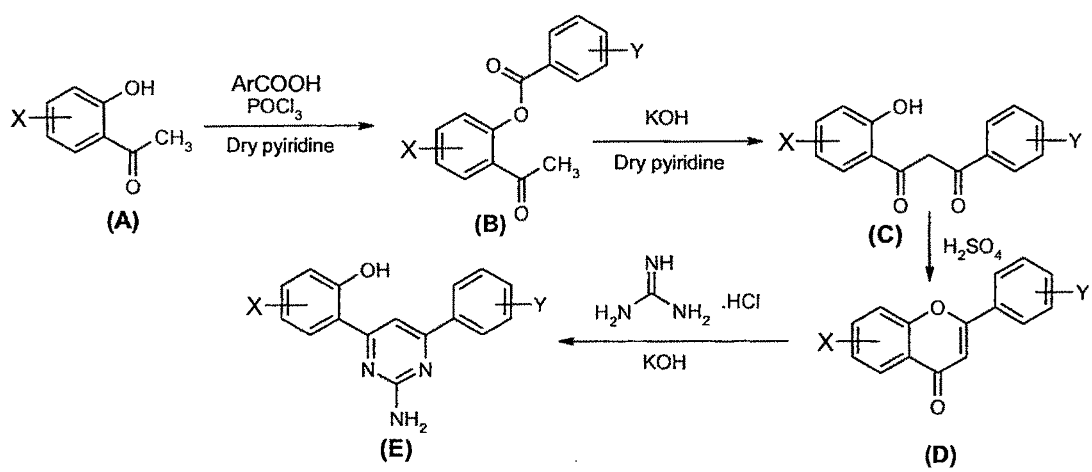
CHAPTER – 5

Summary and Conclusion

The present thesis embodies the work done on 4,6-diaryl-2-aminopyrimidines. The nucleus was an improvisation of the work done previously in our laboratory for HIV-1 activity with a view to improve the selectivity index. During the course of the anti HIV work it was also visualized that the designed molecules would have promising anti platelet activity and anti malarial activity as well. Three types of 2-aminopyrimidnes derivatives were synthesized and discussed in three parts with their respective activities.

Synthetic work

Three series of compounds were synthesized as per **Scheme 2.**



X= Allyloxy, Methoxy, Benzyloxy

Y= H, 4-Methoxy, 3-Methoxy, 3,4-dimethoxy, 2-Methyl, 3-Methyl, 4-Methyl, 2-Cl, 3-Cl, 4-Cl, 2,4-Dichloro, 4-F, 4-Br, 4-NO_2,4-Allyloxy, furan

They are as follows:

4-(4/5-Allyloxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines

4-(4/5-Methoxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines

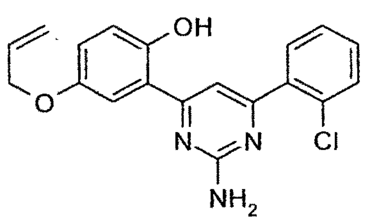
4-(4/5-Benzyloxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines

The substituted 2-hydroxyacetophenone (**A**) derivatives was reacted with various substituted aromatic/ hetero aromatic acid chlorides (generated in situ) through Schotten-Baumann reaction to afford the esters (**B**). Baker-Venkatraman rearrangement of the esters furnished 1,3-propanedione (**C**) derivatives, which were subsequently converted into 2-(substituted phenyl)chromen-4-one (**D**) in acidic medium. On reaction with guanidine hydrochloride 4,6-diaryl-2aminopyrimidine (**E**) were produced.

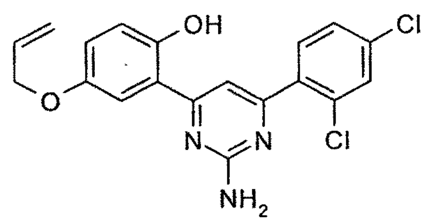
As discussed, substituted 4-(4/5-allyloxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines were synthesized. These compounds structurally resemble the TMC-278 and TMC-125 analogs. Twenty six compounds were synthesized and anti HIV screening was carried out at Rega Institute, Belgium. Some methoxy substituted compounds were also screened for the anti HIV activity.

