A FACILE SYNTHESIS OF BIOLOGICALLY ACTIVE PHTHALIMIDES & ITS ANALOGUES-A STUDY

BY

VARALA RAVI

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THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

TO

KAKATIYA UNIVERSITY

BY

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DEDICATED TO MY BELOVED PARENTS

Who have given me life and Everything

That I possess and who have cherished my success

and finally

to my wife

CERTIFICATE

This research work presented in this thesis has been carried out under my supervision and is a bonafide work of Mr.**VARALA RAVI**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Dated: (**Dr.Srinivas R. Adapa**)

DECLARATION

I have carried out the research work presented in this thesis under the supervision of Dr. Srinivas R. Adapa, Scientist, I&P Chemistry Division, Indian Institute of Chemical Technology, Hyderabad. The work presented is original and has not been submitted in part or full for any degree or diploma to this or any other University.

Dated:

(VARALA RAVI)

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I would not miss this opportunity to express my deep gratitude to my parents, my brother Madhu Babu, my sister Radhika and brother-in-law, Dayanand because of whose support, encouragement and sacrifice this piece of work is completed. I also wish to thank my wife Sridevi, son Master

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MARCH 2006

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Hyderabad 500 007, India.

Abbrevations

BOC	N-*tert*-Butoxycarbonyl
DMAP	4-(Dimethylamino) pyridine
O_3	Ozone
$Na/liq.NH_3$	Sodium/liquid ammonia
PPh_3	Triphenylphosphine
DCC	Dicyclohexyl carbodiimide
$N_2H_4.H_2O$	Hydrazine hydrate
DMS	Dimethylsulfide
Et_3N	Triethylamine
$NaBH_4$	Sodium borohydride
p-TsCl	*para*-Toluene sulfonyl chloride
DIPEA	Diisopropyl ethylamine
PCl_5	Phosporus pentachloride
NMR	Nuclear magnetic resonance
IR	Infra red
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
ee	Enantiomeric excess
HPLC	High performance liquid chromatography
$Pd(OAc)_2$	Palladium acetate
RT	Room temperature

General Remarks

1. All the temperatures are in ^{0}C. All the melting points (on an Electrothermal melting point apparatus) and boiling points are in ^{0}C and are uncorrected.
2. ^{1}H NMR and ^{13}C NMR spectra were recorded either on Brucker WH-90, Brucker AC-200 or DRX-500 spectrometer in $CDCl_3$ containing TMS as an internal standard with chemical shift (δ) expressed in ppm downfield from TMS. The following abbreviations are used: s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet and b= broad.
3. All IR spectra (ν_{max} in cm^{-1}) were recorded neat on Perkin Elmer 1620-F instrument. Elemental analyses were performed by Elementar analyzer; Vario EL (Model) (Germany).
4. Electron-impact (EI) mass spectra were recorded in the form of m/z (intensity relative to base 100) on a VG 7070H Micromass Mass spectrometer at 2000 C, 70eV, with a trop current of 200 μA and 4 KV acceleration.
5. All solvents and reagents were purified and dried by standard procedures. All evaporations were carried out under reduced pressure on Buchi rotary evaporator. Reactions were routinely carried out under an atmosphere of nitrogen.
6. All the reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254 on glass) with UV light, Iodine as probing agents. Column chromatography was performed using Acme silica gel (60-120/100-200 mesh).
7. Optical rotations are measured on HORIBASEPA 300 digital polarimeter at λ 589 nm. Optical purity was checked by comparing the observed $[\alpha]_D$ values with the reported literature $[\alpha]_D$ values.
8. Purity of the compounds was checked by HPLC. HPLC Conditions-Column: Hypersil BDS C_{18}, 5μm, 250 mm x 4.6 mm.

9. The compound numbers, scheme numbers and reference numbers given in each chapter refers to that particular section of the chapter only.

CONTENTS

Chapter IV Synthesis & Applications of N-Phthaloyl Aminoacids

SYNOPSIS

The thesis entitled '**A FACILE SYNTHESIS OF BIOLOGICALLY ACTIVE PHTHALIMIDES & ITS ANALOGUES-A STUDY**' is divided into four chapters.

The title of the thesis clearly reflects the objective, which is to synthesize some biologically relevant drugs containing N-phthaloyl moiety and phthalimide derived compounds and evaluation of their biological activity. **Chapter I** describes the general introduction of phthalimides and their biological importance; synthetic procedure developed in comparision to earlier procedures and application to the synthesis of N-phthaloyl linked 3-thiazolo substituted coumarines and evaluation of their antimycobacterial and antimicrobial activities. **Chapter II** deals with the drugs containing N-phthaloyl moiety such as synthesis of racemic Thalidomide, anti-HIV agent *via* Na/Liq.NH_3 mediated cyclization strategy and drugs derived from phthalimide moiety, eg., synthesis of racemic and enantioselective synthesis of R-Baclofen, a novel $GABA_B$ receptor agonist *via* preparation of N-phthalimido acetaldehyde *in situ* by ozonolysis of N-allyl phthalimide, and subsequent 2-carbon Wittig reaction. Thus formed ester is reacted with 4-chloro boronic acid using Rh-BINAP as chiral reagent. **Chapter III** presents the synthesis and characterization of glycine and mandelic Acid derived phthalimides of biologically relevance (such as anti-microbial and anti-inflammatory). **Chapter IV** deals with the synthesis of synthesis and applications of N-phthaloyl aminoacids in the preparation of 1,5-benzodiazepines acting as Lewis acids, synthesis of novel chiral oxazolines and N-phthaloyl L-aminoacid derived ligands by innovative strategies and chiral oxazoline and chiral Schiff base tetradentate ligand using phthaloyl protecting and deprotecting strategy.

CHAPTER I- Chemistry of Phthalimides

Among heterocyclic scaffolds, phthalimides are of particular biological interest and have been reported as herbicides, insecticides, antipsychotics and antiinflammatory agents. Phthalimide derivatives with phenyl acetic acid and phenyl propionic acid were found to possess anti inflammatory and analgesic properties. Substituted phthalimides are used predominantly as chiral building blocks in organic synthesis and can be used as key intermediates in the preparation of bio-active compounds i.e. antibacterial, analgesic, antifungal, virucidal, plant growth regulator and also in dye industry.

The use of phthalimides as primary amine protecting groups is extensively documented in the chemical literature, especially for α–amino acids. N-Phthaloyl derivatization is one of the most frequently used methods of protection in the synthesis involving compounds with primary amino groups. In addition, the photophysical properties of phthalimides have been studied intensively during the last two decades.

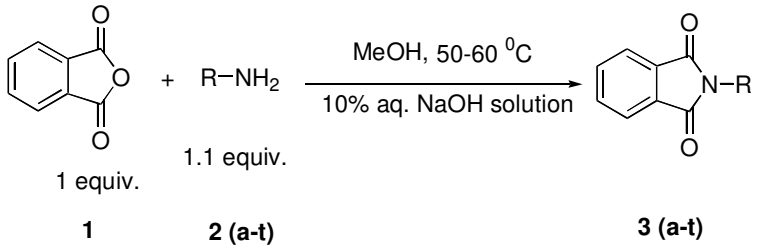
While there are several synthetic procedures for preparing these compounds, limitations as noted below were found. (1) Most of the known procedures for phthalimide formation are compatible only with simple alkyl or aryl substituents on the nitrogen atom. (2) It is difficult to introduce a functional group, especially an electron-donating group, on the phenyl ring of phthalimides. (3) The formation of imide usually requires high reaction temperatures. (4) The use of expensive catalysts (Pd or Ni etc). Thus in order to minimize the usage of raw materials and effluent, product formation should proceed with high levels of atom economy and selectivity.

In view of the tremendous importance of phthalimides, we herein describe an efficient approach for the synthesis of phthalimide derivatives.

Using almost stoichiometric quantities of phthalic anhydride (1 eq.) and substituted amines (1.1 eq) suspended in methanol for the condensation to take place (Scheme 1). The reaction mixture was heated on water bath for the time given to the corresponding amines as shown in Tables 1 and 2, at 50-60 ^{0}C. Added catalytic amount of 10% aq. NaOH solution for the

cyclization of the formed N-phthalamic acids. The mixture was left at the room temperature for overnight and resultant products are formed as crystals. Subsequnt reduction and condensation with appropriate reagent, results in the synthesis of biologically active phthalimide derivatives.

Scheme 1



Structurally and electronically divergent amines were deliberately chosen for the condensation with phthalic anhydride to know the efficacy of present methodology (Table 1).

Table 1. Reaction of phthalic anhydride with structurally divergent amines.

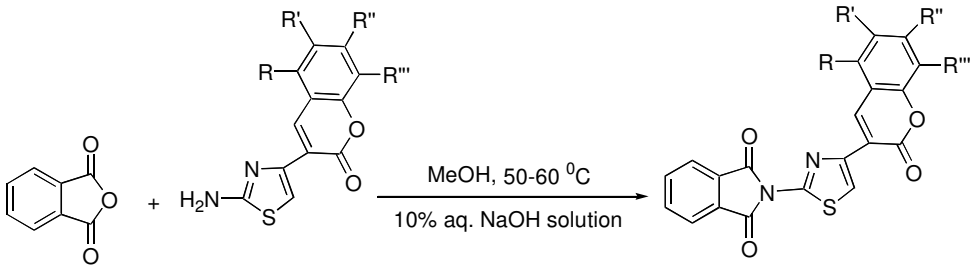
Entry	Amine	Product	Time (min/h)	Isolated yield (%)
1	Cyclohexyl amine (2a)	**3a**	2.5 h	72
2	Aniline (2b)	**3b**	45 min	87
3	4-Methyl aniline (2c)	**3c**	1 h	65
4	Benzyl amine (2d)	**3d**	45 min	78
5	4-Methoxy aniline (2e)	**3e**	1.2 h	76
6	4-Nitro aniline (2f)	**3f**	30 min	92
7	4-Chloro aniline (2g)	**3g**	1 h	81
8	1-(4-Aminophenyl)-1-ethanone (2h)	**3h**	0.75 h	94
9	2-(2-Aminophenyl)acetic acid (2i)	**3i**	2.5 h	88
10	2-Cyano aniline (2j)	**3j**	45 min	95
11	1*H*-Benzo[*d*]imidazol-2-amine (2k)	**3k**	1.45 h	68
12	2-Chloro-1-ethanamine (2l)	**3l**	1.25 h	61

13	2-Aminoethyl cyanide (2m)	**3m**	1.75 h	75
14	2-Aminoethyl methyl sulfite (2n)	**3n**	1.5 h	80
15	1-(2-Aminoethyl)-1,2-triazadien-2-ium (2o)	**3o**	6 h	67
16	4-Chloro-3-fluoroaniline (2p)	**3p**	1.25 h	47
17	1,3-Benzothiazol-2-ylmethanamine (2q)	**3q**	3.5 h	56
18	*tert*-Butyl carbamate (2r)	**3r**	2 h	82
19	2-Amino-1-ethanol (2s)	**3s**	5 h	95
20	1*H*-1,2,3,4-Tetraazol-5-amine (2t)	**3t**	2 h	92

We have studied the functional group tolerance of our developed protocol, using different protected amines. It was noteworthy that, in all cases, -OH, -Cl, -OMs, -CN and $-N_3$ functional groups remained unaffected for the facile condensation to take place. It was also worthwhile to note that good yields could be achieved with different heterocyclic amines such as 1*H*-benzo[*d*]imidazol-2-amine (2k), 1,3-benzothiazol-2-ylmethanamine (2q), 1*H*-1,2,3,4-tetraazol-5-amine (2t) etc.

Apart from the compounds synthesized in Scheme 1, some novel N-phthaloyl linked 3-thiazolo substituted coumarines were also prepared (Scheme 2 and entries 5a-g, Table 2) because of the tremendous importance of the coumarine nucleus which is found in a variety of natural products and exert varied pharmacological effects. There were some limitations for the developed protocol. Amino acids were not tolerated under the present conditions. Base induced racemization was observed for the preparation of N, N-phthaloyl aminoacids.

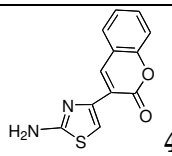
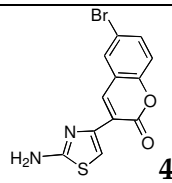
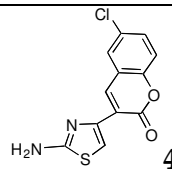
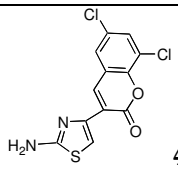
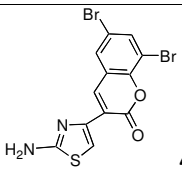
Scheme 2

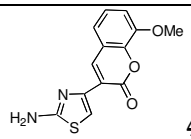
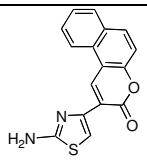


1 **4** **5a-g**

R=R'=R"=R'"=H; R=R"=R'"=H, R'=Br
R=R"=R'"=H, R'=Cl; R=R'=R"=H, R'"=OMe
R=R"=H, R'=Br, R'"=Br; R=R"=H, R'=Cl, R'"=Cl
R=R'=phenyl

Table 2. Reaction of phthalic anhydride with structurally divergent 3-thiazolo substituted coumarines.

Entry	Amine (4a-g)	Product	Time (h)	Isolated yield (%)
1	 **4a**	**5a (ASR-T-01)**	4	82
2	 **4b**	**5b (ASR-T-02)**	6	78
3	 **4c**	**5c (ASR-T-03)**	7	90
4	 **4d**	**5d (ASR-T-04)**	4.5	89
5	 **4e**	**5e (ASR-T-05)**	5	74

6	 **4f**	**5f (ASR-T-06)**	12	58
7	 **4g**	**5g (ASR-T-07)**	8.5	62

We have subjected the compounds (entries 5a-g, Scheme 2) for anti-mycobacterial screening done in TAACF screening programme for the discovery of novel drugs for treatment of mycobacterial infections, Alabama, USA and antimicrobial screening as well.

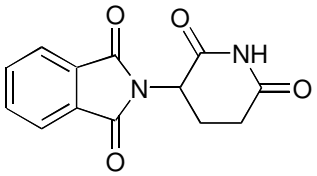
CHAPTER II- Synthesis of Thalidomide and (±)-and (R)-Baclofen

This chapter is divided into two sections. Section-A deals with the racemic synthesis of thalidomide and Section-B deals with the racemic and enantioselective approaches to the synthesis of Baclofen.

Section A: Synthesis of Thalidomide (Anti-HIV/Anti-Leprosy Drug)

Thalidomide (1) has a relatively simple chemical architecture (Figure 1), but exhibits a multitude of physiological activities (as multitarget drug) on mammals.

Figure 1

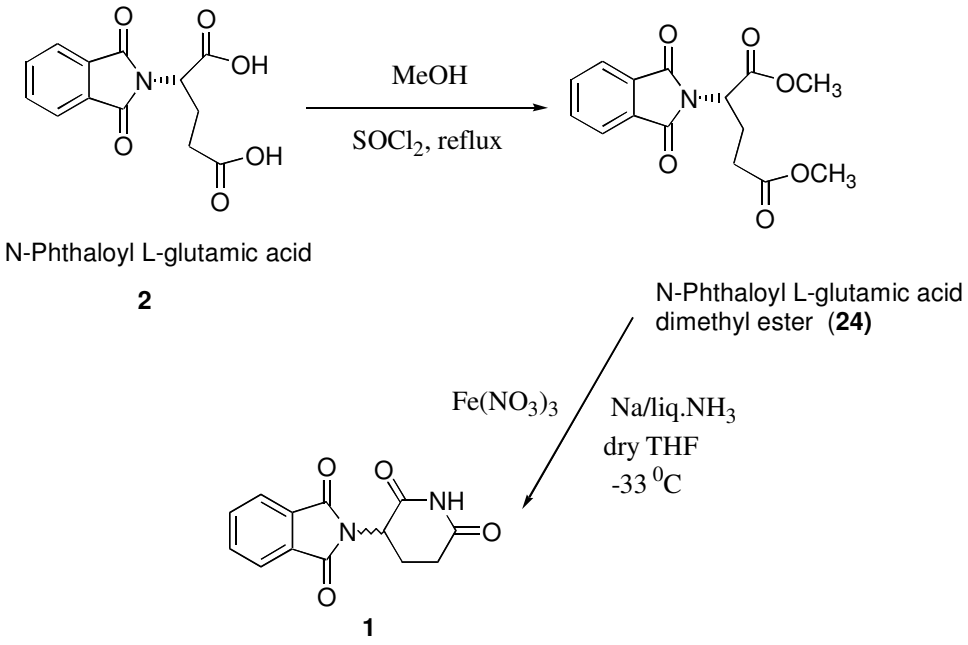


Thalidomide (1)

Considering the newly discovered activity of the drug in treating infectious diseases and being interested in exploring novel routes for the preparation of the phthalimide and arylalkanoic acid derived drugs and analogues, we wish to report two novel methods of synthesizing thalidomide.

Treatment of **1** with thionyl chloride in methanol under reflux for 6 h afforded after usual workup afforded N-phthaloyl L-glutamic acid dimethyl ester **2** as an oil (71%). The following key step is based on the formation of the glutarimide ring from glutaric acid diesters by using the $NaNH_2$/liq.NH_3/$Fe(NO_3)_3$ methodology. To our satisfaction, the ester **2** was cyclized to give the desired compound **6** in a low yield (Scheme 3).

Scheme 3

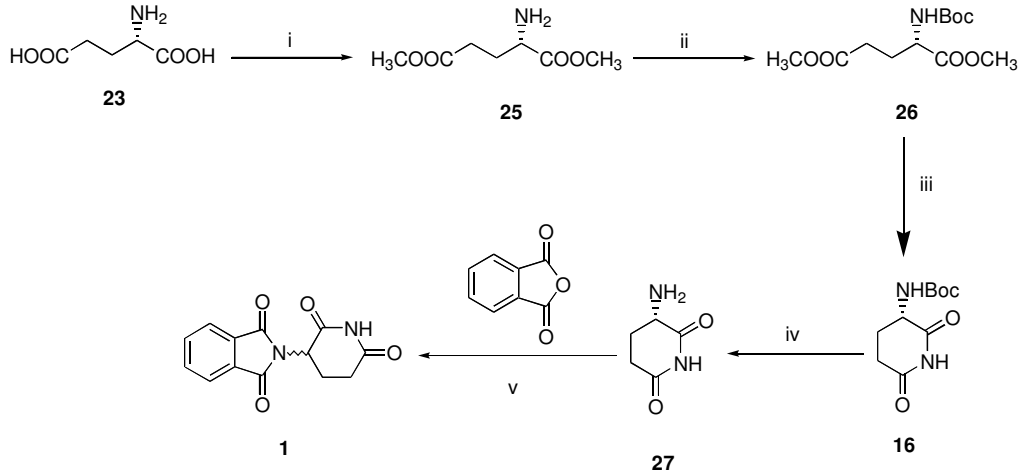


Albeit the chemical yield is low, the above two-step synthesis encouraged us to explore the applicability of this methodology in the large scale synthesis of thalidomide using an alternative strategy starting from L-GA. A facile, efficient, concise, cost effective and scalable synthesis of thalidomide in high overall yield (55%) is presented. Treatment of Boc-protected L-glutamic acid diester *via* Na/liq.NH_3 (-33 ^{0}C) mediated cyclization methodology, produces corresponding glutarimide ring which was subsequently condensed with phthalic anhydride in presence of glacial acetic acid to afford thalidomide and related analogues (Scheme 4).

In summary, the practical short synthesis was developed as an alternative to the previous syntheses of thalidomide using $NaNH_2$/liq. NH_3 methodology for the first time, found to fulfill our initial requirements of economical and

readily available starting materials, high overall yield and ability to be done on multi-gram scale. No exceptional purification (such as use of high melt temperatures, acidic purifications) was required for all intermediates and reagents. General applicability of this methodology could be easily extended to other analogues of thalidomide.

Scheme 4



23 25 26 1 27 16

i) MeOH, SOCl2, reflux; ii) (Boc)2O, DMAP, dioxane-H2O (1:1);iii) $Fe(NO_3)_3$, Na/liq.NH_3, dry THF, -33 ^oC; iv) i) TFA, DCM, 0 ^0C to RT; v) Glacial aceticacid, reflux.

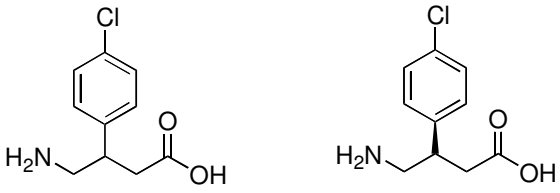
Section B: **Formal Synthesis of (±)-Baclofen via Pd(II)-Bipyridine Catalyzed Conjugative Addition and Enantioselective Synthesis of (R)- (–)-Baclofen, a Novel $GABA_B$ Receptor Agonist, via Rh/BINAP Conjugative Addition**

Baclofen [γ-amino-β-(*p*-chlorophenyl)butyric acid, **1**] is a derivative of γ-aminobutyric acid (GABA). It plays an important role as an inhibitory neurotransmitter in central nervous system (CNS) of mammalians.

R-Baclofen, or (3R)-4-amino-3-(4-chlorophenyl)butanoic acid, (**1a**, Fig. 2), is the only selective and therapeutically available $GABA_B$ agonist known (Lioresal® and Baclon®). Baclofen is commercialized in its racemic form, however literature observations suggested that the biological activity of **1a** resides in the R enantiomer. According to legislation already approved in many countries of the world concerning the commercialization of pharmaceutical products, drugs such as **1a** will soon be sold only in their

enantiomerically pure form. This requirement justifies the need for enantioselective strategies leading to the preparation of these compounds, if possible in a simple and efficient way.

Figure 2



(±)-Baclofen (**1**) (R)-(-)-Baclofen (**1a**)

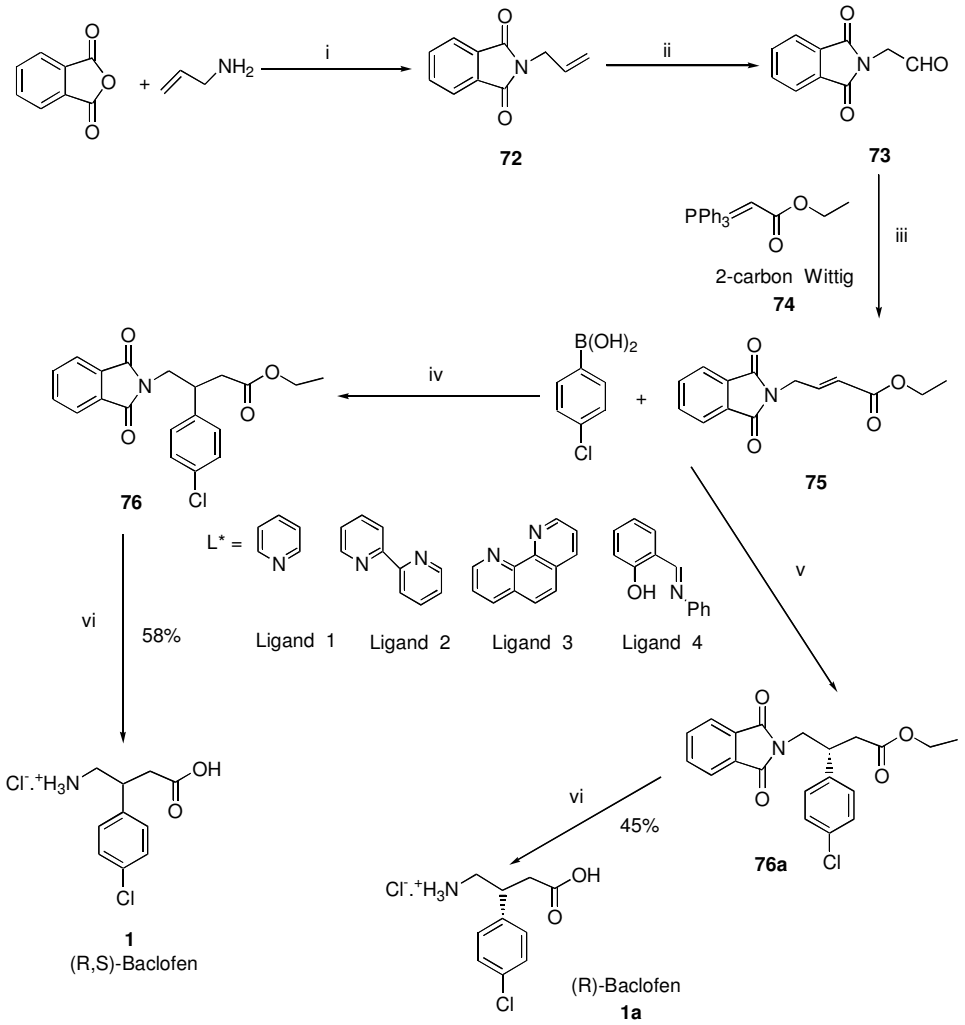
Considering its biological and pharmacological activity of the drug and being interested in exploring novel routes for the preparation of the phthalimide and arylalkanoic acid derived drugs and analogues, we continued our studies using a novel approach for the synthesis of racemic Baclofen and finally Rh/BINAP catalyzed conjugative addition of *p*-chloroboronic acid to achieve enantioselective synthesis of (R)-Baclofen.

Since, this section deals with two important strategies recently developed for the conjugate addition of α,β-unsaturated esters, i.e., a) Pd (II)-Bipyridine-catalyzed catalyzed conjugative addition in the presence of 2,2'-bipyridine and b) introducing stereogenicity into the prochiral molecule *via* Rh/BINAP-catalyzed conjugative addition, a brief account of each was presented in the particular section.

The synthetic strategy for both the syntheses of (R,S)-Baclofen and (R)-(-)-Baclofen was shown in Scheme 5 wherein both the above key steps are essential for the completion of total synthesis of racemic and (R)-Baclofen.

The synthesis commenced with the preparation of N-allyl phthalimide **72** as outlined in Scheme 5.

Scheme 5



Synthesis of (R,S)-Baclofen and R-Baclofen- i) Et_3N, Toluene, reflux, 3.5 h, 95%; ii) O_3, DCM-MeOH, Me_2S, 62%; iii) dry DCM, 0 ^{0}C-RT, 78%; iv) $Pd(OAc)_2$, bipy, H_2O, THF, AcOH, 82%; v) Rh/(S)-BINAP, Cs_2CO_3/Et_3N, Dioxane: H_2O ; vi) $N_2H_4.H_2O$, EtOH, 6N HCl, 58% for 1 and 45% for 1a.

Compound **72** then was subjected to ozonolysis to give compound N-phthalimidoacetaldehyde (**73**) as crystalline white solid which was further was subsequently treated with $PPh_3CHCOOC_2H_5$ (**74**) in dry DCM at room temperature to give the requisite ethyl (2*E*)-4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)but-2-enote (**75**) as colourless crystals. Next, the reaction conditions of the $Pd(OAc)_2$/bipy catalyzed 1,4-conjugative addition were optimized for the synthesis of **76**, a key intermediate using standard reaction conditions, to afford compound **76.**

Above prepared phthalimide protected α,β-unsaturated ester (**75**) was used as the common precursor for the enantioselective synthesis of (R)-Baclofen

using Rh(I)-catalyzed asymmetric conjugate addition of chloroboronic acid as a key step. The reaction conditions of the 1,4-addition were optimized for the synthesis of **76a** using first standard reaction conditions, i.e. 3 mol% of commercially available [Rh(acac)(C_2H_4)$_2$], 4.5 mol% of (S)-BINAP and Na_2CO_3 at 100 ^{0}C for 2 days. Deprotection of the addition product **76** or **76a** to give baclofen hydrochloride was performed in 45% yield by treatment with hydrazine hydrate in 80% hydrazine hydrate and ethanol under reflux conditions for overnight, followed by addition of HCl, affording the desired product **1** and **1a**.

In the present study, a novel, productive approach for the synthesis of baclofen (**1**) in five steps with 22% overall yield *via* Pd(OAc)$_2$/bipy catalyzed conjugative addition of N-phthaloyl α,β-unsaturated ester **75** with 4-chlorophenylboronic acid as a key step was studied. Further, synthesis of R-baclofen (**1a**) in chiron approach using Rh/BINAP asymmetric conjugate addition was also successfully achieved.

CHAPTER III- Glycine & Mandelic Acid Derived Phthalimides

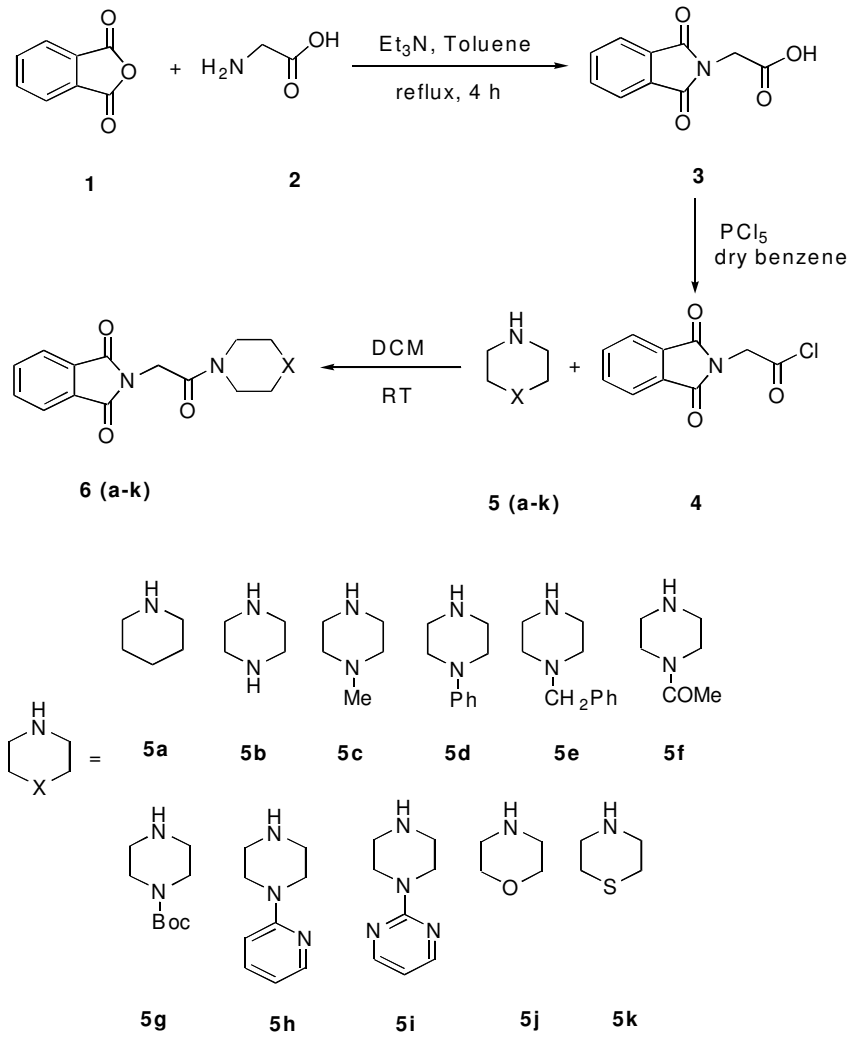
This chapter is divided into two sections.

Section-A deals synthesis, charecterization and biological activities of N-Phthaloyl glycine derived functionalized piperazines and 2-(2-oxo-2-phenylethyl)-1,3-isoindolinedione derivatives. Section-B presents the synthesis of mandelic acid derived phthalimides as a new class of anti-inflammatory and antimicrobial agents.

Section A: Study on N-Phthaloyl Glycine Derived Functionalized ketones and Evaluation of Anti-Microbial Activity

Glycine and γ-aminobutyric acid (GABA) are inhibitory amino acid neurotransmitters in the brain. There are several reports pertaining to the biological activities of N-phthaloyl glycine derivatives. Piperazines and their keto analogues are amongst the most important backbones in today's drug discovery industries. Owing to the high number of positive hits encountered in biological screens with this heterocycle and its congeners, the piperazine

template certainly deserves the title of *"privileged scaffold"* in medicinal chemistry.



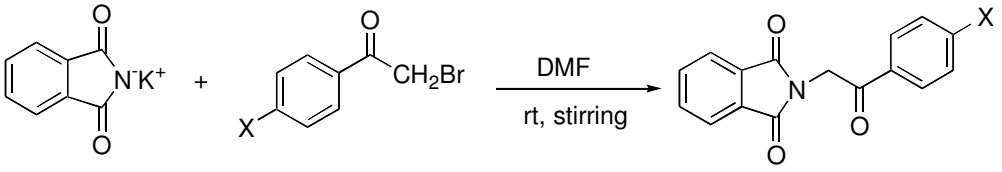
Scheme 6

Moreover, the piperazine scaffold occurs regularly in complex natural products. Thus, it is no wonder that there is a plethora of different synthetic methods that allow for the fast and efficient assembly of these heterocyclic systems.

These findings clearly indicate that N-phthaloyl aminoacid conjugates linked through piperazine moiety side arm with alkane spacers may exhibit good pharmacological activities. A new series of N-phthaloyl glycine derived functionalized piperazines (**6a-k**) were envisaged, resulting from the

combination of N-phthaloyl glycine chloride (**4**) and structurally divergent piperazines (**5a-k**) with potent antimicrobial activity (Scheme 6).

Apart from the synthesis of N-phthaloyl glycine derived functionalized piperazines (**6a-k**), N-phthaloyl functionalized aryl ketones were also synthesized (Scheme 7).



8 **9 (a-j)** **10(a-j)**

X= H, F, Cl, Br, I, OH, CH_3, OCH_3, NO_2, Ph

Scheme 7

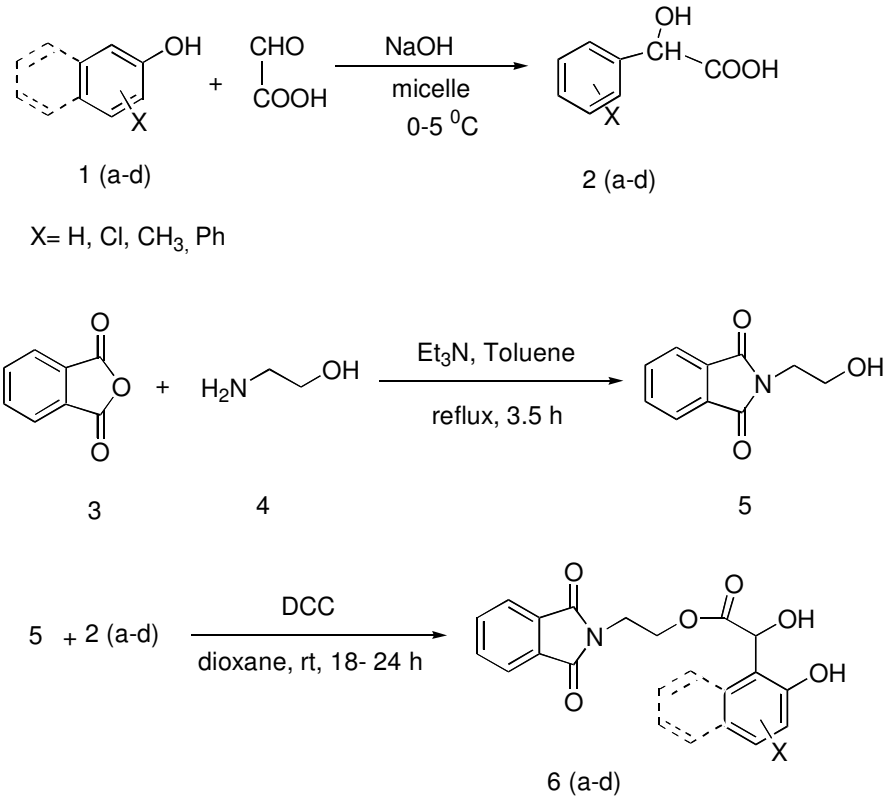
The synthesized compounds [(**6a-k**) and (**10a-j**)] were evaluated for *in vitro* antibacterial as well as antifungal activities.

Section B: Synthesis, Characterization and Biological activities of Mandelic Acid Derived Phthalimides as a New Class of Anti-inflammatory and Antimicrobial Agents

Phthalimide derivatives with phenyl acetic acid and phenyl propionic acid were found to possess anti inflammatory and analgesic properties. N-Hydroxyethyl phthalimide is used as an intermediate in some drugs, dyes and pesticides.

Aromatic hydroxy acids and its derivatives are important biologically and display a range of physiological effects. One such example is the application of mandelic acids in the production of β-lactam antibiotics. A vast literature review reveals that mandelic acid and its derivatives showed anti oxidant, urinary antiseptic, anti HIV, antitumor, antifungal, anti-thrombic effects.

A new hybrid series of 2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(substituted) acetates (**6a-d**) were envisaged resulting from the combination of N-(2-hydroxy ethyl) phthalimide (**5**) and substituted mandelic acids (**2a-d**) as seen, would result in compounds with potent antimicrobial and anti-inflammatory activities (Scheme 8).



Scheme 8

Chapter IV- Synthesis & Applications of N-Phthaloyl Aminoacids

Divided into three sub sections. Section-A deals with the synthesis f N-phthaloyl aminoacids and their application in organic synthesis. Section-B presents the synthesis of N-phthaloyl L-phenyl alanine based chiral oxazoline Section-C descripts the novel chiral Schiff base ligand from N-Phthaloyl L-phenyl alanine derived amides and salicylaldehyde.

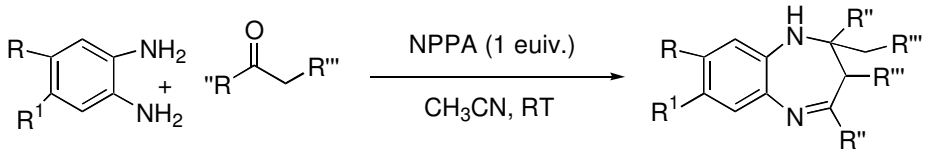
Section A: Synthesis of N,N-Phthaloyl Amino Acids and their Application as Lewis Acids for the Synthesis of 1,5-Benzodiazepines

A brief description of earlier syntheses to N-phthaloyl aminoacids and their application in organo catalysis was discussed by synthesizing N,N-phthaloyl aminoacids with sufficient spectral characterization.

Thus, prepared N,N-phthaloyl aminoacids could be used as Lewis acid promoters by developing a practical procedure for the synthesis of 2,3-

dihydro-1H-1,5-benzodiazepines at ambient temperature using N-phthaloyl L-phenyl alanine (NPPA) in acetonitrile. Due to their accessibility, easy functionalization and potential pharmacological properties, mainly 1,5-benzodiazepine derivatives have received significant attention and the core is indeed a ''privileged scaffold''.

The advantages of the present protocol were mild, short reaction times, study of wide range of electronically divergent substrates, easy work-up, low toxicity, inexpensive, and readily preparable catalyst, that make the procedure an attractive alternative to the existing methods for the synthesis of 1,5-benzodiazepines and can be applied to other organic transformations as well (Scheme 9).



R,R^1=H; R=CH_3, R=H;
R=Cl, R$^{'}$=H; R=NO_2, R$^{'}$=H;
R=CH_3, R^1=CH_3; R=Cl, R^1=Cl;
R=COPh; R^1=H

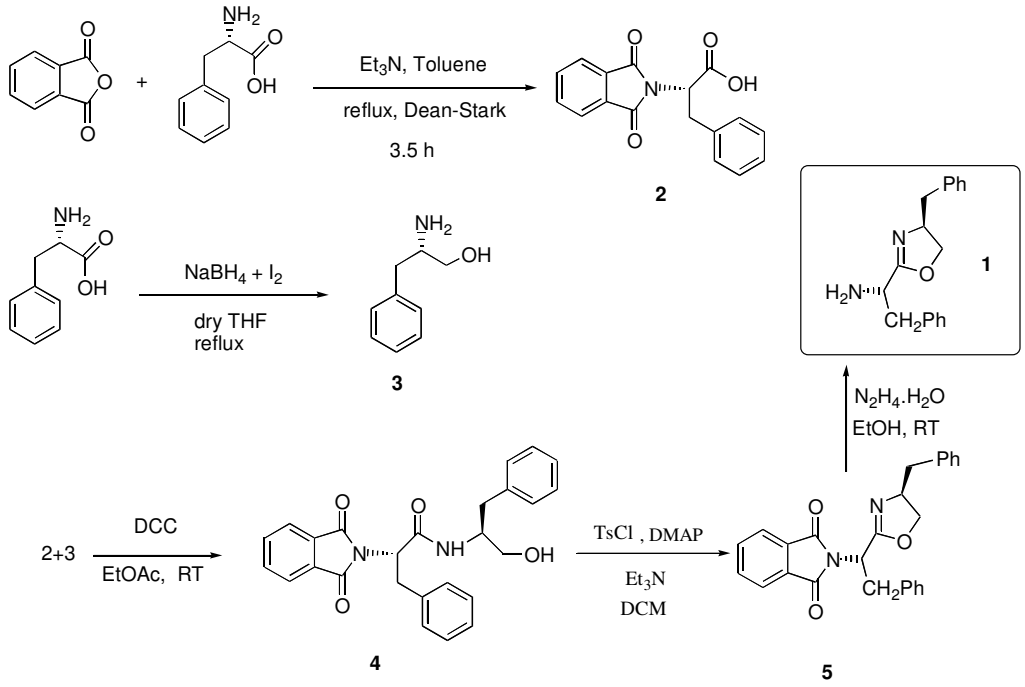
(20 examples)

Scheme 9

Section B: Synthesis of N-Phthaloyl L-Phenylalanine Derived Chiral Oxazoline (1)

The development of new classes of chiral ligands for metal catalyzed asymmetric transformations is an important goal of contemporary organic chemistry. Chiral oxazoline-based ligands are one of those ligands which have attracted significant attention over the past two decades for their potential application in a variety of catalytic asymmetric reactions including diethylzinc addition, allylic alkylation, cyclopropanation, hydrosilylation, olefin hydrogenation, transfer hydrogenation of ketones, and Diels-Alder reactions etc.

In an effort to explore new oxazoline ligand templates for catalytic enantioselective reactions, we have targeted cost-effective N-phthaloyl L-phenyl alanine derived oxazoline amine (Scheme 10).



Scheme 10

The synthetic plan of the oxazoline includes: N-Phthaloylation of various aminoacids and condensing with the divergent chiral aminoalcohols and subsequent cyclization followed by deprotection to give the desired oxazoline **1**. Thus obtained ligands are being investigated for various catalytic asymmetric reactions.

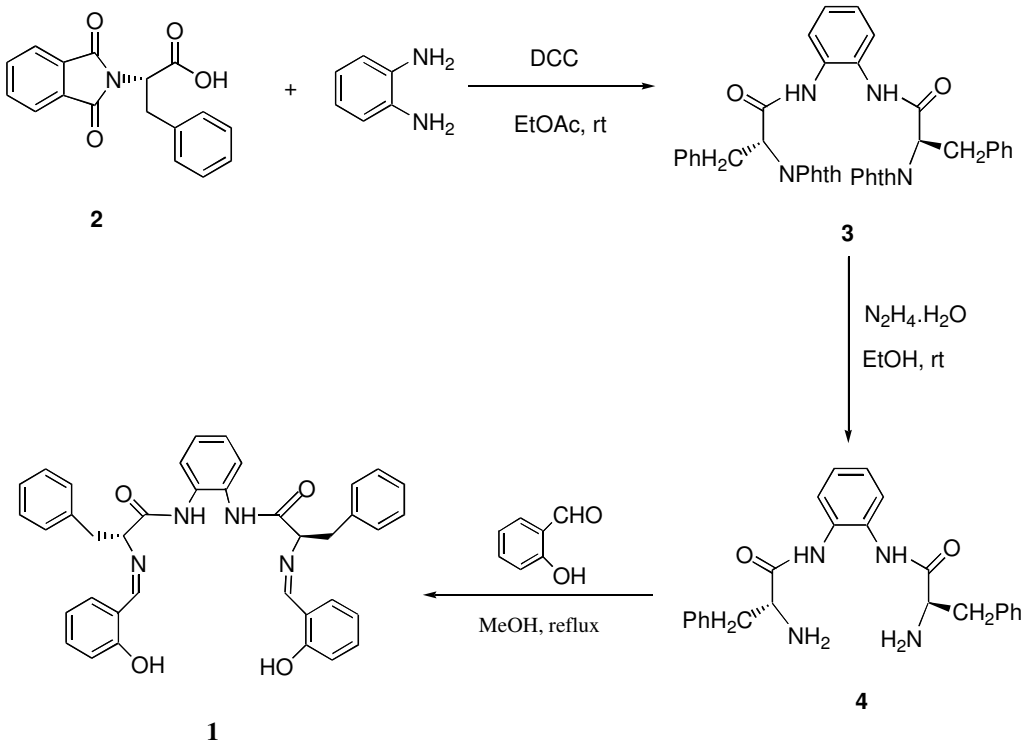
Thus, an elegant description of applications of chiral oxazolines in asymmetric catalysis and recently developed as well as earlier approaches for the synthesis have been aptly described in this section. Apart from that, the synthesis of chiral oxazoline **1** (1S)-1-[(4S)-4-benzyl-4,5-dihydro-1,3-oxazolo-2-yl]-2-phenylethan-1-amine) as a new class of bidentate ligands, designed from N-phthaloyl L-phenyl alanine, was successfully accomplished.

Section-C: Section C: Synthesis of N-Phthaloyl L-Phenylalanine Derived Chiral Schiff Base Ligand

The synthesis of new kind of chiral ligands represents one of the most important factors in the field of asymmetric catalysis. The major parts of most common ligands are bidentate and neutral, like DIOP and BINAP, or dianionic, like TADDOL and BINOL. The chiral chelating ligands that afford metal centres with a chiral environment are essential components for the

development of chiral catalysts. Over the past 25 years, extensive chemistry has surrounded the use of Schiff base ligands in inorganic chemistry.

The present work reports the synthesis and spectroscopic characterization of novel symmetric N-salicylaldehyde ligands using N-phthaloyl protecting and deprotecting strategies (Scheme 11).



Scheme 11

The synthesis was carried out in four easy steps, each with excellent or good yields. At first, employing *N*-phthaloyl protected L-phenylalanine **2**, as starting material, the corresponding diamide adduct **3** was obtained in 90% yield. The N-phthaloyl functions of **3** were cleaved (82% yield) with an ethanolic 80% aq.hydrazine hydrate at reflux for 2.5 h and followed by usual work up. The synthesis of the desired ligands was accomplished by condensation of chiral diamine **4** with salicylaldehyde under reflux in MeOH, followed by crystallization of the corresponding Schiff base **1** in 58% yield.

A short synthesis of a new class of chiral polydentate Schiff base ligand **1**, containing mixed N,O donors was developed. This ligand was easily prepared in good yield starting from low-cost commercially available materials. In fact coordinating the ligand to lanthanides to use in asymmetric catalytic processes would not only has great significance in the fundamental chemistry of these rare earth elements but could also have an important role in the field of MRI contrast agents, biological probes or NMR chiral shift reagents.

1.1.1 INTRODUCTION

The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Imide derivatives are among those organic compounds, which have numerous applications in biology,[1] synthetic[2] and polymer chemistry.[3] Imide refers to any compound which contains the divalent radical "-C(=O)NHC(=O)-". Imide compounds are derived from ammonia or primary amine, where two hydrogen atoms are replaced by a bivalent acid group or two monovalent acid groups, resulting in consisting of two carboxylic acid groups (or one dicarboxylic acid). In other description, Imide is a compound derived from an acid anhydride by replacing the oxygen with the =NH group. Imides are monomers to prepare polyimides that contain repeating imide groups. Aromatic polyimides have better resistance to high temperatures and corrosion than linear polyimides. Frequently, the term of imide refers to the combined forms such as maleimides, phthalimides and succinimides which are used as plastic modifiers to improve heat-resistant, antioxidant and antifoulant properties. They are used as intermediates for the synthesis of cross-linking agents, pesticides, dyes, antiseptics and crystalline adducting agents.[4] They are also useful compounds in the synthesis of primary amines and amino acids for the application in the field of medicine and biological research. N-alkylated phthalimides, made from potassium phthalimide, are used for the synthesis of primary amines (Gabriel synthesis) by the hydrolysis reaction.

Among heterocyclic scaffolds, phthalimides are of particular biological interest and have been reported as herbicides, insecticides, antipsychotics and antiinflammatory agents.[5] Phthalimide, derived from phthalic anhydride with ammonium hydroxide by heating, is used in the synthesis of primary amines and amino acids. It is used to make synthetic indigo and phthalocyanine pigments which have macrocyclic structure showing striking coloring features like porphyrins (biopigments). Phthalimide has isoindole moiety. Indole structure is a motif in nature. Prominent examples include tryptophan

(aromatic side chain amino acid), serotonin (neurotransmitter), auxin (plant growth hormone), and indigo (plant colorant). Phthalimides are used for the preparing of synthetic indigo, pesticides, pigments, dyes, pharmaceuticals, and fungicides. Phthalimide derivatives with phenyl acetic acid and phenyl propionic acid were found to possess anti inflammatory and analgesic properties.[6] Substituted phthalimides are used predominantly as chiral building blocks in organic synthesis and can be used as key intermediates in the preparation of bio-active compounds i.e. antibacterial, analgesic, antifungal, virucidal, plant growth regulator and also in dye industry.

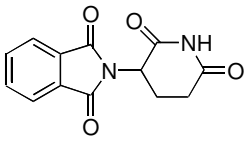
The use of phthalimides as primary amine protecting groups is extensively documented in the chemical literature, especially for α–amino acids. N-Phthaloyl derivatization is one of the most frequently used methods of protection in the synthesis involving compounds with primary amino groups.[7a-b] In addition, the photophysical properties of phthalimides have been studied intensively during the last two decades.[7c]

The biological importance of drugs consisting N-phthaloyl moiety and its derivatives are extensively studied in literature, which can be understood from the Figures 1 and 2.

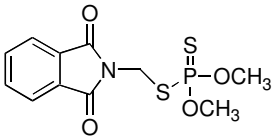
1.1.2 BIOLOGICAL IMPORTANCE

a) Drugs containing N-phthaloyl moiety -Examples:

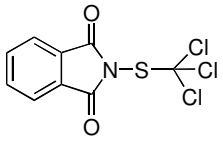
As it can be envisaged from the Figure 1, there are several kinds of pharmaceutical and agricultural related drugs consisting of N-phthaloyl moiety. For example, Phosmet (insecticide and herbicide), Folpet (fungicide, insecticide, germicide), Ditalimfos (fungicide), Captafol (fungicide), Trichlorofenphim (fungicide), Flumioxazin/Valor (pesticide/herbicide), Flumiclorac (herbicide), (S)-Indanofan (herbicide), Cindion-ethyl (weedicide) etc., are the prominent agricultural products widely used in market by agriculturists.



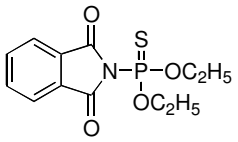
Thalidomide
(Anti-HIV/Anti-Leprosy)



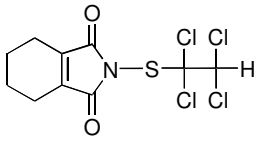
Phosmet (Insecticide, Herbicide)



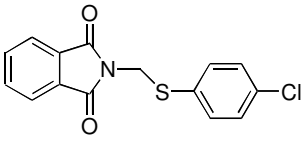
Folpet (Fungicide, Insecticide, Germicide)



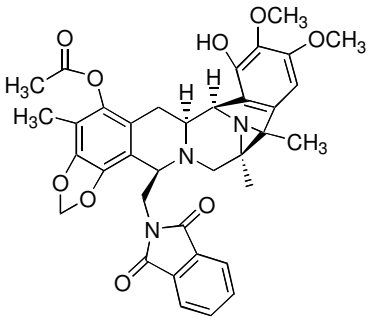
Ditalimfos (Fungicide)



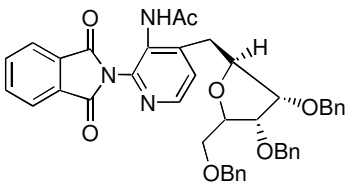
Captafol (Fungicide)



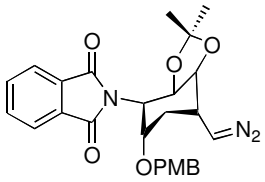
Thiochlorofenphim (Fungicide)



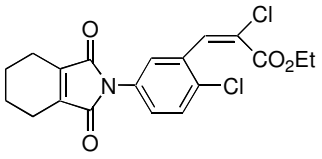
Phthalascidin (Anti-tumor agent)



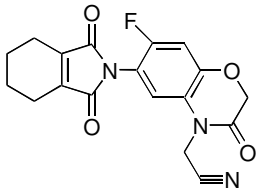
4-Deazaformycin-A
(C-nucleoside antibiotic)



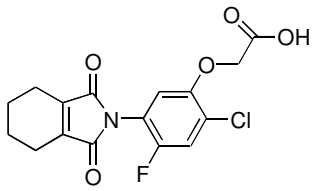
Tunicamycin (Antibiotic)



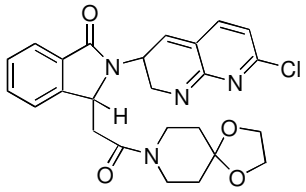
Cinidon-ethyl (Weedicide)



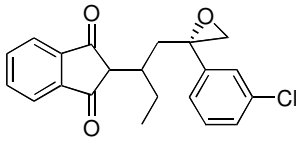
Flumioxazin/Valor
(Pesticide/Herbicide)



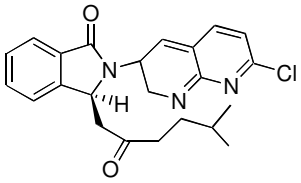
Flumiclorac (Herbicide**)**



Pazinaclone (DN-2327) (Anxiolytic)



(S)-Indanofan (Herbicide)



Pagoclone (GABA) receptor modulator

Figure 1

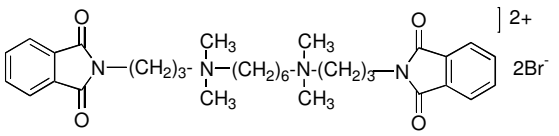
Apart from these agricultural findings, there are certain notable drugs such as Thalidomide (anti-HIV/anti-Leprosy), Phthalascidin (anti-tumor agent),

4-Deazaformycin-A (C-nucleoside antibiotic), Tunicamycin (antibiotic), Pagoclone (GABA receptor modulator), Pazinaclone (anxiolytic) etc., are very beneficial to the mankind.

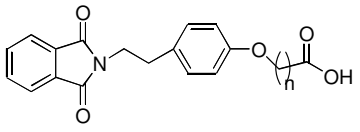
Apart from the drugs consisting N-phthaloyl moiety, there are several phthalimide derived drugs acting on different pharmacological activities with prominent results. For example, LassBio-468 (selective PDE-4 inhibitors), E 2020 or Donepezil (AChE inhibitors), W 84 (allosteric agent), TC-12 and ATC-1 (anti-HIV agents), LK 423 (potent immunomodulators), (R)-PD172938, Buspirone and Lennoxamine (anxiolytic), Zopiclone and Desmethyl zopiclone (hypnotic), Phenytoin (anti-convulsant), 3-(S)-*n*-butyl phthalimide (anti-epileptic), NAN 190 (seratonin $5HT_{1A}$ receptors), AKS 186 (thromboxane A_2 inhibitors), Ameltolide (anti-convulsant) etc., as shown in Figure 2 are some of the glimpses of various outstanding biological activities of phthalimide derivatives.

Hence, it is thought reasonable to give a brief account on the some of the pharmacologically active phthalimide derivatives in Figure 2.

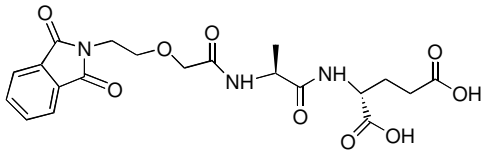
b) Phthalimide derived drugs-Examples:



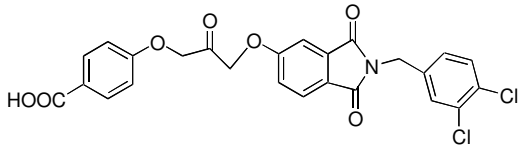
W 84 (Allosteric agent)



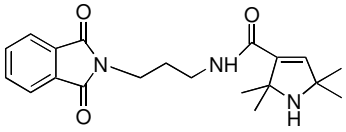
Leukotriene D_4 receptor antagonists



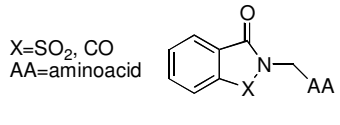
LK 423 (potent immunomodulators)



Cytosolic phospholipase A_2 ($cPLA_2$) inhibitors

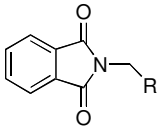


TPC-NH (amine)
Against Postischemic Myocardial Injury

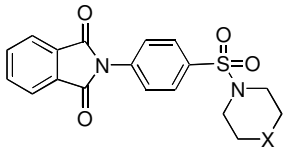


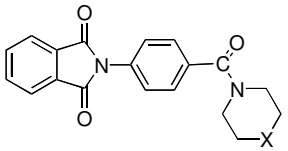
X=SO_2, CO
AA=aminoacid

Inhibitors of Human Leukocyte Elastase, Cathepsin G and Proteinase 3

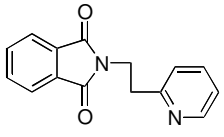


HIV-1 Reverse Transcriptase Inhibitors

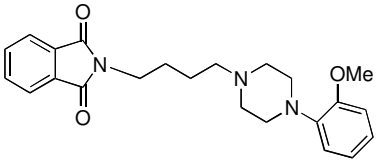




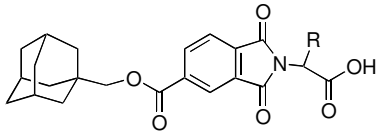
LASSBio 468 (selective PDE-4 inhibitors)



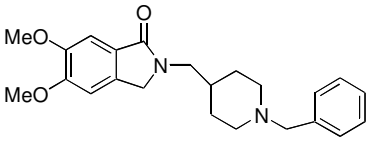
2-[2-(2-pyridyl)ethyl]-1,3-isoindoline dione (Analgesic)



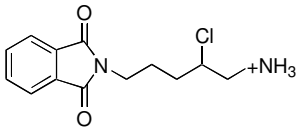
NAN-190 (serotonin 5-HT1A and 5-HT2A receptors)



4-(adamant-1-ylmethoxycarbonyl)-N-(5-carboxypentamethylene) phthalimide (Antimicrobial agent)

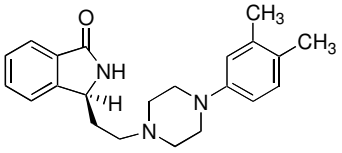


E 2020 (Donepezil)AChE Inhibitors



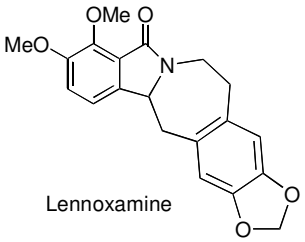
2-chloro-5-phthalimidopentylamine

(selective amine oxidase inhibitors)

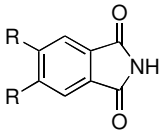


(R)-PD172938

Anxiolytic drugs

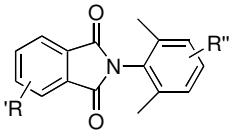


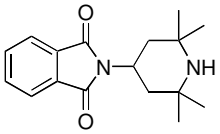
Lennoxamine



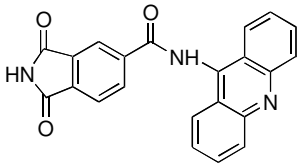
4,5-dianilino-phthalimide

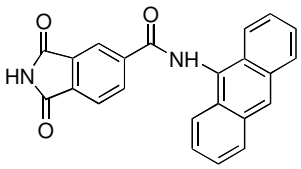
DAPH1 (Tyrosine Kinase Inhibitors)



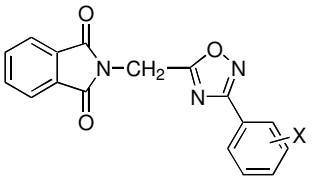


N-Phenyl Phthalimide (Ameltolide/Phenytoin) analogues (anticonvulsant agents)

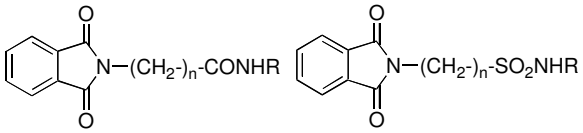




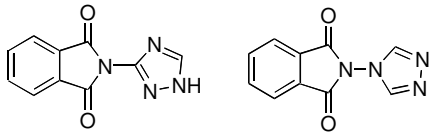
G. lamblia GPRT inhibitors



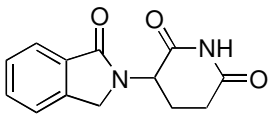
analgesic and antiinflammatory agents



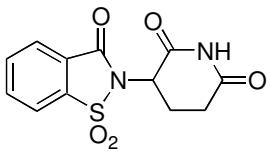
CNS inhibitory agents



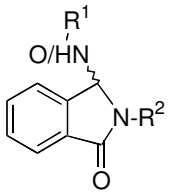
antihypolipidemic agents



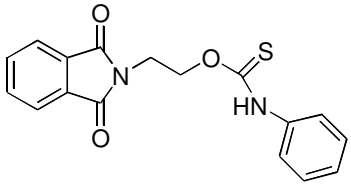
EM-12 (Potent Teratogen)



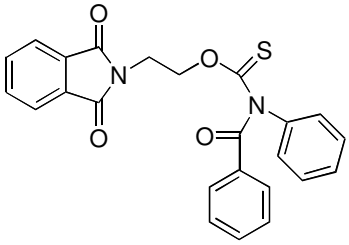
Supidimida (Non-teratogenic)



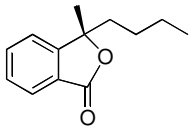
MDM2-p53 inhibitor



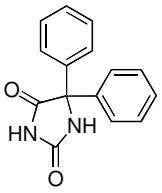
TC 12 (anti-HIV-1 agent)



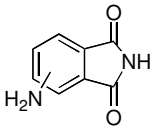
ATC-1 (potent inhibitor of wild-type HIV-I)

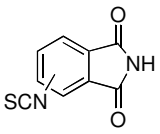


3-(S)-n-butyl phthalimide
(Antiepileptc)

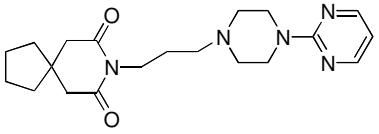


Phenytoin (Anti-convulsant)

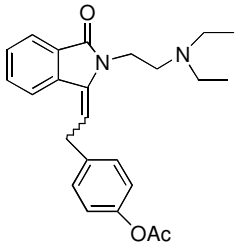




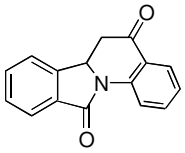
Flourescent protein conjugates

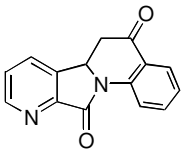


Buspirone (Anxiolytic agent)

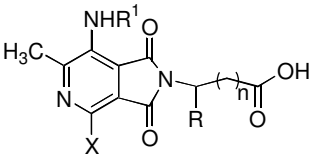


(Anesthetic)

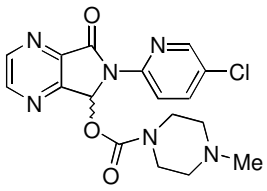




N_2-induced hypoxia antagonists

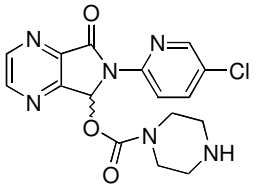


Aldose reductase (AR) inhibitor

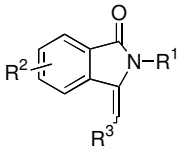


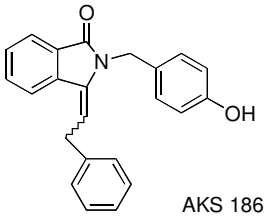
Zopiclone

(Hypnotic agents)

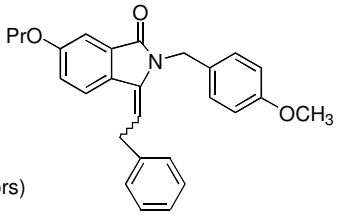


Desmethylzopiclone





AKS 186 (thromboxane A2 inhibitors)



3-(alkyl and aryl)methylene-2,3-dihydro-*1H*-isoindol-1-one (phthalimidine) class of compounds

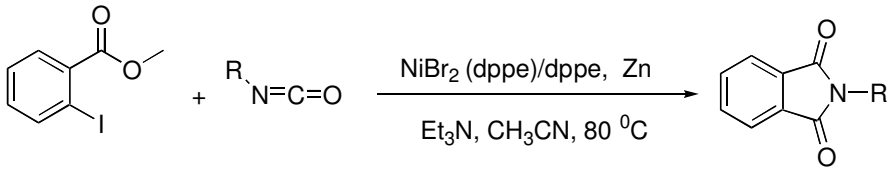
Figure 2

1.1.3 EARLIER SYNTHETIC APPROACHES

Literature search revealed that there are several reports available on the preparation of phthalimides, which are described below.

