Summary

An overview of the work done

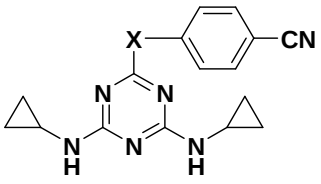
The aim in this thesis entitled "**Study directed towards the development of novel molecular probes from s-triazine nucleus as possible substitute to 'HAART' in anti-HIV chemotherapy"** was to synthesize novel oxadiazolo, pyrimido, imidazo, benzimidazo, thiadiazolo, isoxazolo, pyrazolo, 1,5-benzodiazepino, 1,5-benzothiazepino and 1,5-benzoxazepino substituted analogues of 6-chloro-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine from corresponding amidines, imidate esters, thiosemicarbazone, dimethylaminomethylene ketone and chalcone intermediates.

Greatly encouraged by the impressive bioactive profiles of s-triazine, it was thought in the present work to synthesize s-triazine molecules incorporating in it a wide variety of bioactive pharmocophores. In the synthetic strategies envisaged in the present work, the s-triazine molecule has been selected with this idea in mind, that this molecule on one hand is biologically highly active and on the other hand it can provide a template to hold three bioactive pharmacophores together in the same molecule. It was thought that it could be interesting to access the favourable impact if any, if the above substitution could produce on the biological activity in the new materials through the additive or cumulative effects exercised by each of these moieties. This anticipation was based on the fact that their hetero ring fused derivatives have attracted much attention due to their various biological and medicinal properties. Recently many of these compounds have been proved to be useful as potential agents for the control and treatment of AIDS which has stimulated further interest in these compounds from yet another perspective.

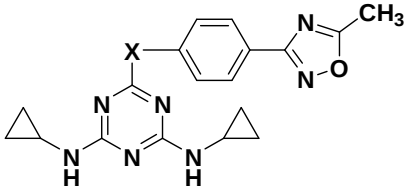
The aim of this study was to design and develop derivatives of s-triazine by incorporating several bioactive pharmacophoric scaffolds which have the previous history of being biologically active. In view of this, heterocyclic scaffolds, such as oxadiazolo, pyrimido, imidazo, benzimidazo, thiadiazolo, isoxazolo, pyrazolo, 1,5-benzodiazepino, 1,5-benzothiazepino and 1,5-benzoxazepino were appended on the 6-position of this molecule through a phenoxyl or a phenylamino bridge utilizing the versatility of the amidines, imidate esters, thiosemicarbazone, dimethylaminomethylene ketone and chalcone precursors, in such a way that these had become a part of a single structure, to assess the favourable impact if any on the biological activity in the new molecule bearing these moieties. It was hoped that their presence in single molecular framework could significantly enhance the bioactivity of the existing drug and would form

interesting targets in future, in synthesis and biological evaluation of the materials belonging to this class of compounds.

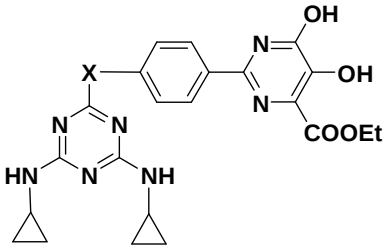
To test this hypothesis a series of compounds **(1-25)** were synthesized to test this hypothesis following the strategies dipicted in the **schemes S-1** to **S-10**. They offered unprecedented opportunities to the chemist to synthesize a wide variety of useful heterocyclic compounds from their reaction with bidentate nucleophiles such as imidate ester **(31-32)** with *o*-phenylenediamine and ethylenediamine, dimethylaminomethylene ketone **(36)** and chalcone **(37)** with hydrazine hydrate and hydroxylamine hydrochloride (for the synthesis of five membered ring), amidines **(29-30)**, dimethylaminomethylene ketone **(36)** and chalcone **(37)** with diethylacetylenedicarboxylate, urea and thiourea (for the synthesis of six memberd ring) and dimethylaminomethylene ketone **(36)** and chalcone **(37)** with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol (for the synthesis of seven membered ring). The present work is designed with the aim to test the feasibility of the application of the above novel synthons **28, 29, 30, 31, 32, 34, 36** and **37** in the synthesis of compounds **(1-25) (Fig-S-1)** following the **schemes S-1-S-10**.



