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Research Article

Inverse Virtual Screening of Some New Pyrazolo-[1,5-a]pyrimidine ; 4,6-Dihetarylpyrimidin-2-amine and Ethyl 2-oxo-4,6-di(hetar-2-yl)cyclohex-3-encarboxylate Heterocyclic Compounds From 1,3-Dihetaryl-2-propen-1-one

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Abstract

An efficient and practical synthesis of 3-(4-alkylphenyl)diazenyl)-5,7-di(hetar-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine, 4,6 Dihetarylpyrimidin-2-amine and Ethyl 2-oxo-4,6-di(hetar-2-yl)cyclohex-3-encarboxylate derivatives. The structures of the various synthesized heterocyclic compounds were assigned on the basis of elemental analysis, IR- and ^{1}H NMR-spectral data, and MS: MS. An inverse virtual screening *in silico* approach has been applied to hetaryl compounds to screen their efficacy against proteins involved in malarial processes, with the aim of directing future experimental assays. Docking studies were performed on a panel of 94 protein targets extracted from the Protein Data Bank, to analyze their possible interactions with the hetaryl compounds that were synthesized.

1. INTRODUCTION

In view of the significant biological activities having pyrimidine nucleus, condensed pyrazolo[1,5-a]pyrimidines, we reported synthesis of several new 3-(4-alkylphenyl)diazenyl)-5,7-di(hetar-2-yl)pyrasolo[1,5-a]pyrimidines , 4,6-Dihetarylpyrimidine-2-amines and Ethyl 2-oxo-4,6-di(hetar-2-yl)cyclohex-3-encarboxylate by the action of appropriate reagents and the cyclization reaction of the synthesized and characterized 1,3-Dihetaryl-2-propen-ones (analogous of chalcone).[1] Scheme 1.

Chalcones are valuable aromatic diaryl-α,β-unsaturated ketones with a ketoethelinic (-CO-CH=CH-) group. Changes in the chalcone structure have offered a high degree of diversity that has proven useful for the development of new biologically active agents [2-4].

The chalcones and their heteroanalogues posse the ability to act as activated unsaturated system in congugated addition reactions of carbanions in presence of acidic or basic catalyst.

Reactions of heterocyclic amines with α,β-unsaturated carbonyl compounds provide a good synthetic methodology for the fusion of a second heterocyclic ring[5].

Thus pyrimidines, fused pyrazolopyrimidines and pyrazoles etc. are nitrogen containing heterocycles that are associated with diverse pharmacological properties as depicted in literature[6-10].

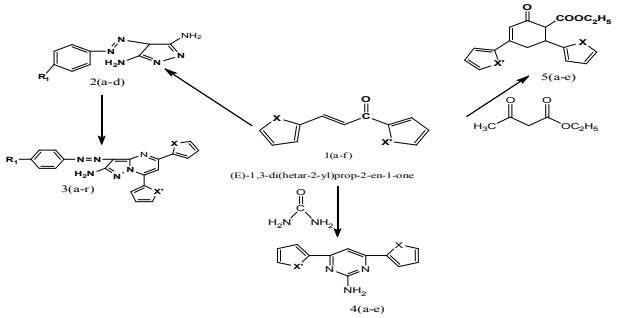
Malaria is a major disease caused by the protozoan parasites of genus Plasmodium with an estimated 3.3 billion people at risk.[11] *Plasmodium falciparum* causes the most severe disease and is predominant in Africa, where more than 90% of all malarial deaths were reported in 2010.[12] Several conventional antimalarials, such as chloroquine and sulphadoxine-pyrimethamine, have been extensively used because of their availability and low cost;[13] however, due to the increasing emergency of drug resistance, artemisinin-based combination therapies (ACTs) are recommended as a first-line therapy.[14]

Phosphoethanolamine N-methyltransferase (PMT) is essential for phospholipid biogenesis in the malarial parasite Plasmodium falciparum. *PfPMT* catalyzes the triple methylation of phosphoethanolamine to produce phosphocholine, which is then used for phosphatidylcholine synthesis by PDB code 4FGZ (EC; 2.1.1.103) .[15]

N-myristoyltransferase (NMT), is an enzyme responsible for protein trafficking in

Plasmodium falciparum, the most lethal species of parasites that cause malaria, is described by PDB code 4B12 (EC; 2.3.1.97).[16]

2. EXPERIMENTAL



Scheme 1 (R= H-, -OCH$_3$, Cl-)

3. RESULTS AND DISCUSSION

3.1 Molecular docking Software used in the study

Molecular docking studies have been conducted using SYBYI 1.1.and MOE. The scoring functions to rank the affinity of ligand bound to the active site of a receptor were determined.

