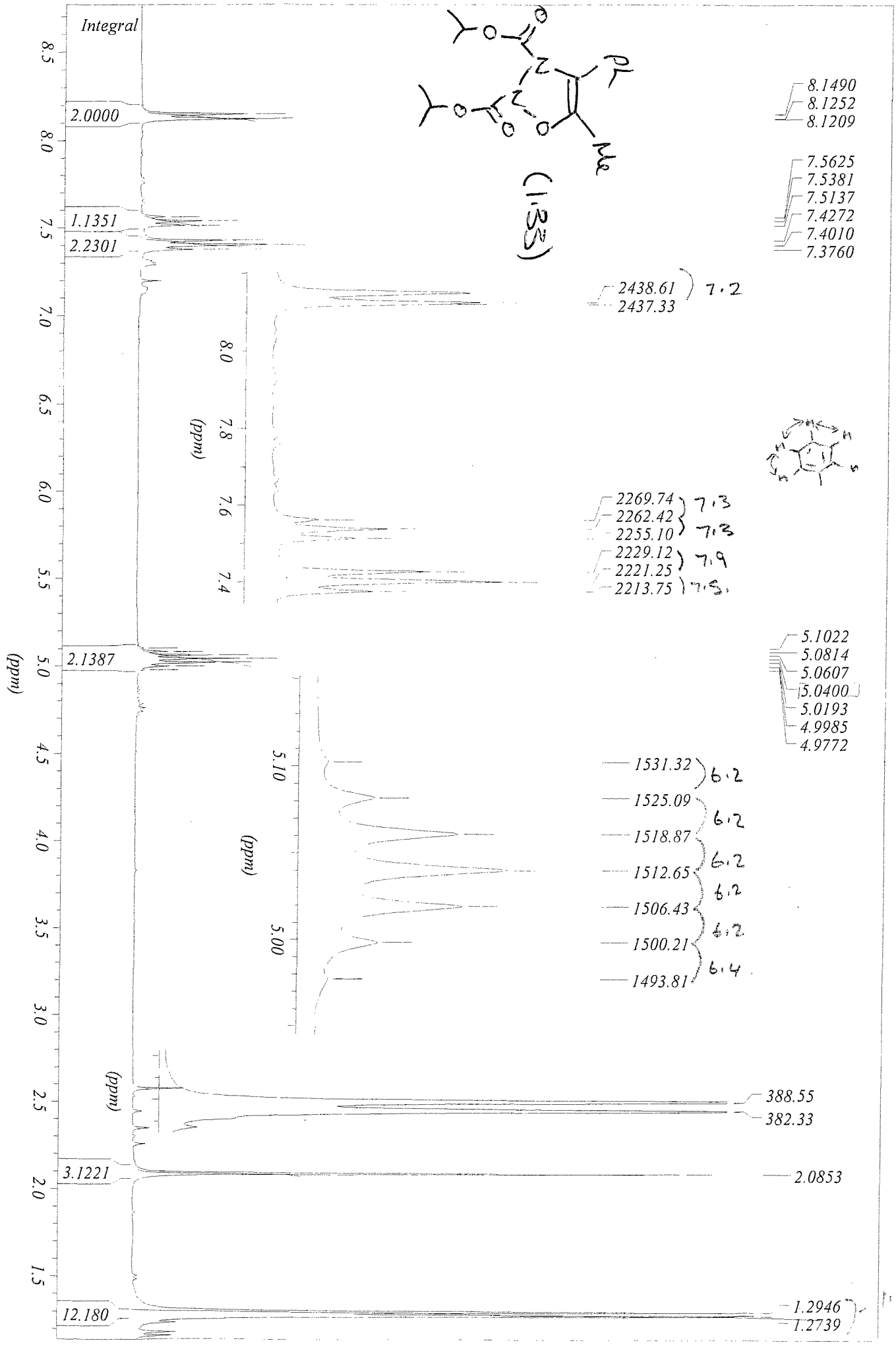
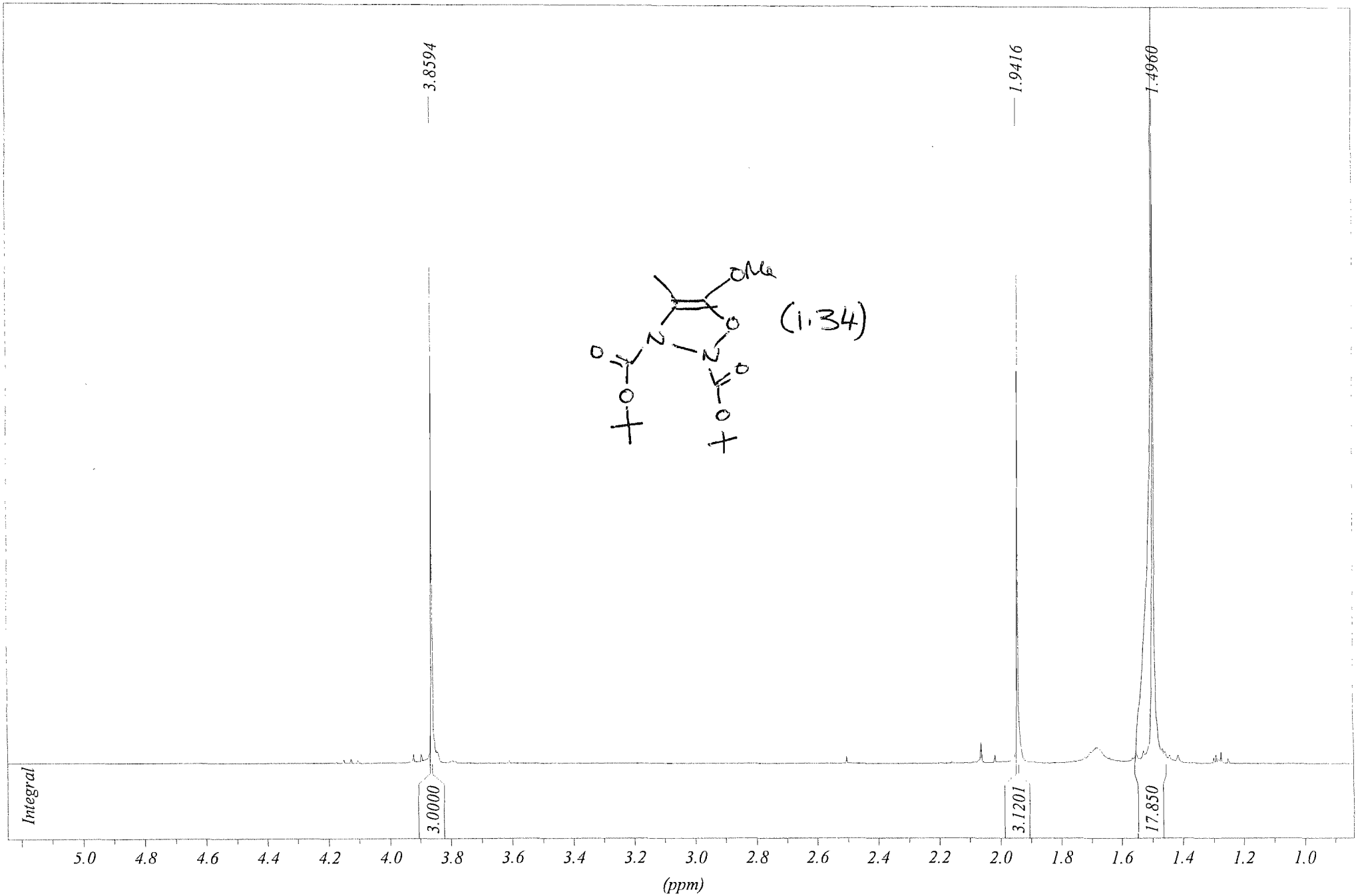
1719.29
1710.51
1703.48
1694.45
4.6061
4.5653
4.5270
4.4869
4.2968
4.2749
4.2573
4.2347
3.8402
3.1804
3.1497
1272.57
1260.28
(1:19)

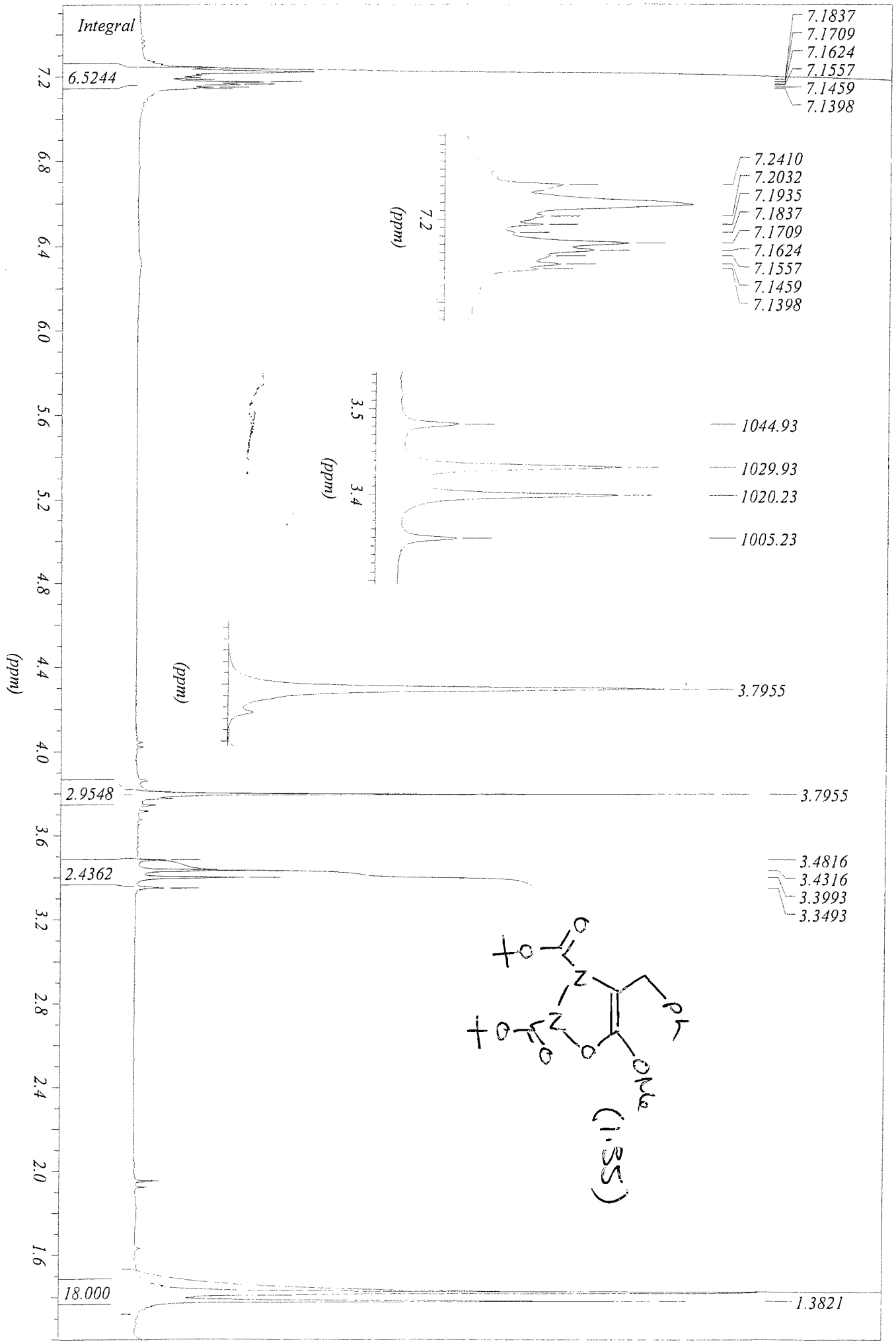

SR4085-30-F1
Integral
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)
2.0000
1.8648
1.9751
9.7095
8.5667
2.9075
9.7095
8.5667
1.2
4.9
4.8
4.20
2.30
2.20
2.10
0.8
1496.10
1489.88
1483.66
1477.26
1471.22
1465.18
1459.15
1453.11
1446.89
6.22
6.22
6.14
6.02
6.04
6.03
6.02
6.22
1265.03
1257.89
1250.75
1243.62
7.14
7.14
7.13
680.84
671.69
664.92
662.54
656.32
653.76
646.99
637.66
631.80
261.68
254.91
247.59
4.9848
4.9641
4.9434
4.9221
4.9019
4.8818
4.8617
4.8416
4.8209
4.2149
4.1912
4.1674
4.1436
4.1793
1.3212
1.3047
1.3004
1.2212
1.1974
2.2685
2.2380
2.2154
2.2075
2.1868
2.1783
2.1557
2.1246
2.1051
1.3248
1.3212
1.3047
1.3004
1.2212
1.1974
0.8719
0.8493
0.8249
6.22
(1.29)
OEt

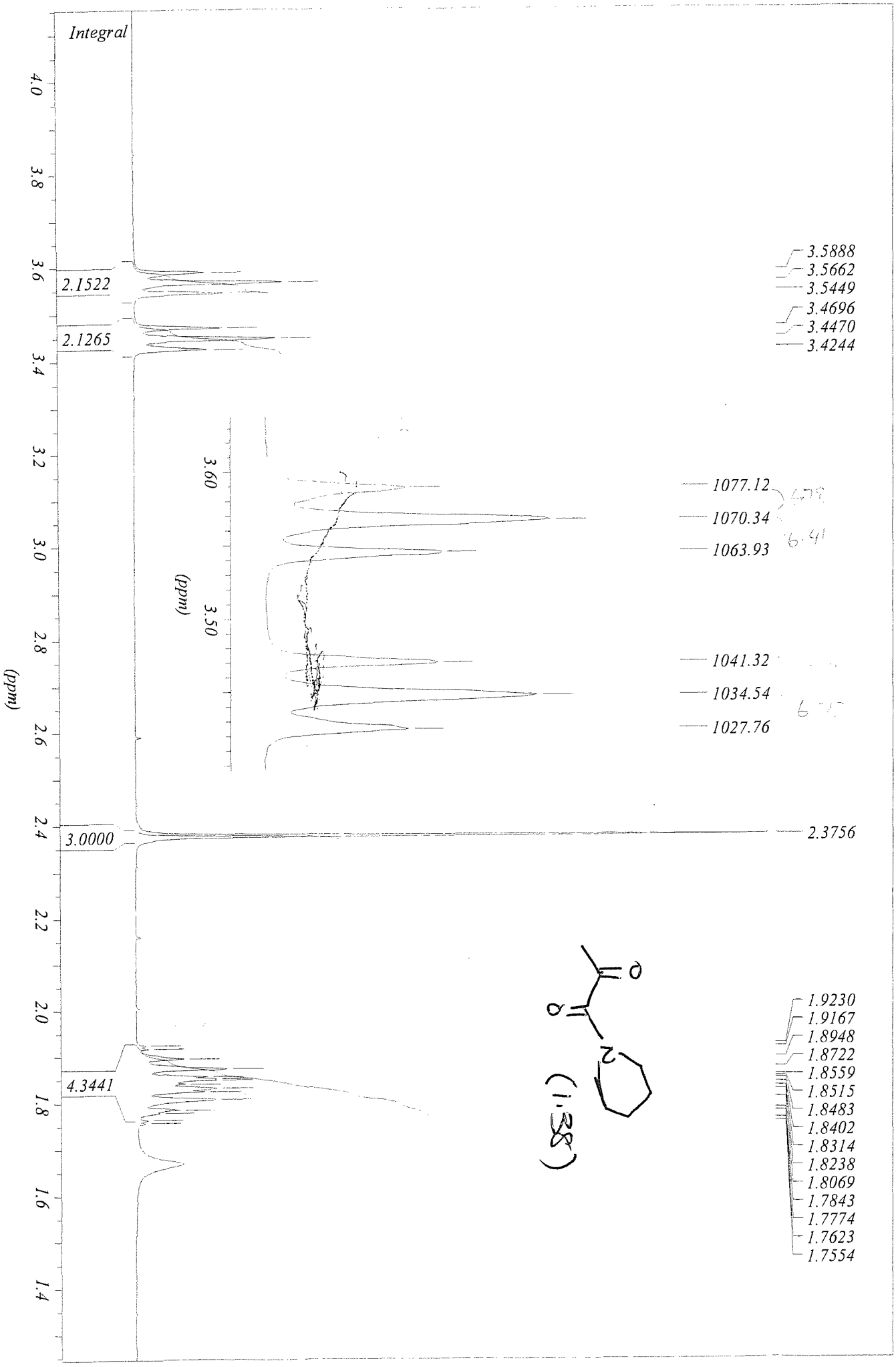

SR4085-21-F1
Integral
(ppm)
2.0000
3.0754
2.0267
3.0577
6.2621
5.9768
1527.91
1521.51
1515.29
1509.07
1507.79
1502.66
1501.57
1495.34
1489.12
1482.90
7.5914
7.5835
7.5707
7.5664
7.5585
7.4360
7.4280
7.4201
7.4171
7.4134
5.0908
5.0695
5.0488
5.0280
5.0238
5.0067
5.0031
4.9823
4.9616
4.9409
3.8680
1.4418
1.4210
1.3967
1.3759
1.2753
1.2540
1.2290
1.2077
432.72
426.50
419.18
412.96
382.77
376.37
368.87
362.46
(131)


Integral
2.0000
1.1351
2.2301
2.1387
3.1221
12.180
(ppm)
8.1490
8.1252
8.1209
7.5625
7.5381
7.5137
7.4272
7.4010
7.3760
2438.61
2437.33
7.2
2269.74
2262.42
2255.10
7.3
7.3
2229.12
2221.25
2213.75
7.9
7.5
5.1022
5.0814
5.0607
5.0400
5.0193
4.9985
4.9772
1531.32
1525.09
1518.87
1512.65
1506.43
1500.21
1493.81
6.2
6.2
6.2
6.2
6.2
6.4
388.55
382.33
2.0853
1.2946
1.2739
(1.33)

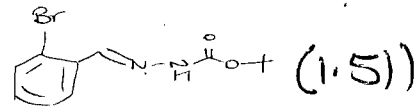
SR4085-46-F1


3.8594
1.9416
1.4960
(1.34)
Integral
3.0000
3.1201
17.850
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
(ppm)


Integral
6.5244
2.9548
2.4362
18.000
7.1837
7.1709
7.1624
7.1557
7.1459
7.1398
7.2410
7.2032
7.1935
7.1837
7.1709
7.1624
7.1557
7.1459
7.1398
1044.93
1029.93
1020.23
1005.23
3.7955
3.7955
3.4816
3.4316
3.3993
3.3493
1.3821
(ppm)
(i.35)


Integral
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
(ppm)
2.1522
2.1265
3.0000
4.3441
2.3756
3.5888
3.5662
3.5449
3.4696
3.4470
3.4244
3.60
3.50
(ppm)
1077.12
1070.34
1063.93
1041.32
1034.54
1027.76
1.9230
1.9167
1.8948
1.8722
1.8559
1.8515
1.8483
1.8402
1.8314
1.8238
1.8069
1.7843
1.7774
1.7623
1.7554

SR4374-80-1



(1.51)

BRUKER

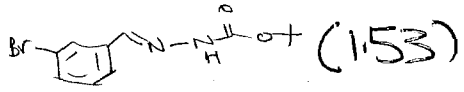
Current Data Parameters
NAME oc1206skr1
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061012
Time 16.35
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 1625.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300063 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.29 Hz

SR4374-80-2



(1.53)

BRUKER

Current Data Parameters

NAME	ocl206skr2
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20061012
Time	16.43
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	1625.5
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

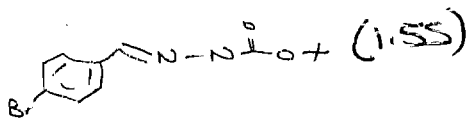
======== CHANNEL f1 ========

NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

F2 - Processing parameters

SI	16384
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	6.38 Hz

SR4374-80-3

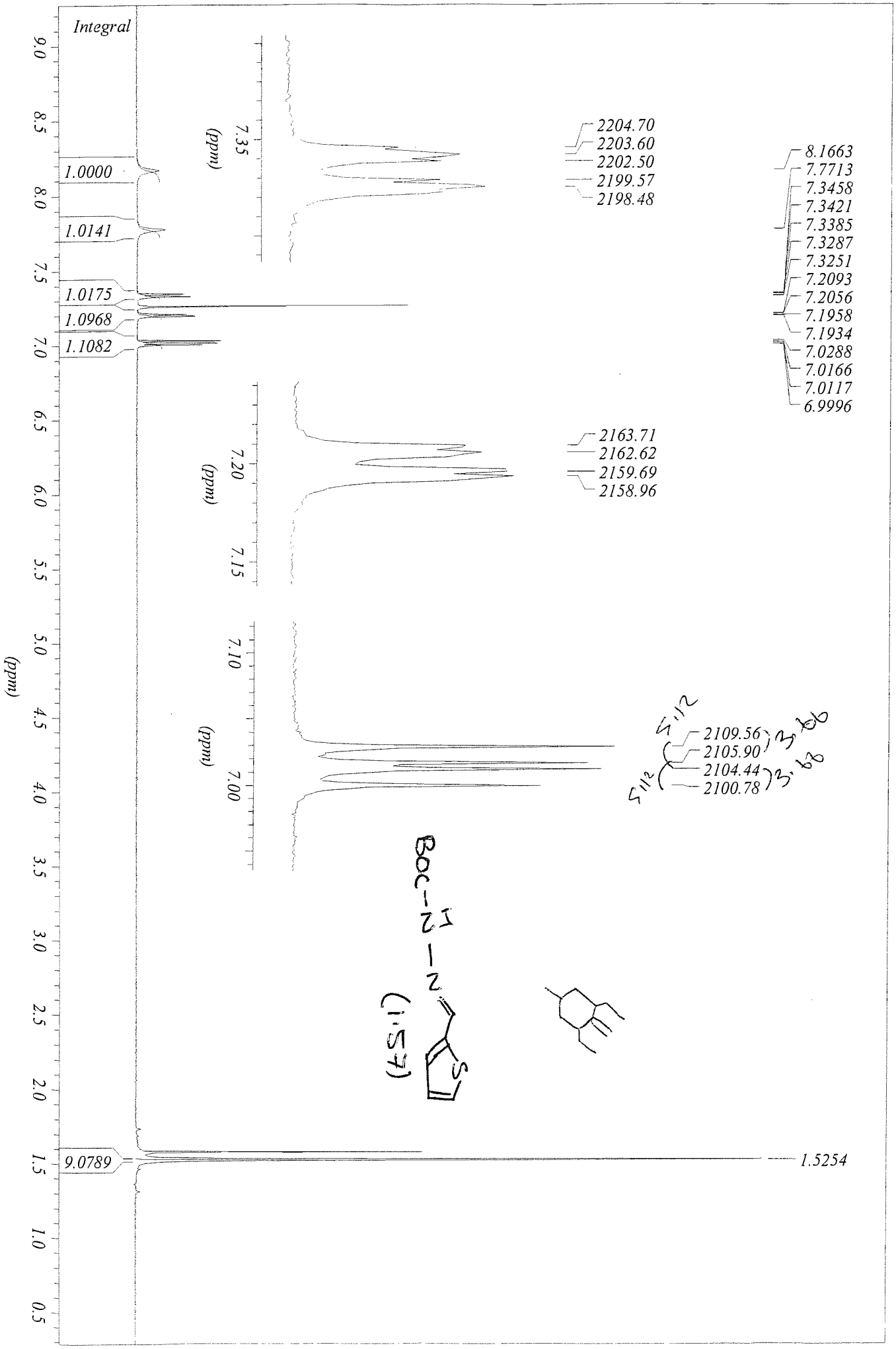


Current Data Parameters
NAME oc1206skr3
EXPNO 10
PROCNO 1

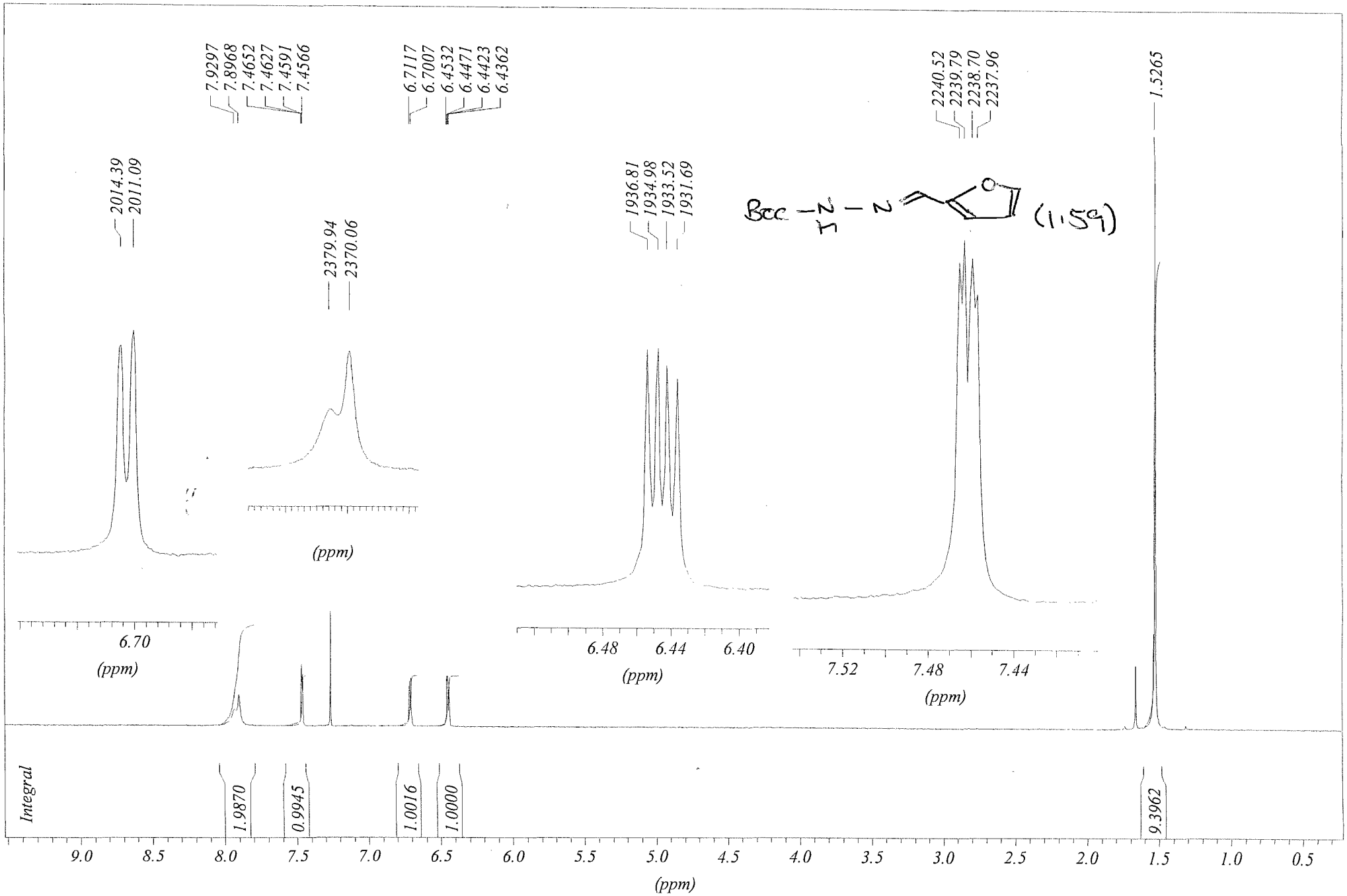
F2 - Acquisition Parameters
Date_ 20061012
Time 16.51
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 1625.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

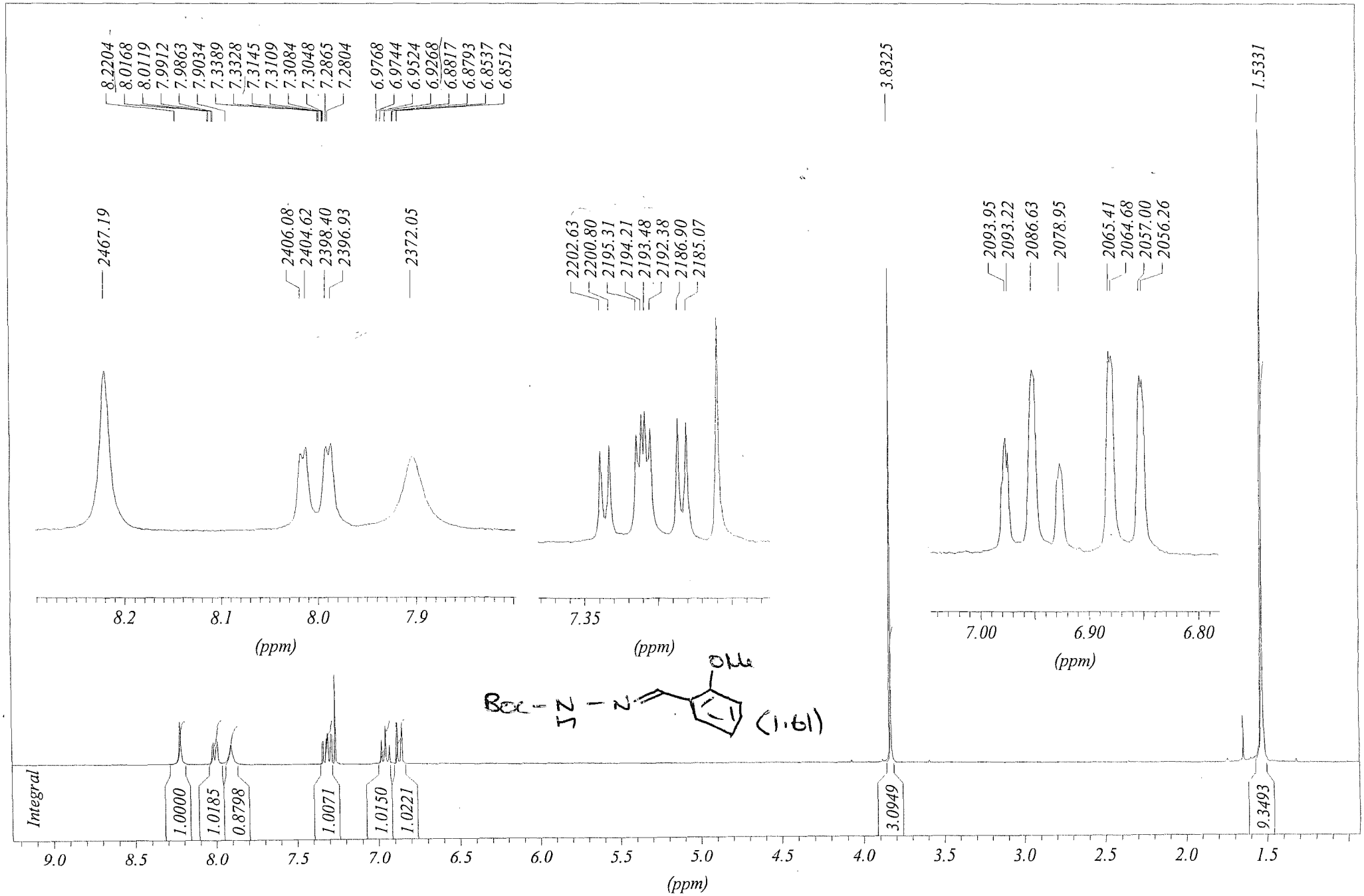
F2 - Processing parameters
SI 16384
SF 300.1300064 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.38 Hz

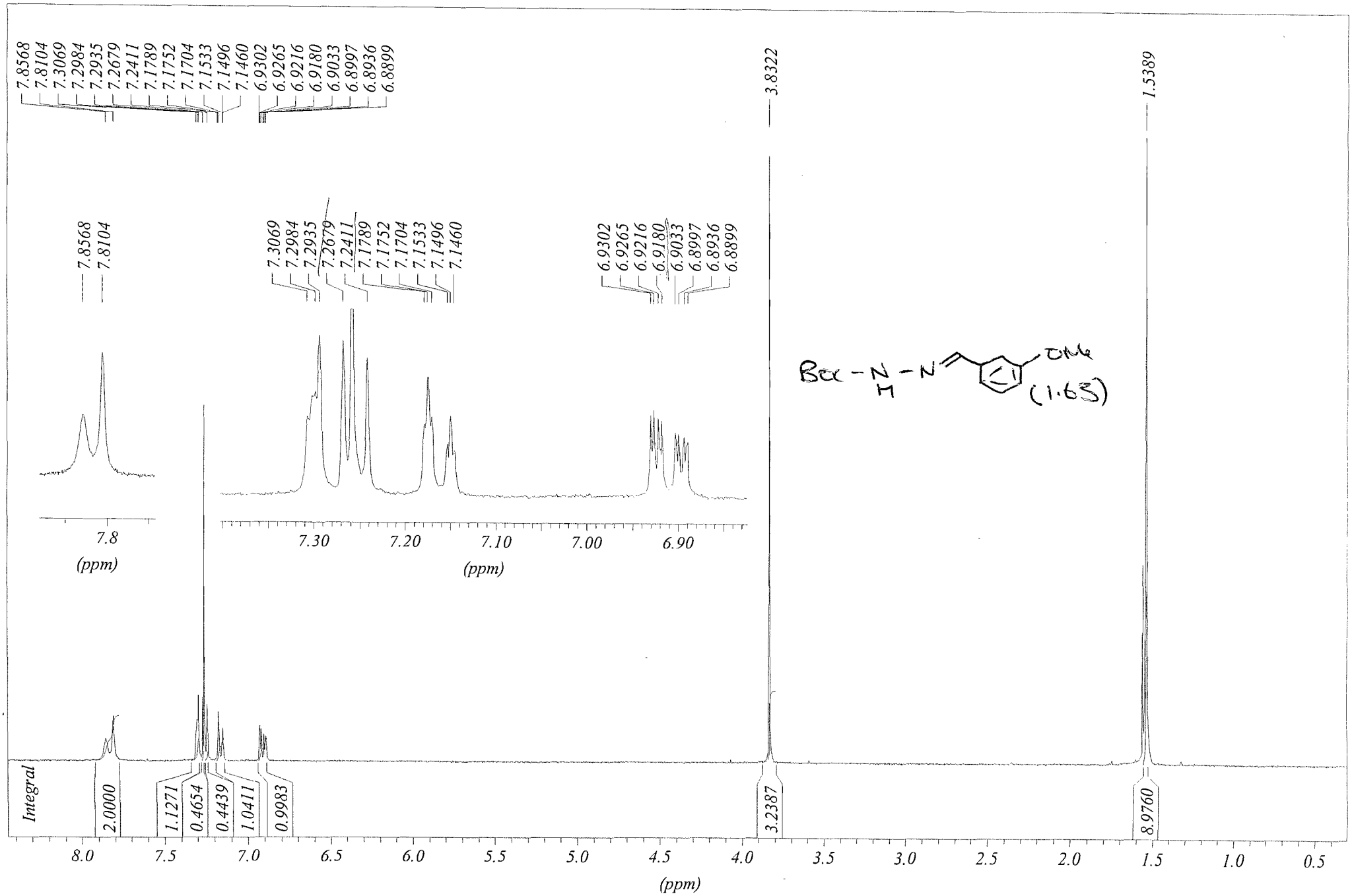

Integral
1.0000
1.0141
1.0175
1.0968
1.1082
9.0789
1.5254
2204.70
2203.60
2202.50
2199.57
2198.48
8.1663
7.7713
7.3458
7.3421
7.3385
7.3287
7.3251
7.2093
7.2056
7.1958
7.1934
7.0288
7.0166
7.0117
6.9996
2163.71
2162.62
2159.69
2158.96
2109.56
2105.90
2104.44
2100.78
5.12
5.12
3.66
3.68
7.35
7.20
7.15
7.10
7.00
(ppm)
Boc-N
N
S
(1.5:1)

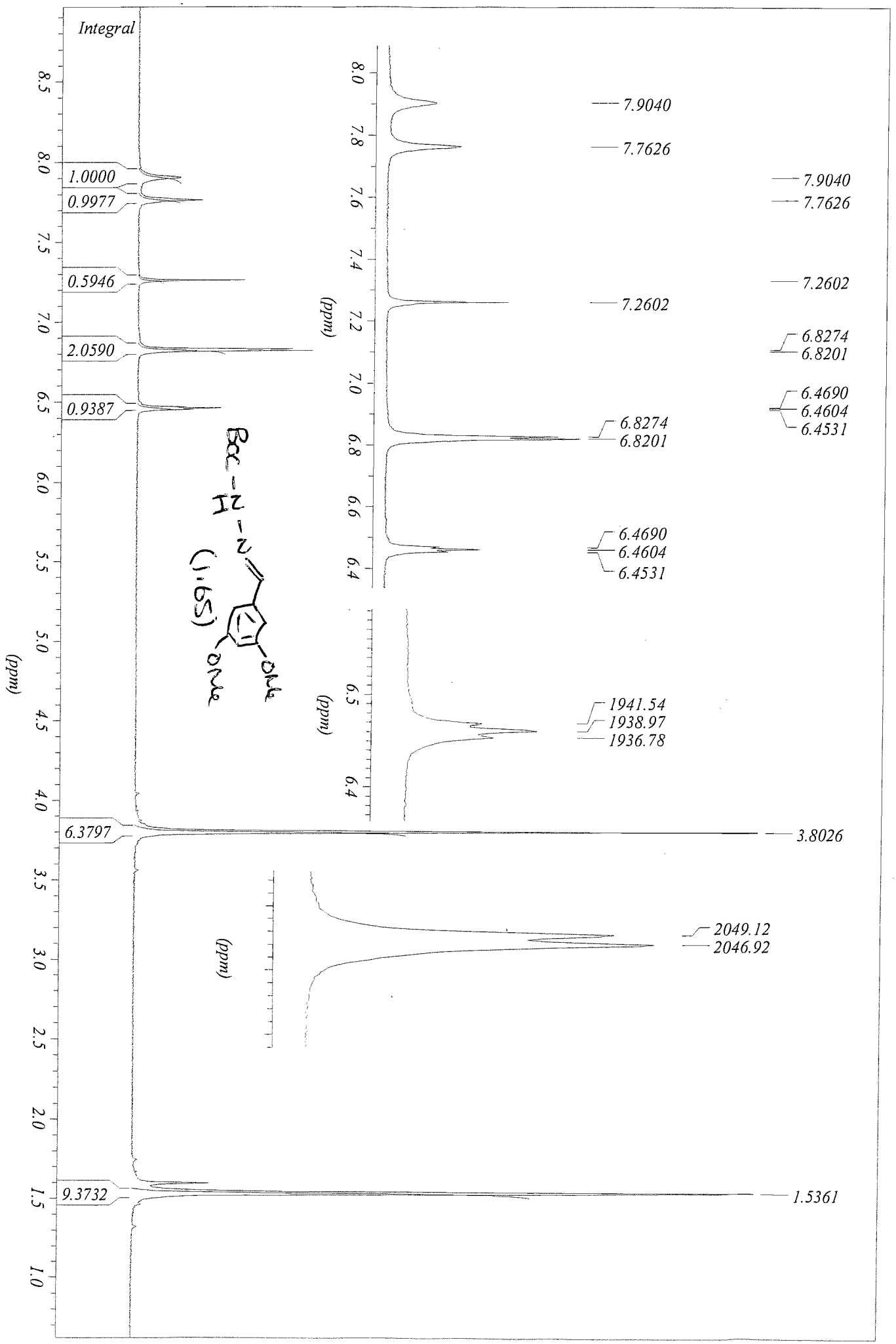
Sr4521-45-A


7.9297
7.8968
7.4652
7.4627
7.4591
7.4566
6.7117
6.7007
6.4532
6.4471
6.4423
6.4362
2240.52
2239.79
2238.70
2237.96
1.5265
2014.39
2011.09
2379.94
2370.06
1936.81
1934.98
1933.52
1931.69
Boc
(1.59)
6.70
(ppm)
(ppm)
6.48
6.44
6.40
(ppm)
7.52
7.48
7.44
(ppm)
Integral
1.9870
0.9945
1.0016
1.0000
9.3962
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

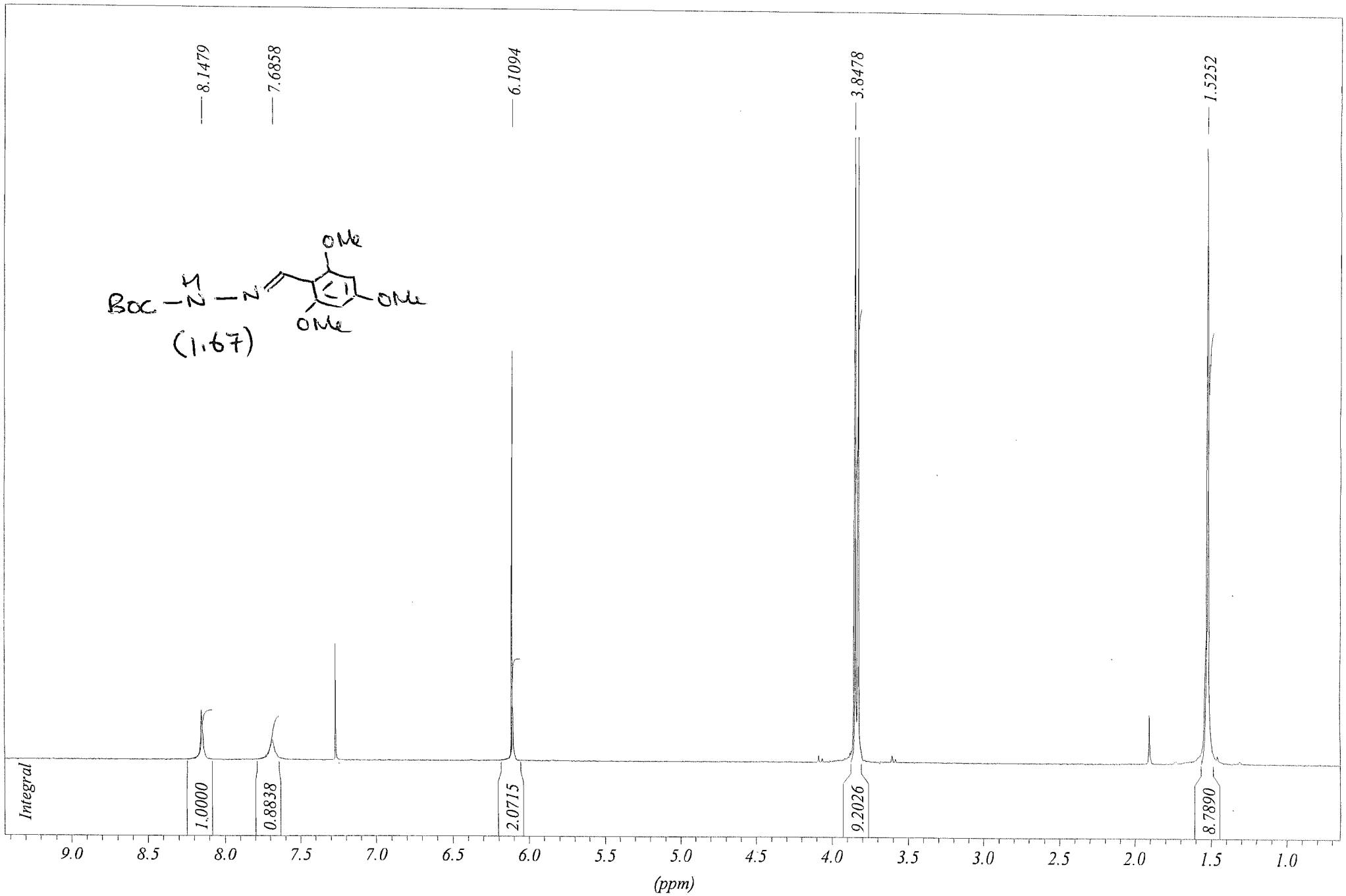
Sr4521-68-1


8.2204
8.0168
8.0119
7.9912
7.9863
7.9034
7.3389
7.3328
7.3145
7.3109
7.3084
7.3048
7.2865
7.2804
6.9768
6.9744
6.9524
6.9268
6.8817
6.8793
6.8537
6.8512
3.8325
1.5331
2467.19
2406.08
2404.62
2398.40
2396.93
2372.05
2202.63
2200.80
2195.31
2194.21
2193.48
2192.38
2186.90
2185.07
2093.95
2093.22
2086.63
2078.95
2065.41
2064.68
2057.00
2056.26
8.2
8.1
8.0
7.9
(ppm)
7.35
(ppm)
7.00
6.90
6.80
(ppm)
Boc
OMe
(1.61)
Integral
1.0000
1.0185
0.8798
1.0071
1.0150
1.0221
3.0949
9.3493
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
(ppm)

