SYNOPSIS

The thesis entitled **"Synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) prodrugs, development of new methods for synthesis of heterocyclic libraries and total synthesis of pinolide"** has been divided into four chapters.

CHAPTER-I : Chapter-I describes Development of pyrrolo[2,1-*c*][1,4]benzodiazepine β-glucoside prodrugs for selective therapy of cancer by ADEPT.

CHAPTER-II : Chapter-II describes Synthesis of new 1,2,3-triazolo heterocyclic scaffolds *via* tandem knoevenagel condensation / azide−alkyne 1,3-dipolar cycloaddition reaction in one pot.

CHAPTER-III : Chapter-III describes Synthesis of new heterocyclics.

SECTION-A : Chapter-III section-A deals with Synthesis of Imidazole derivatives via Silver (I) Carbonate catalysed coupling of vinyl azides with secondary amines.

SECTION-B : Chapter-III section-B deals with Synthesis of 1-aryl-*N* (2-aylimidazo [1,2-a]pyridine-3-yl]methanimine *via* visible-light photoredox catalysis and their cytotoxicity.

CHAPTER-IV : Chapter-IV describes Total synthesis of Pinolide.

CHAPTER-I: Development of pyrrolo[2,1-*c*][1,4]benzodiazepine β-glucoside prodrugs for selective therapy of cancer by ADEPT.

Alkaloids are an important class of natural products, which are known as nitrogenous compounds occurring in plants, toads and animals including mammals and fungi. The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a family of DNA-interactive antitumor antibiotics derived from various *Streptomyces* species. To date thirteen structures which include anthramycin, tomaymycin, DC-81 have been isolated from various *Streptomyces* species (**Figure 1**). The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) interactions with DNA are distinctive since they bind within the minor groove of DNA forming a covalent aminal bond between the C11-position of the central B-ring and the N2 amino group of a guanine base. The cytotoxic and antitumor activity of PBDs is ascribed to their ability to form covalent DNA adducts. Molecular modeling, solution NMR, fluorimetry and DNA foot printing experiments have shown that these molecules have a favored selectivity for Pu-G-Pu sequences and are oriented with their A-rings pointed either towards the 3' or 5' end of the covalently bonded DNA strand.

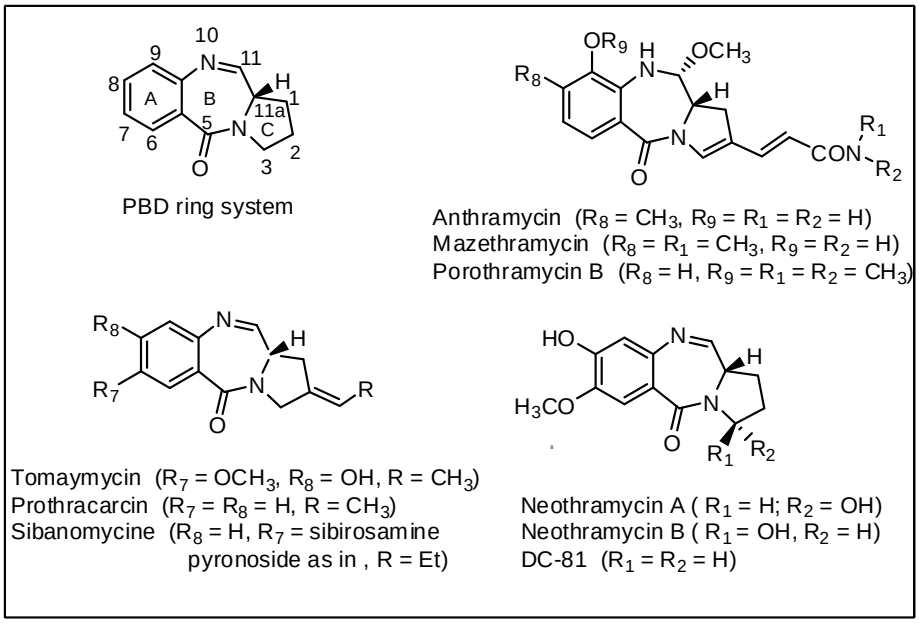


Figure 1: Naturally occurring PBDS

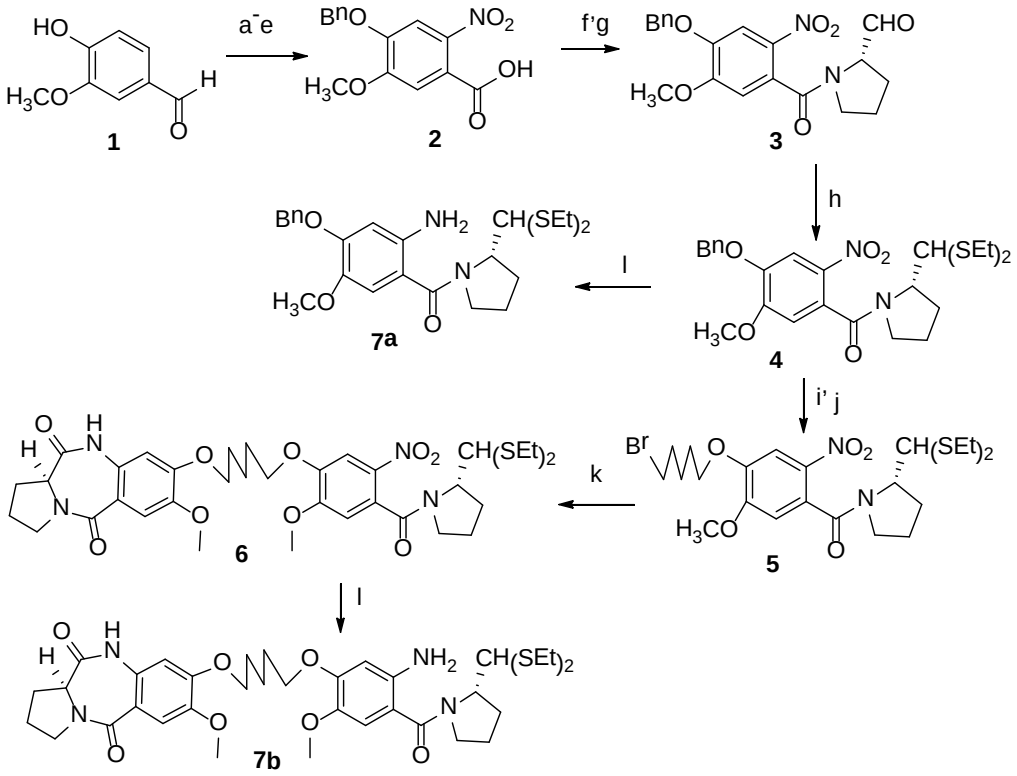
Prodrug:

The term prodrug refers to a pharmacologically inactive compound that is converted to an active drug by metabolic biotransformation. The biotransformation or activation of a prodrug may occur prior, during and after absorption or at specific target sites within the body. Prodrug design may be useful in circumventing problems associated with solubility, absorption and distribution, site specificity, instability, prolonged release, toxicity, poor patient acceptability and formulation problems.

A major limitation of cancer chemotherapy results from the lack of tumour specificity shown by most anticancer drugs. The capability of nearly all of known anticancer agents to differentiate between normal and malignant cells is rather low, leading to several side effects which limits the doses and often leads to discontinuation of the treatment. One approach to prevail over these drawbacks is the development of relatively non-toxic anticancer agents, in a prodrug form, specifically activated in and around the tumour tissue. Several strategies are being explored to improve the selectivity of anti-tumour agents and deliver them at the tumor site by the action of enzymes, thus avoiding destruction of healthy tissues and severe side effects. Prodrug monotherapy (PMT), antibody directed enzyme prodrug therapy (ADEPT) and gene directed enzyme prodrug therapy (GDEPT) are enzyme based approaches that have been developed to target tumour cells selectively.

