Direct Synthesis of Activated Sulfonate Esters and Their Application in Organic Transformations Directed to the Synthesis of Anti-Diabetes type II Peptide-Conjugates

A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of
Doctor of Philosophy in
Chemistry

by

Nani Babu Palakurthy

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Indian Institute of Technology Guwahati

Guwahati-781039

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Dedicated

To

My Grand-Mother

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Dr. Bhubaneswar Mandal

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigations.

Guwahati — Nani Babu Palakurthy

April 2013

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Nani Babu Palakurthy has been working under my supervision since January 2009. I am forwarding his thesis entitled "*Direct Synthesis of Activated Sulfonate Esters and Their Application in Organic Transformations Directed to the Synthesis of Anti-Diabetes type II Peptide-Conjugates*" to be submitted for the Ph.D. degree. I certify that he has fulfilled all the requirements according to the rules of this institute and the investigations embodied in his thesis have not been submitted elsewhere for a degree.

Guwahati
April 2013

Dr. Bhubaneswar Mandal
Supervisor

ACKNOWLEDGEMENT

First and foremost, with a deepest sense of gratitude, I would like to express my sincere thanks to my supervisor, Dr. Bhubaneswar Mandal, who has been a constant source of inspiration for me. His timely help during the crucial phases of my Ph.D. career has made possible to achieve this target. My special thanks to him for his valuable guidance, encouragement, inspiration, creative and scientific ideas which helped me to enhance my knowledge. I am fortunate enough to have his guidance to cultivate scientific thought. I would mention my heartfelt thanks to him for such a wonderful friendly nature that encouraged us to have many scientific discussions and for teachings of life, for which I remain indebted to him.

I would like to acknowledge my sincere gratitude to all my doctoral committee members, Dr. Biplab Mondal, Prof. P. K. Iyer and Dr. S. S. Ghosh, for their intuitive reviewing of my work, advices, constructive criticism and suggestions. I would like to thank all faculty members of the Department of Chemistry of IIT Guwahati for their invaluable suggestions. I express my sincere gratitude and acknowledgement to IIT Guwahati for all the facilities that were made available to me. I am thankful to Mr. Babulal Das (for Single Crystal XRD) of Department of Chemistry and Mr. Chandan Borgohain of Central Instruments Facility (for NMR, LC-MS) and all the non-teaching staff of the Department of Chemistry for their help during my Ph.D. tenure. I thank all my lab members NKC, TK, AS, AP and a special thanks to Dharm Dev for all the laughs, joyful moments, memorable fighting's, for their invaluable cooperation and suggestions. My co-workers Shubhasmin Rana, Sonali Paikaray, Nitesh Kumar are thanked from the bottom of my heart for their extremely helpful hand in my research. I wish to thank

departmental seniors Dr. Siva Murru, Dr. Chandra Moulali Reddy, Dr. Saitanya bayya, Dr. Subash bhai, Dr. Suri Babu Jammi, Dr. Amardeep bayya, Dr. Ramesh Yella, Dr. Naresh Kasoju, Dr. Presenjit, Pilli Santhi Raju, Rajendra Pamula, Adimulam Ramesh, Soma Sekhar Reddy, Laxmi Narayana for lending their hands of support whenever needed. I also take this opportunity to thank all of my Ph.D. batch mates (December, 08) and the other research scholars@chem and all my IITG friends, who have shared their thoughts and views with me.

I further take this precious opportunity to thank Ramana Tamminana for his endless support, friendship, joyful moments, for being my rest upon and finally for proof reading this thesis. My best friends Narasimha Rao Gumma, Sri Ram Murthy, Nageswara Rao Siriginidi, Prakash Nallamlli, Goli Narendra, Sandeep Kumar for their encouragement, support, endless love and affection which had helped me to be focused and even to accomplish this endeavor. Dr.Sunil Kumar, Vasu Pilla, Sravan Kumar specially thanked for being not only best friends but even for their timely help from their respective industry. My other friends Priyadarshini, Mrs. Rajeswari, Mrs. Chandra Kala and Mrs. Krishna Veni are thanked for their time, friendship and timely help. Finally, my Ph. D. endeavor could not have been completed without the endless love, unending support, tolerance and blessings from my family. My teachers, Puli Ramesh Babu mastaru, Vaka venkateswara Rao mastaru, G. V. R. R. Acharyulu mastaru, K. V. R. Acharyulu mastaru, Radha Krishna mastaru and Prof. N. Surya Prakasa Rao, Prof. Bapuji from which my scientific interest is generated and multiplied with time. Therefore, I wish to thank them for all their valuable teachings and emotional attachments. I wish to express my sincere gratitude to my father and mother, sister (Jyothi), brother (Bhaskar Rao). I am also grateful to my cousins Dr. Naveen

Kumar Gummalla, Sirisha, and Aruna and her family members for their affection, belief, encouragement and deep concern for my career. They all are the main soul and inspiration for each and every step that I achieve in my life.

Last but not the least, my grandmother (Karunamma) to whom this thesis is being dedicated, is highly acknowledged for her enormous amount of love, constant and continuous affection and blessings because of which I actually could have been what I am. My highest sense of gratitude for her remains throughout my life.

Nani Babu Palakurthy

Synopsis

The contents of this thesis are divided into five chapters based on the results of the experimental works performed during the complete course of the research period. The introductory chapter of the thesis presents an overview of the therapeutics available so far to prevent the aggregation of the islet amyloid polypeptide (IAPP or Amylin), which causes *Diabetes type II*. Based on the literature reports, five target molecules were designed from our research group. Since the proposed targets were difficult to accomplish using the normal synthetic strategies that were available in literature, our objectives were modified as described later in this chapter. Chapter 2 describes the direct synthesis of all the existing activated forms of the sulfonic acids so that it would facilitate the sulfonamide synthesis. Chapter 3 deals with the synthesis of sulfonamides from one of the activated esters that we have achieved, which is described in Chapter 2, i.e. *O*-sulfonate ester of *N*-hydroxy benzotriazole. Chapter 4 demonstrates the synthesis of *O*-benzyl hydroxamates of various carboxylic acids using the *O*-sulfonate ester of *N*-hydroxy benzotriazoles as the sulfonate esters known to carry out the condensation chemistry between carboxylic acids and amines to give carboxamides. Chapter 5 is divided into two sub chapters such as Chapter 5a and 5b. In Chapter 5a, we discussed the synthesis of sulfonamides using *O*-sulfonate ester of Oxyma which would tolerate the most acid labile functional groups such as trityl (Trt), *tert* butoxy (tBu), *etc*. In Chapter 5b, the synthesis of the targeted peptide conjugates, which is accomplished with Oxyma ester activation strategy, is described.

Chapter 1. Introduction

This chapter highlights the definition of Amylin, causes and consequences of the aggregation of the islet amyloid polypeptide.

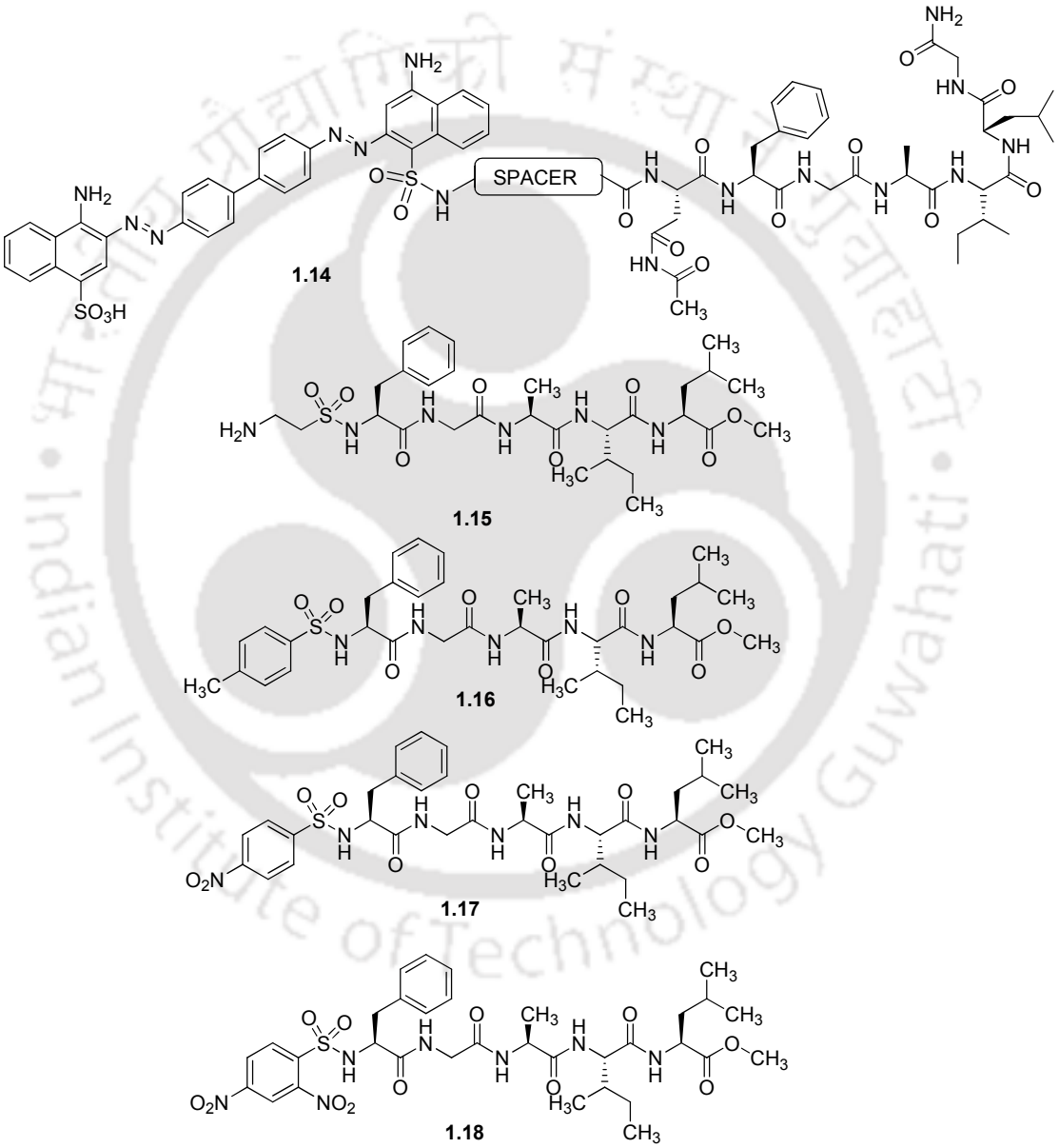
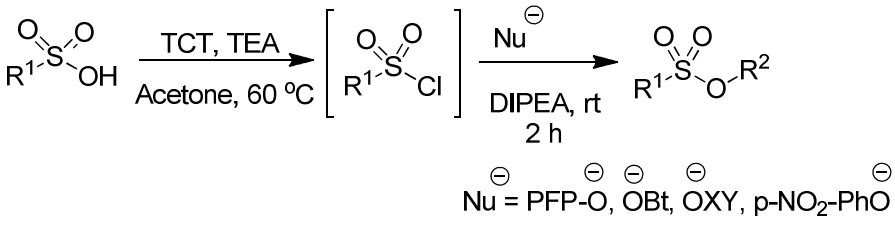


Figure 1

Based on the literature reports, it is believed that the core sequence of Amylin, **NFGAIL**, is responsible for the nucleation process of toxic aggregation that causes the devastating disease, *Diabetes type II*. Therefore, our objectives were set to use the part of this core sequence of the amylin peptide with a slight modification and further to connect with a few small molecules like Congo red, taurine, p-TsOH, 4-nitro benzene sulfonc acid, 2,4-dinitro benzene sulfonic acid, (Figure **1**) *etc*. This objective was further modified into four other objectives as the specified targets are the sulfonamides and all the methods available so far for sulfonamide synthesis were not useful for the synthesis of the target molecules.

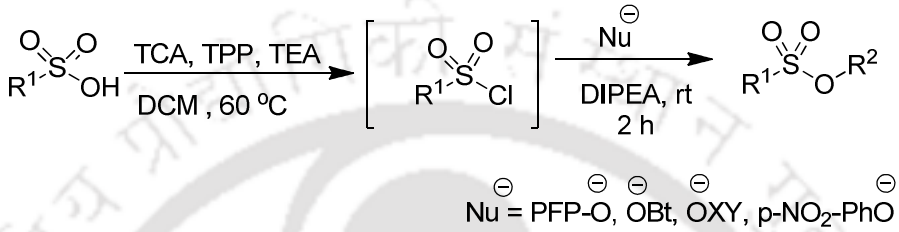
Chapter 2. Direct synthesis of activated sulfonate esters from sulfonic acids

This chapter deals with the synthesis of all the activated sulfonate esters possible to facilitate the synthesis of sulfonamides, so that one of these activation strategies can be adopted for the synthesis of mentioned targets in chapter 1. In this connection, in order to activate the sulfonic acids, our choice of activation was pentafluoro phenol (PFP-OH), para nitro phenol (4-NO_2-C_6H_4-OH i.e. PNP), *N*-hydroxy benzotriazole (HOBt) and Oxyma (HOXY i.e. ethyl 2-cyano-2-(hydroxyimino)acetate). As most of the sulfonate esters can be prepared from the sulfonyl chlorides and many of the sulfonic acids do not have the corresponding sulfonyl chlorides, we decided to make it using 2,4,6-trichloro triazine (TCT) as shown in scheme **1**.



Scheme 1

A variety of substrates underwent this reaction to produce the corresponding sulfonyl chlorides through which the desired activated esters could be achieved in good yields. Furthermore, the same was achieved with trichloro acetonitrile (TCA) and triphenyl phosphine (TPP) in dichloromethane solvent as shown in scheme **2**.

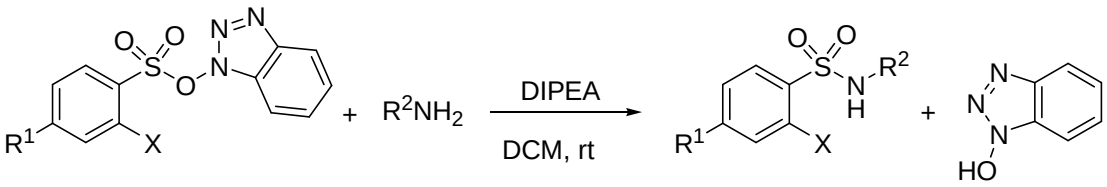


Scheme 2

Chapter 3. Application of *N*-hydroxy benzotriazole esters for sulfonamide synthesis

This chapter demonstrates the use of *O*-sulfonate esters of *N*-hydroxy benzotriazole as the synthetic precursors for the sulfonamides. Previously, it was reported that PFP activation and PNP activation methods are useful for the synthesis of sulfonamides. But all of them needed either longer reaction times, harsh bases and heating conditions. Therefore, keeping the leaving group ability of the HOBt in mind for the nucleophilic attack of the amine, we presumed that this would facilitate the sulfonamide synthesis under ambient and milder conditions. Interestingly, our speculation was practically true and HOBt was found to be better auxiliary than all its counterparts for this transformation. Varieties of amines, e.g. primary, secondary and amino acid esters that include sterically hindered substrates underwent the reaction to furnish the desired sulfonamides in good to excellent yields in presence of DIPEA in dichloromethane solvent as shown in scheme **3**

under ambient and milder conditions. While achieving this, we investigated electronic effects of both sulfonate esters and amines.

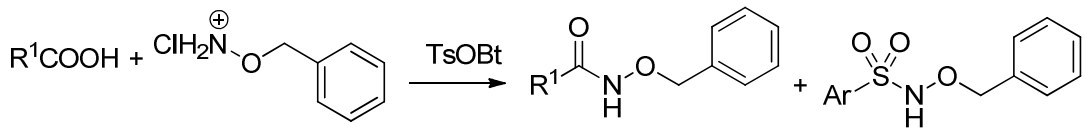


a) $R^1 = CH_3$, X = H
b) $R^1 = NO_2$, X = H
c) R^1 = H, X = NO_2
d) R^1 = H, X = H

Scheme 3

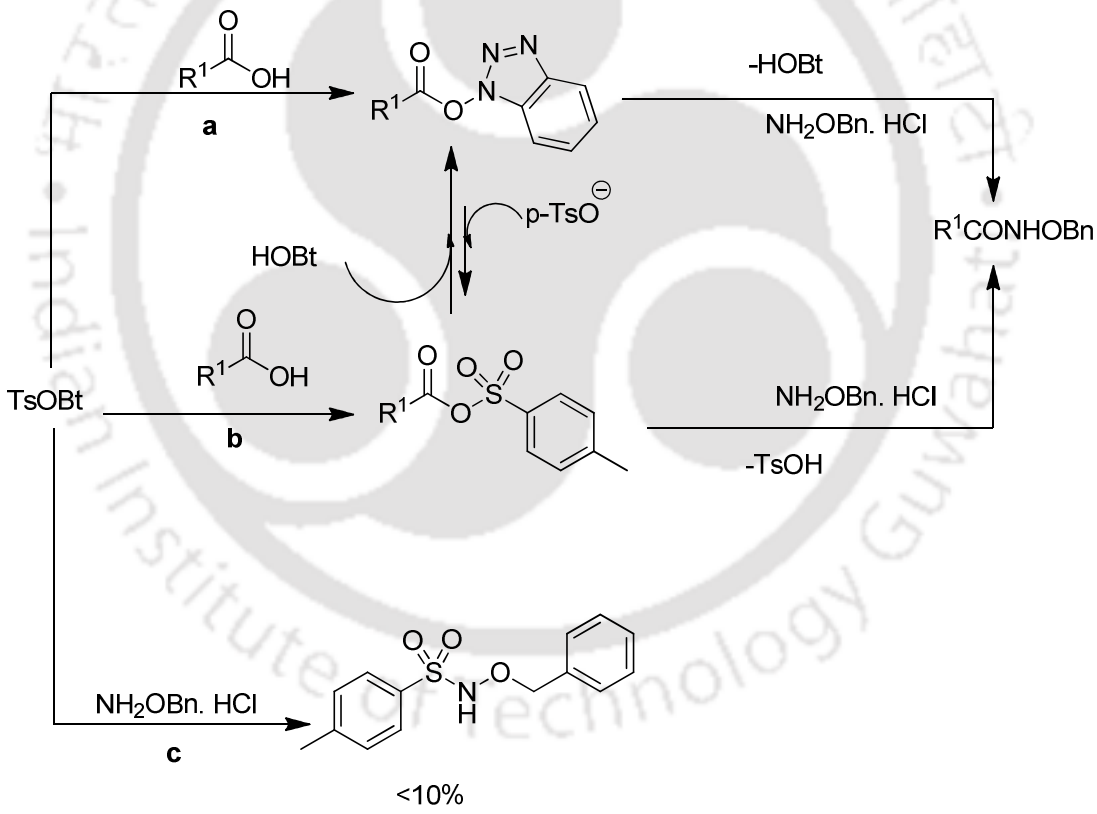
Chapter 4. Application of *O*-sulfonate esters of *N*-hydroxy benzotriazole for the synthesis of *O*-benzyl hydroxamates

This chapter emphasizes the use of *O*-sulfonate esters of *N*-hydroxy benzotriazole as the condensation reagents for the synthesis of *O*-benzyl hydroxamates, an important class of organic compounds that are widely used in medicine. The synthesis of such an important class of compounds was accomplished using the para toluene sulfonic acid ester of *N*-hydroxy benzotriazole (TsOBt), which was found to be the best out of all the sulfonate esters with various substitutions on the benzene ring of the sulfonic acid in acetonitrile solvent along with the DIPEA as base (Scheme **4**). With the optimized conditions, good number of hydroxamtes was synthesized and in none of the cases di- and tri- acylated products were found. In all the cases, the yields were found to be good.



Scheme 4

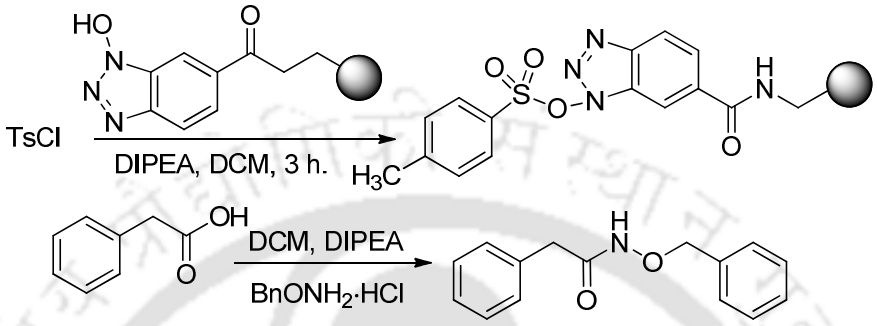
The racemization study was also carried out using the optical rotation and LC-MS. For this, we have synthesized two *C*-terminus free di-peptides with two stereo centers for each using the pentafluoro phenol activation strategy. Synthesis of their respective hydroxamtes employing the present methodology enabled us to know that the present protocol does not cause more than 5% racemization. The ^{1}H-NMR experiments that we carried out to understand the mechanism revealed that HOBt gets released at the end of the reaction as shown in scheme **5**.



Scheme 5

In order to recover and reuse the released HOBt, we employed the solid supported HOBt as shown in scheme **6**. Interestingly, the reaction went to completion within

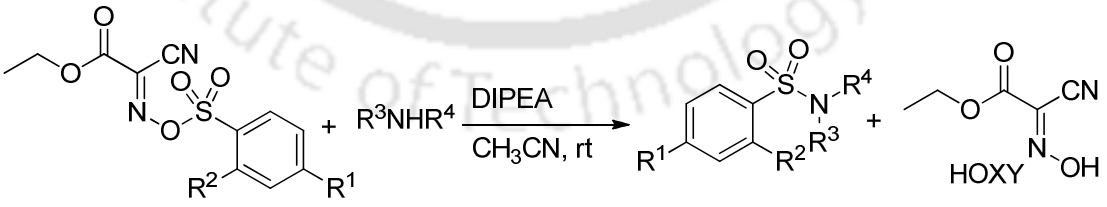
3 h and furnished the desired product in 81% yield. Repeating the same synthesis within the same pot for 6 more cycles did not decrease the yield of the reaction. Therefore, this new solid supported reagent can be used for this transformation for a few more cycles without losing its activity.



Scheme 6

Chapter 5a. Synthesis of sulfonamides using sulfonate esters of Oxyma

This chapter deals with the synthesis of sulfonamides using *O*-sulfonate esters of Oxyma. As HOBt is an explosive on heating, we wanted to find an alternative to it. In this connection, Oxyma was found to be a good candidate for substituting HOBt, since it can tolerate higher temperature and its cost as well as reactivity is similar to that of HOBt.

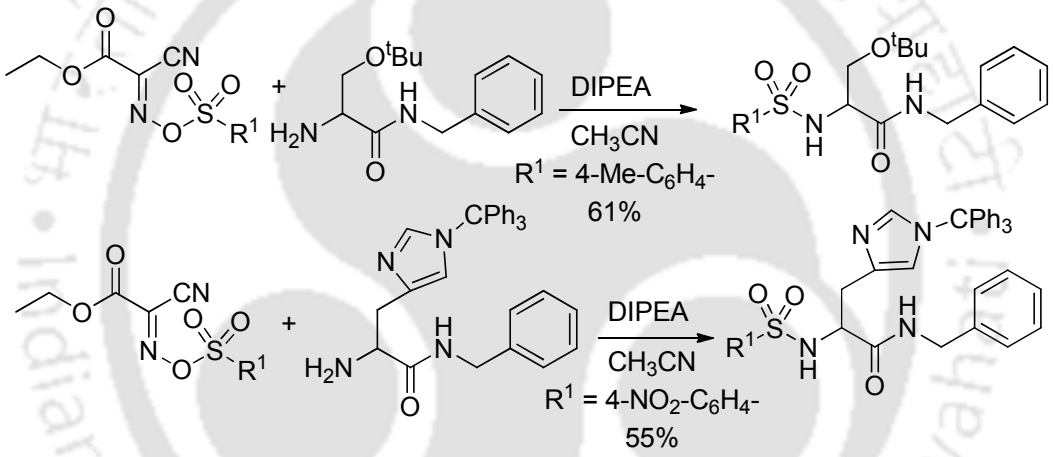


a) $R^1 = H, R^2 = H$
b) $R^1 = CH_3, R^2 = H$
c) $R^1 = NO_2, R^2 = H$
d) $R^1 = H, R^2 = NO_2$
e) $R^1 = NO_2, R^2 = NO_2$

1^o, 2^o amines
Amino acid esters,
Aromatic amine

Scheme 7

Therefore, from *chapter 2*, we further took the activated Oxyma esters of sulfonic acids and envisaged their applicability for sulfonamide synthesis. This strategy is important as it produced the desired product in very good yield when employed the para toluene sulfonate ester of Oxyma and amine in acetonitrile solvent along with DIPEA as shown in scheme **7**. We further proceeded to examine its applicability for varieties of amines that included primary, secondary, sterically hindered amino acid esters. Yields were found to be very good. Interesting part of this chapter is in its applicability for the synthesis of 2,4-dinitrobenzene sulfonamides which make an important class of synthons for variety of functional group transformations.

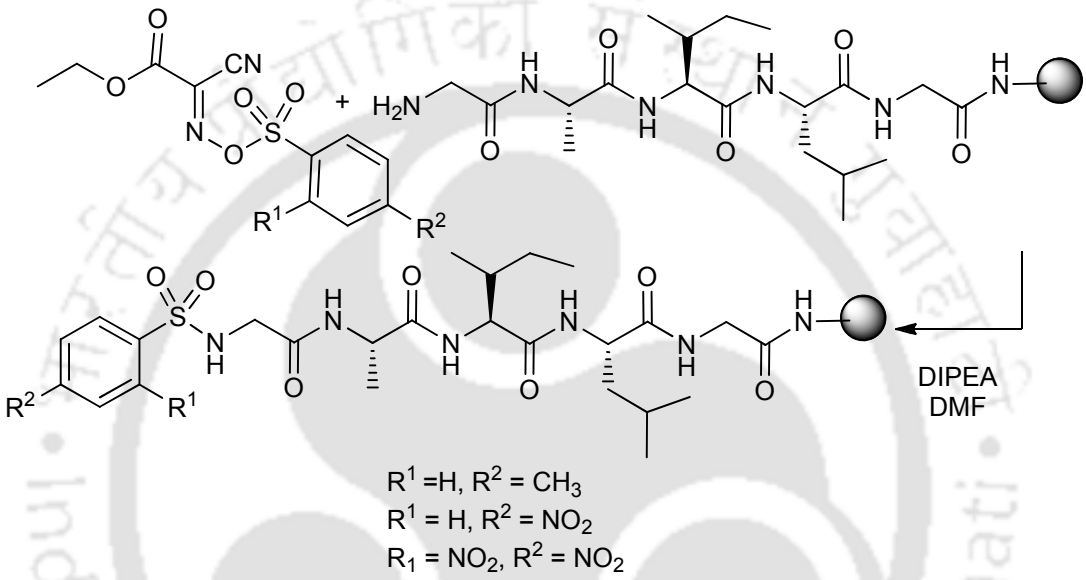


Scheme 8

Having developed the sulfonamide synthesis under ambient and milder condition with the preclusion of HCl production, we investigated the applicability of the present methodology for the synthesis of those substrates that posses the acid labile functional groups such as trityl (Trt) and tertiary butyl (tBu) as shown in scheme **8**. No significant cleavage of any of the protecting groups was noticed.

Chapter 5b. Synthesis of the designed peptide conjugates for inhibition of Amylin aggregation

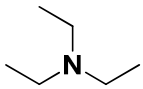
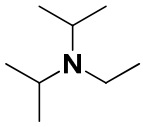
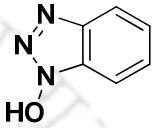
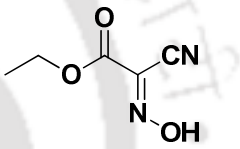
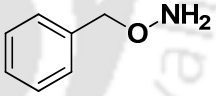
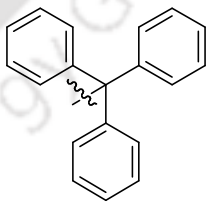
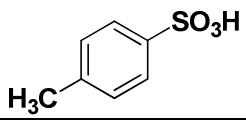
In this chapter, we discussed the synthesis of the target peptides that were specified in *chapter 1* as our premier objectives adopting the previously developed Oxyma activation strategy as shown in scheme **9**. All the peptides were purified using the semi preparative HPLC and characterized with LC-MS. A few of the mentioned targets were synthesized and their activity against amyloid aggregation will be examined by one of my successors from this laboratory.

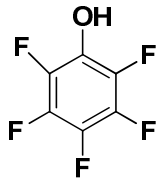
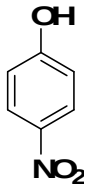
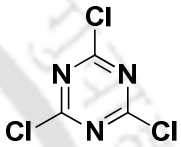
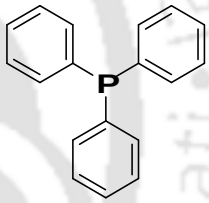
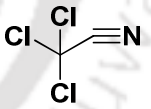
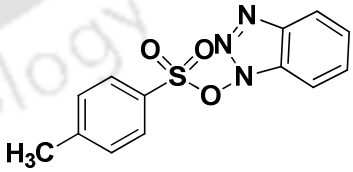
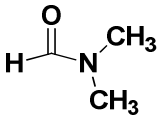


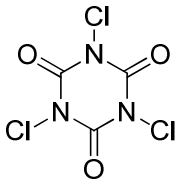
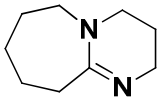
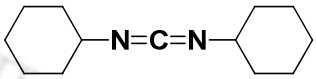
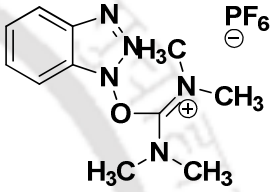
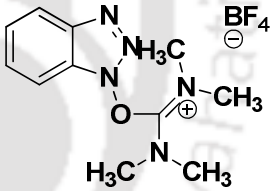
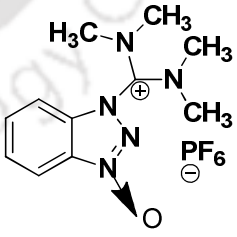
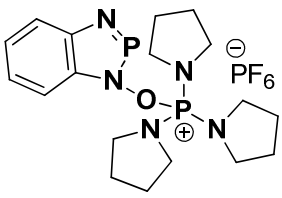
Scheme 9

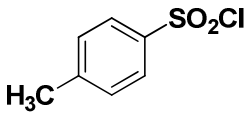
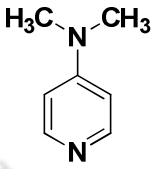
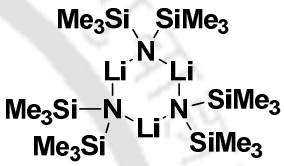
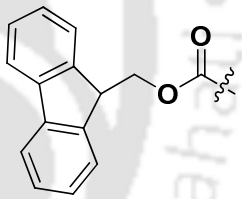
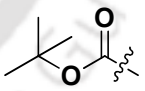
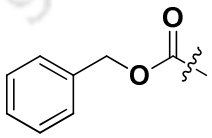
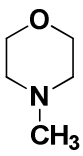
It can be concluded that, we could finally achieve the synthesis of some of the desired peptide-small molecule conjugates, which are important for the drug design against *Diabetes type II*. To achieve that, we had to develop quite a few new synthetic methodologies, without which the synthesis of the mentioned peptide conjugates would not be possible. In the course of this work, we developed reagents that have application in other organic transformations as well.

List of abbreviations

Entry	Abbreviation	Full name	Chemical structure
1	TEA	Triethylamine	
2	DIPEA	di-isopropylamine	
3	HOBt	*N*-hydroxy benzotriazole	
4	HOXY	ethyl 2-cyano-2-(hydroxyimino)acetate	
5	NH_2OBn	*O*-benzyl hydroxylamine	
6	Trt	Trityl	
7	^{t}Bu	Tertiary butyl	
8	p-TsOH	para-Toulene sulfonic acid	

9	PFP-OH	Pentafluorophenol	
10	*P*-NP	para nitrophenol	
11	TCT	Trichlorotriazine	
12	TPP	Triphenyl phosphine	
13	TCA	Trichlro acetonitrile	
13	TsOBt	Toluene-4-sulfonic acid benzotriazol-1-yl ester	
14	DMF	N, N-dimethyl formaamide	
15	TCCA	Trichlo roisocyanuric acid	

			
16	DBU	1,8-Diazabicycloundec-7-ene	
17	DCC	N, N- Dicyclohexyl carbodiimide	
18	HBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate, *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate	
19	TBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate	
20	HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate	
21	PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate	

22	TsCl	4-Methyl-benzenesulfonyl chloride	
23	DMAP	4-Dimethylaminopyridine	
24	LiHMDS	Lithium HexaMethylDiSilazide	
25	Fmoc	9-fluoromethoxy- carbonyl	
26	Boc	tertiary-butoxycarbonyl	
27	Cbz/Z	Benzyloxy carbonyl	
28	NMM	*N*-Methylmorpholine	

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Chapter 1. Introduction

1.1 What is "Amylin"?

The term "amyloid diseases" is used to describe human diseases in which the formation of protein aggregates due to misfolding is in the center of progression of the disease. In this regard, *Diabetes Type II* is one of the most common amyloid diseases worldwide, which generally affects the elderly persons. This disease is the result of aggregation of islet amyloid polypeptide (IAPP, also known as Amylin) which is a 37 residue peptide and is shown in figure **1.1**. It has a disulfide bridge between **2** and **7** cysteine moieties. The sequence "**NFGAIL**", the hydrophobic part of amylin, from residues **22** to **27,** is called the core sequence of the peptide and is believed to be responsible for the initiation of aggregation. Although the aggregation mechanism is still not clearly understood, few reasons, such as, hydrogen bonding, π-π interactions, *etc.* are attributed to the nucleation process, thereby, causing the formation of the toxic fibrils. Aggregation of human islet amyloid polypeptide (IAPP) generates pancreatic amyloid, which is strongly associated with the pathogenesis of *Diabetes type II*. Since no therapy is available for this disease till date, many researchers are involved in this area of research. They are trying to understand the aggregation dynamics and discover a therapy for this disease. As a result of their constant effort to understand the aggregation process, new targets were identified. However, the ideal drug candidate should be water-soluble, non-amyloidogenic, non-cytotoxic and should ideally exhibit IAPP agonistic activity. Simultaneously that should be able to bind IAPP and inhibit its cytotoxic amyloidogenesis process.

Figure 1.1 The primary structure of IAPP

1.2 Literature review for prevention of aggregation of amylin:

A thorough review of the literature revealed that small molecules such as Congo red[1] (**1.1**), nicotine (**1.2**), curcumin (**1.3**), caffeine (**1.4**), taurine (**1.5**) *etc.* are active against the diseases.[2] However, they lack specificity.

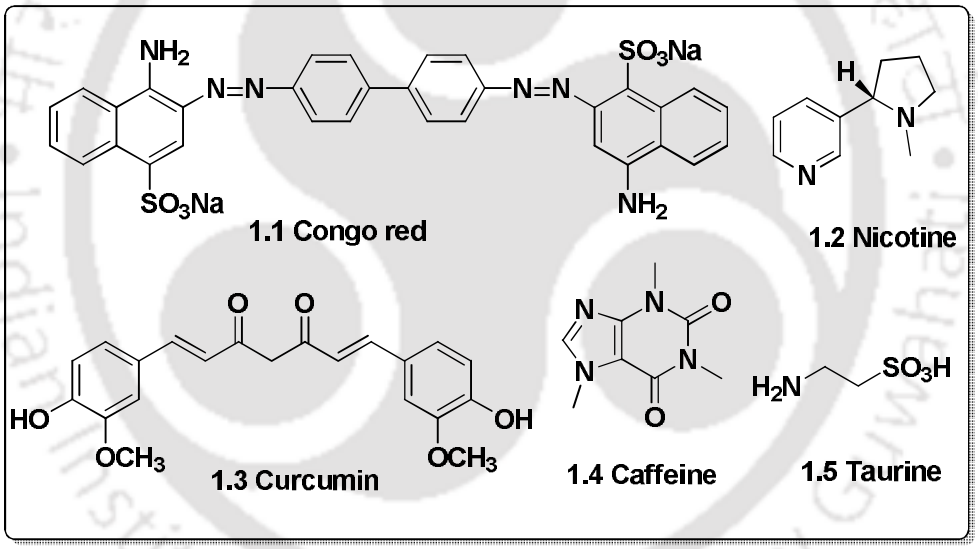


Figure 1.2 Various compounds that have positive disease modifying effect against *Diabetes type II.*

Kapurniotu and co-workers mimicked the original IAPP into a molecular mimic with same 37 residue peptide in which the amino acids at **24** and **26** positions i.e. glycine and iso-leucine are replaced with *N*-methylated glycine and *N*-methylated iso-leucine respectively as it is shown in figure **1.3**. The peptide mimic was able to interact with monomeric IAPP and kinetically

stabilize it against cytotoxic misfolding and self assembly, presumably because of its sequence homology to IAPP. With this mimic, they could demonstrate complete blockage of the aggregation process with low nanomolar activity and reversed IAPP cytotoxic self assembly and fibrillogenesis (Figure **1. 4**).[3]

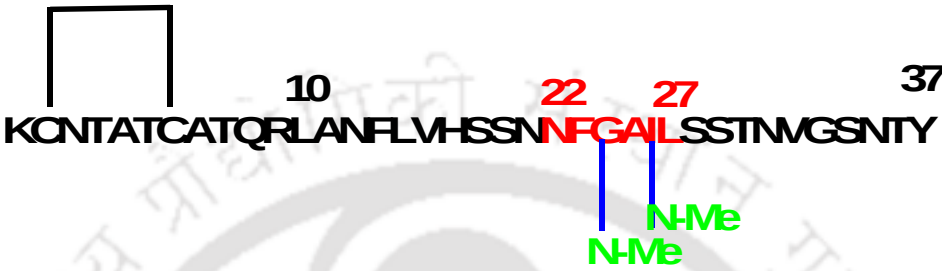


Figure 1.3 *N*-Methylated peptide mimic of Amylin

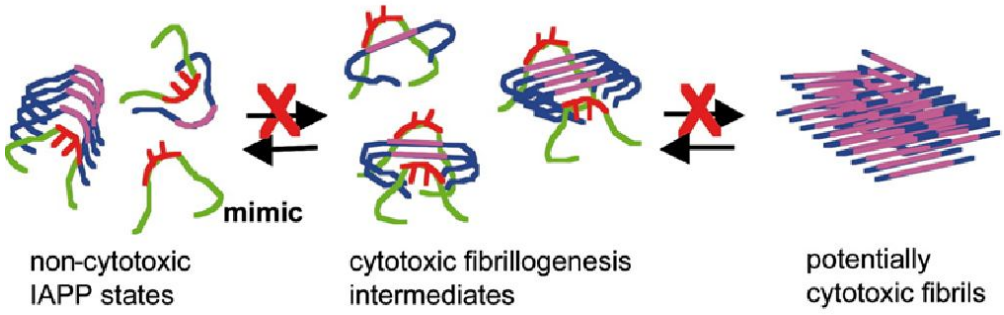


Figure 1.4 Blockage of the process of aggregation of Amylin using the mimicking peptide (courtesy: adopted from Yan, L.; Tataraek-Nossol, M.; Velkova, A.; Kazantzis, A.; Kapurniotu, A. *PNAS.* **2006**, *103*, 2046-2051.)

1.3 Sulfonamides in medicinal chemistry:

1.3.1 Potent therapies for various diseases:

The development of many therapeutic agents has started with sulfanilamide as the lead molecule resulting in the discovery of drugs with a varied spectrum of biological actions. These days, the famous sulfonamides that have extensive marketing are Sildenafil (**1.6**),

Amprenavir (**1.7**), Glibenclamide (**1.8**), Furosemide (**1.9**) *etc*. Sildenafil is used for the treatment of erectile dysfunction whose common name is Viagra®.[4] Amprenavir is a clinically used sulfonamide HIV-1 protease inhibitor. Furosemide is a hypoglycaemic agent.[5] Glibenclamide is used in the treatment of *Diabetes type II* [6] and Furosemide is an effective loop diuretics.[7]

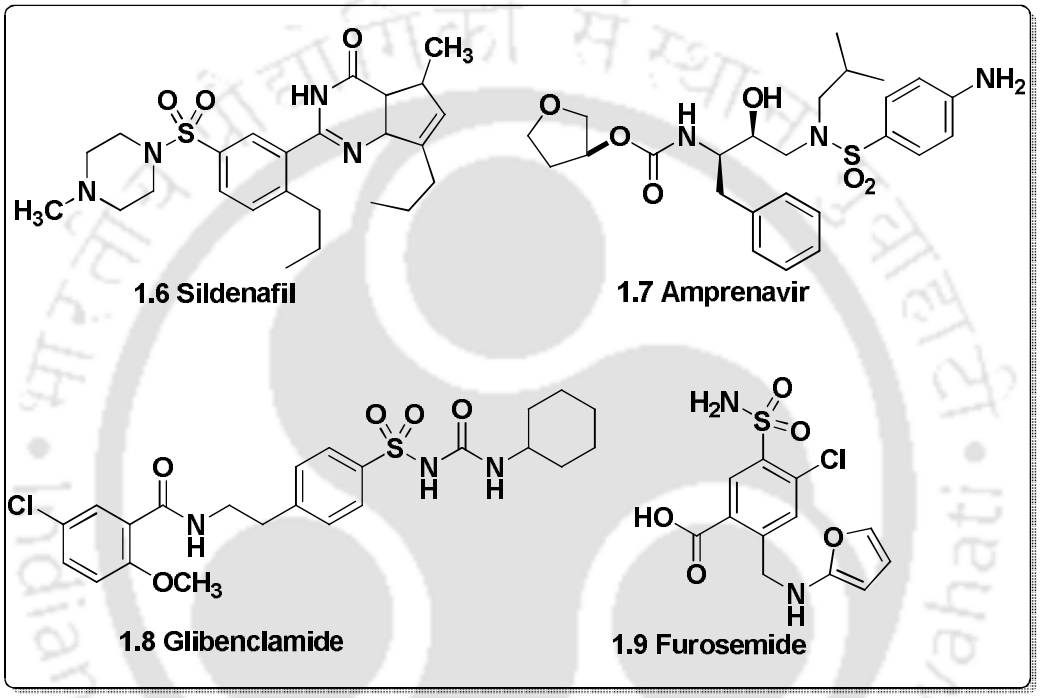


Figure 1.5 Sulfonamides that have wide medicinal usage

1.3.2 Sulfonamides as anti-biotics:

Starting with the first recognized sulfonamide antibacterial, sulfanilamide, was initially employed in 1935. Although sulfonamides were restricted as antibacterial in modern therapy, it is worth highlighting that some of the sulfonamide antibiotics are still in clinical use. Now a day's sulfonamide antibiotics are often used in combination with other drugs, for example, sulfamethoxazole (**1.10**) and trimethoprim are being used together in the treatment of urinary tract infections, acting synergistically to block sequential steps in bacterial folic acid

metabolism. Sulfathiazole (**1.11**) is being used in combination with sulfacetamide and sulfabenzamide in the treatment of bacterial infections.

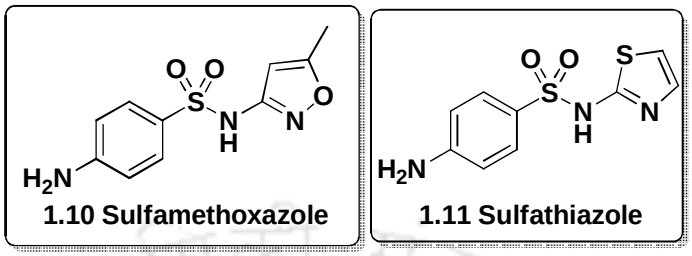


Figure 1.6 Sulfonamides as antibiotics

1.3.3 Sulfonamides and protease inhibitors:

Cysteine proteases are large group of enzymes that are involved in many physiological processes including osteoporosis, Alzheimer's disease and arthritis.[8] They are connected with a huge range of pathological conditions and their inhibition could potentially be an effective chemotherapy in these cases.

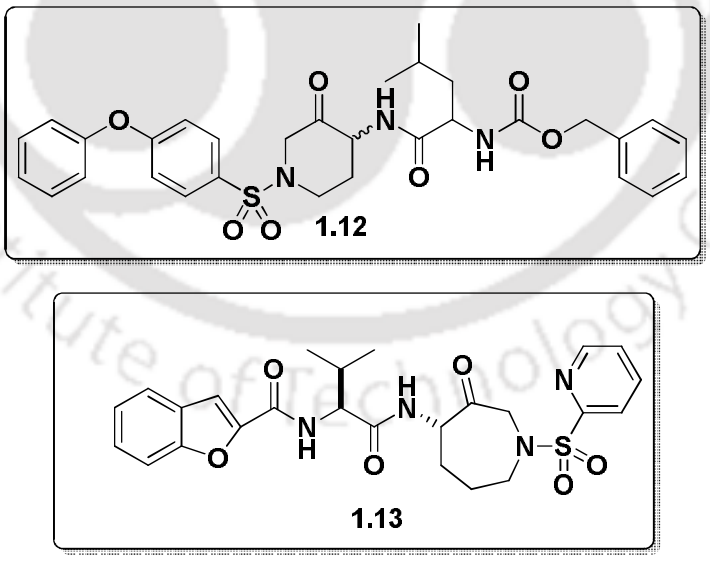
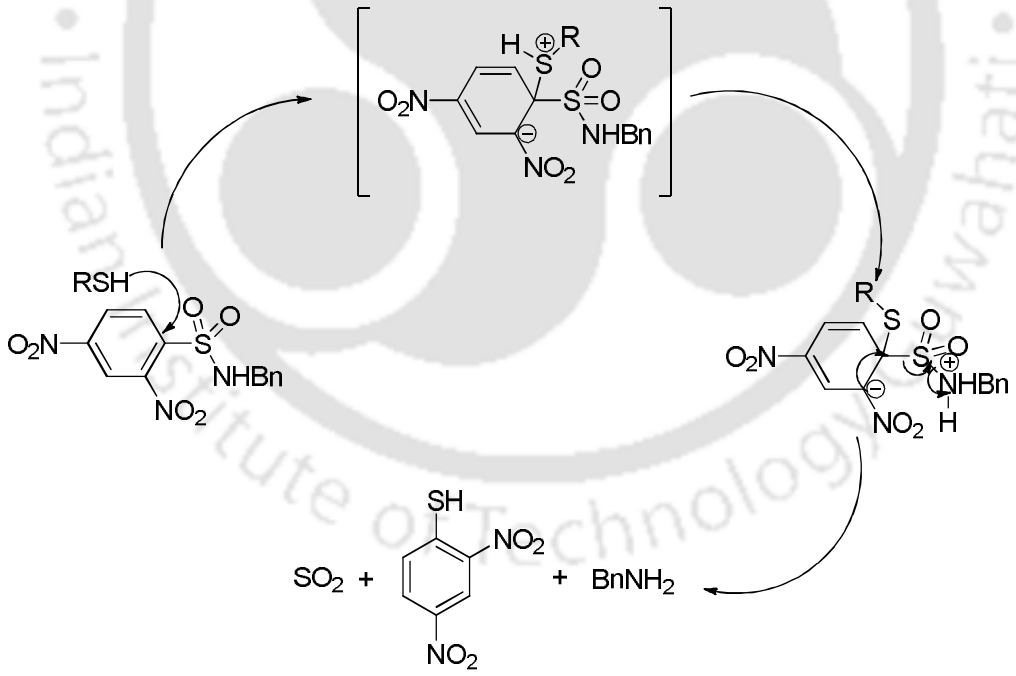


Figure 1.7 Protease inhibitors.

Sulfonamide **1.12** was developed as a subnanomolar peptidomimetic inhibitor with the sulfonamide moiety being incorporated in order to remove the structural liabilities associated with an amide. Veber *et al.* identified sulfonamide **1.13** as a potent reversible inhibitor of both human and rat cathepsin K (Ki = 0.16 nM) which displays good oral bioavailability in rat.[8c]

1.3.4 Other potential uses of sulfonamides in medicinal chemistry:

Tuberculosis affects millions of people each year and co-infection with HIV is an emerging threat. The first line of defense against tuberculosis, a combination of isoniazid with other antibiotics, is becoming ineffective against multi drug-resistant and extensively drug-resistant strains of Mycobacterium tuberculosis (Mtb). Sulfur dioxide (SO_2) is an environmental pollutant like NO and is toxic at elevated concentrations.