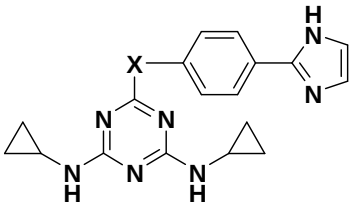
X= NH, O
1,2



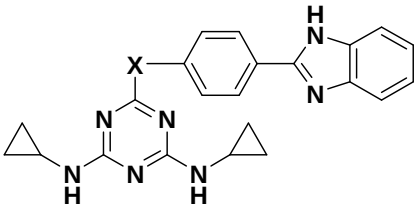
X= NH, O
3,4



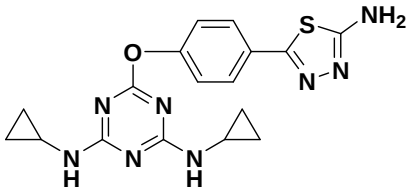
X= NH, O
5,6



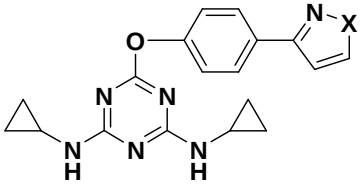
X= NH, O
7,8



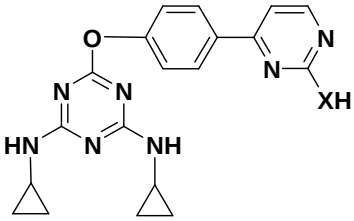
X= NH, O
9,10



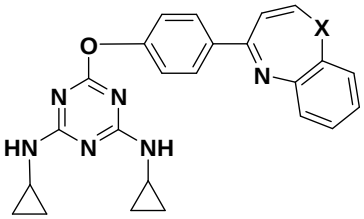
11



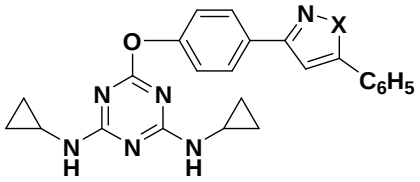
X= NH, O
12,13



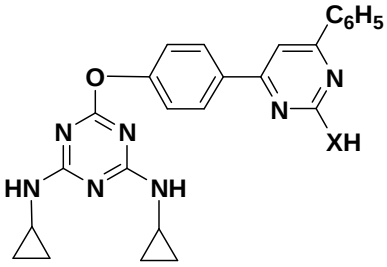
X= O, S
14,15



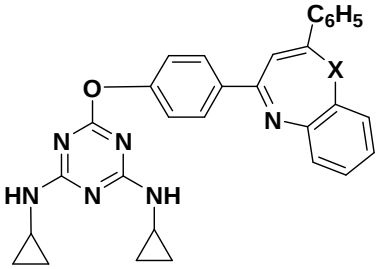
X= NH, S, O
16,17,18



X= O, NH
19, 20



X= O, S
21,22



X= NH, S, O
23,24,25

Fig- S-1

Chapter-I 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 has appeared in the literature for its synthesis and its biological activity. A survey of literature revealed that sufficient scope existed for the further study on the synthesis of the compounds containing this moiety. Various methods which were available in the literature were streamlined for the synthesis of its hetero ring substituted derivatives. Keeping in view the reactivity, availability, synthetic economy, and simplicity in the operational procedure had led us to favour the use of s-triazine.

Chapter-II of the thesis describes a comprehensive review of the methods appeared in the literature for the synthesis amidine derivatives **(29-30),** imidate ester derivatives **(31-32),** thiosemicarbazone deivatives **(34)**, dimethylaminomethylene ketone **(36)** derivatives and chalcone derivatives **(37)** which were used as precursors in the synthesis of wide variety of heterocyclic compounds. The synthesis of these materials was undertaken in view of their versatility of their use as a starting material for the synthesis of various hetero ring substituted compounds with s-triazine as a building block in the subsequent chapters **(Fig.-S-1)**.