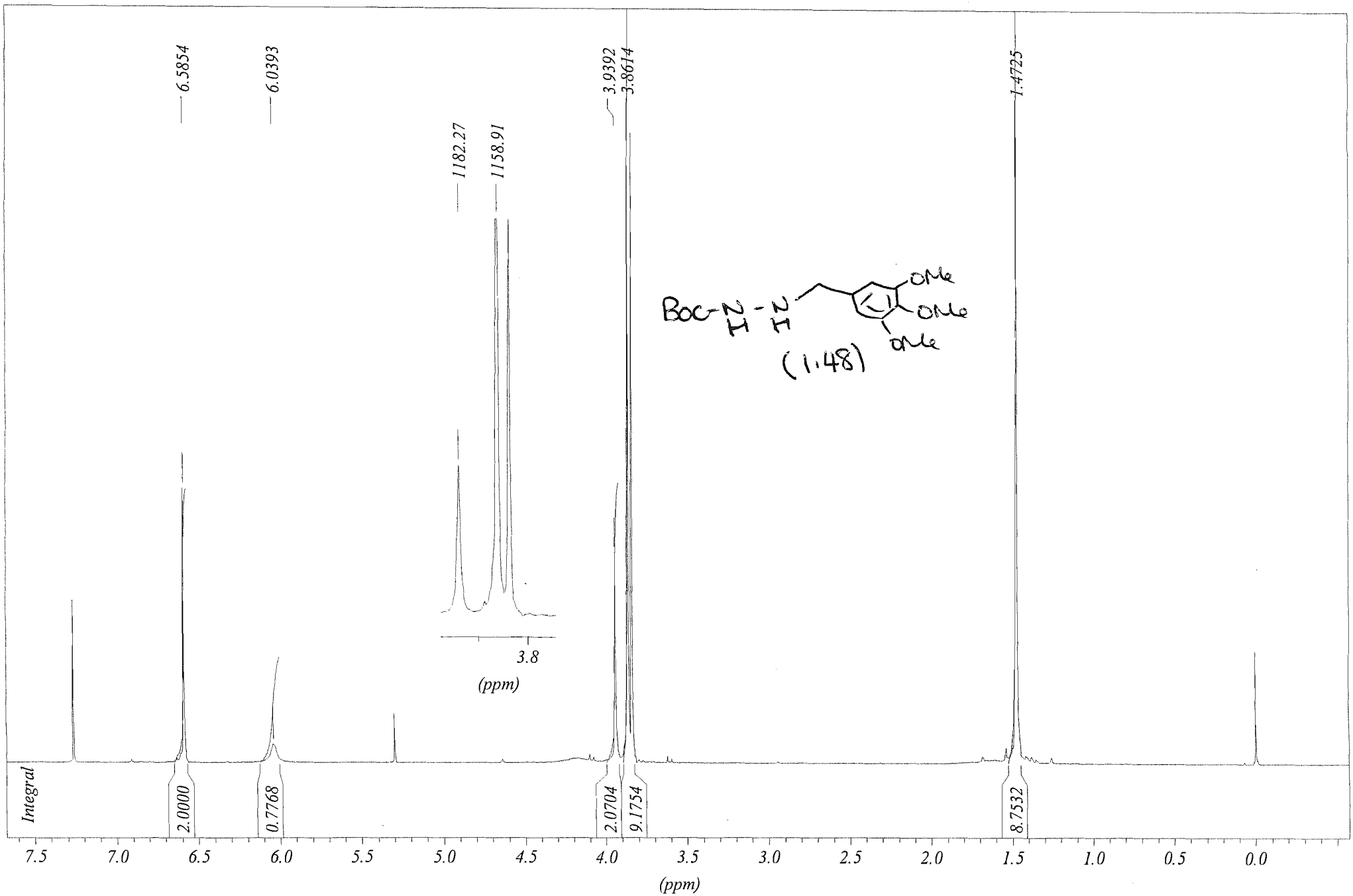

7.8568
7.8104
7.3069
7.2984
7.2935
7.2679
7.2411
7.1789
7.1752
7.1704
7.1533
7.1496
7.1460
6.9302
6.9265
6.9216
6.9180
6.9033
6.8997
6.8936
6.8899
3.8322
1.5389
7.8
(ppm)
7.30
7.20
7.10
7.00
6.90
(ppm)
Boc-N-N
H
OMe
(1.65)
Integral
2.0000
1.1271
0.4654
0.4439
1.0411
0.9983
3.2387
8.9760
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


Integral
1.0000
0.9977
0.5946
2.0590
0.9387
6.3797
9.3732
3.8026
1.5361
7.9040
7.7626
7.2602
6.8274
6.8201
6.4690
6.4604
6.4531
1941.54
1938.97
1936.78
2049.12
2046.92
(ppm)
OMe
OMe
(1.65)

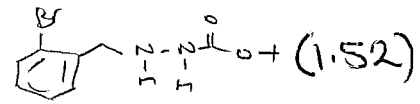
SR4521-68-4


8.1479
7.6858
6.1094
3.8478
1.5252
OMe
OMe
OMe
Boc
N
N
H
(1.67)
Integral
1.0000
0.8838
2.0715
9.2026
8.7890
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

SR4374-18-5


6.5854
6.0393
1182.27
1158.91
3.9392
3.8614
1.4725
Boc-N-N
OMe
OMe
OMe
(1.48)
3.8
(ppm)
Integral
2.0000
0.7768
2.0704
9.1754
8.7532
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

SR4374-82-1



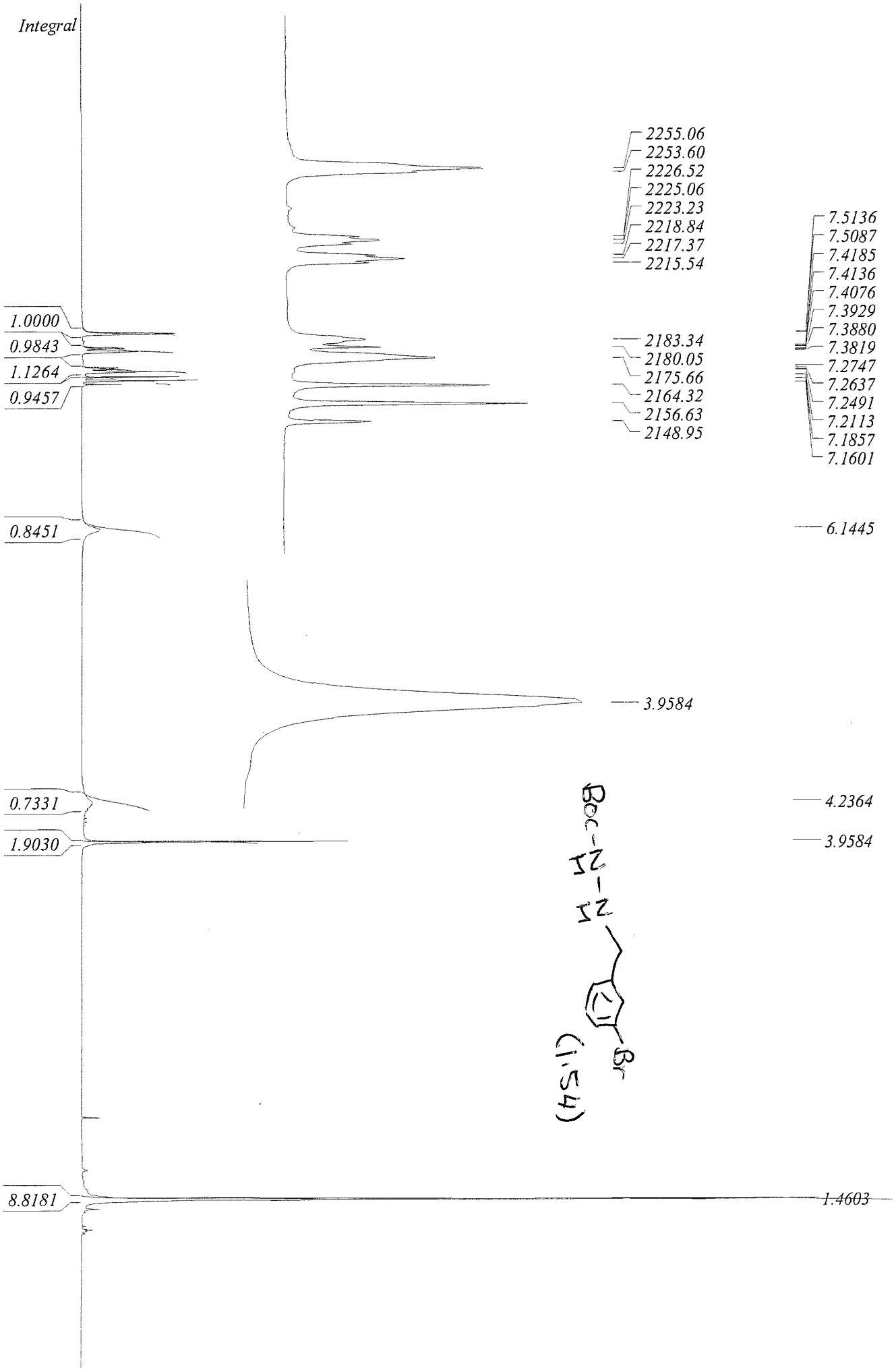
(1.52)

Current Data Parameters
NAME oc1206skr4
EXPNO 10
PROCNO 1

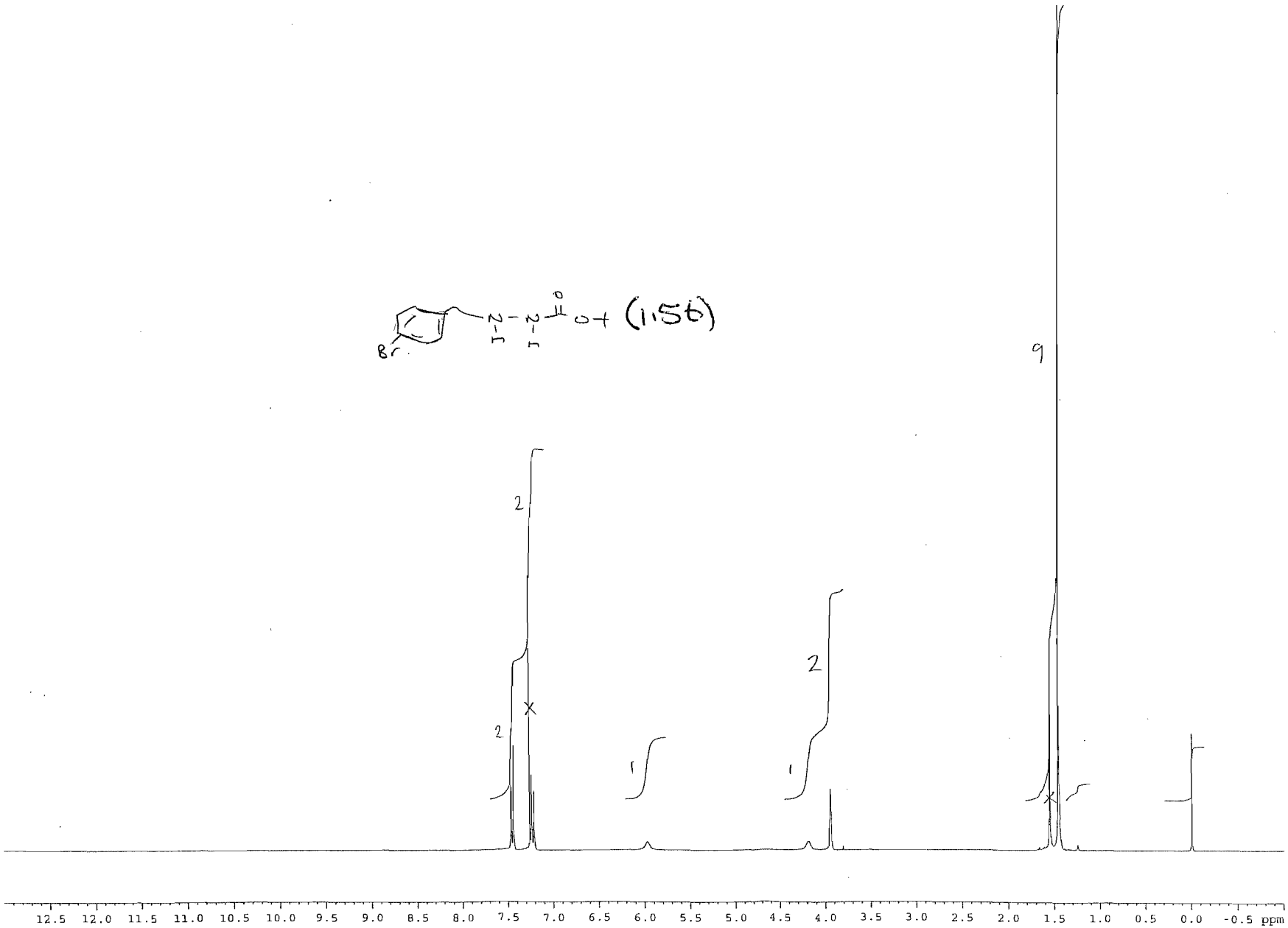
F2 - Acquisition Parameters
Date_ 20061012
Time 16.59
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 1625.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300064 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.35 Hz


Integral
2255.06
2253.60
2226.52
2225.06
2223.23
2218.84
2217.37
2215.54
2183.34
2180.05
2175.66
2164.32
2156.63
2148.95
7.5136
7.5087
7.4185
7.4136
7.4076
7.3929
7.3880
7.3819
7.2747
7.2637
7.2491
7.2113
7.1857
7.1601
1.0000
0.9843
1.1264
0.9457
0.8451
6.1445
3.9584
0.7331
1.9030
4.2364
3.9584
Boc-N-N
Br
(1.54)
8.8181
1.4603

SR4374-B2-3



Current Data Parameters

NAME	oc1206skr5
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

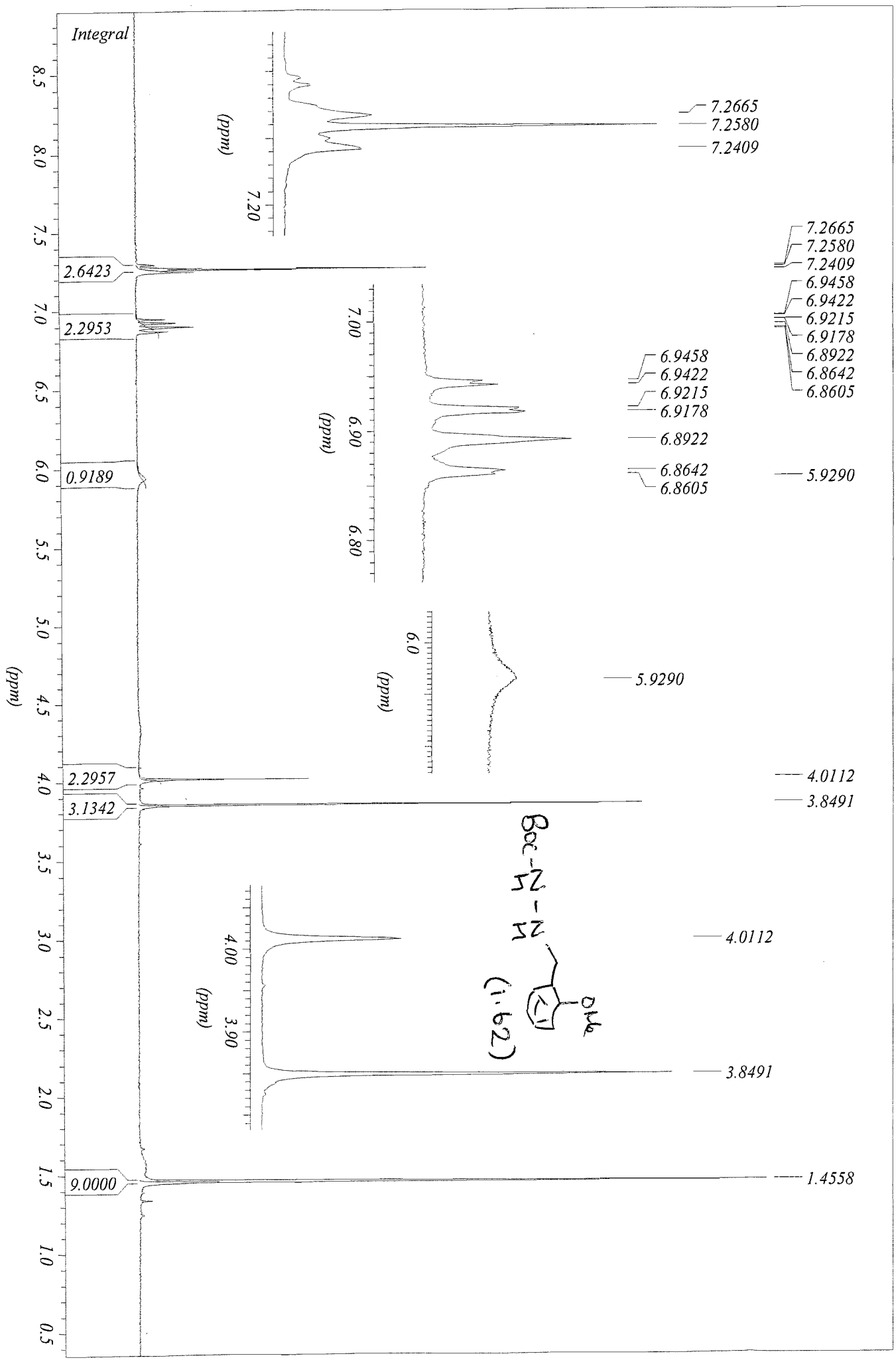
Date_	20061012
Time	17.07
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	1625.5
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

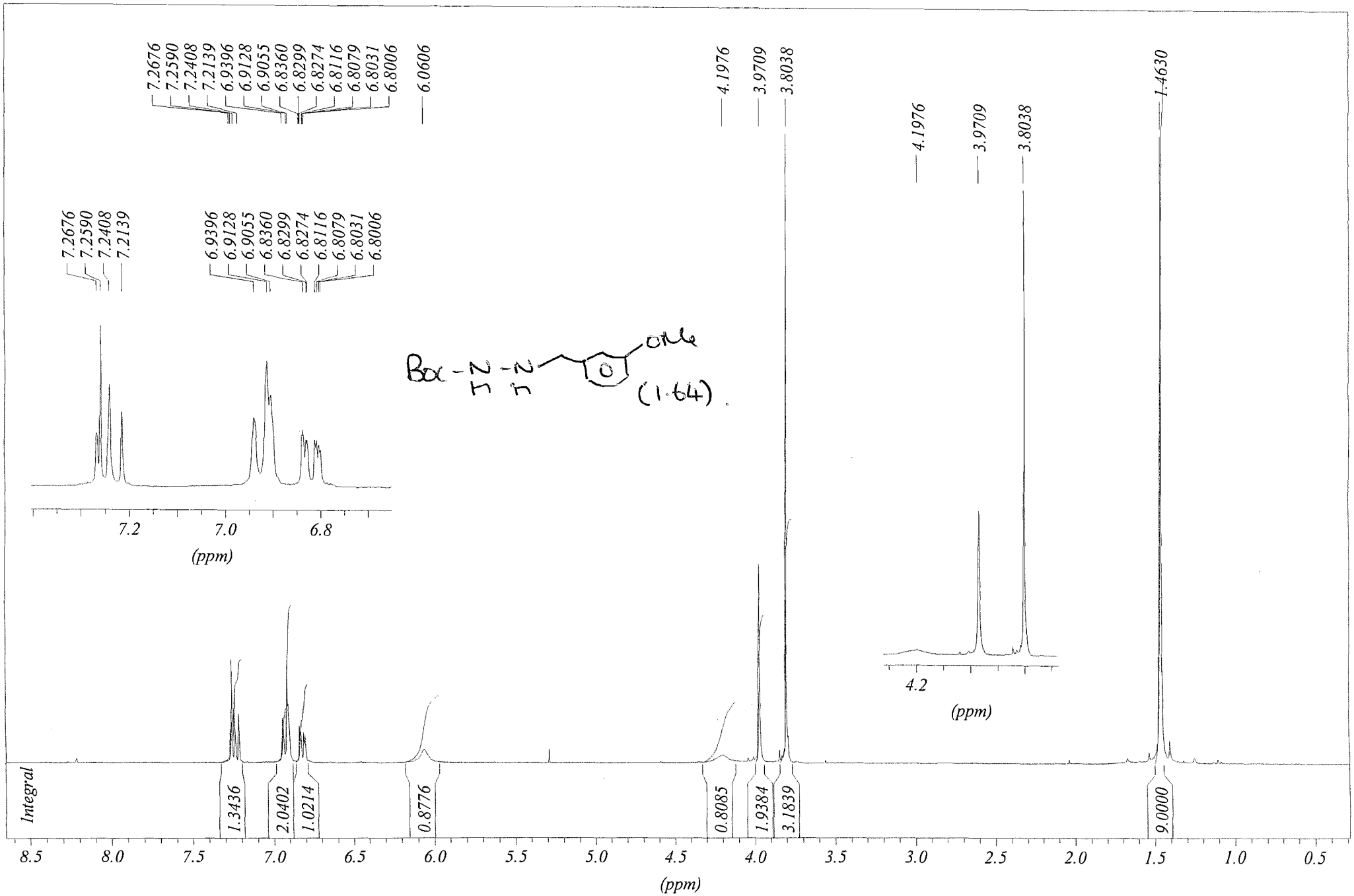
NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

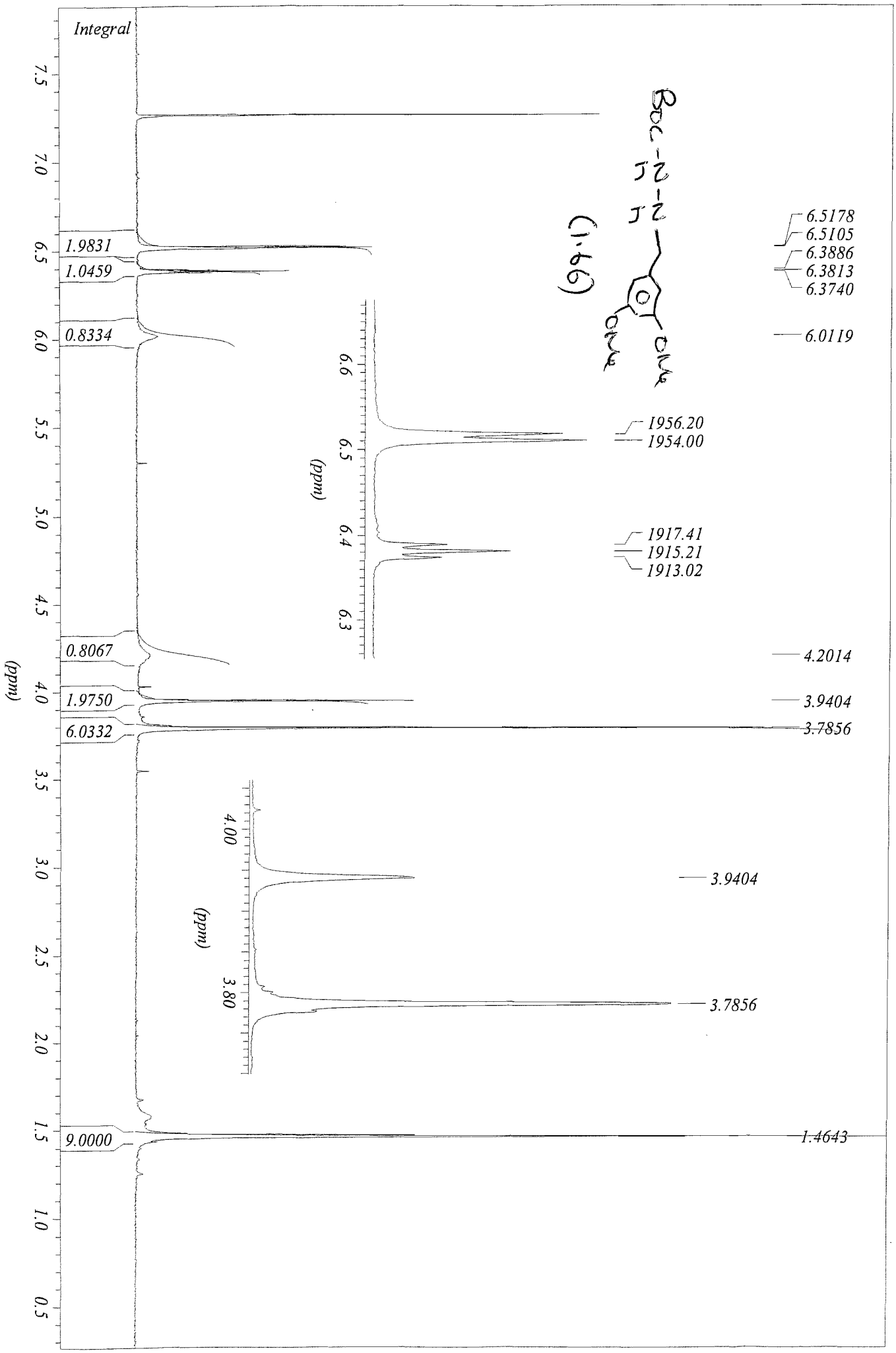
F2 - Processing parameters

SI	16384
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	6.41 Hz

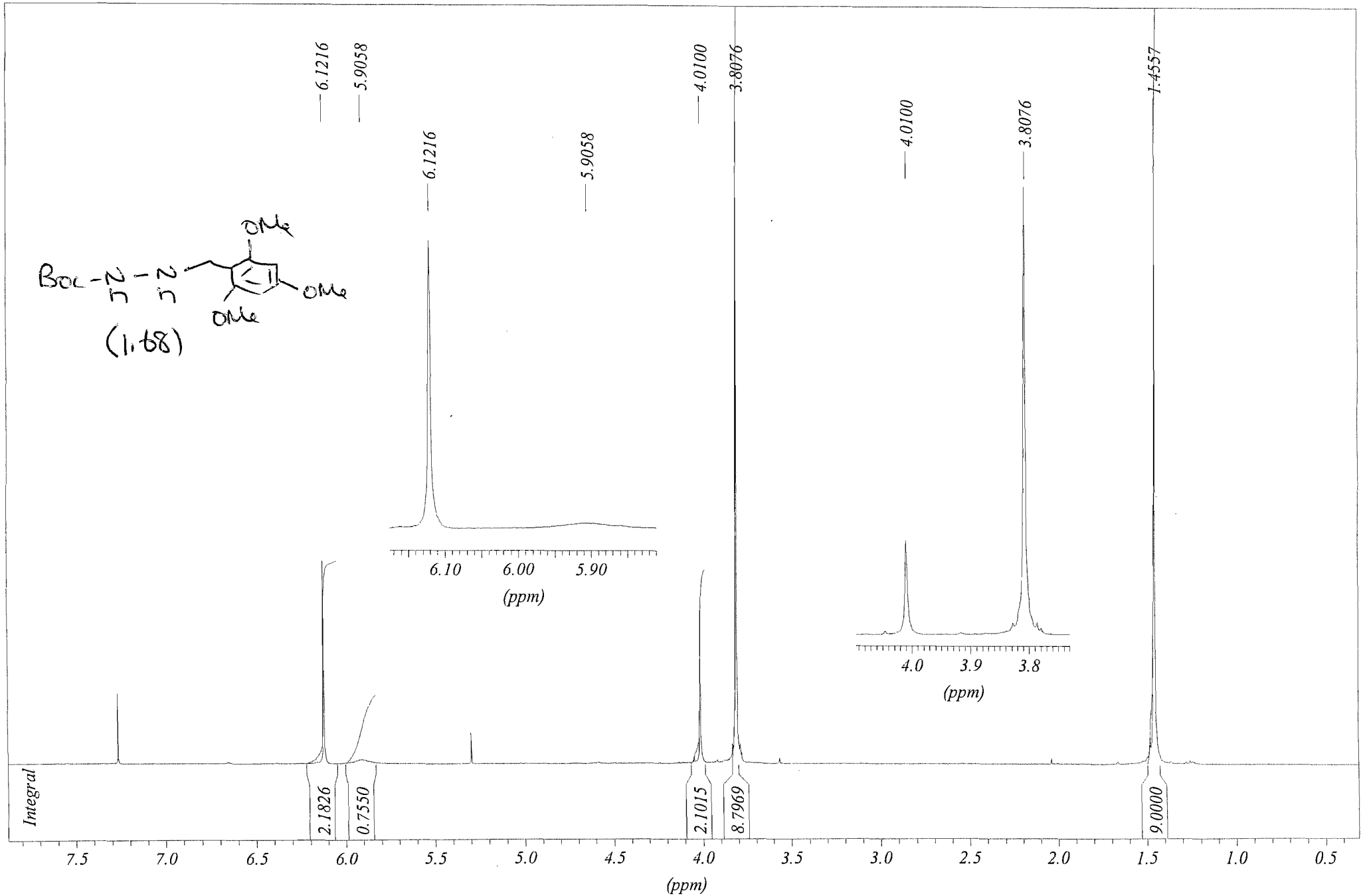

Integral
2.6423
2.2953
0.9189
2.2957
3.1342
9.0000
7.2665
7.2580
7.2409
6.9458
6.9422
6.9215
6.9178
6.8922
6.8642
6.8605
5.9290
4.0112
3.8491
1.4558
(ppm)

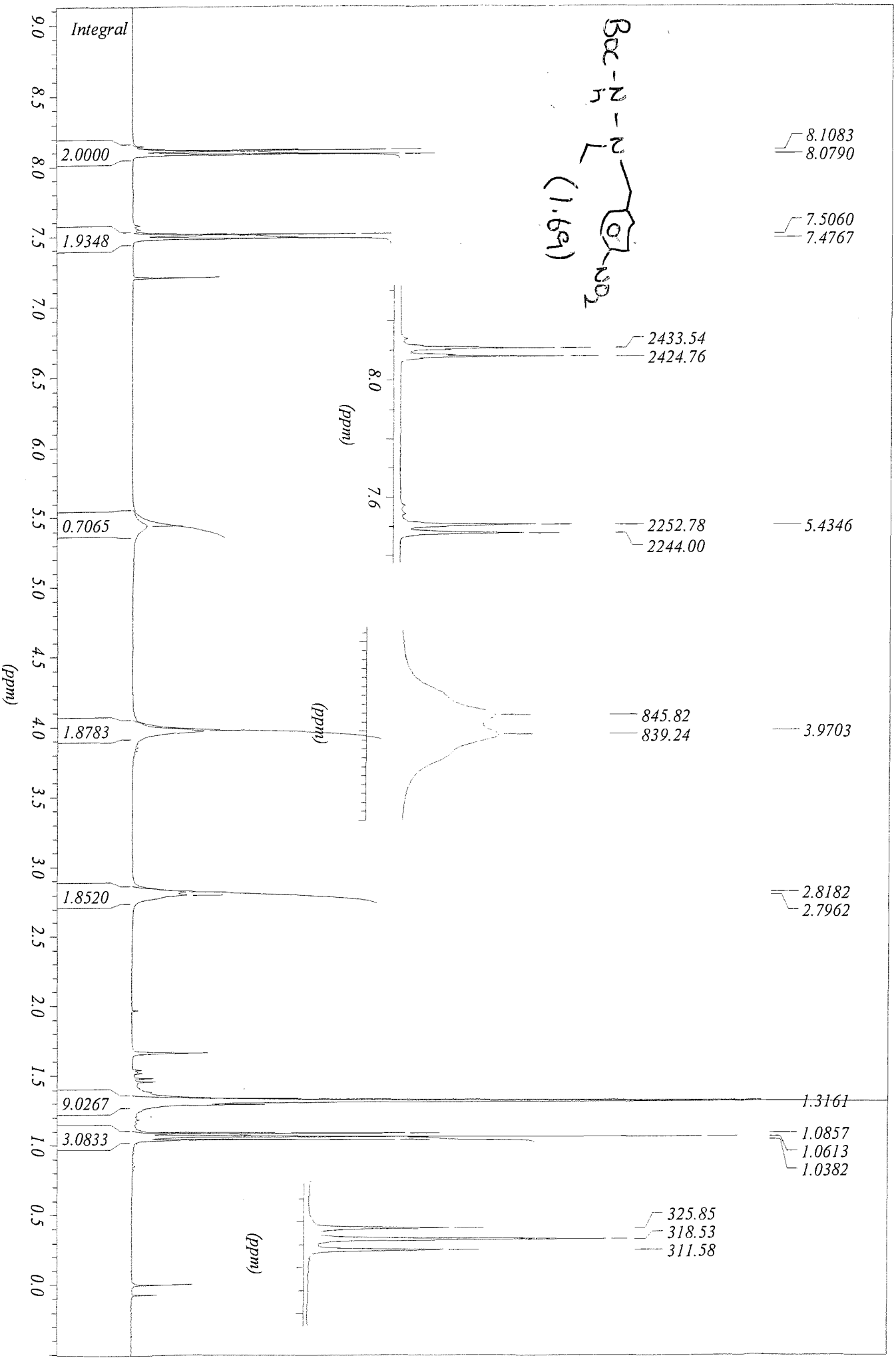
SR4521-73-2

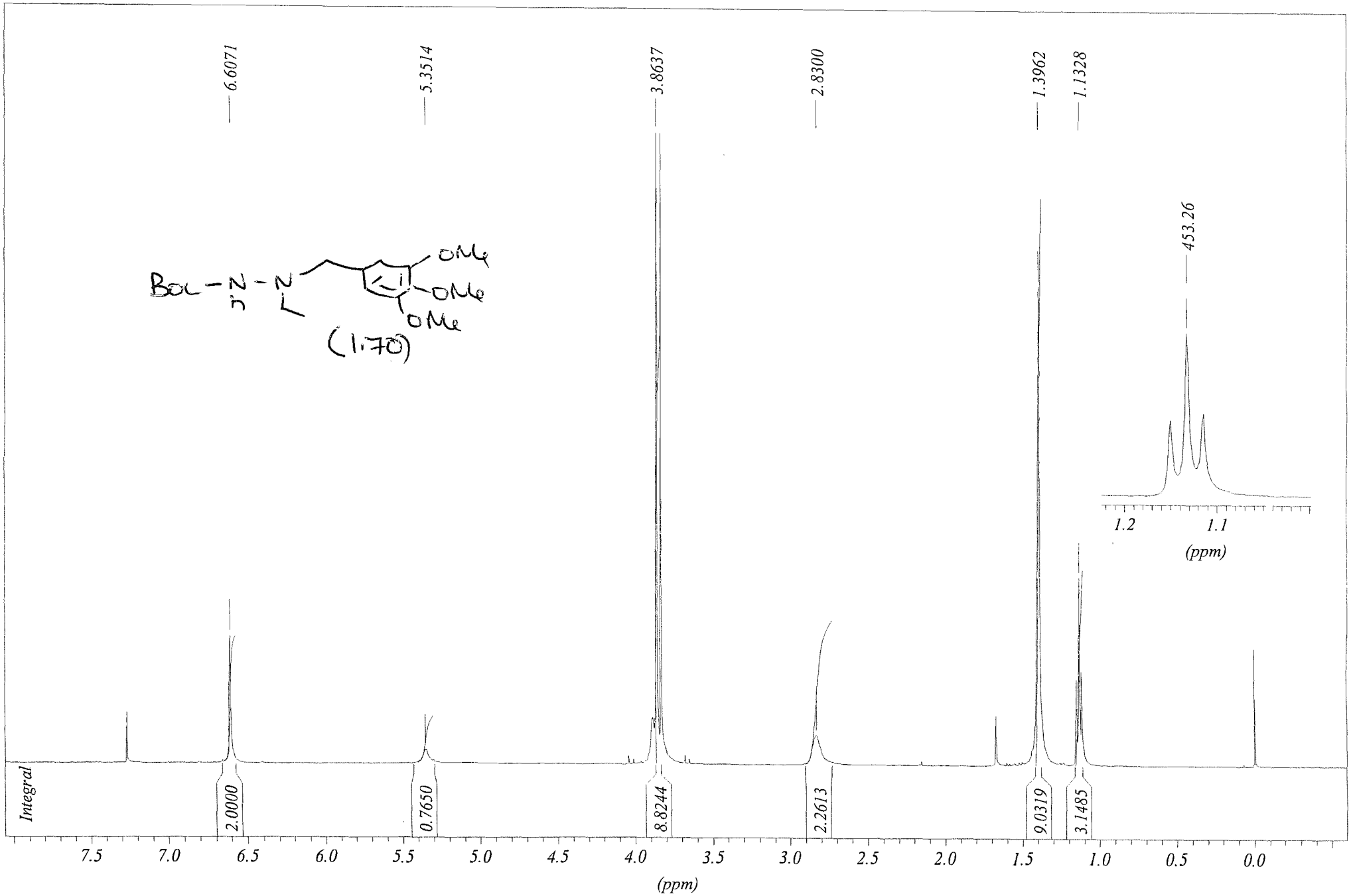

7.2676
7.2590
7.2408
7.2139
6.9396
6.9128
6.9055
6.8360
6.8299
6.8274
6.8116
6.8079
6.8031
6.8006
6.0606
4.1976
3.9709
3.8038
1.4630
Boc-N-N
OMe
(1.64)
7.2
7.0
6.8
(ppm)
4.2
(ppm)
Integral
1.3436
2.0402
1.0214
0.8776
0.8085
1.9384
3.1839
9.0000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

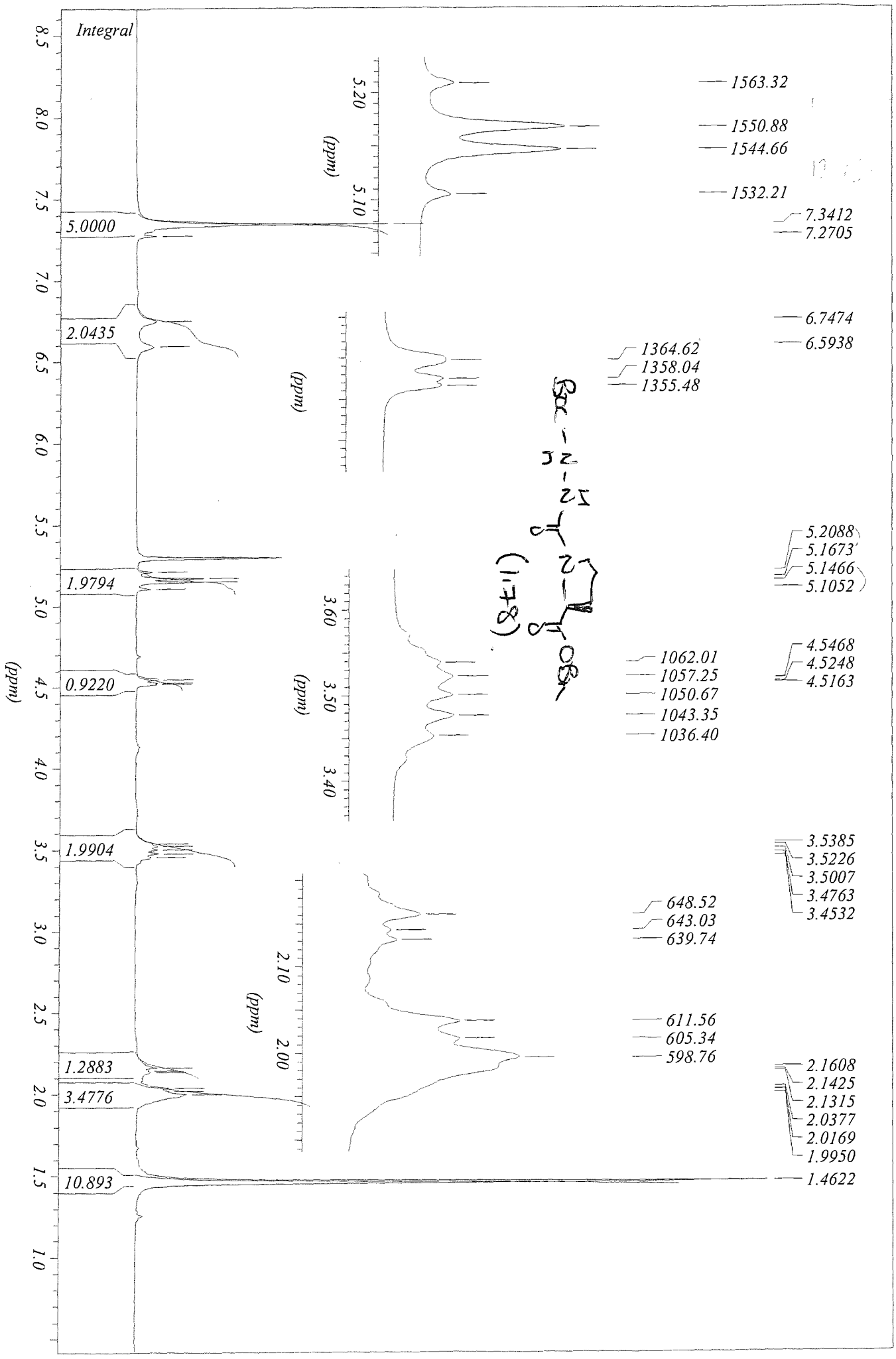

Integral
1.9831
1.0459
0.8334
0.8067
1.9750
6.0332
9.0000
6.5178
6.5105
6.3886
6.3813
6.3740
6.0119
1956.20
1954.00
1917.41
1915.21
1913.02
4.2014
3.9404
3.7856
1.4643
(ppm)
Boc-N-N
OMe
OMe
(1.66)

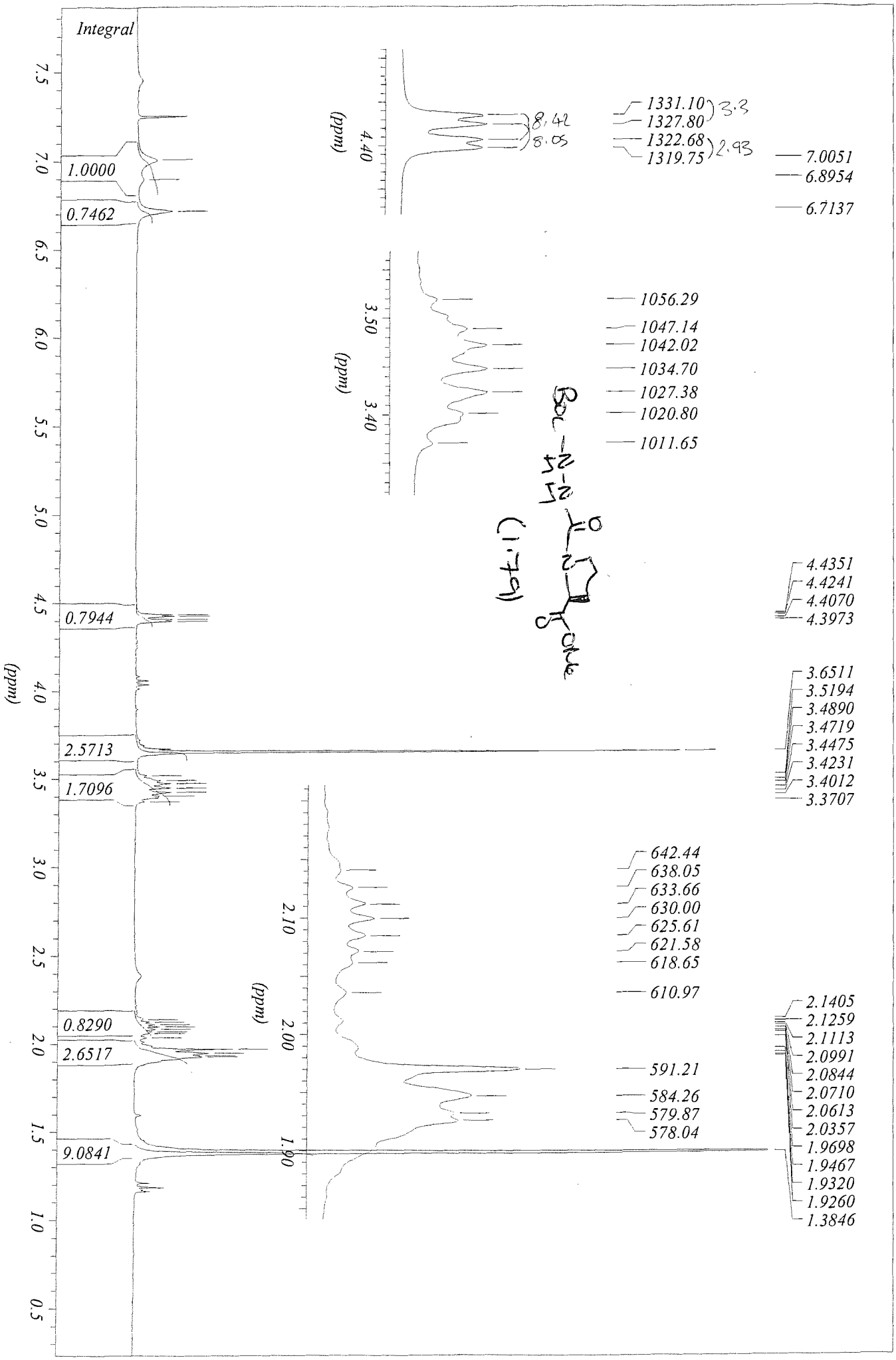
SR4521-73-4


6.1216
5.9058
4.0100
3.8076
1.4557
OMe
OMe
OMe
Boc-N
N
(1.68)
6.10
6.00
5.90
(ppm)
4.0
3.9
3.8
(ppm)
Integral
2.1826
0.7550
2.1015
8.7969
9.0000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