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Table 1: Surflex docking scores and the corresponding binding energies of the designed Heterocyclic Compounds with ***PfPMT*** and ***PfNMT*** and the inhibition

Structure code	Compounds	PDB Code			
		4FGZ		4B12	
		Surflex-Dock ($-\log k_d$)	Surflex-Dock (kcal mol^{-1})	Surflex-Dock ($-\log k_d$)	Surflex-Dock (kcal mol^{-1})
1a	1,3-di(thiophen-2-yl)propen - 1-ones	3.82	-5.19	2.49	-3.38
1b	1-(furan-2-yl)-3-(thiophen-2-yl)propen - 1-ones.	4.16	-5.65	3.55	-4.78
1c	1,3-di(furan-2-yl)propen - 1-ones.	3.72	-5.05	3.03	-4.11
1d	3-(1H-pyrrol-2-yl)-3-(thiophen-2-yl)propen - 1-ones.	3.32	-4.51	3.36	-4.56
1e	1-(1H-pyrrol-2-yl)-3-(furan-2-yl)propen - 1-ones.	4.15	-5.63	4.05	-5.50
1f	3-(furan-2-yl)-1-(thiophen-2-yl)propen - 1-ones.	3.84	-5.22	2.72	-3.70
3a	3-(phenyl)diazenyl)-7,5-di(thiophen-2-yl) pyrazolo[1,5-a]pyrimidin-2-amine.	2.72	-3.70	3.10	-4.21
3b	5,7-di(thieophen-2-yl)-3-((4-chlorophenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine.	3.10	-4.21	2.43	-3.30
3c	5,7-di(thiophen-2-yl)-3-(p-tolydiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine.	2.43	-3.30	3.98	-5.41
3d	5,7-di(thiophen-2-yl)-3-((4-methoxyphenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine.	3.98	-5.41	2.79	-3.79
3e	7-(furan-2-yl)-3-(phenyl)diazenyl)-5-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	2.79	-3.79	3.06	-4.16
3f	7-(furan-2-yl)-3-((4-chlorophenyl)diazenyl)-5-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	3.06	-4.16	3.59	-4.88
3g	7-(furan-2-yl)-3-(p-tolydiazenyl)-5-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	3.59	-4.88	3.01	-4.09
3h	7-(furan-2-yl)-3-((4-methoxyphenyl)diazenyl)-5-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	3.41	-4.63	3.60	-4.89
3i	3-(phenyldiazenyl)-5,7-di(furan-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	3.01	-4.09	5.04	-6.48
3j	3-((4-chlorophenyl)diazenyl)-7,5-di(furan-2-yl) pyrazolo[1,5- a]pyrimidin-2-amine.	4.36	-5.92	3.29	-4.47
3k	5,7-di(furan-2-yl)-3-(p-tolydiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine.	3.60	-4.89	3.60	-4.89
3l	3-((4-methoxyphenyl)diazenyl)-7,5-di(furan-2-yl) pyrazolo[1,5- a]pyrimidin-2-amine.	5.04	-6.48	5.04	-6.48
3m	5-(furan-2-yl)-3-(phenyldiazenyl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	3.29	-4.47	3.29	-4.47
3n	5-(furan-2-yl)-3-((4-chlorophenyl)diazenyl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	3.14	-4.27	3.14	-4.27
3o	5-(furan-2-yl)-7-(thiophen-2-yl)-3-(p-tolyldiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine	2.71	-3.68	2.71	-3.68
3q	3-((4-chlorophenyl)diazenyl)-5-(1H-pyrrol-2-yl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	2.91	-3.95	2.91	-3.95
3r	3-((4-methoxyphenyl)diazenyl)-5-(1H-pyrrol-2-yl)-7-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine	5.64	-7.66	5.64	-7.66
4a	4,6-di(thiophen-2-yl)pyrimidin-2-amine.	3.02	-4.10	3.02	-4.10
4b	4-(furan-2-yl)-6-(thiophen-2-yl)pyrimidin-2-amine.	3.59	-4.88	3.59	-4.88
4c	4,6-di(furan-2-yl)pyrimidin-2-amine.	4.27	-5.80	4.27	-5.80
4d	4-(1H-pyrrol-2-yl)-6-(thiophen-2-yl)pyrimidin-2-amine.	4.41	-5.98	4.41	-5.98
4e	4-(1H-pyrrol-2-yl)-6-(furan-2-yl)pyrimidin-2-amine.	3.74	-5.08	3.74	-5.08
5a	Ethyl 2-oxo-4,6-di(thiophen-2-yl)cyclohex-3-encarboxylate	4.48	-4.09	4.12	-5.60
5b	Ethyl 2-oxo-4-(thiophen-2-yl) -6-(furan-2-yl)cyclohex-3-encarboxylate.	4.95	-4.72	4.52	-614
5d	Ethyl 2-oxo-4-(1H-pyrrol-2-yl) -6-(thiophen-2-yl)cyclohex-3-encarboxylate	5.30	-7.20	5.30	-7.20
5d	Ethyl 2-oxo-4-(1H-pyrrol-2-yl)-6-(furan-2-yl)cyclohex-3-encarboxylate	6.29	-8.23	5.88	-7.99

