Preface

The chemistry of heterocyclic system has evolved into a mojor area of research due to the vast clinical importance, commercial success and pharmacological properties and the benefits which it has given to the society in the treatment of various types of diseases which has been continuously increasing its importance. The discovery that fusion of a different biologiacally active systems onto a single nucleus can serve as a one system with enhanced biological potency of the parent molecule has led to an intensive exploration on the development of various fused heterocyclic sytems, and this had culminated into the chemical collection on the scene of several clinically active substances from oxadiazolo, imidazolo, pyrazolo, pyrido, etc. ring fused to s-triazine nucleus.

Recent studies, based on the s-triazine scaffold towards anti-tumour and anti-HIV activity have led these to be considered as most promising molecules to be employed as lead structures in the discovery of newer medicinally potent chemotherapeutic agents. Encouraged by the improved treatment options which the 'HAART' therapy has provided, it was anticipated that an even still better treatment options could emerge on joining the two active (or more than two) enzyme inhibitors together in the same molecular framework by resorting to such synthetic techniques which allowed these to become the part of the same molecule. The motivation for exploration of this treatment option derived its inspiration on this premise that their presence in tandem in the same molecular framework could contribute significantly to enhance the biological potency in the resulting molecules.

An examination of literature pertaining to the bioactivity of s-triazines revealed that this molecule on the one hand is highly biologically active and on the other hand it provides a template to hold three bioactive pharmacophores together in the same molecule, by allowing the chlorine atoms of 2,4,6-trichloro-1,3,5-triazine to be replaced by oxygen and nitrogen bearing bioactive nucleophilic species. This concept of the drug design has formed the basis in the present study, to seek the structural modification of s-triazine nucleus to generate novel analogues by incorporating onto its nucleus the active pharmacophores like oxadiazole, thiadiazole, imidazole, benzimidazole, isoxazole, pyrazole, pyrimidine and azepine moieties with

the hope to obtain the molecules endowed with high biologically active profiles. It is with this idea in mind that the present study has been framed and has been undertaken.

Chapter I: Introduction

This chapter of the thesis represents an overview of s-triazine with its synthetic aspects, reactivity and physiological aspects. It also gives a brief account of work that have appeared in the literature for its synthesis and biological activity of s-triazine. Various methods which were available in the literature were streamlined for the synthesis of the hetero ring annulated derivatives.

111 *References have been given in this chapter.*

Chapter II: Preparation of starting materials

This chapter of the thesis describes a comprehensive review of the methods which have appeared in the literature on the synthesis of reaction intermediates such as the amidine derivatives**,** imidate ester derivatives**,** thiosemicarbazone deivatives, dimethylaminomethylene ketone and chalcone derivatives derived from phenoxyl and phenylamino substituted derivatives of s-triazine, which were used as precursors in the synthesis of a wide variety of heterocyclic compounds. The synthesis of these materials was undertaken in view of their versatility for their use as a starting material for the synthesis of various hetero ring incorporated analogues of s-triazine as the building block in synthesis in the subsequent chapters.

The following twelve novel compounds have been synthesized in this chapter.

- **(i)** 6-chloro-N,N-dicyclopropyl-1,3,5-triazine-2,4-diamine.
- **(ii)** 4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)benzonitrile.
- **(iii)** 4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxyl)benzonitrile.
- **(iv)** 4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzaldehyde.
- **(v)** 1-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)ethanone.
- **(vi)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-hydroxybenzamidine.
- **(vii)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)-N'-hydroxybenzamidine.
- **(viii)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)-N'-ethylimidate.
- **(ix)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)-N'-ethylimidate.
- **(x)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)benzylidene)thiosemicarbazide.
- **(xi)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-3-(dimethylamino)prop-2-en-1-one.
- **(xii)** (4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-3-phenylprop-2-en-1-one.

82 *References have been given in this chapter.*

Chapter III: Synthesis of isoxazolo, pyrazolo, imidazo, benzimidazo, oxadiazo and thiadiazolo analogues of *s*-triazine linked to it through 2-phenoxyl/phenylamino bridge.

