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Research Article

In Silico Analysis for Anti-Malarial Activity of 2-Anilino 4-Amino Substituted Quinazolines.

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ABSTRACT

In the present work, important structural moieties that govern the anti-malarial activity (3D7) of 2-anilino 4-amino substituted quinazoline derivatives have been identified using consensus pharmacophore modeling. The method encompasses construction of pharmacophore modeling after optimization (MMFF94) followed by field-based alignment of most active three molecules. The study point outs that H-bond donor and acceptor groups as well as aromatic rings are vital for the anti-malarial activity. The outcomes could be advantageous for optimization of 2-anilino 4-amino substituted quinazolines as anti-malarial agents.

KEYWORDS

Pharmacophore modeling, Malaria, 2-anilino 4-amino substituted quinazolines

1. INTRODUCTION

Malaria is neglected disease with high prevalence in developing and undeveloped countries. It is a vector borne disease and *Plasmosdium falciparum* has been identified as the causative agent. The emergence of resistance has worsened the situation; consequently, developing new drugs is very important to eradicate this deadly disease [1-3]. Since, developing a drug is a long and costly process, alternative methods must be employed to have a drug in time.

To accomplish this aim, Computer Aided Drug Designing (CADD) is a method of choice because of advantages like cheaper, eco-benign, easy, fast and outcome focused nature. Hence, it is a better contemporary method for lead optimization. Pharmacophore modeling and QSAR analysis are very common ligand-based drug design (LBDD) thriving methods branches of CADD, especially when the target enzyme is unknown. Consensus pharmacophore modeling is employed widely since it is convenient and recognizes the common pharmacophoric patterns that are linked with the desired activity/property [4-6].

Recently, Gilson *et al* [3] screened2-anilino 4-amino substituted quinazoline derivatives for anti-malarial activity. The tested molecules have good variation in activity profile because of wide alterations in substituents. But they did not describe pharmacophoric features/pattern related with anti-malarial activity of 2-anilino 4-amino substituted quinazolines. Henceforth, in the present work, consensus pharmacophore modeling has been done to identify the significant structural moieties that govern the anti-malarial activity of 2-anilino 4-amino substituted quinazoline derivatives.

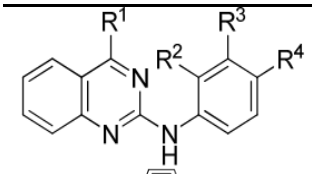
2. MATERIALS AND METHODS

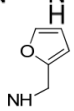
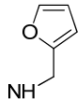
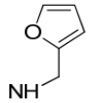
2.1. Dataset

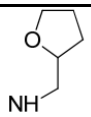
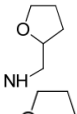
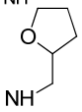
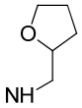
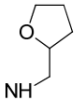
The dataset consists of fifty-six 2-anilino 4-amino substituted quinazoline derivatives with a variety of substituents like heterocyclic rings, -Br, -OCH_3, -F etc., especially positional isomers. Therefore, the present dataset encompasses wide chemical space. The compounds were tested for anti-malarial activity (3D7). The activity values described as EC_{50} (μM) range from 26 to 7700. The dataset has been tabulated in table 1.

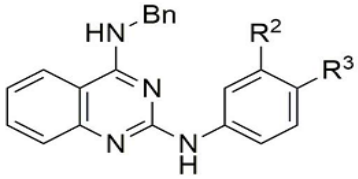
Table 1. Different substituted 2-anilino 4-amino substituted quinazolines along with reported EC_{50}used in the present work.

S. No	R^1	R^2	R^3	R^4	Pf Parasite EC_{50}(μM)

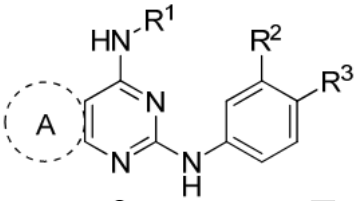


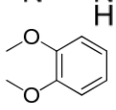
1		H	H	OCH_3	124
2		H	H	OCH_3	7700
3		H	H	OCH_3	1800
4		H	H	OCH_3	329
5		H	-OCH_2O-		7.8
6	$NHCH_3$	H	H	OCH_3	155
7	$NHCH_3$	H	H	F	136
8		H	H	F	418
9		H	H	CH_3	109
10		H	H	Br	125
11		H	H	Cl	113
12		H	H	F	112
14		H	Cl	H	134
15		H	F	H	144
16		F	H	H	317
17		H	H	CO_2CH_3	574
18		H	H	$CH(CH_3)OH$	702