Cheng's Approach (2005)[8]

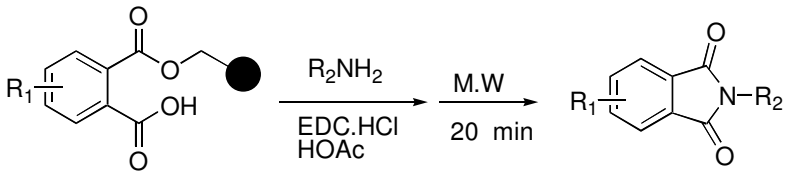
Cheng *et al.* developed a novel approach involving $NiBr_2$(dppe)/dppe/Zn system (Scheme 1) for the preparation of substituted imide and amide derivatives by the reaction of isocyanates with *o*-iodobenzoates and haloarenes in moderate to good yields with excellent tolerance of functional groups.



Scheme 1

Chassaing's Approach (2003)[9]

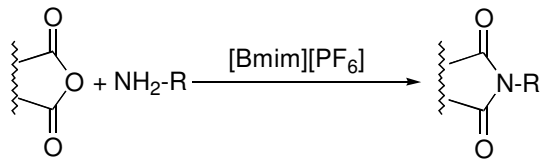
Chassaing *et al.* proposed a solid-phase synthesis of substituted phthalimides. The target compounds are obtained within minutes by a microwave assisted cyclative cleavage in good yields and excellent purities.



Scheme 2

Zheng's Approach (2004)[10]

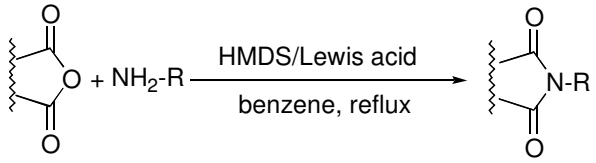
Zheng *et al.* reported synthesis of N-alkyl and N-arylimides in ionic liquids[Bmim][PF_6] or [Bmim][BF_4], a series of succinimide, maleimides and phthalimide derivatives were synthesized from corresponding anhydrides with a variety of primary amines in excellent yields.



Scheme 3

Toru's Approach (1997)[11]

Toru *et al.* reported Lewis acid and hexamethyldisilazane-promoted efficient synthesis of *N*-alkyl- and *N*-arylimide derivatives.

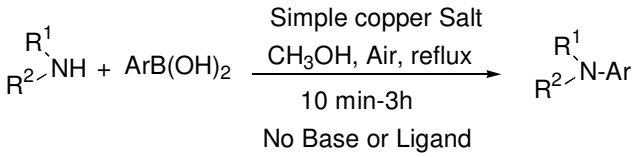


Scheme 4

High-yield synthesis of N-substituted imides was achieved on treatment of amic acids with HMDS in the case of transformation of phthalic anhydride to N-substituted phthalimides in the presence of $ZnBr_2$.

Xie's Approach (2004)[12]

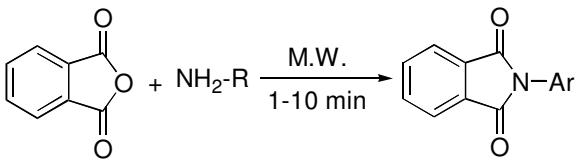
Xie *et al.* reported a simple copper salt catalyzed N-arylation of amines, amides, imides, and sulfonamides with arylboronic acids in MeOH to give *N*-arylimides in excellent yields.



Scheme 5

Li's Approach (2002)[13]

Li *et al.* performed a rapid synthesis of N-aryl phthalimides under microwave irradiation in the absence of solvent in moderate to good yields.

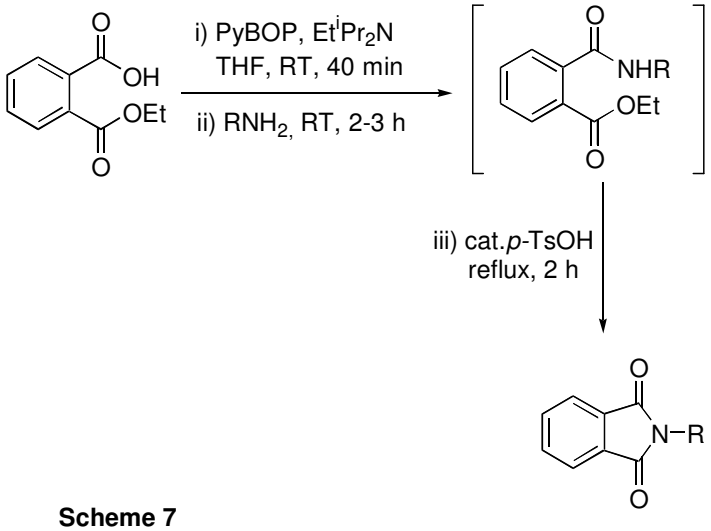


Scheme 6

Riera's Approach (1998)[14]

Riera *et al.* reported a new method for the protection of primary amines or amino alcohols as phthalimides (mild, selective, PyBOP mediated procedure for the conversion of primary amines into phthalimides).

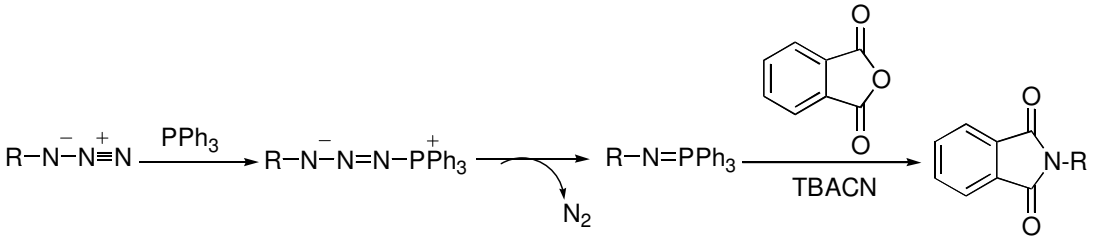
The phthaloyl group is selectively introduced under mild, anhydrous conditions by reacting the amine with 2-(ethoxycarbonyl)benzoic acid activated by PyBOP, followed by the thermally induced cyclization of the resulting phthalamic ester. The reaction conditions are applicable to a variety of primary amines and good yields are obtained in all cases.



Scheme 7

Vilarrasa's Approach (1986)[15]

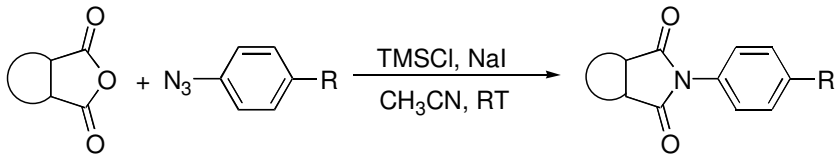
According to Vilarrasa's procedure, N-substituted phthalimides could be obtained in very good yields, under essentially neutral conditions, by mixing or heating an alkyl (or aryl) azide, PPh_3, and phthalic anhydride in benzene or toluene, in the presence of a catalytic amount of TBACN.



Scheme 8

Kamal's Approach (1998)[16]

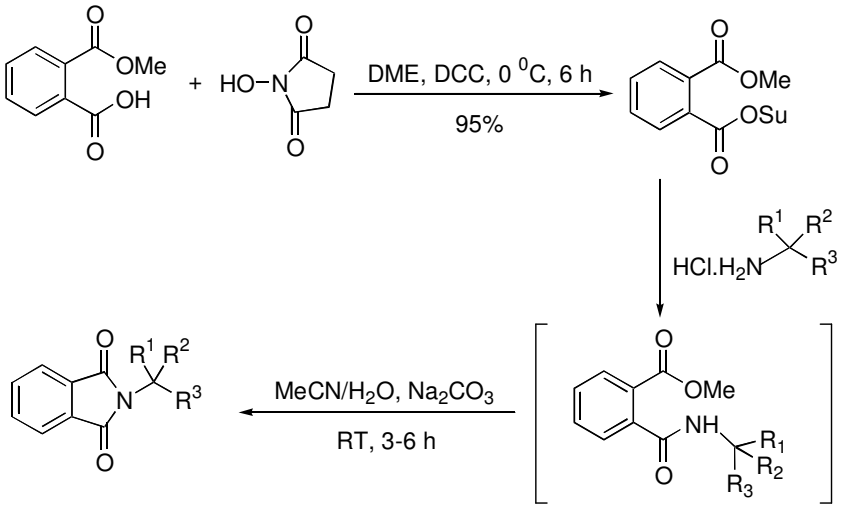
Kamal *et al.* elegantly obtained N-substituted phthalimides and naphthalimides in good to excellent yields, employing chlorotrimethylsilane and sodium iodide (*in situ* generation of iodotrimethylsilane) from corresponding azides and anhydrides under mild conditions.



Scheme 9

Briand's Approach (2002)[17]

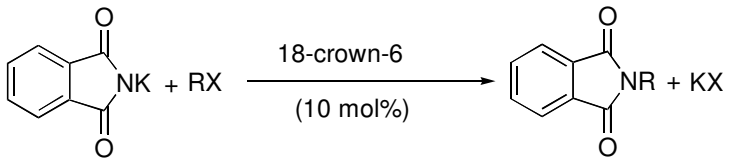
Briand developed a novel protocol using a new, efficient, and readily available reagent, methyl 2-(succinimidooxy)carbonyl)benzoate (MSB), for *N*-phthaloylation of amino acids and amino acid derivatives. The phthaloylation procedure is simple and racemization-free and gives excellent results with R-amino acids, R-amino alcohols, dipeptides, R-amino carboxamides, and R-amino esters.



Scheme 10

Kato's Approach (1982)[18]

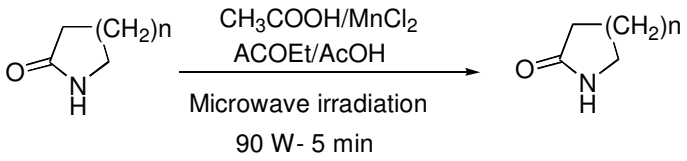
Kato *et al.* reported a facile one-step synthesis of N-substituted phthalimides using a catalytic amount of crown ether to the reaction of potassium phthalimide and alkyl halides in toluene.



Scheme 11

Mansuri's Approach (2005)[19]

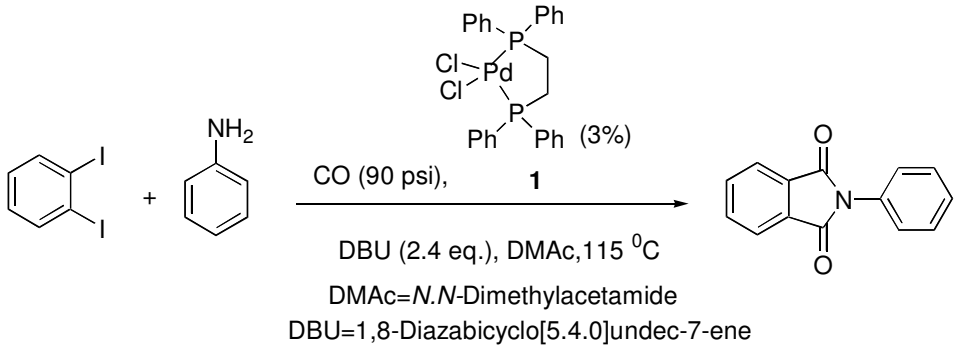
Mansuri *et al.* generated cyclic imides by fast oxidation of lactams using microwave irradiation in the presence of acetic acid and $MnCl_2$.



Scheme 12

Perry's Approach (1991)[20]

Perry *et al.* reported the preparation of N-substituted phthalimides by the Pd-catalyzed carbonylation and coupling of o-dihalo aromatics and primary amines. Optimal conditions established for the reaction using o-diiodobenzene and aniline were DMAc (0.2 M), 115 ^{0}C, 90 psi of CO, 3% $PdCl_2L_2$, and 2.4 equiv of DBU. This process is tolerant of a wide variety of functional groups and gives good yields of the desired products.



Scheme 13

1.1.4 PRESENT WORK

Imide derivatives have numerous applications in biology, synthetic and polymer chemistry.[1-3] Despite their wide applicability, available routes for the synthesis of these compounds are limited.[8-20] Well known methods are;

dehydrative condensation of an anhydride and amine at high temperatures[21a] and the cyclization of the N-substituted amic acid in the presence of acidic reagents.[21d] Direct N-alkylation under Mitsunobu conditions is also a method for the synthesis of imide derivatives.[21a] The condensation of iminophosphoranes with phthaloyl dichloride followed by alkaline hydrolysis also affords phthalimides.[22,23] However, most of these routes have their own synthetic problems when applied to a range of derivatives. Therefore, preparation of functionalized imide derivatives is a major challenge in organic synthesis.

In view of the tremendous importance of phthalimides, the need for developing environmentally safe and eco-friendly methods, demanded by the society, augment the just for their synthetic efficiency. A common method for the preparation of imides is *via* condensation of amine with anhydride or phthalic acid derivatives.[15,22] Another general method is the palladium-catalyzed reaction of phthalimide with iodocompound.[20] While there are several synthetic procedures for preparing these compounds, limitations as noted below were found. (1) Most of the known procedures for phthalimide formation are compatible only with simple alkyl or aryl substituents on the nitrogen atom. (2) It is difficult to introduce a functional group, especially an electron-donating group, on the phenyl ring of phthalimides. (3) The formation of imide usually requires high reaction temperatures. Thus in order to minimize the usage of raw materials and effluent, product formation should proceed with high levels of atom economy and selectivity.

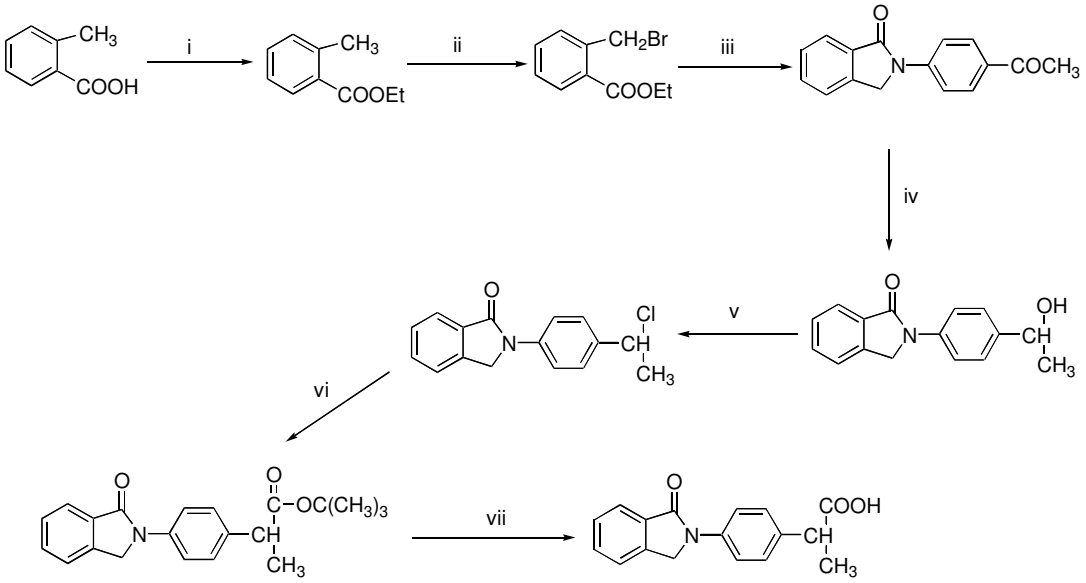
Although there are plenty of reports pertaining to the synthesis of phthalimides in literature shown above, however these methods suffer from disadvantages such as the use of expensive catalysts (Pd or Ni etc.), corrosive solvents, high temperatures, limited use of microwave synthesis when applicable to industrial scale, harsh bases or acids required to condense are the major drawbacks. Some reports using ionic liquids, phase transfer catalysts offer advantages over other procedures employed for the preparation of phthalimides.

1.1.4.1 Objective

Towards this idea, the synthetic application on the phthalimides received much attention in literature and there is demand for the development of a simple mild, efficient and cost-effective procedure for the preparation of phthalimides. We describe herein, an efficient approach for the synthesis of phthalimide derivatives.

1.1.4.2 Results and Discussion

During the course of the synthesis of indoprofen,[25] a potent anti-inflammatory agent and analgesic, we tried to prepare different phthalimide analogues, which were found to possess biological activity.

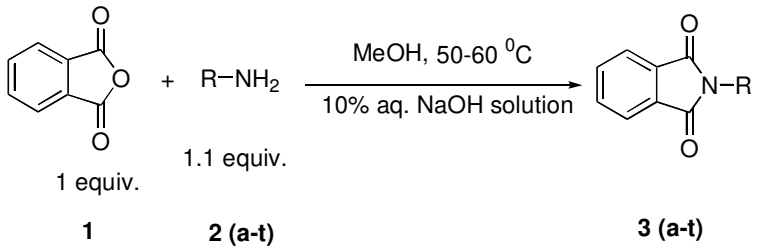


Synthesis of Indoprofen *via* Pd-catalyzed Carbonylation

Scheme14: i) C_2H_5OH, H_2SO_4, 6 h, 64%; ii) NBS, CCl_4, reflux; iii) 4-amino acetophenone, acetone, K_2CO_3, iv) $NaBH_4$, anhyd. methanol; v) Conc. HCl, $CHCl_3$, Rt; vi) $Pd(PPh_3)_2Cl_2$, TEBA (PTC), CO, NaOAc, *t*-butanol; vii) 50% KOH soln, Hydrolysis.

This report describes an improved synthesis of indoprofen *via* Pd catalyzed carbonylation as a key step, developed by Reppe.[23] We have synthesized the target molecule starting from readily available *o*-toluic acid and *p*-amino acetophenone by a sequence of reactions that included oxidative addition of carbonylation as depicted above (Scheme 14).

Using almost stoichiometric quantities of phthalic anhydride (1 eq.) and substituted amines (1.1 eq) suspended in methanol for the condensation to take place (Scheme 15).[27] The reaction mixture was heated on water bath for the time given to the corresponding amines as shown in Tables 1 and 2, at 50-60 ^{0}C. Added catalytic amount of 10% aq.NaOH solution for the cyclization of the formed N-phthalamic acids. The mixture was left at the room temperature for overnight and resultant products are formed as crystals. Subsequnt reduction and condensation with appropriate reagent, results in the synthesis of biologically active phthalimide derivatives. The yields are fairly good and the workup procedure is easier. With optimized experimental conditions for the preparation of phthalimides with phthalic anhydride in hand, the generality of this process has been proved with a wide range of aromatic, aliphatic and heterocyclic amines; the results are illustrated in Table 1.



Scheme 15

Structurally and electronically divergent amines were deliberately chosen for the condensation with phthalic anhydride to know the efficacy of present methodology (Table 1). Aromatic amines reacted faster in comparison to the aliphatic amines in condensation to take place for the formation of N-substituted phthalimides. In general, aldehydes with electron-withdrawing substituents such as –NO_2, -CN, -$COCH_3$ (entries 2f, 2j and 2h) react faster than those with electron-donating substituents such as –CH_3, -OCH_3, -Cl (entries 2c, 2e and 2g).

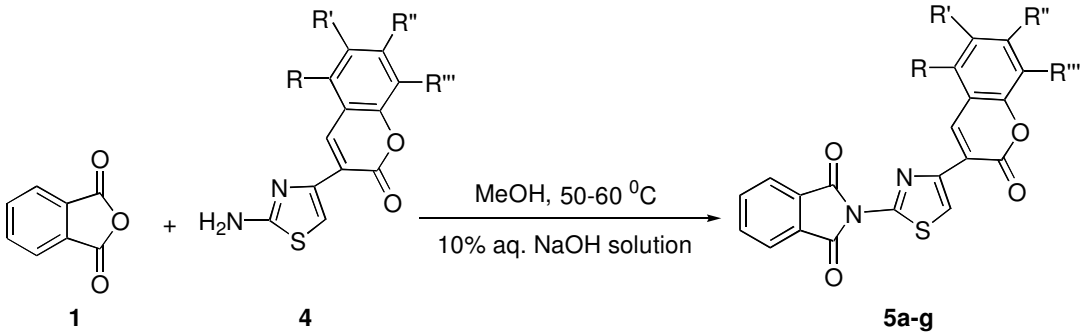
Table 1. Reaction of phthalic anhydride with structurally divergent amines.

Entry	Amine	Product	Time (min/h)	Isolated yield (%)
1	Cyclohexyl amine (2a)	**3a**	2.5 h	72
2	Aniline (2b)	**3b**	45 min	87
3	4-Methyl aniline (2c)	**3c**	1 h	65
4	Benzyl amine (2d)	**3d**	45 min	78
5	4-Methoxy aniline (2e)	**3e**	1.2 h	76
6	4-Nitro aniline (2f)	**3f**	30 min	92
7	4-Chloro aniline (2g)	**3g**	1 h	81
8	1-(4-Aminophenyl)-1-ethanone (2h)	**3h**	0.75 h	94
9	2-(2-Aminophenyl)acetic acid (2i)	**3i**	2.5 h	88
10	2-Cyano aniline (2j)	**3j**	45 min	95
11	1*H*-Benzo[*d*]imidazol-2-amine (2k)	**3k**	1.45 h	68
12	2-Chloro-1-ethanamine (2l)	**3l**	1.25 h	61
13	2-Aminoethyl cyanide (2m)	**3m**	1.75 h	75
14	2-Aminoethyl methyl sulfite (2n)	**3n**	1.5 h	80
15	1-(2-Aminoethyl)-1,2-triazadien-2-ium (2o)	**3o**	6 h	67
16	4-Chloro-3-fluoroaniline (2p)	**3p**	1.25 h	47
17	1,3-Benzothiazol-2-ylmethanamine (2q)	**3q**	3.5 h	56
18	*tert*-Butyl carbamate (2r)	**3r**	2 h	82
19	2-Amino-1-ethanol (2s)	**3s**	5 h	95
20	1*H*-1,2,3,4-Tetraazol-5-amine (2t)	**3t**	2 h	92

Whereas reaction with benzyl amine (entry 4) gave satisfactory yield of 78% in 45 min. We have studied the functional group tolerance of our

developed protocol, using amines 2l, 2m, 2n, 2o, 2s. It was noteworthy that, in all cases, -OH, -Cl, -OMs, -CN and -N_3 functional groups remained unaffected for the facile condensation to take place. It was also worthwhile to note that good yields could be achieved with different heterocyclic amines such as 1*H*-benzo[*d*]imidazol-2-amine (2k), 1,3-benzothiazol-2-ylmethanamine (2q), 1*H*-1,2,3,4-tetraazol-5-amine (2t) etc.

Apart from the compounds synthesized in Table 1, some novel N-phthaloyl linked 3-thiazolo substituted coumarines were also prepared (Scheme 16 and entries 5a-g, Table 2) because of the tremendous importance of the coumarine nucleus which is found in a variety of natural products and exert varied pharmacological effects. Numerous reports have appeared in the literature describing HIV protease inhibiting, α-chymotrypsin inhibiting, analgesic, antimicrobial activity and anticancer activity of 3-heteroaryl coumarines.[24] The amine precursors [3-(2-amino-4-thiazolyl)-2H-1-benzopyran-2-ones] were prepared by the reaction of substituted 3-(2-bromoacetyl) coumarines with thiourea which resulted in the formation of amines **4**, using the literature procedure. [24a,e]

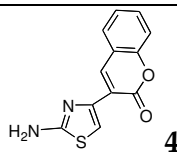
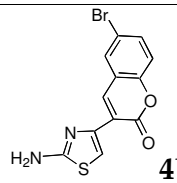
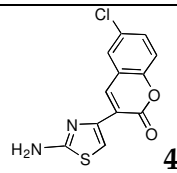
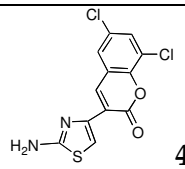
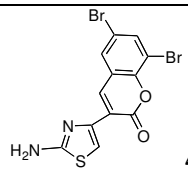
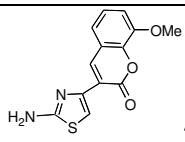
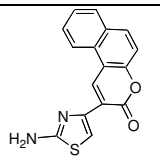


R=R'=R"=R'"=H; R=R"=R'"=H, R'=Br
R=R"=R'"=H, R'=Cl; R=R'=R"=H, R'"=OMe
R=R"=H, R'=Br, R'"=Br; R=R"=H, R'=Cl, R'"=Cl
R=R'=phenyl

Scheme 16

The synthesized compounds were subjected for anti-mycobacterial screening done in TAACF (Tuberculosis Antimicrobial Acquisition and Coordinating Facility), USA and anti microbial activites as well.

Table 2. Reaction of phthalic anhydride with structurally divergent 3-thiazolo substituted coumarines.

Entry	Amine (4a-g)	Product	Time (h)	Isolated yield (%)
1	 **4a**	**5a (ASR-T-01)**	4	82
2	 **4b**	**5b (ASR-T-02)**	6	78
3	 **4c**	**5c (ASR-T-03)**	7	90
4	 **4d**	**5d (ASR-T-04)**	4.5	89
5	 **4e**	**5e (ASR-T-05)**	5	74
6	 **4f**	**5f (ASR-T-06)**	12	58
7	 **4g**	**5g (ASR-T-07)**	8.5	62

There were some limitations for the developed protocol. Amino acids were not tolerated under the present conditions. Base induced racemization was observed for the preparation of N, N-phthaloyl aminoacids.

1.1.5 BIOLOGICAL ACTIVE STUDIES OF NOVEL SYNTHESIZED PHTHALIMIDES

We have subjected the compounds (entries 5a-g, Table 3) for anti-mycobacterial screening done in TAACF screening programme[25] for the discovery of novel drugs for treatment of mycobacterial infections, Alabama, USA and the results are as depicted:

a) Anti-TB Screening: Table 3. Anti-mycobacterial Study-Primary Assay Results:

Primary Assay Data (Level 1)

TAACF

Primary Assay Summary

Dr.Srinivas R. Adapa
Indian Institute of Chemical Technology

S.No	Sample ID	Corp ID	Assay	MIC (μg/mL)	% Inh	Activity
5a	CTPhthalimide-1	ASR-T-01	Alamar	>6.25	1	-
5b	CTPhthalimide-2	ASR-T-02	Alamar	>6.25	0	-
5c	CTPhthalimide-3	ASR-T-03	Alamar	>6.25	3	-
5d	CTPhthalimide-4	ASR-T-04	Alamar	>6.25	0	-
5e	CTPhthalimide-5	ASR-T-05	Alamar	>6.25	33	-
5f	CTPhthalimide-6	ASR-T-06	Alamar	>6.25	29	-
5g	CTPhthalimide-7	ASR-T-07	Alamar	>6.25	12	-

All compounds are initially screened against *Mycobacterium tuberculosis* strain H37Rv at the single concentration, 6.25 μg/mL. Please note the column labeled % Inhibition. Compounds are considered active in the primary screen if, at this concentration, inhibition ≥ 90%. Activity is designated by a **+** in the column labeled Activity.

The data contains primary assay results only over a broad time period. Compounds 5e, 5f showed moderate inhibition found in preliminary assay results. Compounds 5a, 5b, 5c, 5d, 5g showed less/no inhibition during the

preliminary screening for the anti-TB screening. Further levels of screening are currently under progress at TAACF, Alabama, U.S.A.

b) Anti-Microbial Screening:

The synthesized compounds were evaluated for *in vitro* antibacterial activity against various Gram-positive and Gram-negative bacteria by disc diffusion method.[26] All the synthesized compounds were evaluated for their antibacterial activity, compounds 5d and 5g possessed very significant activity against Gram-positive and Gram-negative bacteria and compared with that of the standard (Ciprofloxacin 50 µg/mL).

The minimum inhibitory concentration of the synthesized compounds 5a-g were determined by agar streak dilution method. The minimum inhibitory concentration (MIC) of the synthesized compounds against Gram-positive and Gram-negative bacteria was presented in Table 4. All the compounds posses potent to moderately potent activity against Gram positive and Gram negative bacteria.

Table 4. Minimum inhibitory concentration of synthesized compounds against gram negative and gram-positive bacteria:

No	Compound	Minimum inhibitory concentration			
		Microorganism			
		***Staphylococcus aureus* ATCC9144**	***Bacillus cerceus* ATCC11778**	***Escherichia coli* mutant ATCC25922**	***Klebsiella pneumoniae* ATCC29665**
1	5a	45 µg	44 µg	44 µg	44 µg
2	5b	46 µg	45 µg	44 µg	45 µg
3	5c	44 µg	43 µg	44 µg	45 µg
4	5d	42 µg	41 µg	41 µg	42 µg
5	5e	44 µg	43 µg	44 µg	45 µg
6.	5f	43 µg	43 µg	43 µg	45 µg
7.	5g	40 µg	41 µg	42 µg	41 µg

[a]Size of the inhibition zone by disk diffusion method, control (DMF)=no activity.

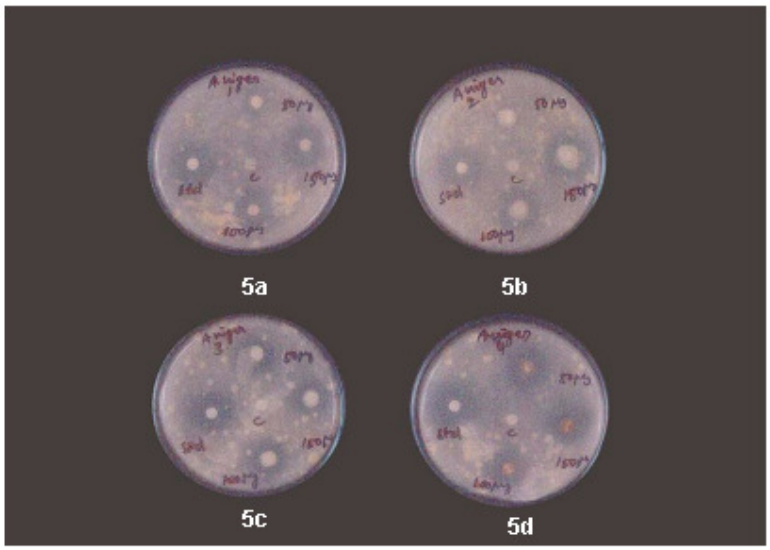
All the synthesized compounds (5a-g) were evaluated for their antifungal activity against *Candida albicans* and *Aspergillus niger* and compared with that of the standard (Ketaconazole) at 50 µg/mL. Table 5 presents the minimum inhibitory concentration (MIC) of the synthesized compounds against *Candida albicans* and *Aspergillus niger*.

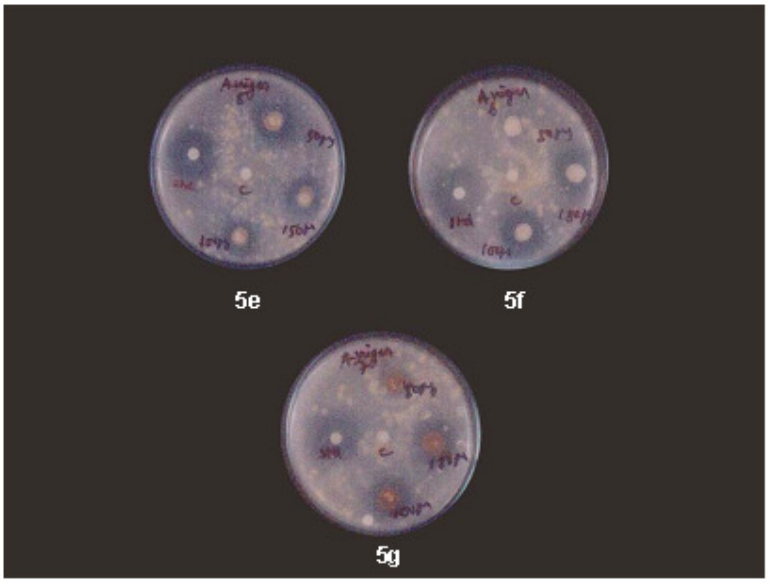
Table 5. Minimum inhibitory concentration of synthesized compounds against Candida albicans and Aspergillus niger:

S.No.	Compounds	Minimum inhibitory concentration (µg/ml)	
		Microorganism	
		Aspergillus niger **ATCC 9020**	***Candida albicans*** **ATTC 2091**
1.	5a	44 µg	43 µg
2.	5b	43 µg	44 µg
3.	5c	43 µg	45 µg
4.	5d	40 µg	41 µg
5.	5e	45 µg	44 µg
6.	5f	45 µg	45 µg
7.	5g	41 µg	42 µg

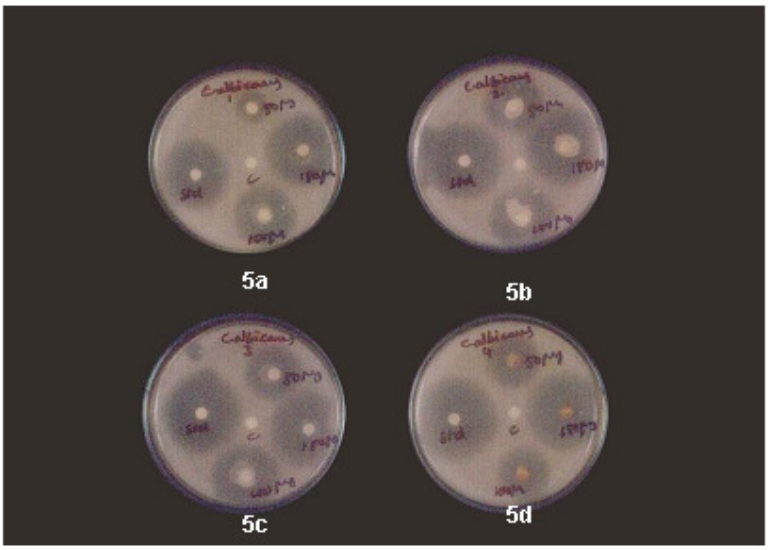
[a]Size of the inhibition zone by disk diffusion method, control (DMF)=no activity.

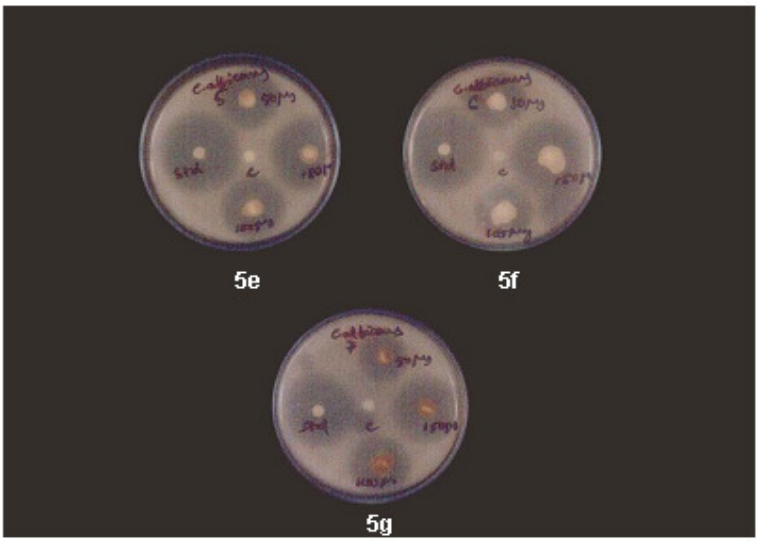
Zone of inhibition of synthesized compounds against *Aspergillus niger*



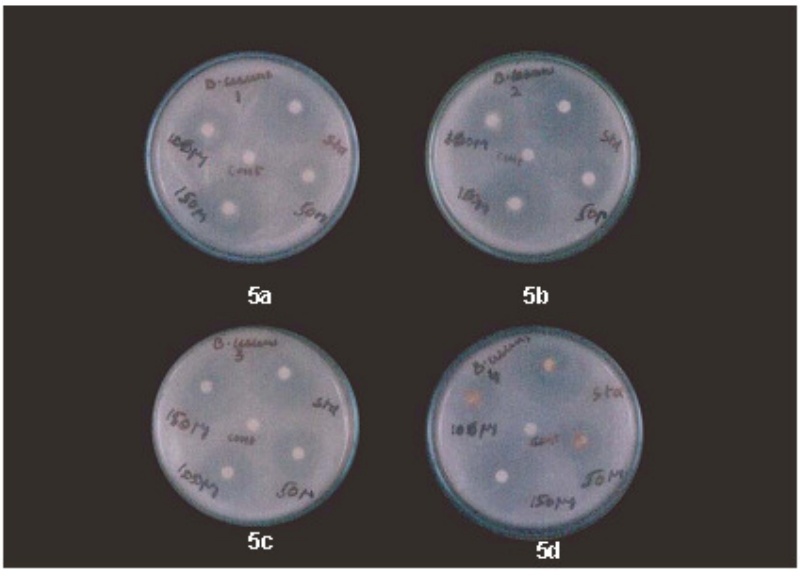


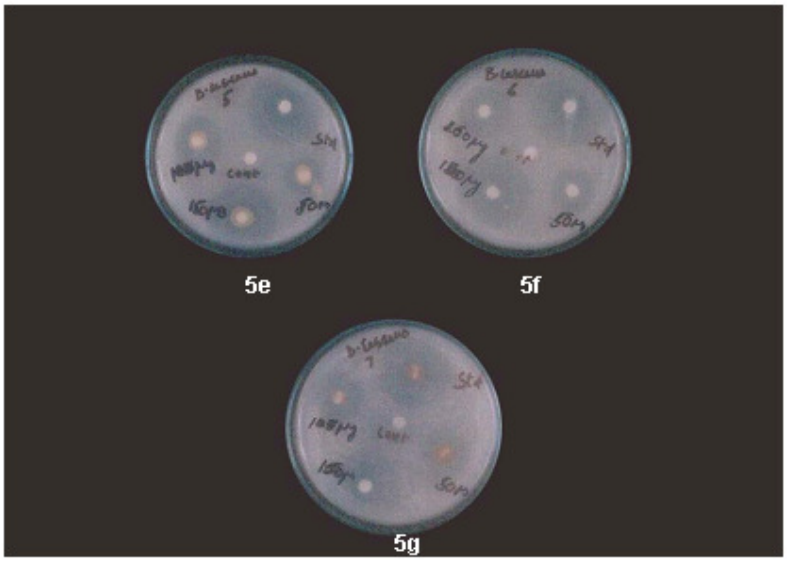
Zone of inhibition of synthesized compounds against *Candida albicans*





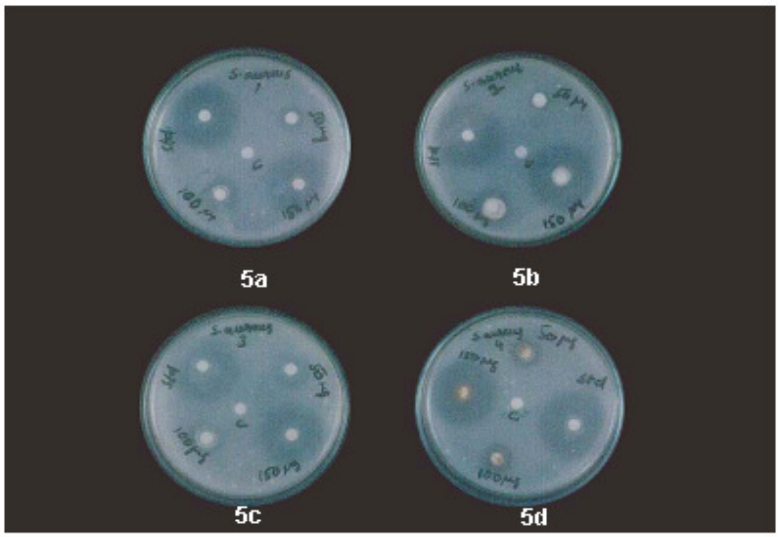
Zone of inhibition of synthesized compounds against *Bacillus cereus*

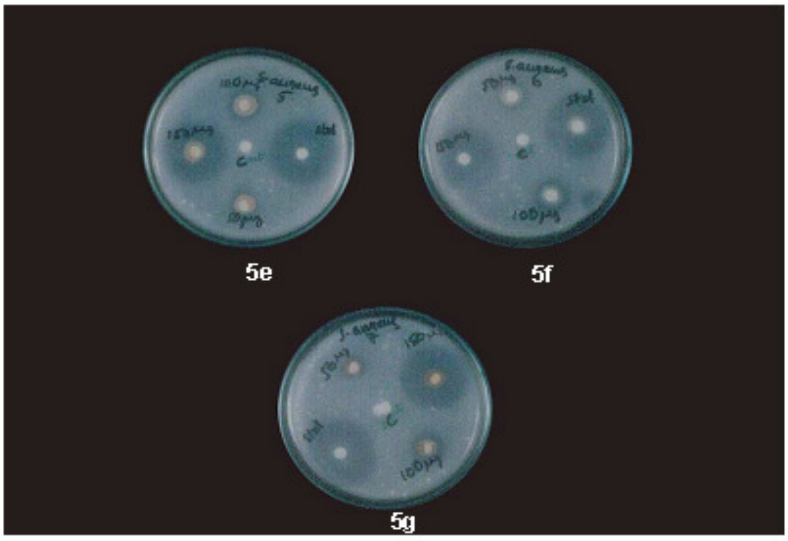




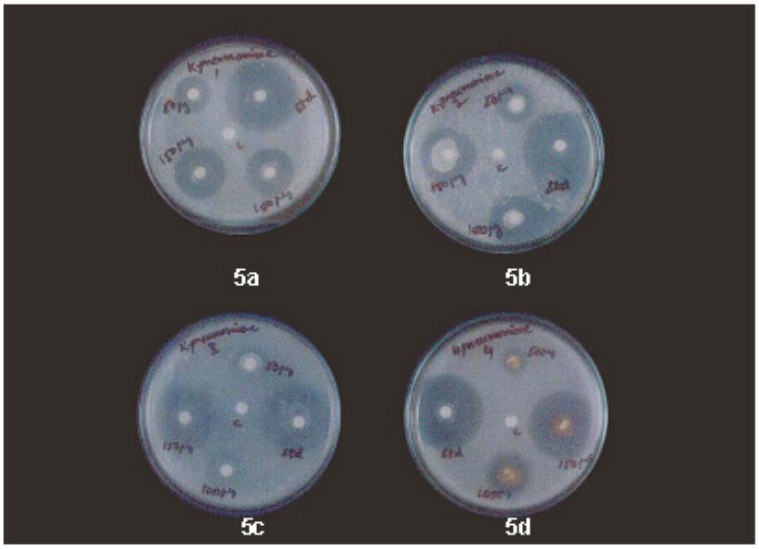
Zone of inhibition of synthesized compounds against

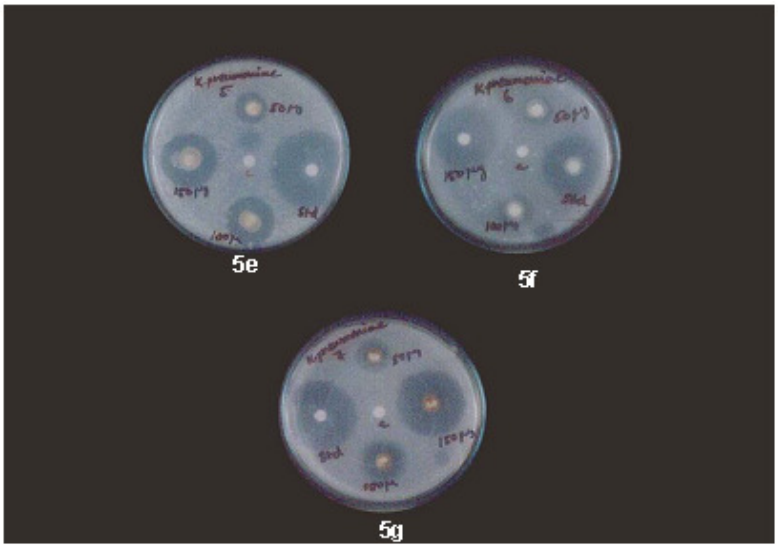
Staphylococcus aureus





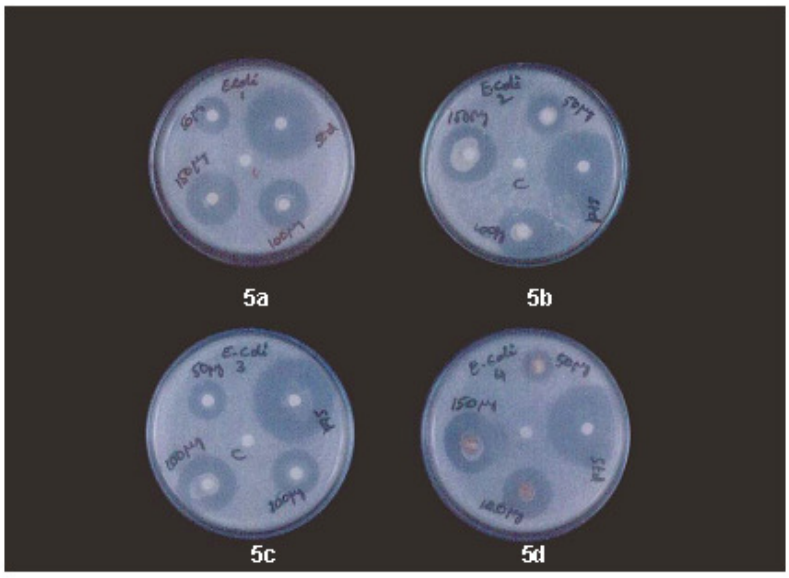
Zone of inhibition of synthesized compounds against *K.pneumonia*

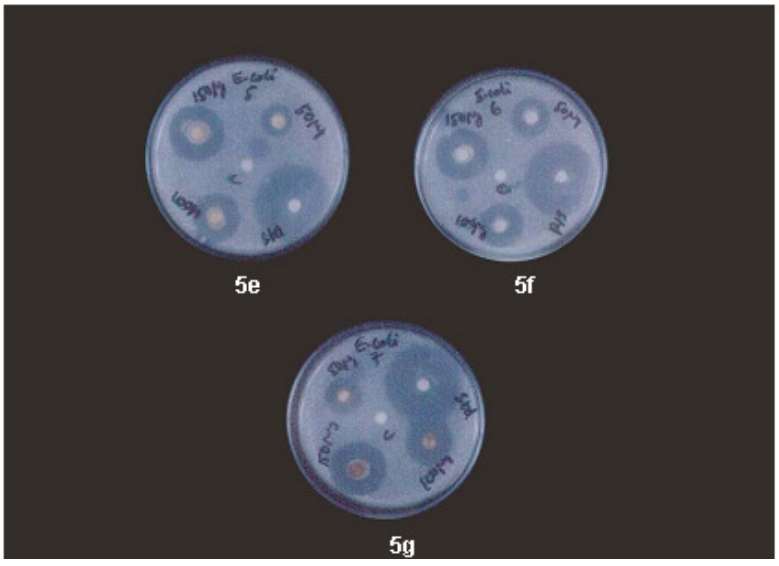




Zone of inhibition of synthesized compounds against

Escherichia coli





1.1.6 CONCLUSION

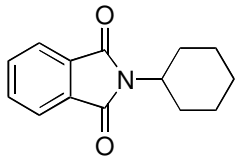
The chemistry of phthalimides is such a vast experience to travel in the sense, the very important scaffold in heterocyclic chemistry not only is used as primary amine protecting groups which are extensively documented in the chemical literature, especially for α–amino acids, but also in the pharmaceutical chemistry as depicted above. The preparation strategy for the synthesis of divergent phthalimides including novel N-phthaloyl linked 3-thiazolo substituted coumarines which have been studied for anti-T.B screening and anti-microbial studies were also presented with sufficient spectral and activity data as well.

1.1.7 EXPERIMENTAL SECTION

Phthalic anhydride (1 mmol) and corresponding amine (1.1 mmol) were added to methanol (2 mL). The reaction mixture was heated on water bath at 50-60 ^{0}C for the time shown in Tables 1 and 2. For the completion of reaction, added catalytic amount of 10% aq. NaOH solution for the cyclization of the formed N-phthalamic acids. The mixture was left at the room temperature for overnight and upon decanting the filtrate, resultant products are formed as crude product, which was further purified by recrystallization to give the corresponding pure N-alkyl or N-arylimide (3a-t, Table 1 and 5a-g, Table 2).[27]

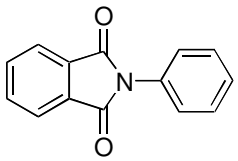
Spectral data for the prepared compounds (3a-t, Table 1):

1. 2-Cyclohexylisoindoline-1,3-dione (3a):



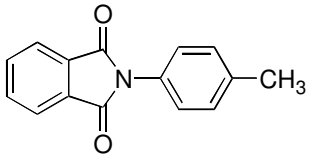
White solid, m.p: 169-171 ^{o}C; IR (KBr): 1770 (m, ν C=O), 1707 (s,ν C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23-1.39 (m, 3 H), 1.68 (d, *J* = 8 Hz, 3 H), 1.83 (d, *J* = 8 Hz, 2 H), 2.18 (d, q, J_1 = 12 Hz, J_2 = 3 Hz, 2 H), 4.08 (t, t, J_1 = 12 Hz, *J*2= 3.5 Hz, 1 H), 7.66 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 7.79 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2H); MS (EI): *m/z* 229 (M^+).

2. 2-Phenylisoindoline-1,3-dione (3b):



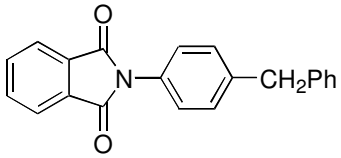
White solid, m.p: 208-210 ^{o}C; IR (KBr): 1732 (m, ν C=O), 1698 (s, ν C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.43 (m, 3 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.78 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 7.95 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.8, 126.6, 128.1, 129.1, 131.8, 134.4, 167.3; MS (EI): *m/z* 223 (M^+).

3. **2-*p*-Tolylisoindoline-1,3-dione (3c):**



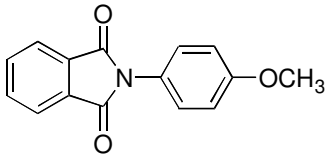
White solid, m.p: 207-209 ^{o}C; IR (KBr): 1746 (m, ν C=O), 1716 (s, ν C=O) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.39 (s, 3 H), 7.29 (s, 4 H), 7.76 (d, d, J_1 =6 Hz, J_2 = 3 Hz, 2 H), 7.93 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H); MS (EI): *m/z* 237 (M^+).

4. **2-Benzylisoindoline-1,3-dione (3d):**



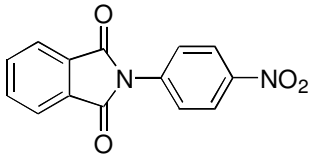
White solid, m.p: 113-115 ^{o}C; IR (KBr): 1770 (m, νC=O), 1702 (s, ν C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.83 (s, 2 H), 7.25 (t, J = 6 Hz, 1 H), 7.31 (t, J = 6 Hz, 4 H), 7.42 (d, J = 6 Hz, 4 H), 7.69 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H) , 7.83 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2H); MS (EI): *m/z* 77, 104, 208, 219, 237, 313.

5. **2-(4-Methoxyphenyl)isoindoline-1,3-dione (3e):**



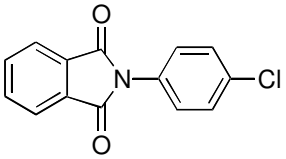
White solid, m.p: 143-145 ^{o}C; IR (KBr): 1704 (s, ν C=O) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ 3.83 (s, 3 H), 7.00 (d, J = 9 Hz, 2 H), 7.31 (d, J = 9 Hz, 2H), 7.76 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 7.93 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H); MS (EI): *m/z* 253 (M^+).

6. 2-(4-Nitrophenyl)isoindoline-1,3-dione (3f):



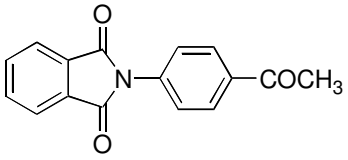
White solid, m.p: 250-252 ^{o}C; IR (KBr): 1731 (s, νC=O), 1715 (s, νC=O), 1520 (s, ν N=O), 1350 (s, ν N=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* =9 Hz, 2 H), 7.83 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 7.99 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 8.36 (d, *J* = 9 Hz, 2 H); MS (EI): *m/z* 268 (M^+).

7. 2-(4-Chlorophenyl)isoindoline-1,3-dione (3g):



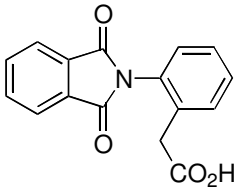
White solid, m.p: 194-196 ^{o}C; IR (KBr): 1716 (m, ν C=O), 1699 (s, ν C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J* = 9 Hz, 2 H), 7.46 (d, *J* = 9 Hz, 2H), 7.79 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 7.94 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H); MS (EI): *m/z* 257 (M^+).

8. 2-(4-Acetlyphenyl)isoindoline-1,3-dione (3h):



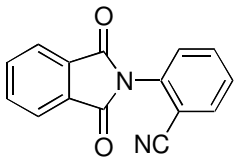
White solid, m.p: 245-247 ^{o}C; IR (KBr): 1748 (m, ν C=O), 1732 (m, ν C=O), 1716 (s, ν C=O), 1683 (s, ν C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3 H), 7.61 (d, *J* = 9 Hz, 2 H), 7.81 (d, d, J_1 = 6 Hz, J_2 = 3 Hz, 2 H), 7.97 (d, d, J_1 = 6 Hz, J_2 =3 Hz, 2 H), 8.09 (d, *J* = 9 Hz, 2 H); MS (EI): *m/z* 265 (M^+).

9. 2-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)phenyl]acetic acid (3i):



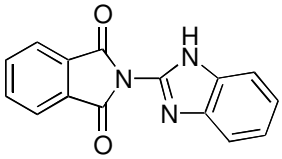
White solid, m.p: 221-223 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61 (s, 2H, CH_2), 7.33-7.45 (m, 4H), 7.80-7.85 (m, 2H), 7.92-7.97 (m, 2H); MS (EI): *m/z* 281 (M^+).

10. 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)benzonitrile (3j):



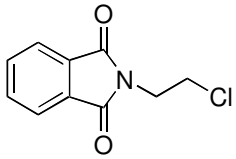
White solid, m.p: 198-199 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (dd, 1H), 7.43-7.62 (m, 3H), 7.77-7.89 (m, 2H), 7.99-8.05 (m, 2H); MS (EI): *m/z* 51, 77, 105,219, 248.

11. 2-(1*H*-benzo[*d*]imidazol-2-yl)-1,3-isoindolinedione (3k):



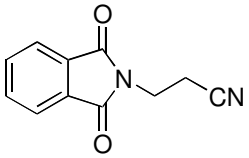
White solid, m.p: 235-237 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01-7.32 (m, 4H), 7.78-8.05 (m, 4H); MS (EI): *m/z* 50, 77, 105,124,149, 160, 263.

12. 2-(2-chloroethyl)-1,3-isoindolinedione (3l):



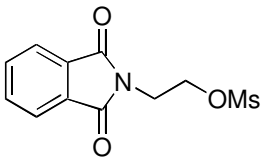
White solid, mp: 223-225 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73-3.77 (t, 2H), 4.00- 4.05 (t, 2H), 7.72-7.75 (m, 2H), 7.85-7.89 (m, 2H); MS (EI): *m/z* 209 (M^+).

13. 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl cyanide (3m):



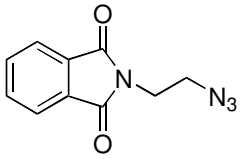
White solid, m.p: 248-250 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77-2.84 (t, 2H), 3.98-4.05 (t, 2H), 7.74-7.78 (m, 2H), 7.87-7.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 134.37, 134.06, 131.34, 123.57, 123.26, 116.85, 33.45, 17.10; MS (EI): *m/z* 200 (M^+).

14. 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)ethyl methyl sulfite (3n):



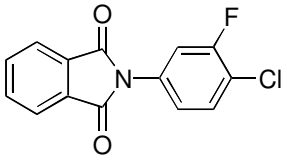
White solid, m.p: 165-167 ^{o}C; IR (KBr): ν 1770, 1702, 1347, 1310, 1178, 987 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 3H), 4.00-4.04 (t, 2H), 4.44-4.47 (t, 2H), 7.72-7.75 (m, 2H), 7.85-7.88 (m, 2H); MS (EI): *m/z* 269, 258, 191, 174, 161, 142, 133, 105, 77.