Heterocyclic compounds have been docked into the active site of PfPMT and PfMNT to investigate their binding interactions. Docking was performed using Surflex-Dock, the 3D (figure A) and 2D (figure B) visualization of the results were carried out using MOE and the Lig-X module of the MOE package. Distances and angles were measured using SYBYL (Tripos Inc.) and Discovery Studio Visualizer (v2.5, Accelyrs Software Inc.). Surflex-dock predicts binding affinities of the ligand-protein complex in the form of –log(Kd). Therefore, scoring values were converted into free energy of binding values using the following equation: kcal/mol=0.59ln(10^{-pk_d}), the result Surflex docking scores have shown a range of values between 6.26-2.43corresponding to binding energy range of -8.55 to -3.30 kcal/mol^{-1} for PDB 4FGZ indicates that the binding interactions of these compounds are similar. This similarity has been confirmed by the stacking and superimposing all the compounds within the binding cavity.

3.2 Hetaryl Chalcone 1(a-f)

The carbonyl group of the compound is interacting with the enzyme via two hydrogen bonds, one with the NH of ASN137 (2.50Å) and another with NH of SER134 (2.06Å) and van der- Waal (hydrophobic) interactions with the residues SER134 and ASN137. Figure (1)

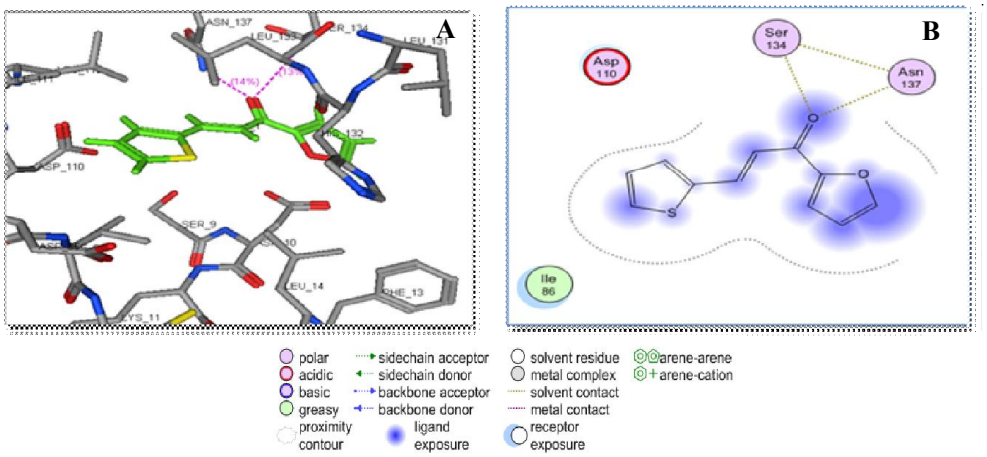


Figure 1: *Binding interactions of Hetaryl chalcone (A) Binding mode of* ***c****ompound 1b (shown as sticks, carbons colored in green, sulfur in yellow and oxygen in red) within the active site of PfPMT. The carbonyl group of (C1) of the compound interacts with ASN137and SER134. (B) 2D picture of hetaryl chalcone (1b) within the active site of PfPMT.*

