TOTAL SYNTHESIS OF TETRAHYDROISOQUINOLINE ALKALOIDS AND NOVEL SYNTHETIC METHODOLOGIES

A SYNOPSIS SUBMITTED TO

ADIKAVI NANNAYA UNIVERSITY, RAJAMAHENDRAVARAM

In the partial fulfillment of the requirements for the award of the degree of

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

By

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SYNOPSIS

The thesis entitled "**Total Synthesis of Tetrahydroisoquinoline Alkaloids and Novel Synthetic Methodologies**" has been divided in to three chapters.

Chapter I: Describes the general introduction of tetrahydroisoquinolines and *tert*-butanesulfinamide. It also deals with total synthesis of tetrahydroisoquinoline alkaloids by using Ellman's reagent**.**

Chapter II: $In(OTf)_3$ catalyzed tandem aza-Piancatelli rearrangement/Michael reaction for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4] thiazine and oxazine derivatives.

Chapter III: Sequential aza-piancatelli rearrangement/friedel-crafts alkylation for the synthesis of pyrrolo[1,2-*d*]benzodiazepine derivatives.

Chapter I : Describes the general introduction of tetrahydroisoquinolines and *tert*-butanesulfinamide. It also deals with total synthesis of tetrahydroisoquinoline alkaloids by using Ellman's reagent.

Introduction: The isoquinoline is a heterocyclic compound, which is frequently found in various biologically active molecules. They are used for many therapeutic applications. The most popular naturally-occurring or synthetic isoquinolines are spasmolytic papaverine (1), the antitussive noscapine (2), the expectorant emetine (3), the angiotensin-converting enzyme inhibitor quinapril (4), the muscle relaxant tubocurarine (5) and the dopaminergic agonist apomorphine (6)(Figure 1**).**

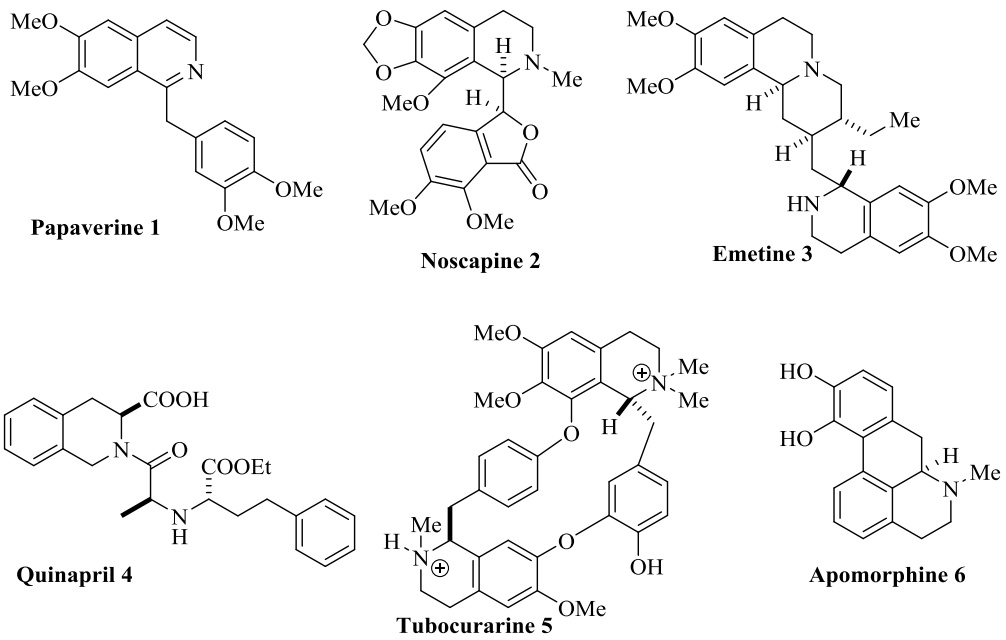
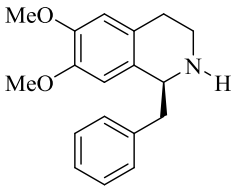


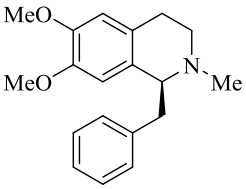
Figure 1 Examples of tetrahydroisoquinoline alkaloids.

