Open Access Research Paper

ISSN: 2349-9818
September - October 2023, Vol. 10 (5), 18-49

Tropical Journal of Pharmaceutical and Life Sciences
(An International Peer Reviewed Journal)
Journal homepage: http://informativejournals.com/journal/index.php/tjpls

Synthesis, Docking and Evaluation of Pyrimidine Derivatives as Anti-Malarial Agents

Amit Kumar Sen*[1] and Rakesh Kr. Jat[2]
[1]Research Scholar, [2]Principal (Professor), Institute of Pharmacy,
Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu (Rajasthan)-333001

ARTICLE INFO:
Received: 24th August 2023**; Received** in revised form: 9th Sept. 2023**; Accepted:** 18th Sept. 2023**; Available online:** 24th Sept. 2023.

Abstract

Malaria is endmic disease of tropical and subtropical contries like India, Pakistan, Srilanka, Bangladesh, South Africa etc. There are lot of fatalities and causalities due to malaria every year. There are lot of drugs have been synthesized for controlling this intermittent fever like chloroquine, hydroxychloroquine, pamaquine, primaquine, artimisininine, sulphadoxine, pyrimethamine, dapsone. The pyrimidine derivative synthetic drugs like sulphadoxine and pyramethamine have potential role to treat malaria with fever side effects. The lead molecule is pyrimdine and various groups are attached to this nucleus for optimizing the activity of lead nucleus and its derivative to treat this dangerous disease.

The main causative organisms are plasmodium falciparm, plasmodium vivex, plasmodium malariae and ovale that cause malaria in patient and transmitted in blood after bitting of female anopheles mosquito that act as vector for plasmodium species.

The docking studies are also performed by software and proper lead compound is identified with docking studies. The synthesis of compounds were carried out in laboratories with microwave synthesis and newer techniques that are fast and less time consuming of better yield of products. Structure activities relationships are studied and optimum activities are obtained by replacing different functional groups and other groups.

Keywords: Molecular docking, Pyrimidine Derivatives, Anti-Malarial Agents, Protozoan disease, Computer aided drug design

Introduction

Malaria is protozoan disease that is caused by plasmodium parasite. The word is derived from mala + aria = (bed air). The species is transmitted by female Anopheles mosquito. Four species are available: - 1) plasmod falciparum (tertian fever) -65% 2) plasmodium vivex (benign tertian malaria)-20% 3) plasmodium malariae (quartan malariae) 4) plasmodium Ovale. When female Anopheles bites, the sporozoites enter in the blood circulation and reach to the liver. In the liver sporozoites mature (average 5-7 days) in the form of

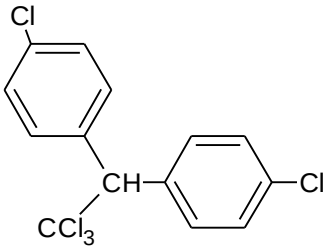
***Corresponding Author:**
Amit Kumar Sen
Institute of Pharmacy,
SJJT University, Jhunjhunu,
Rajasthan-333001, India

schzonts. The schizonts again enter into the circulatory system and invade the erythrocytes in the form of merozoites. After 48 hours these merozoites rupture the erythrocytes that cause chills fever and release of gametocytes. These gametocytes again taking by mosquito and form zygotes and attack the next person.

There are four types of chemotherapy: -

1) **Tissue schizonticides**:- these eradicate extraerythrocytic liver tissue stage of parasites which prevent the entry of parasite in the blood.
2) **Blood schizonticides**:- these destroy the erythrocytics stage of parasite. Mainly chloroquine acts on this phase.
3) **Gametocytocides**:- these kill the sexual forms of the plasmodia which are transmittable to the Anopheles mosquito.
4) **Sporontocides**:-these act against sporozoites and are capable of killing these organisms as soon as enter in the blood stream.

Malaria can be controlled by three different ways. (1) vector elimination by using insecticides like DDT (dichloro-diphenyl-tichloroethane)



2) Drug therapy: -Drug therapy has challenges as the development of antibiotics e.g. resistance to the antibiotics and some adverse drug reactions. (3) Vaccination

Materials and Methods

Quantitative Structure Activity Q.S.A.R.)

This had been near about 50 years since the quantitative structure- exertion relationship (Quantitative Strucute Activity Relationship) paradigm first entered the practice of pharmaceutical chemistry, agrochemistry, toxicology, and ultimately most angles of chemistry85. This stay powers can be concerend to the strengthening of its original hypotheses that exertion was a working of structural formula as described by hydrophobic capacity, electronic attribute, along with sterical parcel as with the fast - fire and extensive progress in computational methods along with computure technology that have been replaced to refine and delineate Quantitative Strucute Activity Relationship is the origination of quantitative medication configuration grounded on the way that the regular packages of the composites are an element of its physiological boundaries.

Computer Aided Drug Design

Computer aided molecular design is frequently divided into fields that concentrate on ligand- or structure-based approaches.

A structure-based approach can also be used when sufficient information about the natural target's structure and list point is available or deducible. In this method, specific ligand-receptor relationships are studied to assist in the identification of new molecules that exert force toward the target. However, knowledge of the target's structure is still limited, if.

Although ligand- grounded design officially encompasses any number of computational methods that only consider the structure of known and implicit ligands, it has become largely synonymous with pharmacophore modeling96-97 and quantitative structure- exertion connections Quantitative Structure exertion Relationship).98-99 Although numerous academic and pharmaceutical discovery laboratories have pioneered these fields for several decades, there is also a significant reliance on commercially available tools like Catalyst 110,111, DISCO112, Any ligand-based method's relative success can be attributed to a number of things, such as its novelty, adaptability, integration with other software and experimental workflows, and demonstrated

scientific validity. However, it should be noted that when a piece of marketable software fails to deliver satisfactorily in a critical review, good performance in these areas does not automatically help the software's devaluation

DOCKING

Molecular docking is a method which preferred orientation of one molecule which bound to each other to form a stable complex into a second.[117] Molecular docking helps to study

"ligand receptor interaction for identifying important amino acid residues of the receptor. It helps to obtained most energetically stable geometry of ligand receptor complex, so that the interaction energy for ligand receptor complex is minimum. This minimum interaction energy is expressed in terms of different scoring function such as dock score. Prediction of affinity of a ligand towards the receptor is called as scoring. The hypothesis is that the ligand which produces minimum score of interaction energy would be the highest pharmacologically active compound.

Proteins, nucleic acids, carbohydrates, and lipids play an important role in signal transduction, such as the relation between biologically relevant molecules. Furthermore, the type of signal produced may be affected by the relative orientation of the two interacting partners (e.g., agonism vs antagonism). Therefore docking is useful for predicting both the type and strength of signal produced.

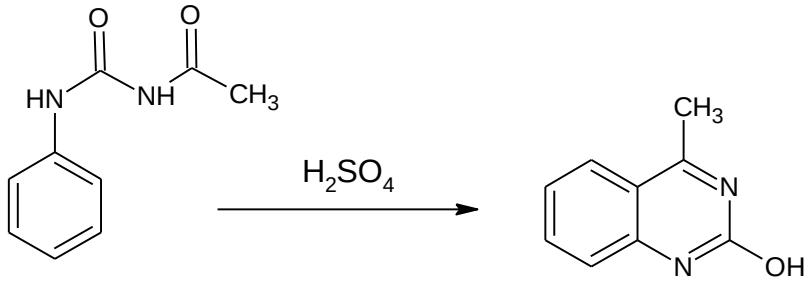
Evaluating The Potential Biological Activity of Some Novel Quinazoline Devices

A Decibel M. P. apparatus was being utilized to find out melting points, which were not adjusted for. All reactions were monitored using pre coated TLC plates using varied mobile phase. We used Thermo Scientific NICOLET 10 spectrophotometers with KBr pellets to capture the infrared spectra. The Bruker Avance II 400 NMR spectrophotometer was used to record 1H NMR spectra. The API- 4000 Quadrupole Mass Spectrometer (ESI) was used to analyse the mass spectrum of substances. The Carlo Erba 1106 CHN analyzer was used for elemental analysis. These techniques are used to determine the raw material identification.

5.1.1 Synthesis of 2- hydrazino - 4 -methylquinazoline (1)

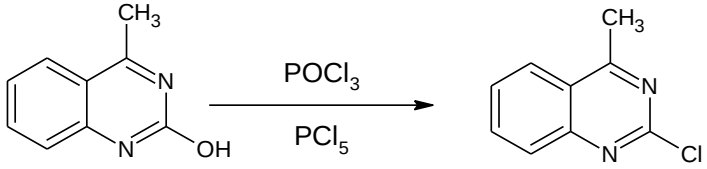
- **Step I: Preparation of 2 - hydroxy - 4 -methylquinazoline**

Sulfuric acid (20 ml) was treated with 25 g (0.1425 mol) of acetoacetanilide for 30 minutes at a temperature below 35 °C. Ammonium hydroxide was used to bring the suspension to a neutral pH. The methanol-derived raw material was filtered, cleaned with water, and then crystallised again. In terms of yield, 83% was discovered, and the melting point was between 220-222 ° C.



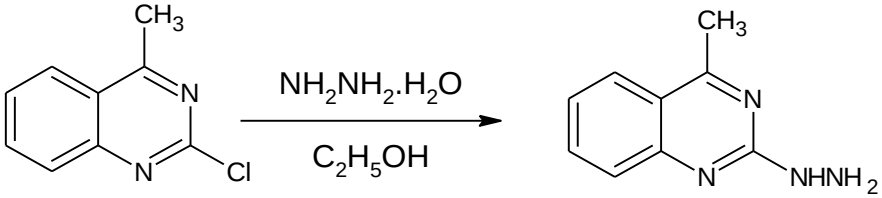
- **Step II: Preparation of 2 - chloro- 4- methylquinazoline**

It took 2 hrs of refluxing a combination of 2 -hydroxy 4-methylquinazoline 4.14g (0.026mol), 9.97g (0.065mol), and 5.41g (0.026mol) of phosphorus pentachloride to produce the final product. After cooling, the reaction mixture was put into an ice-water bath and let to stand for the night. Acidic NaHCO 3 was used to neutralise the pH. The solid was filtered, water washed, dried, and ethanol was used to recrystallize it. One-seventh of a percent of the yield was discovered, and the melting point ranged from 60-61 degrees Celsius.



➢ **Step III: Preparation of 2 -hydrazino- 4 - methylquinazoline (1)**

At 5- 10 C, the 10g of hydrazine hydrate (200mmol) was slowly added to 10ml of HCl (10ml). Then 40ml of ethylene glycol was added, followed by 8.88g (50 mmol) of 2 - chloro- 4 - methylquinazoline, and the mixture was heated under reflux for 2 hours. After cooling, a fine crystalline material separated out, which was then filtered, water washed, and ethanol crystallised again. The melting point was between 140 and 142°C, with a yield of 61%.

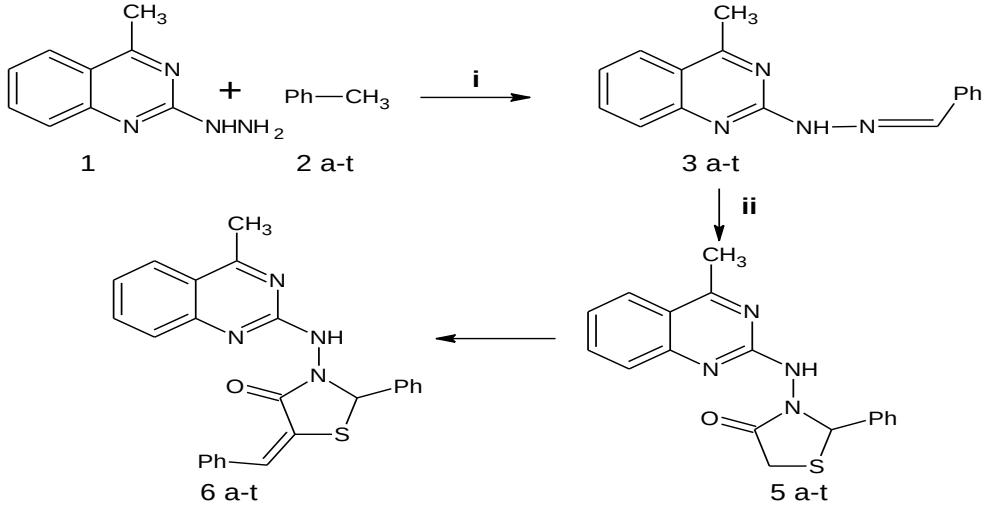


Synthetic strategies adopted

Various substances were synthesised in this investigation using the four synthetic techniques listed below:

➢ **SERIES 1**

Scheme 5.1 depicts the whole series 1 synthetic route, while Table 5.1 provides a list of the produced chemicals.



Scheme: 5.1:-Quinazoline-thiazolidinone arylidene hybrids: synthesis and characterization(5 ar)

Table 5.1: List of synthesized derivatives of series 1 (5- aryl-idene - 3 -(4 - methylquinazolin - 2 - ylamino) -2 - arylthiazol-idin -4 - one)

S.No	Comp	Ar_1	Ar_2
1	5a	C_6H_5	C_6H_5
2	5b	C_6H_5	p-ClC_6H_4
3	5c	C_6H_5	p-$CH_3C_6H_4$
4	5d	C_6H_5	p-ClC_6H_4
5	5e	p-ClC_6H_4	C_6H_5
6	5f	p-ClC_6H_4	p-ClC_6H_4
7	5g	p-ClC_6H_4	p-$CH_3C_6H_4$
8	5h	p-ClC_6H_4	p-$OCH_3C_6H_4$
9	5i	p-$CH_3C_6H_4$	C_6H_5
10	5j	p-$CH_3C_6H_4$	p-ClC_6H_4
11	5k	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$
12	5l	p-$CH_3C_6H_4$	p-$OCH_3C_6H_4$
13	5m	p-$OCH_3C_6H_4$	C_6H_5
14	5n	p-$OCH_3C_6H_4$	p-ClC_6H_4
15	5o	p-$OCH_3C_6H_4$	p-$CH_3C_6H_4$

16	5p	p-$OCH_3C_6H_4$	p-$OCH_3C_6H_4$
17	5q	2-thienyl	C_6H_5
18	5r	2-thienyl	p-$CH_3C_6H_4$

- **Common method of preparation for 1 - ary lidene - 2 -(4 - methylquinazolin - 2 - yl)hydrazines (3a - e) :**

Mixture 1, including 2 – hydrazine – 4 – methylquinazoline, compound 1, and various aldehydes of aromatic nature in EtOH (20 ml) was refluxed in appearance of glacial CH_3COOH uptosix hrs. Quantitatively, resultant solution had been concentrated with pouring it over ice.

Table 5.2: List of arylaldehyde List of arylaldehydes (2a -e) used

S.No	Compound	Quantity(g)
1	B enaldehyde (2a)	1.17
2	p-chlorobenzaldehyde (2b)	1.55
3	p-methylbenzaldehyde (2c)	1.32
4	p-methoxybenzaldehyde (2d)	1.50
5	Thiophene-2-cabaldehyde (2e)	1.23

- **Common preparation Technique forcompound [3-(4- methyl-quinazolin -2 – ylamino)- 2 - aryl thiazolidine - 4 - on (4 a-e)]**

Mercapto ac etic acid (0.003 mol) and a small quantity of anhydrous ZnCl 2 were added to product (3) solution (0.002 mole) in 1,4 – di-oxane (60 millilitter). Sodium bicarbonate solution had been used to neutralise the mixture after it had been refluxed for 10 to 12 hours. The surplus solvent had been distilled off and the mixture had been cooled. Cold water was used to wash the solid material after it had been filtered. Re-crystallization of the resultant solid in ethanol was carried out (99 percent).

