Summary
The present thesis entitled “Studies on the synthesis, characterization and anti-microbial study of face ‘c’ annulated analogues of 1, 5-benzodiazepines” deals with the synthesis of novel imidazolo, benzimidazolo, oxadiazolo, isoxazolo, pyrazolo, pyrimido, thiadiazolo, 1,5-benzodiazepino, 1,5-benzothiazepino, 1,5-benzoazepino incorporated analogue of 1,5-benzodiazepines linked on its 2-position through an oxyphenyl and amino phenyl bridge.

Ubiquity of 1,5-benzodiazepine in chemical literature is undoubtedly a consequence of the multifarious biological response, which they elicit in combating a variety of body ailments. The use of this class of compounds is not merely confined to the management of anxiety or stress related conditions and as neoplastic agents but their additional novel applications have been continuously emerging. The recent demonstrations that these compounds can serve as potential agents for the control and treatment of AIDS has stimulated further interest in these compounds from yet another perspective.

The proven record of the synthetic potential of the amidines, imidate esters, thiosemicarbazone, dimethylaminomethylene ketones and chalcones in heterocyclic synthesis aroused our interest, in the present work, in the design and development of the new analogues of 1,5-benzodiazepine which contained several bioactive pharmacophoric scaffolds such as imidazole, benzimidazole, oxadiazole, isoxazole, pyrazole, pyrimidine, thiadiazole, 1,5-benzodiazepine, 1,5-benzothiazepine, 1,5-benzoazepine on the 2-position of this molecule, linked through a phenoxy/phenylamino spacer, utilizing the versatility of the above mentioned precursors. The aim of this study was to incorporate these pharmacophores which had the previous history of being biologically active on to the bioactive nucleus of 1,5-benzodiazepine on the premise that their presence in tandem in a single molecular framework could contribute significantly to the biological efficacy in the resulting molecules. The literature is replete with examples showing that the incorporation of bioactive pharmacophores on to the existing drug molecules sometimes exert a profound influence on the overall biological profiles of the parent molecules.
A wide array of biological potentials of 1,5-benzodiazepine, oxadiazoles, isoxazoles, pyrazoles, pyrimidines, thiaziazoles, imidazoles, benzimidazoles, 1,5-benzodiazepines, 1,5-benzothiazepines, 1,5-benzoxazepines has stimulated intense global efforts to develop their structural analogues, where different constitution and biological activity could allow them to be used as novel chemotherapeutic agents.

This prompted us to undertake the study to develop such molecules in which the above bioactive pharmacophores were brought together in such a way so as to become the part of the same molecule. The idea behind formulating such a study was to assess the favorable impact if any, these produced on the biological activity in the new materials through the additive or cumulative effect exercised by each of these moieties. If their role to produce a positive impact on activity was established, such structures were likely to form interesting targets in future, in the synthesis and biological evaluation of these materials. To test this hypothesis a series of compounds 1-24 shown in (Fig. S-1) were required to be obtained by synthesis. A perusal of the structure of FDA approved anti-HIV agent etravirine (A) revealed that its molecule essentially consisted of the following three vital fragments viz;

(i) The p-aminobenzonitrile fragment
(ii) The p-hydroxy benzonitrile fragment
(iii) The 4-amino pyrimidyl fragment.

In addition to etravirine there are other compounds possessing a pyrimidine ring in their molecules viz. raltegravir etc, which have recently emerged as the most powerful HIV-integrase inhibitors for the treatment of HIV-1 infection. One of these contains an oxadiazole ring, apart from the presence of the pyrimidine nucleus in its molecule. The presence of a cyano group in the above fragments were likely to offer an unprecedented opportunity to a chemist for its elaboration to the oxadiazole and imidazole rings, following the reported procedure for its formation, from the nitrile group in the literature. The cyano group contained in etravirine has so far not been functionalized to produce the oxadiazole and imidazole (and other) five membered rings) in its molecule. The present study intended to explore the possibility of incorporating these nuclei in the proposed structures 1-8 (Fig. S-1).
The **Schemes: S-1 to S-4** has been drawn to show the strategies which were employed for the synthesis of the compounds 1-2 from amidines 31, imidate esters 32, thiosemicarbazone 33, dimethylaminomethylene ketones 34 and chalcones 35 intermediates. These synthons were chosen as these have been known to offer unprecedented opportunity to a chemist in the synthesis of a wide variety of useful heterocyclic compounds from their reactions with bidentate nucleophiles such as o-phenylenediamine, ethylenediamine, hydrazine hydrate, hydroxylamine hydrochloride etc. on (to form five membered rings), with urea, thiourea, acetamidine and guanidine (to form six membered rings) with o-phenylenediamine, o-aminophenol and o-aminothiophenol (to form seven membered rings). The aim in the present work was to examine the feasibility of the application of the above synthons 27, 31, 32, 33, 34 and 35 in the synthesis of compounds 1-24 following the schemes outlines in S-1 to S-4.
**Chapter-I** of the thesis give a brief introductory idea of the synthetic aspects, reactivity and physiological aspects of 1,5-benzodiazepines. In addition to this it presents a comprehensive review of the practical and handy methods that have appeared in the literature for the synthesis of amidines 31, imidate esters 32, thiosemicarbazone 33 dimethylamino methylene ketones 34 and chalcones 35 which were employed as precursors in the subsequent chapters, in the present work in the synthesis of the heterocyclic materials in the subsequent chapters as shown in Fig. S-1.