The chiral *N*-*tert*-butanesulfinamide is a versatile chiral auxiliary for the asymmetric induction in the preparation of synthetically useful chiral amines. Addition of an organometallic reagent to C=N bond of an enantiopure sulfinimine is one of the most elegant methods for the synthesis of chiral amines. The electron-withdrawing sulfinyl group is highly stereodirecting and activates the C=N bond effectively in nucleophilic addition reactions, and can easily be removed to provide the enantiopure amine derivatives. However, the use of this useful chiral auxiliary in the total synthesis of complex natural products is still unexplored to a great extent. Inspired by its potential application in natural products synthesis, we attempted the total synthesis of (*S*)-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (A), (*S*)-1-benzyl-6,7-dimethoxy-

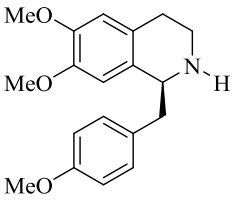
N-methyl-1,2,3,4-tetrahydro-isoquinoline (B), (-)-*O*-*O*-dimethylcoclaurine (C) and (+)-*O*-methylarmepavine (D).



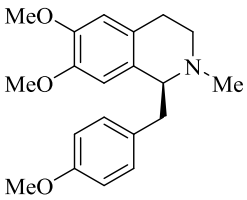
(*S*)-1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**A**)



(*S*)-1-Benzyl-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (**B**)



(-)-*O*-*O*-Dimethylcoclaurine (**C**)

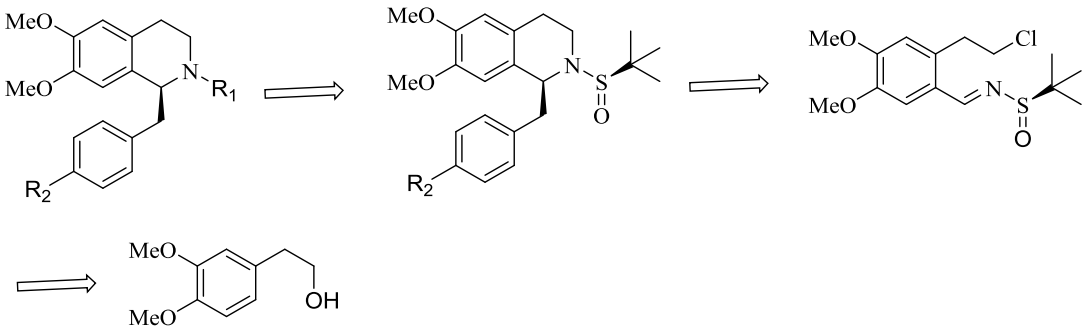


(+)-*O*-Methylarmepavine (**D**)

Present work

Retrosynthetic analysis

Our retrosynthetic approach for the synthesis of (*S*)-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (A), (*S*)-1-benzyl-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydro-isoquinoline (B), (-)-*O*-*O*-dimethylcoclaurine (C) and (+)-*O*-methylarmepavine (D) is outlined in (**Scheme 1).** Accordingly we envisioned that the above targets could be accessed from the compound A, B, C and D which was proposed to be obtained from enantiopure N-sulfinyl imine by two consecutive reactions *viz* Grignard addition and chloroamide cyclization. The aldimine (4) could be prepared by the condensation of (*R*)-*tert*-butanesulfinamide with an aldehyde (3). The required aldehyde was prepared from 3, 4 Dimethoxy phenyl ethyl alcohol (1).