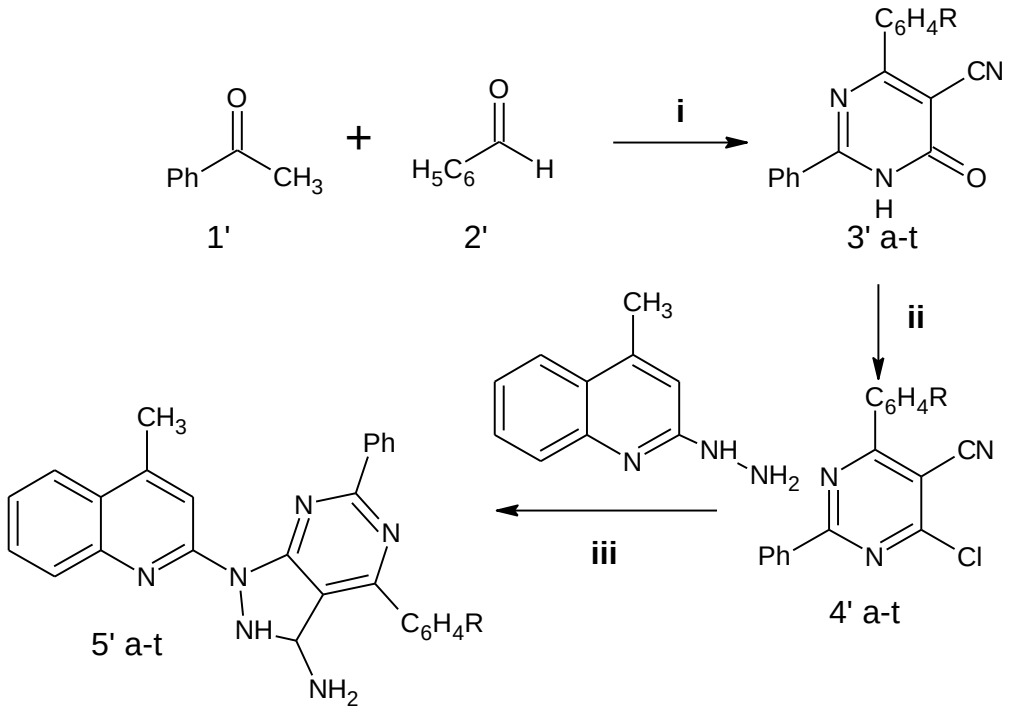
Following a 12-hour reflux process, the solution was emptied into a container filled with ice-cold water and the resulting named compounds were analysed. Recrystallization from dioxane was used to purify the final product, which was then further purified using the same method.

Thiazolidin-ones along with their aryl-idene derivative had been prepared and synthesis was carried out satisfactorily according to the prescribed process. Conversion of 2-NH-NH_2 – 4 methylquinazoline along various organic aldehydes under acid circumstances yielded compounds (3a -e). The thioglycolic acid reaction in dioxane was used to convert the hydrazine intermediates to thiazolidinone (4a -e). After a long process of reaction in Glacial acetic acid, the desired chemicals (Z) - 5- Ary lidene - 3- (4 –methylquinazoline -2-ylamino)- 2- aryl thiazolidine - 4 had been produced.

Due to the presence of a carbonyl group, a second distinctive FTIR signal was identified in the region of 1650-1660 cm - 1 for compounds (4a-e). The synthesis of the thiazolidinone ring was verified by 1H NMR singlets for C -CH 2-S and N-CH-S at 5.29 and 6.77 ppm. It was verified that the reaction had progressed from the thiazolidinone derivatives to the desired target arylidene derivatives when singlet disappeared at 5.29 for two protons and fresh singlet emerged at 5.88 for a single proton. In the end, mass and elemental analysis revealed the structures of all produced substances.

5.1.3 SERIES 2

Scheme 5.2 outlines the whole series 2 synthetic method, and the list of chemicals created is provided in Table 5.6 (Figure 5.2).



Scheme 5.2:- Synthesis of Quinazoline - pyrazolopyrimidine Analogues

Table 5.6 List of synthesized derivatives of series 2(1- (4– methylquinazoline - 2 – yl) – 4,6 – di-aryl - 1H – pyrazolo[3, 4 -b]pyrimidine - 3 -amines)

S.No.	Comp	Ar	Ar’
1.	5’a	C_6H_5	C_6H_5
2.	5’b	C_6H_5	p-F C_6H_4
3.	5’c	C_6H_5	p-$OCH_3C_6H_4$
4.	5’d	C_6H_5	2-thienyl
5.	5’e	p-$CH_3C_6H_4$	C_6H_5
6.	5’f	p-$CH_3C_6H_4$	p-F C_6H_4
7.	5’g	p-$CH_3C_6H_4$	p-$OCH_3C_6H_4$
8.	5’h	p-$CH_3C_6H_4$	2-thienyl
9.	5’i	p-$CH_3C_6H_4$	p-$CH_3C_6H_4$
10.	5’j	p-$OCH_3C_6H_4$	C_6H_5
11.	5’k	p-$OCH_3C_6H_4$	p-F C_6H_4
12.	5’l	p-$OCH_3C_6H_4$	p-$OCH_3C_6H_4$
13.	5’m	p-$OCH_3C_6H_4$	2-thienyl
14.	5’n	p-$OCH_3C_6H_4$	p-$CH_3C_6H_4$
15.	5’o	p-ClC_6H_4	C_6H_5
16.	5’p	p-ClC_6H_4	p-F C_6H_4
17.	5’q	p-ClC_6H_4	p-$OCH_3C_6H_4$
18.	5’r	p-ClC_6H_4	p-$CH_3C_6H_4$
19.	5’s	p-F C_6H_4	C_6H_5
20.	5’t	p-F C_6H_4	p-$CH_3C_6H_4$

- **Preparation of 2 - oxo - 4, 6 – di-phenyl -1,2 - di-hydropyrimidinee - 3 - carbon itrile derivative (3'a- t):**

According to the literature, the synthesis was carried out. Ammonium acetate, 6.17gm (0.08mol), ethyl cyanoacetate, 1.13gm (0.01mol), aromatic aldehydes (0.01mol), and ketones (0.01mol) were dissolved in n-butanol (20ml) and refluxed for three hours. After filtering, the ethanol was added.

Table 5.7: List of ketones used

S.No	Name	Quantity(g)
1	Acetophenone	1.20
2	p-methylacetophenone	1.34
3	p-methoxyacetophone	1.50
4	p-chloroacetophenone	1.55
5	p-fluoroacetophenone	1.38

Table 5.8: List of aldehydes used

S.No	Name	Quantity(g)
1	Benzaldehyde	1.06
2	p-flourobenzaldehyde	1.24
3	p-methoxybenzaldehyde	1.36
4	Thiophene2-cabaldehyde	1.12
5	p-methylbenzaldehyde	1.20

Table 5.9 Characterization Data of "2 -oxo - 4,6 - diaryl - 1,2 -dihydropyrimidine -3 -carbonitrile derivaties (3'a-t)"

S.No.	Comp	%yield	M.pt. (^{o}C)
C11	3'a	85%	292-294
12	3'b	88%	295-296
13	3'c	79%	301-303
14	3'd	83%	286-288
15	3'e	76%	298-299
16	3'f	81%	293-294
17	3'g	79%	308-310
18	3'h	77%	289-290
19	3'i	80%	300-302
20	3'j	75%	309-310
21	3'k	76%	303-304
22	3'l	77%	315-316
23	3'm	81%	293-295
24	3'n	77%	301-302
25	3'o	82%	303-305
26	3'p	81%	309-310
27	3'q	79%	305-306
28	3'r	73%	298-299
29	3's	79%	288-289
30	3't	76%	299-301

- **Preparation of 2- chloro -4,6 - dip henylnicotinonitrile derivative (4'a- t):**

Pyrimidone product 3 (0.005 mol), p hosphorus pentachloride (hosphorus pentachloride), and phosphorus oxychloride (phosphorus oxychloride) were heated for three hours in a water bath. It was next necessary to neutralise the reaction mixture with a weak ammonia solution, which was placed into an ice-cold bath. The chloro derivative, - t), was prepared by filtering and recrystallizing the isolated solid from ethanol.

Table 5.11: Characterization Data of 2 - chloro - 4,6 - diaryl - 1,2 -dihydropyrimidinee -3 - carbonitries (4'a - t)

S.No.	Comp	%yield	M.pt. (°C)
1	4'a	65%	160-162
2	4'b	68%	167-169
3	4'c	69%	180-181
4	4'd	70%	173-175
5	4'e	71%	160-161
6	4'f	65%	171-172
7	4'g	70%	166-168
8	4'h	62%	189-190
9	4'i	71%	181-182
10	4'j	59%	173-175
11	4'k	67%	176-177
12	4'l	66%	161-163
13	4'm	72%	168-169
14	4'n	65%	188-189
15	4'o	70%	172-173
16	4'p	68%	182-183
17	4'q	63%	167-169
18	4'r	69%	175-177
19	4's	61%	166-168
20	4't	63%	171-172

- **Preparation of "1 - (4- methylquinazolin - 2 - yl)- 4,6 - diaryl - 1H - pyrazolo[3,4-b]pyrimidine - 3- amine derivatives (5'a- t)" :**

According to process outlined, the prepared products have been created. It was added with excess of 2 ith excess of 2-hydrazino-hydrazino- 4-methyl quinazolone quinazolone (1), 2.07g (0.012 moles), and the mixture was refluxed for 12 hours with this amount of chloro derivatives (0.03 moles). 5'a-t was obtained by cooling, filtering, and re-crystallizing the solution from acetic acid.

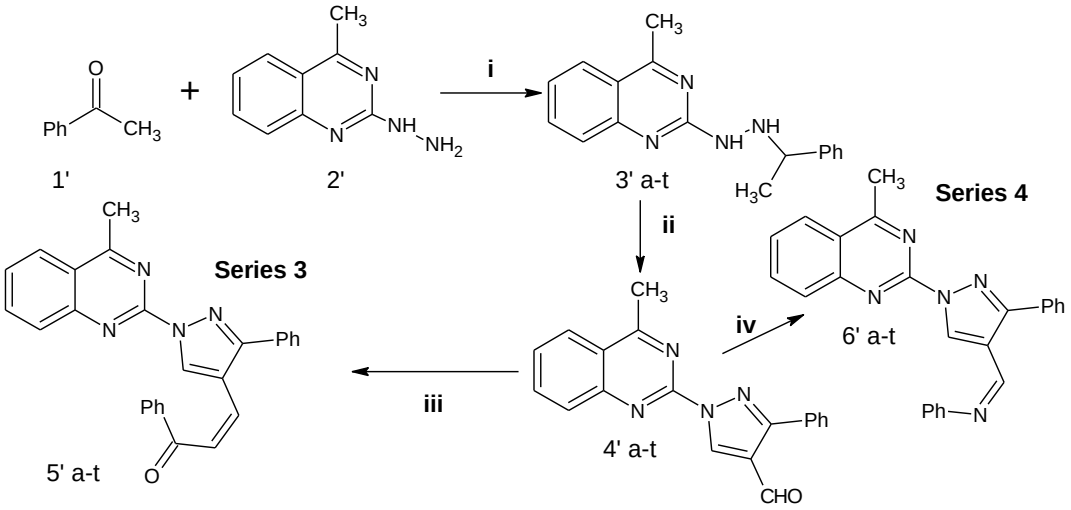
- **Data Interpretation of "1 - (4 -methylquinazolin - 2 - yl)- 4,6 - diaryl -1H - pyrazolo[3,4-b]pyrimidine -3 - amines (Series 2)"**

Various organic aldehydes, $CNCH_2COOC_2H_5$, along with extra amount of CH_3COONH_4 in butyl alcohol were combined with substituted acetophenones to produce the appropriate derivatives (3'a-t). IR spectrum of substances validated the 70 to generate matching derivatives - t). There were absorption bands at 3439 cm-1, 2223 cm-1 and 1640 cm-1, respectively, in the infrared spectra of the chemicals, which indicated that the synthetic product had been synthesised. The pyrazolo - pyrimidinee compounds (5'a - t) were obtained by reacting the chloro derivatives with the 2-hydrazino-4-methylquinazoline (1). There are two peaks in the IR spectra that correlate to C=N at 1601cm-1 and 3454 and 3342 cm-1, respectively, which correspond to the NH

2 band. 1 H NMR showed that NH2 had been present in the final target product because of a large peak at 5.60. The structure of produced chemicals was validated by their elemental analysis and spectral data.

SERIES 3

List of chemicals produced in Table 5.13 is shown in Scheme 5.3, which outlines the whole synthetic process of series 3.



Scheme 5.3:- Synthesis of Chalcone (5''a-v) schiff's base (6''a-s). Condition and chemicals: i) "1 - 2 drops Glacial acetic acid, Ethanol, Stir, 60°C, 6 hr. ii) DMF, POCl3, Stir, 55 - 60°C, 5 hr. iii) Acetic acid, Sodium acetate, re flux, 4 hours iv) Glacial acetic acid, Ethanol, reflux, 8 hr.

Table 5.13: List of synthesized derivatives of series 3 "(3 - (1- (4- methylquinazolin -2 - yl) - 3 - aryl- 1H -pyrazol -4 - yl)- 1 - arylprop- 2 -en - 1 - ones)"

S.No.	Comp	Ar	Ar'
1.	5"a	C_6H_5	C_6H_5
2.	5"b	C_6H_5	p-$CH_3C_6H_4$
3.	5"c	C_6H_5	p-$OCH_3C_6H_4$
4.	5"d	C_6H_5	p-ClC_6H_4
5.	5"e	p-ClC_6H_4	C_6H_5
6.	5"f	p-ClC_6H_4	p-ClC_6H_4
7.	5"g	p-ClC_6H_4	p-$CH_3C_6H_4$
8.	5"h	p-ClC_6H_4	p-$OCH_3C_6H_4$
9.	5"i	p-ClC_6H_4	2-thienyl
10.	5"j	p-ClC_6H_4	C_6H_5
11.	5"k	p-$OCH_3C_6H_4$	p-$OCH_3C_6H_4$
12	5"l	p-$OCH_3C_6H_4$	p-$CH_3C_6H_4$
13	5"m	p-$OCH_3C_6H_4$	p-ClC_6H_4
14	5"n	p-$OCH_3C_6H_4$	2-thienyl
15	5"o	2-thienyl	C_6H_5
16	5"p	2-thienyl	p-$OCH_3C_6H_4$
17	5"q	2-thienyl	p-$CH_3C_6H_4$
18	5"r	2-thienyl	p-ClC_6H_4
19	5"s	$C_6H_4CH_3$	C_6H_5
20	5"t	$C_6H_4CH_3$	p-$OCH_3C_6H_4$
21	5"u	$C_6H_4CH_3$	p-$CH_3C_6H_4$
22	5"v	$C_6H_4CH_3$	p-ClC_6H_4

- **General experimental method for preparation of 1 - (4- methylquinazolin - 2 – yl)- 2 - (1-arylethylidene)hydrazines (3''a- e)**

Various ketones were added for a combination of 2-hydrazine-4-methylquinazoline and products (1) 2.07 g (0.012mol) in EtOH (20 ml) (0.012 mol). For six hours at 60°C, the mixture was mixed with one drop of glacial acetic acid. Filtration and ethanol washing were used to generate the final solution.

Table 5.14: List of Acetophenones used

S.No.	Name	Quantity(g)
1	Acetophenone (1"a)	1.44
2	p-chloroacetophenone (1"b)	1.86
3	p-methoxyacetophenone (1"c)	1.8
4	2-acetylthiophene (1"d)	1.5
5	p-methylacetophenone (1"e)	1.62

- **General experimental method for preparation of 1 - (4- methylquinazolin - 2 – yl) - 3 - phenyl–1H - pyrazole- 4 -carbaldehyde (4''a- e)**

To the Vilsmeier-Haack reagent, Hydrazone (0.006mol) was added, and the reaction mixture was agitated at 55- 60 °C for 5 hours with the addition of Dimethyl formamide, 13 ml, along with Phosphorus Oxy Chloride (2.3 equivalent). A cold water rinse and neutralisation with sodium hydroxide were then performed on the solution. After the solid was filtered, washed, and re-crystallized from ethanol, it was ready to be dissolved.