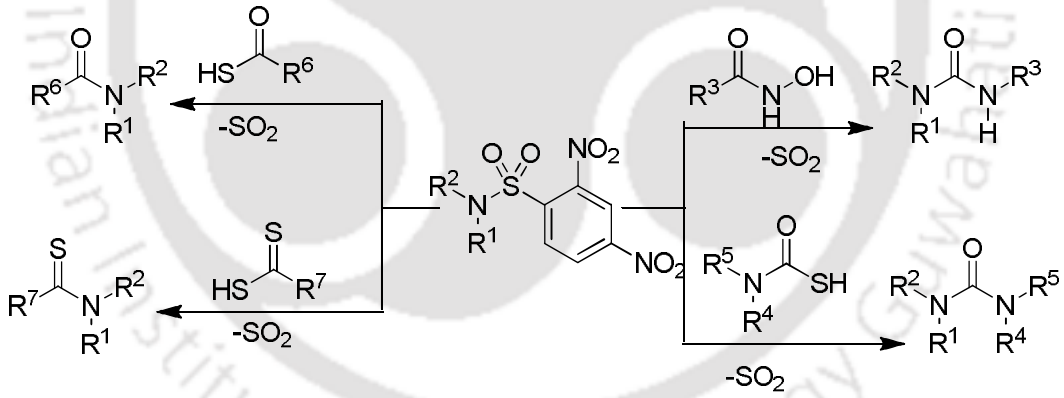
Scheme 1.1

Although mechanisms of its cytotoxicity are yet unclear, SO_2 at elevated concentrations is known to induce oxidative damage to biomacromolecules such as proteins, lipids and DNA.

However, despite its well-documented cytotoxic effects, SO_2 has been routinely used as an antibiotic and antioxidant in wine-making. Barring certain individual cases of allergies, sulfur dioxide is well-tolerated in humans. Thus, it was envisaged that the susceptibility of bacteria to the deleterious effects of SO_2 could be exploited to develop new SO_2-based tuberculosis drug candidates. To tap its therapeutic potential and possibly avoid undesirable side effects, controlled delivery of SO_2 is necessary. In this connection, Konkimalla *et al.* developed a methodology to unleash the SO_2 *in vivo* in a controlled manner from 2,4-dinitrobenzene sulfonamides and could have successfully demonstrated the use as a potential therapy for tuberculosis (Scheme **1.1**).[9]

1.4 Sulfonamides as synthons in organic chemistry:

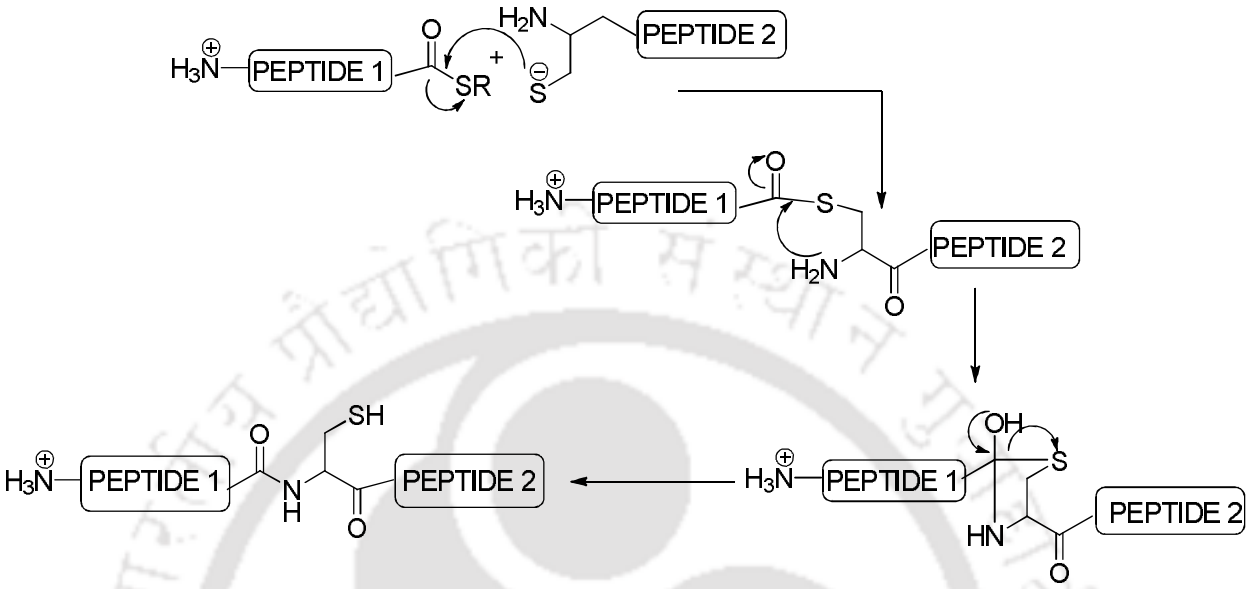
1.4.1 2,4-Dinitrobenzene sulfonamides as the synthons:



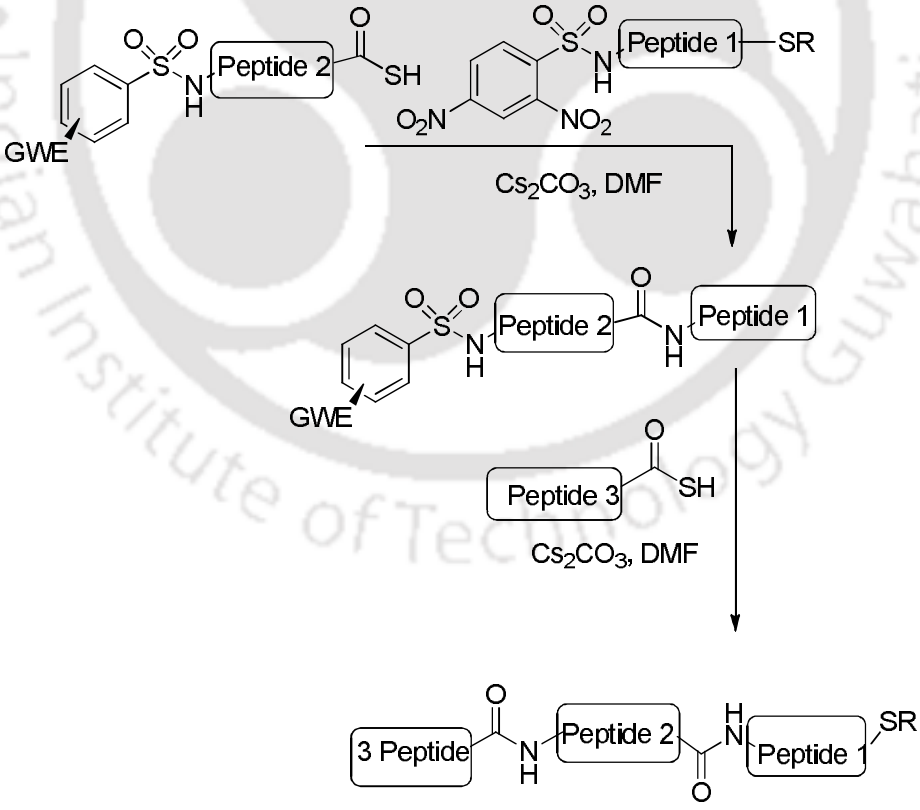
Scheme 1.2

2,4-dinitrobenzene sulfonamides are extensively developed for the synthesis of various functionalities such as ureas, thio-ureas, amides and thio-amides by the elimination of sulfur dioxide (SO_2) as shown in scheme **1.2** by Tomkinson *et al.* which opened an important way for the synthesis of longer peptides and glycopeptides. More on this will be discussed in the subsequent section.[10]

1.4.2 2,4-Dinitro benzene sulfonamides as synthons for Native Chemoselective Ligation (NCL):



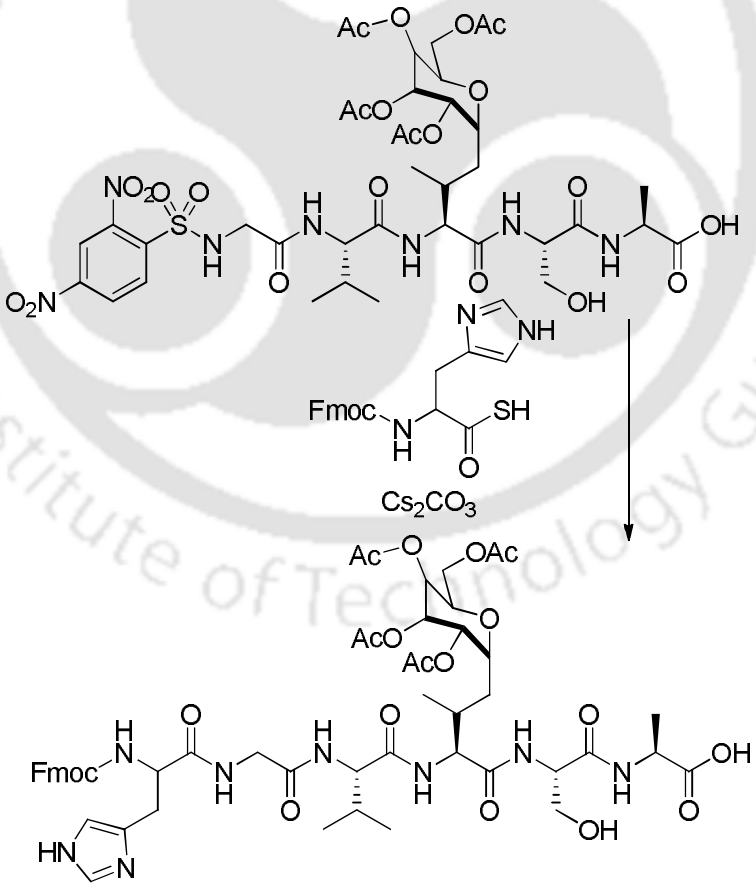
Scheme 1.3



Scheme 1.4

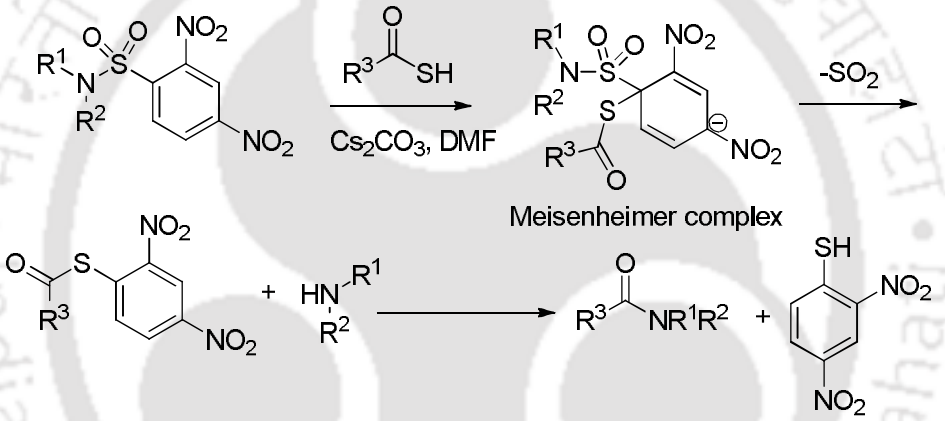
Following the mentioned report by Tomkinson, Crich *et al.* extended the same strategy for the synthesis of longer peptides as the advanced Native Chemoselective Ligation (NCL). NCL is a strategy that was introduced by Stephen Kent[11] and further advanced by Danishefsky in which longer peptides could be synthesized by the reaction of *C*-terminus thio-ester of one peptide with another peptide bearing cysteine at the *N*-terminus (Scheme **1.3**).[12]

In order to develop an alternative for the synthesis of longer peptides, Crich developed the following strategy through Meisheinheimer's complex as an intermediate from 2,4-dinitrobenzene sulfonamides (Scheme **1.4**).[13] The same strategy is further extended for the synthesis of glycopeptides by Sucheck *et al*. as shown in scheme **1.5**.[14]



Scheme 1.5

The mechanism of the coupling of the two peptides is shown in scheme **1.6**. The nucleophilic attack of the thio acid of the second peptide on the 2,4-dinitrobenzene sulfonamide derivative of the first peptide would lead to the formation of the Meisenheimer complex which ideally rearranges to expel sulfur dioxide and forms the highly reactive 2,4-dinitro thio-phenolate of the second peptide and *N*-terminus free first peptide (Scheme **1.6**). The *in situ* generated starting materials for the coupling would get coupled with each other to furnish the desired peptide in high yield.



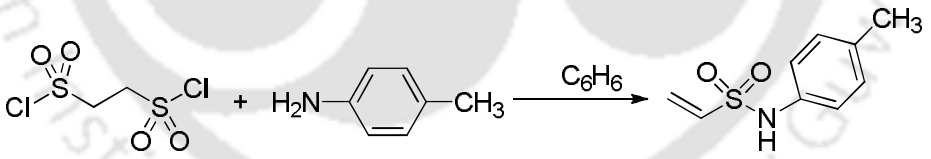
Scheme 1.6

Although these methodologies were very good strategies for the synthesis of various peptides, the fundamental draw-backs were associated with the synthesis of 2,4-dinitrobenzene sulfonamide derivatives over solid phase apart from the technical difficulties to synthesize thio-esters and thio-acids of the respective peptides. Since the production of the stoichiometric amounts of HCl is inevitable as the synthesis was carried out from the putative 2,4-dinitrobenzene sulfonyl chloride and the *N*-terminus free peptide, it was difficult to extend the same strategy for the solid phase resins. Some resins are cleaved in acidic conditions. Such

methods are also not compatible to acid labile functional groups such as Boc, ^{t}Bu, Trt *etc.* This problem was addressed in the following chapters.[15]

1.5 Sulfonamide synthesis: Available literature methods

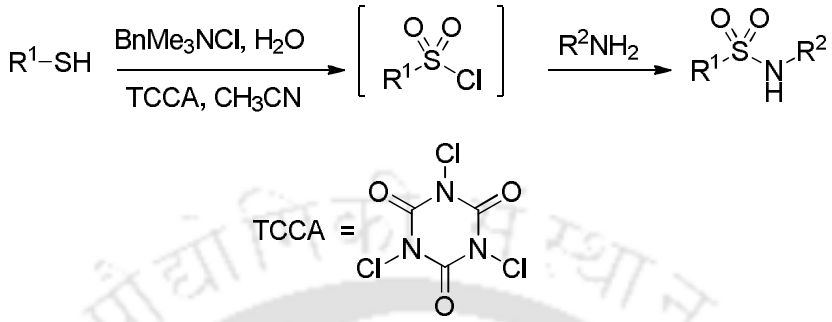
Due to the abundance and value of sulfonamides in pharmaceutical industries, it is vital that there are efficient and diverse ways of synthesizing them. Until recently, sulfonamides have almost exclusively been synthesized from the highly reactive sulfonyl chlorides. Sulfonyl chlorides, in turn, are commonly synthesized from the appropriate sulfonic acid by treatment with thionyl chloride, chlorosulfonic acid, phosphorus oxychloride/phosphorus pentachloride, or by oxidation of thiols/sulfides with chlorine gas.[16] Syntheses of sulfonamides utilizing simple alkyl sulfonyl chlorides were reported at around 1903. Koburger *et al.* (Scheme **1.7**) showed that it was possible to obtain reactions with the normally non-nucleophilic anilines, whereas Forster *et al.* provided an interesting example in the synthesis of a camphor-derived sulfonamide.[17]



Scheme 1.7

In the application of chlorine gas to affect the oxidation of thiols/sulfides to sulfonyl chlorides the use of excess oxidant and/or aqueous acid can be potentially unfavorable in the case of sensitive substrates. Bonk *et al.* developed a one pot synthesis of sulfonamides in which an ice-cooled solution of thiol, H_2O and $BnMe_3NCl$ was treated with trichloroisocyanuric acid (TCCA) followed by the amine (Scheme **1.8**).[18]

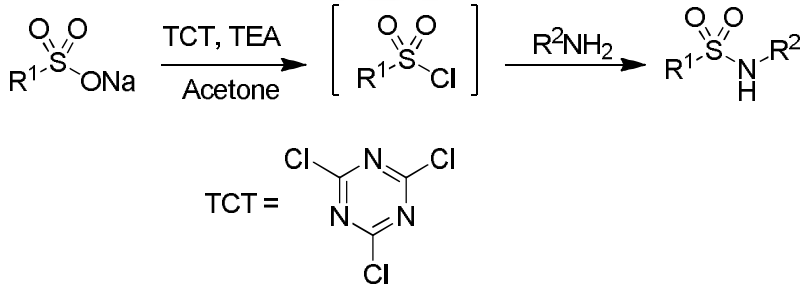
Key to this method is the generation of chlorine gas by mixing benzyltrimethylammonium chloride with TCCA and thus the *in situ* preparation of the sulfonyl chloride. This is a mild



Scheme 1.8

protocol that minimizes both the amount of oxidant required and the aqueous component. A selection of alkyl and aryl thiols were subjected to these conditions and provided sulfonamides in good yields.

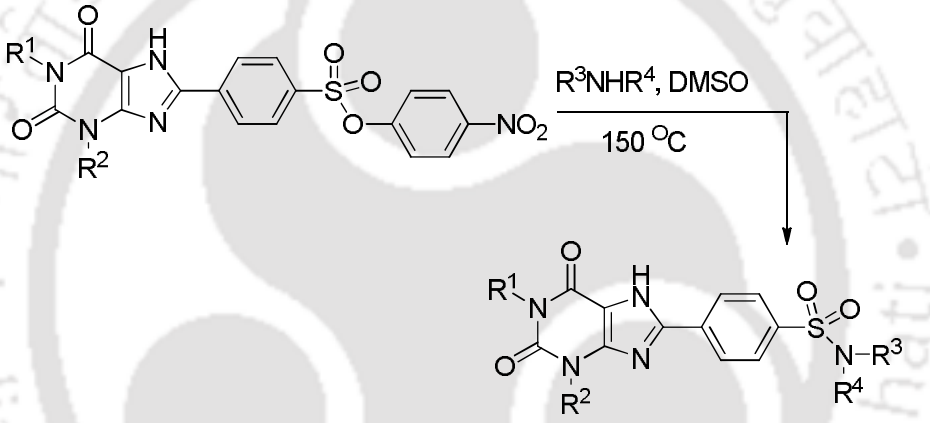
De Luca *et al.* have developed a microwave assisted synthesis to generate sulfonamides directly from the sulfonic acid or its sodium salt. They form sulfonyl chloride *in situ* under microwave conditions using the mild chlorinating agent 2,4,6-trichloro-[1,3,5]-triazine (TCT) in acetone with triethylamine. After filtration, NaOH and the amine were added and the reaction mixture was exposed to further microwave irradiation. This methodology worked well for alkyl, aryl and heteroaromatic sulfonic acids giving the sulfonamides in good yields (Scheme **1.9**).[19]



Scheme 1.9

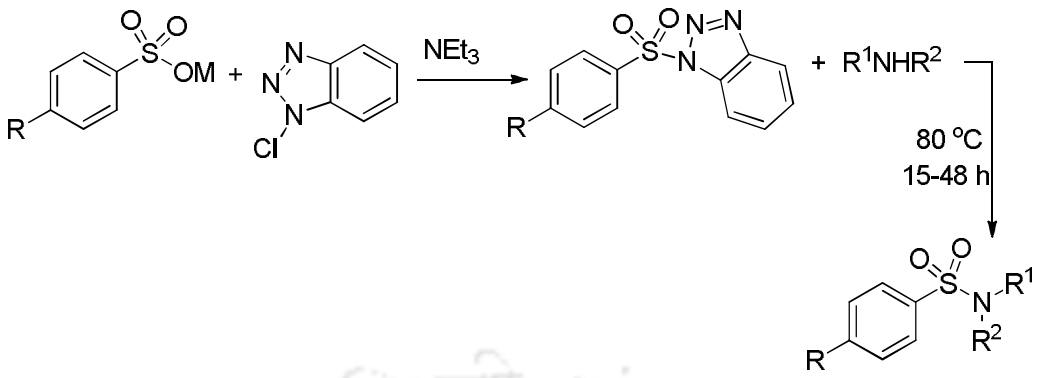
Although commonly used in the synthesis of sulfonamides, sulfonyl chlorides are difficult to prepare, handle and often are not amenable to long term storage. These issues have led to the development of alternative methods for sulfonamide synthesis.

In the preparation of Adenosine A receptor antagonists, *Muller et al.* were unsuccessful in the synthesis of xanthin-8-yl benzene sulfonamides from the corresponding sulfonic acids *via* sulfonyl chloride. To overcome this issue, the *p*-nitrobenzene sulfonates were prepared and the sulfonamides synthesized by displacement of the *p*-nitrophenol (Scheme **1.10**).[20]



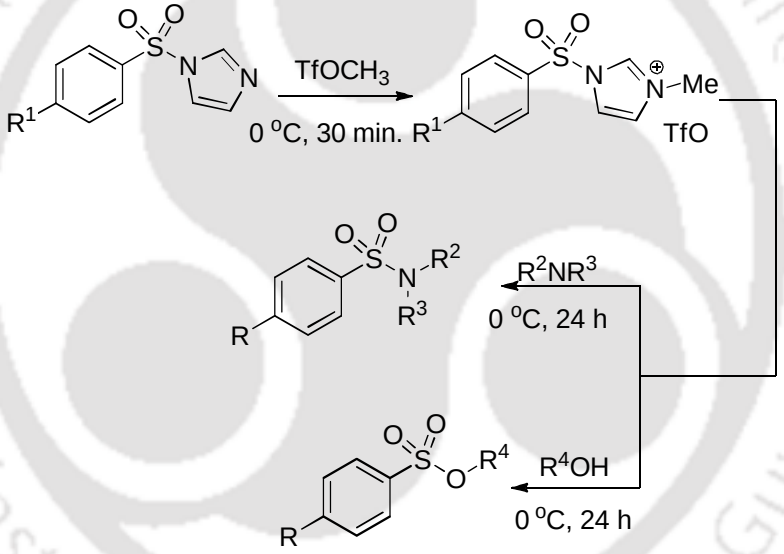
Scheme 1.10

Katritzky *et al.* have utilized the sulfonylbenzotriazolyl moiety as a replacement to sulfonyl chlorides in the synthesis of sulfonamides. They initially synthesized the sulfonylbenzotriazoles from the corresponding sulfonate metal salts 1-Chloro-1H-benzotriazole in presence of triethyl amine as base, and it is followed by the reaction with the respective amine at 80° C yielded the desired sulfonamide (Scheme **1.11**).[21]



Scheme 1.11

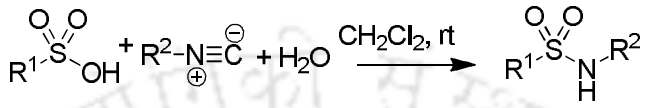
A variety of alkyl and aryl sulfonyl benzotriazoles were synthesized *via* the above mentioned approach in good yields (41-93%) and these were used to synthesize a range of sulfonamides



Scheme 1.12

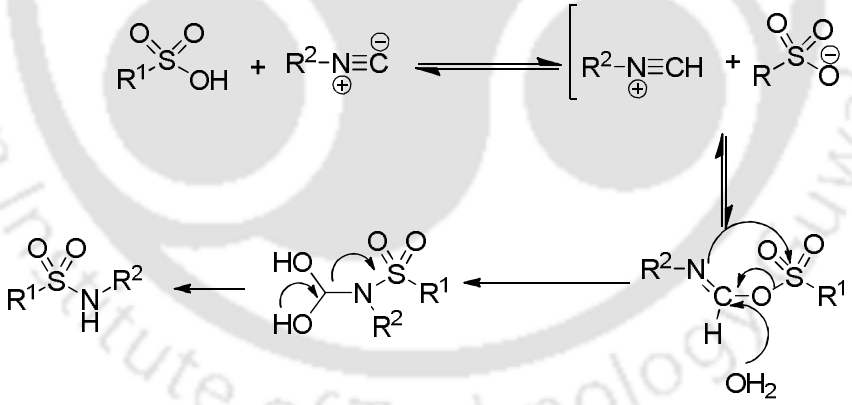
in good yields. Alkyl/aryl sulfonyl imidazoles have also been employed in the synthesis of sulfonamides; here the imidazole needs to be activated for it to become an effective leaving group. This is achieved by alkylation using methyl triflate to give the imidazolium triflate. When amines were added to these salts the desired sulfonamides were obtained in good yield (Scheme **1.12**).[22]

There are few methods available for the synthesis of sulfonamides from the corresponding sulfonic acids. One such route was developed by Shaabani *et al.* whereby the sulfonamides are formed *via* the reaction of sulfonic acids, isocyanides and water in dichloromethane at ambient temperature. The sulfonamides were isolated in good yield.[23]



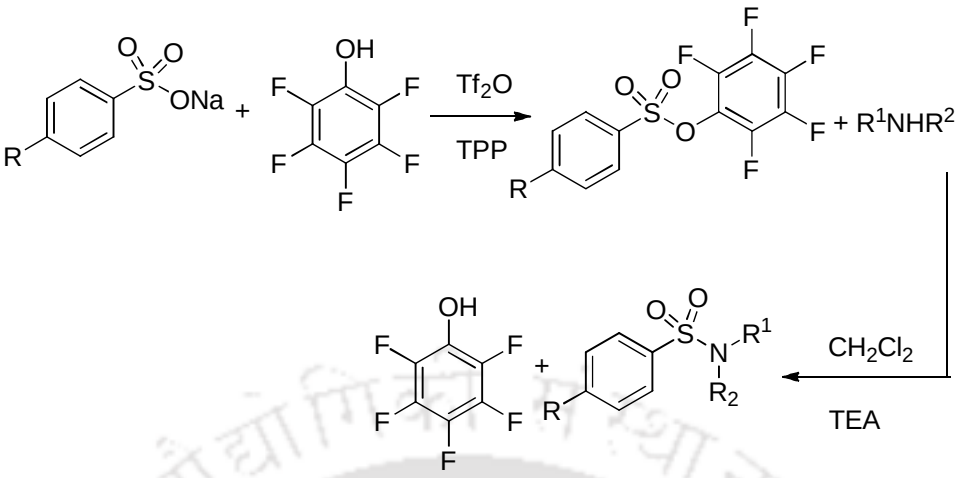
Scheme 1.13

This reaction doesn't occur in the absence of water and they have proposed the following mechanism (Scheme **1.14**). It is believed that protonation of the isocyanide by the sulfonic acid occurs to generate an intermediate, which on quenching with water produces the second intermediate and thus elimination of formic acid gives the sulfonamide.



Scheme 1.14

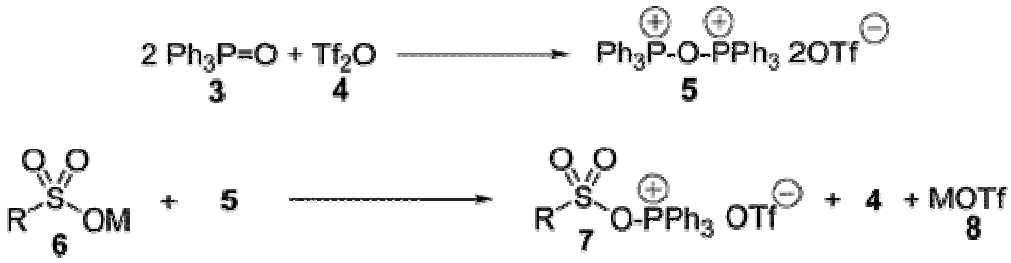
Caddick *et al.* have developed pentafluoro phenyl (PFP) sulfonate esters as alternatives to sulfonyl chlorides in the synthesis of sulfonamides. The sulfur centre is susceptible to nucleophilic attack, especially by amines, to make sulfonamides (Scheme **1.15**).[24]



Scheme 1.15

PFP sulfonate esters are generally crystalline solids making them amenable to long term storage and providing ease of handling. They have also proven to be stable to aqueous acid and base partitioning and column chromatography. Extensive investigations were carried out into the nature of this class of compounds demonstrating their versatility in the synthesis of sulfonamides.

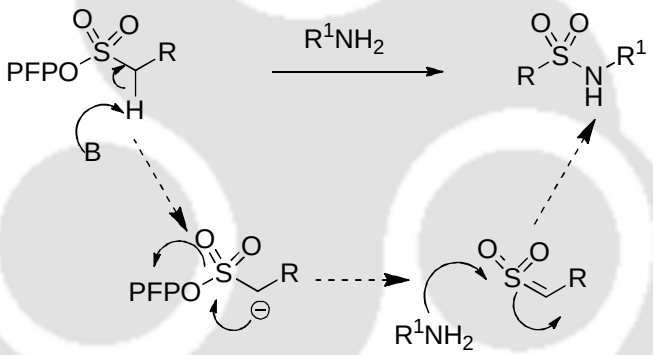
Despite the plethora of coupling reagents used in the synthesis of amides until recently there existed no analogous route to the synthesis of sulfonamides or sulfonate esters from sulfonic acids. Hence, initially the PFP sulfonate esters needed to be synthesized from the appropriate sulfonyl chloride. This was impractical and limited the range of esters that could be produced. A successful route to the desired sulfonate esters was found by activation of sulfonic acid salts using triphenylphosphine ditriflate. The intermediate is sufficiently activated to undergo reaction with nucleophiles such as the PFP anion, with the formation of the P=O π bond believed to be the driving force for the reaction.



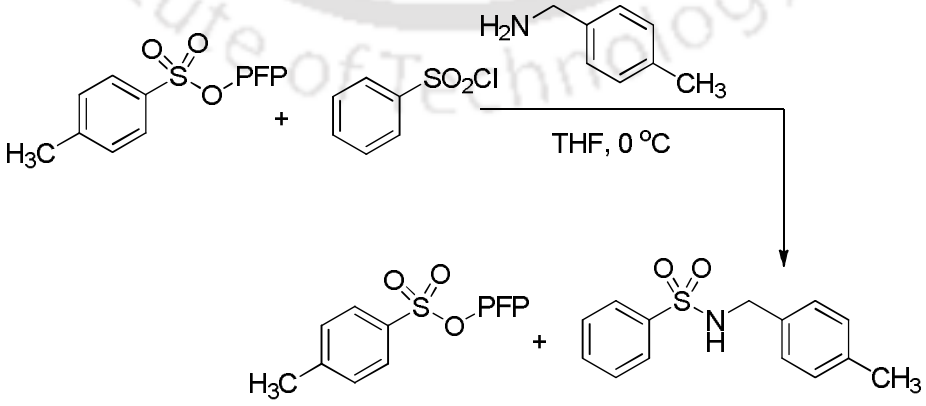
Scheme 1.16

This methodology was proven to be robust displaying high functional group tolerance and giving excellent yields and can also be applied in the direct synthesis of sulfonamides from sulfonic acid salts.

The reactivity of the PFP sulfonate esters is of two types. Alkyl-PFP-esters are believed to react *via* a sulfene intermediate which is formed by deprotonation of the α-C-H.

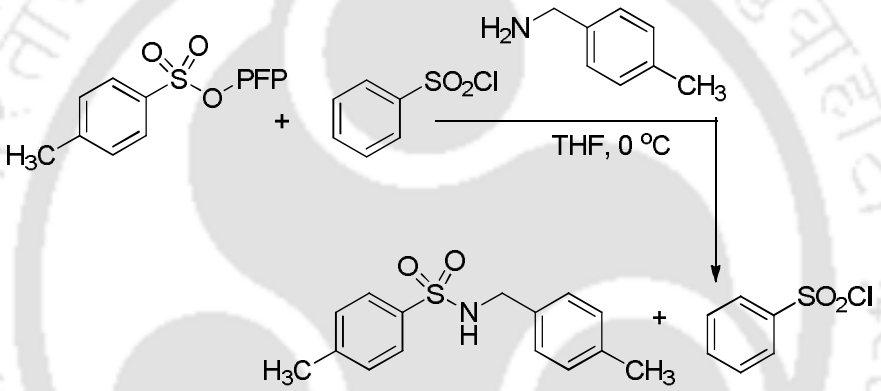


Scheme 1.17



Scheme 1.18

PFP sulfonates are less reactive than sulfonyl chlorides and therefore require higher temperatures and stronger bases (at 65 °C with DBU). This observation was further supported by the preferential nucleophilic attack by an amine on a sulfonyl chloride in the presence of a PFP sulfonate. Scheme **1.18** shows the reaction of one equivalent of 4-methylbenzylamine with a mixture of benzene sulfonyl chloride and PFP tosylate which gave solely the product derived from reaction with the sulfonyl chloride.



Scheme 1.19

A major advantage of PFP sulfonate esters over sulfonyl chlorides is their ability to react under aqueous conditions to give the desired sulfonamide in good yields. This was demonstrated when a 1:1 mixture of benzene sulfonyl chloride and PFP tosylate in an aqueous medium (1:1 methanol/water) were treated with one equivalent of amine. This reaction yielded only sulfonamide which was derived from the PFP tosylate and the amine (Scheme **1.19**).

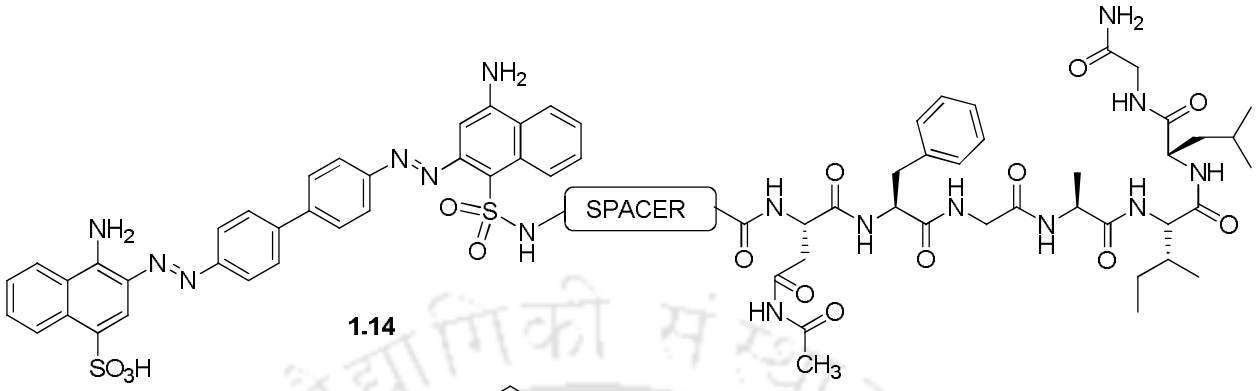
The aryl PFP sulfonates bearing electron donating groups and sterically hindered amines react more slowly and often require increased temperatures. Wilden *et al.* envisaged that a

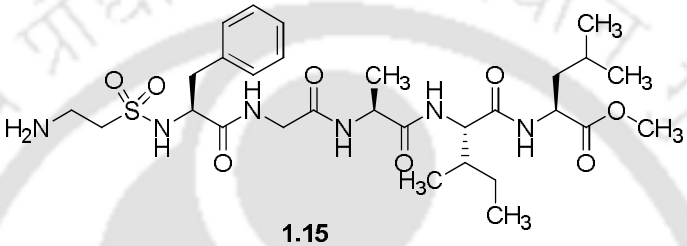
nucleophilic catalyst would increase the rate and efficacy of these reactions. Indeed when the aminolysis reaction is performed in the presence of tetrabutyl ammonium chloride, an acceleration of the rate is observed.

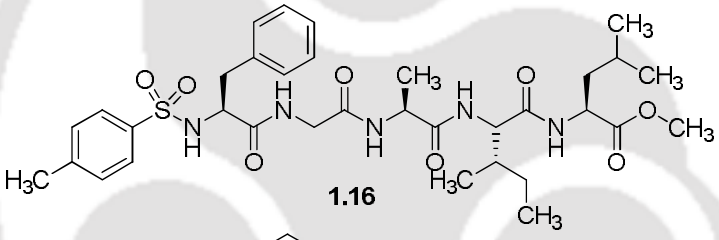
Overall, the PFP sulfonate ester methodology was shown to be robust and broad in its application with alkyl, benzylic, heterocyclic and aromatic PFP sulfonate esters reacting with primary, secondary and sterically hindered amines in moderate to good yields.

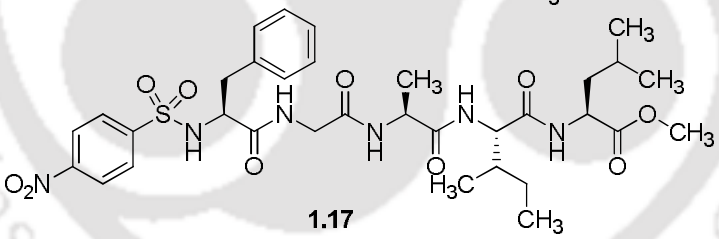
Having found all the above mentioned literature methods after several trials, we came to know that, none of these methods is applicable to the present targets and we decided to develop new methods for the synthesis of sulfonamides under ambient and milder conditions. To accomplish the task, the objectives we have set are as follows.

1.6 Objectives:









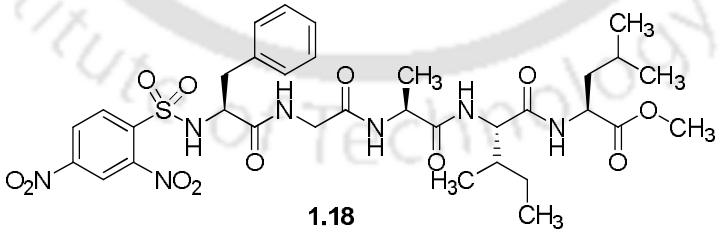


Figure 1.8 Our designed molecules for the therapeutic use against *Diabetes Type II*

We first wanted to device a drug design strategy against *Diabetes type II*. With the background discussed in section **1.1** and **1.2**, we thought it could be a good idea to make some peptide-small molecule conjugates. We have designed our targets in a way that (a) the hydrophobic core sequence of Amylin is intact which is to facilitate recognition to homologous core sequence of the native Amylin. (b) Congo red, taurine or other small molecules are attached to it to render the conjugate non cytotoxic. This strategy should increase the specificity of the small molecules. Compounds of this series are supposed to be potential drug leads for *Diabetes type II.* A few of such targets as the **NFGAIL** conjugates of Congo red, taurine and a few other sulfonic acid derivatives are shown in figure **1.8.**

Since all of the designed targets are sulfonamides, a thorough literature survey was performed to know the available synthetic methods which as discussed in the previous section. However, none was found to be suitable for us, as we wanted a method which should be compatible to acid labile protecting groups so that the whole synthesis can be carried out on solid phase. Compatibility to Fmoc based peptide synthesis was also important. To reach to the global target we specified a few immediate objectives, which are as follows:

1) Activation of the sulfonic acids in such a manner that, they undergo amidation to form sulfonamides under ambient conditions such that the acid labile functional groups and solid phase resins can sustain.

2) Direct synthesis of the activated sulfonate esters as the corresponding sulfonyl chlorides are not commercially available for many of the sulfonic acids.

3) Application of these activation strategies for the synthesis of peptide conjugates of Congo red and other small molecules for the therapeutic use against *Daibetes Type II*.

4) Utilization of these activated sulfonate esters for other related organic transformations**.**

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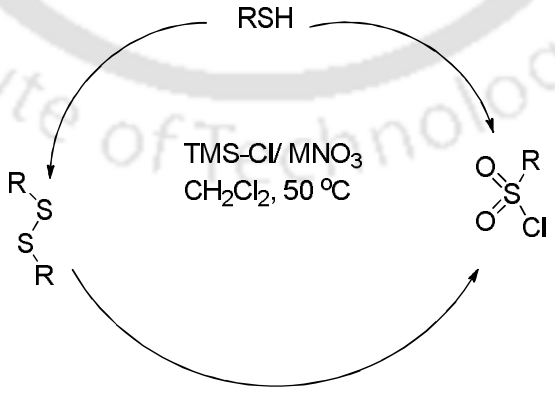
Chapter 2. Direct Synthesis of Activated Sulfonate Esters from Sulfonic Acids

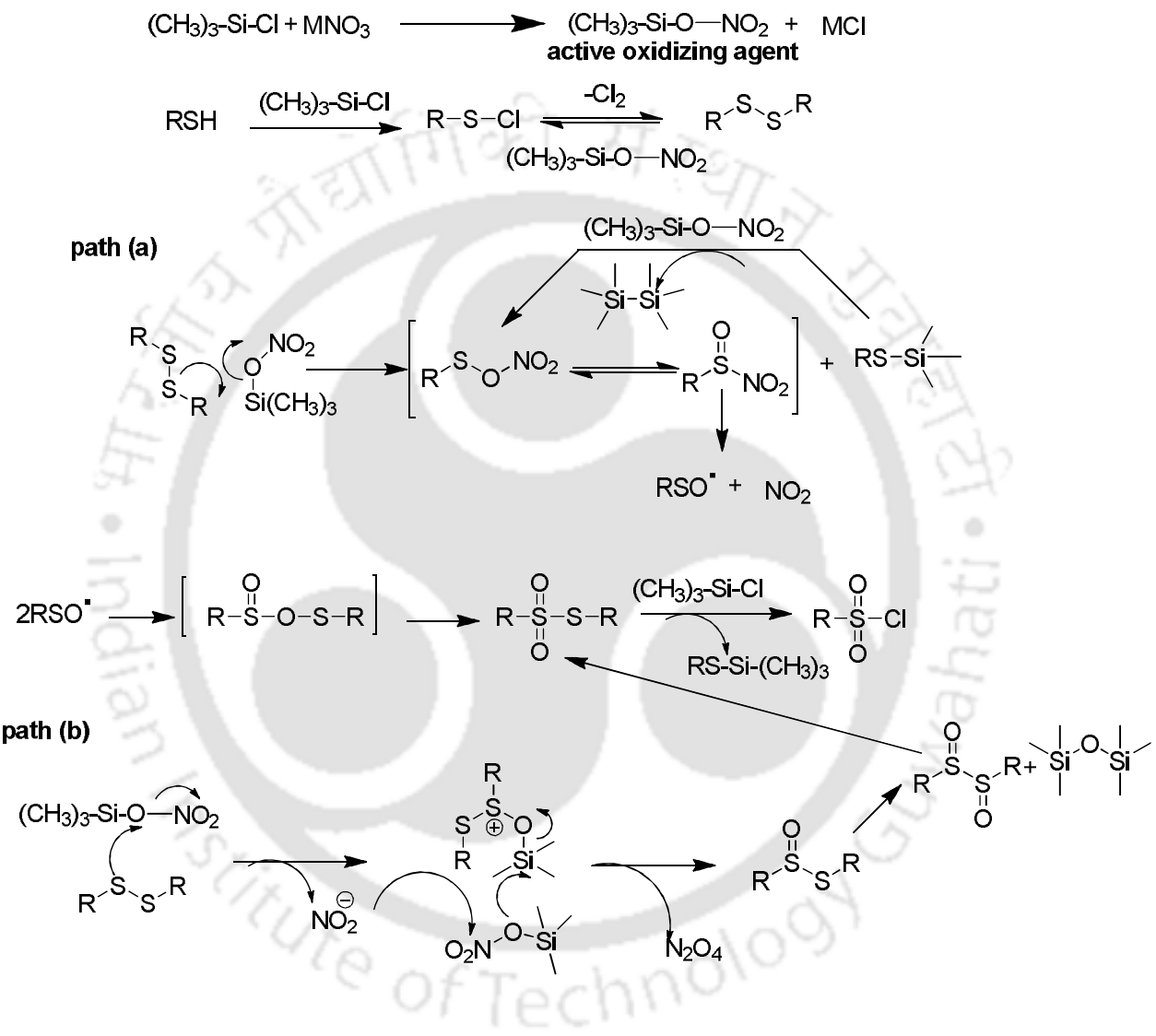
2.1 Introduction:

The direct synthesis of activated sulfonates esters is an important transformation. Not many literature reports are available for achieving this transformation. Apart from the lack of literature reports, from the synthetic point of view it is important to develop a method for the activation of sulfonic acids into various activated esters e.g. *para*-nitrophenol, pentafluoro phenol, *N*-hydroxy benzotriazole, ethyl 2-cyano-2-(hydroxyimino) acetate (Oxyma) *etc.*, so that there could be an alternative for the putative sulfonyl chlorides for the nucleophilic substitution reaction to generate sulfonamides, sulfonate esters, *etc.* Sulfonyl chlorides are severe lung effecting substrates.[1] It is known for practical difficulties in handling and long storage as they are very reactive species. Furthermore, not many of the sulfonyl chlorides are commercially available. In order to address the lack of commercial availability for the sulfonyl chlorides, the following seem to be promising methodologies.



Scheme 2.1

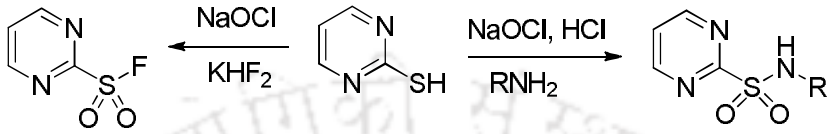
George *et al.* reported a method in which the sulfonyl chlorides can be made from the thiols using trimethyl silyl chloride and a metal nitrate in substitution of aqueous chlorine as shown in scheme **2.1**. The mechanism of this transformation is depicted in scheme **2.2**.[2]



Scheme 2.2

Wright *et al.* developed a strategy for the synthesis of sulfonyl chlorides and sulfonyl fluorides at low temperature (-25 °C) by using 3.3 equiv of aqueous sodium hypochlorite. This reaction is rapid, avoids the use of chlorine gas and succeeds with substrates that have

previously been found to afford little or none of the sulfonamide product with other procedures. This method allows for the preparation of the sulfonyl fluorides, which are stable enough to be purified and stored, making those potentially useful monomers in parallel chemistry efforts as shown in the scheme **2.3**.[3]



Scheme 2.3

In this regard, the very first of its kind activation of the sulfonic acid into their corresponding pentafluro phenol sulfonate esters was reported by Caddick group in which they have used harsh reagent such as triflic anhydride (described in *chapter 1*, Scheme **1.15**). In addition to that, the activated ester strategies offer excellent advantages such as chemoselectivity (Scheme **1.18**), temperature dependant selectivity (Scheme **1.19**) that render a huge application in the natural product synthesis. Following this, they have extended the same strategy in synthesizing the trichloro phenol esters of various sulfonic acids keeping the fact in mind that pentafluoro phenol is a costly substrate, where as the trichloro phenol is cheaper than its counterpart by two-fold.

Furthermore, the other activation methods that are available so far are para nitro phenol (Scheme **1.10**), benzotriazole (Scheme **1.11**), in which the long reaction times and heating conditions are the draw-backs, where as in imidazolium triflate (Scheme **1.12**) *etc.* the harsh reagent like triflic acid usage is necessary.[4]

Additionally, as it was described in the *chapter 1*, we were trying to develop a method for the HCl free synthesis of sulfonamides so that it could be compatible with all the acid labile substrates and acid labile solid phase resins for the synthesis of probable drug candidates that

may have substantial activity against *Diabetes type II*. In this connection, the sulfonic acids of our interest to be activated are Congo red and 8-amino naphthalene sulfonic acid. None of these sulfonic acids has corresponding sulfonyl chlorides. Secondly, derivatization of the peptides **NFGAIL, LPPFFAED**, and **LVFFAED** as sulfonamides over solid phase would be great, though no report was found that could be used over solid phase. Thus, we undertook the challenge of activating the sulfonic acids into all kinds of activated sulfonate esters so that they would facilitate the sulfonamide synthesis under ambient and milder conditions and can also be compatible with the acid labile resins.

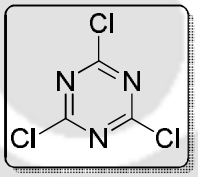


Figure 2.1 Trichlorotriazine

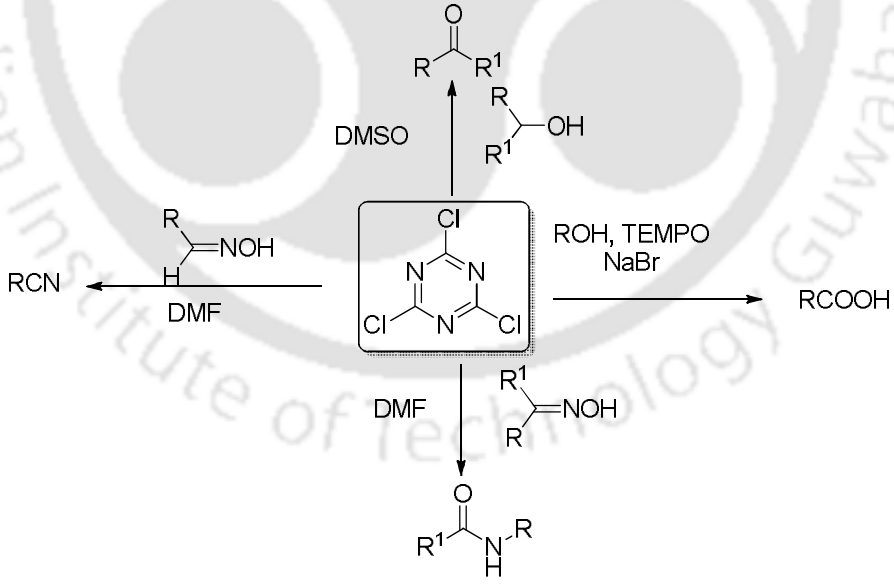


Figure 2.2 Synthetic utility of TCT

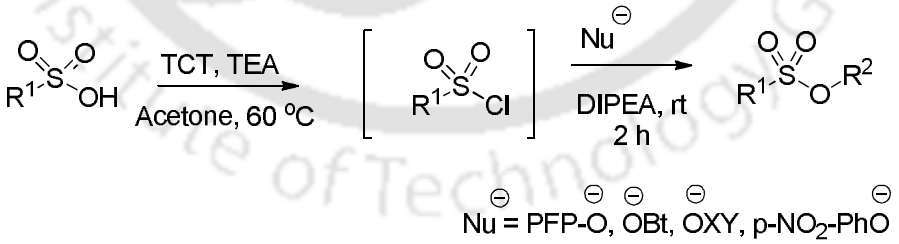
The thorough literature search for the synthesis of sulfonyl chlorides from the sulfonic acids revealed that there are quite a few methods available out of which we became interested in

two methodologies, in which trichlorotriazine (TCT, Figure **2.1**)[5] and trichloroacetonitrile (TCA) along with triphenylphosphine (TPP) in acetone and dichloromethane solvents were used respectively.[6]

Giacomelli *et al*. used TCT in an extensive manner to carry out various transformations such as carboxylic acids to hydroxamtes, primary and secondary alcohols to aldehydes and ketones respectively, aldoximes to nitriles, alcohols to acids, to synthesize isonitriles (Figure **2.2)** and ketoximes to secondary amides *etc.* It is a very good replacement for all the chlorinating reagents such as thionyl chloride, sulfonyl chloride, *etc*.[7] Although a good number of methods for the activation of carboxylic acids into an activated form were failed when employed for the activation of sulfonic acids, indeed TCT worked well for the activation of sulfonic acids as well as carboxylic acids.[8]

2.2 Results and discussion:

As it was shown in scheme **2.4** (method **a**)**,** we tried a reaction with *para*-toulene sulfonic acid and *N*-hydroxy benzotriazole to get the corresponding ester.