3.3. 3-(p-substituted phenyldiazenyl)-5, 7-di(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine. 3(a-r)

18 Pyrazolo [1,5-a]pyrimidine analogues (5,7-di(hetaryl-2-yl)-3-((4-subestitutedphenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine.) were docked into the active site of enzyme. Regarding the binding interactions, compounds have similar pattern of hydrogen-bonding, as the oxygen in furan ring is hydrogen-bonded to the nitrogen atom of ASN137 as shown in figure 2.

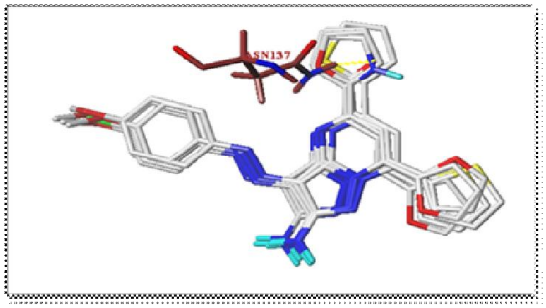


Figure 2: Ensemble of the docked Pyrazolo[1,5-a]pyrimidine within PfPMT binding site. It is revealed a same trend of hydrogen bonding (yellow dashed lines) with ASN137residue.

3.4 4, 6-di(hetar-2-yl)pyrimidin-2-amine. 4(a-e)

5 Pyrimidine analogues (4,6-di(hetar-2-yl)pyrimidin-2-amine) were docked into the active site of enzyme. The 4d compound has been selected from the docked pyrimidine, on basis of scoring and binding interaction. The hydrogen bond has been observed between the amino group of pyrimidine and negative oxygen of ASP (2.43Å).

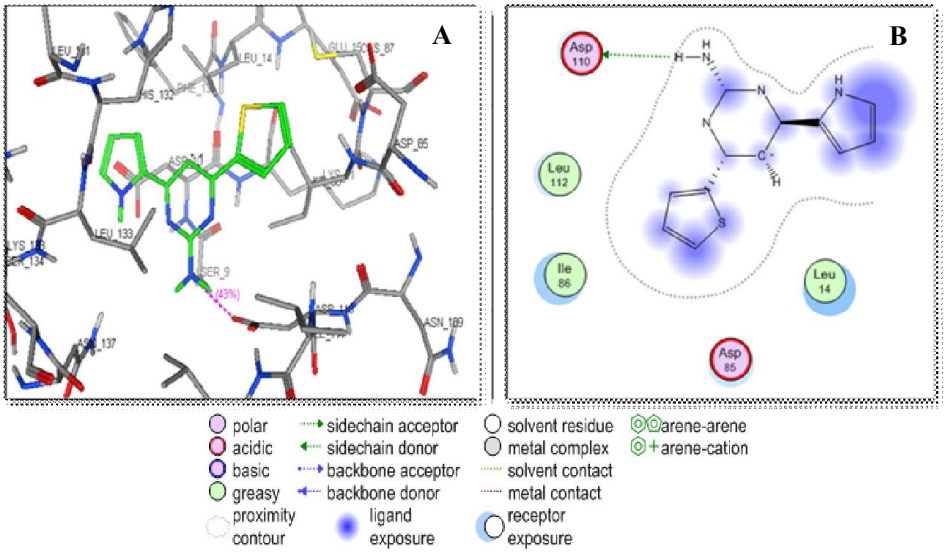


Figure 3: Binding interactions of 4,6-di(hetar-2-yl)pyrimidin-2-amine**.** (A) Binding mode of **c**ompound 4d (shown as sticks, carbons colored in green, nitrogen in blue and sulfur in yellow) within the active site of PfPMT. (B) 2D picture of pyrimidine 4d within the active site of PfPMT.