This chapter describes the incorporation of oxadiazolo, imidazo, benzimidazo, thiadiazo, isoxazolo and pyrazolo derivatives on to the s-triazine nucleus through phenoxyl/ phenylamino linkage from the corresponding amidine, imidate ester, dimethylaminomethylene ketone and chalcone derivatives from their reactions with bidentate nucleophiles in one pot reaction.

The following eleven novel compounds have been synthesized in this chapter.

(i) N^2,N^4-dicyclopropyl-N^6-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl)-1,3,5-triazine-2,4,6- triamine.
(ii) 6-(4-(5-methyl-1,2,4-oxadiazol-3-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4,-diamine.
(iii) N^2-(4-(1*H*-imidazol-2-yl)phenyl)-N^4,N^6-dicyclopropyl-1,3,5-triazine-2,4,6-triamine.
(iv) 6-(4-(1*H*-imidazol-2-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(v) N^2-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenyl)-N^4,N^6-dicyclopropyl-1,3,5-triazine-2,4,6-triamine.
(vi) 6-(4-(1*H*-benzo[*d*]imidazol-2-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(vii) 6-(4-(5-amino-1,3,4-thiadiazol-2-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(viii) 6-(4-(5-isoxazol-3-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(ix) 6-(4-(5-phenylisoxazol-3-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(x) 6-(4-(1*H*-pyrazol-3-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(xi) 6-(4-(5-phenyl-1*H*-pyrazol-3-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.

176 *References have been given in this chapter.*

Chapter IV: Synthesis of pyrimido incorporated analogues of s-triazine linked through an aminophenyl and oxyphenyl bridge.

This chapter describes the synthesis of pyrimidine ring incorporated analogues of s-triazine formed by the cyclocondensation of respective dimethylamino methylene ketone and chalcone derivatives with bidentate nucleophiles.

The following five novel compounds have been synthesized in this chapter.

(i) Ethyl2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-ylamino)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate.
(ii) Ethyl2-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate.

(iii) Ethyl4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)pyrimidine-2-thiol.
(iv) Ethyl4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidin-2-ol.
(v) Ethyl4-(4-(4,6-bis(cyclopropylamino)-1,3,5-triazin-2-yloxy)phenyl)-6-phenylpyrimidine-2-thiol.

39 *References have been given in this chapter.*

Chapter V: Synthesis of benzodiazepino, benzothiazepino, benzoxazepino incorporated analogues of 1,3,5-s-triazine linked on its 6-position through an phenoxyl bridge.

This chapter of the thesis describes the synthesis of benzodiazepino, benzothiazepino and benzoxazepino incorporated analogues of s-triazine formed by the cyclocondensation of corresponding chalcone and dimethylaminomethylene ketone derivatives with *o*-phenylenediamine, *o*-aminothiophenol and *o*-aminophenol, respectively.

The following six novel compounds have been synthesized in this chapter.

(i) 6-(4-((2Z,4E)-1*H*-benzo[b][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(ii) 6-(4-((2Z,4E)-benzo[b][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(iii) 6-(4-((2Z,4E)-benzo[b][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(iv) 6-(4-((2Z,4E)-2-phenyl-1*H*-benzo[b][1,4]diazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(v) 6-(4-((2Z,4E)-2-phenylbenzo[b][1,4]thiazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.
(vi) 6-(4-((2Z,4E)-2-phenylbenzo[b][1,4]oxazepin-4-yl)phenoxy)-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine.

72 *References have been given in this chapter.*

Chapter VI: Evaluation of anti-microbial activity of the synthesised compounds

This chapter of the thesis describes the antimicrobial screening of the compounds synthesized against bacterial species such as *S. aureus* and *E.coli* and fungal species such as *F.solani* and *A.niger* by agar cup method against the standard drug streptomycin for bacteria and fluconazole for fungi at concentrations 400, 200, 100 μg/ml.

13 *references have been given in this chapter.*

Summary

An overview of the work done has been given at the end of the thesis.