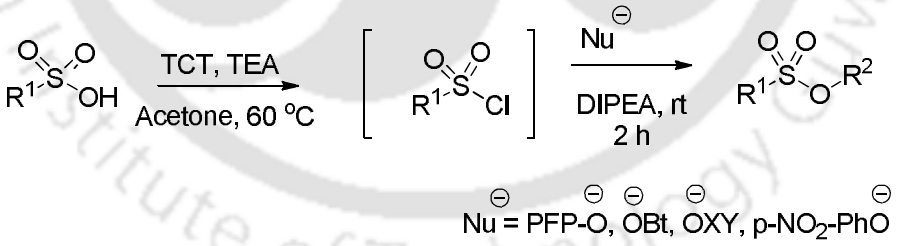


Scheme 2.4

Interestingly, with 1 mmol of p-TsOH, 1 mmol of TCT along with 1 mmol of di-isopropyl ethyl amine (DIPEA) or triethyl amine (TEA) in acetone solvent at reflux for 1 h followed by the addition of 1 mmol of HOBt and 1 mmol of DIPEA yielded the desired product i.e. TsOBt

in very good yield. That has encouraged us to peruse further to extend the applicability of this reaction to various sulfonic acids and various leaving groups such Oxyma, pentafluoro phenol, para nitro phenol (Scheme **2.5**). Then, we went on to synthesize the varieties of sulfonate esters of various sulfonic acids such as benzene sulfonic acid (entries **1-4**, Table **2.1**), p-TsOH (entries **5-8**, Table **2.1**), sodium salt of sodium salt of dodecyl benzene sulfonic acid (entries **9-12**, Table **2.1**) and medicinally important sulfonic acid esters such as 8-amino naphthalene sulfonic acid (entries **13-16**, Table **2.1**). But, it is noteworthy to mention that in case of 8-amino naphthalene sulfonic acid, it is important to protect the amino group with an appropriate protecting group to prevent the corresponding sulfonamide formation. In our case, we have chosen the benzoyl protection so as to stop the further sulfonamide formation. In all the cases, the yields were isolated to be good to excellent.

Adopting the second method that was specified below i.e. TCA instead of TCT in dichloromethane solvent even yielded the desired product TsOBt in very good yield with *p*-TsOH and HOBt as the model substrates (Scheme **2.5**, method **b**).



Scheme 2.5

With the optimized conditions in hand for the method **b** as well, we proceeded further for the synthesis of all the sulfonate esters that we have synthesized using previous method i.e. method **a**. In all the cases the yields were quite good and comparable with that of the method **a** with few exceptions in which the yield was differed by the 5-10% when compared with the

Table 2.1 Synthesis of various activated sulfonated esters from corresponding sulfonic acids.

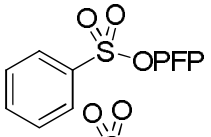
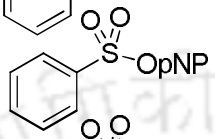
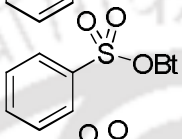
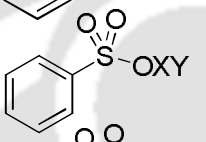
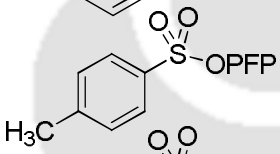
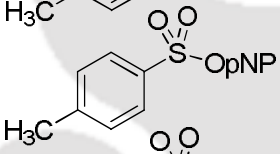
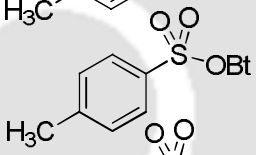
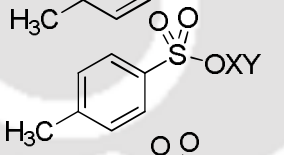
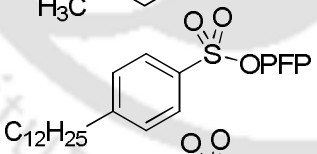
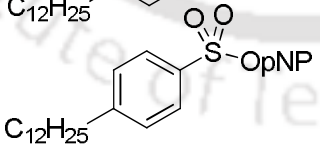
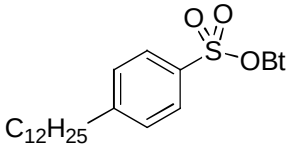
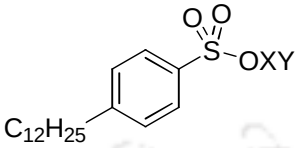
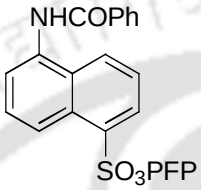
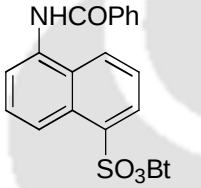
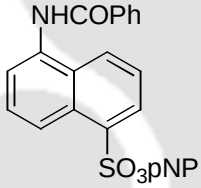
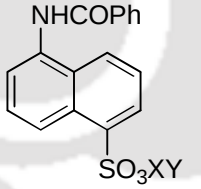
entry	sulfonate ester	method[a]	yield[b]	time (h)[c]
1		a	96	1
		b	88	1
2		a	91	1
		b	90	1
3		a	84	1
		b	84	1
4		a	94	1
		b	98	1
5		a	81	1
		b	86	1
6		a	91	1
		b	92	1
7		a	78	1
		b	89	1
8		a	76	1
		b	68	1
9		a	68	1
		b	74	1
10		a	76	1
		b	71	1

Table **2.1** Continues…..

entry	sulfonate ester	method[a]	yield[b]	time (h)[c]
11		a	78	1
		b	81	1
12		a	88	1
		b	78	1
13		a	58	1
		b	58	1
14		a	69	1
		b	55	1
15		a	66	1
		b	61	1
16		a	72	1
		b	65	1

[a]Method details are given in the experimental section. [b]Yields refer to isolated yield after column chromatography. [c]TLC is checked for every 10 min.

previous method. The advantage of this method over the previous is, it precludes the handling difficulty with the side product that gets generated with the trichlorotriazine which is a potential explosive on exposure to moisture.

2.3 Conclusion:

In conclusion, using TCT we demonstrated the synthesis of activated sulfonate esters of various sulfonic acids under milder conditions with reasonably good yields, which is first of its kind. Furthermore, we envisaged another synthetic route that facilitated the same synthesis using TPP. These methods enable the sulfonamide synthesis for those sulfonic acids that lack commercially available, parent sulfonyl chlorides.

2.4 Experimental Section:

2.4.1 General information:

All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. Thin layer chromatograms were run on glass plates coated with silica gel G for TLC, using solvent systems EtOAc/Hexane. All the compounds were purified by column chromatography using 60-120 mesh silica gel from Spectrochem (India). ^{1}H-NMR (400 MHz for ^{1}H) was recorded using DRX-400 Varian spectrometer using $CDCl_3$ as solvent unless mentioned otherwise. Chemical shifts were reported in parts per million (ppm), internal reference (0.05% to 1%) tetra methyl silane. Coupling constants (*J*) were reported in Hz singlet(s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). Low resolution mass spectra were recorded on a Micromass Q-TOF ESI MS instrument (model HAB273). HRMS was recorded on 6500 Q-TOF LC/MS system. IR was recorded on a Perkin Elmer spectrum FT-IR one spectrometer. Data for previously reported compounds (cited therein) matched well with our observed data.

2.4.2 General procedure for the synthesis of activated sulfonate esters (method a):

The representative procedure for the synthesis of **TsOBt** is given here and is common for all. In an oven dried 25 mL round bottom flask, to the sulfonic acid (1 mmol, acetone 1 mL) added triethyl amine/ DIPEA (1 mmol) followed by the addition of 2,4,6 trichloro triazine (1 mmol). Then it was refluxed at 60 ˚C while being monitored by the TLC. After complete conversion to the respective sulfonyl chlorides, it was filtered off over Celite®. To the filtrate, the nucleophilic alcohol along with base DIPEA/ TEA (1 mmol) added and continued to stir the reaction mixture at room temperature. After completion of the reaction, it was washed with 5% $NaHCO_3$ (2×10 ml), 5% HCl (2×10 ml) and with brine (2×10 ml). Then it was dried over Na_2SO_4 followed by concentration under reduced pressure. Then it was purified by recrystallization using hexane and dichloromethane solvents (Although recrystallization was commonly employed, column chromatography was used wherever it was needed).

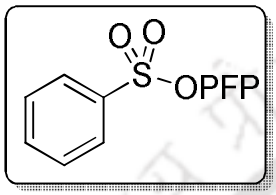
2.4.3 General procedure for the synthesis of activated sulfonate esters (method b):

The representative procedure for the synthesis of **TsOBt** is given here and is common to all the substrates. In an oven dried 25 mL round bottom flask, the sulfonic acid (1 mmol, dichloromethane 1 mL), trichloro acetonitrile, triphenyl phosphine and triethyl amine (1 mmol) was taken. Then it was refluxed at 60 ˚C while being monitored by the TLC. After complete conversion to the respective sulfonyl chlorides, the nucleophilic alcohol along with base DIPEA/ TEA (1 mmol) was added and continued to stir the reaction mixture at room temperature. After completion of the reaction, it was washed with 5% $NaHCO_3$ (2×10 ml), 5% HCl (2×10 ml) and with brine (2×10 ml). Then it was dried over Na_2SO_4 followed by concentration under reduced pressure. Then it was purified by recrystallization using hexane

and dichloromethane solvents (Although recrystallization was commonly employed, column chromatography was used wherever it was necessary).

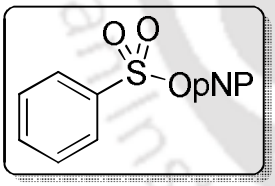
2.5 Characterization data:

1) Benzenesulfonic acid pentafluorophenyl ester (Table 2.1, entry 1):



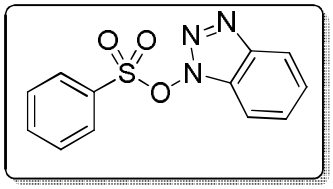
R_f product 0.54 (EtOAc/Hexane, 1:9) Yield (method **a** 96%, method **b** 88%) colourless solid. IR (KBr, ν/cm^{-1}) 2864 1620, 1446, 1335, 1124, 1024, 910 .^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98-7.96 (d, 2H, 2×Ar**H**), 7.75-7.73 (m, 1H, 1×Ar**H**), 7.61-7.58 (m, 2H, 2×Ar**H)**. ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 148.4, 139.2, 137.7, 134.2, 130.4, 128.4, 129.9, 122.4; LRMS (ESI) m/z [M+H]$^+$: 324.99, found : 324.99.

2) Benzenesulfonic acid paranitrophenyl ester (Table 2.1, entry 2):



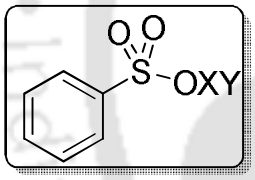
R_f product 0.51 (EtOAc/Hexane, 1:9), Yield (method **a** 91%, method **b** 90%), pale yellow crystalline solid. IR (KBr, ν/cm^{-1}) 2875 1644, 1338, 1158, 883. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98-7.96 (d, 1H, Ar**H**), 8.04-8.01 (d, 2H, 2×Ar**H**), 7.98-7.96 (d, 2H, 2×Ar**H**), 7.80-7.76 (m, 3H, 3×Ar**H**), 7.23-7.19 (m, 2H, 2×Ar**H)**. ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 163.8, 145.9, 143.7, 134.1, 130.2, 125.9, 125.4, 120.3; LRMS (ESI) m/z [M+H]$^+$: 280.02, found : 280.02.

3) Benzenesulfonic acid paranitrophenyl ester (Table 2.1, entry 3):



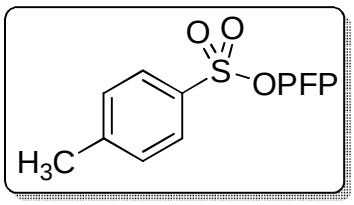
R_f product 0.54 (EtOAc/Hexane, 1:9), Yield (method **a** 84% method **b** 84**%)**, colourless solid. IR (KBr, ν/cm^{-1}) 3404, 1620, 1446, 1393, 1158, 1017, 910 .^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98-7.96 (d, 1H, Ar**H**), 7.91-7.90 (d, 1H, Ar**H**), 7.88-7.87 (d, 1H, Ar**H**), 7.80-7.76 (m, 1H, Ar**H**), 7.61-7.53 (m, 4H, 4×Ar**H**), 7.43-7.38 (m, 1H, Ar**H)**. ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 136.4, 129.9, 129.7, 129.4, 128.4, 125.9, 125.4, 120.3, 109.3; LRMS (ESI) m/z $[M+H]^+$: 276, found: 276.04.

4) Benzenesulfonic acid Oxyma ester (Table 2.1, entry 4):



R_f product 0.48 (EtOAc/Hexane, 1:4) Yield (method **a** 94% method **b** 98%), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3093, 2977, 1754, 1591, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.02 (m, 2H, 2×Ar**H**), 7.75-7.73 (m, 1H, 1×Ar**H**), 7.62-7.59 (m, 2H, 2×Ar**H**), 4.41-4.36 (q, 2H, C**H**$_2$), 1.37-1.33 (t, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.9, 135.8, 133.1, 131.5, 129.7, 129.4, 106.1, 64.7, 13.8; HRMS (ESI) m/z Calcd. for $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 283.0389, found: 283.0384.

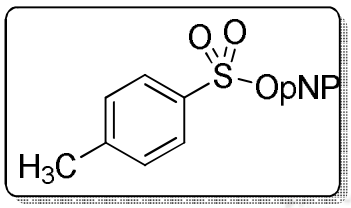
5) Toluene-4-sulfonic acid pentafluorophenyl ester (Table 2.1, entry 5):



Yield (method **a** 81%, method **b** 86%), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3093, 1373 936, 7214. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.81-7.79 (d, 2H, 2×Ar**H**), 7.41-7.38 (d,

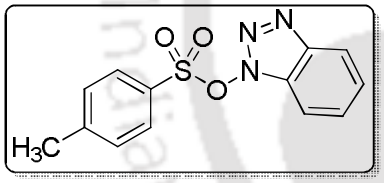
2H, 2×Ar**H**), 2.44(s, 3H, C**H**$_3$). LRMS(ESI) m/z Calcd. for $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 337.01, found: 337.01.

6) Toluene-4-sulfonic acid paranitrophenyl ester (Table 2.1, entry 6):



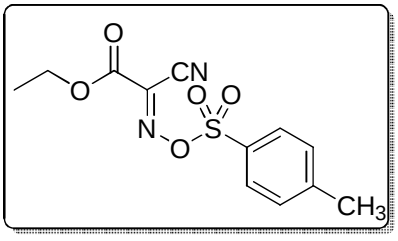
R_f product 0.48 (EtOAc/Hexane, 1:4) Yield (method **a** 91%, method **b** 92%), colorless crystalline solid. IR (KBr, ν/cm^{-1}), 2977, 1754, 1347, 1591, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.02 (m, 2H, 2×Ar**H**), 7.75-7.73 (m, 1H, 1×Ar**H**), 7.62-7.59 (m, 2H, 2×Ar**H**), 4.41-4.36 (q, 2H, C**H**$_2$), 1.37-1.33 (t, 3H, C**H**$_3$); HRMS (ESI) m/z Calcd. for $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 294.04, found: 294.04.

7) Toluene-4-sulfonic acid *N*-hydroxy benzotriazole ester (Table 2.1, entry 7):



R_f product 0.61 (EtOAc/Hexane, 1:4) Yield (method **a** 78% method **b** 89%), white crystalline solid. IR (KBr, ν/cm^{-1}) 3305, 1752, 1539, 1439, 1358, 1169, 1126, 976, 856, .^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.0 (m, 1H, Ar**H),** 7.81-7.77 (m, 2H, 2×Ar**H),** 7.67-7.56 (m, 2H, 2×Ar**H**), 7.49-7.39 (m, 3H, 3×Ar**H**), 2.50 (s, 3H, C**H**$_3$). LRMS (ESI) m/z $[M+H]^+$: 290.O5, found: 290.05

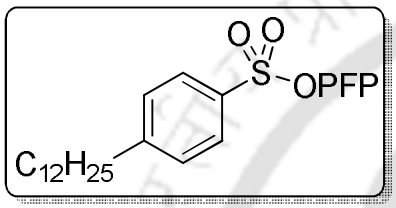
8) Toluene-4-sulfonic acid *Oxyma* ester (Table 2.1, entry 8):



R_f product 0.46 (EtOAc/Hexane, 1:4), Yield (method **a** 76% method **b** 68%), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3011, 2923, 1759, 1593, 949, 769. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86-7.84 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.35-7.33 (d, 2H,

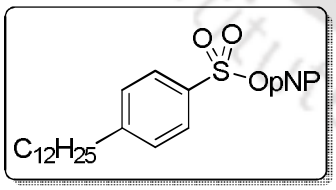
J = 8 Hz, 2×Ar**H**), 4.37-4.31 (q, 2H, C**H**$_2$), 2.41 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.6 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.0, 147.5, 131.5, 130.4, 130.1, 129.5, 106.2, 64.6, 21.9, 13.9; LRMS (ESI) m/z Calcd. for $C_{12}H_{13}N_2O_5S$ $[M+H]^+$: 297.05, found: 297.05.

9) 4-Dodecyl-benzenesulfonic acid pentafluorophenyl ester (Table 2.1, entry 9):



R_f product 0.42 (EtOAc/Hexane, 1:4) Yield (method **a** 68%, method **b** 74%) white crystalline solid. IR (KBr, ν/cm^{-1}) 1358, 1169, 1126, 976, 856.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 (m, 2H, 2×Ar**H**), 7.51 (m, 2H, 2×Ar**H**), 2.51-2.49 (q, 2H, C**H**$_2$-Ar), 1.61-1.60 (m, 2H, C**H**$_2$), 1.37-1.29 (m, 18H, 9×C**H**$_2$), 0.90 (t, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 162.4, 147.5, 144.7, 136.1, 134.4, 130.4, 129.7, 127.2, 118.2, 34.2, 31.9, 30.1, 22.9, 14.6; HRMS (ESI) m/z Calcd. for $[M+H]^+$: 493.1834; found: 493.1828.

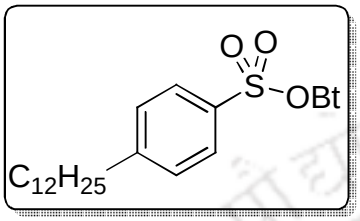
10) 4-Dodecyl-benzenesulfonic acid paranitrorophenyl ester (Table 2.1, entry 10):



R_f product 0.41(EtOAc/Hexane, 2:3), Yield (method **a** 76% method **b** 71**%)**, colorless crystalline solid. IR (KBr, ν/cm^{-1}) 1586, 1362, 1162, 918, 749. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.05 (m, 2H, 2×Ar**H**), 7.91 (m, 2H, 2×Ar**H**), 7.88 (m, 2H, 2×Ar**H**), 6.85 (m, 2H, 2×Ar**H**), 2.51-2.49 (q, 2H, C**H**$_2$-Ar), 1.61-1.60 (m, 2H, C**H**$_2$), 1.37-1.29 (m, 18H, 9×C**H**$_2$), 0.92 (t, 2H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.4,

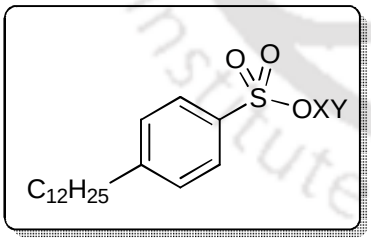
143.5, 140.3, 128.6, 127.2, 118.2, 34.2, 31.9, 30.1, 22.9, 14.6; $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 448.2158, found: 448.2158.

11) 4-Dodecyl-benzenesulfonic acid *N*-hydroxy benzotriazole ester (Table 2.1, entry 11):



R_f product 0.37 (EtOAc/Hexane, 2:3), Yield (method **a** 78%, method **b** 81%), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 2923, 1759, 1573, 1351, 941, 757. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98 (m, 2H, 2×Ar**H**), 7.84 (m, 2H, 2×Ar**H**), 7.48 (m, 2H, 2×Ar**H**), 7.45 (m, 2H, 2×Ar**H**), 2.47-2.46 (m, 2H, C**H**$_2$-Ar), 1.60-1.58 (m, 2H, C**H**$_2$), 1.39-1.29 (m, 18H, 9×C**H**$_2$), 0.93 (t, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.7, 128.9, 128.4, 33.8, 31.3, 29.7, 22.9, 14.3; HRMS (ESI) m/z Calcd. for $C_{12}H_{13}N_2O_5S$ $[M+H]^+$: 444.2321, found: 444.2319.

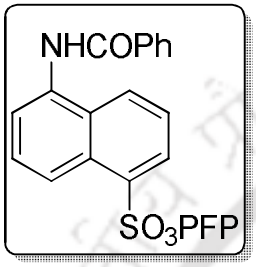
12) 4-Dodecyl-benzenesulfonic acid Oxyma ester (Table 2.1, entry 12):



R_f product 0.46 (EtOAc/Hexane, 2:3) Yield (method **a** 88%, method **b** 78%), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 2256, 1591, 1457, 1368, 920, 734. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 (m, 2H, 2×Ar**H**), 7.51 (m, 2H, 2×Ar**H**), 4.41-4.36 (q, 2H, C**H**$_2$), 2.49-2.46 (q, 2H, C**H**$_2$), 1.62-1.60 (m, 2H, C**H**$_2$), 1.37-1.29 (m, 21H, 9×C**H**$_2$, C**H**$_3$), 0.94 (t, 3H, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.9, 159.7, 129.7, 128.4, 110.1, 64.7, 34.2, 31.9, 30.1, 22.9, 14.6, 13.8;

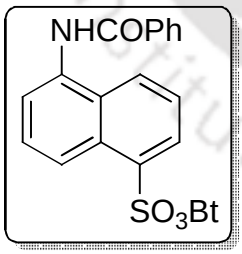
HRMS (ESI) m/z Calcd. for $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 451.2267, found: 451.2234.

13) 5-Benzoylamino-naphthalene-1-sulfonic acid pentafluorophenyl ester (Table 2.1, entry 13):



R_f product 0.31 (EtOAc/Hexane, 2:3), Yield (method **a** 58%, method **b** 58%), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 2258, 1614, 1335, 1591, 942. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.08-8.05 (m, 3H, 3×Ar**H**), 7.53-7.50 (d, 2H, 2×Ar**H**), 7.41-7.39 (m, 3H, 3×Ar**H**), 7.11-7.09 (m, 3H, 3×Ar**H**), 6.91 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.9, 140.1, 135.8, 134.6, 133.5, 131.1, 129.7, 129.4, 127.3, 124.6, 124.0, 123.8, 123.5, 123.0, 117.1 109.5; HRMS (ESI) m/z Calcd. for $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 493.0407, found: 493.0401.

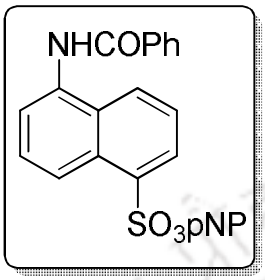
14) 5-Benzoylamino-naphthalene-1-sulfonic acid benzotriazol-1-yl ester (Table 2.1, entry 14):



R_f product 0.29 (EtOAc/Hexane, 2:3) Yield (method **a** 69%, method **b** 55%) colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3086, 2256, 1620, 1591, 1380. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.00 (m, 5H, 5×Ar**H**), 7.59(br s, 1H, N**H**), 7.55-7.53 (m, 2H, 2×Ar**H**), 7.47-7.45 (m, 4H, 4×Ar**H**), 7.12-7.09 (m, 3H, 3×Ar**H**), 6.81(m, 1H, 1×Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.6, 143.8, 142.6, 135.8, 131.5, 129.9, 127.7, 124.3,

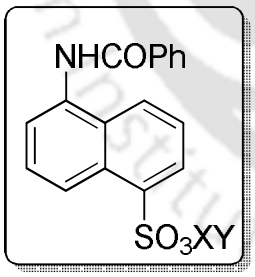
116.1, 110.1; HRMS (ESI) m/z Calcd. for $C_{23}H_{16}N_4O_4S$ $[M+H]^+$: 444.0892, found: 444.0891.

15) Benzoylamino-naphthalene-1-sulfonic acid 4-nitro-phenyl ester (Table 2.1, entry 15):



R_f product 0.21 (EtOAc/Hexane, 2:3) Yield (method **a** 66%, method **b** 61), colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3098, 2241, 1754, 1525, 1335, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.06-7.92 (m, 6H, 6×Ar**H**), 7.58-7.44 (m, 4H, 4×Ar**H**), 7.16-7.13 (m, 2H, 2×Ar**H**), 6.55-6.65(m, 2H, 2×Ar**H**), 6.94 (m, 2H, 2×Ar**H**). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.4, 163.4, 143.3, 141.6, 141.1, 133.5, 130.9, 129.4, 128.6, 127.3, 126.1, 126.4, 125.6, 125.1, 124.8, 124.7, 124.3, 124.1, 116.8; HRMS (ESI) m/z Calcd. for $C_{23}H_{16}N_2O_6S$ $[M+H]^+$: 448.0729, found: 448.0719.

16) 5-Benzoylamino-naphthalene-1-sulfonic acid Oxyma ester (Table 2.1, entry 16):



R_f product 0.21 (EtOAc/Hexane, 2:3) Yield (method **a** 72%, method **b** 65%) colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3093, 2977, 2254, 1754, 1634, 1591, 1361, 921. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.02 (m, 3H, 3×Ar**H**), 7.56-7.50 (m, 3H, 3×Ar**H**), 7.42-7.38 (m, 3H, 3×Ar**H**), 7.18-7.15 (m, 2H, 2×Ar**H**), 4.36-4.31 (q, 2H, C**H**$_2$), 1.36-1.31 (t, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.3, 163.8, 160.9, 142.4, 140.5, 135.2, 133.7, 131.0, 129.1, 128.4, 124.9,

106.1, 64.7, 13.8; HRMS (ESI) m/z Calcd. for $C_{22}H_{17}N_3O_6S$ $[M+H]^+$: 451.0838, found: 451.0831.

2.6 References:

1) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. Direct conversion of thiols to sulfonyl chlorides and sulfonamides. *J. Org. Chem*. **2009**, *74*, 9287-9291.

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7) a) Lidia, D. L.; Giampaolo, G.; Maurizio, T. An easy and convenient synthesis of Weinreb amides and hydroxamates. *J. Org. Chem.* **2001**, *66*, 2534–2537; b) Lidia, D. L.; Giampaolo, G.; Andrea, P. A mild and efficient alternative to the classical swern oxidation. *J. Org. Chem.* **2001**, *66*, 7907-7909; c) Lidia, D. L.; Giampaolo, G.; Andrea, P. Beckmann rearrangement of oximes under very mild conditions. *J. Org. Chem.* **2002**, *67*, 6272-6274; d) Lidia, D. L.; Giampaolo, G.; Simonetta, M.; Andrea, P. Trichloroisocyanuric/TEMPO oxidation of alcohols under mild conditions: A close investigation. *J. Org. Chem.* **2003**, *68*, 4999-5001.

8) Caddick, S.; Wilden, J. D.; Judd, D. B. Direct synthesis of sulfonamides and activated sulfonate esters from sulfonic acids. *J. Am. Chem. Soc.* **2004**, *126*, 1024-1025.

2.7 Selected spectra for representative compounds:

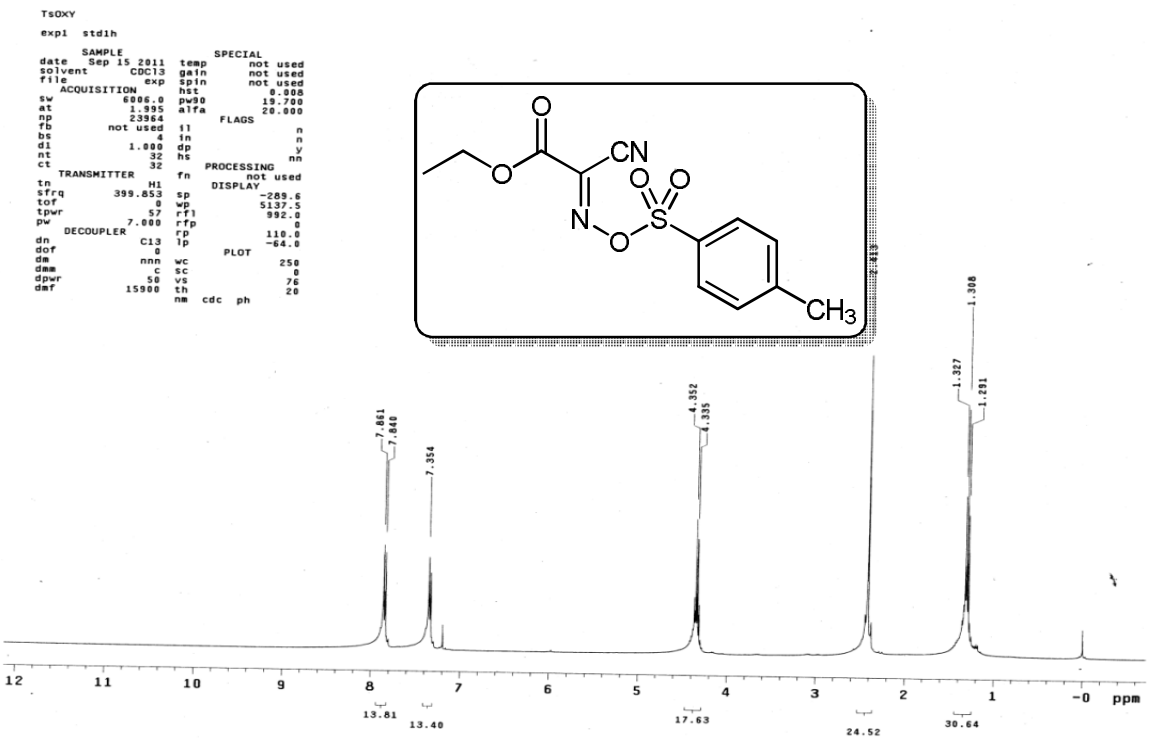


Figure 2S.1 (Table **2.1**, entry **8**)

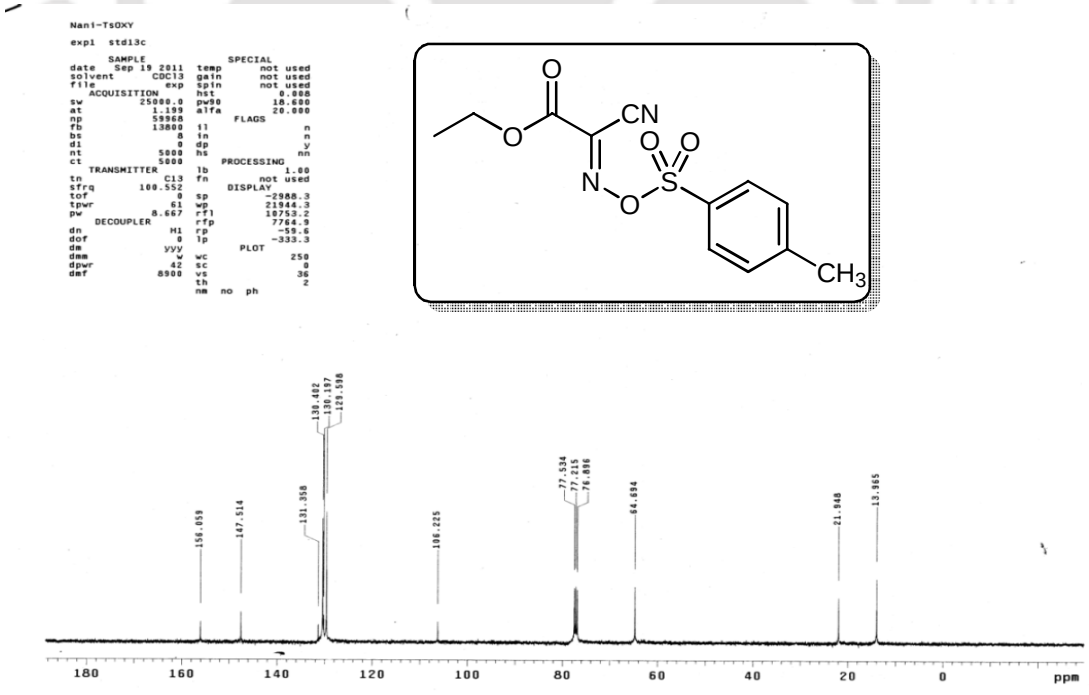


Figure 2S.2 (Table **2.1**, entry **8**)

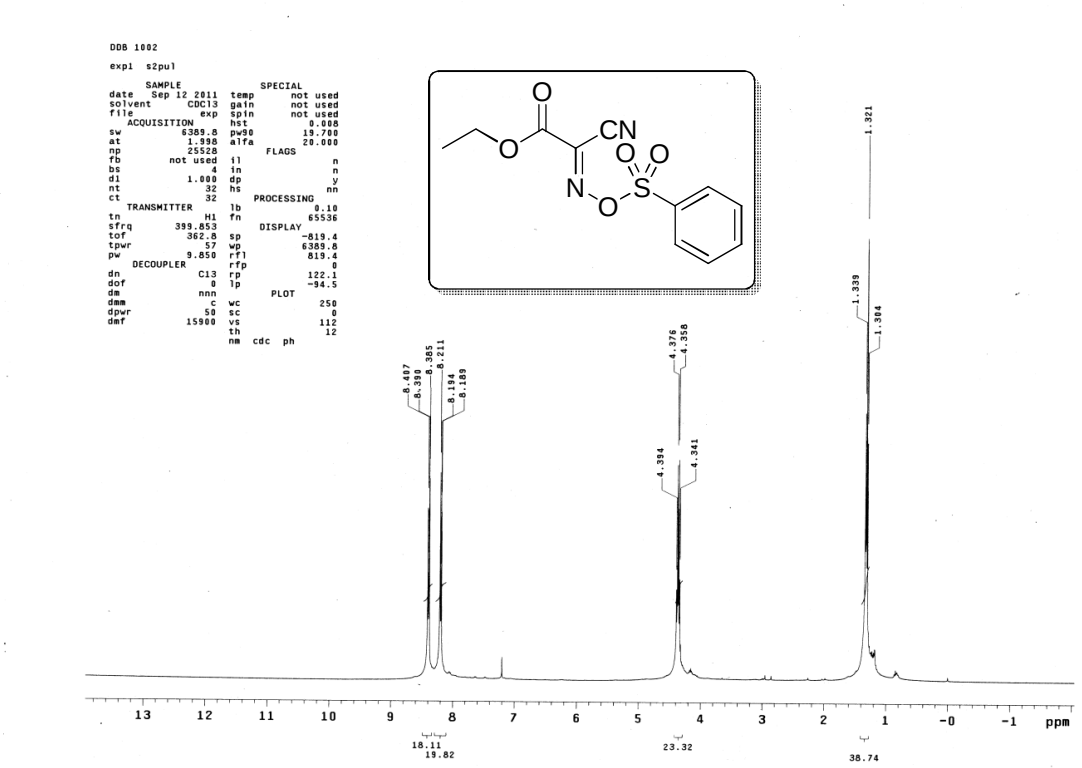


Figure 2S.3 (Table **2.1,** entry **4)**

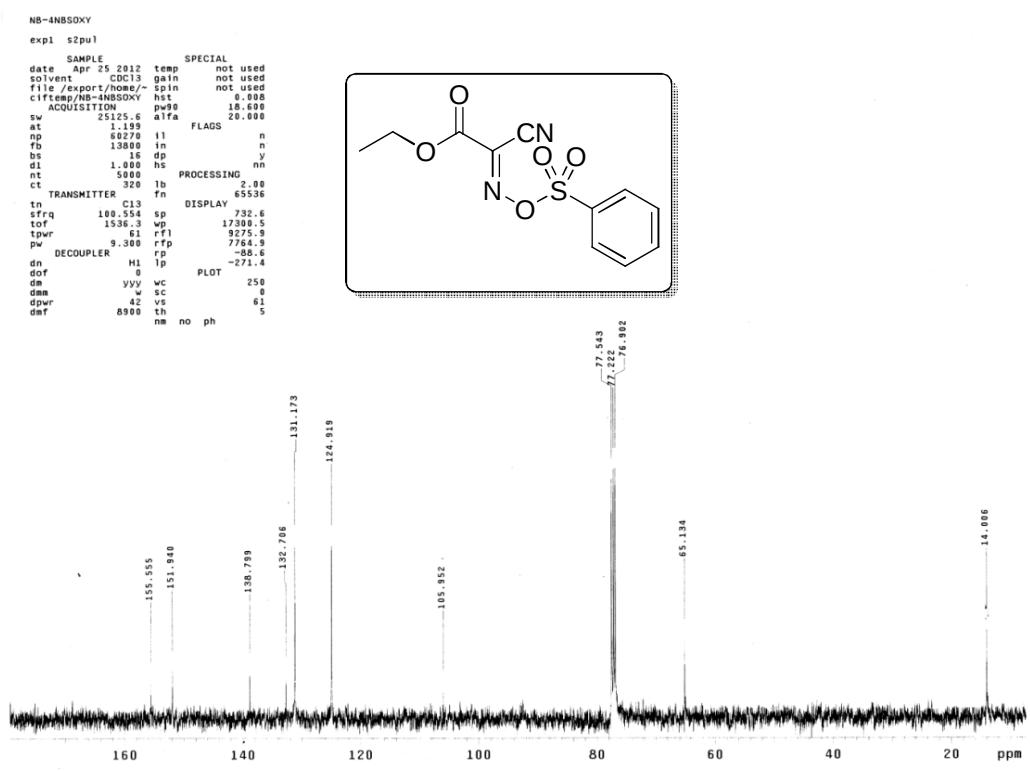


Figure 2S.4.

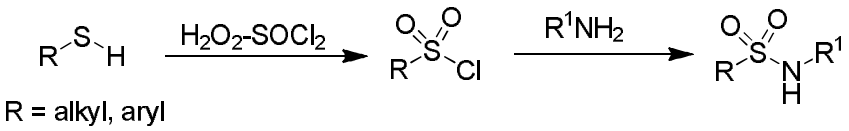
Chapter 3. Application of *N*-Hydroxy Benzotriazole Esters for Sulfonamide Synthesis

3.1 Introduction:

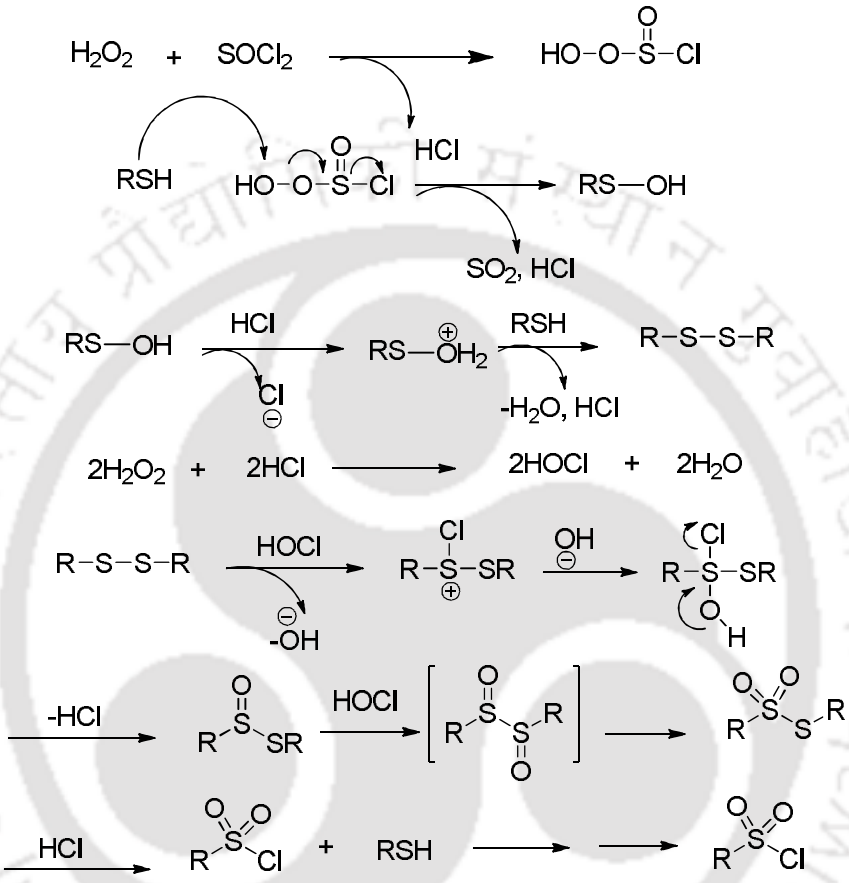
Since sulfonyl chlorides are reactive species it is difficult to store them for a long period of time. They are severe lungs effecting substrates. Furthermore, many of the sulfonic acids do not have the corresponding sulfonyl chlorides that are commercially available.[1] Certain drawbacks are associated with the available methods for the synthesis of sulfonyl chlorides also. For example, use of expensive or less easily available reagents, vigorous reaction conditions, long reaction time, tedious manipulations in the isolation of the pure products and side reactions, *etc*.[2] Therefore, it is important to develop the alternative methods that can be substitution for the chloride moiety of the sulfonyl chlorides to overcome these draw-backs.

Hence, it was sought to develop the methodologies for the synthesis of sulfonyl chlorides from sulfonic acids as shown in the following section (few methodologies are already discussed in the *Chapter 1*, Scheme **1.8**, Scheme **1.9** and Scheme **1.13**).[3]

Soheilizad *et al.* developed a method for the synthesis of sulfonyl chlorides from thiols using hydrozen peroxide and thionyl chloride and in turn sulfonamides with very good yields (Scheme **3.1**). Apart from the very good yields, it could obviate the purification problems as well as the use of costly and harsh reagents. The mechanism of this reaction is shown in scheme **3.2**.[4]

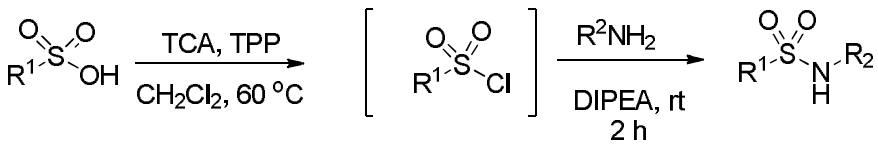


Scheme 3.1



Scheme 3.2

There was another report by *Meshram et al.* in which the sulfonyl chlorides were prepared from the corresponding sulfonic acids directly using trichloroacetonitrile and triphenyl phosphine as the chlorinating source (Scheme **3.3**).[5]



Scheme 3.3

In addition to these methodologies, while attempting to synthesize the adenosine based sulfonamide, Muller *et al.* have noticed that the reaction between corresponding sulfonyl chloride and amine with various experimental conditions were found to be not successful (*chapter 1*, Scheme **1.10**).[6] Thus, they had to develop the activation method using *para*-nitrophenol ester as activation and could have accomplished desired product with high yield. This inspired many to activate the sulfonic acids into various activated esters to furnish sulfonamides.

In this connection, Caddick *et al.* contributed in activating the sulfonic acids as corresponding sulfonate esters of pentafluorophenol (PFP) and 2,4,6-trichlro phenol (TCP). In the context of natural product synthesis it is often important to carry out sulfonylation of amines in presence of more than one amine functionality. Therefore, chemoselective synthesis of sulfonamides is an important transformation to avoid formation of undesired side products. Since PFP sulfonate esters are less reactive than sulfonyl chlorides and therefore require higher temperatures and harsh bases (65 °C with DBU). This chemo-selectivity was observed by the preferential nucleophilic attack by an amine on a sulfonyl chloride in the presence of a PFP sulfonate. Scheme **1.18** (*chapter* 1) shows the reaction of one equivalent of 4-methylbenzylamine with a mixture of benzenesulfonyl chloride and PFP tosylate which gave solely the product derived from the reaction with sulfonyl chloride by Caddick *et al*.[7]

Although, these methodologies were good for the specific purposes, yet there were few draw-backs associated with them. For example, the use of poly-halogenated compounds and non-ambient conditions were inevitable though contrary to the green chemistry recommendations. Furthermore, as our drug discovery endeavor is concerning to the synthesis of the specified peptide based targets (Figure **1.5**), it was necessary to develop an alternative activation

protocol of sulfonic acids that would facilitate the sulfonamide synthesis. Effort to design alternative activation strategy of sulfonic acids not only may reduce handling problems but also it may sometimes generate more reactive alternative as shown in scheme **3.1**.

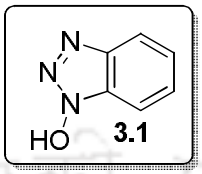
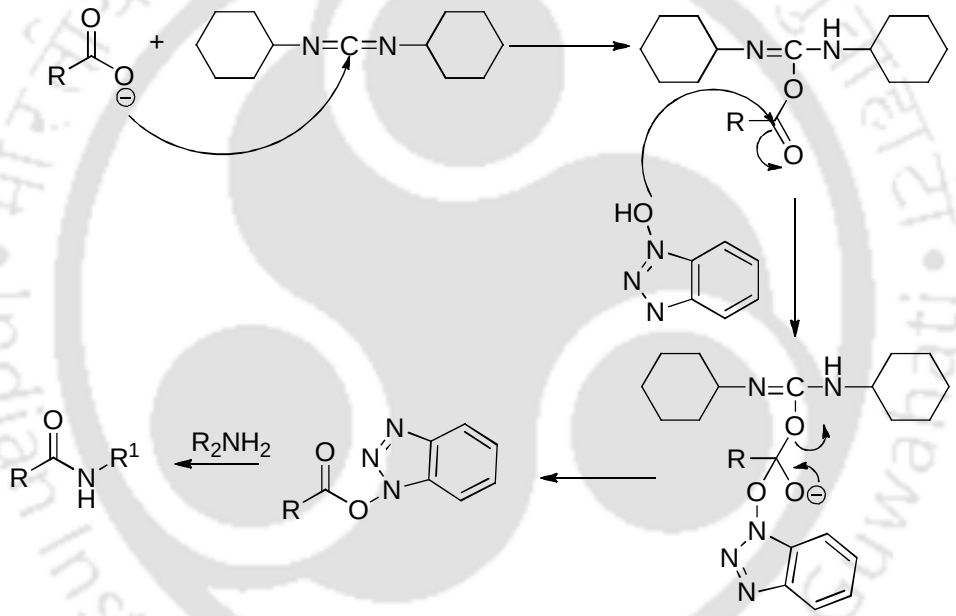


Figure 3.1 *N*-Hydroxy benzotriazole



Scheme 3.4

On the other hand, sometimes it may lower the reactivity of the activated sulfonate esters that offer remarkable chemoselectivity. We wondered whether *N*-Hydroxy benzotriazole (HOBt) **3.1** could be used for devising such an alternative activation of sulfonic acids. HOBt is a potential reagent for peptide synthesis and is used for activation of the carboxylic acid end to the corresponding HOBt ester which would then be prone to nucleophilic attack of alcohols,

amines and amino acids to produce esters, amides and peptides in combination with dicyclohexyl carbodiimide (DCC) as shown in scheme **3.4**. Furthermore, this is best known as racemization suppressant while dealing with the chiral molecules in particular the amino acids.[8]

Hydroxy-benzotriazole based reagents probably represent the widest class of coupling reagents. Although difference in reactivity was reported by few scientists there is practically no difference, as exemplified by Hachman. HBTU, TBTU and HMBDU *etc.* are HOBt derived coupling reagents which usually perform very well. Surprisingly, the potential explosive properties of these reagents are almost always disregarded.[9]

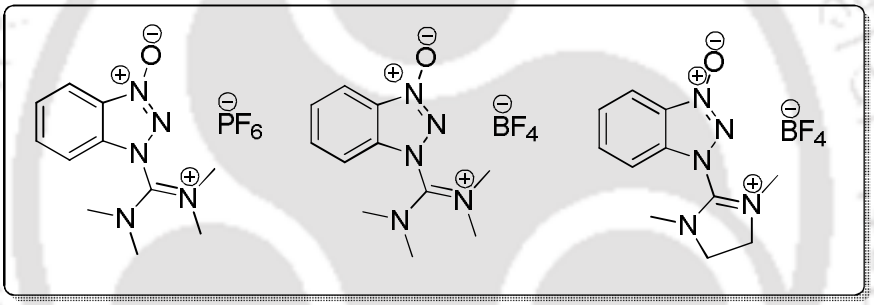


Figure 3.2 HOBt peptide coupling reagents with F as anion

Li *et al.* designed and synthesized immonium/carbonium type coupling reagents, such as BOMI, BDMP, BPMP *etc.* which showed the best results, achieving 90% conversion within 10 min during the coupling of Z-Gly-Phe-OH with Val-OMe (Anteunis test). In addition to that, epimerization was low, BOMI displaying 3.1% and BDMP 2.3% of the DL-isomer. However, these reagents were not compared to the classic reagents such as HATU or PyBOP. As an application, these reagents were used to carry out the total synthesis of Cyclosporine O, an immunosuppressive agent.[10]

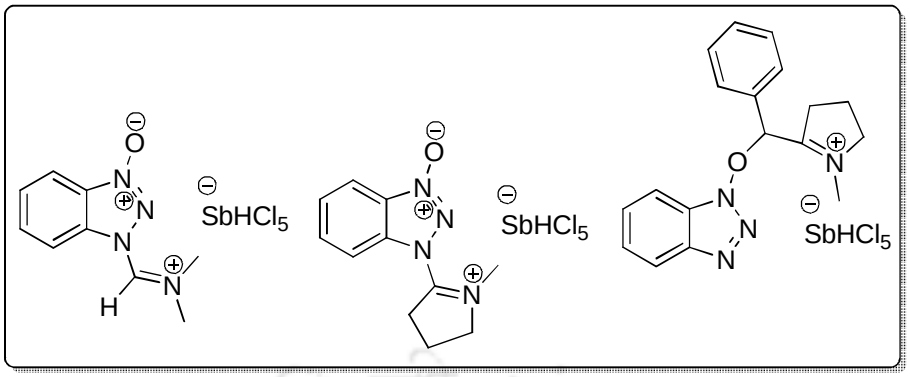
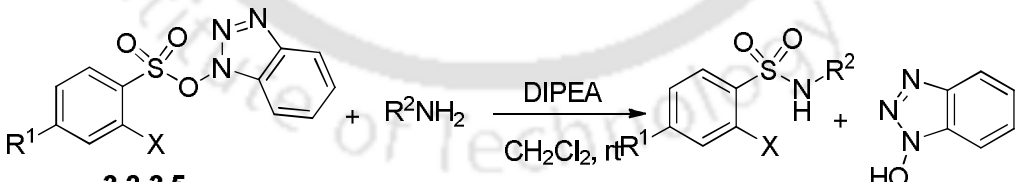


Figure 3.3 HOBt derived peptide coupling reagents with Sb as anion

3.2 Results and discussion:

We first prepared the *N*-hydroxy benzotriazole sulfonate ester of *p*-TsOH (**3.2**) by the reaction of pTsCl and HOBt in the presence of base. Then, analogues of that were prepared varying substitution on the aromatic ring of the sulfonic acid (**3.3-3.5**). Having the *N*-Hydroxy benzotriazole sulfonate ester of *p*-TsOH at hand, we took the benzyl amine as the model substrate to examine its reactivity in DCM solvent along with DIPEA as base (Scheme **3.5**). Interestingly, we found its reactivity was good to produce the corresponding sulfonamide. Thus, we went to envisage generality to varieties of amines.