15. 2-(2-azidoethyl)-1,3-isoindolinedione (3o):



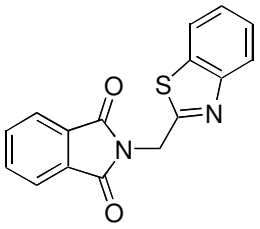
White solid, m.p: 212-214 ^{o}C; IR (KBr): ν 2110, 1774, 1713, 1614, 1395, 1021, 719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.54-3.61 (t, 2H), 3.85-3.91 (m, 2H), 7.67-7.77 (m, 2H), 7.85-7.90 (m, 2H); MS (EI): *m/z* 216 (M^+).

16. 2-(4-chloro-3-fluorophenyl)-1,3-isoindolinedione (3p):



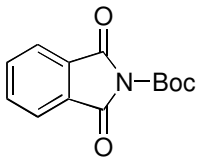
White solid, m.p: 278-279 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.28 (dd, 1H), 7.33-7.40 (m, 1H), 7.55-7.60 (dd, 1H), 7.78-7.82 (m, 2H), 7.89-7.98 (m, 2H); MS (EI): *m/z* 275 (M^+).

17. 2-(1,3-benzothiazol-2-ylmethyl)-1,3-isoindolinedione (3q):



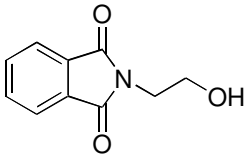
White solid, m.p: >300 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.28 (s, 2H), 7.07-7.47 (m, 4H), 7.74-7.81 (m, 2H), 7.89-8.03 (m, 2H); MS (EI): *m/z* 294 (M^+).

18. *tert*-butyl 1,3-dioxo-2-isoindolinecarboxylate (3r):



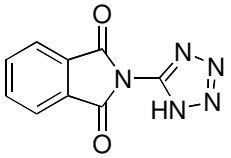
White solid, m.p: 176-177 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 9H), 7.72-7.78 (m, 2H), 7.88-7.96 (m, 2H); MS (EI): *m/z* 247 (M^+).

19. 2-(2-hydroxyethyl)-1,3-isoindolinedione (3s):



White crystalline solid, m.p: 126-128 ^{0}C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.96-8.00 (m, 2H), 8.05-8.08 (m, 2H), 3.87-3.98 (m, 4H). IR (KBr) cm^{-1}: 3472, 1767, 1697, 1428, 1057, 725. MS (EI): *m/z* (M^+): 77, 105, 148, 160, 191.

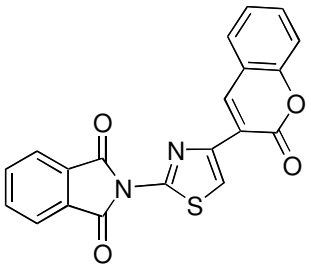
20. 2-(1*H*-1,2,3,4-tetraazol-5-yl)-1,3-isoindolinedione (3t):



White solid, m.p: 234-235 ^{o}C; IR (KBr): ν 3285, 1801, 1778, 1695, 1621, 1367, 1067, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (br s, 1H, NH), 7.46-7.58 (m, 2H), 7.98-6.10 (m, 2H); MS (EI): *m/z* (M^+): 215.

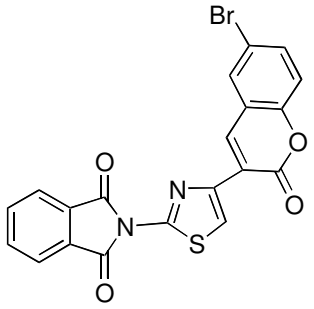
Spectral data for the prepared compounds (5a-g, Table 2):

1. 2-[4-(2-oxo-2*H*-3-chromenyl)-1,3-thiazol-2-yl]-1,3-isoindolinedione (Entry 5a):



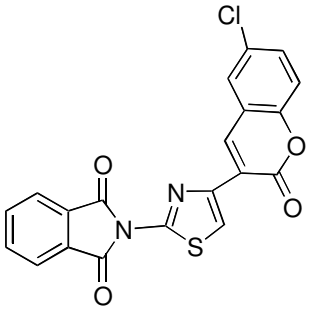
Pale green solid, m.p: 212-214 ^{0}C; IR (KBr): ν 3087, 1793, 1731, 1627, 1478, 1343, 1084, 1001, 783, 711 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.35-7.46 (m, 4H), 7.52-7.65 (m, 3H), 7.99-8.05 (dd, 2H), 8.17 (s, 1H). MS (FAB): *m/z* 55, 77, 89, 107, 137, 154, 176, 289, 307, 329, 375 $(M+H)^+$.

2. **2-[4-(6-bromo-2-oxo-2*H*-3-chromenyl)-1,3-thiazol-2-yl]-1,3-isoindolinedione (Entry 5b):**



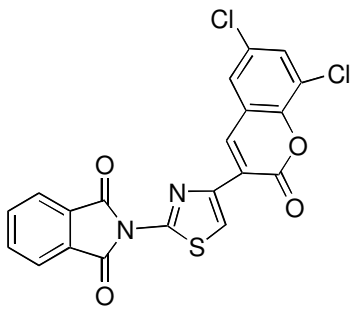
Yellow solid, m.p: 278-280 ^{0}C; IR (KBr): ν 3074, 1793, 1727, 1338, 1096, 784, 711, 592 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.40-7.44 (d, 3H), 7.59-7.85 (m, 3H), 7.98-8.23 (m, 2H), 8.48 (s, 1H). MS (FAB): *m/z* 57, 73, 108, 147, 207, 221, 239, 281, 327, 454 $(M+H)^+$.

3. **2-[4-(6-chloro-2-oxo-2*H*-3-chromenyl)-1,3-thiazol-2-yl]-1,3-isoindolinedione (Entry 5c):**



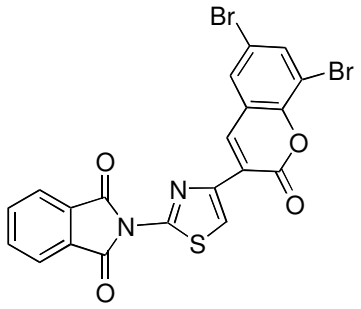
Light yellow solid, m.p: 252-254 ^{0}C; IR (KBr): ν 3088, 1768, 1708, 1462, 1301, 1108, 1046, 728, 630, 538 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.45-7.52 (d, 3H), 7.65-7.90 (m, 3H), 8.01-8.25 (m, 2H), 8.44 (s, 1H). MS (FAB): *m/z* 65, 76, 104, 148, 149, 232, 249, 347, 409 $(M+H)^+$.

4. **2-[4-(5,7-dichloro-2-oxo-2*H*-3-chromenyl)-1,3-thiazol-2-yl]-1,3-isoindolinedione (Entry 5d):**



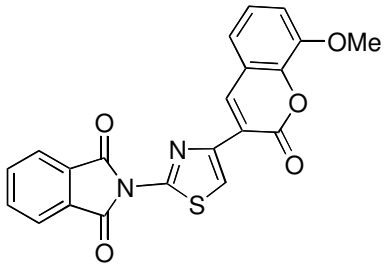
Yellow solid, m.p: 238-240 ^{0}C; IR (KBr): ν 3067, 1766, 1712, 1458, 1402, 1276, 1099, 1054, 732, 624, 542 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.58 (s, 1H), 7.92-8.25 (m, 4H), 8.38-8.55 (d, 2H), 8.65 (s, 1H). MS (FAB): *m/z* 55, 67, 77, 95, 107, 120, 136, 154, 279, 289, 307, 339, 369, 409, 427, 444 $(M+H)^+$.

5. **2-[4-(5,7-dibromo-2-oxo-2*H*-3-chromenyl)-1,3-thiazol-2-yl]-1,3 isoindolinedione (Entry 5e):**



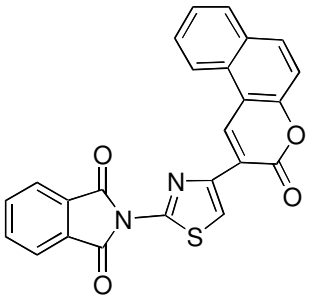
Yellow solid, m.p: >300 ^{0}C; IR (KBr): ν 3056, 1772, 1732, 1368, 1209, 1097, 1104, 962, 638, 458 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.55 (s, 1H), 7.89-8.30 (m, 4H), 8.41-8.52 (d, 2H), 8.60 (s, 1H). MS (FAB): *m/z* 55, 81, 95, 120, 154, 307, 403, 445, 499, 533 $(M+H)^+$.

6. **2-[4-(8-methoxy-2-oxo-2*H*-3-chromenyl)-1,3-thiazol-2-yl]-1,3-isoindolinedione (Entry 5f):**



Yellow solid, m.p: 202-203 ^{0}C; IR (KBr): ν 3027, 2985, 1767, 1721, 1656, 1493, 1377, 1207, 1089, 939, 642 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 4.04 (s, 3H), 7.39-7.60 (m, 3H), 8.05-8.22 (m, 3H), 8.55-8.65 (d, 2H), 8.82 (s, 1H). MS (FAB): *m/z* 55, 91, 121, 136, 154, 271, 305, 344, 378, 405 $(M+H)^+$.

7. **2-[4-(3-oxo-3*H*-benzo[*f*]chromen-2-yl)-1,3-thiazol-2-yl]-1,3-isoindolinedione(Entry 5g):**



Green solid, m.p: 262-263 ^{0}C; IR (KBr): ν 3083, 1774, 1726, 1624, 1555, 1209, 1099, 995, 783, 741 cm^{-1}; ^{1}H NMR (300 MHz, DMSO): δ 7.46-7.62 (m, 3H), 7.75-7.83 (m, 3H), 8.01-8.22 (m, 4H), 8.65 (d, 1H), 9.40 (d, 1H). MS (FAB): *m/z* 55, 81, 107, 154, 295, 337, 425 (M +H)$^{+}$.

1.1.8 REFERENCES

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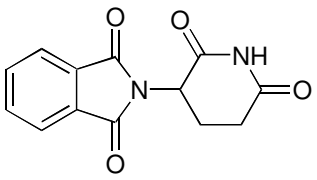
2.1.1. INTRODUCTION

Thalidomide (CAS number 50-35-1), (N-α-phthalimido glutarimide or 2-(2,6-dioxo-3-piperidyl) isoindoline-l,3-dione) (Figure 1) is a glutamic acid derivative that was first introduced as a nontoxic sedative and safe alternative to barbiturates (non-barbiturate hypnotic), in the late 1950s,[1] by Chemie Grunenthal in Germany under the brand name of Contergan. Its notorious human teratogenic effects: babies exposed to thalidomide *in utero* during the first 34-50 days of pregnancy were born with severe life-threatening birth defects, i.e. severe congenital abnormalities in babies born to mothers using it for morning sickness and phocomelia led to its withdrawal in 1963 (Figure 2).[2]

Figure 1



Thalidomide (1)

Thalidomide: from tragedy to promise

*Thalidomide (**1**) has a relatively simple chemical architecture, but exhibits a multitude of physiological activities (as multitarget drug) on mammals. Despite its unfortunate history, thalidomide has attracted scientific interest again because of its recently discovered action against inflammatory diseases and cancer. Interest in thalidomide was initially rekindled in the mid-1960s after the approval of FDA, United States in 1998, by its effect on erythema nodosum leprosum (ENL).[3] That such an infamous drug should become available again gives an indication of the degree to which it has been rehabilitated. When old drugs find new, unexpected uses, there is usually a considerable element of serpendity involved-a chance observation leads to a completely new indication for the drug. So it has been with thalidomide, but it would have taken amazing perception to have predicted in the 1960s. Thalidomide is probably the most infamous drug ever to have been brought to market.*

Figure 2 ('**Thalidomide Babies**'*)*

Its broad range of biological activities stems from its ability to moderate cytokine action in cancer and inflammatory diseases. Early studies examined its anxiolytic, mild hypnotic, antiemetic, and adjuvant analgesic properties. Subsequently, thalidomide was found to be highly effective in managing the cutaneous manifestations of leprosy, being superior to Aspirin in controlling leprosy-associated fever. Recent research has shown promising results with thalidomide in patients with myeloma, myelodysplastic syndrome, a variety of infectious diseases, autoimmune diseases, cancer, and progressive body weight loss related to advanced cancer and AIDS. Among the recent discoveries in cancer therapeutics, the revival of thalidomide ranks as one of the most surprising and intriguing. Thalidomide differs from most other anti-cancer agents because of its low level of toxicity (except teratogenicity).

Over 12,000 affected children were born with skeletal abnormalities, an event that led to a major reform of drug approval procedures in the United States and elsewhere. The basis of these fetal abnormalities is unknown, although the drug has subsequently been found to have a broad range of biological effects on cytokine secretion, immune function, angiogenesis, cell adhesion, and cell proliferation. Which of these mechanisms account for its clinical activities and teratogenic effects remains an unresolved issue.

Recent studies have demonstrated consistent responses in graft-versus-host disease (GVHD) and in cancer, including multiple myeloma, myelodysplasia,

Kaposi's sarcoma, and several other solid tumors such as Behcet's disease, tuberculosis, inflammatory bowel disease, Sjogren's syndrome, rheumatoid arthritis, and other collagen and vascular diseases.[4,5] An abbreviated history of thalidomide is given in Table 1**.**

Table 1. <u>The (re) discovery of thalidomide</u>

Year	Observation
1953	First synthesis by '*Chemie Grunental'* in Germany.
1956	Introduced to market in Germany under the brand name '***Contergan***'.
1957	Introduced to European and Canadian markets as a sleeping aid.
1958	First report on peripheral neuritis in some patients on long-term use.
1960	By this year used widely in Europe, UK and Canada to ameliorate nausea in pregnancy.
1961	First reports about the birth defects and further reports on peripheral neuropathies.
1961	Reports on twelve thousand cases of human fetal abnormalities related to use of thalidomide in pregnant women.
1963	Thalidomide withdrawn from the market.
1964	Reports showing curative effect of thalidomide in patients with erythema nodosum leprosum.
1966	Demonstrated effect against graft-versus-host reaction in animal models.
1980	Immunosuppressive and anti-inflammatory thalidomide analogs identified in preclinical setting.
1986	Thalidomide showed therapeutic response in patients with graft-versus-host disease.
1989	First report on plasma pharmacokinetics and urinary excretion.
1990	Active against pharyngeal and esophageal.ulcerations in Behcet's syndrome.

1991 Inhibits tumor-necrosis factor a production and angiogenes in experimental system.

1992 Inhibition of replication of human immunodeficiency virus type 1 (HIV-1) *in vitro*.

1996 Synthesis of thalidomide analogs and demonstration of their immunosuppressive and anti-inflammatory efficacy.

1998 Food and Drug Administration (FDA) approval for therapeutic use inactivity patients with erythema nodosum leprosum. Activity against HIV-associated Kaposi's sarcoma reported.

1999 Antitumor activity of thalidomide in refractory multiple myeloma and possible activity against various solid malignant tumors. Immuno modulatory effects reported. Clinical testing of analogs started.

Despite the growing interest for this drug and its analogues, we still have only limited data on its metabolism, pharmacology, pharmacokinetics, and mechanism of action.

2.1.2 PHARMACOLOGY

2.1.2.1 Mechanism of Action

Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In patients with erythema nodosum leprosum (ENL) the mechanism of action is not fully understood. Available data from *in vitro* studies and preliminary clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-α (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration. For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with ENL (Figure 3), however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients.

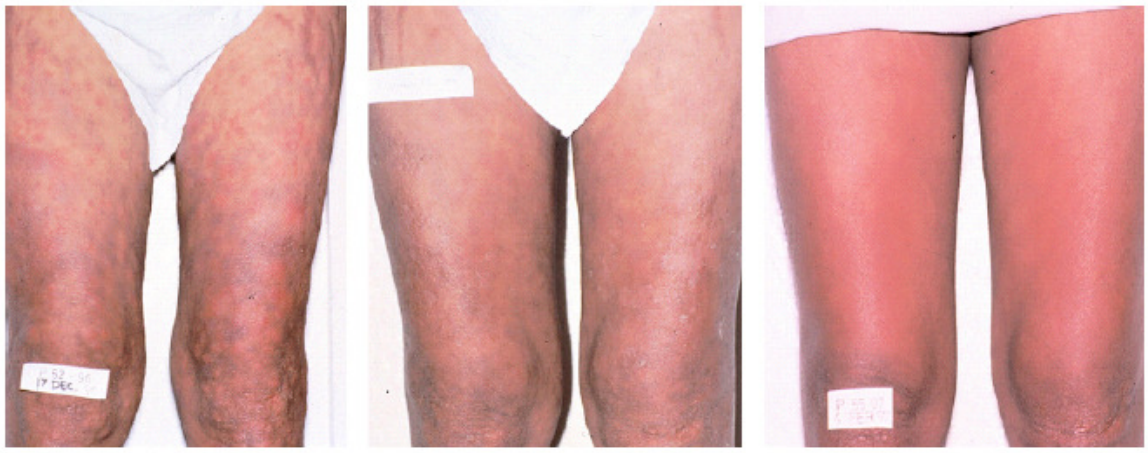


Figure 3

2.1.2.2 Pharmacokinetics and Drug Metabolism

Absorption

The absolute bioavailability of thalidomide from THALOMID® (thalidomide) capsules has not yet been characterized in human subjects due to its poor aqueous solubility. In studies of both healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations (T_{max}) of THALOMID® (thalidomide) ranged from 2.9 to 5.7 hours indicating that THALOMID® (thalidomide) is slowly absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner. This lack of C_{max} dose proportionality, coupled with the observed increase in T_{max} values, suggests that the poor solubility of thalidomide in aqueous media may be hindering the rate of absorption load should be measured after the first and third months of treatment and every 3 months thereafter.

Precautions

The only type of thalidomide exposure known to result in drug-associated birth defects is as a result of direct oral ingestion of thalidomide. Currently no specific data are available regarding the cutaneous absorption or inhalation of thalidomide in women of childbearing potential and whether these exposures may result in any birth defects. Patients should be instructed to not

extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion. If there is contact with non-intact thalidomide capsules or the powder contents, the exposed area should be washed with soap and water.

Thalidomide has been shown to be present in the serum and semen of patients receiving thalidomide. If healthcare providers or other caregivers are exposed to body fluids from patients receiving THALOMID® (thalidomide), appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to THALOMID® (thalidomide) or washing the exposed area with soap and water.

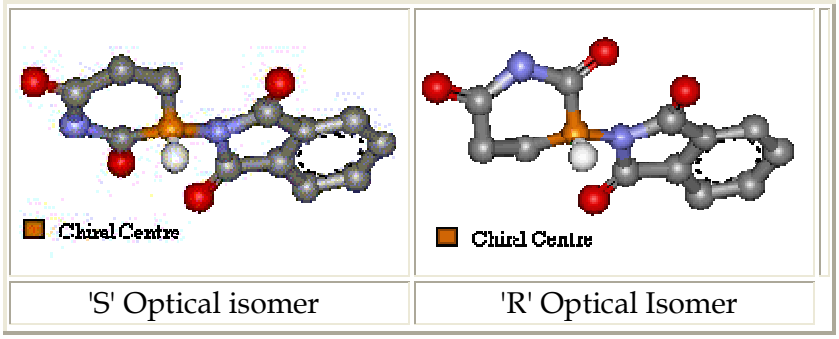
2.1.3 CHIRALITY-STUDY OF MECHANISM OF RACEMIZATION

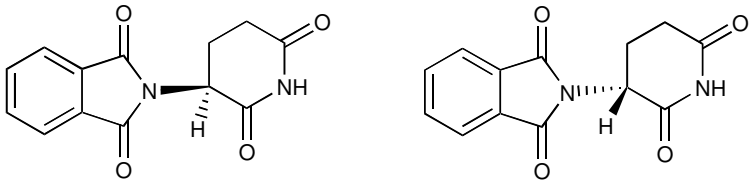
Many chiral drugs must be made with high enantiomeric purity due to toxic activity of the 'wrong' enantiomer. An example of this is thalidomide which is racemic - that is, it contains both left and right handed isomers in equal amounts (Figure 4). One enantiomer is effective against morning sickness, and the other is teratogenic. It should be noted that the enantiomers are converted to each other *in vivo*. That is, if a human is given D-thalidomide or L-thalidomide, both isomers can be found in the serum. Hence, administering only one enantiomer will not prevent the teratogenic effect in humans.

Since thalidomide has a stereogenic carbon atom, it exists as two enantiomers. The diagram to the right shows the molecule without hydrogens. Notice that two of the groups attached to the chiral centre are part of the same ring structure. They are classified as two different groups. Since moving around from the chiral centre the order of atoms is different each way. It is said the chiral atom has two different views around the ring. Laboratory tests after the thalidomide disaster showed that in some animals the 'S' enantiomer was teratogenic but the 'R' isomer was an effective sedative. It is now known that even when a stereo selective sample of thalidomide (only one of the optical isomers) is created, if administered p^H in the body, can cause racemizing. This means that both enantiomers are formed in a roughly

equal mix in the blood. So, even if a drug of only the 'R' isomer had been created, the disaster would not have been averted.

Two Images To Show the Enantiomers Of Thalidomide





S-(-)-Thalidomide

L-(-)-Thalidomide

R-(+)-Thalidomide

D-(+)-Thalidomide

Figure 4

Mechanism for Racemization:

It is a classically quoted example of a drug developed as a racemate in which only one isomer, the S-isomer, carries the negative side effect, teratogenicity.[6a,7] It has been shown that the strongly acidic hydrogen atom at the stereogenic center of thalidomide rapidly epimerizes under physiological conditions at p^H 7.4, 37 ^{0}C, rendering bioassay of enantiomers difficult due to chiral lability *in vitro* and *in vivo*.[7a,15] The reverse reactions operate on an achiral compound and thus produce a racemic mixture of enantiomers (Figure 5).

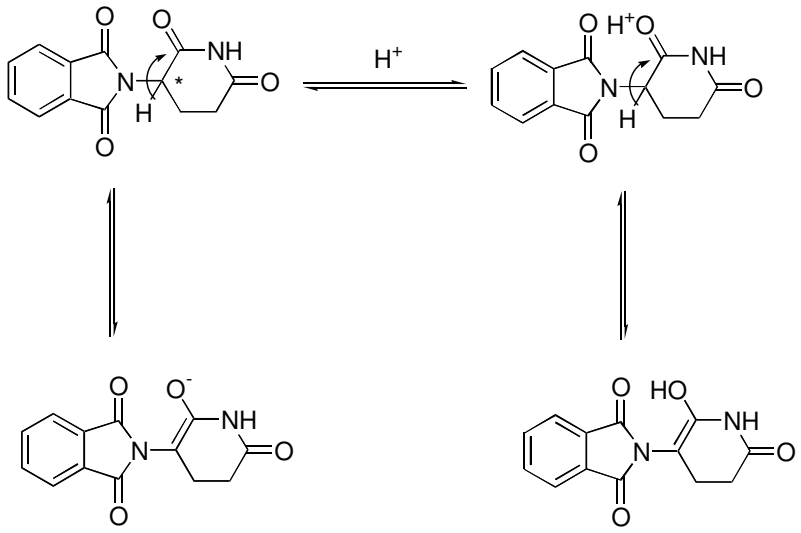


Figure 5

Tests with mice in 1961 suggested that only one enantiomer was teratogenic while the other possessed the therapeutic activity. Unfortunately, subsequent test with rabbits showed that both enantiomers had both activities. In one sense this is not surprising, because it is likely that the same mode of action is operative in both functions (in many cases it seems to be prevention of *angiogenesis*, the development of new blood vessels). In another sense the shared activity seems surprising, because one might expect the enantiomers to interact quite differently (diastereomerically) with the chiral, resolved molecules of nature. The solution of this second riddle is that the enantiomers interconvert (the compound racemizes) under physiological conditions. Thus the drug is being sold as a racemate.

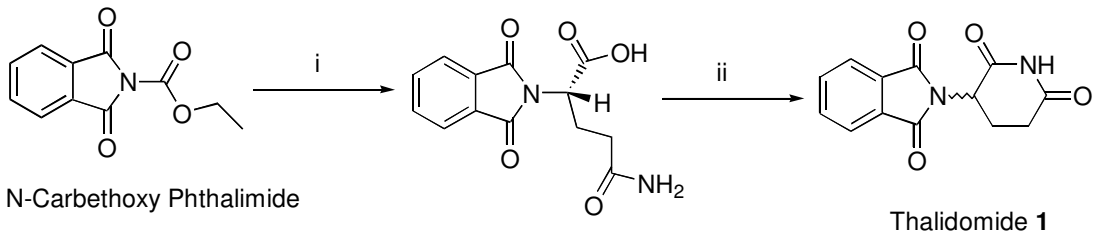
2.1.4 EARLIER APPROACHES

Literature search revealed that there are several reports available on the synthesis of thalidomide (**1**), which are described below.

Muller's Approach-I (1999)[7a]

G.W. Muller *et al.* developed a concise synthesis of thalidomide in a two-step synthesis (Scheme 1). The sequence requires no purifications. Treatment of L-glutamine with N-carbethoxyphthalimide produces N-phthaloyl-L-glutamine. Cyclization of N-phthaloyl-L-glutamine to afford thalidomide is

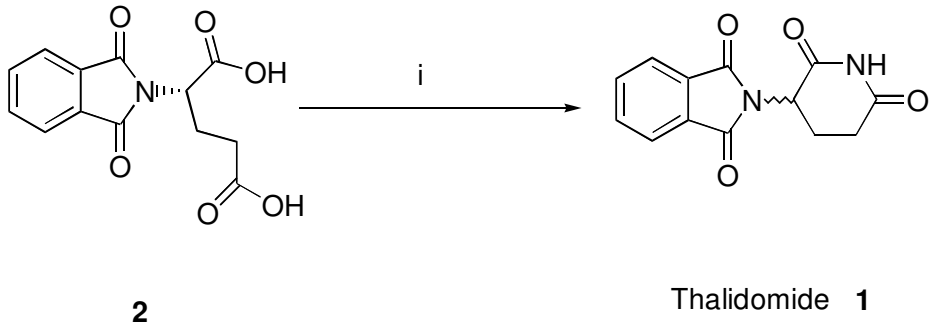
accomplished by treatment with CDI in the presence of a catalytic amount of DMAP.



Scheme 1: (i) a) L-glutamine, Na_2CO_3, b) 4N HCl (aq.); (ii) CDI, DMAP.

Galons's Approach (1999)[7d]

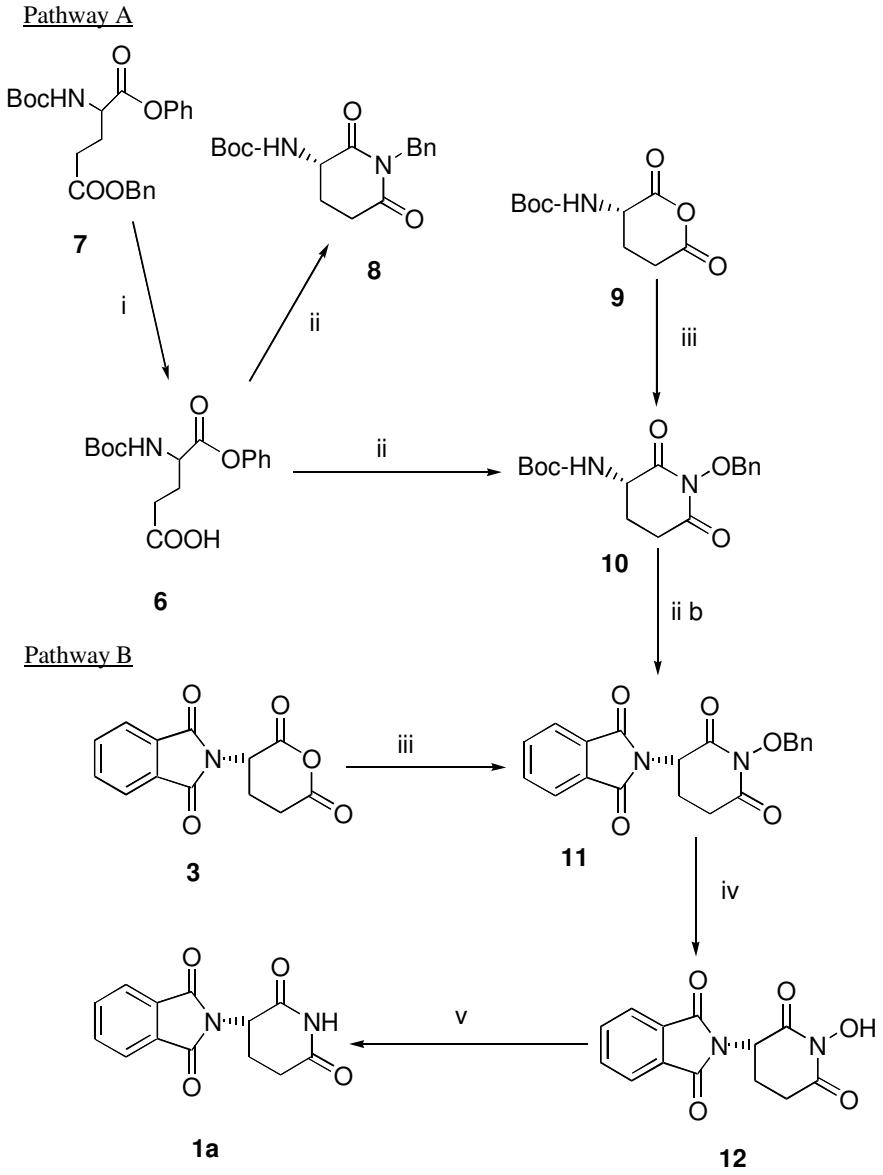
H. Galons *et al.* have provided a single step asymmetric synthesis of thalidomide in which they used trifluroacetamide on reacting with diacids in the presence of N-ethyl-N-dimethyl-aminopropylcarbodiimide and of 1-hydroxybenzotriazole to afford cyclic imides of different ring size (Scheme 2).



Scheme 2: i) CF_3CONH_2, EDCCl, HOB^t.

Robin's Approach (1995)[7c]

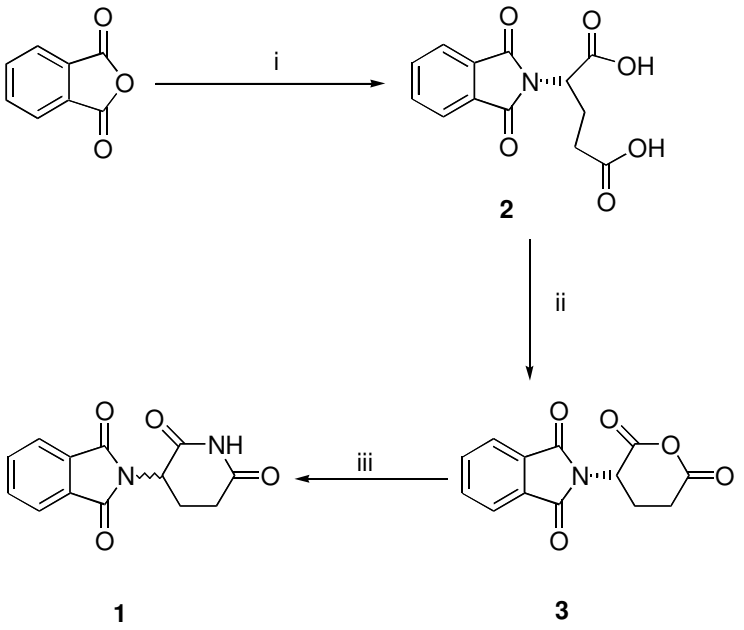
S. Robin *et al.* conveniently reported the second asymmetric synthesis of thalidomide and some of its derivatives (Scheme 3). Benzyloxyamine reacted with Boc-glutamic-α-phenyl ester in the presence of carbodiimide to give Boc-amino-N-benzyloxypiperidinone. Deprotection of the amino group followed by phthaloylation led to N-benzyloxyphthalimide which was then converted into thalidomide.



Scheme 3: (i) a) PhOH, DCC, pyr, EtOAc; b) $BnONH_2$, EDC, HOB^t; ii) a) HCl, gas, DCM; b) phthalic anhydride, Et_3N, THF; (iii) $BnONH_2$, DCC, pyr, DCM; iv) H_2, Pd-C, MeOH; v) $BrCH_2COPh$, Et_3N, CH_3CN, DMAP cat.

Reepmeyer's Approach-I (1987)[8]

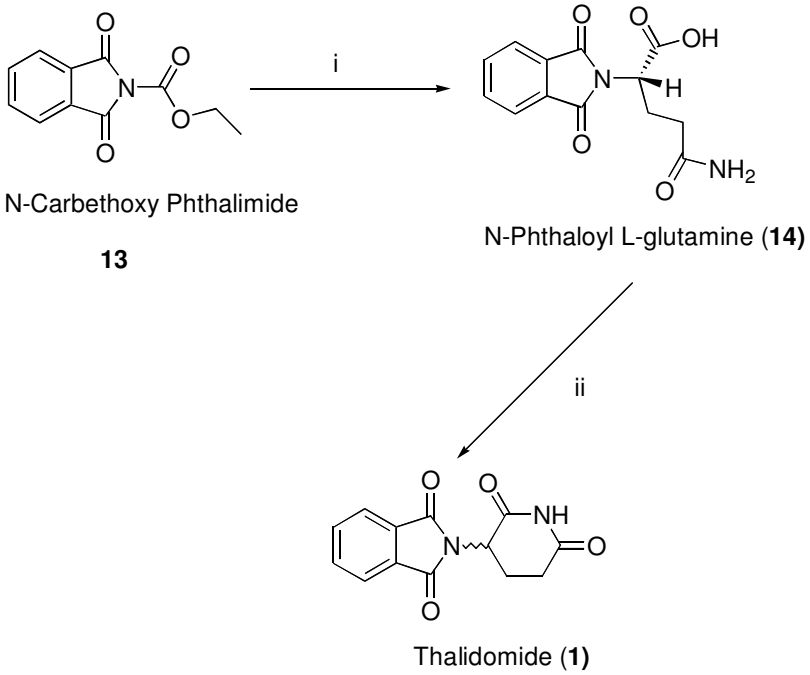
Reepmeyer *et al.* prepared thalidomide traditionally as outlined in Scheme 4. This is a fairly simple three-step sequence. The last step in this synthesis involves a high-temperature melt reaction that afford crude thalidomide requiring multiple recrystallizations.



Scheme 4: (i) L-glutamic acid, pyridine, reflux; (ii) Ac_2O; (iii) urea, melt.

Reepmeyer's Approach-II:[9]

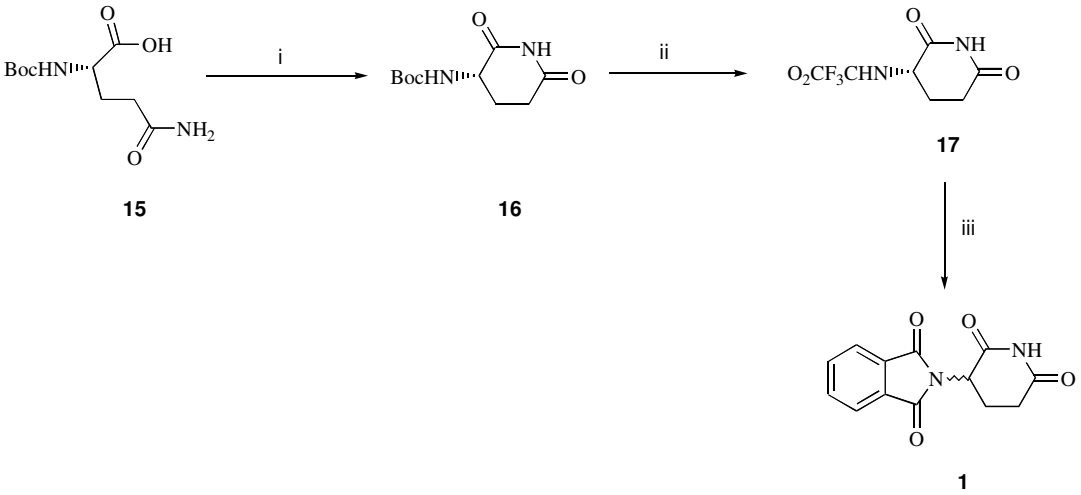
Reepmeyer described an efficient synthesis of R-or S-Thalidomide by the treatment of L-/D-glutamine with N-carbethoxyphthalimide and intramolecular cyclization using the following reagents to furnish the desired drug (Scheme 5).



Scheme 5: i) Na_2CO_3, H_2O; ii) $SOCl_2$, DCM, pyridine, Et_3N, -30 ^{0}C.

Greig's Approach (2002)[10]

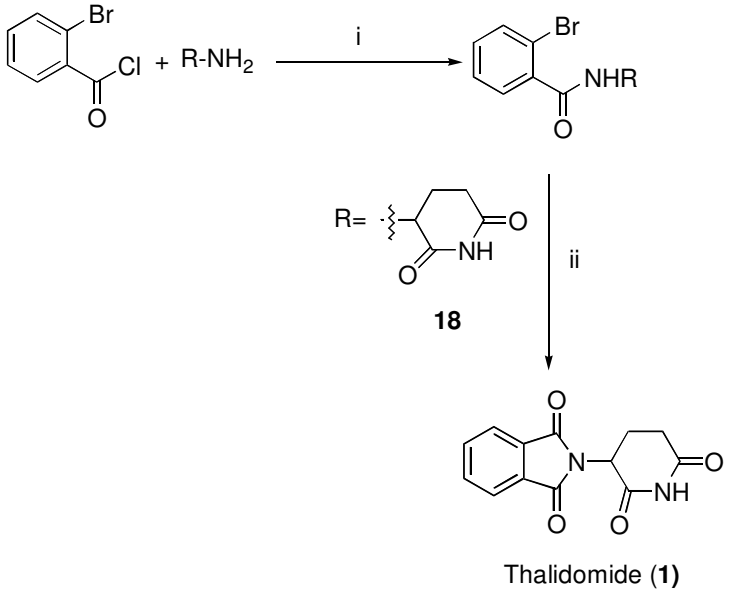
Greig *et al.* reported the synthesis of thalidomide by refluxing *tert*-butoxycarbonyl-L-glutamine with carbonyldiimidazole (CDI) I THF and followed by the shown steps below to furnish thalidomide in 69% yield (Scheme 6).



Scheme 6: i) CDI, THF; ii) CF_3COOH, DCM; iii) phthalic anhydride, Et_3N, THF.

Langstorm's Approach (2001)[7f]

Langstorm *et al.* have reported the synthesis of thalidomide by palladium-mediated carbonylation in presence of CO in THF (Scheme 7).

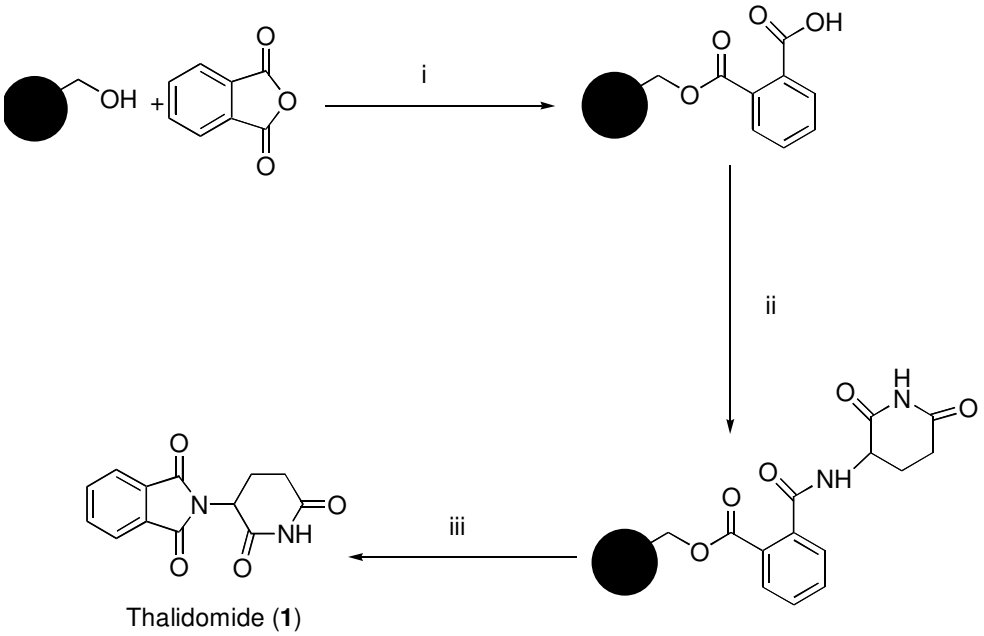


Scheme 7

Scheme 7: i) H_2O-dioxane; ii) $Pd(PPh_3)_4$, CO, THF.

Li's Approach (2002)[7h]

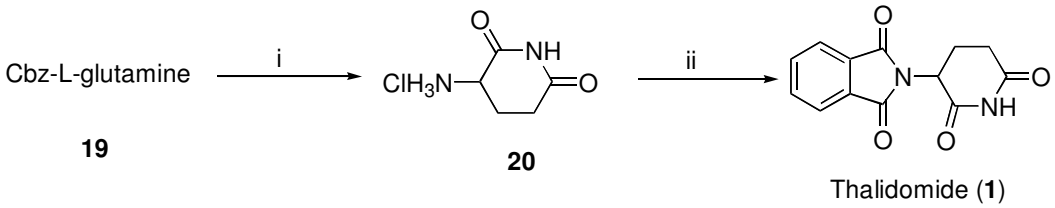
Li, P-K *et al.* have described a novel solid-phase synthesis of thalidomide using a synthetic strategy that involved the coupling of hydroxymethyl polystyrene with phthalic anhydride to form the resin linked acid, followed by reaction with primary amines and acid/base workup (Scheme 8).



Scheme 8: i) Et_3N, DMAP, DMF, RT; ii) DIC, HOB^t, α-amino glutarimide, DMF, RT; iii) 5% TFA, Toluene.

Muller's Approach-II (1999)[7g]

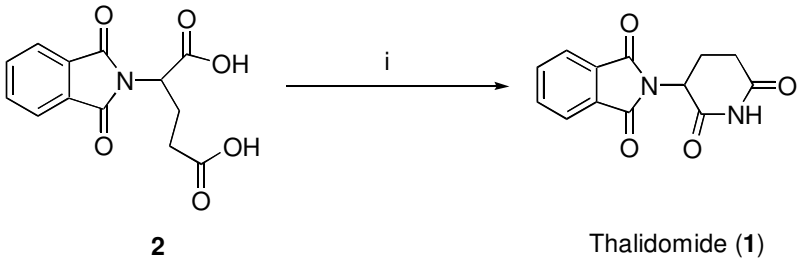
G.W. Muller *et al.* synthesized thalidomide from commercially available Cbz-L-glutamine with CDI in THF affording the Cbz-glutarimide and followed by the steps afforded the corresponding drug (Scheme 9).



Scheme 9: i) a) CDI, THF, reflux, b) H_2, 10% Pd/C, EtOAc, 4N HCl; ii) a) AcOH, reflux, b) 10% Pd/C, acetone.

Seijas Approach (2001)[11]

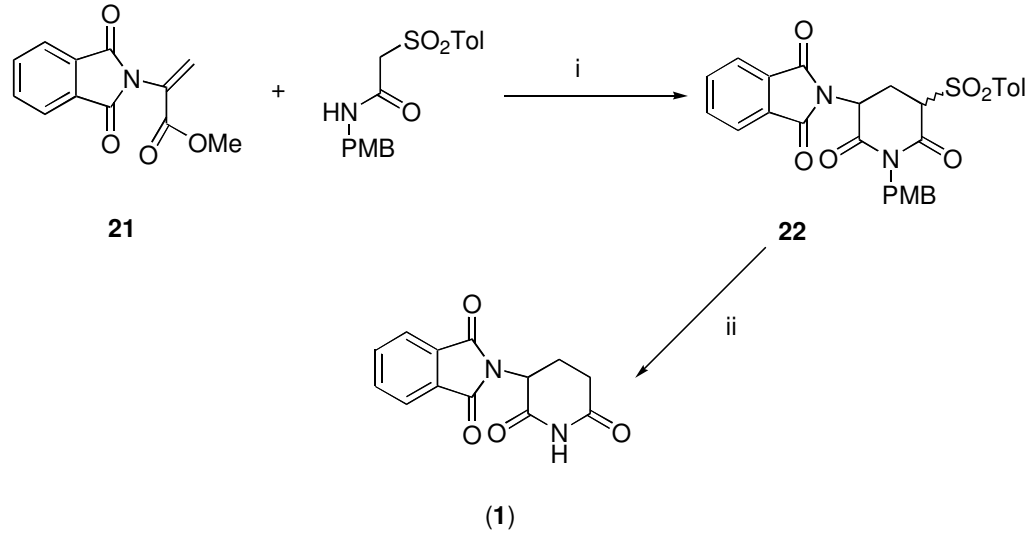
Seijas *et al.* have reported in only one-step using N-phthaloyl L-glutamic acid in high yield by microwave irradiation in the presence of urea or thiourea (Scheme 10).



Scheme 10: i) urea/thiourea, μW, X=O, 63%; X= S, 85%.

Chang's Appraoach-I (2003)[7i]

Chang *et al.* have reported the synthesis of thalidomide and various substituted glutarimides *via* a formal [3+3] cycloaddition strategy (Scheme 11).



Scheme 11: i) NaH; ii) a) 6% Na/Hg, b) CAN, $MeCN_{(aq)}$.

2.1.5 PRESENT WORK

2.1.5.1 Objective

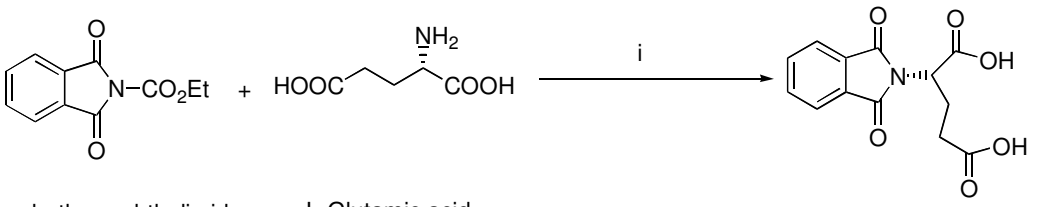
Syntheses of thalidomide have been well documented in the literature.[7-11] Celgene corporation has made significant progress in the synthesis of the drug. Although these synthetic procedures seem straightforward

transformations, they suffer from several drawbacks on the large scale preparation: (1) involving a high-temperature melt reaction requiring multiple recrystallizations[8]; (2) use of costly starting materials/reagents in the steps involved for the preparation; (3) low overall yields. Usually the above syntheses leave as the final step the formation of the glutarimide ring. The conditions employed include the condensation of liquid and/or gas ammonia with generic cyclic anhydrides,[12] the cyclization of an amide-acid with CDI/DMAP,[7a] the reaction of diacid chlorides with lithium nitride,[13] the reaction of a primary and a secondary amide reacted with $AlCl_3$,[14] and the reaction of urea/thiourea with a cyclic anhydride.[7a] These conditions can often cause low yields, by-product formation and longer reaction times. Unfortunately, none of these routes is very practical in terms of industrial scale-up operations.

To address the above difficulties involved in the preparation of thalidomide, better isolation protocols coupled with replacements of costlier reagents such as L-glutamine which is five times costlier than L-glutamic acid, N-phthaloyl DL-glutamic anhydride, CDI (1,1′-carbonyl diimidazole), $Pd(PPh_3)_4/CO$[7f] etc., became the twin objectives of our approach. Considering the newly discovered activity of the drug in treating infectious diseases and being interested in exploring novel routes for the preparation of the phthalimide and arylalkanoic acid derived drugs and analogues, we have successfully developed two novel methods for the synthesis of thalidomide.

2.1.6 RESULTS AND DISCUSSION

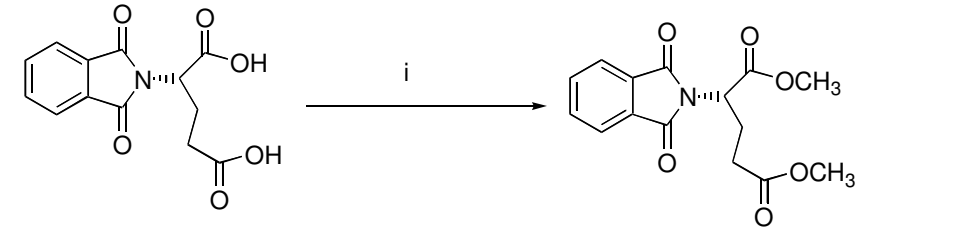
Our initial attempt involved the reaction of L-glutamic acid **23** (L-GA) with a solution of Na_2CO_3 in water and N-carbethoxy phthalimide (**4**) using a standard procedure to furnish N-phthaloyl L-glutamic acid **2** as colourless crystals in 60% yield (Scheme 12).[16]



N-carbethoxy phthalimide **4** + L-Glutamic acid **23** → N-Phthaloyl L-glutamic acid **2**

Scheme 12: i) Na_2CO_3, H_2O, 0 ^{0}C to RT.

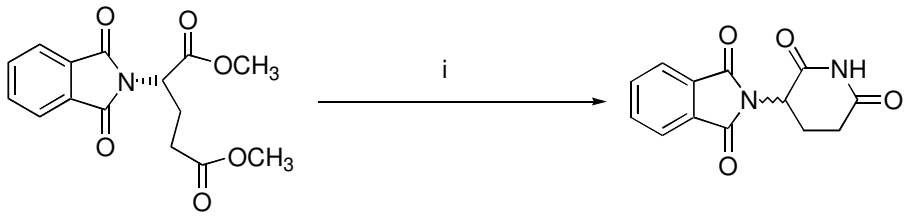
The compound **2** was characterized by the formation of multiplet at δ 5.05-5.18 *Hz* (1H, CH-N) by ^{1}H NMR spectrum and the optical purity of the compound was found to be 94.6%. Treatment of **2** with thionyl chloride in methanol under reflux for 6 h afforded after usual workup afforded N-phthaloyl L-glutamic acid dimethyl ester **24** as a colourless oil in 71% yield (Scheme 13).[17] The esterification was proved by signals at 3.62 (3H, singlet) and 3.73 (3H, singlet) respectively. The characteristic CH-N proton showed a signal at δ 4.91 (dd, *J*=5.0 *Hz*, *J*=9.0 *Hz*, 1H) from the ^{1}H NMR spectrum. The characteristic doublet at 4.91 slightly shifted up field compared to the proton (CH-N) confirmed the formation of **24**. The optical purity of the ester was found to be 97.2% ($[\alpha]^{25}_D$= - 168.8 (c=1.4, $CHCl_3$).



N-Phthaloyl L-glutamic acid **2** → N-Phthaloyl L-glutamic acid dimethyl ester (**24**)

Scheme 13: i) MeOH, $SOCl_2$, reflux.

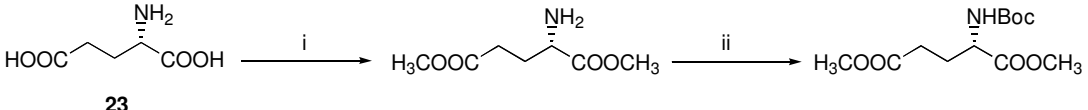
The following key step is based on the formation of the glutarimide ring from glutaric acid diesters by using the $NaNH_2$/liq.NH_3/$Fe(NO_3)_3$ methodology, as evidenced in the previous report by Kinoshita.[18] To our satisfaction, the ester **24** was cyclized to give the desired compound **1** (Scheme 14) in a low yield (1.14 g, 45%).



24 **1**

Scheme 14: i) $Fe(NO_3)_3$, Na/liq.NH_3, dry THF, -33 ^oC.

Albeit the chemical yield is low, the above two-step synthesis encouraged us to explore the applicability of this methodology in the large scale synthesis of thalidomide using an alternative strategy starting from L-GA (**23**). The starting material for this approach is an inexpensive commonly available reagent and the results from our study are presented herein. The starting material which was converted into dimethyl ester **25** as light yellowish oil in 95% yield (Scheme 15).[19] The ester was further acidified and converted into its hydrochloride salt for the optical rotation value. The rotation found to be $[\alpha]^{25}_D$= + 22.8 (c=2, MeOH) and by comparing from the literature data, optical purity of the salt was found to be 93.8%. Based on HPLC data (t_R=5.888 min), purity of the compound was 98.98 (area%) at 230 nm.



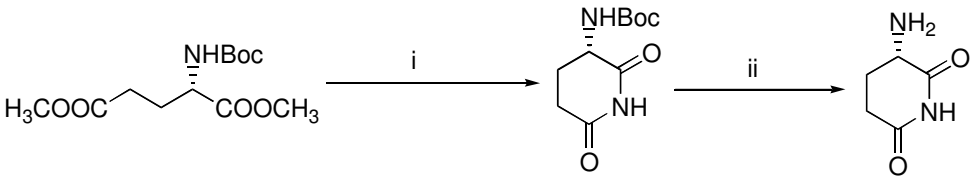
23 **25** **26**

Scheme 15: i) MeOH, $SOCl_2$, reflux; ii) $(Boc)_2O$, DMAP, dioxane-H_2O (1:1).

The ester **25** was then protected with $(Boc)_2O$ in a mixture of dioxane and water with a catalytic amount of DMAP at room temperature for 12 h to afford *tert*-butoxycarbonyl L-glutamic acid dimethyl ester **26** as an oil (88%, Scheme 15).[20]

The formation of Boc-protected ester was confirmed by signal at δ 1.43 (s, 9H) and clear doublet of doublet signal at 4.27 (1H, CH-N), two NH signals at δ 5.17 and 7.89 from ^{1}H NMR spectrum. The rotation found to be $[\alpha]^{25}_D$= + 12.5 (c=2, $CHCl_3$) and by comparing from the literature data, optical purity of **26** was found to be 96.89%. Based on HPLC data (t_R=7.243 min), purity of the compound was 98.37 (area%) at 230 nm.

The ester was treated with Na/liq.NH_3 at -33 ^{0}C in dry THF which was already found to be practically applicable and cyclized to afford the glutarimide **16** as white crystals in 2 h (68%, Scheme 16).[21] The characteristic stereogenic proton signal (CH-N) at δ 4.21 with coupling constants of *J*=6.2 *Hz*, *J*=11.0 *Hz* (dd, 1H) confirmed the cyclization of **26**. Further, its ^{13}C-NMR spectrum showed signals at δ 172.4, 172.0, 155.4 respectively due to the three carbons bearing carbonyl groups and disappearance of methyl groups of the ester in the region of and δ 45-60. The observed optical rotation is –58.2 (c=1.05, MeOH), showing the optical purity of 93.4%. The purity of the **26** from HPLC data (t_R=6.069 min), revealed 95.05 purity (area%) of the compound at 210 nm.



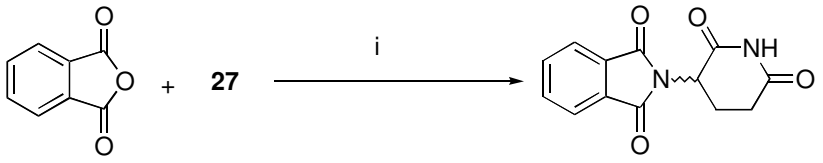
26 **16** **27**

Scheme 16: i) $Fe(NO_3)_3$, Na/liq.NH_3, dry THF, -33 ^{o}C; ii) i) TFA, DCM, 0 ^{0}C to RT.

This imide was characterized and then deprotected with trifluoroacetic acid in CH_2Cl_2 in 1.5 h to remove the protective group to generate corresponding aminoglutarimide trifluoroacetate **27** in quantitative yield (Scheme 16). The characteristic CH-N proton showed a signal at δ 4.32 (dd, *J*=5.4 *Hz*, *J*=13 *Hz*, 1H) and the free amine protons at δ 11.32 from the ^{1}H NMR spectrum.

Without further purification, this compound **27** was reacted with phthalic anhydride in refluxing glacial acetic acid in the presence of triethylamine to furnish thalidomide **1** in 65% yield (Scheme 17). Various solvents such as THF, DMF and toluene were used for the condensation to take place. The reaction was sluggish and took longer reaction times (1-2 days) in THF and DMF, which are not practically viable in large scale synthesis, whereas

azeotropic removal of water via Dean-Stark is needed in case of toluene as solvent (8 hrs). We now disclose that glacial acetic acid as solvent is quite efficient in the condensation giving in 2 hrs complete conversion. In the ^{1}H-NMR spectrum of thalidomide, the four protons of the aromatic ring resonate as a symmetrical multiplet at δ 7.82. The signal from H-1 δ appears as a doublet of doublets (*J*=5.4 and 12.8) at δ 5.16. The remaining four protons on the piperidinedione ring appear as three sets of multiplets at δ 2.08, 2.55, and 2.88. The amine proton resonates as a broad singlet at ca. δ 11.00. In the ^{13}C-NMR spectrum of thalidomide three signals at δ 173.2, 170.2 and 167.6 attributable to the four carbonyl carbon atoms and three signals at 135.3, 131.7 and 123.8 attributable to the six aromatic carbon atoms are clearly discernable. The three remaining carbon atoms of the piperidinedione ring resonate at 49.5 (C-1), 31.4 (C-5), and 22.5 (C-6), respectively.



1

Scheme 17: i) Glacial aceticacid, reflux.

The purity of the **1** from HPLC data (t_R=6.997 min), revealed 96.96 purity (area%) of the compound at 230 nm. Racemization of the product occurs in this step, which was proved by Chiral HPLC studies. The overall yield of the synthesis *via* Scheme 15-17 is 55%. Na/liq.NH_3 mediated cyclization of glutamic acid diester is for the first time shown to be a good tool and useful in the synthesis of thalidomide. While both routes to the desired compound were ultimately successful, the approach outlined in Schemes 15-17 proved to be more amenable to multi-gram scale preparations due to the crystallinity and purity of intermediates in that route.[22]

2.1.7 CONCLUSION

In summary, the practical short synthesis was developed as an alternative to the previous syntheses of thalidomide using $NaNH_2$/liq. NH_3 methodology for the first time, found to fulfill our initial requirements of economical and

readily available starting materials, high overall yield and ability to be done on multi-gram scale. No exceptional purification (such as use of high melt temperatures, acidic purifications) was required for all intermediates and reagents. General applicability of this methodology could be easily extended to other analogues of thalidomide.

2.1.8 EXPERIMENTAL SECTION

L-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) pentanedioic acid (2)

L-Glutamic acid **23** (5.0 g, 34.32 mmol), was dissolved in a solution of (10.42 g, 98.44 mmol) of sodium carbonate in 50 mL water. After cooling the mixture to 0 ^{o}C, (10.42 g, 47.50 mmol) well-ground N-carbethoxyphthalimide (**4**) was added and the white suspension was stirred for 5 min at 0 ^{o}C, and 40 min at room temperature and then filtered. The filtrate was acidified to pH 2.5 with 6 M HCl. The colourless oil that separated slowly crystallized out upon cooling. The colorless crystals were collected after 2 days at 5 ^{o}C to give **2** (7.9 g, 28.55 mmol, 60% yield) as solid, m.p 160 ^{o}C.

IR (neat): ν 2920, 2880, 1716 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 2.40-2.80 (m, 4H, CH_2-CH_2), 5.05-5.18 (m, 1H, CH), 7.75-7.95 (m, 4H).

[α]$_D^{25}$ = - 42.6 (c=1, EtOH);[15]

Optical purity: 94.6 %.

L-Dimethyl-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) pentanedioate (24)

To a solution of N-phthaloyl L-glutamic acid **2** (5.0 g, 18.05 mmol) in methanol (100 mL) was added, dropwise, thionyl chloride (25 mL). The reaction mixture was refluxed for 6 h. The solvent was removed under reduced pressure, dissolved in ethyl acetate (500 mL), and then washed with saturated aqueous Na_2CO_3 solution (2×100 mL) and water (2×100 mL). The ethyl acetate layer was dried over Na_2SO_4 and then evaporated, leaving oil, which upon purification by silica gel chromatography, using CH_2Cl_2:EtOAc (1:1) as the eluent, gave compound N-phthaloyl L-glutamic acid dimethyl ester **24** (3.91 g, 12.82 mmol, 71% yield) as an oil.

***IR (neat*)**: ν 1746 (C=O), 1743 (C=O), 1714(C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 2.35-2.41 (m, 2H), 2.44-2.51 (m, 1H), 2.56-2.67 (m, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.91 (dd, *J*= 5Hz, *J*= 9Hz, 1H), 7.72-7.75 (m, 2H), 7.84-7.87 (m, 2H).

^{13}C NMR (75 Hz, CDCl3): δ (ppm)= 164.7 (C=O), 134.2 (Arom CH×2), 132.7 (Arom C), 123.5 (Arom CH×2), 52.7 (CO_2CH_3), 51.6 (CO_2CH_3), 51.0 (CHN), 30.5 (CH_2CH_2CHN), 24.2 (CH_2CH_2CHN).