Table 5.15: List of 1 - (4- methylquinazolin- 2 -yl)- 2 - (1 -ar ylethylidene)hydrazines used

Sr. No.	IUPAC Name	Quantity (g)
1	1-(4-methylquinazolin-2yl) – 2-(1 –phenylethyli-dene) hydrazin(3"a)	1.64
2	1-(1-(4 – chlorophenyl)ethyli-dene) – 2-(4 – methylquinazolin – 2 – yl) hydrazin (3"b)	1.84
3	1-(1-(4 – methoxyphenyl)ethyli-dene) – 2-(4 – methylquinazolin – 2 – yl) hydrazin (3"c)	1.8
4	1-(4- methylquinazolin – 2 – yl) – 2-(1-(thiophen – 2 – yl) ethyli-dene)- hydrazin (3"d)	1.68
5	1-(4- methylquinazolin – 2 – yl) – 2-(1 – p –tolylethyli-dene)hydrazin (3"e)	1.72

- **Common Practical methodology for preparation of "3 - (1- (4- methylquinazolin - 2- yl)- 3 - aryl - 1H - pyrazol-4 - yl)- 1 - aryl prop- 2 - en - 1 –ones" (5 a - v) 75 3 - aryl - 1H - pyrazol-4 - yl)- 1 - aryl prop- 2 - en - 1 -one s (5a - v)**

CH_3COONa (6 milli mol) along with CHO pyrrazole, (4 milli mol) were used to buffer a mixture of different organic benzophenones (2.5 milli mol) in 18.25 milliliter CH_3COOH. After 4 hours of refluxing, the reaction mixture was dumped into a bowl of ice cold water. Filtrated, rinsed along H_2O, also then recrystallizationalong with CH_3COOH-Dimethyl Formamide(2:1) to obtain desired chemicals.

Table 5.16: List of "1-(4 -methylquinazolin - 2- yl) -3 -aryl-1H- pyrazol – 4"

Sr. No.	IUPAC Name	Quantity (g)
1	1-(4 – methylquinazolin-2yl) – 3 – phenyl-1H – pyrazole – 4-carbaldehyde (4"a)	0.94
2	3-(4– chlorophenyl) – 1-(4 – methylquinazolin – 2 – yl)-1H – pyrazole – 4-carbaldehyde (4"b)	1.04
3	3-(4 – methoxyphenyl) – 1-(4 – methylquinazolin-2 – yl)-1H – pyrazole – 4-carbaldehyde (4"c)	1.03
4	1-(4- methylquinazolin – 2 – yl) – 3-(thiophen – 2 – yl)-1H – pyrazole – 4-carbaldehyde (4"d)	0.96
5	1-(4- methylquinazolin – 2 – yl) – 3 – p – tolyl-1H – pyrazole – 4-carbaldehyde (4"e)	0.98

- **Data interpretation of "3 - (1- (4- methylquinazolin - 2 - yl)-3 - aryl - 1H - pyrazol- 4 - yl)- 1 - aryl prop- 2 - en - 1- ones" (Series 3)**

After the Vilsmeier - Haack reaction, the chalcon analogue (4"a-e) were transformed into their chalcone analogues (5 a-v) by ClaisenSchimdt condense. IR, 1 H NMR, mass spectrometry, and elemental analyses validated the structure of all synthesised target series. IR. There were two C-H stretch peaks that corresponded to the aldehyde group around 2735 and 2768 per centimeter that vanished following the preparation of chalcone, as shown by IR analysis.

The preparation of hydrazon has heen validated by appearance of a wide singlet of NH at 8.3 in 1HNMR spectra. the next synthesis yielded two features that peaked at around 9.4 and 10.14 (the protons at C5 and C6), respectively. Chalcone's, unsaturation was also proven by a proton almost at 7.6 that was deshielded, confirming the doublet. The J parameters along with ethylene proton had been received to be roughly 15.5 Hz, which suggested creation for the transisomer, according to this study. Analysis of elements and mass spectra helped prove the structure's existence.

SERIES 4

Scheme 5.3 depicts the series 4 synthetic process in its entirety, while Table 5.17 lists the chemicals generated along the way.

Table 5.17: List of syn thesized derivatives of series 4(N- {[1 - (4 – methylquinazolin -2 - yl)- 3 - aryl- 1H- pyrazol- 4- yl]methyl-idene}arylines)

S.No.	Comp	Ar	Ar'
1.	6"a	C_6H_5	C_6H_5
2.	6"b	C_6H_5	p-$CH_3C_6H_4$
3.	6"c	C_6H_5	p-$OCH_3C_6H_4$
4.	6"d	C_6H_5	p-ClC_6H_4
5.	6"e	p-ClC_6H_4	C_6H_5
6.	6"f	p-ClC_6H_4	p-ClC_6H_4
7.	6"g	C_6H_5Cl	p-$CH_3C_6H_4$
8.	6"h	C_6H_5Cl	p-ClC_6H_4
9.	6"i	$C_6H_4OCH_3$	C_6H_5
10.	6"j	$C_6H_4OCH_3$	p-$CH_3C_6H_4$
11.	6"k	p-$OCH_3C_6H_4$	p-$OCH_3C_6H_4$
12	6"l	p-$OCH_3C_6H_4$	p-ClC_6H_4

13	6”m	2-thienyl	C_6H_5
14	6”n	2-thienyl	p-$CH_3C_6H_4$
15	6”o	2-thienyl	p-$OCH_3C_6H_4$
16	6”p	$C_6H_4CH_3$	C_6H_5
17	6”q	$C_6H_4CH_3$	p-$CH_3C_6H_4$
18	6”r	$C_6H_4CH_3$	p-$OCH_3C_6H_4$
19	6”s	$C_6H_4CH_3$	p-$OCH_3C_6H_4$

- **Common practical methodoly for preparation of “N -{[1 - (4- methylquinazolin -2 - yl)-3 - aryl - 1H- pyrazol- 4 - yl]methylidene}arylines” (6 a- s) :**

Formyl pyrazole derivatives (4"a-e) (0.001 mol) were interacting with different aromatic anilines (0.01) in ethanol (20 ml) in the appearance of 1- 2 drops of glacial CH_3COOH for eight hours to produce the desired series of sciff's bases. Using filtering, water washing, and ethanol recrystallization, the target series (6'a-s) was separated.

Table 5.19: List of aromatic anilines used

S.No.	Name	Quantity(g)
1	Aniline	0.93
2	p-methylaniline	1.07
3	p-methoxyaniline	1.23
4	p-chloroaniline	1.27

- **Data interpretation of “N - {[1- (4- methylquinazolin - 2- yl)- 3- aryl - 1H - pyrazol-4 - yl]methylidene}arylines” (Series 4)**

The schiff's base (6"a-s) of 4-formyl pyrazoles was established by spectroscopic methods as the reaction progressed. Before synthesising Schiff base, the aldehydic group's IR distinctive peak vanished. The existence of a singlet at 8.55 in 1HNMR spectra, which corresponds to CHO of pyrazole, verified the synthesis of in the study. Analysis of elements and mass spectra verified the structure's identity.

General experiment of Synthesis, characterization and biological evaluation of quinazoline-conjugated chalcone derivatives

In medicinal chemistry, chalcone scaffold is found to be very much interesting moiety. Taking this into consideration, synthesis of versatile design heterocyclic derivatives with better pharmacological properties can be designed. Chalcone possesses reactive chemical structure, easy to make and additionally it shows promising activities.

Heterocycles containing chalcone core are known to possess several biological activities like antiinflammatory, antiviral, anticancer, bactericidal,[7] and insecticidal. **Figure 5.1** shows some potent biologically active chalcone derivatives in clinical use. Medieagenin **AS**, Menchiwanin **AT** and Licochalcone-A**AU** shows *in-vitro* antimalarial, anticancer, antibacterial and antiviral properties.

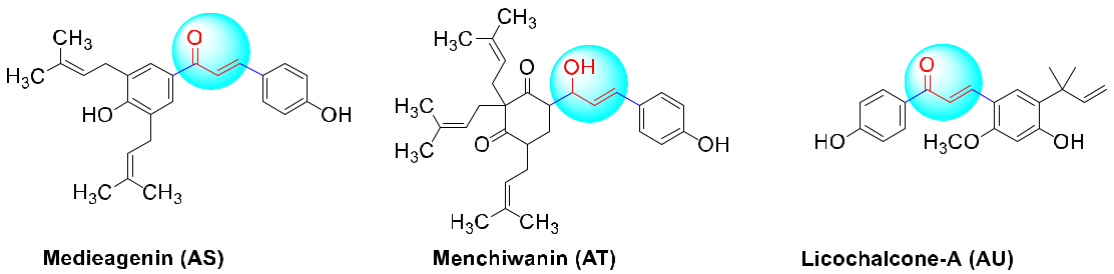


Figure 5.1: Biologically active chalcones derivatives.

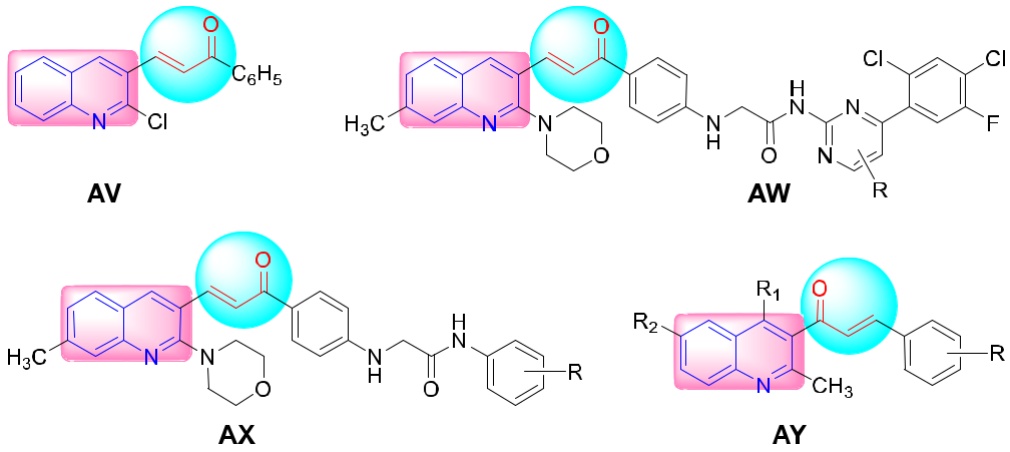


Figure 5.2: Biologically active quinoline-conjugated chalcone derivatives.

The quinazoline-derived chalcone derivatives are well acknowledged and found to be fascinating scaffold in drug discovery research.

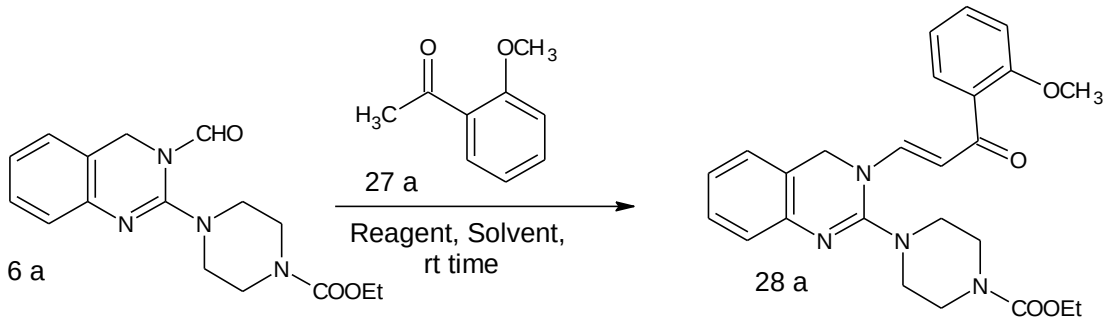
Some biological active quinazoline-conjugated chalcone derivatives are represented in **Figure 5.2**. Compound **AV** is reported to possess good antibacterial activity against all strains.[15] Compound **AW** is reported to be highly potent against *B. subtilis*. Further, compound **AX** is reported to be highly active against *E. coli* and *S. aureus* strains respectively.[16]Similarly, the derivatives of compound **AY** are reported to possesses good antimicrobial activity.

From above literature survey it is revealed that, quinazoline-derived chalcones need to be extensively studied further to check probability of getting highly potent novel heterocycles.

Result and Discussion

Chemistry

In the current chapter, Compound **6** is considered as a key starting material for synthesis of quinazoline-conjugated chalcone derivatives **28**.



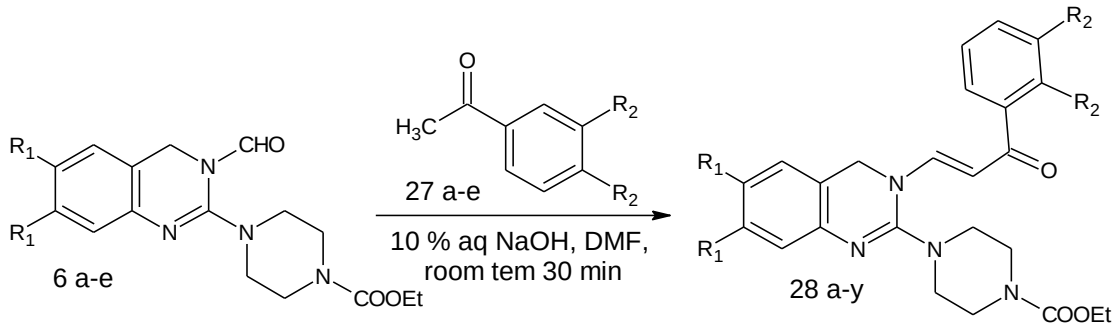
Scheme 5.4: Reaction of compound **6a** with 2-methoxy acetophenones **27a**.

Table 5.20: Optimization conditions for the synthesis of compound **28a**.[a]

Entry	Reagent	Solvent	Temp. (°C)	Reaction time (hr)	% Yield[b]
1	**aq. NaOH**	**DMF**	**rt**	**0.5**	**92**
2	aq. KOH	DMF	rt	0.5	83
3	aq. NaOH	EtOH	rt	5	82
4	aq. NaOH	MeOH	rt	6	83
5	Aq.K_2CO_3	DMF	rt	7	78

[a]All reactions were carried out on 0.668 mmol. of**6a** (1.0 equiv.), 1.05 equiv. of **27c**, 1.5 equiv. of base at rt unless otherwise noted. [b]Isolated yield.

As shown in **Scheme 5.4**, **Table 5.20**, several reaction conditions were screened for the synthesis of quinazoline-conjugated chalcone derivatives **28**. The best result was obtained, when synthesis of chalcone was carried out by reaction of compound **6b** and 2-methoxy acetophenone **27a** using aq. sodium hydroxide in presence of DMF at room temperature (entry 1, 92%).



Scheme 5.5: Synthesis of quinazoline-conjugated chalcone derivatives **28a-y**.

Table 5.21: Synthesis of quinazoline-conjugated chalcone derivatives **28a-y**.

