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Research Article

Consensus Pharmacophore Modeling Analysis for Human Cellular Cytotoxicity (Hepg2) Activity of 2-Anilino 4-Amino Substituted Quinazolines.

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ABSTRACT
In the present work, extensive and consensus pharmacophore modeling has been performed to find the key structural features required for Human Cellular Cytotoxicity (HepG2) activity for congeneric 2-anilino 4-amino substituted quinazolines. The methodology involves field-based alignment of most active three molecules followed generation of pharmacophore modeling. The analysis reveals that H-bond donor and acceptor groups as well as aromatic rings are important for the activity profile. The results could be beneficial for future optimization of 2-anilino 4-amino substituted quinazolines.

KEYWORDS
Pharmacophore modeling, HepG2, 2-anilino 4-amino substituted quinazolines**.**

1. INTRODUCTION

Hep G2 is a human liver cancer cell line and a widely used *in vitro* model system for studying liver metabolism, toxicity of xenobiotics and polarized human hepatocytes, especially lipids in human hepatocytes. It has been employed to explore intracellular trafficking and dynamics of bile canalicular and sinusoidal membrane proteins [1,2].Hence, while drug developing it is important to test and optimize a drug candidate for HepG2 activity.

To achieve this goal, Computer Aided Drug Designing (CADD) is modern method widely used. CADD is preferred method for lead optimization due to advantages like cost effective, eco-friendly, robust, rapid and result oriented nature. Pharmacophore modeling and QSAR analysis are highly popular ligand-based drug design approaches under the umbrella of CADD, especially when the target enzyme is not known. Consensus pharmacophore modeling has gained high attention as it is useful to identify the common pharmacophoric features that are associated with the desired activity [3-5].

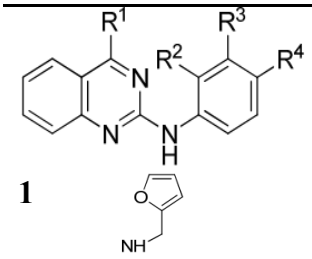
Recently, Gilson *et al* [6] reported HepG2 screening for 2-anilino 4-amino substituted quinazolines. The compounds have varying activity due to good variation in substituents. However, they did not report pharmacophoric pattern and features associated with HepG2 activity of 2-anilino 4-amino substituted quinazolines. Hence, in the present work, consensus pharmacophore modeling has been performed to find the important structural features required for Human Cellular Cytotoxicity (HepG2) activity of congeneric 2-anilino 4-amino substituted quinazolines.

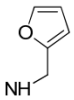
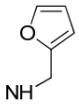
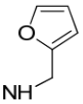
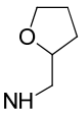
2. MATERIALS AND METHODS

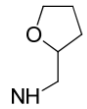
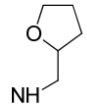
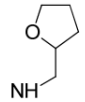
2.1. Dataset

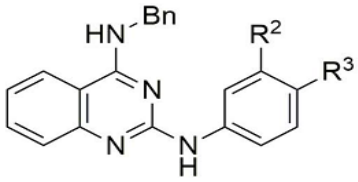
The dataset consists of fifty-five congeneric 2-anilino 4-amino substituted quinazolines with substituents like –Cl, -F, -OCH_3, etc. Thus, the present dataset covers acceptable chemical space. The compounds were screened for Human Cellular Cytotoxicity using HepG2 growth inhibition assay using Cell Titre-Glo. The activity values reported as EC_{50} (µM) range from 2.5 to 38.3. 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.

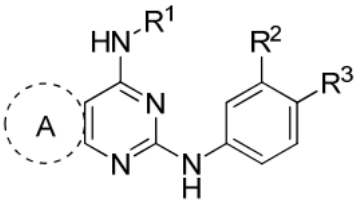
S. No	R^1	R^2	R^3	R^4	HepG2 EC_{50}(µM)
					
1		H	H	OCH_3	2.5

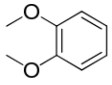
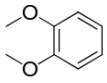
2		H	H	OCH_3	25.6
3		H	H	OCH_3	15.9
4	$NHCH_3$	H	H	OCH_3	26.1
5		H	-OCH_2O-		7.8
6	$NHCH_3$	H	H	F	16.2
7		H	H	F	20.1
8		H	H	CH_3	5.9
9		H	H	Br	19.0
10		H	H	Cl	7.4
11		H	H	F	4.9
12		H	Cl	H	5.0
14		H	F	H	8.6
15		F	H	H	21.3
16		H	H	CO_2CH_3	33.5
17		H	H	$CH(CH_3)OH$	12.6
18		H	H	$C(O)NH_2$	34.6
19		H	H	$C(O)NH_2$	20.0
20		H	H	NHAc	38.3