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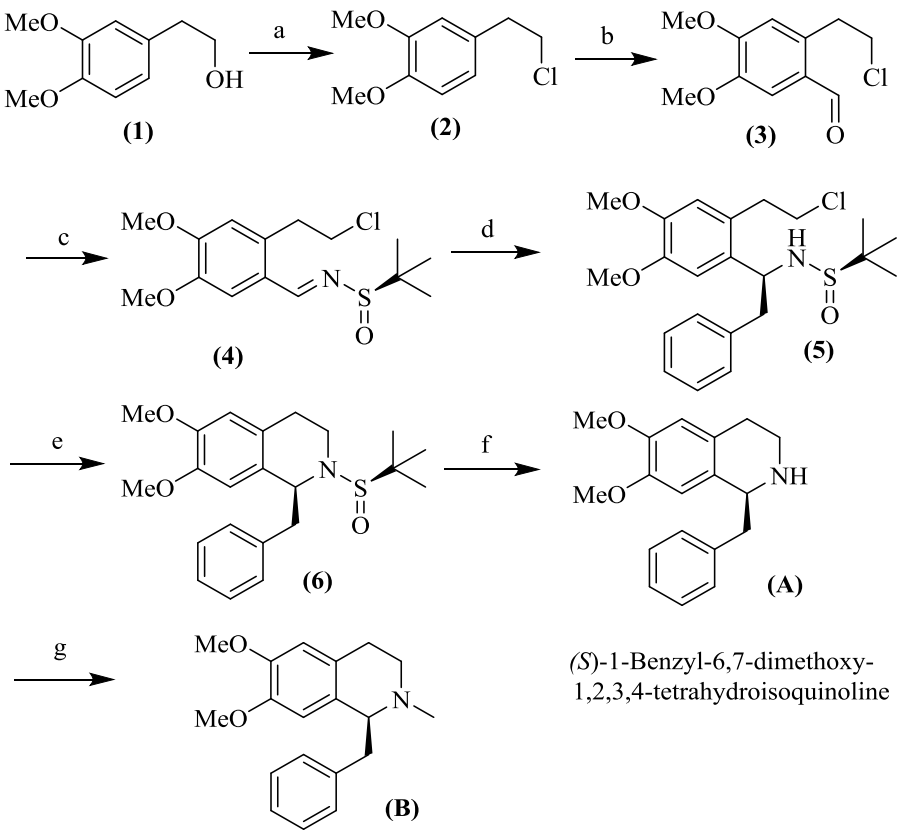
R_1= H, R_2 = H;(*S*)-1-Benzyl-6,7-dimethoxy- 1,2,3,4-tetrahydroisoquinoline (A)
R_1= Me, R_2 = H;(*S*)-1-Benzyl-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline(B)
R_1= H, R_2 = OMe;(-)-O-O-dimethylcoclaurine (C)
R_1= Me, R_2 = OMe;(+)-O-methylarmepavine (D)

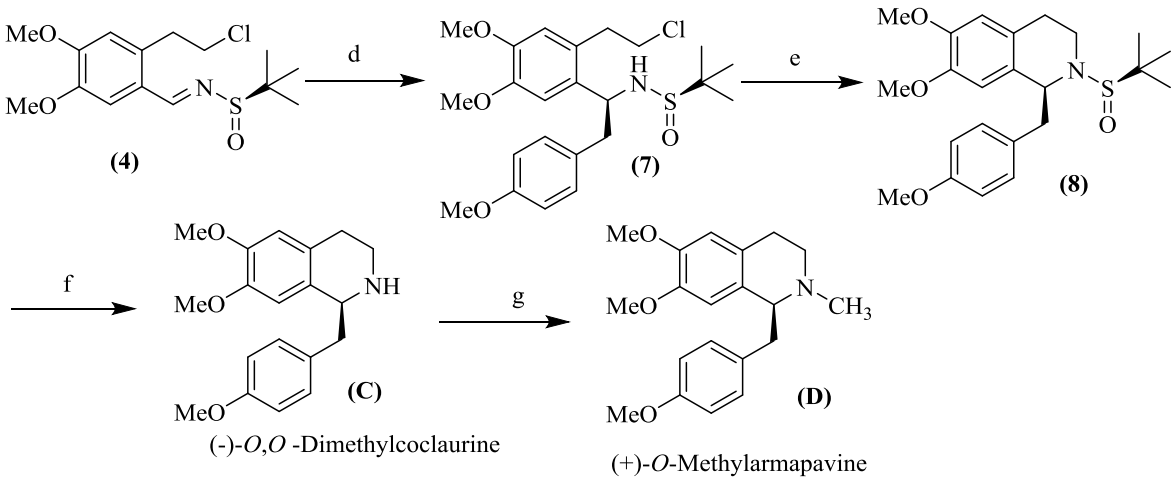
Scheme 1 Retrosynthetic analysis

We began our synthesis from commercially available 3,4 Dimethoxy phenyl ethyl alcohol (**1)** which on chlorination with thionyl chloride, resulted corresponding chloro derivative (**2)** in 96% yield, which on further treatment with dichloro(methoxy)methane in presence of tin chloride gave the chloro aldehyde (**3)** in 90 % yield. Accordingly, *N*-sulfinyl imine (4) was prepared in 92% yield from chloro aldehyde (**3)** and (*R*)-*tert*-butylsulfinamide in the presence of copper sulphate in dichloromethane. A subsequent addition of benzylmagnesium bromide to *N*-sulfinyl imine (**4**) furnished the 1-benzyl derivative (**5)** in 91% yield. Base promoted chloroamide cyclization in the presence of NaH in DMF at room temperature gave the 1-benzyltetrahydroisoquinoline derivative (**6)** in 88% yield. Deprotection of sulfinyl group from compound **(6)** by using dioxane-HCl gave the (*S*)-1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**A**) in 93%. Finally, the *N*-methylation of **A** by using 38% HCHO, $NaBH_4$ in MeOH at 0-25 ^{O}C over 3 h, gave *N*-methyl derivatives **B** in 96% yield (**Scheme 2**).