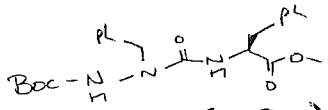

Integral
2.0000
1.9348
0.7065
1.8783
1.8520
9.0267
3.0833
8.1083
8.0790
7.5060
7.4767
2433.54
2424.76
2252.78
2244.00
5.4346
845.82
839.24
3.9703
2.8182
2.7962
1.3161
1.0857
1.0613
1.0382
325.85
318.53
311.58
(ppm)


6.6071
5.3514
3.8637
2.8300
1.3962
1.1328
453.26
1.2
1.1
(ppm)
Integral
2.0000
0.7650
8.8244
2.2613
9.0319
3.1485
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


Integral
5.0000
2.0435
1.9794
0.9220
1.9904
1.2883
3.4776
10.893
(ppm)
1563.32
1550.88
1544.66
1532.21
7.3412
7.2705
6.7474
6.5938
1364.62
1358.04
1355.48
1062.01
1057.25
1050.67
1043.35
1036.40
648.52
643.03
639.74
611.56
605.34
598.76
5.2088
5.1673
5.1466
5.1052
4.5468
4.5248
4.5163
3.5385
3.5226
3.5007
3.4763
3.4532
2.1608
2.1425
2.1315
2.0377
2.0169
1.9950
1.4622

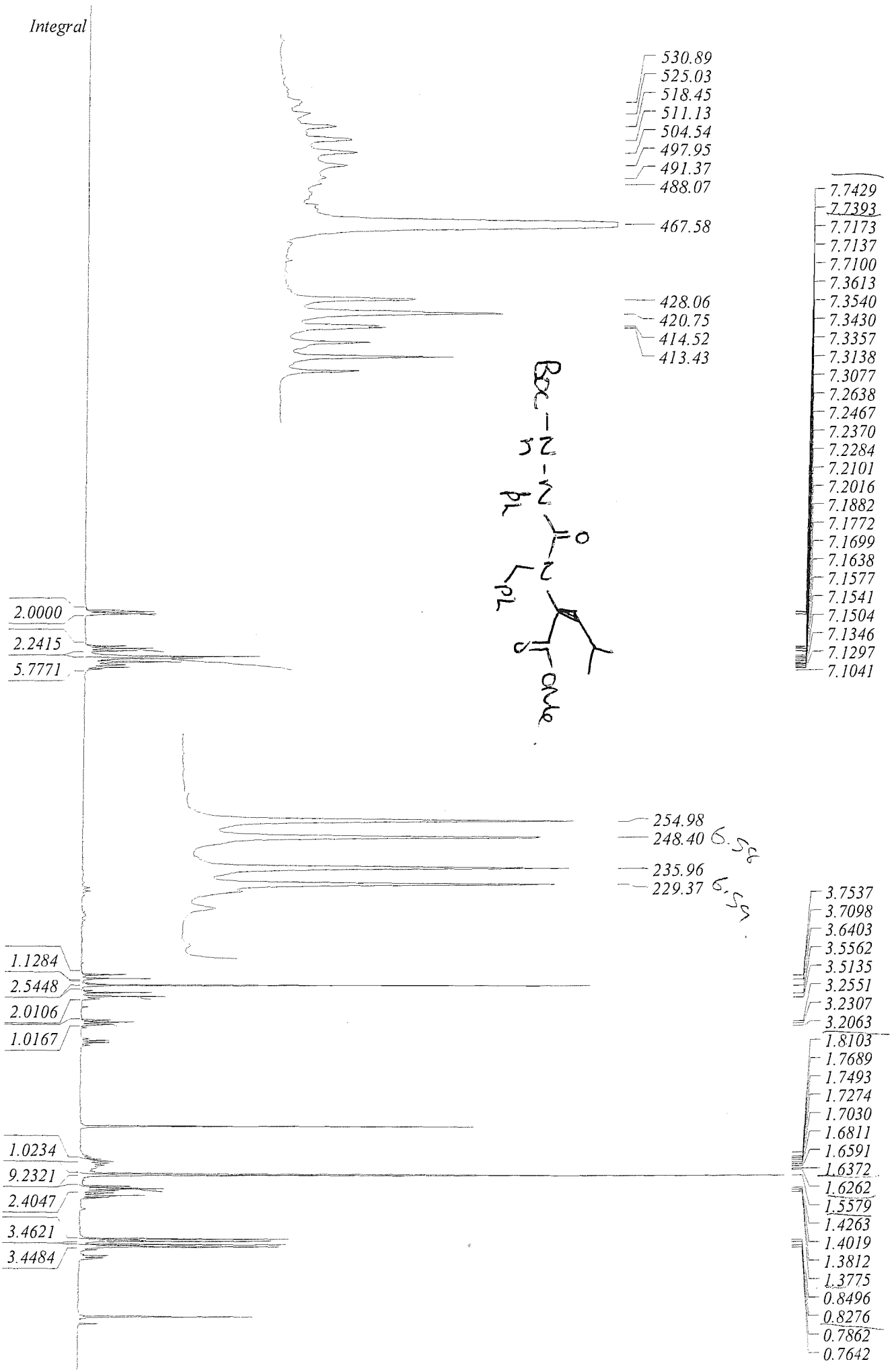

Integral
1.0000
0.7462
0.7944
2.5713
1.7096
0.8290
2.6517
9.0841
(ppm)
8.42
8.05
1331.10
1327.80
1322.68
1319.75
3.3
2.93
7.0051
6.8954
6.7137
1056.29
1047.14
1042.02
1034.70
1027.38
1020.80
1011.65
4.4351
4.4241
4.4070
4.3973
3.6511
3.5194
3.4890
3.4719
3.4475
3.4231
3.4012
3.3707
642.44
638.05
633.66
630.00
625.61
621.58
618.65
610.97
591.21
584.26
579.87
578.04
2.1405
2.1259
2.1113
2.0991
2.0844
2.0710
2.0613
2.0357
1.9698
1.9467
1.9320
1.9260
1.3846
Boc-N
(1.79)

SR4374-2



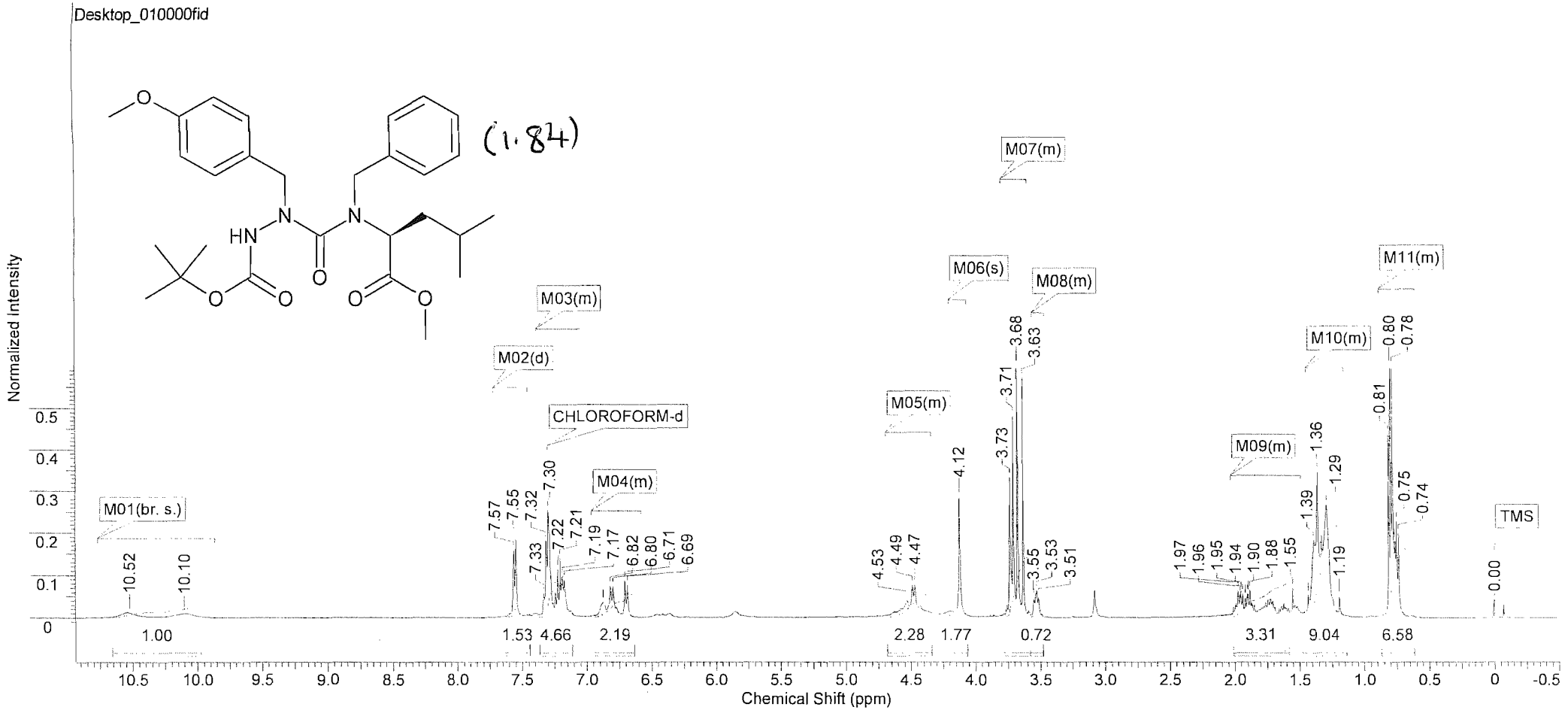
(1.82)


```
Current Data Parameters
NAME                 oc1606skr1
EXPNO                        10
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20061016
Time                     13.01
INSTRUM                  av300
PROBHD     5 mm QNP 1H/13
PULPROG                  zg30
TD                      32768
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                   5995.204 Hz
FIDRES                0.182959 Hz
AQ                    2.7329011 sec
RG                        406.4
DW                       83.400 usec
DE                        6.00 usec
TE                       303.2 K
D1                    1.00000000 sec
MCREST                0.00000000 sec
MCWRK                 0.01500000 sec

======== CHANNEL f1 ========
NUC1                         1H
P1                       12.10 usec
PL1                       3.00 dB
SFO1            300.1315006 MHz

F2 - Processing parameters
SI                       16384
SF              300.1300286 MHz
WDW                         EM
SSB                          0
LB                        0.30 Hz
GB                           0
PC                        1.00
SR                       28.55 Hz
```


Integral
530.89
525.03
518.45
511.13
504.54
497.95
491.37
488.07
467.58
428.06
420.75
414.52
413.43
7.7429
7.7393
7.7173
7.7137
7.7100
7.3613
7.3540
7.3430
7.3357
7.3138
7.3077
7.2638
7.2467
7.2370
7.2284
7.2101
7.2016
7.1882
7.1772
7.1699
7.1638
7.1577
7.1541
7.1504
7.1346
7.1297
7.1041
2.0000
2.2415
5.7771
254.98
248.40
235.96
229.37
6.56
6.54
3.7537
3.7098
3.6403
3.5562
3.5135
3.2551
3.2307
3.2063
1.8103
1.7689
1.7493
1.7274
1.7030
1.6811
1.6591
1.6372
1.6262
1.5579
1.4263
1.4019
1.3812
1.3775
0.8496
0.8276
0.7862
0.7642
1.1284
2.5448
2.0106
1.0167
1.0234
9.2321
2.4047
3.4621
3.4484

SR4374-11-F1

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.60 - 0.88 (m, 6 H) 1.15 - 1.44 (m, 9 H) 1.49 - 2.03 (m, 3 H) 3.46 - 3.56 (m, 1 H) 3.58 - 3.79 (m, 6 H) 4.12 (s, 2 H) 4.34 - 4.69 (m, 2 H) 6.58 - 6.96 (m, 2 H) 7.05 - 7.38 (m, 5 H) 7.56 (d, *J*=6.53 Hz, 2 H) 10.31 (br. s., 1 H)



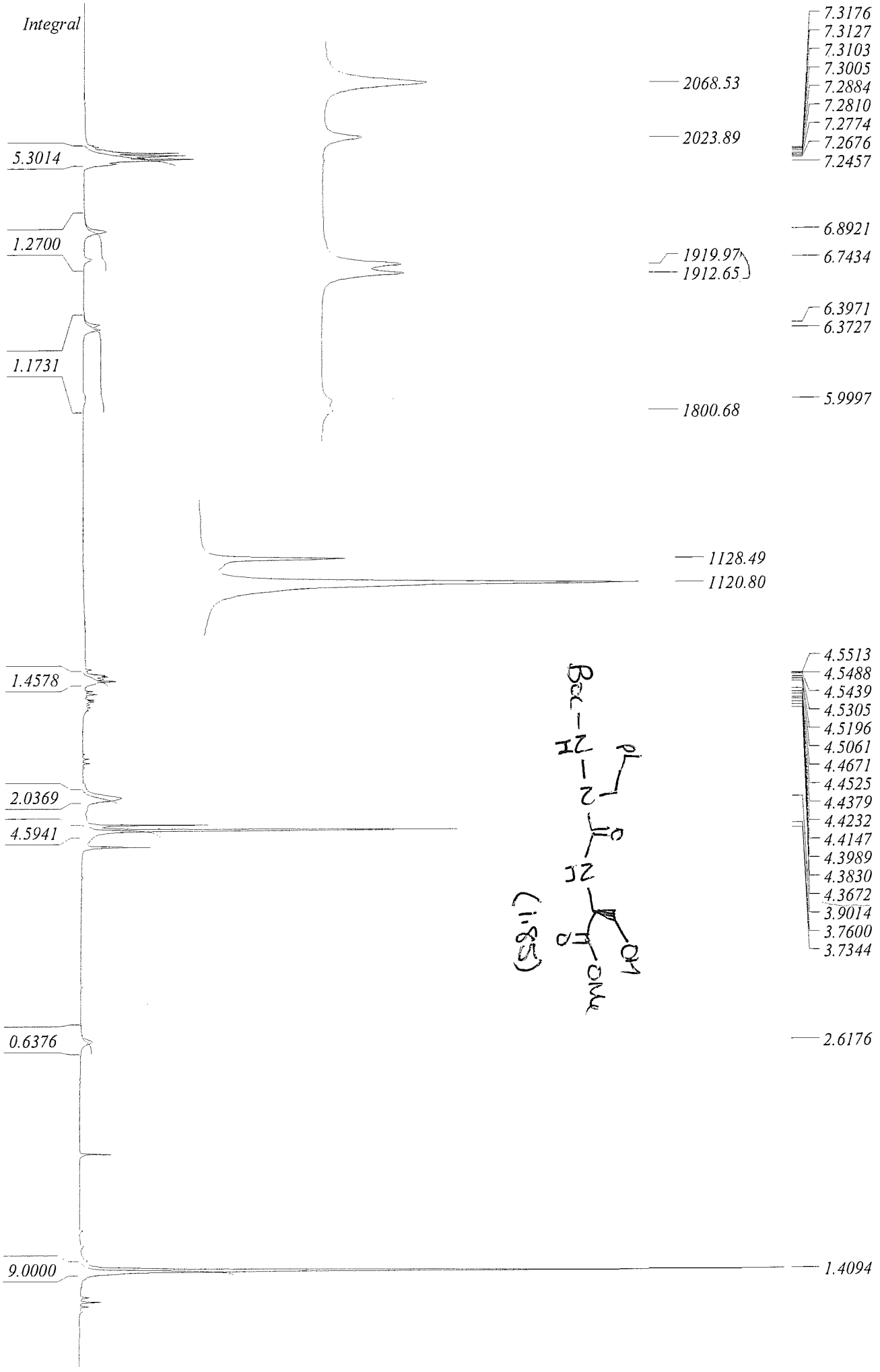
No.	(ppm)	(Hz)	Height
1	0.00	0.0	0.0130
2	0.74	294.6	0.1988
3	0.75	301.2	0.2280
4	0.77	306.2	0.1792
5	0.78	312.7	0.5937
6	0.80	318.7	0.7456
7	0.81	325.3	0.4399
8	1.19	476.8	0.0481
9	1.29	516.5	0.2669
10	1.33	530.5	0.1616
11	1.34	534.6	0.1479

No.	(ppm)	(Hz)	Height
12	1.36	544.1	0.3465
13	1.39	556.1	0.1828
14	1.43	573.2	0.0521
15	1.55	621.4	0.0691
16	1.88	753.4	0.0643
17	1.90	758.9	0.0542
18	1.90	761.9	0.0562
19	1.92	768.0	0.0461
20	1.94	775.5	0.0545
21	1.95	781.0	0.0612
22	1.96	784.0	0.0526

No.	(ppm)	(Hz)	Height
23	1.97	789.5	0.0621
24	3.51	1405.4	0.0466
25	3.53	1411.4	0.0640
26	3.55	1420.0	0.0424
27	3.63	1453.6	0.5704
28	3.68	1470.7	1.0000
29	3.71	1483.7	0.4811
30	3.73	1493.3	0.3321
31	4.12	1649.4	0.2859
32	4.47	1787.9	0.0766
33	4.49	1795.4	0.0755

No.	(ppm)	(Hz)	Height
34	4.53	1812.0	0.0405
35	6.69	2675.3	0.0762
36	6.71	2683.8	0.0869
37	6.80	2720.0	0.0736
38	6.82	2728.5	0.0746
39	6.87	2749.6	0.0346
40	7.17	2870.6	0.0890
41	7.19	2877.6	0.0978
42	7.21	2884.1	0.1392
43	7.22	2890.6	0.1135
44	7.24	2897.7	0.0598

No.	(ppm)	(Hz)	Height
45	7.30	2919.7	0.2536
46	7.32	2927.3	0.1809
47	7.33	2933.3	0.0567
48	7.55	3020.6	0.1833
49	7.57	3027.2	0.1569
50	10.10	4042.6	0.0091
51	10.52	4211.2	0.0112


Integral
5.3014
1.2700
1.1731
1.4578
2.0369
4.5941
0.6376
9.0000
2068.53
2023.89
1919.97
1912.65
1800.68
1128.49
1120.80
7.3176
7.3127
7.3103
7.3005
7.2884
7.2810
7.2774
7.2676
7.2457
6.8921
6.7434
6.3971
6.3727
5.9997
4.5513
4.5488
4.5439
4.5305
4.5196
4.5061
4.4671
4.4525
4.4379
4.4232
4.4147
4.3989
4.3830
4.3672
3.9014
3.7600
3.7344
2.6176
1.4094

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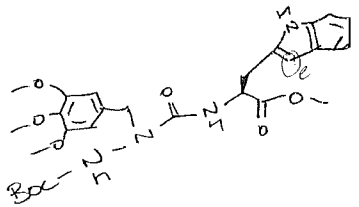


(1.86)

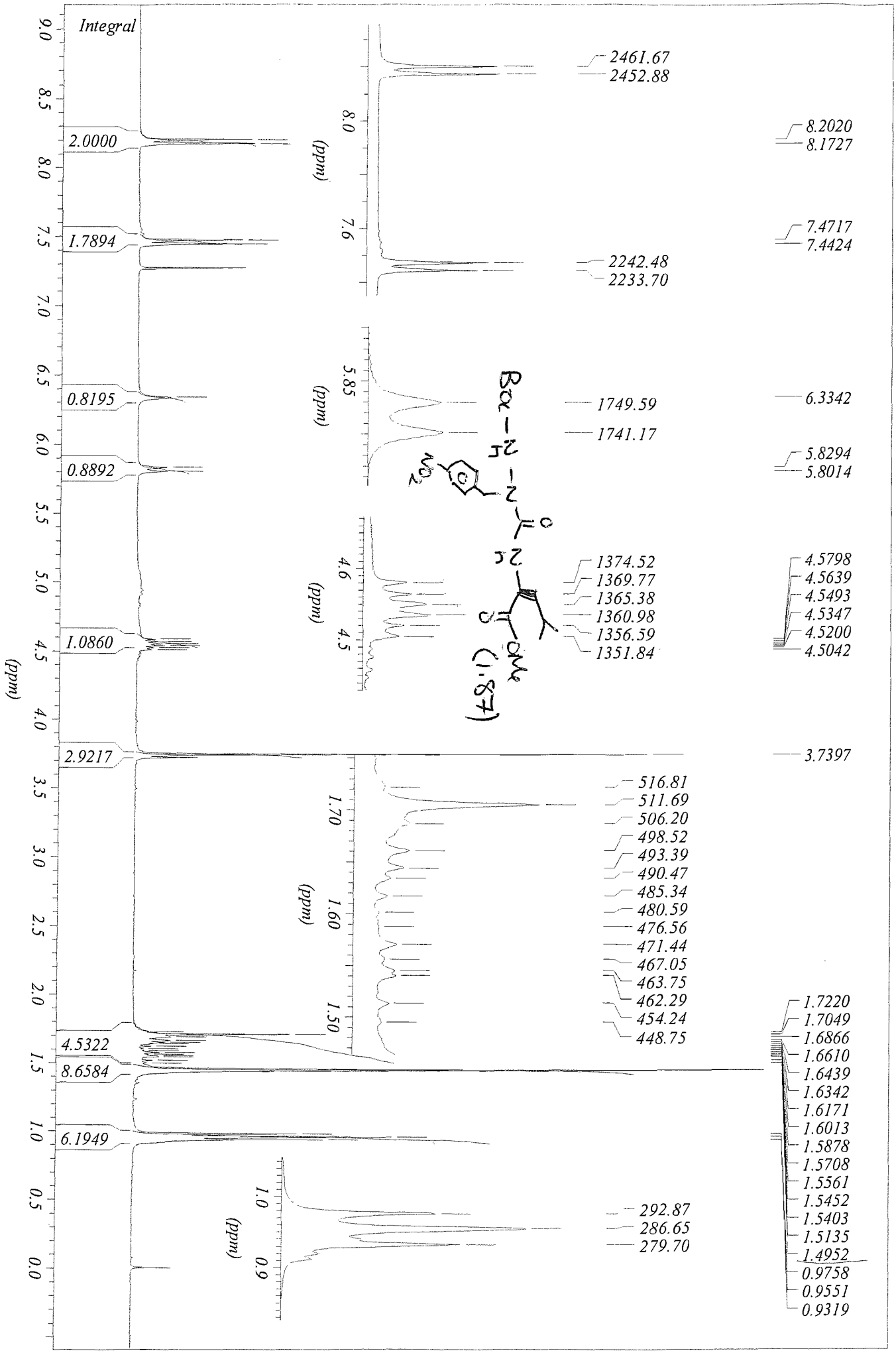
BRUKER

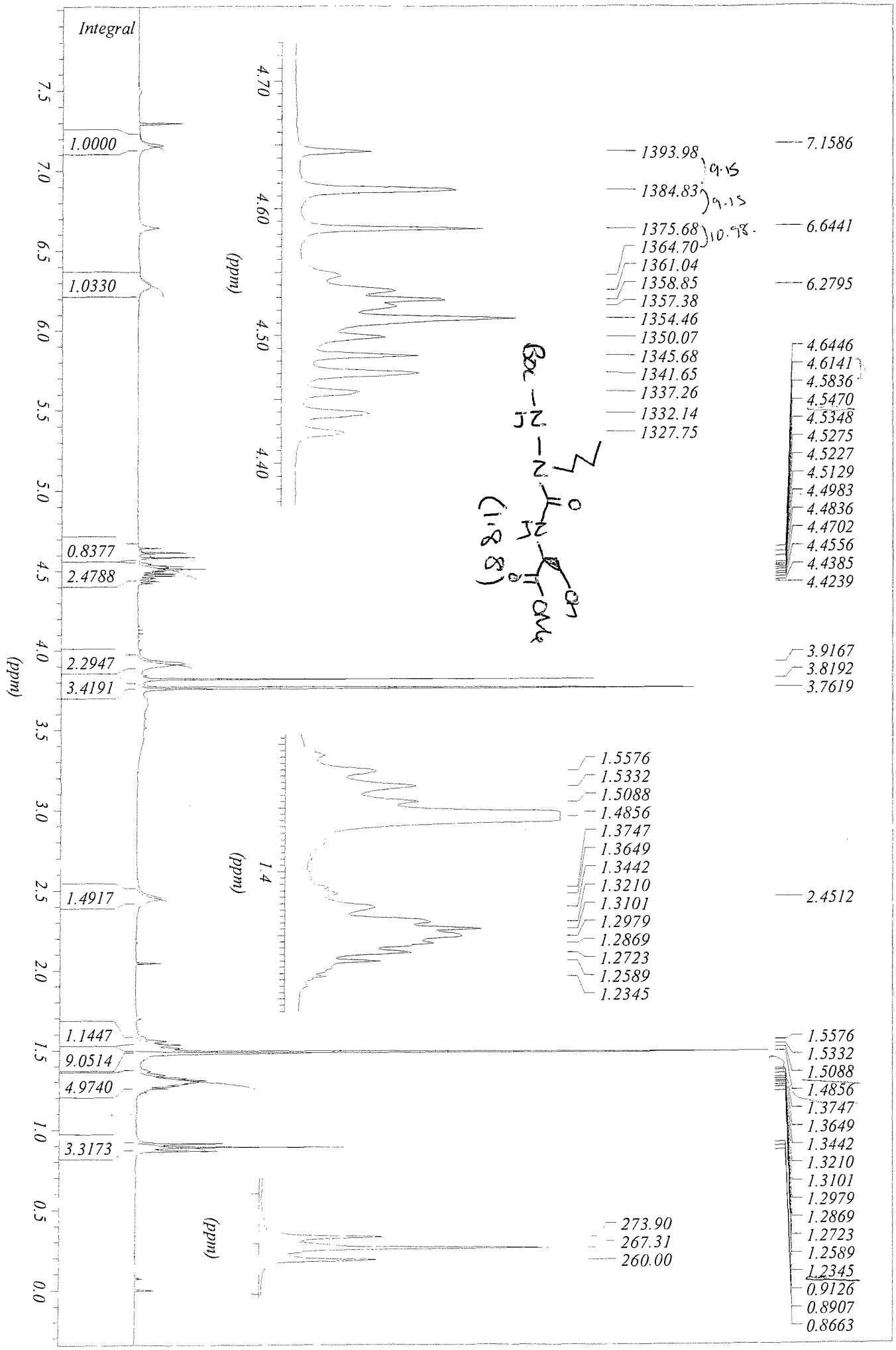
Current Data Parameters
NAME oc1606skr3
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061016
Time 13.17
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 812.7
DW 83.400 usec
DE 6.00 usec
TE 303.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

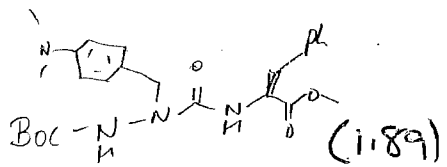
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300070 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 7.02 Hz


Integral
2.0000
1.7894
0.8195
0.8892
1.0860
2.9217
4.5322
8.6584
6.1949
(ppm)
2461.67
2452.88
2242.48
2233.70
8.2020
8.1727
7.4717
7.4424
1749.59
1741.17
6.3342
5.8294
5.8014
1374.52
1369.77
1365.38
1360.98
1356.59
1351.84
4.5798
4.5639
4.5493
4.5347
4.5200
4.5042
3.7397
516.81
511.69
506.20
498.52
493.39
490.47
485.34
480.59
476.56
471.44
467.05
463.75
462.29
454.24
448.75
1.7220
1.7049
1.6866
1.6610
1.6439
1.6342
1.6171
1.6013
1.5878
1.5708
1.5561
1.5452
1.5403
1.5135
1.4952
0.9758
0.9551
0.9319
292.87
286.65
279.70
Boc
(1.87)


Integral
1.0000
1.0330
0.8377
2.4788
2.2947
3.4191
1.4917
1.1447
9.0514
4.9740
3.3173
(ppm)
1393.98
1384.83
1375.68
1364.70
1361.04
1358.85
1357.38
1354.46
1350.07
1345.68
1341.65
1337.26
1332.14
1327.75
9.15
9.15
10.98
7.1586
6.6441
6.2795
4.6446
4.6141
4.5836
4.5470
4.5348
4.5275
4.5227
4.5129
4.4983
4.4836
4.4702
4.4556
4.4385
4.4239
3.9167
3.8192
3.7619
2.4512
1.5576
1.5332
1.5088
1.4856
1.3747
1.3649
1.3442
1.3210
1.3101
1.2979
1.2869
1.2723
1.2589
1.2345
0.9126
0.8907
0.8663
273.90
267.31
260.00
(1.88 g)

SR4374-46



Current Data Parameters

NAME	dc1505skr1
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20051215
Time	11.33
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

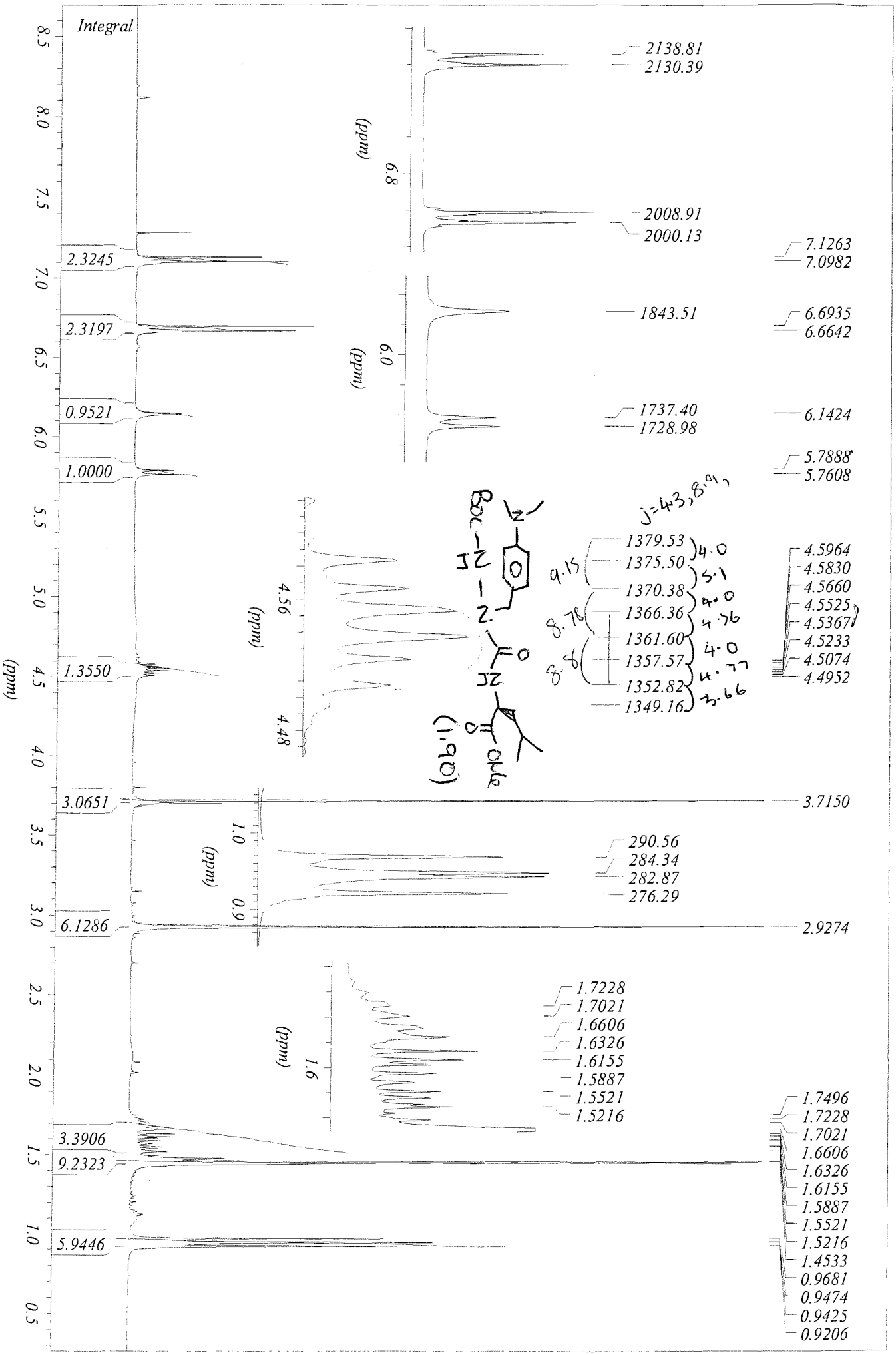
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

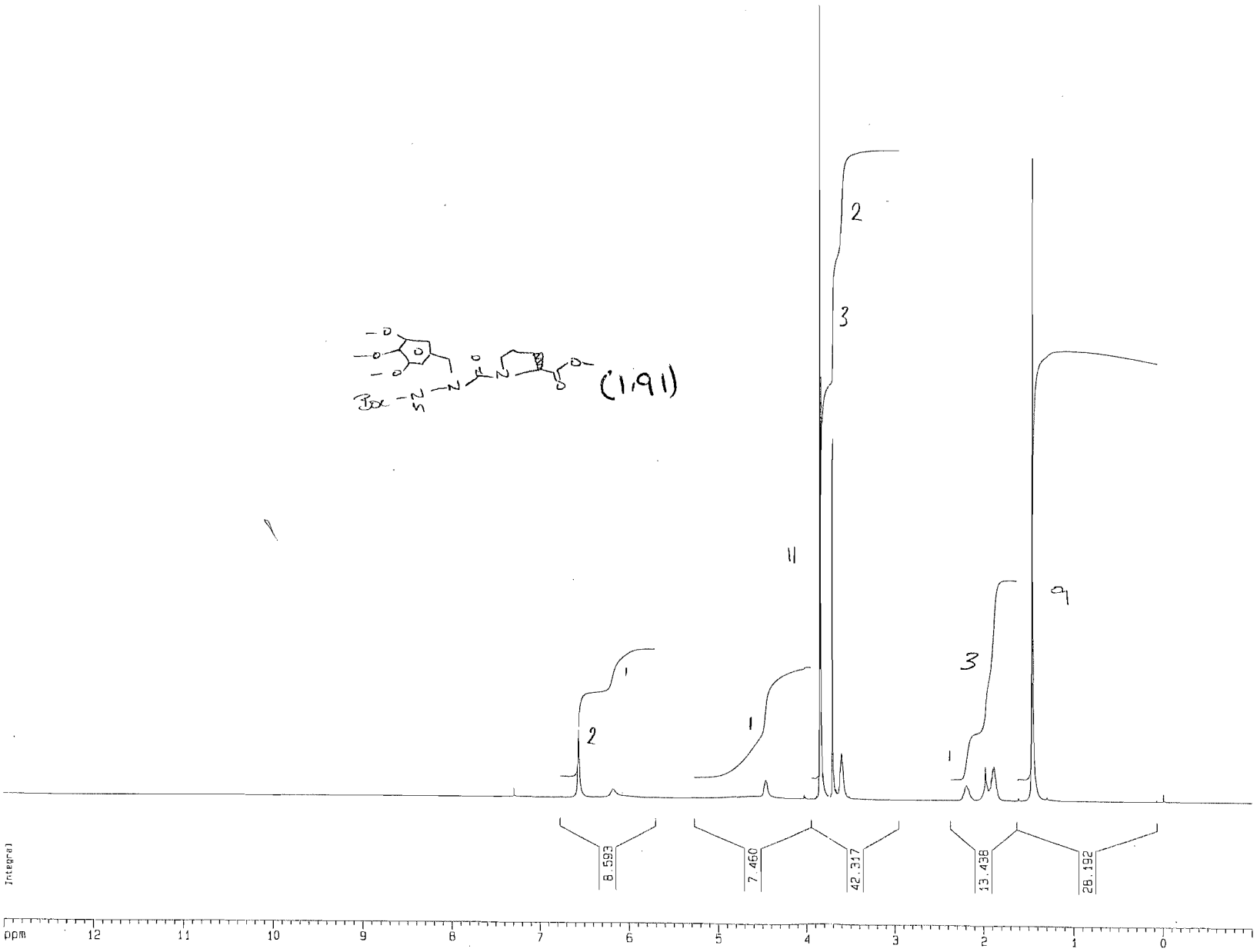
SI	16384
SF	400.1300214 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	21.44 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm


Integral
2.3245
2.3197
0.9521
1.0000
1.3550
3.0651
6.1286
3.3906
9.2323
5.9446
2138.81
2130.39
2008.91
2000.13
1843.51
1737.40
1728.98
7.1263
7.0982
6.6935
6.6642
6.1424
5.7888
5.7608
4.5964
4.5830
4.5660
4.5525
4.5367
4.5233
4.5074
4.4952
3.7150
2.9274
1.7496
1.7228
1.7021
1.6606
1.6326
1.6155
1.5887
1.5521
1.5216
1.4533
0.9681
0.9474
0.9425
0.9206
1379.53
1375.50
1370.38
1366.36
1361.60
1357.57
1352.82
1349.16
J=4.3, 8.9 Hz
9.15
8.78
8.8
4.0
5.1
4.0
4.76
4.0
4.77
3.66
290.56
284.34
282.87
276.29
(1.90)
(ppm)

SR4374-35



Current Data Parameters

NAME	dc1505skr4
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20051215
Time	16.00
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	28.5
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

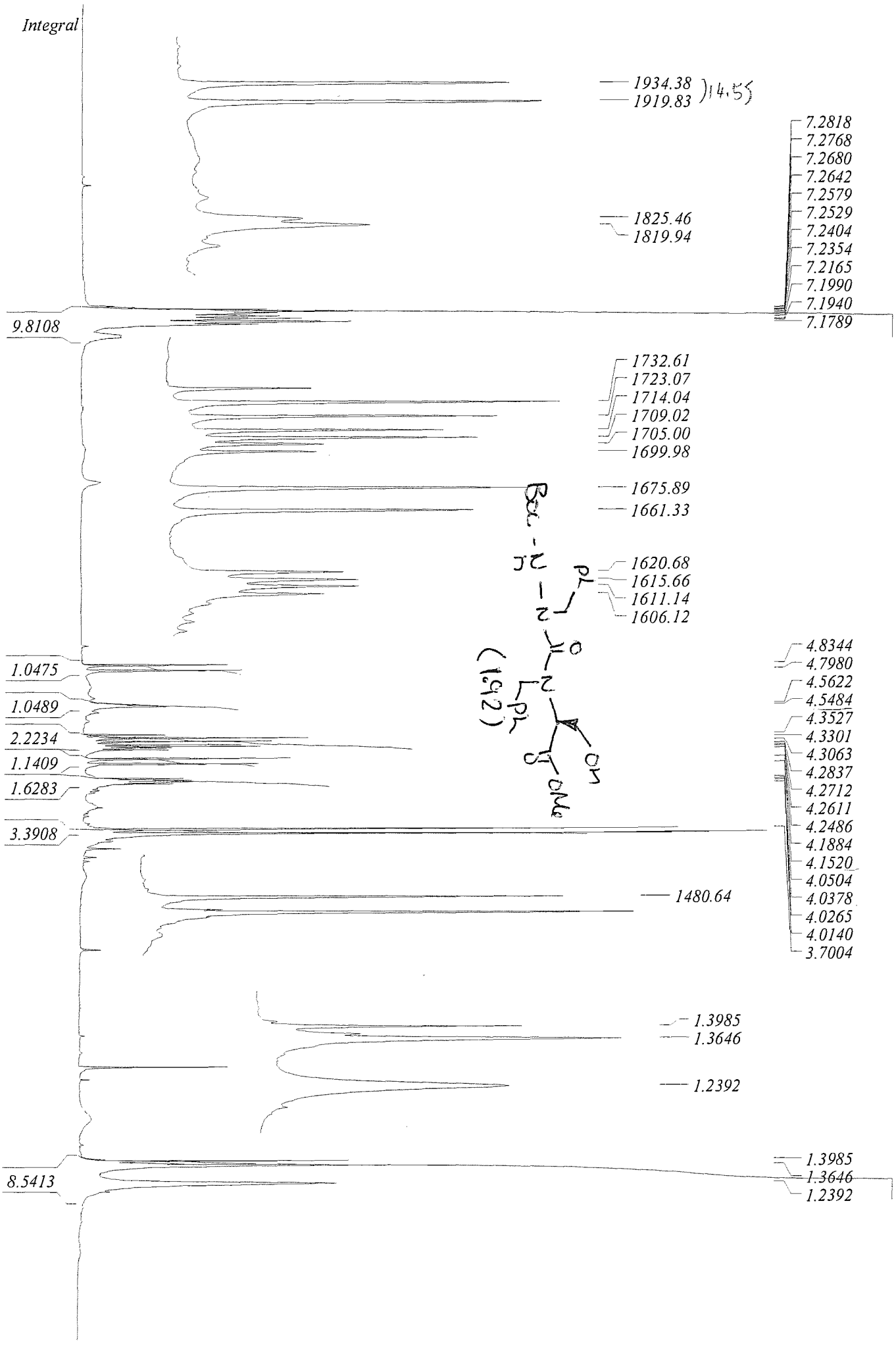
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

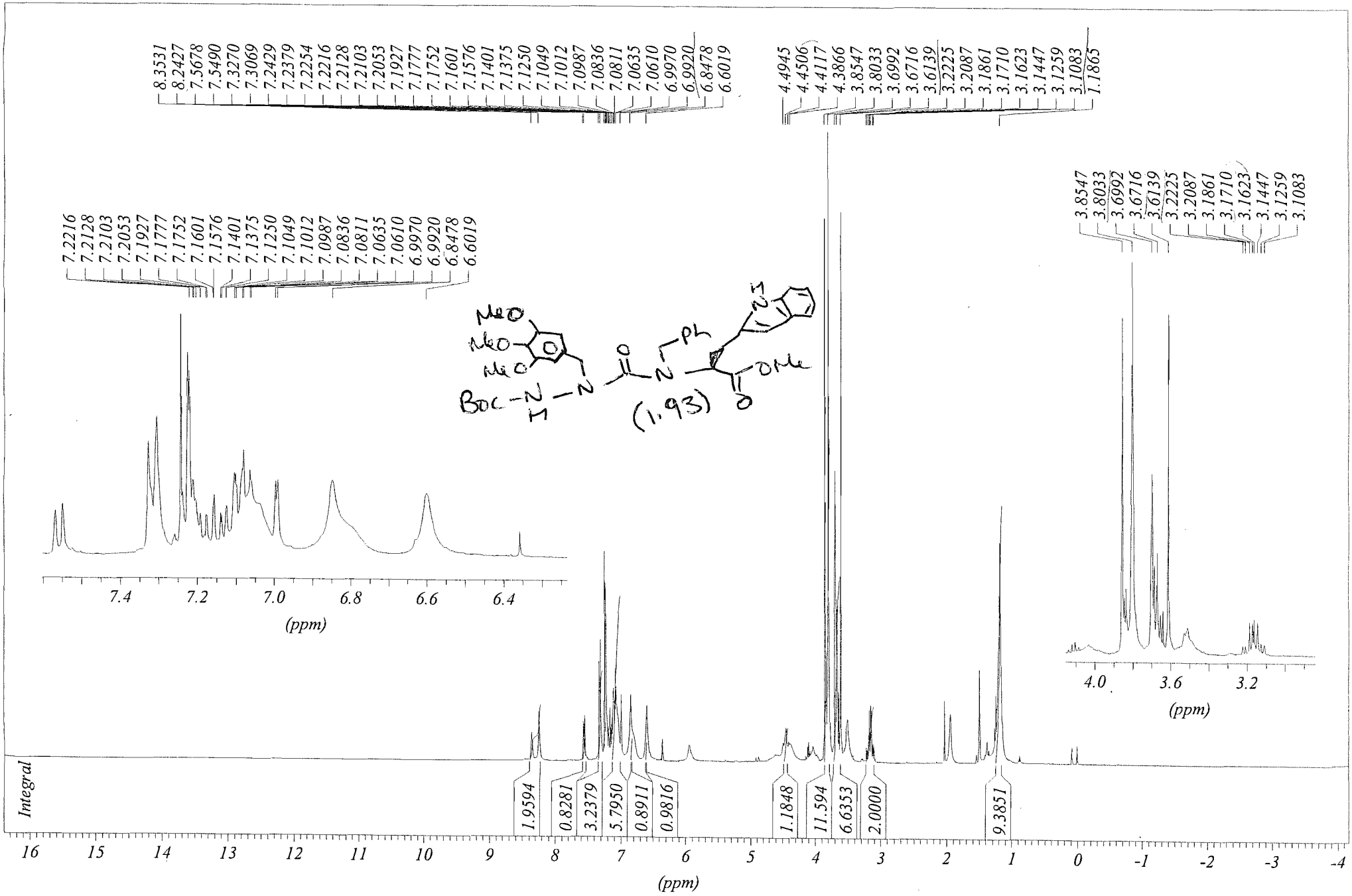
SI	16384
SF	400.1300053 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	5.27 Hz