3.2) $R^1 = CH_3$, X = H
3.3) $R^1 = NO_2$, X = H
3.4) R^1 = H, $X = NO_2$
3.5) R^1 = H, X = H

Scheme 3.5

Table 3.1. Synthesis of various sulfonamides using *N*-Hydroxy benzotriazole esters.

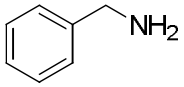
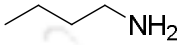
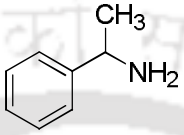
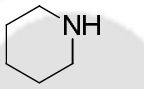
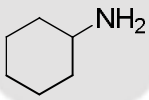
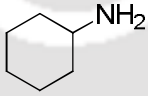
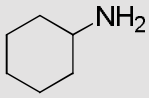
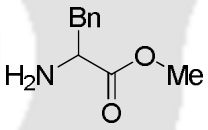
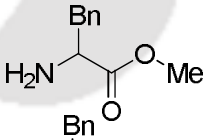
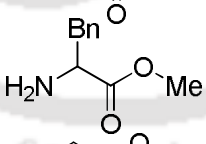
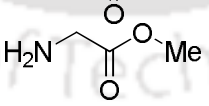
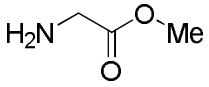
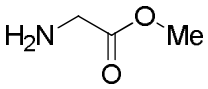
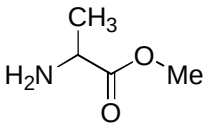
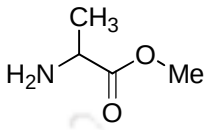
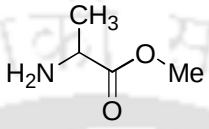
entry	sulfonate ester	amine	time (h)[b]	yield (%)[c]
1	$R^1 = CH_3$, X = H		1.5	75
2	$R^1 = CH_3$ X = H		2.5	60
3	$R^1 = CH_3$ X = H		2	84
4	$R^1 = CH_3$ X = H		2	91
5	$R^1 = CH_3$ X = H		2.5	80
6	$R^1 = H$ X = H		1	84
7	$R^1 = NO_2$ X = H		1	90
8[a]	$R^1 = CH_3$ X = H		--	n.d.
9	$R^1 = H$ X = H		7	34
10	$R^1 = NO_2$ X = H		2.5	47
11	$R^1 = CH_3$ X = H		2	71
12	$R^1 = NO_2$ X = H		1.5	82
13	$R^1 = H$ X = NO_2		1.5	79

Table **3.1** continues……

entry	sulfonate ester	amine	time (h)[b]	yield (%)[c]
14	$R^1 = CH_3$ X = H		2.5	65
15	$R^1 = NO_2$ X = H		2.5	76
16	$R^1 = H$ $X = NO_2$		2.5	67

[a]The reaction was continued till 10 h and from TLC no new spot was noticed and hence the reaction was aborted. [b]TLC was checked for every 30 min. [c]Yield refers to the isolated yield after column chromatographic purification. All the reported products were characterized with ^{1}H-NMR, IR and ESI-MS. All the new compounds were characterized completely.

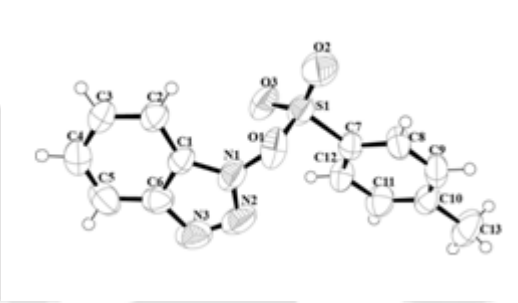


Figure 3.3. ORTEP diagram of TsOBt with 50% ellipsoid (CCDC # 834974).

As it was shown in Table **3.1** all the amines that include primary and secondary, underwent the reaction to furnish the products in excellent yields. The same method was extended to amino acid esters, which also showed similar reactivity except for sterically hindered methyl ester of phenylalanine. Reaction of TsOBt with methyl ester of phenylalanine did not progress at all. However, increasing the electrophilicity by removing the electron donating methyl group on benzene ring of the sulfonyl chloride showed better reactivity by resulting 34% isolated yield, although the reaction took longer time (7 h). On the other hand, further

increment of electrophilicity by inserting an electron withdrawing group increased the yield (47%) and reduced the reaction time as well (2.5 h). By this observation, we summerise that this scheme is sensitive to the steric and electronic factors of the substrates of the sulfonate esters and nature of the amine being used. Therefore, we took up few more examples. The same difference in reactivity was even found when cyclohexyl amine was used with variation of the substitution on the benzene ring of the sulfonate esters. When electron donating methyl group was present the reaction took little longer time (2.5 h), the reaction time was reduced to 1 h when methyl group was removed and an electron withdrawing group was inserted. The variation of the position of the nitro group also influences the reaction yield.

3.3 Conclusion:

As one of our objectives, we found an alternative to pentafluorophenol, trichlorophenol, *p*-nitrophenol *etc*. to facilitate the sulfonamide synthesis by eliminating sulfonyl chlorides. Yet, it is a practical problem to synthesize the HOBt activated esters of sulfonic acids directly from the sulfonic acids as heating conditions were necessary. In order to overcome this difficulty, the work was extended further, which is included in one of the following chapters.

3.4 Experimental Section:

3.4.1 General information:

All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. All the sulfonyl chlorides were freshly recrystallized before use. Melting points were uncorrected and determined with a Buchi-540 apparatus. Thin layer chromatograms were run on glass plates coated with silica gel G for TLC, using solvent

systems EtOAc/Hexane. All the compounds were purified by column chromatography using 60-120 mesh silica gel from Spectrochem (India). ^{1}H-NMR (400 MHz for ^{1}H) was recorded using DRX-400 Varian spectrometer using $CDCl_3$ as solvent unless mentioned otherwise. Chemical shifts were reported in parts per million (ppm), internal reference (0.05% to 1%) tetra methyl silane. Coupling constants (*J*) were reported in Hz singlet(s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). Low resolution mass spectra were recorded on a Micromass Q-TOF ESI MS instrument (model HAB273).

3.4.2 General procedure for the synthesis of sulfonamides from sulfonate esters *N*-Hydroxy benzotrizoles:

An oven dried 25 mL R.B. flask equipped with magnetic stir bar was loaded with TsOBt (289 mg, 1 mmol) in DCM (1 mL) followed by DIPEA (1 equiv.). Then amine (1 equiv.) was added followed by 1 mL of DCM for amines and 1.5 mL of 1:3 DMF: DCM mixture for amino acid esters. The progress of the reaction was checked by TLC. After completion of the reaction, the reaction mixture was diluted with 10 mL of DCM and organic layer was washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), and saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$. Then it was dried in vacuum and purified by column chromatography.

3.4.3 General procedure for the synthesis of sulfonate esters of *N*-Hydroxy benzotriazole esters:

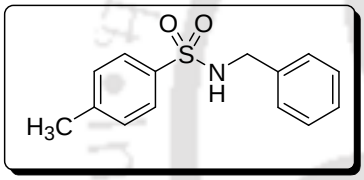
An oven dried 25 mL two necked R.B. flask equipped with magnetic stir barwas loaded with HOBt (1 mmol) in DCM (5 mL) followed by the addition of DIPEA (1 equiv.) under nitrogen at 0˚ C. Then the respective sulfonyl chloride (1 equiv.) was added drop wise for about 20 min

along with 1 mL of DCM. Then it was continued to stir at room temperature while being monitored by the TLC. After completion of the reaction, the reaction mixture was diluted with 10 mL of DCM and organic layer was washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), and saturated NaCl solution (2×10 mL), then the organic layer collected and dried over anhydrous $CaCl_2$. Finally it was dried in vaccuo and purified by column chromatography.

3.5 Characterization data:

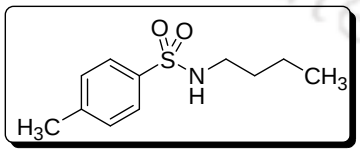
3.5.1 Characterization data for sulfonamides:

1) *N*-Benzyl-4-methylbenzenesulfonamide (entry 1, Table 3.1):



R_f product 0.58 (EtOAc/Hexane, 1:4), Yield 75%, white solid, mp 87-89 °C. IR (KBr, ν/cm^{-1}) 3262, 3027, 1594, 1492, 1450, 1320, 1156. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77-7.75 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.31-7.26 (m, 5H, 5×Ar**H**), 7.20-7.18 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 4.74 (br s, 1H, N**H**), 4.11 (s, 2H, C**H**$_2$), 2.43 (s, 3H, C**H**$_3$). LRMS (ESI) m/z 261 $[M]^+$.

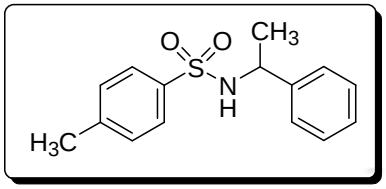
2) *N*-Butyl-4-methylbenzenesulfonamide (entry 2, Table 3.1):



R_f product 0.52 (EtOAc/Hexane, 1:4), Yield 60%, white solid, mp 44 °C. IR (KBr, ν/cm^{-1}) 3470, 3090, 1652, 1358, 1163.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77-7.75 (d, 2H, *J* = 8 Hz, 2xAr**H**), 7.31-7.29 (d, 2H, *J* = 8 Hz, 2xAr**H**), 5.12 (br s, 1H, N**H**), 2.91 (t, 2H, *J* = 6.8 Hz, NHC**H**$_2$), 2.42 (s, 3H, C**H**$_3$), 1.45-1.41 (m, 2H, NHCH$_2$C**H**$_2$), 1.30-1.25 (m,

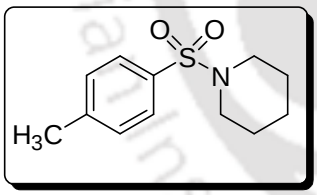
2H, **CH$_2$**CH$_3$), 0.85-0.83 (t, 3H, *J* = 5.6 Hz, CH$_2$**CH$_3$**). LRMS (ESI) m/z 228 $[M+H]^+$.

3) 4-Methyl-*N*-(1-phenylethyl)benzenesulfonamide (entry 3, Table 3.1):



R_f product 0.46 (EtOAc/Hexane, 1:4) Yield 70%, white solid, mp 44 °C. IR (KBr, ν/cm^{-1}) 3307, 2931, 2854, 1926, 1597, 1494, 1427, 1159, 1092, 925. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55-7.53 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 7.09-7.07 (d, 5H, *J* = 8 Hz, 5×Ar**H**), 7.02-7.01 (m, 2H, 2×Ar**H**), 5.22-5.21 (d, 1H, *J* = 3.6 Hz, N**H**), 4.38-4.35 (t, 1**H**, *J* = 12 Hz, C**H**Ar), 2.29 (s, 3H, ArC**H$_3$**), 1.33-1.32 (d, 3H, *J* = 6.8 Hz, CHC**H$_3$**). LRMS (ESI) m/z 276 $[M+H]^+$.

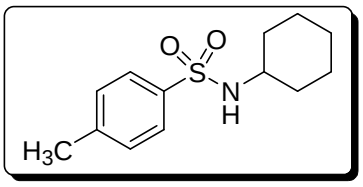
4) 1-Tosylpiperidne (entry 4, Table 3.1):



R_f product 0.42 (EtOAc/Hexane, 1:4), Yield 80%, white solid, mp 91-93 °C. IR (KBr, ν/cm^{-1}) 2946, 1739, 1446, 1337, 1263. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64-7.62 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.33-7.31 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 2.97 (t, 4H, *J* = 5.6 Hz, 2×C**H$_2$**), 2.43 (s, 3H, C**H$_3$**), 1.66-1.61 (m, 4H, 2×C**H$_2$**), 1.42-1.39 (m, 2H, C**H$_2$**). LRMS (ESI) m/z 240 $[M+H]^+$.

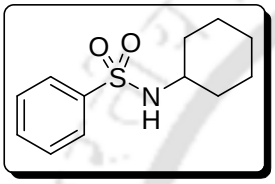
5) *N*-Cyclohexyl-4-methylbenzenesulfonamide (entry 5, Table 3.1):

R_f product 0.61 (EtOAc/Hexane, 1:4) Yield 80%, white solid, mp 87-89 °C. IR (KBr, ν/cm^{-1}) 3328, 2937, 1755,



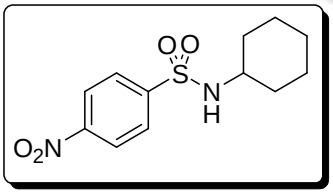
1684. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79-7.77 (d, 2H, *J* = 8.4 Hz, 2xAr**H**), 7.32-7.28 (d, 2H, *J* = 8.4 Hz, 2xAr**H**), 4.97 (br s, 1H, N**H**), 3.11-3.09 (m, 1H, NHC**H**), 2.42 (s, 3H, C**H$_3$**), 1.74-1.72 (m, 4H, 2xNHCHC**H$_2$**), 1.63-1.60 (m, 4H, 2xNHCHCH$_2$C**H$_2$**), 1.27-1.07 (m, 2H, NHCHCH$_2$CH$_2$C**H$_2$**). LRMS (ESI) m/z 254 $[M+H]^+$.

6) *N*-Cyclohexylbenzenesulfonamide (entry 6, Table 3.1):



R_f product 0.53 (EtOAc/Hexane, 1:4), Yield 86%, yellow oil. IR (KBr, ν/cm^{-1}) 3288, 2855, 1728, 1443, 1161, 1074. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.83-7.81(d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 7.48-7.40 (m, 3H, 3xAr**H**), 4.98-4.96 (d, 1H, *J* = 7.6 Hz, N**H**), 3.06-3.02 (m, 1H, NHC**H**), 1.67-1.52 (m, 4H, 2xNHCHC**H$_2$**), 1.27-1.15 (m, 4H, 2×NHCHCH$_2$C**H$_2$**), 1.02-1.00 (m, 2H, NHCHCH$_2$CH$_2$C**H$_2$**). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 141.6, 132.5, 129.1, 127.0, 52.7, 33.9, 25.2, 24.7; LRMS (ESI) m/z 262.07 $[M+Na]^+$.

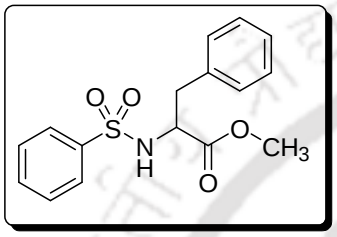
7) *N*-Cyclohexyl-4-nitrobenzenesulfonamide (entry 7, Table 3.1):



R_f product 0.51 (EtOAc/Hexane, 1:4) Yield 89%, yellow solid. IR (KBr, ν/cm^{-1}) 3288, 2928, 1608, 1525, 1160, 1073. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.31-8.28(d, 2H, *J* = 9.3Hz, 2×Ar**H**), 8.06-8.02 (d, 2H, *J* = 8.8 Hz, 2xArH), 4.75(br s, 1H, N**H**), 3.15-3.11 (m, 1H, NHC**H**), 1.70-1.58 (m, 4H, 2xNHCHC**H$_2$**), 1.26-1.08 (m, 4H,

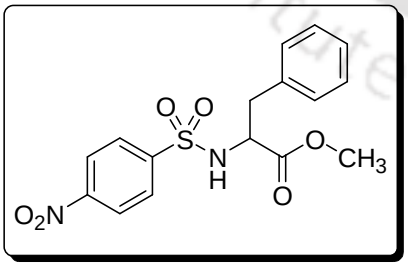
2×NHCHCH$_2$C**H**$_2$), 1.05-1.03 (m, 2H, NHCHCH$_2$CH$_2$C**H**$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.9, 147.6, 128.2, 124.4, 53.2, 33.9, 25.0, 24.7; LRMS (ESI) m/z 285.31 $[M+Na]^+$.

8) Methyl 3-phenyl-2-(phenylsulfonamido)propanoate (entry 9, Table 3.1):



R_f product 0.24 (EtOAc/Hexane, 1:4) Yield 34%, colorless oil. IR (KBr, ν/cm^{-1}) 3435, 2929, 1743, 1447, 1164, 1036,.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm (400 MHz, $CDCl_3$) 7.69-7.66 (m, 2H, 2xAr**H**), 7.47-7.45 (d, 2H, *J* = 7.2 Hz, 1xAr**H**), 7.39-7.36 (t, 4H, 2xAr**H**), 7.19-7.16 (m, 4H, 4xAr**H**), 5.11-5.09 (d, 1H, N**H**), 4.16-4.12(m, 1H, C**H)**, 4.06(s, 3H, C**H$_3$**), 3.44-3.37 (m, 1H, C**H**HAr), 2.97-2.95 (m, 1H, C**H**HAr), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.4, 139.8, 135.1, 132.9, 129.5, 129.1, 128.7, 127.4, 127.2, 56.9, 52.5, 39.5; LRMS (ESI) m/z 320.08 $[M+H]^+$.

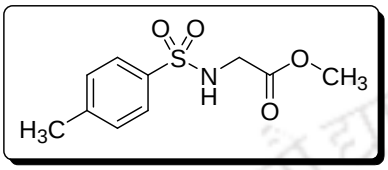
9) Methyl 2-(4-nitrophenylsulfonamido)-3-phenylproponoate (entry 10, Table 3.1):



R_f product 0.23 (EtOAc/Hexane, 1:4) Yield 83%, pale yellow solid, mp 153 °C. IR (KBr, ν/cm^{-1}) 3272, 1722, 1523, 1347, 1313, 1168, 1092, 1008, 855, 739. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm (400 MHz, $CDCl_3$) 8.16-8.14 (d, 2H, *J* = 8 Hz, 2xAr**H**), 7.78-7.76 (d, 2H, *J* = 8 Hz, 2xAr**H**), 7.16-7.14 (m, 3H, 3xAr**H**), 6.99-6.96 (m, 2H, 2xAr**H**), 5.30 (s, 1H, N**H**), 4.21-4.16 (m, 1H, C**H**), 3.54 (s, 3H, -OC**H$_3$**),

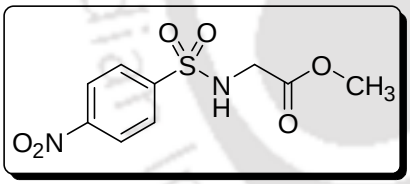
3.07-3.02 (dd, 1H, J_1 = 5.6 Hz, J_2 = 4.8 Hz, C**H**HAr), 3.00-2.94 (dd, J_1 = 7.2 Hz, J_2 = 7.2 Hz, 1H, CH**H**Ar). LRMS (ESI) m/z 365 $[M+H]^+$.

10) Methyl 2-(4-methylphenylsulfonamido)acetate (entry 11, Table 3.1):



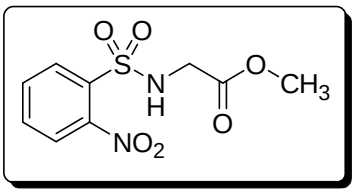
R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 75%, white solid, mp 151 °C. IR (KBr, ν/cm^{-1}) 3262, 2943, 1729, 1532, 1350, 1336, 1236, 1159, 830, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77-7.74 (d, 2H, J = 8 Hz, 2×Ar**H**), 7.32-7.30 (d, 2H, J = 8. Hz, 2×Ar**H**), 5.06 (br s, 1H, N**H**), 3.80 (d, 2H, J = 4 Hz, CH_2), 3.64 (s, 3H, -OC**H**$_3$), 2.43 (s, 3H, C**H**$_3$). LRMS (ESI) m/z 244 $[M+H]^+$.

11) Methyl 2-(4-nitrophenylsulfonamido)acetate (entry 12, Table 3.1):



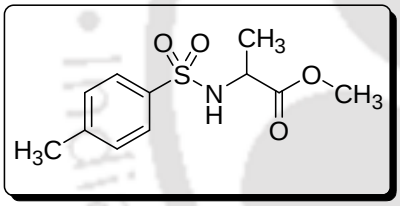
R_f product 0.26 (EtOAc/Hexane, 1:4) Yield 75%, pale yellow solid. IR (KBr, ν/cm^{-1}) 3344, 1743, 1541, 1403, 1369, 1347, 1225, 1163, 1127, 837, 785.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36-8.34 (d, 2H, J = 9.2 Hz, 2×Ar**H**), 8.06-8.04 (d, 2H, J = 8.8 Hz, 2×Ar**H**), 5.35 (br s, 1H, N**H**), 3.86 (d, 2H, J = 4 Hz, C**H**$_2$), 3.65 (s, 3H, -OC**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.8, 152.3, 148.4, 126.4, 124.2, 50.4, 41.8; LRMS (ESI) m/z 275 $[M+H]^+$.

12) Methyl 2-(2-nitrophenylsulfonamido)acetate (entry 13, Table 3.1):



R_f product 0.58 (EtOAc/Hexane, 1:9) Yield 75%, pale yellow solid. IR (KBr, ν/cm^{-1}) 3305, 1752, 1539, 1439, 1358, 1208, 1169, 976.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.11-8.08 (m, 1H, Ar**H**), 7.95-7.92 (m, 1H, Ar**H**), 7.76-7.73 (m, 2H, 2×Ar**H**), 6.08 (br s, 1H, N**H**), 4.02 (s, 2H, C**H$_2$**), 3.61 (s, 3H, -OC**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.0, 147.6, 135.8, 133.5, 132.8, 129.4, 122.5, 52.6, 48.7; LRMS (ESI) m/z 275 $[M+H]^+$.

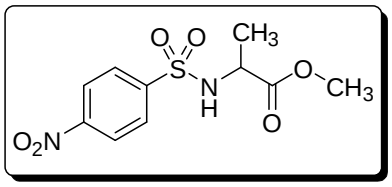
13) Methyl 2-(4-methylsulfonamido)proponoate (entry 14, Table 3.1):



R_f product 0.58 (EtOAc/Hexane, 1:9) Yield 75%, white solid, mp 137-139 °C. IR (KBr, ν/cm^{-1}) 3342, 3026, 1734, 1589, 1340, 1160. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.74-7.72 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 7.30-7.28 (d, 2H, *J* = 8. Hz, 2×Ar**H**), 5.37 (d, 1H, *J* = 8.4 Hz, N**H**), 4.00-3.96 (q, 1H, *J* = 7.2 Hz, C**H**), 3.54 (s, 3H, -OCH_3), 2.42 (s, 3H, C**H$_3$**), 1.38-1.37 (d, 2H, *J* = 7.2 Hz, C**H$_3$**). LRMS (ESI) m/z 258 $[M+H]^+$.

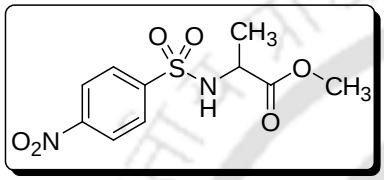
14) Methyl 2-(4-nitrophenylsulfonamido)proponoate (entry 15, Table 3.1):

R_f product 0.22 (EtOAc/Hexane, 1:4) Yield 75%, pale yellow solid, mp 111-113 °C. IR (KBr, ν/cm^{-1}) 3257, 1736, 1525, 1350, 1176, 1087, 973, 863.^{1}H NMR (400 MHz,



$CDCl_3$) δ ppm 8.38-8.35 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 8.07-8.05 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 5.62 (d, 1H, *J* = 8 Hz, N**H**), 4.12-4.08 (m, 1H, C**H**), 3.60 (s, 3H,-OC**H**$_3$), 1.44-1.42 (d, 3H, *J* = 7.2 Hz, C**H**$_3$). LRMS (ESI) m/z 289 $[M+H]^+$.

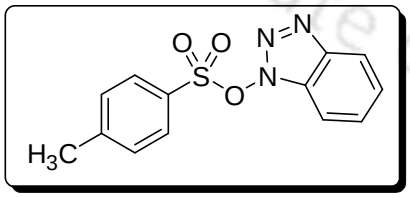
15) Methyl 2-(4-nitrophenylsulfonamido)proponoate (entry 16, Table 3.1):



R_f product 0.22 (EtOAc/Hexane, 1:4) Yield 75%, pale yellow solid, mp 111-113 °C. IR (KBr, ν/cm^{-1}) 3257, 1736, 1525, 1350, 1176, 1087, 973, 863.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38-8.35 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 8.07-8.05 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 5.62 (d, 1H, *J* = 8 Hz, N**H**), 4.12-4.08 (m, 1H, C**H**), 3.60 (s, 3H,-OC**H**$_3$), 1.44-1.42 (d, 3H, *J* = 7.2 Hz, C**H**$_3$). LRMS (ESI) m/z 289 $[M+H]^+$.

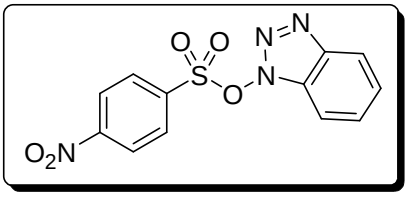
3.5.2 Characterization data of *N*-Hydroxy benzotriazole sulfonate esters

1) 1*H*-Benzo[*d*][1,2,3]triazol-1-yl 4-methanebenzenesulfonate



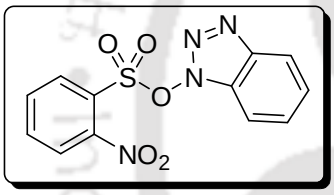
R_f product 0.61 (EtOAc/Hexane, 1:4), Yield 89%, white crystalline solid. IR (KBr, ν/cm^{-1}) 3305, 1752, 1539, 1439, 1358, 1169, 1126, 976, 856, .^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-8.0 (m, 1H, Ar**H),** 7.81-7.77 (m, 2H, 2×Ar**H**), 7.67-7.56 (m, 2H, 2×Ar**H**), 7.49-7.39 (m, 3H, 3×Ar**H**), 2.50 (s, 3H, C**H**$_3$). LRMS (ESI) m/z 290 $[M+H]^+$.

2) 1*H*-Benzo[*d*][1,2,3]triazol-1-yl 4-nitrobenzenesulfonate[7]



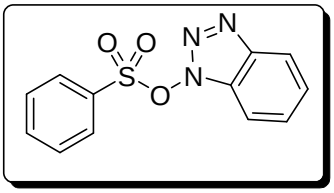
R_f product 0.52 (EtOAc/Hexane, 1:4) Yield 69%, pale yellow solid. IR (KBr, ν/cm^{-1}) 3375, 1752, 1539, , 1358, 1169, 1126, 976, 856, .^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.41-8.39 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 8.09-8.07(d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.98-7.95(m, 1H, Ar**H**), 7.66-7.57 (m, 2H, 2×Ar**H**), 7.43-7.40 (m, 1H, Ar**H**). LRMS (ESI) m/z 320 $[M]^+$ 321 $[M+H]^+$.

3) 1*H*-Benzo[*d*][1,2,3]triazol-1-yl 2-nitrobenzenesulfonate[7]



R_f product 0.58 (EtOAc/Hexane, 1:4) Yield 49%, pale yellow solid. IR (KBr, ν/cm^{-1}) 3305, 1752, 1539, 1439, 1358, 1169, 1126, 976, 856. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.11-8.08 (m, 1H, Ar**H**), 7.95-7.92 (m, 1H, Ar**H**), 7.76-7.73 (m, 4H, 4×Ar**H**), 7.40 (m, 2H, 2×Ar**H**). LRMS (ESI) m/z 321 $[M+H]^+$

4) 1*H*-Benzo[d][1,2,3]triazol-1-yl benzenesulfonate[7]



R_f product 0.54 (EtOAc/Hexane, 1:9) Yield 64%, colourless solid. IR (KBr, ν/cm^{-1}) 3404, 1620, 1446, 1393, 1158, 1017, 910 .^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.98-7.96 (d, 1H, Ar**H**), 7.91-7.90 (d, 1H, Ar**H**), 7.88-7.87 (d, 1H, Ar**H**), 7.80-7.76 (m, 1H, Ar**H**), 7.61-7.53 (m, 4H, 4×Ar**H**), 7.43-7.38 (m, 1H, Ar**H)**. ^{13}C NMR (100 MHz, $CDCl_3$) δ

ppm 136..4, 129.9, 129.7, 129.4, 128.4, 125.9, 125.4, 120.3, 109.3; LRMS (ESI) m/z 276 $[M+H]^+$.

Crystallographic data compound 1

1*H*-Benzo[*d*] [1, 2, 3] triazol-1-yl 4-methanebenzenesulfonate (TsOBt)

Crystal data: CCDC # 834974

	1*H* benzo[*d*][1, 2, 3] triazol-1-yl 4-methanebenzenesulfonamide
Formula	$C_{13}\ H_{11}\ N_3\ O_3\ S$
Mol. wt.	289.31
Crystal system	Triclinic
Space group	'C2/c'
Temperature /K	296 (2)
Wavelength /Å	0.71073
a /Å	19.828(2)
b /Å	9.5788(10)
c /Å	15.5044(17)
α/°	90.00
β/°	112.462(6)
γ/°	90.00
V/ $Å^3$	2721.4(5)
Z	8

Density/Mgm^{-3}	1.412
F(000)	1200
Total no. of reflections	3305
Reflections, $I > 2\sigma(I)$	2336
Max. 2θ/°	28.45
Ranges (h, k, l)	-26<= h <=22,-12<= k <=12 -20<= l <=17
Complete to 2θ (%)	96.2
Refinement method	Full-matrix least-squares on F^2
WR_2(all data)	0.1310
Gof (F^2)	1.008
R indices [$I > 2\sigma(I)$]	0.0410
R indices (all data)	0.0618

3.6 References:

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2) (a) Caddick, S.; Wilden, J. D.; Wadman, S. J.; Bush, H. D.; Judd, D. B. A new route to sulfonamides via intermolecular radical addition to pentafluorophenyl vinylsulfonate and subsequent aminolysis. *Org. Let*t. **200**2, *4*, 2549-2551; (b) Caddick, S.; Hamza, D.; Wadman, S.; Wilden, J. D. Solid-phase intermolecular radical reactions 2: Synthesis of *C*-glycopeptide mimetics via a novel acrylate acceptor. *Org. Lett.* **2002**, *4*, 1775-1777.

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3.7 Representative spectra:

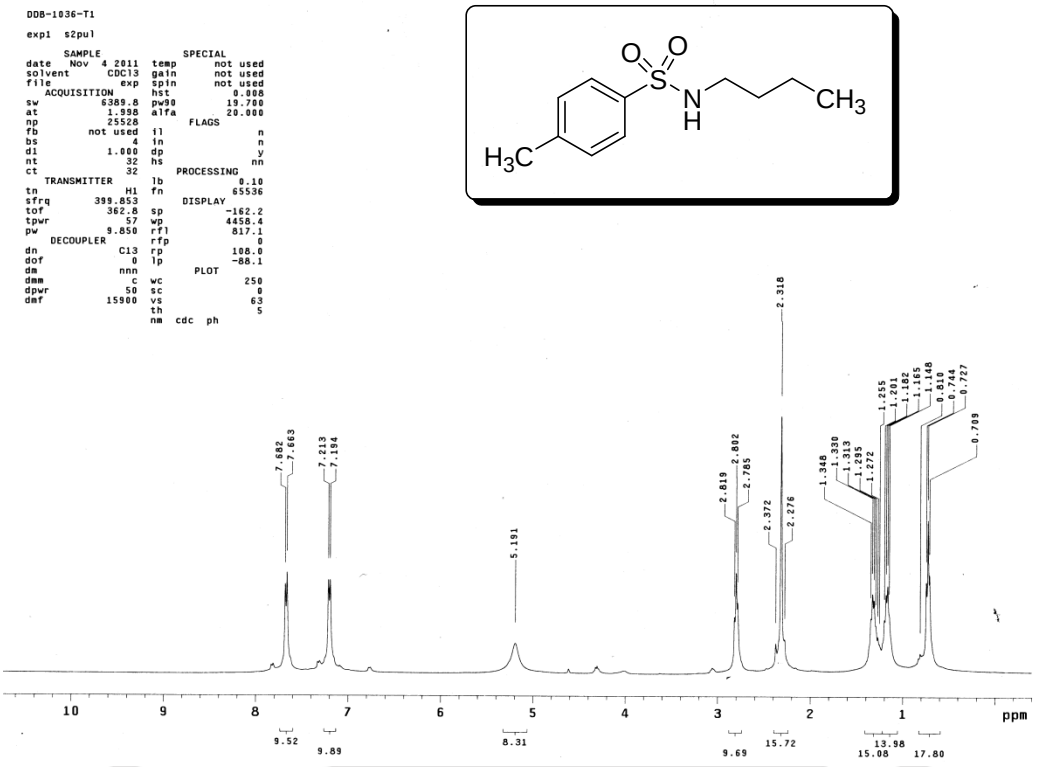


Figure S3.1 (Table **3.1**, entry **2**)

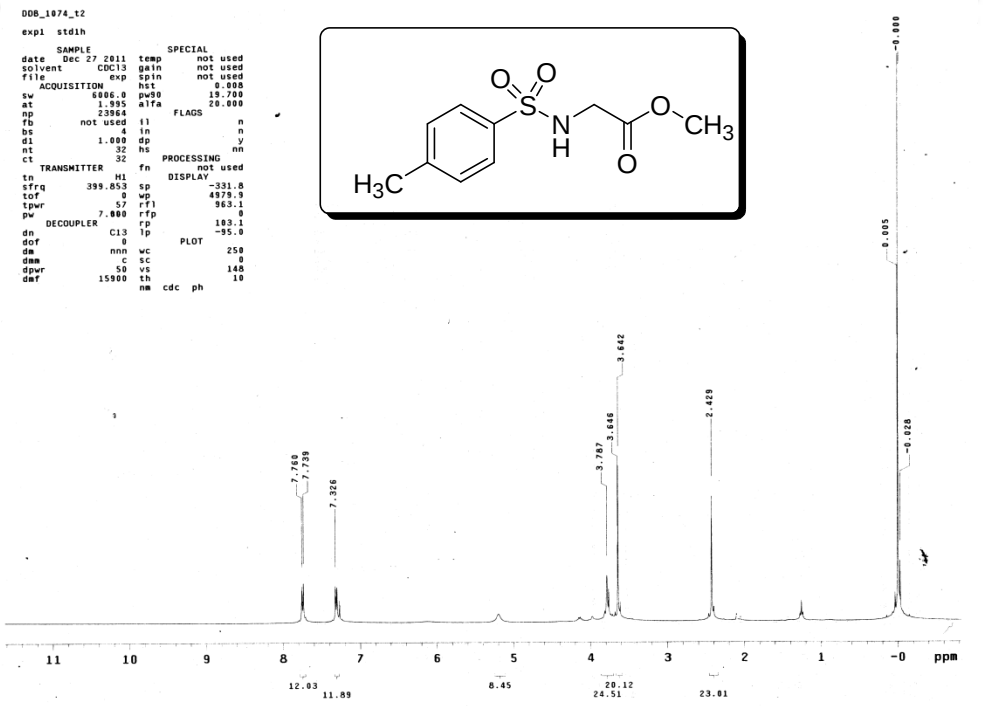


Figure S3.2 (Table **3.1,** entry **11)**

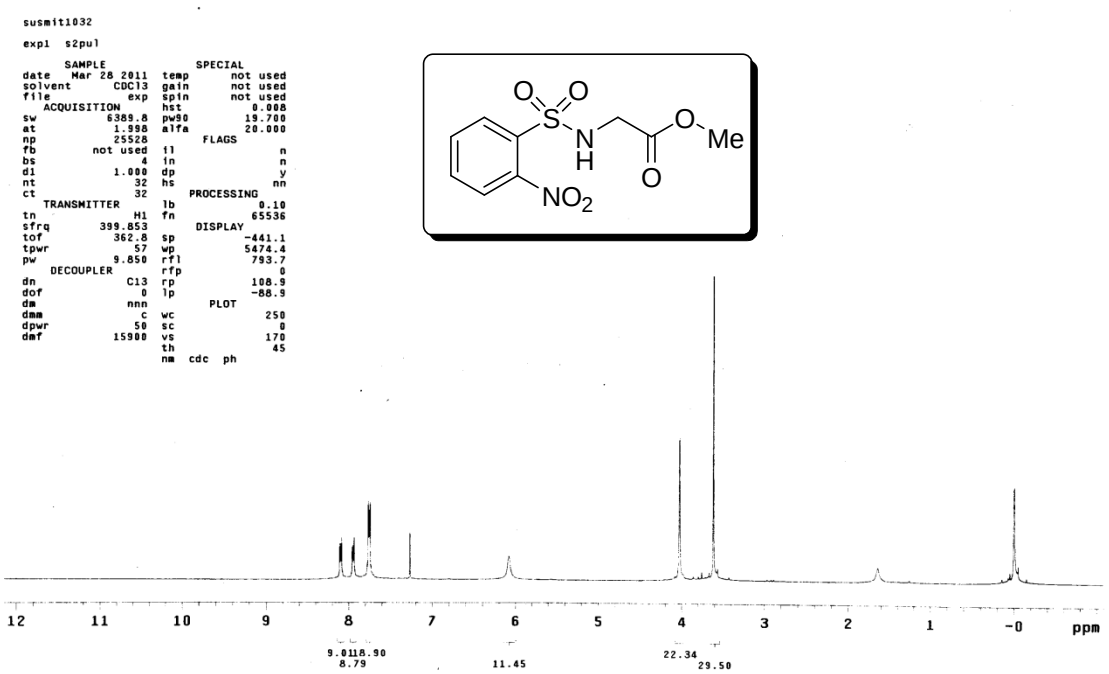


Figure S3.3 (Table **3.1,** entry **13)**

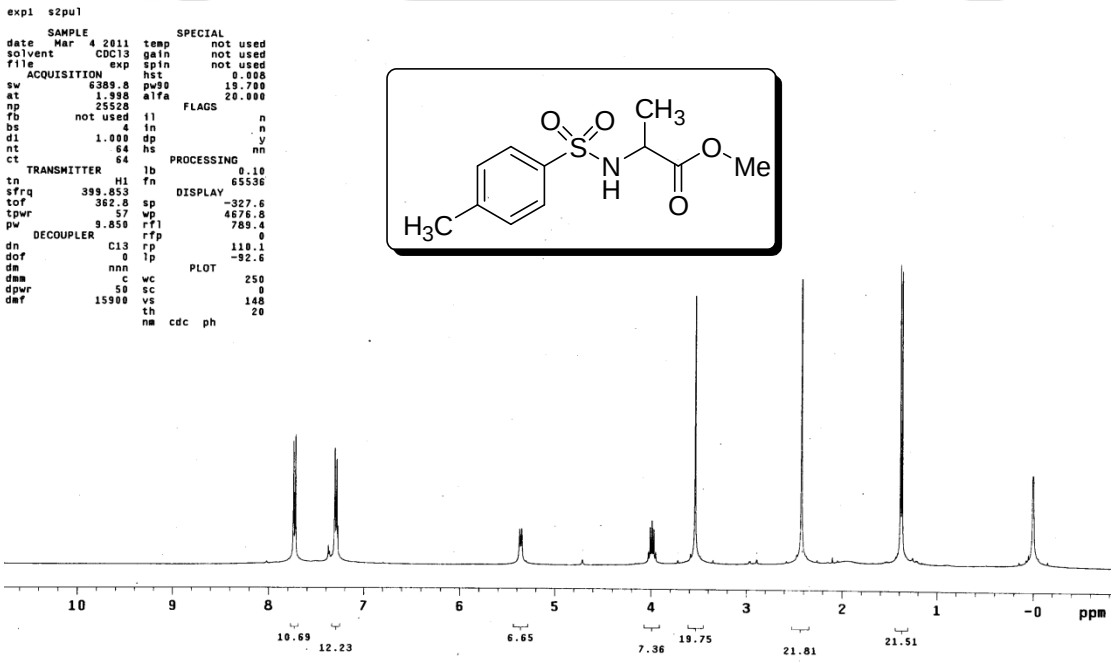


Figure S3.4 (Table **3.1**, entry **14**)

Chapter 4. Synthesis of *O*-Benzyl Hydroxamtes Employing the *N*-Hydroxy Benzotriazole Esters of Sulfonic Acids

4.1 Introduction:

In continuation to the development of the activated sulfonate esters as useful auxiliaries for certain organic transformations,[1] we wanted further to demonstrate the synthesis of one important class of organic compounds i.e. hydroxamates, using sulfonate esters. Sulfonate esters are in use as coupling reagents for the reaction between acids and alcohols, amines or amino acids to produce esters, carboxamides and peptides respectively. Hydroxamic acids are also important class of organic compounds that have the following medicinal applications.

4.1.1 Hydroxamic acids as metal ion chelators:

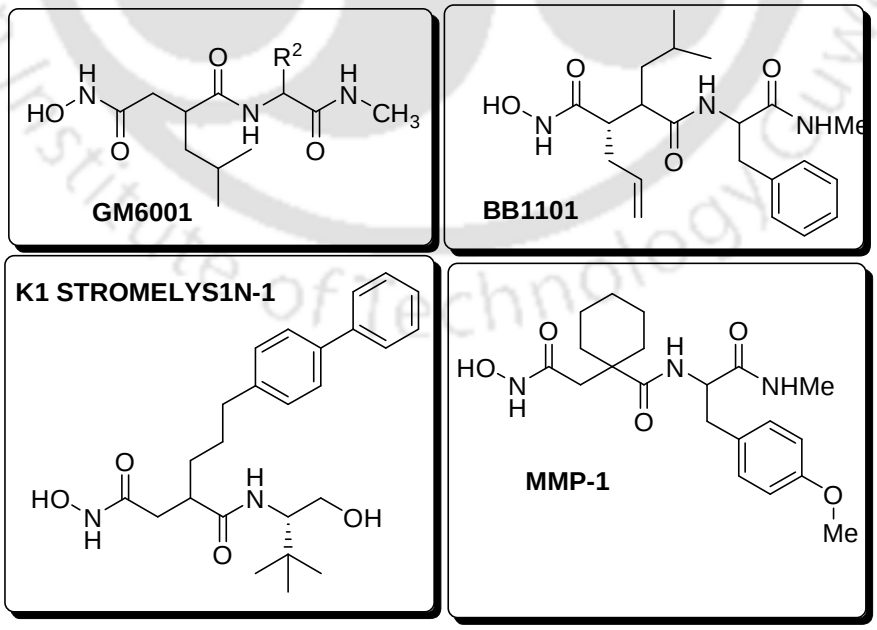


Figure 4.1 Matrix metalloprotease enzyme inhibitors

Matrix metalloproteinases (MMPs), also called matrixins, are a family of structurally related zinc-containing enzymes that mediate the breakdown of connective tissue and are therefore targets for therapeutic inhibitors in many inflammatory, malignant and degenerative diseases. The important structural constituent of MMP's is hydroxamic acids (Figure **4.1**).[2]

4.1.2 Hydroxamates in siderophores:

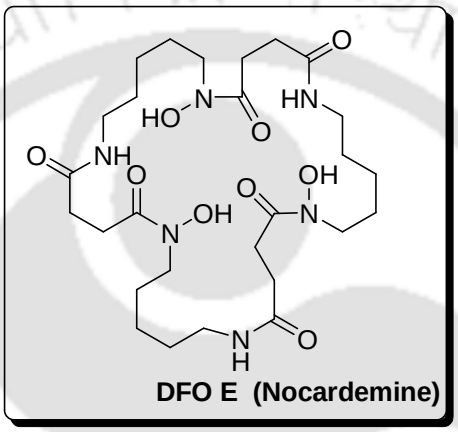


Figure 4.2 Siderophore

Iron plays an essential role in the evolution of nearly all forms of life on earth. Although iron is one of the most abundant elements on the planet, its pivotal role depended on the development of effective methods for its assimilation. Ionic forms of iron especially iron (III), its most common state, are insoluble under physiological conditions. To circumvent the solubility problem, many microbial plant and even higher organisms synthesize and utilize specific low molecular weight iron chelators called siderophores.[3] One of such siderophores is shown in Figure **4.2**.

4.1.3 Pseudo-peptides:

Structural manipulations of biologically active peptides are often performed in order to improve the properties of these peptides for research in drug development. An important class of these compounds is the back bone modified peptides or "pseudo-peptides", such as aza-peptide and oxa-peptides (Figure **4.3**).[4] Aza peptides are those in which the alpha carbon of an amino acid in a peptide chain is replaced by nitrogen atom, where as if the replacement is with oxygen, then it is called oxa-peptide. Therefore, the hydroxamic acids fall into such an important class of backbone modified peptides that give room for the development of new drugs in medicinal chemistry.

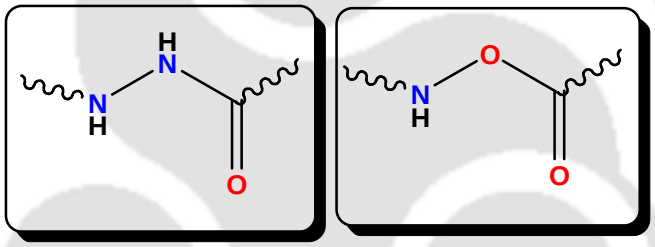
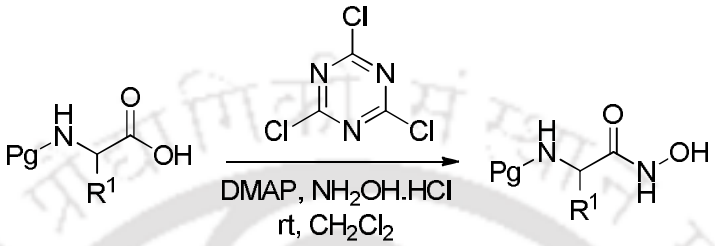


Figure 4.3 Back-bone modified peptides

4.1.4 Synthetic methods:

Normally, hydroxamic acids are prepared using the reaction between carboxylic acid and the unprotected hydroxyl amine hydrochloride using different kinds of methods. For example, carboxylic acids along with $NH_2OH.HCl$ and strong bases in presence of a coupling reagent furnish the desired product with few drawbacks. To list a few drawbacks of this strategy, the formation of di and tri acylated products, *O*-acylation to produce the esters, the difficulty to choose solvent as $NH_2OH.HCl$ is a salt, *etc*. In spite of all the difficulties listed above, Giampaolo *et al.* has reported a very good method to synthesize unprotected hydroxamic acids

using trichlorotriazine or cyanuric chloride (TCT) (Scheme **4.1**). It is noteworthy that TCT has to be prepared from the dangerous precursors such as HCN and the by-product comes from the reaction is extremely hygroscopic and a potential explosive on treatment with water, which makes this method under utilized for this transformation.[5]



Scheme 4.1

Therefore, to avoid such handling difficulties, it is important to start with either *O/N*-protected hydroxyl amines and at the end of the reaction these protections shall be removed with an appropriate reagent. Although, copious methodologies are available for the synthesis hydroxamates/hydroxamic acids and Weinerb amides from the acids and the corresponding *O/N*-protected hydroxyl amines using several peptide coupling reagents, such as BOP, PyBOP, DCC, EDC, CDI, PPAA, TBTU, DEPC, 2-chloro- and 2-bromo-1-methylpyridinium iodides,[6] the following are the recent reports in this field.