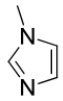
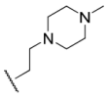
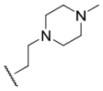
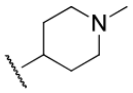
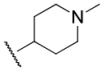
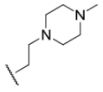
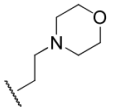
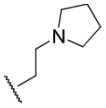
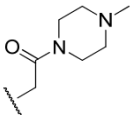
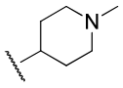
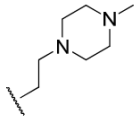
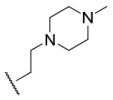
21		H	-OCH_2O-	8.6	
22		H	OCH		7.7
23		OCH_3	H	H	24.5
24		OCH_3	H		15.8
25		OCH_3	OCH_3	H	20.1

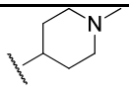
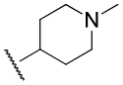


26	--	H	OCH_3	--	8.5
27	--	H	OCH_2CH_3	--	4.5
28	--	H	F	--	5.1
29	--	H	CF_3	--	6.4
30	--	Cl	Br	--	2.9
31	--	Cl	F	--	6.3
32	--	F	Cl	--	6.6
33	--	(N)	CF_3	--	8.9



34			H	F	5.5
35		Bn	H	F	2.8
36		Bn	H	F	17.8

37		Bn	H	F	12.4
38		Bn	H	F	18.2
39		Bn	H	F	18.7
40		Bn	H	F	9.0
41		Bn	H	F	26.0
42			Cl	F	8.9
43			F	Cl	12.3
44			Cl	F	11.5
45			F	Cl	11.1
46	Ar		H	F	27.9
47	Ar		H	F	15.3
48	Ar		H	F	30.1
49	Ar		H	F	26.5
50	Ar		H	F	30.4
51	Ar		H	Cl	11.5
52	Ar		Cl	F	6.1
53	Ar		F	Cl	7.5

54	Ar		Cl	F	5.1
55	Ar		F	Cl	5.1

2.2. Structure drawing, optimization and alignment

The structures were drawn using ChemSketch 12 freeware; optimization was accomplished using MMFF94 force field available in TINKER. Then, the optimized structures were aligned using Open3d Align software. The aligned structures were subjected to pharmacophore modeling using LIQUID plugin following the default settings [3-5].

3. RESULTS AND DISCUSSION

The pharmacophore analysis reveals that the activity is correlated with five structural features. The most important pharmacophoric feature includes the presence of three aromatic rings due to their hydrophobic nature. Interestingly, these three rings form a triangle like arrangement. The pharmacophore also consists of two H-bond donor groups situated within the triangle of aromatic rings. The following figures depict this consensus pharmacophoric pattern along with their respective distances (shown using green color).

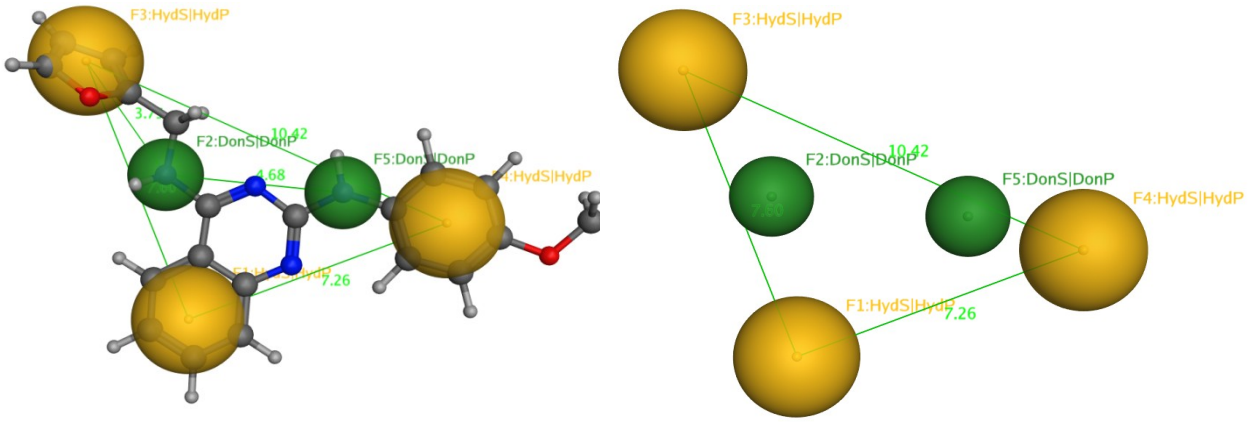


Figure 1. Consensus pharmacophoric pattern using the most active molecule 1 as a representative only (Yellow: Hydrophobic, Green: H-bond donor groups).

4. CONCLUSION

Therefore, in future optimizations, the triangular arrangement of three aromatic rings must be kept along with two H-bond donor groups for retention of activity for HepG2 cell line.

5. REFERENCES

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