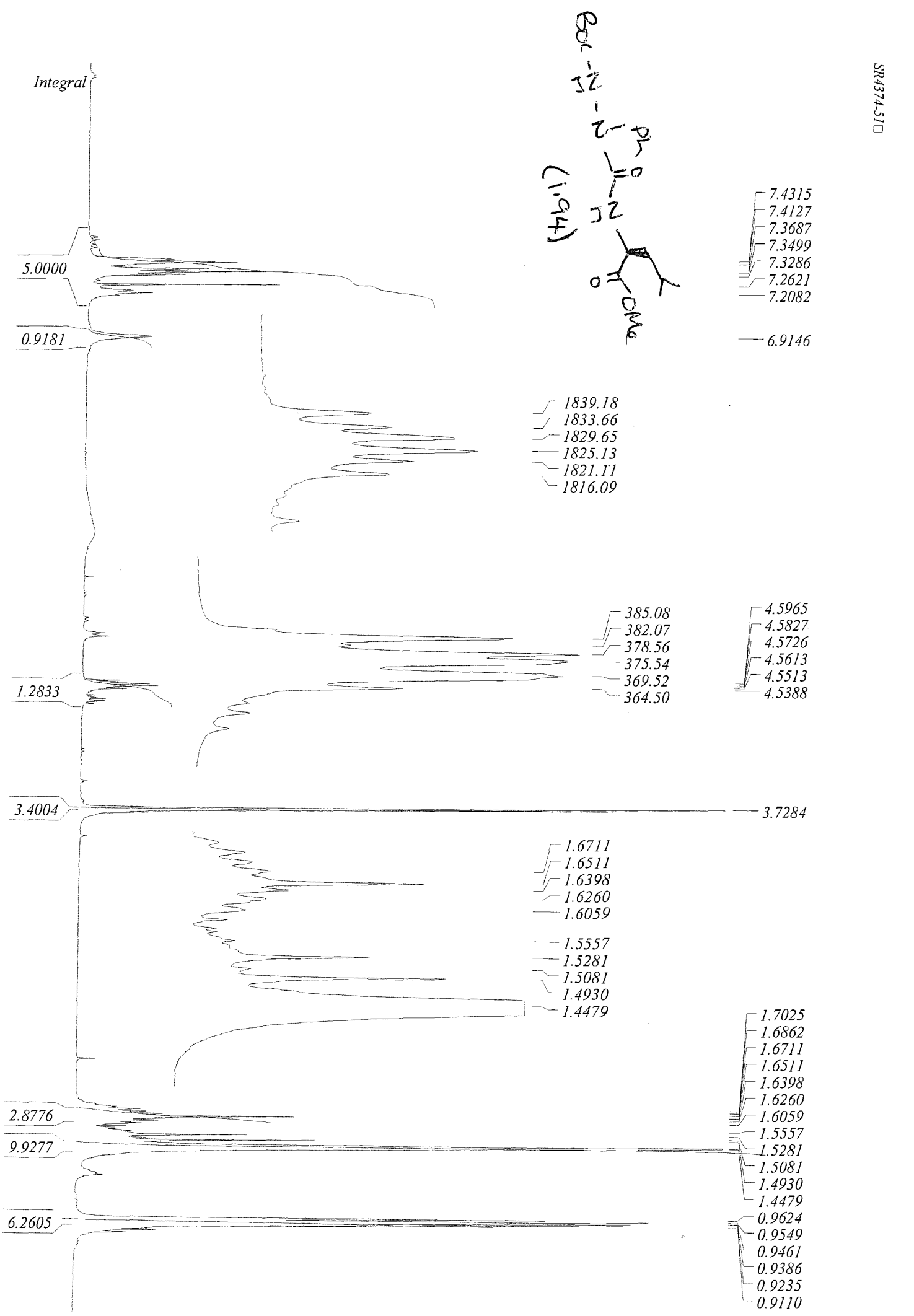
1D NMR plot parameters

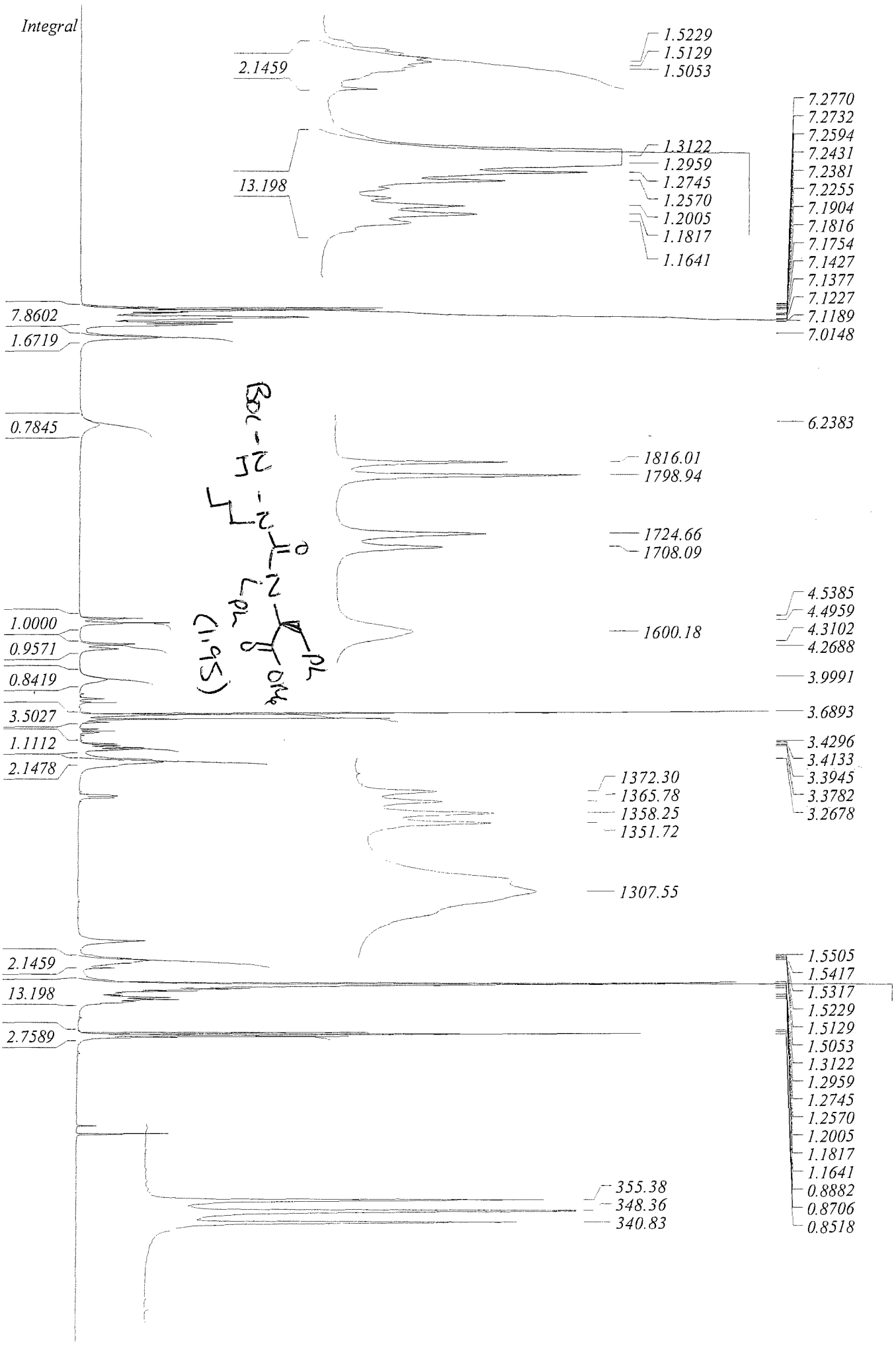
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

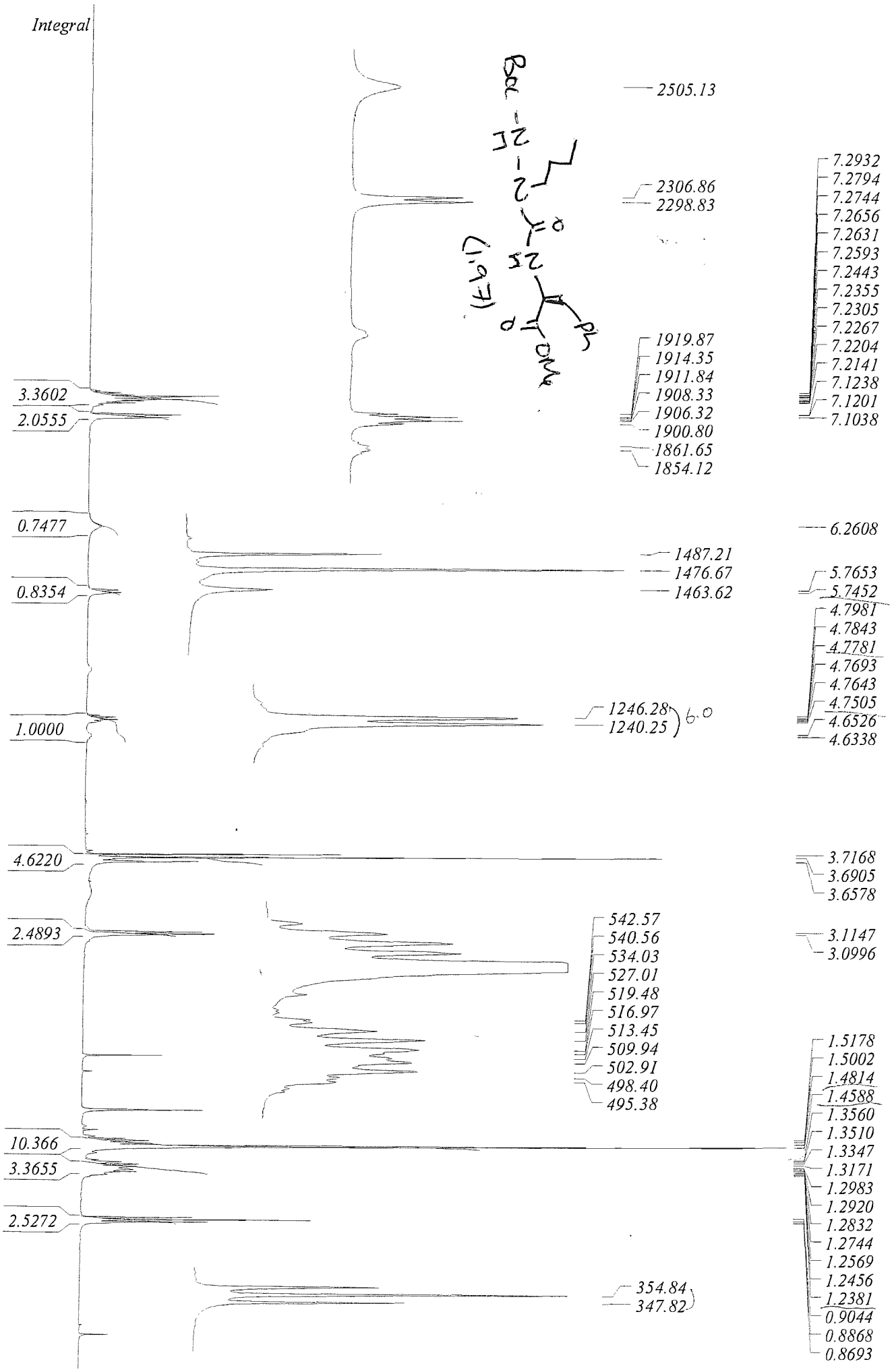

SR4374-85-F3
Integral
1934.38
1919.83
14.55
1825.46
1819.94
7.2818
7.2768
7.2680
7.2642
7.2579
7.2529
7.2404
7.2354
7.2165
7.1990
7.1940
7.1789
9.8108
1732.61
1723.07
1714.04
1709.02
1705.00
1699.98
1675.89
1661.33
1620.68
1615.66
1611.14
1606.12
Bzl-N
Pl
N
O
Pl
(1.92)
O
OMe
OH
4.8344
4.7980
4.5622
4.5484
4.3527
4.3301
4.3063
4.2837
4.2712
4.2611
4.2486
4.1884
4.1520
4.0504
4.0378
4.0265
4.0140
3.7004
1.0475
1.0489
2.2234
1.1409
1.6283
3.3908
1480.64
1.3985
1.3646
1.2392
1.3985
1.3646
1.2392
8.5413

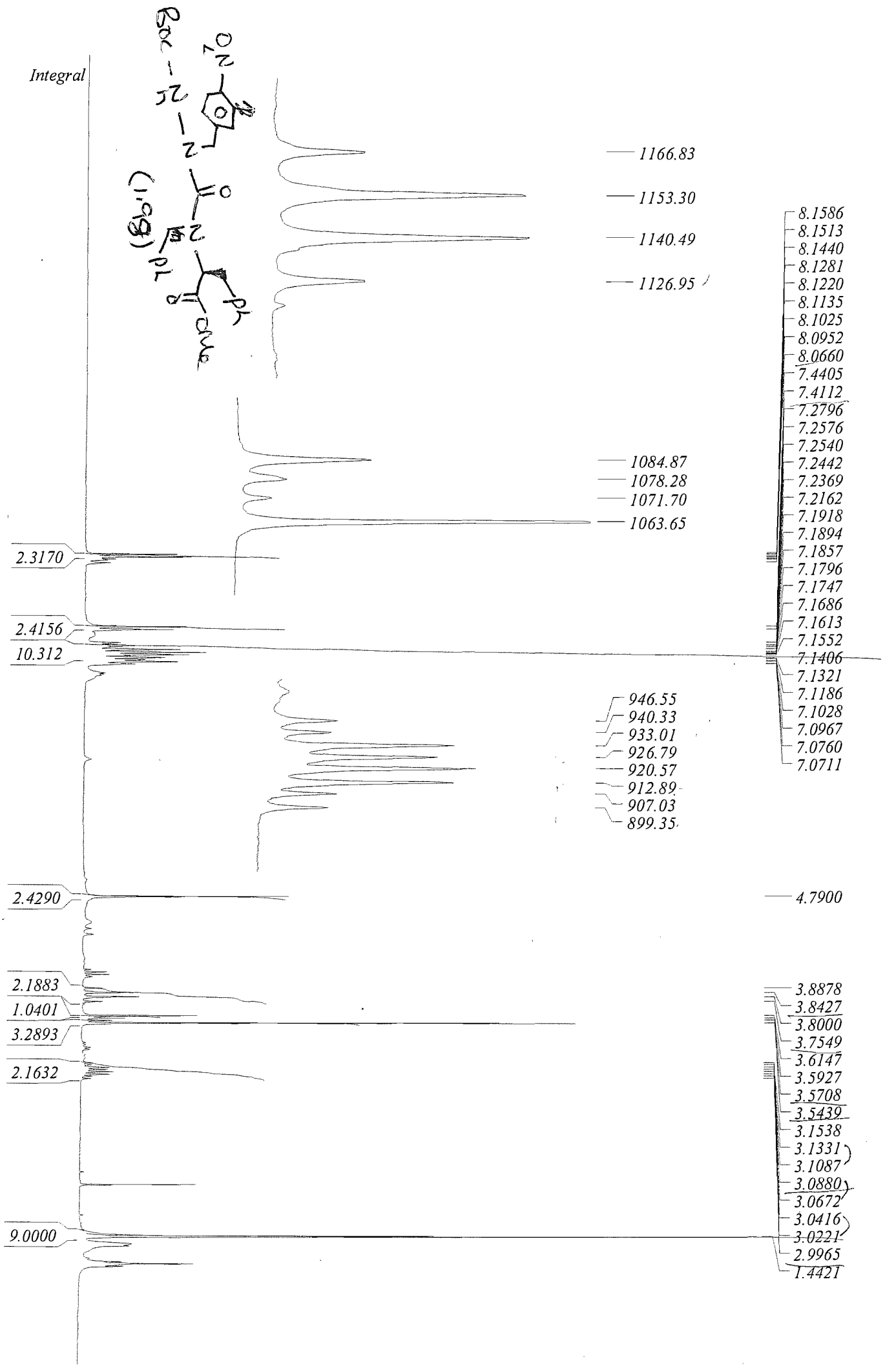
SR4374-43-F1□


8.3531
8.2427
7.5678
7.5490
7.3270
7.3069
7.2429
7.2379
7.2254
7.2216
7.2128
7.2103
7.2053
7.1927
7.1777
7.1752
7.1601
7.1576
7.1401
7.1375
7.1250
7.1049
7.1012
7.0987
7.0836
7.0811
7.0635
7.0610
6.9970
6.9920
6.8478
6.6019
4.4945
4.4506
4.4117
4.3866
3.8547
3.8033
3.6992
3.6716
3.6139
3.2225
3.2087
3.1861
3.1710
3.1623
3.1447
3.1259
3.1083
1.1865
MeO
MeO
MeO
Boc-N
N
N
Ph
OMe
(1.93)
7.4
7.2
7.0
6.8
6.6
6.4
(ppm)
4.0
3.6
3.2
(ppm)
Integral
1.9594
0.8281
3.2379
5.7950
0.8911
0.9816
1.1848
11.594
6.6353
2.0000
9.3851
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
-4
(ppm)

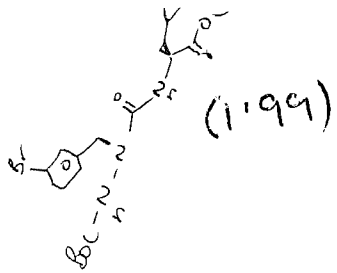

SR4374-51
Integral
5.0000
0.9181
1.2833
3.4004
2.8776
9.9277
6.2605
7.4315
7.4127
7.3687
7.3499
7.3286
7.2621
7.2082
6.9146
1839.18
1833.66
1829.65
1825.13
1821.11
1816.09
385.08
382.07
378.56
375.54
369.52
364.50
4.5965
4.5827
4.5726
4.5613
4.5513
4.5388
3.7284
1.6711
1.6511
1.6398
1.6260
1.6059
1.5557
1.5281
1.5081
1.4930
1.4479
1.7025
1.6862
1.6711
1.6511
1.6398
1.6260
1.6059
1.5557
1.5281
1.5081
1.4930
1.4479
0.9624
0.9549
0.9461
0.9386
0.9235
0.9110


SR4374-70-F1D
Integral
2.1459
13.198
2.7589
1.1112
3.5027
0.8419
0.9571
1.0000
1.6719
7.8602
0.7845
2.1459
13.198
2.7589
1.5229
1.5129
1.5053
1.3122
1.2959
1.2745
1.2570
1.2005
1.1817
1.1641
7.2770
7.2732
7.2594
7.2431
7.2381
7.2255
7.1904
7.1816
7.1754
7.1427
7.1377
7.1227
7.1189
7.0148
6.2383
4.5385
4.4959
4.3102
4.2688
3.9991
3.6893
3.4296
3.4133
3.3945
3.3782
3.2678
1816.01
1798.94
1724.66
1708.09
1600.18
1372.30
1365.78
1358.25
1351.72
1307.55
355.38
348.36
340.83
1.5505
1.5417
1.5317
1.5229
1.5129
1.5053
1.3122
1.2959
1.2745
1.2570
1.2005
1.1817
1.1641
0.8882
0.8706
0.8518


Integral
2505.13
2306.86
2298.83
1919.87
1914.35
1911.84
1908.33
1906.32
1900.80
1861.65
1854.12
7.2932
7.2794
7.2744
7.2656
7.2631
7.2593
7.2443
7.2355
7.2305
7.2267
7.2204
7.2141
7.1238
7.1201
7.1038
3.3602
2.0555
0.7477
0.8354
1.0000
4.6220
2.4893
10.366
3.3655
2.5272
1487.21
1476.67
1463.62
1246.28
1240.25
6.0
6.2608
5.7653
5.7452
4.7981
4.7843
4.7781
4.7693
4.7643
4.7505
4.6526
4.6338
3.7168
3.6905
3.6578
3.1147
3.0996
542.57
540.56
534.03
527.01
519.48
516.97
513.45
509.94
502.91
498.40
495.38
1.5178
1.5002
1.4814
1.4588
1.3560
1.3510
1.3347
1.3171
1.2983
1.2920
1.2832
1.2744
1.2569
1.2456
1.2381
0.9044
0.8868
0.8693
354.84
347.82


Integral
1166.83
1153.30
1140.49
1126.95
1084.87
1078.28
1071.70
1063.65
946.55
940.33
933.01
926.79
920.57
912.89
907.03
899.35
8.1586
8.1513
8.1440
8.1281
8.1220
8.1135
8.1025
8.0952
8.0660
7.4405
7.4112
7.2796
7.2576
7.2540
7.2442
7.2369
7.2162
7.1918
7.1894
7.1857
7.1796
7.1747
7.1686
7.1613
7.1552
7.1406
7.1321
7.1186
7.1028
7.0967
7.0760
7.0711
4.7900
3.8878
3.8427
3.8000
3.7549
3.6147
3.5927
3.5708
3.5439
3.1538
3.1331
3.1087
3.0880
3.0672
3.0416
3.0221
2.9965
1.4421
2.3170
2.4156
10.312
2.4290
2.1883
1.0401
3.2893
2.1632
9.0000

SR4374-89-F1



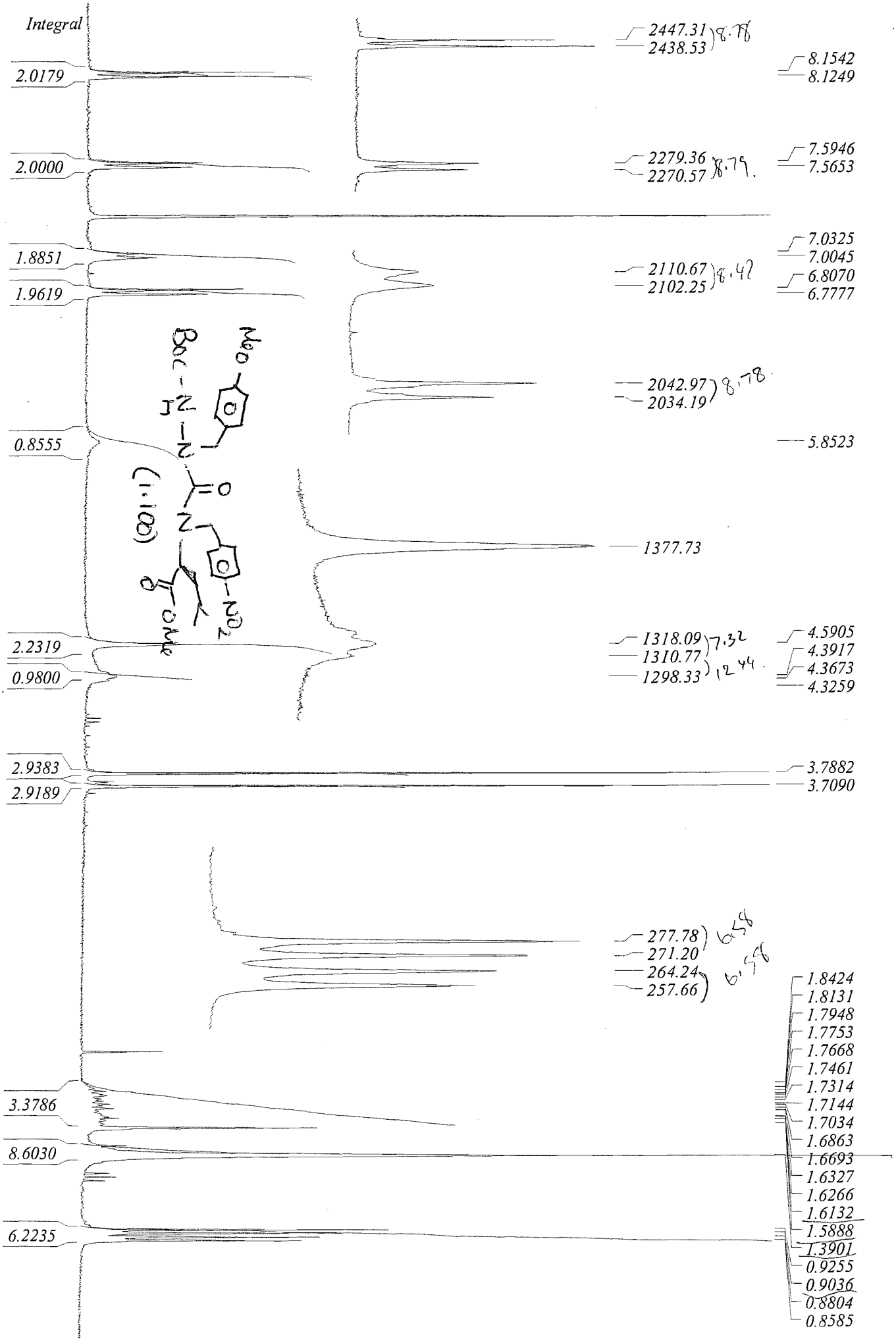
(1.99)

Current Data Parameters
NAME oc1606skr7
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061016
Time 16.10
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 406.4
DW 83.400 usec
DE 6.00 usec
TE 303.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

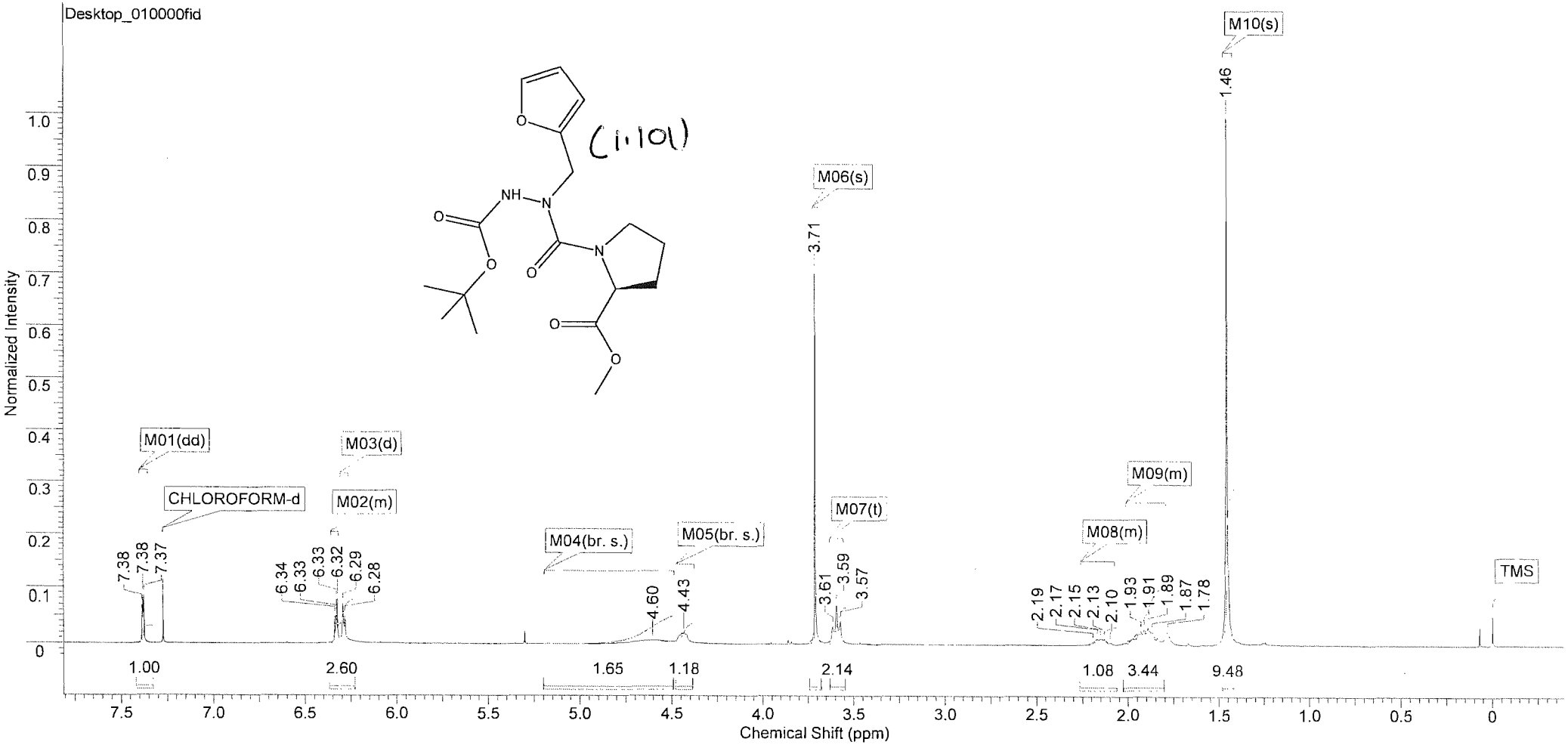
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300052 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 5.18 Hz


Integral
2.0179
2.0000
1.8851
1.9619
0.8555
2.2319
0.9800
2.9383
2.9189
3.3786
8.6030
6.2235
2447.31
2438.53
8.78
8.1542
8.1249
2279.36
2270.57
8.79
7.5946
7.5653
7.0325
7.0045
2110.67
2102.25
8.47
6.8070
6.7777
2042.97
2034.19
8.78
5.8523
1377.73
1318.09
1310.77
1298.33
7.32
12.44
4.5905
4.3917
4.3673
4.3259
3.7882
3.7090
277.78
271.20
264.24
257.66
6.58
6.58
1.8424
1.8131
1.7948
1.7753
1.7668
1.7461
1.7314
1.7144
1.7034
1.6863
1.6693
1.6327
1.6266
1.6132
1.5888
1.3901
0.9255
0.9036
0.8804
0.8585
Boc-N-N
H
O
N
O
NO2
MeO
OMe
(1.00)

SR4521-53-F1

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.46 (s, 9 H) 1.79 - 2.01 (m, 3 H) 2.07 - 2.26 (m, 1 H) 3.59 (t, *J*=6.40 Hz, 2 H) 3.71 (s, 3 H) 4.43 (br. s., 2 H) 4.60 (br. s., 1 H) 6.29 (d, *J*=2.93 Hz, 1 H) 6.31 - 6.35 (m, 1 H) 7.38 (dd, *J*=1.83, 1.10 Hz, 1 H)



No.	(ppm)	(Hz)	Height
1	1.46	437.6	1.0000
2	1.78	535.3	0.0238
3	1.87	560.6	0.0234
4	1.89	567.2	0.0319
5	1.91	573.4	0.0284
6	1.93	579.2	0.0260

No.	(ppm)	(Hz)	Height
7	2.10	629.7	0.0040
8	2.13	638.9	0.0109
9	2.15	645.1	0.0124
10	2.17	649.9	0.0124
11	2.19	657.6	0.0062
12	3.57	1071.4	0.0424

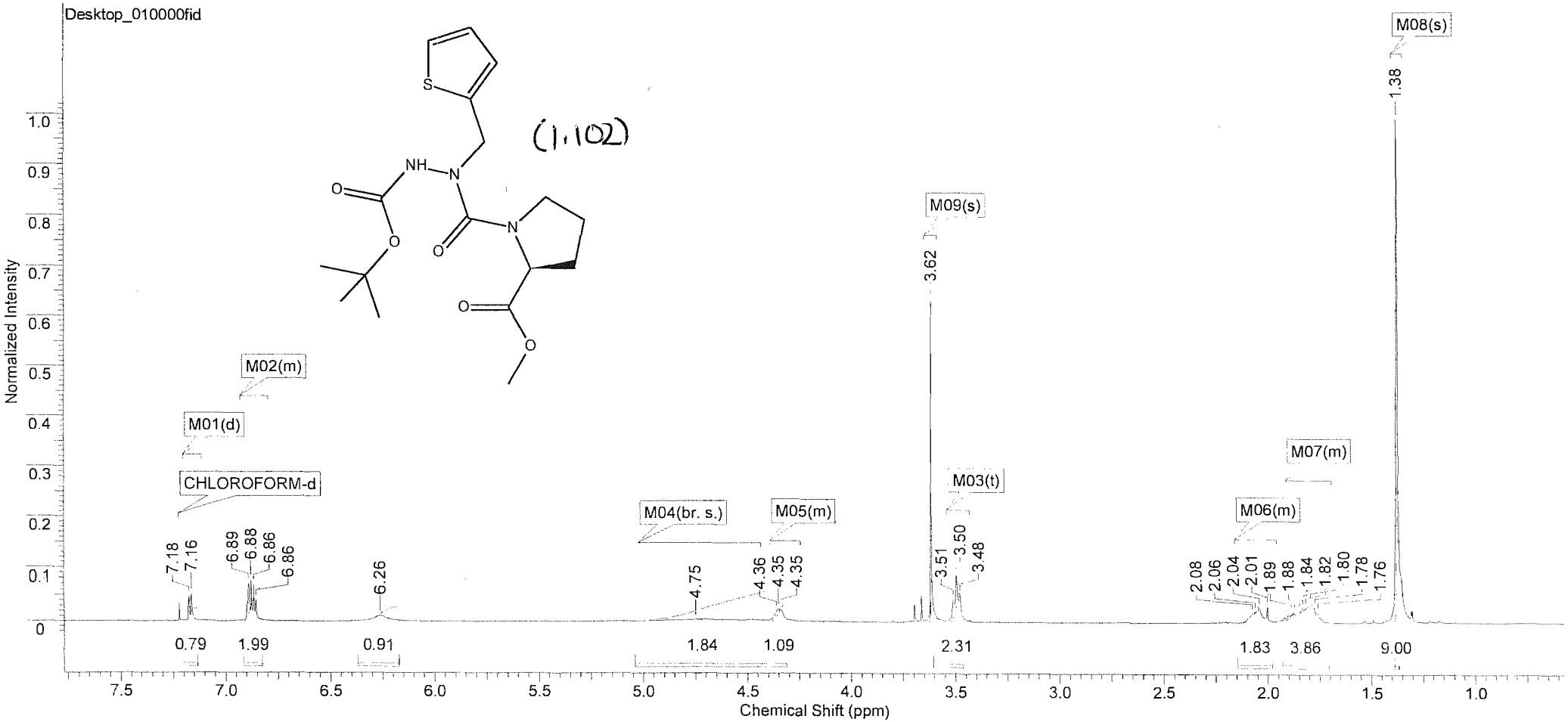
No.	(ppm)	(Hz)	Height
13	3.59	1078.0	0.0696
14	3.61	1084.2	0.0326
15	3.71	1113.1	0.7032
16	4.43	1329.7	0.0197
17	4.60	1380.6	0.0071
18	6.28	1885.2	0.0499

No.	(ppm)	(Hz)	Height
19	6.29	1888.1	0.0721
20	6.32	1896.6	0.0798
21	6.33	1898.4	0.0794
22	6.33	1899.8	0.0524
23	6.34	1901.7	0.0494
24	7.37	2213.1	0.0845

No.	(ppm)	(Hz)	Height
25	7.38	2214.2	0.0754
26	7.38	2214.9	0.0854
27	7.38	2216.0	0.0694

SR4521-69-F2

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.38 (s, 9 H) 1.70 - 1.92 (m, 3 H) 1.96 - 2.16 (m, 2 H) 3.50 (t, *J*=6.53 Hz, 2 H) 3.62 (s, 3 H) 4.25 - 4.39 (m, 1 H) 4.75 (br. s., 2 H) 6.80 - 6.93 (m, 2 H) 7.17 (d, *J*=5.02 Hz, 1 H)



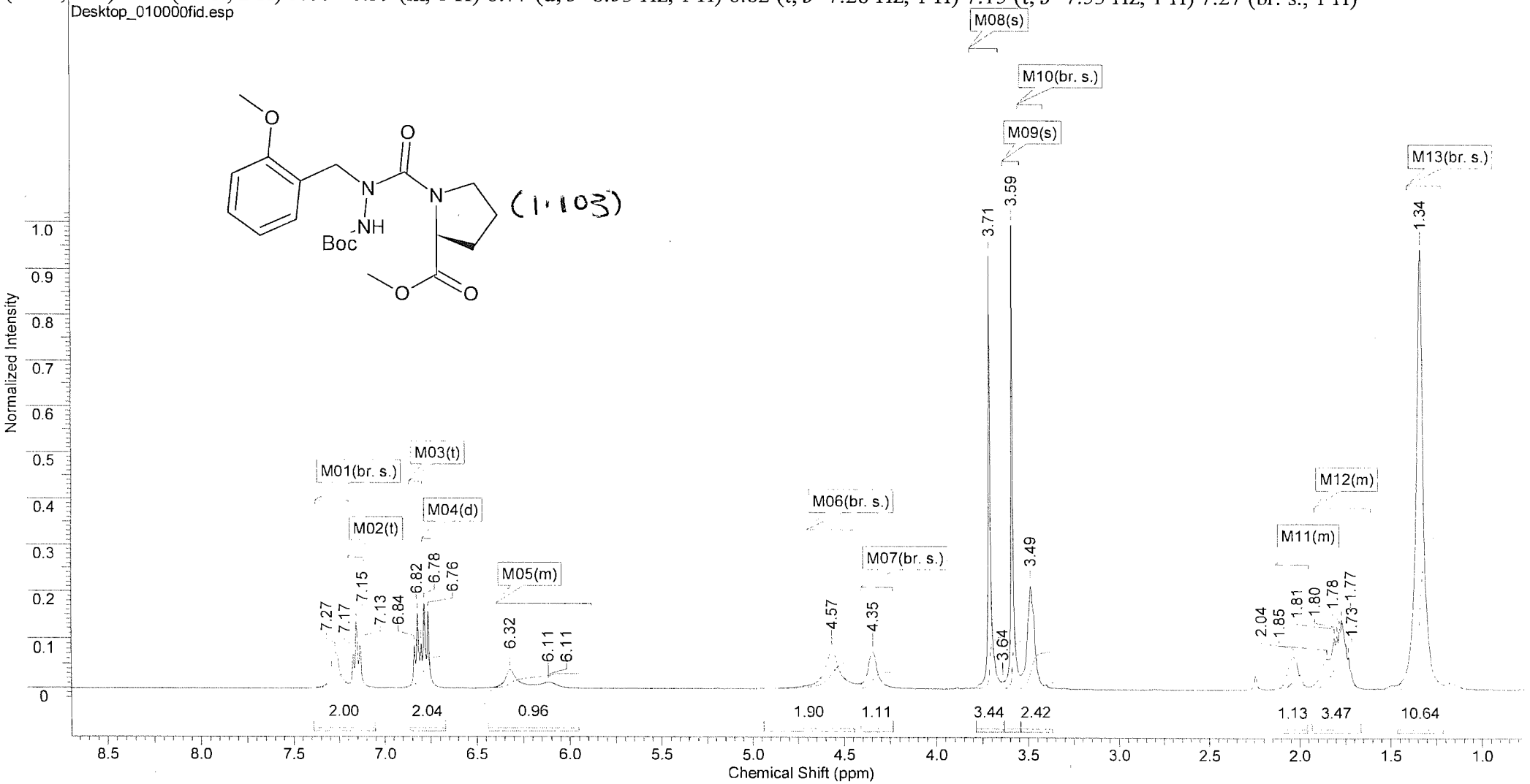
No.	(ppm)	(Hz)	Height
1	1.38	552.1	1.0000
2	1.76	704.7	0.0191
3	1.78	711.2	0.0275
4	1.80	719.3	0.0372
5	1.82	728.3	0.0274
6	1.84	734.3	0.0271
7	1.88	750.4	0.0176

No.	(ppm)	(Hz)	Height
8	1.89	755.4	0.0166
9	2.01	802.6	0.0310
10	2.04	818.2	0.0288
11	2.06	826.2	0.0197
12	2.08	831.2	0.0173
13	3.48	1392.4	0.0537
14	3.50	1398.9	0.0866

No.	(ppm)	(Hz)	Height
15	3.51	1405.4	0.0423
16	3.62	1447.6	0.6353
17	4.35	1738.7	0.0229
18	4.35	1742.2	0.0241
19	4.36	1745.7	0.0199
20	4.75	1900.3	0.0040
21	6.26	2505.2	0.0099

No.	(ppm)	(Hz)	Height
22	6.86	2743.1	0.0403
23	6.86	2746.6	0.0672
24	6.88	2751.6	0.0756
25	6.89	2756.6	0.0698
26	7.16	2866.0	0.0514
27	7.18	2871.1	0.0462

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.34 (br. s., 9 H) 1.61 - 1.92 (m, 3 H) 1.95 - 2.13 (m, 1 H) 3.49 (br. s., 2 H) 3.59 (s, 3 H) 3.71 (s, 3 H) 4.35 (br. s., 1 H) 4.57 (br. s., 2 H) 5.88 - 6.39 (m, 1 H) 6.77 (d, *J*=8.53 Hz, 1 H) 6.82 (t, *J*=7.28 Hz, 1 H) 7.15 (t, *J*=7.53 Hz, 1 H) 7.27 (br. s., 1 H)



No.	(ppm)	(Hz)	Height
1	0.00	0.4	0.0284
2	1.34	536.5	0.9510
3	1.73	694.1	0.0665
4	1.77	709.2	0.1441
5	1.78	714.2	0.1256
6	1.80	719.7	0.1092

No.	(ppm)	(Hz)	Height
7	1.81	725.7	0.1058
8	1.85	741.8	0.0621
9	2.04	815.6	0.0663
10	3.49	1395.3	0.2157
11	3.59	1435.5	1.0000
12	3.64	1455.6	0.0149

No.	(ppm)	(Hz)	Height
13	3.71	1484.7	0.9337
14	4.35	1738.6	0.0743
15	4.57	1827.5	0.0791
16	6.11	2443.9	0.0112
17	6.11	2446.4	0.0112
18	6.32	2528.2	0.0379

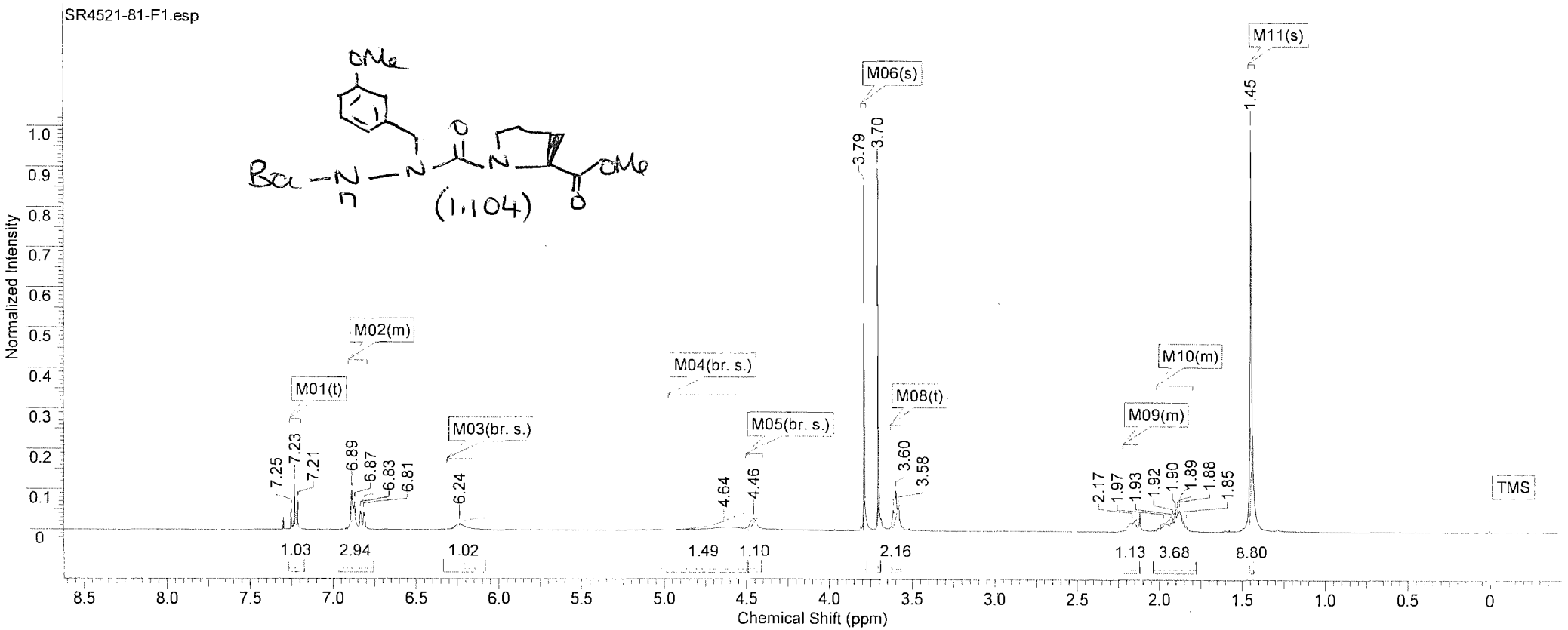
No.	(ppm)	(Hz)	Height
19	6.76	2705.4	0.1584
20	6.78	2713.9	0.1769
21	6.80	2720.9	0.0900
22	6.82	2728.5	0.1538
23	6.84	2735.5	0.0870
24	7.13	2854.4	0.0857