Anti HIV activity

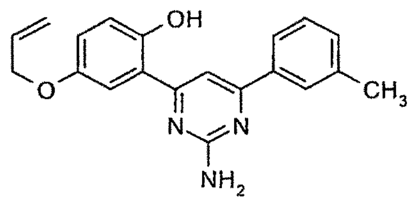
The viability of both HIV and mock-infected cells was assessed spectrophotometrically via the in-situ reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into formazan. The primary anti-HIV screening of newly synthesized 2-aminopyrimdines shows that compound **18**, **19** and **26** possess IC_{50} value 1.34, 0.34 and 1.88 in μM respectively. Unfortunately, this compound also possesses cytotoxicity at same concentration. We also screened the 4-(4/5-methoxy-2-hydroxy phenyl)-6-(substituted phenyl)-2-aminopyrimidnes which is discussed in Part II. In that series compounds **29** and **31** possess IC_{50} value 6.44 and 0.52 in μM respectively.



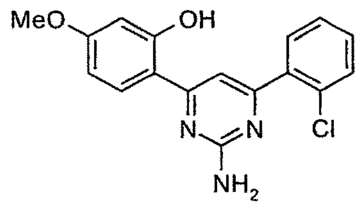
(18) IC_{50}=1.34



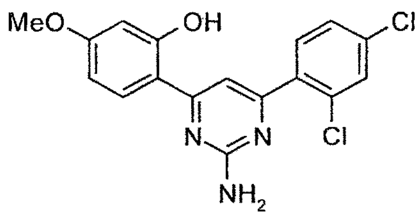
(19) IC_{50}=0.34



(26) IC_{50}= 1.88



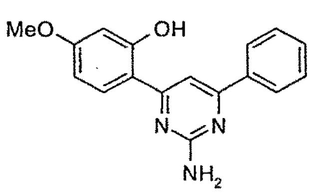
(29) IC_{50}=6.44



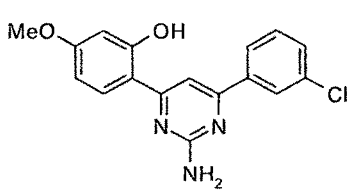
(31) IC_{50}=0.52

Anti platelet activity

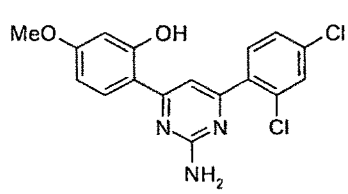
4-(4/5-Methoxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines were synthesized. As discussed in Part II these compounds have some features which are required for anti platelet drugs. Eighteen compound were screened for anti platelet activity on whole blood using ADP as inducer of platelet aggregation. Whole Blood Aggregometer, Chronolog Corporation, Haverton, PA, USA was used. Compound **31** is the most potent compound was found twice as potent as aspirin. Also compounds **30, 34, 35, 37, 38** and **41** produce more than 60 % inhibition and compounds **27, 33 and 40** were found equipotent to aspirin.