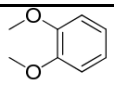
19		H	H	$C(O)NH_2$	691
20		H	H	$C(O)NH_2$	569
21		H	H	NHAc	274
22		H	$-OCH_2O-$		8.6
23		H	OCH	H	230
24		OCH_3	H	H	526
25		OCH_3	H		1100
26		OCH_3	OCH_3	H	1300



27	--	H	OCH_3	--	264
28	--	H	OCH_2CH_3	--	159
29	--	H	F	--	77
30	--	H	CF_3	--	105
31	--	Cl	Br	--	137
32	--	Cl	F	--	56
33	--	F	Cl	--	121
34	--	(N)	CF_3	--	102



35			H	F	57

36		Bn	H	F	41
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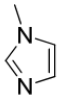
38		Bn	H	F	636
39		Bn	H	F	57
40		Bn	H	F	866
41		Bn	H	F	1200
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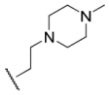
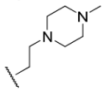
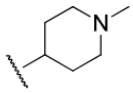
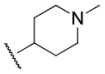
43			Cl	F	110
44			F	Cl	128
45			Cl	F	134
46			F	Cl	283
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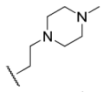
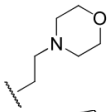
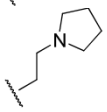
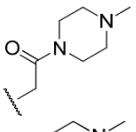
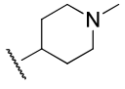
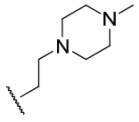
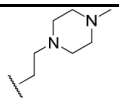
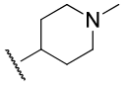
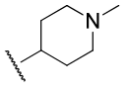
48	Ar		H	F	42
49	Ar		H	F	118
50	Ar		H	F	77
51	Ar		H	F	64
52	Ar		H	Cl	51
53	Ar		Cl	F	26

54	Ar		F	Cl	27
55	Ar		Cl	F	35
56	Ar		F	Cl	28

2.2. Structure drawing, optimization and alignment

ChemSketch 12 freeware was used to draw all the structures, followed by structure optimization using MMFF94 force field available in TINKER. In the next step, Open3dAlign software was used to align all the optimized structures. The aligned structures were imported in PyMOl 2.2forconsensus pharmacophore modeling using LIQUID plugin fusing the default settings [4-6].

3. RESULTS AND DISCUSSION

The consensus pharmacophore modeling identified that the anti-malarial activity is associated with seven pharamcophoric features. The central pharmacophoric feature contains the occurrence of three aromatic rings in a triangular arrangement. These three aromatic rings contribute toward hydrophobic nature of the molecule. The pharmacophore pattern also comprises of two H-bond donor groups positioned inside the trio of lipophilic aromatic rings. The pharmacophoric pattern also includes two lipophilic centers close to one of the rings. The following figure depicts this consensus pharmacophoric pattern along with their respective distances (shown using green color).

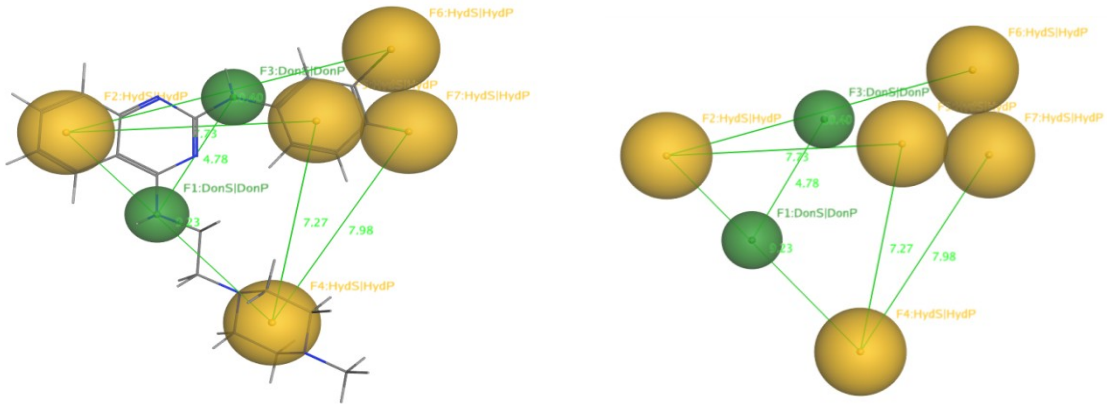


Figure 1. Consensus pharmacophoric pattern using the active molecule 26 as a representative only (Yellow: Hydrophobic, Green: H-bond donor groups)

4. CONCLUSION

Consequently, in future optimizations, the three-cornered arrangement of hydrophobic aromatic rings, two H-bond donor groups and two additional lipophilic center close to one of the rings must be retained for retention of anti-malarial activity.

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