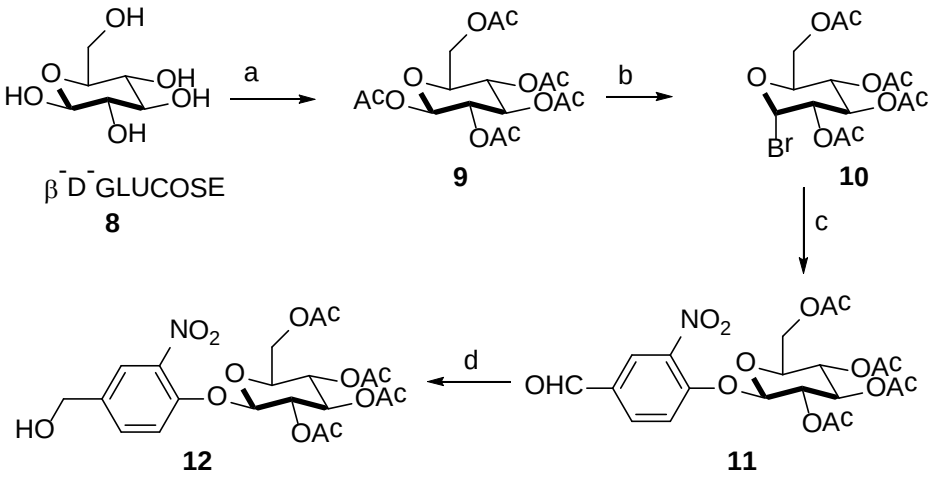
SYNTHESIS OF PBD-GLUCOSIDE PRODRUGS

The synthesis of PBD precursors (2-amino-4-(benzyloxy)-5-methoxy-1,4-phenylene)carbonyl](2*S*)-pyrrolidine-2-carboxaldehyde diethylthioacetal (**7a**) and 8-(5-(5-amino-4-((*S*)-2-(bis(ethylthio)methyl)pyrrolidine-1-carbonyl)-2-methoxyphenoxy)pentyloxy)-7-methoxy-2,3-dihydro-1*H*-benzo[e]pyrrolo[1,2,-a][1,4]diazepine-5,11(10*H*,11a*H*)-dione (**7b**) was carried out employing vanillin as the starting material (Scheme 1).



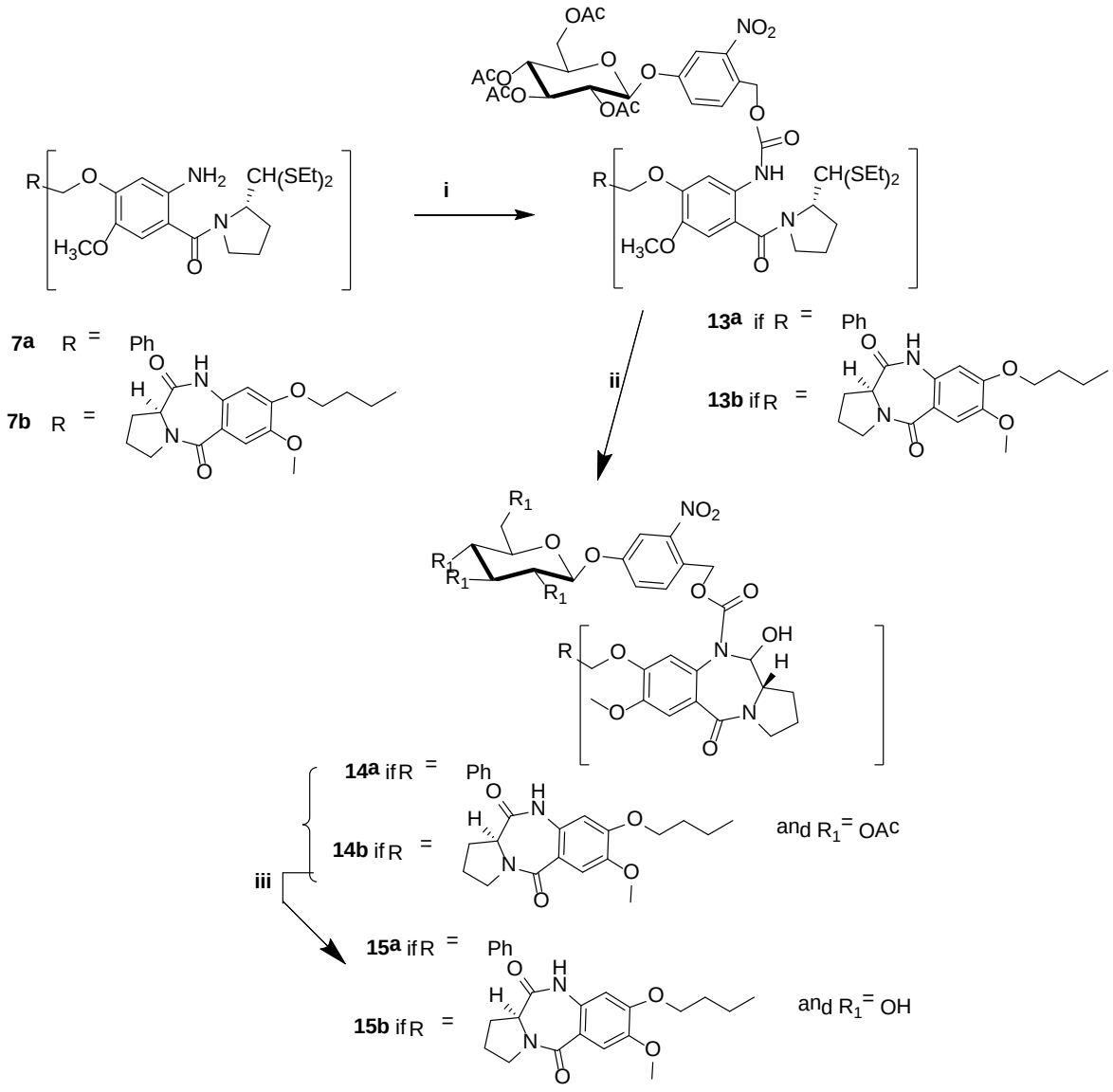
Scheme 1: Reagents and conditions: a) NH_2SO_3H, $NaClO_2$, H_2O, 1 h; b) H_2SO_4, MeOH, 15 h; c) BnBr, K_2CO_3, acetone,reflux, 12 h; d) HNO_3-H_2SO_4, $SnCl_4$, CH_2Cl_2, -25^oC, 5 min; e) 2n LiOH, THF, MeOH, H_2O (3:1:1), rt, 12 h; f) C_6H_6, $SOCl_2$, l-prolinemethyl ester hydrochloride,THF/H_2O, Et_3N, 0 ^oC; g) DIBAL-H, CH_2Cl_2,- 78 ^oC, 45 min; h) EtSH-TMSCl,$CHCl_3$, rt, 16–18 h; i) BF_3.OEt-EtSH, CH_2Cl_2, 12 h; j) 1,5-dibromopropane, K_2CO_3, acetonitrile, reflux, 12 h. k) PBD lactam, acetone, reflux, 12h ; l) $SnCl_2 \cdot 2H_2O$, MeOH, reflux,4 h.

The synthesis of β–glucoside promoiety (**12**) was prepared starting from β-D-glucose (**8**), which on acetylation and alpha bromination gave compound **10** which is on reacting with 4-hydroxy-3-nitrobenzaldehyde gave compound **11**, followed by reduction with $NaBH_4$ afforded the desired product **12** (Scheme 2).



Scheme 2: **Reagents and conditions:** a) Ac_2O, CH_3COONa, reflux, 2 h; b) CH_2Cl_2, HBr-CH_3COOH, 3 h; c) CH_3CN, Ag_2O, 4-hydroxy-3-nitrobenzaldehyde, 3 h; d) $CHCl_3$, $(CH_3)_2CHOH$, $NaBH_4$.

The coupling of the PBD intermediates with the self-immolative β–glucoside promoiety was carried out using the intermediates **7a, 7b** and 4-β–D-2,3,4,6-tetra-O-acetyl glucopyranosyloxy-3-nitrophenyl methanol (**12**) via an isocyanate intermediate. The deprotection of diethylthioacetal group of these intermediates (**13a,13b**) resulted in ring closure to provide carbinolamine carbamate compounds **14a, 14b** which on deacetylation using NaOMe in methanol gave the target molecules **15a** and **15b** (Scheme 3).



Scheme 3: **Reagents and conditions:** i) a) Et_3N, $CO(COCl_3)_2$, 25 min, rt; b) **12**, cat. dibutyl tindilaurate, rt, 6-8 h; ii) $HgCl_2$, $CaCO_3$, CH_3CN/H_2O, 4:1, rt, 12 h: (iii) MeOH, cat. NaOMe, 0-5 ^oC, 30 min.

Pyrrolobenzodiazepine β-glucoside prodrug activation by enzymatic toxification of the PBD-glucoside prodrugs as shown in Figure 2.