It is evident from the **scheme: S-1** that 6-chloro-N^2,N^4-dicyclopropyl-1,3,5-triazine-2,4-diamine served as a key intermediate in the preparation of various reactive synthons **29, 30, 31, 32, 34, 36** and **37** respectively. Nitrile, obtained by the reaction of **28** with *p*-aminobenzonitrile and *p*-hydroxybenzaldehyde, on reaction with CH_3OH and KOH produceds amidine derivatives **(29-30)** which on reacion with HCl gas in methanol formed imidate ester derivatives **(31-32)**. Compound **36** on its reaction with *p*-hydroxybenzaldehyde yielded **33** which on further reaction with thiosemicarbazide produced thiosemicarbazone **34,** this on reacting with *p*-hydroxyacetophenone gave **35** which on further reaction, with DMF/DMA produced dimethylaminomethylene ketone **36,** and with benzaldehyde it formed chalcone **37**. Chalcones and dimethylaminomethylene ketone have been reported to undergo reactions with bidentate nucleophiles to form five, six and seven membered heterocyclic rings, therefore they were used for the synthesis of these heterocyclic derivatives.

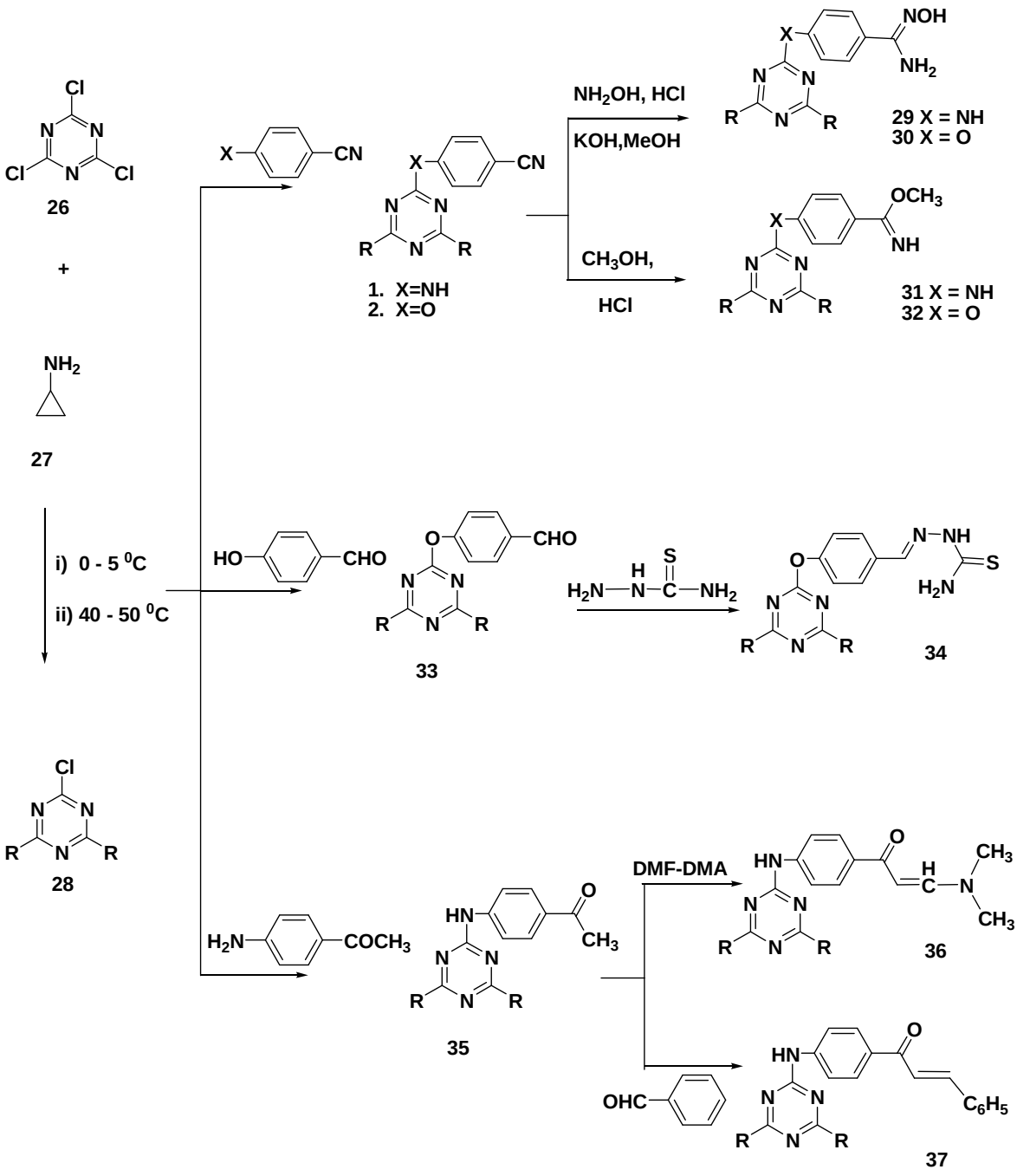
Chapter-III (Scheme: S: 2-5 and 8) of this summary describes the synthesis of oxadiazole derivative **(3-4)** by the cyclocondensation of the amidine derivatives **(29, 30) (Scheme: S-2)** with acetyl chloride together with the synthesis of imidazole and benzimidazole derivatives **(7-10)** by

