It consists of two parts: Part A concerning the syntheses and anticancer and antiplatelet activity of 1,4-diazepines and Part B concerning the work on syntheses, biological studies and molecular modeling studies of pyrimidines for anti HIV activity.

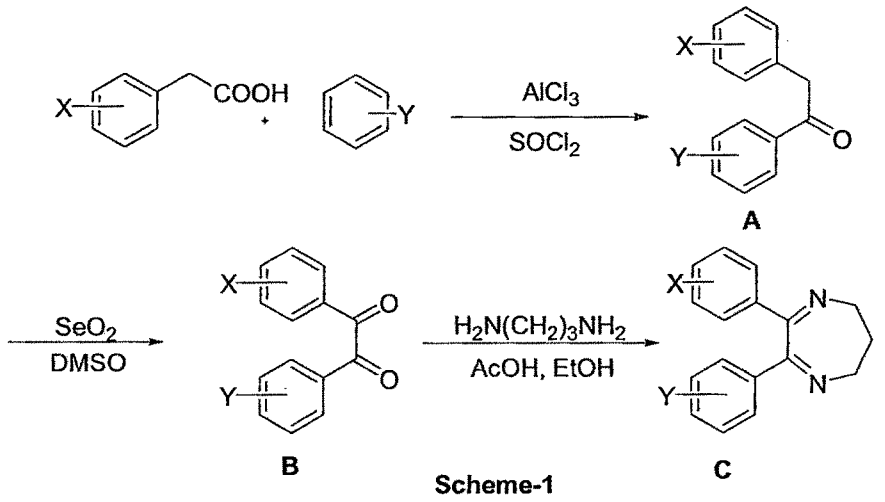
Part A –Synthesis, Antiproliferative and Antiplatelet activity of 1,4-diazepines

Although a vast majority of benzodiazepines are clinically used as CNS depressants, reports of such compounds with various activities are available in literature. The benzodiazepine field offers promising avenues for research in antiplatelet, anticancer, antiHIV etc. The present study details the synthesis of two monocyclic diazepines possessing diaryl rings at different positions and their biological activity.

1. 2,3-diaryl-6,7-dihydro-5*H*-1,4-diazepine
2. 5,7-diaryl-2,3-dihydro-1*H*-1,4-diazepine

1. 2,3-diaryl-6,7-dihydro-5*H*-1,4-diazepine

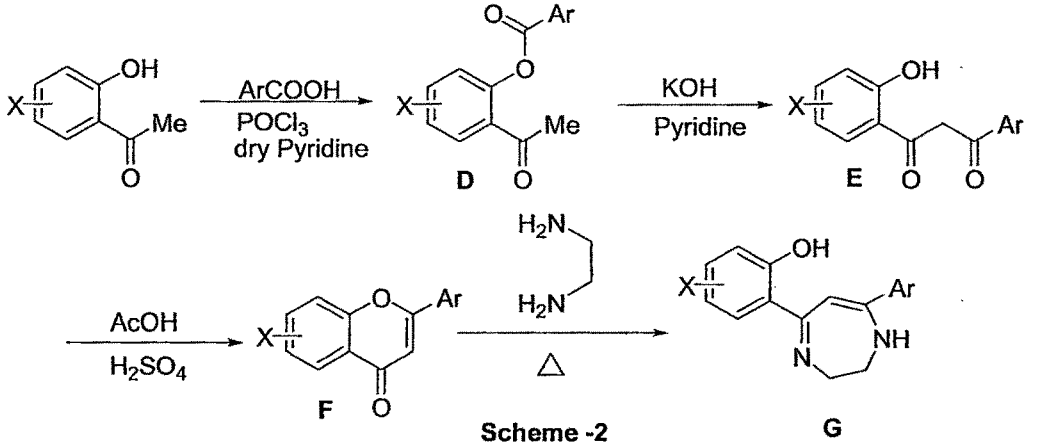
Friedel–Crafts acylation reaction of substituted phenylacetic acids with substituted benzene in presence of anhydrous aluminium chloride as a catalyst afforded 1,2-diaryl-1- ethanones **(A)**. The ethanones were oxidized with selenium dioxide under microwave condition to give 1,2-diarylethane-1,2-diones **(B)**. The 2,3-diaryl-6,7-dihydro-5*H*-1,4-diazepines **(C)** were obtained by cyclization with 1,3-propanediamine The general scheme adopted to synthesize 2,3-diaryl-6,7-dihydro-5*H*-1,4-diazepine is given below **(Scheme 1)**:



Scheme-1

2. 5,7-diaryl-2,3-dihydro-1*H*-1,4-diazepine

The 2-hydroxyacetophenone derivatives were reacted with various substituted aromatic/hetero aromatic acid chlorides (generated in situ) through Schotten-Baumann reaction to afford the esters **(D)**. Baker-Venkatraman rearrangement of the esters furnished 1,3-propanedione derivatives **(E)**, which were subsequently converted into 2-(substituted phenyl)chromen-4-one **(F)** in acidic medium. The formation of diazepines **(G)** was accomplished by cyclocondensation of the 2-(substituted phenyl)chromen-4-one with ethylenediamine. The general scheme adopted to synthesize 5,7-diaryl-2,3-dihydro-1*H*-1,4-diazepine is given below **(Scheme 2)**:



Scheme -2

All the synthesized compounds were characterized by their spectral and chemical analysis. The data are presented under presented under the respective compounds and are in accordance with the chemical structure.