3.5 Ethyl 2-oxo-4,6-di(hetar-2-yl)cyclohex-3-encarboxylate. 5(a-e)

Docking results of compound 5e is visualized (figure 4). Three hydrogen bonds have been observed, the first one is formed between the carbonyl group of the cyclohexenone moiety and the NH of ILE111 (1.9Å). The second hydrogen bond between the ester carbonyl group of the compounds and the NH of the ILE86 (1.90Å), the third hydrogen bond between NH of the pyrrol ring and OH of the ASP110 (2.39 Å), The second and third observation could be used to explain the absence of those hydrogen bonds when the result was visualized using the MOE but was observed when visualized with SYBYL.

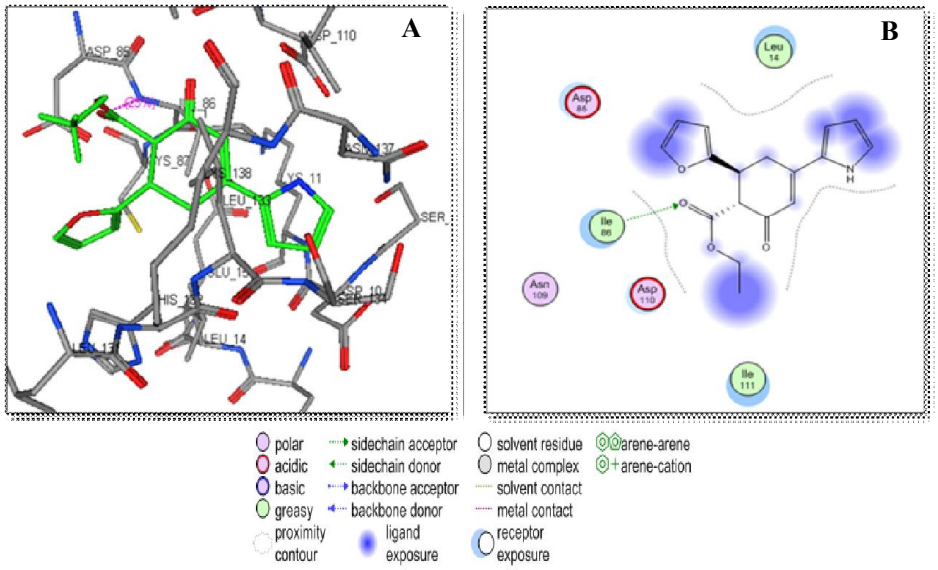


Figure 4: Binding interactions of Cyclohexenone**.** (A) Binding mode of **c**ompound 5e (shown as sticks, carbons colored in green nitrogen in blue and oxygen in red) within the active site of PFPMT. The carbonyl group (C2) of the compound interacts with ILE111 amino group (B) 2D picture of cyclohexenone 5e within the active site of PfPMT.

3.6 Heterocyclic Chalcone (1e)

1-(1H-pyrrol-2-yl)-3-(furan-2-yl)propen-1-one has been selected from the docked heterocyclic chalcone, on basis of scoring and binding interaction. The docking result of compound 1e is shown in (figure 4.4). Docking results have revealed hydrogen bond between NH of pyrrol ring with carbonyl of THR197 with a distance of 1.99Å. Figure (5)