the reaction of imidate ester derivative **(31-32)** with ethylenediamine and *o*-phenylenediamine respectively **(Scheme: S-3),** and thiadiazole derivative **(11)** by the reaction of **36** with thiosemicarbazide followed by its reaction with ammonium iron sulfate **(Scheme: S-4),** also the synthesis of isoxazole **(12, 19)** and pyrazole **(13, 20)** derivatives by the reaction of dimethyaminomethylene ketone **(36)** and chalcone **(37)** with hydroxylamine hydrochloride and hydrazine hydrate respectively **(Scheme: S-2 and S-8).**

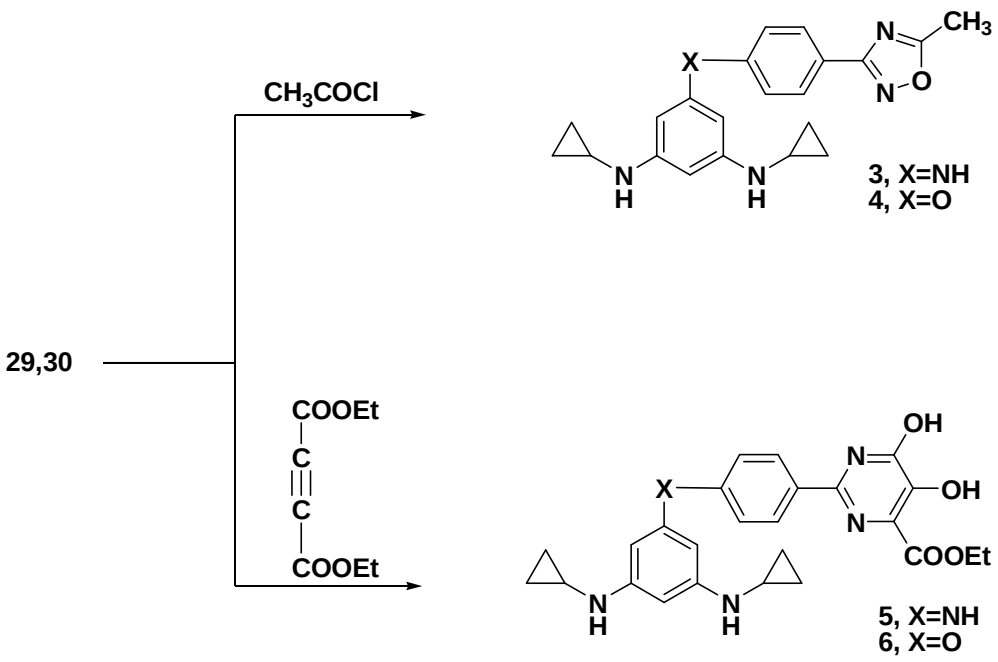
Chapter-IV (Scheme: S: 2, 6 and 9) of the thesis describes the synthesis of pyrimidine ring substituted derivatives of s-triazine **(5-6, 14-15, 21-22).** Pyrimidine derivatives were synthesized by the reaction of amidine derivatives **(29-30)** with diethyl acetylenedicarboxylate **(Scheme: S-2)** and by the reaction of dimethylaminomethylene ketone **(36)** and chalcone **(37)** with urea and thiourea **(Scheme: S-6 and S-9).**

Chapter-V (Scheme: S: 7 and 10) of the summary describes the synthesis of seven membered ring compounds **(16-18, 23-25)** by the reaction of dimethylaminomethylene ketone derivatives **(36)** and chalcone **(37)** with *o*-phenylenediamine, *o*-aminothiophenol and *o*-aminophenol respectively.