Entry	Comp.	R1	R2	% Yield[a]
1	**28a**	H	2-OCH3	92
2	**28b**	H	2-F	84
3	**28c**	H	4-F	80
4	**28d**	H	2,4-F	77
5	**28e**	H	4-Cl	75
6	**28f**	6-CH3	2-OCH3	88
7	**28g**	6-CH3	2-F	85
8	**28h**	6-CH3	4-F	82
9	**28i**	6-CH3	2,4-F	80
10	**28j**	6-CH3	4-Cl	79
11	**28k**	6-OCH3	2-OCH3	87
12	**28l**	6-OCH3	2-F	85
13	**28m**	6-OCH3	4-F	81
14	**28n**	6-OCH3	2,4-F	83
15	**28o**	6-OCH3	4-Cl	79
16	**28p**	7-F-8-CH3	2-OCH3	84
17	**28q**	7-F-8-CH3	2-F	82
18	**28r**	7-F-8-CH3	4-F	85
19	**28s**	7-F-8-CH3	2,4-F	78
20	**28t**	7-F-8-CH3	4-Cl	74
21	**28u**	7-F	2-OCH3	91
22	**28v**	7-F	2-F	88
23	**28w**	7-F	4-F	87

24	**28x**	7-F	2,4-F	82
25	**28y**	7-F	4-Cl	82

Effect of substitution at quinazoline core and at acetophenone for the synthesis of chalcone derivatives was studied in the current chapter. Unsubstituted and 6-CH3, 6-OCH3, 7-F-8-CH3, 7-F substituted quinazoline ring along with 2-OCH3, 2-F, 4-F, 2,4-F and 4-Cl substitution at phenyl ring of acetophenones were selected for the synthesis of quinazoline-conjugated chalcone derivatives **28**. **Table 5.21** reflects that, good to excellent yield was obtained. As far as the substitution at phenyl ring is concerned, higher yield was obtained with -OCH3 substituent as compared to other substituents. On the other hand, lower yield was obtained in case of Cl substitution. In remaining compounds, comparable yield was obtained.

The structure of the quinazoline-conjugated chalcone **28a** had been detected by ^{1}Proton NMR, ^{13}Carbon Nuclear Magnetic Resonance along with 2D NMR spectroscopy analysis. ^{1}Proton Nuclear Magnetic Resonance (**Figure 5.3**) to compound **28a**, single at chemical shift 3.74 for 3H was assigned to OCH_3 protons for carbamate along with single at chemical shift 3.91 for three H was given to methoxy protons present on phenyl ring. Proton belonging to piperazine ring appeared as two multiplets at δ 3.67-3.55 (2 x CH2) and δ 3.39-3.30 (2 x CH2), respectively. Proton belonging to double bond appeared as doublet at δ 7.74 and δ 7.46 with coupling constant J = 15 Hz. This confirms the formation of quinazoline-conjugated chalcone derivatives. Further, the quinazoline proton appeared in the range δ 8.22 - δ 7.38 and the protons belonging to phenyl ring appeared in the range δ 7.60 - δ 7.02.

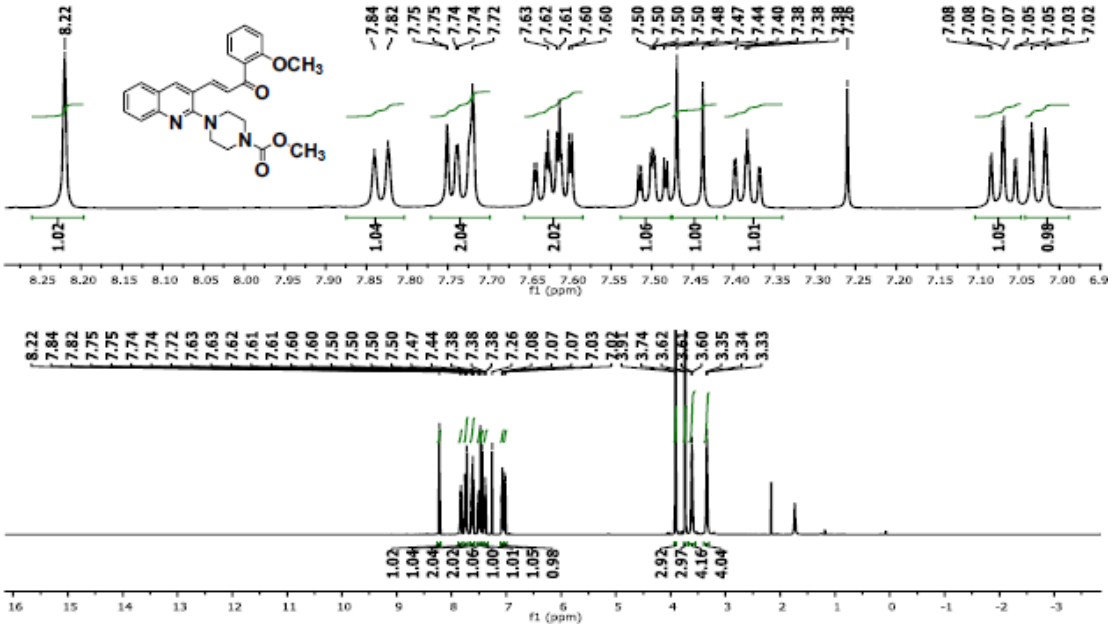


Figure 5.3:^{1}H NMR (500 MHz, CDCl3) spectrum of compound **28a**.

In ^{13}C NMR spectrum, (**Figure 5.4**) signlet at chemical shift 52.67 had been given to methoxy C of carbamate and signlet at chemical shity 55.83 had been identified to methoxy C on phenyl ring at C2 position. Signals at δ 50.21 and δ 43.66 were assigned to CH2 groups of piperazine ring. The presence of two CH2 groups were confirmed by D-135 NMR as shown in **Figure 5.4**.

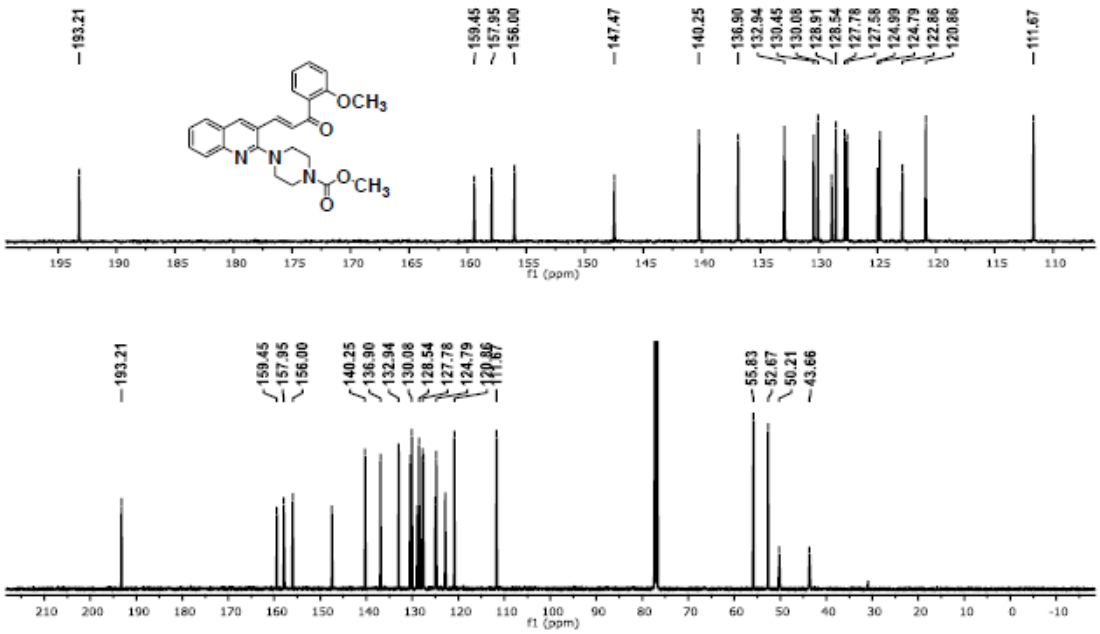


Figure 5.4: C NMR (126 MHz, CDCl3) spectrum of compound **28a**.

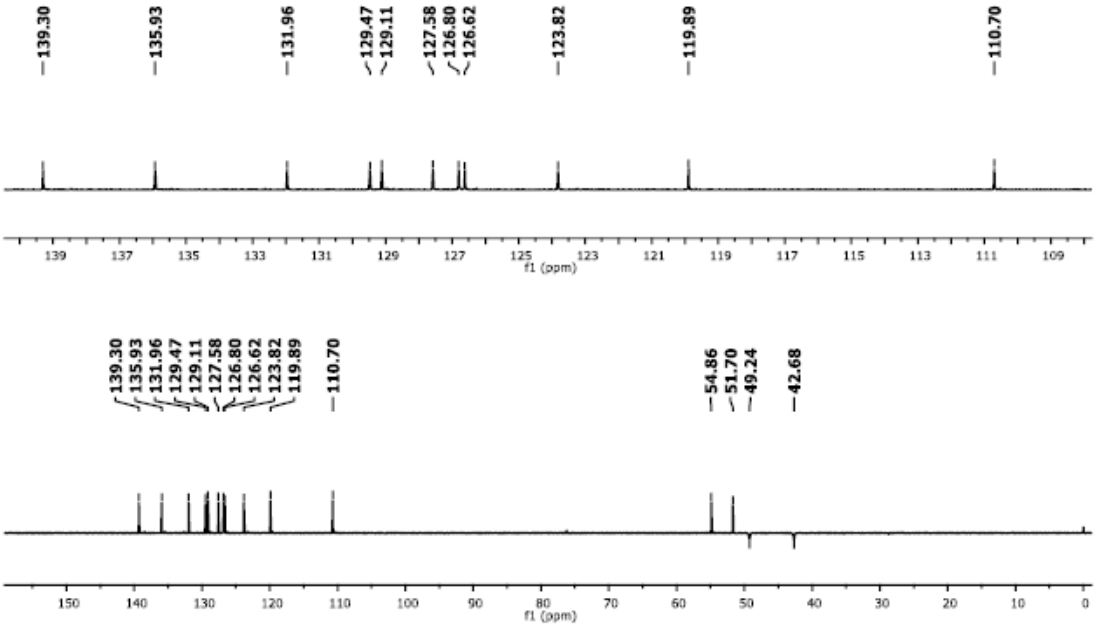


Figure 5.5: DEPT-135 NMR spectrum of compound **28a**.

In aromatic region, carbonyl carbon of carbamate was found to appear at δ 156.00 and the conjugated ketonic carbon appeared at δ 193.21. The aromatic carbons of quinazoline ring, double bond and phenyl ring appeared between δ 159.45-111.67. The spectral data mentioned above confirms the formation of compound **28a**.

The above assigned chemical shifts were further confirmed by 2D NMR spectroscopic techniques like COSY and HSQC. As shown in **Figure 5.5**, proton '**a**' at δ 8.22 of quinazoline ring does not show any co-relation with other protons. On the other hand, proton '**d**' at δ 7.38 (J = 8.0 Hz) exhibited co-relation with proton '**e**' and proton '**b**' at δ 7.83 (J = 8.4 Hz) is showed co-relation with proton '**c**'. Proton '**f**' at δ 7.74 (J = 16 Hz) showed co-relation with proton '**g**' at δ 7.46 (J = 16 Hz). In context with protons of phenyl ring, proton '**i**' at δ 7.02 displayed co-relation with proton '**h**' at δ 7.07, proton '**j**' at δ 7.50 and proton '**k**' at δ 7.61. On the basis of this, protons identified by COSY were correlated with carbon atoms by HSQC spectroscopy as shown in **Figure 5.6**. On the basis of above discussed spectral data, the formation of (*E*)-methyl 4-(3-(3-(2-methoxyphenyl)-3-oxoprop-1-enyl)-quinazolin-2-yl)-piperazine-1-carboxylate-**28a** was confirmed.

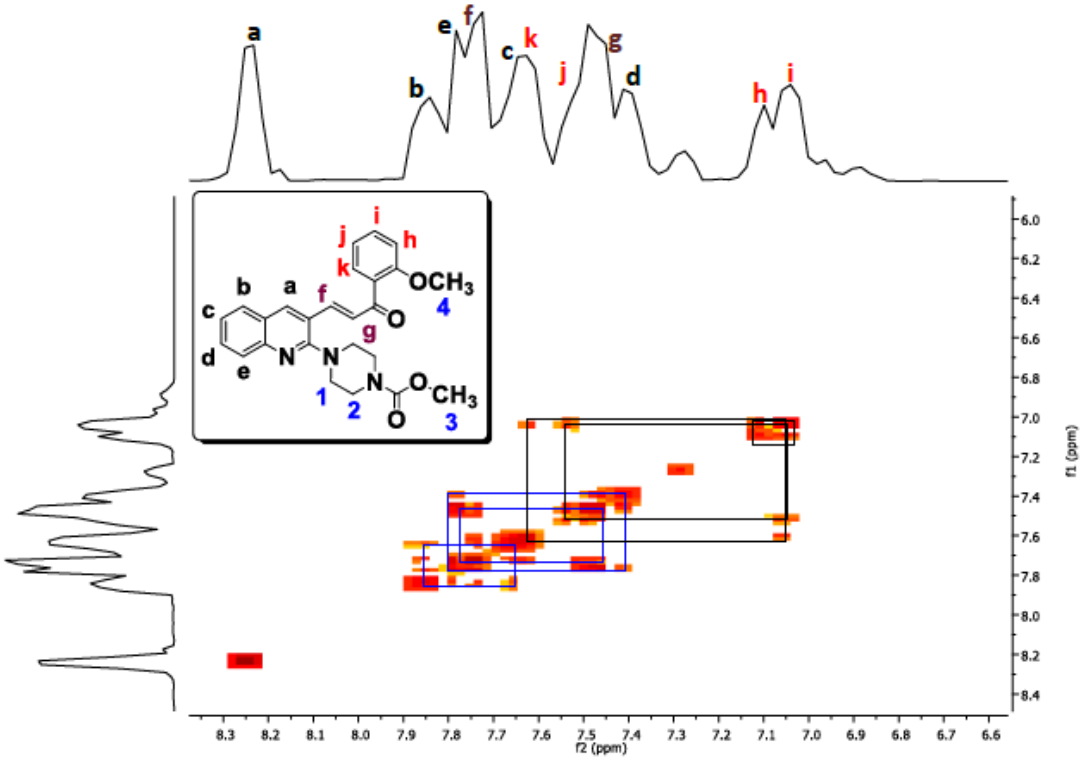


Figure 5.6: COSY NMR (δ 8.4 - δ 6.5) spectrum of compound **28a**.

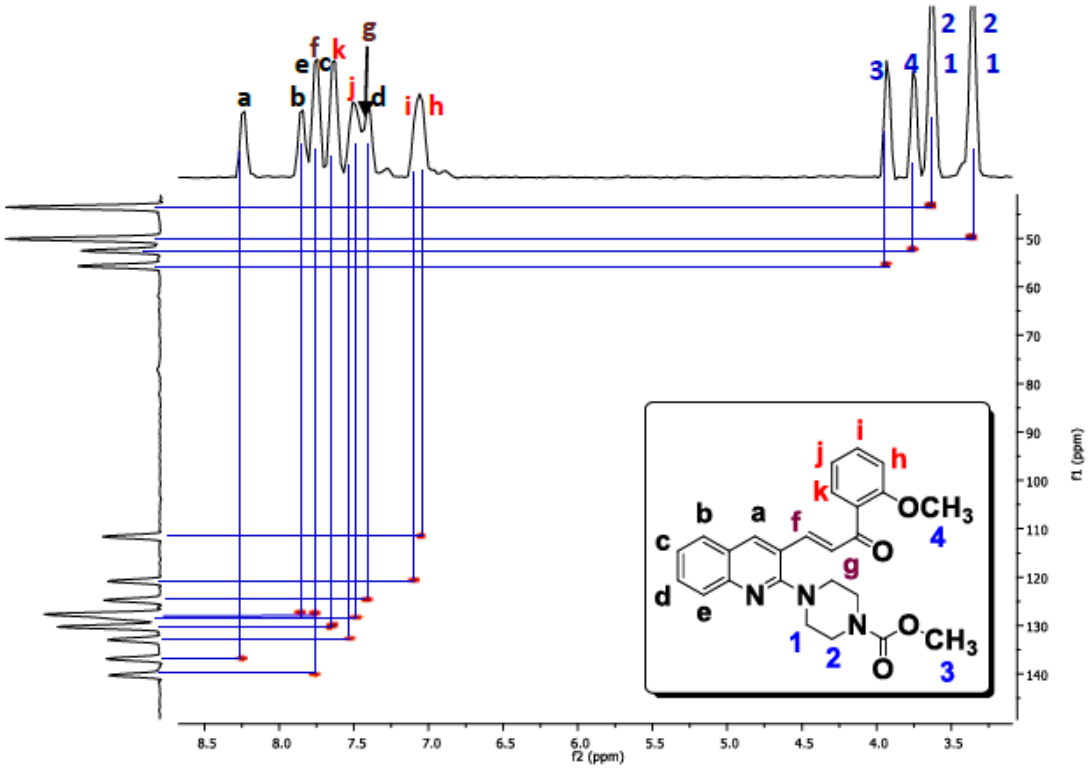


Figure 5.7: HSQC NMR spectrum of compound **28a**.