4.1.5 Using peptide coupling reagents:

The following thiouronium salts have been used for the synthesis of hydroxamates from the acids directly which could be prepared from the reaction of tetramethylurea or DMPU with oxalyl chloride and a catalytic amount of DMF.

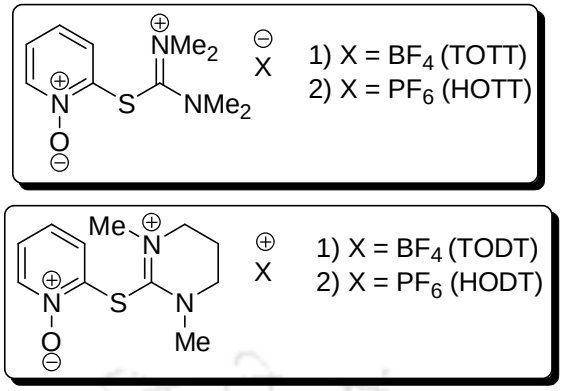
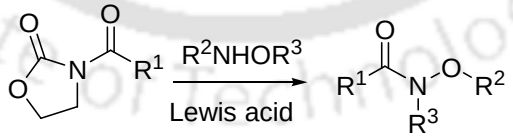


Figure 4.4 Coupling reagents used for hydroxamic acid synthesis

The corresponding chloro-uronium salts were treated with sodium tetra-fluoroborate or potassium hexafluorophosphate and subsequently with *N*-Hydroxy-2-pyridinethione. The new uronium salts TOTT and TODT (Figure **4.4**) were obtained in 60% and 81% yield, respectively.[7]

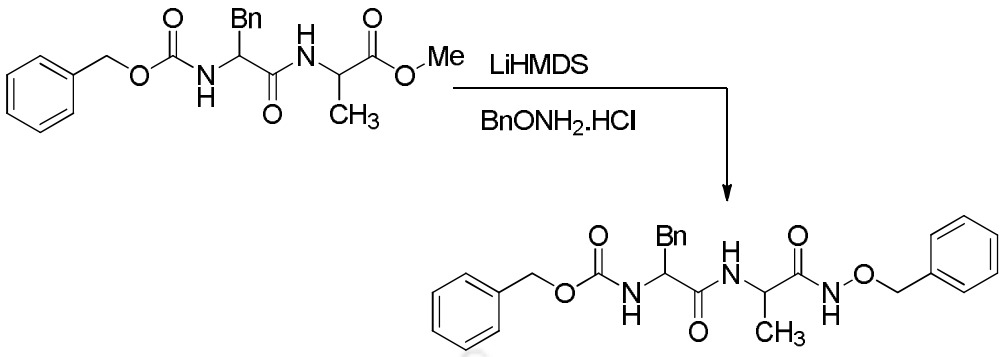
4.1.6 Activation of carboxylic acids as *N*-Acyloxazolidinones:

Sibi *et al.* reported a novel activation method for the synthesis of *O*-protected hydroxamates with samarium triflate as catalyst. This methodology works well with respect to the retention of stereochemistry with chiral acids and with the yields for sterically hindered acids as well (Scheme **4.2**).[8]



Scheme 4.2

Zanda *et al.* developed a simple and high yielding one-step method for the synthesis of hydroxamate derivatives directly from a range of unactivated esters and the anion of *O*-benzyl-hydroxylamine generated *in situ* (Scheme **4.3**).



Scheme 4.3

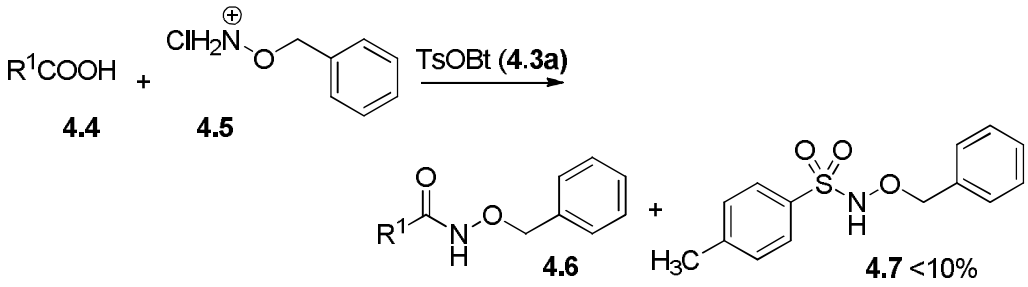
The reaction was found to take place in minutes at -78 °C using lithium hexamethyl disilylaizde (LIHMDSA). Very importantly, the method was successfully employed with enolizable esters, including chiral R-amino acid esters and peptides with no trace of racemization/epimerization at the R carbon detected.[9]

As one of our objectives was to develop the activated sulfonate esters as an auxiliary to carry out certain transformations, we wanted to extend their applicability for the synthesis of protected hydroxamates of various acids.

4.2 Results and discussion:

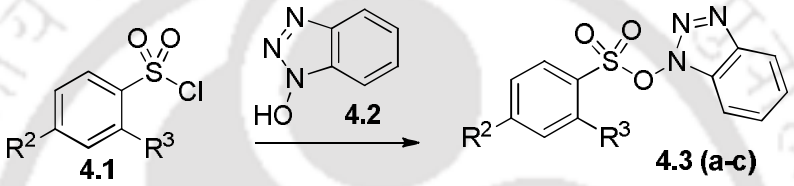
Initially, we took up the phenyl acetic acid, TsOBt (**4.3a**) and DIPEA and stirred for 5 min. Then pre-neutralized *O*-benzyl hydroxyl amine hydrochloride (1 mmol with 1 mmol of DIPEA in 1 mL acetonitrile) was added and resulting, mixture was stirred at room temperature.

Interestingly, the coupling took place within 2 h and gave the desired product (**4.6**) in good yield along with a little amount of sulfonamide of *O*-benzyl hydroxyl amine of *p*-toulene sulfonic acid (**4.7**). In order to explore the chemistry of this particular transformation, we



Scheme 4.4

synthesized various sulfonate esters (**4.3a-c**) as shown in the scheme **4.5** and Table **4.1** using a reported procedure (*chapter 2*).[1d]



Scheme 4.5

Table 4.1 Synthesis of various sulfonate esters of HOBt

entry	R^2, R^3	yield (%)[a]	time(h)[b]
4.3a	$R^2 = CH_3$, $R^3 = H$	1.5	84
4.3b	$R^2 = NO_2$, $R^3 = H$	1.5	81
4.3c	$R^2 = H$, $R^3 = NO_2$	1.5	80

[a] Yields refer to the isolated yields after column chromatography. [b] TLC is checked for every 30 min. All the products were completely character-ized with ^{1}H-NMR, ^{13}C-NMR ESI-MS, *etc*.

Having various sulfonate esters at hand, we further proceeded to examine the ability of each of these coupling reagents (**4.3a-c**) for this transformation. Although the insertion of electron withdrawing group accelerated the reaction, generation of the sulfonamide corresponding to the *O*-benzyl hydroxyl amine side product (**4.7**) was more. Therefore, we continued to perform this reaction with TsOBt.

Table 4.2 Synthesis of hydroxamic acids using sulfonate esters of HOBt.

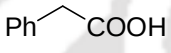
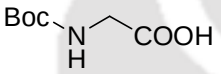
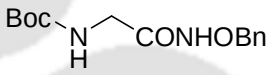
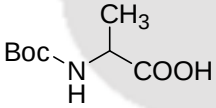
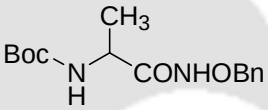
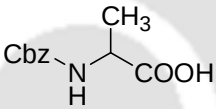
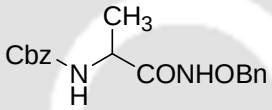
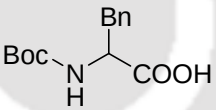
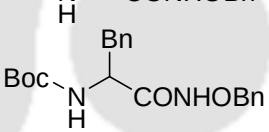
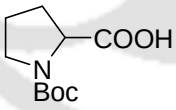
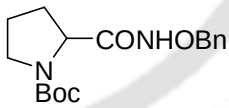
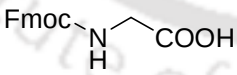
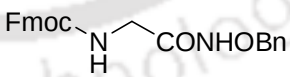
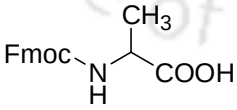
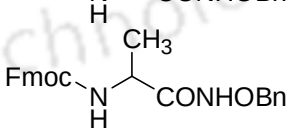
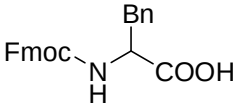
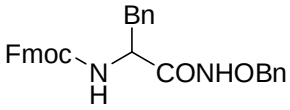
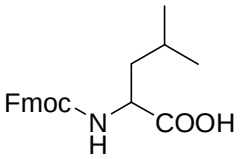
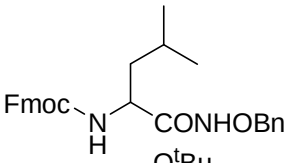
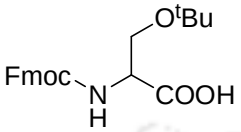
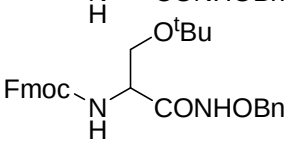
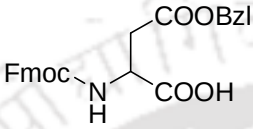
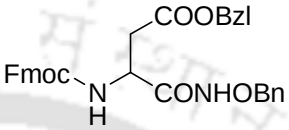
entry	carboxylic acid	product	yield (%)[a]
1	$H_3C-COOH$	$H_3C-CONHOBn$	80
2	Ph−COOH	Ph−CONHOBn	76
3	*m*-Cl—Ph·COOH	*m*-Cl—Ph·CONHOBn	81
4	*m*-NO_2-C_6H_4-COOH	*m*-NO_2-C_6H_4-CONHOBn	76
5	*p*-NO_2-C_6H_4-COOH	*p*-NO_2-C_6H_4-CONHOBn	79
6			84
7			86
8			79
9			86
10			71
11			76
12			84
13			75
14			64

Table **4.2** continues…….

entry	carboxylic acid	product	yield (%)[a]
15			56
16			61
17			56

[a] Yields refer to the isolated yields after column chromatography. TLC was checked for every 30 min. All the unreported products were characterized completely. Reported compounds were ch-aracterized with ^{1}H-NMR, IR, ESI-MS and matched with the reported data.

The reactivity of TsOBt was moderate and produced the desired product (**4.6**) in good to excellent yield in spite of the fact that the formation of the side product persisted and ranged from 5-10% depending on the steric bulk of the acid. The base and solvent screening experiments revealed that DIPEA and acetonitrile were the best for these conditions. The current methodology was compatible with aliphatic carboxylic acid (entries **1** and **6**, Table **4.2**) aromatic acids (entries **2-5**, Table **4.2**). The yields were good to excellent in all the cases and no di and tri-acylated products were observed in the reaction mixture. The present method was compatible with all common *N*-protecting groups (entries **7-17**, Table **4.2** and entries **1** and **2**, Table **4.3**). Also the present methodology was compatible with side chain protecting groups such as, *tert*-butyl ether (entry **16**, Table **4.2**) and benzyl ester (entry **17,** Table **4.2**).

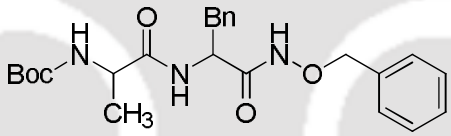
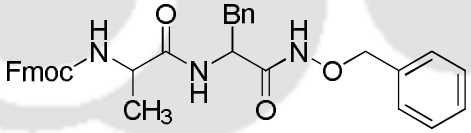
Apart from the functional group tolerance, the important advantage of this method lied in the applicability to the sterically hindered amino acids such as alanine (entries **8-9** and **13**, Table

4.2), phenyl alanine (entries **10** and **14**, Table **4.2**) and leucine (entry **15**, Table **4.2**). In all these cases, reaction yields were found to be good but less than their sterically less hindered analogues.

4.2.1 Tests for racemization:

Sulfonate esters in condensation chemistry found to cause no/less racemization. In our observation, when compared with optical rotation of the reported literature for the (entries **8** and **10**, Table **4.2**), the rotation values were found to be close to the reported values and can be concluded that this transformation does not cause significant racemization.[6a, 8]

Table 4.3. Synthesis of hydroxymic acids of peptides

entry	product	yield (%)[a]
1		69
2		61

[a]Yields refer to the isolated yields after column chromatography TLC is checked for every 30 min. All the products were completely characterized with ^{1}H-NMR, ^{13}C-NMR, IR, ESI-MS.

The present methodology was also extended to the synthesis of hydroxamates of di-peptides. Two di-peptides were synthesized using the pentafluorophenol activation strategy and then

converted to the corresponding *O*-benzyl hydroxamates using the current methodology (Table **5.3**).

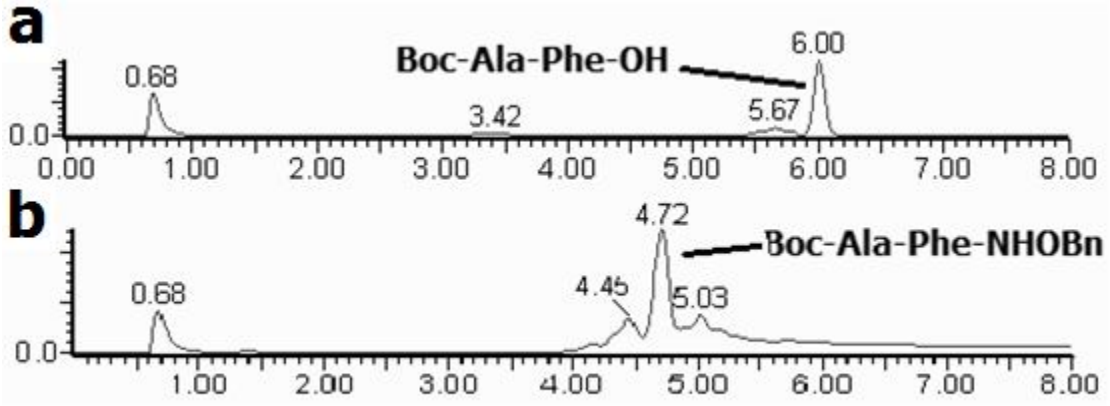


Figure 4.5 LC-MS chromatograms for Boc-Ala-Phe-OH (**a**) and Boc-Ala-Phe-NHOBn (**b**) using Millipore water and acetonitrile solvent with 0.1% formic acid while using 254 nm

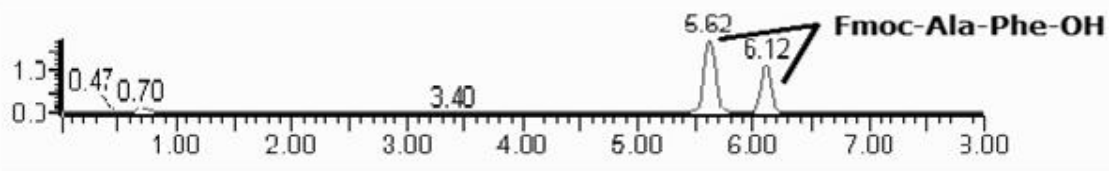


Figure 4.6 LC-MS chromatogram for Fmoc-Ala-Phe-OH using Millipore water and acetonitrile solvent with 0.1% formic acid while using 254 nm.

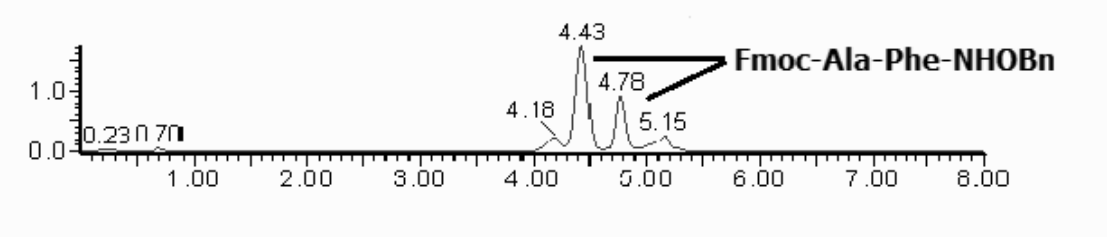


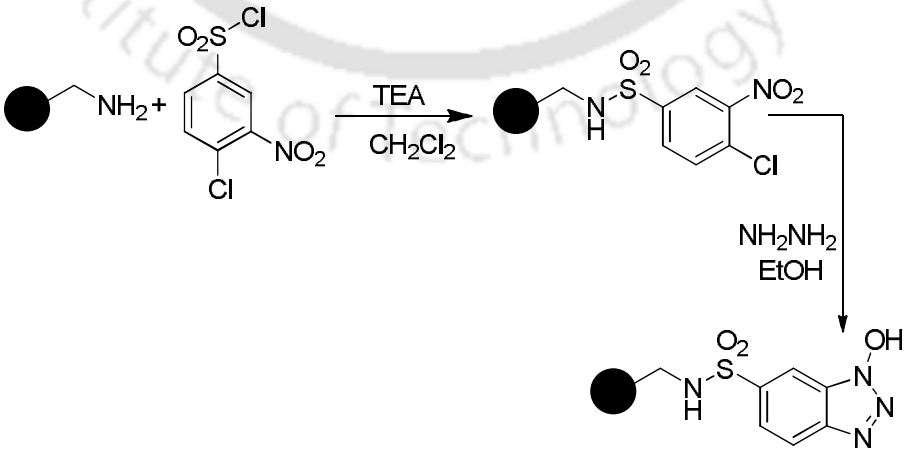
Figure 4.7 LC-MS chromatogram for Fmoc-Ala-Phe-NHOBn using Millipore water and acetonitrile solvent with 0.1% formic acid while using 254 nm.

An investigation on the extent of racemization was performed using LCMS. The diastereomeric ratio that was noticed in case of the *C*-terminus free di-peptide i.e. Boc-Ala-

Phe-OH (Figure **4.5a**) and Fmoc-Ala-Phe-OH (Figure **4.6**) was found to be retained after the application of the present protocol i.e. even after synthesizing the Boc-Ala-Phe-NHOBn and Fmoc-Ala-Phe-NHOBn (Figure **4.5b-4.7**), which confirmed the fact that this protocol does not cause much racemization i.e.less than 5%.

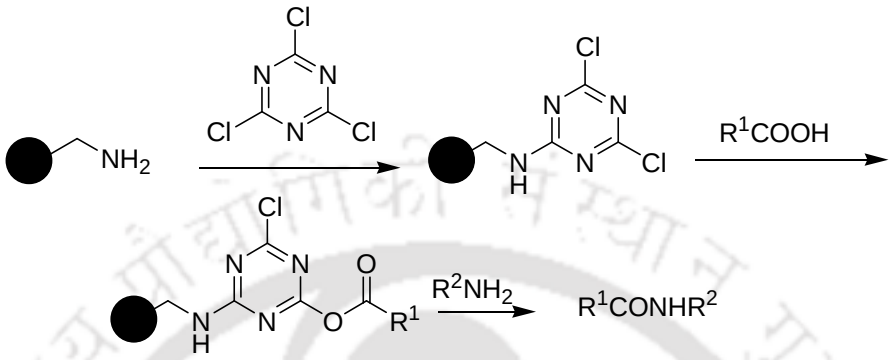
4.2.2 Recovery and recyclability of HOBt using solid supported TsOBt:

Additionally, one of the major difficulties encountered during the synthesis of chemical combinatorial libraries is conciliating the need for highly diverse arrays of compounds with their heterogeneous behavior. Organic synthesis by solid phase methods is, therefore, emerging as a tool for clean synthesis of compounds. Tethering starting materials or reagents to an insoluble polymer allows spectacular simplifications in handling steps, rendering the automation of the process much easier. In this case, unlike classical solid phase synthesis, the reagents remain attached to the insoluble matrix, while the desired product is easily recovered by mere washing with the respective solvent(s). In this connection, in 1997 Tartar *et al.* have synthesized the solid supported HOBt and used for coupling reaction of an amine and an acid along with DCC (Scheme **4.6**).[10]



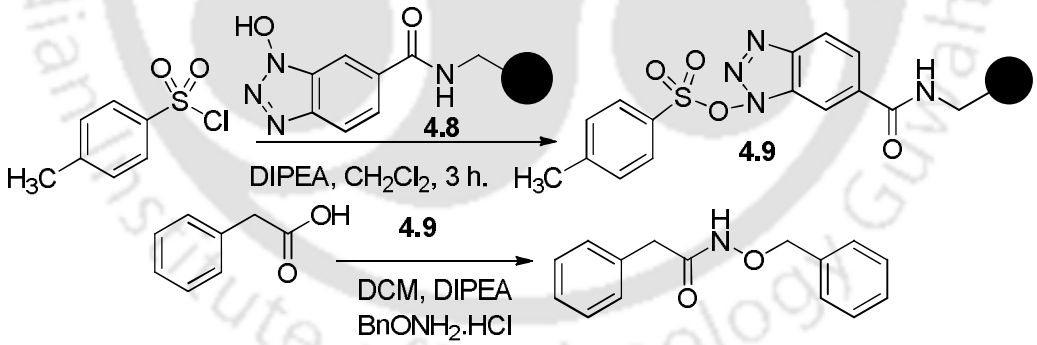
Scheme 4.6

Following the above mentioned report, in 1999 taddei *et al.* have designed another solid supported trichlorotriazine and used for the same transformation (Scheme **4.7**). But, in this case, the reagent can't be re-used as it was not possible to regenerate.[11]



Scheme 4.7

In spite of the fact that these two were very effective methodologies for condensation chemistry, these reagents must be synthesized on the resin in a multistep procedure. In few cases such reagents are commercially available, but the resins are expensive and rather sensitive to prolonged storage.



Scheme 4.8

Therefore, in order to extend the applicability of the present protocol such that it facilitates the reuse and recyclability, we wanted to synthesize the soild supported TsOBt (**4.9**) with tosyl chloride and solid supported HOBt (**4.8**). Interestingly, we found the reaction was successful and further it could be employed for condensation reaction between phenyl acetic acid and pre-neutralized NH_2OBn successfully (Scheme **4.8**) and checked the recovery-reusability of

the solid supported HOBt for three times. Each time the result was good as it was shown in table **4.4**.

Table 4.4 Recovery and recyclibilty of solid supported HOBt

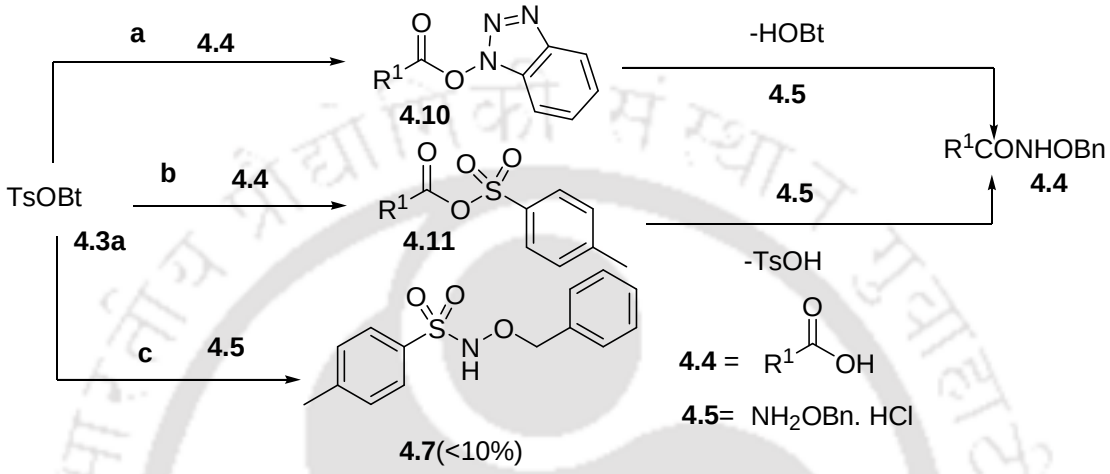
entry	acid	cycle	yield
1	Phenyl acetic acid	I	81
		II	80
		III	80
2	Fmoc- Gly-OH	I	82
		II	82
		III	80
		IV	76
		V	75
		VI	71
3	Fmoc- Phe-OH	I	58
		II	58
		III	57
		IV	58
		V	54
		VI	52

[a]The yields refer to the isolated yields after work up Characterization data of the products were matched with those of the previously synthesized products, table 4.2.

4.2.3 Mechanism:

The reaction mechanism can be depicted as shown in the scheme **4.9** based on the possible products. The desired *O*-benzyl hydroxamates (**4.6**) can be generated following the path **a** and **b**. On the other hand, direct attachment of the *O*-benzyl hydroxyl amine on the sulfur center of the reagent **4.3a** (path **c**) and the intermediate **4.11** can lead to the formation of the byproduct

4.7. As it was shown in scheme **4**, the formation of both the intermediates (**4.10** and **4.11**) was identified by IR and ^{1}H-NMR spectroscopy. In our model reaction, the peaks at δ 4.04-4.03 was assigned as glycinic CH_2 protons of Fmoc glycine (Figure **4.8, A**). A set a of two peaks emerged out at δ 3.72-3.71 and δ 3.56-3.49 after 2 min.



Scheme 4.9

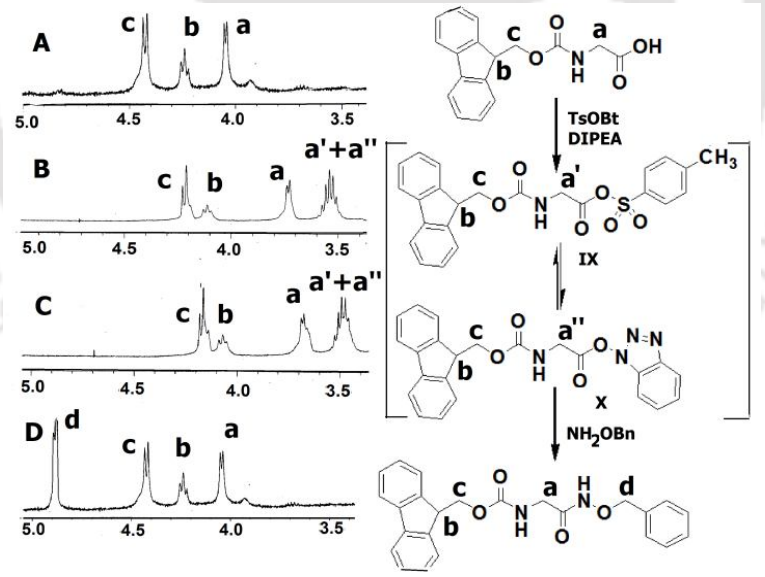
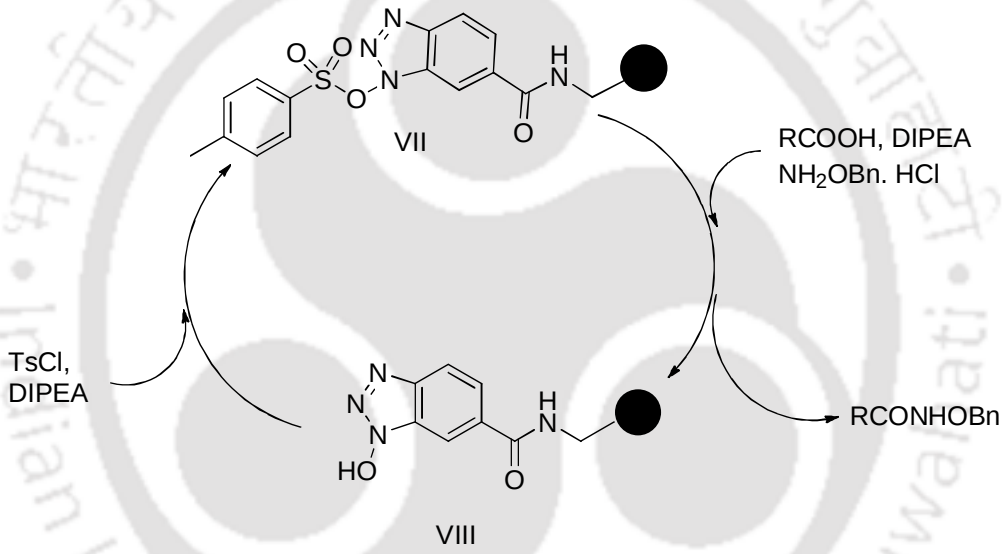


Figure 4.8. Evidence of the mechanism from ^{1}H NMR

(**A**) Selected region of the NMR spectra of Fmoc-Gly-OH, (**B**) the same after 2 min. of mixing Fmoc-Gly-OH and TsOBt, (**C**) the same after 10 min. of mixing Fmoc-Gly-OH and TsOBt, and (**D**) the same of Fmoc-Gly-NHOBn.

(**B**) of the addition of TsOBt to the Fmoc-Gly-OH along with the DIPEA in acetonitrile solvent, which persisted as long as the amine component was not added (**C**). These peaks were probably for the formation of the intermediates **4.10** and **4.11**, which is similar to that of the observations of Carpino *et al.* Furthermore, in IR spectra, the C=O stretching frequencies corresponding to the sulfonate ester at 1370 cm^{-1} and HOBt ester at 1756 cm^{-1} respectively were observed. Furthermore, recyclability of the reagent i.e. solid supported HOBt has been explained as shown in the following scheme **4.10.**



Scheme 4.10

4.3. Conclusion:

In conclusion, we have demonstrated the *O*-benzyl hydroxamate synthesis using the sulfonate ester of *N*-Hydroxy benzotriazole, which was successfully applied to wide verities of acids that include amino acids with various side chain protecting groups and common *N*-protecting groups such as Boc, Cbz and Fmoc under milder and ambient conditions in a green solvent, acetonitrile. This strategy was successfully applied to the synthesis of *O*-benzyl hydroxamates

of di-peptides also. Gratifyingly, the method enjoys the success with solid supported HOBt which facilitates the recovery of *N*-Hydroxybenzotriazole and was successfully reused up to three cycles without losing its efficiency. This process even facilitates the isolation of product without purification using column chromatography. And also the yields isolated were found to be good.

4.4 Experimental Section:

4.4.1 General information:

All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. *O*-Benzyl hydroxyl ammonium chloride was purchased from Alfa Aeser. Melting points were uncorrected and determined with a Buchi-540 apparatus. Thin layer chromatograms were run on glass plates coated with silica gel G for TLC, using solvent systems EtOAc/Hexane. All the compounds were purified by column chromatography using 60-120 mesh silica gel from Spectrochem (India). ^{1}H-NMR (400 MHz for ^{1}H) was recorded using DRX-400 Varian spectrometer using $CDCl_3$ as solvent unless mentioned otherwise. Chemical shifts were reported in parts per million (ppm), internal reference (0.05% to 1%) tetra methyl silane. Coupling constants (*J*) were reported in Hz singlet(s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). Low resolution mass spectra were recorded on a Micromass Q-TOF ESI MS instrument (model HAB273). HRMS was recorded on 6500 Q-TOF LC/MS system. IR was recorded on a Perkin Elmer spectrum FT-IR one spectrometer. LC-MS was performed on WATERS Q-TOF instrument. Specific rotation was measured on Rudolph Research Analytical instrument

Autopol 1 at 589 nm, 27.1 °C, temperature correction off. Data for previously reported compounds (cited therein) matched well with our observed data.

4.4.2 General procedure for the synthesis of Sulfonate esters of *N*-Hydroxy benzotriazole:

The representative procedure for the synthesis of **TsOBt** is common to all in Table **4.1** from entry **4.3a** to **4.3c** and is as follows. An oven dried 25 mL R.B. flask equipped with magnetic stir bar, was loaded with HOBt (1 mmol, 1 equiv.) which was dissolved in 1 mL of dry CH_2Cl_2. To this, DIPEA (1 mmol, 1 equiv) was added under nitrogen. Then, it was cooled to 0 °C, followed by the slow addition of tosyl chloride using a syringe over 30 mins. Then, the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was washed with saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$. Then it was dried in *vaccuo* and purified by recrystallization using hexane and CH_2Cl_2.

4.4.3 General procedure for the synthesis of *O*-benzyl hydroxamtes:

The representative procedure for the synthesis of *N*-Benzyloxy-benzamide is common to all in Table **4.2** and is as follows. An oven dried 25 mL R.B. flask equipped with magnetic stir bar, was loaded with benzoic acid (1 mmol, 1 equiv.), TsOBt (1 mmol, 1 equiv.) and DIPEA (2equiv., 2 mmol) and was dissolved in 1 ml of acetonitrile at 0 °C, followed by the slow addition of pre-neutralized NH_2OBn with DIPEA (1equiv. 1 mmol). Then, the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with EtOAc followed by concentration under reduced pressure and was washed with 5% $NaHCO_3$ (2× 10 mL), 5% HCl (2×10 mL) (for Boc protected acids, HCL was not used) and saturated NaCl solution (2×10

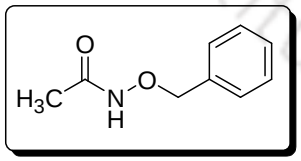
mL). Then the organic fraction was collected and dried over anhydrous $CaCl_2$. Then it was dried in *vaccuo* and purified by recrystallization using hexane and CH_2Cl_2.

4.4.4 General procedure for the synthesis of *O*-benzyl hydroxamates with solid supported reagent:

The solid supported HOBt was swelled for 20 min using dichloromethane as solvent with rotator in a sintered 5 mL syringe. To this, 1.5 equiv. of tosyl chloride along with 2 equiv. of DIPEA was added and rotated for 2 h. Then the reaction mixture was washed for 5 times with CH_2Cl_2. To this, 2.5 equiv of the phenyl acetic acid along with 2 equiv of DIPEA was added and continued to rotate for more 20 min.Finally, the pre-neutralized mixture of $NH_2OBn.HCl$ and DIPEA in DCM 1 mL was added and stirred for 3 h. Then it was washed with DCM for 5 times and finally with 5% $NaHCO_3$ (2× 3 mL), 5% HCl (2×3 mL) and brine (2×10 mL). That afforded the desired product 81%, 80% and 80% for 3 cycles when the same solid supported HOBt was used repeatatively.

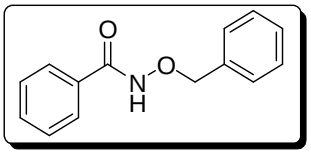
4.5 Characterisation data:

1) *N*-Benzyloxy-acetamide (Entry1, Table 4.2):



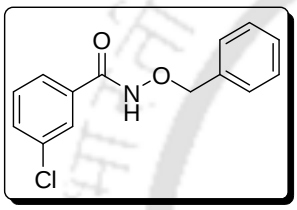
R_f product 0.56 (EtOAc/Hexane, 1:4), Yield (182 mg, 80%), colorless crystals. IR (KBr, ν/cm^{-1}) 1754, 1650, 1591, 1365, 1150, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56-7.43 (m, 5H, 5×Ar**H**), 4.99(s, 2H, C**H**$_2$), 2.18 (s, 3**H**, C**H**$_3$); LRMS (ESI) m/z 228.09 $[M+H]^+$.

2) *N*-Benzyloxy-benzamide (Entry 2, Table 4.2):



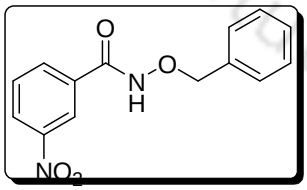
R_f product 0.61 (EtOAc/Hexane, 1:4), Yield (173 mg, 76%), colorless crystals. IR (KBr, ν/cm^{-1}) 3093, 2977, 1535, 1095, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.56-7.43 (m, 10H, 10×Ar**H**), 4.99(s, 2H, C**H**$_2$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 228.10, found: 228.10.

3) *N*-Benzyloxy-2-nitro-benzamide (Entry 3, Table 4.2):



R_f product 0.57 (EtOAc/Hexane, 1:4) Yield (207 mg, 81%), yellow colorless crystals. IR (KBr, ν/cm^{-1}) 3099, 2797, 1741, 1561, 769. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.01 (br s, 1H, N**H**), 8.44 (s, 1H, 1×Ar**H**), 8.26-8.28 (d, 1H, *J* = 8.4 Hz, 1×Ar**H**), 7.98-7.96 (d, 1H, *J* = 7.6 Hz, 1×Ar**H**), 7.56-7.52 (t, 1H, *J* = 8.0 Hz, 1×Ar**H**), 7.35-7.30 (m, 4H, 4×Ar**H**), 7.18 (s, 1H, 1×Ar**H**), 4.94(s, 2H, C**H**$_2$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 261.05, found: 261.05.

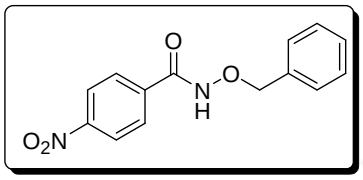
4) *N*-(Benzyloxy)-3-nitroorobenzamide (Entry 4, Table 4.2):



R_f product 0.53 (EtOAc/Hexane, 1:4), Yield (215 mg, 76%), colorless crystals. IR (KBr, ν/cm^{-1}) 2993, 1733, 1574, 971, 758. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.58 (br s, 1H, N**H**), 8.20-8.15 (m, 2H, 2×Ar**H**), 7.77-7.75 (d, 1H, *J* = 8.8 Hz, 1×Ar**H**), 7.34-7.33 (m, 5H, 5×Ar**H**), 7.19 (s, 1H, 1×Ar**H**), 4.98 (s, 2H,

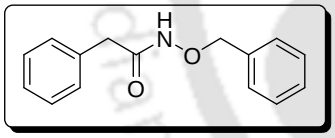
C**H**$_2$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 273.08, found: 273.08.

5) *N*-Benzyloxy-4-nitro-benzamide (Entry 5, Table 4.2):



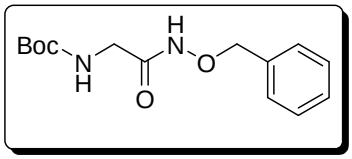
R_f product 0.53 (EtOAc/Hexane, 1:4), Yield (215 mg, 79%), colorless crystals. IR (KBr, ν/cm^{-1}) 2993, 1733, 1574, 971, 758. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.58 (br s, 1H, N**H**), 8.20-8.15 (m, 2H, 2×Ar**H**), 7.77-7.75 (d, 1H, *J* = 8.8 Hz, 1×Ar**H**), 7.34- 7.33 (m, 5H, 5×Ar**H**), 7.19 (s, 1H, 1×Ar**H**), 4.98 (s, 2H, C**H**$_2$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 273.08, found: 273.08.

6) *N*-Benzyloxy-2-phenyl-acetamide (Entry 6, Table 4.2):



R_f product 0.52 (EtOAc/Hexane, 1:4) Yield (203 mg, 84%), yellow color solid. IR (KBr, ν/cm^{-1}) 3113, 2986, 1748, 1591, 958. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.50 (br s, 1H, N**H**), 7.38-7.17 (m, 10H, 10×Ar**H**), 4.84 (s, 2H, C**H**$_2$), 3.44 (s, 2H, C**H**$_2$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 242.11, found: 242.11.

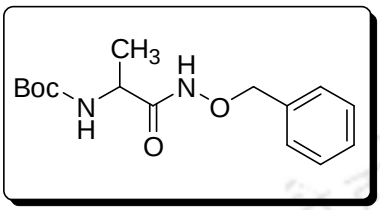
7) (Benzyloxycarbamoyl-methyl)-carbamic acid *tert*-butyl ester (Entry 7, Table 4.2):



R_f product 0.48 (EtOAc/Hexane, 1:4) Yield (241 mg, 86%), colorless solid; IR (KBr, ν/cm^{-1}) 3093, 2897, 1754, 1620, 983, 886. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.68 (br s, 1H, N**H**), 7.41-7.27 (m, 5H, 5×Ar**H**), 5.50 (br s, 1H, N**H**), 4.88 (s, 2H,

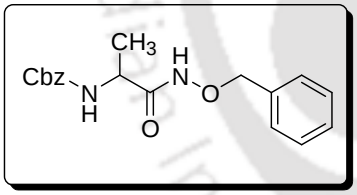
C**H**$_2$), 3.67 (s, 2H, C**H**$_2$), 1.44 (s, 9H, C(C**H**$_3$)$_3$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 281.15, found: 281.15.9

8) (1-Benzyloxycarbamoyl-ethyl)-carbamic acid *tert*-butyl ester (Entry 8, Table 4.2):



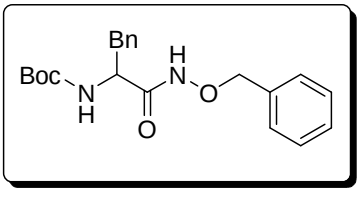
R_f product 0.48 (EtOAc/Hexane, 1:4), Yield (233 mg, 79%), colorless semi solid, mp 96 °C. IR (KBr, ν/cm^{-1}) 3164, 2974, 1751, 15941, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.41 (br s, 1H, N**H**), 7.38-7.34 (m, 5H, 5×Ar**H**), 5.12 (br s, 1H, N**H**), 4.88 (s, 2H, C**H**$_2$), 4.05 (q, 1H, C**H**), 1.41 (s, 9H, C(C**H**$_3$)$_3$), 1.33-1.31 (d, 3H, J = 6.8 Hz, C**H**$_3$); $[\alpha]_D$ = -55.1°, 25 °C, c =1.1, $CHCl_3$ LRMS (ESI) m/z Calcd. for $[M+H]^+$: 295.16, found: 295.16.

9) (1-Benzyloxycarbamoyl-ethyl)-carbamic acid benzyl ester (Entry 9, Table 4.2):



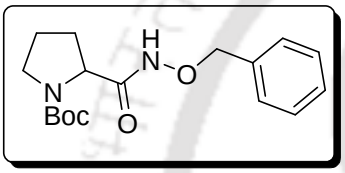
R_f product 0.49 (EtOAc/Hexane, 1:4), Yield (282 mg, 86%), colorless solid, mp 121-124 °C (Lit. 121-122 °C). IR (KBr, ν/cm^{-1}) 3102, 2973, 1752, 1568, 760. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.79 (br s, 1H, NH), 7.37-7.26 (m, 10H, 10×Ar**H**), 5.10-5.04 (t, J = 11.6 Hz, 2H, C**H**$_2$), 4.89 (s, 2H, C**H**$_2$), 4.07 (m, 1H, α-C**H**), 1.36-1.34 (d, J = 6.8 Hz, 3H, C**H**$_3$); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 329.15, found: 329.15.

10) (1-Benzyloxycarbamoyl-2-phenyl-ethyl)-carbamic acid *tert*-butyl ester: (Entry 10, Table 4.2): R_f product 0.51 (EtOAc/Hexane, 1:4), Yield (263 mg, 71%), Colorless solid. mp. 129-130 °C (Lit. 129-131 °C). IR (KBr, ν/cm^{-1}) 3328, 1754, 1664. ^{1}H NMR (400 MHz, $CDCl_3$)



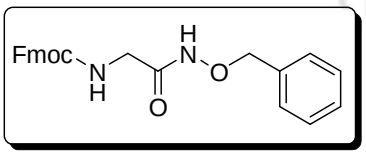
δ ppm 8.50 (br s, 1H, N**H**), 7.29-7.17 (m, 10H, 10×Ar**H**), 5.01 (br s, 1H, N**H**), 4.77(s, 2H, C$\mathbf{H_2}$), 4.67 (m, 1H, α-C**H**), 4.13-4.11 (d, *J* = 6.8 Hz, 1H, C$\mathbf{H_a}$H$_\mathbf{b}$), 3.07-2.96 (m, 1H, CH$_\mathbf{a}$**H$_\mathbf{b}$**) 1.36 (s, 9H, -C(C$\mathbf{H}_3$)$_3$); $[\alpha]_D$ = –26.4 [25 °C, *c* 1.1, $CHCl_3$]; LRMS (ESI) m/z Calcd. for $[M+H]^+$: 371.19, found: 371.19.

11) tert-Butyl 2-(benzyloxycarbamoyl)pyrrolidine-1-carboxylate (Entry 11, Table 4.2):



R_f product 0.43 (EtOAc/Hexane, 1:4), Yield (243 mg, 76%), colorless liquid, IR (KBr, ν/cm^{-1}) 3093, 2977, 1754, 1591, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79-7.74(d, 2H, 2×Ar**H**), 7.42-7.29 (m, 4H, 4×Ar**H**), 4.94 (s, 2H, C$\mathbf{H_2}$), 4.18 (m, 1H, C**H**), 3.44(br s, 2H, C$\mathbf{H_2}$), 2.04 (m, 2H, C$\mathbf{H_2}$), 1.41 (S, 9H, C(C$\mathbf{H}_3$)$_3$), 1.27-1.22 (m, 2H, C$\mathbf{H_2}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.9, 135.8, 133.1, 131.5, 129.7, 129.4, 106.1, 64.7, 13.8; LRMS (ESI) m/z Calcd. for $[M+H]^+$:321.18, found: 321.18.

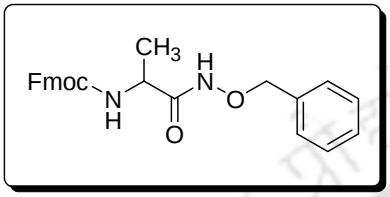
12) (Benzyloxycarbamoyl-methyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (Entry 12, Table 4.2):



R_f product 0.42 (EtOAc/Hexane, 1:4), Yield (354 mg, 84%), colorless liquid, IR (KBr, ν/cm^{-1}) 3093, 2977, 1754, 1591, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75-7.73 (d, *J* = 7.6 Hz, 2H, 2×Ar**H**), 7.56 (br s, 3H, 3×Ar**H**), 7.40-7.27 (m, 8H, 8×Ar**H**), 5.43 (br s, 1H, N**H**), 4.86 (s, 2H, C$\mathbf{H_2}$), 4.38-4.36 (d, *J*

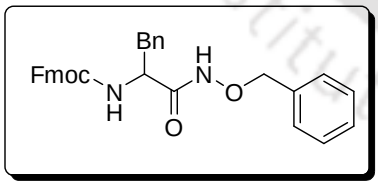
= 7.6 Hz, 4H, C**H**$_2$), 4.21-4.19 (t, *J* = 7.2 HZ, 1H, C**H**); LRMS (ESI) m/z Calcd. for $[M+H]^+$: 425.14, found: 425.14.

13) (1-Benzyloxycarbamoyl-ethyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (Entry 13, Table 4.2):



R_f product 0.42(EtOAc/Hexane, 1:4), Yield (296 mg, 75%), Colorless solid, mp 145-147 °C (Lit. 146-148 °C). IR (KBr, ν/cm^{-1}) 3093, 2977, 1754, 1591, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76-7.75 (d, 2H, *J* = 7.6 Hz, 2×Ar**H**), 7.57 (br s, 3H, 3×Ar**H**), 7.41-7.39 (m, 3H, 3×Ar**H**), 7.28-7.26 (m, 5H, 5×Ar**H**), 5.35 (br s, 1H, N**H**), 4.40 (br s, 4H, 2×(C**H**$_2$)), 4.23-4.20 (m, 2H, 2×CH), 1.48-1.46 (d, *J* = 6.8 Hz, 3H, CH_3); LRMS (ESI) m/z Calcd. for $[M+Na]^+$: 417.18, found: 417.18.

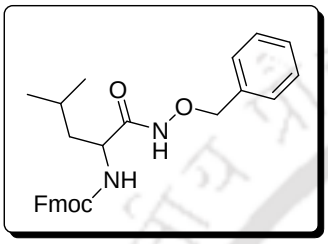
14) (1-Benzyloxycarbamoyl-2-phenyl-ethyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (Entry 14, Table 4.2):



R_f product 0.46 (EtOAc/Hexane, 1:4), Yield (315 mg, 64%), white solid, IR (KBr, ν/cm^{-1}) 3411, 2928, 1714, 1599, 1396, 1047, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73-7.71 (d, *J* = 7.6 Hz, 3H, 3×Ar**H**), 7.50-7.7 (t, *J* = 7.2 Hz, 3H, 3×Ar**H**), 7.37-7.33 (m, 4H, 4×Ar**H**), 7.24-7.21 (m, 8H, 8×Ar**H**), 5.41 (br s, 1H, N**H**), 4.64 (br s, 1H, N**H**), 4.39-4.37 (t, *J* = 6.4 Hz, 2H, C**H**$_2$), 4.25 (s, 2H, C**H**$_2$), 4.14-4.08 (m, 2×1H, 2×CH), 3.18-3.17 (m, 1H, C**H**$_a$H$_b$), 3.06-3.05 (m, 1H, CH$_a$**H**$_b$); ^{13}C NMR (100

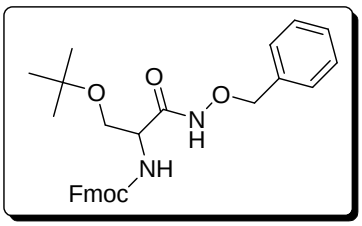
MHz, $CDCl_3$) δ ppm 175.2, 170.8, 143.7, 141.1, 129.4, 128.3, 127.5, 126.9, 126.8, 125.0, 119.8, 66.7, 47.1, 37.8; HRMS (ESI) m/z Cald. for $[M+H]^+$: 493.2127, found: 493.2159.