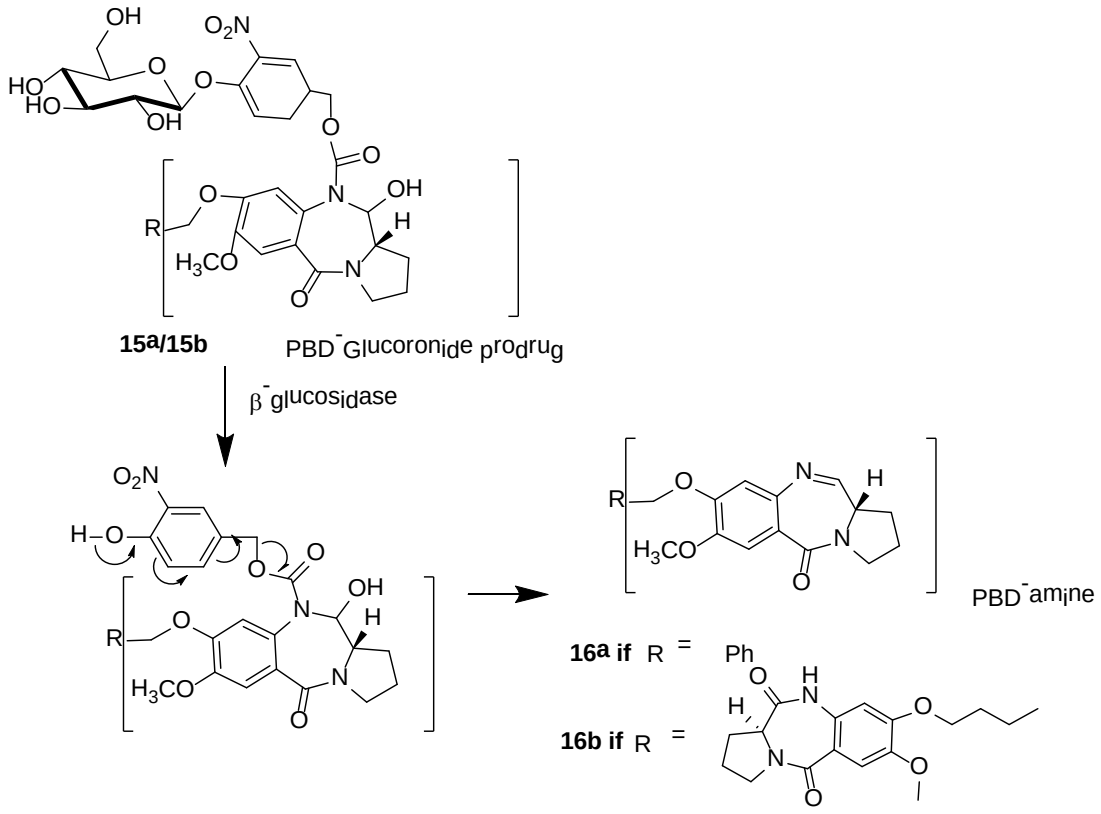
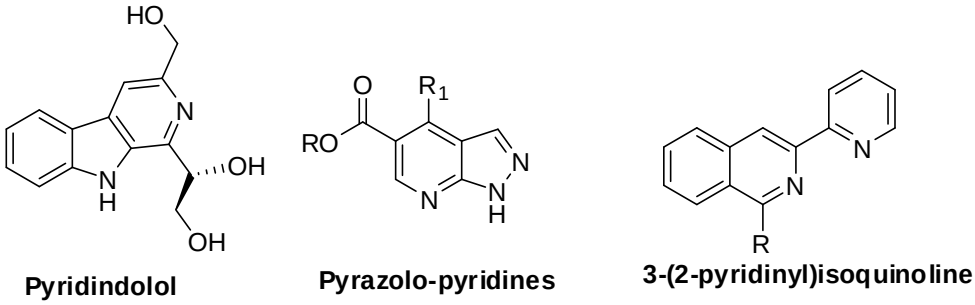


Figure 2: Pyrrolobenzodiazepine β-glucoside prodrug activation

PBD glucoside prodrugs **15a** and **15b** were synthesized and evaluated for their potential use in selective therapy of solid tumors by ADEPT. These compounds were evaluated for their anticancer activity in two human cancer cell lines, i.e, MCF-7 and A375. The MTT assay was performed incomparison to the parent drug and in the presence and absence of β-glucosidase enzyme. All the compounds have shown significant cytotoxic activity in the presence of the enzyme. The preliminary studies reveal that the prodrugs are much less toxic compared to the parent moieties. These prodrugs are activated by sweet almonds β-glucosidase to form the active cytotoxic moiety signifying their utility in ADEPT of cancer.

CHAPTER-II: Synthesis to 1,2,3-triazolo-heterocyclic scaffolds via tandem Knoevenagel condensation/azide-alkyne 1,3-dipolar cycloaddition reaction in one pot

The azide−alkyne 1,3-dipolar cycloaddition reaction has attracted an enormous amount of interest over the past decade. Today it is widely used in classical organic/combinatorial synthesis, medicinal chemistry/drug discovery programs, and has also made a major impact in polymer/material science and in the field of chemical biology. Intramolecular azide−alkyne cycloaddition provides an elegant access to interesting two annulated cyclic ring system. Thus, developing one pot, novel tandem process for intramolecular azide/internal alkyne 1,3-dipolar cycloaddition would open a rapid access to diverse heterocyclic scaffold. In this chapter a tandem process which involves an intermolecular Knoevenagel condensation-intramolecular azide/internal alkyne 1,3-dipolar cycloaddition reaction in one pot that eventually leads to very interesting fused 1,2,3-triazoloheterocycles. The β-carboline, pyrazolo-pyridine and isoquinoline heterocycles are very important scaffolds as they are found in numerous synthetic and natural products of biological and pharmacological interest (Figure 3).



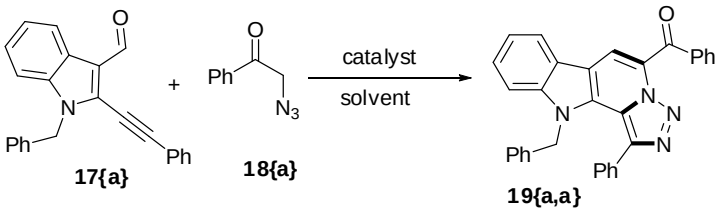
Pyridindolol **Pyrazolo-pyridines** **3-(2-pyridinyl)isoquinoline**

Figure 3

Synthesis of 1,2,3-Triazolo-Heterocyclic Scaffolds

Indole is considered as a privileged scaffold and is found in a plethora of synthetic and natural products of medicinal interest. Starting from 2-(arylethynyl)-indole-3-carbaldehyde **17** and phenacyl azide **18**, the proposed tandem Knoevenagel condensation-azide/internal alkyne 1,3-dipolar cycloaddition reaction should lead to the formation of fused 1,2,3-triazolo-β-carbolines **19**.

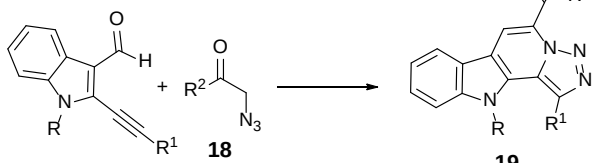
Table 1. Optimization of One Pot, Tandem Knoevenagel Condensation-Azide/Internal Alkyne 1,3-Dipolar Cycloaddition Reaction[a]



17{a} **18{a}** **19{a,a}**

entry	catalyst/ additive[d]	catalyst/ additive (mol %)	solvent	temperature[c]	yield of 34{a,a} (%)[b]
1	piperidine	20	ethanol	rt	12
2	piperidine	20	ethanol	reflux	NI
3	DBU	20	ethanol	rt	8
4	NaOH	20	ethanol	rt	NI
5	p-TsOH	20	ethanol	rt	NI
6	AcOH	20	ethanol	rt	NI
7	$Sc(OTf)_3$	20	ethanol	rt	NI
8	PA	20	ethanol	rt	35
9	PA	50	ethanol	rt	55
10	PA	100	ethanol	rt	88
11	PA	150	ethanol	rt	88
12	PA	100	ethanol	reflux	87
13	PA	100	acetonitrile	rt	81
14	PA	100	methanol	rt	87

[a] **17{a}**(0.20 mmol), **18{a}**(0.20 mmol), solvent (2.0 mL), catalyst, stirr, 24 h. [b]Isolated unoptimized yields. NI = Not isolated. [c]rt = room temperature. [d]PA = piperidinium acetate.