X-Ray Crystallography

The crystal data have been deposited at the Cambridge Crystallographic Data Centre (CCDC Nos. 2130556). Compound **28h** was dissolved in DCM and hexane. Further it was kept on standing for crystallization. The growth of colourless crystal was observed.

Asymmetric unit cell contains one molecule of **28h**. The bond lengths, bond angles and torsional angles are shown in **Table 5.3**.

The F1-C23 bond length is 1.365(3) Å and one C–N bond lengths C7-N1 is (1.3211(3) Å clearly indicates aromatic nitrogen atom is present. The two C–N bond lengths of N2-C11 and N3-C12 are 1.470(3) Å and 1.471(3) Å respectively.[18-20] The torsional angles for N1-C7-C8-C9, C2-C3-C4-C5, N2-C11-C12-N3 and N3-C13-C14-N2 are found to be -5.7(5)◦, 0.1(5)◦, -53.3(3)◦ and 56.9(3)◦ respectively.

Molecular geometry from SC-XRD revealed that, nitrogen containing ring in the quinazoline core is not in the same plane as that of another ring and is observed to be slightly twisted.

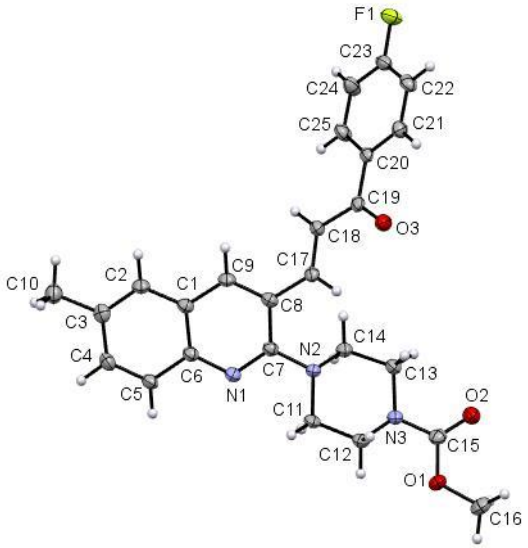


Figure 5.8: ORTEP diagram of compound **28h**.

- **BIOLOGY**

All synthesized compounds were evaluated for their antibacterial and anticancer activities.

Result and Discussion

Procurement of data set

Extensive literature survey on recent studies of cysteine proteases inhibitors resulted in a data set comprising of papers[125-128] from which 242 compounds were selected.

The compounds selected from the data set had both structural as well as activity profile diversity. It had several groups of molecules such as thiosemicarbazone derivatives, azadipeptide nitriles, phenylurenyl chalcone derivatives, and 2-Pyrimidinecarbonitrile derivatives.

All the 242 compounds were drawn using MDL ISIS 2.5 and thoroughly checked for any error.

Pharmacophore generation through PHASE

The drawn structures were imported onto on a Windows-based operating system on a HP workstation with the Maestro (v.9.0.109) module of the Schrödinger molecular modeling package.

Training Set And Test Set

For the purpose of generating a pharmacophore the data set of 242 compounds was divided into training and test set. Preparation of training set is a very important step in the pharmacophore generation. A good training set ensures a better pharmacophoric features which in turn leads to statistical significance.

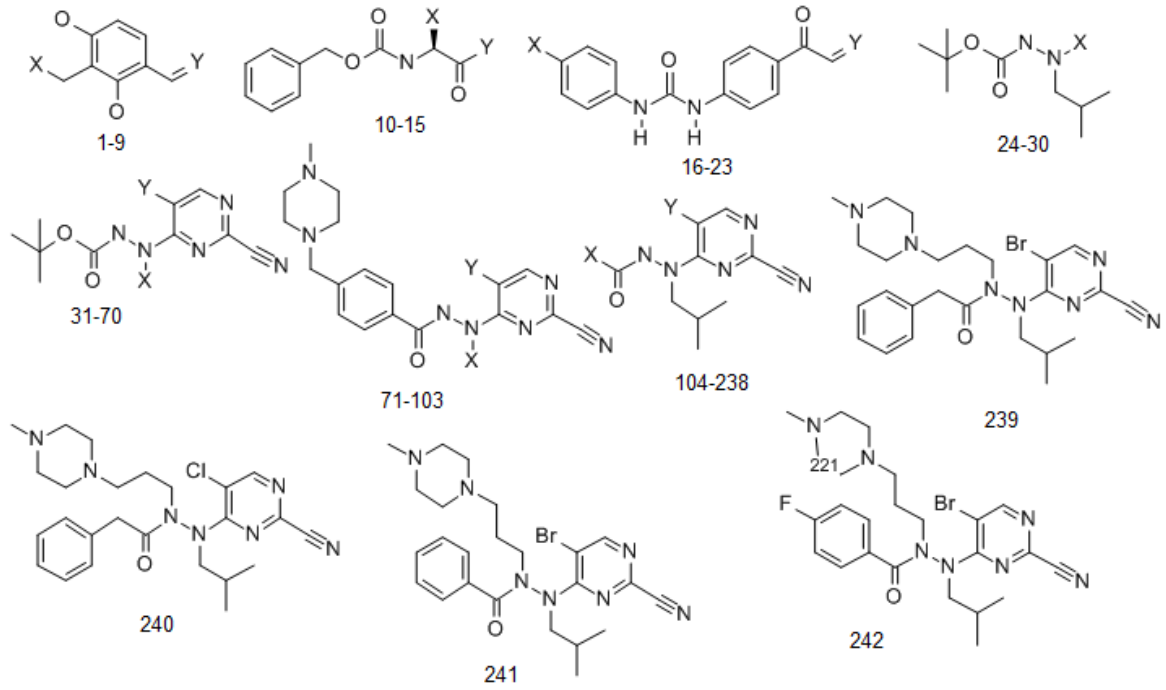
Criteria for Training Set Selection

1. At least 16 compounds should be in the training set.
2. Activity range of compounds should be at least four orders of magnitude.
3. Each order must be represented by at least 3 compounds.
4. Most active and the most inactive compound must be included in the training set.

5. If molecules having similar structures are present then for inclusion in the training set they must differ by an order of magnitude otherwise the most active compound is picked.
6. If molecules having similar activity is reported but structurally different then both are picked otherwise most active is picked.

The **Quantitative Structure Activity Relationship** studies were performed using four series of structurally diverse compounds namely thiosemicarbazone derivatives, azadipeptide nitriles, phenylurenyl chalcone derivatives, and 2-Pyrimidinecarbonitrile derivatives comprising 242 compounds (activity ranges from 0.0002µM to 28µM) reported in literature [125-128] by adopting the Maestro (v.9.0.109) module of the Schrödinger molecular modeling package.

The data set comprises of the following compounds:



Pharmacophore generation through Phase module

Molecular structures of all ligands used to create pharmacophore models are shown in the Table 1. Prior to the modeling, the sd file of ligands input in DSV 2.0 were imported into the project table and minimized with the Maestro (v.9.0.109) module of the Schrödinger molecular modeling package.

Ligand Preparation

These structures were then incorporated into the LigPrep (v.2.3) module of Schrödinger. The protonation state for all ionizable groups was set at neutral pH = 7. Specified chiralities were retained for stereoisomer generation and also original states were retained in case of any ionization for any state. A conformational search was performed with the confgen method to derive representative conformers for each ligand in the data sets. Number of conformers per rotatable bond and maximum number of conformers per structure were set to 100 and 1000 respectively. Force field applied was OPLS 2005 and RMSD of 1 Å was set to eliminate redundant conformers. Thus only unique structures were retained during the conformational search.

Construction of 3D Quantitative Structure Activity Relationship Model

The 3D QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP study was carried out with the PHASE (v.3.1) program of the Schrodinger molecular modeling package. The pIC_{50} values were used instead of IC_{50} values for each ligand in the training and test sets by calculating -log [IC_{50}].

Pharmacophore sites were derived for the different conformations. The specific interactions between a target and a ligand depend on a structural complementarity between functional groups presented in the ligand and coordinating residues from the binding pocket. PHASE classifies these chemical features as hydrogen bond acceptors (labeled as A), hydrogen bond donors (labeled as D), hydrophobic groups (labeled as H), negatively charged groups (labeled as N), positively charged groups (labeled as P), and aromatic rings (labeled as R).

PHASE uses the most active compounds (high affinity) in the training set to build the pharmacophores. To define a common pharmacophore or hypothesis, PHASE employs an analysis of k point pharmacophores derived from the conformational sets of active compounds and then identifies all spatial arrangements with pharmacophore features that are shared by those molecules. In this study, activity threshold for the selection of active and inactive ligands was set (pIC_{50}> -0.480, was considered as active and pIC_{50}< -4.450, was considered as inactive). Thus, a common pharmacophore must match a minimum required number of active ligands, which was set as 75 in this study. Essential features were generated using the "Create site" tool in the Phase which resulted in various variants. Among different variants the combination of AAHHR features was selected for further studies.

A plot between the pIC_{50} values of observed versus estimated activity demonstrated a good correlation coefficient ($r2$ training= 0.8273) for training set molecules, indicating the good predictive ability of the pharmacophore (Fig 7).

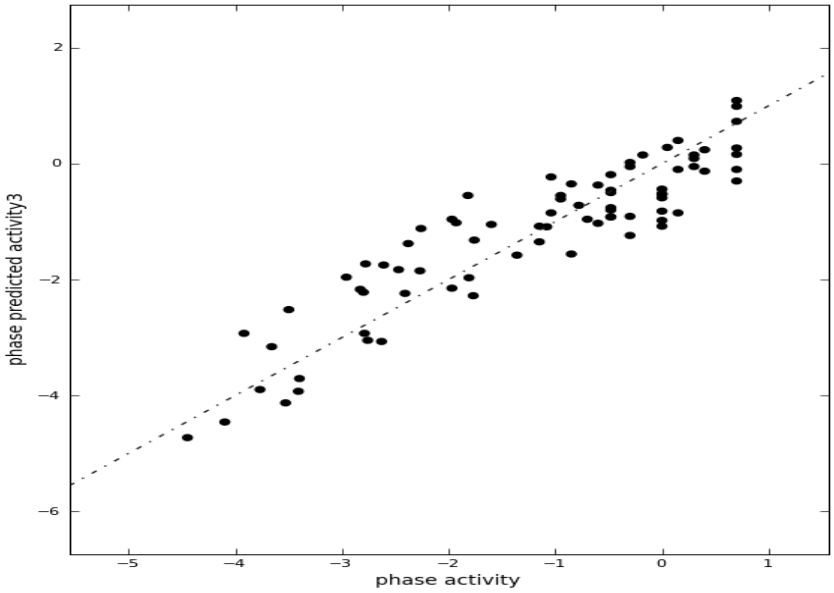


Fig 5.2: Correlation graph between observed and predicted activity of training set (r^2 training=0.8273)

Pharmacophoric representation of the most potent compound 14_251 (A) of the data set showed the presence of nicotino hydrazide group at C-6 position having a carbonyl group providing acceptor feature (A4) to the molecule, whereas cyano pyrimidine ring provided the ring aromatic feature (R9) and bromine group and cyano group attached to the cyano pyrimidine ring provided for the hydrophobic (H6) and acceptor feature (A1) respectively. The isobutyl group provides for the hydrophobic feature (H7) of the pharmacophore. The same study carried with the least active compound of the data set , 9_6, (IC_{50} =28µM) depicted the absence of proper mapping of even one of the function except for the close proximity between the A4 and the oxo group in benzyl (S)-1-((S)-1-cyanoethylamino)-1-oxo-3-phenylpropan-2-ylcarbamate. (Fig 8).

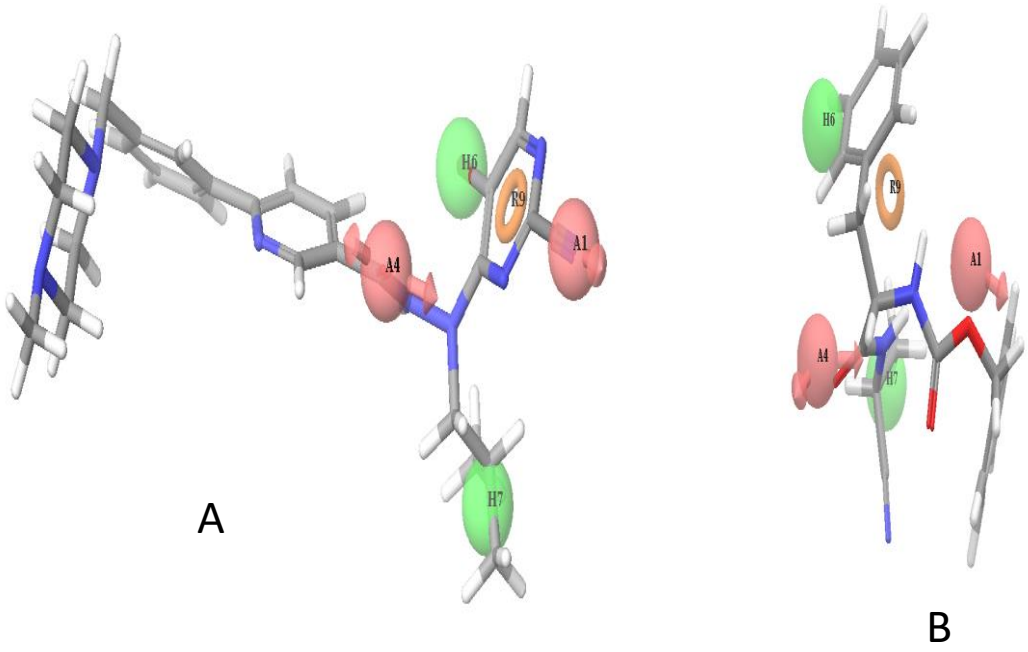


Fig.3 (A) Mapping of the most active compound **14_251** of the training set.
(B) Mapping of the least active compound **9_6** of the training set.

Test set validation

The generated model was further assessed by its predictability on the test set containing 163 compounds from the same data set. The overall correlation coefficient value of (r^2 test= 0.6028) between the observed and estimated activity of the test set molecule was indicative of its good predictive quality (Fig 9).