***EIMS*:** *m/z*= 305 (M^+, 0.1%), 273 (18), 186 (100).

[α]$_D^{25}$ = - 168.8 (c=1.4, $CHCl_3$);[16]

Optical purity: 97.2 %.

2-(2,6-dioxo-3-piperidyl) isoindoline-1,3-dione (1) (Scheme 14)

To a stirred solution of sodium amide [29.5 mmol mmol; prepared *in situ* from sodium metal (0.68 g) and ammonia in the presence of a catalytic amount of iron (III) nitrate in liquid ammonia (150 mL)] was added a solution of the N-phthaloyl L-glutamic acid dimethyl diester **24** (3 g, 9.83 mmol) in dry THF (100 mL) at -33^0 C. After stirring for 1.5 h, ammonium chloride (8.0 g) was added and the ammonia is allowed to evaporate. Water (100 mL) was added to the residue and the mixture is extracted with chloroform (3×20 mL). The extract was dried with Na_2SO_4 and concentrated and column purified on silica gel with chloroform/acetone (9:1) to afford thalidomide **1** (1.14 g, 4.43 mmol, 45% yield) as a white powder. mp 275-276 ^{0}C.

L-1,5-Dimethyl-2-aminopentanedioate (25)

To a solution of L-glutamic acid **23** (12 g, 81.6 mmol) in dry methanol (250 mL) was added, thionyl chloride (40.16 g, 326 mmol) using a dropping funnel at 0 ^{0}C over a period of 30 min. Then, the reaction mixture was stirred at room temperature for 12 hrs under vigorous stirring. Then, the solvent was evaporated under reduced pressure, diluted with aq. $NaHCO_3$ and extracted with dichloromethane (5×200 ml). The organic layer was washed with H_2O, brine, dried over anhydrous Na_2SO_4. Evaporation of the solvent gave diester (12.86g, 73.47 mmol, 95% yield) as light yellowish oil.

IR (neat): ν 3255, 2957, 1741, 1691, 1435, 1220 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)= 4.25-4.32 (q, 1H, CH), 3.30-3.38 (br s, 4H, Ar, 2H), 3.60-3.71 (s, 3H,), 3.78-3.90 (s, 3H), 2.37-2.45 (d, 1H, CH_2), 2.25-2.34 (m, 1H, CH_2).

$[\alpha]_D^{25}$ for L-Glutamic acid dimethyl ester hydrochloride: + 22.8 (c=2, MeOH);[18]

Optical purity: 93.8 %.

HPLC retention time (t_R)= 5.888 min (Purity (area %)-98.98 at 230 nm).

L-1,5-Dimethyl-2-[(*tert*-butoxycarbonyl)amino] pentanedioate (26)

A solution of diester **25** (12g, 68.6 mmol) and di-*tert* butyl dicarbonate (17.8 g, 81.6 mmol) in a mixture of dioxane and water (1:1) with a catalytic amount of DMAP was allowed to room temperature and continued stirring for 12 hrs. Then, solvent was evaporated, the residue was diluted with aq. $NaHCO_3$ and extracted with DCM (5×100 mL). The organic layer was washed with water (3×100 mL), dried over anhydrous Na_2SO_4. Evaporation of the solvent gave NH-Boc protected diester **26** (16.6 g, 60.34 mmol, 88% yield) as clear colourless oil.

IR ($CHCl_3$): ν 3436, 3025, 2981, 1732, 1714, 1503, 1369, 1168 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 5.17 (br s, 1H, NH), 4.27 (dd, 1H, CH), 3.80- 3.98 (s, 3H), 3.62-3.78 (s, 3H), 2.34-2.45 (t, 2H), 2.10-2.25 (m, 1H), 1.85-2.00 (m, 1H), 1.43 (s, 9H).

EIMS: *m/z*= 276 $(M+1)^+$(1), 219 (22), 216 (48), 187 (25), 174(31), 160 (63), 142 (41), 116 (99), 84 (86) 57 (100).

Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.26; H, 7.81; N, 5.05.

$[\alpha]_D^{25}$ = +12.5 (c=2, $CHCl_3$);[19]

Optical purity: 96.89 %.

HPLC retention time (t_R) = 7.243 min (Purity (area %)-98.37 at 230 nm).

L-*tert*-butyl *N*-[2,6-dioxohexahydro-3-pyridinyl] carbamate (16)

To a stirred solution of sodium amide [65.46 mmol; prepared *in situ* from sodium metal (1.5 g) and ammonia in the presence of a catalytic amount of iron (III) nitrate in liquid ammonia (250 mL)] was added a solution of the NH-

Boc protected glutamic acid diester **26** (6 g, 21.82 mmol) in dry THF (150 mL) at –33 ^{0}C. After stirring for 2 h, ammonium chloride (10 g) was added and the ammonia is allowed to evaporate. Water (200 mL) was added to the residue and the mixture is extracted with chloroform (3×200 mL). The extract was dried with Na_2SO_4 and concentrated and column purified on silica gel with chloroform/acetone (9:1) to afford **16** (3.38 g, 13.11 mmol, 68% yield) as white crystals. mp 212-214 ^{0}C.

IR(KBr): ν 3362, 3231, 1731, 1692, 1534, 1358, 1190 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm)= 7.92 (br s, 1H, CONHCO), 5.30 (br s, 1H, NHCO), 4.21 (dd, *J*=6.2 Hz, *J*=11.0 Hz, 1H), 2.63-2.75 (m, 1H), 2.45 (m, 1H), 1.87- 1.95 (m, 2H), 1.40 (s, 9H).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ (ppm)= 172.4, 172.0, 155.4, 78.2, 50.6, 31.0, 28.0, 24.4.

EIMS**:** *m/z* **=** 228 (M^+).

Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.68; H, 7.07; N, 12.28; O, 28.07. Found: C, 52.64; H, 7.12; N, 12.74; O, 27.55.

[α]$_D^{25}$ = - 58.2 (c=1.05, MeOH);^{20}

Optical purity: 93.4 %.

HPLC retention time**:** *(t_R)* = 6.069 min (Purity (area %)-95.05 at 210 nm).

Aminoglutarimide trifluoroacetate (27)

To compound **16** (2.5 g, 9.69 mmol) in DCM (200 mL) at 0 ^{o}C was added TFA (20 mL) slowly and was allowed to stand for vigorous stirring at room temperature for 3.5 hrs. After the reaction was complete by TLC, the solvent was rotavaped to furnish free amine compound (2.63 g, quant) as a solid.

^{1}H NMR (300 MHz, DMSO-d$_6$): δ (ppm)= 11.37 (s, 1H, NH), 8.68 (br, 2H), 4.32 (dd, *J*= 5.4Hz, *J*=13Hz, 1H), 2.72-2.86 (m, 2H), 2.09-2.25 (m, 2H).

(2-(2,6-dioxo-3-piperidyl) isoindoline-1,3-dione) (1) (Scheme 17)

To aminoglutarimide trifluoroacetate **27** (2g, 8.26 mmol), phthalic anhydride (1.02 g, 7 mmol), and Et_3N (2.43 mL) was added and kept under reflux conditions for 2 h in glacial acetic acid (75 mL). Monitored TLC, after completion the reaction mixture was poured into ice. The desired compound

was obtained by filtration by Buckner funnel *in vacuo* as powder which was further crystallized from ethyl acetate to give thalidomide **1** (1.15 g, 4.48 mmol, 65 %) as white solid. mp 275-276 ^{0}C.

IR (KBr): ν 3194, 3097, 2912, 1778, 1707, 1388, 1205, 726 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)=11.00 (s, 1H, NH), 7.78-8.03 (br s, 4H, Ar, 2H), 5.15 (dd, *J*= 12.8, 5.4Hz, 1H, CHCO), 2.72-2.89 (m, 1H, CH_2CO), 2.47- 2.69 (m, 2H, CH_2 CH_2), 2.01-2.13 (m, 1H, CH_2).

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)= 173.2, 170.2, 167.6, 135.3, 131.7, 123.8, 49.5, 31.4, 22.5.

EIMS: *m/z*= 258 (M^+).

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.91; N, 10.84; O, 24.78. Found: C, 60.43; H, 3.85; N, 10.83; O, 24.89.

HPLC retention time**:** *(t_R)* = 6.997 min (Purity (area %)-96.96 at 230 nm).

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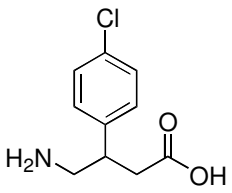
2.2.1. INTRODUCTION (Section B)

Baclofen (CAS No: 1134-47-0), [γ-amino-β-(*p*-chlorophenyl)butyric acid, **1**] is a derivative of γ-aminobutyric acid (GABA). It plays an important role as an inhibitory neurotransmitter in central nervous system (CNS) of mammalians.[1] A simple amino acid has two major receptor subtypes, $GABA_A$ and $GABA_B$. These receptors play a distinct role in central and peripheral nervous system through ion-channel regulation.[2] The overall physiological effect is transmission inhibition, pre and post-synaptically mediated by $GABA_A$ sites and pre-synaptically by $GABA_B$ sites. However, baclofen is the only potent and selective $GABA_B$ agonist known so far against bicuculline receptor.[3] In contrast to that of simple GABA, baclofen is the most lipophilic and can penetrate to blood/brain barrier. Consequently, baclofen helps to reduce the excitatory effect of active compounds such as benzodiazepine, barbiturate, etc.[4] The deficiency of GABA is associated with diseases that exhibit neuromuscular dysfunctions such as epilepsy, Huntigton, Parkinsons' disease etc.[5] Baclofen is one of the most promising drugs in treatment of the paroxysmal pain of trigeminal neuralgia[6] as well as spasticity of spinal without influencing the sedation.[7]

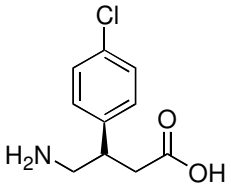
R-Baclofen, or (3R)-4-amino-3-(4-chlorophenyl)butanoic acid, (CAS No: 69308-37-8), (**1a**, Fig. 1), is the only selective and therapeutically available $GABA_B$ agonist known (Lioresal® and Baclon®). Baclofen is commercialized in its racemic form, however literature observations suggested that the

biological activity of **1a** resides in the R enantiomer. According to legislation already approved in many countries of the world concerning the commercialization of pharmaceutical products, drugs such as **1a** will soon be sold only in their enantiomerically pure form. This requirement justifies the need for enantioselective strategies leading to the preparation of these compounds, if possible in a simple and efficient way.

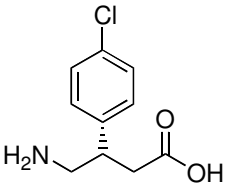
Figure 1.



(±)-Baclofen (**1**)



(R)-(-)-Baclofen (**1a**)



(S)-(+)-Baclofen (**1b**)

2.2.2 PHARMACOLOGY OF BACLOFEN

Bowery *et al*.[1,2] has demonstrated that baclofen helps to decrease the neurotransmitter release in mammalian central nervous system by action at the GABA receptor. This effect is associated with the stereospecificity of (R)-(–)-baclofen (**1a**) isomer being 100-fold more active in producing neural depression than (S)-(+)-baclofen (**1b**) isomer. The $GABA_B$ receptors of peripheral and central nervous systems are associated with many biological processes including analgesia, muscle relaxation, hypertension, increased gastric mutility and inhibition of the liberation of corticotropin releasing hormone. There are only few agonist and antagonists available concerning these factors.

Baclofen is one of them and used in treatment of spasticity, a serious disease characterized by increase muscle tone, usually perceived muscle tightness or achiness in the limbs.[8] These symptoms are normally associated with multiple sclerosis. Although baclofen is commercially available in its racemic form, only the (R)-enantiomer (**1a**) shows entire medicinal activity.[1, 9]

2.2.2.1 Pharmacokinetics

Baclofen is rapidly and almost completely absorbed from the gastrointestinal tract. The peak plasma concentration occurs 1 to 3 hours following ingestion, but the rate and extent of absorption vary between patients. The volume of distribution is 0.7 L/kg and the protein-binding rate is about 30%. Some baclofen does cross the blood-brain barrier with concentrations in the CSF of approximately 12% of those found in the plasma. Within 72 hours, 70 to 80% of the dose is excreted in urine mainly as unchanged baclofen while approximately 15% is metabolised in the liver by deamination to β-(*p*-chlorophenyl)-γ-hydroxybutyric acid which is pharmacologically inactive. The elimination half-life of baclofen is 3 to 4 hours in plasma and about 5 hours in CSF. In patients with severely impaired renal function, a marked increase in serum concentrations of baclofen and toxic symptoms have been observed although a moderate reduction in renal function does not adversely affect the disposition of baclofen. Moderate hepatic dysfunction has no major effect of the pharmacokinetics of baclofen.

Baclofen, USP is a white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in

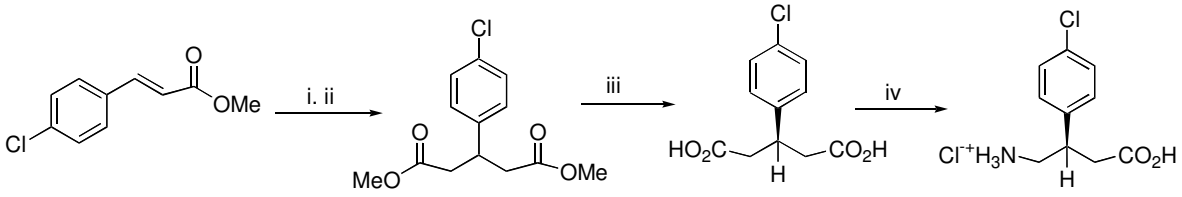
methanol and insoluble in chloroform. Each tablet, for oral administration, contains 10 mg or 20 mg Baclofen. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, hydrous dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

2.2.3 EARLIER APPROACHES

Literature search revealed that there are several reports available on the synthesis of (R)-(–)-baclofen (**1a**). They are concerned mostly with resolution, chemo-enzymatic or enantioselective synthesis, which are described below.

Chenevert's approach (1991)[10]

Chenevert *et al.* have achieved the synthesis of both (R)- and (S)-baclofen by enantioselective hydrolysis of intermediate **3** using Chymotrypsin enzyme (Scheme 1). Michael addition of dimethyl malonate with **2** followed by demethoxycarbonylation afforded the key intermediate **3**. It was then subjected to enantioselective hydrolysis with Chymotrypsin enzyme to afford chiral monoester **4** in 98% ee and 85% yield. The chiral monoester **4** upon Curtius rearrangement followed by acid hydrolysis gave (R)-(–)-baclofen (**1a**).



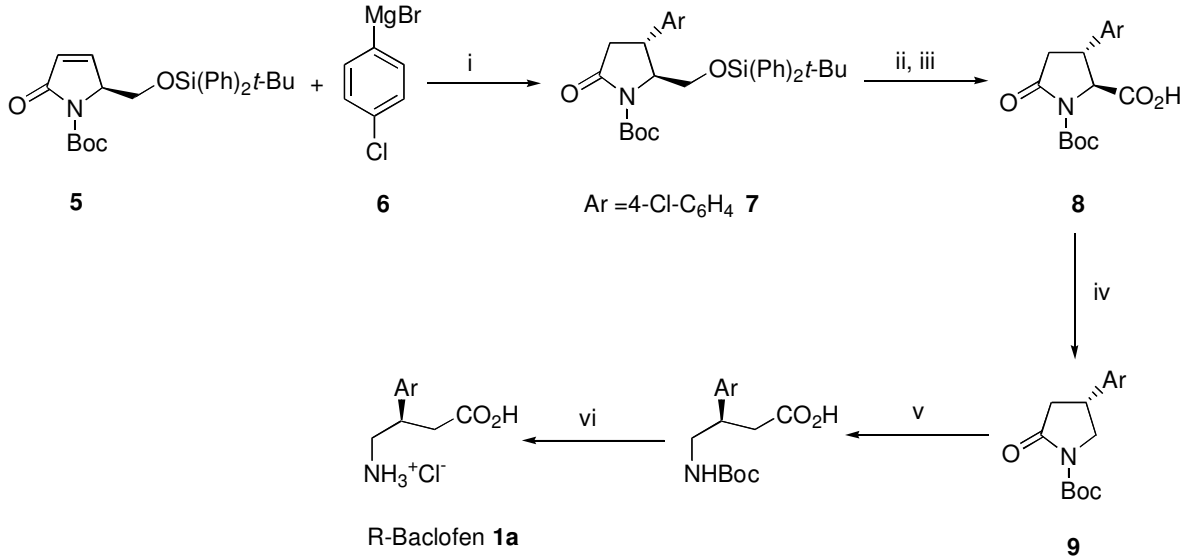
2 **3** **4** R-Baclofen **1a**

Scheme 1: (i) Dimethyl malonate, CH_3ONa, THF, reflux; (ii) NaCl, H_2O, DMSO, 160 ^{0}C; (iii) α-Chymotrypsin, phosphate buffer, pH 7.7, 25 ^{0}C; (iv) a)

Ethyl chloroformate, Et_3N, acetone, 0 ^oC; b) NaN_3, H_2O, acetone; c) toluene, reflux; d) HCl. H_2O.

Herdeis's approach (1992)[11]

Herdeis's strategy to synthesize (R)-baclofen (**1a**) involved stereoselective Michael addition of (S)-pyroglutamic acid derivative **5** with Grignard reagent **6** (Scheme 2).

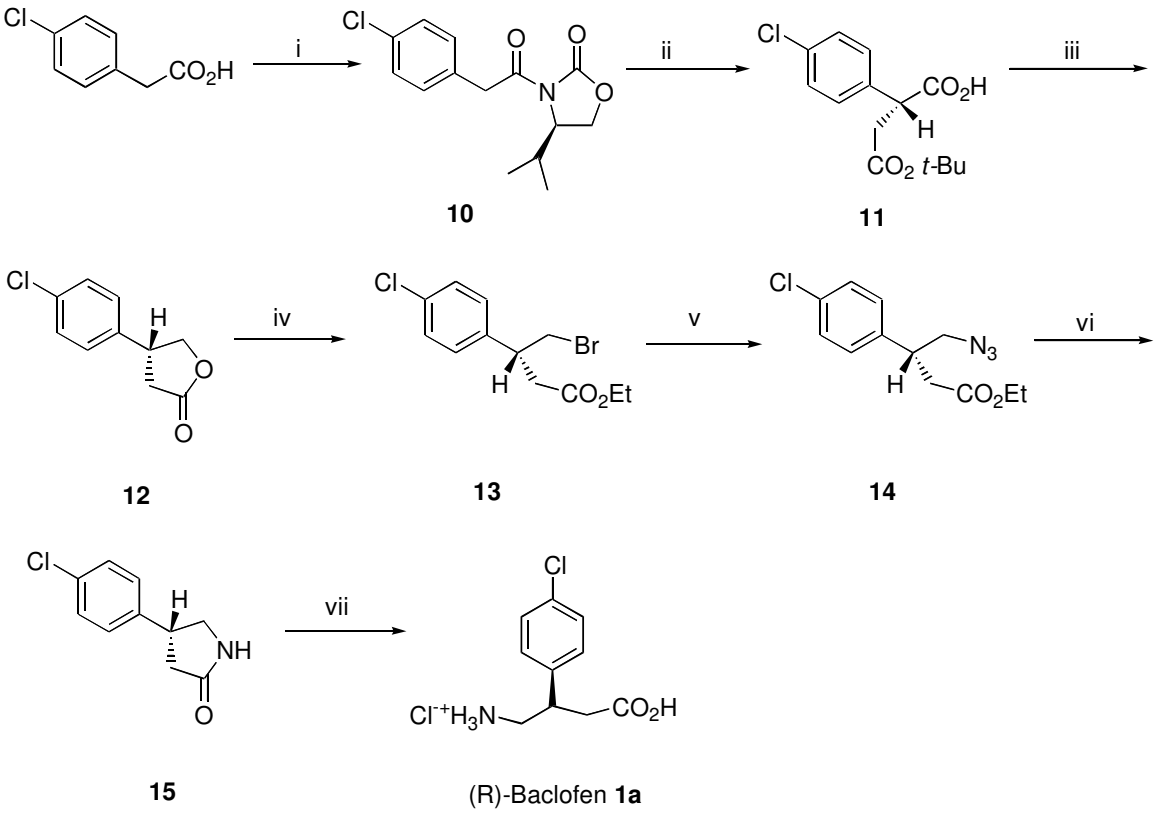


Scheme 2: (i) CuBr.Me_2S, Et_2O, -35 ^0C, 20 min; -78 ^0C, TMS-Cl, NH_4Cl; (ii) Et_3NHF, RT, 4-5days; (iii) $RuCl_3$, $NaIO_4$, CH_3CN: CCl_4 (2:1), H_2O; (iv) N-methyl morpholine, isobutyl chloroformate, -15 ^0C, N-hydroxy-2-thiopyridone, Et_3N, THF, 2 h; (v) aq. 1M LiOH, 1.5 h; (vi) 6M HCl, reflux, 3 h.

Schoenfelder's approach (1993)[12]

Schoenfelder's strategy makes use of enantioselective alkylation of chiral 2-(4-chlorophenyl) acetyl oxozolidone (**10**). The oxazolidone 10 was prepared from 2-(4-chlorophenyl)acetic acid and was then converted to chiral *t*-butyl-2-(4-chlorophenyl)succinate **11** in two steps. Chemoselective reduction of the acid functionality of **11** followed by dehydration gave γ-butyrolactone **12**. The

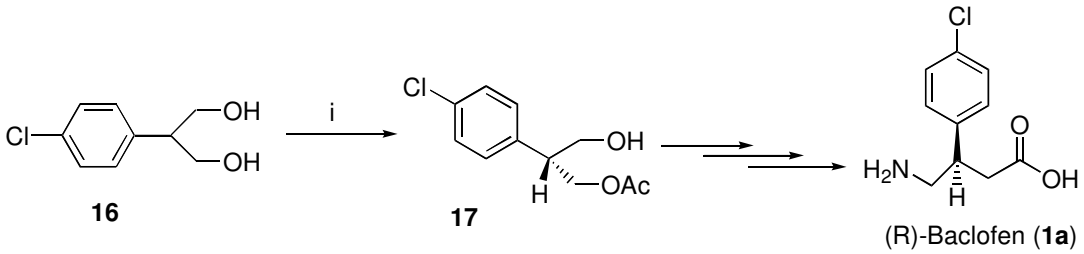
lactone **12** was then converted to azidoester **14**, which on reduction followed by cyclization gave lactam **15**. Lactam **15** was then hydrolyzed with HCl to afford (R)-baclofen (**1a**) hydrochloride salt (Scheme 3).



Scheme 3: (i) a) $ClCO^tBu$, Et_3N; b) Li-oxazolidine, THF, -78 ^0C; (ii) a) NaHMDS, $BrCH_2CO^tBu$, -78 ^0C; b) H_2O_2-LiOH; (iii) a) BH_3.DMS; b) *p*-TSA, toluene, reflux; (iv) EtOH, HBr; (v) NaN_3, DMSO; (vi) a) PPh_3, H_2O; b) DMAP, toluene, reflux; (vii) 6 M HCl, reflux.

Desjardins's approach (1994)[13]

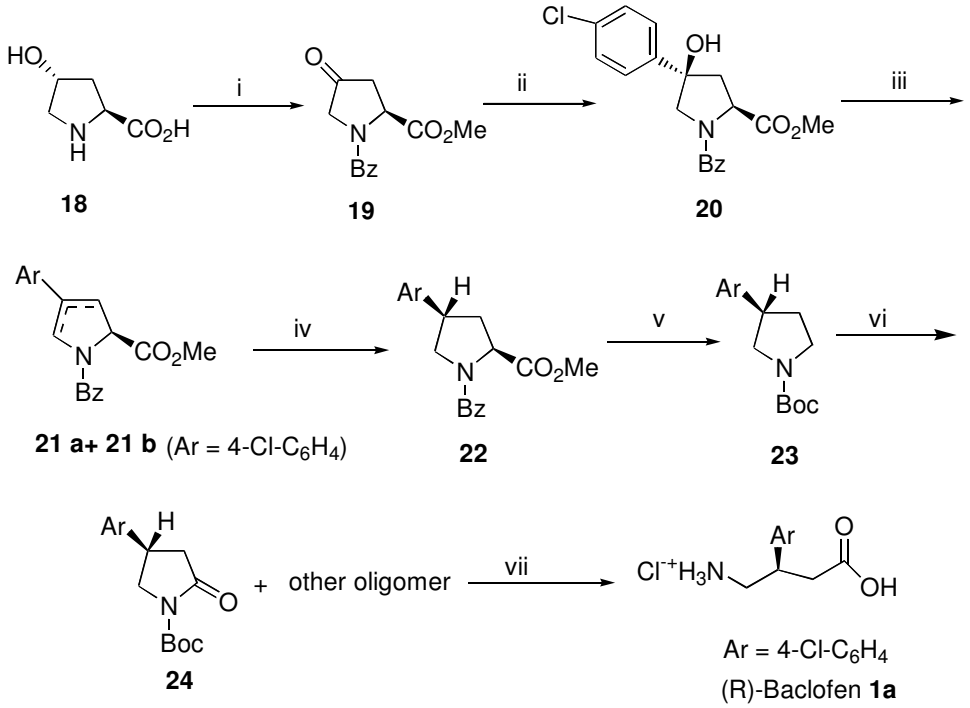
In Desjardins's approach lipase was used to carry out the enantioselective acetylation of 2-(4-chlorophenyl)-1,3-propane diol (**16**) to give optically active mono acetate **17** as a key step. The mono acetate **17** was further converted to (R)-baclofen (Scheme 4).



Scheme 4: (i) Lipase, Ac_2O.

Yashifuji's approach (1995)[14]

Yashifuji's approach consists of chiral trans-4-hydroxy-L-proline (**18**) as a chiral precursor for the synthesis of both (R)- and (S)- baclofen (Scheme 5). The strategy is based on the following two key steps (i) a stereoselective hydrogenation of dehydroproline derivative **21a** and **21b**, controlled by C_2-carboxyl functionality (ii) an effective Ru catalyzed oxidation of pyrrole **23** to pyrrolidone **24**.

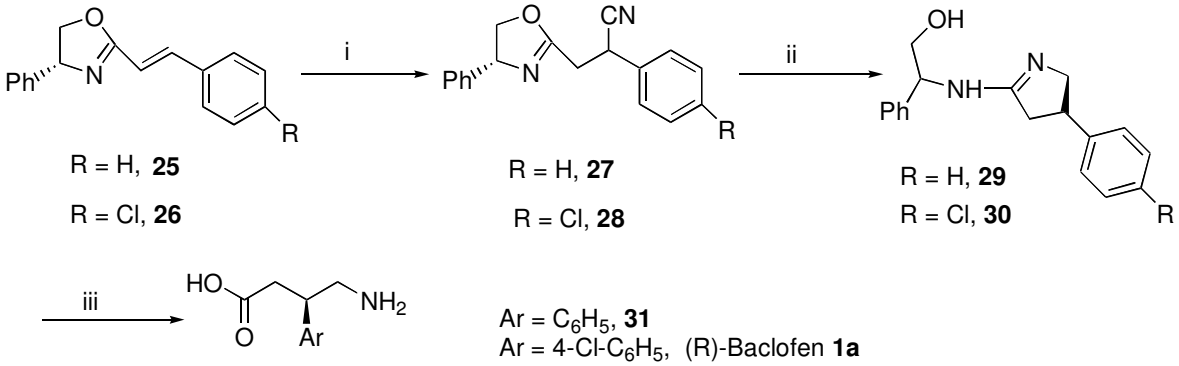


Scheme 5: (i) a) MeOH; b) benzoyl chloride, Et_3N; $COCl_2$, DMSO, Et_3N, -78 ^{0}C; (ii) 4-Cl-Ph-Br, Mg, $CeCl_3$, Et_2O, RT; (iii) $SOCl_2$, pyridine, RT; (iv) Pt, H_2 (1

atm), RT, 6N HCl, AcOH, 110 ^{0}C; (v) a) cyclohexanol, 2-cyclohexene-1-one, 155 ^{0}C; b) *tert*. Butoxy chloride; (vi) RuO_2, aq. $NaIO_4$, AcOEt: H_2O, RT; (vii) 6N HCl, reflux.

Langlois's approach (1997)[15]

Using Langlois's method both (R)-4-amino-3-phenylbutyric acid (**31**) and (R)-baclofen (**1a**) have been synthesized in 50% ee. The chiral precursors, α,β-unsaturated oxazoline **25** and **26**, were derived from the reaction of (R)-phenylglycinol with the corresponding cinnamic acids and these were subjected to hydrocyanation reaction to afford cyanooxazolines **27** and **28**. Subsequently, these were reduced to imides **29** and **30** respectively. Finally, imides **29** and **30** were hydrolyzed to give (R)- (**31**) and (R)-baclofen (**1a**) respectively (Scheme 6).

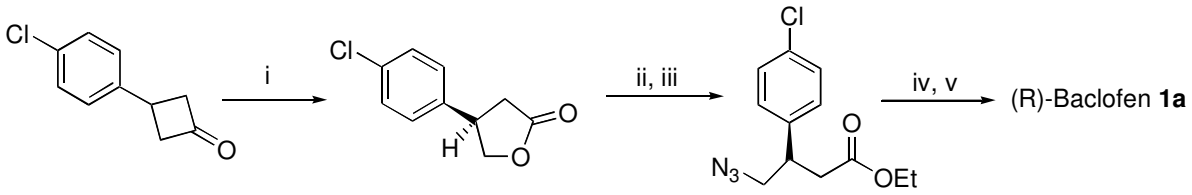


Scheme 6: (i) a) $AlEt_2CN$, DCM, -30 ^{0}C, RT, 48 h, 50 % de; (ii) $NaBH_4$, $NiCl_2$, THF: H_2O (2:1); (iii) 2N NaOH: EtOH, 14 h.

Mazzini's approach (1997)[16]

Mazzini *et al*. have synthesized (R)-baclofen *via* chemoenzymatic Baeyer-Villiger oxidation as a key step (Scheme 7). 3-(4-Chlorophenyl) cyclobutanone (**32**) was subjected to enantioselective Baeyer-Villiger oxidation in presence of

Cunninghamell echinulata (NRLL 3655) enzyme to obtain (3R)-chlorophenyl-γ-butyrolactone **33** in 30% yield and >99% ee which was further converted to azidoester **34**. Subsequently, hydrolysis with NaOH and Pd-catalyzed hydrogenation afforded (R)-baclofen (**1a**).

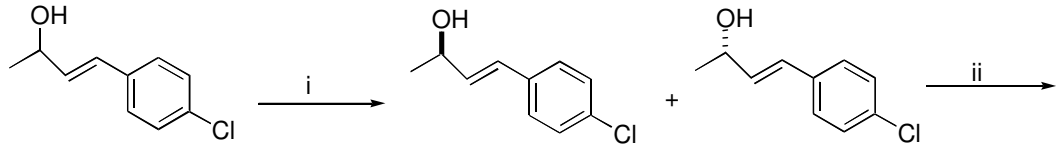


32 **33** **34**

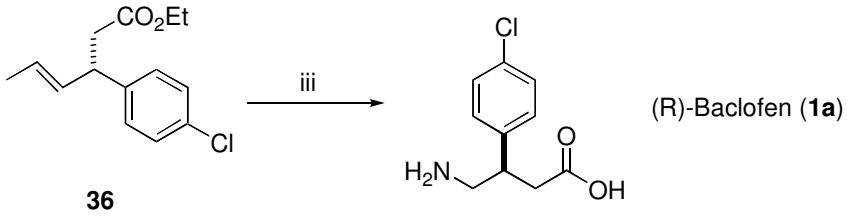
Scheme 7: (i) culture C. echinulata; (ii) Me_3SiI, EtOH, DCM, 0 ^{0}C to RT; (iii) NaN_3, DMF, 75 ^{0}C; (iv) 2M NaOH, conc. HCl, RT; (v) Pd-C, H_2, Et_2O/EtOH, RT.

Brenna's approach (1997)[17]

Brenna's approach involves enzymatic resolution of substituted allyl alcohol **35a** in presence of Porcine pancreas lipase (PPL, Sigma type II) to yield optically active allylic alcohol **35b** in >99% ee as key step (Scheme 8). Subsequently, it was transformed to ester **36** via Claisen orthoester rearrangement, which on ozonolysis followed by reductive amination afforded (R)-baclofen (**1a**).



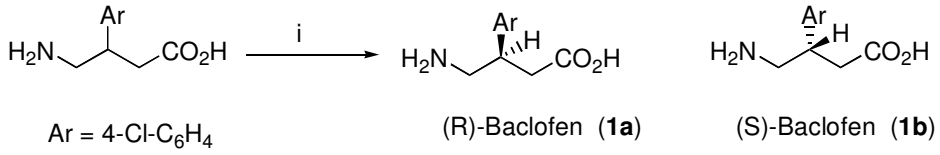
35a (S)-E-(-)-**35b**



Scheme 8: (i) PPL, *t*-butylmethyl ether, vinyl acetate; (ii) $CH(OEt)_3$, propanoic acid, 125-130 ^{0}C; (iii) O_3, DCM-MeOH (1:1), NH_4OAc, $NaBH_3CN$, -78 ^{0}C, 12 h, 2M NaOH, HCl, RT.

Levadoux's approach (1998) [18]

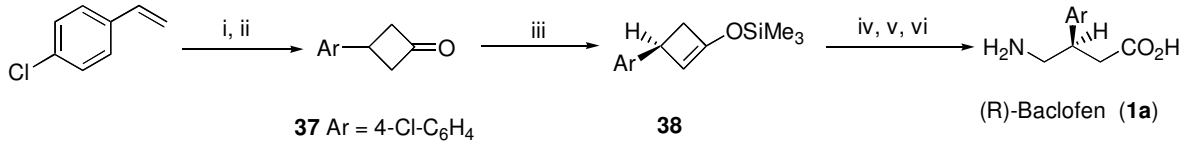
Levadoux *et al.* have developed a process for obtaining optically active baclofen and its analogues by Streptomyces microrganism-mediated resolution (Scheme 9).



Scheme 9: (i) Streptomyces microorganism.

Resende's approach (1999)[19]

Resende's approach involves enantioselective deprotonation of **37** with lithium (S, S')-α,α'-dimethylbenzylamide followed by silylation afforded the chiral silylenol ether **38** in 70% yield and 98% ee. Finally, it was transformed to (R)-baclofen (**1a**) in three steps (Scheme 10).

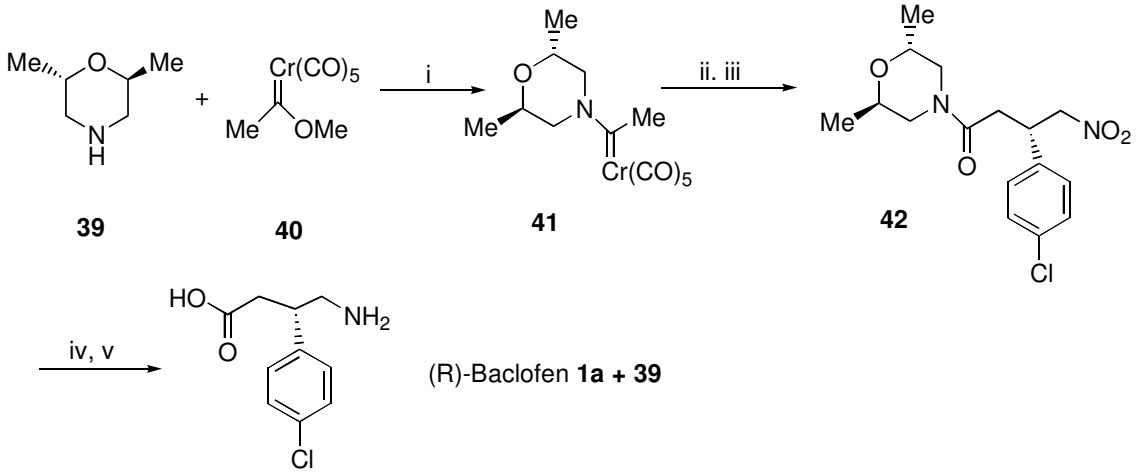


Scheme 10: (i) Zn-Cu, $POCl_3$, CCl_3COCl, Et_2O, RT, 12 h; (ii) Zn/AcOH, RT, 14 h; (iii) Lithium (S, S')-α, α^1-dimethylbenzylamide, THF, TMSCl, -100 ^{0}C; 15

min; (iv) O_3, DCM, -78 ^{0}C, 40 min; (v) Me_2S, -78 ^{0}C to RT, 12 h; (vi) $NaBH_3CN$, NH_4OAc, 12 h, 6N HCl (one pot sequence).

Licandro's approach (2000)[20]

Licandro *et al*. have achieved the synthesis of (R)-baclofen (**1a**) using diastereoselective Michael addition of enantiopure Cr-carbene complex **41** to *p*-chloronitrostyrene to give **42** (Scheme 11). The optically active chromium-carbene complex **41** was obtained by condensation of (S,S)-2,6-diemethylmorpholine(**39**)with pentacarbonyl(methoxymethylcarbene)chromium (**40**). The nitro group in **42** was then reduced with Raney-Ni and finally hydrolyzed with 6M HCl to afford (R)-baclofen (**1a**).

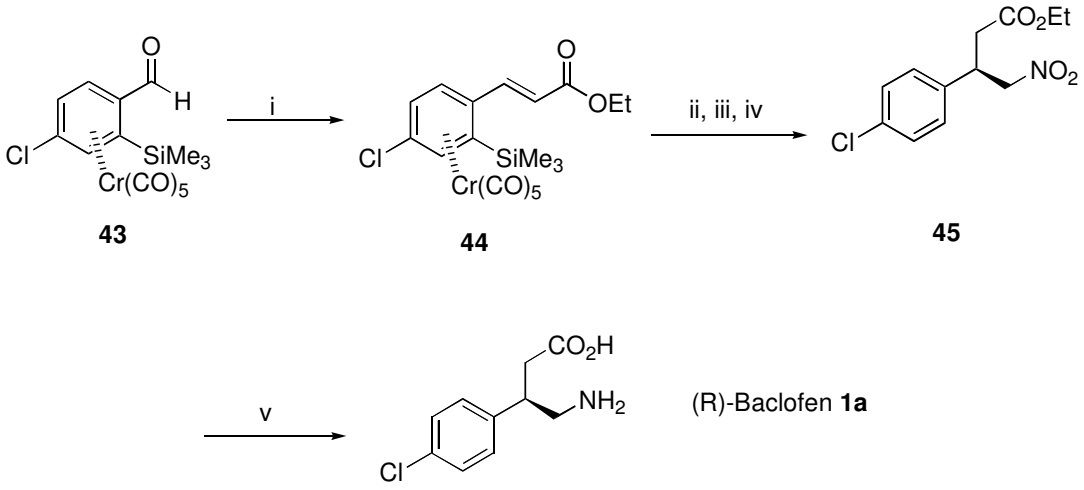


Scheme 11: (i) aminolysis (ii) *n*-BuLi, THF, -97 ^{o}C, *p*-Cl-PhCH=$CHNO_2$; (iii) CAN, acetone, RT, 4 h; (iv) Raney-Ni, dry-MeOH, 5 atm, 1 h; (v) 6M HCl, reflux, 8 h.

Baldoli's approach (2000)[21]

Baldoli's approach involves stereoselective Michael addition of nitromethane to chiral chromium(0) complex **44** as a key step. The chiral aldehyde **43** was

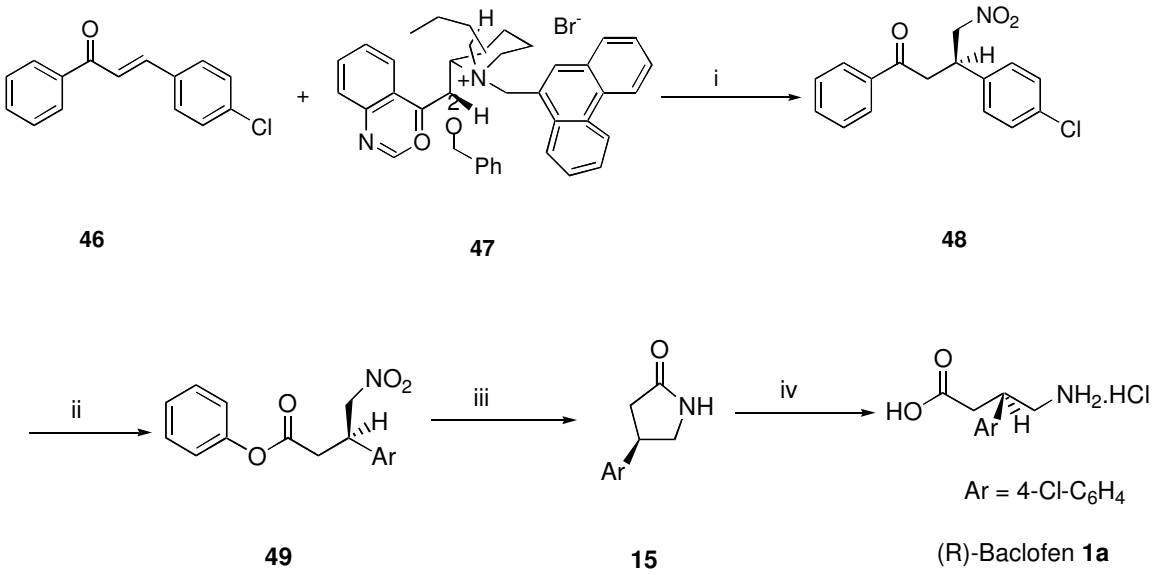
obtained by resolution of its diastereoisomeric-semioxamazone derivative. Aldehyde **43** was subjected to Wittig-Horner reaction to obtain ester **44** (Scheme 12). The Michael addition of nitromethane onto ester **44** followed by desilylation and de-complexation yielded nitroester **45**. Finally, hydrogenation of nitroester **45** followed by hydrolysis afforded (R)-baclofen (**1a**).



Scheme 12: (i) $(EtO)_2OPCH_2CO_2Et$, $(Me_3Si)_2NLi$, THF, RT; (ii) CH_3NO_2, K_2CO_3, TEBA, RT; (iii) Bu_4NF, DCM, RT; (iv) hν, air, DCM; (v) a) PtO_2, H_2, MeOH, RT; b) 6N HCl, reflux.

Corey's approach (2000)[22]

In Corey's approach chiral quaternary ammonium salt **47** was used as a chiral catalyst for the enantioselective Michael addition of nitromethane to α,β-enone **46** to afford nitroketone **48**. Nitroketone **48** was converted to nitroester **49** followed by reduction of nitro group in **49** to give lactam **15**, which was hydrolyzed to afford (R)-baclofen (**1a**) as a hydrochloride salt (Scheme 13).

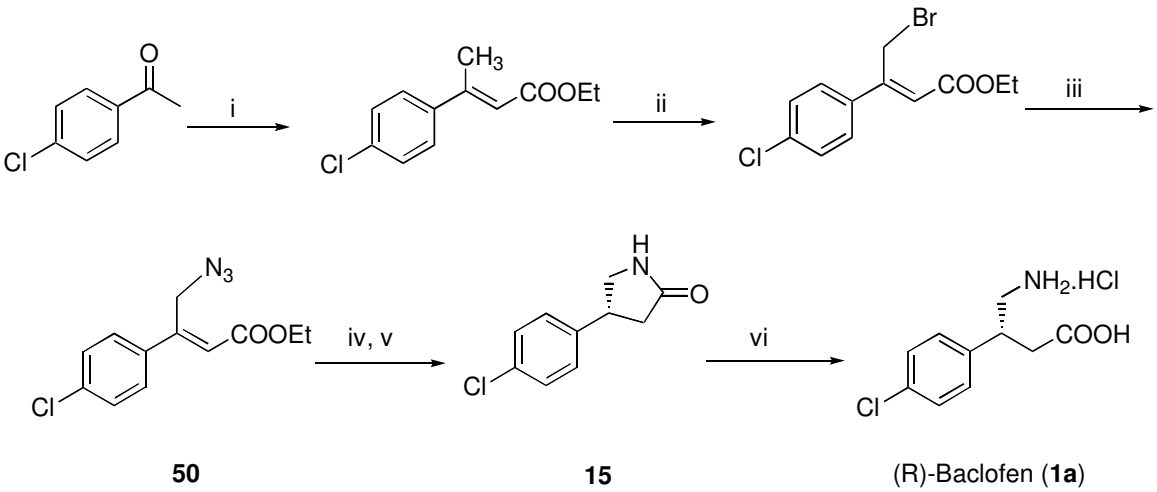


46 **47** **48** **49** **15** (R)-Baclofen **1a**

Scheme 13: (i) CH_3NO_2, CsF, toluene, -40 ^{0}C, 36 h; (iii) *m*-CPBA, EDC, reflux, 36 h; (iii) $NaBH_4$, $NiCl_2$, MeOH, 23 ^{0}C, 10 min; (iv) 5N HCl, reflux, 4 h.

Sudalai's approach (2002)[23]

a) Sudalai group has developed a simple method for the enantioselective synthesis of (R)-baclofen (**1a**) using asymmetric reduction of azido ester **50** using Ru(II)-(S)-BINAP complex to give lactam **15** which on hydrolysis gave (R)-baclofen (Scheme 14).

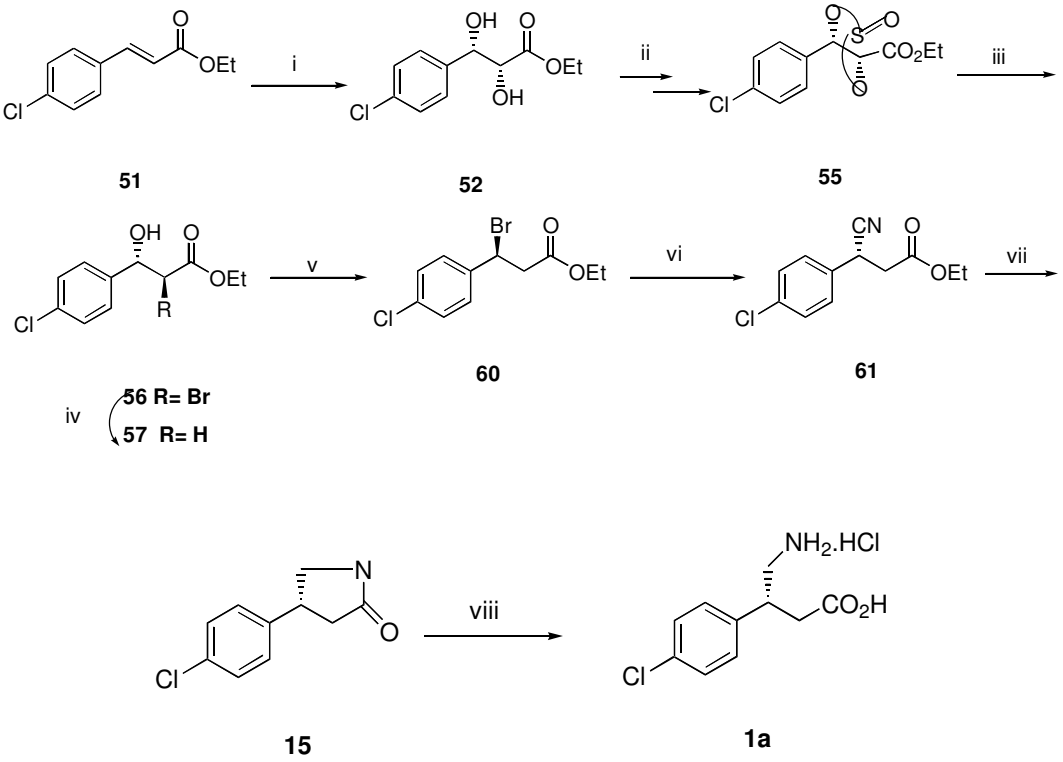


50 **15** (R)-Baclofen (**1a**)

Scheme 14: i) Br-CH_2CO_2Et, Zn, benzene, reflux, *p*-TSA, toluene, 120 ^{0}C; (ii) NBS, AIBN, CCl_4, reflux, 10 h; (iii) NaN_3, EtOH: H_2O (80:20), 80 ^{0}C, 8 h; (iv) Rh

(II)-(S)-BINAP, H_2 (200 psi), MeOH, 50 ^{0}C, 20 h; (v) $CoCl_2$, $NaBH_4$, H_2O, 25 ^{0}C, 30 min; (vi) 20% HCl, 100 ^{0}C, 3 h.

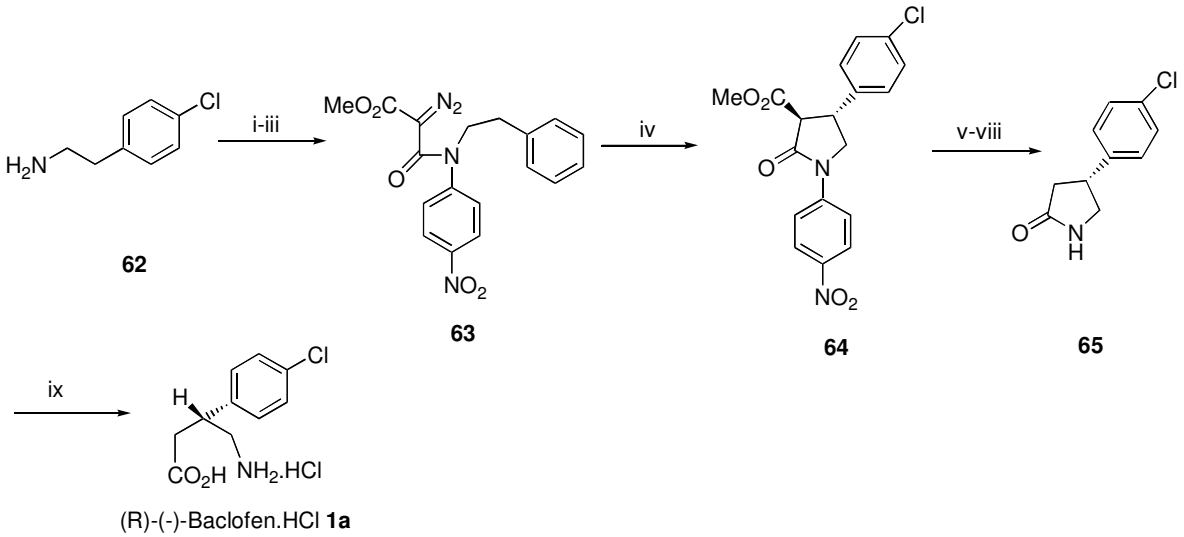
b) Another synthetic strategy for (R)-baclofen (**1a**) by the same group is shown in Scheme 15 wherein Os catalyzed asymmetric dihydroxylation (AD) constitutes a key step in introducing chirality into the molecule.



Scheme 15: i) cat. OsO_4, $(DHQ)_2$-PHAL, $K_3Fe(CN)_6$, $MeSO_2NH_2$, K_2CO_3, t-BuOH-H_2O (1:1), 0-25 ^{0}C, 24 h, 95%; ii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 ^{0}C, 30 min; iii) a) cat. $RuCl_3.3H_2O$, $NaIO_4$, CH_3CN: H_2O (80:20), 0 ^{0}C, 10 min. b) anhydrous LiBr, 25 ^{0}C, 45 min. c) 20% H_2SO_4, Et_2O, 25 ^{0}C, 4 h; (iv) Bu_3SnH, AIBN, benzene, 80 ^{0}C; (v) PBr_3, pyridine, Et_2O, -20 to 0 ^{0}C; (vi) NaCN, DMF, 70 ^{0}C, 18 h; (vii) $NiCl_2.H_2O$, $NaBH_4$, MeOH, 25 ^{0}C, 1 h; (vii) 6N HCl, reflux, 16 h, 78%, $[\alpha]_D$ = -1.70 (c=0.6, H_2O), 85%.

Hashimoto's approach (1998)[24]

Hashimoto *et al.* developed a site- and enantioselective intramolecular C-H insertion of α-methoxycarbonyl-α-diazoacetamides by exploiting a *p*-nitrophenyl group as the N-substituent and dirhodium (II) tetrakis[N-phthaloyl-(S)-*tert*-leucinate] as catalyst, leading to the formation of 4-substituted 2-pyrrolidine derivatives of up to 82% ee. The efficiency of the present protocol has been verified well by a short-step synthesis of (R)-(-)-baclofen (Scheme 16).

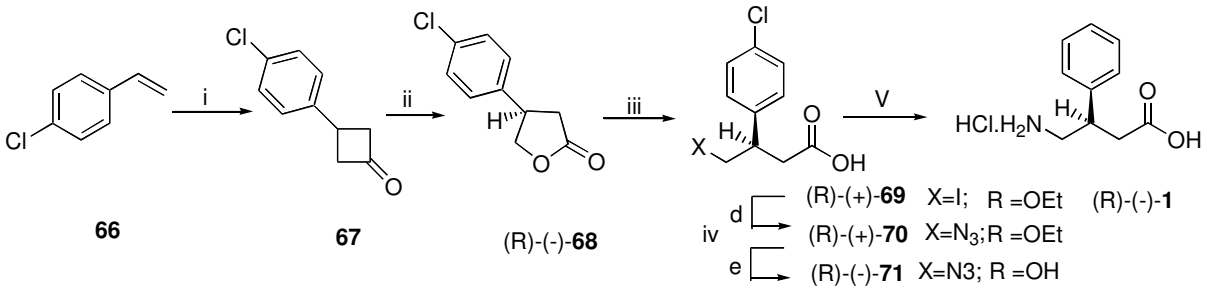


Scheme 16: i) 4-fluoro nitrobenzene, K_2CO_3, EtOH, 160 ^{0}C, 18 h; ii) MeO_2CCH_2COCl, Et_3N, CH_2Cl_2, 0 ^{0}C, 2 h; iii) *p*-acetamidobenzenesulfonyl azide, DBU, CH_3CN, 0 ^{0}C, 3 h; iv) Rh_2[S-PTTL)$_4$ (2 mol%), DCM, 23 ^{0}C, 6 h, 83%; v) NaCl, aq.DMSO, 160 ^{0}C, 2 h, 96%; vi) Fe, AcOH, reflux, 2 h; vii) CAN, CH_3CN, 0 ^{0}C, 1.5 h, 81%; viii) recrystallization from EtOAc: *n*-hexane, 99%; ix) 6N HCl, reflux, 6 h.

Furstoss's approach (1997)[25]

A seven-step enantioselective synthesis of (R)-(-)-baclofen **1a** is described. The strategy developed involved, as a key step, a microbiologically mediated

Baeyer-Villiger oxidation of the prochiral 3-(4'-chlorobenzyl)-cyclobutanone **67** which led to the optically pure (R)-(-)-4 lactone. This was further transformed throughout chemospecific reactions into the target molecule (R)-(-)-1(Scheme 17).



Scheme 17: i) a) Cl_3COCl, Et_2O, $POCl_3$, reflux; b) Zn, AcOH, reflux, 65%; ii) Culture of C.echimulata, 31%; iii) Me_3SiI, EtOH, CH_2Cl_2, 0 ^{0}C to RT, 95%; iv) NaN_3, DMF, 75 ^{0}C, 95%; v) a) 2M, NaOH, RT; b) HCl, RT, 16 h, 95%; vi) a) H_2 1 atm, Pd-C, Et_2O/EtOH, RT; HCl $_{gas}$, 80% overall.

2.2.4 PRESENT WORK

2.2.4.1 Objective

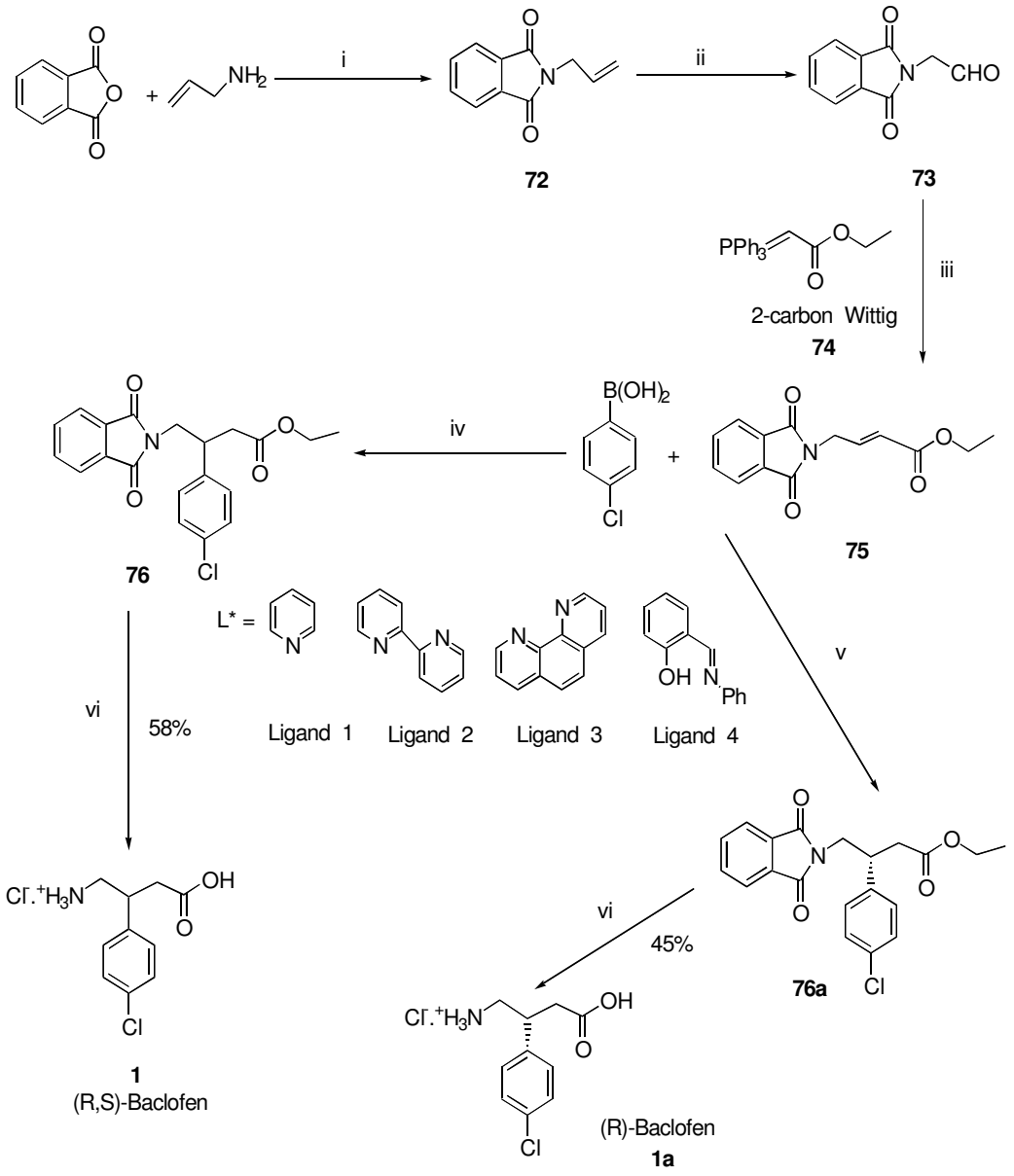
Although racemic baclofen (**1**) is commercially available in bulk quantities, its entire biological activity is associated only with the (R)-enantiomer 1a. Various methods such as resolution, chemo-enzymatic or enantioselective synthesis have been developed to synthesize (R)-baclofen (**1a**) (vide supra). However, these methods suffer from disadvantages such as low overall yields, separation of diastereoisomers and the use of expensive reagents. In this context, a more practical approach for the synthesis of (R)-baclofen (**1a**) is highly desirable. Considering its biological and pharmacological activity of the drug and being interested in exploring novel routes for the preparation of

the phthalimide and arylalkanoic acid derived drugs and analogues, we continued our studies using a novel approach for the synthesis of racemic Baclofen and finally Rh/BINAP catalyzed conjugative addition of *p*-chloroboronic acid to achieve enantioselective synthesis of (R)-Baclofen.

Since, this section deals with two important strategies recently developed for the conjugate addition of α,β-unsaturated esters, ie. a) Pd(II)-Bipyridine-catalyzed catalyzed conjugative addition in the presence of 2,2′-bipyridine and b) introducing stereogenicity into the prochiral molecule *via* Rh/BINAP-catalyzed conjugative addition, a brief account of each was presented in the following sections.

The synthetic strategy for both the syntheses of (R,S)-Baclofen and (R)-(-)-Baclofen was shown in Scheme 18 wherein both the above key steps are essential for the completion of total synthesis of racemic and (R)-Baclofen.