No.	(ppm)	(Hz)	Height
25	7.15	2862.0	0.1360
26	7.17	2869.5	0.0669
27	7.27	2908.7	0.0719

SR4521-81-F1

22/11/2006 18:20:25

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.45 (s, 9 H) 1.80 - 2.02 (m, 4 H) 2.13 - 2.22 (m, 1 H) 3.60 (t, *J*=6.27 Hz, 2 H) 3.70 (s, 3 H) 3.79 (s, 3 H) 4.46 (br. s., 1 H) 4.64 (br. s., 1 H) 6.24 (br. s., 1 H) 6.79 - 6.91 (m, 3 H) 7.23 (t, *J*=8.03 Hz, 3 H)



No.	(ppm)	(Hz)	Height
1	1.45	578.2	1.0000
2	1.84	735.3	0.0137
3	1.85	740.9	0.0283
4	1.88	751.4	0.0524

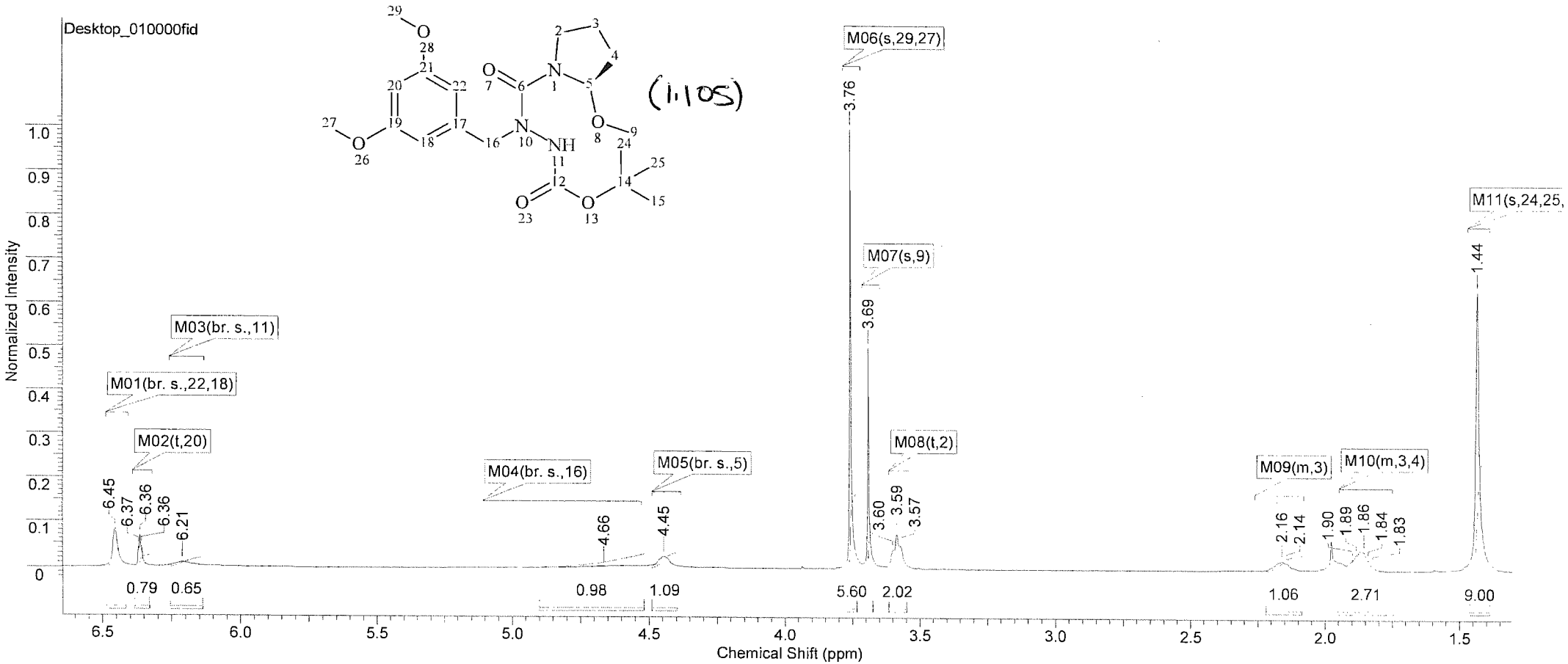
No.	(ppm)	(Hz)	Height
5	1.89	755.4	0.0549
6	1.90	761.4	0.0487
7	1.92	767.5	0.0337
8	1.93	772.0	0.0226

No.	(ppm)	(Hz)	Height
9	1.97	789.5	0.0209
10	2.17	866.3	0.0233
11	3.58	1433.0	0.0607
12	3.60	1439.5	0.0992

No.	(ppm)	(Hz)	Height
13	3.61	1445.6	0.0516
14	3.70	1481.7	0.9002
15	3.79	1515.8	0.8614
16	4.46	1782.9	0.0284

Formula $C_{20}H_{31}N_3O_6$	FW	409.4766

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.44 (s, 9 H) 1.75 - 1.95 (m, 3 H) 2.08 - 2.26 (m, 1 H) 3.59 (t, *J*=6.02 Hz, 2 H) 3.69 (s, 3 H) 3.76 (s, 6 H) 4.45 (br. s., 1 H) 4.66 (br. s., 2 H) 6.21 (br. s., 1 H) 6.36 (t, *J*=2.01 Hz, 1 H) 6.45 (br. s., 2 H)



No.	Atom	Exp. Shift (ppm)	Multiplet
1	24	1.44	M11
2	25	1.44	M11
3	15	1.44	M11
4	3	1.86	M10
5	4	1.86	M10
6	3	2.15	M09
7	2	3.59	M08

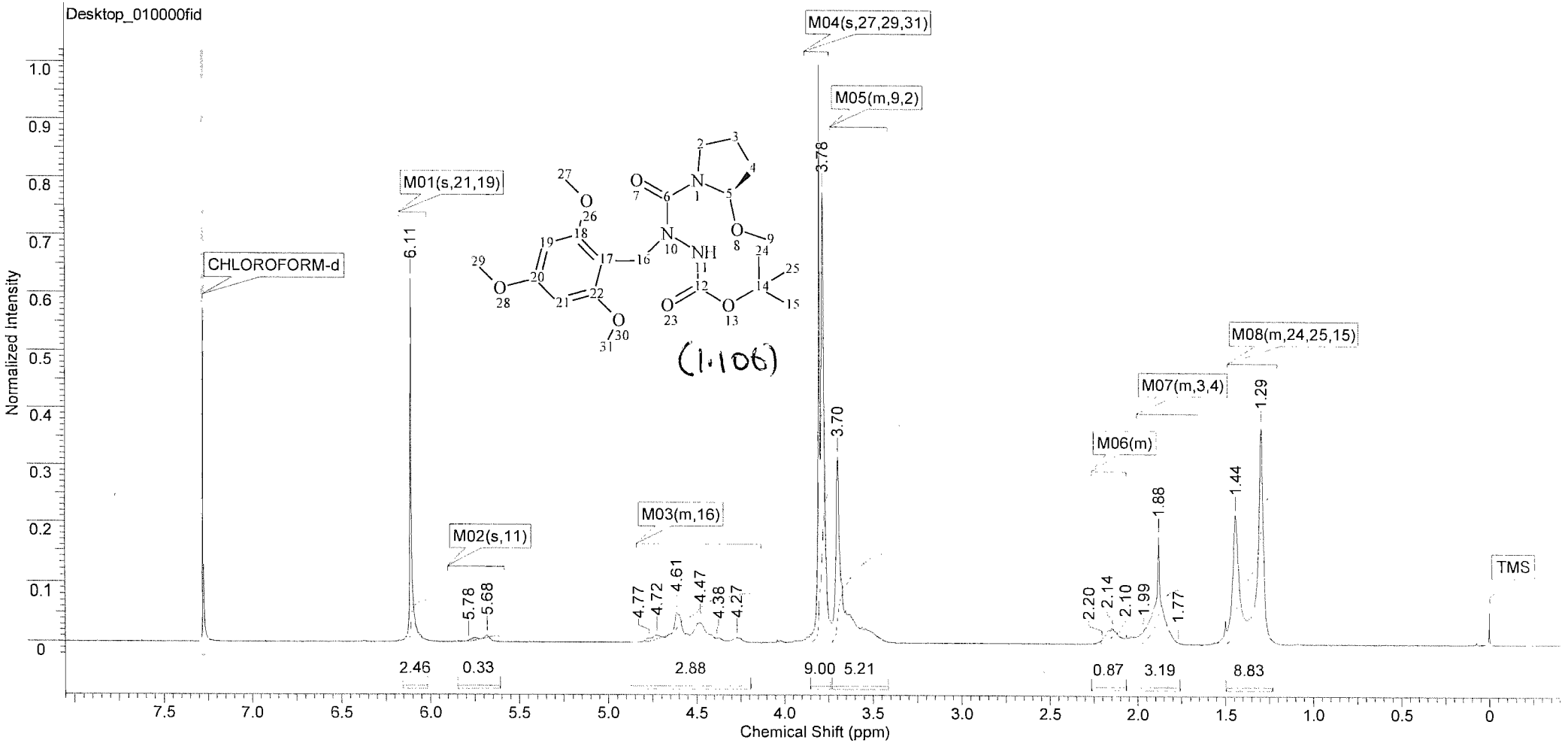
No.	Atom	Exp. Shift (ppm)	Multiplet
8	9	3.69	M07
9	29	3.76	M06
10	27	3.76	M06
11	5	4.45	M05
12	16	4.66	M04
13	11	6.21	M03
14	20	6.36	M02

No.	Atom	Exp. Shift (ppm)	Multiplet
15	22	6.45	M01
16	18	6.45	M01

SR4521-85-F2

Formula $C_{21}H_{33}N_3O_7$	FW	439.5026

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.20 - 1.49 (m, 9 H) 1.66 - 2.01 (m, 3 H) 2.07 - 2.26 (m, 1 H) 3.42 - 3.74 (m, 5 H) 3.78 (s, 9 H) 4.13 - 4.84 (m, 3 H) 5.73 (s, 1 H) 6.11 (s, 2 H)



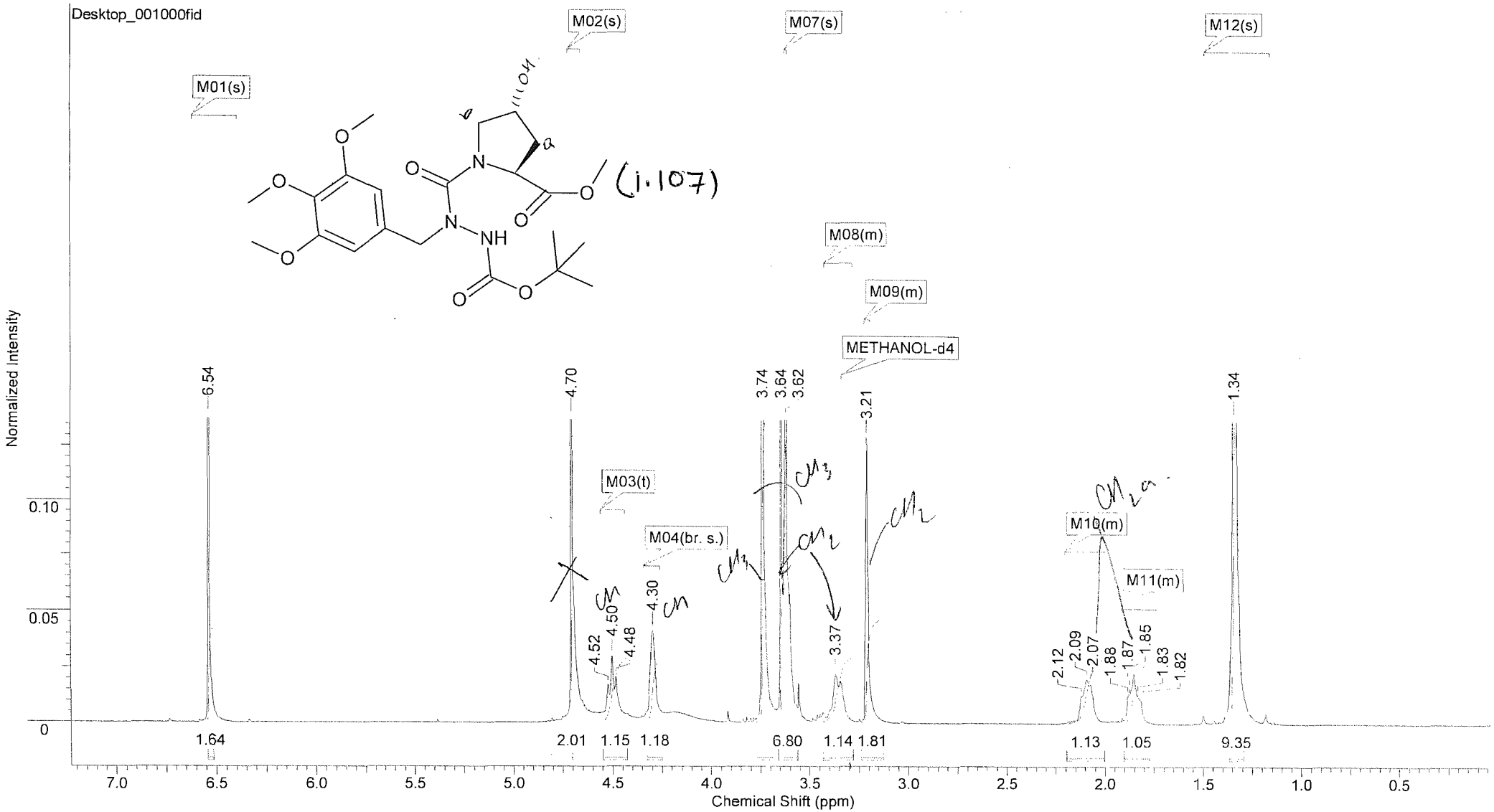
No.	Atom	Exp. Shift (ppm)	Multiplet
1	24	1.37	M08
2	25	1.37	M08
3	15	1.37	M08
4	3	1.88	M07
5	4	1.88	M07

No.	Atom	Exp. Shift (ppm)	Multiplet
6	9	3.70	M05
7	2	3.70	M05
8	27	3.78	M04
9	29	3.78	M04
10	31	3.78	M04

No.	Atom	Exp. Shift (ppm)	Multiplet
11	16	4.54	M03
12	11	5.73	M02
13	21	6.11	M01
14	19	6.11	M01

SR4521-34-F1

1H NMR (400 MHz, METHANOL-d_4) δ ppm 1.34 (s, 9 H) 1.74 - 1.91 (m, 1 H) 1.98 - 2.20 (m, 1 H) 3.19 - 3.22 (m, 2 H) 3.28 - 3.43 (m, 1 H) 3.62 (s, 3 H) 3.64 (s, 3 H) 3.74 (s, 6 H) 4.30 (br. s., 1 H) 4.50 (t, J=8.28 Hz, 1 H) 4.70 (s, 2 H) 6.54 (s, 5 H)



No.	(ppm)	(Hz)	Height
1	1.34	536.6	0.9040
2	1.82	726.8	0.0116
3	1.83	731.8	0.0135
4	1.85	739.9	0.0234

No.	(ppm)	(Hz)	Height
5	1.87	748.4	0.0163
6	1.88	752.4	0.0133
7	2.07	828.7	0.0183
8	2.09	836.2	0.0206

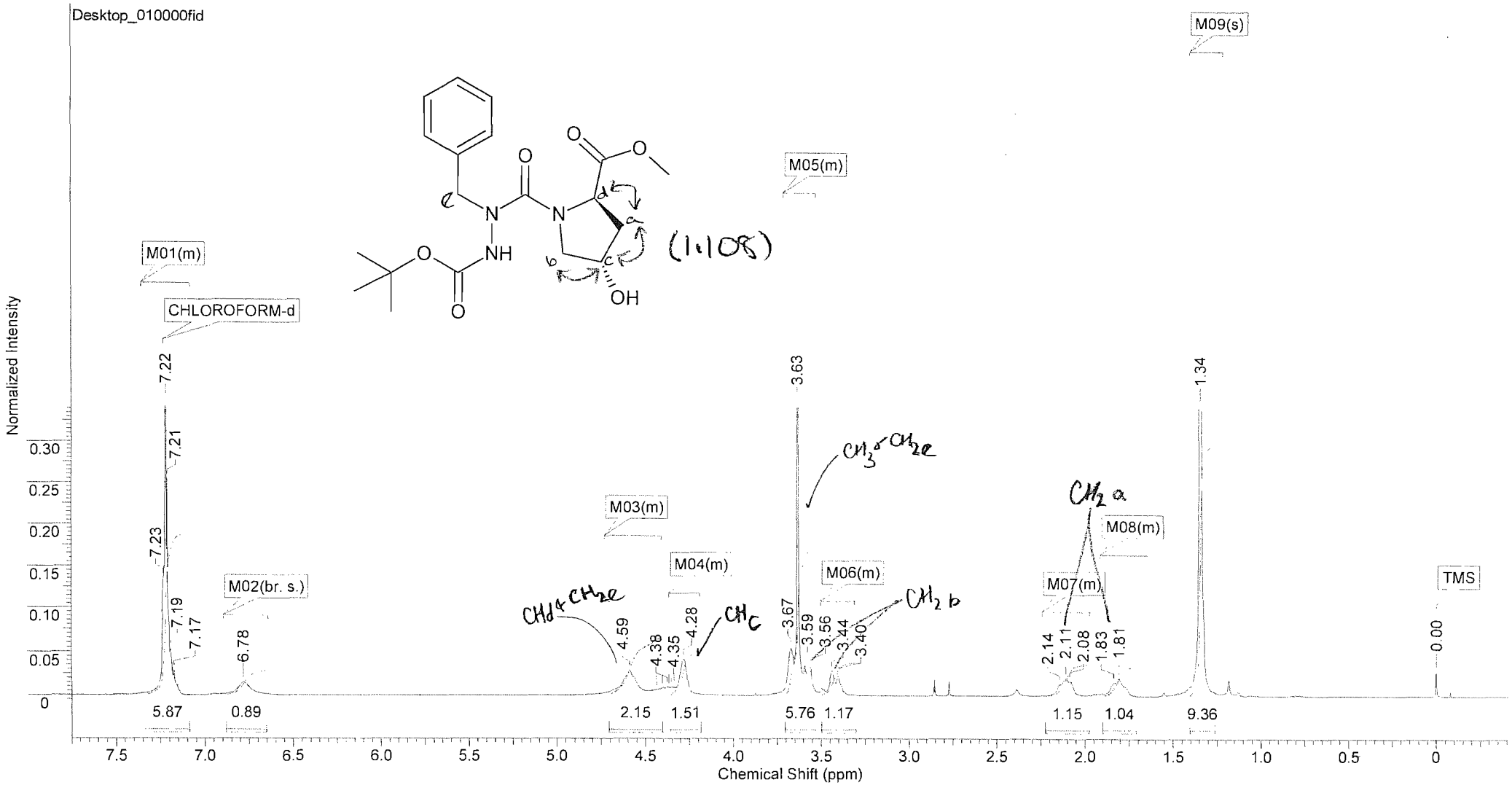
No.	(ppm)	(Hz)	Height
9	2.12	846.8	0.0129
10	3.21	1284.4	0.1302
11	3.37	1346.7	0.0226
12	3.62	1448.1	0.4591

No.	(ppm)	(Hz)	Height
13	3.64	1458.1	0.5745
14	3.74	1495.8	1.0000
15	4.30	1718.6	0.0416
16	4.48	1792.4	0.0212

No.	(ppm)	(Hz)	Height
17	4.50	1800.4	0.0304
18	4.52	1809.0	0.0177
19	4.70	1881.8	0.5802
20	6.54	2615.1	0.2710

SR4521-100-F1

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.34 (s, 9 H) 1.65 - 1.91 (m, 1 H) 1.97 - 2.24 (m, 1 H) 3.31 - 3.50 (m, 1 H) 3.52 - 3.71 (m, 5 H) 4.19 - 4.37 (m, 1 H) 4.41 - 4.73 (m, 2 H) 6.78 (br. s., 1 H) 7.08 - 7.35 (m, 5 H)



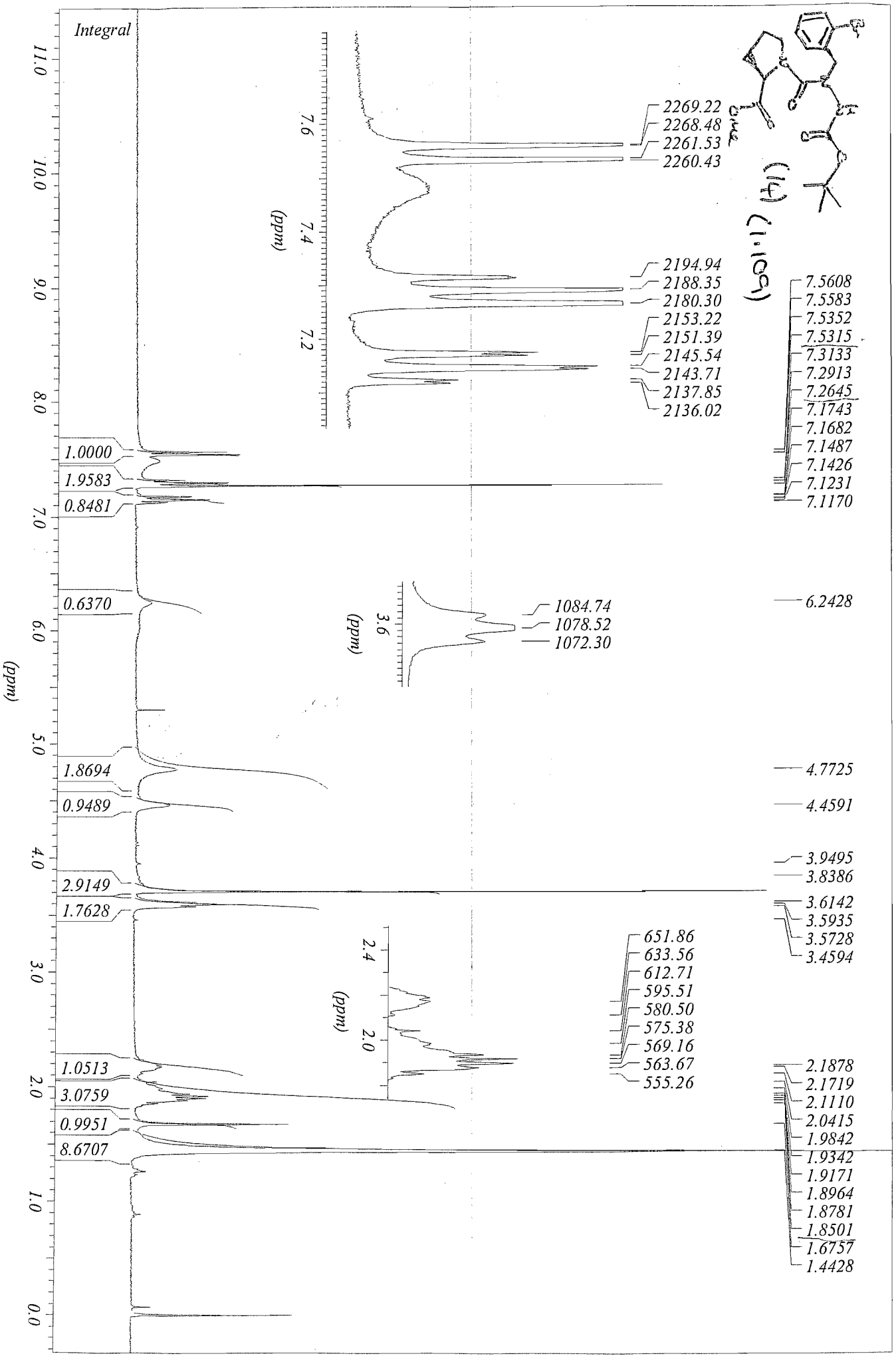
No.	(ppm)	(Hz)	Height
1	0.00	0.0	0.0296
2	1.34	403.2	1.0000
3	1.81	541.9	0.0207
4	1.83	550.7	0.0158
5	2.08	625.7	0.0169
6	2.11	632.7	0.0205

No.	(ppm)	(Hz)	Height
7	2.14	642.9	0.0139
8	3.40	1021.3	0.0221
9	3.44	1031.9	0.0287
10	3.56	1068.1	0.0330
11	3.59	1077.6	0.0343
12	3.63	1090.1	0.5839

No.	(ppm)	(Hz)	Height
13	3.67	1101.4	0.0540
14	4.28	1285.5	0.0423
15	4.34	1301.6	0.0101
16	4.35	1306.0	0.0096
17	4.36	1310.0	0.0097
18	4.38	1313.6	0.0106

No.	(ppm)	(Hz)	Height
19	4.40	1321.3	0.0092
20	4.44	1331.9	0.0075
21	4.59	1377.0	0.0286
22	6.78	2036.0	0.0150
23	7.17	2153.1	0.0289
24	7.19	2158.9	0.0524

No.	(ppm)	(Hz)	Height
25	7.21	2164.0	0.2550
26	7.22	2167.0	0.4541
27	7.23	2171.0	0.1362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9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.0000
1.9583
0.8481
0.6370
1.8694
0.9489
2.9149
1.7628
1.0513
3.0759
0.9951
8.6707
7.6
7.4
7.2
2269.22
2268.48
2261.53
2260.43
2194.94
2188.35
2180.30
2153.22
2151.39
2145.54
2143.71
2137.85
2136.02
3.6
1084.74
1078.52
1072.30
2.4
2.0
651.86
633.56
612.71
595.51
580.50
575.38
569.16
563.67
555.26
7.5608
7.5583
7.5352
7.5315
7.3133
7.2913
7.2645
7.1743
7.1682
7.1487
7.1426
7.1231
7.1170
6.2428
4.7725
4.4591
3.9495
3.8386
3.6142
3.5935
3.5728
3.4594
2.1878
2.1719
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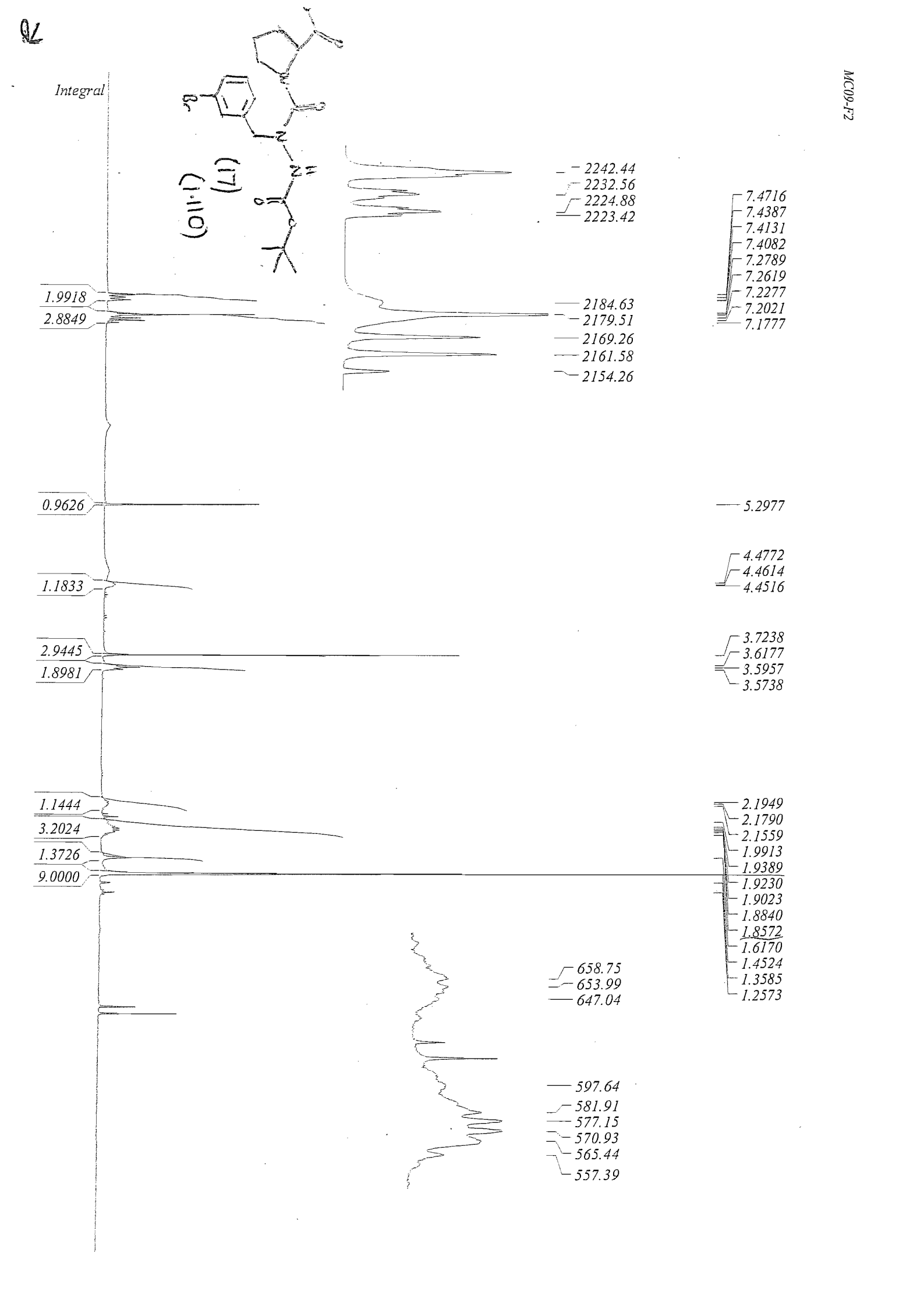
1.8964
1.8781
1.8501
1.6757
1.4428


Integral
(i-110)
(17)
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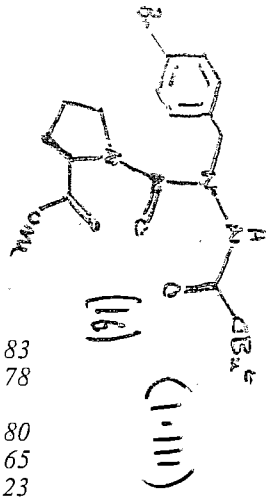
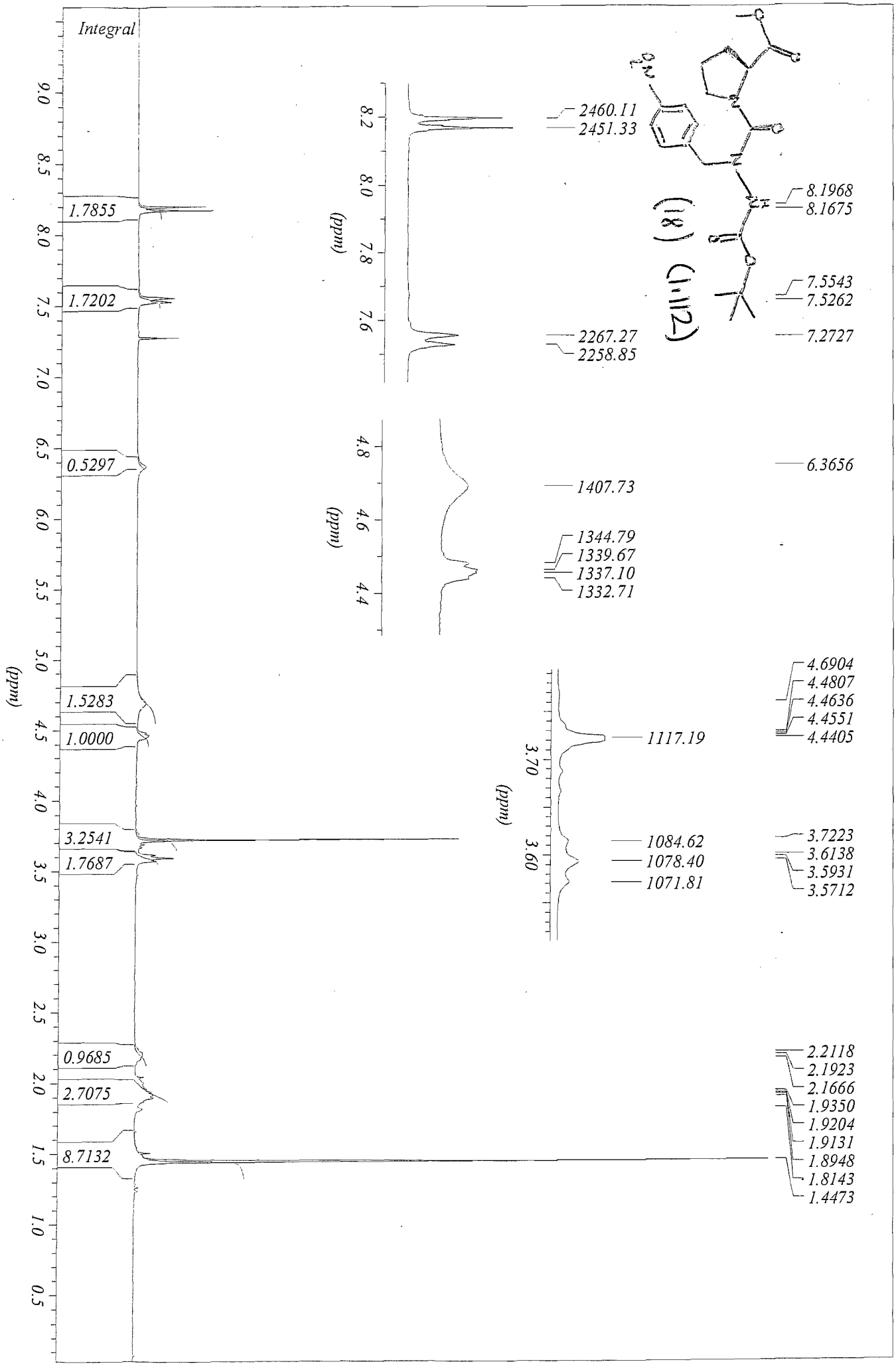
0.9626
1.1833
2.9445
1.8981
1.1444
3.2024
1.3726
9.0000
2242.44
2232.56
2224.88
2223.42
2184.63
2179.51
2169.26
2161.58
2154.26
658.75
653.99
647.04
597.64
581.91
577.15
570.93
565.44
557.39
7.4716
7.4387
7.4131
7.4082
7.2789
7.2619
7.2277
7.2021
7.1777
5.2977
4.4772
4.4614
4.4516
3.7238
3.6177
3.5957
3.5738
2.1949
2.1790
2.1559
1.9913
1.9389
1.9230
1.9023
1.8840
1.8572
1.6170
1.4524
1.3585
1.2573

09

MC-07-F2



(16) (I-III)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8.7132
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2451.33
2267.27
2258.85
1407.73
1344.79
1339.67
1337.10
1332.71
1117.19
1084.62
1078.40
1071.81
8.1968
8.1675
7.5543
7.5262
7.2727
6.3656
4.6904
4.4807
4.4636
4.4551
4.4405
3.7223
3.6138
3.5931
3.5712
2.2118
2.1923
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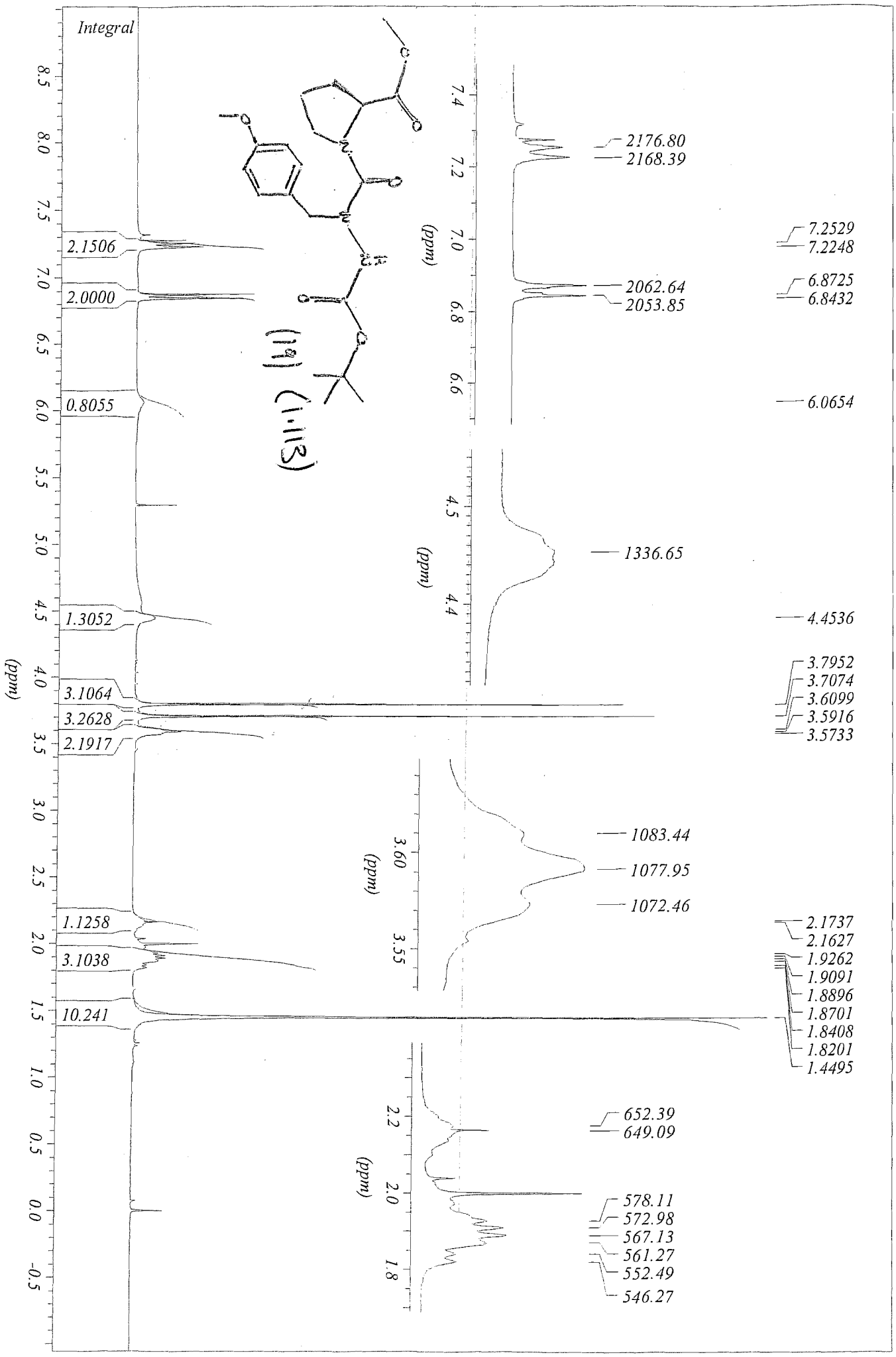
1.9350
1.9204
1.9131
1.8948
1.8143
1.4473
(18) (1:1:2)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3.2628
2.1917
1.1258
3.1038
10.241
(ppm)
2176.80
2168.39
2062.64
2053.85
1336.65
1083.44
1077.95
1072.46
652.39
649.09
578.11
572.98
567.13
561.27
552.49
546.27
7.2529
7.2248
6.8725
6.8432
6.0654
4.4536
3.7952
3.7074
3.6099
3.5916
3.5733
2.1737
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1.8896
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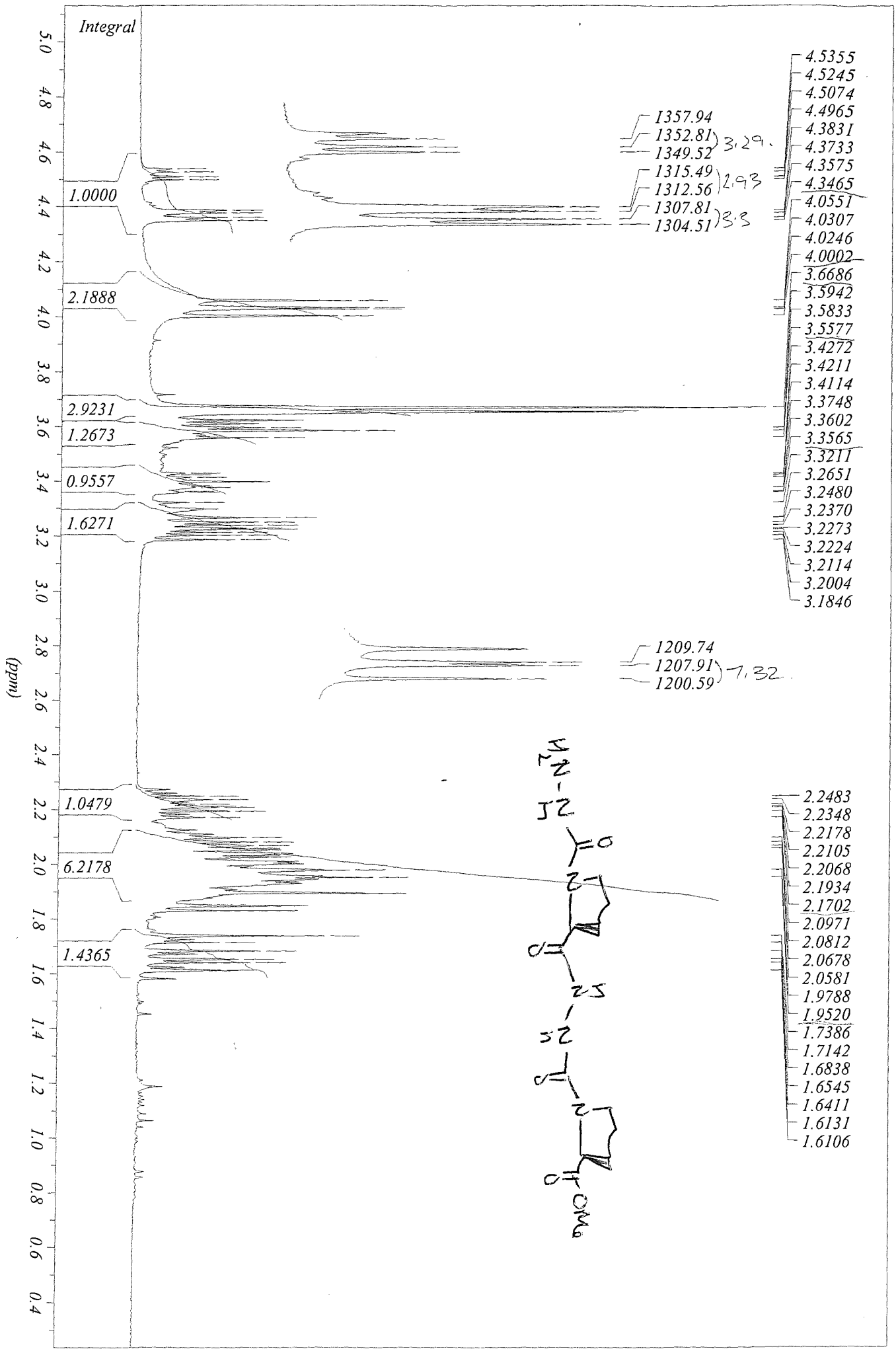
1.8408
1.8201
1.4495