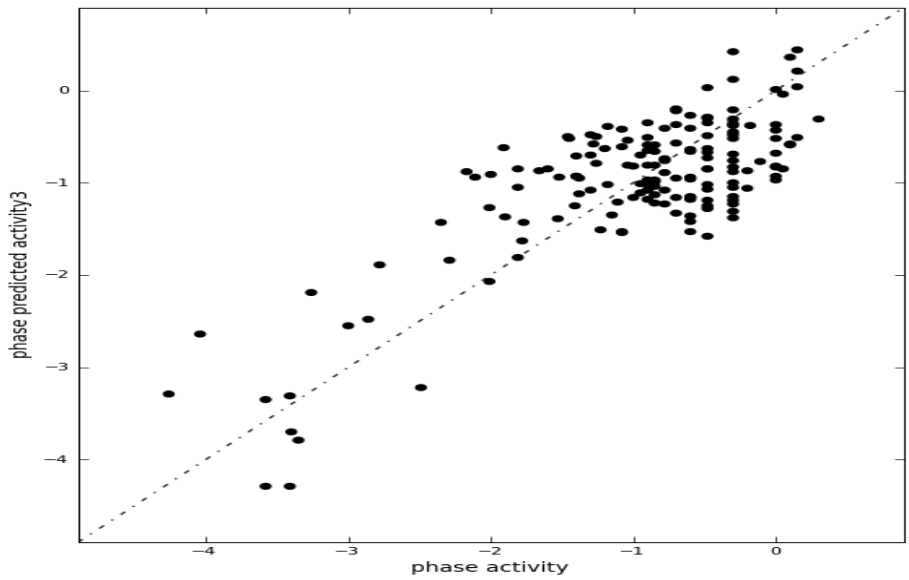


Fig 4: Correlation graph between observed and predicted activity of test set (r^2 test= 0.6028)

The docking studies

The docking studies were performed using GOLD version 3.1.Among all conformations of the ligands used in QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP study theconformation of the Phase pharmacophore based alignment was submitted to the docking studies. The co-crystallized structure of Falcipian-2 (PDB ID: 3BPF) in complex with its inhibitor E-64 was selected for the docking studies. Protein was prepared by protein preparation wizard available inSchrodingerpackage. The co-crystallized ligand E-64 was used for the selection of active site. The most and the least active ligands used in the pharmacophore were docked at the active site of the protein.

The docking studies at the Falcipian-2 active site with the most active molecule (viz.14_251) of the dataset clearly showed (Fig.10) that the nitrogen group present in nicotinohydrazide moiety was involved in H-bonding with Asn-173 and a close contact was shown by the C-4 carbon of the pyrimidinee nucleus with Cys-42. The isobutyl moiety very well went into a hydrophobic pocket made of Leu-84, Ala-175 and Ile-85 whereas the bromine group and oxo group are close to Trp-206 and Cys-42. These findings well corroborates with common pharmacophore of Phase. The docking studies at the Falcipian-2 active site with the most inactive molecule (viz.9_6) (Fig.11) of the dataset showed H-bonds between the cyano group and His-174 and nitrogen group and Asn-173 of the cyanoethylamino moiety. There is also a H-bond and close contact between hydrogen and nitrogen of carbamate moiety with Gly-83 which does not corroborates with the Phase pharmacophore.

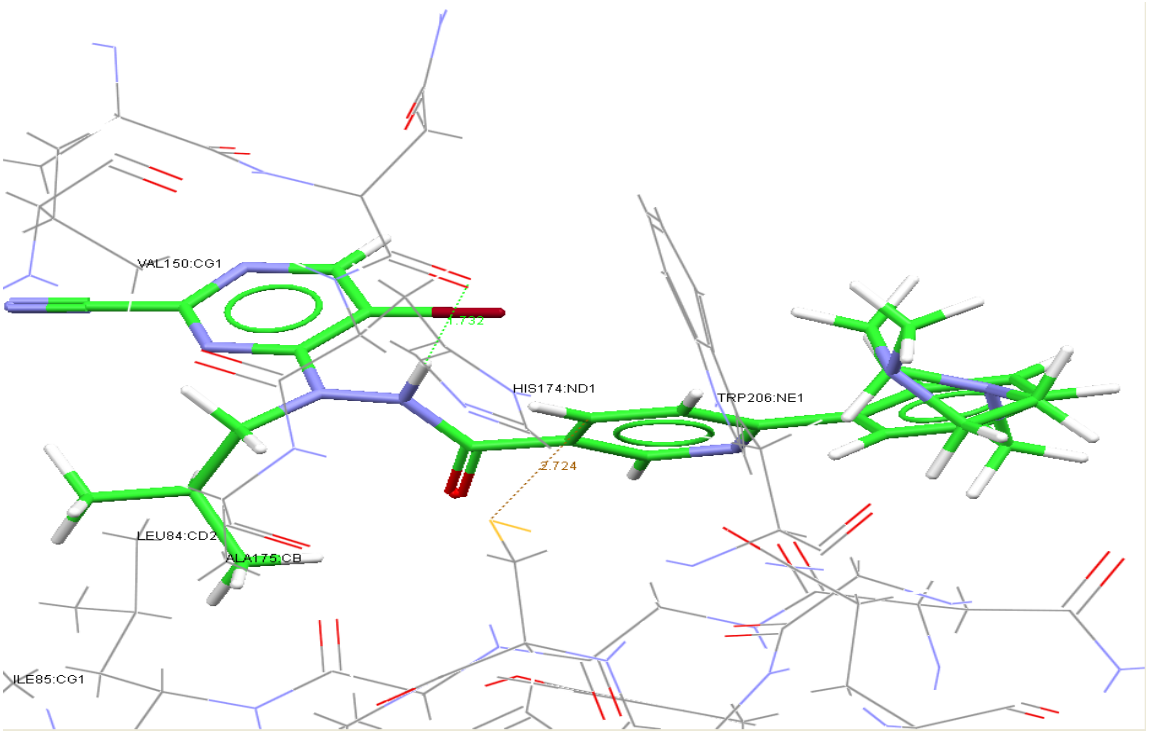


Fig.5: Docked pose of the most active molecule (14_251).

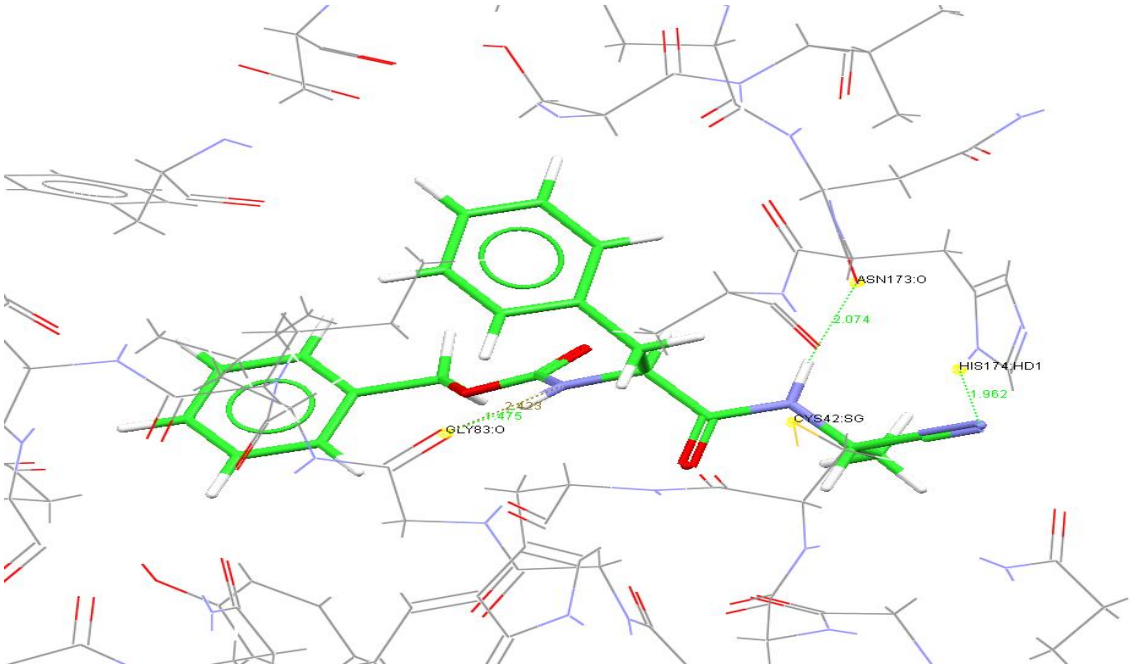
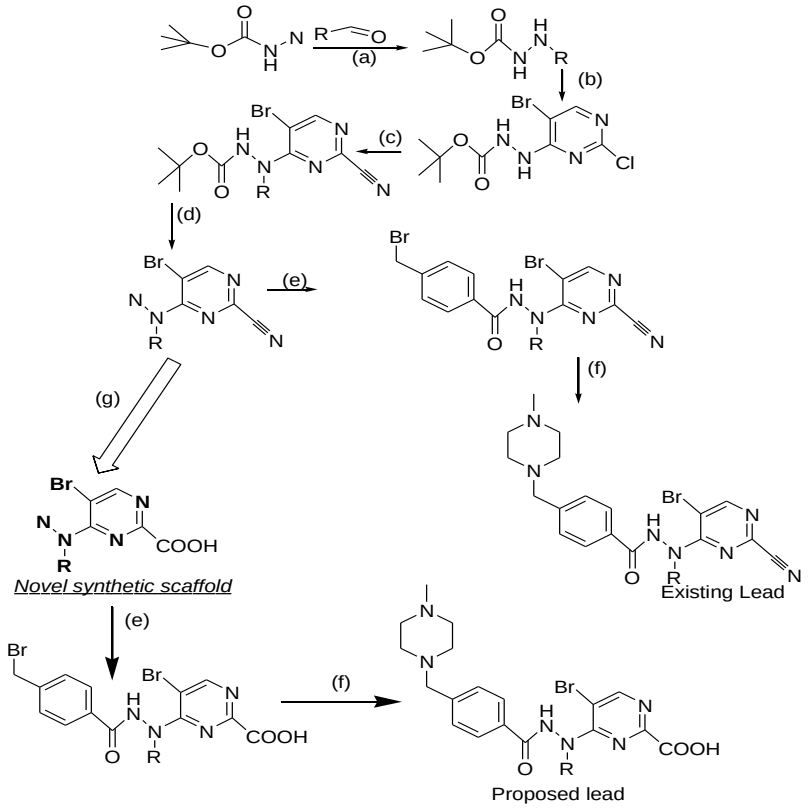


Fig.6 Docked pose of the least active molecule (9_6).

Synthetic Protocol

Novel synthetic scaffold can be generated by incorporating pharmacophoric 3D feature based interactions. The synthesis of 2-Cyano pyrimidine derivatives takes place by the following process[32b]:



Reagents and conditions: (a) aldehyde or ketone, NaBH3CN, AcOH, rt; (b) 5-bromo-2,4 dichloropyrimidine, DIPEA, i-PrOH; (c) potassium cyanide, 1,4-diazabicyclo[2.2.2]octane, 9:1 DMSO-H2O; (d) p-toluenesulfonic acid, ACN, rt; (e) 4-bromomethylbenzoyl bromide, DIPEA; (f) N-methylpiperazine, DIPEA, THF, rt.

Introduction of –COOH group (Step- G) by the hydrolysis of –CN in the presence of aqueous acid i.e. hydrochloric acid gives a novel synthetic scaffold [(129)]. The –COOH group is responsible for contributing a negative ionizable feature which may play an active role in its accumulation inside the vacuole of parasite.

The step (d) will be continued as mentioned in the literature for the introduction of 4-((4-methylpiperazin-1-yl) methyl) benzamide for stabilizing and increasing the lipophilic character of the molecule[32b].

Summary and Conclusion

Summary

A pharmacophore based on common pharmacophoric features was developed and validated by the r^2 and q^2 of training and test sets respectively. The developed pharmacophore corroborated well in the docking studies.

A synthesis protocol has been proposed to develop new scaffold to target Falcipian-2 and act as novel anti-malarial agents.

The study of the pharmacophore generated by Phase demonstrated that the A1, A4, H7, H6 and R9 features are the essential requirements for activity. The docking studies also corroborated well with the Phase pharmacophore as it showed that the oxo group of the most active compound was in close proximity with the Cys-42 residue, (an important residue in cysteine proteases mechanism) which could be involved in covalent bond formation which would lead to inhibition of Falcipian-2 and the corresponding Phase feature is acceptor feature (A4). The isobutyl group of the most active compound also docks into the hydrophobic pocket made of Leu-84, Ala-175 and Ile-85 corresponding to the hydrophobic feature of Phase pharmacophore (H7). Bromine of the cyanopyrimidine ring and the ring itself moves into hydrophobic pocket made of Val-150 which corresponds to hydrophobic (H6) and ring aromatic (R9) feature of the Phase pharmacophore.

Thus these studies may help in design and synthesis of selective inhibitors of Falcipian-2 with the aim of the development of novel anti-malarial drugs.

HETEROCYCLIC COMPOUNDS- Some or all of the atoms in the molecules of a heterocyclic compound(also spelled heterocycle) are connected in rings that contain at least one atom of a substance other than carbon. Heterocyclic compounds are members of a large group of naturally occurring compounds that are distinguished from one another by this unique structural feature . The term heterocyclic is derived

prefix hetero, which means other or one of a type, refers to the noncarbon atoms, or heteroatoms, that are contained within the ring. The presence of at least one ring structure indicates that this category of compound contains at least one ring structure. Heterocyclic compounds make up a significant portion of the essential biological components for continued existence. Nucleic acids, the molecules that are responsible for transmitting genetic information, are made up of lengthy chains of heterocyclic devices that are connected to one another using a wide variety of different kinds of materials. Heterocyclic compounds account for the vast majority of psychoactive substances, including a variety of naturally occurring pigments, minerals, and antibiotics. Synthetic heterocycles, which may come in the form of medications, insecticides, pigments, and polymers, are essential to the operation of the modern society. Heterocyclic compounds are a significant class of molecules due to the fact that they are found in a broad variety of herbal products and pharmaceutical medicines derived from both marine and terrestrial sources. A few of the tablets that havebeen given the OK include heterocyclic ring structures as part of their active pharmacophoric component. Inthe pharmaceutical sector, large heterocyclic ring structures offer an unbeatable competitive advantage as small lead compounds. This is because nitrogen heterocyclic compounds serve as the building blocks of many essential bioactive molecules. They are well-known in the fields of herbicides, fungicides, and other chemicals with a focus on usefulness. It is heartening to learn that heterocyclic compounds are responsible for over half of all known chemical compounds and for nearly ninety percent of all pharmaceuticals that are now in circulation. Most of

these drugs fall under the heterocyclic category and have ring structures with three to six members. But it's becoming more and more obvious that medium-sized ring (7-9 members)heterocyclic compounds are important heterocyclic motifs of biological importance in the creation of medications. Many different physiological effects have been associated to ring-containing compounds including oxepine, oxocin, azepine, azocine, diazepine, dioxazepine, oxazepine, thiazepine, and their benzo-fused equivalents. About 350 distinct azepine structures and more than 2,000 distinct oxepine structureshave been linked to pharmacological effects. Compounds having medium-sized rings that include more than one form of hetero element have emerged as critical medicines in recent years. As a consequence of this, synthetic and medicinal chemists have taken an interest in the synthesis of heterocyclic compounds that include rings of a medium size. Because of enthalpic and entropic challenges, the synthesis of compounds with medium-sized rings is notoriously difficult. In addition, hazardous conformational functions add even another layer of complexity to the situation. Therefore, as a result of this, the door has been opened for thestudy and development of cutting-edge methods that may be used to get access to these ring-basedsystems. The application of recently established metallic-mediated distinctions as a method for resolving a number of these issues has been applauded by a significant number of individuals who follow the most recent developments in scientific research pertaining to this field. Another industry that encourages the employment of innovative synthetic methods is the pharmaceutical industry. The following sections will highlight some of these developments and categorize them according to the sort of permission procedure being discussed. The development of greener methods for working with compounds that have medium-sized rings has made use of a wide variety of enabling techniques. In a nutshell, one is able to assess thedevelopment that has been done. BASIC CHARACTERISTICS OF HETEROCYCLIC COMPOUNDS In the realm of chemistry, some of the most well-known substances are pyrimidinee, pyrrole, furan, and thiophene, which are all examples of simple heterocyclic compounds. There are five carbon atoms and one nitrogen atom included inside the ring structure of pyrimidinee. Earrings inside the molecules of pyrrole, furan, and thiophene each include one nitrogen, oxygen, or sulfur atom in addition to either five or six carbon atoms. Pyrimidinee and pyrrole are both examples of nitrogen heterocycles. This means that the molecules of both of these compounds include carbon as well as nitrogen atoms inside the rings. When subjected to intense