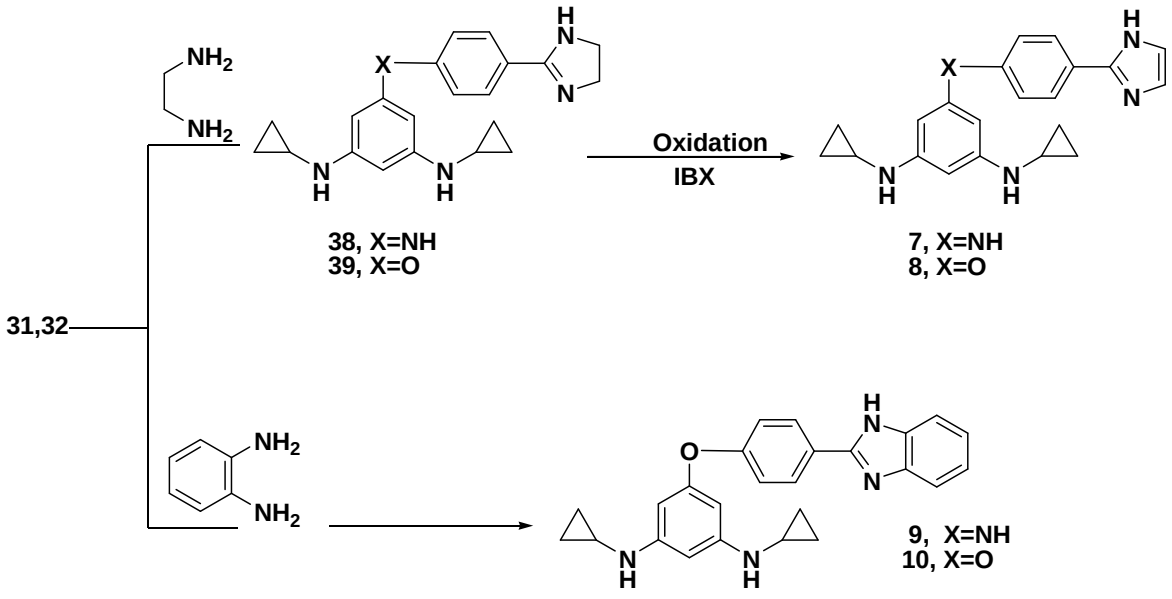
Chapter-VI of the summary describes the results which have emanated by the invitro screening of the few selected synthesized compounds. Antibacterial and antifungal activity of oxadiazoles, imidazoles, benzimidazoles, thiadiazole, pyrazoles, isoxazoles pyrimidines and azepines incorporated onto the s-triazine nucleus were tested against *E*.coli, *S*.aureus, *A*.niger and *F*.solani against the standard drugs streptomycin and fluconazol following the cup-plate method at concentrations 400, 200, 100 μg/ml. The zone of inhibition was measured and the activity data of the compounds were represented in tabular form, bar diagram form and through photographic plates.


26
+
27
i) 0 - 5 ^{0}C
ii) 40 - 50 ^{0}C
28
X
CN
1. X=NH
2. X=O
NH_2OH, HCl
KOH,MeOH
CH_3OH,
HCl
NOH
NH_2
29 X = NH
30 X = O
OCH_3
NH
31 X = NH
32 X = O
HO
CHO
33
H_2N—N—C—NH_2
34
H_2N
COCH$_3$
35
DMF-DMA
36
OHC
C_6H_5
37