15) (9*H*-Fluoren-9-yl)methyl 1-(benzyloxyamino)-4-methyl-1-oxopentan-2-ylcarbamate (Entry 15, Table 4.2):



R_f product 0.51 (EtOAc/Hexane, 2:4), Yield (257 mg, 56%), white solid, IR (KBr, ν/cm^{-1}) 3432, 2923, 1670, 1539, 1289, 741. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.50 (br s, 1H, NH), 7.74-7.72 (d, *J* = 7.6 Hz, 2H, 2×Ar**H),** 7.52-7.50 (d, *J* = 7.2 Hz, 2H, 2×Ar**H**), 7.37-7.24 (m, 9H, 9×Ar**H**), 5.5-5.51 (d, *J* = 8.8 Hz, 1H, NH), 4.86 (s, 2H, CH_2), 4.80 (s, 2H, 2×Ar**H)** 4.34-4.30 (m, 1H, CH), 4.27-4.23 (m, 1H, CH), 4.13-4.07 (m, 2H, C**H$_a$H$_b$**), 1.59-1.52 (m, 1H, CH), 0.88 (br s, 6H, 2×CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.4, 166.3, 143.8, 141.8, 136.0, 129.5, 128.7, 127.9, 127.2, 125.2, 120.1, 84.2, 75.7, 67.2, 47.2, 42.3; HRMS (ESI) m/z Calcd. for $[M+H]^+$: 459.2284, found: 459.2298.

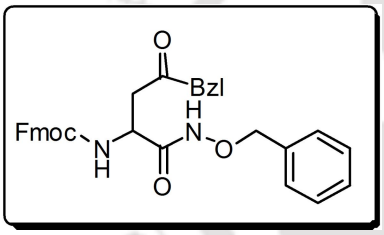
16) (1-Benzyloxycarbamoyl-2-*tert*-butoxy-ethyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (Entry 16, Table 4.2):



R_f product 0.48 (EtOAc/Hexane, 1:4) Yield (299 mg, 61%), white solid, mp 154-157 °C. IR (KBr, ν/cm^{-1}) 3309, 2974, 1672, 1537, 1298, 738. ^{1}H NMR (400 MHz, DCl_3) δ ppm 9.20 (br s, 1H, N**H**), 7.74-7.73 (d, *J* = 7.6 Hz, 2H, 2×Ar**H**), 7.57-7.55 (d, *J*

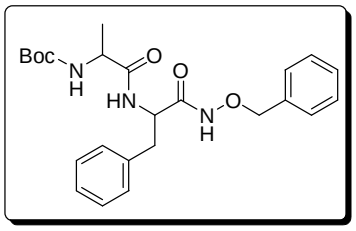
= 7.6 Hz, 2H, 2×Ar**H**), 7.39- 7.25 (m, 9H, 9×Ar**H**), 5.74-7.53 (d, *J* = 5.6 Hz, 1H, N**H**), 4.94-4.85 (d, *J* = 10.4 Hz, 2H, C**H**$_2$), 4.37-4.35 (d, *J* = 6.2 Hz, 2H, C**H**$_2$), 4.20-4.16 (t, *J* = 6.8 Hz, 1H, C**H**), 4.10-4.09 (m, 1H, C**H**), 3.70-3.69 (m, 1H, C**H**$_a$H$_b$), 3.30-3.29 (m, 1H, CH$_a$**H**$_b$), 1.10 (s, 9H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.2, 166.2, 143.7, 141.3, 129.1, 128.6, 127.7, 125.1, 120.0, 74.5, 67.2, 61.2, 47.1, 29.7, 27.2 HRMS (ESI) m/z Calcd. for $[M+H]^+$: 489.2389, found: 489.2294.

17) (1-Benzyloxycarbamoyl-3-oxo-4-phenyl-butyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (Entry 17, Table 4.2):



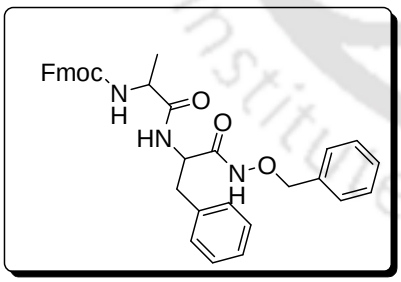
R_f product 0.39 (EtOAc/Hexane, 2:3) Yield (299 mg, 56%), white solid, mp 108-111 °C. IR (KBr, ν/cm^{-1}) 3093, 2977, 1754, 1591, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.95 (br s, 1H, NH), 7.76-7.75 (d, *J* = 7.6 Hz, 2H, 2×Ar**H)**, 7.57-7.55 (d, *J* = 7.6 Hz, 2H, 2×Ar**H)** 7.41-7.23 (m, 14H, 14×Ar**H**), 5.74-5.73 (d, *J* = 5.6 Hz, 1H, N**H**), 5.13 (s, 2H, C**H**$_2$), 4.87 9s, 2H, C**H**$_2$), 4.45 (t, 1H, C**H**), 4.39-4.37(d, *J* = 6.8 Hz, 2H, C**H**$_2$), 4.18-4.15 (m, 2H, 2×C**H**), 3.02-2.97 (m, 1H, C**H**$_a$H$_b$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.9, 135.8, 133.1, 131.5, 129.7, 129.4, 106.1, 64.7, 13.8; LRMS (ESI) m/z Calcd. for $[M+H]^+$: 551.2182, found: 551.2374.

18) *tert*-Butyl 1-(1-(benzyloxyamino)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (Entry 1, Table 4.3):



R_f product 0.36 (EtOAc/Hexane, 2:3) Yield (349 mg, 79%), white solid, 125-128 °C. IR (KBr, ν/cm^{-1}) 3340, 2978, 1725, 1577, 1210, 978. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28-7.26 (m, 4H, 4×Ar**H**), 7.23-7.19 (m, 4H, 4×Ar**H**), 6.85-6.83 (d, 2H, *J* = 7.2 Hz, 2×Ar**H**), 5.62 (br s, 1H, 1×N**H**), 5.24 (br s, 1H, N**H**), 4.50 (s, 2H, C$\mathbf{H_2}$), 4.46 (m, 1H, C**H**), 3.05 (m, 1H, C**H**), 3.05 (br s, 2H, C$\mathbf{H_a}\mathbf{H_b}$), 1.37 (s, 9H, -C(C$\mathbf{H_3}$)$_3$, 1.16-1.15 (d, 3H, *J* = 6.0 Hz, C$\mathbf{H_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.2, 170.8, 156.1, 143.7, 143.6, 141.2, 135.1, 128.6, 128.4, 128.3, 127.7, 127.0, 125.0, 119.9, 77.2, 67.4, 67.1, 50.1, 47.0, 36.4; HRMS (ESI) m/z Calcd. for $[M+K]^+$: 479.1826 found: 479.1823.

19) (9*H*-Fluoren-9-yl)methyl 1-(1-(benzyloxyamino)-1-oxo-3-phenylpropan-2-ylamino)-1-oxopropan-2-ylcarbamate (Entry 2, Table 4.3):



R_f product 0.48 (EtOAc/Hexane, 2:3), Yield (445 mg, 79%), white solid, mp 115-117 °C. IR (KBr, ν/cm^{-1}) 3233, 2929, 1693, 1535, 1082, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28-7.26(m, 4H, 4×Ar**H**), 7.23-7.19 (m, 6H, 6×Ar**H**), 6.85-6.83 (d, 1H, *J* = 7.2 Hz, 1×N**H**), 5.24 (br s, 1H, 1×N**H**), 4.50(s, 2H, C$\mathbf{H_2}$), 3.77- 3.74 (m, 1H, α-C**H**), 3.05 (br s, 2H, C$\mathbf{H_a}\mathbf{H_b}$), 1.37 (s, 9H, -C(C$\mathbf{H_3}$)$_3$, 1.16-1.15 (d, 3H, *J* = 6.0 Hz, C$\mathbf{H_3}$) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.6, 172.3, 156.7, 155.5, 143.8, 143.6, 140.6, 137.2, 135.0, 133.2, 129.1,

129.1, 128.6, 127.9, 127.6, 127.4, 126.9, 126.0, 125.1, 123.7, 120.9, 119.8, 77.2, 74.6, 74.4, 65.6, 60.3, 53.3, 53.2, 49.9, 47.5, 46.6, 36.7, 34.0, 33.3, 31.6, 29.6, 25.3, 25.0, 25.2, 21.0; HRMS (ESI) m/z Calcd. for $[M+K]^+$: 564.2498, found: 564.2456.

4.7 References:

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stereoselective aldol addition. *Synthesis* **1989**, 856-858; h) Tamaka, K.; Ogita, T.; Tanzawa, K.; Sugimura, Y. Synthesis and determination of the absolute configuration of matlystatin B. *Tetrahedron. Lett.* **1993**, *34*, 683-686; i) Nikam, S. S.; Kornberg, B. E.; Johnson, D. R.; Doherty, A. M. Synthesis of hydroxamic acids: $PdBaSO_4$ as a new catalyst for the deprotection of *O*-benzyl hydroxamates. *Tetrahedron Lett*. **1995**, *36*, 197-200; j) Gibson, C. L.; Handa, S. An expedient synthesis of (R)-(+)-umbelactone. *Tetrahedron: Asymmetry* **1996**, *7*, 1281-1284; k) Brenner-Wei ß, G.; Giannis, A.; Sandhoff, K. Uncatalyzed condensation between aryl-1,2-diamines and diethyl bromomalonate: A one-pot access to substituted ethyl 3-hydroxyquinoxaline-2-carboxylates. *Tetrahedron* **1992**, *48*, 5855-5860.

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4.6 Representative spectra for the selected compounds:

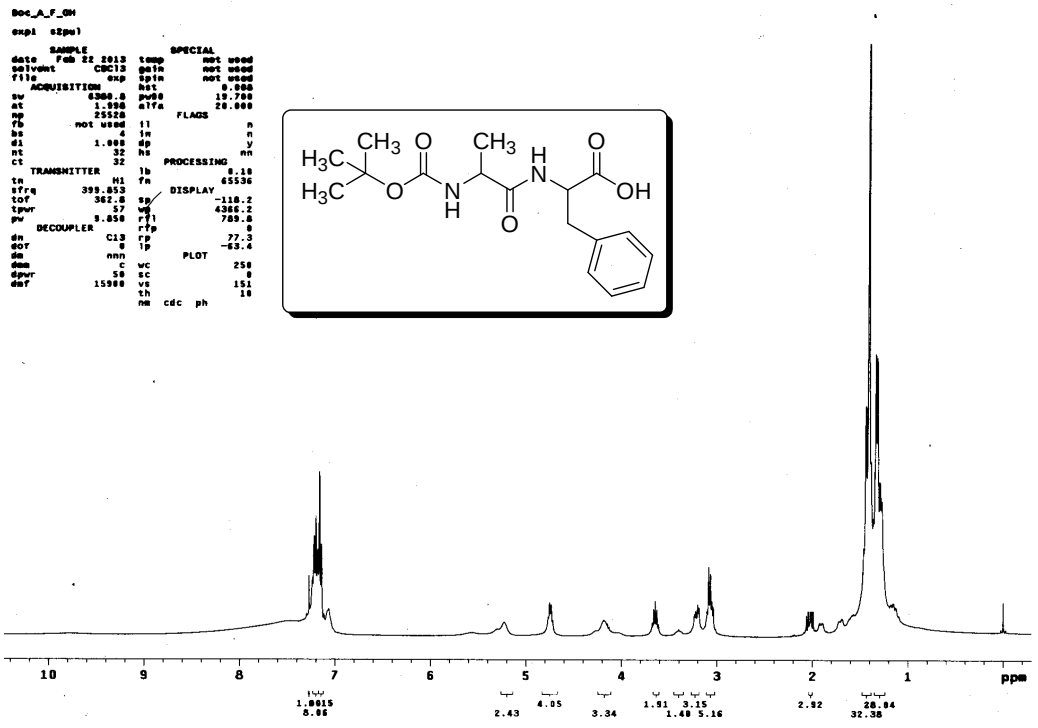


Figure 5S.4

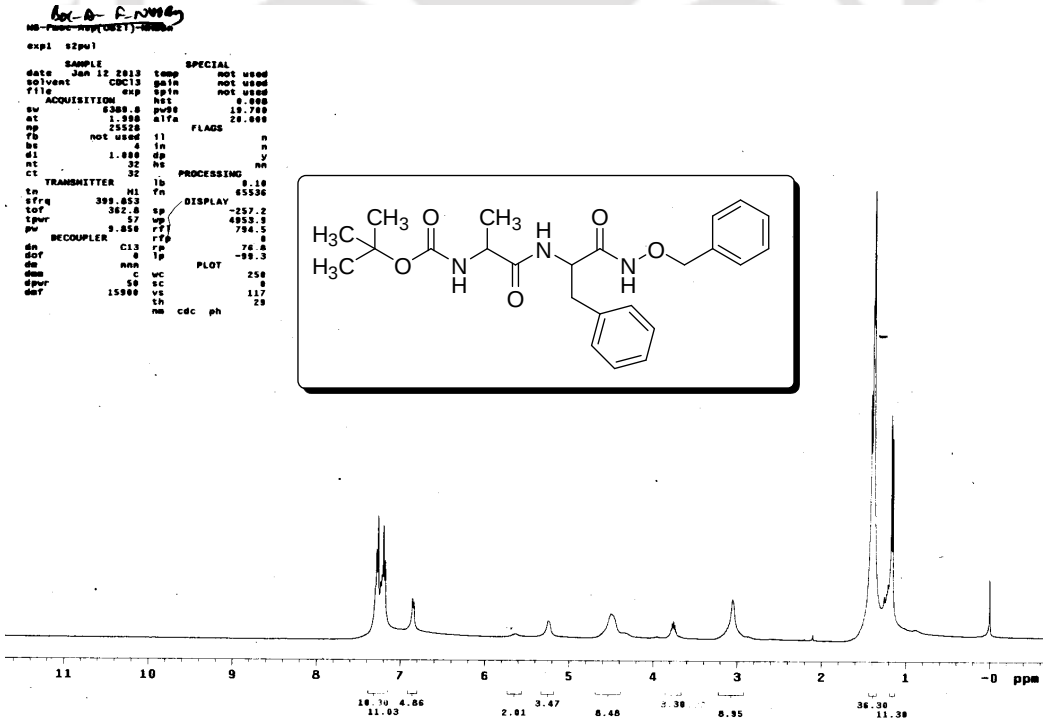


Figure 5S.5 (Table **4.3,** entry **1)**

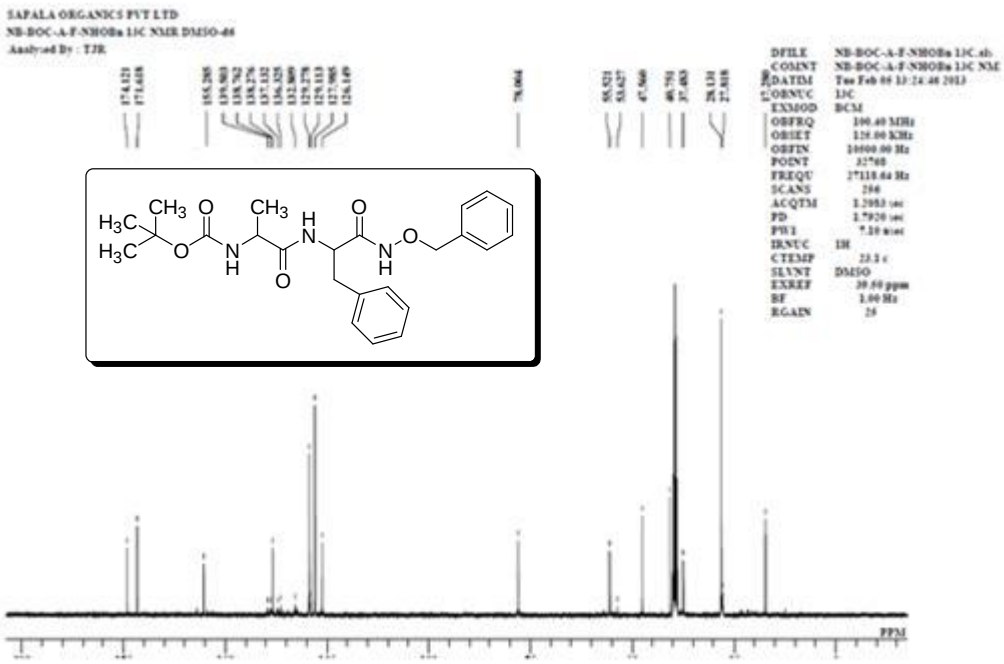


Figure 5S.6 (Table **4.3,** entry **1)**

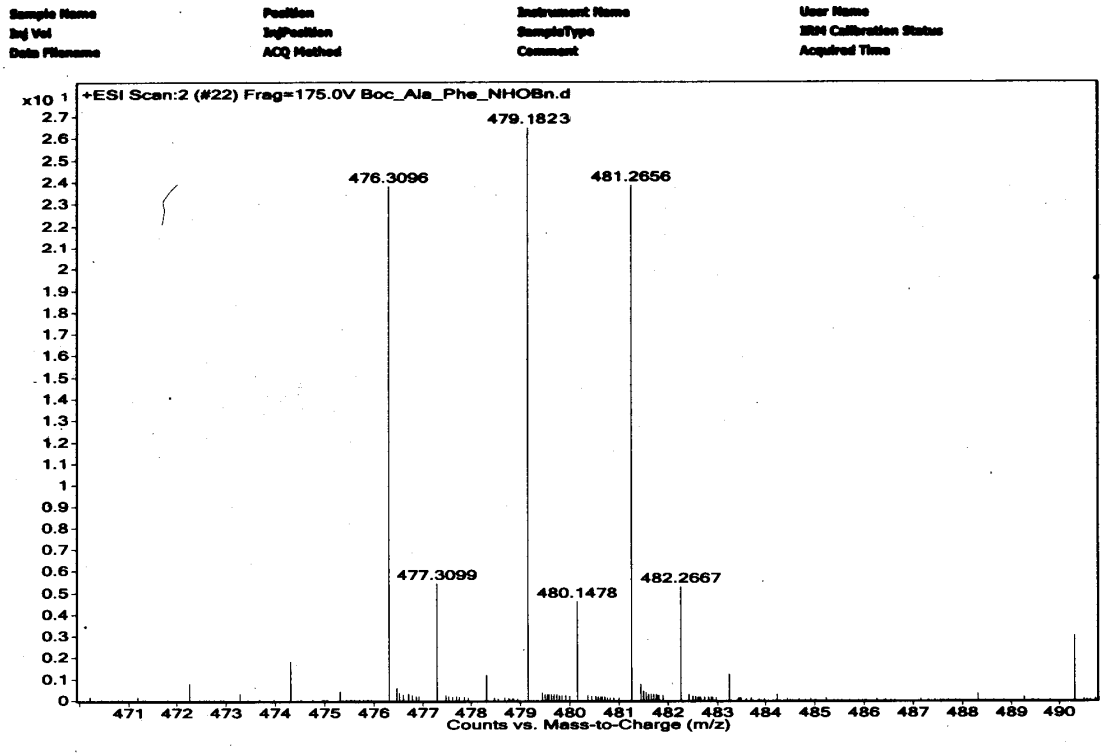


Figure 5S.7. Calcd. mass for $[M+K]^+$: 479.1826 found: 479.1823. (entry 1, table 3) **(**Table **4.3,** entry **1)**

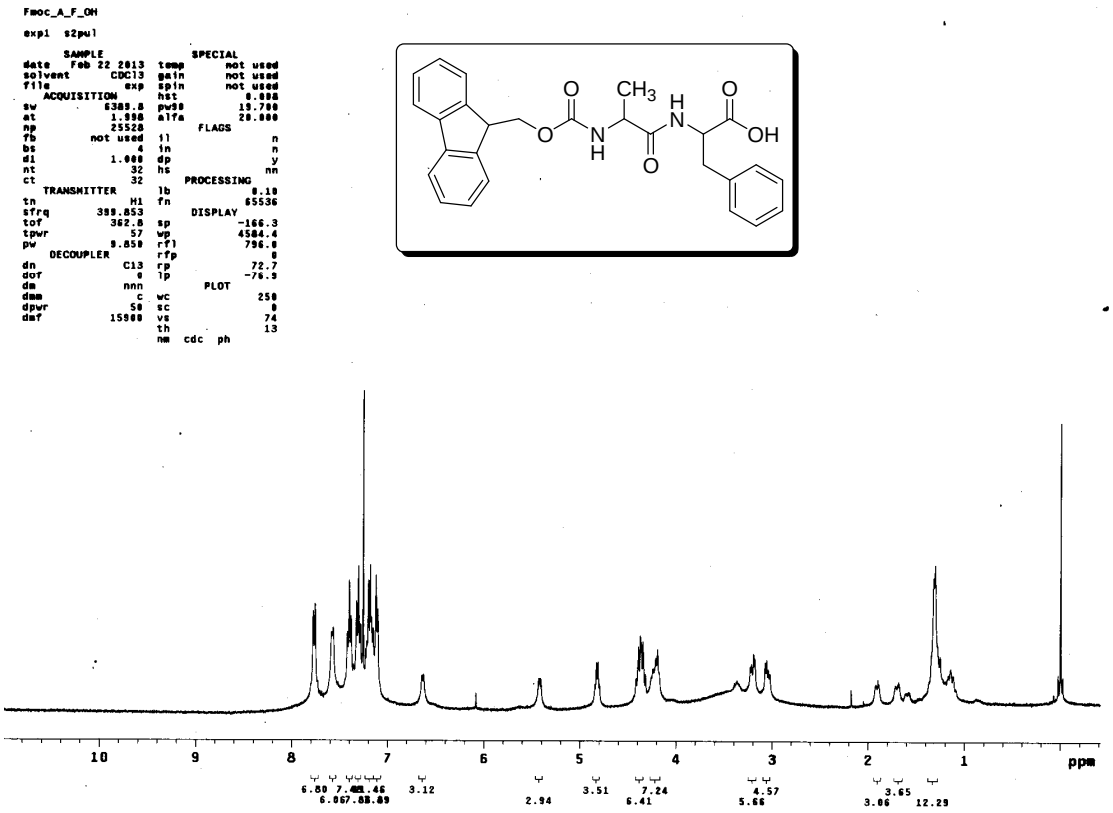


Figure 5S.8

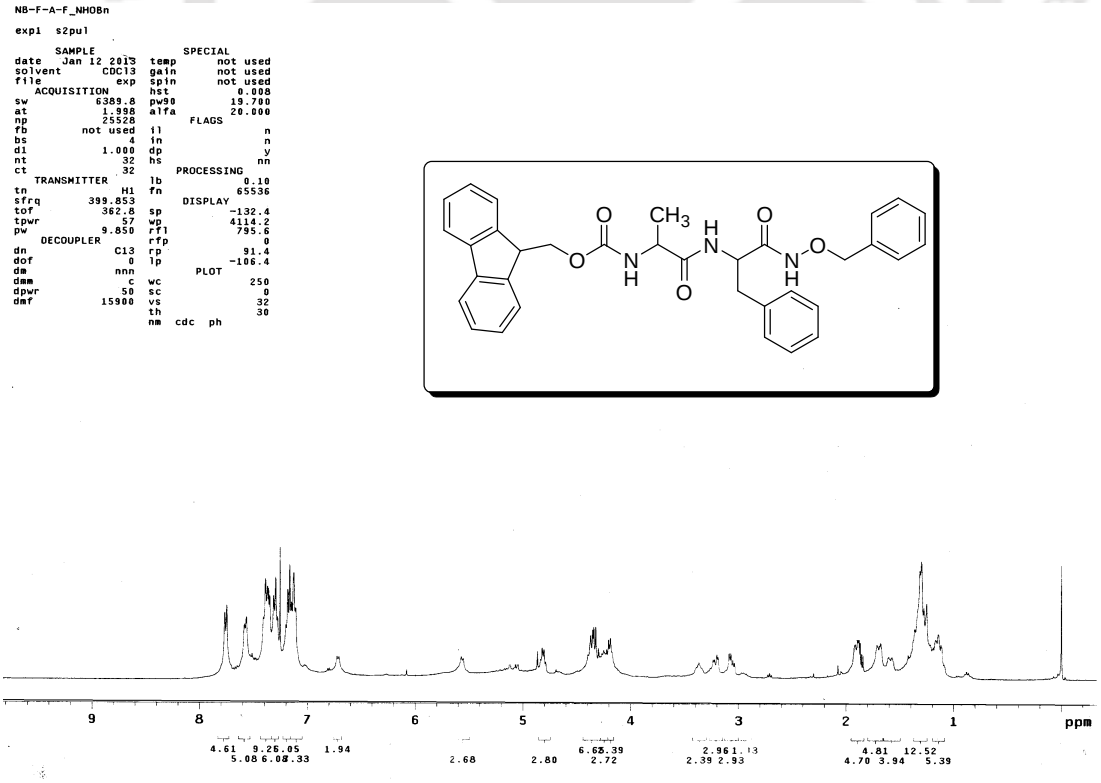


Figure 5S.9 (Table **4.3,** entry **2)**

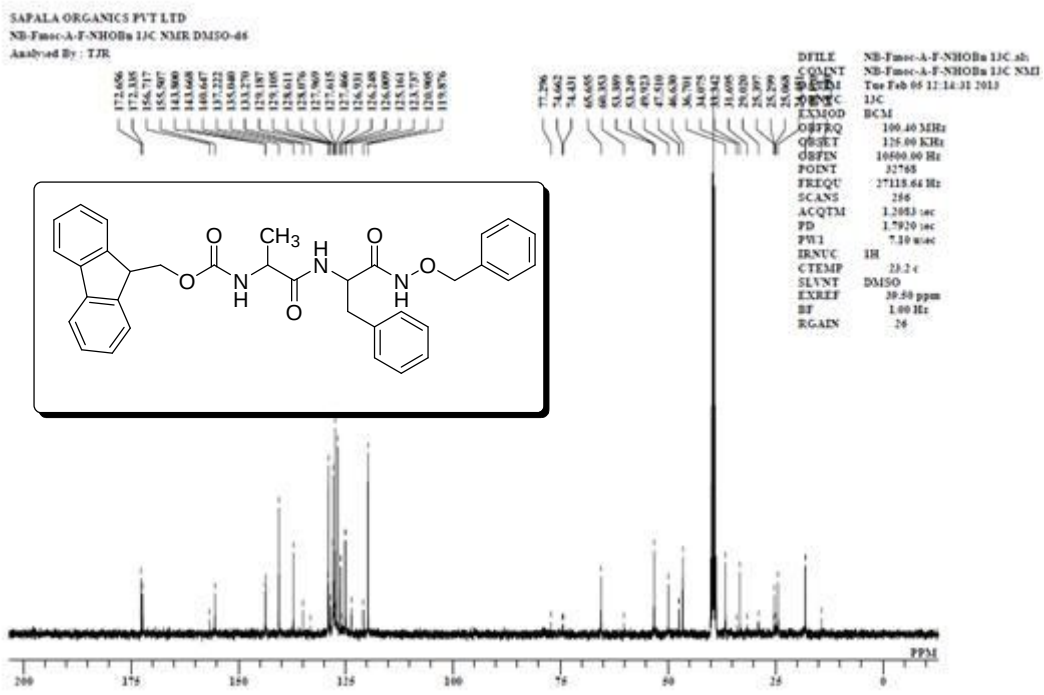


Figure 5S.10 (Table **4.3,** entry **2)**

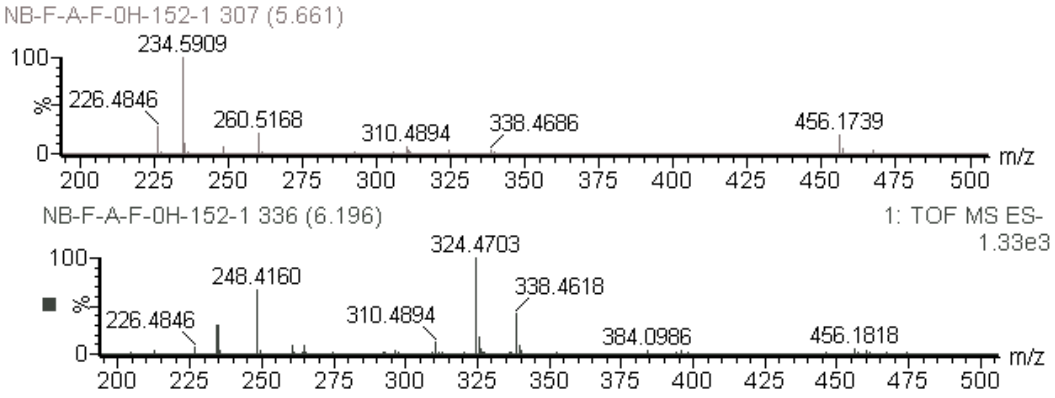


Figure 5S.11 MS spectra for the compound Fmoc-Ala-Phe-OH at two different retention times (Rt 5.6, upper panel) and (Rt 6.1, lower panel)

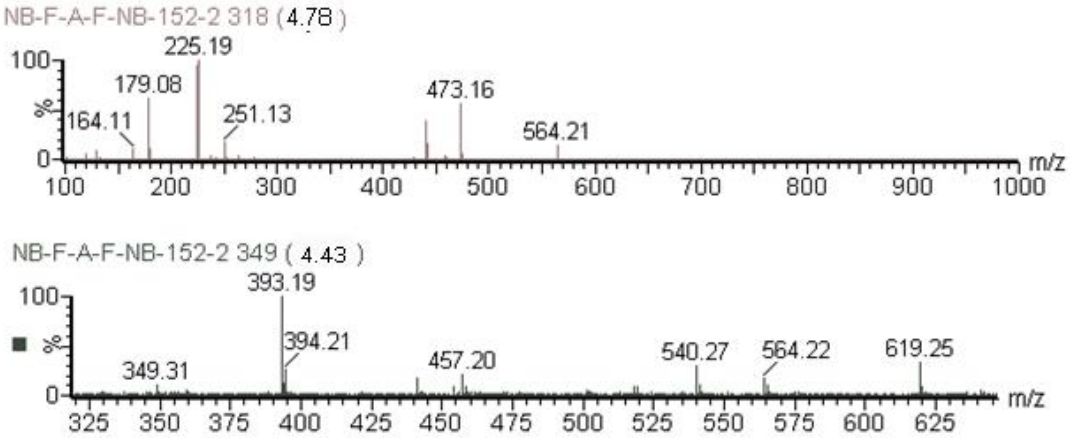


Figure 5S.114.2. MS spectra for the compound Fmoc-Ala-Phe-NHOBn, at two different retention times (Rt 4.8, upper panel) and (Rt 4.4, lower panel).

Chapter 5a. Synthesis of Sulfonamides Using Sulfonate Esters of Oxyma

5a.1 Introduction

Having explained the need for the activation of sulfonic acids into a form which undergoes the amidation to produce sulphonamides in the previous chapter,[1] we further wanted to develop another method for the same transformation as *N*-hydroxy benzotriazole (HOBt)[2] is an explosive material on heating. In addition to this handling draw-back, the method we previously demonstrated could not be applied for the less nucleophilic amines such anilines, applicability to acid labile functional groups and solid phase resins.

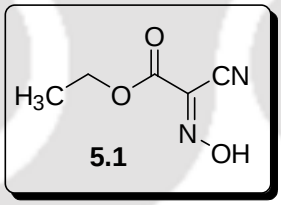
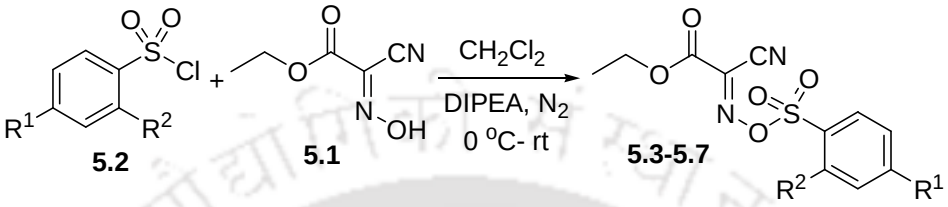


Figure 5.1 Oxyma [ethyl 2-cyano-2-(hydroxyimino)acetate]

In recent times Oxyma (**5.1**) [ethyl 2-cyano-2-(hydroxyimino)acetate] was found to be a very good replacement for HOBt in peptide synthesis which can be even heated (unlike HOBt).[3] Yet, it holds all the advantages of HOBt such as racemization suppressant and a very good leaving group. Therefore, we wanted to check whether Oxyma can be a replacement for the HOBt in the synthesis of sulfonamides using the Oxyma ester activation protocol while retaining all the benefits of previous activation methods with exclusion of all the demerits.[4]

Furthermore, the ability of Oxyma to withstand various temperatures opens a way to prepare corresponding sulphonate esters too.

5a.2 Results and Discussion



Scheme 5a.1

Table 5a.1 Synthesis of various sulfonate esters

entry	sulfonyl chloride (**5.2**)	time (h)[a]	yield (%)[b]
5.3	R^1 = H; R^2 = H	2	79
5.4	R^1 = CH_3; R^2 = H	2	81
5.5	R^1 = NO_2; R^2 = H	1.5	64
5.6	R^1 = H; R^2 = NO_2	1.5	63
5.7	R^1 = NO_2: R^2 = NO_2	1.5	71

[a] TLC is checked for every 30 min. [b] The yields were referred to the isolated yields after column chromatography.

At first, we prepared a few Oxyma esters from sulfonyl chlorides with various substitutions (**5.3-5.7**) using a reported protocol (Scheme **5.1**).[1] All the sulfonate esters were characterized with ^{1}H-NMR, ^{13}C-NMR and ESI-MS. *p*-NO_2-$C_6H_4SO_3XY$ was characterized using single crystal XRD (Figure **1**) also.

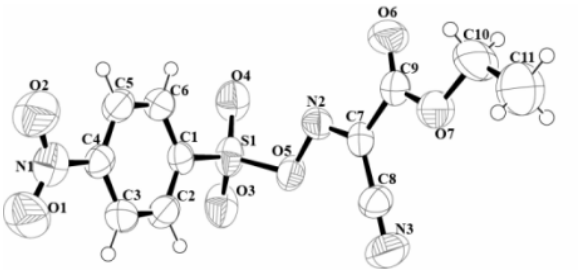
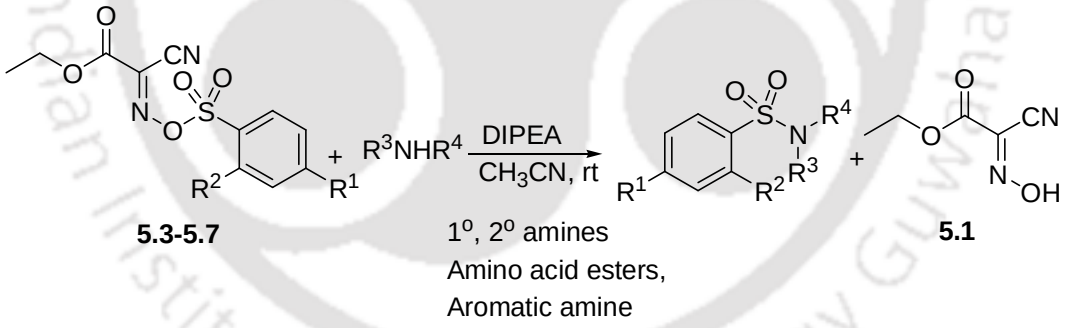


Figure 5a.1 ORTEP diagram for 4-NO_2–Ph–SO_3XY, with 50 % probability ellipsoids

Having the activated esters in hand, we investigated their ability to undergo amidation with various amines (Scheme **5a.2**) in green solvents. Intially, we took (E)-Ethyl 2-cyano-2-(tosyloxyimino)acetate **(**TsOXY) and benzyl amine 1 equiv. each, in presence of 1 equiv. of DIPEA in acetonitrile. The reaction progressed smoothly and generated the desired product in very good yield within 2 h. This encouraged us to persue further to verify applicability of this method to various amines. Although, the reactions work equally good in CH_2Cl_2, we proceeded with acetonitrile keeping green chemistry aspects in mind.



Scheme 5a.2

This methodology is applicable to a wide variety of amines that include primary (entries **1-7**, Table **5a.2**), protected hydroxyl amine (Entry **8** &**9,** Table **5a.2**), secondary (entries **10-13,** Table **5a.2**) and amino acid esters including that with sterically hindered side chains (entries **14-19,** Table **5a.2**). This methodology is also sensitive to the eletronic and the steric factors as its previous counterpart (HOBt).

Table 5a.2 Synthesis of various sulphonamides

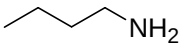
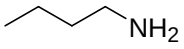
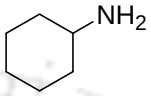
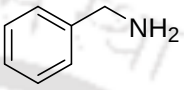
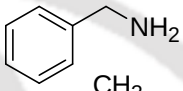
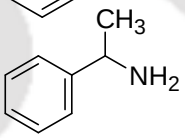
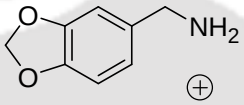
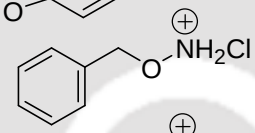
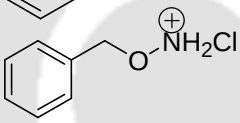
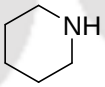
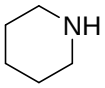
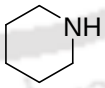
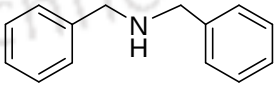
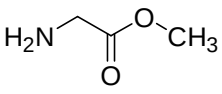
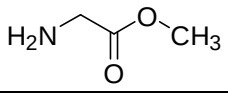
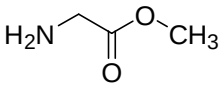
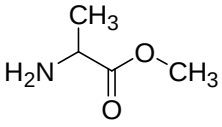
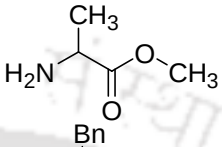
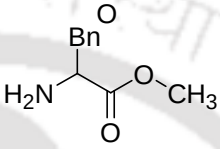
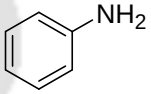
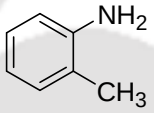
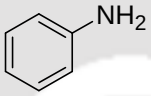
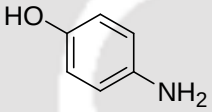
entry	sulfonate ester	amine	yield (%)[a]
1	$R^1 = CH_3$, $R^2 = H$		84
2	$R^1 = NO_2$, $R^2 = NO_2$		86
3	$R^1 = CH_3$, $R^2 = H$		89
4	$R^1 = CH_3$, $R^2 = H$		79
5	$R^1 = NO_2$, $R^2 = NO_2$		83
6	$R^1 = CH_3$, $R^2 = H$		61
7	$R^1 = CH_3$, $R^2 = H$		69
8	$R^1 = CH_3$, $R^2 = H$		73
9	$R^1 = H$, $R^2 = NO_2$		76
10	$R^1 = CH_3$, $R^2 = H$		90
11	$R^1 = H$, $R^2 = H$		92
12	$R^1 = NO_2$, $R^2 = H$		96
13	$R^1 = CH_3$, $R^2 = H$		54
14	$R^1 = CH_3$, $R^2 = H$		84
15	$R^1 = NO_2$, $R^2 = H$		88

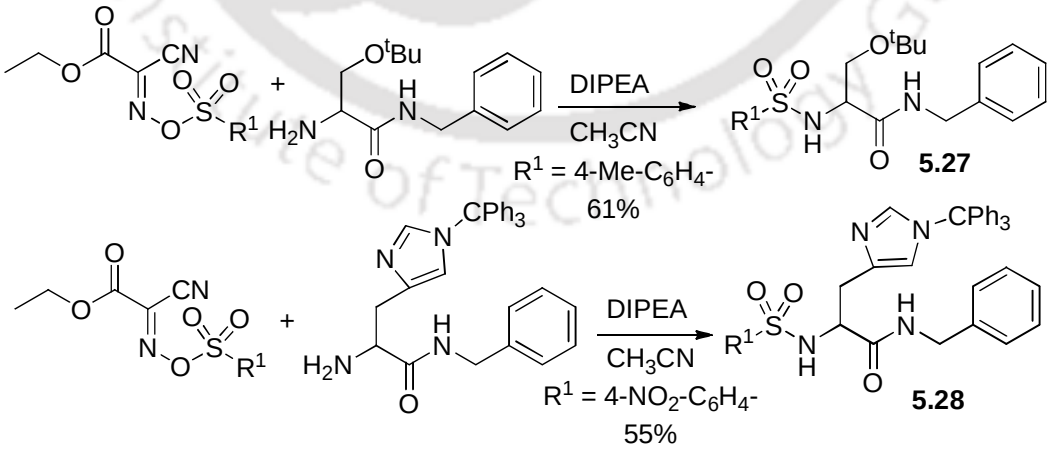
Table **5a.2** continues….

entry	sulfonate ester	amine	yield (%)[a]
16	R^1 = H, R^2 = NO_2		84
17	R^1 = CH_3, R^2 = H		79
18	R^1 = NO_2, R^2 = NO_2		74
19	R^1 = NO_2, R^2 = NO_2		68
20[b]	R^1 = CH_3, R^2 = H		n.d.
21[b]	R^1 = CH_3, R^2 = H		n.d.
22[c]	R^1 = NO_2, R^2 = H		24
23[c]	R^1 = NO_2, R^2 = H		30

[a] Yields refer to the isolated product after column chromatography. All the reported products were characterized using ^{1}H NMR and compared with the reported data, the rest are characterized fully and data provided in supporting information. [b] The reaction was aborted as there was no progress even after 5 h. [c] It took 3 h for the completion of the reaction.

For example, in the case of entries **4** and **6**, when sterically hindered amine was subjected to the reaction conditions, yield was found to be lower than its sterically less hindered analogue. Similar argument holds for the decreament in the yields of the reactions indicated in entries **15** and **19** respectively.

The important advantages of this method lies in the applicability for the synthesis of 2,4- di nitrobenzene sulfonamides (2,4-dNBS) of less nucleophilic and sterically hindered amines. 2,4-dNBS of peptides are of great synthetic importance as they are synthetic precursors for native chemoselective ligation (NCL) as it was described in the *chapter **1***, scheme **1.4**,[5]. Apart from this, 2,4-dNBS are in use as the synthetic precursors for ureas, thioureas, and thioamides.[6] In addition to their synthetic importance, they have recently drawn attention as antituberculosis drugs as they act as pro-drugs for the in vivo generation of SO_2.[7] It is noteworthy that the reaction did not progress when the less nucleophilic aniline was employed with TsOXY (entry **20** and **21** Table **5a.2**) but interestingly, the insertion of an electron withdrawing group at *para* position of sulfonic acids in the sulfonate ester i.e. 4-NbsOxy has dramatically yielded the corresponding sulfonamide of less nucleophilic aniline, though the yield was found to be less (24%). In the case of 4-hydroxy aniline i.e. entry **23**, Table **5a.2**, the yield was relatively more than its previous counterpart i.e. unsubstituted aniline. Hence it can be concluded from these observations that the present methodology is sensitive to the steric and electronic factors.



Scheme 5a.3

In order to examine, whether the present protocol can tolerate the acid labile groups, we took H-Ser(*t*Bu)-NHBn and H-His(Trt)-NHBn (Scheme **5a.3**), and subjected to the reaction conditions. Interestingly, significant cleavage of any of these groups was not noticed.

Therefore, the current strategy of synthesizing the sulphonamides of substrates that have acid labile functionalities makes the sulphonate esters of Oxyma a better auxiliary in the synthesis of natural products and in peptide chemistry.

5a.3 Conclusion:

In peroration, we have shown a novel activation of sulfonic acid as corresponding Oxyma esters, which are new class of peptide coupling reagents[1] and has the following advantages: (i) room temperature reactions, (ii) very good to excellent yields, (iii) shorter time of the reaction compared to the other activation methods, (iv) easy handling and purification, (v) avoidance of the bases like DBU, NMM, NMP, NaH *etc.*, (vi) a wide substrate scope (vii) applicability to those substrates that have acid labile groups such as Trt and *t*Bu and (viii) compatibility with Fmoc based solid phase peptide synthesis strategy. Moreover, the current methodology gives a way for easy synthesis of dNBS derivatives, which are important as antituberculosis drugs. Apart from these, Oxyma is a better auxiliary than its counterparts i.e. HOBt, PFP, *p*-NO_2PhOH and TCP in terms of green chemistry practice. Furthermore, if desired, the by-product, Oxyma can be recovered easily and reused for reagent preparation, which can be used in the same pool. Although the present methodology could necessitate the use of sulfonyl chlorides for reagent preparation, it gives access to the HCl free sulfonamide synthesis under milder conditions. Taking advantage of this acid free sulfonamide synthesis method, the synthesis of some biologically important peptide conjugates was performed and is discussed in the following part of this chapter.

5a.4 Experimental Section:

5a.4.1 General information:

All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. Melting points were uncorrected and determined with a Buchi-540 apparatus. Thin layer chromatograms were run on glass plates coated with silica gel G for TLC, using solvent systems EtOAc/Hexane. All the compounds were purified by column chromatography using 60-120 mesh silica gel from Spectrochem (India). ^{1}H-NMR (400 MHz for ^{1}H) was recorded using DRX-400 Varian spectrometer using $CDCl_3$ as solvent unless mentioned otherwise. Chemical shifts were reported in parts per million (ppm), internal reference (0.05% to 1%) tetra methyl silane. Coupling constants (*J*) were reported in Hz singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). Low resolution mass spectra were recorded on a Micromass Q-TOF ESI MS instrument (model HAB273). HRMS was recorded on 6500 Q-TOF LC/MS system. IR was recorded on a Perkin Elmer spectrum FT-IR one spectrometer. LC-MS was performed on WATERS Q-TOF instrument. HPLC was carried out on WATERS instrument with UV detector under 254 nm and 214 nm. Specific rotation was measured on Rudolph Research Analytical instrument Autopol 1 at 589 nm, 27.1 °C, temperature correction off. Data for previously reported compounds (cited therein) matched well with our observed data.

5a.4.2 General procedure for the synthesis of sulfonate esters from sulfonyl chloride and Oxyma:

An oven dried 25 mL R.B. flask, equipped with a magnetic stir bar, was loaded with Oxyma (1 mmol, 1 equiv.) which was dissolved in 1 mL of dry CH_2Cl_2. To this, DIPEA (1 mmol, 1

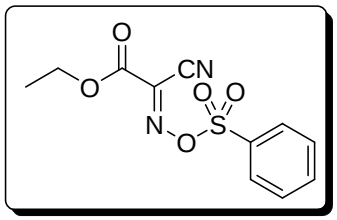
equiv) was added under nitrogen. Then it was cooled to 0 °C, followed by the slow addition of sulfonyl chloride (1 mmol, 1 equiv.), predissolved in dry DCM using a syringe over 30 mins. Then, the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was washed with saturated NaCl solution (2×10 mL) and dried over anhydrous $CaCl_2$. Then it was dried in *vaccuo* and purified by recrystallization using hexane and CH_2Cl_2.

5a.4.3 General procedure for the synthesis of sulfonamides from the sulfonate esters of Oxyma:

An oven dried 25 mL round bottomed flask, equipped with magnetic stir bar, was loaded with Oxyma sulfonate (1 mmol, 1 equiv.) dissolved in 1 mL of CH_3CN. To this, the solution of amine (1 mmol, 1 equiv.) and DIPEA (1 mmol, 1 equiv.) in 1 mL of CH_3CN was added slowly over 2 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated using rotary evaporator and then diluted with 10 mL of ethyl acetate and washed with 5% HCl (3×10 mL), 5% $NaHCO_3$ (3×10 mL), and saturated NaCl solution (2×10 mL) and dried over anhydrous Na_2SO_4. Then it was dried in *vaccuo* and purified by column chromatography.

5a.5 Characterization data:

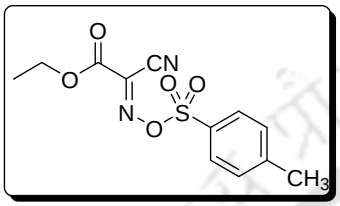
1) (E)-Ethyl 2-cyano-2-(phenylsulfonyloxyimino)acetate (Table 5a.1, Entry 1):



R_f product 0.48 (EtOAc/Hexane, 1:4), Yield 223 mg, 79%, colorless crystalline solid, mp 96 °C. IR (KBr, ν/cm^{-1}) 3093, 2977, 1754, 1591, 942, 764. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04-5.02 (m, 2H, 2×Ar**H**), 7.75-7.73 (m, 1H, 1×Ar**H**), 7.62-7.59 (m,

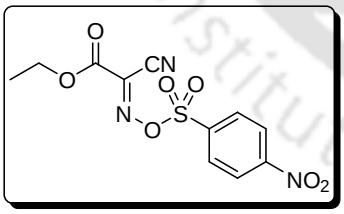
2H, 2×Ar**H**), 4.41-4.36 (q, 2H, C**H**$_2$), 1.37-1.33 (t, 3H, C**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.9, 135.8, 133.1, 131.5, 129.7, 129.4, 106.1, 64.7, 13.8; HRMS (ESI) m/z Calcd. for $C_{11}H_{11}N_2O_5S$ $[M+H]^+$: 283.0389, found: 283.0384 .