heating, a variety of biological materials give out minute amounts of pyrimidinee and pyrrole, which are constituents of the molecules that make up the materials themselves. During the 1850s, the two compounds were found combined for the first time in an oily combination that had been produced by intensely heating bones. The manufacture of pyrimidinee and pyrrole may currently be achieved via the use of synthetic processes. The manufacturing of dyes and pharmaceuticals is where these compounds get the greatest financial return on investment. In addition to its use as a solvent, a denaturant of alcohol, and an auxiliary inthe dyeing process, pyrimidinee is also used as an additive to rubber, a waterproofing agent, and a denaturant of methanol. The chemical production of other chemicals often involves the usage of furan, which is a heterocycle that contains oxygen (including pyrrole). The production of nylon intermediates requires the use of furfural, which may be obtained from oat hulls and corncobs. Furfural is a material that is chemically linked to furan and has some of the same properties. Benzene and the sulfur heterocycle thiophene have a number of chemical and physical properties in common. Benzene is the more well-known of the two. It was found for the first time during the process of purifying benzene and is a common contamination of benzene eobtained from herbal sources. As is the case with many other types of compounds, it is often trans formedinto different forms. In the latter part of the nineteenth century, the chemicals known as furan and thiophene were both isolated for the first time. The structural and molecular characteristics of heterocyclic compounds become more apparent when contrasted with those of natural molecules that do not include heteroatoms. Comparable to substances that are composed of carbon-cyclic atoms Organic molecules are characterizedby their presence of a carbon skeleton, sometimes known as a "backbone," to which hydrogen (H), oxygen, and other heteroatoms are linked. The capacity of individual carbon atoms to form chemical bonds is one that cannot be found in any other element.

We talk about a cyclic compound, also known as a carbocyclic oralicyclic compound, whenever two or more chains are joined at their terminals to create a ring. This may happen whenever there are two or more chains. Carboxylic compounds are converted into heterocycliccompounds whenmolecules are exchanged for heteroatoms. Cyclopentane (C5H10) is an example of a carbocyclic compound; the common notation used to show its molecular structure uses chemical symbols in place of the atoms ofthe components, and lines in place of the bonds between the atoms. These formulas are frequently expressed in polygonal form for the sake of ease of writing. One example of this is the formula for cyclopentane, in which each vertex represents an atom of carbon. By exchanging one of the carbon atoms in cyclopentane for a nitrogen atom, the related molecule pyrrolidine is made. Structure of pyrrolidine is as follows: It is possible to anticipate the production of more heterocyclic compounds as derivatives of cyclopentane via the use of similar components through the use of different rings.

The most fundamental components of organic compounds are hydrocarbons, which consist only of the elements carbon and hydrogen. In saturated hydrocarbons, every single one of the carbon atoms is bound to either another carbon atom or a hydrogen atom. Saturated hydrocarbons do not include any unbounded carbon atoms. Those that contain double or triple bonds between their carbon atoms are thought to be unsaturated, while aromatic compounds are thought to have at least one ring in which the atoms are linked due to the fact that each carbon in these compounds may receive up to four different substituents at thesame time. Aromatic molecules, on the other hand, are highly stable and do not readily undergo additionprocesses. This is in contrast to other unsaturated compounds. The ring's stability and lack of reactivity maybe attributed to the presence of three pairs of electrons, which have been given the name pi lectrons. These electrons are coupled with the ring's triple bonds. The term aromatic sextet refers to a collection of six electrons that, when brought together, provide a very stable structure. This structure is linked to the aromaticring as a whole as opposed to the atoms that make up the aromatic ring. How Heterocyclic Compounds Get Their Names The task of identifying heterocyclic compounds is made more difficult by the fact that in addition to the globally recognized scientific nomenclature, there are also several vernacular names for these compounds. When appended to heteroatom prefixes, variety prefixes, such as dioxa- and triaza-,specify the number of heteroatoms of a certain sort. We are able to indicate the presence of a variety of heteroatoms by combining the prefixes stated above in the recommended order of oxa-, thia-, and aza- Inaddition, the proportion ofconnected foris indicated by prefixes dihydro-, tetrahydro-, etc. in partly saturated rings. These prefixes are used to signify partiallysaturated rings. For the purpose of assigning Arabic numerals for lowest possible numbers to the heteroatoms. If there is an oxygen atom, the numbering scheme begins with an oxygen atom (if present), and if there is a sulfur or nitrogen atom, the numbering scheme When counting the number of nitrogen atoms that are bonded together, one must start with the nitrogen atom that has the substituent. In a compound with maximum unsaturation, the fact that there are multiple possible configurations of double bonds can be denoted by labeling. This fact indicates that there are multiple possible configurations of double bonds. There are significant conceptual differences between homologous and heterologous sets.

References

1. Ashley E, McGready R, Proux S, Nosten F. Malaria .*Travel Med. Infect. Dis*. **2006**; 4: 159-173.
2. Kumar A, Katiyar SB, Agawal A, Chauhan PMS. Perspective in Antimalarial Chemotherapy.*Curr.Med. Chem*. **2003**; 10: 1137-1150.
3. http://www.who.int/mediacentre/factsheets/fs094/en/index.html.
    a) http://www.rollbackmalaria.org/wmr2005/pdf/intro_section.pdf.
    b) http://www.rollbackmalaria.org/wmr**2005**/pdf/section2.pdf.
4. www.niaid.nih.gov/topics/malaria/documents/malaria.pdf.
5. Kumar A, Katiyar SB, Agawal A, Chauhan PMS.Perspective in antimalarial chemotherapy .*Curr. Med. Chem*. **2003**; 10: 1137-1150.

6. Stocks PA, Raynes KJ, Ward SA. Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery (Ed.: P. J. Rosenthal), Humana, Totowa. **2001**; 235-253.
7. Wellems TE, Plowe CV. Chloroquine resistant malaria .*J. Infect. Dis*. **2001**; 184: 770-776.
8. Hastings IM. The origins of antimalarial drug resistance .*Trends Parasitol*. **2004**; 20:512-518.
9. Ginsburg H.Acta Trop. Should chloroquine be laid to rest? **2005**; 96:16-23.
10. Meshnick SR. Why does quinine still work after 350 years of use? *Parasitol. Today***1997**; 13:89-90.
11. Kevin BJ. Effectiveness of antimalarial drugs. *N. Engl. J. Med*. **2005**; 352: 1565-1577.
12. Suh KN, Kain KC, Keystone JS. Malaria. *Can. Med. Assoc. J*. **2004**; 170: 1693- 1702.
13. Pasvol G.Management of severe malaria: interventions and controversies. Infect. Dis. Clin. N. Am. **2005**; 19: 211-240.
14. http://www.who.int/malaria/docs/TreatmentGuidelines**2006**.pdf.
15. Taylor WRJ, White NJ. Antimalarial drug toxicity: a review .*Drug Saf*. **2004**; 27: 25-61.
16. Haynes RK, Vonwiller SC. From Qinghao, Marvelous Herb of Antiquity, to the Antimalarial Trioxane Qinghaosu - and Some Remarkable New Chemistry .*Acc. Chem. Res.***1997**; 30: 73-79.
17. Schmuck G, Roehrdanz E, Haynes RK, Kahl R. Neurotoxic Mode of Action of Artemisinin Antimicrob. *Agents Chemother*. **2002**:46: 821-827.
18. Franck X, Fournet A, Prina E, Mahieux R, Hocquemiller R, Figadere B. Biological evaluation of substituted quinazolines. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3635.
19. Winter RW, Cornell KA, Johnson LL, Isabelle LM, Hinrichs DJ, Riscoe MK. Hydroxy anthraquinazones as antimalarial agents. *Bioorg. Med.Chem. Lett*. **1995**, *5*, 1927.
20. Francois G, Timperman G, Eling W, Assi LA, Holenz J, Brigmann G. Naphthylisoquinazoline alkaloids against malaria: evaluation of curative potentials of dioncophylline C and dioncopeltine A against *Plasmodium berghei* in vivo. *Antimicrob. Agents Chemother*. **1997**, *41*, 2533.
21. Konig GM, Wright AD, Sticher O, Fronczek F. Two new sesquiterpenes isothiocyanates from marine sponge *Acanthella klethra*. *J. Nat. Prod*. **1992**, *55*, 633.
22. Radloff PD, Philipps J, Nkeyi M, Hutchinson D, Kremsner PG. Atovaquone and proguanil for *Plasmodium falciparum* malaria. *Lancet,* **1996**, *347*, 1511.
23. Chen M, Christensen SB, Zhai L, Rasmussen MH, Theander TG, Frokjaer S, Steffansen B, Davidsen J, Kharazmi A. The novel oxygenated chalcone, 2,4-dimethoxy-4'-butoxychalcone, exhibits potent activity against human malaria parasite Plasmodium falciparum in vitro and rodent parasites Plasmodium berghei and Plasmodium yoelii in vivo*J. infect. Dis.***1997**, *176*, 1327.
24. Francois G, Bringmann G, Dochez C, Schneider C, Timperman G. Assi, L. A. Activities of extracts and naphthylisoquinazoline alkaloids from Triphyophyllum peltatum, Ancistrocladus abbreviatus and Ancistrocladus barteri against Plasmodium berghei (Anka strain) in vitro.*J.Ethanopharmacol.***1995**, *46*, 115.
25. Singh SB, Zink DL, Polishook JD, Dombrowski AW, Darkin-Rattray SJ, Schmatz DM, Goetz MA. Apicidins: Novel cyclic tetrapeptides as coccidiostats and antimalarial agents from Fusarium pallidoroseum. *Tetrahedron Lett*. **1996**;37:8077.
26. Ancelin M, Calas M, Vidal-Sailhan V, Herbute S, Ringwald P, Vial H. Potential inhibitors of Plasmodium phospholipid metabolism with a broad spectrum of in vitro antimalarial activities. *Antimicrob Agents Chemother.* **2003**; 47:2590.
27. Martin RE, Henry RI, Abbey JL, Clements JD, Kirk K. The 'permeome' of the malaria parasite: an overview of the membrane transport proteins of Plasmodium falciparum. *Genome Biol.* **2005**; 6:R26.
28. Roberts F, Roberts CW, Johnson JJ, et al. Evidence for shikimate pathway in apicomplexan parasites. *Nature.***1998**; 393:801.
29. Jomaa H, Jochen W, Sanderbrand S, et al. Inhibitors of the nonmevalonate pathway of isoprenoid biosynthesis as antimalarial drugs. *Science.***1999**; 285:1573.

30. Doerig C, Endicott J, Chakrabarti D. Cyclin-dependent kinase homologues of Plasmodium falciparum. *Int J Parasitol.* **2002**; 32:1575.
31. [a]. Blackman M. Proteases involved in erythrocyte invasion by the malaria parasite: function and potential as chemotherapeutic targets. *Curr Drug Targets.* **2000**; 1:59.
32. [b]. Coteron M. jose, et al. Falcipian Inhibitors: Optimization Studies of the 2-Pyrimidinecarbonitrile Lead Series. *Jounral of Medicinal Chemistry* . 2010.
33. Salmon BL, Oksman A, Goldberg DE. Malaria parasite exit from the host erythrocyte: a two-step process requiring extraerythrocytic proteolysis. *Proc Natl Acad Sci USA.* **2000**; 98:271.
34. Bailly E, Jambou R, Savel J, Jaureguiberry G. Plasmodium falciparum: differential sensitivity in vitro to E-64 (cysteine protease inhibitor) and Pepstatin A (aspartyl protease inhibitor). *J Protozool.* **1992**; 39: 593.
35. Singh A, Rosenthal PJ. Comparison of efficacies of cysteine protease inhibitors against five strains of *Plasmodium falciparum*. *Antimicrob Agents Chemother.* **2001**; 45:949.
36. Pandey KC, Wang SX, Sijwali PS, Lau AL, McKerrow JH, Rosenthal PJ. The *Plasmodium falciparum* cysteine protease Falcipian-2 captures its substrate, hemoglobin, via a unique motif. *Proc Natl Acad Sci USA.* **2005**; 102:9138.
37. Rosenthal PJ, Olson JE, Lee GK, Palmer JT, Klaus JL, Rasnick D. Antimalarial effects of vinyl sulfone cysteine proteinase inhibitors. *Antimicrob Agents Chemother.* **1996**; 40:1600.
38. Lee BJ, Singh A, Chiang P, et al. Antimalarial activities of novel synthetic cysteine protease inhibitors. *Antimicrob Agents Chemother.* **2003**; 47:3810.
39. Barrett AJ, Rawlings ND. Evolutionary lines of cysteine peptidases. *Biol. Chem*. **2001**; 382: 727.
40. Barrett AJ, Rawlings ND, Woessner JF. Handbook of Proteolytic Enzymes. Academic Press, San Diego, CA.**1998**.
41. Turk V, Turk B, Turk D. Lysosomal cysteine proteases: facts and opportunities. *Eur. Mol. Biol. Org. J.* **2001**; 20: 4629.
42. Wu Y, Wang X, Liu X, Wang Y. Data-mining approaches reveal hidden families of proteases in the genome of malaria parasite. *Genome Res*. **2003**; 13: 601.
43. Rosenthal PJ. Protease inhibitors, in: Rosenthal PJ (Ed.), Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery. Humana Press, Totowa, NJ, **2001**: 325.
44. Shenai BR, Rosenthal PJ. Reducing requirements for hemoglobin hydrolysis by *Plasmodium falciparum* cysteine proteases. *Mol. Biochem. Parasitol*. **2002**; 122:99.
45. Francis SE, Sullivan Jr DJ, Goldberg DE. Hemoglobin metabolism in the malaria parasite *Plasmodium falciparum*. *Annu. Rev. Microbiol*.**1997b**: 51: 97.
46. McKerrow JH, Sun E, Rosenthal PJ, Bouvier J. The proteases and pathogenicity of parasitic protozoa. *Annu. Rev. Microbiol*.**1993**; 47: 821.
47. Lew VL, Tiffert T, Ginsburg H. Excess hemoglobin digestion and the osmotic stability of *Plasmodium falciparum*-infected red blood cells. *Blood***2003**; 101: 4189.
48. Bailly E, Jambou R, Savel J, Jaureguiberry G. Plasmodium falciparum: differential sensitivity in vitro to E-64 (cysteine protease inhibitor) and Pepstatin A (aspartyl protease inhibitor). *J. Protozool*. **1992**; 39:593.
49. Dluzewski AR, Rangachari K, Wilson RJ, Gratzer WB. Plasmodium falciparum: protease inhibitors and inhibition of erythrocyte invasion. *Exp. Parasitol*.**1986**; 62: 416.
50. Rosenthal PJ, McKerrow JH, Aikawa M, Nagasawa H, Leech JH. A malarial cysteine proteinase is necessary for hemoglobin degradation by Plasmodium falciparum. *J. Clin. Invest.***1988**; 82: 1560.
51. Gluzman IY, Francis SE, Oksman A, Smith CE, Duffin KL, Goldberg DE. Order and specificity of the Plasmodium falciparum hemoglobin degradation pathway. *J. Clin. Invest*. **1994**; 93: 1602.