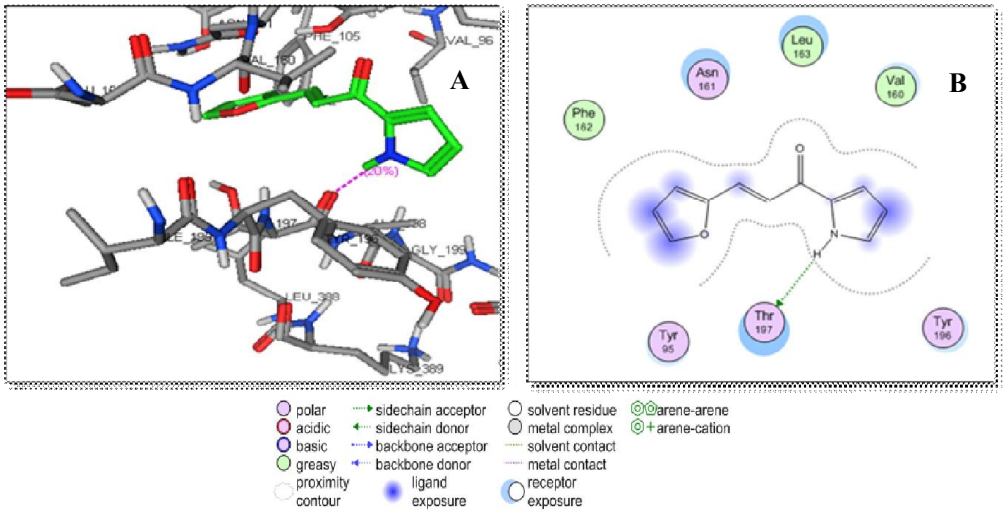


Figure 5: Binding interactions of Heterocyclic Chalcone**.** (A) Binding mode of **c**ompound 1e (shown as sticks, carbons colored in green, oxygen in red, and nitrogen in blue) within the active site of PfMNT. (B) 2D picture of Heterocyclic Chacone within the active site of PfMNT.

3.7 3-(p-substituted phenyldiazenyl)-5,7-di(thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-2-amine. 3r

The 3r compound has been selected from the docked pyrazol[1,5-a]pyrimidine, on basis of scoring and binding interaction. Three hydrogen bonds have been observed. The first between the amine group of compound and carbonyl group VAL160 (1.91Å), the second between of pyrazolo[1,5-a]pyrimidine with OH group of the THR197 (2.51 Å) and the third hydrogen bond between diazenyl with the THR197 (2.73 Å).The second and third observation could be used to explain the absence of those hydrogen bonds when the result was visualized using the MOE but was observed when visualized with SYBYL. Figure (6)

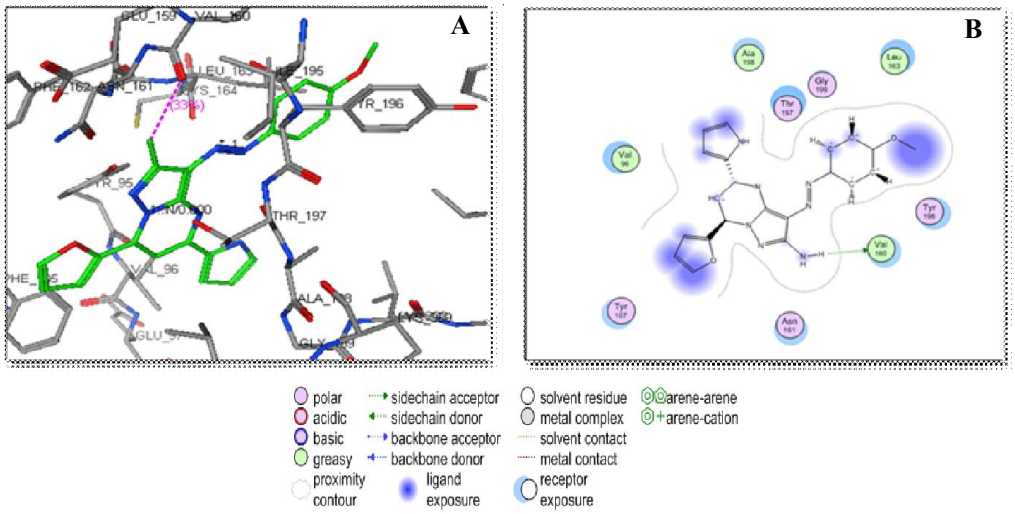


Figure 6: Binding interactions of Pyrazolo[1,5-a]pyrimidine**.** (A) Binding mode of **c**ompound 3r (shown as sticks, carbons colored in green, nitrogen in blue and oxygen in red) within the active site of PfNMT. (B) 2D picture of pyrazolo[1,5-a]pyrimidine 3r within the active site of PfNMT.

3.8 4,6-di(het-2-yl)Pyrimidine-2-amine

The 4d compound has been selected from the docked 4,6-di(thiophen-2-yl)pyrimidin-2-amine, on basis of scoring and binding interaction. One hydrogen bond has been observed between NH of pyrrol ring of the compound and carbonyl group of VAL160 (1.95Å). Figure (7)