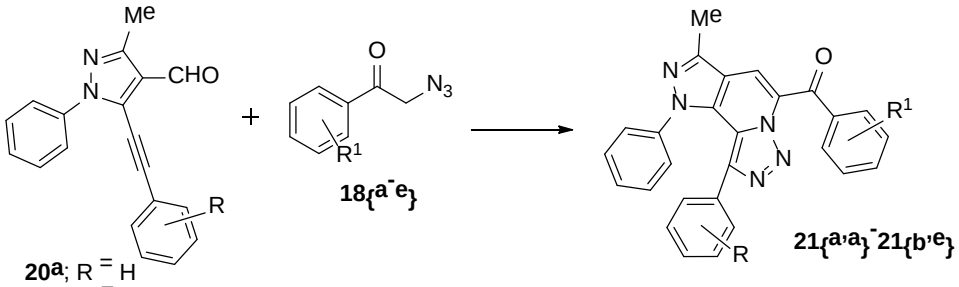


17 **18** **19**

19{a,a} R = Bn, R^1 = Ph, R^2 = Ph (88%)
19{a,b} R = Bn, R^1 = Ph, R^2 = 4-Cl-C_6H_4 (83%)
19{a,c} R = Bn, R^1 = Ph, R^2 = 4-F-C_6H_4 (91%)
19{a,d} R = Bn, R^1 = Ph, R^2 = 4-MeO-C_6H_4 (86%)
19{a,e} R = Bn, R^1 = Ph, R^2 = 4-Ph-C_6H_4 (90%)
19{a,f} R = Bn, R^1 = Ph, R^2 = 4-Me-C_6H_4 (80%)
19{a,g} R = Bn, R^1 = Ph, R^2 = 3-MeO-C_6H_4 (82%)
19{a,h} R = Bn, R^1 = Ph, R^2 = 4-(pyrrolidin-1-yl)phenyl (80%)
19{b,a} R = Bn, R^1 = 4-MeC_6H_4, R^2 = Ph (81%)
19{b,b} R = Bn, R^1 = 4-MeC_6H_4, R^2 = 4-Cl-C_6H_4 (80%)
19{b,e} R = Bn, R^1 = 4-MeC_6H_4, R^2 = 4-Ph-C_6H_4 (83%)
19{b,f} R = Bn, R^1 = 4-MeC_6H_4, R^2 = 4-Me-C_6H_4 (81%)
19{c,b} R = Bn, R^1 = *n*-pentyl, R^2 = 4-Cl-C_6H_4 (80%)
19{c,f} R = Bn, R^1 = *n*-pentyl, R^2 = 4-Me-C_6H_4 (81%)
19{d,b} R = Me, R^1 = *n*-pentyl, R^2 = 4-Cl-C_6H_4 (78%)
19{d,f} R = Me, R^1 = *n*-pentyl, R^2 = 4-Me-C_6H_4 (80%)

Scheme 4. Synthesis of a library of fused 1,2,3-triazolo-β-carbolines: **Reagents and conditions**: one equivalent piperidinium acetate, EtOH, rt, 24 h.

To our delight, substrate **20** smoothly reacted with phenacyl azides **18** in ethanol at room temperature using one equivalent piperidinium acetate as an additive leading to high yields of fused pyrazole-1,2,3-triazolopyridyls **21**.



20a; R = H
20b; R = Me

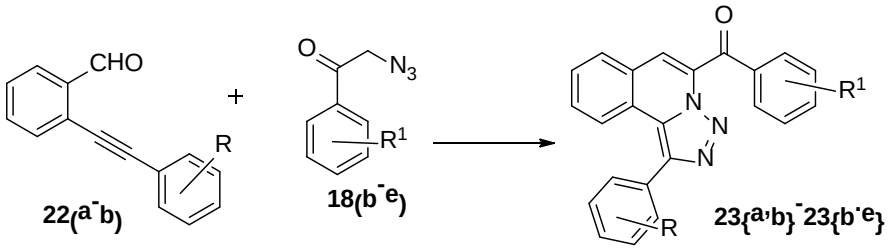
18{a-e}

21{a,a}-21{b,e}

21{a,a}; R = R1= H (93%)
21{a,b}; R = H, R1= 4-chloro (90%)
21{a,c}; R = H, R1= 4-fluoro (89%)
21{a,d}; R = H, R1= 4-methoxy (88%)
21{a,e}; R = H, R1= 4-phenyl (89%)
21{b,a}; R = 4-methyl, R1= H (91%)
21{b,b}; R = 4-methyl, R1= 4-chloro (93%)
21{b,c}; R = 4-methyl, R1= 4-fluoro (90%)
21{b,d}; R = 4-methyl, R1= 4-methoxy (85%)
21{b,e}; R = 4-methyl; R1= 4-phenyl (91%)

Scheme 5. Synthesis of fused pyrazole-1,2,3-triazolopyridyls Libraries**: Reagents and conditions:** one equivalent piperidinium acetate, EtOH, rt, 24 h.

Next, a series of fused 1,2,3-triazoloisoquinolines **23** were synthesized by refluxing 2-alkynylaryl aldehydes **22** and phenacyl azides **18** in ethanol using one equivalent of piperidinium acetate as an additive.



22(a-b)

22 a if R= H

22 b if R= Me

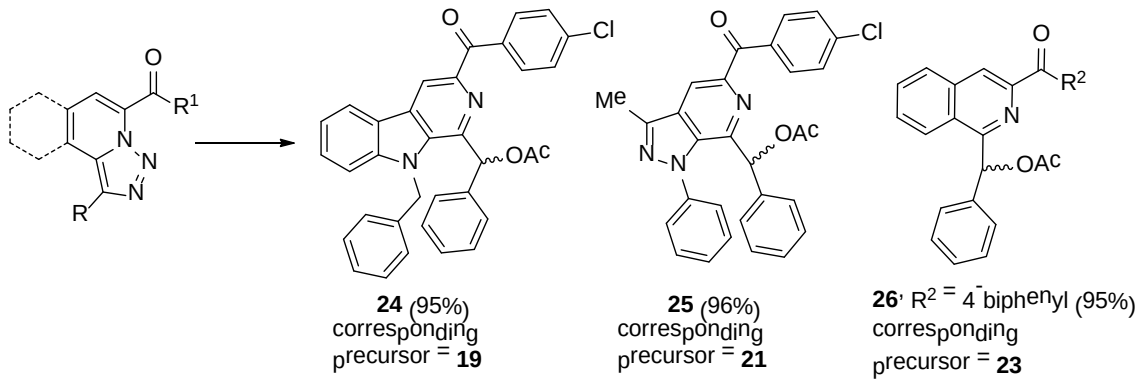
18(b-e)

23{a,b}-23{b-e}

23{a,b}; R = H, R1= 4-chloro (85%)
23{a-c}; R = H, R1 = 4-fluoro (89%)
23{a-d}; R = H, R1= 4-methoxy (82%)
23{b-b}; R = 4-methyl, R1= 4-chloro (89%)
23{b-c}; R = 4-methyl, R1= 4-fluoro (91%)
23{b-d}; R = 4-methyl, R1= 4-methoxy (78%)
23{b,e}; R = 4-methyl, R1=4-phenyl (89%)

Scheme 6. Synthesis of 1,2,3-triazoloisoquinolines: **Reagents and conditions:** one equivalent piperidinium acetate, EtOH, reflux, 24 h.

Fused 1,2,3-triazolo-heterocycles **19, 21** and **23** are very interesting heterocycles in terms of their biological and pharmacological potentials since they bear privileged scaffolds (β-carboline, pyrazolo-pyridine, and isoquinoline) as a part of their chemical structure. Moreover we found that these fused 1,2,3-triazolo-heterocycles **19, 21** and **23** could be converted to β-carboline **24**, pyrazolo-pyridine **25** and isoquinoline **26** by refluxing the corresponding precursor in acetic acid. Thus, these new fused heterocycles provide efficient and alternative routes for β-carboline, pyrazolo-pyridine and isoquinoline (Scheme 7).



Scheme7. Conversion of fused 1,2,3-triazolo-heterocycles to corresponding β-carboline, pyrazolo-pyridine, and isoquinoline: **Reagents and conditions :** AcOH, reflux, 12 h**.**

An atom economical, tandem, four-centered, one-pot, two-step method has been developed leading to the formation of structurally diverse heterocyclic scaffolds. The generality and scope of the strategy has been demonstrated on three distinct substrates (indole, pyrazole and benzene). Furthermore, efficient conversion of these heterocyles into various other pharmacologically important β-carboline, pyrazolopyridine and isoquinoline has been illustrated.

CHAPTER-III/Section-A: Synthesis of imidazole derivatives via silver (I) carbonate catalysed coupling of vinyl azides with secondary amines.

Imidazo[1,2-a]pyridines are very important heterocycles which have been found to be the core scaffold of many natural products and drugs (**Figure 4**). They have received considerable interest from the pharmaceutical industry because of their important biological activities and interesting therapeutic properties including antibacterial, antifungal, antiviral, antiulcer and anti-inflammatory behavior.