Scheme 2 Reagents and conditions: a) $SOCl_2$, $CHCl_3$, 0-65 ^{o}C, 4h, 96%; b) Cl_2CHOMe, $SnCl_4$, CH_2Cl_2, 0-25 ^{o}C, 8h, 90%; c) (*R*)-*tert*-butylsulfinamide, $CuSO_4$, CH_2Cl_2, 25 ^{o}C, 12h, 92%; d) $PhCH_2MgBr$, CH_2Cl_2, −78 ^{o}C, 2h, 91%; e) NaH, DMF, 0-25 ^{o}C, 3h, 88%; f) 1,4-dioxane.HCl, MeOH, 0-25 ^{o}C, 2h; 93%; g) 37% HCHO, $NaBH_4$, MeOH, 0-25 ^{o}C, 3h, 95%.

In a similar manner, the addition of *p*-methoxybenzylmagnesium chloride to *N*-sulfinylimine **4** afforded the corresponding 1-*p*-methoxybenzyl derivative (**7**) in 88% yield (Scheme 3). A subsequent base promoted cyclization of chloroamide gave the 1-*p*-methoxybenzyltetrahydroisoquinoline (**8**) in 86% yield. Deprotection of sulfinyl group from compound (**8**) by using dioxane-HCl gave the (-)-*O*, *O*-dimethylcoclaurine (**C)** in 91% yield. Finally, the *N*-methylation of C using 37% formaldehyde and sodium borohydride in MeOH at 0-25 ^{o}C over 3h gave the *N*-methyl derivatives (**D)** in 94% yield.



Scheme 3 Reagents and conditions: d) *p*-methoxybenzylmagnesiumchloride, CH_2Cl_2, −78 ^{o}C, 2h, 88%; e) NaH, DMF, 0-25 ^{o}C, 3h, 86%; f) 1,4-dioxane.HCl, MeOH, 0-25 ^{o}C, 1h, 91%; (g) 37% HCHO, $NaBH_4$, MeOH, 0-25 ^{o}C, 3h, 94%.

In summary, we have demonstrated an efficient strategy for the total synthesis of tetrahydroisoquinoline alkaloids such as (*S*)-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**A**), (*S*)-1-benzyl-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroiso quinoline (**B**), (–)-*O*-*O*-dimethylcoclaurine (**C**) and (+)-*O*-methylarmepavine (**D**) using *tert*-butylsulfinamide as a chiral auxiliary. The use of readily available chiral auxiliary to introduce the chirality of these alkaloids makes this approach simple, convenient and attractive.

Chapter II : In(OTf)$_3$ catalyzed tandem aza-Piancatelli rearrangement/ Michael reaction for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4] thiazine and oxazine derivatives.

Introduction

The heterocyclic compounds which containing hetreo atoms such as nitrogen, sulphur and oxygen possess an enormous significances in the field of medicinal chemistry, particularly the Oxazine and Thiazine containing analogues/derivates have been attracted by many researchers in the field of synthesis because of their various wide range of biological activities. The benzo[*b*][1,4]oxazine and thiazine structural units are frequently found in various biologically active molecules (**Figure 2**). They are known to display aldose- reductase inhibitory activity and potential therapeutic properties. In addition to this, benzoxazinones exhibit a diverse range of pharmacological properties such as anti-candina albicans, antifungals, kinase inhibitors, antagonism to progesterone receptor, antitumor, antiviral, antithrombotic, antimycobacterial, anti-inflammatory, antidiabetic and hypolipidaemic effects. Furthermore, 2-arylidene-4-aminoalkyl-2*H*-1,4-benoxazin-(4*H*)-ones and related compounds were found to exhibit significant CNS (central nervous system) depression. Thus, benzo[*b*][1,4]oxazines have recognized as privileged structures for the generation of drug like libraries in drug-discovery. Consequently, various methods have been devised for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine or thiazine derivatives.