SR4272-46-F1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6.2178
1.4365
(ppm)
1357.94
1352.81
1349.52
3.29
1315.49
1312.56
1307.81
1304.51
2.93
3.3
1209.74
1207.91
1200.59
7.32
4.5355
4.5245
4.5074
4.4965
4.3831
4.3733
4.3575
4.3465
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4.0307
4.0246
4.0002
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3.5942
3.5833
3.5577
3.4272
3.4211
3.4114
3.3748
3.3602
3.3565
3.3211
3.2651
3.2480
3.2370
3.2273
3.2224
3.2114
3.2004
3.1846
2.2483
2.2348
2.2178
2.2105
2.2068
2.1934
2.1702
2.0971
2.0812
2.0678
2.0581
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1.7142
1.6838
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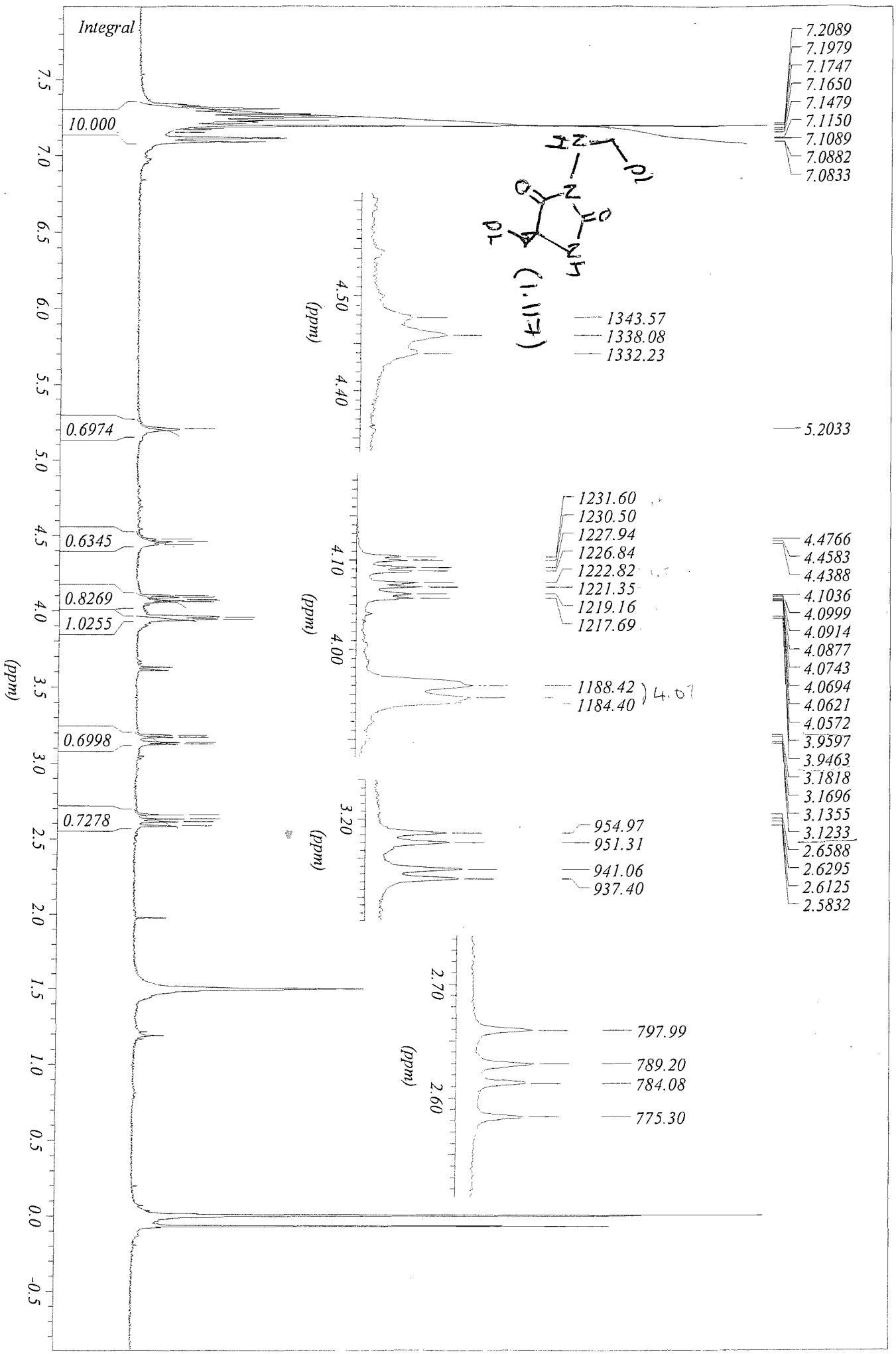
1.6411
1.6131
1.6106


Integral
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0.7278
(ppm)
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7.1979
7.1747
7.1650
7.1479
7.1150
7.1089
7.0882
7.0833
5.2033
4.4766
4.4583
4.4388
4.1036
4.0999
4.0914
4.0877
4.0743
4.0694
4.0621
4.0572
3.9597
3.9463
3.1818
3.1696
3.1355
3.1233
2.6588
2.6295
2.6125
2.5832
1343.57
1338.08
1332.23
1231.60
1230.50
1227.94
1226.84
1222.82
1221.35
1219.16
1217.69
1188.42
1184.40
954.97
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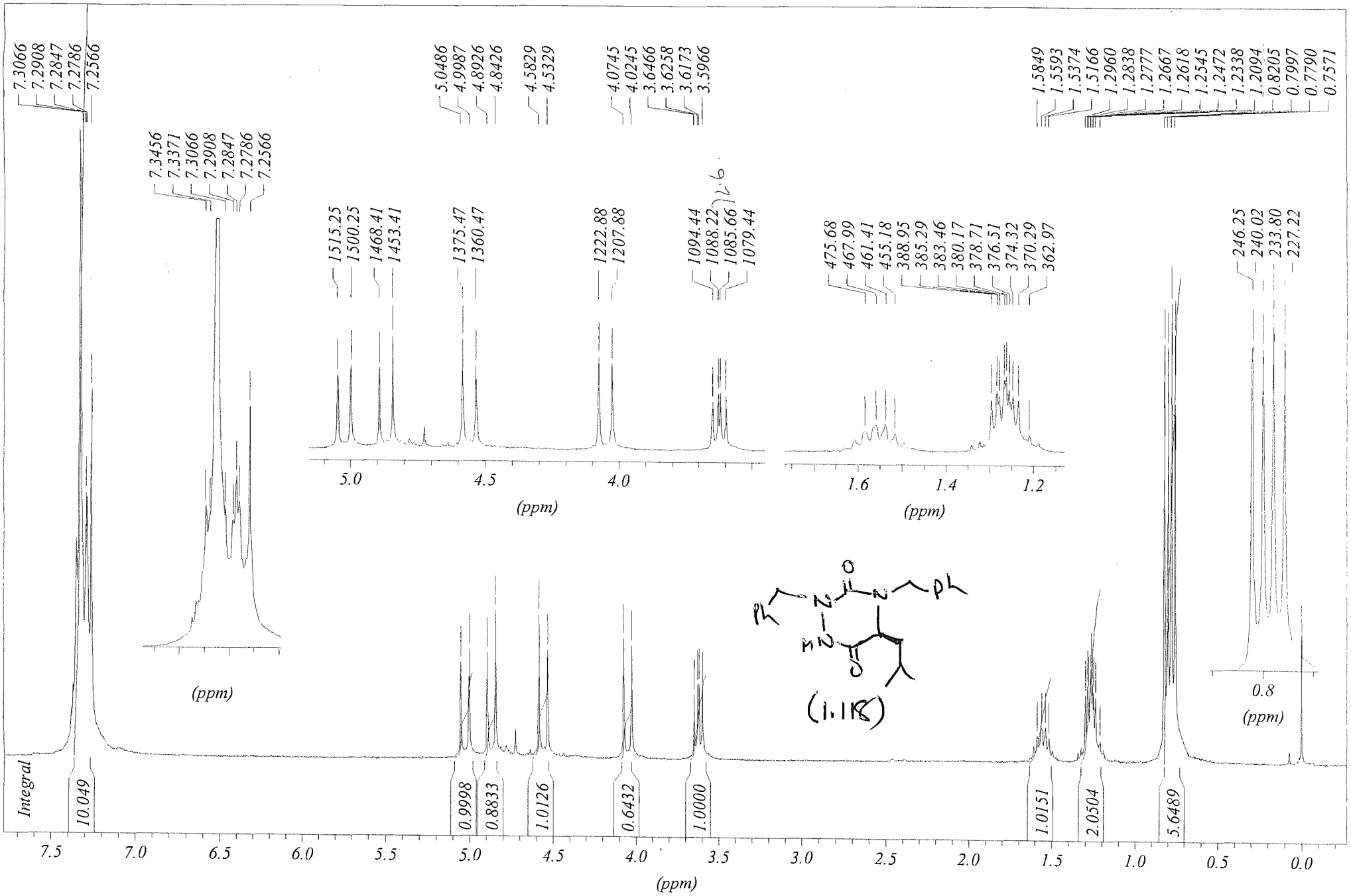
789.20
784.08
775.30
(1.117)
4.07


7.3066
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7.2566
5.0486
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4.8426
4.5829
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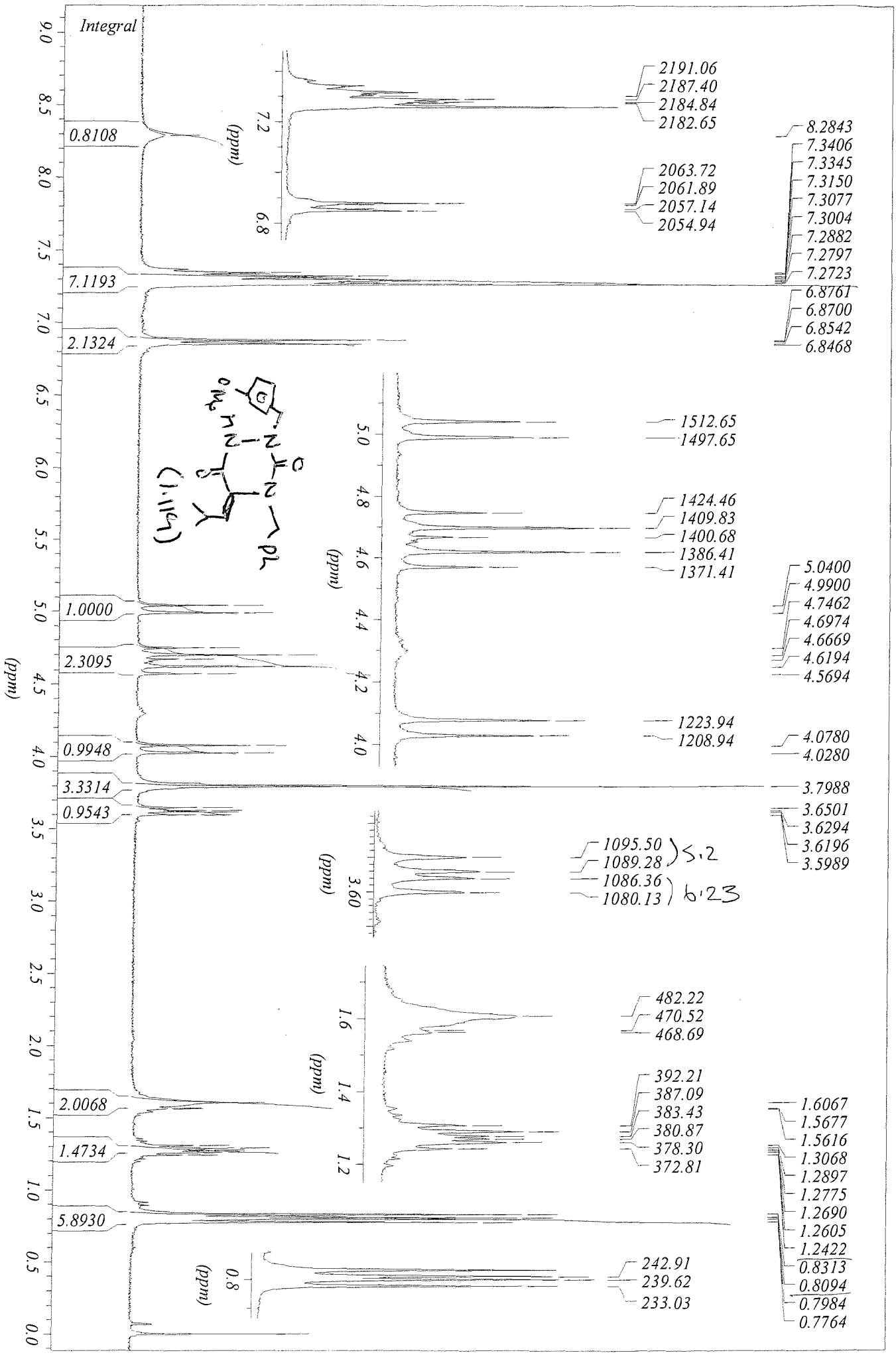
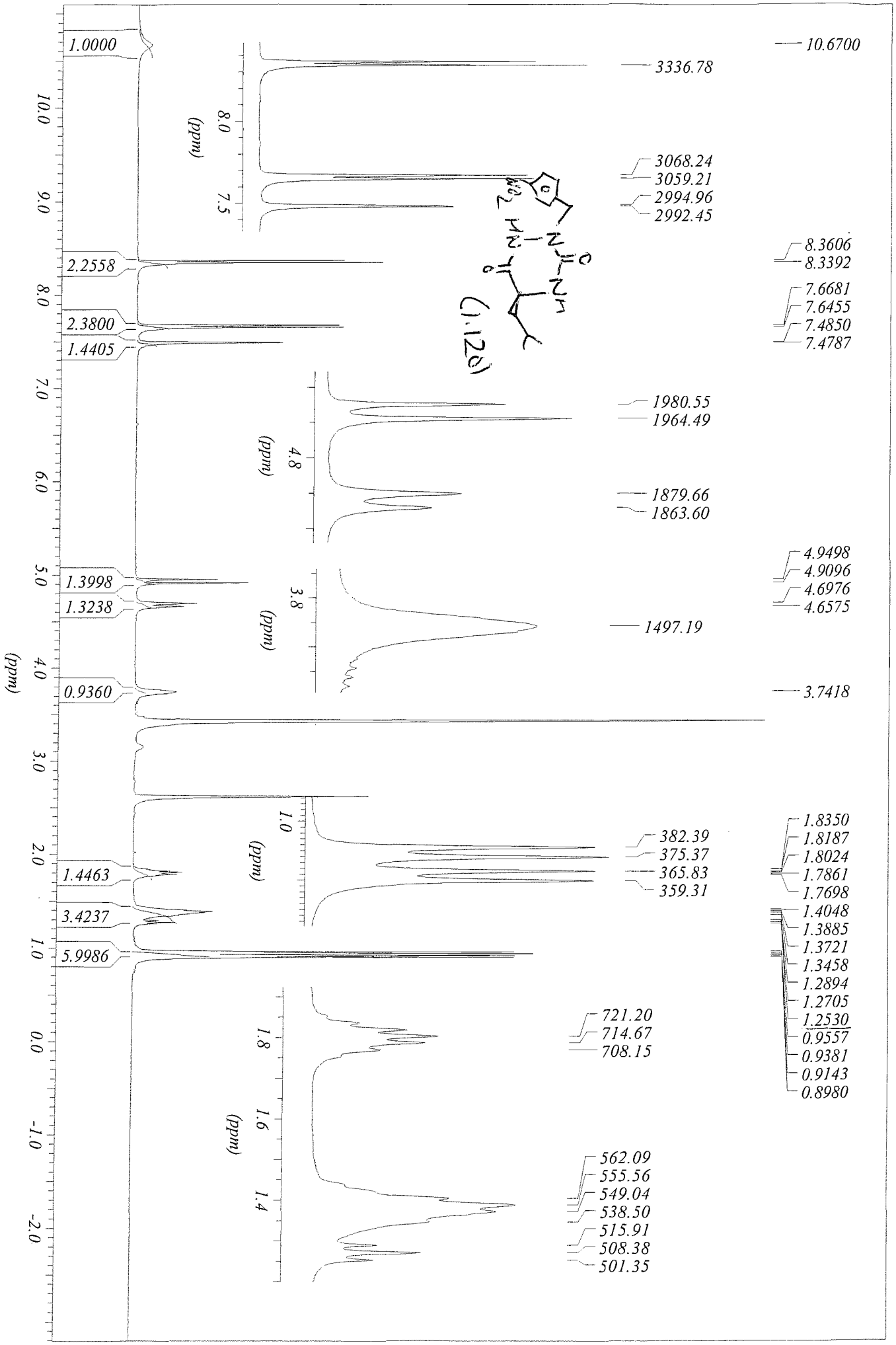
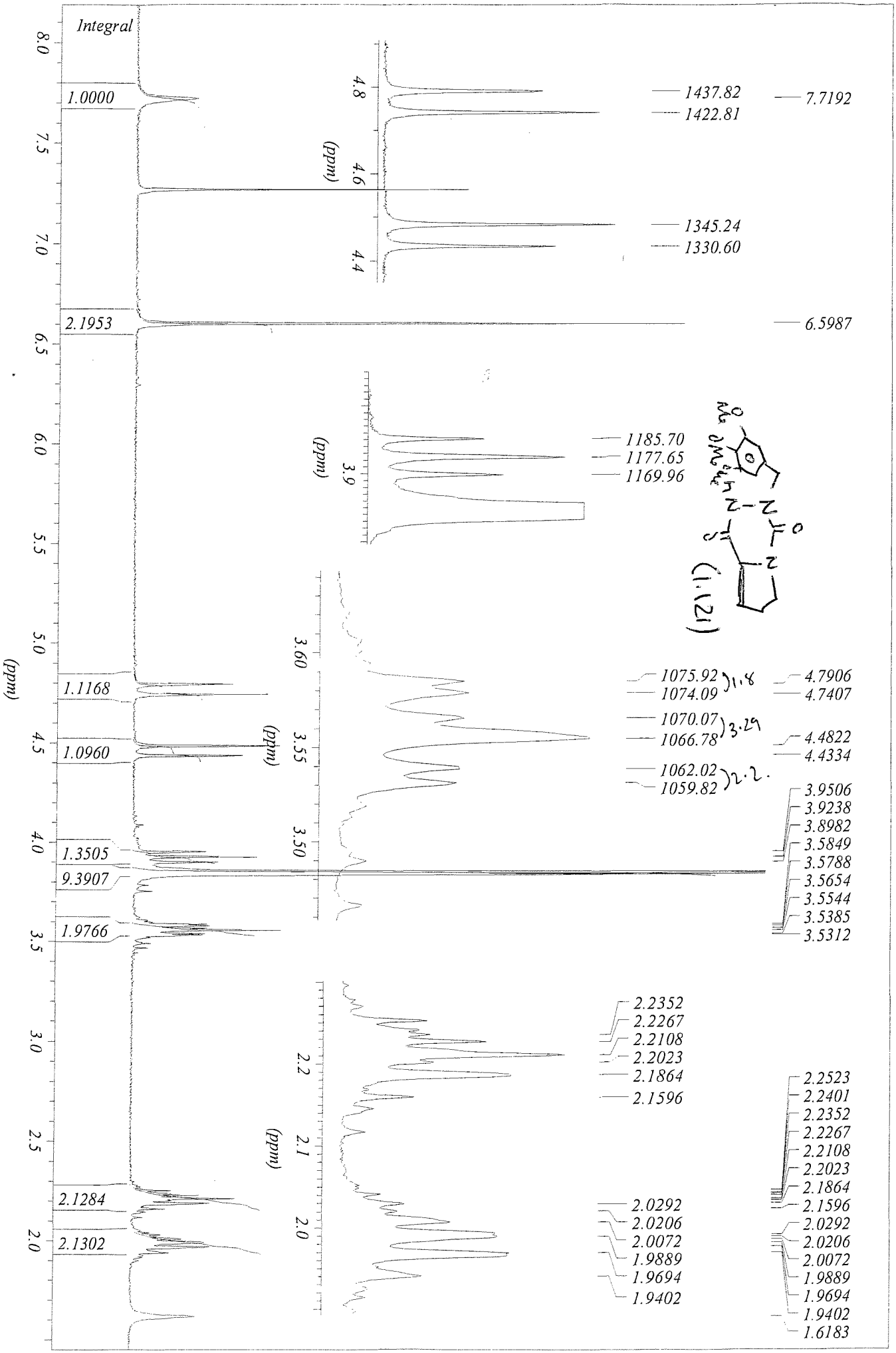
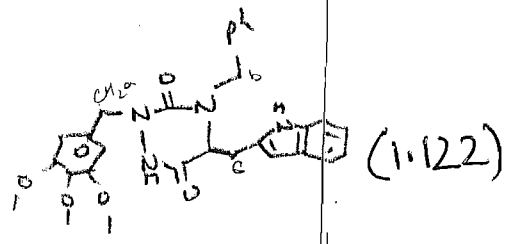
4.0745
4.0245
3.6466
3.6258
3.6173
3.5966
1.5849
1.5593
1.5374
1.5166
1.2960
1.2838
1.2777
1.2667
1.2618
1.2545
1.2472
1.2338
1.2094
0.8205
0.7997
0.7790
0.7571
7.3456
7.3371
7.3066
7.2908
7.2847
7.2786
7.2566
1515.25
1500.25
1468.41
1453.41
1375.47
1360.47
1222.88
1207.88
1094.44
1088.22
1085.66
1079.44
2.6
475.68
467.99
461.41
455.18
388.95
385.29
383.46
380.17
378.71
376.51
374.32
370.29
362.97
246.25
240.02
233.80
227.22
5.0
4.5
4.0
(ppm)
1.6
1.4
1.2
(ppm)
(ppm)
0.8
(ppm)
Integral
10.049
0.9998
0.8833
1.0126
0.6432
1.0000
1.0151
2.0504
5.6489
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)
Ph
N
O
N
Ph
HN
O
(1.1K)


Integral
0.8108
7.1193
2.1324
1.0000
2.3095
0.9948
3.3314
0.9543
2.0068
1.4734
5.8930
2191.06
2187.40
2184.84
2182.65
2063.72
2061.89
2057.14
2054.94
8.2843
7.3406
7.3345
7.3150
7.3077
7.3004
7.2882
7.2797
7.2723
6.8761
6.8700
6.8542
6.8468
1512.65
1497.65
1424.46
1409.83
1400.68
1386.41
1371.41
1223.94
1208.94
5.0400
4.9900
4.7462
4.6974
4.6669
4.6194
4.5694
4.0780
4.0280
3.7988
3.6501
3.6294
3.6196
3.5989
1095.50
1089.28
1086.36
1080.13
482.22
470.52
468.69
392.21
387.09
383.43
380.87
378.30
372.81
1.6067
1.5677
1.5616
1.3068
1.2897
1.2775
1.2690
1.2605
1.2422
0.8313
0.8094
0.7984
0.7764
242.91
239.62
233.03
(ppm)


1.0000
2.2558
2.3800
1.4405
1.3998
1.3238
0.9360
1.4463
3.4237
5.9986
10.6700
3336.78
3068.24
3059.21
2994.96
2992.45
8.3606
8.3392
7.6681
7.6455
7.4850
7.4787
1980.55
1964.49
1879.66
1863.60
4.9498
4.9096
4.6976
4.6575
1497.19
3.7418
382.39
375.37
365.83
359.31
1.8350
1.8187
1.8024
1.7861
1.7698
1.4048
1.3885
1.3721
1.3458
1.2894
1.2705
1.2530
0.9557
0.9381
0.9143
0.8980
721.20
714.67
708.15
562.09
555.56
549.04
538.50
515.91
508.38
501.35
(1.12g)
(ppm)


Integral
1.0000
2.1953
1.1168
1.0960
1.3505
9.3907
1.9766
2.1284
2.1302
1437.82
1422.81
1345.24
1330.60
7.7192
6.5987
1185.70
1177.65
1169.96
1075.92
1074.09
1070.07
1066.78
1062.02
1059.82
4.7906
4.7407
4.4822
4.4334
3.9506
3.9238
3.8982
3.5849
3.5788
3.5654
3.5544
3.5385
3.5312
2.2352
2.2267
2.2108
2.2023
2.1864
2.1596
2.0292
2.0206
2.0072
1.9889
1.9694
1.9402
2.2523
2.2401
2.2352
2.2267
2.2108
2.2023
2.1864
2.1596
2.0292
2.0206
2.0072
1.9889
1.9694
1.9402
1.6183
(ppm)

SR4374-45-F1



(1.122)

Current Data Parameters

NAME	ocl006skr6
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

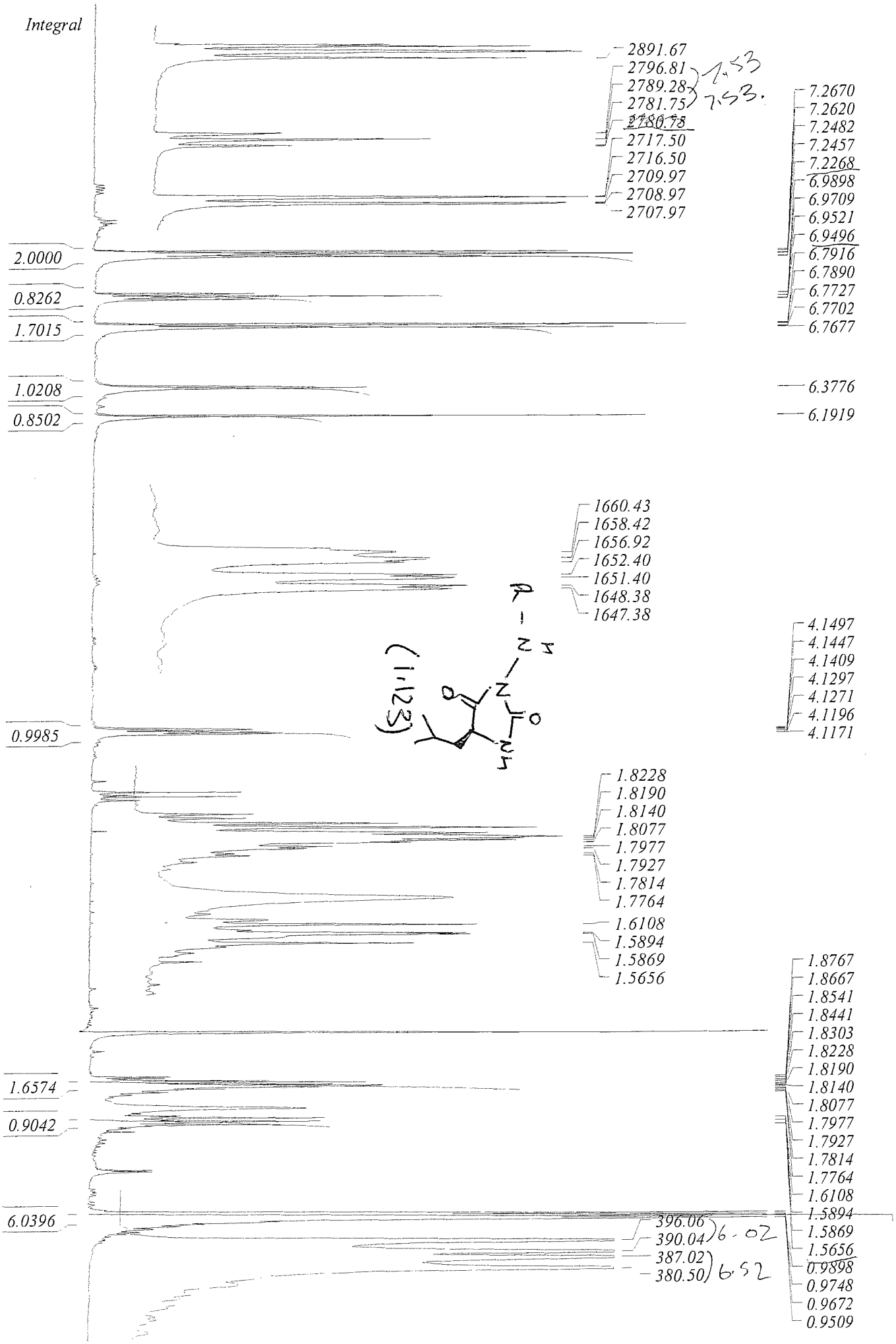
Date_	20061010
Time	20.50
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	1625.5
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

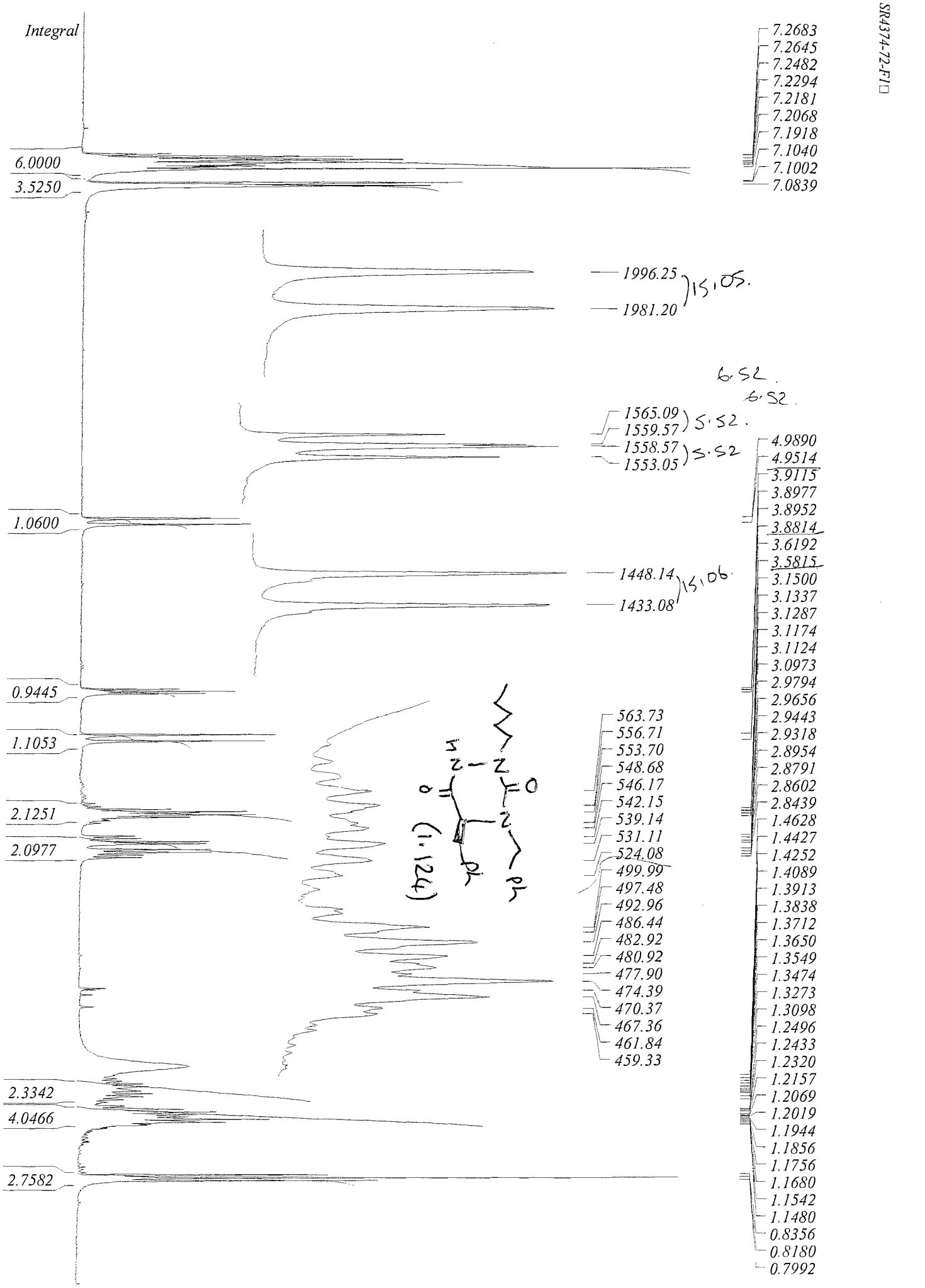
======== CHANNEL f1 ========

NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

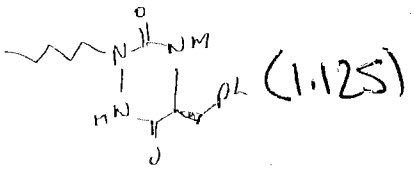
F2 - Processing parameters

SI	16384
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	6.39 Hz


Integral
2891.67
2796.81
2789.28
2781.75
2780.75
2717.50
2716.50
2709.97
2708.97
2707.97
1.53
7.53.
7.2670
7.2620
7.2482
7.2457
7.2268
6.9898
6.9709
6.9521
6.9496
6.7916
6.7890
6.7727
6.7702
6.7677
2.0000
0.8262
1.7015
1.0208
0.8502
6.3776
6.1919
1660.43
1658.42
1656.92
1652.40
1651.40
1648.38
1647.38
4.1497
4.1447
4.1409
4.1297
4.1271
4.1196
4.1171
0.9985
1.8228
1.8190
1.8140
1.8077
1.7977
1.7927
1.7814
1.7764
1.6108
1.5894
1.5869
1.5656
1.8767
1.8667
1.8541
1.8441
1.8303
1.8228
1.8190
1.8140
1.8077
1.7977
1.7927
1.7814
1.7764
1.6108
1.5894
1.5869
1.5656
0.9898
0.9748
0.9672
0.9509
1.6574
0.9042
6.0396
396.06
390.04
387.02
380.50
6.02
6.52


Integral
6.0000
3.5250
1.0600
0.9445
1.1053
2.1251
2.0977
2.3342
4.0466
2.7582
7.2683
7.2645
7.2482
7.2294
7.2181
7.2068
7.1918
7.1040
7.1002
7.0839
1996.25
1981.20
15.05.
6.52.
6.52.
1565.09
1559.57
1558.57
1553.05
5.52.
5.52
4.9890
4.9514
3.9115
3.8977
3.8952
3.8814
3.6192
3.5815
3.1500
3.1337
3.1287
3.1174
3.1124
3.0973
2.9794
2.9656
2.9443
2.9318
2.8954
2.8791
2.8602
2.8439
1.4628
1.4427
1.4252
1.4089
1.3913
1.3838
1.3712
1.3650
1.3549
1.3474
1.3273
1.3098
1.2496
1.2433
1.2320
1.2157
1.2069
1.2019
1.1944
1.1856
1.1756
1.1680
1.1542
1.1480
0.8356
0.8180
0.7992
1448.14
1433.08
15.06.
563.73
556.71
553.70
548.68
546.17
542.15
539.14
531.11
524.08
499.99
497.48
492.96
486.44
482.92
480.92
477.90
474.39
470.37
467.36
461.84
459.33
(1.124)

SR4374-79-F1



(1.125)

Current Data Parameters

NAME	oc1906skr2
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20061019
Time	15.26
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	228.1
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

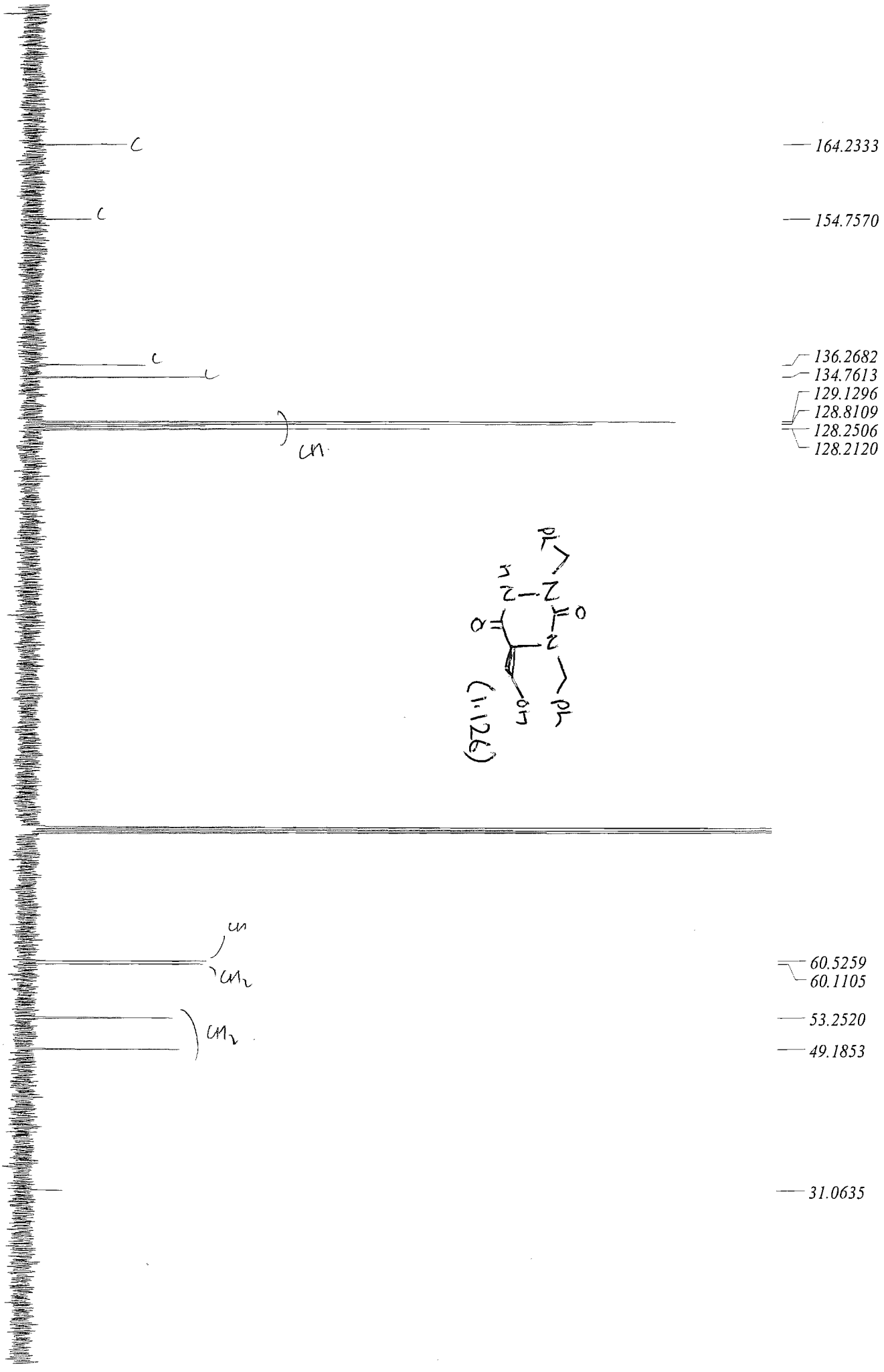
F2 - Processing parameters

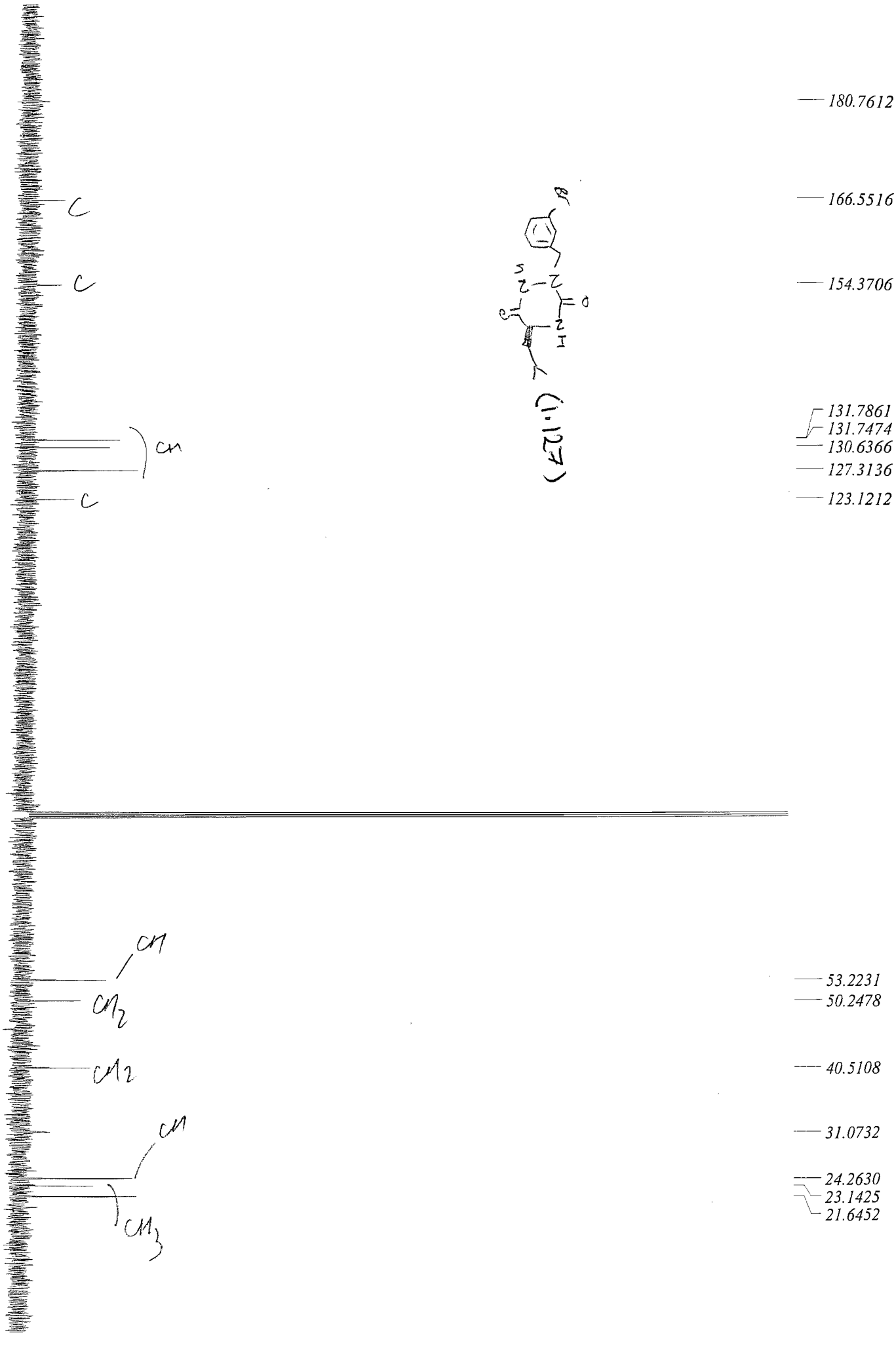
SI	16384
SF	400.1300476 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	47.56 Hz

1D NMR plot parameters

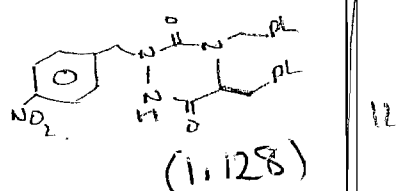
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

SR4374-88□


164.2333
154.7570
136.2682
134.7613
129.1296
128.8109
128.2506
128.2120
60.5259
60.1105
53.2520
49.1853
31.0635


180.7612
166.5516
154.3706
131.7861
131.7474
130.6366
127.3136
123.1212
53.2231
50.2478
40.5108
31.0732
24.2630
23.1425
21.6452

SR4374-93-F1



(1.128)

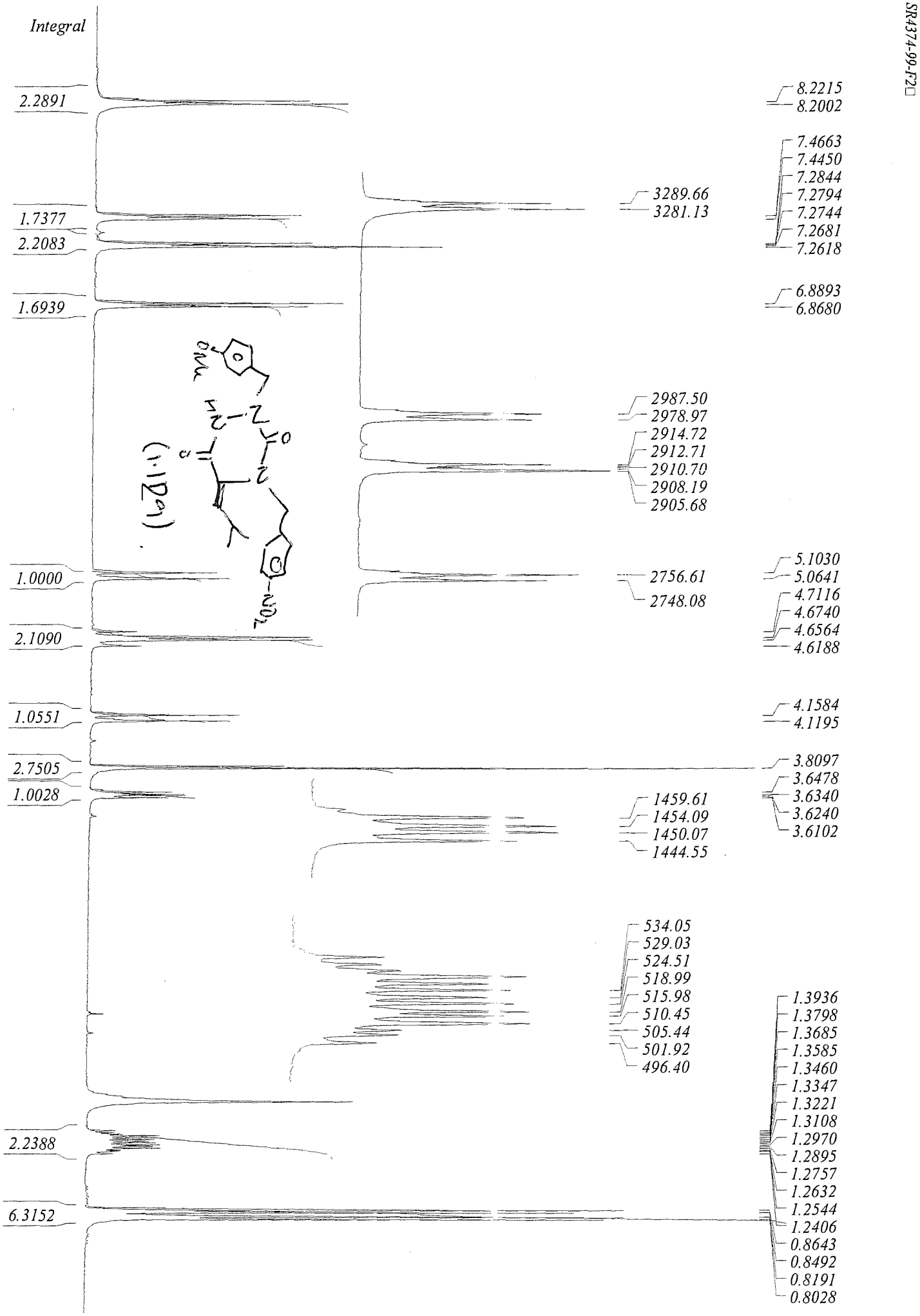
Current Data Parameters
NAME oc1006skr1
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20061010
Time 20.06
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 1625.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