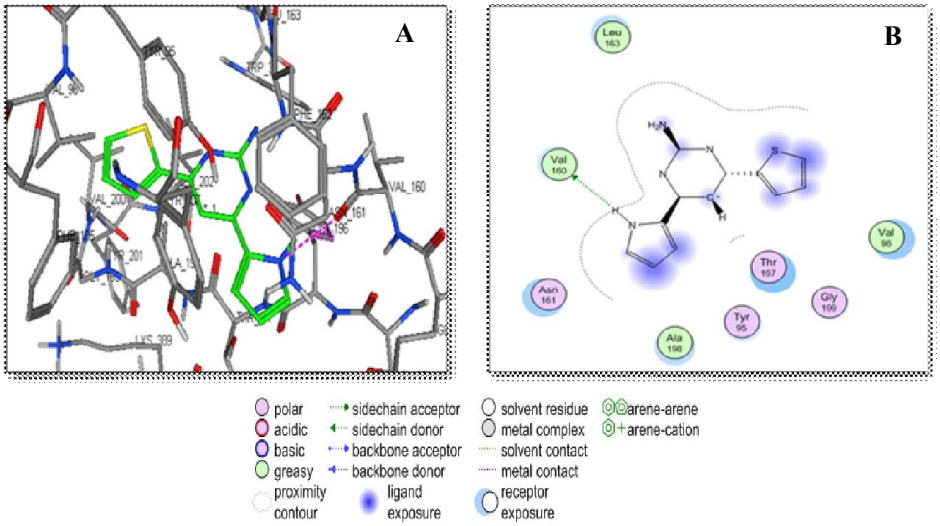
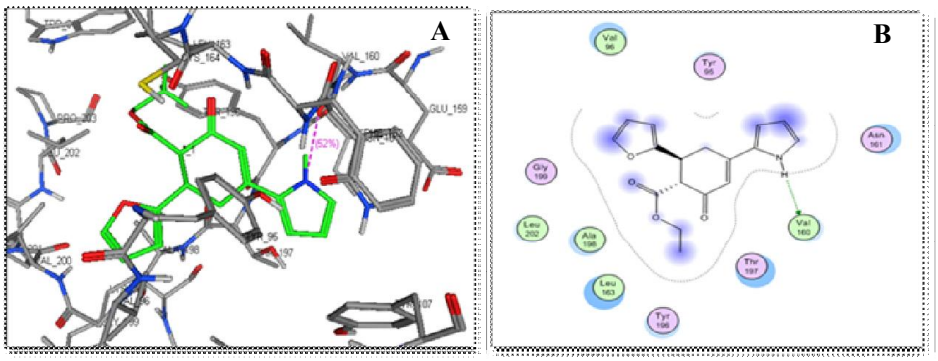


Figure 7: Binding interactions of 4,6-di(hetar-2-yl)pyrimidin-2-amine**.** (A) Binding mode of **c**ompound 4d (shown as sticks, carbons colored in green, nitrogen in blue and sulfur in yellow) within the active site of PfNMT. (B) 2D picture of pyrimidine 4d within the active site of PfNMT.

3.9 Ethyl 2-oxo-4,6-di(hetar-2-yl)cyclohex-3-encarboxylate. 5e

This compound has been selected from the docked cyclohexenone, on basis of scoring and binding interaction. The docking results of compound 4e (figure 8). One hydrogen bond has been observed between the NH of the pyrrol ring and OH of the VAL160 (1.78 Å). Figure (8)



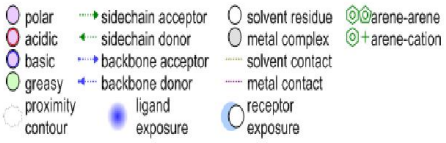


Figure 8: Binding interactions of Cyclohexenone**.** (A) Binding mode of **c**ompound 5e (shown as sticks, carbons colored in yellow and oxygen in red) within the active site of PfMNT. The amino group of pyrrol ring of the compound interacts with VAL160. (B) 2D picture of cyclohexenone 5e within the active site of PfMNT

Phosphoethanolamine N-methyltransferase (PMT) is an emergingnbiochemical target in *P. falciparum*. Plasmodium PMT (PfPMT) is an S-adenosylmethionine (SAM)-dependent methyltransferase that converts phosphoethanolamine (pEA) into phosphocholine
(pCho). In the case of Plasmodium, rapid membrane biogenesis and phospholipid biosynthesis are required for growth and replication when it infects human erythrocytes.[17,18]
The enzyme N-myristoyltransferase (NMT) represents a promising drug target [19] because it has been shown to be essential in many organisms.[20]