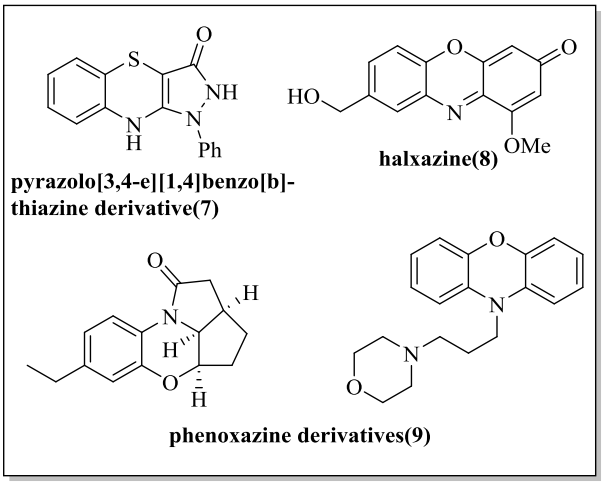
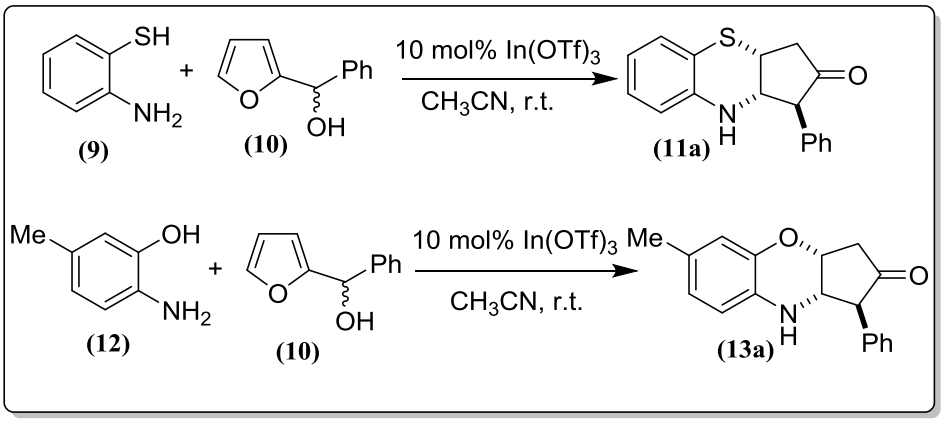


Figure 2 Examples of biologically active benzo[*b*][1,4]oxazine and thiazine derivatives.

Aza-Piancatelli rearrangement/Michael reaction methodology

The furan-2-yl(phenyl)methanol(10) derivatives undergo smooth aza-Piancatelli rearrangement with 2-aminothiophenol(9) and 2-aminophenol(12) in the presence of 10 mol% $In(OTf)_3$ in acetonitrile at room temperature to afford the corresponding 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine(11a) or oxazine(13a) derivatives respectively in good yields with high selectivity in short reaction times (**Scheme 4**).



Scheme 4 aza-Piancatelli rearrangement/Michael reaction methodology.

The required alcohol was prepared for the Aza-Piancatelli rearrangement/Michael reaction from known procedure.

Structure determination

The structure of the compound **13b** was characterized by detailed NMR studies including 2-D double quantum filtered correlation spectroscopy (DQFCOSY) and nuclear Overhauser effect spectroscopy (NOESY). The ^{1}H NMR experiments provided coupling constants between $^{3}J_{\text{H1-H2 (}pro\text{-}R\text{)}}$, = 4.4, $^{3}J_{\text{H1-H4}}$ = 3.1 and $^{3}J_{\text{H3-H4}}$ = 10.7 and $^{3}J_{\text{H1-H2 (}pro\text{-}S\text{)}}$ ~0 Hz. From these coupling values along with the presence of a nOe correlations, H2(*pro-R*)/H4 (medium intensity) and H2(*pro-S*)/H3 (weak intensity), the 5-membered *cis*-fused ring was found to take a twist conformation. In addition a ω-coupling, $^{4}J_{\text{H3-H2(}pro\text{-}S\text{)}}$ = 1.6 Hz and nOe correlation between H5/H6 further supports the structure. An energy minimized structure is consistent with the NMR findings which are given in (**Figure 3**).