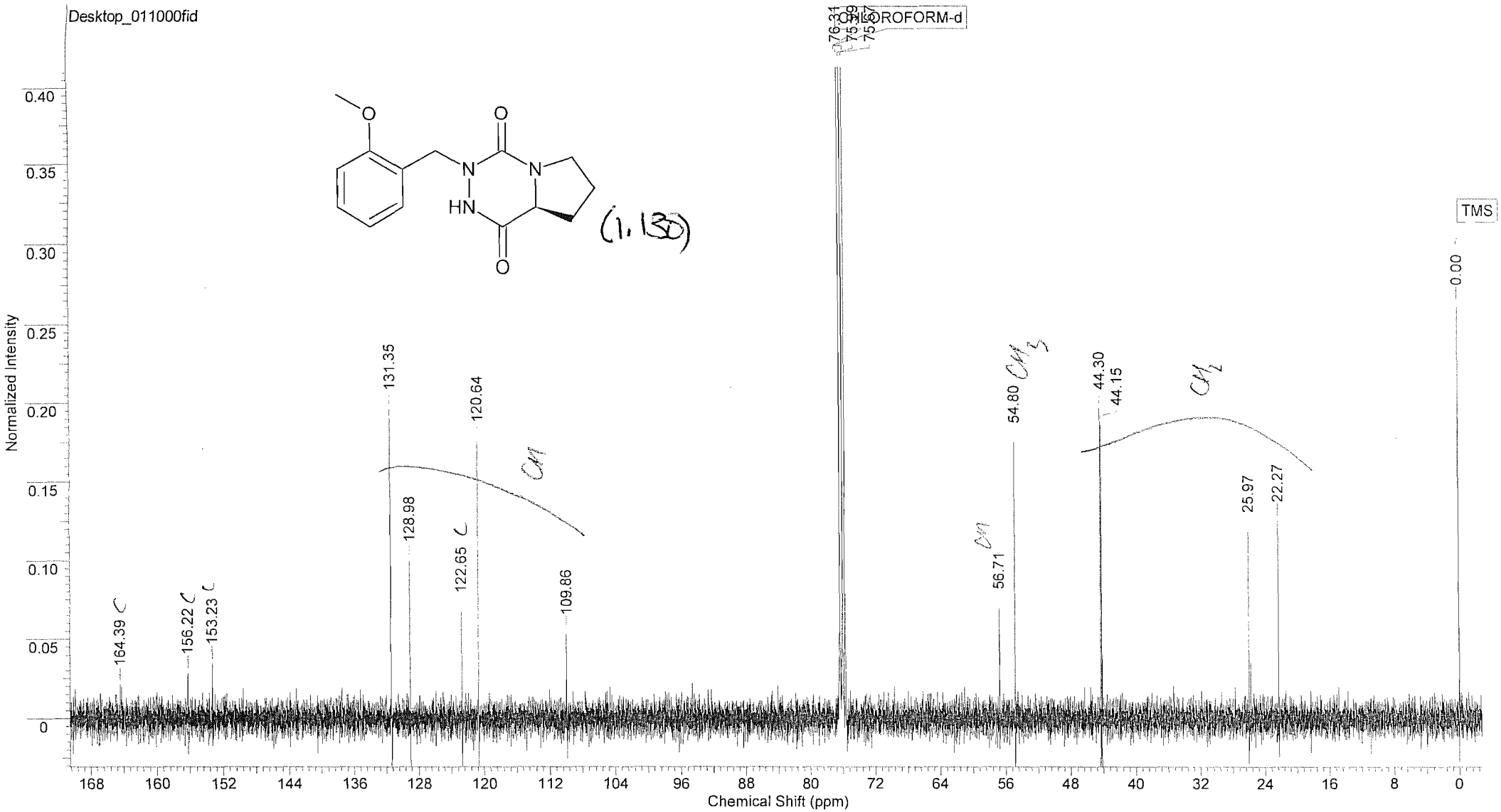
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300063 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.28 Hz

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm


SR4374-99-F2
Integral
2.2891
1.7377
2.2083
1.6939
1.0000
2.1090
1.0551
2.7505
1.0028
2.2388
6.3152
8.2215
8.2002
7.4663
7.4450
7.2844
7.2794
7.2744
7.2681
7.2618
6.8893
6.8680
3289.66
3281.13
2987.50
2978.97
2914.72
2912.71
2910.70
2908.19
2905.68
2756.61
2748.08
5.1030
5.0641
4.7116
4.6740
4.6564
4.6188
4.1584
4.1195
3.8097
3.6478
3.6340
3.6240
3.6102
1459.61
1454.09
1450.07
1444.55
534.05
529.03
524.51
518.99
515.98
510.45
505.44
501.92
496.40
1.3936
1.3798
1.3685
1.3585
1.3460
1.3347
1.3221
1.3108
1.2970
1.2895
1.2757
1.2632
1.2544
1.2406
0.8643
0.8492
0.8191
0.8028

SR4521-97-F3



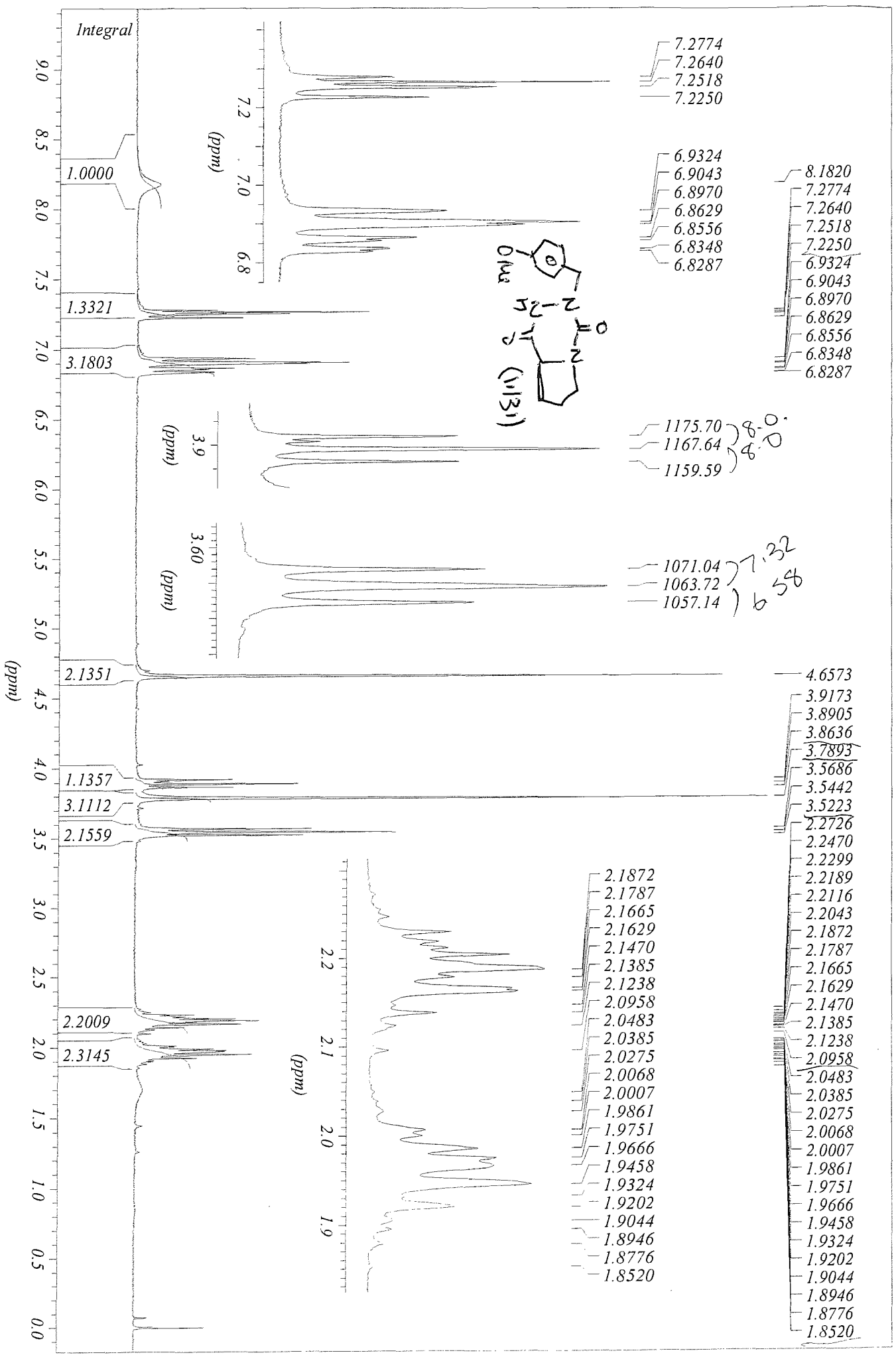
No.	(ppm)	(Hz)	Height
1	0.00	0.0	0.2626
2	22.27	2241.2	0.1256
3	25.97	2613.4	0.1188
4	44.15	4442.5	0.1866

No.	(ppm)	(Hz)	Height
5	44.30	4458.1	0.1968
6	54.80	5514.5	0.1756
7	56.71	5706.0	0.0696
8	75.67	7614.8	0.9242

No.	(ppm)	(Hz)	Height
9	75.99	7646.9	0.9922
10	76.31	7679.0	1.0000
11	109.86	11054.4	0.0534
12	120.64	12139.0	0.1763

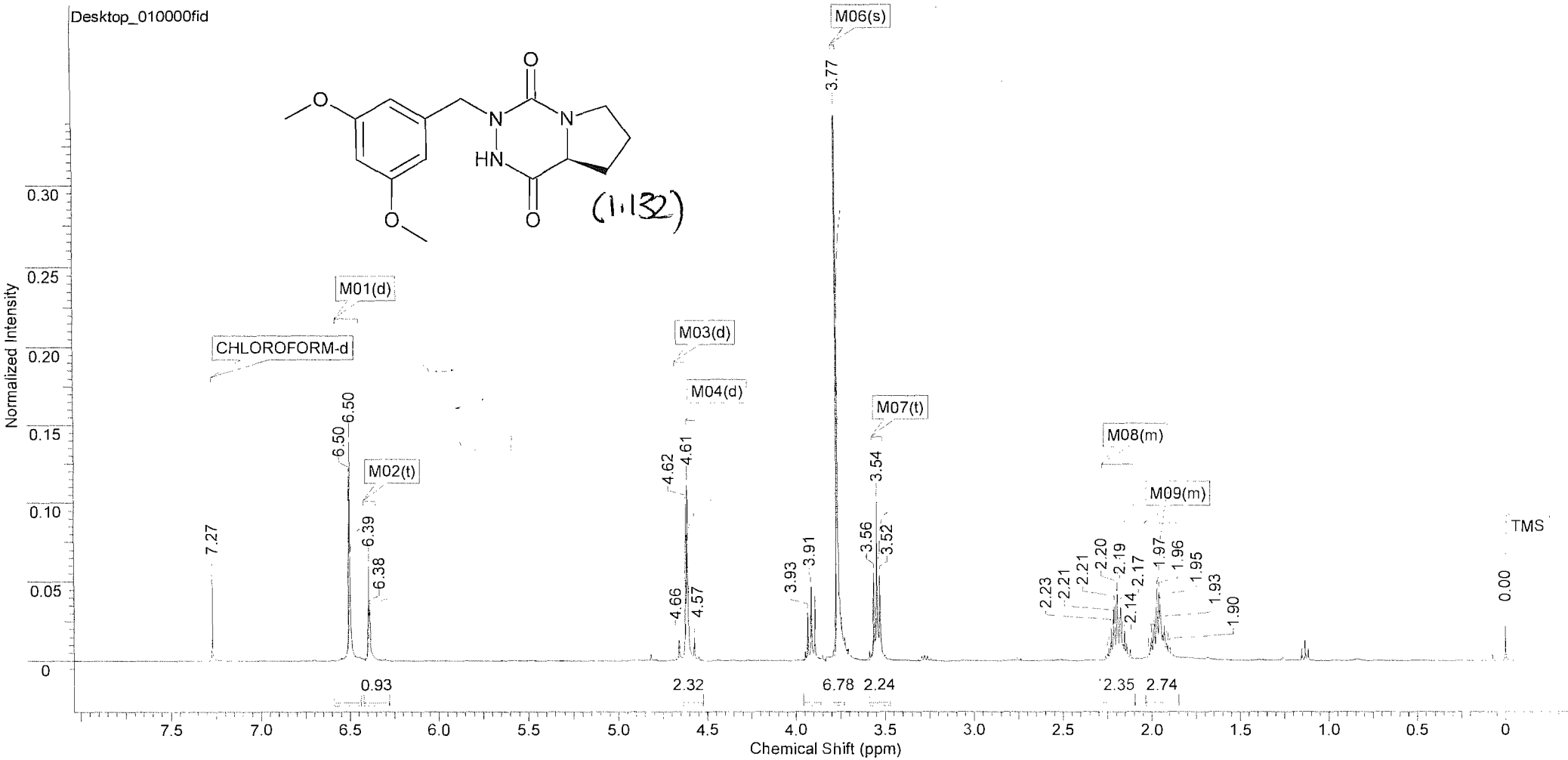
No.	(ppm)	(Hz)	Height
13	122.65	12342.1	0.0675
14	128.98	12978.7	0.0998
15	131.35	13216.8	0.1966
16	153.23	15419.2	0.0348

No.	(ppm)	(Hz)	Height
17	156.22	15719.5	0.0285
18	164.39	16541.7	0.0213


Integral
1.0000
1.3321
3.1803
2.1351
1.1357
3.1112
2.1559
2.2009
2.3145
(ppm)
7.2774
7.2640
7.2518
7.2250
6.9324
6.9043
6.8970
6.8629
6.8556
6.8348
6.8287
1175.70
1167.64
1159.59
1071.04
1063.72
1057.14
4.6573
3.9173
3.8905
3.8636
3.7893
3.5686
3.5442
3.5223
2.2726
2.2470
2.2299
2.2189
2.2116
2.2043
2.1872
2.1787
2.1665
2.1629
2.1470
2.1385
2.1238
2.0958
2.0483
2.0385
2.0275
2.0068
2.0007
1.9861
1.9751
1.9666
1.9458
1.9324
1.9202
1.9044
1.8946
1.8776
1.8520

SR4660-01-F1

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.85 - 2.04 (m, 2 H) 2.09 - 2.28 (m, 2 H) 3.54 (t, *J*=7.03 Hz, 2 H) 3.77 (s, 6 H) 3.91 (t, *J*=8.03 Hz, 1 H) 4.59 (d, 1 H) 4.64 (d, 1 H) 6.39 (t, *J*=2.26 Hz, 1 H) 6.50 (d, *J*=2.01 Hz, 2 H)



No.	(ppm)	(Hz)	Height
1	0.00	0.0	0.0245
2	1.90	758.4	0.0083
3	1.91	763.4	0.0097
4	1.91	766.0	0.0111
5	1.93	771.0	0.0224
6	1.94	775.0	0.0169
7	1.95	780.0	0.0361
8	1.96	783.0	0.0436

No.	(ppm)	(Hz)	Height
9	1.97	787.5	0.0456
10	1.99	795.1	0.0256
11	2.00	800.6	0.0148
12	2.02	806.6	0.0058
13	2.12	847.8	0.0074
14	2.14	856.3	0.0109
15	2.15	860.8	0.0190
16	2.17	869.3	0.0342

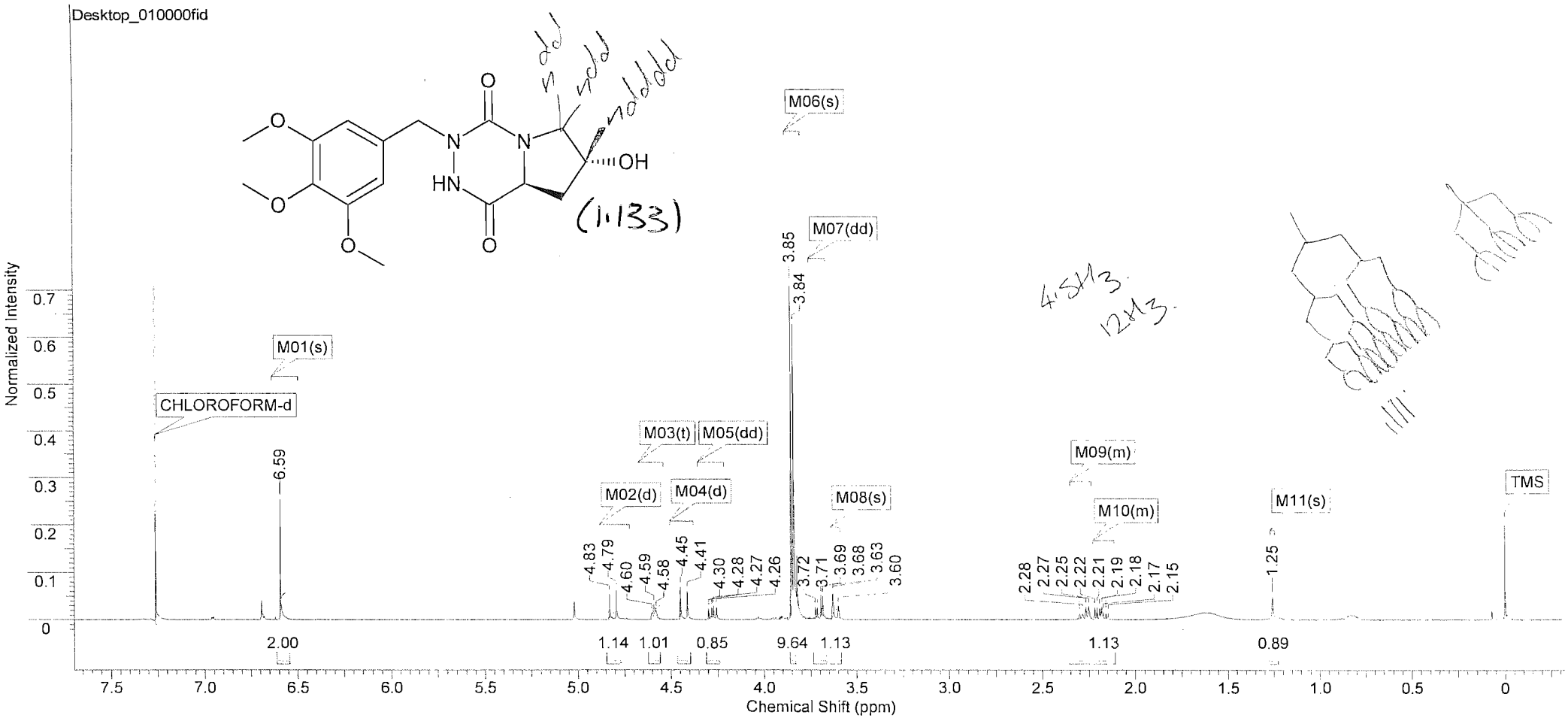
No.	(ppm)	(Hz)	Height
17	2.19	876.9	0.0417
18	2.20	878.4	0.0450
19	2.21	883.4	0.0353
20	2.21	885.9	0.0264
21	2.23	891.4	0.0206
22	2.24	896.5	0.0082
23	2.25	899.0	0.0048
24	3.52	1410.4	0.0537

No.	(ppm)	(Hz)	Height
25	3.54	1417.0	0.1007
26	3.56	1424.5	0.0557
27	3.77	1506.8	1.0000
28	3.89	1557.0	0.0326
29	3.91	1565.0	0.0466
30	3.93	1573.1	0.0303
31	4.57	1829.0	0.0148
32	4.61	1844.1	0.1112

No.	(ppm)	(Hz)	Height
33	4.62	1847.6	0.0993
34	4.66	1863.2	0.0137
35	6.38	2554.8	0.0331
36	6.39	2556.9	0.0597
37	6.40	2559.4	0.0333
38	6.50	2599.5	0.1391
39	6.50	2601.5	0.1172
40	7.27	2908.2	0.0547

SR4521-58

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.25 (s, 1 H) 2.11 - 2.23 (m, 1 H) 2.23 - 2.35 (m, 1 H) 3.61 (s, 1 H) 3.70 (dd, 1 H) 3.85 (s, 9 H) 4.28 (dd, *J*=10.29, 6.27 Hz, 1 H) 4.43 (d, *J*=15.06 Hz, 1 H) 4.59 (t, *J*=4.52 Hz, 1 H) 4.81 (d, *J*=15.06 Hz, 1 H) 6.59 (s, 2 H)



No.	(ppm)	(Hz)	Height
1	1.25	501.9	0.0501
2	2.15	858.8	0.0134
3	2.16	863.3	0.0139
4	2.17	869.3	0.0154
5	2.18	872.4	0.0285
6	2.19	876.9	0.0252
7	2.21	882.9	0.0266

No.	(ppm)	(Hz)	Height
8	2.22	887.4	0.0260
9	2.25	900.5	0.0273
10	2.27	907.0	0.0276
11	2.28	914.0	0.0138
12	2.30	920.5	0.0127
13	3.60	1440.0	0.0292
14	3.63	1452.1	0.0565

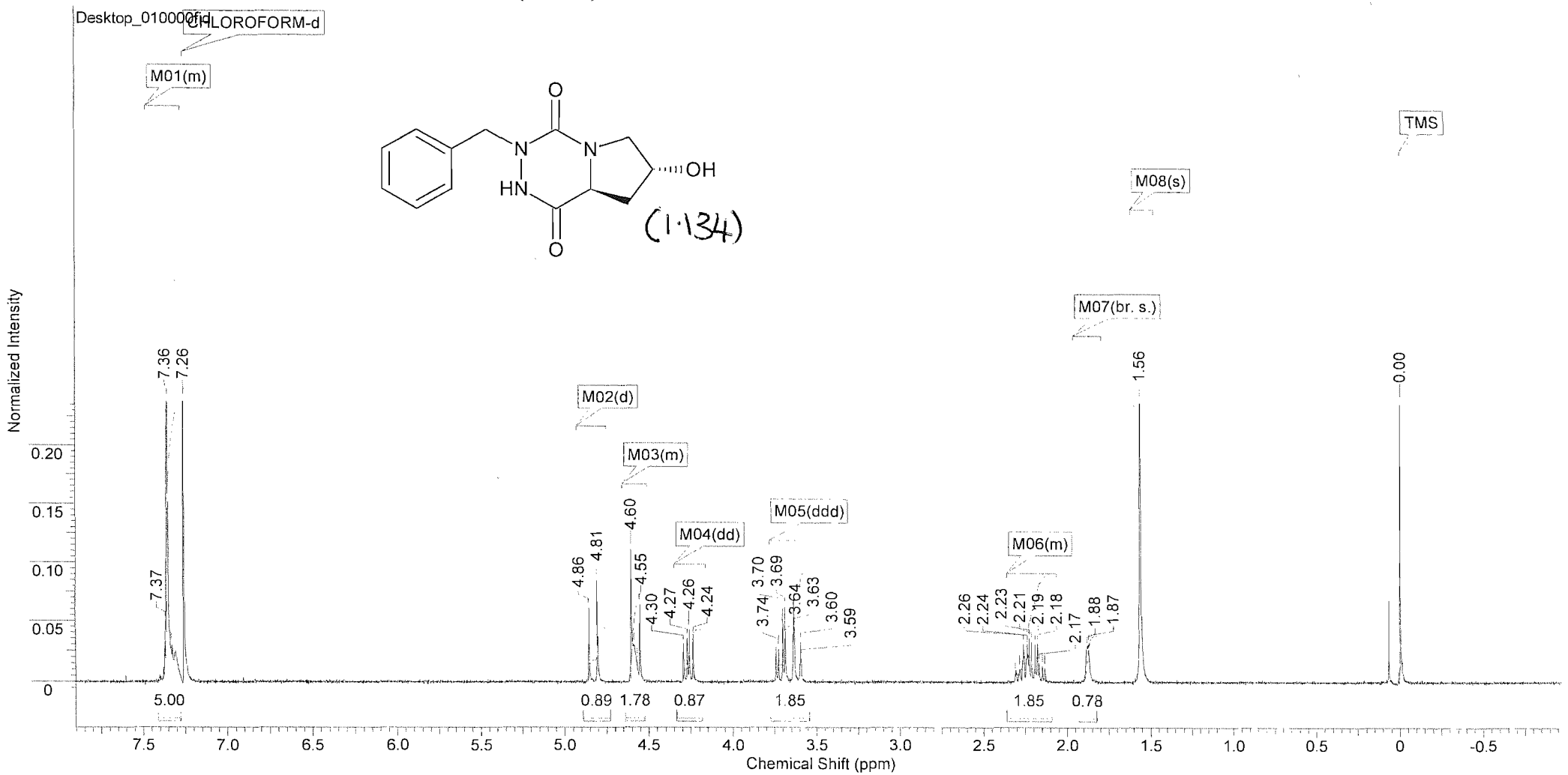
No.	(ppm)	(Hz)	Height
15	3.68	1473.7	0.0501
16	3.69	1478.2	0.0510
17	3.71	1485.7	0.0264
18	3.72	1490.2	0.0268
19	3.84	1536.4	0.6295
20	3.85	1541.9	1.0000
21	4.26	1703.1	0.0258

No.	(ppm)	(Hz)	Height
22	4.27	1709.1	0.0289
23	4.28	1713.1	0.0251
24	4.30	1719.6	0.0233
25	4.41	1764.8	0.0610
26	4.45	1779.9	0.0699
27	4.58	1832.1	0.0203
28	4.59	1836.6	0.0326

No.	(ppm)	(Hz)	Height
29	4.60	1841.1	0.0149
30	4.79	1917.4	0.0623
31	4.83	1932.4	0.0535
32	6.59	2637.2	0.2534

SR4660-02-F2

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.56 (s, 3 H) 1.88 (br. s., 1 H) 2.06 - 2.36 (m, 1 H) 3.66 (ddd, 1 H) 4.27 (dd, *J*=10.61, 6.95 Hz, 1 H) 4.51 - 4.65 (m, 2 H) 4.83 (d, *J*=15.00 Hz, 1 H) 7.27 - 7.48 (m, 5 H)



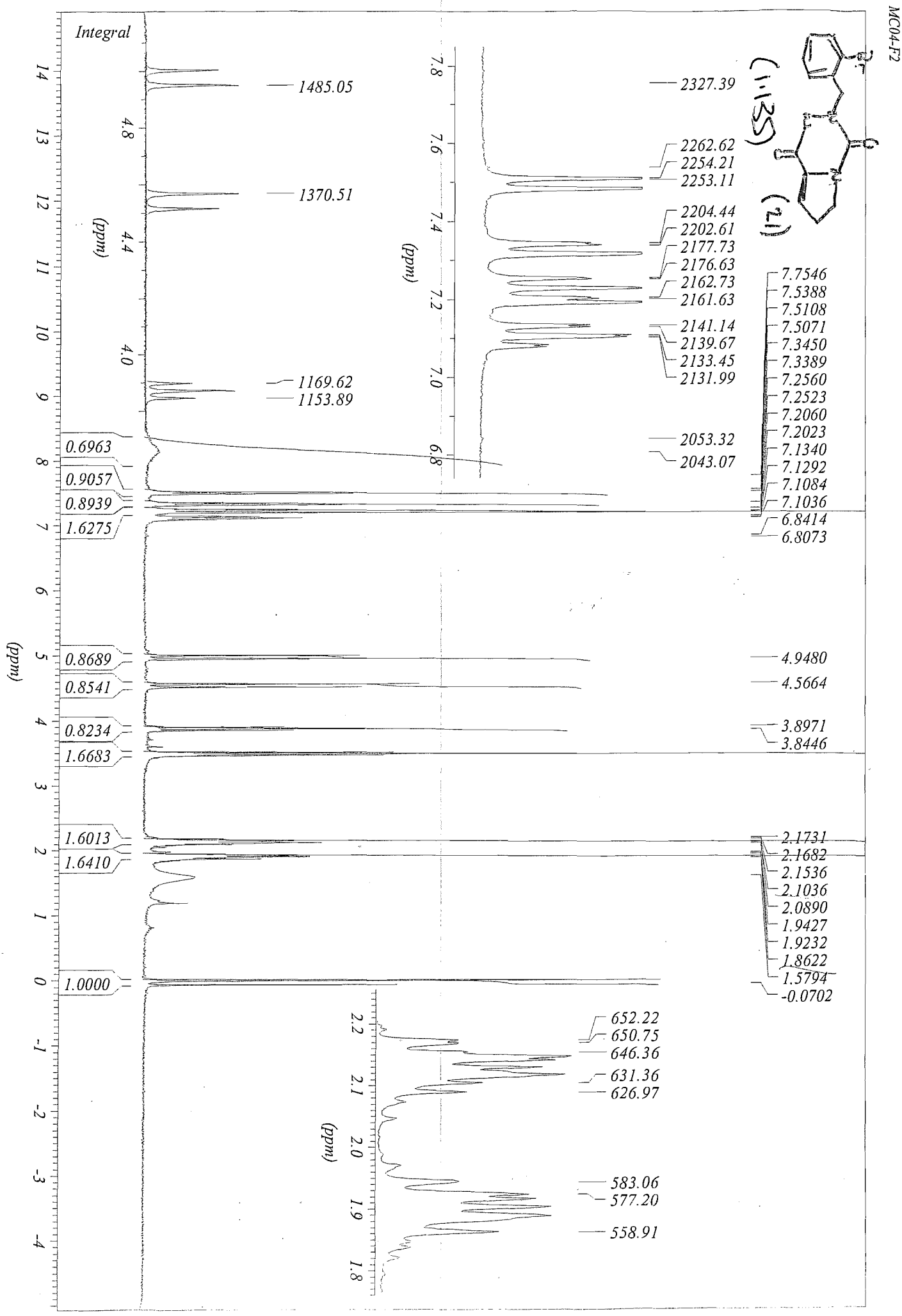
No.	(ppm)	(Hz)	Height
1	0.00	0.0	0.4441
2	1.56	469.5	0.3930
3	1.87	562.4	0.0312
4	1.88	565.3	0.0292
5	2.13	640.7	0.0113
6	2.15	645.1	0.0128
7	2.17	651.0	0.0156
8	2.18	654.3	0.0317

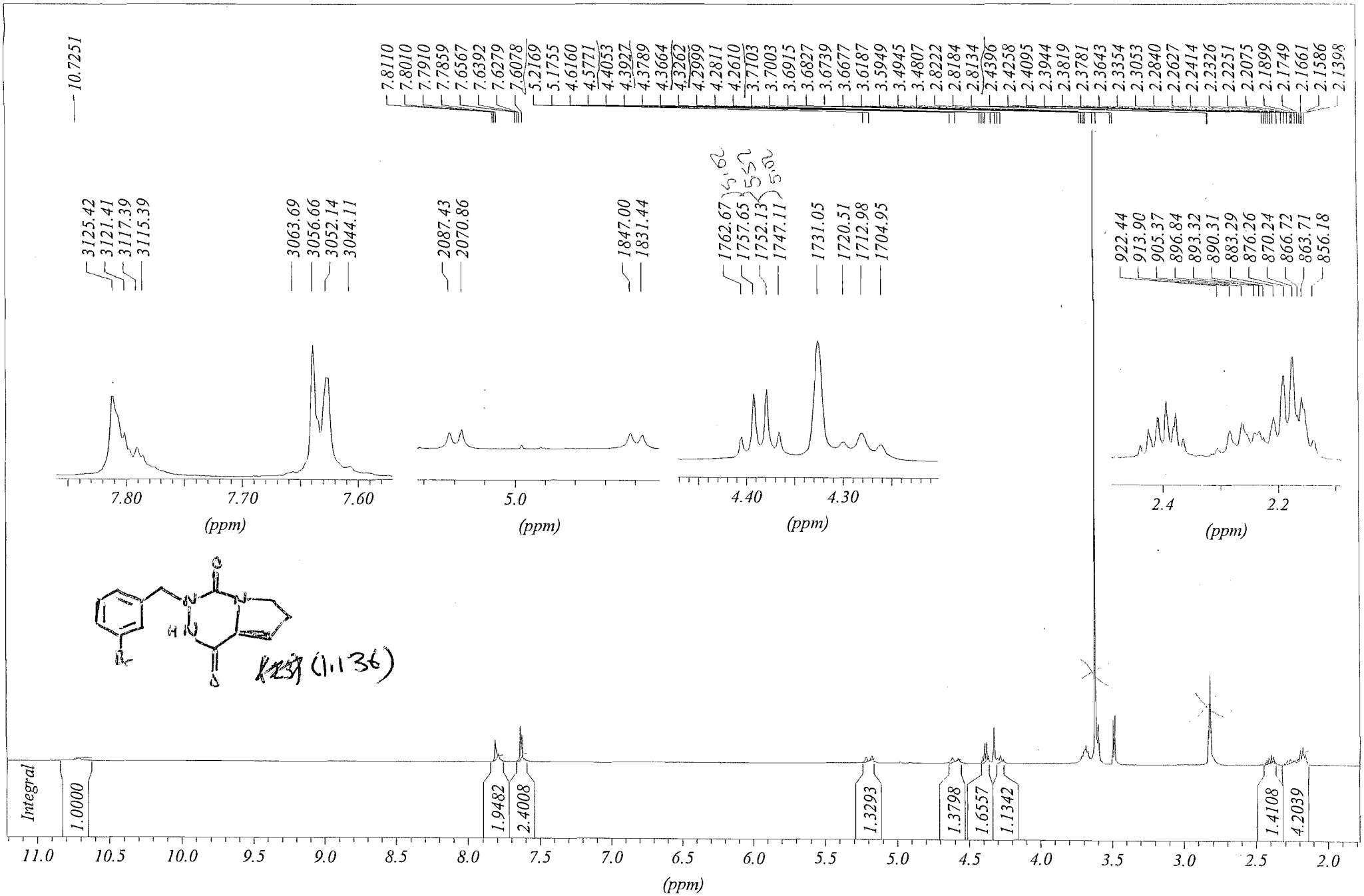
No.	(ppm)	(Hz)	Height
9	2.19	658.7	0.0312
10	2.21	664.5	0.0329
11	2.23	668.9	0.0356
12	2.24	672.6	0.0312
13	2.26	679.1	0.0312
14	2.29	686.1	0.0107
15	2.31	694.1	0.0066
16	3.59	1077.6	0.0186

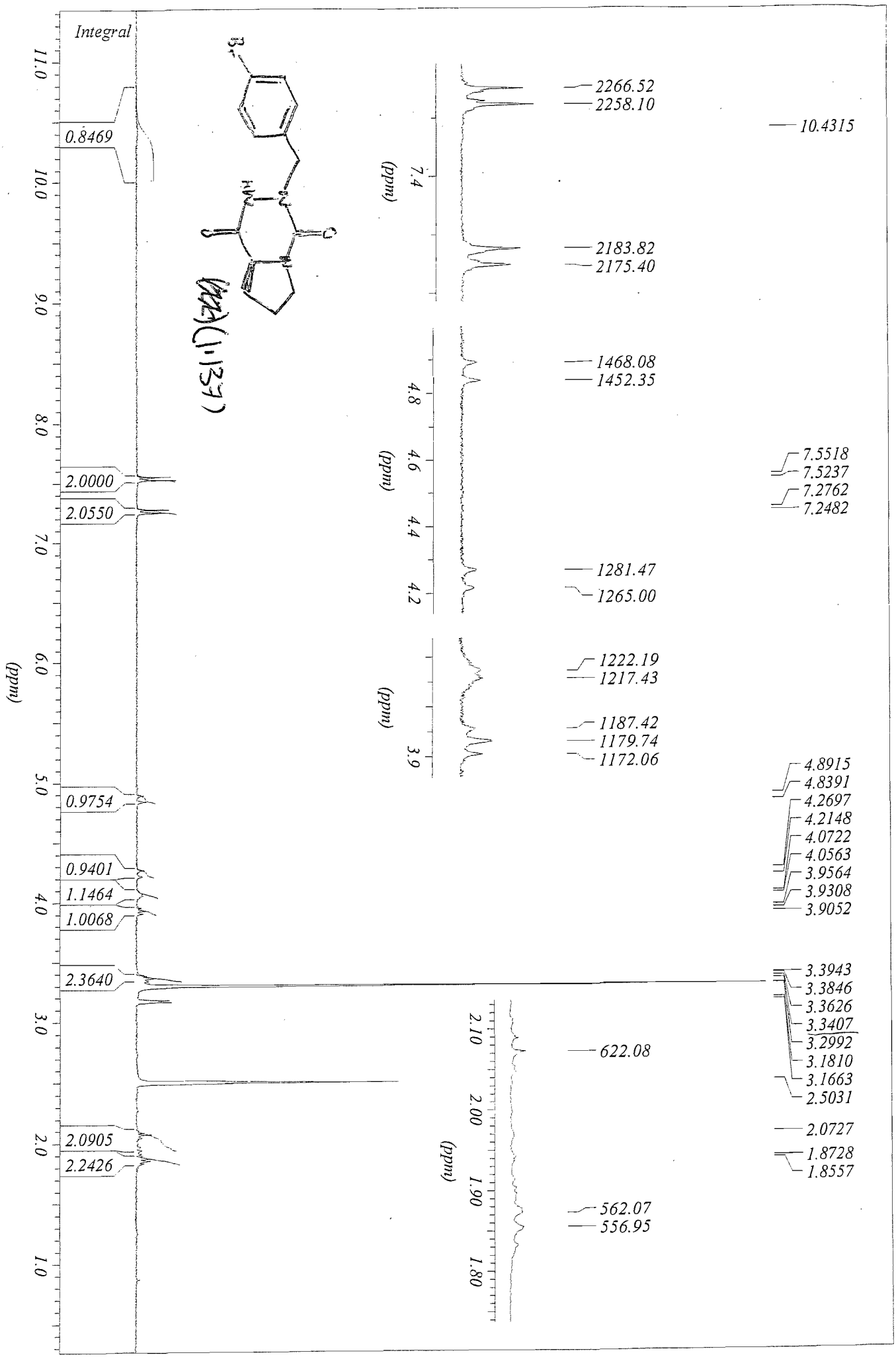
No.	(ppm)	(Hz)	Height
17	3.60	1079.1	0.0325
18	3.63	1090.1	0.0453
19	3.64	1092.6	0.0391
20	3.69	1106.5	0.0632
21	3.70	1110.9	0.0618
22	3.73	1118.6	0.0265
23	3.74	1123.0	0.0284
24	4.24	1271.6	0.0375

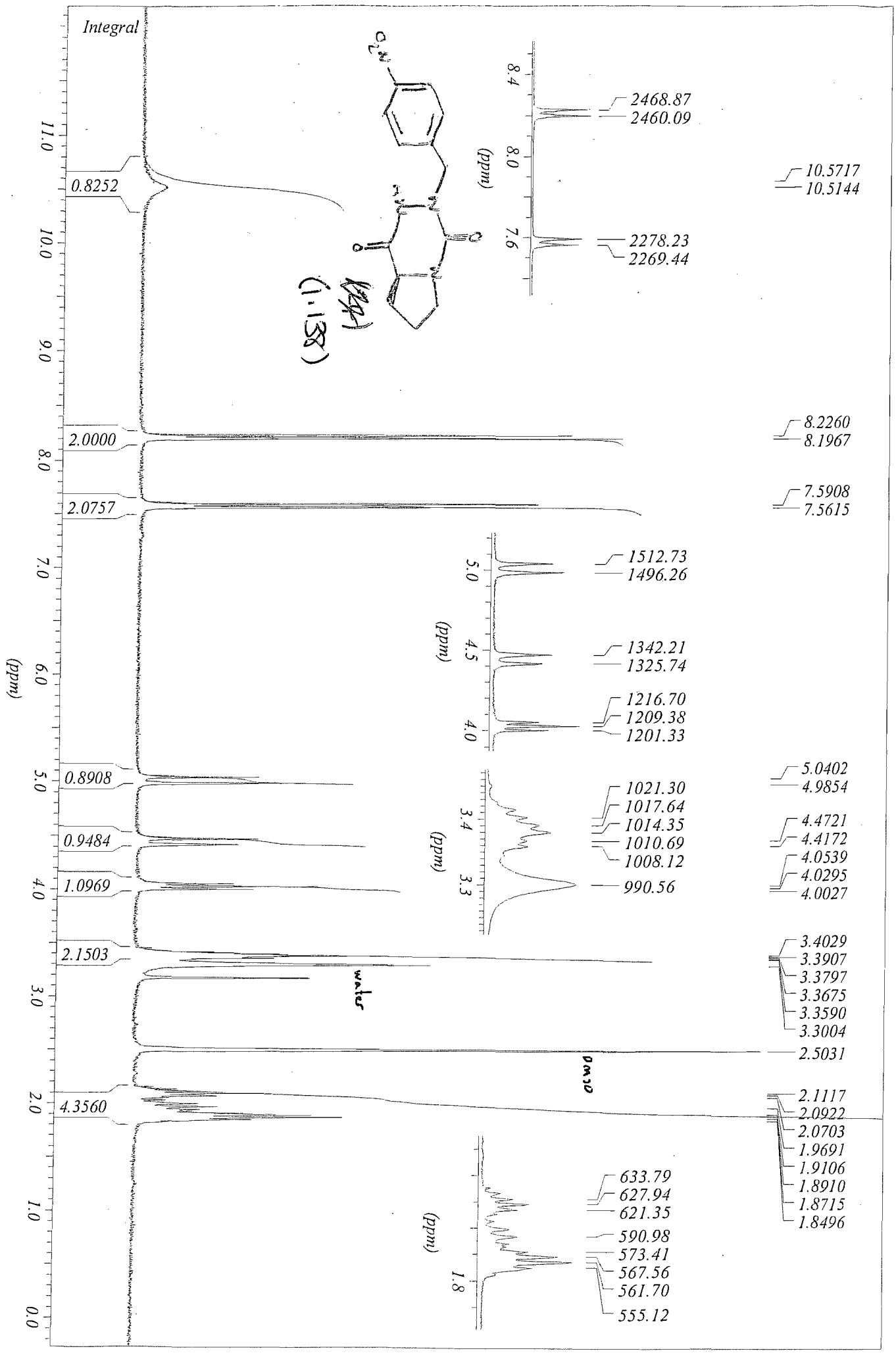
No.	(ppm)	(Hz)	Height
25	4.26	1278.2	0.0433
26	4.27	1281.8	0.0358
27	4.30	1289.1	0.0305
28	4.55	1366.7	0.0643
29	4.57	1371.5	0.0163
30	4.59	1376.6	0.0300
31	4.59	1378.0	0.0308
32	4.60	1381.7	0.1113

No.	(ppm)	(Hz)	Height
33	4.81	1442.4	0.0847
34	4.86	1457.5	0.0621
35	7.26	2178.7	1.0000
36	7.33	2201.4	0.0293
37	7.36	2208.0	0.4813
38	7.37	2210.9	0.0500