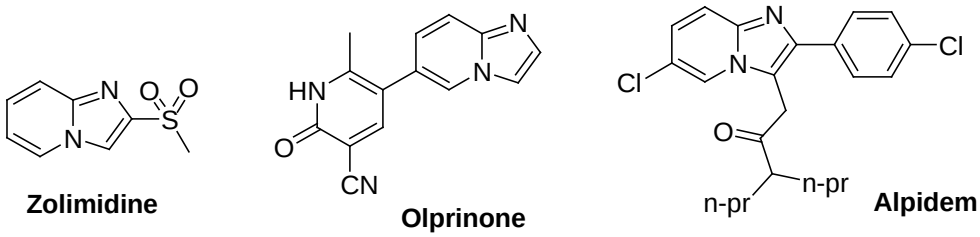
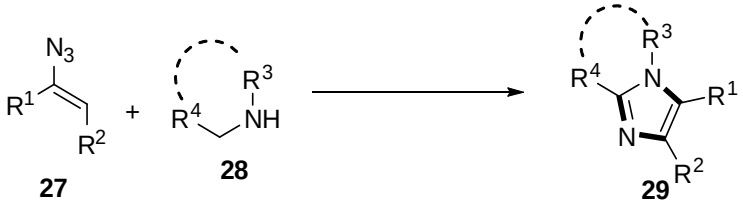


Figure 4

Synthesis of imidazole derivatives (22a-v) *via* silver(I)carbonate mediated coupling of vinyl azides with secondary amines

Given our interest towards developing newer synthetic transformations, in this section we report a straightforward protocol to access structurally diverse imidazoles through Ag_2CO_3 mediated coupling of vinyl azides with secondary amines (scheme 8). It is worth to note that the synthetic strategy described herein involves functionalization of sp^3C-H bonds adjacent to the secondary nitrogen.

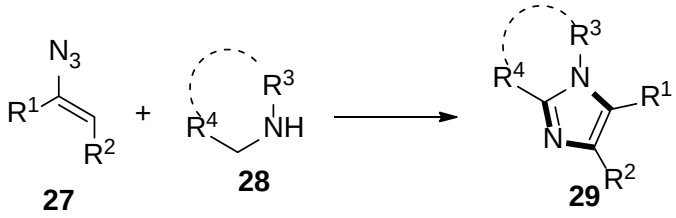
Table 2. Coupling of vinyl azide **27a** with 1,2,3,4-tetrahydroisoquinoline **28a** to yield imidazole **29a**[a]



entry	catalyst/oxidant	solvent	T (°C)	yield,[b] %
1	CuI (10 mol %) / H_2O_2 (10 eq.)	toluene	90	ND
2	CuI (10 mol %) / TBHP (10 eq.)	toluene	90	ND
3	AgOTf (10 mol %) / TBHP (10 eq.)	toluene	90	ND
4	MnO_2 (100 mol %)	toluene	90	ND
5	DDQ (100 mol %)	toluene	90	ND
6	$PhI(OAc)_2$ (100 mol %)	toluene	90	ND
7	Ag_2CO_3 (100 mol %)	toluene	90	45
8	Ag_2CO_3 (150 mol %)	toluene	90	91
9	Ag_2CO_3 (200 mol %)	toluene	90	92

10	Ag_2CO_3 (150 mol %)	toluene	reflux	75
11	Ag_2CO_3 (150 mol %)	toluene	60	55[c]
12	Ag_2CO_3 (100 mol %)	THF	reflux	48
13	Ag_2CO_3 (100 mol %)	CH_3CN	reflux	54
14	Ag_2CO_3 (50 mol %) TBHP (10 eq.)	toluene	90	31
15	Ag_2CO_3 (150 mmol)	toluene	90	65[d]
16	Ag_2CO_3 (300 mmol)	toluene	90	91[d]

[a]Reaction conditions: vinyl azide **27a** (0.5 mmol), 1,2,3,4-tetrahydroisoquinoline **28a** (0.5 mmol), catalyst/oxidant, solvent (5 mL), stir in open air, 12 h.[b]Isolated yields. [c]Reaction was run for 24 hours. [d]The reaction was carried out under a nitrogen atmosphere. TBHP = t-Butyl hydroperoxide, ND = The desired product was not detected on TLC.

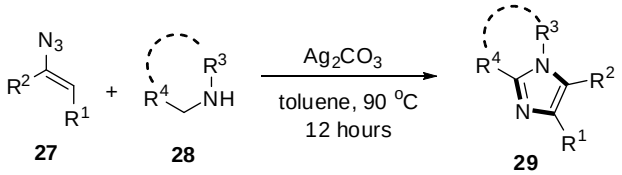


Scheme 8. Synthesis of fused imidazoles: **Reagents and conditions:** 150 mol% Ag_2CO_3, toluene, 90 ^oC, 12 h.

Having optimized reaction conditions at hand (**Table 1**, entry 8), we tried to explore the scope of the Ag_2CO_3 mediated coupling of vinyl azides and secondary amines to yield imidazoles. Vinyl azides **27a-j** and **27m** were obtained from Knoevenagel condensation of phenacyl azides with aldehydes whereas vinyl azides **27k-l** were obtained from corresponding styrenes. A number of vinyl azides derived from aromatic aldehydes bearing halogen and electron withdrawing functional group gave very high yields (90-95%) of desired imidazole derivatives. Vinyl azides derived from electron rich aromatic aldehydes, heteroaromatic aldehydes and aliphatic aldehydes gave relatively lower yields (68-81%) of the imidazole derivatives. Lower yields of the imidazoles with these vinyl

azides might be correlated with the increased side reactions of the 2*H*-azirines derived from such azides. Vinyl azides derived from styrene gave very high yields (91-95%) of the desired imidazole. Vinyl azides derived from phenacyl azides bearing halogen, electron withdrawing as well as electron releasing functional group worked well leading to the high yields of imidazoles.

In terms of secondary amines, the reaction gave high yields of the imidazoles **8** with 1,2,3,4-tetrahydroisoquinoline **28a** and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **28b.** (The reaction also worked well and gave high yields (79-81%) of desired imidazoles using N-benzyl anilines **28c** and **28d**. However, it gave relatively lower yields (65%) of imidazoles using dibenzyl amine **28e**.



27 **28** **29**

27a: R^1=4-Br-Ph-; R^2=Ph-CO-
27b: R^1=4-NO_2-Ph-; R^2=Ph-CO-
27c: R^1=3,4,5-tri-OMe-Ph-; R^2=Ph-CO-
27d: R^1=Furyl-Ph-; R^2=4-OMe-Ph-CO-
27e: R^1=Furyl-Ph-; R^2=4-F-Ph-CO-
27f: R^1=4-Cl-Ph-; R^2=4-NO_2-Ph-CO-
27g: R^1=C_3H_8-; R^2=4-OMe-Ph-CO-
27h: R^1=3,4-di-OMe-Ph-; R^2=4-Cl-Ph-CO-
27i: R^1=4-CN-Ph-; R^2=4-OMe-Ph-CO-
27j: R^1=4-Cl-Ph-; R^2=4-NO_2-Ph-CO-
27k: R^1=Ph-; R^2=H
27l: R^1=4-Me-Ph-; R^2=H
27m: R^1=4-Cl-Ph-; R^2=4-OMe-Ph-CO-

28a: THIQ
28b: 6,7-dimethoxy-THIQ
28c: R^3=Ph-; R^4=Ph-
28d: R^3=4-OMe-Ph-; R^4=Ph-
28e: R^3=Ph-CH_2-; R^4=Ph-