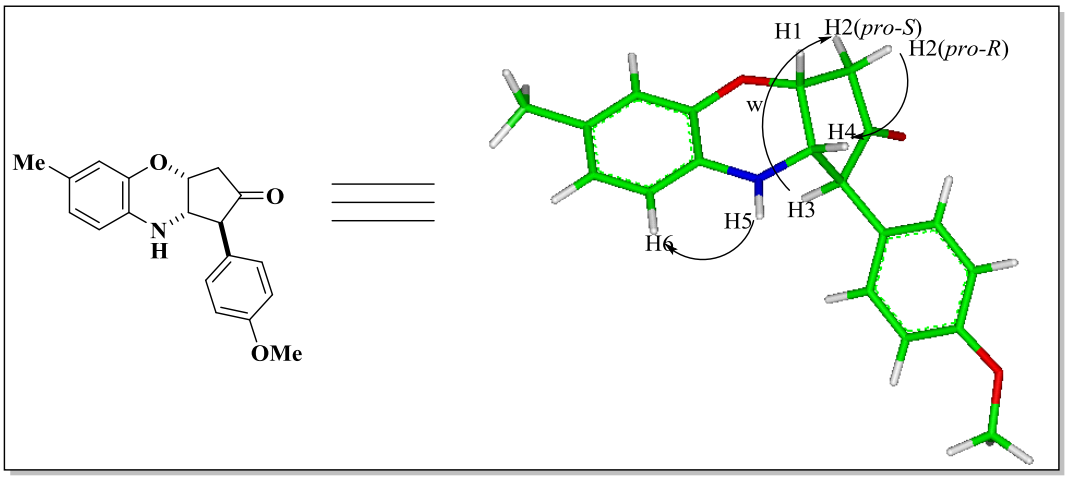


Figure 3 Characteristic nOe's and energy minimized structure of 1**3b**

X-ray crystal structure

The structure of **13c** was confirmed by X-ray crystallography (**Figure 4**).

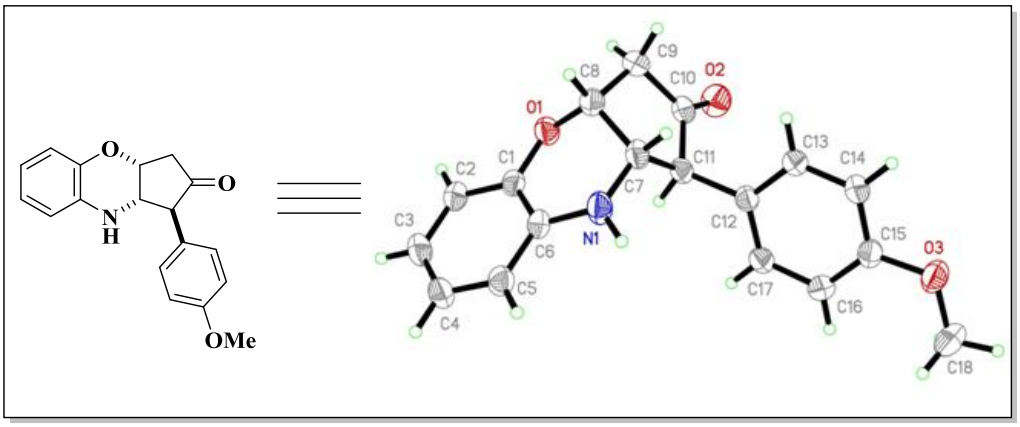


Figure 4 ORTEP diagram of **13c**

In summary, we have demonstrated a novel strategy for the synthesis of 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine and oxazine derivatives *via* a tandem aza-Piancatelli/Michael reaction between furan-2-yl(phenyl)methanols and 2-aminothiophenols and 2-aminophenols respectively. This is the first report on the synthesis of annulated 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine and oxazine derivatives by means of aza-Piancatelli rearrangement.

Chapter III : Sequential aza-Piancatelli rearrangement/Friedel-Crafts alkylation for the synthesis of pyrrolo[1,2-*d*]benzodiazepine derivatives

Introduction: Benzodiazepine derivatives are found to display a wide range of pharmacological properties such as anti-convulsant, anti-anxiety, sedative, anti-inflammatory, antidepressant and hypnotic agents. In particular, pyrrolobenzo diazepines are orally active arginine vasopressin (AVP, V_1 & V_2) receptor antagonists[3] Indeed, V_2 receptor antagonists are useful for the treatment of congestive heart failure, liver cirrhosis, nephrotic syndrome, and hyponatremia (**Figure 5**).