Scheme 18: Synthetic Strategy for the synthesis of (±)-Baclofen and (R)-Baclofen:



Synthesis of (R,S)-Baclofen and R-Baclofen

Scheme 18: i) Et_3N, Toluene, reflux, 3.5 h, 95%; ii) O_3, DCM-MeOH, Me_2S, 62%; iii) dry DCM, 0 ^{0}C-RT, 78%; iv) $Pd(OAc)_2$, bipy, H_2O, THF, AcOH, 82%; v) Rh/(S)-BINAP, Cs_2CO_3/Et_3N, Dioxane: H_2O ; vi) $N_2H_4.H_2O$, EtOH, 6N HCl, 58% for **1** and 45% for **1a**.

2.2.4.1 Pd(II)-Bipyridine Catalyzed Conjugative Addition-(±)-Baclofen

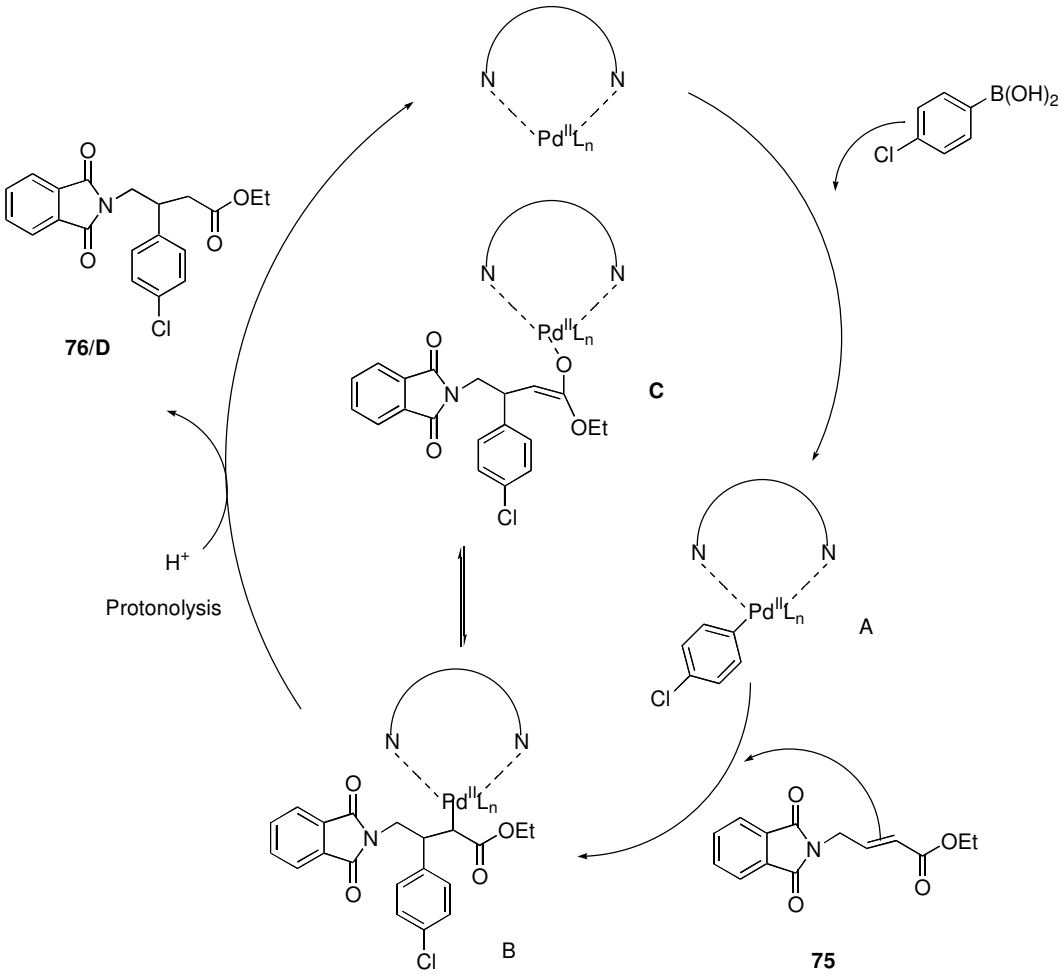
The 1,4-conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a powerful tool for the construction of C-C bonds.[26] While the Rh(I)-catalyzed conjugate addition of organo-boron, silicon, and tin reagents to α,β-unsaturated carbonyl compounds has been well developed,[26d] the reports on Pd-catalyzed conjugate addition are rare. Different kinds of oganometallic reagents[27] have been attempted in Pd-catalyzed conjugate addition. Most of them were troubled by the formation of the Heck-type coupling products. The reason might be that a palladium catalyst yields C-bound enolates in the insertion of enones into a C-Pd bond in contrast to the formation of O-bound enolates in the insertion of enones into a C-Rh bond.[26, 27h, 28] β-Hydride elimination will easily occur in the former case, resulting in the formation of the Heck-type coupling products. Recently, Miyaura reported that the cationic Pd(II) complexes can catalyze the conjugate addition of arylboronic acids with enones, affording the addition products in excellent yields,[27h,i] and the detailed mechanism was also reported.[29]

From the reported Pd(II)-catalyzed conjugate addition of arylboronic acid to enones, it was known that the easily occurring β-hydride elimination represents the main drawback of the reaction.[27g,28] Thus, a method of suppressing β-hydride elimination is important in developing Pd(II)-catalyzed conjugate additions. In our ongoing studies in the Pd(II)-catalyzed nucleophile-alkene-α,β-unsaturated carbonyl coupling through nucleopalladation and conjugate addition, we found that the presence of halide ions (Cl-, Br-, and I-)[30] and bidentate nitrogen ligands (e.g.,

2, 2[1]-bipyridine and phenanthroline)[31] are crucial for inhibiting the β-hydride elimination. In all of these reactions, the carbon-palladium bonds were formed from the nucleopalladation (nucleophiles= halides, nitrogen, and oxygen) of the alkenes or alkynes, and it occurred to us whether the conjugate addition reaction could take place with the carbon-palladium bond formed from the transmetallation of arylboronic acid and Pd(II) species.

First, transmetallation generates the arylpalladium species A from *p*-chloroboronic acid and palladium acetate, which was followed by insertion of the ester **75** into the carbon palladium bond to give palladium enolate B or C. The presence of bipy inhibits the β-hydride elimination of the C-Pd bond in B. Protonolysis of B or C gives the corresponding conjugate addition products D in a protonic medium with the regeneration of the divalent palladium species. The protonic medium will also lead to the protonolysis of arylpalladium species A, which may be stabilized by the coordination of bipy.[32]

The possible mechanism for this divalent palladium catalyzed reaction was proposed as shown in Scheme 19.



Scheme 19: $Pd(OAc)_2$/bipy Catalyzed Conjugative Addition of *p*-chloroboronic acid to ester 75: Proposed Mechanism

2.2.4.2 Rh/BINAP Catalyzed Asymmetric Conjugative Addition of *p*-chloroboronic acid to ester 75:

In the past 20 years there has been dramatic growth in the use of transition metal catalysts in synthetically important organic transformations. Recently, more attention has been paid to rhodium catalysts in the formation of carbon-carbon bonds. While showing new and complementary reactivity to other catalyst systems, rhodium catalysis may permit the development of more environmentally benign processes. As the reactions can be frequently

performed in the presence of water or even in water as the exclusive solvent. The carbon-carbon bond lies at the heart of organic chemistry, and our ability to synthesize new and interesting organic molecules is inextricably linked to the discovery of new methods. In recent years, organic chemists have increasingly employed transition metal catalysts as instruments for C-C bond forming processes. The prevalence of these reactions is illustrated by the many processes involving palladium that bear the names of those who discovered them. These include the Kumada-Corriu,[33] Mirozoki-Heck,[34] Stille,[35] Suziki-Miyaura,[36] and Tsuji-Trost[37] reactions that permit the cross-coupling of substrates in ways that would have previously been thought impossible.[38] Increasingly, the application of these reactions is becoming a cornerstone in the efficient construction of complex organic molecules.

Due to the tremendous versatility and utility of palladium in the formation of C-C bonds, much effort has been devoted for the development of new reactions with novel applications, continuing reported. In the past five years, there has been a renewed focus on rhodium catalysts in C-C bond forming reactions. Rhodium catalysts have recently been used with organometallic reagents in the formation of new C-C bonds. From a synthetic perspective, these reactions can couple with common reagents in several ways that have not been demonstrated with other metal catalysts. Many of the new reactions that are catalyzed by rhodium complexes show promising utility from an environmental perspective as water can be used as a cosolvent or the sole solvent in many cases. Rhodium has also been found use in C-C bond

forming reactions that do not employ organometallic reagents. Notable examples include rhodium-catalyzed cycloadditions,[39] hydroacylation reactions,[40] and allylic functionalizations.[41,42]

1,4-Conjugate addition of organometallics to activated alkenes is an important process in organic chemistry. The use of metal catalysts in combination with an organometallic reagent has been particularly effective in this regard. Perhaps the most commonly used metal is copper, but reports with other metals have also appeared. Frequently, Grignard reagents, organolithiums, or diorganozincs are employed as the organometallic component while they provide high yields in many cases, issues of chemoselectivity accompany limit their use. Of particular importance is the search for enantioselective 1,4-addition reactions, significant advances have been made, particularly with copper catalysts and Grignard or diorgano zinc reagents. Success with these reactions typically requires the use of low temperatures and strictly anhydrous reaction conditions. The rhodium-catalyzed reactions presented in this section represent an attractive alternative to copper-catalyzed additions as they are insensitive to the presence of water, occur under mild conditions, and can be carried out with a wide range of substrates. Furthermore, they employ mild organometallic reagents that are not prone to background reactions and are compatible with aryl nucleophiles that can be problematic with copper catalysis.

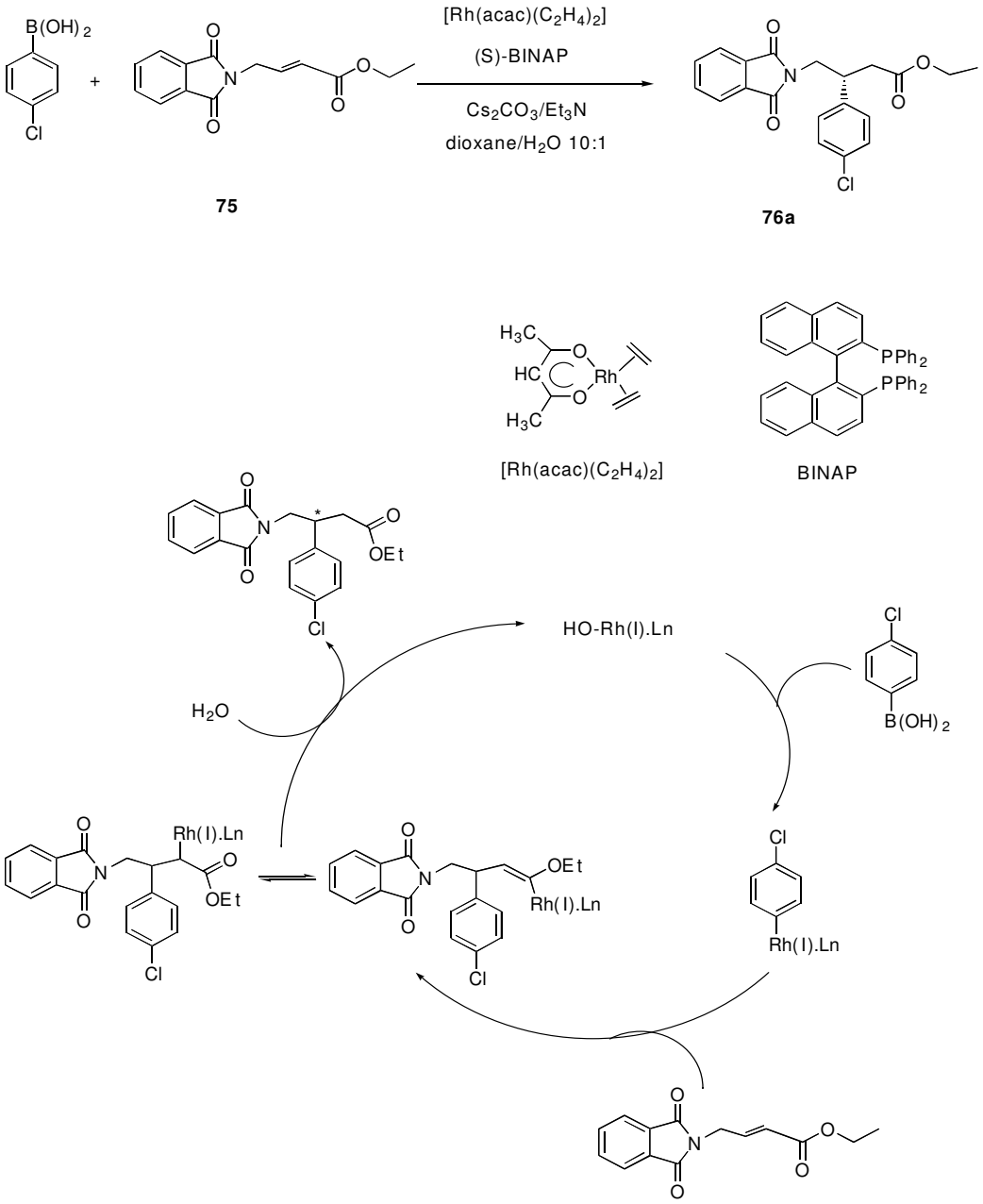
In 1997, Miyaura reported that rhodium (I) complexes catalyze the 1,4-addition of aryl and alkenyl boronic acids to enones in excellent yield.[30]

Using [Rh(acac)$(CO)_2$]as the rhodium(I) source, a variety of ligands were examined.

Bis (phosphine) ligands possessing large bite angles were shown to give the best results. The mild reaction conditions found to avoid aldol condensations of the substrates and products, which can be problematic under basic conditions. Even enals selectively undergo 1,4-additions demonstrating the mildness and high chemoselectivity associated with these reactions.

In 1998, Hayashi reported the first enantioselective variant of this transformation.[49a] To achieve high yields and enantioselectivity, the solvent was changed to a 10/1 mixture of dioxane and water, the temperature was increased to 100^0C, and the rhodium source was changed from [Rh(acac)$(CO)_2$] to [Rh(acac)$(C_2H_4)_2$]. The change in rhodium source was done to facilitate the in situ generation of the rhodium-BINAP complex which is slow when the dicarbonyl complex is employed.

The catalytic cycle has been proposed to involve the transmetallation of *p*-chloroboronic acid to a rhodium (I) complex to give an arylrhodium (I) complex, the coordination of the ester **75** (Scheme 20) to rhodium followed by insertion into the Rh-C bond to afford an equilibrium mixture and, finally the hydrolysis of the rhodium enolate with water to provide the requisite addition product **76a**.



Scheme 20: Enantioselective synthesis of Rh/BINAP Catalyzed Conjugative Addition of *p*-chloroboronic acid to ester 4: Proposed Mechanism

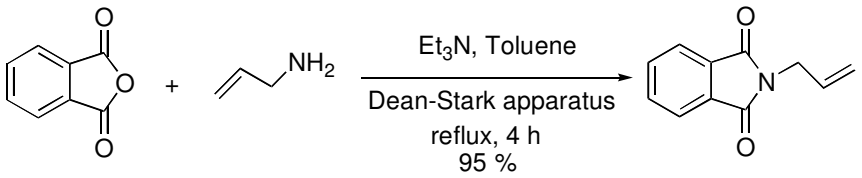
2.2.5 RESULTS AND DISCUSSION

Some examples for the racemic synthesis of Baclofen and its derivatives are given in ref.26. Initially, the synthesis of baclofen was carried out, as outlined in Scheme 18.

Method A: Pd(II)-bipy Catalyzed Conjugative Addition for the Synthesis of (R, S)-Baclofen

The synthesis commenced with the preparation of N-allyl phthalimide by condensing commercially available phthalic anhydride with allyl amine in the presence of triethylamine as base and toluene as solvent for 3.5 h under reflux *via* azeotropic removal of water using Dean-Stark apparatus to yield 95% N-allyl phthalimide (**72**) as crystalline solid (Scheme 21).[25b]

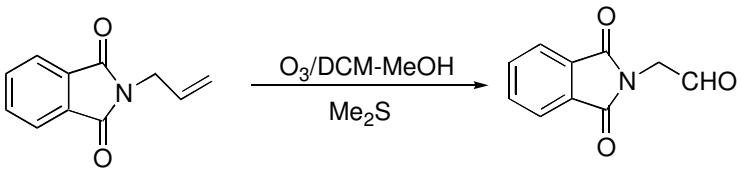
Scheme 21



72

Allylic bond of the olefine **72** is further confirmed by the ^{1}H-NMR spectrum, which showed doublets at δ 5.17 and 5.23 respectively with the coupling constants *J*= 17.3 Hz and 11.31 Hz. The five membered cyclic phthalimide formation is evidenced by C=O stretching at 1773 (s) and 1703 cm^{-1}. Compound **72** then was subjected to ozonolysis using 9:1; 200 mL of DCM-MeOH at –78 ^{0}C for 30 min, followed by usual workup and further recrystallization from DCM-hexane to give compound N-phthalimidoacetaldehyde (**73**) as crystalline white solid,[43] in 62% yield.

Scheme 22

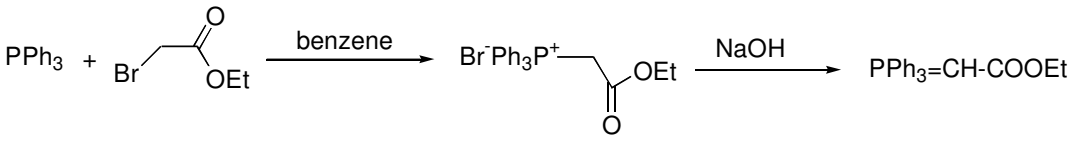


72 **73**

The formation of phthalimidoactaldehyde **73** (Scheme 22) was confirmed by the disappearance of ^{1}H-NMR signals of allylic protons and formation of aldehydic proton, which was proved by the appearance of proton signal at 9.63 Hz of ^{1}H NMR and signal at 193.5 Hz in ^{13}C NMR.

2-carbon Wittig ylide **74** was prepared as given in the Scheme 23.

Scheme 23

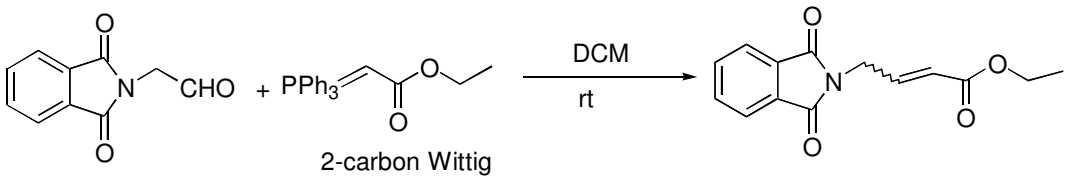


74

Preparation of 2-carbon Wittig

The aldehyde **73** was subsequently treated with $PPh_3CHCOOC_2H_5$ (**74**) in dry DCM at room temperature to give the requisite ethyl (*2E*)-4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)but-2-enote (**75**) as colourless crystals in 78% yield (Scheme 24). The *E* selectivity is proved by comparing literature ^{1}H NMR signal coupling constant, *J*=6.1Hz. A clear doublet at δ 5.77 (two protons) and multiplet at 6.81 (one proton) revealed the presence of olefinic ester group. A sharp signal at 1714 cm^{-1} corresponding to ester C=O is observed from IR spectrum. ^{13}C NMR also showed the presence of olefin by signals at 122.8 and 140.6 respectively, confirming the trans-geometry of the double bond of α,β-unsaturated ester. Its mass spectrum also showed the molecular ion peak at *m/z* 259 corresponding to the ester **75**. A brief account of the very important Wittig olefination is presented below in order to understand various aspects pertaining to the *E* selectivity.

Scheme 24



73 **74** **75**

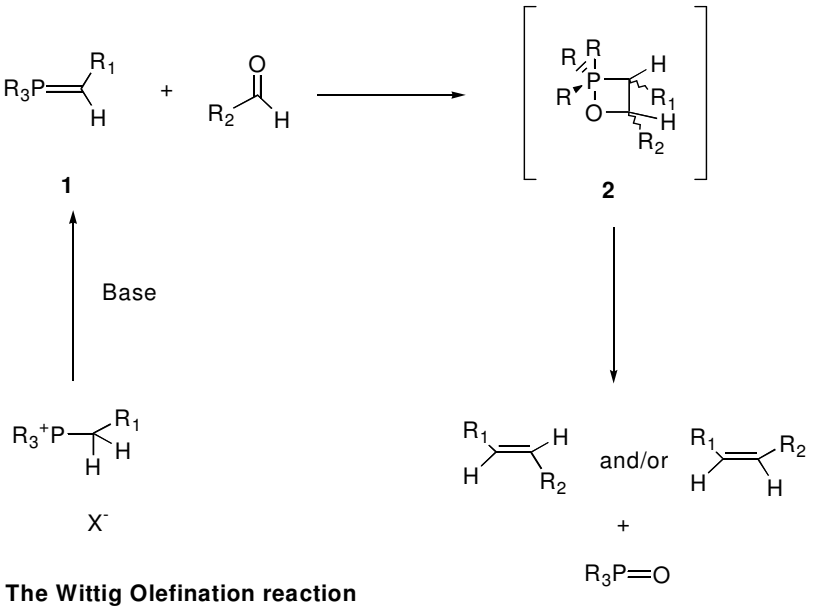
Wittig olefination:

The Wittig olefination reaction is one of the most important methods in synthetic organic chemistry (Figure 2).[45] This reaction involves the nucleophilic attack of an alkyl or phenyl P-substituted phosphorus ylide on an aldehyde or ketone to form an alkene (or a mixture of geometrically isomeric alkenes) and a phosphine oxide (4). The reaction path that leads to the products is thought to proceed through two main steps: the formation of an oxaphosphetane intermediate (Wittig half-reaction) and the decomposition of the oxaphosphetane to form the products. It has been found experimentally that the formation of the oxaphosphetane determines the stereoselectivity of the reaction. The stereoselectivity of the Wittig reaction is dependent on several factors such as the nature of the substituents on the phosphorus atom, the ylidic carbon, the carbonyl group, and the experimental conditions, such as ionic strength of the media, base utilized, presence of additives and catalyst, solvent polarity, concentration, pressure, and temperature.

The Wittig reaction of stabilized ylides (R_1= CN, COOR) with aldehydes is remarkably E stereoselective.[45, 46] Although the E-stereoselectivity can be readily rationalized in terms of the faster formation of the thermodynamically more stable E-oxaphosphetanes, this behavior is in contrast to the unusual

Z-stereoselectivity observed in reactions of unstabilized ylides (R_1= alkyl in Figure 2). The E stereoselectivity of the Wittig reaction of stabilized ylides is not greatly affected by experimental conditions, such as the presence of soluble metal ions, changes of reaction temperature, and concentrations of the reactants.

Figure 2.



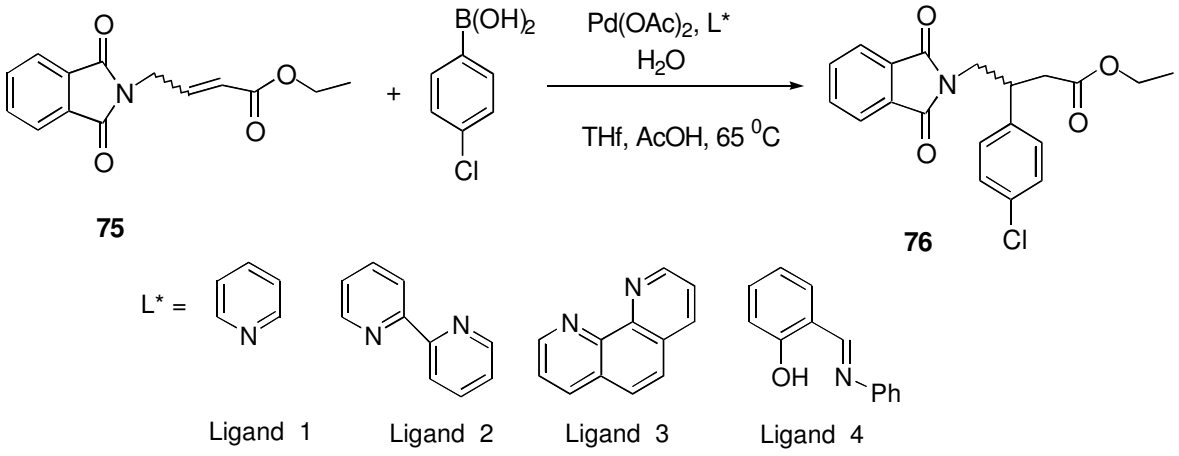
The Wittig Olefination reaction

However, substituents on the phosphorus atom and the solvent employed have a pronounced effect on the yields of these reactions; i.e., replacement of the usual phenyl groups on the phosphorus atom of the ylide by alkyl groups promotes the Wittig reaction with less electrophilic aldehydes or even ketones and also increases the already marked E-stereoselectivity; under other circumstances, these aldehydes and ketones would be relatively unreactive. Thus, stabilized P-phenyl substituted ylides, by far the most common case for the Wittig reaction, are highly E-stereoselective, whereas the corresponding unstabilized ones are highly Z-stereoselective. This observation suggests that

the reaction profiles of these two different types of ylides are essentially different; i.e., for unstabilized ylides, oxaphosphetane formation is fast, and the rate-determining step of the reaction is the oxaphosphetane decomposition, whereas oxaphosphetane formation is slow and is the rate determining in the Wittig reaction of stabilized ylides. However, there might be a small possibility that oxaphosphetanes are not stable intermediates in the Wittig reaction of stabilized ylides.

Next, the reaction conditions of the 1,4-conjugative addition were optimized for the synthesis of **76**, a key intermediate using standard reaction conditions employed by Lu et al,[44] i.e. ester **75** (1 equiv.), 4-chloro phenylboronic acid (3 equiv.), $Pd(OAc)_2$ (0.385 mmol), bipy (0.2 mmol) and HOAc:THF (2:1) at 40 ^{0}C for 2 days (Scheme 25). Several ligands (L*) were screened as shown in Scheme 25, such as pyridine, bipyridyl, 1,10-phenanthroline and N-salicylideneaniline, but bipyridyl afforded the desired product in excellent yield over other ligands chosen.

Scheme 25



While the Rh(I)-catalyzed conjugate addition of organo-boron, silicon, and tin reagents to α,β-unsaturated carbonyl compounds has been well developed and applied for the synthesis of baclofen,[47] the reports on Pd-catalyzed conjugate addition are rare. Under these conditions, compound **76** was obtained as colourless crystals in 82% yield. The conjugate addition of 4-chlorophenylboronic acid to the ester **75** was proved by the disappearance of olefinic protons and a signal at δ 3.75 in ^{1}H NMR spectrum correspond to the β-addition of boronic acid to the α,β-unsaturated ester. The proposed mechanism for the $Pd(OAc)_2$/bipy catalyzed conjugate addition of *p*-chloroboronic acid to ester **75**, is already exemplified in detail in 2.1.4.1 of Scheme 19.

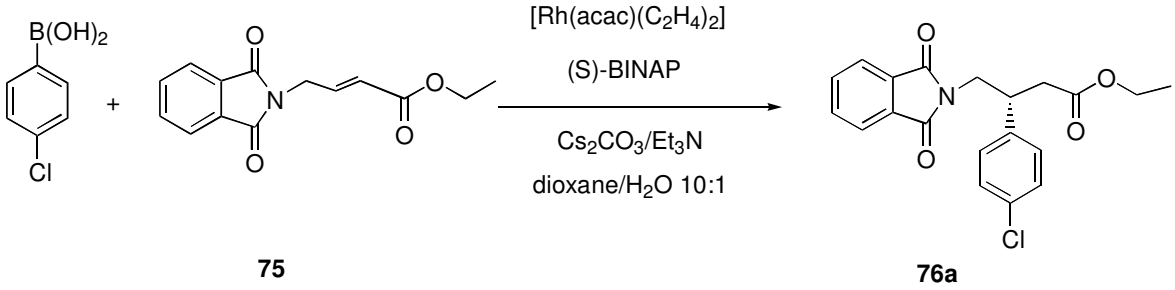
Final conversion of compound **76** into (±)-baclofen (**1**) was accomplished by deprotection in 80% hydrazine hydrate and ethanol under reflux conditions for overnight, followed by addition of HCl, affording the desired product in 22% overall yield in five steps. Consequently, succeeded in the synthesis of baclofen as its hydrochloric salt and comparison of the spectral data of the product **1** with literature data proved the achievement of desired target. Pd(II)-bipy catalyzed conjugative addition methodology is shown for the first time to be a good tool and useful in the synthesis of racemic baclofen.

Method B: Chiron Approach for the Synthesis of (R)-Baclofen via Rh/BINAP Catalyzed Conjugative Addition

Above prepared phthalimide protected α,β-unsaturated ester (**75**) was used as the common precursor for the enantioselective synthesis of (R)-Baclofen using Rh(I)-catalyzed asymmetric conjugate addition of chloroboronic acid as a key step (Scheme 26).

This type of reaction was discovered by Miyaura et al. in 1997[48] and further developed into an enantioselective version in collaboration with Hayashi *et al*.[49] The reaction conditions of the 1,4-addition were optimized for the synthesis of **76a** using first standard reaction conditions, i.e. 3 mol% of commercially available $[Rh(acac)(C_2H_4)_2]$, 4.5 mol% of (S)-BINAP and Na_2CO_3 at 100 ^{0}C for 2 days.[50]

Scheme 26

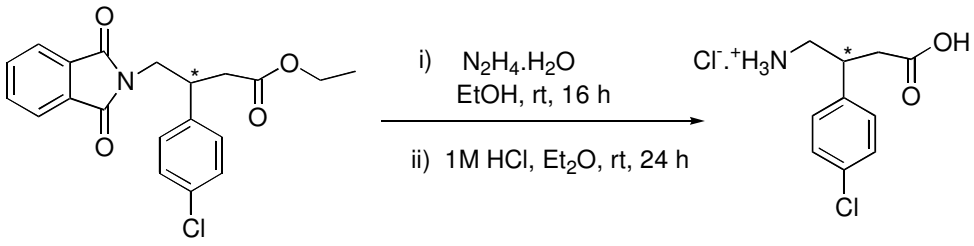


75 **76a**

Under these conditions, (R)-**76a** was obtained in 78% yield and 72% ee. As the chloroboronic acid is partially hydrolyzed under the standard conditions, the amount of boronic acid was increased to 5 equivalents; it was found that with Et_3N instead of Cs_2CO_3 the product was obtained in 65% yield with 88% ee, using (S)-BINAP as ligand. It is noteworthy that the use of Et_3N as base resulted in a rate enhancement and the starting material was consumed completely after 24 hours at 100 ^{0}C. The proposed mechanism for the

Rh/BINAP-catalyzed asymmetric conjugate addition of *p*-chloroboronic acid to ester **75**, was already exemplified in detail in 2.1.4.2 of Scheme 20.

Scheme 27



76/ 76a **1/ 1a**

Deprotection of the addition product **76a** to give baclofen hydrochloride was performed in 45% yield by treatment with hydrazine hydrate in 80% hydrazine hydrate and ethanol under reflux conditions for overnight, followed by addition of HCl, affording the desired product (Scheme 27). Comparision of the optical rotation of the product **1a** {$[\alpha]_D$ –1.64 (c=0.32, H_2O) with literature data proved the absolute configuration to be R with 96.5% ee.[51]

2.2.6 CONCLUSION

In the present study, a novel, productive approach for the synthesis of baclofen (**1**) in five steps with 22% overall yield *via* $Pd(OAc)_2$/bipy catalyzed conjugative addition of N-phthaloyl α,β-unsaturated ester **75** with 4-chlorophenylboronic acid as a key step was studied. Further, synthesis of R-baclofen (**1a**) in chiron approach using Rh/BINAP asymmetric conjugate addition was also successfully achieved.[52]

2.2.7 EXPERIMENTAL SECTION

a) **N-Allylphthalimide** (**72**). Phthalic anhydride (7 g, 47.28 mmol), allyl amine (3.56 mL, 47.60 mmol) and triethyl amine (0.7 mL) in toluene (500 mL) were heated under reflux in nitrogen atmosphere for 3.5 h while azeotropic removal of water using a Dean-Stark apparatus. Stopped heating and the solvent was removed under reduced pressure. Ethyl acetate was added to the reaction mixture, and the organic phase was washed with dil. HCl (1M) to eliminate the unreacted starting materials, dried over magnesium sulphate and filtered to give a colourless crystalline solid **72** in 95% yield (8.4 g).

Physical State: Colourless crystalline solid; m.p: 68-70 ^{0}C.

IR (neat): ν 3022, 2921, 1773, 1703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 4.27 (d, 2H), 5.15-5.28 (dd, 2H), 5.67-5.89 (m, 1H), 7.70- 7.81 (m, 2H), 7.82-7.88 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 40.0, 117.7, 123.3, 131.5, 132.1 134.0, 167.9.

EIMS: *m/z*= 76, 104, 130, 169, 187.

b) **N-phthalimido acetaldehyde** (**73**). To N-allyl phthalimide **72** (5 g, 26.73 mmol), dissolved in 9:1; 200 mL of DCM-MeOH and ozone was bubbled through the solution at –78 ^{0}C for 30 min until a blue colour persisted. The mixture was purged N_2 until the blue colour disappears at the same temperature. DMS (35 mL, 1.2 mol) was added and the mixture was allowed to warm to room temperature and stirred for 16 h at which point it was concentrated in vacuo. The residue was crystallized from DCM/hexane to give the desired compound **73** as white solid in 62% yield (3.13 g).

Physical State: Crystalline white solid; m.p: 110-112 ^{0}C.

IR (neat): ν 2931, 1777, 1716, 1613, 1466, 1400 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 4.56 (s, 2H), 7.71- 7.80 (m, 2H), 7.82-7.91 (m, 2H), 9.63 (s, 1H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 47.36, 123.67, 131.12, 131.99, 134.35, 167.63, 193.0.

EIMS: *m/z*= 50, 63, 78, 104, 133, 160 (M-29), 161(M-28).

Anal. Calcd for $C_{10}H_7NO_3$ (%): C, 63.49; H, 3.73; N, 7.40. Found: C, 63.54; H, 3.91; N, 7.32.

c) **Preparation of Wittig ylide 74** (**$Ph_3PCHCOOEt$**).

To the clear solution of triphenyl phosphine (TPP) (1.1 equiv.) in benzene was added ethyl 2-bromoacetate (1 equiv) slowly and kept stirring for overnight at room temperature. Lump like solid was formed and the reaction mixture was filtered and washed with benzene several times to remove unreacted TPP and dried well. To the dried solid (1 equiv.), NaOH solution (15%) (1.2 equiv.) was added and kept for stirring. After 2 h, solid separated out, filtered and after several water washings, obtained pure white solid of $Ph_3PCHCOOEt$.

d) **Ethyl-4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)but-2-enote (75)**. To a stirred solution of N-phthalimido acetaldehyde (2.5 g, 13.23 mmol, 1 equiv.) (**73**) in dry DCM (30 mL), was added $Ph_3PCHCOOEt$ (1.5 equiv.) (**74**) at 0 ^{0}C. After addition, the reaction mixture was brought to room temperature and stirred for another 2.5 h. The reaction mixture was quenched with water and

diluted with DCM. The organic layer was separated, washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography (hexane: ethyl acetate 3:1) afforded the compound **75** as colourless crystals in 78% yield (2.67 g).

Physical State: Colurless crystalline solid; mp 93-95 ^{0}C.

IR (neat): ν 2923, 2361, 1773, 1714, 1389, 715 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= 1.14 (t, *J*=6.1 Hz, 3H), 4.05 (q, *J*=6.1 Hz, 2H), 4.34 (d, *J*=5.5 Hz, 2H), 5.77 (d, *J*=6.1 Hz, 1H), 6.81 (m, 1H), 7.69-7.78 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 13.9, 37.9, 60.2, 122.8, 123.2, 131.6, 133.9, 140.6, 165.2, 167.2.

EIMS: *m/z*= 259 (M^+).

Anal. Calcd for $C_{14}H_{13}NO_4$ (%): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.69; H, 5.13; N, 5.35.

e) **Procedure A (Pd/bipy catalyzed conjugate addition): Ethyl 4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-(4-chlorophenyl) butanoate (76)**. To a Schlenk tube were added 4-chloro phenylboronic acid (3.6 g, 23.1 mmol), ester **75** (2 g, 7.7 mmol), $Pd(OAc)_2$ (86.24 mg, 0.385 mmol), bipy (0.24 g, 0.20 mmol), HOAc (0.2 mL), THF (0.1 mL), and H_2O (0.05 mL) under argon. The mixture was stirred and heated at 40 °C for 2 days until the substrate disappeared as monitored by TLC. The reaction mixture was neutralized with saturated $NaHCO_3$ and then extracted with Et_2O. The combined ether solution was washed with brine solution, dried ($MgSO_4$), and concentrated. The residue

was purified by flash chromatography (EtOAc/petroleum ether 1:20) to give the product **76** as a colourless crystalline solid in 82% yield (2.35 g).

f) **Procedure B (Rh/BINAP catalyzed conjugate addition): Ethyl (3R)-3-(4-chlorophenyl)-4-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl)butanoate (76a).** A solution of $[Rh(acac)(C_2H_4)_2]$ (1.00 mg, 3.87 μmol, 0.03 equiv) and (S)-BINAP (3.62 mg, 5.81 μmol, 0.045 equiv in anhydrous dioxane (2 mL) was stirred for 2 hours at ambient temperature under nitrogen. Cs_2CO_3 (84.1 mg, 258 μmol, 2 equiv), *p*-chloroboronic acid (645 μmol, 5 equiv), phthalimide protected α,β-unsaturated ester **75** (129 μmol, 1 equiv) and H_2O (0.2 mL) were successively added at room temperature and the mixture was heated at 100 ^{0}C for 2 days. Added EtOAc (15 mL) and the mixture was extracted with H_2O (10 mL). The organic layer was dried and concentrated *in vacuo*. Flash chromatography (silica gel, EtOAc-petroleum ether, 15:85) furnished **76a** in 65% yield.

Physical State: Colurless crystalline solid; mp 113-115 ^{0}C.

HPLC: DAICEL Chiralpak AD-H column; length: 25 cm + 1 cm precolumn; flow: 0.5 mL/min; eluent: *n*-hexane-*i*-PrOH (70:30); t_R (S) 27.4 min, t_R (R) 36.7 min.

IR (neat): ν 3433, 2968, 2925, 2852, 1773, 1708, 1397, 718, 672, 525 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)= (t, *J*=7.1 Hz, 3H), 2.69 (m, 2H), 3.75 (m, 1H), 3.91 (m, 4H), 7.23 (m, 4H), 7.70-7.76 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm)= 14.0, 38.5, 40.2, 42.9, 60.5, 123.3, 128.7, 129.1, 131.8, 133.0, 134.1, 138.9, 168.0, 171.1.

EIMS: *m/z*= 371 (M^+).

Anal. Calcd for $C_{20}H_{18}ClNO_4$ (%): C, 64.61; H, 4.88; N, 3.77. Found: C, 64.39; H, 4.87; N, 3.82.

g) **4-Amino-3-(4-chlorophenyl)butyric acid hydrochloride (1/1a).** Compound **76** or **76a** (5.39 mmol) (2 g), in ethyl alcohol (75 mL) and 80% aq. hydrazine hydrate (5 mL) were heated at reflux for overnight. The mixture was left at room temperature for 10 h, the precipitate formed was filtered off, washed with ethanol (10 mL). After addition of 6N HCl (3.5 mL), the filtrate was concentrated to half of its volume, the formed precipitate was filtered off and the filtrate was concentrated again to furnish the desired compound **1/1a** as crystalline solid in 58% and 45% yields respectively (0.74 g, 0.58 g).

Physical State: Colurless solid; m.p.198-200 °C (lit.[9a] 195°C);

Optical rotation: $[\alpha]_D^{25}$ = - 1.64 (c 0.32, H_2O), lit. $[\alpha]_D^{25}$ =2.0 (c 0.6, H_2O); ee= 96.5%.

IR (KBr, λ_{max}): ν 3000, 1720, 1580, 1490, 1410, 1200, 1190, 1125, 1010, 950, 825 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm)= 2.65–2.91 (AB part from ABX, J_{AB}=16.6 Hz, J_{AX}=6.9 Hz, J_{BX}=7.7 Hz, 2H), 3.10–3.39 (AB part from ABX, J_{AB}=12.8 Hz, J_{AX}=6.0 Hz, J_{BX}=8.9 Hz, 2H), 3.64–3.72 (m, 1H), 7.41–7.43 (m, 4H).

^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm)= 37.7, 48.5, 128.8, 128.9, 131.2, 141.8, 176.0.

EIMS: *m/z*= 213 (M^+).

Anal. Calcd for $C_{10}H_{12}ClNO_2$ (%): C, 56.21; H, 5.66; N, 6.56; Found: C, 56.15; H, 5.72; N, 6.54.

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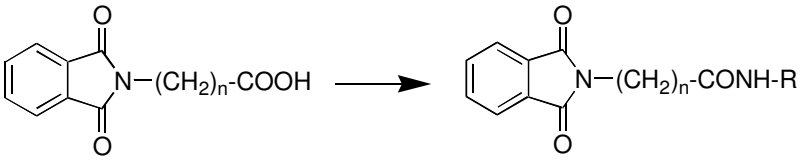
3.1.1. INTRODUCTION

Glycine and γ-aminobutyric acid (GABA) are inhibitory amino acid neurotransmitters in the brain. Their structures have been incorporated into several compounds, which showed anticonvulsant properties in several models[1-3] including phthalimido derivatives of glycine and its monoalkyl amides[4] and dialkyl amides[5] as well as phthalimides of GABA. [4-9]

.1.1 General survey of N-Phthaloyl glycine derivatives, Functionalized tones and Piperazines

Scriba *et al*.[8] reported the synthesis and anticonvulsant activity of *N*, *N*-phthaloyl derivatives of central nervous system inhibitory amino acids (Figure 1). The compounds were tested for anticonvulsant activity according to standard procedures, which included the maximal electroshock seizure test and the seizure threshold test with subcutaneous pentylenetetrazole, eg., N-phthaloyl glycine amides, the N, N-phthaloyl GABA amides (Figure 2).



1a-g

	n	R
1a	1	H
1b	1	C_2H_5
1c	1	$CH(CH_3)_2$
1d	1	CH_2-Ph
1e	3	H
1f	3	Ph
1g	3	$CH(CH_3)_2$

Figure 1

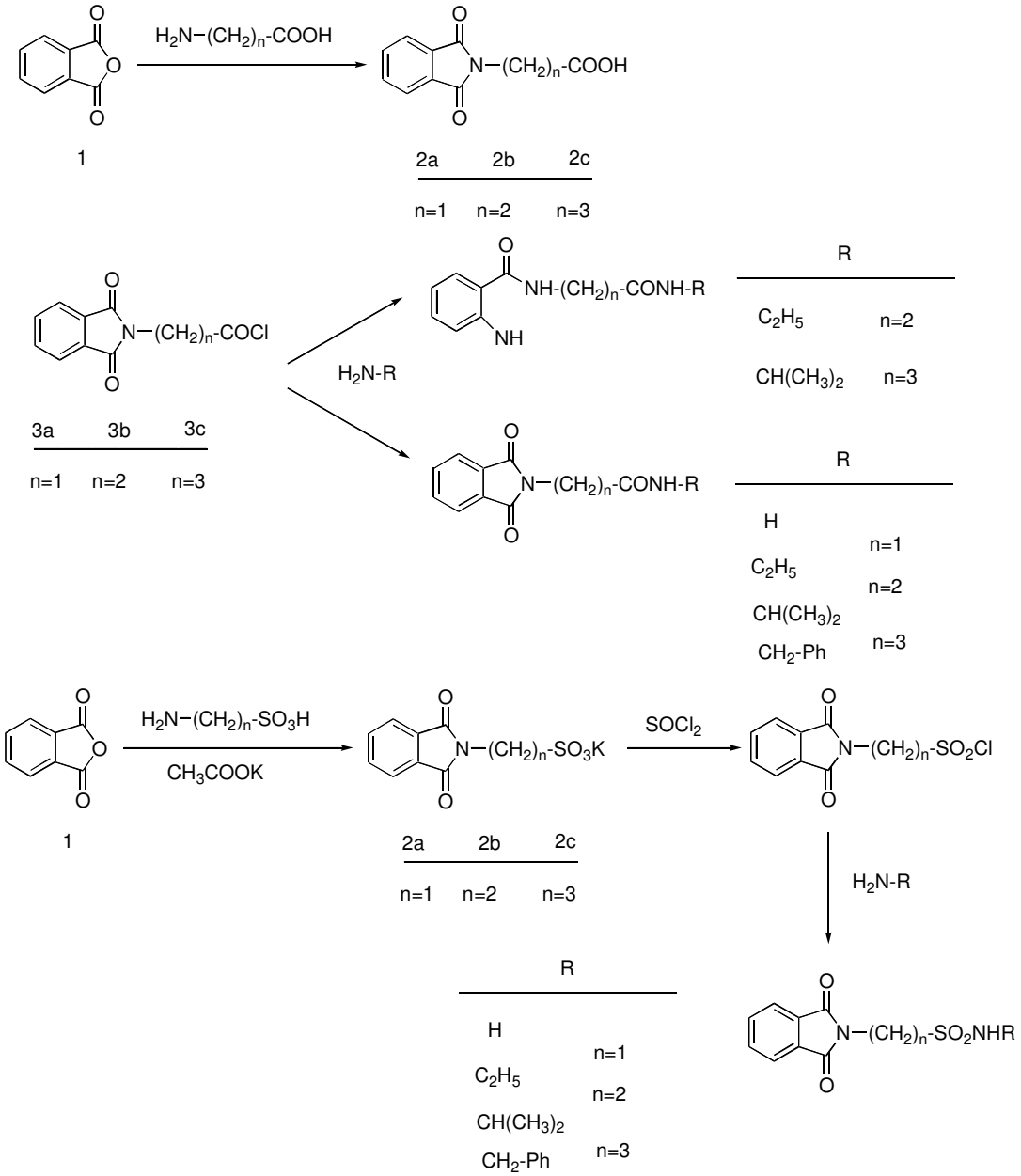


Figure 2. Anticonvulsant activity of N, N-phthaloyl derivatives of central nervous system inhibitory amino acids.

Abdohallahi *et al.*[10] have recently reported N-phthaloyl glycine derived benzoxazinone analogues (Figure 3), which are found to be having antiphlogistic, hypnotic and antimicrobial activities.

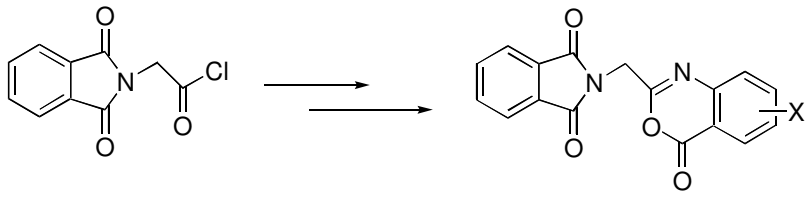


Figure 3

R. M. Srivatsava *et al*.[11] synthesized a new class of oxadiazolo-phthalimides (Figure 4) as peripheral analgesics derived from N-phthaloyl glycine.

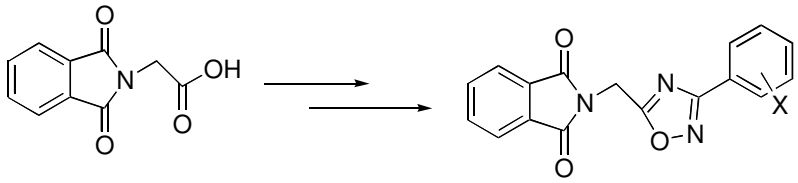


Figure 4

N-phthaloylamino acid hydroxamates of general formula $C_6H_4(CO)_2N$-X-CONHOH (X = amino acid residue) contain two biologically active groups in their structures, phthalimido and *N*-hydroxyamido (Figure 5).[9]

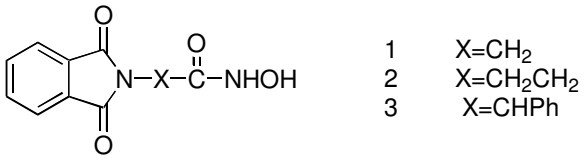


Figure 5

Phthalimides have been known for a long time as plant growth regulators, bacteriostatics and fungicides.[12] Thalidomide is the best-known phthalimide, a hypnotic/ sedative drug with teratogenic effect. Nevertheless, thalidomide has never completely vanished as a therapeutic substance. The drug was found to have a powerful anti-inflammatory effect owing to its ability to inhibit the production of the cytokine tumor necrosis factor alpha (TNF-α), a potent stimulator of inflammation, cellular necrosis and tissue damage in general. It is also effective for mycobacterial infection in the central nervous system such as tuberculous meningitis caused by *Mycobacterium bovis* or *Mycobacterium bacillus*.[13] The other active part in phthalimidohydroxamate structures is the *N*-hydroxyamido group (hydroxamic acid). Some natural hydroxamic acids, products of various microorganisms and fungi, act as

growth factors or possess antitumour and antibacterial activity.[14] In biomedical sciences, hydroxamic acid moieties are used in the design of therapeutics targeted at cancer, cardiovascular diseases, Alzheimer's disease, malaria, allergic and infective diseases, metal poisoning and other metal overload diseases, *e.g*. after transfusions in the genetic blood disease Cooley's anemia.

Barreiro *et al.*[15] synthesized novel N-phenyl-phthalimide functionalized derivatives having antiinflammatory activity (Figure 6).

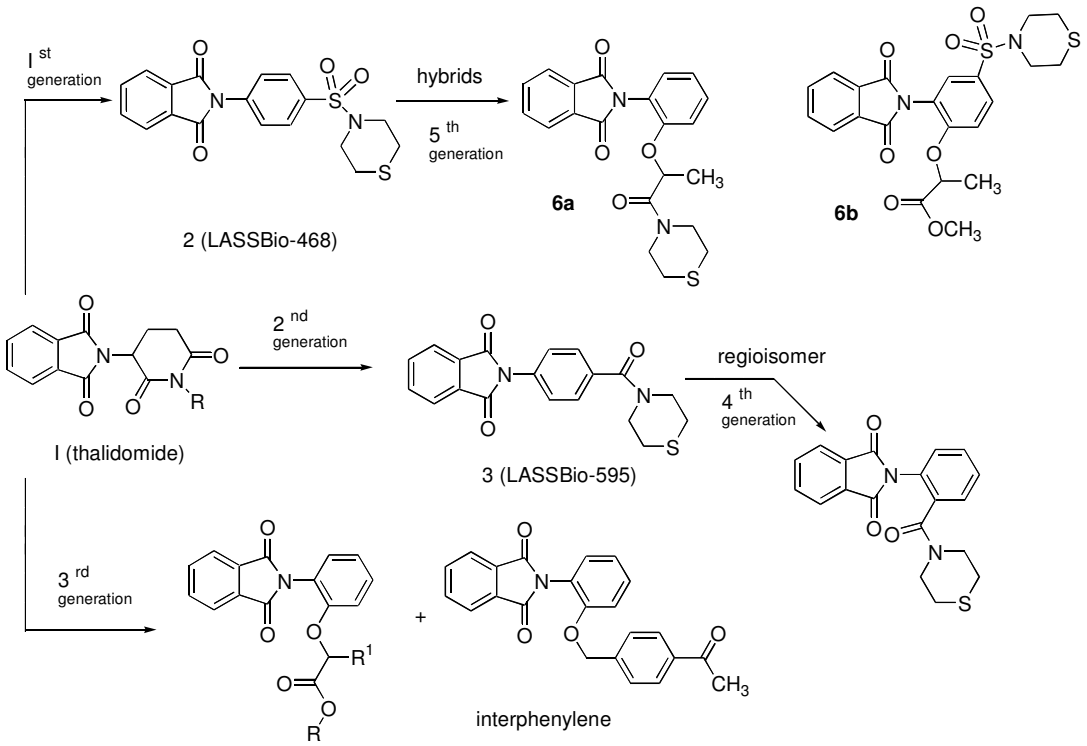


Figure 6

Recently, Lima *et al.*[16] demonstrated that LASSBio-468 (2-[4-(1,4-thiazinan-4-ylacid) phenyl]-1,3-isoindolidinedione) a new synthetic thalidomide analogue, could inhibit the TNF-α production induced by lipopolysaccharide (LPS), *in vivo*.

Again Barreiro *et al.* extended the synthesis and anti-inflammatory activity of new N-phenyl-phthalimide sulfonamides (Figure 7) and the isosters N-phenyl-phthalimide amides, designed as hybrids of thalidomide and aryl sulfonamide phosphodiesterase inhibitor.[17]

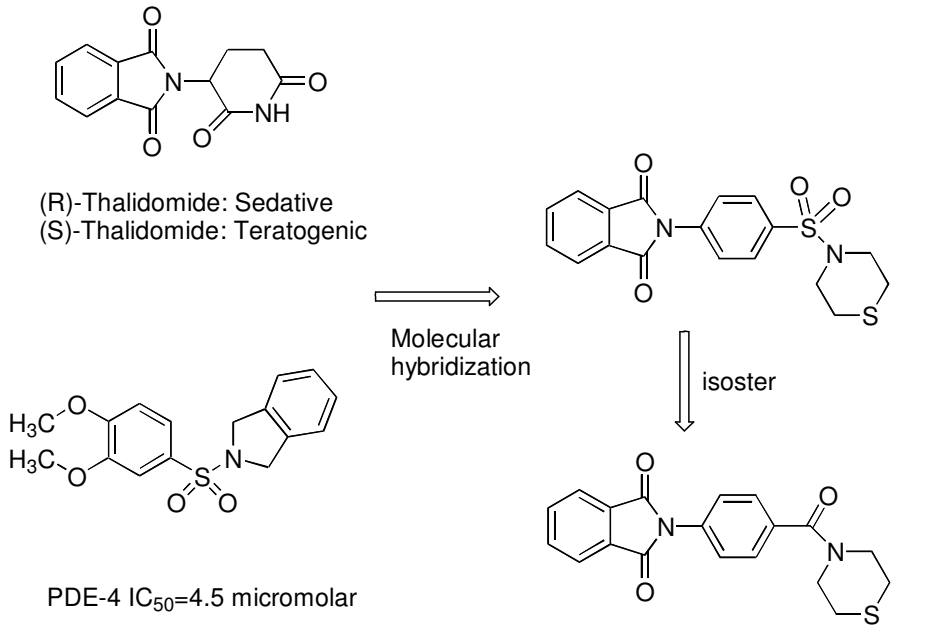
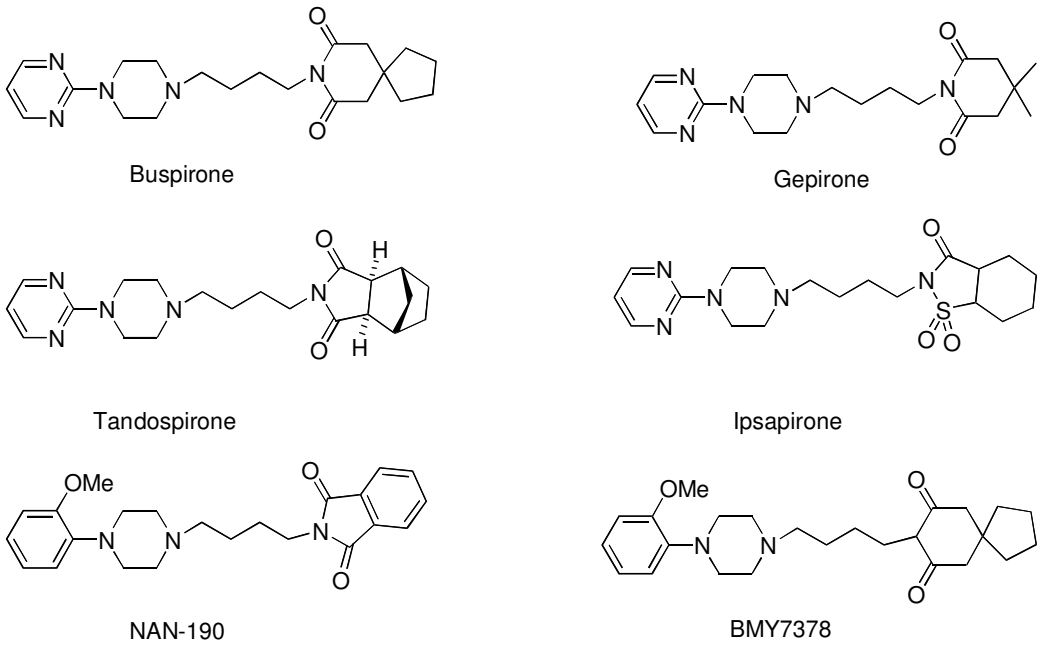


Figure 7

New and efficient antidepressants, 1-aryl-3-(4-arylpiperazin-1-yl)propane derivatives were designed, synthesized, and evaluated for 5-HT reuptake inhibition and 5-HT_{1A} receptor antagonism (Figure 8).[18, 19]



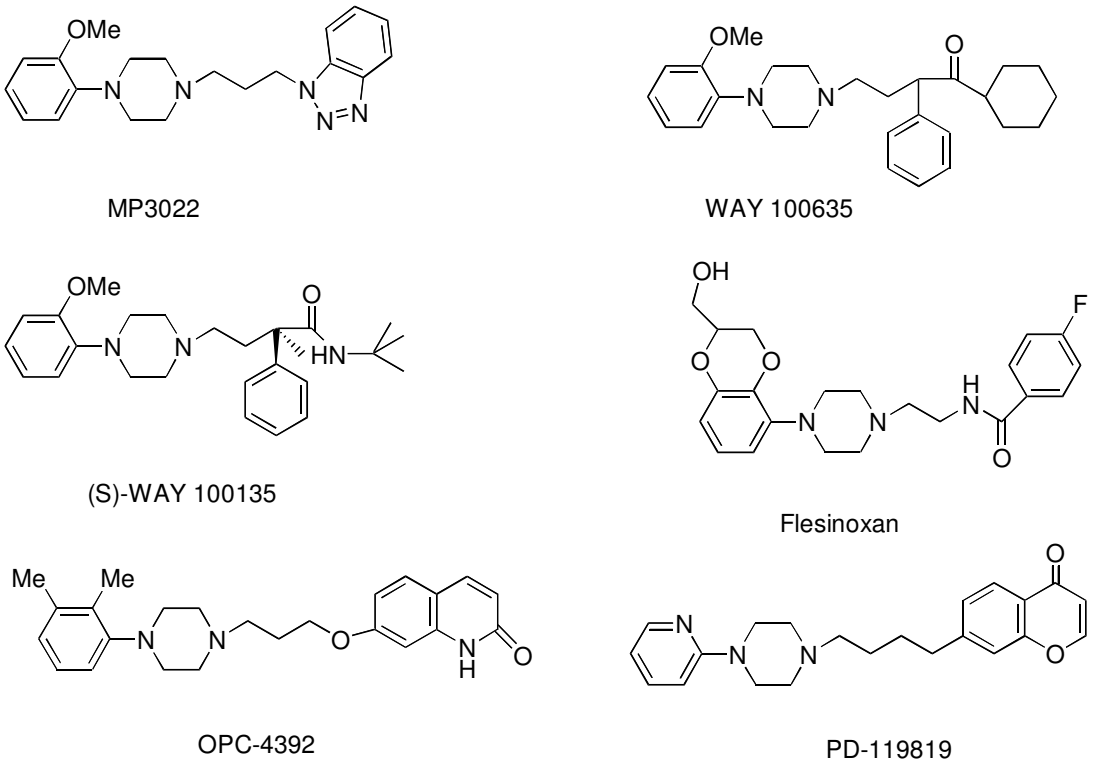


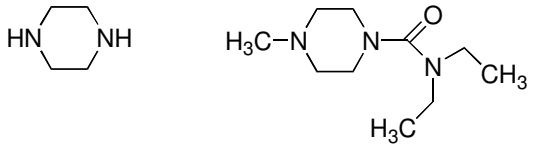
Figure 8

Quantitative structure-activity relationships (QSAR) was performed to correlate the physicochemical properties, ie, electronic, hydrophobic, and steric properties with the HIV-1 reverse transcriptase inhibitory activity of phthalimide derivatives.[20]

Some related functionalized ketones of biological importance

Piperazines and their keto analogues are amongst the most important backbones in today's drug discovery industries. Owing to the high number of positive hits encountered in biological screens with this heterocycle and its congeners, the piperazine template certainly deserves the title of "*privileged scaffold*" in medicinal chemistry. (Privileged scaffolds are molecular backbones with versatile binding properties representing a frequently occurring binding motif, and providing potent and selective ligands for a range of different biological targets). Moreover, the piperazine scaffold occurs regularly in complex natural products. Thus, it is no wonder that there is a plethora of different synthetic methods that allow for the fast and efficient assembly of these heterocyclic systems.