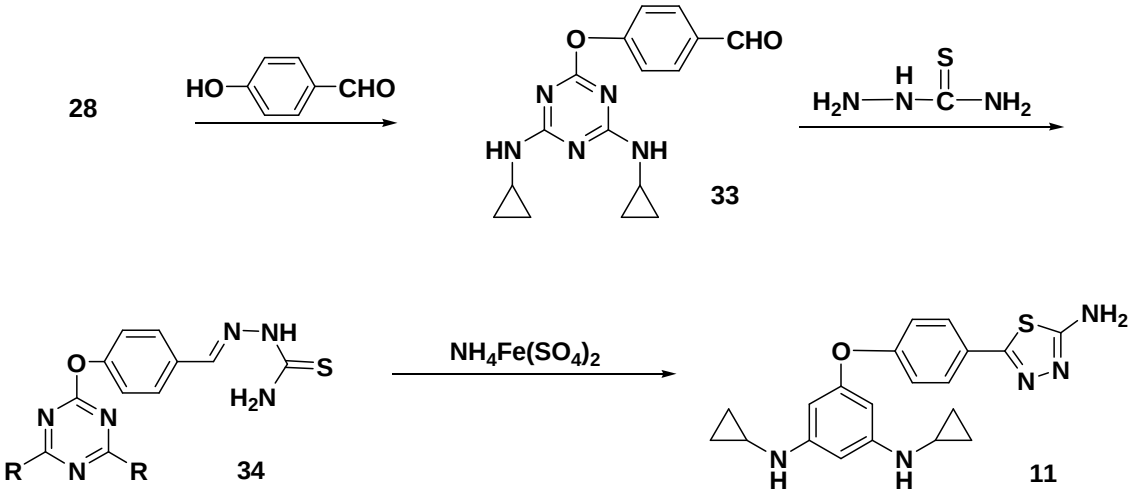
Scheme-S-1



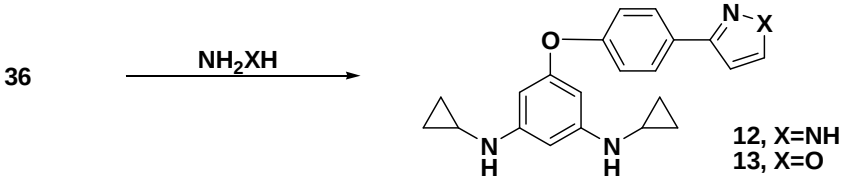
Scheme-S-2



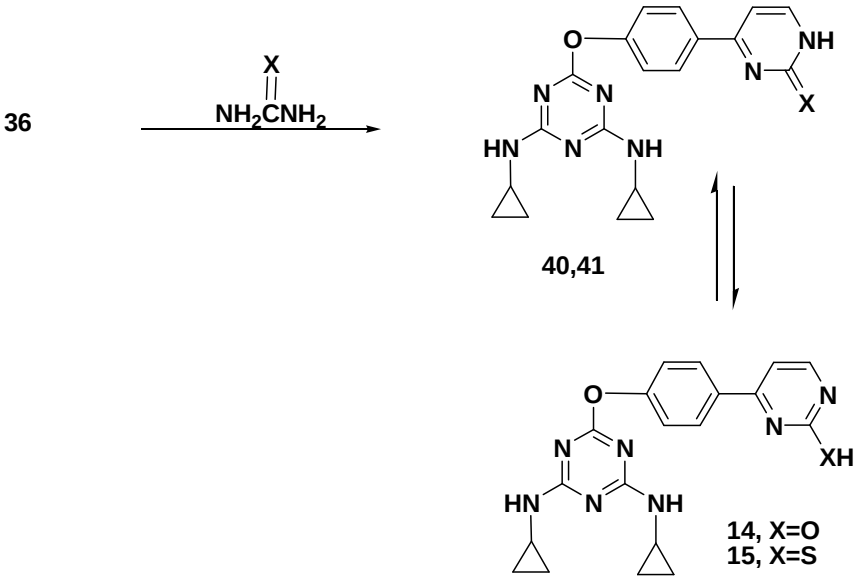
Scheme-S-3



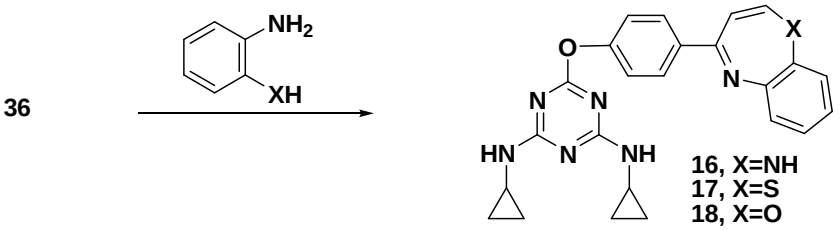
Scheme-S-4



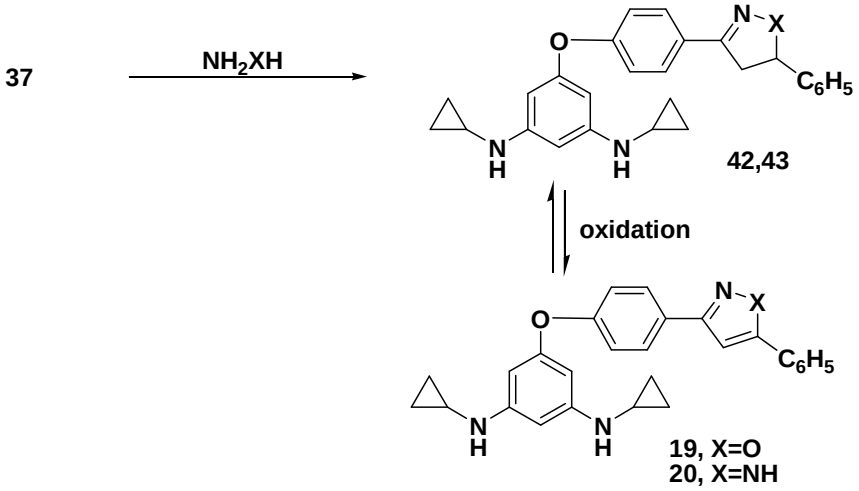