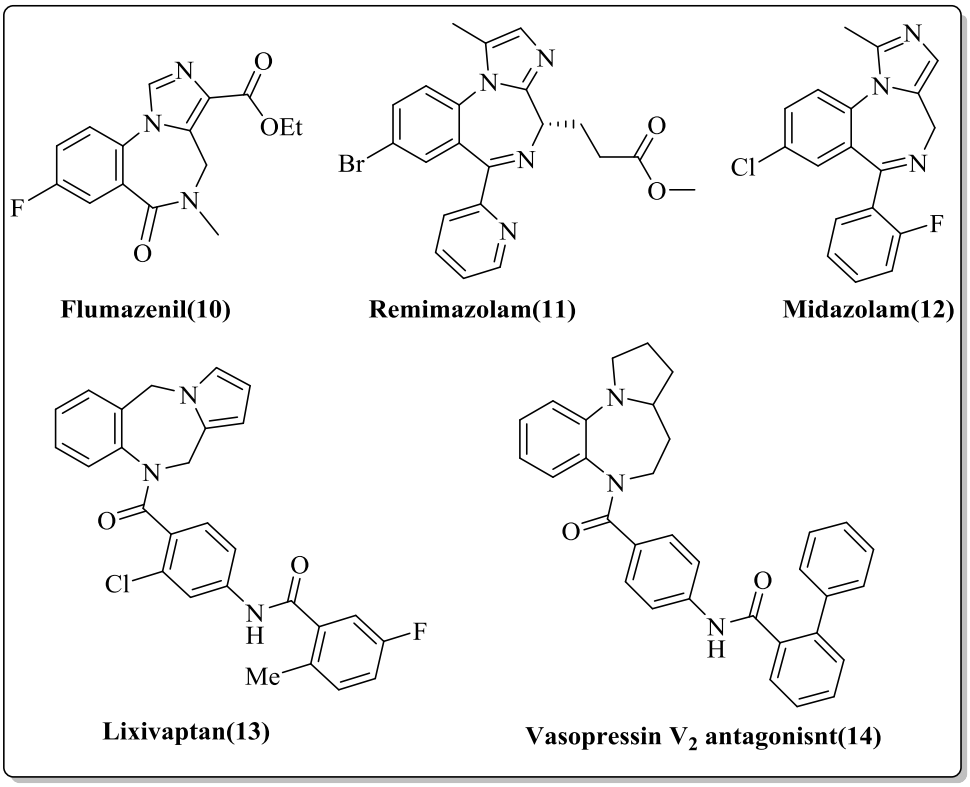
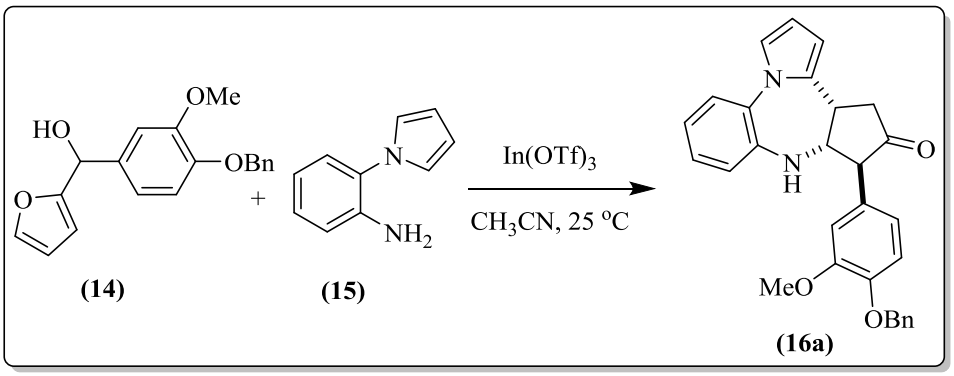