Simple piperazine can be regarded as azo-piperidine, itself is still employed as an anthelmintic for the treatment of pinworm (*Enterobius vermicularis)* and round worm (*Ascaris lumbricoides*) infections, for instance DEC (dimethyl carbamazine) is currently the primary therapeutic agent for the treatment of filariasis (Figure 9).

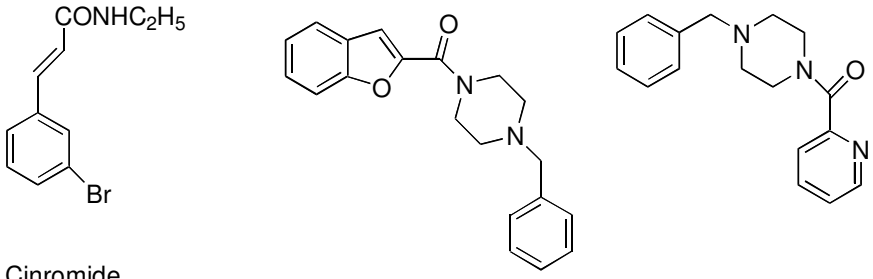


Piperazine Diethyl carbamazine (DEC)

Figure 9

Some of the functionalized piperazines show CNS sedative and antidepressant properties (Figure 10).[21]

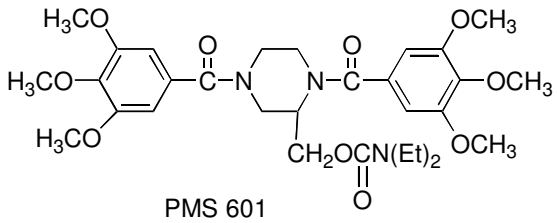
Cinromide - *CNS sedative*; **Befuraline** and **Piberaline -** *Antidepressants*



Cinromide Befuraline Piberaline

Figure 10

Examples of functionalized piperazines showing platelet-activating factor antagonists with anti-HIV-1 activity (Figure 11).[22]



PMS 601

Figure 11

Examples of functionalized piperazines showing α_1-adrenoreceptor blocking and antioxidant properties eg., Prazosin (Figure 12).[23]

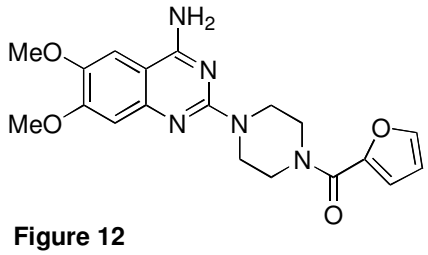
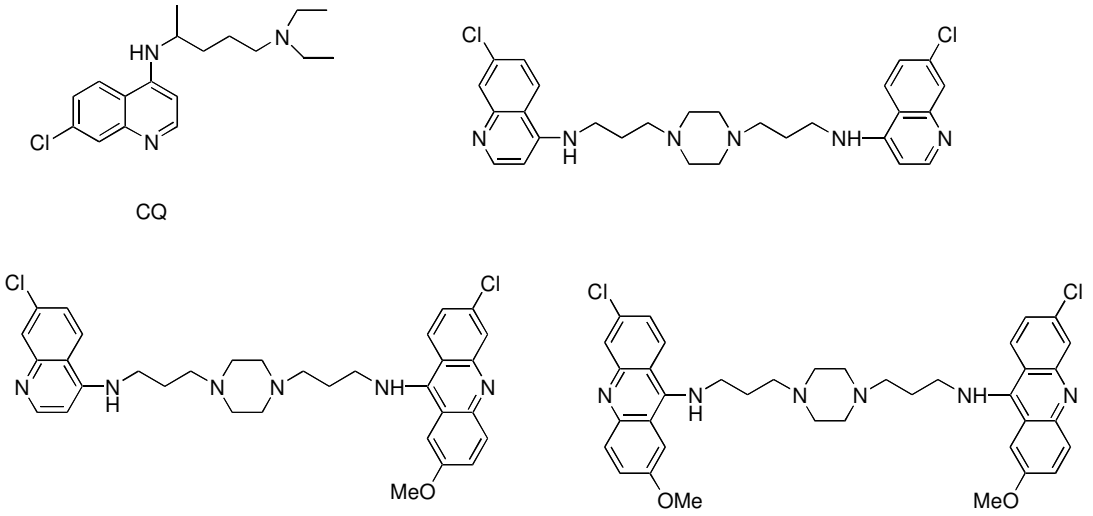


Figure 12

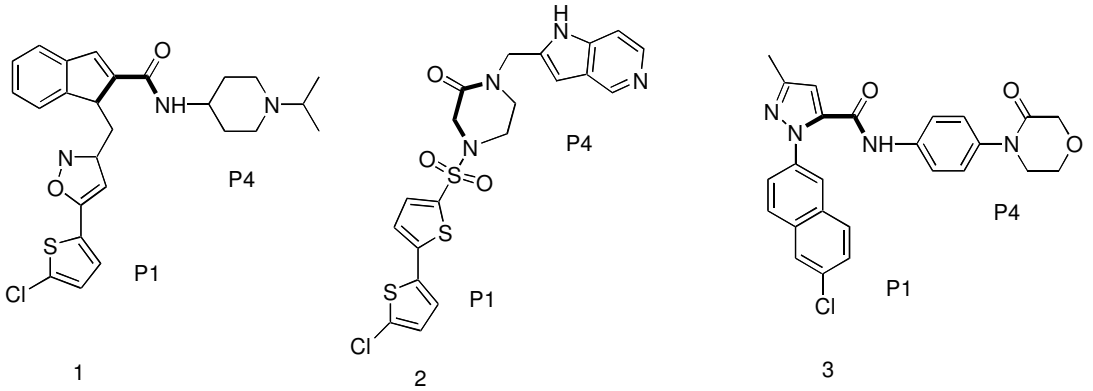
1,4-bis(3-aminopropyl)piperazine linker and a large variety of terminal groups were also synthesized. The aim was to prove that in related bisquinoline, it is the second quinoline moiety that is responsible for cytotoxicity and that it is not an absolute requirement for overcoming resistance to chloroquine (CQ) (Figure 13).[24]



CQ

Figure 13

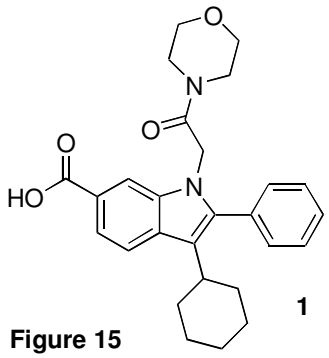
Some examples of substituted indole scaffolds acting as P4 and P1 Inhibitors (Figure 14).[25]



1 2 3

Figure 14

Allosteric indole-*N*-acetamide inhibitors, typified by **1** (Figure 15), that are potent inhibitors of the NS5B enzyme and show promising activity in the replicon assay.[26]



1

Figure 15

Discovery of a 3-Amino-6-phenyl-pyridazine derivative as a new synthetic antineuroinflammatory compound (Figure 16).[27]

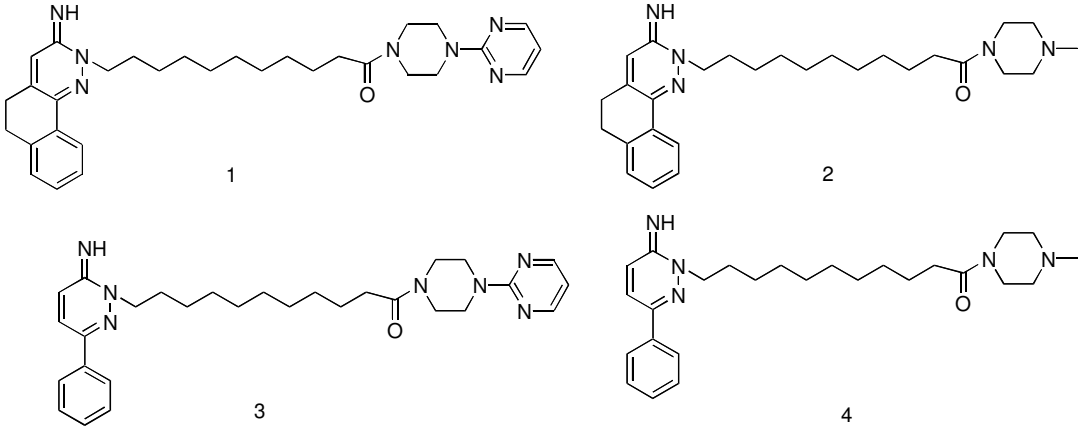


Figure 16

3.1.2 PRESENT WORK

3.1.2.1 Objective

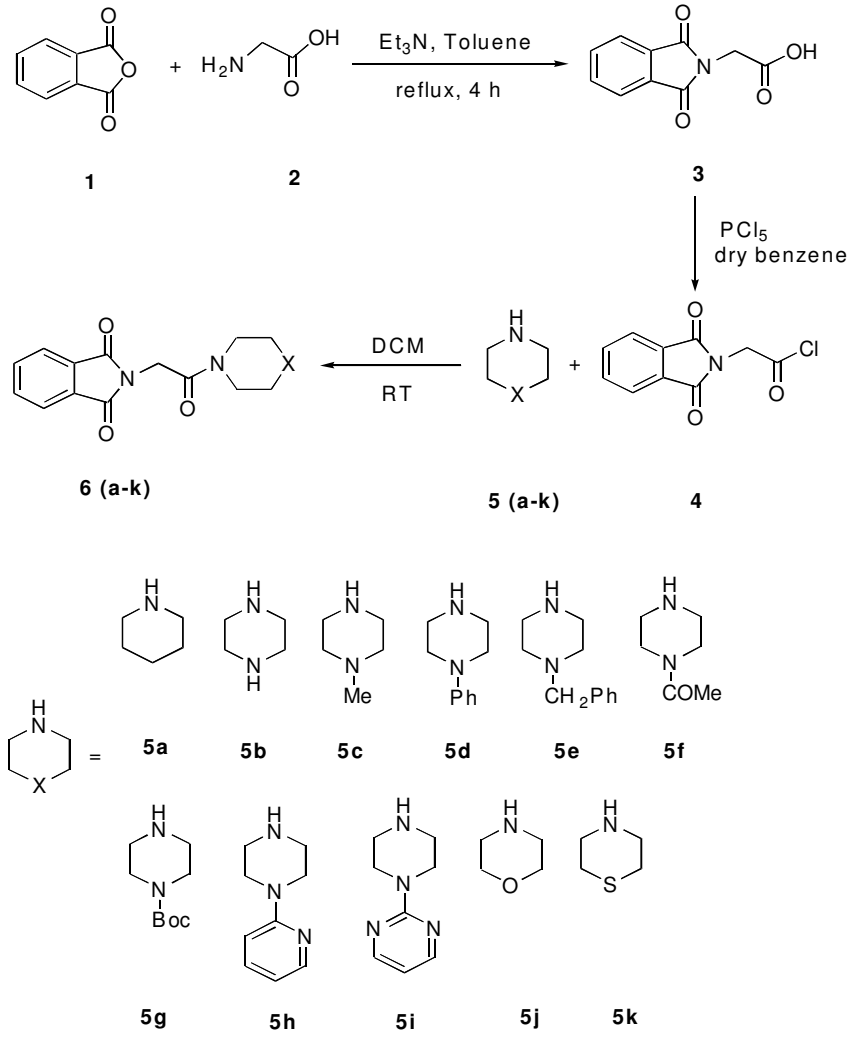
These findings clearly indicate that N-phthaloyl aminoacid conjugates linked through piperazine moiety side arm with alkane spacers may exhibit good pharmacological activities.

3.1.2.2 Synthesis and Characterization of N-Phthaloyl glycine derived functionalized piperazines

A new series of N-phthaloyl glycine derived functionalized piperazines (**6a-k**) were envisaged, resulting from the combination of N-phthaloyl glycine chloride (**4**) and structurally divergent piperazines (**5a-k**) with potent antimicrobial activity (Scheme 1).

Chemistry

In the present study, N-phthaloyl glycine chloride **4** was prepared in two steps.



Scheme 1. Synthesis of N-Phthaloyl glycine derived functionalized piperazines

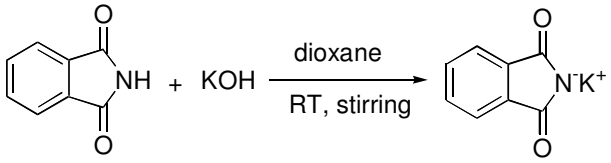
Initially, N-phthaloyl glycine **3** was prepared by condensing phthalic anhydride and glycine in the presence of triethyl amine, toluene under reflux conditions using Dean-Stark apparatus to afford as a white crystalline solid in 95% yield. Next, several chlorination procedures were adapted *viz*., i)

PCl_5/dry benzene, ii) $SOCl_2$, Et_3N, iii) oxalyl chloride/DCM, but involving procedure i) the corresponding 2-phthalimido acetyl chloride could be obtained in excellent yield. A mixture of **3** and phosphorus pentachloride in dry benzene at 50-55 ^{0}C for 1 h and after usual work up and further recrystallization using benzene: pet.ether to afford compound **4** as off-white solid in 92% yield.

To a solution of acyl chloride **4** was allowed to react with commercially available functionalized piperazine derivatives (**5a-k**) in DCM at ambient temperature to give the acylamide derivatives **6a-k** in good yields. The formation of **3** was confirmed by the ^{1}H-NMR spectrum, which showed a singlet at δ 4.25 (CH_2) and its mass spectrum showed the molecular ion peak at *m/z* 205. The characterization of acyl chloride **4** was proved by the singlet at δ 4.78 (CH_2) and molecular ion peak at *m/z* 225. Acyl amides (**6a-k**) were fully characterized by sufficient spectral data and were subjected to anti-microbial screening as well.

3.1.2.3 Synthesis and Characterization of α-Phthalimido Functionalized Ketones

Apart from the synthesis of N-phthaloyl glycine derived functionalized piperazines (**6a-k**), N-phthaloyl functionalized aryl ketones were also synthesized. Preparation of potassium phthalimide was a key step to accomplish this. Equimolar mixture of phthalimide and KOH were dissolved in dioxane and stirred for overnight at room temperature, resulting a milky suspension (Scheme 2), and the solvent was removed *in vacuo* to afford potassium phthalimide (**8**) as white solid having m.p>300 ^{0}C.[31]

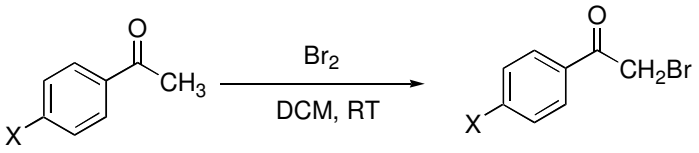


7 **8**

Scheme 2

The α-bromide-ketones were prepared (**9a-j**),[32] as shown in Scheme 3. One equiv. of molecular bromine was added dropwise to a solution of 1.1 equiv.

substituted acetophenones in DCM, followed by usual work-up procedure afforded the desired α-bromide-ketones (Scheme 3).

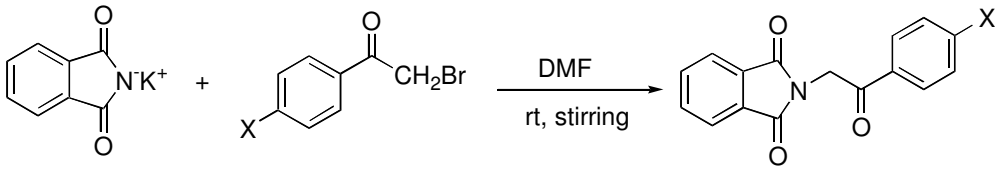


8 **9**

X= H, F, Cl, Br, I, OH, CH_3, OCH_3, NO_2, Ph

Scheme 3

Next target was set to synthesize α-phthalimido functionalized ketones (Scheme 4),[33] To a solution of α-bromide-ketones (10 mmol) in DMF (10 mL) was added 110 mol% potassium phthalimide with stirring at ambient temperature, followed by usual work up and further purification by recrystallizing in ethanol, afforded the corresponding desired products (**10a-j)** in moderate to excellent yields.



8 **9 (a-j)** **10(a-j)**

X= H, F, Cl, Br, I, OH, CH_3, OCH_3, NO_2, Ph

Scheme 4

Finally, the desired α-phthalimido functionalized ketones were also subjected to anti-microbial screening.

3.1.3 Studies on Biological activity of N-Phthaloyl glycine derived functionalized piperazines and functionalized ketones:

Evaluation of antimicrobial activity

The synthesized compounds [(**6a-k**) and (**10a-j**)] were evaluated for *in vitro* antibacterial activity against various bacteria such as *Staphylococcus aureus* ATCC 9144, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922 and Klebsiella pneumoniae ATCC 29665 by disc diffusion method. All the

synthesized compounds were evaluated for their antibacterial activity, all compounds possessed insignificant activity against Gram-positive and Gram-negative bacteria and compared with that of the standard (Ciprofloxacin 50 μg/ml). The antifungal activity of the compounds was tested against C. *albicans* (ATCC 2091) and A. *niger* (ATCC 9029) using sabouraud dextrose agar medium (Hi-Media Laboratories, India), all compounds possessed insignificant activity against the fungi and compared with that of the standard (Ketoconazole 50 μg/ml).

The minimum inhibitory concentration of the synthesized compounds were determined by agar streak dilution method.

Paper disc diffusion method

The sterilized[34] (autoclaved at 120 ^{0}C for 30 min) medium (40-50 ^{0}C) was innoculated (1 mL/100 mL of medium) with the suspension (105 cfu mL^{-1}) of the microorganism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (200 mg mL^{-1} in dimethyl formamide) was placed on the solidified medium. The plates were preincubated for 1 h at room temperature and incubated at 37 ^{0}C for 24 and 48 h for antibacterial and antifungal activities, respectively. Ciprofloxacin (100 □g/disc) and ketoconazole (100 □g/disc) was used as standard for antibacterial and antifungal activities, respectively.

Minimum inhibitory concentration (MIC)

MIC[35] of the test compounds were determined by agar streak dilution method. A stock solution of the synthesized compound (100 mg mL^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity and sabouraud dextrose agar medium for antifungal activity). A specified quantity of the medium (40-50 ^{0}C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. Suspension of the microorganism were prepared to contain approximately 10^5 cfu mL^{-1} and applied to plates with serially diluted

compounds in dimethyl formamide to be tested and incubated at 37 ^{0}C for 24 and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate.

No significant antimicrobial activity was observed for the compounds (**6a-k**) and (**10a-j**).

3.1.4 CONCLUSION

In the present study, synthesis of N-phthaloyl glycine derived functionalized piperazines (**6a-k**) and N-phthaloyl functionalized aryl ketones (**10a-j**) were accomplished. All the compounds were completely characterized using spectroscopic data and subjected to anti-microbial screening as well.

3.1.5 EXPERIMENTAL SECTION

a) Spectral data of N-phthaloyl glycine derived functionalized piperazines:

1. Preparation of N-phthaloyl glycine (2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl)acetic acid (3):[28]

The preparation **3** for the synthesis of the title compound is as follows: A mixture of phthalic anhydride (7 g, 42.29 mmol), glycine (3.60g, 47.61 mmol) and triethyl amine (0.7 mL) in toluene (250 mL) was heated under reflux for 4 h while azeotropic removal of water using Dean-Stark apparatus.[2] The reaction mixture was concentrated at reduced pressure, added ethyl acetate to the residue, washed the organic phase with dilute HCl (1N) to eliminate the unreacted triethylamine, dried over $MgSO_4$, concentrated to yield the N-phthaloyl glycine **3** as a solid (9.22 g, 95%).

White crystalline solid; Mp: 193-195 ^{0}C; IR (KBr): ν 3426, 2985, 2933, 1772, 1726, 1413, 1245, 1245, 954, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25 (s, 2H), 7.77 (m, 2H), 7.82 (m, 2H); Mass (EI): *m/z* 205, 160, 104, 76, 41.

2. Preparation of N-phthaloyl glycine chloride (2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethanoyl chloride) (4):

Procedure A: A mixture of N-phthaloyl glycine (**3**) (4.5g, 22 mmol) and phosphorus pentachloride (4.5 g, 22 mmol) in dry benzene was heated in an oil bath at 50-55 ^{0}C for 1 hour. The slightly yellowish solution was separated from the remaining phosphorus pentachloride by filtration. After concentration to dryness under reduced pressure, the solid was recrystallized from benzene: pet. ether and dried under reduced pressure to give the corresponding 2-phthalimido acetyl chloride **4** as solid (4.48 g, 92%).[29]

Procedure B: N-phthaloyl glycine (**3**) (4.5g, 22 mmol) was placed in a 100 mL round-bottom flask and then thionyl chloride (20 mL) was added. After adding one drop of triethylamine, the mixture was refluxed for 8 h. Toluene (75 mL) was added to the flask, and by distillation of toluene, the excess thionyl chloride was removed. The resulting acyl chloride **4** (2.86 g, 58 %)was used directly for the next step.[10]

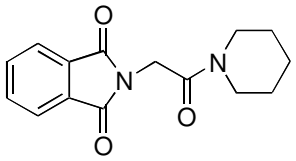
Procedure C: *N*-phthaloyl glycine **1** (4.5 g, 22 mmol, 1 eq.) was dissolved in anhydrous THF (50 mL) under N2 atmosphere and pyridine was added (0.3 mL). Under vigorous stirring, a 2.05 M solution of oxalyl chloride (3.90 g, 30.7 mmol, 1.4 eq.) in anhydrous DCM (15 mL) was added dropwise at room temperature over 1 hour. The solution was heated at 40 °C for 10 more minutes and concentrated to 20 mL; anhydrous Et_2O (20 mL) was added and the mixture was filtered through a pad of charcoal and Celite®. The filter cake was washed with dry Et_2O (100 mL) and the solvent was removed under reduced pressure yielding **4** as an off-white powder (3.85 g, 78 %), which was kept under N2.[30]

Off-white powder, Mp: 83-85 ^{0}C; IR (KBr): ν 3478, 2979, 2935,1851, 1771, 1718, 1608, 1406, 1252, 934, 712, 522 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78 (s, 2H), 7.70-7.81 (m, 2H), 7.85-7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.64, 124.01, 131.59, 134.77, 166.60, 169.19; Mass (EI): *m/z* 225, 161 (M-COCl), 105, 76, 50.

3. General procedure for the preparation of acylamides (6a–k)

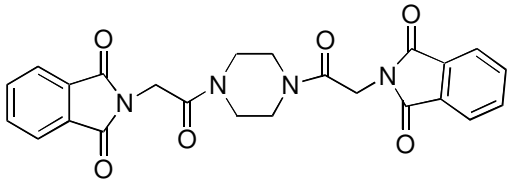
To a solution of acyl chloride derivative (**4**) (5 mmol) in 50 mL of methylene chloride, were added the functionalized piperazine derivatives (**5a-k**, 5.5 mmol). Stirred the reaction mixture for about 30 min, at room temperature, the reaction was monitored by TLC. The corresponding phthalimide derivatives were isolated by addition of 50mL of methylene chloride and extraction with 10% aq HCl and brine. Dried the organic layer over anhyd. Na_2SO_4 and concentrated at reduced pressure to give the acylamide derivatives **6a-k** in good yields.[8]

6a) 2-(2-oxo-2-piperidinoethyl)-1,3-isoindolinedione:



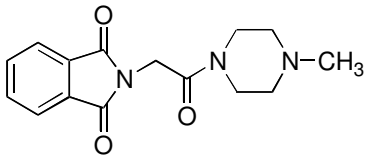
White crystalline solid, Yield 68%, Mp: 193-195 ^{0}C; IR (KBr): ν 3426, 2985, 2933, 1772, 1726, 1413, 1245, 1245, 954, 712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.58-1.74 (m, 6H), 2.95-2.97 (t, 1H), 3.48-3.56 (t, 3H), 4.42 (s, 2H), 7.69-7.72 (m, 2H), 7.85-7.90 (m, 2H); Mass (EI): *m/z* 272.

6b) 2-(2-4-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)acetyl]piperazino-2-oxoethyl)-1,3-isoindolinedione:



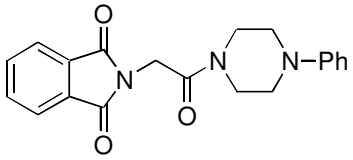
White crystalline solid, Yield 55%, Mp: 185-187 ^{0}C; IR (KBr): ν 3470, 3020, 2926, 2808, 2766, 1774, 1723, 1661, 1450, 1395, 1237, 955, 746, 537 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.38-3.54 (t, 8H), 4.50 (s, 2H), 7.77-7.83 (m, 2H), 7.85-7.96 (m, 2H); Mass (FAB): *m/z* 461$(M+H)^+$.

6c) **2-[2-(4-methylpiperazino)-2-oxoethyl]-1,3-isoindolinedione**:



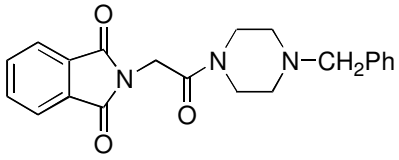
White solid, Yield 75%, Mp: 131-133 ^{0}C; IR (KBr): ν 3470, 2924, 2857, 1775, 1722, 1647, 1455, 1395, 1289, 960, 717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H), 2.35-2.52 (t, 4H), 3.50-3.72 (t, 4H), 4.46 (s, 2H), 7.70-7.75 (m, 2H), 7.82-7.92 (m, 2H); Mass (EI): *m/z* 287, 232, 162, 143, 100, 71, 59.

6d) **2-[2-oxo-2-(4-phenylpiperazino)ethyl]-1,3-isoindolinedione**:



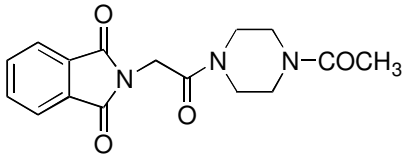
White crystalline solid, Yield 80%, Mp: 201-203 ^{0}C; IR (KBr): ν 3471, 3048, 2985, 2920, 1776, 1713, 1643, 1452, 1394, 1223, 1114, 959, 711 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.32-3.55 (t, 4H), 3.64-3.80 (t, 4H), 4.47 (s, 2H), 6.95- 7.13 (m, 3H), 7.21-7.25 (dd, 2H), 7.78-8.02 (m, 4H) Mass (EI): *m/z* 349, 198, 160, 132, 120, 77, 43.

6e) **2-[2-(4-benzylpiperidino)-2-oxoethyl]-1,3-isoindolinedione**:



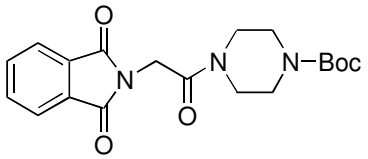
Black solid, Yield 82%, Mp: 110-112 ^{0}C; IR (KBr): ν 3458, 3266, 2931, 1773, 1723, 1410, 1248, 1118, 955, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.41-2.61 (t, 4H), 3.38 (s. 2H), 3.49-3.65 (t, 4H), 4.42 (s, 2H), 7.26-7.34 (m, 5H), 7.68-7.74 (m, 2H), 7.83-7.89 (m, 2H) Mass (EI): *m/z* 363, 160, 146, 104, 91, 43.

6f) **2-[2-(4-aceylpiperidino)-2-oxoethyl]-1,3-isoindolinedione**:



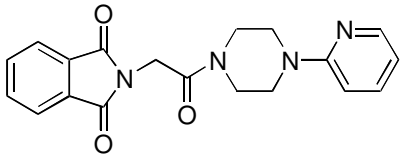
Dark brown solid, Yield 45%, Mp: 256-258 ^{0}C; IR (KBr): ν 3484, 2983, 2885, 1777, 1712, 1688, 1484, 1293, 960, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.35-3.39 (t, 4H), 3.46-3.53 (t, 4H), 4.49 (s, 2H), 7.72-7.76 (m, 2H), 7.86-7.92(m, 2H); Mass (EI): *m/z* 315.

6g) ***tert*-butyl 4-[2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)acetyl]-1-piperazinecarboxylate**:



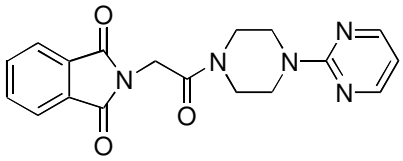
White solid, Yield 90%, Mp: 164-166 ^{0}C; IR (KBr): ν 3474, 2926, 2855, 1779, 1717, 1643, 1463, 1394, 1230, 1113, 958, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 9H), 3.39-3.41 (t, 4H), 3.56-3.74 (t, 4H), 4.45 (s, 2H), 7.68-7.74 (m, 2H), 7.84-7.89 (m, 2H); Mass (EI): *m/z* 373.

6h) **2-2-oxo-2-[4-(2-pyridyl)piperazino]ethyl-1,3-isoindolinedione**:



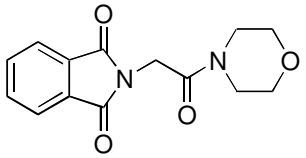
White crystalline solid, Yield 88%, Mp: 220-221 ^{0}C; IR (KBr): ν 3457, 3055, 2908, 1777, 1709, 1689, 1594, 1439, 1242, 958, 725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.49-3.71 (t, 4H), 3.81-3.99(t, 4H), 4.49 (s, 2H), 6.49-6.53 (m, 2H), 7.69-7.73 (m, 1H), 7.85-7.90 (m, 2H), 8.24-8.30 (m, 3H); Mass (EI): *m/z* 350.

6i) **2-2-oxo-2-[4-(2-pyrimidinyl)piperazino]ethyl-1,3-isoindolinedione**:



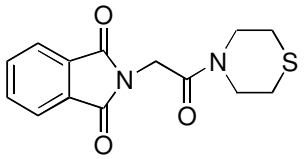
Dark brown flakes, Yield 92%, Mp: 148-151 ^{0}C; IR (KBr): ν 3469, 3023, 2934, 1774, 1716, 1668, 1581, 1444, 1378, 1236, 952, 719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.58-2.91 (t, 4H), 3.33-3.69 (t, 4H), 4.46 (s, 2H), 6.58 (dd, 1H), 7.66-7.86 (m, 4H), 8.12 (d, 2H); Mass (EI): *m/z* 351.

6j) **2-(2-morpholino-2-oxoethyl)-1,3-isoindolinedione**:



Yellow flakes, Yield 85%, Mp: 128-130 ^{0}C; IR (KBr): ν 3448, 2988, 2892, 1777, 1708, 1455, 1278, 1198, 970, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48-3.63 (t, 4H), 3.68-3.85 (t, 4H), 4.43(m, 2H), 7.71-7.77 (m, 2H), 7.86-7.91(m, 2H); Mass (EI): *m/z* 274, 246, 233, 220, 162, 134, 115, 87, 58.

6k) **2-[2-oxo-2-(1,4-thiazinan-4-yl)ethyl]-1,3-isoindolinedione**:



Red solid, Yield 58%, Mp: 118-120 ^{0}C; IR (KBr): ν 3455, 3010, 2898, 1773, 1715, 1484, 1284, 1201, 962, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59-2.81 (t, 4H), 3.77-3.88 (t, 4H), 4.40 (s, 2H), 7.66-7.75 (m, 2H), 7.84-7.95 (m, 2H); Mass (EI): *m/z* 290.

b) Spectral data of α-Phthalimido Functionalized Ketones:

Preparation of potassium phthalimide (8):

Equimolar mixture of phthalimide and KOH were dissolved in dioxane and stirred for overnight at room temperature to form a milky suspension, and the solvent was removed *in vacuo* to afford potassium phthalimide **8** as white solid,[31] which turns into yellow upon exposure to moisture. Soluble in water; Mp= >300 ^{0}C.

Preparation of α-bromide-ketone (9a-j):

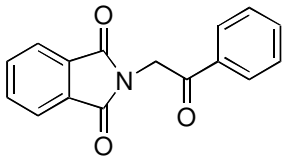
To a solution of substituted acetophenones (4 mmol), added bromine (4.4 ml, 0.2 mol) dropwise in DCM (20 ml) during 10 min, and the reaction mixture was held under stirring at room temperature for 2-5 h. The solvent was evaporated *in vacuo* to afford the desired α-bromide-ketones.

General procedure for the synthesis of phthalimide ketones (10a-j):

In a dried flask, to a solution of α-bromide-ketone (10 mmol) in DMF (10 mL) was added 110 mol% potassium phthalimide with stirring (the reaction could be carried out in the air without special handling; potassium phthalimide was not completely dissolved in the DMF). The reaction was carried out at room temperature and monitored by TLC. After the reaction was complete, the

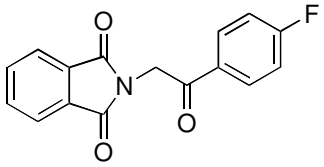
reaction mixture was poured into water (250 mL). The desired products were collected by filtration. The products were further purified by recrystallization from ethanol or isopropanol.

10a) **2-(2-oxo-2-phenylethyl)-1,3-isoindolinedione**:



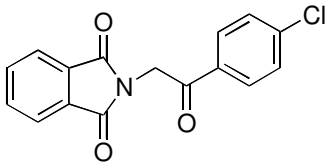
White solid, Yield 78%; IR (KBr, cm^{-1}): ν 2984, 2889, 2864, 1772, 1702, 1698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.86-7.83 (m, 2H), 7.72-7.69 (m, 2H), 7.61-7.56 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.10 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 191.39, 168.28, 134.78, 134.54, 134.44, 132.61, 129.29, 128.54, 123.92, 44.60; FAB-MS: *m/z* 74, 105, 133, 195, 196, 237, 266 $(M+H)^+$.

10b) **2-[2-(4-fluorophenyl)-2-oxoethyl]-1,3-isoindolinedione**:



White solid, Yield 62%; IR (KBr, cm^{-1}): ν 2991, 2878, 2858, 1777, 1708, 1689, 735, 638, 527; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02-7.99 (m, 2H), 7.87-7.85 (m, 2H), 7.73-7.71 (m, 2H), 7.15 (t, *J* = 8.5 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.89, 168.23, 134.58, 132.56, 131.24, 123.96, 116.73, 116.52, 116.35, 44.43; EI-MS: *m/z* 50, 76, 104, 147, 264, 283 $(M)^+$.

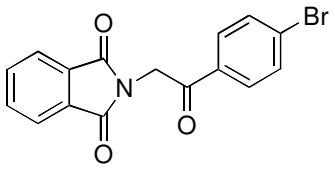
10c) **2-[2-(4-chlorophenyl)-2-oxoethyl]-1,3-isoindolinedione**:



White solid, Yield 74%; IR (KBr, cm^{-1}): ν 2985, 2887, 1774, 1705, 1108, 927, 834, 755; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99-7.87 (m, 4H), 7.75-7.40 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 5.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.35, 168.22, 141.01, 134.61,

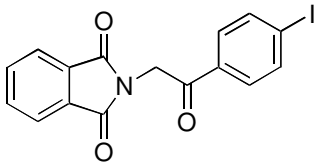
133.11, 132.56, 129.94, 129.67, 124.01, 44.48; EI-MS: *m/z* 50, 77, 104, 140, 160, 299 $(M)^+$.

10d) **2-[2-(4-bromophenyl)-2-oxoethyl]-1,3-isoindolinedione**:



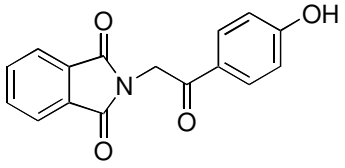
Yellow solid, Yield 80%; IR (KBr, cm^{-1}): ν 2998, 2884, 1767, 1699, 1213, 941, 858, 735, 527; ^1H NMR (300 MHz, $CDCl_3$): δ 7.89-7.84 (m, 4H), 7.75-7.72 (m, 2H), 7.66-7.63 (m, 2H), 5.06 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.53, 168.21, 134.61, 133.51, 132.68, 132.56, 129.99, 129.77, 124.02, 44.45; EI-MS: *m/z* 50, 76, 104, 141, 160, 183, 344 $(M)^+$.

10e) **2-[2-(4-iodophenyl)-2-oxoethyl]-1,3-isoindolinedione**:



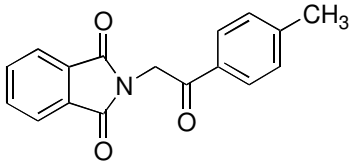
White solid, Yield 85%; IR (KBr, cm^{-1}): ν 2977, 2889, 1775, 1705, 1245, 978, 885, 764, 578; ^1H NMR (300 MHz, $CDCl_3$): δ 7.85-7.79 (m, 4H), 7.72-7.52 (m, 2H), 7.60-7.64 (m, 2H), 5.04 (s, 2H); FAB-MS: *m/z* 109, 119, 133, 175, 211, 370, 392 $(M)^+$.

10f) **2-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,3-isoindolinedione**:



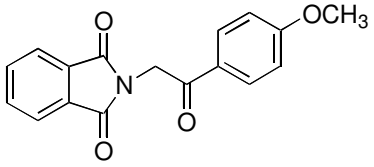
White solid, Yield 45%; IR (KBr, cm^{-1}): ν 3468, 2998, 2957, 2885, 1778, 1704, 1448, 1235, 848, 735; ^1H NMR (300 MHz, $CDCl_3$): δ 7.89-7.75 (m, 4H), 7.71-7.63 (m, 2H), 7.27-7.15 (m, 2H), 5.06 (s, 2H); FAB-MS: *m/z* 282 $(M)^+$.

10g) **2-[2-(4-methylphenyl)-2-oxoethyl]-1,3-isoindolinedione**:



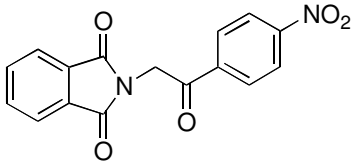
White solid, Yield 82%; IR (KBr, cm^{-1}): ν 2985, 2978, 2964, 1772, 1704, 1398, 1294, 1187, 848, 756; ^1H NMR (300 MHz, $CDCl_3$): δ 7.88-7.83 (m, 4H), 7.73-7.69 (m, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 5.08 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.92, 168.33, 145.41, 134.50, 132.65, 132.33, 130.05, 129.88, 128.60, 123.91, 44.50, 22.17; EI-MS: *m/z* 65, 91, 104, 119, 148, 279 $(M)^+$.

10h) **2-[2-(4-methoxyphenyl)-2-oxoethyl]-1,3-isoindolinedione**:



Shiny creamy solid, Yield 68%; IR (KBr, cm^{-1}): ν 2974, 2968, 2944, 1779, 1701, 1464, 1378, 1278, 1194, 1011, 938; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.9 Hz, 2H), 7.85-7.80 (m, 2H), 7.72-7.67 (m, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.05 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.76, 168.36, 164.54, 134.48, 132.63, 130.84, 127.79, 123.87, 114.46, 55.94, 44.27; EI-MS *m/z*: 50, 64, 77, 92, 105, 108, 136, 161, 213, 295 $(M)^+$.

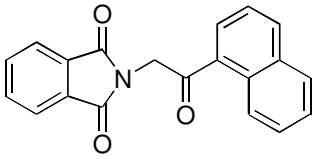
10i) **2-[2-(4-nitrophenyl)-2-oxoethyl]-1,3-isoindolinedione**:



Yellow solid, Yield 92%; IR (KBr, cm^{-1}): ν 2984, 2765, 1772, 1701, 1444, 1413, 1378, 1213, 958, 864, 737, 532; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.9 Hz, 2H),

7.85-7.80 (m, 2H), 7.72-7.67 (m, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.05 (s, 2H), 3.83 (s, 3H); EI-MS: *m/z* 310 $(M)^+$.

10j) **2-[2-(4-hydroxyphenyl)-2-oxoethyl]-1,3-isoindolinedione**:



Yellow solid, Yield 65%; IR (KBr, cm^{-1}): ν 2985, 2935, 2857, 2856, 1781, 1709; ^1H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, *J* = 9.4 Hz, 1H), 8.06 (m, 2H), 7.92 (m, 3H), 7.77-7.75 (m, 2H), 7.56 (m, 3H), 5.16 (s, 2H); FAB-MS: *m/z* 316 $(M)^+$.

3.1.6 REFERENCES

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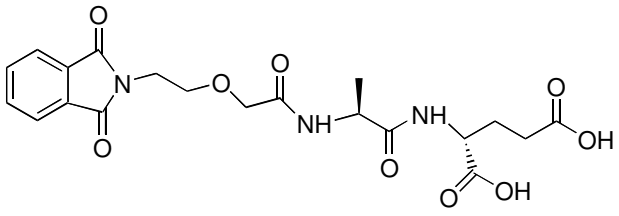
3.2.1. INTRODUCTION

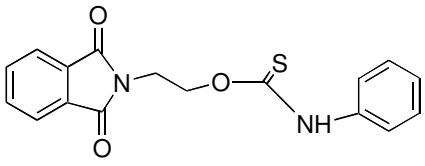
3.2.1.1 History of Ethanolamine Phthalimide Derivatives

Among heterocyclic scaffolds, phthalimides are prominent and widely used as drugs, pharmaceuticals as well as agrochemicals.[1-4] Phthalimide derivatives with phenyl acetic acid and phenyl propionic acid were found to possess anti inflammatory and analgesic properties.[5] Phthalimides are also used in the preparation of synthetic indigo, pigments and dyes. N-Hydroxyethyl phthalimide is used as an intermediate in some drugs, dyes and pesticides.

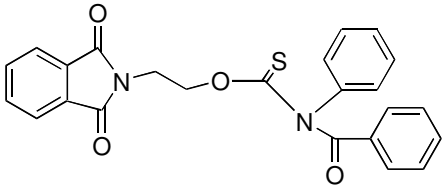
Some new lipophilic MDP analogues such as phthalimido desmuramyl dipeptides were synthesized by replacing N-acetylmuramic acid part with different N-phthaloylated aminoacids.[6-7] The most promising compound in this series is LK 423 (Figure 1) with some interesting immunomodulating activities.



LK 423 (potent immunomodulators)



TC 12 (anti-HIV-1 agent)



ATC-1 (potent inhibitor of wild-type HIV-1)

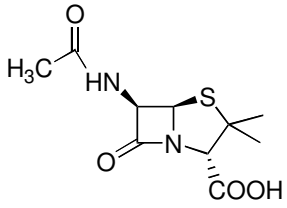
Figure 1

It was found to augment the capacity to produce interleukin-10 in the spleen cells of cyclophosphamide-treated mice,[8] and it alleviated the dextran sulfate sodium-induced colitis in rodents.[9] LK 423 is thus a candidate substance to be developed as an anti-inflammatory pharmaceutical agent.[9]

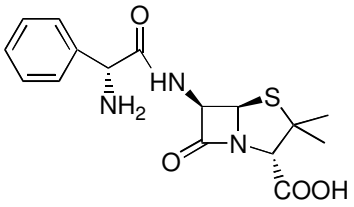
The compound was also able to stimulate the production of tumor necrosis factor in *in vitro* phorbol 12-myristate 13-acetate and ionomycin-stimulated cultures of human peripheral blood mononuclear cells.[10]

3.2.1.2 History of Mandelic acid Derivatives

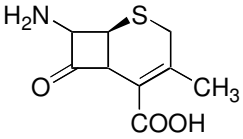
Aromatic hydroxy acids and its derivatives are important biologically and display a range of physiological effects. One such example is the application of mandelic acids in the production of β-lactam antibiotics (Figure 2).[11] A vast literature review reveals that mandelic acid and its derivatives showed anti oxidant,[12] urinary antiseptic,[13] anti HIV,[14] antitumor,[15] antifungal,[16] anti-thrombic effects.[17] They are also used as additives in cosmetics, detergents and moulding of concrete, insect repellants and corrosion inhibitors.



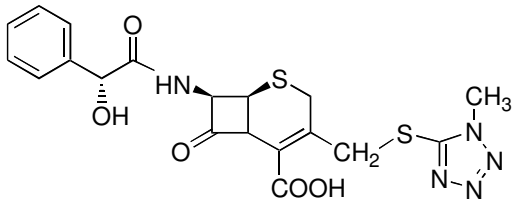
Pencillin G



Ampicillin



Cephalosporin



Cefamandole

Figure 2. β-Lactam antibiotics and the relevance of aminohydroxy acids in the side chains

Florence Pojer *et al.*[18] reported the biosynthesis of Chlorobiocin. The aminocoumarin antibiotics nevobiocin and clorobiocin were synthesized from β-hydroxy-tyrosyl-s-NOVH with mandelic acid moiety (Figure 3). The biosynthesis of this moiety has now been identified by biochemical and molecular biological studies.

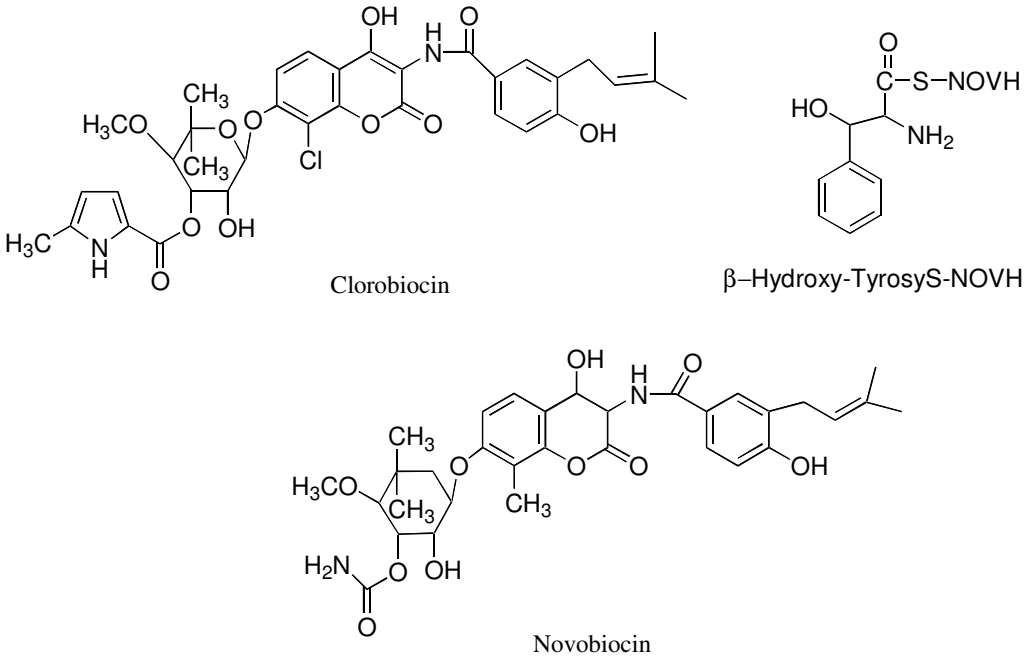


Figure 3

Jean-Michel Vatele *et al.*[19] reported the synthesis of Antitumor Goniothalamus styryllactones with mandelic acid moiety (Figure 4).

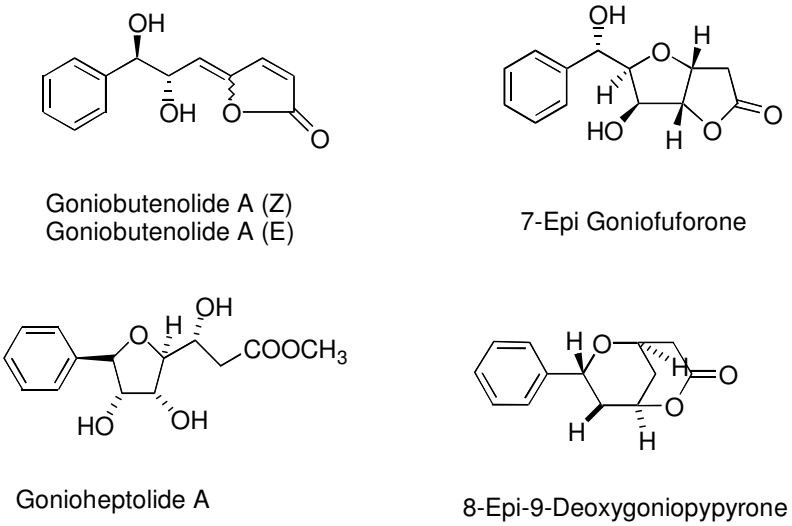
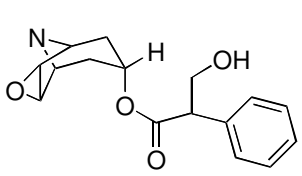
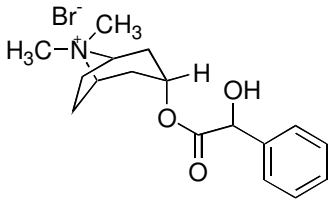


Figure 4

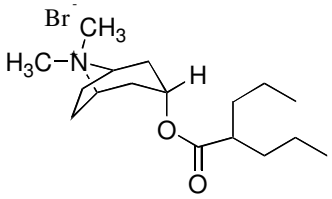
Patrick M. Woster[20] reported naturally occurring Solanaceous alkaloids containing mandelic moiety possess antichlonergic activity (Figure 5).



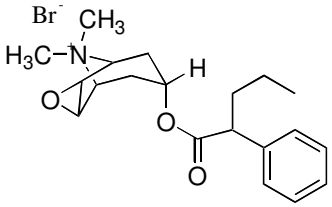
(-)-Scopalamine, Hyoscine
(+)-Atroscine



Homoatropine
methyl bromide



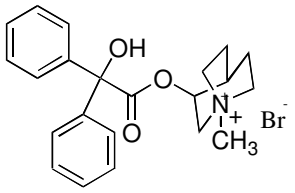
Anisotropine methyl bromide



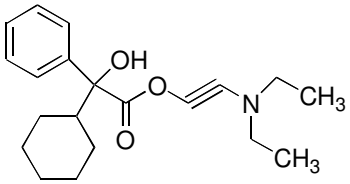
Methyl Scopalamine methyl bromide

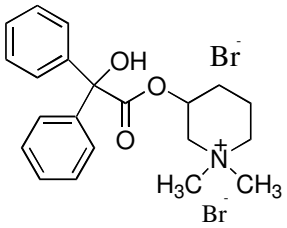
Figure 5

Some synthetic anticholenergic agents - Aminoalcohol esters (Figure 6):



Clidinium bromide
(Qaurazan)





Mepenzole (Cantil)

Figure 6

Zaneveld *et al.*[21] reported the use of mandelic acid condensed polymer (SAMMA), a new antimicrobial contraceptive agent, for vaginal prophylaxis. It inhibits sperm function, and has broad spectrum anti microbial activity, and is highly safe.

Rocchietti *et al.*[22] reported that the usage of acylage from *E. coli* immobilised on glyoxyl agarose by multipoint interaction in the hydrolysis of mandelic acid isopropyl amide at pH 6.5 and at 4°C. These results suggest

that the immobilization of PGA from *E.coli* on different supports may be a useful tool to modulate the catalytic properties.

Lesac *et al.*[23] has reported the synthesis of novel chiral dopents based on optically active *p*-substituted mandelic acids (Figure 7).

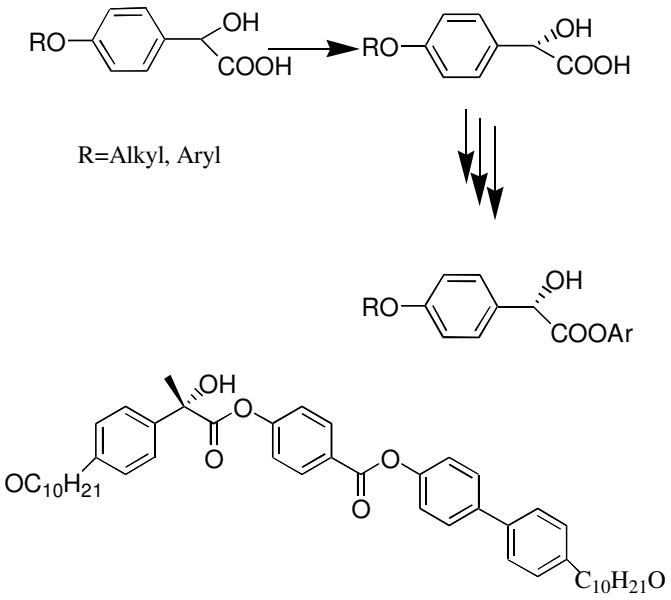


Figure 7

Ting Su *et al.*[24] have reported the design and synthesis of glycolic and mandelic acid derivatives as factor X_a inhibitors. A series of glycolic and mandelic acid derivatives were synthesized and investigated for their factor X_a inhibitory activity.

Chun Yoon *et al.*[25] have reported the synthesis and properties of naphtho difuranones by the reaction of 1,5-dihydroxy napthalene with an appropriate mandelic acid.

Marcus A. Tius *et al.*[26] have reported that cryptophycin 337 is an analogue of the potent anti tumor antibiotic activity. (R)-mandelic acid was used as the sole source of asymmetry for the synthesis of unit - A of this molecule.

B. C. Herold *et al.*[27] have reported the microbicidal activity for prevention of human immuno deficiency virus and Herpes simplex virus entry of mandelic acid condensed polymer (SAMMA). SAMMA is highly

effective against all CCR5 and CXCR4 isolates of HIV in primary human macrophages and peripheral blood mononuclear cells.

Boddie *et al*.[28] have used the mandelic acid (3%) as the germicide in the testing of the germicidal activities of five different teat dip classes against 3 bovine mycoplasma species. Nawrut *et al*.[29] have reported the reaction of (±)-O-acetylmandeyol-chloride with the respective compounds gives the respective products, having antitumor activity.

Pearman *et al*.[30] have reported the antimicrobial activity of urine of paraplegic patients receiving methylamine mandelate.

Ley *et al*.[12] have synthesized 3,4-dihydroxy and hydroxy mandelic acid dopamides with antioxidant property (Figure 8).

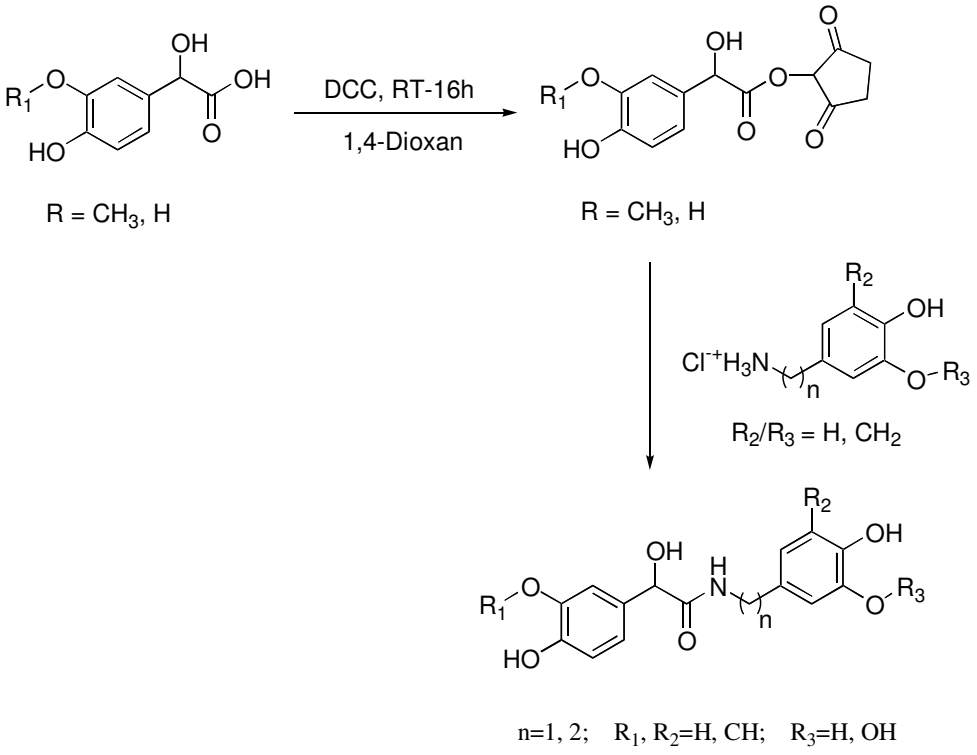
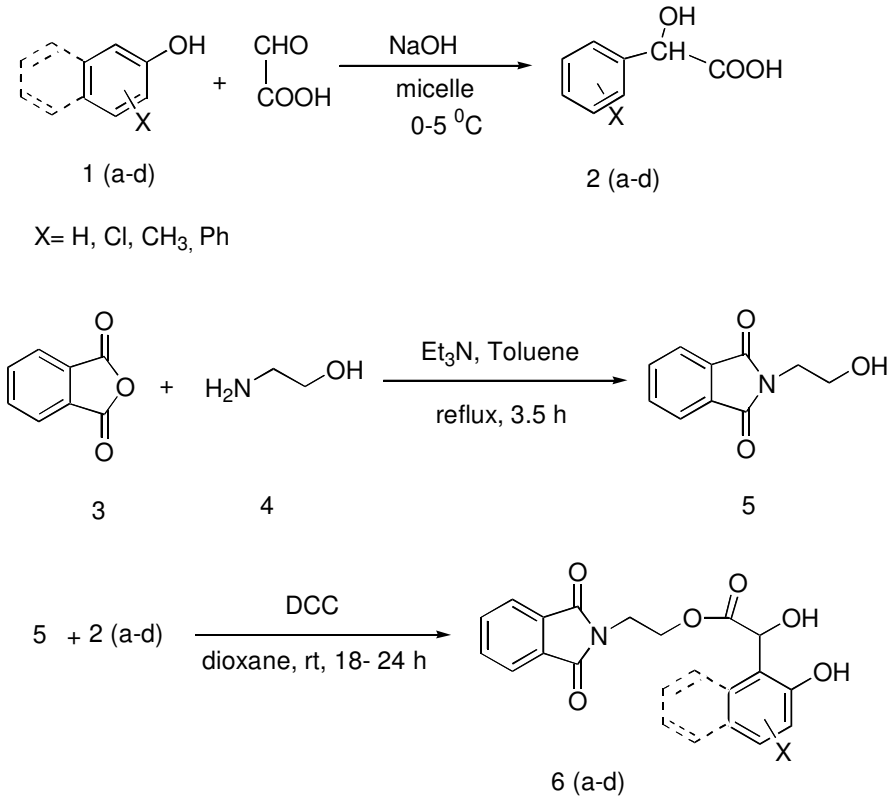


Figure 8. Synthesis of hydroxymandelic acid amides

3.2.2 PRESENT WORK

3.2.2.1 Objective: Synthesis, Characterization of Hybrid Molecules (Mandelic Acid Derived Phthalimides)

A new hybrid series of 2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(substituted) acetates (**6a-d**) were envisaged resulting from the combination of N-(2-hydroxy ethyl) phthalimide (**5**) and substituted mandelic acids (**2a-d**) as seen, would result in compounds with potent antimicrobial and anti-inflammatory activities.



Scheme 1. Synthesis of Mandelic acid derived Phthalimides

In the present study, substituted mandelic acids (**2a-d**) were prepared by reacting a mixture of NaOH solution with the corresponding substituted phenols and glyoxalic acid in the presence of a phase transfer catalyst (CTAB). N-(2-hydroxy ethyl) phthalimide (**5**) was prepared by treatment of phthalic anhydride with ethanolamine and triethyl amine in toluene. Compound **5** was allowed to condense with the above prepared substituted mandelic acids

(**2a-d**) in the presence of dioxane/water to obtain the desired new series of 2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(substituted) acetate (**6a-d**).

3.2.3 Biological activities of Mandelic Acid Derived Phthalimides

a) Biological investigation

The *in vitro* antibacterial (Staphylococcus aureus ATCC 9144, Bacillus cereus ATCC 11778, Escherichia coli ATCC 25922 and Klebsiella pneumoniae ATCC 29665) and antifungal (Candida albicans ATCC 2091 and Aspergillus niger ATCC 9029) activities of the compounds were evaluated by paper disc diffusion method. The sterlized[31] (autoclaved at 120 ^{0}C for 30 min) medium (40-50 ^{0}C) was inoculated (1 mL/100 mL of medium) with the suspension (105 cfu mL^{-1}) of the microorganisms (matched to Mc Farland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (200 µg mL^{-1} in dimethyl formamide) was placed on the solidified medium. The plates were preincubated for one hour at room temperature and incubated at 37 ^{0}C for 24 and 48 hours for anti bacterial and anti-fungal activities respectively. Ciproflaxacin (100 µg/disc) and ketoconazole (100 µg/disc) were used as standard for antibacterial and anti-fungal activities respectively. The observed zone of inhibition is presented in Table-1. And also all the compounds exhibited potent to moderately potent antibacterial and antifungal activities. The compounds were active against all the tested microorganisms compared to ciproflaxacin as standard and with minimum inhibitory concentrations (MIC) values of 40-

45 µg, 41-44 µg, 41 µg, 41-44 µg, 40-45 µg and 41-44 µg against *S.aureus*, *B.cereus*, *E.coli*, *K.pneumoniae*, *A.niger* and *Candida albicans* respectively.