52. Rosenthal PJ. Plasmodium falciparum: effects of proteinase inhibitors on globin hydrolysis by cultured malaria parasites. *Exp. Parasitol*. **1995**; 80: 272.
53. Gamboa de Dominguez ND, Rosenthal PJ. Cysteine proteinase inhibitors block early steps in hemoglobin degradation by cultured malaria parasites. *Blood*.**1996**; 87: 4448.
54. Francis SE, Banerjee R, Goldberg DE. Biosynthesis and maturation of the malaria aspartic hemoglobinases plasmepsins I and II. *J. Biol. Chem*. **1997a**; 272: 14961.
55. Debrabant A, Delplace P. Leupeptin alters the proteolytic processing of P126, the major parasitophorous vacuole antigen of Plasmodium falciparum. *Mol. Biochem. Parasitol*.**1989**; 33: 151.
56. Hadley T, Aikawa M, Miller LH. Plasmodium knowlesi: studies on invasion of rhesus erythrocytes by merozoites in the presence of protease inhibitors. *Exp. Parasitol*.**1983**; 55: 306.
57. Lyon JA, Haynes JD, Diggs CL, Chulay JD, Pratt-Rossiter JM. Plasmodium falciparum antigens synthesised by schizonts and stabilised at the merozoite surface by antibodies when schizonts mature in the presence of growth inhibitory immune serum. *J. Immunol*.**1986**; 136: 2252.
58. Salmon BL, Oksman A, Goldberg DE. Malaria parasite exit from the host erythrocyte: a two-step process requiring extraerythrocytic proteolysis. *Proc. Natl Acad. Sci*. USA.**2001**: 98: 271.
59. Wickham ME, Culvenor JG, Cowman AF. Selective inhibition of a two-step egress of malaria parasites from the host erythrocyte. *J. Biol. Chem*.**2003**; 278: 37658.
60. Rosenthal PJ. Protease inhibitors, in: Rosenthal PJ (Ed.), Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery. Humana Press, Totowa, NJ. **2001** pp. 325.
61. Breton CB, Blisnick T, Jouin H, Barale JC, Rabilloud T, Langsley G, Pereira da Silva LH. Plasmodium chabaudi p68 serine protease activity required for merozoite entry into mouse erythrocytes. *Proc. Natl Acad. Sci*. USA. **1992**; 89: 9647.
62. Hadley T, Aikawa M, Miller LH. Plasmodium knowlesi: studies on invasion of rhesus erythrocytes by merozoites in the presence of protease inhibitors. *Exp. Parasitol*. **1983**; 55: 306.
63. Greenbaum DC, Baruch A, Grainger M, Bozdech Z, Medzihradszky KF, Engel J, DeRisi J, Holder AA, Bogyo M. A role for the protease Falcipian 1 in host cell invasion by the human malaria parasite. *Science*.**2002**; 298: 2002.
64. Williamson KC, Fujioka H, Aikawa M, Kaslow DC. Stage-- specific processing of Pfs230, a Plasmodium falciparum transmission blocking vaccine candidate. *Mol. Biochem. Parasitol*.**1996**; 78: 161.
65. Brooks SR, Williamson KC. Proteolysis of Plasmodium falciparum surface antigen, Pfs230, during gametogenesis. Mol. Biochem. *Parasitol*.**2000**; 106: 77.
66. Eksi S, Czesny B, Greenbaum DC, Bogyo M, Williamson KC . Targeted disruption of Plasmodium falciparum cysteine protease, Falcipian 1, reduces oocyste production, not erythrocyte stage growth. *Mol. Microbiol*.**2004**; 53: 243.
67. Chiyanzu I, Elizabeth H, Jiri G, Rosethal PJ, Mckerrow J, Chibale K. Synthesis and evaluation of isatins and thiosemicarbazone derivatives against Cruzain, Falcipian-2, and Rhodesain. *Bioorg. Med. Chem. Lett*. **2003**; 13: 3527.
68. Greenbaum DC, Mackey Z, Hansell E, Doyle, P, Gut, J, Caffrey C R, Lehrman J, Rosenthal P J, Mckerrow J, Chibale K. Synthesis and SAR of parasiticidal thiosemicarbazone Cysteine Protease inhibitors against *Plasmodium Falciparum*, T. Brucei, T. Cruzi. *J. Med. Chem*. **2004**; 47: 3212.
69. Rosenthal P J, Dahl EL. Biosynthesis, localization and processing of Falcipian cysteine proteases of *Plasmodium falciparum*. *Molecular & Biochemical Parasitology*, **2005**; 139: 205.
70. Chiyanzu I, Clarkson C, Smith PJ, Lehman J, Gut J, Rosenthal PJ, Chibale K. Design Synthesis and anti-plasmodial evaluation in vitro of new 4-aminoquinazoline isatin derivatives. *Bioorg. & Med. Chem*. **2005**; 13: 3249.

71. Dominguez JN, Leon C, Rodrigues J, Gut J, Rosenthal PJ. Synthesis and Evaluation of new antimalarial phenylurenyl chalcone derivatives. J. *Med. Chem*. **2005**; 48: 3654.
72. Valente C, Guedes RC, Moreira R, Iley J, Gut J, Rosenthal PJ. Dipeptide vinyl sultams: Synthesis via the Wittig-Horner reaction and activity against papain, Falcipian-2 and *Plasmodium falciparum*. *Bioorg. & Med. Chem. Lett*. **2006**; 16: 4115.
73. Chipeleme A, Gut J, Rosenthal PJ, Chibale K. Synthesis and biological evaluation of phenolic Mannich bases of benzaldehyde and thiosemicarbazone derivatives against the cysteine protease Falcipian-2 and a chloroquine resistant strain of *Plasmodium falciparum*. *Bioorg. & Med. Chem.***2007**; 15: 273.
74. Verissimo E, Berry N, Gibbons P, Cristiano MLS, Rosenthal PJ, Gut J, Ward SA, O'Neill PM. Design and synthesis of novel 2-pyridone peptidometic Falcipian 2/3 inhibitors. *Bioorg. &Med. Chem. Lett*. **2008**; 18: 4210.
75. Loser R, Gut J, Rosenthal PJ, Frizler M, Gutschow M, Andrews KT. Antimalarial activity of azadipeptide nitriles. *Bioorg. &Med. Chem. Lett*. **2010**; 20: 252.
76. Hans RH, Guantai EM, Lategan C, Smith PJ, Wan B, Franzblau SG, Gut J, Rosenthal PJ, Chibale K. Synthesis, antimalarial and anti tubercular activity of acetylenic chalcones. *Bioorg. & Med. Chem. Lett*. **2010**; 20: 942.
77. Kerr ID, Lee JH, Pandey KC, Harrison A, Sajid M, Rosenthal PJ, Brinen LS. Structures of Falcipian-2 and Falcipian-3 Bound to Small molecule Inhibitors: Implications for Substrate Specificity. *J. Med. Chem*. **2009**; 52, 852.
78. Sijwali PS, Shenai BR, Gut J, Singh A, Rosenthal PJ. Expression and characterization of the *Plasmodium falciparum* haemoglobinase Falcipian-3. *Biochem. J*. **2001b**; 360:481.
79. Rosenthal PJ. Cysteine poteases of malaria parasite. *Int. J. of Parasitol*. **2004;** 34:1489.
80. Garcia LGE, Rodriguez JB. Current status and progress made in malaria chemotherapy. *Curr. Med. Chem*. **2007**; 14: 289.
81. Goldberg DE. Semin. Cell Biol. Hemoglobin degradation in *Plasmodium* infected red blood cells.**1993**; 4: 355.
82. Rosenthal PJ. Cysteine proteases of malaria parasites.*Int. J. Parasitol*. **2004**; 34: 1489.
83. Ersmark K, Samuelson B, Hallberg A.Plasmepsins as potential targets for new antimalarial therapy. *Med. Res. Rev*. **2006;** 26: 626.
84. Rosenthal PJ, Sijwali P S, Singh A., Shenai BR. Cysteine proteases of malaria parasite: targets for chemotherapy. *Curr. Pharm. Des*. **2002**, 8: 1659.
85. Hansch, C.; Leo, A.; *Substituent Constants for Correlation Analysis in Chemistry and Biology*, John Wiley & Sons, New York, **1979**.
86. Livingstone, DJ. Perspective: "The charactarization of chemical structure using molecular properties. A Survey". *J. Chem. Inf. Comput. Sci.***2000**; 40: 195.
87. Hansch C, Kurup A, Garg R, Gao H. A review of QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP lacking positive hydrophobic terms*Chem. Rev.***2001**; 101: 619.
88. Crum-Brown A, Fraser TR. On the connection between chemical constitution and physiological action. Part1. On the physiological action of the ammonium bases, derived from Strychia, Brucia, Thebaia, Codeia, Morphia and Nicotia. *Trans. R. Soc. Edinburgh.* **1868**; 25: 151.
89. Richet C, Seancs C R. Comptes Rendus des Seances de la Societe de Biologie et de ses Filiales. *Soc. Biol. Ses. Fil.***1893**; 9: 775.
90. Meyer H. "Welche eigenschaft der anaesthetica bedingt inre Narkotische wirkung?" *Arch. Exp. Pathol. Pharmakol.***1899**; 42: 109.
91. Overton, E.; *Studien Uber die Narkose*, Fischer, Jena, Germany, **1901**.
92. Ferguson J. The use of chemical potential as indices of toxicity. *Proc. R. Soc. London Ser. B.***1939**; 127: 387-404.

93. Hammett LP. *Chem. Rev.***1935**; 17: 125.
94. Hammett LP. '*Physical Organic Chemistry*', 2nd ed., McGraw-Hill, New York, **1970**.
95. Taft RW. *J. Am. Chem. Soc.***1952**; 74: 3120.
96. Guner OF. Pharmacophore perception, development, and use in drug design. International University Line, La Jolla, CA.**2000**.
97. Van Drie JH. Pharmacophor discovery- lessons learned. *Curr Pharm Design*. **2003**; 9:1649.
98. Topliss JG. Quantitative structure-activity relationships of drugs, Vol 19. Academic Press, New York. **1983.**
99. Martin YC. Quantitative drug design: a critical introduction. Marcel Dekker, New York.**1978**.
100. Hansch C, Fujita T. *J Am Chem Soc*. **1964**; 86:1616**.**
101. Gund P, Wipke WT, Langridge R. Computer searching of a molecular structure file for pharmacophoric patterns. Elsevier, Amsterdam. **1974**, 3: 33.
102. Kier LB, Hall LH .Molecular connectivity in chemistry and drug research. Academic Press, London. **1976**.
103. Hancsh C, Leo A. Substituent constants for correlation analysis in chemistry and biology. Wiley, New York. **1979**.
104. Hopfinger AJ. A QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP investigation of dihydrofolate reductase inhibition by Baker triazines based upon molecular shape analysis. *J Am Chem Soc*. **1980**;102:7196.
105. Van Drie JH, Weininger D, Martin YC. ALADDIN: an integrated tool for computer-assisted molecular design and pharmacophore recognition from geometric, steric, and substructure searching of 3-D molecular structures. *J Comput- Aided Mol Design.***1989**; 3:225.
106. Lauri G, Bartlett PA. CAVEAT: A program to facilitate design of organic molecules. *J Comput-Aided Mol Design*. **1994**; 8:51.
107. Van Drie JH. Strategies for the determination of pharmacophoric 3D database queries. *J Comput-Aided Mol Design*. **1997**; 11:39.
108. Chen X, Rusinko A, III Young SS. Recursive partitioning analysis of a large structure-activity data set using 3-D descriptors. *J Chem Inf Comput Sci* .**1998**;38:1054.
109. Chen X, Rusinki A, III Tropsha A, Young SS. *J Chem Inf Comput Sci*.**1999**; 39:887.
110. Greene J, Kahn S, Savoj H, Sprague P, Teig S. *J Chem Inf Comput Sci* .**1994**;34:1297.
111. Barnum D, Greene J, Smellie A, Sprague P. Identification of common functional configuration among molecules. *J Chem Inf Comput Sci*.**1996**; 36:563.
112. Martin YC, In Hansch C, Fujita T. Classical and 3D QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP in agrochemistry. American Chemical Society, Washington, DC. **1995**; 318.
113. Jones G, Willett P, Glen RC. A genetic algorithm for flexible molecular overlay and pharmacophore elucidation. *J Comput-Aided Mol Design*. **1995**; 9:532.
114. Cramer RD, Patterson DE, Bunce JD. COMFA: Effect of shape on binding of steroids to carrier proteins. *J Am Chem Soc*. **1988**; 110:5959.
115. Van Drie JH, In Guner OF .Pharmacophore perception, development, and use in drug design. International University Line, La Jolla, CA. **2000**; 517–530.
116. Phase, version 3.1, Schrodinger, LLC. New York, NY, 2009.
117. Lengauer T, Rarey M. "Computational methods for biomolecular docking". *Curr. Opin. Struct. Biol.* **1996**;6 (3): 402.
118. Shoichet BK, Kuntz ID, Bodian DL. "Molecular docking using shape descriptors". *Journal of Computational Chemistry* .**2004**;13 (3): 380.

119. Cai W, Shao X, Maigret B. "Protein-ligand recognition using spherical harmonic molecular surfaces: towards a fast and efficient filter for large virtual throughput screening". *J. Mol. Graph. Model*. **2002**;20 (4): 313.
120. Morris RJ, Najmanovich RJ, Kahraman A, Thornton JM. "Real spherical harmonic expansion coefficients as 3D shape descriptors for protein binding pocket and ligand comparisons". *Bioinformatics*. **2005**;21 (10): 2347.
121. Kahraman A, Morris RJ, Laskowski RA, Thornton JM. "Shape variation in protein binding pockets and their ligands". *J. Mol. Biol*. **2007**; 368 (1): 283.
122. Suresh PS, Kumar A, Kumar R, Singh VP. "An in silico [correction of insilico] approach to bioremediation: laccase as a case study".J. Mol. Graph. Model. 2008; 26 (5): 845.
123. Chipeleme A, Gut G, Rosenthal PJ, Chibale K. Synthesis and biological evaluation of phenolic Mannich bases of benzaldehyde and thiosemicarbazone derivative against the cysteine protease Falcipian2 and a chloroquine resistant strain of *P. falciparum*. *Bioorg. & Med. Chem*. **2007**; 15: 273.
124. Chiyanzu I, Gut J, Rosenthal PJ, Chibale K. Synthesis and evaluation of isatins and thiosemicarbazone derivatives against cruzain, Falcipian2 and Rhodesain. *Bioorg. & Med. Chem. Lett*. **2003**; 13: 3527.
125. Dominguez JN, Leon C. Synthesis and evaluation of new antimalarials Phenyl urenyl chalcone derivative. *J. Med. Chem*. **2005**; 48: 3654.
126. Gut J, Rosenthal PJ. Falcipian inhibitors: optimization studies of the 2- pyrimidino carbonitrile lead series. *J. Med. Chem*. **2010**.
127. Gund P. In *Pharmacophore Perception, Development, and Drug Design*; Gunner, O. F., Ed.; International University Line: La Jolla,CA, **2000**; 3.
128. Smellie A, Teig SL, Poling TP. Promoting Conformational Variation. *J. Comput. Chem.* **1995**; 16: 171.

How to cite this article: Amit Kumar Sen, and Rakesh Kr. Jat. "SYNTHESIS, DOCKING AND EVALUATION OF PYRIMIDINE DERIVATIVES AS ANTI-MALARIAL AGENTS". *Tropical Journal of Pharmaceutical and Life Sciences*, vol. 10, no. 5, Sept. 2023, pp. 18-49, https://informativejournals.com/journal/index.php/tjpls/article/view/145.

Published by:
Informative Journals
Jadoun Science Publishing Group India