Figure 5 Biologically active tricyclic benzodiazepinone derivatives

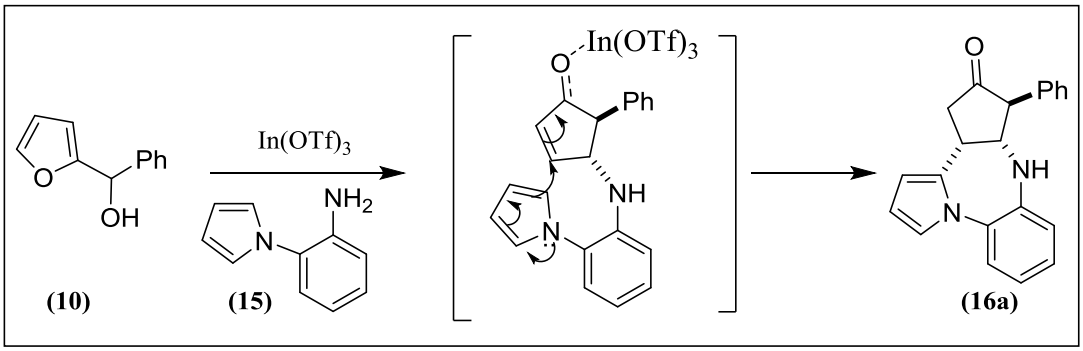
Aza-Piancatelli rearrangement/Friedel-Crafts alkylation methodology

2-Furylcarbinols(14) undergo a smooth aza-Piancatelli rearrangement followed by Friedel-Crafts alkylation with a bifunctional substrate, (1*H*-pyrrol-1-yl)aniline(15) in the presence of 10 mol% $In(OTf)_3$ in acetonitrile at room temperature to afford the corresponding hexahydrobenzo[*b*]cyclopenta[*f*]pyrrolo[1,2-*d*][1,4]diazepin-11(4a*H*)-one(16a) scaffolds in good yields (Scheme 5).



Scheme 5 Domino aza-Piancatelli rearrangement/Friedel-Crafts alkylation.

The essential alcohol and (1*H*-pyrrol-1-yl)aniline were synthesized from known procedures for the aza-Piancatelli rearrangement/Friedel-Crafts alkylation.



Scheme 6 proposed a possible reaction path way

Structure determination:

The structure and relative stereochemistry of **16b** were established by detailed NMR studies including 2-D double quantum filtered correlation spectroscopy (DQFCOSY) and nuclear Overhauser effect spectroscopy (NOESY). The large coupling constant between H2-H3 ($^3J_{H2\text{-}H3}$=11.1 Hz) along with the presence of *nOe* cross correlations between H2/H5', H5'/H16, H3/H4, H5/H19, H4/H19, H6/H8, H11/H14 indicates the trycyclic system is *cis*- fused to cyclopentenone ring with fluorophenyl ring being relatively *trans*- oriented as shown in **Figure 6**.

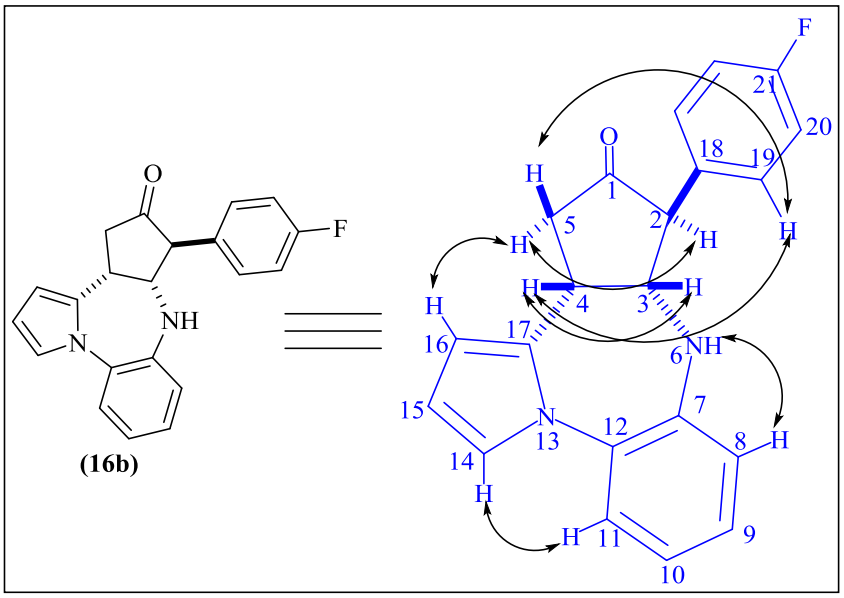


Figure 6 Characteristic *nOe* cross peaks of **16b**

In conclusion, we have developed a novel strategy for the efficient synthesis of benzo[*b*]cyclopenta[*f*]pyrrolo[1,2-*d*][1,4]diazepin-11(9*H*)-one derivatives through a cascade of aza-Piancatelli reaction followed by Friedel-Crafts alkylation. This is the first report on the synthesis of biologically relevant *cis*-fused pyrrolobenzodiazepinone scaffolds by means of aza-Piancatelli rearrangement.