29{a,a}: R^1=4-Br-Ph-; R^2=Ph-CO-;R^3+R^4=THIQ
29{b,a}: R^1=4-NO_2-Ph-; R^2=Ph-CO-;R^3+R^4=THIQ
29{c,a}: R^1=3,4,5-tri-OMe-Ph-; R^2=Ph-CO-;R^3+R^4=THIQ
29{d,a}: R^1=Furyl-Ph-; R^2=4-OMe-Ph-CO-;R^3+R^4=THIQ
29{e,a}: R1=Furyl-Ph-; R2=4-F-Ph-CO-;R3+R4=THIQ
29{f,a}: R^1=4-Cl-Ph-; R^2=4-NO_2-Ph-CO-;R^3+R^4=THIQ
29{g,a}: R^1=C_3H_8-; R^2=4-OMe-Ph-CO-;R^3+R^4=THIQ
29{h,a}: R^1=3,4-di-OMe-Ph-; R^2=4-Cl-Ph-CO-;R^3+R^4=THIQ
29{i,a}: R^1=4-CN-Ph-; R^2=4-OMe-Ph-CO-;R^3+R^4=THIQ
29{j,a}: R^1=4-Cl-Ph-; R^2=4-NO_2-Ph-CO-;;R^3+R^4=THIQ
29{d,b}: R^1=Furyl-Ph-; R^2=4-OMe-Ph-CO-;R^3+R^4=6,7-di-OMe-THIQ
29{k,a}: R^1=Ph-; R^2=H;R^3+R^4=THIQ
29{k,b}: R1=Ph-; R2=H;R3+R4=6.7-di-OMe-THIQ
29{l,a}: R^1=Ph-; R^2=H;R^3+R^4=THIQ
29{m,c}: R^1=4-Cl-Ph-; R^2=4-OMe-Ph-CO-;R^3=Ph-;R^4=Ph-;
29{b,c}: R^1=4-NO_2-Ph-; R^2=Ph-CO-;R^3=Ph-;R^4=Ph-;
29{b,d}: R^1=R^1=4-NO_2-Ph-; R^2=Ph-CO-;R^3=4-OMe-Ph-;R^4=Ph-;
29{b,e}: R^1=4-NO_2-Ph-; R^2=Ph-CO-;R^3=Ph-CH_2;R^4=Ph-;
29{m,a}: R^1=4-Cl-Ph-; R^2=4-OMe-Ph-CO-;R^3+R^4=THIQ
29{c, b}: R^1=3,4,5-tri-OMe-Ph-; R^2=Ph-CO-;R^3+R^4=6.7-di-OMe-THIQ
29{b,d}: R^1=R^1=4-NO_2-Ph-; R^2=Ph-CO-;R^3+R^4=6.7-di-OMe-THIQ

Scheme 9: Synthesis of fused imidazole libraries

In conclusion, we have developed a straightforward methodology for the synthesis of fused imidazoles through Ag_2CO_3 mediated coupling of vinyl azides with secondary amines under air and moisture tolerant mild reaction conditions. A series of 22 different imidazole derivatives were synthesized in high yields using the optimized protocol. A few control experiments were carried out to reveal the mechanistic insights of the reaction.

CHAPTER-III/Section-B: Synthesis of 1-aryl-*N* (2-arylimidazo[1,2-a]pyridine-3-yl]methanimine *via* visible-light photoredox catalysis and their cytotoxicity

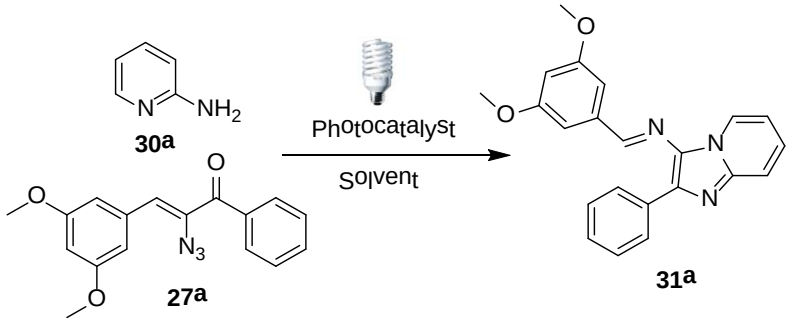
The reaction is said to be photochemical reaction when activation energy is provided in the form of light. Photochemistry is the sub-discipline of chemistry which deals with the study of the interactions between atoms or molecules with light. In our day-to-day life, photochemistry involves in many important processes.

Synthesis of 1-aryl-*N*-(2-arylimidazo[1,2-a]pyridin-3-yl)methanimine *via* visible-light photoredox catalysis

At the onset, coupling of 2-aminopyridine **30a** and vinyl azide **27a** was taken as a model reaction and the effect of light, photo catalyst, and solvent was studied (Table 3). We screened all these preferred solvents for our reaction which was performed using 5 mol% of $Ru(bpy)_3Cl_2.6H_2O$ as a photo catalyst in the presence of white LED light (15 W). Among all these solvent tested ethyl acetate was found the best giving 94% yield of **31a** in a reaction time of 6 h (Table 3, entry 5). In other solvents such as water, acetone, ethanol, 2-propanol, methanol, methyl ethyl ketone, 1-butanol and t-butanol the reaction was not successful (Table 3, entries 1-10). The photo catalyst loading could be reduced to 2 mol% without reducing the product yield (Table 3, entry 11). Further reduction of the catalyst loading led to a lower yield of **31a** (Table 3, entry 12). No product was observed in absence of light or photo catalyst (Table 3, entries 13-14). However it is worth noting here that the reaction gave **31a** in 81 % yield under refluxing condition (Table 3, entry 15). It is

because the 2*H*-azirine can be generated under both the thermal and photochemical decompositions. The product **31a** could be obtained in high yields under both the thermal (81%) and photochemical conditions (94%) though both the pathways have their own merits and demerits. The thermal conversion was slightly inferior in terms of yield and also it required conventional energy to promote the reaction though it does not require any metal catalyst. The photochemical conversion gave better yields but it required a photocatalyst to harvest the light energy. Since the natural sunlight offers cost efficient sustainable energy source for photochemical reactions, we performed the synthesis of **31a** using the sun-light and got 75% yield of **31a** in two bright sunny days (Table 3, entry 16).

Table 3: Optimization of photoredox catalytic synthesis of 1-aryl-*N*-(2-arylimidazo[1,2-a]pyridin-3-yl)methanimine[a]



Entry	Photocatalyst	Solvent	yield(%) [b] (31a)
1	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Water	ND
2	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Acetone	ND
3	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Ethanol	20%
4	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	2-Propanol	15%
5	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Ethyl Acetate	94%
6	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Methanol	20%
7	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Methyl ethyl ketone	ND
8	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	1-Butanol	ND

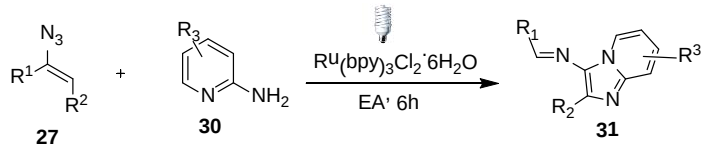
9	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	t-Butanol	ND
10	$Ru(bpy)_3Cl_2.6H_2O$ (5 mol%)	Ethanol-water (1:1)	20%
11	**$Ru(bpy)_3Cl_2.6H_2O$ (2 mol%)**	**Ethyl Acetate**	94%
12	$Ru(bpy)_3Cl_2.6H_2O$ (1 mol%)	Ethyl Acetate	70%
13[c]	$Ru(bpy)_3Cl_2.6H_2O$ (2 mol%)	Ethyl Acetate	ND
14	No catalyst	Ethyl Acetate	15%
15[d]	No catalyst	Ethyl Acetate	81%
16[e]	$Ru(bpy)_3Cl_2.6H_2O$ (2 mol%)	Ethyl Acetate	75%
17	$Ru(bpy)_3(PF_6)_2$ (2 mol%)	Ethyl Acetate	80%
18	Rose Bengal (2 mol%)	Ethyl Acetate	ND
19	Eosin-y	Ethyl Acetate	ND
20	$Ir(ppy)_3$ (5 mol%)	Ethyl Acetate	85%

[a]Reaction conditions: **27a** (0.5 mmol), **30a** (0.5 mmol), photocatalyst, solvent (10 mL) and a 15 W white LED bulb kept at a distance of 10 cm (approx.) from the reaction vessel. [b]Yields of the isolated products after column chromatography. [c] The reaction was run in dark. [d]The reaction mixture was refluxed for 6h. [e]The reaction mixture was exposed to direct sun-light for two days. ND = the desired product was not detected on TLC.

In order to improve the yield of the product, we also examined several photoredox catalysts. Tris(2,2'bipyridyl)dichlororuthenium(II)hexahydrate, and visible light were found to be essential for this reaction. In the absence of any of the reagents/reaction

parameters either the product was not detected (N.D.) or was formed in trace amounts (**Table 3**).

The generality and the scope of the present photo catalytic protocol were examined across a range of vinyl azides **27a** by incorporating various substituents (aryl, alkyl and heterocyclic moieties) as well as functional groups such as MeO, NO_2, Cl, Br, and CN **(scheme 10**). The yield was >77%, in all these reactions clearly indicating their potential for industrial applications. Especially, product **31** was obtained in good to excellent yields (78–95%). Vinyl azides derived from aromatic α-azido ketones containing electron withdrawing or donating functional groups gave quantitative yields. Similarly, vinyl azides derived from heteroaromatic aldehydes also gave the desired imidazo[1,2-*a*]pyridine derivatives. Using this reaction, several functional groups, such as halogen, alkyl and esters were easily added to 2-aminopyridines. Moreover, the reaction was also successful with 1-aminoisoquinoline and gave the desired imidazo[2,1-*a*]isoquinoline in excellent yield (>90%).