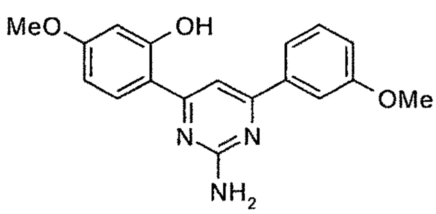
(27) 42.67 %



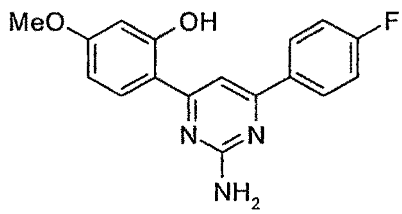
(30) 65.84 %



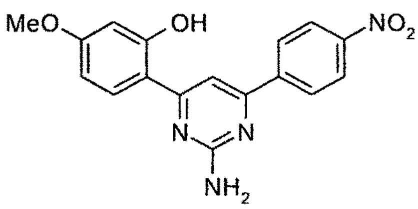
(31) 77.47 %



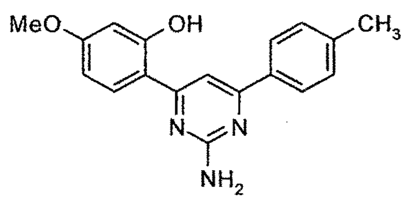
(33) 51.19 %



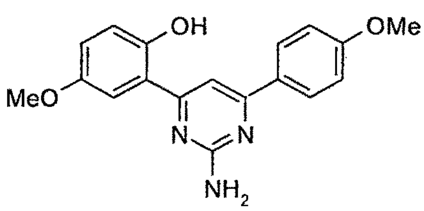
(34) 64.01 %



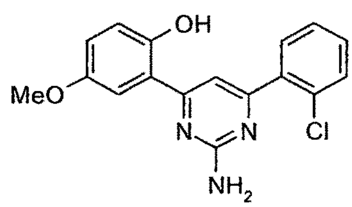
(35) 62.82 %



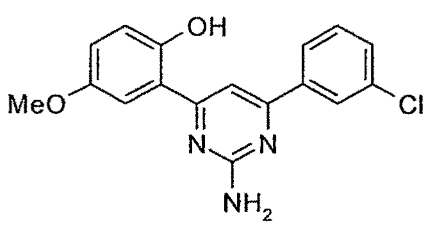
(37) 58.52 %



(38) 64.28 %



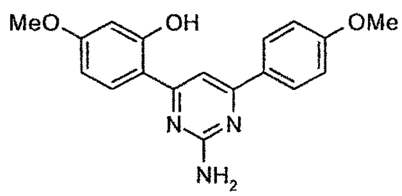
(40) 55.13 %



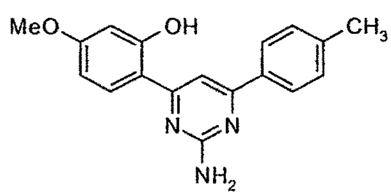
(41) 66.85 %

Anti malarial activity

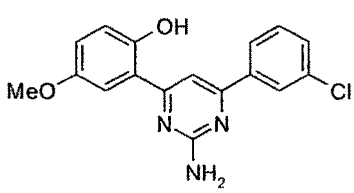
4-(4/5-Benzyloxy substituted-2-hydroxy phenyl)-6-(substituted phenyl)-2-amino pyrimidines and 4-(4/5-Methoxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines were synthesized by scheme 1. As discussed in Part III, these compounds were screened for anti malarial activity. The screening of compound was carried out at Department of Biochemistry, The M.S. University of Baroda, Vadodara. Sixteen synthesized compounds were screened. Compounds **32** and **48** were found most active compared to standard drug with IC_{50} value **1.78** and **1.61** μg/ml respectively. Compounds **35, 41, 46** and **47** were moderately active with IC $_{50}$ value **<10.**



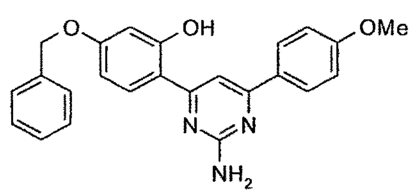
(32) IC_{50}=1.78



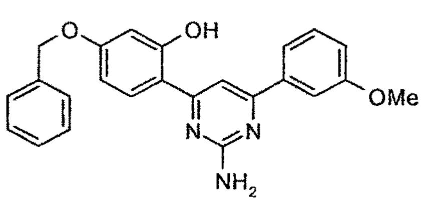
(35) IC_{50}=8.71



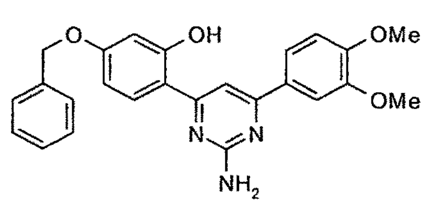
(41) IC_{50}=9.53



(46) IC_{50}=5.01



(47) IC_{50}=7.61



(48) IC_{50}= 1.61

Conclusion

4-(4/5-allyloxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines were screened for its anti HIV activity. We hypothesized that substitution of unsaturated group and methoxy group would provide better binding interaction with NNIBP. The primary anti-HIV screening of newly synthesized 2-aminopyrimdines shows the improvisation in the biological activity but compounds also possess cytotoxicity at same concentration.

4-(4/5-Methoxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines were synthesized and screened for its anti platelet activity, this moiety share some common features which were important for the anti platelet activity. Some compounds shows very good anti platelet activity with ADP induced platelet aggregation.

4-(4/5-Benzyloxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines and 4-(4/5-Methoxy substituted-2-hydroxyphenyl)-6-(substitutedphenyl)-2-aminopyrimidines were screened for its anti malarial activity. These compounds bear the structural requirement for classical DHFR inhibitors. We performed the anti malarial screening using malarial parasites. Two compounds were found to have activity comparable to chloroquine

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