A survey of literature on 1,5-benzodiazepines revealed that sufficient scope existed in a further study on the synthesis of the compounds derived from this nucleus. The proposed investigation was undertaken with a view to streamline the various methods which were available in the literature for the synthesis of the heteroring incorporated analogues of 1,5-benzodiazepines. Considerations of reactivity, compound availability, synthetic economy, and simplicity in the operational procedure has led us to favor the use of 1,5-benzodiazepines appended with amidines 31, imidate esters 32, thiosemicarbazone 33, dimethylamino methylene ketones 34 and chalcones 35 in their synthesis. In view of the wide spread application of amidines, imidate esters, thiosemicarbazone, dimethylamino methylene ketones, chalcones as versatile synthons in the synthesis of wide variety of heterocyclic compounds, it was considered worthwhile to employ these materials in the present work, to the synthesis of oxadiazolo, imidazolo, benzimidazolo, thiadiazolo, pyrazolo, isoxazolo, pyrimido, 1,5-benzodiazepino, 1,5-benzoxazepino, and 1,5-benzothiazepino incorporated analogues of 1,5-benzodiazepines linked on to its 2-position through an oxyphenyl and aminophenyl spacer.
Chapter-II of the thesis describes the synthesis of starting materials from 2-thiomethyl ether substituted 1,5-benzodiazepine which was in turn obtained from the sequence of reactions shown in scheme S-1a. Carbonyl compounds with an adjacent CH$_2$ group have been known to undergo reaction with CS$_2$ and CH$_3$I in the presence of a base to form the corresponding oxoketenedithioacetal derivatives. Oxoketene dithioacetal react with bidentate nucleophiles to form the heterocyclic rings. This property of oxoketene dithioacetal derived from cyclohexanone was utilized in the present work in the synthesis of 1,5-benzodiazepine 27 from 26. It reacted smoothly with o-phenylenediamine to form the 1,5-benzodiazepine nucleus containing a thiomethyl ether function at its 2-position. The synthesis of these materials was undertaken with a view to examine their versatility as starting materials, in the synthesis of various heteroring annulated products 1-24 shown in Fig. S-1. Compound 25 and 26 were utilized as most suitable building blocks for the preparation of 27, 31, 32, 33, 34 and 35 respectively.

It is evident from the Scheme: S-1a that 2-thiomethyl ether substituted analogue of face ‘c’ cyclohexano annulated 1,5-benzodiazepine 27 formed the key intermediates in the preparation of reactive synthons 31, 32, 33, 34 and 35 which were available on its reaction with (i) p-hydroxybenzonitrile/p-aminobenzonitrile followed by reaction of the obtained nitrile with hydroxylamine in methanol and KOH to give amidines 31, (ii) and with hydrochloric acid gas in ethanol to give imidate esters 32. In another operation 27 was treated with p-hydroxy benzaldehyde and p-hydroxy acetophenone to give 29 and 30 respectively. It has been known that carbonyl compounds containing an adjacent methylene group react with benzaldehyde (in presence of fused sodium acetate in glacial acetic acid) to generate the corresponding chalcones. In a similar manner, their reaction with dimethylformamide dimethylacetal (DMF-DMA) produces (dimethylamino methylene) ketones, which have been reported to undergo reactions with bidentate nucleophiles to give heterocyclic compounds. Compound 27 reacted with thiosemicarbazide to give the corresponding thiosemicarbazone 33. Compound 30 when was treated with dimethylformamide dimethylacetal (DMF-DMA) gave
dimethylamino methylene ketones 34, and with benzaldehyde it formed chalcone 35 respectively.