3.10 Heterocyclic chalcone

The synthesized heterocyclic chalcones are different on 1,3-di hetaryl ring. It has been noticed that hetaryl rings didn't play a crucial role on the activities of these compounds with the active site of Phosphoethanolamine N-methyltransferase (PMT) enzyme but the carbonyl group was played a crucial role on the activities of these compounds.
The hetaryl rings have played a crucial role on the activities of these compounds with the active site of N-myristoyltransferase (NMT) enzyme.
The pyrrol ring in 1e compound has been shown ΔG value -5.50 kcal mol^{-1} in PDB code 4B12 is better than 1d compound with ΔG value -4.56 kcal mol^{-1} that indicates that the thiophene ring decreases the activity of the compound with active site of the N-myristoyltransferase (NMT) enzyme.

3.11 Pyrazolo[1,5-a]pyrimidine

5,7-di(hetar-2-yl)-3-((4-substituted phenyl)diazenyl)pyrazolo[1,5-a]pyrimidin-2-amine, the methoxy substitutent at C3 has played a crucial role on the activities of the compounds with the active site of Phosphoethanolamine N-methyltransferase (PMT) enzyme. The order of this compound with 4FGZ according to docking was 5.64 corresponding ΔG value -7.99 kcal mol^{-1}. The substitutent at C3 and 5,7-di(hetar-2-yl) ring are played a crucial role on the activities of the compounds with the active site of N-myristoyltransferase (NMT) enzyme. Compounds such as 3c, 3d, 6m and 3r have shown v-good activity with the active site of the N-myristoyltransferase (NMT) enzyme. The order of these compounds according to docking poses was 6.48, 6.49, 6.02 and 6.50 corresponding ΔG values -8.80,-8.82,-8.18 and -8.83 kcal mol^{-1} respectively.

3.12 4,6-di(hetar-2-yl) pyrimidin-2-amine

The amino group is played a crucial role on the activities of the compounds with the active site of Phosphoethanolamine N-methyltransferase (PMT) enzyme. compound such as 4d shown good activity with the active site of Phosphoethanolamine N-methyltransferase (PMT) enzyme PDB code 4FGZ. The order of this compound according to docking was 4.41 corresponding ΔG values.
-5.98 kcal mol^{-1} there are no effect of hetaryl rings. The compound 4d with PDB code 4B12, the pyrrol ring at C4 is played a crucial role on the activities of the compounds with the active site of N-myristoyltransferase (NMT) enzyme. The order of this compound according to docking poses was 3.82 corresponding ΔG values -5.19 kcal mol^{-1} respectively.

3.13 Cyclohexenone

Ethyl 2-oxo-4,6-di(hetaryl-2-yl)cyclohex-3-encarboxylate derivatives. compound 5e shows the highest activity with Phosphoethanolamine N-methyltransferase (PMT) enzyme. The order of this compound according to docking is 6.26 corresponding to ΔG value -8.55 kcal mol^{-1}. The ester group has played a crucial role on the activities of the compounds.

On the other hands compound 5e also is having highest activity with active site of enzyme N-myristoyltransferase (NMT) here the amino group of the pyrrol ring interacts with the enzyme thus playing a crucial role in activity of the compound. The order of this compound according to docking was 5.88 corresponding ΔG value -7.99 kcal mol^{-1}. The compound 5a is less active compared with 5e, followed by 5b then 5d. Through this result the activity of these compounds with the active site of N-myristoyltransferase (NMT) enzyme depend on electro-negativity of hetero atom of hetaryl ring.

3. CONCLUSION

The parent aromatic compounds of this family are pyrrole, furan, and thiophene. These compounds have played an important role in increasing the biological activity of the compounds seen in the inverse docking results. The impact of these five membered rings appeared clearly in the biological activity of cyclohexenones.
During this study about 33 compounds were synthesized and designed using molecular docking technique; the compounds have been designed, synthesized and screened for 94 enzymes selected from PDB. Two enzymes have been chosen depending on the score. The docking and the biological activities have been remarkably consistent in terms of docking binding energies (kcal/mol^{-1}) and percent of inhibition. Docking study on those compounds has provided valuable information about the structural basis of binding. This study has also supported the structure – activity relationships, highlighting the importance of and hydrophobic, beside the hydrogen bonds between the compound and active site of the enzyme

4. ACKNOWLEDGEMENT

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