The (MIC)[32] of the test compounds were determined by agar streak dilution method. A stock solution of the synthesized compounds (100 µg mL^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity and sabouraud dextrose agar medium for anti-fungal activity). A specified quantity of the medium (40-50 ^{o}C) containing the compound was poured into a petridish to give a depth of 3-4mm and allowed to solidify. Suspension of the microorganism were prepared to contain approximately 10 cfu mL^{-1} and applied to plates with serially diluted compounds with dimethyl formamide to be tested and

The observed MIC is presented in Table-1.

Antimicrobial activity of the synthesized compounds

In vitro activity-Zone of inhibition(MIC)

	B.cereus	**S.aureus**	**K.pneumoniae**	**E.coli**	**C.albicans** **A.niger**
	(ATCC9144)	(ATCC11778)	(ATCC25922)	(ATCC29665)	(ATCC2091) (ATCC9029)
6a	24(45)	24(25)	24(44)	25(44)	24(44) 17(43)
6b	27(46)	25(45)	26(44)	25(45)	25(43) 16(44)

6c	25(44)	23(43)	27(44)	28(45)	25(43)
16(45)					
6d	32(42)	30(41)	28(41)	32(42)	28(40)
20(15)					
Ciproflaxacin	35(1.2)	32(1.4)	33(0.9)	36(1.2)	-
(50□g/disc)					
Ketaconazole	-	-	-	-	33(2.2)
20(8.9)					
(50□g/disc)					

Zone of inhibition in mm, MIC in □g mL^{-1}

incubated at 37 °C for 24 and 48 h for bacteria and fungi respectively. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate. The observed MIC is presented in Table-1. Acute oral toxicity test was performed for all the synthesized compounds (6a-d) as per organization of economic co-operation and development (OECD) guidelines.

The *in vivo* anti-inflammatory activity of the synthesized compounds (6a-d) was evaluated by carrageenan induced acute paw oedma in rats taking carrageenan as control and indomethacin as standard.

Pharmacology

The synthesized compounds were evaluated for anti-inflammatory activity by using carrageenan induced acute paw oedema method (Table 2). Acute oral toxicity tests were performed for all the synthesized compounds as per organization of economic co-operation and development (OECD) guidelines.

Statistical analysis (ANOVA followed by Dunnett's test) was performed for anti-inflammatory activity to ascertain the significance of the exhibited activity. The test compounds and the standard drugs were administered in the form of a suspension (1% w/v of tween-80 as vehicle)

Animals

Inbred Wistar rats 150-250mg were preserved in colony cages at 25±2^{0}c, relative humidity 45-55% under 12 hrs light and dark cycle. The animals were fed with standard animal feed and water *ad libitum*. All the animals were acclimatized for a week before use.

Acute Oral Toxicity

Acute oral toxicity[14] was performed as per OECD guidelines (acute toxic class method). The toxicity of the compounds were tested by using stepwise procedure, each step using 3 rats of a single sex. The rats were on fast prior to dosing (food was withheld but not water) for 3-4 hrs. The synthesized compounds were suspended in Tween-80 and administered in a dose of 2000 mg/kg body weight, was selected for the evaluation of anti-inflammatory activity.

Anti-inflammatory activity

The anti-inflammatory activity[15] was determined by carrageenan-induced acute paw oedema in rats. Wistar rats of either sex were selected by random sampling technique and used for the study. Indomethacin 20 mg/kg was administered as standard drug for comparison. The test compounds were administered orally by intragastric tube. After half an hour of administration of test compounds, 0.1 mL of carrageenan was injected into the lateral malleolus of the sub plantar region of the left hind paw. The inflammation of

the paw was measured for all the animals by using Plathysmograph before the administration of the carrageenan and after the administration of the carrageenan at 60, 120, 180, 240 and 300 min. The percentage protection of the compounds was calculated as follows:

All the compounds exhibited highly significant to moderately significant anti-inflammatory activity (Figures 9 and 10). Among the four compounds 6b and 6c at 200 mg/kg (p.o) showed significant reduction in paw oedema when compared to the compound 6a and 6d. The compound 6b&c showed 70% protection, compound 6d showed 65% and compound 6a showed 60% protection. The standard indomethacin showed 75% protection. The compounds did not cause mortality up to 2000 mg/kg in acute oral toxicity studies (OECD-423 guidelines) and were considered as safe (X-unclassified).

Anti-inflammatory activity of the synthesized compounds 6a-d

Carrageenan induced Paw Oedema

Group	1 hr	2 hr	3 hr	4 hr	5 hr
Group I Control 1% CMC (1 ml/kg)	0.18 ± 0.003	0.26 ± 0.006	0.32 ± 0.005	0.36 ± 0.004	0.42 ± 0.005
Group II Compound – I (200 mg/kg)	0.17 ± 0.003** (5.55)	0.22 ± 0.007** (15.38%)	0.21 ± 0.003** (34.37%)	0.18 ± 0.005*** (50%)	0.16 ± 0.007*** (60%)
Group III	0.17 ± 0.004**	0.21 ± 0.004**	0.18 ± 0.004***	0.15 ± 0.006***	0.12 ±

Compound – II (200 mg/kg)	(5.55%)	(19.53%)	(43.75%)	(58.33%)	0.004*** (70%)
Group IV Compound – III (200 mg/kg)	0.15 ± 0.002** (16.66%)	0.19 ± 0.007** (26.92%)	0.21 ± 0.003*** (50%)	0.13 ± 0.004*** (63.88%)	0.12 ± 0.004*** (70%)
Group V Compound – IV (200 mg/kg)	0.15 ± 0.004** (16.66%)	0.19 ± 0.004** (26.92%)	0.21 ± 0.004** (34.37%)	0.20 ± 0.003*** (44.44%)	0.16 ± 0.003*** (65%)
Group VI Standard Indomethacin (10 mg/kg)	0.17 ± 0.003*** (5.55%)	0.19 ± 0.007*** (26.92%)	0.16 ± 0.005*** (50%)	0.12 ± 0.003*** (66.66%)	0.14 ± 0.002*** (75%)

All values are mean ± SEM values using 6 animals in each group.

Significant differences with respect to control group was evaluated by ANOVA, Dunnets 't' test. *P < 0.05, **P < 0.01, ***P < 0.001.

$$\text{Percentage protection} = \frac{\text{control-test}}{\text{control}} \times 100$$

The data are presented in the Table-2.

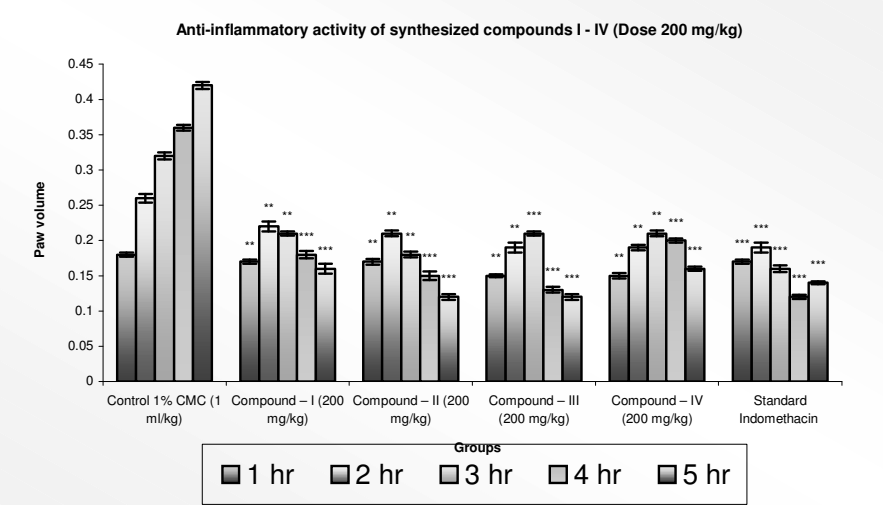


Figure 9

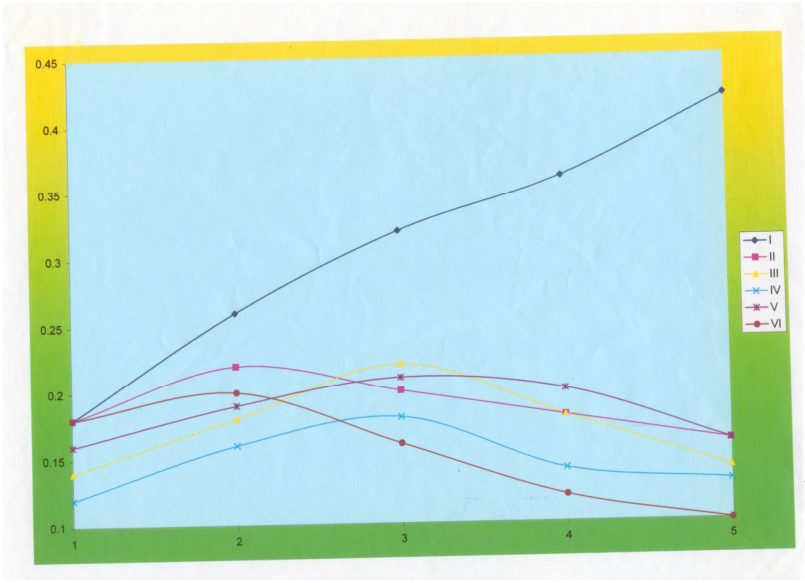


Figure 10

3.2.4 CONCLUSION

In the present study, a new series of 2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(substituted phenyl) acetates (**6a-d**) were synthesized and characterized by IR, ^{1}H NMR, mass spectral and elemental analysis, found to possess both antiinflammatory and antimicrobial activities. Among the compounds tested for anti-inflammatory, compound **6b** and **6c** showed significant activity and compound **6d** showed potent anti bacterial activity and potent anti fungal activity. The anti-inflammatory activity was

determined by carragean induced acute paw oedema in rats. The results were discussed in the text. The *in vitro* antibacterial and antifungal activities of the compounds were evaluated by paper disc diffusion method. The minimum inhibitory concentrations (MIC) of the compounds were also determined by agar streak dilution method.

3.2.5 EXPERIMENTAL SECTION

i) General procedure for the synthesis of substituted mandelic acids (2a-d):

To a mixture of substituted phenol (8.7 mL, 100 mmol) in NaOH solution (4 g, 50 ml, 100 mmol), cetyl trimethyl ammonium bromide (CTAB-phase transfer catalyst) (2 mL, 0.005 mmol solution), glyoxalic acid (5.5 mL, 100 mmol) added dropwise for 1 hr at 0-5 °C under stirring which continued for 4-5 hrs. Completion of the reaction was confirmed by TLC. The reaction mixture was acidified with HCl to pH 6 and extracted into benzene. The aqueous layer was further acidified by HCl to pH 2, saturated with brine solution and extracted into ethyl acetate, dried the organic layer over sodium sulphate and evaporated under reduced pressure. The obtained products were recrystallized from benzene (**2a-d**).

2-(4′-Hydroxyphenyl)-2-hydroxyethanoic acid (2a)

Off-white solid, Yield: 90%, m.p. 102-104 ^{0}C; IR (KBr, cm^{-1}): ν 3469, 3229, 2941, 2472, 1928, 1692, 1260, 1072, 853; ^{1}H NMR (DMSO-d$_6$): δ 3.65 (s, 1H, CHOH), 4.92 (s, 1H, CHOH), 6.61-6.78 (m, 2H, aromatic), 7.13-7.28 (m, 2H, aromatic), 7.82 (br s, 1H, OH, Ar); EI-MS (*m/z*) (%): 168, 153, 142, 124, 94, 77; Elemental analysis (CHN): C 57.15, H 4.80, O 38.06 (for $C_8H_8O_4$); found C 57.02, H 4.92, O 38.14.

2-(3′-Chloro-4′-hydroxyphenyl)-2-hydroxyethanoic acid (2b)

Off-white solid, Yield: 85%, m.p. 119-122 ^{0}C; IR (KBr, cm^{-1}): ν 3447, 3194, 2929, 2583, 1902, 1750, 1711, 1437, 1187, 1091, 811; ^{1}H NMR (DMSO-d$_6$): δ 2.6 (s, 1H, CHOH), 4.91 (s, 1H, CHOH), 6.85-7.45 (m, 3H, aromatic), 9.01 (br, 1H, COOH). EI-MS (*m/z*) (%): 202, 157, 141, 121, 111, 93, 69; Elemental analysis

(CHN): C 47.43, H 3.48, Cl 17.50, O 31.59 (for $C_8H_7ClO_4$); found C 47.14, H 3.56, Cl 17.32, O 31.78.

2-(3′-Methyl-4′-hydroxyphenyl)-2-hydroxyethanoic acid (2c)

Off-white solid, Yield: 75%, m.p. 78-80 ^{0}C; IR (KBr, cm^{-1}): ν 3495, 3309, 2924, 2026, 1715, 1263, 1061; Mass (*m/z*) (%): 182, 138, 110, 91; ^{1}H NMR (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 4.86 (s, 1H, CHOH), 5.20 (s, 1H, OH), 6.68-7.07 (m, 3H, aromatic), 7.63 (br s, 1H, OH), 8.71 (1H, COOH); Anal ($C_9H_{10}O_4$) (C, H, N): C 59.34, H 5.53, N 3.77, O 35.13; found C 59.18, H 5.60, N 3.85, O 35.21.

2-(6′-Hydroxynaphthyl)-2-hydroxyethanoic acid (2d)

Light yellow solid, Yield: 62%, m.p. 116-118 ^{0}C; IR (KBr, cm^{-1}): ν 3407, 3256, 1725, 1627, 1431, 1263, 1075, 809: ^{1}H NMR (DMSO-d_6): δ 5.56 (s, 1H, CHOH), 5.95 (br s, 1H, OH), 7.10-8.12 (m, 6 H), 9.56 (br s, 1H, COOH). EI-MS (*m/z*) (%): 218, 173, 144, 127; Elemental analysis (CHN): C 66.05, H 4.62, O 29.33 (for $C_{12}H_{10}O_4$); found C 66.23, H 4.80, O 29.08.

ii) General procedure for the synthesis of N-(2-hydroxy ethyl)phthalimide (5):

A mixture of phthalic anhydride (7 g, 42.29 mmol) and ethanolamine (3.75 g, 42.42 mmol) and triethyl amine (0.7 mmol) in toluene (500 mL) was heated under reflux for 4 hrs under azeotropic removal of water using Dean-Stark apparatus. The reaction mixture was concentrated at reduced pressure, added ethyl acetate to the residue, and the organic phase was washed with 1N HCl solution (20 mL) to eliminate the unreacted triethylamine, dried over $MgSO_4$, concentrated to yield the N-(2-hydroxy ethyl)phthalimide (**5**) as a white crystalline solid.

White crystalline solid, Yield: 95%, m.p. 126-128 ^{0}C; IR (KBr, cm^{-1}): ν 3472, 3046, 2953, 1767, 1697, 1428, 1394, 1057, 725; ^{1}H-NMR ($CDCl_3$) δ: 7.96-8.00 (m, 2H), 8.05-8.08 (m, 2H), 3.87-3.98 (m, 4H); IR (KBr) cm^{-1}: 3472, 1767, 1697, 1428, 1057, 725. EI MS: *m/z* (M^+): 160 (M-CH_2OH), 148, 105, 77; Elemental analysis (CHN): C 62.82, H 4.74, N 7.33, O 25.11 (for $C_{10}H_9NO_3$); found C 61.98, H 4.86, N 7.40, O 25.03.

c) General method of synthesis 6a-d

A mixture of substituted mandelic acid (3.5 g, 20 mmol) and N-(2-hydroxy ethyl)phthalimide (4 g, 20 mmol) in 1,4-Dioxan (20 mL) were taken in a round bottomed flask under nitrogen. Added N, N-dicyclohexyl carbidimide (4.5 g, 20 mmol) to the mixture at room temperature and stirred for 48h. The byproduct was precipitated out and then filtered. The filtrate thus obtained was extracted with chloroform. The combined layer was rotavaped under reduced pressure. The product obtained was recrystallized from ethyl acetate, and confirmed by TLC (Scheme 1).

2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(4-hydroxy phenyl) acetate (6a)

Yield: 62%, m.p. 104-106 ^{0}C; IR (KBr, cm^{-1}): ν 3418, 3263, 2857, 1767, 1682, 759; ^{1}H NMR (DMSO-d_6): δ 3.98 (t, 2H, CH_2), 4.12 (t, 2H), 4.91 (s, 1H, CHOH), 6.65-7.32 (m, 4H), 7.98-8.01 (m, 2H), 8.12-8.20 (m, 2H); FAB-MS (*m/z*) (%): 341, 281, 241, 160, 147, 104, 91, 77, 55; Elemental analysis (CHN): C 63.34, H 4.43, N 4.10, O 28.12 (for $C_{18}H_{15}NO_6$): found C 63.18, H 4.52, N 3.98, O 28.03.

2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-(3-chloro-4-hydroxyphenyl)-2-hydroxy acetate (6b)

Yield: 60%, m.p. 108-110 ^{0}C; IR (KBr, cm^{-1}): ν 3426, 3287, 2857, 1760, 1694, 759, 793; ^{1}H NMR (DMSO-d_6): δ 3.08 (s, 1H, CHOH), 4.02 (t, 2H, CH_2), 4.16 (t, 2H),

5.20 (s, 1H, CHOH), 6.68- 7.23 (m, 3H), 7.98-8.10 (m, 2H), 8.15-8.22 (m, 2H); FAB-MS (*m/z*) (%): 375, 341, 281, 241, 207, 174, 147, 107, 73, 55; Elemental analysis (CHN): C 57.54, H 3.76, Cl 9.43, N 3.73, O 25.55 (for $C_{18}H_{14}ClNO_6$); found C 57.60, H 3.80, Cl 9.28, N 3.79, O 24.98.

2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(4-hydroxy-3-methyl phenyl) acetate (6c)

Yield: 58%, m.p. 116-118 ^{0}C; IR (KBr, cm^{-1}): ν 3470, 3365, 2855, 1781, 1713, 755; ^{1}H NMR (DMSO-d_6): δ 2.14 (s, 3H), 3.94 (t, 2H, CH_2), 4.07 (t, 2H, CH_2), 4.90 (s, 1H, CHOH), 6.68-7.10 (m, 3H) 8.00-8.20 (m, 4H); FAB-MS (*m/z*) (%): 355, 307, 281, 225, 136, 91, 77, 73; Elemental analysis (CHN): C 67.25, H 5.05, N 4.13, O 23.57 (for $C_{19}H_{17}NO_5$); found C 67.32, H 5.10, N 4.08, O 23.70.

2-(1,3-dioxo-2,3-dihydro-1H-2-isoindolyl) ethyl 2-hydroxy-2-(6-hydroxy-2-naphthyl) acetate (6d)

Yield: 67%, m.p. 106-108 ^{0}C; IR (KBr, cm^{-1}): ν 3471, 3360, 2859, 1780, 1703, 755. ^{1}H NMR (DMSO-d_6): δ 4.01 (t, 2H, CH_2), 4.22 (t, 2H, CH_2), 5.60 (s, 1H, CHOH), 6.12 (br s, 1H, CHOH), 7.12-7.18 (m, 3H), 7.86-8.02 (m, 2H), 8.13-8.25 (m, 2H); Mass (*m/z*) (%): 391, 226, 154, 136, 107, 98, 77, 51. Elemental analysis (CHN): C 61.46, H 4.61, N 3.77, O 30.16 (for $C_{22}H_{17}NO_6$); found C 61.23, H 4.72, N 3.94, O 29.82.

3.2.6 REFERENCES

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4.1.1 INTRODUCTION

Among heterocyclic scaffolds, phthalimides are of particular biological interest with numerous applications in biology and synthetic chemistry.[1] Moreover, the fact that the phthaloyl group can easily be cleaved under mild conditions makes it very advantageous for the protection of amino groups during syntheses.[2] However, available routes for the synthesis of N,N-phthaloyl amino acids are limited.[3-6] Among these, the fusion of amino acids with phthalic anhydride is a widely used methodology.[2a,3] For some amino acids good yields are obtained, but in some cases the conditions used are so drastic that racemization occurs.[2a,4a,c] Furthermore, amino acids with functionalized side chains failed to give the desired phthaloylated products.[4b] The extent of this racemization was limited by performing the reactions in boiling solvents and the presence of bases such as triethylamine.[4] In such reactions, the medium should be kept neutral by slow distillation of the base and the water formed to allow cyclization of the intermediate phthalamic acids.[4a,c] Under prolonged heating, however, partial hydrolysis of the phthaloyl derivative to the intermediate phthalamic acid was sometimes observed.[4c]

Another important progress in the N-phthaloylation of aminoacids was brought about by the introduction of N-carbethoxyphthalimide by Nefkens *et al*.[5] The mild conditions under which this reagent causes phthaloylation makes it more attractive than the above described procedures. However, low yields were experienced when N-carbethoxyphthalimide was used with amino alcohol or hindered amino acids.[8] Further problems resulting from contamination by phthalimide which co-crystallization with the reagent during its preparation[7] or by partial decomposition of the N-carbethoxyphthalimide to (ethoxycarbonyl) phthalamic acid and phthalic acid has also been reported.[8]

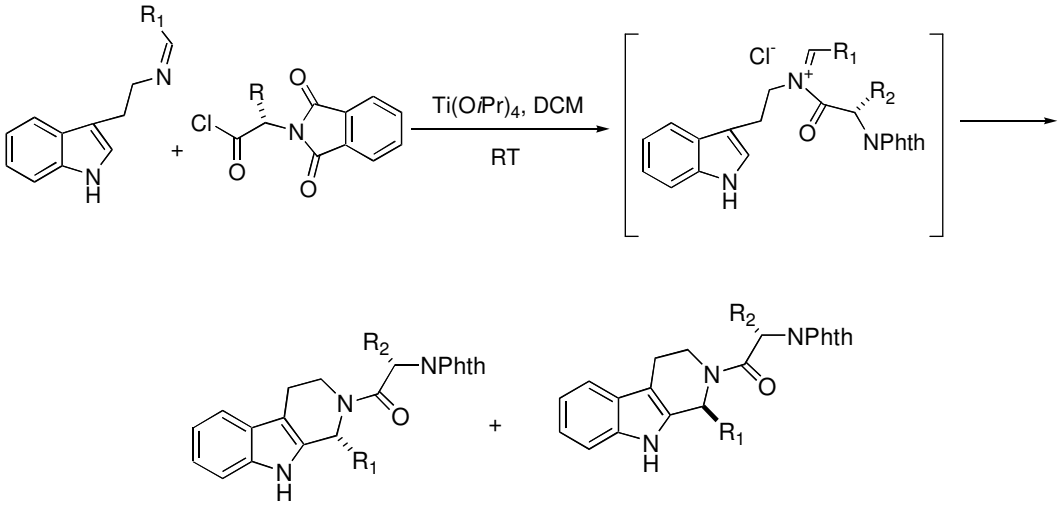
More recently, the phthaloylation of primary aminoacid with 3-chloro-3-(dimethoxyphosphoryl)isobenzofuran 1(3H)-one was investigated.[6] This phosphoryl derivative prepared from the lachrymatory and moisture

sensitive phthaloyl chloride, reacted with aliphatic amines and nonfunctionalized amino acids to afford the corresponding N-phthaloyl derivatives in very good yields.[6a]

Other procedures have been described for N-phthaloylation of amino carboxamides, amino alcohols, amino nitriles, amino esters, and oligonucleotides.[1g,9] However, none of them is applicable to the N-phthaloylation of free amino acids. Sheehan *et al.*[2] have shown that phthaloylation by the fusion of an amino acid with phthalic anhydride can lead to racemization if the reaction temperature is higher than 150 ^{0}C. More recently it has been reported[4] that some substituted amino acids like N-benzylcysteine undergo racemization if the fusion temperature exceeds 110 ^{0}C. Balenovic and Gaspert[10] have developed a two-step procedure applicable to aminoacids which involves the cyclization of a phthalamic ester obtained by the reaction of an amino acid with O-carbethoxythiobenzoic acid.

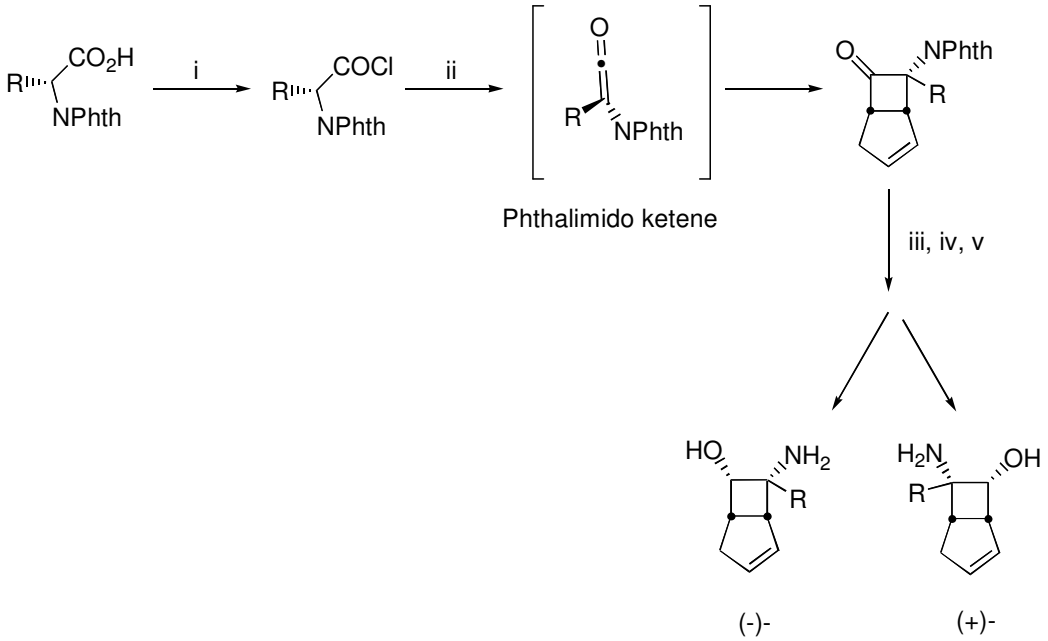
4.1.2 APPLICATIONS OF N,N-PHTHALOYL AMINO ACIDS

N,N-Phthaloyl-protected amino acid chlorides were employed as chiral auxillary groups for asymmetric Pictet-Spengler reactions which is one of the most important methods in heterocyclic and natural product chemistry by Waldmann *et al* (Scheme 1).[11]



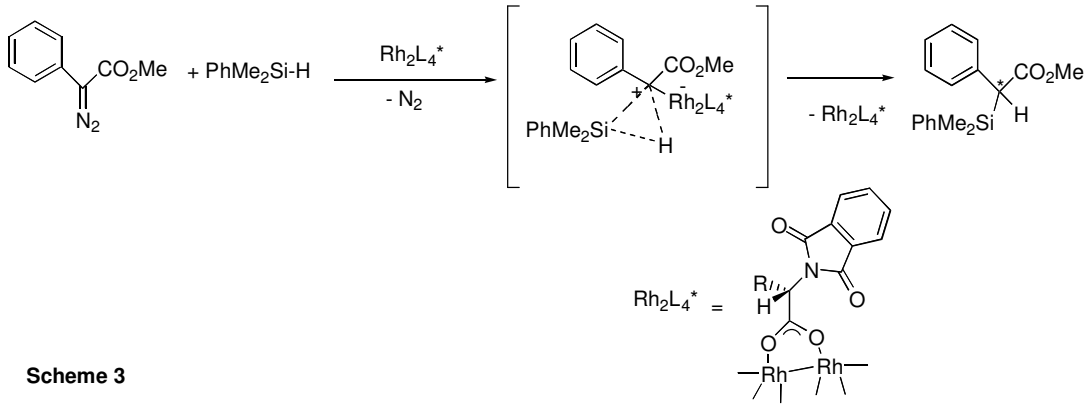
Scheme 1

N,N-Phthaloyl-protected amino acid chlorides can be versatile precursors for the synthesis of N-O chelating ligands for enantioselective catalysis as evidenced by Roberts *et al* (Scheme 2).[12]



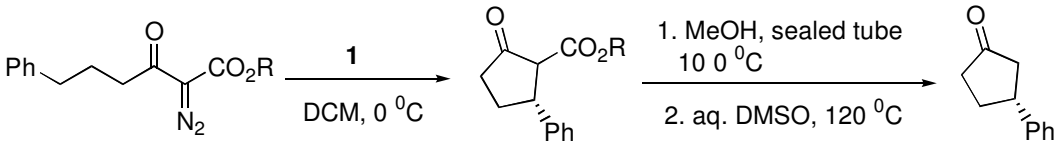
Scheme 2. i) pyridine, $(COCl)_2$, THF; ii) Et_3N, DCM, cyclopentadiene; iii) NaBH4, *i*-PrOH/H_2O; iv) AcOH, 90 ^{0}C; v) L-/D-Asp,*i*-PrOH/MeOH; vi) Et_3N, DCM, indene

Hashimoto *et al.*[13] elegantly employed dirhodium (II) carboxylates incorporating N-phthaloyl-(S)-amino acids as chiral bridging ligands for the enantioselective insertion reactions of methyl phenyldiazoacetate into Si-H bond of Silanes (Scheme 3).

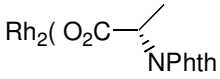


Scheme 3

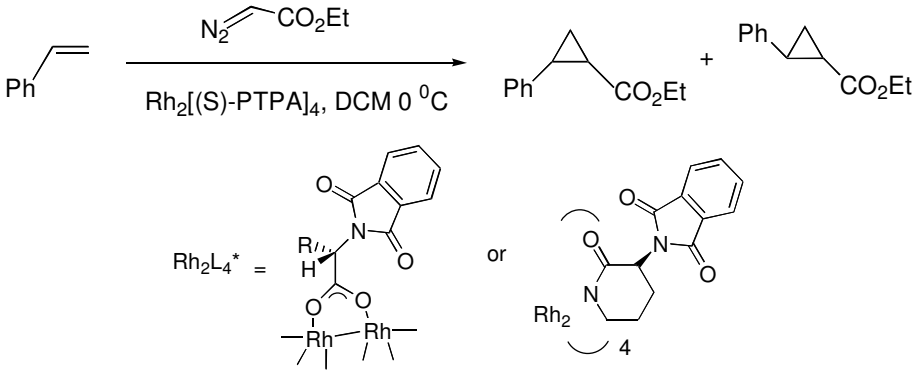
According to Ikegami *et al.*[14] (Scheme 4) the enantioselectivity in C-H insertion reactions of α-diazo β-keto esters catalyzed by dirhodium (II) tetrakis [N-phthaloyl-(S)-phenylalaninate] was found to be substantially improved by evaluation of the alkoxy group of the ester moiety.



Scheme 4

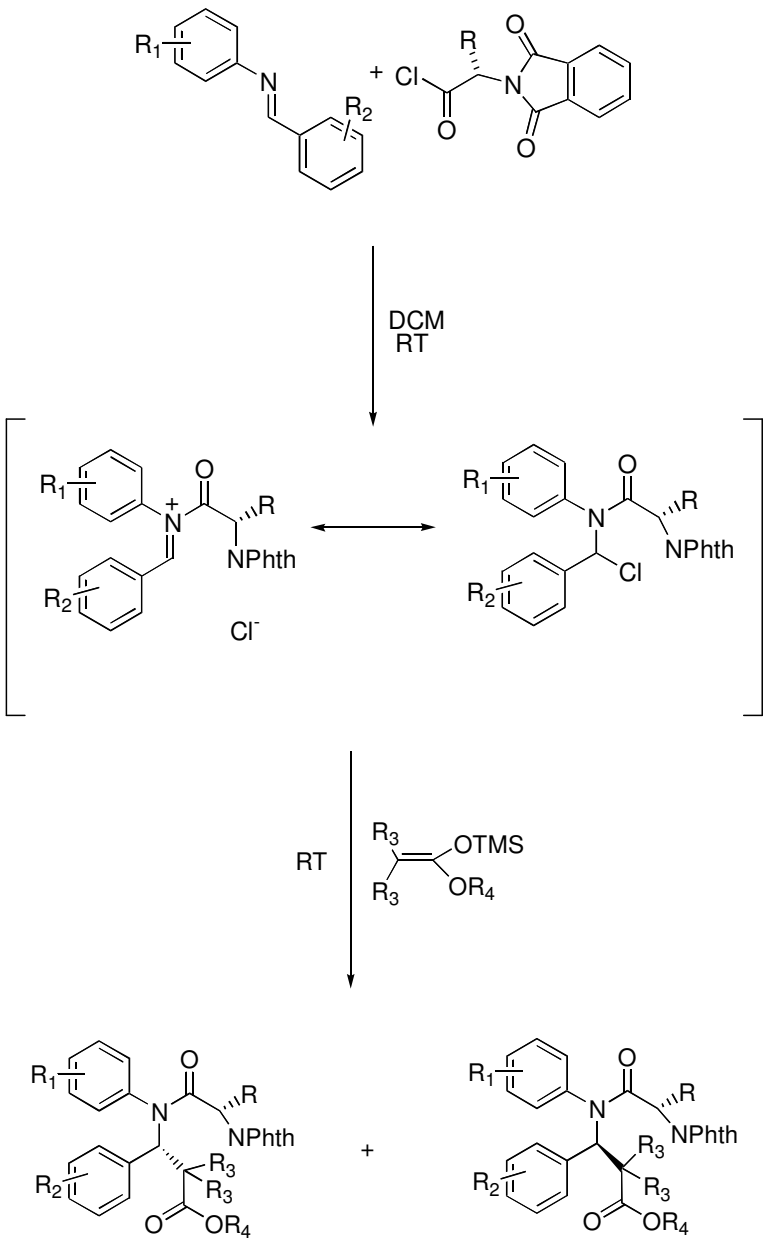
1= $Rh_2(O_2C$  NPhth

Again, Hashimoto *et al.*[15] applied dirhodium (II) tetrakis[3(S)-phthalimido-2-piperidinonate] as a novel dirhodium(II)carboxamidate catalyst for asymmetric cyclopropanation (Scheme 5).



Scheme 5

Waldmann *et al.* employed N,N-phthaloylamino acids as chiral auxillaries in asymmetric Mannich type reaction (Scheme 6).[16] If Schiff bases are treated with N,N-phthaloyl-protected amino acid chlorides and the silylketene acetals at room temperature the N-acylated β-amino acid esters are formed in a smooth reaction in moderate to high yields and with good to excellent diastereomer ratios.



Scheme 6

Apart from the literature data given above for the application of N,N-phthaloyl L-aminoacids as efficient chiral precursors, in this section, another newly developed characteristic nature as Lewis acid promoters was exemplified by application for the synthesis of 1,5-benzodiazepines. At first, the summary of the prepared N,N-phthaloyl L-aminoacids is given in Table 1, according to the procedure given by Vidal *et al.*[17].

Table 1. N,N-phthaloyl L-aminoacids Synthesized:

Entry	M.P (^{0}C)	$[\alpha]^{25}_D$	Physical state
N-Phthaloyl glycine (**1**)	193-195 ^{0}C	_	Off-white amorphous solid
N-Phthaloyl L-Phenyl alanine (**2**)	181-185 ^{0}C	$[\alpha]_D$ –202, c=1.00, EtOH.	White solid
N-Phthaloyl L-Leucine (**3**)	118-120 ^{0}C	$[\alpha]_D$ –24.2, c=3.46, EtOH.	**White crystalline solid**
N-Phthaloyl L-Glutamic acid (**4**)	160-162 ^{0}C	$[\alpha]_D$ –49, c=3, Dioxane.	Colourless solid
N-Phthaloyl L-Valine (**5**)	110-112 ^{0}C	$[\alpha]_D$ –71.7, c=1.46, EtOH.	**White amorphous** powder
N-Phthaloyl L- Methionone (**6**)	124-126 ^{0}C	$[\alpha]_D$ –49, c=3, Dioxane	Light yellowish solid
N-Phthaloyl L-Cysteine (**7**)	120-122 ^{0}C	$[\alpha]_D$ –49, c=3, Dioxane	Brown solid
N-Phthaloyl L-Iso Leucine (**8**)	123-125 ^{0}C	$[\alpha]_D$ –56, c=1, MeOH	**White crystalline** solid
N-Phthaloyl L-Serine (**9**)	70-72 ^{0}C	$[\alpha]_D$ –68.8, c=1, Dioxane	**Colourless powder**
N-Phthaloyl L-Tryptophan (**10**)	192-194 ^{0}C	$[\alpha]_D$ -275 (c=1.0, EtOH)	**Yellow solid**

4.1.3 PRESENT WORK

4.1.3.1. Objective- Synthesis of 1,5-Benzodiazepines

Due to their accessibility, easy functionalization and potential pharmacological properties, mainly 1,5-benzodiazepine derivatives have received significant attention and the core is indeed a ''privileged scaffold'' found in compounds

active against a variety of target types including peptide hormones (such as CCK), interleukin converting enzymes (ICE) and potassium blockers (I_k).[18] More recently, the area of biological interest of 1,5-benzodiazepines has been

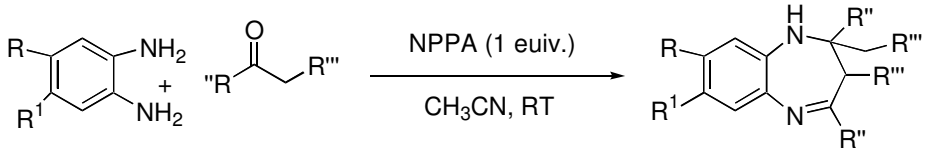
extended to various diseases such as cancer, viral infection (non-nucleoside inhibitors of HIV-1 reverse transcriptase), cardiovascular disorders.[19] In addition, 1,5-benzodiazepines show antidepressive, antifungal, antibacterial, antifeedant, antiinflammatory, analgesic and anticonvulsant activities.[20] Besides these derivatives are also used as dyes for acrylic fibre[21] in photography. Moreover, 1,5-benzodiazepines are valuable synthons used for the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[22]

Despite their importance as pharmacological, industrial and synthetic intermediates, comparatively few methods for their preparation are reported in the literature, a great number of which have appeared only very recently employing BF_3-etherate,[23a] $NaBH_4$,[23b] polyphosphoric acid or SiO_2,[23c] $MgO/POCl_3$,[23d] $Yb(OTf)_3$,[23e] Al_2O_3/P_2O_5 or AcOH under microwave conditions,[23f,g] Amberlyst-15 in ionic liquid,[23h] $CeCl_3.7\ H_2O/NaI$ supported on silica gel,[23i] and $InBr_3$,[23j] 1-butyl-3-methylimidazolium bromide ([bmim]Br),[23k] $Sc(OTf)_3$,[23l] CAN[23m] as catalysts or as stoichiometric reagents. However, many of these methods have some drawbacks such as low yields of the products,[23a,23b] high temperatures,[23c] drastic reaction conditions,[23d] long reaction times,[23c] and relatively expensive reagents.[23e, i, j, l] Therefore, there is further scope to explore efficient methods for the synthesis of 1,5-benzodiazepines using a milder, non-hazardous and inexpensive organo reagent. Earlier reports have explored aminoacids, carboxylic acids including aliphatic and aromatic acids as efficient Lewis acid catalysts for various organic transformations.[24]

In continuation of our interest in developing novel synthetic methodologies, particularly carbon-carbon, carbon-heteratom bond formations,[25] and being interested in the use of N,N-phthaloyl aminoacids as eco-friendly reagents for organic synthesis, we undertook a study of the utility of several N,N-phthaloyl aminoacids as Lewis acid catalysts for the synthesis of 1,5-benzodiazepines (Scheme 7).

4.1.4 RESULTS AND DISCUSSION

Initially evaluated the feasibility of a reaction on *o*-phenylenediamine (*o*-PD) (1 mmol) and acetophenone (2.2 mmol) using N-phthaloyl L-phenyl alanine (1 mmol) at ambient temperature in methanol as solvent to afford the corresponding 1,5-benzidiazepine in 65% yield in 24h.



R,R^1=H; R=CH_3, R=H;
R=Cl, R$^{'}$=H; R=NO_2, R$^{'}$=H;
R=CH_3, R^1=CH_3; R=Cl, R^1=Cl;
R=COPh; R^1=H

(20 examples)

Scheme 7

Encouraged by this result, different reaction parameters were studied. The reaction was performed in different solvents such as CH_3CN, CH_3CN-H_2O, $CHCl_3$, MeOH, and H_2O. Acetonitrile (81%) and chloroform (75%) were found to be the best solvents in terms of yields and reaction time. The reaction in solvent free conditions resulted in poor yields, compared to the yields obtained in acetonitrile as solvent. Among the various acids depicted in Table 2, N-phthaloyl L-phenyl alanine (hereafter, NPPA) was found to be the most effective catalyst in terms of conversion and reaction rates, giving the corresponding 1,5-benzodiazepine in 12 h (81% yield).

Next, the optimization of NPPA was found that 1 equiv. of NPPA needed to promote reaction. No reaction was observed in the absence of the acid even after stirring for 4 days, thus highlighting the role of the NPPA as a promoter.

Table 2. Reaction with *o*-Phenylenediamine with acetophenone catalyzed by various acids

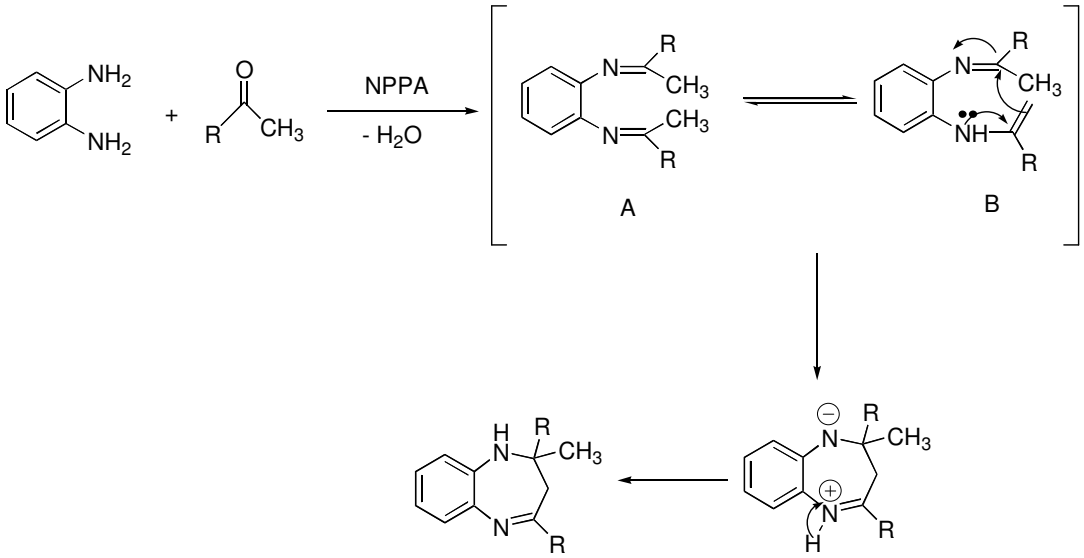
Entry	Acid	Time (h)	Yield (%)
1	Benzoic acid	24	80
2	4-Nitro benzoicacid	15	85
3	3- Bromo benzoicacid	24	65
4	Phenyl acetic acid	24	58
5	D(-)Mandelic acid	24	72
6	*p*-tolunesulphonic acid	24	30
7	Cinnamic acid	24	32
8	Anthranilic acid	24	28
9	Malonic acid	36	44
10	2-picolinic acid	36	35
11	N-phthaloyl glycine	24	22
12	N-phthaloyl L-phenyl alanine	12	81
13	N-phthaloyl L-leucine	72	N
14	N-phthaloyl L-isoleucine	24	N
15	N-phthaloyl L-valine	24	68
16	N-phthaloyl L-serine	24	55
17	N-phthaloyl L-glutamic acid	24	77
18	N-phthaloyl L-methionine	24	48
19	N-phthaloyl L-cysteine	24	N
20	N-phthaloyl L-tryphtophan	12	78

G.C Yield %
NR= No Reaction

Any excess NPPA beyond this loading did not show any further increase in conversion and yield. Use of less than the required catalyst loading, resulted in poor yields. The optimum yields of the product were obtained when a 1:2.2 ratio of *o*-phenylenediamine to ketone was used.

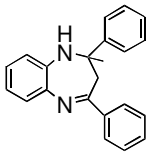
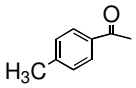
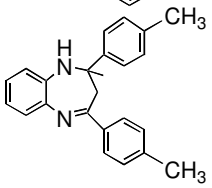
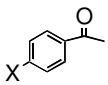
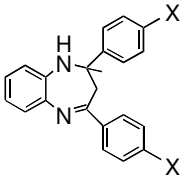
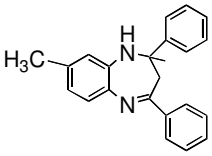
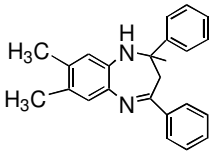
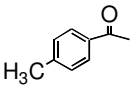
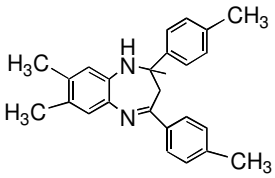
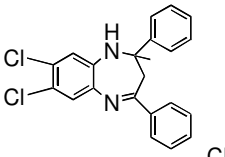
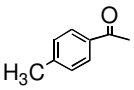
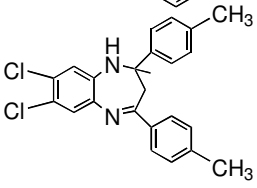
Having established the optimized reaction conditions, successfully synthesized a wide variety of biologically relevant 1,5-benzodiazepines using NPPA at room temperature, and the results are shown in Table 3. In all cases, the reaction was clean and complete within 4-48 h. Electronically divergent

acetophenones were employed as novel substrates for the synthesis of corresponding 1,5-benzodiazepines in moderate to excellent yields (Table 3, entries 1-9). All the products were completely characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. The benzodiazepines were the only products obtained and the rest of the material was essentially starting material. The scope and generality of the present procedure was extended to various aliphatic ketones as well (Table 3, entries 10-13). The reaction of substituted *o*-phenylenediamines with acetone under similar conditions gave good yields of corresponding benzodiazepines (62-80%, Table 3, entry 10). It is noteworthy that, in the reaction with an unsymmetrical ketone such as 2-butanone, the ring closure occurred selectively giving a single product in 10 h (85%, Table 3, entry 11). Cyclic ketones such as cyclopentanone and cyclohexanone (Table 3, entries 12 and 13) also reacted well to afford the corresponding fused ring benzodiazepines in moderate yields. The mechanism of the reaction probably involves an intramolecular imine-enamine cyclization promoted by NPPA (Scheme 8), as already reported by Jung and coworkers when using polyphosphoric acid or SiO_2.[23c]


NH2
NH2
+
O
R
CH3
NPPA
- H2O
R
N
CH3
CH3
N
R
A
R
N
CH3
NH
R
B
H
N
R
CH3
N
R
N
R
CH3
N
H
R

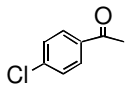
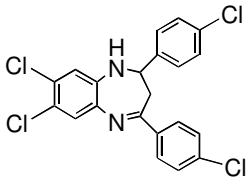
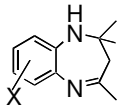
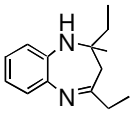
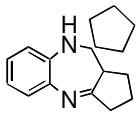
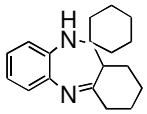
Scheme 8

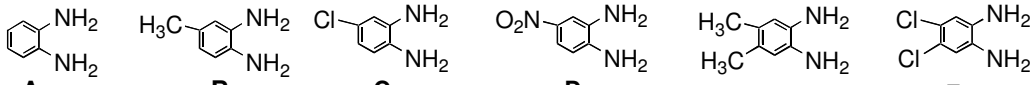
Table3. NPPA-catalyzed synthesis of 1,5-benzodiazepines.

Entry	Diamine	Ketone	Benzodiazepine	Time (h)	Yields (%)[a]
1	A			12	81[23i]
2	A			10	78
3	A	 X=Cl, 3a X=Br, 3b X=I, 3c		24 28 18	82 74 68
4	B			36	55[23i]
5	E			10	82[23j]
6	E			8	90
7	F			36	82
8	F			48	58

(Contd.)

Table 3 (Contd).

Entry	Diamine	Ketone	Benzodiazepine	Time (h)	Yields (%)[a]
9	F			40	65
10	A B C D E F	 X,15a=R, R^1=H X, 15b=R=CH_3, R^1=H X, 15c=R=Cl, R^1=H X, 15d=R=NO_2, R^1=H X, 15e=R=CH_3, R^1=CH_3 X, 15f=R=Cl, R^1=Cl		5 7 4 10 8 5	77,15a[23j] 67,15b[23i] 80,15c[23j] 64,15d[23j] 62, 15[23j] 78,15f
11	A			10	85[23j]
12	A			12	72[23j]
13	A			14	65[23j]

Diamine: 

A **B** **C** **D** **E** **F**

[a] Yields refer to the isolated pure products after column chromatography.

4.1.5 CONCLUSION

In conclusion, a brief description of earlier syntheses to N-phthaloyl aminoacids and their application in organo catalysis was discussed by synthesizing N,N-phthaloyl aminoacids with sufficient spectral characterization.

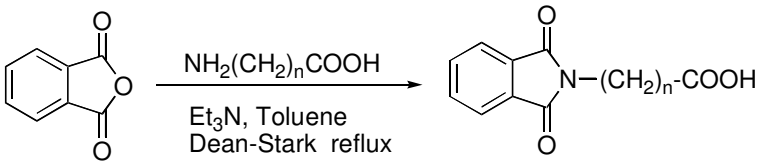
Thus, prepared N,N-phthaloyl aminoacids could be used as Lewis acid promoters by developing a practical procedure for the synthesis of 2,3-dihydro-1H-1,5-benzodiazepines at ambient temperature using NPPA in acetonitrile. The advantages of the present protocol were mild, short reaction times, study of wide range of electronically divergent substrates, easy work-up, low toxicity, inexpensive, and readily preparable catalyst, that make the

procedure an attractive alternative to the existing methods for the synthesis of 1,5-benzodiazepines and can be applied to other organic transformations as well.

4.1.6 EXPERIMENTAL SECTION

4.1.6.1 Synthesis of N-Phthaloyl Amino Acids:

General Scheme:



General Procedure:

A mixture of corresponding L-amino acid (47.61 mmol), phthalic anhydride (7 g, 47.29 mmol) and triethylamine (0.7 mL) in toluene (250 mL) was refluxed under nitrogen for 4 h with azeotropic elimination of water with a Dean-Stark apparatus. After removing the solvent at reduced pressure, ethyl acetate was added and the organic phase was washed with dilute HCl (1 M) to eliminate the unreacted amino acid, dried over $MgSO_4$, filtered and concentrated to give the desired N-phthaloyl aminoacid. The title compounds (Table 1) were synthesized according to the above procedure.

Spectral data for the synthesized N,N-Phthaloyl Amino Acids (Table 1):

N-Phthaloyl glycine (entry 1):

IR (KBr): ν 3426, 2985, 2933, 1772, 1726, 1413, 1245, 1245, 954, 712 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$): δ 4.25 (s, 2H), 7.77 (m, 2H), 7.82 (m, 2H); Mass (EI): *m/z* 205, 160, 104, 76, 41

(S)-N^{α}-Phthaloyl phenylalanine (entry 2):

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.61 (d, *J*=8.7 Hz, 2H), 5.25 (t, *J*=8.7 Hz, 1H), 7.20 (m, 5H), 7.65-7.84 (m, 4H), 9.38 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 34.5, 53.2, 126.6, 126.9, 128.6, 128.9, 131.5, 134.2, 136.5, 167.5, 174.5; MS (FAB): *m/z* 65, 76, 104, 148, 149, 232, 249, *m/z* 296 $(M+H)^+$, 318 $(M+Na)^+$

(S)-N^{α}-Phthaloyl leucine (entry 3):

IR (KBr): ν 3426, 2957, 2870, 2619, 2130, 1777, 1716, 1582, 1406, 846, 669 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.92 (d, 6H), 1.45 (dd, 1H), 1.80-1.98 (t, 1H), 2.25- 2.30 (t, 1H), 4.90 (d, 1H), 7.72-7.75 (m, 2H), 7.80-7.84 (m, 2H), 10.58 (brs, 1H, COOH); MS (EI): *m/z* 261 $(M)^+$, 216, 205, 187, 160, 132, 104, 76, 461.

(S)-N^{α}-Phthaloyl glutamic acid (entry 4):

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.40-2.80 (m, 4H, CH_2-CH_2), 5.05-5.18 (m, 1H, CH), 7.75-7.95 (m, 4H); MS (FAB): *m/z* 278 $(M+H)^+$.

(S)-N^{α}-Phthaloyl valine (entry 5):

^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.88 (d, *J*=6.8 Hz, 3H), 1.13 (d, *J*=6.7 Hz, 3H), 2.45 (m, 1H), 4.58(d, *J*=8.4 Hz, 1H), 7.70 (m, 2H), 7.84 (m, 2H), 8.08 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 6.19.6, 21.0, 28.5, 57.7, 123.7, 131.7, 134.3, 167.8, 173.9; MS (FAB): *m/z* 248 $(M+H)^+$, 270 $(M+Na)^+$.

(S)-N^{α}-Phthaloyl methionine (entry 6):

IR (KBr): ν 3124, 2966, 2917, 1776, 1745, 1712, 1389, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.96-2.15 (m, 2H), 2.32-2.50 (t, 3H), 4.94-5.05 (dd, 1H), 7.61-7.74 (m, 2H), 7.78-7.90 (m, 2H); MS (EI): *m/z* 279 $(M)^+$, 205, 187, 173, 132, 104, 86, 61.

(S)-N^{α}-Phthaloyl isoleucine (entry 8):

IR (KBr): ν 3240, 2965, 2928, 2902, 2876, 1752, 1684, 1466, 1192, 729 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.87 (t, *J*=7.2 Hz, 3H), 1.14 (d, *J*=6.7 Hz, 3H), 1.51 (m, 2H), 2.53 (m, 1H), 4.70 (d, *J*=8.4 Hz, 1H), 7.75 (m, 2H), 7.86 (m, 2H), 8.49 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 10.9, 16.8,25.9, 34.4, 57.1, 123.6, 131.7, 134.3, 167.9, 174.0; MS (FAB): *m/z* 262 $(M+H)^+$, 216, 205, 187, 160, 104, 76, 41.

(S)-N^{α}-Phthaloyl serine (entry 9):

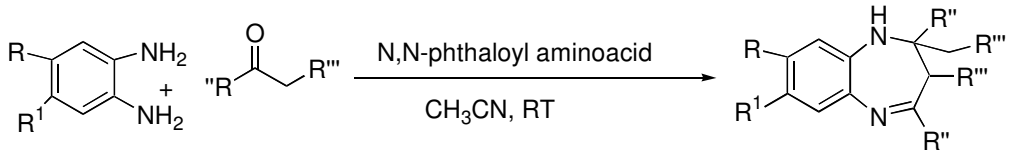
^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.90 (dd, *J*=11.6 Hz, *J*=9.2 Hz, 1H), 5.14 (dd, *J*=11.6 Hz, *J*=4.7 Hz, 2H), 5.38 (dd, *J*=9.2 Hz, *J*=4.7 Hz, 1H), 7.72 (m, 2H), 7.86 (m, 2H), 8.05 (br s, 1H, OH); MS (FAB): *m/z* 236 $(M+H)^+$.

(S)-N^{α}-Phthaloyl tryphtophan (entry 10):

^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.55 (d, J=6.5 Hz, 2H), 5.10 (m, 1H), 6.84-7.02 (m, 3H), 7.23 (d, *J*=7.9 Hz, 2H), 7.47(d, *J*=7.7 Hz, 2H), 7.78 (s, 4H), 10.72 (s, 1H), 13.25 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 24.0, 52.6, 109.6, 111.3, 117.8, 118.3, 120.9, 123.2, 126.8, 130.8, 134.7, 35.9, 167.1,170.2; MS (FAB): *m/z* 335 $(M+H)^+$, 357 $(M+Na)^+$.

4.1.6.2 Synthesis of 1,5-Benzodiazepines Promoted by N,N-Phthaloyl Aminoacids:

General Scheme:



R,R^1=H; R=CH_3, R=H;
R=Cl, R=H; R=NO_2, R=H;
R=CH_3, R^1=CH_3; R=Cl, R^1=Cl;
R=COPh; R^1=H

General Procedure:

To a suspension of N-phthaloyl aminoacid (1 mmol) in acetonitrile (3 mL), added successively *o*-phenylenediamine (1 mmol) and acetophenone (2 mmol) at room temperature. Stirred for appropriate time, the reaction mixture was extracted with DCM (2×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to funish the crude product, which was purified by silica gel column chromatography (EtOAc/Hexane 1:5) to afford the corresponding pure product. For known compounds, references are given in Table 3.

Spectral data for the novel synthesized 1,5-benzodiazepines (Table 3):

Entry 2: Pale yellow crystalline solid, mp 98-99 ^{0}C; IR (KBr): ν 3318, 1630, 1598 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.26 (s, 3H), 2.32 (s, 3H), 2.98 (d, 1H, *J*=13.38 Hz), 3.05 (d, 1H, *J*=13.38 Hz), 3.43(br s, NH), 6.76 (m, 1H), 7.01 (m, 6H), 7.23 (m, 1H), 7.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.75, 21.16, 29.85, 42.97, 73.06, 121.28, 121.38, 125.18, 126.03, 127.15, 128.50, 128.67, 128.92, 129.22, 136.45, 137.0, 138.18, 139.76, 140.32, 144.98, 166.82; MS(EI): *m/z* = 340 (M^+).

Entry 3a: Pale yellow crystalline solid, mp 143-145 ^{0}C. IR (KBr): ν 3269, 1636, 1593, 765 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (s, 3H), 2.75-2.82 (d, 1H, *J*=13.28 Hz), 2.92-3.02 (d, 1H, *J*=13.28 Hz), 3.25 (br s, NH), 6.68-6.75 (m, 1H), 6.92-7.02 (m, 1H), 7.12-7.20 (m, 5H), 7.38-7.52 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 29.73, 42.85, 73.37, 121.43, 121.95, 126.58, 127.01, 128.23, 128.32, 128.58, 133.01,137.55, 137.72, 139.84, 145.78, 165.94; MS (EI): *m/z*= 381 (M^+).

Entry 3b: Brown solid, mp 102-104 ^{0}C. IR (KBr): ν 3325, 1640, 1589, 574 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.87 (d, 1H, *J*=12.84 Hz), 3.00 (d, 1H, *J*=13.60 Hz), 2.65 (br s, NH), 6.98 (m, 1H), 7.00 (m, 6H), 7.22 (m, 1H), 7.47 (m, 4H); MS (FAB): *m/z*= 471 (M^++1).

Entry 3c: Pale yellow crystalline solid, mp 143-144 ^{0}C; IR (KBr): ν 3259, 1636, 1579, 462 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.71 (s, 3H), 2.85 (d, 1H, *J*=13.60 Hz), 2.99 (d, 1H, *J*=12.84Hz), 3.32 (br s, NH), 6.73-6.75 (m, 1H), 6.98-7.03 (m, 2H), 7.21-7.33 (m, 5H), 7.53-7.58 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=30.26, 43.37, 74.10, 93.38, 97.40, 122.07, 122.56, 127.28, 128.24, 129.23,129.28, 137.84, 137.98, 139.40, 140.39, 147.64, 166.81; MS (FAB): *m/z*= 565 (M^++1).

Entry 6: Pale yellow crystalline solid; mp 102-103 ^{0}C; IR (KBr): ν 3325, 1636, 1594 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (s, 3H), 2.26-2.36 (s, 6H), 2.45(s, 3H), 2.58 (s, 3H), 2.91(d, 1H, *J*=12.84 Hz), 3.03 (d, 1H, *J*=13.60 Hz), 3.29 (br s, NH), 6.56 (s, 1H), 7.02-7.07 (m, 1H), 7.24-7.28 (m, 4H), 7.47-7.53 (m, 2H), 7.83-7.87 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 19.12, 21.10, 29.88, 43.06, 72.88, 122.34, 125.24, 127.05, 128.44, 128.76, 128.94, 129.58, 129.60, 134.58, 136.56, 137.26, 137.96, 139.68, 166.76; MS (EI): *m/z* = 368 (M^+).

Entry 7: Yellow crystalline solid, mp 158-160 ^{0}C; IR (KBr): ν 3304, 1638, 1603, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 3H), 2.93 (d, 1H, *J*=13.60 Hz), 3.12 (d, 1H, *J*=12.84 Hz), 3.49 (br s, NH), 6.88 (s, 1H), 7.13-7.30 (m, 5H), 7.36 (s, 1H), 7.50-7.53 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 29.97, 43.23, 72.97, 121.90, 124.14, 125.33, 127.30, 128.35, 128.76, 130.13, 137.84, 139.26, 146.83, 168.81; MS (EI): *m/z* = 381 (M^+).