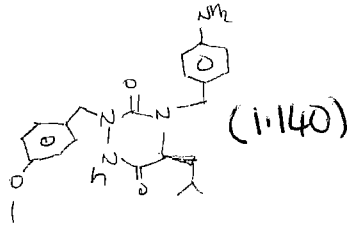

MC04-F2
Integral
1485.05
1370.51
1169.62
1153.89
0.6963
0.9057
0.8939
1.6275
0.8689
0.8541
0.8234
1.6683
1.6013
1.6410
1.0000
(ppm)
2327.39
2262.62
2254.21
2253.11
2204.44
2202.61
2177.73
2176.63
2162.73
2161.63
2141.14
2139.67
2133.45
2131.99
2053.32
2043.07
7.7546
7.5388
7.5108
7.5071
7.3450
7.3389
7.2560
7.2523
7.2060
7.2023
7.1340
7.1292
7.1084
7.1036
6.8414
6.8073
4.9480
4.5664
3.8971
3.8446
2.1731
2.1682
2.1536
2.1036
2.0890
1.9427
1.9232
1.8622
1.5794
-0.0702
652.22
650.75
646.36
631.36
626.97
583.06
577.20
558.91
(1-135)
(21)


10.7251
7.8110
7.8010
7.7910
7.7859
7.6567
7.6392
7.6279
7.6078
5.2169
5.1755
4.6160
4.5771
4.4053
4.3922
4.3789
4.3664
4.3262
4.2999
4.2811
4.2610
3.7103
3.7003
3.6915
3.6827
3.6739
3.6677
3.6187
3.5949
3.4945
3.4807
3.8222
2.8184
2.8134
2.4396
2.4258
2.4095
2.3944
2.3819
2.3781
2.3643
2.3354
2.3053
2.2840
2.2627
2.2414
2.2326
2.2251
2.2075
2.1899
2.1749
2.1661
2.1586
2.1398
3125.42
3121.41
3117.39
3115.39
3063.69
3056.66
3052.14
3044.11
2087.43
2070.86
1847.00
1831.44
1762.67
1757.65
1752.13
1747.11
1731.05
1720.51
1712.98
1704.95
922.44
913.90
905.37
896.84
893.32
890.31
883.29
876.26
870.24
866.72
863.71
856.18
7.80
7.70
7.60
(ppm)
5.0
(ppm)
4.40
4.30
(ppm)
2.4
2.2
(ppm)
Integral
1.0000
1.9482
2.4008
1.3293
1.3798
1.6557
1.1342
1.4108
4.2039
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
(ppm)


Integral
0.8469
2.0000
2.0550
0.9754
0.9401
1.1464
1.0068
2.3640
2.0905
2.2426
(ppm)
2266.52
2258.10
2183.82
2175.40
1468.08
1452.35
1281.47
1265.00
1222.19
1217.43
1187.42
1179.74
1172.06
622.08
562.07
556.95
10.4315
7.5518
7.5237
7.2762
7.2482
4.8915
4.8391
4.2697
4.2148
4.0722
4.0563
3.9564
3.9308
3.9052
3.3943
3.3846
3.3626
3.3407
3.2992
3.1810
3.1663
2.5031
2.0727
1.8728
1.8557


Integral
0.8252
2.0000
2.0757
0.8908
0.9484
1.0969
2.1503
4.3560
water
DMSO
(ppm)
2468.87
2460.09
2278.23
2269.44
10.5717
10.5144
8.2260
8.1967
7.5908
7.5615
1512.73
1496.26
1342.21
1325.74
1216.70
1209.38
1201.33
1021.30
1017.64
1014.35
1010.69
1008.12
990.56
5.0402
4.9854
4.4721
4.4172
4.0539
4.0295
4.0027
3.4029
3.3907
3.3797
3.3675
3.3590
3.3004
2.5031
2.1117
2.0922
2.0703
1.9691
1.9106
1.8910
1.8715
1.8496
633.79
627.94
621.35
590.98
573.41
567.56
561.70
555.12

SR4521-05-F1



(1.140)

Current Data Parameters

NAME	nv2205skr1
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20051122
Time	14.48
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

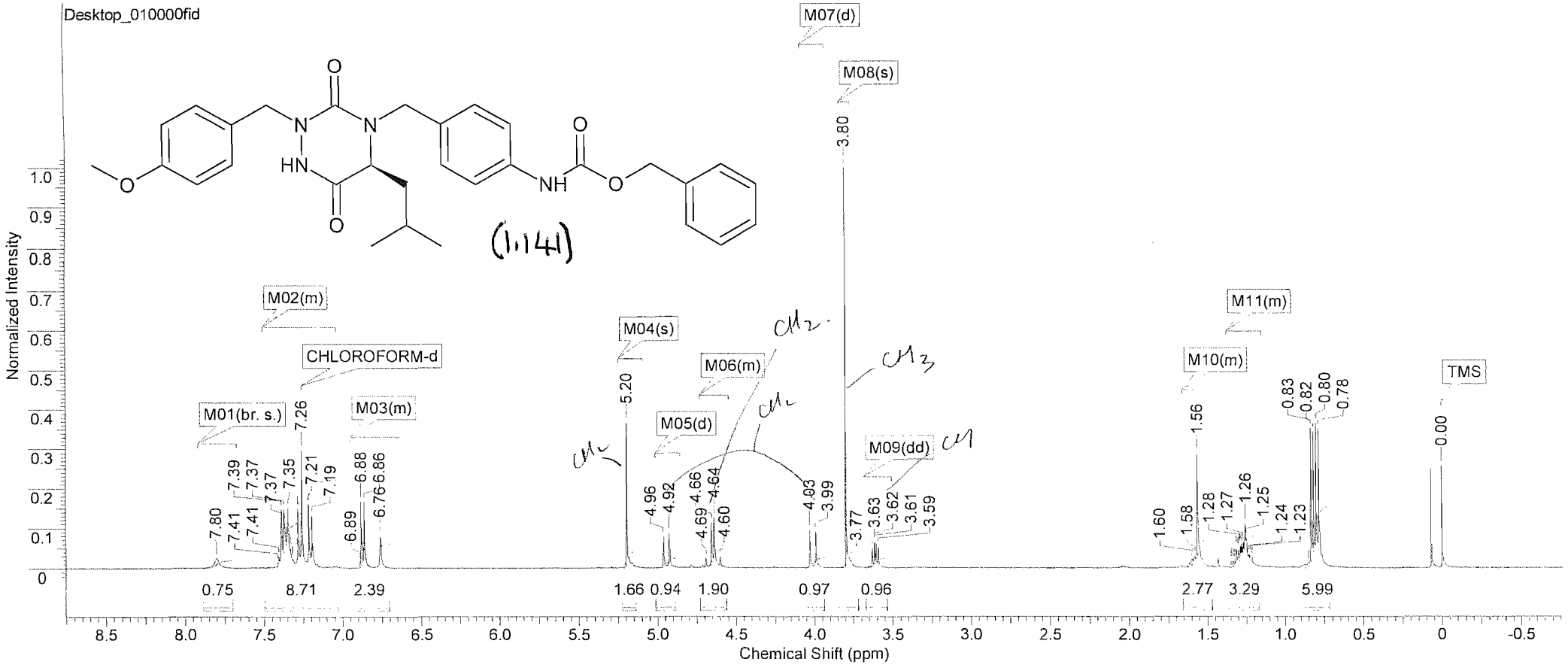
SI	16384
SF	400.1300194 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	19.37 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

SR4374-15-F2

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.15 - 1.37 (m, 2 H) 1.48 - 1.66 (m, 1 H) 3.61 (dd, *J*=9.54, 6.02 Hz, 1 H) 3.78 (s, 3 H) 4.01 (d, *J*=15.06 Hz, 1 H) 4.54 - 4.73 (m, 2 H) 4.94 (d, *J*=15.06 Hz, 1 H) 5.20 (s, 2 H) 6.63 - 6.95 (m, 3 H) 7.04 - 7.51 (m, 10 H) 7.80 (br. s., 1 H)



No.	(ppm)	(Hz)	Height
1	0.00	0.0	0.2570
2	0.78	313.7	0.3522
3	0.80	320.7	0.3674
4	0.82	327.3	0.3439
5	0.83	333.8	0.3526
6	0.85	340.8	0.0150
7	1.21	485.9	0.0267
8	1.23	491.4	0.0341
9	1.24	494.4	0.0341
10	1.25	499.4	0.0761
11	1.26	502.4	0.1124
12	1.27	508.0	0.0660

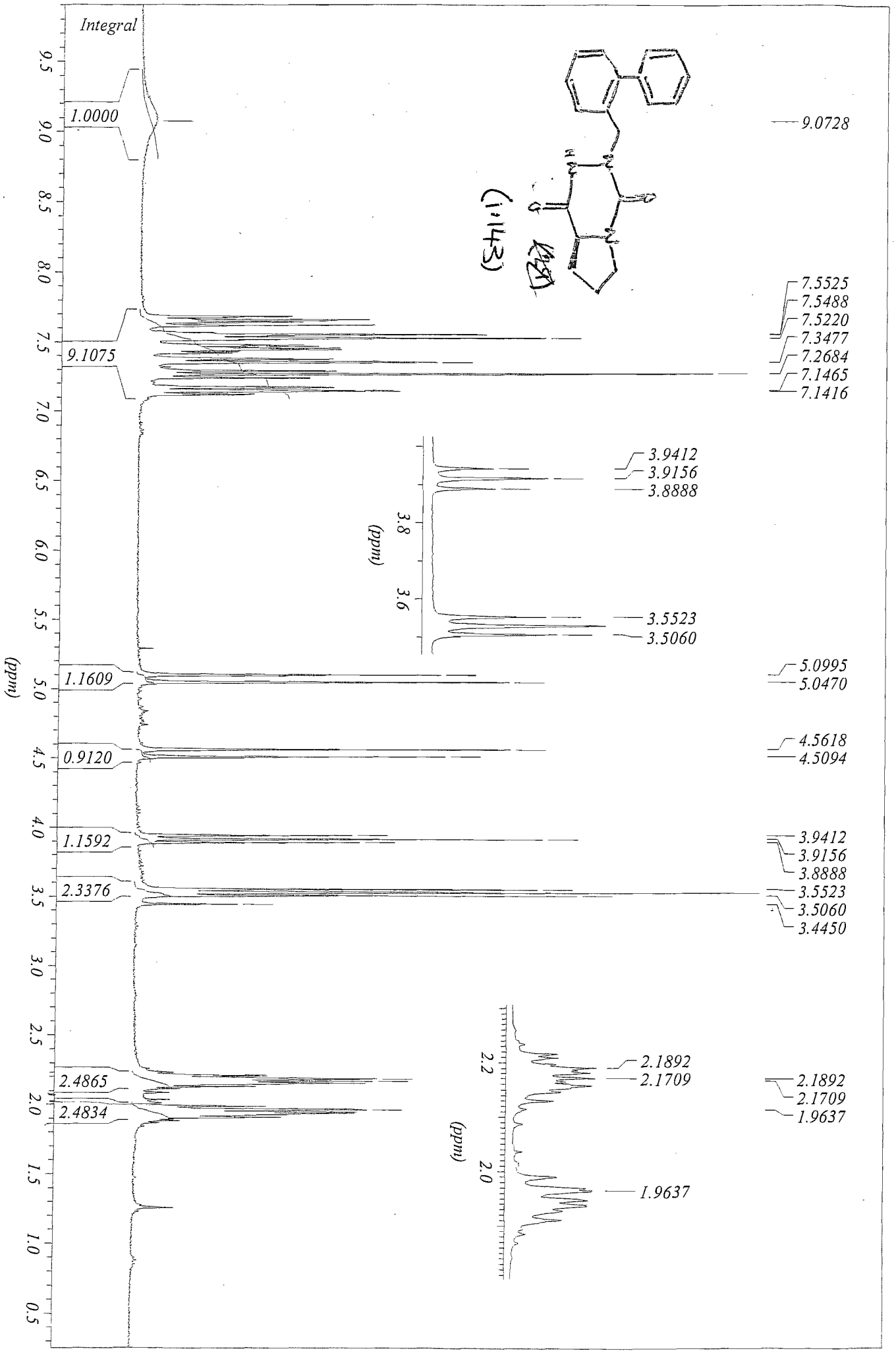
No.	(ppm)	(Hz)	Height
13	1.28	511.0	0.0568
14	1.28	514.0	0.0621
15	1.29	516.5	0.0558
16	1.30	520.5	0.0463
17	1.31	526.0	0.0491
18	1.32	530.0	0.0181
19	1.34	534.6	0.0184
20	1.35	539.6	0.0169
21	1.56	625.4	0.2874
22	1.58	632.9	0.0300
23	1.60	639.5	0.0211
24	1.60	642.0	0.0216

No.	(ppm)	(Hz)	Height
25	3.59	1437.5	0.0539
26	3.61	1443.6	0.0604
27	3.62	1447.1	0.0661
28	3.63	1453.1	0.0515
29	3.77	1507.8	0.0198
30	3.80	1519.9	1.0000
31	3.99	1597.2	0.0918
32	4.03	1612.2	0.0962
33	4.60	1840.6	0.0283
34	4.64	1855.6	0.1259
35	4.66	1862.7	0.1143
36	4.69	1877.2	0.0245

No.	(ppm)	(Hz)	Height
37	4.92	1970.6	0.0869
38	4.96	1985.7	0.0797
39	5.20	2079.0	0.3669
40	6.76	2704.9	0.0786
41	6.86	2745.1	0.1661
42	6.88	2753.6	0.1682
43	6.89	2756.6	0.0183
44	7.19	2878.1	0.1320
45	7.21	2886.6	0.1618
46	7.26	2904.2	0.2987
47	7.28	2914.2	0.1499
48	7.32	2928.8	0.0240

No.	(ppm)	(Hz)	Height
49	7.33	2933.3	0.0502
50	7.35	2939.3	0.1504
51	7.37	2947.9	0.1140
52	7.37	2949.9	0.1479
53	7.39	2955.9	0.1472
54	7.41	2963.4	0.0300
55	7.41	2965.9	0.0155
56	7.80	3121.5	0.0254

14.9


Integral
1.0000
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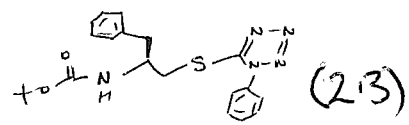
1.1609
0.9120
1.1592
2.3376
2.4865
2.4834
9.0728
7.5525
7.5488
7.5220
7.3477
7.2684
7.1465
7.1416
3.9412
3.9156
3.8888
3.5523
3.5060
5.0995
5.0470
4.5618
4.5094
3.4450
2.1892
2.1709
1.9637
(ppm)

SR4521-06-F2



(23)

Current Data Parameters

NAME	nv2105skr4
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20051121
Time	13.42
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	1625.5
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

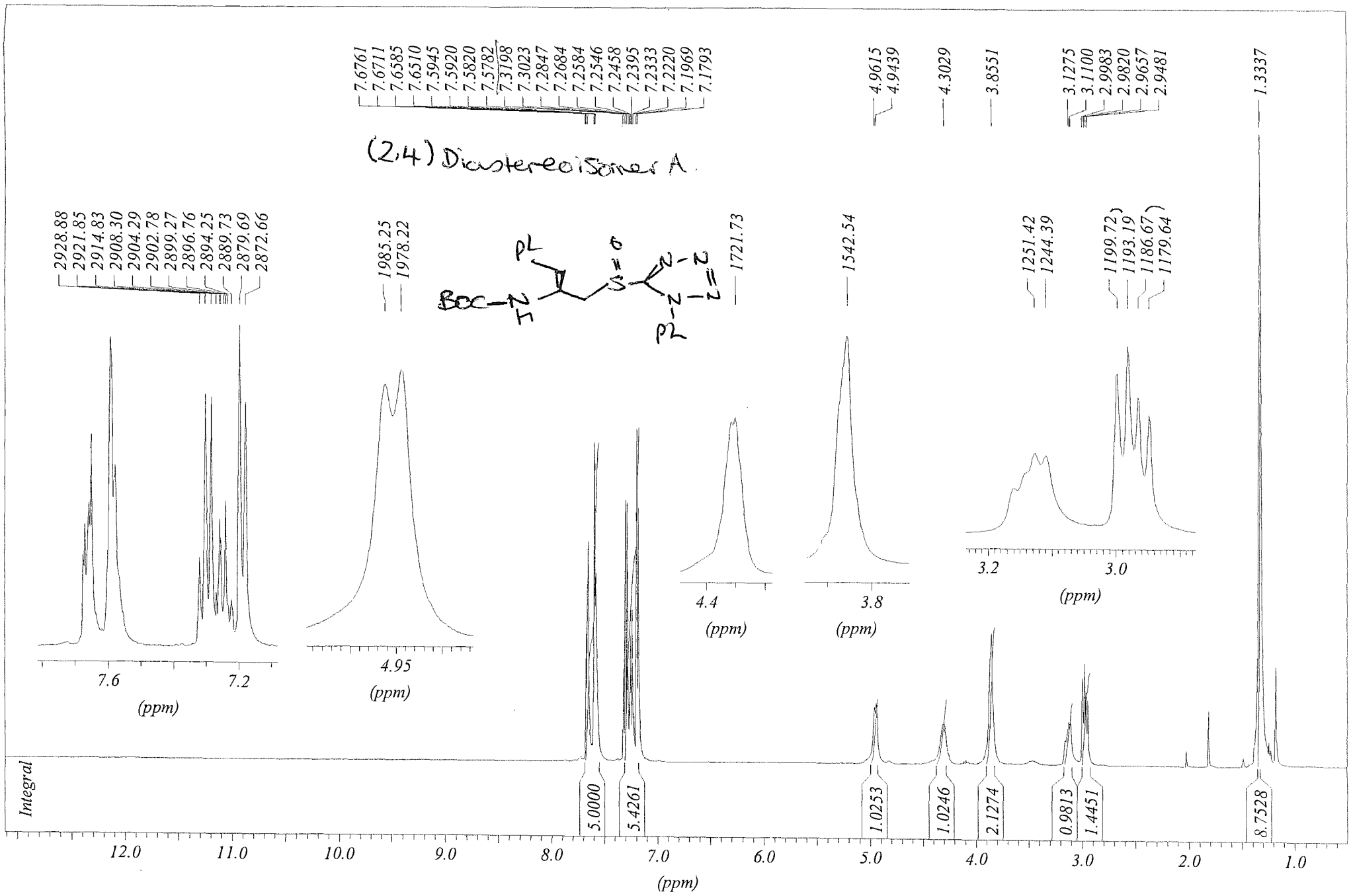
======== CHANNEL f1 ========

NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

F2 - Processing parameters

SI	16384
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	6.23 Hz

SR4521-8-F1□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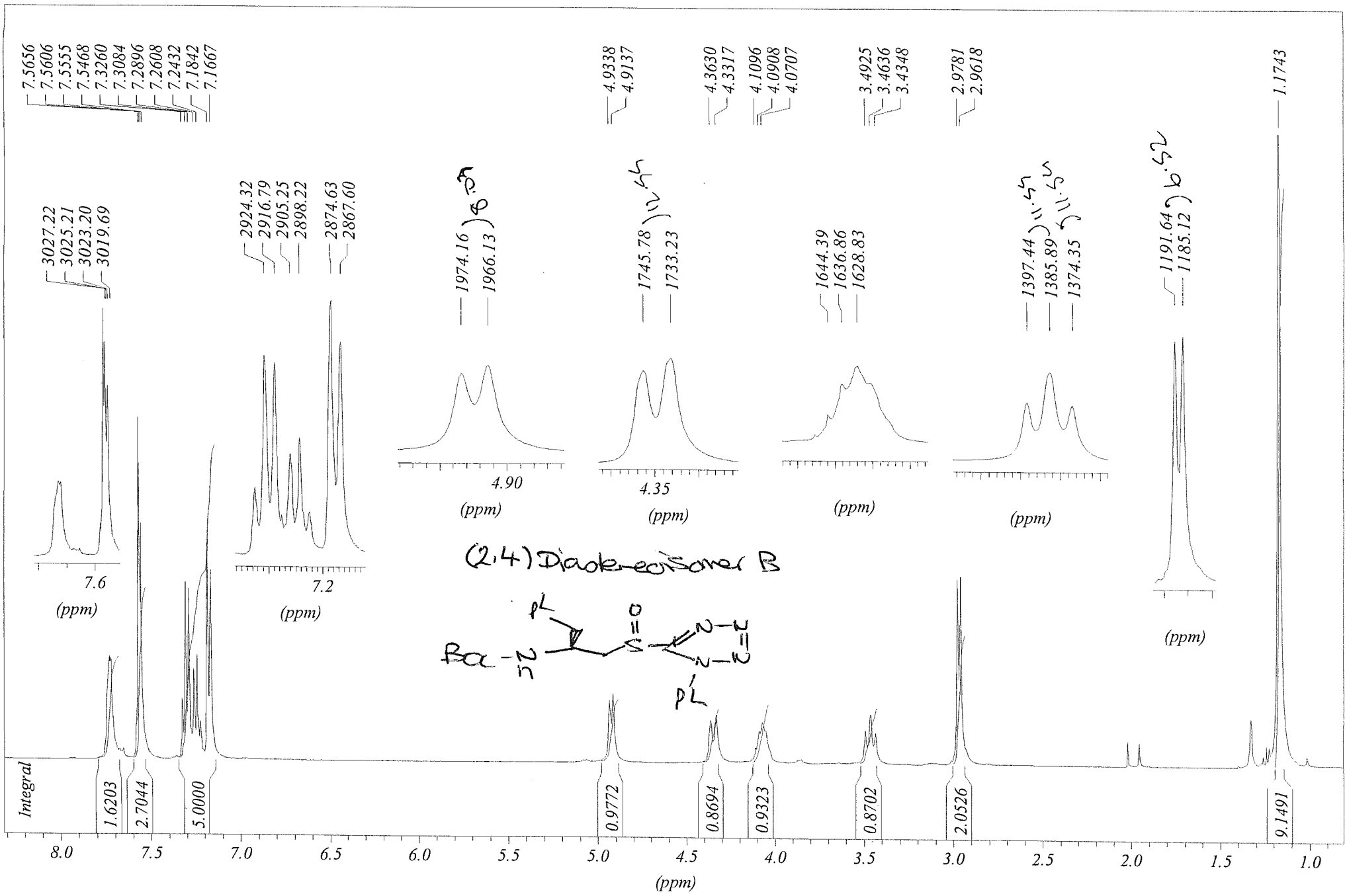
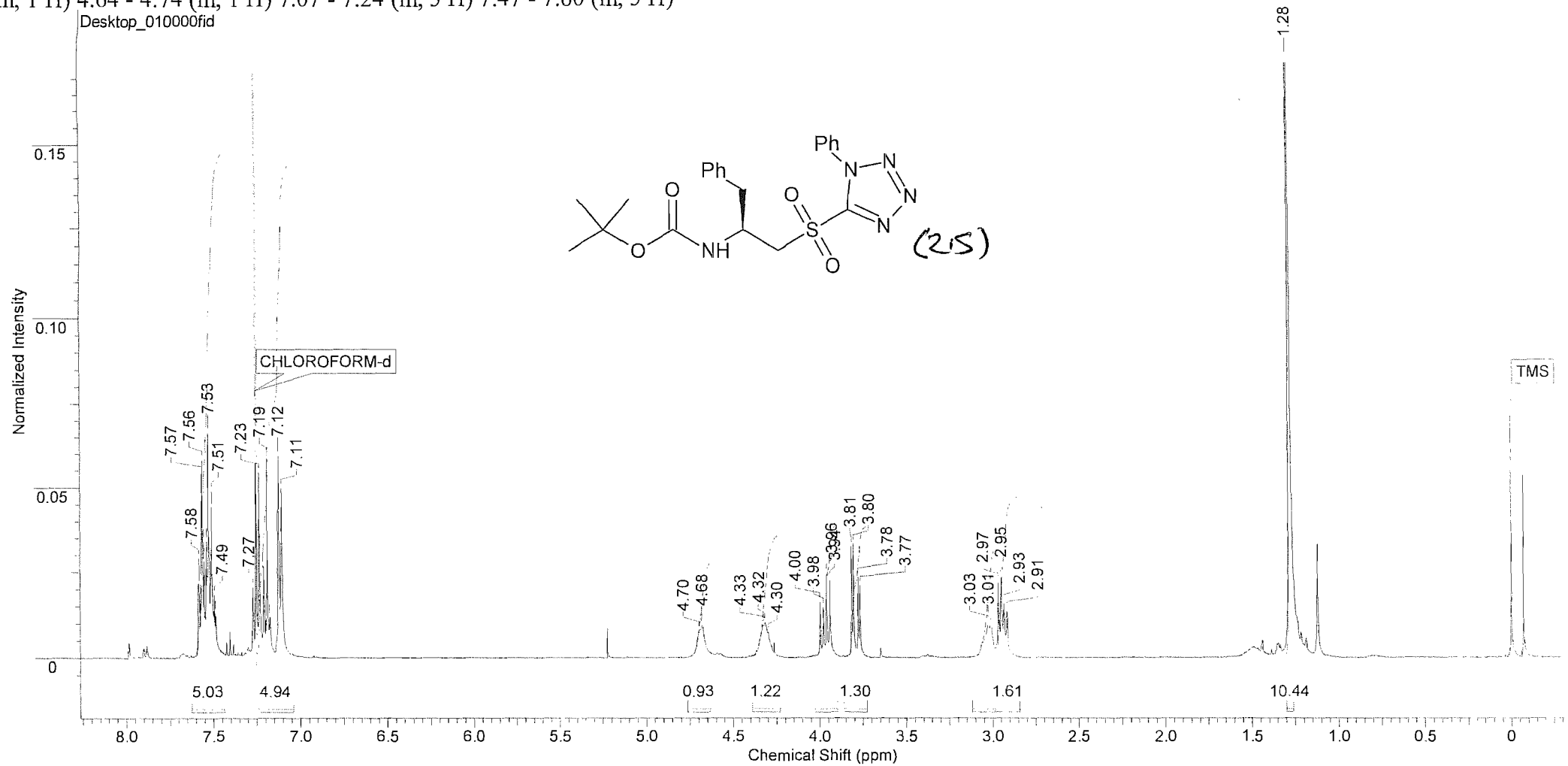
7.6510
7.5945
7.5920
7.5820
7.5782
7.3198
7.3023
7.2847
7.2684
7.2584
7.2546
7.2458
7.2395
7.2333
7.2220
7.1969
7.1793
4.9615
4.9439
4.3029
3.8551
3.1275
3.1100
2.9983
2.9820
2.9657
2.9481
1.3337
(2,4) Diastereoisomer A.
2928.88
2921.85
2914.83
2908.30
2904.29
2902.78
2899.27
2896.76
2894.25
2889.73
2879.69
2872.66
1985.25
1978.22
1721.73
1542.54
1251.42
1244.39
1199.72
1193.19
1186.67
1179.64
Boc
PL
P2
7.6
7.2
(ppm)
4.95
(ppm)
4.4
(ppm)
3.8
(ppm)
3.2
3.0
(ppm)
Integral
5.0000
5.4261
1.0253
1.0246
2.1274
0.9813
1.4451
8.7528
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)

SR4521-08-F2□


7.5656
7.5606
7.5555
7.5468
7.3260
7.3084
7.2896
7.2608
7.2432
7.1842
7.1667
4.9338
4.9137
4.3630
4.3317
4.1096
4.0908
4.0707
3.4925
3.4636
3.4348
2.9781
2.9618
1.1743
3027.22
3025.21
3023.20
3019.69
2924.32
2916.79
2905.25
2898.22
2874.63
2867.60
1974.16
1966.13
1745.78
1733.23
1644.39
1636.86
1628.83
1397.44
1385.89
1374.35
1191.64
1185.12
7.6
(ppm)
7.2
(ppm)
4.90
(ppm)
4.35
(ppm)
(ppm)
(ppm)
(ppm)
(2,4) Diastereoisomer B
Integral
1.6203
2.7044
5.0000
0.9772
0.8694
0.9323
0.8702
2.0526
9.1491
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

SR4521-08

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.28 (s, 9 H) 2.94 (dd, 1 H) 2.99 - 3.08 (m, 1 H) 3.79 (dd, *J*=15.06, 4.52 Hz, 1 H) 3.97 (dd, 1 H) 4.23 - 4.38 (m, 1 H) 4.64 - 4.74 (m, 1 H) 7.07 - 7.24 (m, 5 H) 7.47 - 7.60 (m, 5 H)



(25)

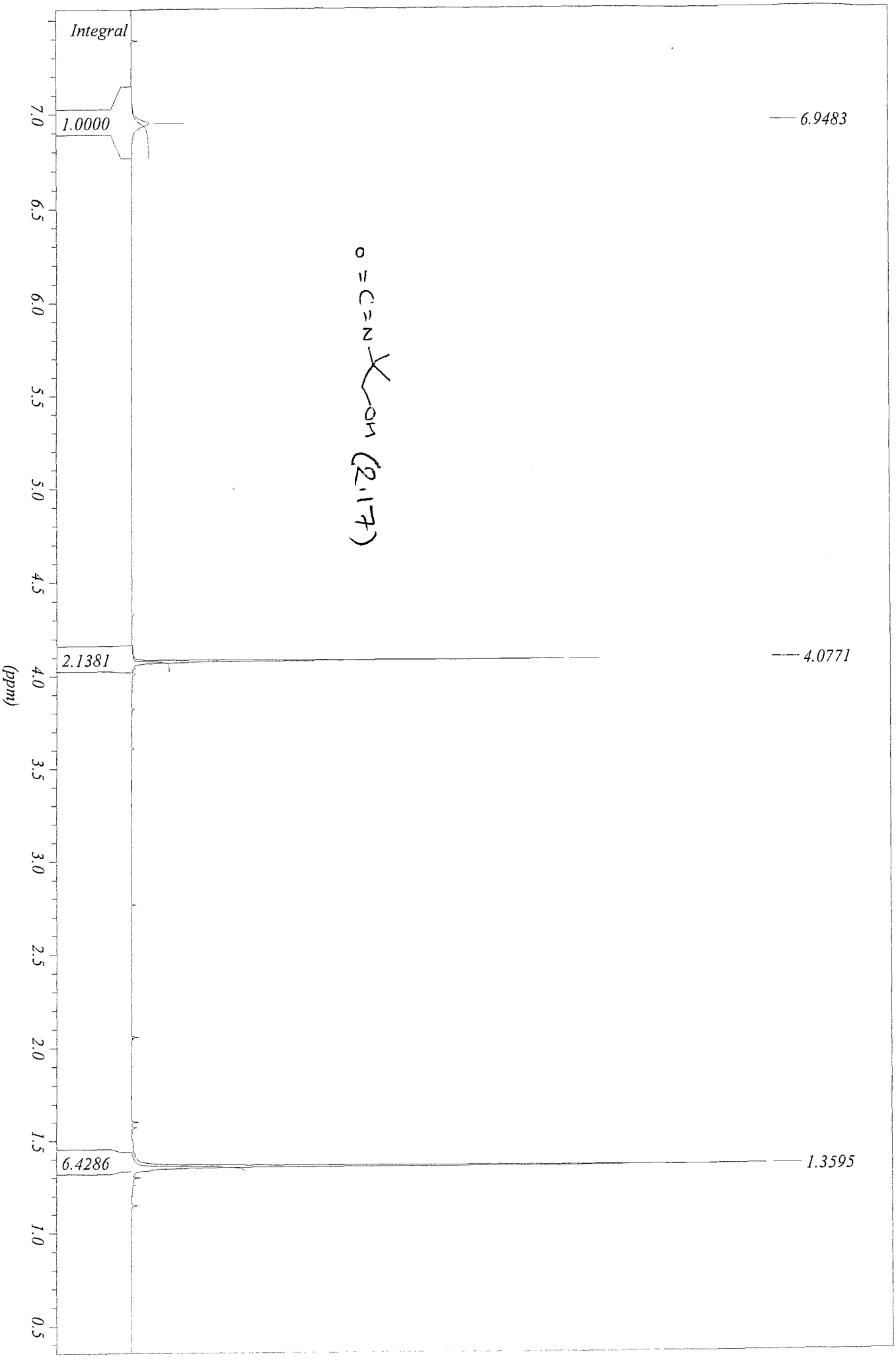
No.	(ppm)	(Hz)	Height
1	1.28	513.5	1.0000
2	2.91	1166.0	0.0138
3	2.93	1173.0	0.0158
4	2.95	1179.5	0.0233
5	2.97	1186.6	0.0219
6	3.01	1204.1	0.0099
7	3.03	1211.2	0.0097
8	3.77	1506.8	0.0210
9	3.78	1511.3	0.0235

No.	(ppm)	(Hz)	Height
10	3.80	1521.9	0.0332
11	3.81	1526.4	0.0325
12	3.94	1576.1	0.0225
13	3.96	1584.1	0.0246
14	3.98	1591.1	0.0148
15	4.00	1599.2	0.0164
16	4.30	1719.6	0.0073
17	4.32	1726.7	0.0103
18	4.33	1730.7	0.0094

No.	(ppm)	(Hz)	Height
19	4.68	1872.2	0.0095
20	4.70	1879.2	0.0080
21	7.11	2843.0	0.0499
22	7.12	2850.0	0.0596
23	7.17	2870.6	0.0120
24	7.19	2875.6	0.0593
25	7.21	2885.1	0.0269
26	7.23	2894.7	0.0544
27	7.27	2909.2	0.0207

No.	(ppm)	(Hz)	Height
28	7.49	2995.0	0.0133
29	7.49	2997.0	0.0184
30	7.51	3003.6	0.0491
31	7.51	3006.1	0.0286
32	7.53	3011.1	0.0664
33	7.54	3015.1	0.0342
34	7.55	3021.6	0.0342
35	7.56	3025.2	0.0584
36	7.57	3027.2	0.0537

No.	(ppm)	(Hz)	Height
37	7.57	3029.7	0.0178
38	7.58	3033.7	0.0291


Integral
1.0000
2.1381
6.4286
6.9483
4.0771
1.3595
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)
O=C=N-X-OH (2,17)

Departmental Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
Contact: Dr Mark E Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.

Identification code	**2006sot1277 (SR4521–99–82)**
Empirical formula	$C_{14}H_{17}N_3O_3$
Formula weight	275.31
Temperature	120(2) K
Wavelength	0.6905 Å
Crystal system	Monoclinic
Space group	*P*21
Unit cell dimensions	a = 6.766(5) Å
	b = 9.745(7) Å β = 98.750(8)°
	c = 10.262(8) Å
Volume	668.7(9) Å^3
Z	2
Density (calculated)	1.367 Mg / m^3
Absorption coefficient	0.098 mm^{-1}
F(000)	292
Crystal	Plate; colourless
Crystal size	0.10 × 0.10 × 0.001 mm^3
θ range for data collection	2.82 – 25.42°
Index ranges	$-8 \le h \le 8$, $-11 \le k \le 12$, $-12 \le l \le 12$
Reflections collected	4278
Independent reflections	1414 [R_{int} = 0.0706]
Completeness to θ = 25.42°	98.6 %
Absorption correction	None
Max. and min. transmission	0.9999 and 0.9903
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1414 / 1 / 186
Goodness-of-fit on F^2	0.846
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0471, $wR2$ = 0.1214
R indices (all data)	$R1$ = 0.0636, $wR2$ = 0.1401
Largest diff. peak and hole	0.198 and –0.245 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except the NH which was freely refined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	−365(5)	11727(4)	2841(4)	30(1)	1
C2	−2413(6)	10999(4)	2658(4)	33(1)	1
C3	−1919(5)	9475(4)	2958(4)	31(1)	1
C4	−209(5)	9582(4)	4111(4)	27(1)	1
C5	1250(5)	8386(4)	4289(4)	26(1)	1
C6	2567(5)	11209(4)	4555(4)	27(1)	1
C7	5064(5)	10330(4)	6449(4)	29(1)	1
C8	4528(5)	9788(4)	7733(4)	29(1)	1
C9	5774(5)	8863(4)	8492(4)	32(1)	1
C10	5345(6)	8438(4)	9725(4)	37(1)	1
C11	3672(6)	8945(5)	10186(4)	36(1)	1
C12	2380(5)	9839(4)	9414(4)	30(1)	1
C13	2793(5)	10282(4)	8190(4)	30(1)	1
C14	−557(6)	11245(5)	9243(5)	41(1)	1
N1	894(4)	10805(3)	3767(3)	28(1)	1
N2	3439(4)	10154(3)	5339(3)	30(1)	1
N3	3064(4)	8775(3)	4953(3)	28(1)	1
O1	3260(4)	12391(3)	4617(3)	33(1)	1
O2	899(4)	7218(3)	3887(3)	33(1)	1
O3	721(4)	10238(3)	9952(3)	41(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–N1	1.480(5)	C7–N2	1.468(5)
C1–C2	1.543(5)	C7–C8	1.514(6)
C2–C3	1.543(5)	C8–C9	1.389(5)
C3–C4	1.528(5)	C8–C13	1.413(5)
C4–N1	1.477(5)	C9–C10	1.402(6)
C4–C5	1.520(5)	C10–C11	1.383(6)
C5–O2	1.221(5)	C11–C12	1.393(6)
C5–N3	1.364(5)	C12–O3	1.380(5)
C6–O1	1.241(5)	C12–C13	1.397(6)
C6–N1	1.346(5)	C14–O3	1.432(5)
C6–N2	1.382(5)	N2–N3	1.413(5)
N1–C1–C2	102.6(3)	C8–C9–C10	120.4(4)
C1–C2–C3	104.8(3)	C11–C10–C9	119.7(4)
C4–C3–C2	101.8(3)	C10–C11–C12	120.3(4)
N1–C4–C5	107.8(3)	O3–C12–C11	115.3(3)
N1–C4–C3	102.7(3)	O3–C12–C13	124.0(3)
C5–C4–C3	116.2(3)	C11–C12–C13	120.7(3)
O2–C5–N3	122.8(3)	C12–C13–C8	118.9(3)
O2–C5–C4	125.8(3)	C6–N1–C4	120.1(3)
N3–C5–C4	111.4(3)	C6–N1–C1	123.8(3)
O1–C6–N1	125.4(4)	C4–N1–C1	112.4(3)
O1–C6–N2	122.4(3)	C6–N2–N3	120.1(3)
N1–C6–N2	112.2(3)	C6–N2–C7	124.6(3)
N2–C7–C8	112.6(3)	N3–N2–C7	114.2(3)
C9–C8–C13	119.9(4)	C5–N3–N2	120.9(3)
C9–C8–C7	120.6(3)	C12–O3–C14	117.1(3)
C13–C8–C7	119.4(3)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	23(2)	28(2)	38(2)	4(2)	2(1)	1(2)
C2	24(2)	28(2)	45(2)	−1(2)	4(2)	2(2)
C3	22(2)	26(2)	46(2)	3(2)	2(2)	−2(1)
C4	17(2)	23(2)	42(2)	0(2)	5(1)	−2(1)
C5	19(2)	23(2)	37(2)	3(2)	7(1)	0(1)
C6	18(2)	27(2)	37(2)	−3(2)	6(1)	−2(1)
C7	15(2)	29(2)	42(2)	0(2)	1(1)	−2(1)
C8	24(2)	24(2)	38(2)	−2(2)	−1(2)	−4(2)
C9	25(2)	25(2)	45(2)	−1(2)	1(2)	0(2)
C10	35(2)	26(2)	46(2)	6(2)	−5(2)	2(2)
C11	38(2)	28(2)	40(2)	4(2)	4(2)	−4(2)
C12	26(2)	27(2)	37(2)	−2(2)	4(2)	−3(2)
C13	24(2)	23(2)	40(2)	0(2)	−2(1)	−1(1)
C14	24(2)	47(2)	52(2)	0(2)	8(2)	3(2)
N1	22(2)	24(2)	40(2)	2(1)	7(1)	−1(1)
N2	20(1)	24(2)	44(2)	−2(1)	−1(1)	−2(1)
N3	21(1)	23(2)	39(2)	0(1)	2(1)	0(1)
O1	25(1)	24(1)	49(2)	0(1)	5(1)	−2(1)
O2	25(1)	24(2)	50(2)	−4(1)	5(1)	−2(1)
O3	38(2)	43(2)	45(2)	4(1)	12(1)	8(1)

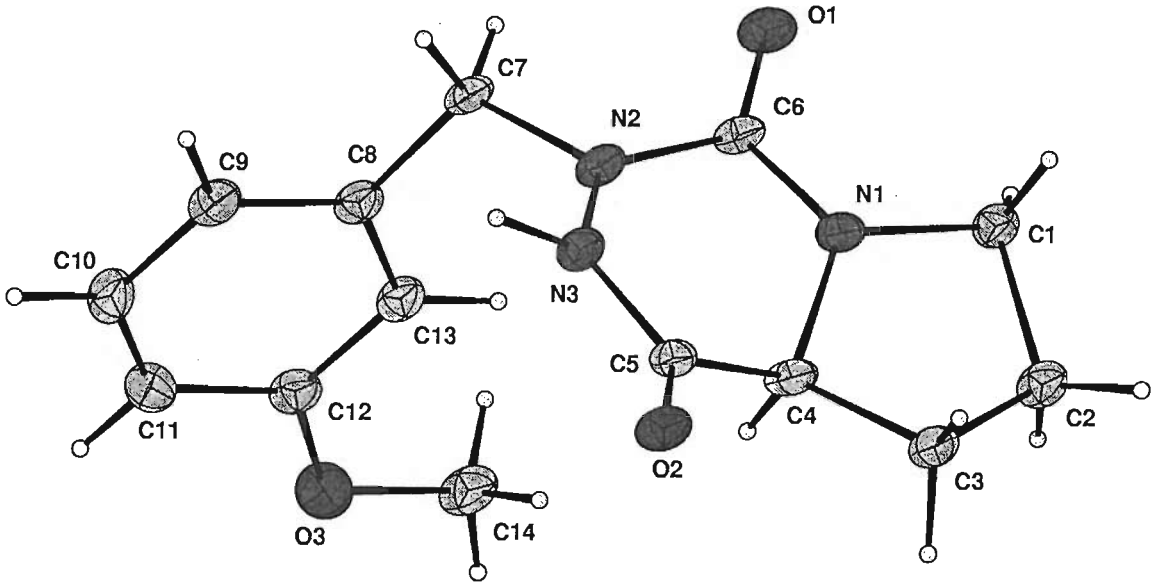
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	158	11805	1994	36	1
H1B	−450	12654	3223	36	1
H2A	−3113	11114	1745	39	1
H2B	−3268	11372	3276	39	1
H3A	−3079	8980	3214	38	1
H3B	−1485	9008	2192	38	1
H4	−757	9749	4949	33	1
H7A	5396	11317	6551	35	1
H7B	6269	9844	6250	35	1
H9	6923	8517	8175	39	1
H10	6200	7805	10240	44	1
H11	3404	8683	11034	43	1
H13	1922	10904	7672	36	1
H14A	163	12117	9241	61	1
H14B	−1746	11372	9669	61	1
H14C	−963	10935	8333	61	1
H99	4230(80)	8190(60)	5200(50)	53(15)	1

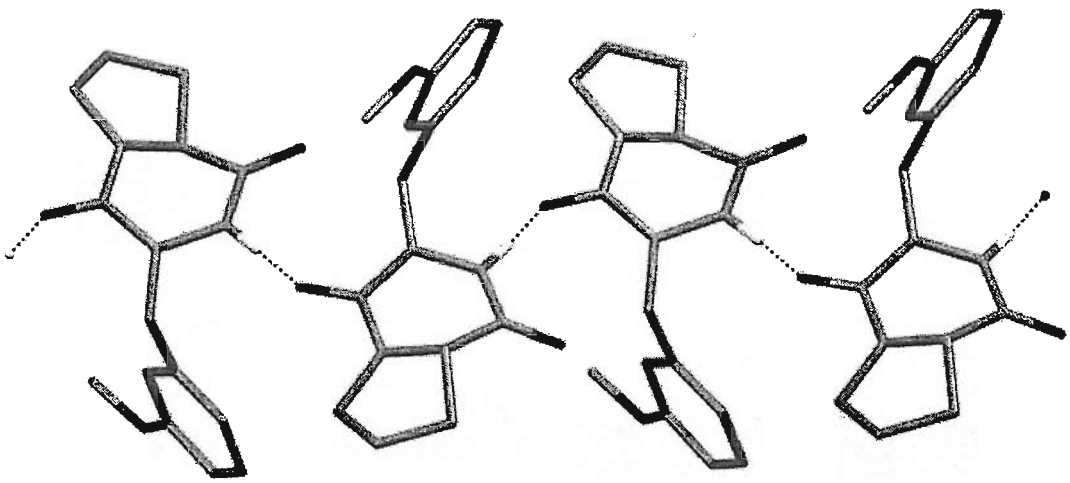
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
N3–H99···O1^{i}	0.98(5)	1.85(5)	2.805(4)	165(5)

Symmetry transformations used to generate equivalent atoms:
(i) −x+1,y−1/2,−z+1



Thermal ellipsoids drawn at the 35% probability level



Hydrogen bonded chains extend along the b axis