Chapter-III of the thesis describes the strategy which was adopted in the desired synthesis of oxadiazole, imidazole, benzimidazole, thiaimidazole, isoxazole and pyrazole incorporated analogues of 1,5-benzodiazepines 1, 2, 3, 4, 5, 6, 7, 8 from the cyclocondensation of amidine derivatives 31, imidate ester derivatives 32, thiosemicarbazone 33, dimethylamino methylene ketone 34 and chalcone 35 with appropriate reagents Scheme-2(a-e). Amidine derivatives 31 reacted with acetyl chloride to afford oxadiazole derivatives 1. The reaction of imidate ester 32 with ethylenediamine, o-phenylenediamine [and subsequent oxidation of 2a with 2-iodoxybenzoic acid (IBX)] afforded the corresponding imidazole and benzimidazole derivatives 2, 3 respectively (Scheme-2b). The thiazole derivatives 4 was obtained from the thiosemicarbazone 33 on its reaction with ammonium iron sulphate (Scheme-2c). The treatment of dimethylamino methylene ketones 34 with hydroxylamine hydrochloride and hydrazine hydrate in methanol afforded the corresponding isoxazole and pyrazole derivatives 5 and 6 respectively. In a likewise manner compounds 7 and 8 were obtained by the reaction of chalcone 35 with hydroxylamine hydrochloride and hydrazine hydrate in methanol followed by subsequent oxidation with 2-iodoxybenzoic acid (IBX) Scheme-2(d,e).

Chapter-IV of the thesis describes the synthesis of pyrimidine ring incorporated derivatives of 1,5-benzodiazepine 9-18. The reaction of dimethylamino methylene ketone 34 with urea and thiourea afforded the corresponding pyrimidine derivatives 9 and 10 respectively as shown in (Scheme-3a). In a likewise manner, the synthesis of other additional pyrimidine ring incorporated derivatives 11 and 12 were achieved by the cyclocondensation of dimethylamino methylene ketones 34 with acetamidine and guanidine respectively (Scheme-3b). In a similar manner the reaction of chalcone with urea and thiourea afforded the corresponding pyrimidine derivatives 13 and 14 respectively as shown in (Scheme-3c). The reaction of 2-thiomethyl ether incorporated face ‘c’ cyclohexano annulated 1,5-benzodiazepine analogues 27 with aminopyrimidine bearing pharmacophores afforded the corresponding pyrimidine ring bearing derivatives 15-18 respectively (Scheme-3d).
Literature is replete with examples illustrating the importance of α,β-unsaturated ketones (the chalcones) and dimethylamino methylene ketones in heterocyclic synthesis. These compounds are prone to undergo reaction with bidentate nucleophiles to form five, six, and seven membered heterocyclic rings. The formation of five and six membered rings from the reactions with active synthons containing these functionalities were examined in chapter-III and IV respectively, where the synthesis of isoxazole, pyrazole and pyrimidine ring were described.

Chapter-V of the thesis, examined the synthesis of 1,5-benzodiazepine, 1,5-benzoxazepine and 1,5-benzothiazepine ring condensed derivatives 19-21 which were achieved by the cyclocondensation of dimethylamino methylene ketones 34 with o-phenylenediamine, o-aminothiophenol and o-aminophenol respectively, as shown in (Scheme-4a). In a likewise manner, versatility of the chalcone 35 in the formation of seven membered rings compounds from their reaction with o-phenylenediamine, o-aminothiophenol and o-aminophenol followed by their oxidation with 2-iodoxybenzoic acid (IBX) (Scheme-4b) was explored to give 22, 23 and 24 respectively. These protocols smoothly furnished the desired products in moderate to good yield.

Chapter-VI of the thesis describes the results which emanated, on screening of the antibacterial and antifungal activity of a few selected compounds synthesized in each chapters- II, III, IV and V respectively. Antibacterial and antifungal properties of oxadiazole, imidazole, benzimidazole, thiazole, pyrazole, isoxazole, pyrimidine, 1,5-benzodiazepine, 1,5-benzoxazepine, 1,5-benzothiazepine ring incorporated products of 1,5-benzodiazepine were screened against E. coli, B. subtilis, A. niger, F. solani using Ciprofloxin and Flucanazole as references and employing the standard disc diffusion method at concentrations 400, 200, 100 µg/ML respectively. The zone of inhibition of each compound was recorded using the standard techniques.

Each chapter comprised of an introductory part, followed by results and discussion, experimental section, relevant schemes, tables and figures. Sufficient
literature pertaining to the work has been appended in each chapter and the formation of products has been rationalized by giving plausible mechanism of the reactions. All the synthesized compounds in chapter-II, III, IV and V have been purified by column chromatography, preparative TLC and characterized by their elemental analysis and spectral data.

Scheme-S-1a

Scheme-2a
Summary

Scheme-2b

Scheme-2c

Scheme-2d
Summary

Scheme-2e

Scheme-3a
Scheme-3b

Scheme-3c
Scheme-3d
Scheme-4a

Scheme-4b