Scheme-S-5



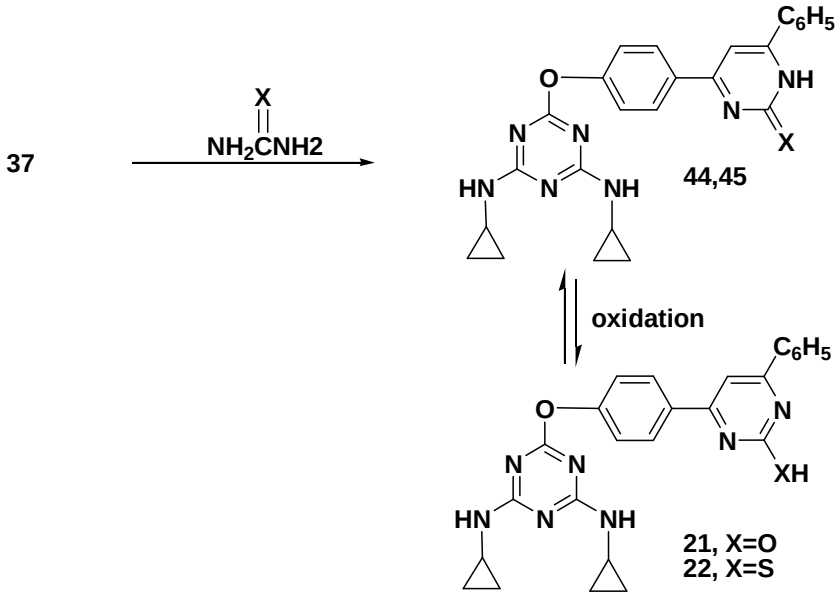
Scheme-S-6



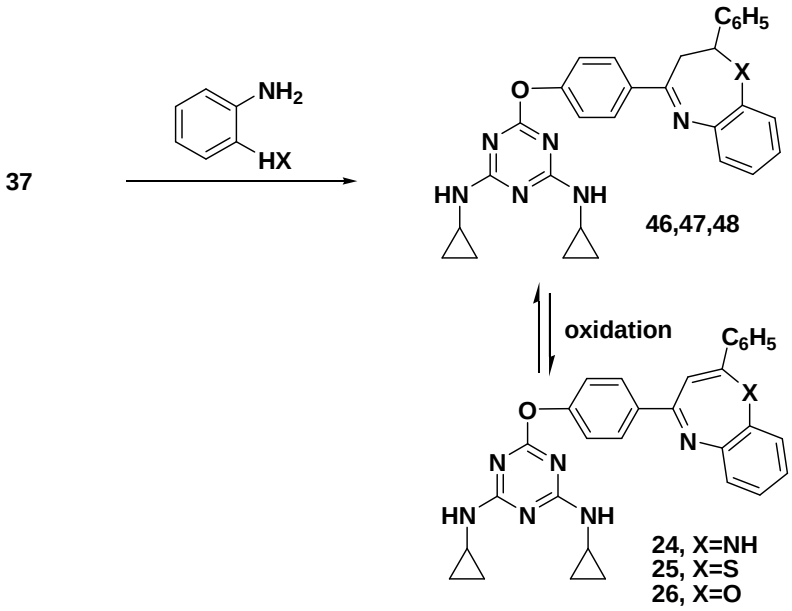
Scheme-S-7



Scheme-S-8



Scheme-S-9


37
NH2
HX
C6H5
X
O
N
N
N
HN
N
NH
46,47,48
oxidation
C6H5
X
O
N
N
N
HN
N
NH
24, X=NH
25, X=S
26, X=O

Scheme-S-10