The biological work carried out has been discussed under following sub heads:

- Antiproliferative activity
- Antiplatelet activity

Antiproliferative activity

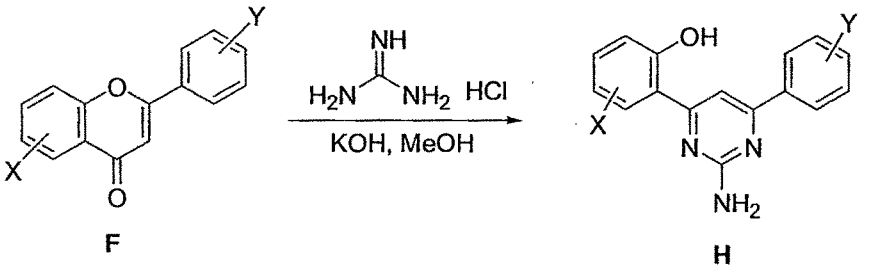
The 2,3 and 5,7-diaryl diazepines were screened against various human leukemic cancer cell lines- Jurkat, HL60, Molt3, NCEB-1 and K562 for antileukemic activity. None of the 2,3-diarydiazepines showed encouraging activity. Among the 5,7-diaryl diazepine series, compound **49c** demonstrated high cytotoxic activity against the K562 and Jurkat cell lines with an IC_{50} values of 4.55 and 8.47 μM respectively.

Antiplatelet activity

The 2,3-diaryl-6,7-dihydro-5H-1,4-diazepines **(44a-r)** were evaluated to inhibit platelet aggregation of female Sprague-Dawley rat platelet-rich plasma induced by arachidonic acid. From these studies **44i** was the most active one with 36.4% inhibition. Compound **44o** showed 28.3% inhibition with two fold greater activity as compared to aspirin (14%). The compound **44h, 44k** and **44m** showed moderately good activity.

Part B- Synthesis and Anti-HIV activity of 4,6-diaryl-2-aminopyrimidines

During the synthesis of 5,7-diaryl-2,3-dihydro-1*H*-1,4-diazepine it was recognized that the common intermediate chromen-4-one derivative **(F)**, on reaction with guanidine hydrochloride produced 4,6-diaryl-2-amino pyrimidines **(H)** **(Scheme 3)**. These compounds structurally resemble the TMC analogs. TMC 125 (delaviridine) is an approved candidate as antiHIV-1 agent.



Scheme 3

Anti-HIV screening

The viability of both HIV- and mock-infected cells was assessed spectrophotometrically via the *in situ* reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into formazan. The parent compound of the series, **50a** was found to be active against HIV-infected cells with an IC_{50} value of 3.22 μM and its selectivity index is 10.

Docking studies

We validated our hypothesis by performing automated docking studies of the active compounds using Autodock 3.0 version. Inspection of conformation of the compound **50a** at the non nucleoside binding site (NNBS) led to the following conclusions: The phenyl groups show lack of hydrophobic binding with the surrounding residues of NNBS viz., Tyr 181, Tyr 188, Trp 229 (distance 10.74 Å), Phe 227 (4.64 Å). The phenyl ring attached to the 4th position of the

pyrimidine ring interacts with Asp 110 (distance 4.43 Å) and Asp 186 (distance 3.61 Å) which are at proximity to the polymerase active site. The hydrogen of the hydroxyl group of the phenyl ring forms a hydrogen bond with Leu 228 (distance 2.0 Å). The amino group hydrogens hydrogen bond with Glu 224 (distance 3.32 Å) and His 221 (distance 3.28 Å).

Conclusion

The 2,3-diaryl-6,7dihydro-5*H*-1,4-diazepines screened for both antileukemic and antiplatelet activities. From the results of the above studies, some compounds this class of diazepines showed very good antiplatelet activity when arachidonic acid induced platelet aggregation. Further studies are required to prove their mechanism of action. This group of compounds lack antileukemic activity.

The antileukemic results of 5,7-diaryl-2,3-dihydro-1*H*-1,4-diazepines indicate that a few compounds show promising activity. They can be further optimized by introducing different substitutions in both aryl rings and diazepines ring.

In case of the 4,6-diaryl-2-aminopyrimidine, we hypothesize that a linker group between one of the aromatic residues and the pyrimidine ring in the ligand would provide better binding interactions which may therefore contribute to better antiHIV-1 activity.