27a: R^1=4-Br-Ph-; R^2=Ph-CO-
27b: R^1=4-NO_2-Ph-; R^2=Ph-CO-
27e: R1=Furyl-Ph-; R2=4-F-Ph-CO-
27m: R^1=4-Cl-Ph-; R^2=4-OMe-Ph-CO-
27n: R^1=3,5-di-OMe-Ph-; R^2=-Ph-CO-
27o: R^1=-Ph-; R^2=4-Cl-Ph-CO-
27p: R^1=3,5-di-OMe-Ph-; R^2=4-Cl-Ph-CO-
27q: R^1=3,4,5-tri-OMe-Ph-; R^2=4-Cl-Ph-CO-
27r: R^1=-Napthyl-; R^2=-Ph-CO-
27s: R^1=4-NO_2-Ph-; R^2=4-Cl-Ph-CO-
27t: R^1=3-NO_2-Ph-; R^2=-Ph-CO-
27u: R^1=4-Br-Ph-; R^2=4-Cl-Ph-CO-
27v: R^1=4-NO_2-Ph-; R^2=4-OMe-Ph-CO-
27w: R^1=4-Cl-Ph-; R^2=3-OMe-Ph-CO-
27x: R^1=4-NO_2-Ph-; R^2=3-OMe-Ph-CO-
27y: R^1=3,5-di-OMe-Ph-; R^2=4-CN-Ph-CO-
27z: R^1=4-CN-Ph-; R^2=-Ph-CO-
30a: 2-amino pyridine
30b: 4-Chloro 2-amino pyridine
30c: 4-Carboxy methyl 2-amino pyridine
30d: 4-methyl 2-amino pyridine
30e: 2-amino quinoline

31a: R^1=4-Br-Ph-; R^2=Ph-CO-;R^3=H
31b: R^1=4-NO_2-Ph-; R^2=Ph-CO-;R^3=H
31c: R^1=3-phenoxy-Ph-; R^2=Ph-CO-;R^3=H
31d: R^1=3-Me-Ph-; R^2=4-Cl-Ph-CO-;R^3=H
31e: R^1=Furyl-Ph-; R^2=4-F-Ph-CO-;R^3=H
31f: R^1=3,5-di-OMe-Ph-; R^2=4-Cl-Ph-CO-;R^3=4-Cl-
31g: R^1=3,5-di-OMe-Ph-; R^2=4-Cl-Ph-CO-;R^3=-4-COOMe-
31h: R^1=4-NO_2-Ph-; R^2=4-OMe-Ph-CO-;R^3=benzene-
31i: R^1=4-NO_2-Ph-; R^2=3-OMe-Ph-CO-;R^3=4-Me-
31m: R^1=4-Cl-Ph-; R^2=4-OMe-Ph-CO-;R^3=H
31n: R^1=3,5-di-OMe-Ph-; R^2=-Ph-CO-;R^3=H
31o: R^1=-Ph-; R^2=4-Cl-Ph-CO-;R^3=H
31p: R^1=3,5-di-OMe-Ph-; R^2=4-Cl-Ph-CO-;R^3=H
31q: R^1=3,4,5-tri-OMe-Ph-; R^2=4-Cl-Ph-CO-;R^3=H
31r: R^1=-Napthyl-; R^2=-Ph-CO-;R^3=H
31s: R^1=4-NO_2-Ph-; R^2=4-Cl-Ph-CO-;R^3=H
31t: R^1=3-NO_2-Ph-; R^2=-Ph-CO-;R^3=H
31u: R^1=4-Br-Ph-; R^2=4-Cl-Ph-CO-;R^3=H
31v: R^1=4-NO_2-Ph-; R^2=4-OMe-Ph-CO-;R^3=H
31w: R^1=4-Cl-Ph-; R^2=3-OMe-Ph-CO-;R^3=H
31x: R^1=4-NO_2-Ph-; R^2=3-OMe-Ph-CO-;R^3=H
31y: R^1=3,5-di-OMe-Ph-; R^2=4-CN-Ph-CO-;R^3=H
31z: R^1=4-CN-Ph-; R^2=-Ph-CO-;R^3=H

Scheme 10: 1-aryl-*N*-(2-arylimidazo[1,2-a]pyridin-3-yl)methanimines

In conclusion, we have disclosed a new, one-pot procedure for the synthesis of 1-aryl-*N*-(2-arylimidazo[1,2-a]pyridin-3-yl)methanimines **(31a-x)** by employing vinyl azides and 2-aminopyridines as starting materials. Some of these compounds also showed cytotoxic activity in the selected human cancer cell lines.

CHAPTER-IV: Total Synthesis of Pinolide

The ten-membered lactonic compounds (nonenolides) have commonly been isolated from fungal sources. These compounds contain interesting structural features having various stereogenic centres and different functionalities. They also possess important biological properties such as cytotoxic, antibacterial, antifungal and herbicidal activities.

As part of our studies directed towards the synthesis of 10-membered lactones (Figure 6) and other biologically active molecules, we herein report an efficient approach for the total synthesis of pinolide by employing cost-effective and readily available starting material D-mannitol.

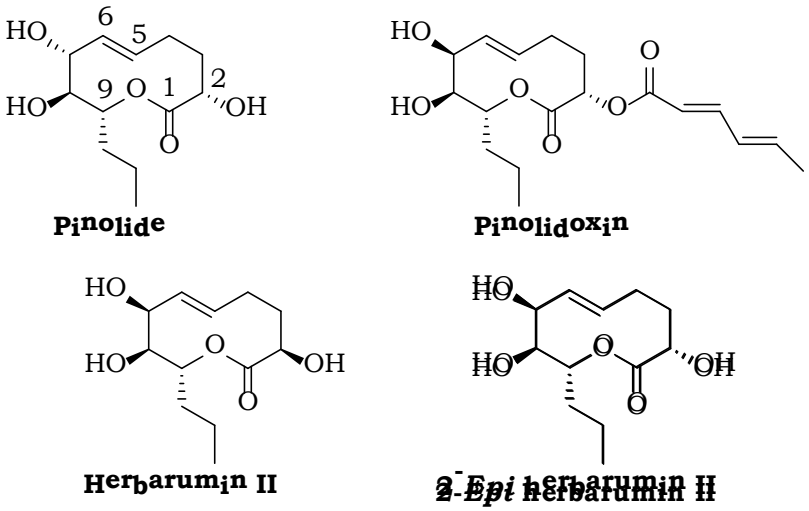
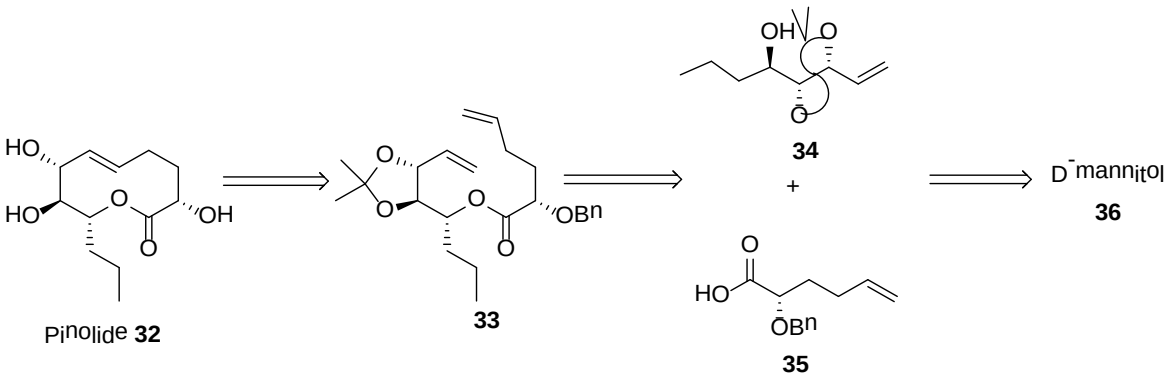