Entry 8: Pale yellow solid, mp 179-180 ^{0}C; IR (KBr): ν 3434, 1636, 1597, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.75 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 2.95 (d, 1H, *J*=13.60 Hz), 3.09 (d, 1H, *J*=13.60 Hz), 3.50 (br s, NH), 6.88 (s, 1H), 7.05-7.09 (t, 3H), 7.28 (s, 1H), 7.38-7.44 (t, 3H), 7.50-7.53 (d, 2H); MS (EI): *m/z* = 409 (M^+).

Entry 9: Pale yellow crystalline solid, mp 199-200 ^{0}C; IR (KBr): ν 3325, 1630, 1594 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.77 (s, 3H), 2.88 (d, 1H, *J*=13.60 Hz), 3.11 (d, 1H, *J*=13.60 Hz), 3.48 (br s, NH), 6.92 (s, 1H), 7.21-7.25 (m, 4H), 7.38 (s, 1H), 7.45-7.51 (m, 4H); MS (FAB): *m/z* = 451 (M^++1).

Entry 10f: Reddish crystalline solid, mp 92-94 ^{0}C; IR (KBr): ν 3325, 1636, 1590 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ =1.35 (s, 6H), 2.26 (s, 2H), 2.34 (s, 1H), 6.78(s, 1H), 7.18 (s, 1H); MS (EI): *m/z*= 257 (M^+).

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4.2.1 INTRODUCTION

The development of methodologies for an efficient asymmetric synthesis is one of the most important areas of synthetic organic chemistry. The synthesis of biologically relevant natural and unnatural organic molecules in optically pure form is of central interest in medicinal chemistry and related disciplines. Variations in the stereochemistry of molecular probes for a target enzyme or receptor sites very often display dramatic differences in their binding properties and biological activities. For meaningful biological studies it is important, if not mandatory, to synthesize such agents in enantiomerically pure form. Recent advances in molecular biology and modern instrumentation techniques have led to a better understanding of many complex human diseases at the molecular level. Concurrent with these remarkable achievements have come new challenges and opportunities for asymmetric synthesis. Thus, from the design of enzyme inhibitors to the synthesis of receptor agonists or antagonists and bioactive natural products, asymmetric synthesis is of fundamental significance in biology and medicine. The search for new ligands in asymmetric catalysis is a field of continuing interest. To facilitate practical applications, new ligands should be easy to prepare from simple and easily accessible starting materials.

Asymmetric synthesis is the most powerful and commonly used method for preparation of chiral molecules. In 1904, Marckwald gave a definition which is still accepted today:[1] ''Asymmetric syntheses are these reactions which would produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes.'' In 1971, the definition was modified by Morrison and Mosher in order to include the various cases of asymmetric induction.[2] ''Asymmetric synthesis is a reaction in which an achiral unit in an ensamble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts.''

The growth of this core technology has given rise to enormous economic potential in the manufacture of pharmaceuticals, animal health products, agrochemicals, fungicides, pheromones, flavors, and fragrances. This subject is an essential component of molecular science and technology in the 21st century. Recent progress has spurred various interdisciplinary research efforts directed toward the creation of molecularly engineered novel functions. Figure 1 illustrates a general principle of asymmetric catalysis, which provides an ideal way for multiplying molecular chirality.

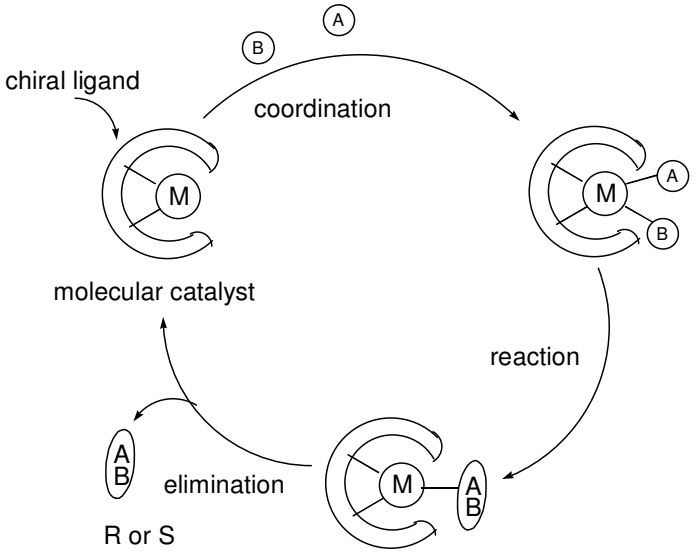


Figure 1. A general principle of asymmetric catalysis with chiral organo-metallic molecular catalysis. M=metal; A, B =reactant and substrate.

Asymmetric synthesis can be divided into:

• *Substrate controlled asymmetric synthesis*: when optically active compound is used as starting material, the stereochemical outcome of the reaction is influenced by already existing chiral centres. This method is often used in the synthesis of natural products.

• *Auxiliary controlled asymmetric synthesis*: when a chiral auxiliary is temporarily attached to an achiral substrate, the product of this addition is chiral and the stereochemical outcome of the reaction is influenced by newly formed stereocenter. Most of the chiral auxiliaries are prepared from optically active amino acids, terpenes and α-hydroxy acids.

• *Reagent controlled asymmetric synthesis*: the asymmetric induction is obtained by means of chiral reagent. Most of the chiral reagents are bases, reducing agents or hydroboration reagents.

• *Asymmetric catalysis*: the small amount of a chiral catalyst is used which is increasing the rate of the reaction as well as inducing enantioselectivity without being consumed.

4.2.2 APPLICATIONS OF CHIRAL OXAZOLINES

Enantiomerically pure amino acids, amino alcohols, amines, alcohols and epoxides play an increasingly important role as intermediates in pharmaceutical industry and agro chemistry. About 80% of the active compounds produced by pharmaceutical companies are chiral and it is estimated that this fraction will be increased in future, with the development of new methods. One of the important growth factors is an impressive progress made by academic research in the field of asymmetric catalysts and transformations.[3]

The advances in asymmetric synthesis have now reached the point that many organic molecules can be prepared with near complete enantioselectivity. This technology is particularly sophisticated in the generation of new stereogenic centers in the presence of existing chiral centers. A number of asymmetric catalysts or so called 'abiological catalysts' are approaching an efficiency and selectivity comparable to enzymes such as in the asymmetric hydrogenation of dehydroamino acids utilizing chiral bis-phosphine-rhodium complexes, asymmetric isomerization of allylic amines with Rh(I)-BINAP complexes, asymmetric epoxidation of allylic alcohols, asymmetric epoxidation of unfunctionalised olefins, asymmetric reductions with chiral oxazaborolidenes and asymmetric dihydroxylation reactions. The advantage of abiological catalysts, however, is the availability of either enantiomer of the target molecule. Today there is enormous emphasis on the design and development of efficient chiral catalysts for enantioselective synthesis and this field has become one of the most intense areas of organic chemical research.

The oxazoline scaffold is prevalent both in natural products[4] and ligands for asymmetric catalysis.[5,6] Consequently, the synthesis of oxazolines has generated intense interest among organic chemists. In asymmetric catalysis, bis(oxazolines) have evolved as a "privileged" ligand structure, while other structurally divergent oxazolines have received considerably less attention.[7] Chiral oxazoline-based ligands have attracted significant attention over the past 15 years for their potential application in a variety of catalytic asymmetric reactions[1] including allylic alkylation, cyclopropanation, hydrosilylation, olefin hydrogenation, transfer hydrogenation of ketones, and Diels-Alder reactions. Generally chiral oxazolines are easy to prepare in high enantiomeric purity and can form effective catalytic complexes with a variety of metals.[8]

Besides the intrinsic advantages of oxazoline ligands, such as easy accessibility, modular nature, stability towards hydrolysis and oxidation, and facile coordination to a wide range of transition metals, an important advantage of oxazoline ligands is that the stereogenic centres neighbouring the coordinating nitrogen atom of the oxazoline ring, are held in close proximity to the metal thus exerting a strong and direct influence on the stereochemical outcome of metal catalyzed processes.[9]

The large majority of these ligands are derived from readily available chiral amino alcohols in a few high-yielding synthetic steps. As a consequence, the enantiocontrolling stereo center resides on the carbon atom neighboring the coordinating nitrogen of the oxazoline ring and, therefore, in close proximity to the metal active site, thus having a direct influence on the stereochemical outcome of the reaction. Since the first report in 1986 of the use of chiral oxazoline-based ligands in asymmetric catalysis,[9] a diverse range of ligands with one, two, or more oxazoline rings incorporating various heteroatoms, additional chiral elements, and specific structural features have been used with a great success in a wide range of asymmetric reactions.

Synthesis of Oxazolines

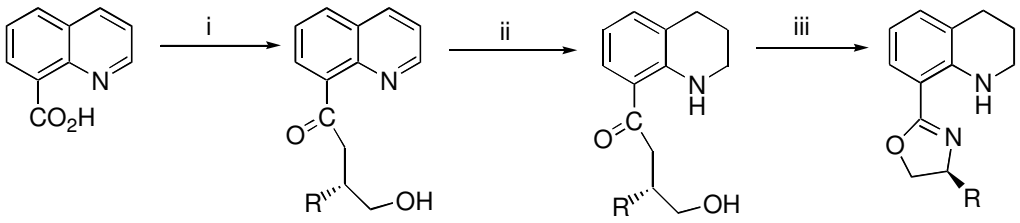
Oxazolines are powerful structural elements, which have been incorporated in many chiral ligands successfully used in asymmetric catalysis. However, despite their obvious benefits they have not as yet been used as building blocks to form other functional groups in chiral ligands. Oxazolines can be synthesized by several routes. The most general methods are: (a) the ring-expansion reaction of acylaziridines; (b) the N-cyclofunctionalization of a double bond starting from a vicinal O-functionality, or the O-cyclofunctionalization of a double bond starting from an N-functionality; or (c) the formation of a C–C bond by an aldol condensation.

4.2.3 EARLIER SYNTHETIC APPROACHES FOR THE SYNTHESIS OF CHIRAL OXAZOLINES

Herein, presented are some recent, original strategies that have been utilized in the synthesis of chiral oxazolines.

Zhou's Approach (2002)[21]

Zhou *et al.* synthesized chiral 1,2,3,4-tetrahydroquinolinyl-oxazoline compounds from 8-quinoline carboxylic acid and enantiomerically pure amino alcohols.

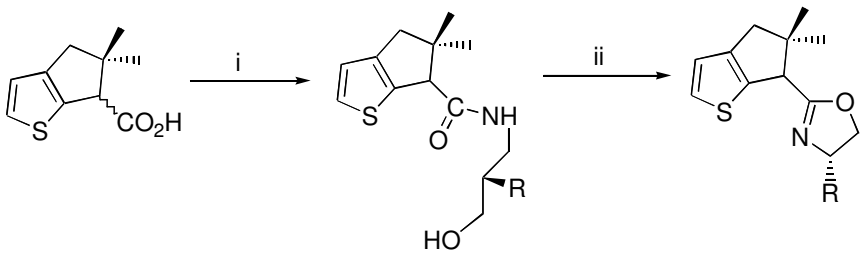


Scheme 1

Scheme 1: i) $SOCl_2$, then amino alcohol or $EtOH/H^+$, then amino alcohol; ii) Ni-Al, KOH; iii) CH_3SO_3H.

Ricci's Approach (2004)[19]

Ricci *et al.* have reported the synthesis of novel bidentate ligands with two stereogenic centres with an oxazoline moiety linked to a rigid cyclopenta[b]thiophene, 5,6,-dihydro backbone in which the sulfur atom is part of a strong π-donor structure.

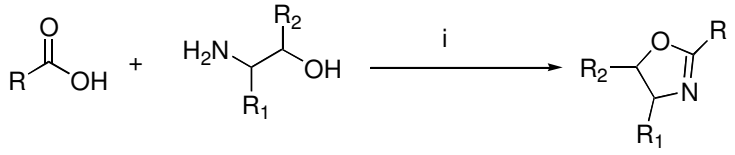


Scheme 2

Scheme 2: i) DCC, then amino alcohol; ii) *p*-TsCl, DMAP, dry Et_3N, DCM.

Sigman's Approach (2002)[10a]

According to Sigman's procedure, the acid and β-amino alcohol were treated with CCl_4, PPh_3, and a base to generate the oxazoline in a single step.

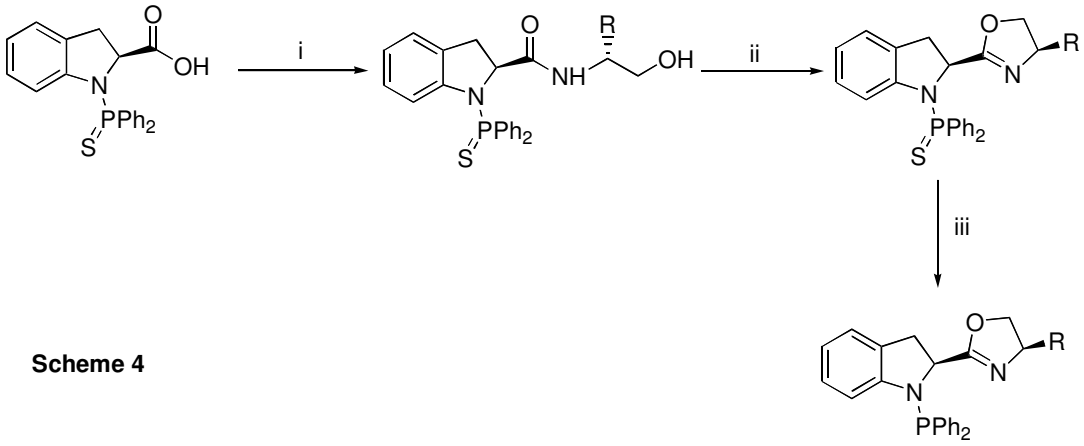


Scheme 3

Scheme 3: i) PPh_3, CH_2Cl_2, $(i\text{Pr})_2\text{Et}$; CCl_4, DCM, one pot.

Niedercorn's Approach (2004)[15g]

Niedercorn *et al.* have reported the synthesis of chiral aminophoshine-oxazoline derived auxiliaries *via* series of reactions.



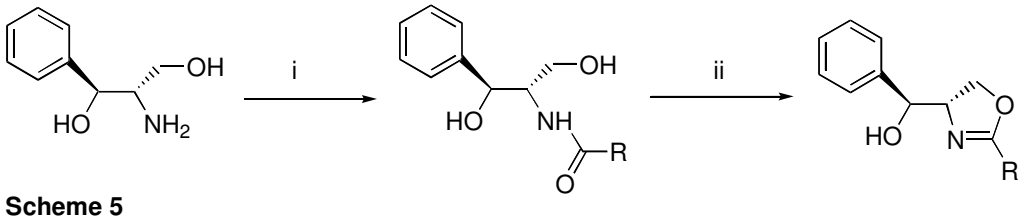
Scheme 4

Scheme 4: i) BOP, Et_3N, CH_3CN, amino alcohol; ii) *p*-TsCl, DMAP, dry Et_3N, DCM; iii) Ni Raney, THF.

Gong's Approach (2003)[15h]

Gong *et al.* reported the synthesis of chiral oxazolines, beginning with an amidation of (1S,2S)-2-amino-1-phenyl-propane-1,3-diol with RCOCl and

$(RCO)_2O$ to provide amides and further using Evan's procedure[7e] provided the corresponding chiral oxazolines in good to excellent yields.

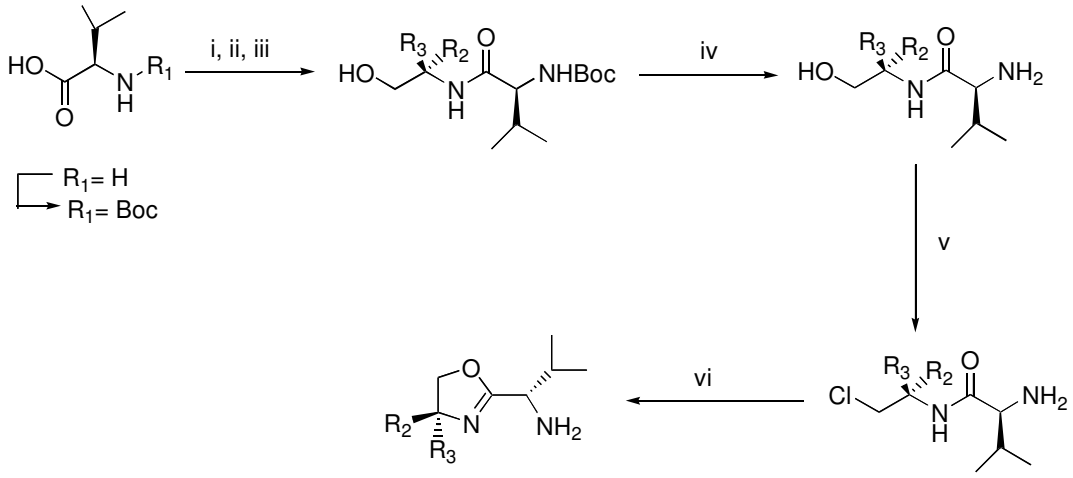


Scheme 5

Scheme 5: i) RCOCl or $(RCO)_2O$, Et_3N, DCM, reflux; ii) *p*-TsCl, Et_3N, DCM, reflux.

Adolfsson's Approach (2005)[15i]

Adolfsson *et al.* elegantly synthesized 2-(aminomethyl)-oxazolines as high modular scaffolds from α-amino acids and 1,2-amino alcohols.

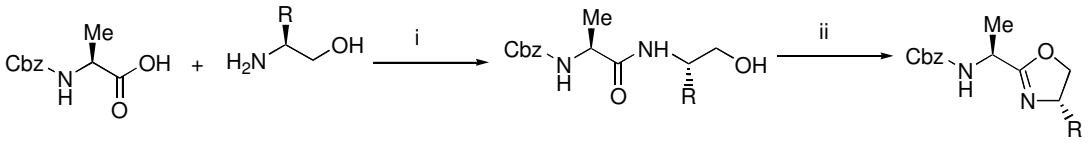


Scheme 6

Scheme 6: i) $(Boc)_2O$, NaOH, THF/H_2O, 25 ^{0}C; ii) Bu*i*OCOCl, NMM, THF, -15 °C; iii) 1,2-amino alcohol, THF, 25 °C; iv) HCl (aq, 3 M), MeOH; v) $SOCl_2$, 1,2-dichloroethane, 70 °C; vi) NaOH, EtOH, reflux.

Gilbertson's Approach (2002)[23]

Gilbertson and Lan presented an approach that allows for the synthesis of phosphine-oxazoline ligands by the synthesis using Burgess reagent.



Scheme 7

Scheme 7: i) EDC, HOBt; ii) Burgess reagent, THF RT.

4.2.4 **PRESENT WORK**

4.2.4.1 **Objective**

In an effort to explore new oxazoline ligand templates for catalytic enantioselective reactions, targeted the synthesis of oxazoline amines using N-phthaloyl protecting and deprotecting approaches (Figure 2). This oxazoline template contains three noteworthy features: (1) introduction of multiple chiral centers in which a variety of different substituents can be integrated, (2) the building blocks are commercially accessible with many available from the chiral pool, and (3) the pendant amine can be systematically elaborated. Markedly, this scaffold is also present in biologically relevant natural products.[4b-e]

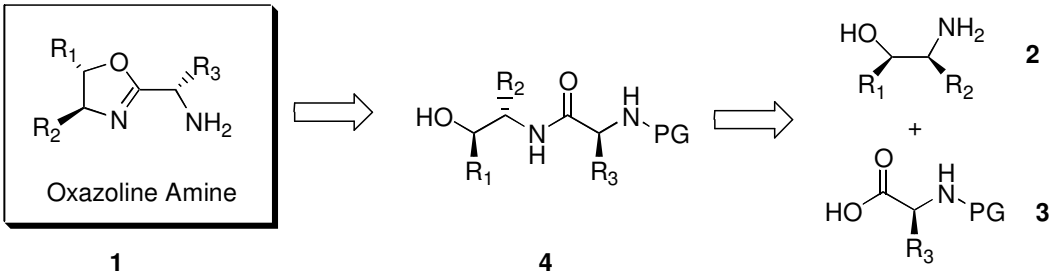


Figure 2. Oxazoline amine synthetic plan

The formation of chiral oxazolines is a straightforward process starting from a carboxylic acid or carboxylic acid derivative and a suitable chiral 1,2-amino alcohol. The ease with which R-amino acids can be transformed into 1,2-amino alcohols opens up a wide variety of enantiomerically pure ligand building blocks. Thus, vast structural variations of the 1,2-amino alcohol. The central building block in this class of ligands is a highly modular symmetric scaffold, 2-(aminomethyl) oxazoline (1).[11]

Herein, we disclose our preliminary attempts on the preparation of a N-phthaloyl L-phenyl alanine derived ligand based on this oxazoline scaffold.

4.2 RESULTS AND DISCUSSION

a) Synthesis of chiral oxazoline 1 (1S)-1-[(4S)-4-benzyl-4,5-dihydro-1,3-oxazolo-2-yl]-2-phenylethan-1-amine)

The synthetic plan of the oxazoline amine[11] reveals that the oxazoline core can be synthesized by cyclic dehydration of a β-hydroxyamide (Figure 2). This is the most common method for oxazoline synthesis and is achieved by converting the hydroxyl group into a good nucleofuge.[7] The β-hydroxyamides can be accessed through amide bond formation using commercially available β-amino alcohols and suitably protected α-amino acids.

In order to realize a synthetically concise approach, the protecting group on the amino functionality of the α-amino acid must be stable to the basic conditions of the reaction and cannot be cleaved under acidic conditions since oxazolines are generally acid sensitive. Earlier reports ruled out the possibility of several protecting groups for particular reasons. The trifluroacetamide protecting group led to racemization of the α-amino acid under the reaction conditions.[12] In contrast, the Cbz-, Boc-, and Alloc-protected α-amino acids all cyclized cleanly, but removal of these protecting groups proved to be difficult.[13] Although use of the Fmoc-protecting group,[10b] found to be very productive, the expensive commercially available Fmoc-protected α-amino acids as a mild deprotection protocol, emphasized the need of experimenting with much cheaper and stable N-phthaloyl group as the protecting group towards the synthesis of chiral oxazolines.

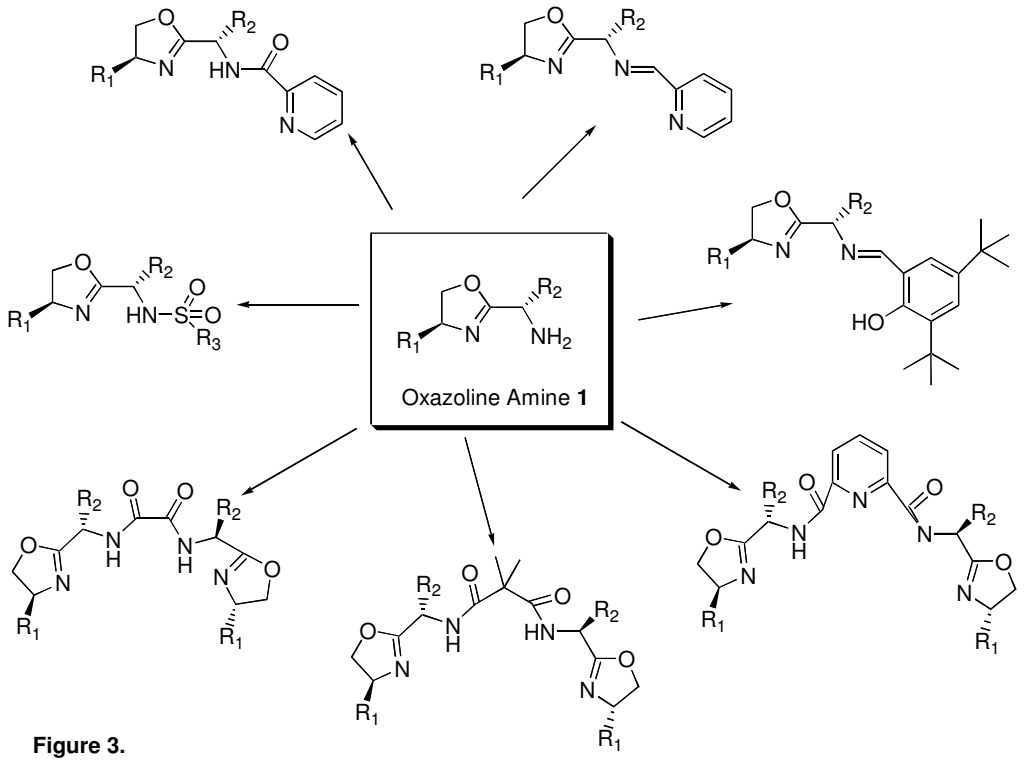


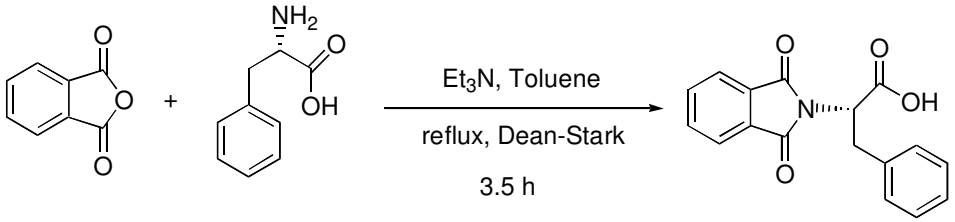
Figure 3.

Hence, the highly modular scaffolds represented by 2-(aminomethyl) oxazolines are certainly qualified as ligands or ligand precursors for asymmetric catalysis. Taken advantage of the ease with which enantiomerically pure 2-(aminomethyl)oxazolines are prepared and devised an array of ligand structures based on this precursor (Figure 3). 2-(aminomethyl)oxazolines **1** have previously been used in various synthetic applications, e.g., peptide synthesis and as substrates for asymmetric alkylation reactions.[14] Surprisingly, this highly modular class of oxazolines has not yet to any larger extent, been applied as ligands in asymmetric catalysis.[15]

Though, the structure of 2-(aminomethyl) oxazolines, presents multiple opportunities for the preparation of ligands suitable for catalytically active transition metals. The parent compound **1** can be used by itself, functioning as a bidentate ligand, or the primary amine functionality can be further derivatized into a number of different interesting ligand structures. Since the basic structure is constructed from R-amino acids and 1,2-amino alcohols, the formation of 2-(aminomethyl)oxazolines containing two or three stereocenters

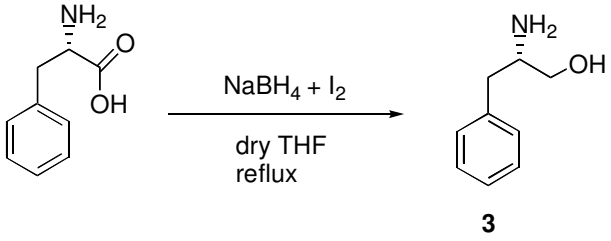
is rather straightforward, taking advantage of the wide array of building blocks available in the chiral pool.[16]

With the goal to set to prepare the desired N-phthaloyl L-amino acid derived chiral oxazoline, initially the study was limited to ligands based on the amino acid L-phenyl alanine. At first, N-phthaloyl L-phenylalanine (**2**) was prepared in 90% yield by condensing phthalic anhydride and L-phenyl alanine and catalytic amount of triethyl amine in toluene under Dean-Stark conditions as depicted in Scheme 8.[17]



Scheme 8

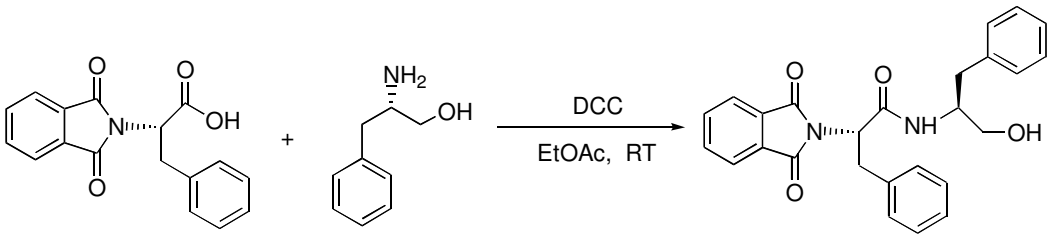
The compound **2** was characterized by the formation of multiplet at δ 5.27 (1H, CH) by ^{1}H NMR spectrum and the optical purity of the compound was found to be 97.4%. Reduction of L-phenyl alanine to L-phenyl alaninol **3** was done using $NaBH_4$+I_2 in THF in 63% yield as a semi-white solid (Scheme 9).[18] The rotation was found to be $[\alpha]^{25}_D$= - 22.8 (c=1.2, 1N HCl) which is in accordance with the literature data.



Scheme 9

A concern with this method was the possibility of racemization of the chiral centre on the α-amino acid during the activation for the coupling of the above prepared N-phthaloyl L-phenylalanine (**2**) and L-phenylalaninol (**3**) as precursors for the formation of β-hydroxyamides[19] can be accessed through amide bond formation. DCC in ethyl acetate was found to be the ideal coupling reagent for the successful coupling (Scheme 10). Importantly, no

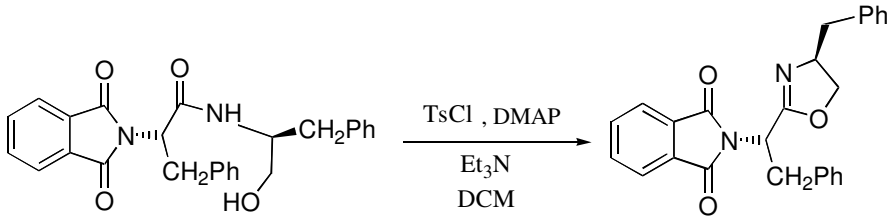
detectable racemization of the α-amino acid is observed. The amide **4** was formed as semi-white solid in 62% yield with optical rotation of $[\alpha]^{25}_{D}$= -78.0 (c=1.0, $CHCl_3$).



2 **3** **4**

Scheme 10

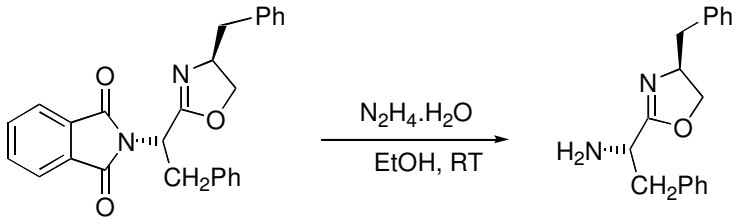
Using several optimized conditions for the literature for the formation of oxazoline ring, taken up the study of cyclization of the formed β-hydroxyamide **4** in the presence of i) *p*-TsCl, DMAP, dry Et_3N in DCM developed by Evans[7e] ii) $MeSO_3H$[20] iii) PPh_3, DIPEA, CCl_4 in DCM,[21] iv) Burgess reagent (Methyl *N*-(triethylammoniumsulphonyl)carbamate), etc.[22] Among the tested procedures, Evans' procedure seemed to work efficiently for the desired cyclization to give the oxazoline **5** as semi-white solid in 45% yield (Scheme 11). The optical rotation of the oxazoline **5** was found to be $[\alpha]^{25}_{D}$= - 102.4 (c=1.0, $CHCl_3$).



4 **5**

Scheme 11

With the scope of this procedure examined, the stage was set for the crucial deprotection reaction.



5 **1**

Scheme 12

Final conversion of compound **5** into 2-(aminomethyl) oxazoline **1** was accomplished by deprotecting in 80% hydrazine hydrate and ethanol under reflux conditions for overnight, followed by addition of HCl, affording amine functionalized oxazoline **1** in 58% yield (Scheme 12) as viscous oil with an observed optical rotation of $[\alpha]^{25}_{D}$= –98.6 (c=0.45, $CHCl_3$).

4.2.5 CONCLUSION

In conclusion, an elegant description of applications of chiral oxazolines in asymmetric catalysis and recently developed as well as earlier approaches for the synthesis have been aptly described in this section. Apart from that, the synthesis of chiral oxazoline **1** (1S)-1-[(4S)-4-benzyl-4,5-dihydro-1,3-oxazolo-2-yl]-2-phenylethan-1-amine) as a new class of bidentate ligands, designed from N-phthaloyl L-phenyl alanine, was successfully completed.[23]

4.2.6. EXPERIMENTAL SECTION

1. Preparation of (2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanoic acid (2)

A mixture of L-Phenyl alanine (3.93 g, 23.8 mmol), phthalic anhydride (3.5 g, 23.64 mmol) and triethylamine (0.35 mL) in toluene (250 mL) was heated under reflux under nitrogen atmosphere for 3.5 h with azeotropic removal of water with a Dean-Stark apparatus. After removal of the solvent under reduced pressure, ethyl acetate was added and the organic phase was washed with dilute HCl (1 M) to eliminate the unreacted phenyl alanine, dried over $MgSO_4$, filtered and concentrated to give the desired N-phthaloyl L-phenyl alanine **2** as white solid (6.32 g, 90%).

White solid, Mp: 181-185 ^{0}C.

***[α]*$^{25}_{D}$** = -198.4 (*c*=1.00, EtOH)

IR (KBr cm^{-1}): ν 3265, 3027, 2920, 1746, 1697, 1493, 1396, 1218, 1100, 1070, 939, 630.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* (in ppm) 3.61 (d, *J*=8.7 Hz, 2H), 5.25 (t, *J*=8.7 Hz, 1H), 7.20 (m, 5H), 7.65-7.84 (m, 4H), 9.38 (bs, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): *δ* (in ppm) 34.5, 53.2, 126.6, 126.9, 128.6,128.9, 131.5, 134.2, 136.5, 167.5, 174.5.

FAB-MS: 65, 76, 104, 148, 149, 232, 249, *m/z* 296 $(M+H)^+$, 318 $(M+Na)^+$.

2. Reduction of L-Phenyl alanine to L-Phenyl alaninol (3)

$NaBH_4$ (11g, 290 mmol) was dissolved in 450 mL of dried THF. To a solution of L-phenyl alanine (20 g, 121 mmol) was cooled to 0 ^{0}C in a ice bath. To this mixture was added molecular I_2 (30.74 g, 121 mmol) in THF dropwise in half an hour and then allowed to stir at reflux for 18 hours. Then it was cooled to room temperature. To this milky reaction mixture, was added methanol until it becomes clear (approximately 1 L). After stirring for half an hour, the solvent was removed by rotavapor producing a white paste, which was dissolved in 4 L of 20% aqueous KOH. The solution was stirred for 4 hours and extracted with 4x1 L of methylene dichloride (MDC) and the organic extracts were dried over Na_2SO_4 and was evaporated. The white semisolid residue was recrystallised from toluene to yield 11.53 g of **3** (63%).

Semi-white solid, Mp: 93-94 ^{0}C.

***[α]*$^{25}_{D}$** = -22.8 (c=1.2, 1N HCl)

IR (KBr cm^{-1}): ν 3356, 3298, 2875, 2365, 1953, 1877, 1759, 1708, 1577, 1492, 1453, 1338, 1122, 1064, 973, 753, 698, 553.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* (in ppm) 2.35 (br s, 3H), 2.45-2.51 (dd, 1H), 2.72-2.80 (dd, 1H), 3.04- 3.15 (m, 1H), 3.31-3.39 (m, 1H), 3.57-3.62 (m, 1H), 7.12-7.20 (m, 3H), 7.21-7.29 (m, 2H).

FAB-MS: 91, 120, *m/z* 152 $(M^+ + H)$.

3. Preparation of *N*1-[(1*S*)-1-benzyl-2-hydroxyethyl]-(2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanamide (4)

To a stirred solution of N-phthaloyl L-phenyl alanine (5 g, 17 mmol) and L-phenyl alaninol (2.56 g, 17 mmol) in EtOAc (50 mL), a solution of DCC (1.2 mmol) in EtOAc was added in dropwise over a period of 20 min at room temperature, the mixture was stirred for 6 hours, the white precipitate formed was filtered under reduced pressure, the filtrate was washed twice with a 5% solution of citric acid (250 mL) and evaporated. The residue was purified by SiO_2 gel coloumn chromatography (eluent 20% ethyl acetate: hexane) to yield the desired amide **4** (4.49 g, 62%).

Semi-white solid, Mp: 202-204 ^{0}C.

[α]$^{25}_D$ = -78.0 (*c*=1.00, $CHCl_3$)

IR (KBr cm^{-1}): ν 3450, 3364, 3314, 2928, 2856, 1773, 1718, 1655, 1539, 1383, 1232, 1095, 958, 719, 528.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* (in ppm) 3.12-3.22 (dd, 4H), 3.98-4.2 (m, 2H), 4.51 (m, 1H), 4.95 (dd, 1H), 4.92 (br s, 1H), 5.42 (br s, 1H), 7.15-7.40 (m, 10H), 7.56-7.80 (m, 4H).

FAB-MS: 55, 69, 107, 163, 250, 310, 369, 411, *m/z* 429 (M^++H).

4. Synthesis of N-Phthaloyl Protected Oxazoline: (2-(1*S*)-1-[(4*S*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]-2-phenylethyl-1,3-isoindolinedione) (5)

To the solution of amide (2.44 g, 5.7 mmol) in DCM (40 mL) dded successively at room temperature *p*-TsCl (1.63 g, 8.5 mmol), DMAP (350 mg, 5 mol%) and dry Et_3N (1.73 g, 2.4 mL, 17 mmol). After 12 hours, 10% $NaHCO_3$ solution (50 mL) was added and the solution was stirred for half an hour and then extracted with DCM (2×20 mL). The organic layer was dried over Na_2SO_4, filtered and the filtrate purified by EtOAc/hexane (1:9) to derive the corresponding oxazoline **5** in 45% yield (1.05 g).

Semi-white solid, Mp: 160-162 ^{0}C.

[α]$^{25}_D$ = -102.4 (*c*=1.00, $CHCl_3$)

IR (KBr cm^{-1}): ν 3010, 2982, 2928, 2814, 1779, 1666, 1380, 1311, 1201, 1078, 977, 772, 512.

^{1}H NMR (300 MHz, $CDCl_3$): δ (in ppm) 2.62 (m, 1H), 3.20 (m, 1H), 3.61 (dd, 2H), 4.02 (m, 1H), 4.15-4.45 (m, 2H), 5.15 (dd, 1H), 7.01-7.28 (m, 10H), 7.61-7.82 (m, 4H).

FAB-MS: 55, 77, 91, 105, 154, 250, 307, *m/z* 411 (M^++H).

Elemental Analysis (for $C_{26}H_{22}N_2O_3$ in %): C 76.08, H 5.40, N 6.82.

5. Synthesis of Amine-Functionalized Oxazoline: (*(1S)*-1-[(*4S*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]-2-phenylethan-1-amine) (1)

Compound **5** (0.73 g, 1.77 mmol) in ethyl alcohol (50 mL) and 80% aq.hydrazine hydrate ($N_2H_4.H_2O$) (5 mL) were refluxed for 2.5 h. The mixture was left at room temperature for overnight, the precipitate formed was filtered off and washed with ethanol. After addition of 6N HCl (25 mL) the filtrate was concentrated off to half of its volume, the precipitate was filtered off and concentrated again to yield a solid, which was recrystallised from ethanol/ethyl ether to give 0.29 g (58%) of pure compound as viscous oil **1**.

Viscous oil.

$[\alpha]^{25}_D$ = -98.6 (*c*=0.45, $CHCl_3$)

IR (neat, cm^{-1}): ν 3356, 2988, 2956, 2911, 1456, 1328, 1120, 927, 756, 527.

^{1}H NMR (300 MHz, $CDCl_3$): δ (in ppm) 2.12-2.18 (dd, 2H), 2.32-2.40 (dd, 2H), 3.61 (dd, 1H), 4.12- 4.44 (m, 2H), 7.09-7.37 (m, 10H).

EI-MS: *m/z* 280 (M^+).

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4.3.1 INTRODUCTION

The synthesis of new kind of chiral ligands represents one of the most important factors in the field of asymmetric catalysis. The major parts of most common ligands are bidentate and neutral, like DIOP and BINAP,[1] or dianionic, like TADDOL[2] and BINOL.[3] The chiral chelating ligands that afford metal centres with a chiral environment are essential components for the development of chiral catalysts. Over the past 25 years, extensive chemistry has surrounded the use of Schiff base ligands in inorganic chemistry.

Hugo Schiff described the condensation of an aldehyde and an amine leading to a Schiff base which are considered "privileged ligands"[4] in 1864.[5] Schiff base ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. In fact, Schiff bases are able to stabilize many different metals in various oxidation states, controlling the performance of metals in a large variety of useful catalytic transformations. The present study will focus on the different ways of preparing metal complexes and their use in catalytic processes. Generally, active catalytic Schiff base metal complexes are obtained *in situ*, and are not well characterized. However, the appropriate choice of metal precursor and the reaction conditions are crucial for catalytic properties. Finally, a particular class of Schiff bases will also be discussed. When two equivalents of salicylaldehyde are combined with a diamine, a particular chelating Schiff base is produced. The so-called Salen ligands, with four coordinating sites and two axial sites open to ancillary ligands, are very much like porphyrins, but more easily prepared. Although the term Salen was used originally only to describe the tetradentate Schiff bases derived from ethylenediamine, the more general term Salen-type is used in the literature to describe the class of [O,N,N,O] tetradentate bis-Schiff base ligands (Figure 1). Among higher denticity ligands are the tetradentate salen ligands, used for example in asymmetric epoxidation, epoxide ring opening and aziridination.[6, 7]

Basic guidelines for the design, synthesis and application of metal Schiff base complexes in catalysis will thus be surveyed with the emphasis on the relevant problems in producing active and useful complexes.

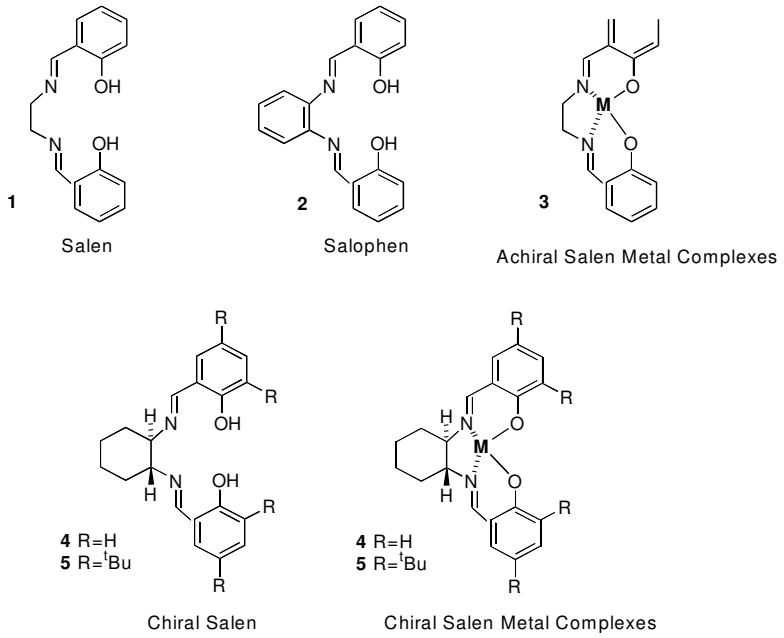


Figure 1. Different Salen ligands and M(Salen) complexes.

The complexation steps: different routes

In many catalytic applications Schiff base metal complexes are prepared *in situ* by producing a reaction between the Schiff base and available and well-defined metal complexes. This approach is clearly simple and suitable for catalytic applications. Essentially, five different synthetic routes can be identified for the preparation of Schiff base metal complexes (Figure 2).

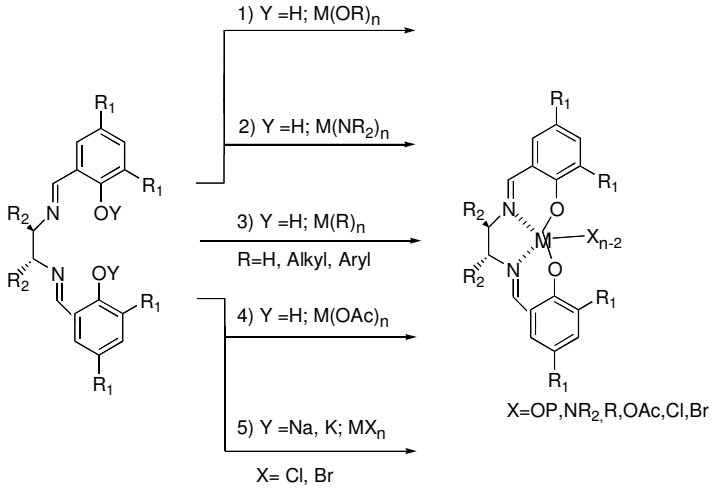


Figure 2. The complexation steps: different routes

Salen–type chiral Schiff base ligands have received considerable attention during the last decades, mainly because their steric and electronic properties can be easily adopted by choosing the right chiral amine and aldehyde precursors. In this context for example Jacobsen catalyst (Figure 3) and other similar transition metal complexes with symmetrical and unsymmetrical ligands have been developed and used as catalyst for many kind of processes.[8]

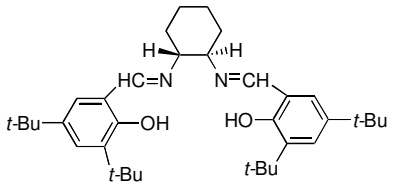


Figure 3. Jacobsen Catalyst

4.3.2 APPLICATIONS OF CHIRAL SCHIFF BASE LIGANDS

High-pressure (10KBar) reaction of 2-methyl furan with alkyl glyoxylates catalyzed by chiral (salen) Co(II) complex afforded the Friedel-Crafts products both in good yields and enantioselectivity (Figure 4).[9]

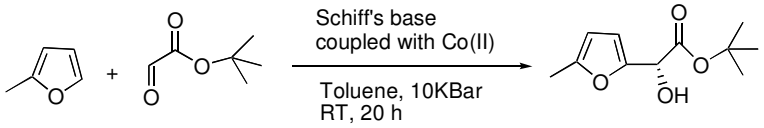


Figure 4

A series of new chiral N_4-Schiff bases, containing amine or sulfonamide functionalities have been synthesized. Coupled with ruthenium catalysts, these Schiff bases induce interesting results in the hydrogenation of acetophenone: complete conversion and 76% ee were obtained with the catalytic system $Ru(PPh_3)_3Cl_2$/(1R,2R)-N,N-bis-(2-*p*-tosylaminobenzylidene)-1,2-diphenylethylenediamine. A very important phosphine co-ligand effect was observed on both activity and enantioselectivity of the catalysts. However, without the co-ligand, we obtained an enantioselectivity for the (R)-enantiomer, whereas with nonchiral co-ligand an enantioselectivity for the (S)-enantiomer was observed (Figure 5).[10]

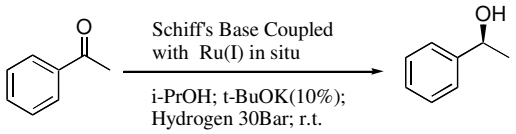


Figure 5

Schiff base complexes are able to stabilize titanium in a low oxidation state and enable the control of simple diastereoselection in the pinacol coupling of the aromatic aldehydes **(Figure 6).**[11]

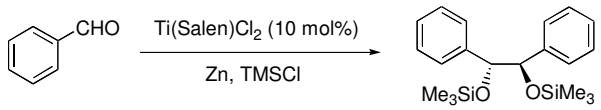


Figure 6

The use of chiral Al (salen) Cl complex in the addition of HCN to imines gave 2^0 amines in an enantiomerically pure form (Figure 7).[12]

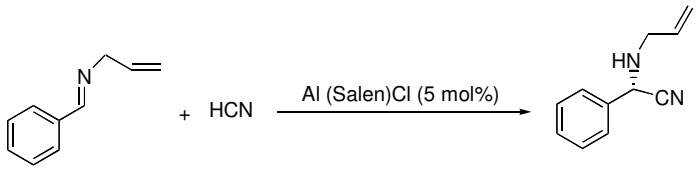


Figure 7

The addition of alkynyl to ketones can be done using Zn(Salen) as a catalyst, leading to new perspectives in the formation of quaternary stereocenters (Figure 8).[13]

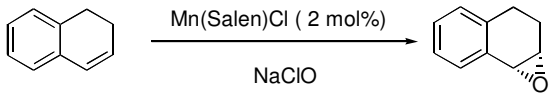


Figure 8

Nguyen reported that ruthenium(II) Salen complexes were a very efficient catalyst for the cyclopropanation of olefins (Figure 9).[14] The key discovery of the synthesis was the stabilization of the intermediate Ru(II)Salen by pyridine.

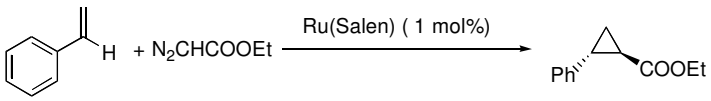


Figure 9

Schiff bases have an important role to perform as polymerization catalysts, and are able to stabilize a reactive cationic nickel complex. The Schiff bases

are able to act as a metallaic crown, and an interesting structure containing different metals can result. Ni(Salen) bearing another metal can behave as a bifunctional catalyst, as prepared by Kozlowski (Figure 10).[15]

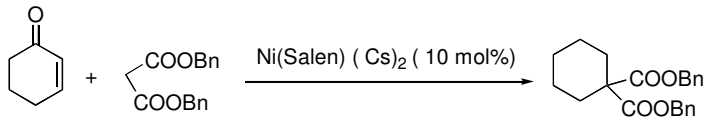


Figure 10

Salen can act as a bifunctional catalyst, mimicking the common aminoalcohols widely used in Zn-mediated additions of Et_2Zn to aldehydes. Zn(Salen) has the ability to promote the addition of other organometallic reagents as well. Alkynylation has attracted considerable interest in recent years, as propargylic alcohols are valuable synthetic precursors (Figure 11).[16]

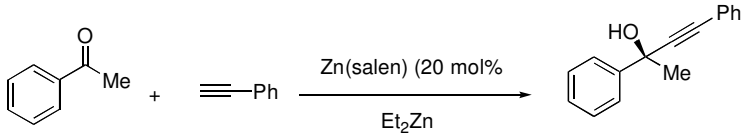


Figure 11

4.3.3 PRESENT WORK

4.3.3.1 Objective

An interesting class of salen analogue transition metal complexes is that one having N-salicylaldehyde chiral aminoacidatos as ligands; studied as non-enzymatic models for pyridoxal-amino acid system.[17] To this aim several copper (II),[18] zinc (II)[18] and vanadium (IV) or (V)[19] salicylaldehyde aminoacidatos have been synthesized and structurally characterized. As part of ongoing studies on using lanthanide salts as catalysts in synthetic organic chemistry,[20-22] the present work reports the synthesis and spectroscopic characterization of novel symmetric N-salicylaldehyde ligands based on chiral amino acid-derived subunits of structure **L** (Figure 12).

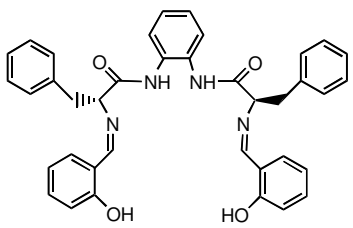
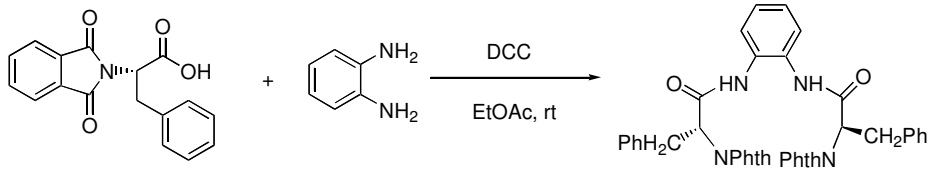


Figure 12

Complexes of trivalent lanthanides aminoacidato complexes have been the subjects of several physicochemical studies,[23] but very few reports on the catalytic activity of such complexes have been found in the literature.[24] Ligand **L** contains from four up to six coordination sites; its core is based upon two nitrogen imine atoms and two hydroxyl functions, which are known to coordinate strongly to transition metal centers,[18] and two amide moieties. The synthesis was carried out in four easy steps, each with excellent or good yields.

4.3.3.2 RESULTS AND DISCUSSION:

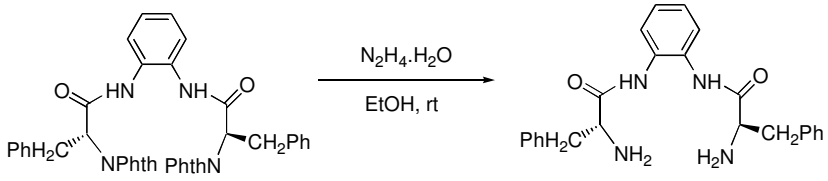
At first, N-phthaloyl L-phenyl alanine **2** was subjected to the coupling reaction with *o*-phenylenediamine (2:1 ratio) by using 2 equiv. of dicyclohexyl carbodiimide (DCC) as condensating agent in EtOAc at room temperature.



2 **3**

Scheme 1

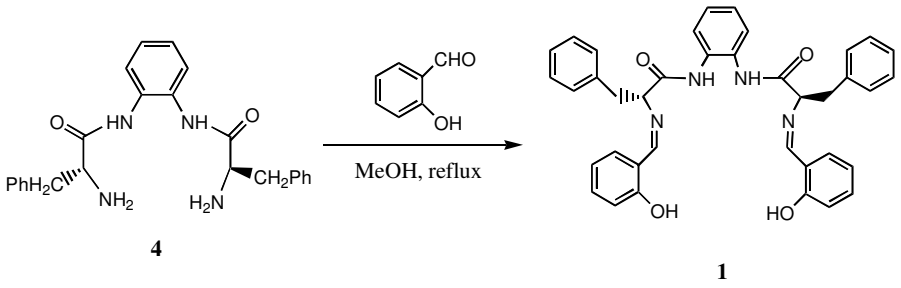
Employing *N*-phthaloyl protected L-phenylalanine **2**, as starting material, the corresponding diamide adduct **3** was obtained in 90% yield, respectively, after SiO_2 gel column chromatography using CH_2Cl_2/MeOH (99:1) as eluent.



3 **4**

Scheme 2

The N-phthaloyl functions of **3** were cleaved (82% yield) with a ethanolic 80% aq.hydrazine hydrate at reflux for 2.5 h and followed by usual work up. This high yielding two-step synthesis of diamino diamides of structure like **4** needs to be pointed out as they represent useful synthons for tetra and pentadentate macrocyclic tetramide ligands.[18]



4 **1**

Scheme3

The synthesis of the desired ligands was accomplished by condensation of chiral diamine **4** with salicylaldehyde under reflux in MeOH, followed by crystallization of the corresponding Schiff base **1** in 58% yield. This ligand is insoluble at room temperature in a non-polar solvent such as *n*-hexane, benzene or toluene, but exhibits a very good solubility in slightly polar solvents such as dichloromethane, acetonitrile, acetone or tetrahydrofuran. This compound is also stable for several days at room temperature in the solid state.

4.3.4 CONCLUSION

In conclusion, a short synthesis of a new class of chiral polydentate Schiff base ligand **1**, containing mixed N, O donors was developed. This ligand was easily prepared in good yield starting from low-cost commercially available materials. In fact coordinating the ligand to lanthanides to use in asymmetric catalytic processes would not only has great significance in the fundamental chemistry of these rare earth elements but could also have an important role in the field of MRI contrast agents, biological probes or NMR chiral shift reagents.

4.3.5 EXPERIMENTAL SECTION

1. Synthesis of *N*1-(2-[(2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanoyl]aminophenyl)-(2*S*)-2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl)-3-phenylpropanamide (3):

To a stirred solution of N-phthaloyl L-phenyl alanine **2** (5 g, 16.95 mmol) and *o*-phenylenediamine (0.915 g, 8.47 mmol) in EtOAc (50 mL), a solution of DCC (3.49 g, 16.95 mmol) in EtOAc (25 mL) was added drop wise over a period of 20min at room temperature. After the addition was complete

the mixture was stirred for 6 h, the white precipitate formed was filtered under reduced pressure, the filtrate was washed twice with a 5% solution of citric acid (100 mL) and evaporated. The residue was purified by SiO_2 gel column chromatography (eluent CH_2Cl_2/MeOH, 99:1) to give the desired compound **3** in 90% yield (10.10 g, 15.21 mmol).

Yellow crystalline solid, Mp: 108-109 ^{0}C.

[α] $^{25}_D$ = -128.0 (*c*=1.00, $CHCl_3$)

IR (KBr cm^{-1}): ν 3328, 3028, 2928, 2851, 1777, 1716, 1629, 1530, 1383, 720.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* 3.42-3.53 (dd, 4H), 5.10-5.18 (m, 2H), 6.89-7.38 (m, 14H), 7.55-68 (m, 4H), 7.70-7.82 (m, 4H),

8.70 (br s, 2H, NH).

FAB-MS: 55, 69, 91, 154, 225, 250, 377, 592, *m/z* 663 $(M+H)^+$.

2. Synthesis of *N1*-(2-[(2S)-2-amino-3-phenylpropanoyl]aminophenyl)-(2S)-2-amino-3-phenylpropanamide (4):

Compound **3** (8.0 g, 12.06 mmol) in ethyl alcohol (75 mL) and 80% aq. $N_2H_4.H_2O$ (1 mL) were heated at reflux for 2 h. The mixture was left at room temperature for 0.5 h, and then the precipitate was filtered off and washed with ethanol After addition of 6N HCl (25 mL), the filtrate was concentrated to half of its volume, the precipitate was filtered off and the filtrate was concentrated again to give the desired diamine **4** in 82% yield (3.98 g, 9.9 mmol).

White solid, Mp: 265-266 ^{0}C.

[α] $^{25}_D$ = -22.43 (*c*=1.00, MeOH)

IR (KBr cm^{-1}): ν 3300, 3057, 2987, 2863, 1708, 1688.

^{1}H NMR (300 MHz, CDCl$_3$): *δ* 2.76 (dd, 2H, J_{1-2}=8.8 Hz, J_{1-3}=14.6 Hz), 3.33 (dd, 2H, J_{1-2}=4.2 Hz, J_{1-3}=14.6 Hz), 3.74 (dd, 2H, J_{1-2}=4.2 Hz, J_{1-3}=8.8 Hz) 7.14–7.64 (m, 14H).

^{13}C NMR (75 MHz, CDCl$_3$): *δ* 40.7, 56.5, 124.6, 125.9, 126.9, 128.7, 129.3, 129.9, 137.9, 173.5 132.2, 133.2, 160.5, 167.8, 170.7

FAB-MS: 55, 77, 91, 120, 136, 154, 225, 256, 307, 386, *m/z* 403 $(M+H)^+$.

3. Synthesis of Schiff base (1)*: N*1-2-[((2*S*)-2-[1-(2-hydroxyphenyl)methylidene]amino-3-phenylpropanoyl)amino]phenyl-(2*S*)-2-[1-(2-hydroxyphenyl)methylidene]amino-3-phenylpropanamide

To a stirred solution of compound **4** (3 g, 7.46 mmol) in MeOH (30 mL), added salicylaldehyde (1.82 g, 14.92 mmol) and the mixture was allowed held at reflux for 2 h, and then cooled; the white precipitate formed was filtered under reduced pressure, washed with a little cold MeOH and collected to give the Schiff base **1** in 58% yield (2.64 g).

White solid, Mp: 275-276 ^{0}C.

[α] $^{25}_D$ = -36.98 (*c*=1.00, $CHCl_3$)

IR (KBr cm^{-1}): ν 3300, 1660, 1628.

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 3.24 (dd, 2H, J_{1-2}=8.9 Hz, J_{1-3}=13.3 Hz), 3.49 (dd, 2H, J_{1-2}=3.6 Hz, J_{1-3}=13.3 Hz), 4.20 (dd, 2H, J_{1-2}=3.6 Hz, J_{1-3}=8.9 Hz), 6.78–7.49 (m, 22H).

^{13}C NMR (75 MHz, $CDCl_3$): *δ* 41.2, 76.2, 117.0, 118.3, 119.2, 125.0, 126.4, 127.0, 28.5, 128.7, 129.5, 129.8, 132.2, 133.3, 136.6, 160.5, 167.9, 169.9.

FAB-MS: 73, 91, 107, 149, 224, 270, 298, 386, 464, 566, *m/z* 611 $(M+H)^+$.

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He is member of several editorial and reviewer boards of various chemistry journals. He is also Life member in several established scientific bodies. He worked in Pharma Industry also for a period of one year as Scientist. Till dated, he has 13 years of vast experience in research and nearly 3 years in teaching field.