2) (E)-Ethyl 2-cyano-2-(tosyloxyimino)acetate (Table 5a.1, Entry 2):



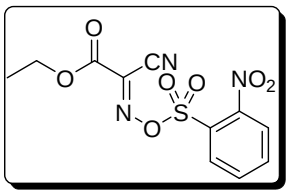
R_f product 0.46 (EtOAc/Hexane, 1:4), Yield 240 mg, 81%, colorless crystalline solid, mp 70-71 °C. IR (KBr, ν/cm^{-1}) 3011, 2923, 1759, 1593, 949, 769. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.86-7.84 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.35-7.33 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 4.37-4.31 (q, 2H, C**H**$_2$), 2.41 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.6 Hz, C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.0, 147.5, 131.5, 130.4, 130.1, 129.5, 106.2, 64.6, 21.9, 13.9; LRMS (ESI) m/z Calcd. for $C_{12}H_{13}N_2O_5S$ $[M+H]^+$: 297.05, found: 297.05.

3) (E)-Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate (Table 5a.1, Entry 3):



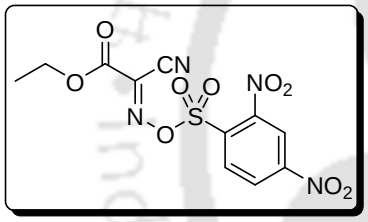
R_f product 0.42 (EtOAc/Hexane, 1:4), Yield 209 mg, 64%, pale yellow solid, mp 111 °C. IR (KBr, ν/cm^{-1}) 3113, 2991, 1768, 1604, 932, 745.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.40-8.39 (d, 2H, *J* = 6.8 Hz, 2×Ar**H**), 8.21-8.8.18 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 4.39-4.34 (q, 2H, C**H**$_2$), 1.39-1.30 (t, 3H, *J* = 6.8 Hz, C**H**$_3$), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.5, 151.9, 138.7, 132.7, 131.1, 124.9, 105.9, 65.1, 14.0; LRMS (ESI) m/z Calcd.for $C_{11}H_{10}N_3O_7S$ $[M+H]^+$: 328.02, found: 328.02.

4) (E)-Ethyl 2-cyano-2-(2-nitrophenylsulfonyloxyimino)acetate (Table 5a.1, Entry 4):



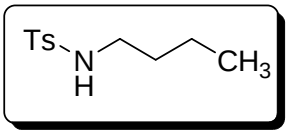
R_f product 0.58 (EtOAc/Hexane, 1:4), Yield 206 mg, 63%, colorless crystalline solid, mp 113 °C. IR (KBr, ν/cm^{-1}) 3103, 2988, 1748, 1544, 928, 742. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.27-8.25 (d, 1H, *J* = 8.0 Hz, 1×Ar**H**), 7.95-7.85 (m, 3H, 3×Ar**H**), 4.47-4.42 (q, 2H, C**H**$_2$), 1.40-1.37 (t, 3H, C**H**$_3$), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 155.6, 148.0, 137.1, 133.4, 132.8, 126.3, 125.5, 105.9, 65.1, 13.9; HRMS (ESI) m/z Calcd. for $C_{11}H_{10}N_3O_7S$ $[M+H]^+$: 328.0239, found : 328.0237 .

5) (E)-Ethyl 2-cyano-2-(2,4-dinitrophenylsulfonyloxyimino)acetate (Table 5a.1, Entry 5):



R_f product 0.39 (EtOAc/Hexane, 1:4) Yield 264 mg, 71%, yellow crystalline solid, mp 109 °C. IR (KBr, ν/cm^{-1}) 3121, 2989, 1752, 1602, 985, 767.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.91-8.90 (d, 1H, *J* = 2.4 Hz, 1×Ar**H**), 8.54-8.50 (m, 1H, 1×Ar**H**), 7.95-7.92 (d, 1H, *J* = 9.2 Hz, 1×Ar**H**), 4.51-4.46 (q, 2H, 2×C**H**$_2$), 1.40-1.37 (t, 3H, C**H**$_3$), ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 156.1, 154.2, 144.0, 137.5, 131.7, 129.6, 118.8, 106.6, 64.9, 14.0; HRMS (ESI) m/z Calcd. for $C_{11}H_9N_4O_9S$ $[M+H]^+$: 373.0090, found: 373.0098.

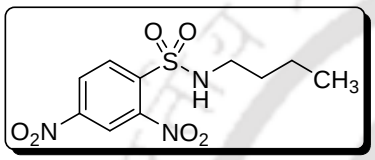
6) *N*-Butyl-4-methylbenzenesulfonamide (Table 5a.2, Entry 1):



R_f product 0.52 (EtOAc/Hexane, 1:4), Yield 275 mg, 84%, white solid, mp 44 °C. IR (KBr, ν/cm^{-1}) 3470, 3090, 1652, 1358, 1163. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77-7.75 (d,

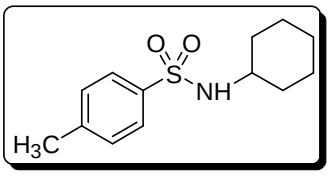
2H, *J* = 8 Hz, 2xAr**H**), 7.31-7.29 (d, 2H, *J* = 8 Hz, 2xAr**H**), 5.12 (br s, 1H, N**H**), 2.91 (t, 2H, *J* = 6.8 Hz, NHC**H**$_2$), 2.42 (s, 3H, C**H**$_3$), 1.45-1.41 (m, 2H, NHCH$_2$C**H**$_2$), 1.30-1.25 (m, 2H, **CH**$_2$CH$_3$), 0.85-0.83 (t, 3H, *J* = 5.6 Hz, CH$_2$**CH**$_3$). LRMS (ESI) m/z Calcd. for $C_{11}H_{18}NO_2S$ $[M+H]^+$: 228.10, found: 228.10.

7) *N*-Butyl-2,4-dinitro-benzenesulfonamide (Table 5a.2, Entry 2):



R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 261 mg, 86%, pale yellow solid, mp 151 °C. IR (KBr, ν/cm^{-1}) 3262, 2943, 1729, 1532, 1350, 1336, 1236, 1159, 830, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.14-9.13 (d, 1H, *J* = 2.4 Hz, 1×Ar**H**), 8.56 (s, 1N**H**), 8.28-8.28 (d, 1H, J_1 = 2.4 Hz, J_1 = 2.8 Hz 1×Ar**H**), 6.94-6.91 (d, 1H, 1×Ar**H**), 3.44-3.40 (m, 2H, -C**H**$_2$CH$_2$-), 1.81-1.74 (m, 2H, -CH$_2$C**H**$_2$CH$_2$), 1.54-1.48 (m, 2H, -CH$_2$CH$_2$C**H**$_2$-), 1.03-0.98 (m, 3H, CH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 148.3, 135.5, 130.1, 129.9, 123.9, 114.1, 43.2, 30.6, 20.0, 13.5; LRMS (ESI) m/z Calcd. for $C_{10}H_{14}N_3O_6S$ $[M+H]^+$: 304.06, found: 304.06.

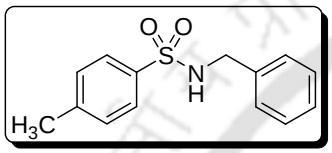
8) *N*-Cyclohexyl-4-methylbenzenesulfonamide (Table 5a.2, Entry 3):



R_f product 0.61 (EtOAc/Hexane, 1:4), Yield 226 mg, 89%, white solid, mp 87-89 °C. IR (KBr, ν/cm^{-1}) 3328, 2937, 1755, 1684. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79-7.77 (d, 2H, *J* = 8.4 Hz, 2xAr**H**), 7.32-7.28 (d, 2H, *J* = 8.4 Hz, 2xAr**H**),

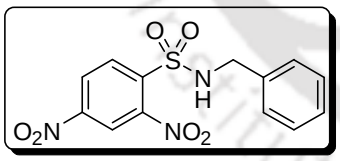
4.97 (br s, 1H, N**H**), 3.11-3.09 (m, 1H, NHC**H**), 2.42 (s, 3H, C**H**$_3$), 1.74-1.72 (m, 4H, 2xNHCHC**H**$_2$), 1.63-1.60 (m, 4H, 2xNHCHCH$_2$C**H**$_2$), 1.27-1.07 (m, 2H, NHCHCH$_2$CH$_2$C**H**$_2$). LRMS (ESI) m/z Calcd. For $C_{13}H_{20}NO_2S$ $[M+H]^+$: 254.12, found: 254.12.

9) *N*-Benzyl-4-methylbenzenesulfonamide (Table 5a.2, Entry 4):



R_f product 0.58 (EtOAc/Hexane, 1:4), Yield 206 mg, 79%, white solid, mp 87-89 °C. IR (KBr, ν/cm^{-1}) 3262, 3027, 1594, 1492, 1450, 1320, 1156. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77-7.75 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.31-7.26 (m, 5H, 5×Ar**H**), 7.20-7.18 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 4.74 (br s, 1H, N**H**), 4.11 (s, 2H, C**H**$_2$), 2.43 (s, 3H, C**H**$_3$). LRMS (ESI) m/z Calcd. for $C_{14}H_{16}NO_2S$ $[M]^+$: 261.02, found: 261.02 .

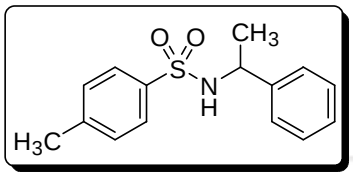
10) *N*-Benzyl-2,4-dinitro-benzenesulfonamide (Table 5a.2, Entry 5):



R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 298 mg, 83%, white solid, mp 151 °C. IR (KBr, ν/cm^{-1}) 3379, 3096, 2346, 1532, 1336, 1159. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.16-9.15 (t, 1H, *J* = 2.4 Hz, 1×Ar**H**), 8.91 (s, 1H, 1N**H**), 8.24-8.21 (dd, 1H, J_1 = 2.4 Hz, J_2 = 2.8 Hz, 1× ArH), 7.43-7.26 (m, 5H, 5×Ar**H**), 6.92-6.90 (d, 1H, *J* = 5.2 Hz, 1×Ar**H**), 4.66-4.64 (d, 2H, J_1 = 5.6 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 148.3, 136.2, 135.7, 130.6, 130.2, 129.2, 128.2, 127.1,

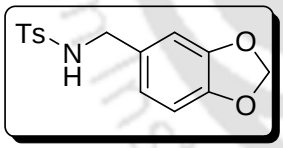
124.0, 114.6, 47.4. LRMS (ESI) m/z Calcd. for $C_{13}H_{12}N_3O_6S$ $[M]^+$: 338.04, found: 338.04 .

11) 4-Methyl-*N*-(1-phenylethyl)benzenesulfonamide (Table 5a.2, Entry 6):



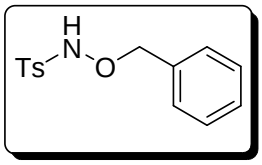
R_f product 0.46 (EtOAc/Hexane, 1:4), Yield 168 mg, 61%, white solid, mp 78 °C. IR (KBr, ν/cm^{-1}) 3307, 2931, 2854, 1926, 1597, 1494, 1427, 1159, 1092, 925. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55-7.53 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 7.09-7.07 (d, 5H, *J* = 8 Hz, 5×Ar**H**), 7.02-7.01 (m, 2H, 2×Ar**H**), 5.22-5.21 (d, 1H, *J* = 3.6 Hz, N**H**), 4.38-4.35 (t, 1**H**, *J* = 12 Hz, C**H**Ar), 2.29 (s, 3H, ArC**H**$_3$), 1.33-1.32 (d, 3H, *J* = 6.8 Hz, CHC**H**$_3$). LRMS (ESI) m/z Calcd. for $C_{15}H_{18}NO_2S$ $[M+H]^+$: 276.10, found: 276.10.

12) *N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methylbenzenesulfonamide (Table 5a.2, Entry 7):



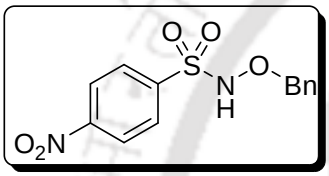
R_f product 0.59 (EtOAc/Hexane, 2:3), Yield 211 mg, 69%, white solid, mp 139 °C lit (134-137 °C). IR (KBr, ν/cm^{-1}) 3268, 1586, 1337, 1263, 1089, 926. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64-7.62 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.33-7.31 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 6.58-6.65 (m, 3H, 2×Ar**H**), 5.9 (s, 2H, C**H**$_2$), 4.92 (t, *J* = 6.4 Hz, N**H**), 4.20 (d, *J* = 6.4 Hz, 2H, -C**H**$_2$), 2.43 (s, 3H, C**H**$_3$). LRMS (ESI) m/z Calcd. For $C_{15}H_{16}NO_4S$ $[M+H]^+$: 306.08, found: 306.08.

13) *N*-Benzyloxy-4-methyl-benzenesulfonamide (Table 5a.2, Entry 8):



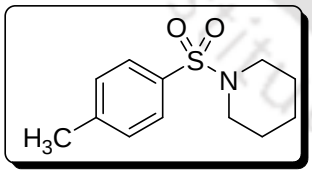
R_f product 0.46 (EtOAc/Hexane, 1:6), Yield 202 mg, 73%, white solid, mp 74°C lit (72 °C). IR (KBr, ν/cm^{-1}) 3268, 1586, 1337, 1263, 1089, 926. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82-7.80 (d, 2H, *J* = 8.0 Hz, 2×Ar**H**), 7.37-7.26 (m, 7H, 7×Ar**H**), 4.97 (s, 2H, C**H**$_2$), 2.43 (s, 3H, C**H**$_3$); LRMS (ESI) m/z Calcd. for $C_{14}H_{16}NO_3S$ $[M+H]^+$: 278.08, found: 278.07.

14) *N*-Benzyloxy-4-nitro-benzenesulfonamide (Table 5a.2, Entry 9):



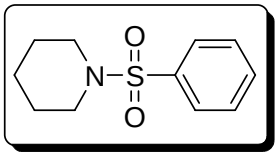
R_f product 0.42 (EtOAc/Hexane, 1:4), Yield 234 mg, 76%, white solid, mp 91-93 °C. IR (KBr, ν/cm^{-1}) 2946, 1742, 1451, 1337, 1248. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.02 (d, 1H, 1×Ar**H**), 8.71-8.69 (dd, 1H, *J* = 2.8Hz, 1×Ar**H**), 8.41-8.38 (dd, 1H, *J* = 2.6Hz, 1×Ar**H**), 8.18-8.04 (m, 2H, 2×Ar**H**), 8.76-7.26 (m, 4H, 4×Ar**H**), 5.06 (s, 2H, C**H**$_2$); LRMS (ESI) m/z Calcd. for $C_{13}H_{13}N_2O_5S$ $[M+H]^+$: 309.05, found: 309.05.

15) 1-Tosylpiperidine (Table 5a.2, Entry 10):



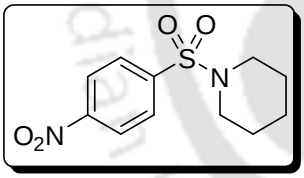
R_f product 0.42 (EtOAc/Hexane, 1:4), Yield 216 mg, 90%, white solid, mp 82 °C. IR (KBr, ν/cm^{-1}) 2946, 1739, 1446, 1337, 1263. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64-7.62 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.33-7.31 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 2.97 (t, 4H, *J* = 5.6 Hz, 2×C**H**$_2$), 2.43 (s, 3H, C**H**$_3$), 1.66-1.61 (m, 4H, 2×C**H**$_2$), 1.42-1.39 (m, 2H, C**H**$_2$). LRMS (ESI) m/z Calcd for $C_{12}H_{18}NO_2S$ $[M+H]^+$: 240.10, found 240.10.

16) 1-Benzenesulfonyl-piperidine (Table 5a.2, Entry 11):



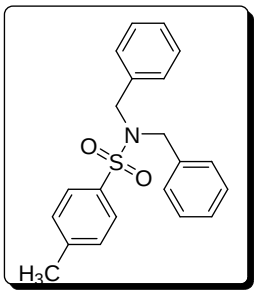
R_f product 0.42 (EtOAc/Hexane, 1:4), Yield 207 mg, 92%, white solid, mp 91-93 °C. IR 1630, 1485, 1470, 1450, 1340, 1180 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.64-7.62 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.33-7.31 (d, 3H, *J* = 8.4 Hz, 3×Ar**H**), 2.97 (m, 4H, *J* = 5.6 Hz, 2×C**H**$_2$), 1.66-1.61 (m, 4H, 2×C**H**$_2$), 1.42-1.39 (m, 2H, C**H**$_2$). LRMS (ESI) m/z Calcd. for $C_{11}H_{16}NO_2S$ $[M+H]^+$: 226.09, found: 226.09.

17) 1-(4-Nitrophenylsulfonyl)piperidine (Table 5a.2, Entry 12):



R_f product 0.51 (EtOAc/Hexane, 1:4), Yield 281 mg, 96%, yellow solid, mp 174 °C. IR (KBr, ν/cm^{-1}) 3113, 2928, 1608, 1525, 1160, 1073. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.32-8.30 (d, 2H, *J* =8.8Hz, 2×Ar**H**), 7.88-7.86(d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 2.99-2.94 (m, 4H, 2×-NC**H**$_2$), 1.62-1.55(m, 4H, 2×-NCH$_2$C**H**$_2$), 1.40-1.37 (m, 2H, NHCH$_2$CH$_2$C**H**$_2$). LRMS (ESI) m/z Calcd. for $C_{11}H_{15}N_2O_4S$ $[M+Na]^+$: 293.10, found: 293.10.

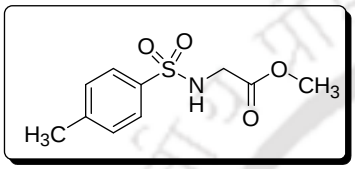
18) *N,N*-Dibenzyl-4-methylbenzenesulfonamide (Table 5a.2, Entry 13):



R_f product 0.38 (EtOAc/Hexane, 1:4), Yield 189 mg, 54%, colorless crystalline solid. IR (KBr, ν/cm^{-1}) 3012, 2976, 1739, 1455, 1337, 1263. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 7.72-7.70 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.29-7.27 (d, 2H, *J* =

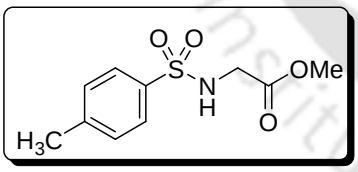
8.0 Hz, 2×Ar**H**), 7.20-7.18 (m, 6H, 6×Ar**H**), 7.04-7.01 (m, 4H, 4×Ar**H**), 4.29 (s, 4H, 2×C**H**$_2$), 2.42 (s, 3H, C**H**$_3$). LRMS (ESI) m/z Calcd. for $C_{21}H_{21}NO_2S$ $[M+]^+$: 351.13, found: 351.13 .

19) Methyl 2-(4-methylphenylsulfonamido)acetate (Table 5a.2, Entry 14):



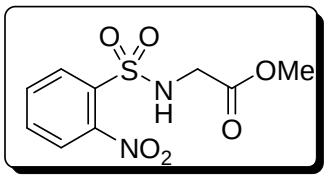
R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 204 mg, 84%, white solid, mp 151 °C. IR (KBr, ν/cm^{-1}) 3262, 2943, 1729, 1532, 1350, 1336, 1236, 1159, 830, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77-7.74 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 7.32-7.30 (d, 2H, *J* = 8.2 Hz, 2×Ar**H**), 5.06 (br s, 1H, N**H**), 3.80 (d, 2H, *J* = 4 Hz, CH_2), 3.64 (s, 3H, -OC**H**$_3$), 2.43 (s, 3H, C**H**$_3$). LRMS (ESI) m/z $[M+H]^+$.Calcd. for $C_{10}H_{14}NO_4S$ $[M+H]^+$: 244.06, found: 244.06.

20) (4-Nitro-benzenesulfonylamino)-acetic acid methyl ester (Table 5a.2, Entry 15):



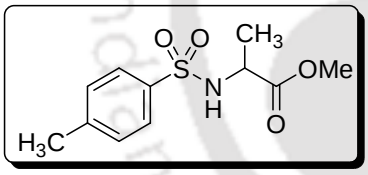
R_f product 0.26 (EtOAc/Hexane, 1:4), Yield 241 mg, 88%, pale yellow solid. Mp 94-95°C. IR (KBr, ν/cm^{-1}) 3344, 1743, 1541, 1403, 1369, 1347, 1225, 1163, 1127, 837, 785.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.36-8.34 (d, 2H, *J* = 9.2 Hz, 2×Ar**H**), 8.06-8.04 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 5.35 (br s, 1H, N**H**), 3.86 (d, 2H, *J* = 4 Hz, C**H**$_2$), 3.65 (s, 3H, -OC**H**$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.8, 152.3, 148.4, 126.4, 124.2, 50.4, 41.8; LRMS (ESI) m/z Calcd.for $C_9H_{10}N_2O_6S$ $[M+]^+$: 274.03, found: 274.02.

21) (2-Nitro-benzenesulfonylamino)-acetic acid methyl ester (Table 5a.2, Entry 16):



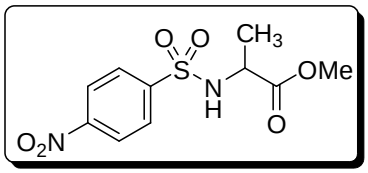
R_f product 0.58 (EtOAc/Hexane, 1:9), Yield 230 mg, 84%, pale yellow solid, mp 109 °C. IR (KBr, ν/cm^{-1}) 3305, 1752, 1539, 1439, 1358, 1208, 1169, 976. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.11-8.08 (m, 1H, Ar**H**), 7.95-7.92 (m, 1H, Ar**H**), 7.76-7.73 (m, 2H, 2×Ar**H**), 6.08 (br s, 1H, N**H**), 4.02 (s, 2H, C**H$_2$**), 3.61 (s, 3H, -OC**H$_3$**). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.0, 147.6, 135.8, 133.5, 132.8, 129.4, 122.5, 52.6, 48.7; LRMS (ESI) m/z Calcd. for $C_9H_{11}N_2O_6S$ $[M+H]^+$: 275.03, found: 275.02.

21) Methyl 2-(4-methylsulfonamido)proponoate (Table 5a.2, Entry 17):



R_f product 0.58 (EtOAc/Hexane, 1:9), Yield 203 mg, 79%, white solid, mp 137-139 °C. IR (KBr, ν/cm^{-1}) 3342, 3026, 1734, 1589, 1340, 1160. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.74-7.72 (d, 2H, *J* = 8 Hz, 2×Ar**H**), 7.30-7.28 (d, 2H, *J* = 8.3 Hz, 2×Ar**H**), 5.37 (d, 1H, *J* = 8.4 Hz, N**H**), 4.00-3.96 (q, 1H, *J* = 7.2 Hz, C**H**), 3.54 (s, 3H, -OCH_3), 2.42 (s, 3H, C**H$_3$**), 1.38-1.37 (d, 3H, *J* = 7.2 Hz, C**H$_3$**). LRMS (ESI) m/z Calcd. for $C_{11}H_{16}NO_3S$ $[M+H]^+$: 242.08, found: 242.08.

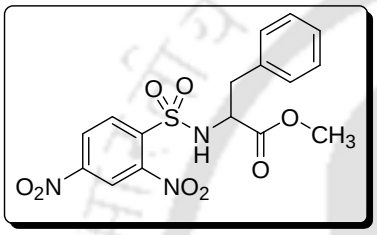
22) Methyl 2-(2,4-dinitrophenylsulfonamido)propanoate (Table 5a.2, Entry 18):



R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 247 mg, 74%, colorless foam. IR (KBr, ν/cm^{-1}) 2934, 1727, 1548, 1346,

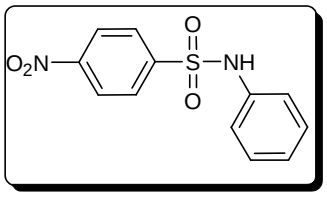
1332, 830, 735. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.75 (d, 1H, *J* = 2.4 Hz, 1×Ar**H**), 8.29 (dd, 1H, J_1 = 2.4 Hz, J_1 = 2.8 Hz 1×Ar**H**), 6.14(dd, 1H, 1×Ar**H**), 4.32(m, 1H, α-C**H**), 3.59(s, 1H, N**H**), 3.56(s, 3H, OCH_3), 1.53(d, 3H, *J* = 7.2 Hz C**H**$_3$).; LRMS (ESI) m/z Calcd. for $C_{10}H_{12}N_3O_8S$ $[M+H]^+$: 334.03, found: 334.05.

23) Methyl 2-(4-nitrophenylsulfonamido)-3-phenylproponoate (Table 5a.2, Entry 19):



R_f product 0.23 (EtOAc/Hexane, 1:4), Yield 193 mg, 53%, pale yellow solid, mp 153 °C. IR (KBr, ν/cm^{-1}) 3272, 1722, 1523, 1347, 1313, 1168, 1092, 1008, 855, 739.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm (400 MHz, $CDCl_3$) 8.16-8.14 (d, 2H, *J* = 8 Hz, 2xAr**H**), 7.78-7.76 (d, 2H, *J* = 8 Hz, 2xAr**H**), 7.16-7.14 (m, 2H, 2xAr**H**), 6.99-6.96 (m, 2H, 2xAr**H**), 5.30 (s, 1H, N**H**), 4.21-4.16 (m, 1H, C**H**), 3.54 (s, 3H, -OC**H**$_3$), 3.07-3.02 (dd, 1H, J_1 = 5.6 Hz, J_2 = 4.8 Hz, C**H**HAr), 3.00-2.94 (dd, J_1 = 7.2 Hz, J_2 = 7.2 Hz, 1H, CH**H**Ar). LRMS (ESI) m/z Calcd. for $C_{16}H_{17}N_2O_6S$ $[M+H]^+$: 365.08, found: 365.08.

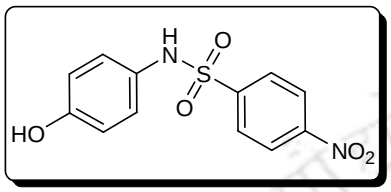
24) 4-Nitro-*N*-phenylbenzenesulfonamide (Table 5a.2, Entry 22):



R_f of product 0.38 (EtOAc/Hexane, 2:3), Yield 67 mg, 24%, pale yellow crystalline solid, mp.172 °C. IR (KBr, ν/cm^{-1}) 3279, 1337, 1159, 836, ^{1}H NMR (400 MHz, CDCl3) 8.32-8.30 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 7.90-7.88 (d, 1H, *J* = 8.4 Hz, 1×Ar**H**), 7.29 (t, 2H, *J* = 6.8 Hz, 2×Ar**H**), 7.21 (t, 1H, *J* =

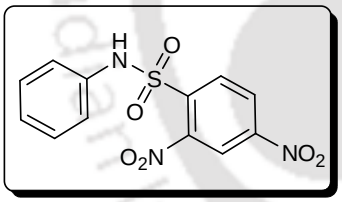
7.2 Hz, 1×Ar**H**), 7.22–7.18 (m, 1H, 1×Ar**H**), 7.08 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 6.57 (br s, 1N**H**); LRMS (ESI) m/z Calcd. for $C_{12}H_{11}N_2O_4S$ $[M+H]^+$: 279.04, found: 279.04.

25) *N*-(4-Hydroxyphenyl)-4-nitrobenzenesulfonamide (Table 5a.2, Entry 23):



R_f product 0.21 (EtOAc/Hexane, 3:2). Yield 88 mg, 30 % White solid. mp. 172 °C. IR (KBr, ν/cm^{-1}) 3320 , 1324, 1159, 920, 1H NMR (400 MHz, $CDCl_3$) 8.34-8.32 (d, *J* = 8.8 Hz, 2×Ar**H**), 7.99- 7.97 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 6.72-6.69 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 6.52-6.50(d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 3.73(br s, 1H, O**H**); LRMS (ESI) m/z Calcd. for $[M+H]^+$: $C_{12}H_{11}N_2O_5S$ 295.03, found: 295.03.

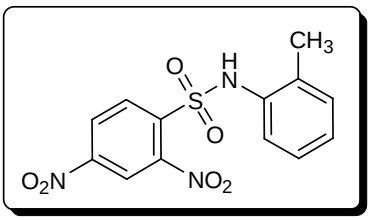
26) 2,4-Dinitro-*N*-phenylbenzenesulfonamide (Table 5a.2, Entry 24):



R_f product 0.26 (EtOAc/Hexane, 1:4), Yield 181 mg, 56%, pale yellow solid, mp 112-115 °C. IR (KBr, ν/cm^{-1}) 3344, 1743, 1541, 1403, 1369, 1347, 1225, 1163, 1127, 837, 785.^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.72 (s, 1H, 1×Ar**H**), 9.18(s, 1H, 1×Ar**H**), 8.17-8.15(d, 1H, *J* = 9.6 Hz, 1×Ar**H**), 7.50-7.47(m, 2H, 2×Ar**H**), 7.42-7.38 (m, 1H, 1×Ar**H**), 7.31-7.25(m, 2H, 2×Ar**H)** LRMS (ESI) m/z Calcd. for $C_{12}H_{10}N_3O_6S$ $[M+H]^+$: 324.02, found: 324.02.

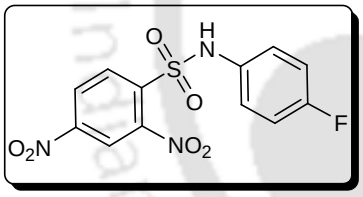
27) 2,4-Dinitro-*N*-*o*-tolylbenzenesulfonamide (Table 5a.2, Entry 25):

R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 229 mg, 68%, white solid, mp 151 °C. IR (KBr, ν/cm^{-1}) 3262, 2943, 1729,



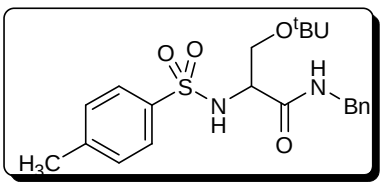
1532, 1350, 1336, 1236, 1159, 830, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.82 (s, 1H, 1×Ar**H**), 9.17(d, 1H, *J* = 2.8 Hz, 1×Ar**H**), 8.75-8.74 (d, 1H, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1Ar×**H**), 8.41-8.38 (dd, 1H, J_1 = 2.8 Hz, J_2 = 2.8 Hz, 1×Ar**H**), 8.15-8.12 (dd, 1H, *J* = 2.8. Hz, 1×Ar**H**), 7.82-7.78 (m, 1H, 1×Ar**H)**, 7.40-7.24 (m, 2H, 2×Ar**H**), 2.26 (s, 3H, C**H$_3$**); HRMS (ESI) m/z Calcd. for $C_{13}H_{12}N_3O_6S$ $[M+H]^+$: 338.0447, found: 338.0448.

28) *N*-(4-Fluoro-phenyl)-2,4-dinitro-benzenesulfonamide (Table 5a.2, Entry 26):



R_f product 0.21 (EtOAc/Hexane, 1:6), Yield 270 mg, 79%, white solid, mp 129 °C. IR (KBr, ν/cm^{-1}) 3286, 1552, 1350, 1165. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.04 (s, 1H, NH), 8.87 (s, 1H, 1×Ar**H**), 8.60-8.58 (d, 1H, *J* = 8.6 Hz, 1×Ar**H**), 8.19-8.16 (dd, 1H, J_1 = 1.9 Hz, J_2 = 2.4 Hz, 1×ArH), 7.14-7.15 (m, 4H, 4×Ar**H**); LRMS (ESI) m/z Calcd. for $C_{12}H_9FN_3O_6S$ $[M+H]^+$: 342.01, found: 342.01.

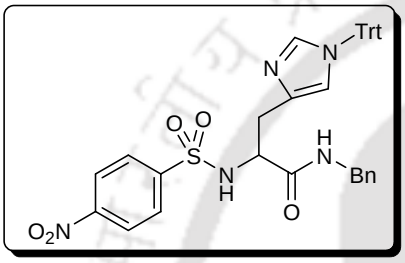
29) *N*-Benzyl-3-*tert*-butoxy-2-(toluene-4-sulfonylamino)-propionamide (compound 5a.27):



R_f product 0.09 (EtOAc), Yield 259 mg, 61%, red color semi solid,. IR (KBr, ν/cm^{-1}) 3276, 1552, 1364, 1165. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.91-7.89 (d, 2H, *J* = 8.4 Hz, 2×Ar**H**), 7.72 7.66 (m, 2H, 2×Ar**H**), 7.40-7.35 (m, 3H, 3×Ar**H**), 7.30-7.27 (m, 2H, 2×Ar**H**), 5.71 (s, 2H, CH_2),

4.41-4.36(m, 2H, CH_2), 3.78 (m, 1H, α-CH), 2.46 (s, 3H, CH_3), 1.36 (s, 9H, $C(CH_3)_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.2, 144.6, 142.1, 136.7, 109.9, 109.2, 100.6, 76.1, 68.1, 61.6, 54.2, 46.7, 34.6, 19.9; HRMS (ESI) m/z Calcd. for $C_{21}H_{29}N_2O_4S$ $[M+H]^+$: 406.1926, found: 406.1926.

30) *N*-Benzyl-3-(4-nitro-benzenesulfonyl)-2-(1-trityl-1H-imidazol-4-ylmethyl)-propionamide: (compound 5a.28):



R_f product 0.12 (EtOAc), Yield 369 mg, 55%, yellow color semi solid,. IR (KBr, ν/cm^{-1}) 3344, 1749, 1552, 1210, 1165. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.21-8.19 (d, 2H, 9.2 Hz, 2×Ar**H**), 8.08-8.06 (d, 2H, *J* = 8.8 Hz, 2×Ar**H**), 7.84-7.81 (t, 1H, -C**H**=N-), 7.63-7.61(d, 1H, NH), 7.32-7.06 (m, 20H, Ar**H**), 6.64(s, 1H, -C**H**=C); 4.32(s, 2H, CH_2), 3.86(m, 1H, α-CH), 3.06-2.95(m, 2H, CH_2): ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 175.0, 161.1, 154.5, 146.6, 142.1, 139.2, 138.1, 136.7, 130.4, 129.2, 128.8, 128.0, 127.6, 127.2, 126.5, 120.6, 73.9, 54.2, 49.9, 30.6.; HRMS (ESI) m/z Calcd. for $C_{39}H_{35}N_4O_5S$ $[M+H]^+$: 672.2281, found: 672.2281.

5a.6 References:

1) Khattab, S. N. Sulfonate esters of 1-hydroxypyridin-2(1*H*)-one and ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma) as effective peptide coupling reagents to replace 1-

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5) a) Karmakar, P.; Talan, R. S.; Sucheck, S. J. Mixed-phase synthesis of glycopeptides using a *N*-peptidyl-2,4-dinitrobenzenesulfonamide–thioacid ligation strategy. *Org. Lett.* **2011,** *13*¸ 5298-5301; b) Crich, D.; Sharma, I. Triblock peptide and peptide thioester synthesis with

reactivity-differentiated sulfonamides and peptidyl thioacids. *Angew Chem. Int. Ed.* **2009**, *48*, 7591-7594.

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7) a) Malwal, S. R.; Sriram, D.; Yogeeswari, P.; Konkimalla, V. B.; Chakrapani, H. Design, synthesis, and evaluation of thiol-activated sources of sulfur dioxide (SO_2) as antimycobacterial agents. *J. Med. Chem.* **2012**, *55*, 553-557; b) Malwal, S. R.; Sriram, D.; Yogeeswari, P.; Chakrapani, H. Synthesis and antimycobacterial activity of prodrugs of sulfur dioxide (SO_2). *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3603-3606.

5a.7 Selected spectra for representative compounds:

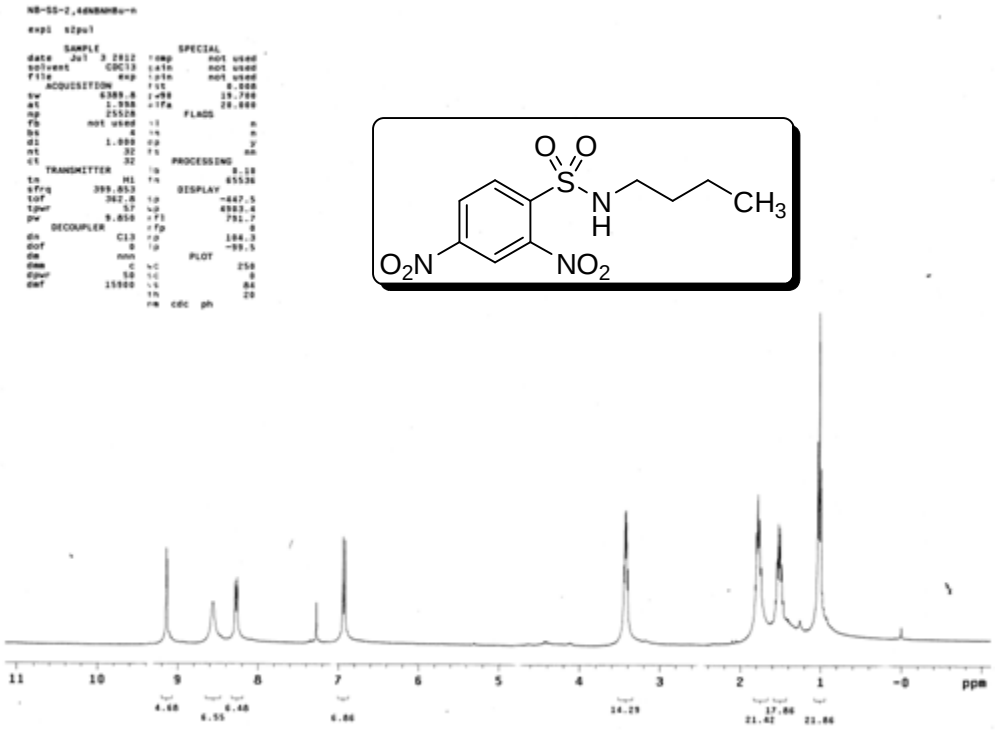


Figure 5aS.1 (Table **5a.2**, entry **2**)

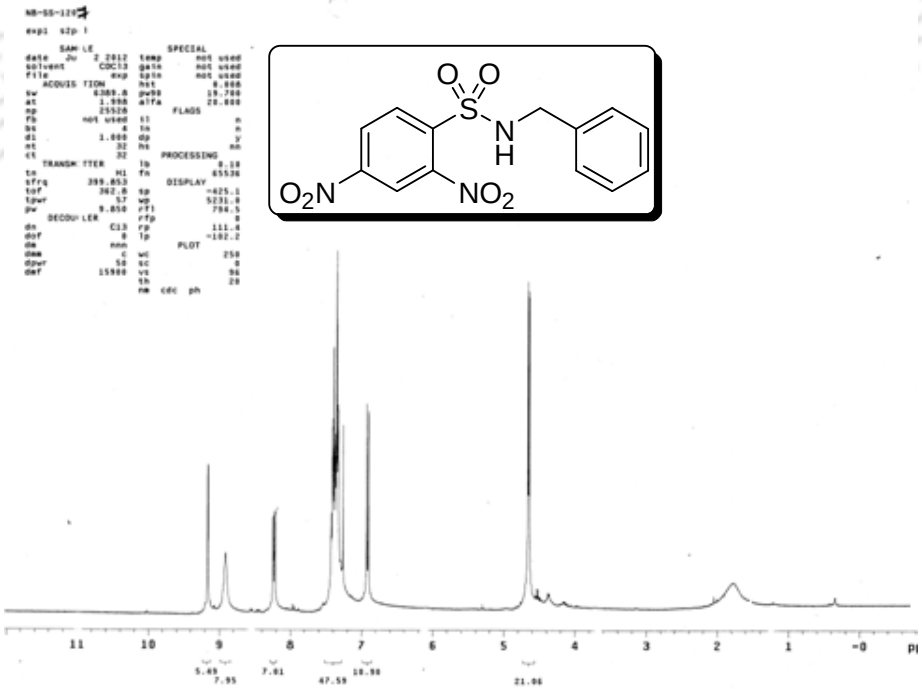


Figure 5aS.2 (Table **5a.2,** entry **5)**

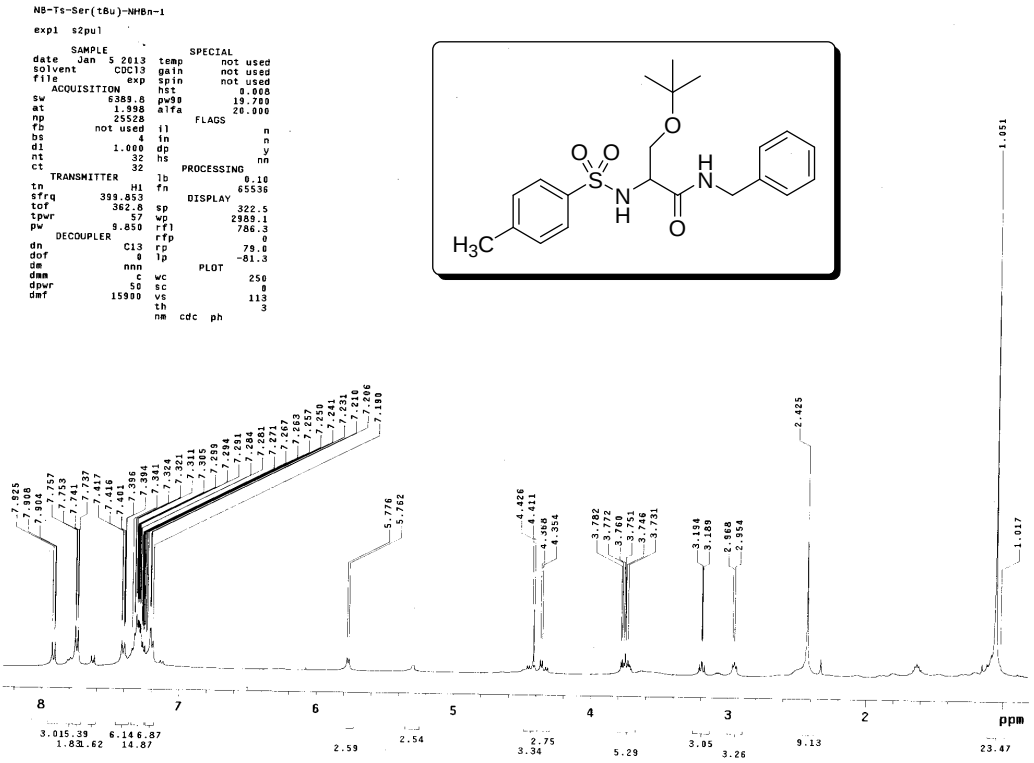


Figure 5aS.3 (5.27)

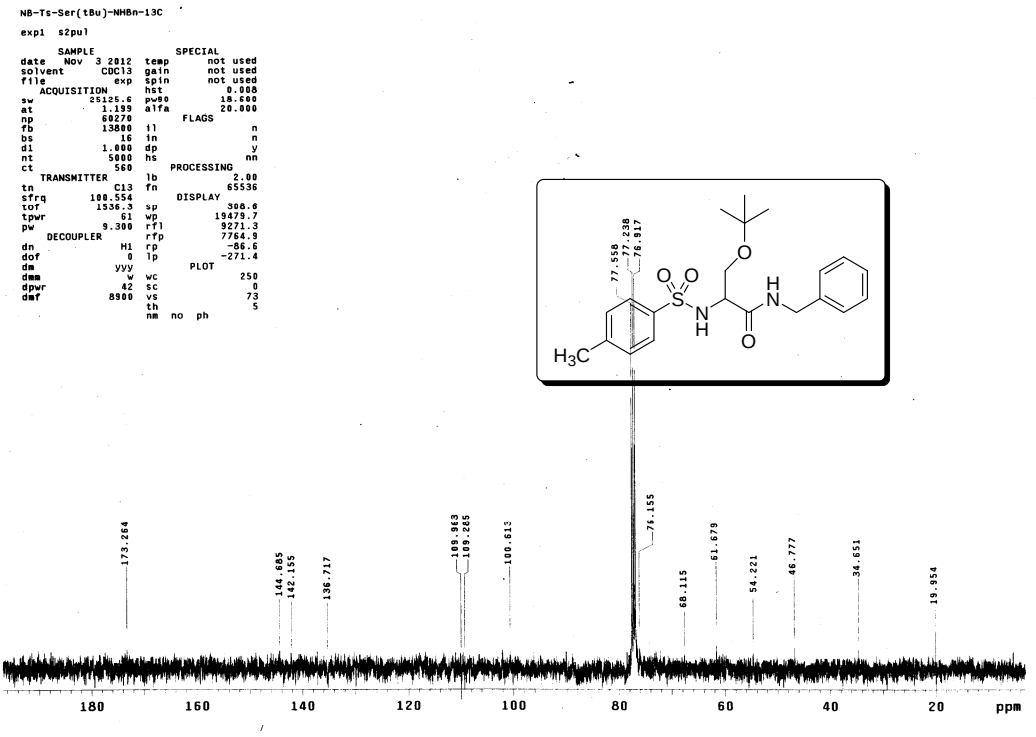


Figure 5aS.4 (5a.27)

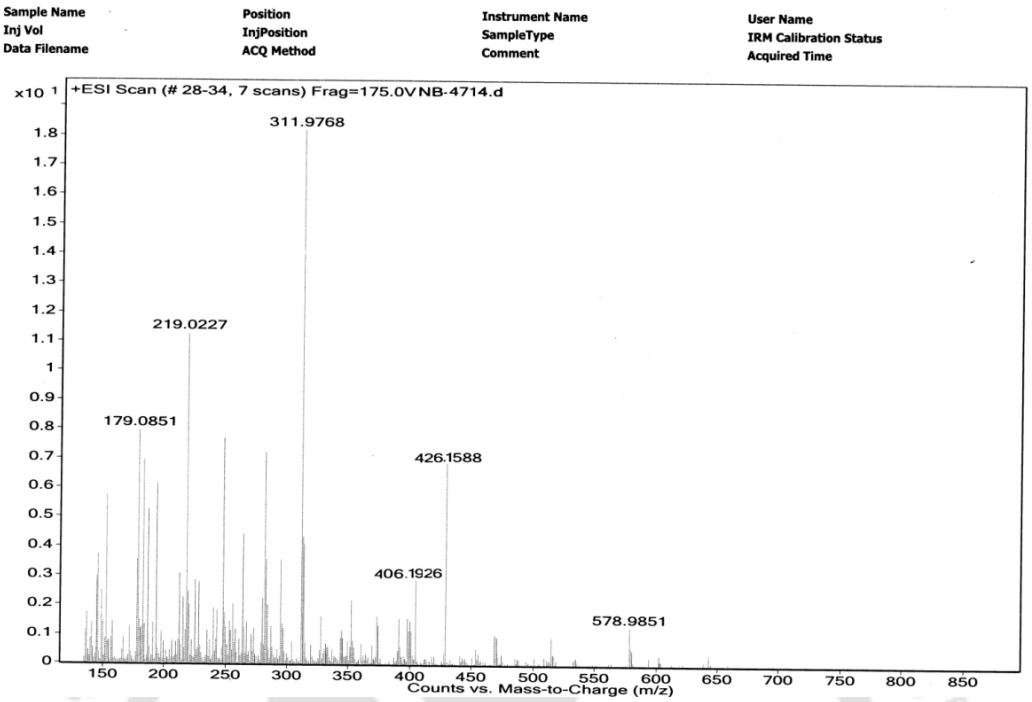


Figure 5aS.5 Calculated mass for formula $C_{21}H_{28}N_2O_4S$ is 406.1926 and found 405.1926 $[M+H]^+$ (**5a.27)**

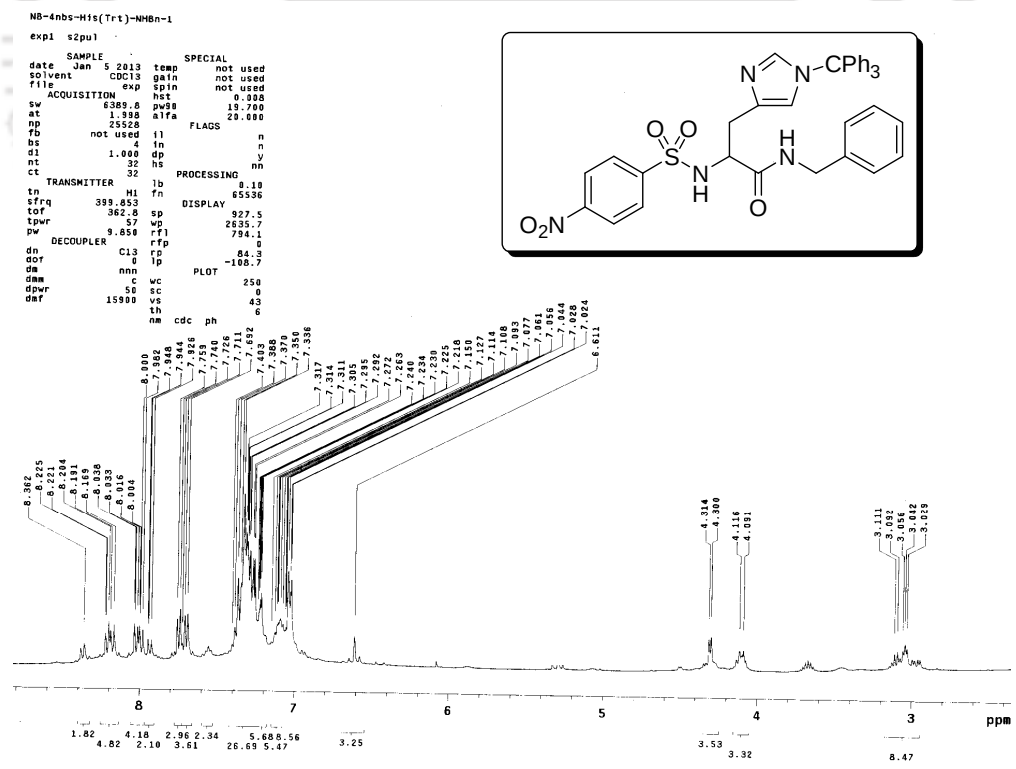


Figure 5aS.6 (5a.28)