Figure 5

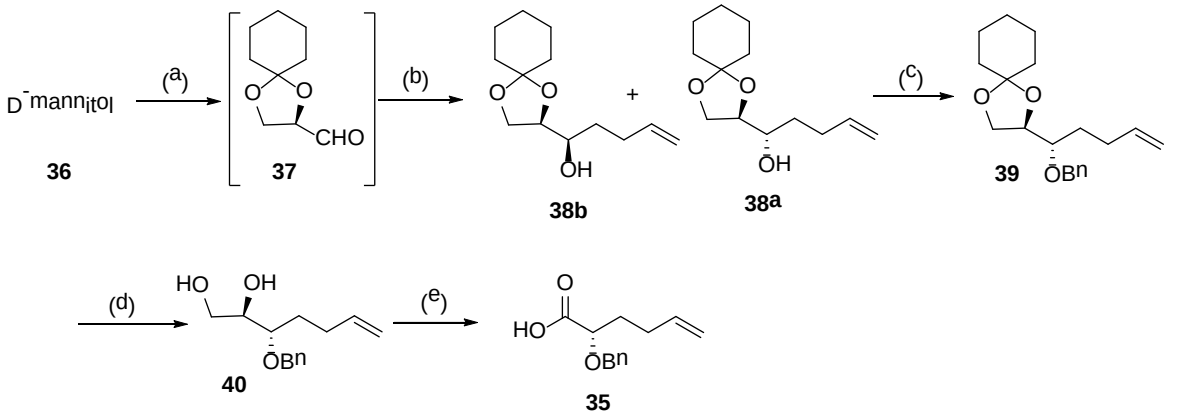
The retro synthetic concept has been outlined in Scheme 10, it depicts that the target compound pinolide could be achieved via ring closing metathesis (RCM) of diene ester**,** which inturn could be obtained via esterification of olefinic acid fragment and

olefinic alcohol fragment. Both olefinic acid (**35**) and olefinic alcohol (**34**) fragments for the target compound could be obtained from D-mannitol after several manipulations.



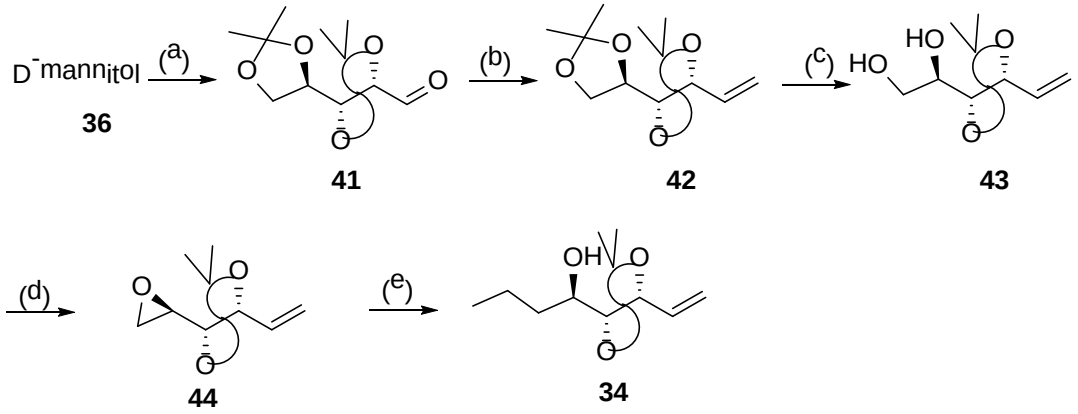
Scheme 11. Retrosynthetic analysis of pinolide

One of the core fragments, olefinic acid fragment **35** was prepared from D-mannitol **36,** as depicted in Scheme-11. Initially D-mannitol was converted to aldehyde **37,** followed by subjecting to Grignard reaction (Mg/homoallylbromide/I_2/THF) furnished the *anti*-diastereomeric alcohol **38a** in 69% yield, along with *syn*-diastereomeric alcohol **38b** in 12% yield. After separation of these two diastereomers, alcoholic functional group of **38a** was protected with benzylbromide in dry THF by using NaH as a base to afford benzyl ether derivative **39** in 89% yield. The cyclohexanone protecting group of **39** was deprotected by using trifluoro acetic acid (TFA) in THF: H_2O (9:1) and the corresponding diol **40** was obtained in 83% yield. The diol **40** upon treatment with sodium metaperiodate in CH_3CN:H_2O (4:1) furnished the corresponding aldehyde, and which without further purification underwent over oxidation with $NaClO_2$, NaH_2PO_4 in DMSO furnished the olefinic acid fragment **35** in 75% yield.



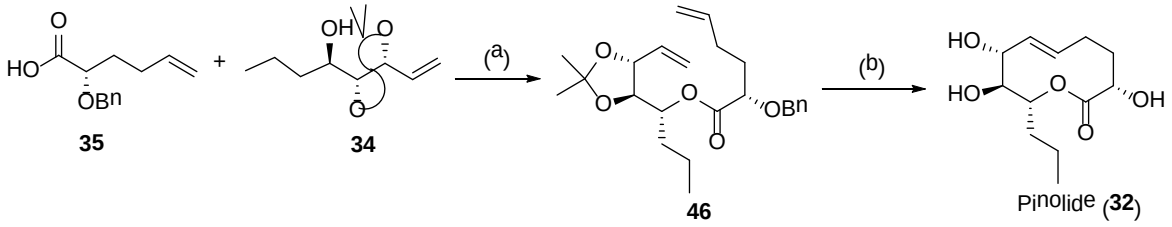
Scheme 12. Reagents and conditions: (a) (i) cyclohexanone, $BF_3.Et_2O$, $CH(OEt)_3$, DMSO, rt, 8 h; (ii) $NaIO_4$, aq CH_3CN(60%), rt, 1h; (b) Mg, homoallyl bromide, THF, 0 ^oC to rt, 2 h, 68%; (c) NaH, BnBr, THF, 0 ^oC to rt, 4 h, 89%; (d) TFA (THF/H_2O 9:1) 0 ^oC to rt, 6 h, 84%; (e) (i) $NaIO_4$, CH_3CN:H_2O (4:1), 90 min; (ii) $NaClO_2$, NaH_2PO_4, DMSO, H_2O, 75% over two steps.

Olefinic alcohol fragment **34** was also prepared from D-mannitol **36**, as depicted in Scheme-12. Aldehyde **41** was prepared from D-mannitol. This crude aldehyde **41** was subjected to Wittig olefination with MeTPPBr and *t*-BuOK in dry THF to furnish the olefin **42** in 58% yield. Terminal acetonide group in **42** was selectively deprotected by using $CuCl_2.2H_2O$ in CH_3CN and the corresponding diol **43** was obtained in 83% yield.[11] Primary alcohol group in **43** was selectively converted as tosyl ether by treating with TsCl, cat. Bu_2SnO and triethylamine in CH_2Cl_2 to furnish the monotosylated compound, this crude monotosylated compound was taken up for the cyclization using K_2CO_3 in methanol to afford the epoxide **44** in 75% yield. Regioselective opening of epoxide **44** was carried out with ethyl magnesium bromide in the presence of cuprous iodide in dry THF at −35 ^oC to afford the olefinic alcohol fragment **34** in 81% yield.



Scheme 13. Reagents and conditions: (a) (i) 2,2,DMP, PTSA, rt, (ii) Conc.HCl in MeOH, O ^{0}C (iii) $NaIO_4$, THF:H_2O (b) MeTPPBr, *t*-BuOK, THF, 0 ^{o}C to rt, 6 h, 58%; (c) $CuCl_2.2H_2O$, CH_3CN, 0 ^{o}C, 30 min, 83 %; (d) (i) TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, 2 h; (ii) K_2CO_3, MeOH, 0 ^{o}C, 1 h, 75% over two steps; (e) C_2H_5MgBr, CuI (cat), THF, −35 ^{o}C, 3 h, 81%.

Olefinic acid fragment **35** and olefinic alcohol fragment **34** were coupled according to steglich esterification procedure to obtain diene ester **46** in 84% yield. Upon treatment of **46** with the Grubbs' first generation catalyst in CH_2Cl_2 at reflux conditions for 16 h followed by treated with with $TiCl_4$ in dichloromethane at 0 °C to afford the target pinolide (**32**) in 81% yield as shown in Scheme 14. The ^{1}H and ^{13}C NMR spectral data and optical rotation of pinolide **32** were in excellent agreement with the data previously reported in literature.



Scheme 14. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 0 ^{o}C to rt, 3 h, 80%; (b) **Gr-I**, dry CH_2Cl_2, reflux, 16 h, then $TiCl_4$, CH_2Cl_2, 0 ^{o}C , 2 h, 65%.

In conclusion, stereoselective total synthesis of pinolide has been achieved from D-mannitol. In this approach out of four stereocenters in the pinolide three were obtained from the starting material D-mannitol and the remaining centre was established by the Grignard reaction.