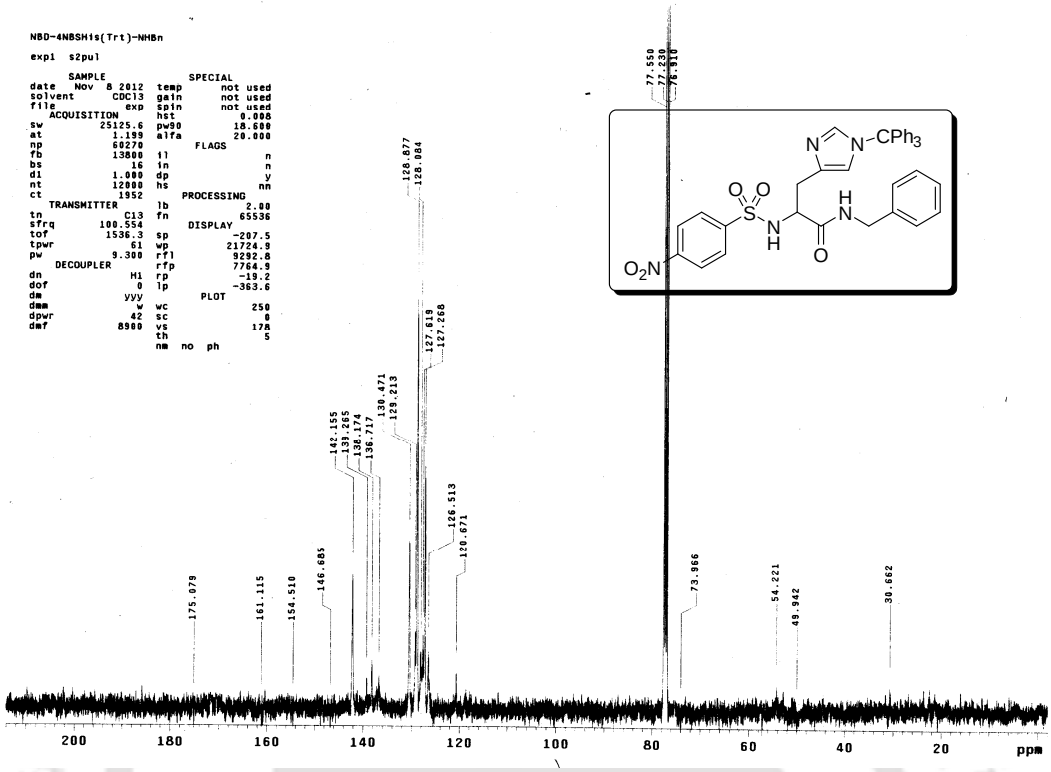


Figure 5aS.7 (5a.28)

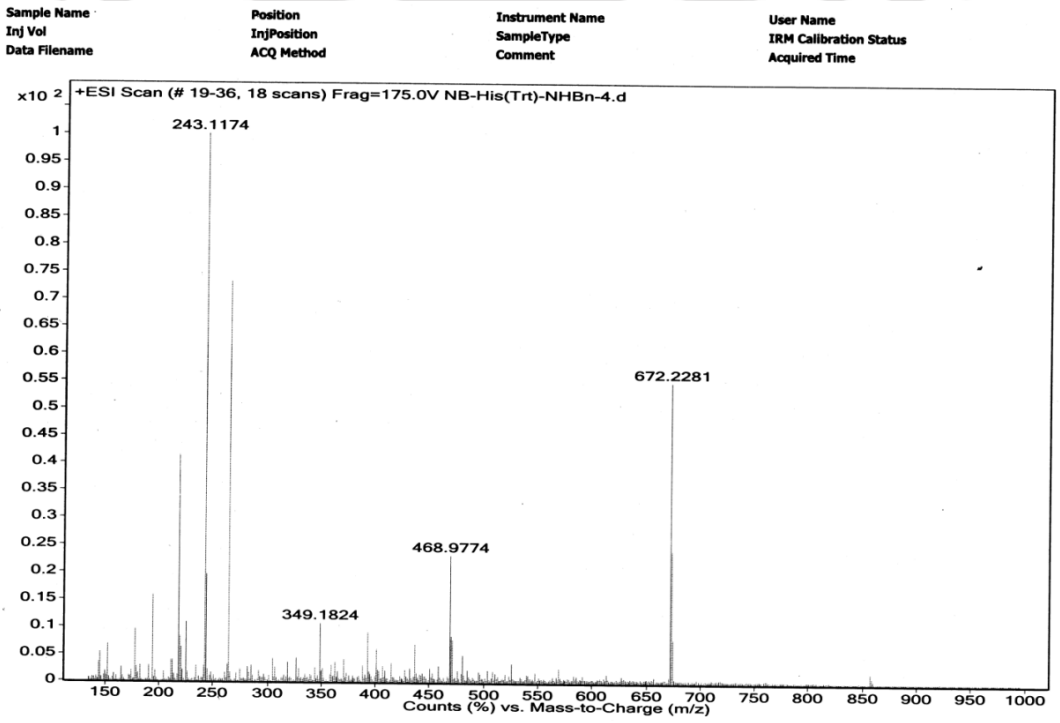


Figure 5aS.8 Calculated mass for $C_{38}H_{34}N_5O_5S$ is 672.2281 and found 672.2281 $[M+H]^+$ **(5a.28)**

Crystallographic data compound 1

(E)-Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate

Crystal data: CCDC(# 877997)

	(E)-Ethyl 2-cyano-2-(4-nitrophenylsulfonyloxy-imino)acetate (Table **4a.1**, entry **3**)
Formula	C_{11} H_9 N_3 O_7 S
Mol. wt.	327.28
Crystal system	monoclinic
Space group	P 21/n
Temperature /K	296(2) K
Wavelength /Å	0.71073
a /Å	8.3883(6)
b /Å	6.8216(6)
c /Å	25.4392(19)
α/°	90.00
β/°	98.735(4)

γ/°	90.00
V/ $Å^3$	1438.8(2)
Z	4
Density/Mgm^{-3}	1.511
F(000)	672.0
Total no. of reflections	2521
Reflections, I > 2σ(I)	831
Max. 2θ/°	25.250
Ranges (h, k, l)	10≥ 8≤30
Complete to 2θ (%)	97.1
Refinement method	Full-matrix least-squares on F^2
WR_2 (all data)	0.1614
Gof (F^2)	0.813
R indices [I > 2σ(I)]	0.0460
R indices (all data)	0.0776

Table 5aS.1

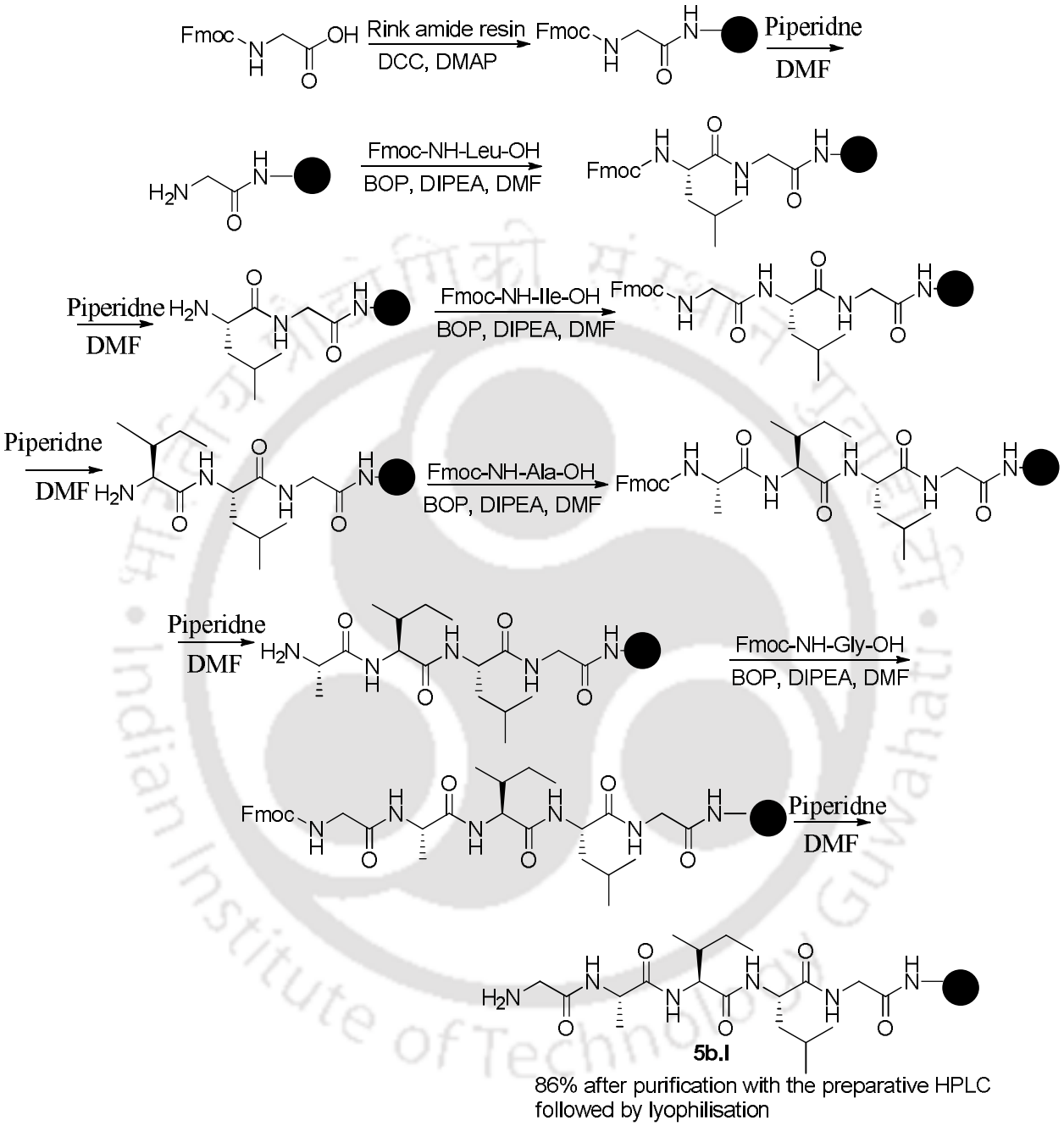
Chapter 5b. Synthesis of the Designed Peptide Conjugates for Inhibition of Amylin Aggregation

5b.1 Introduction:

As it was described in the *chapter 1*, section **1.6**, we wanted to finally synthesize the conjugates of various sulfonic acids i.e. Congo red, taurine, p-TsOH, 2-NO_2-C_6H_4-SO_3H, 2,4-C_6H_3-SO_3H, *etc.* and selected sequence of the IAPP or Amylin peptide. IAPP or Amylin peptide is responsible for causing *Diabetes type II*, an age related disease. And the selected sequence is called the core sequence of Amylin, which is responsible for self aggregation of the peptide. Proposed peptide-small molecule conjugates are expected to inhibit the aggregation of amylin, thereby help as lead molecule for drug design against diabetes type II. In this connection, having developed few activation methods such as *N*-hydroxy benzotriazole activation and Oxyma activation we wanted to further explore the applicability of these methods for the synthesis of mentioned peptide derivatives under ambient and milder conditions.

5b.2 Results and discussion:

We chose the Oxyma activation method to apply for the synthesis of the above mentioned targets. We have coupled the desired amino acid residues on Rink amide MBHA resin following Fmoc/*t*But protection technique and made **GAILG** peptide over solid phase (Scheme **5b.1**). The first coupling was carried out using DCC/DMAP to couple the glycine residue with the Rink amide resin.



Scheme 5b.1

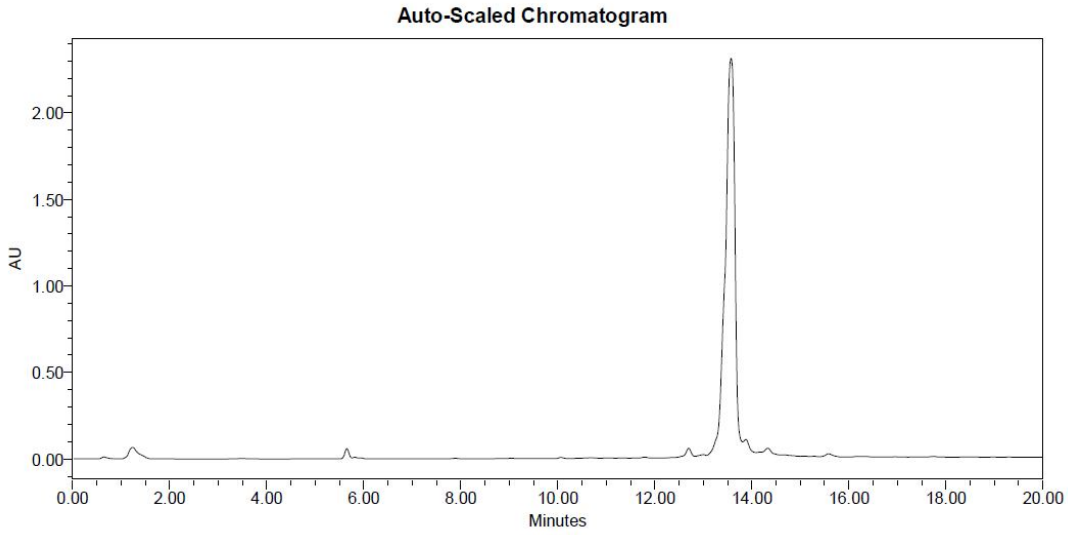


Figure 5b.1 HPLC chromatogram for the peptide Fmoc-GAILG-NH_2

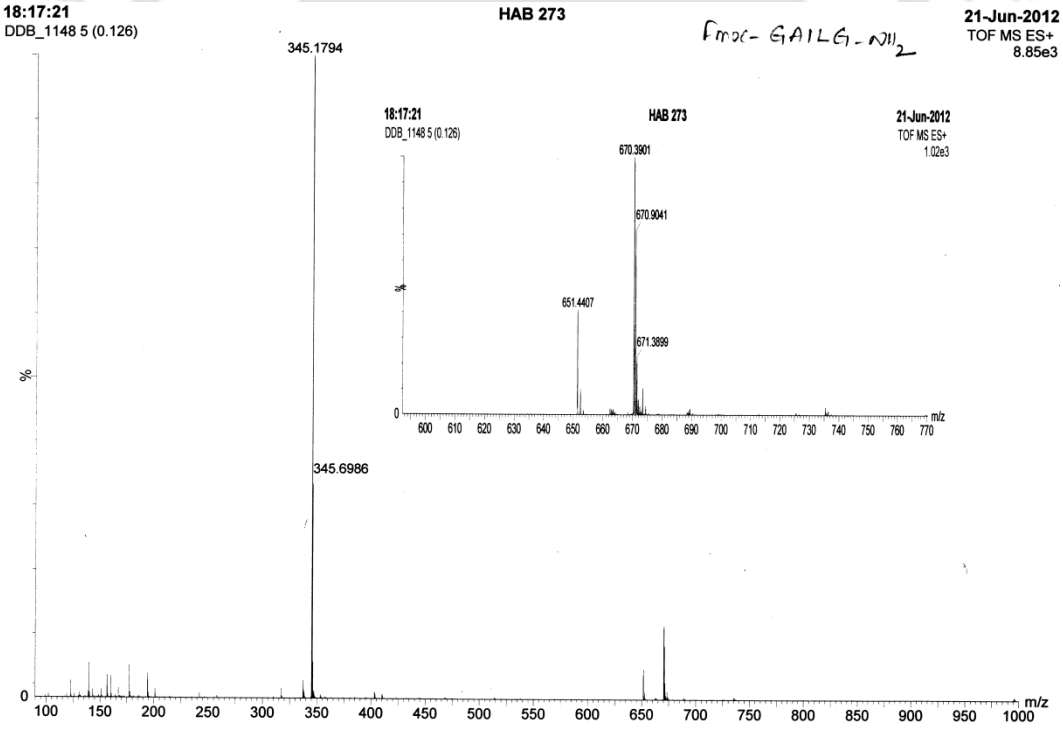


Figure 5b.2 Mass spectrum for the peptide Fmoc-GAILG-NH_2

The rest of the coupling was carried out with BOP in DMF solvent. In each case the Fmoc was deprotected using piperidne. After completion of the peptide synthesis the test cleavage was done and it was characterized using LC-MS. Having the proof of the formation of Fmoc-**GAILG** (**5b.1**), we proceeded further to cleave a small part of the peptide from the resin using trifluoroacetic acid. Then it was precipitated using cold ether. The peptide obtained in this way was characterized using HPLC and ESI-MS. HPLC chromatogram was shown in figure **5b.1** and the ESI-MS was shown in **5b.2**.

Later**,** the Fmoc group was cleaved using piperidine /DMF, an aliquot was cleaved from the resin and injected in HPLC for checking its purity. The HPLC profile of GAILG-NH_2 was shown in figure **5b.3.**

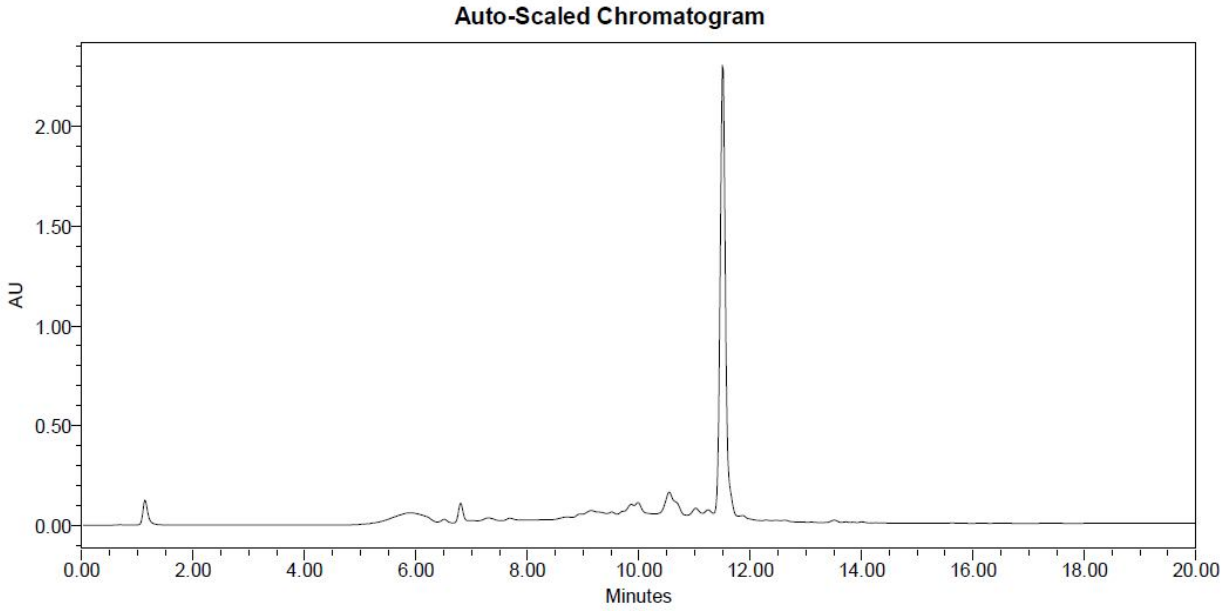
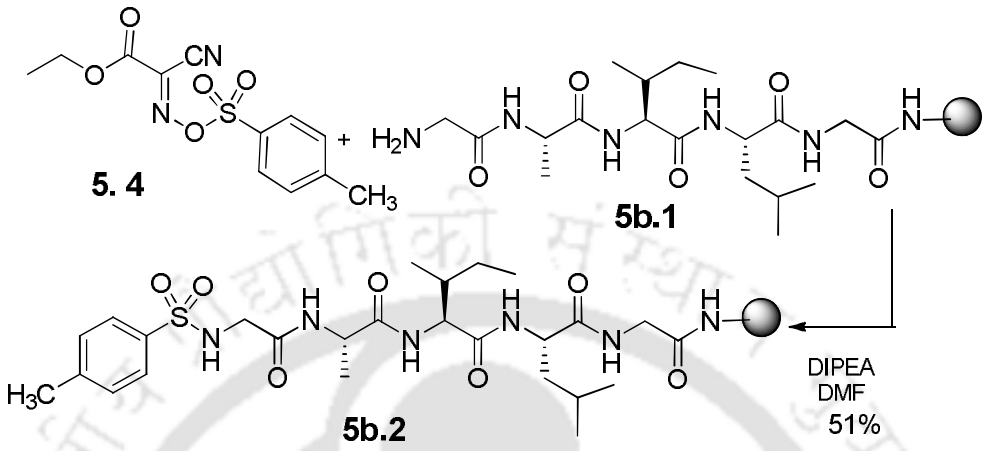


Figure 5b.3 HPLC chromatogram for the peptide NH_2-GAILG-NH_2

The *O*-sulfonate esters of Oxyma with various substitution on benzene ring such as 4-methyl, 4-nitro, 2,4,-dinitro were prepared as it was mentioned in the *chapter 5,* scheme **5a.1.** First, we employed it in the reaction between **5.4** and **5b.1** at room temperature using DIPEA as

base and DMF as solvent (Scheme **5b.2**). Interestingly the coupling took place within 14 h and yielded the desired product in good yield.[1]



Scheme 5b.2

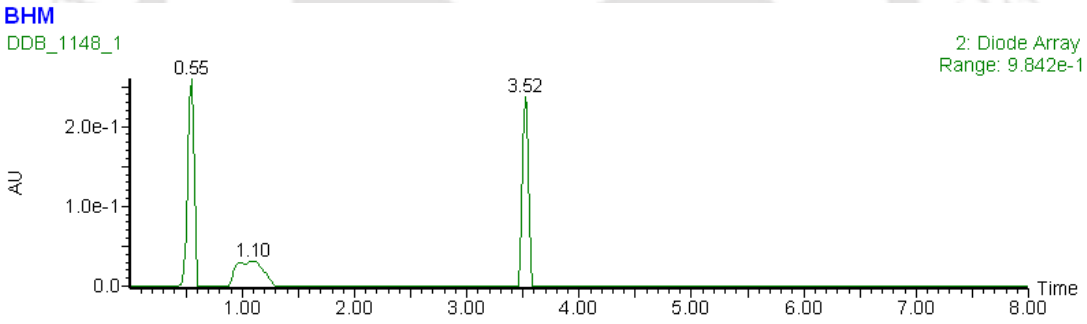


Figure 5b.4 UPLC chromatogram for **Ts-GAILG-NH$_2$ (5b.2)**

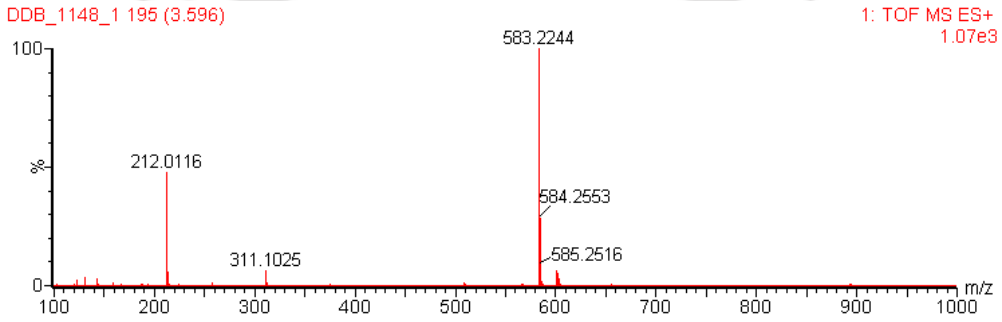
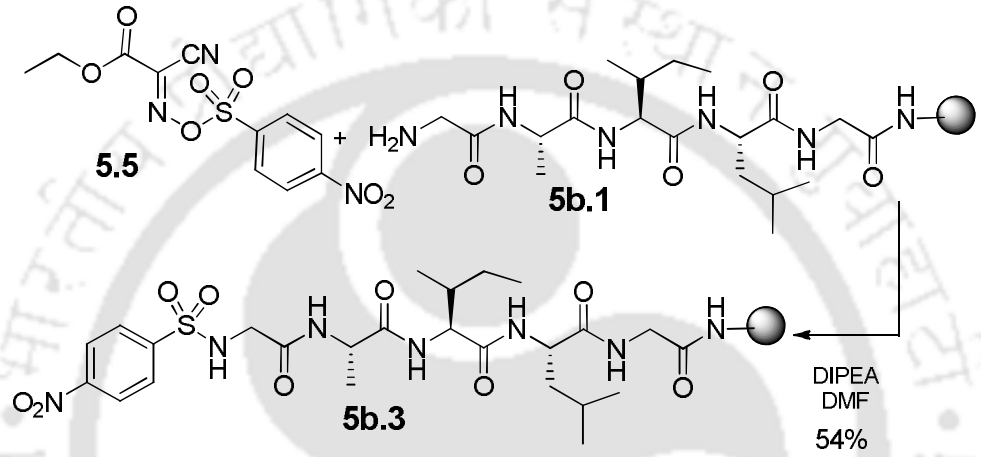


Figure 5b.5 ESI-MS spectrum of **Ts-GAILG-NH$_2$ (5b.2),** Calculated mass for $C_{26}H_{43}N_6O_7S$ is 583.29 and found 583.22 as $[M+H]^+$

After completion of the coupling, the whole peptide was cleaved from the resin and precipitated using cold ether. The characterization of this peptide was carried out with LC-MS followed by purification with semi preparative HPLC. The HPLC chromatogram of the purified peptide-p-TsOH conjugate was shown in figure **5b.4** and the LC-MS was shown figure **5b.5**.



Scheme 5b.3

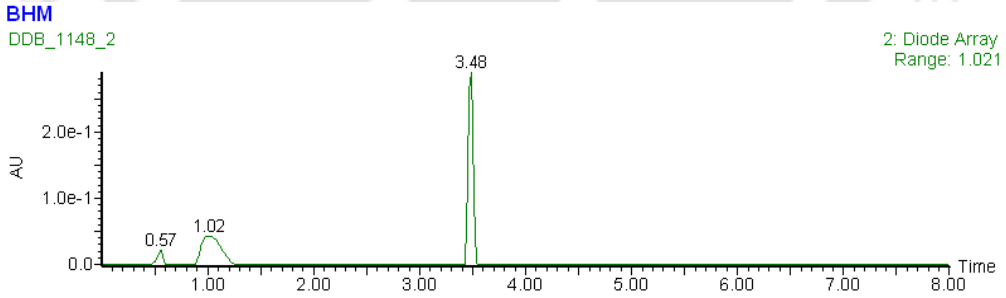


Figure 5b.6. UPLC chromatogram of 4-NO_2 benzene sulfonamide of GAILG-NH_2 (**5b.3**)

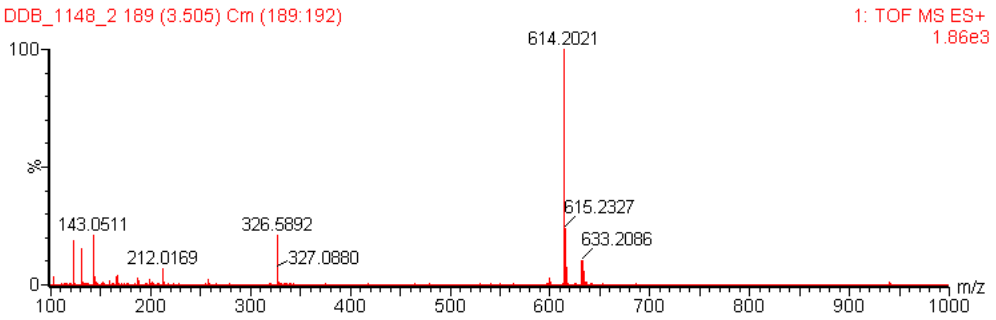
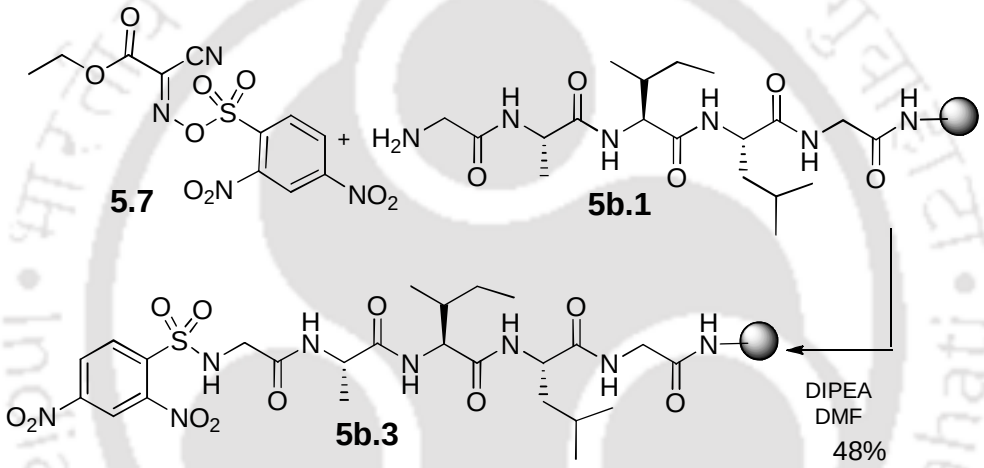


Figure 5b.7 ESI-Mass spectrum for the purified peptide 4-NO_2-$C_6H_6SO_2$-GAILG-NH_2. (**5b.3**)

Calculated mass for $C_{25}H_{39}NaN_7O_9S$ is 14.29 and found 614.20 as $[M+H]^+$



Scheme 5b.4

Then, the peptide conjugate **5b.3** was synthesized employing the same conditions as shown in the scheme **5b.3** and the characterization details are shown in the figure **5b.6** and figure **5b.7**

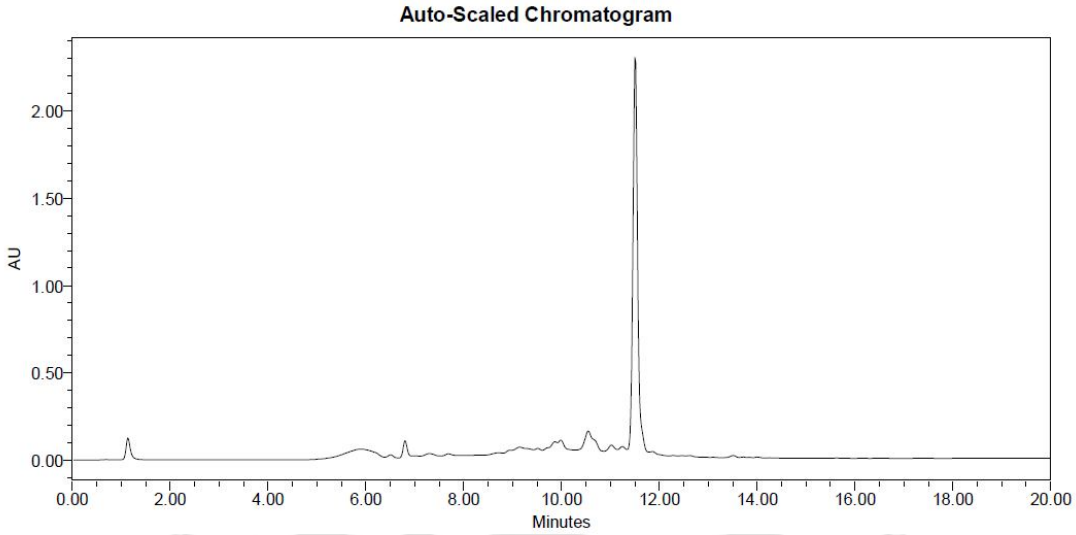


Figure 5b.8 HPLC chromatogram of purified 2,4-dinitrobenzenesulfonamide of GAILG-NH_2 (**5b.3**)

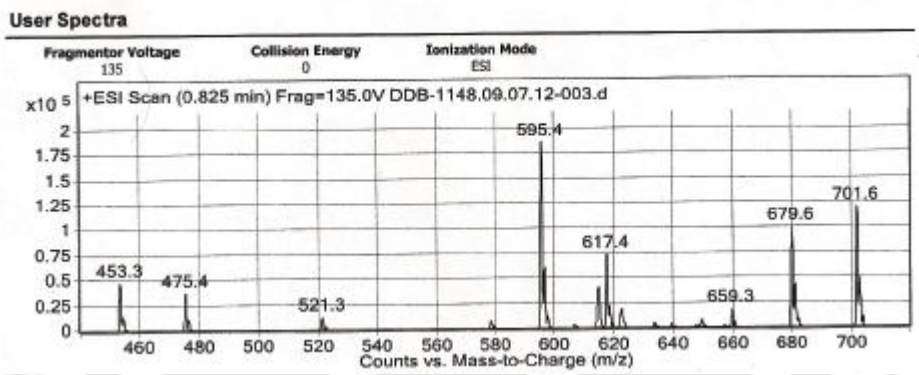


Figure 5b.9 ESI-MS spectrum of the purified peptide 2,4-dinitro-$C_6H_6SO_2$-GAILG-NH_2. Calculated mass for $C_{25}H_{39}N_8O_{11}S$ is 659.24 and found 659.30 as $[M+H]^+$ (**5b.3**).

Similarly, **5.7** and **5b.1** were coupled with the same conditions and the reaction was found to be completed after allowing it to be rotated for overnight (Scheme **5b.4**). The isolated yield was found to be good in spite of the fact that **5.7** is very reactive and hence less stable under these conditions. Compound **5b.3** was characterized with semi preparative HPLC followed by MS as shown in figure **5b.8** and figure **5b.9** respectively.

5b.3 Conclusion:

In conclusion, we have adopted the Oxyma activation method, discussed in the first part of this chapter, for the synthesis of the peptide-small molecule conjugates (mentioned in *chapter 1*), which was main target of the works described in this thesis. Finally we have been successful in synthesizing three of them at present.[2] The present synthetic methodology was compatible with the acid labile resins and acid labile functional groups, such as trityl (Trt) and tertiary butoxy (tBu) which also strengthens NCL as it was mentioned in the *chapter 1,* scheme **1.2** and **1.3**. The rest of the peptide conjugates will be synthesized in due course of time followed by evaluation of their activity against prevention of the aggregation of the IAPP in our group.

5b.4 General procedure for the synthesis of sulphonamide derivatives of peptide from the sulphonate esters of Oxyma on solid phase:

To the resin connected peptide that was synthesized using solid phase peptide synthesis strategy following Fmoc/^{t}But protection technique on Rink amide MBHA resin, 2/3 equivalents of the corresponding sulfonate esters were added along with DIPEA (2.5 equiv.) in 1 mL of DMF into a sintered syringe and subjected to gentle rotation using a blood tube rotator. The reaction was monitored using Kaiser's Test. After completion, the reaction mixture was thoroughly washed with DMF for 5 times. Finally attachment of the sulfonic acid derivatives was performed using suitable reagents as mentioned above. Then the peptide was cleaved from the resin using TFA/DCM cleavage cocktail followed by precipitation using cold ether. Then it was purified using semi preparative HPLC followed by lyophilization. The yields reported were for peptides purified as mentioned above.

References:

1) Partha, K.; Rommel, S. T.; Steven, J. S. Mixed-Phase Synthesis of Glycopeptides Using a *N*-Peptidyl-2,4-dinitrobenzenesulfonamide–Thioacid Ligation Strategy *Org. Lett.* **2011**, *13*, 5298–5301.

2) Palakurthy, N. B; Dev, D.; Rana, S.; Nadimpally, K. C.; Mandal B.* Sulphonamide synthesis via Oxyma-O-sulphonates: Compatibility to acid sensitive groups and SPPS, *Eur. J. Org. Chem*. **2013**, *13*, 2627-2633.

6. Conclusions and Outlook

The whole structure of the thesis can be depicted as shown in the figure **1**. In total we have attempted to activate all the possible aryl sulfonic acids (within our laboratory) as it was described the *chapter 2* which will solve the problem of non availability of the commercial sulfonyl chlorides. Furthermore, these activation strategies are helpful to achieve chemoselectivity, which would offer many advantages in the total synthesis of natural products.

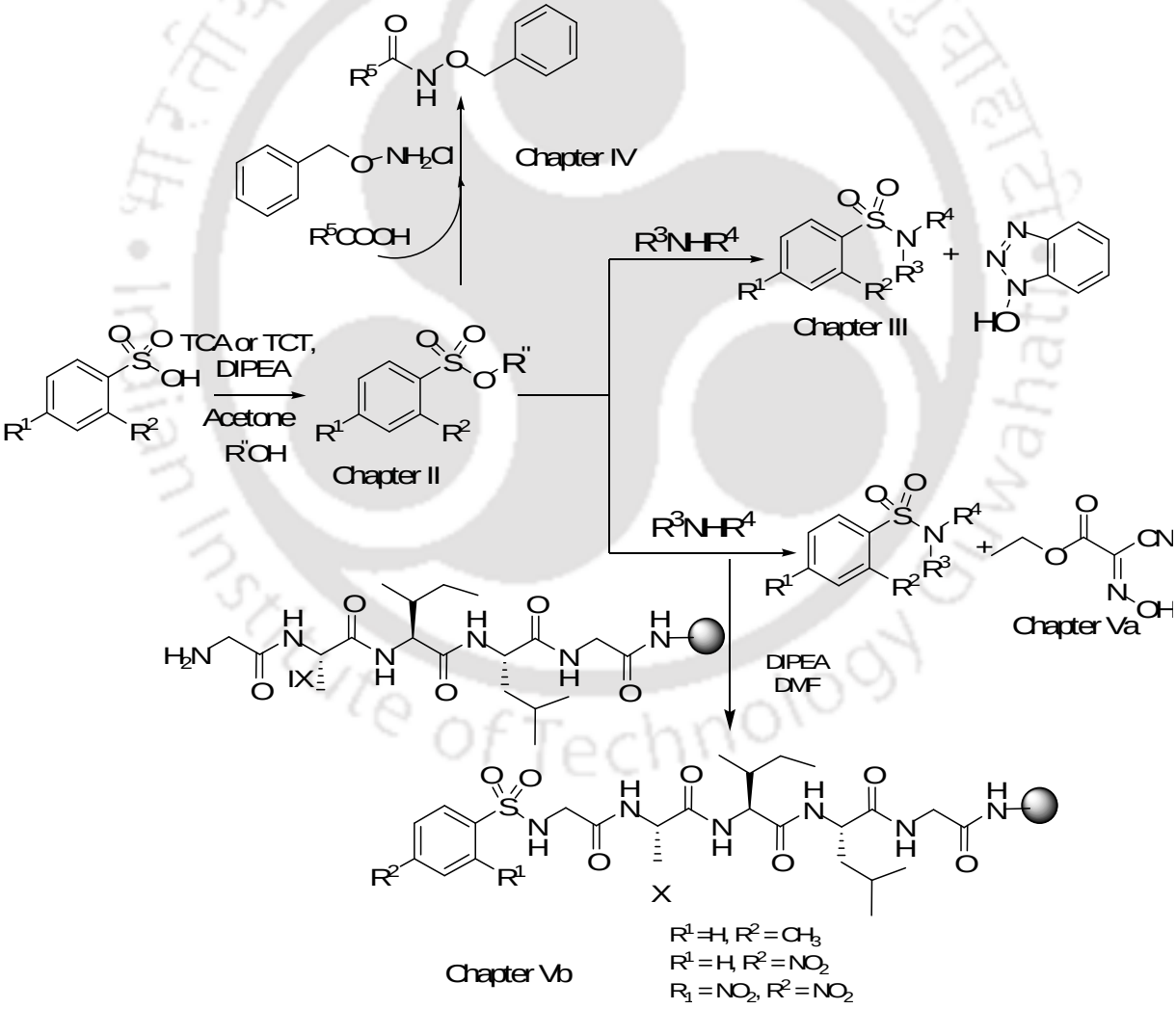


Figure 1

Having achieved the direct synthesis of activated sulfonate esters, we took one of the activated forms i.e. sulfonate esters of *N*-hydroxy benzotriazole and we used it for sulfonamide synthesis, which is the subject matter of *chapter 3*. Although the use of chlorinating asgents cannot be precluded at the previous step, it gives an access for the HCl free sulfonamide synthesis. In continuation to our interest in the activated sulfonate esters as useful synthetic auxiliaries, we further demonstrated the synthesis of the *O*-benzyl hydroxamates of various acids using TsOBt in *chapter 4*. This protocol, as it was shown, does not cause more than 5% racemization in case of chiral amino acids. Additionally, we have investigated the mechanism in detail. Furthermore, we developed the solid supported TsOBt using resin connected HOBt, which was successfully recycled and recovered for three cycles without losing its activity to carry out the condensation chemistry.

In *chapter 5a*, we took up another activated form of the sulfonate esters from *chapter 2* and used it for sulfonamide synthesis. Since HOBt is a potentially explosive material on heating, Oxyma was found to be very good and handy replacement not only in terms laboratory practice, but also in terms of reactivity. This could be applied to those substrates that posses acid labile functional groups such as trityl and tertiary butoxy apart from the applicability for the synthesis of sulfonamides of less nucleophilic anilines and 2,4 dinitro benzene sulfonamides which are an important class of organic synthons for quite a good number of functional group transformations.

In *chapter 5b*, the previously developed activation strategy i.e. Oxyma activation was used to accomplish the synthesis of specified peptide-small molecule conjugates that are expected to

have potential therapeutic activity in preventing the aggregation of the islet polypeptide (IAPP), thereby can be a remedy for *Diabetes type* II. This was the primary target of our work.

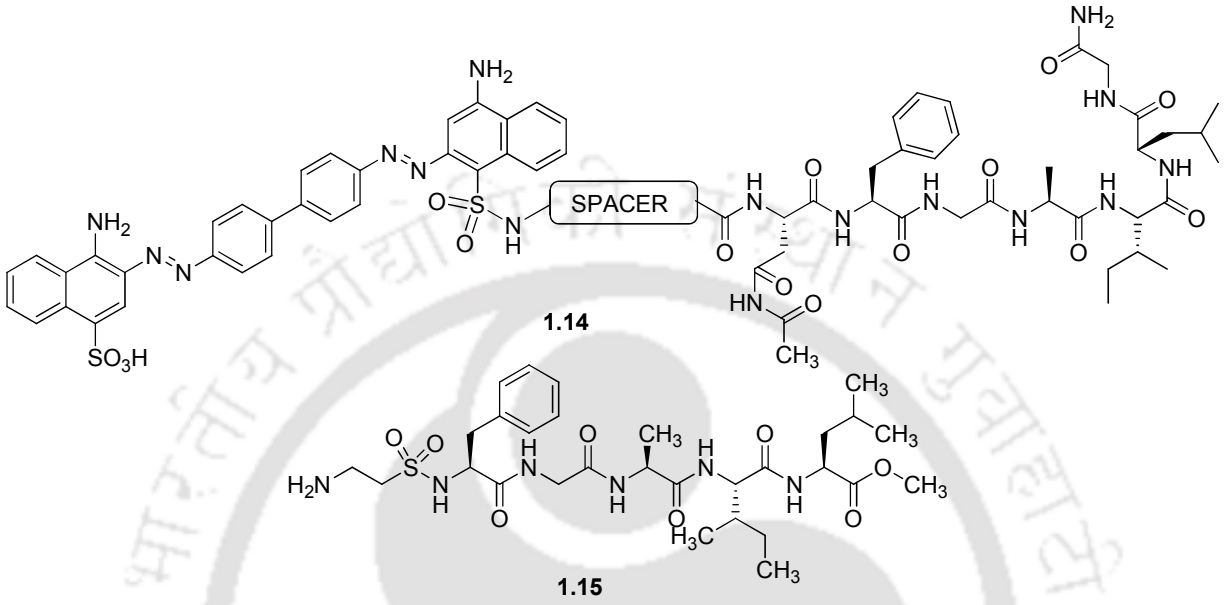


Figure 2

However, it deserves mention that some of the designed peptides could not be synthesized. Those are shown in figure **2**. One of my successors from this laboratory will synthesize them using the developed methodologies and test their activity against inhibition of aggregation of Amylin shortly.

7. Research Outcome

7a. List of publications

1) Palakurthy, N. B.; Mandal, B.* Sulfonamide synthesis using *N*-hydroxybenzotriazole sulfonate: an alternative to pentafluorophenyl (PFP) and trichlorophenyl (TCP) esters of sulfonic acids. *Tetrahedron Lett.* **2011**, *52*, 7132-7134.

2) Nadimapally, K. C.; Talluri, K.; Palakurthy, N. B.; Saha, A.; Mandal, B.* Catalyst and solvent-free amidation of inactive esters of *N*-protected amino acids. *Tetrahedron Lett.* **2011**, *51*, 2579-2582.

3) Palakurthy, N. B; Dev, D.; Rana, S.; Nadimpally, K. C.; Mandal B.* Sulphonamide synthesis via Oxyma-O-Sulphonates: Compatibility to acid sensitive groups and SPPS *Eur. J. Org. Chem.* **2013**, *13*, 2627-2633.

4) Dev, D.; Palakurthy, N. B; Kumar, N.; Mandal, B.* *O*-Sulfonate esters promoted synthesis of Nitriles from Aldoximes. *Tetrahedron Lett*. **2013**, *54*, 4397-4400

5) Palakurthy, N. B; Dev, D.; Paul, A.; Paikaray, S.; Chaudhury, S.; Mandal, B.* Synthesis of *O*-Benzyl Hydroxamates Employing the Sulfonate Esters of *N*-Hydroxybenzotriazole. *RSC Advances* **2013**, *xx***,** xxxx-xxxx. **DOI:** 10.1039/C3RA44294B (just accepted).

6) **Palakurthy, N. B.**; Dev, D.; Rana, S.; Nadimpally, K. C.; Mandal, B.* Sulfonamide Synthesis via Oxyma-O-sulfonates—Compatibility to Acid Sensitive Groups and Solid-Phase Peptide Synthesis. CHEMINFORM, **2013**, *44*, XXXX-XXXX. DOI:10.1002/chin.201340075.

7) Dev, D.; **Palakurthy, N. B**.; Kumar, N.; Mandal, B. * An unexpected involvement of Ethyl-2-cyano-2-(hydroxyimino) acetate cleaved product in the promotion of the synthesis of nitriles from aldoximes: A mechanistic perception. CHEMINFORM, **2013**, *47*, XXXX-XXXX. DOI: 10.1002/chin.201347061.

8) Palakurthy, N. B; Kumar, N.; Mandal, B.* Direct synthesis of activated sulfonate esters. (Manuscript under preparation).

9) Palakurthy, N. B; Rana, S.; Dev, D.; Mandal, B.* Investigation on the Oxyma as an additive to the 2,4,6-trichlorobenzoyl chloride (Yamaguchi's reagent) (Manuscript under preparation).

10) Dev, D.; Palakurthy, N. B.; Mandal, B. * *O*-sulfonate esters of Oxya promoted Esterification. (Manuscript under preparation).

7b. Conference papers

1. DBU catalyzed Peptide Synthesis from Benzyl Esters of amino acids. Palakurthy, N. B.; Saha, A.; Manna, M.; Mandal, B. *Frontiers in Chemical Sciences (FICS-2010),* Indain Institute of Technology Guwahati, Decemebr 3-4, **2010.**

2. A Facile and Acid Free Sulfonamide Synthesis under Ambeint and Milder Conditions. Palakurthy, N. B.; Dev, D.; Rana, S.; Nadimpally, K. C.; Mandal, B. *Internationl Symposium on Chemistry and Chemical Biology of Natural Products (CCBNP-2012)*, Indian Institute of Chemical Technology, Hyderabad, August 2-4, **2012.**

3. A Facile and Faster Synthesis of Nitriles Using Sulfonate Esters of Oxyma. Dev, D.; Palakurthy, N. B.; Mandal, B. *Internationl Symposium on Chemistry and Chemical Biology of*

Natural Products (CCBNP-2012), Indian Institute of Chemical Technology, Hyderabad, August 2-4, **2012.**

4. Sulfonate esters as useful synthetic reagents. **Palakurthy, N. B**.; Dev, D.; Mandal, B.* ***1st Annual International Conference (AIC-1) & Industry – CCRS Congress (ICC) 2013***, Sanketika Vidya Parishad Engineering College, Visakhapatnam, July 13-14, **2013**.