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Design of Chalcones of 7-Azaindole as Raf-B Inhibitors

D. Giles*, V.N. Saiprabha, G. Yeshna

Acharya and BM Reddy College of Pharmacy, Achit Nagar Post, Bengaluru – 560 107, Karnataka, India.

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ABSTRACT

The present work deals with the design of 7-azaindole derivatives for its Raf-B inhibition. All the designed compounds follows Lipinski's rule of five. *In silico* ADME predictions of all the designed compounds suggests that none of the compounds have problem with bioavailability. The compounds were designed on the binding affinity towards the Raf-B inhibition. It was observed that few of the designed compounds were found to have significant interaction with the active site of the receptor. The compounds possessing 3-hydroxyl-2-methyl as substitution in chalcone was found to possess maximum docking score than other designed compounds.

1. Introduction

The Raf family kinases consist of three isoforms: A-Raf, B-Raf and C-Raf. B-Raf represents an interesting target for anticancer drug development as it is mainly involved in the Ras–Raf–MEK–ERK signal transduction pathway participating in cell proliferation and cell survival [1, 2]. B-Raf kinase is found to frequently mutate in melanomas, with the Val600/Glu600 (V600E) transition representing the most common mutation [3], accounting for over 90% in all of the B-Raf oncogenic mutants reported to date. Furthermore, this mutation type causes B-Raf to signal independently from upstream regulation [4]. The clinical approval of Vemurafenib and Dabrafenib for the treatment of metastatic melanoma bearing the B-RafV600E mutation has further confirmed that B-RafV600E may be an attractive target for anticancer therapy [5].

Molecular docking is used routinely to predict the binding strength of ligands in the target [6]. The efficacy of molecular docking may be significantly enhanced through discriminatory analysis for the selection of docking scores [7].

7-azindole derivatives have been found to be an important scaffold in the anticancer drug like Vemurafenib [8]. Chalcone derivatives have been an important class of compounds which is used as anticancer agents [9]. Hence conjugating the azaindole ring with chalcone could improve the binding affinity of compound which in turn the pharmacological activity increases.

As part of our continued interest in drug design of Raf-B inhibitors as anticancer agents, the present strategy, involves designing for chalcone derivatives of 7-azaindole as Raf-B inhibitors by docking study.

2. Experimental Methods

2.1 Drug-Likeness Evaluation

Drug-likeness rules are used for fast calculation of drug-like properties of a molecule. The predicted drug-likeness properties [10] like molecular weight, AlogP, Hydrogen bond donars, Hydrogen bond acceptors and number of rotatable bonds were reported in Table 1.

2.2 ADME Studies

All the designed compounds were subjected to absorption, distribution, metabolism and excretion descriptors using Discovery Studio 3.5. This study provides the insight into the pharmacokinetic property of the designed compounds [11]. The results were depicted in Fig. 1.

Table 1 Drug-likeness evaluation of the designed compounds

Ligand	No of H-bond donor	No of H-bond acceptor	Molecular weight (g/mol)	logP	No of rotatable bonds
1.	2	4	298.724	3.466	3
2.	4	5	279.293	2.055	3
3.	4	5	279.293	2.055	3
4.	2	4	278.305	3.288	3
5.	2	4	278.305	3.288	3
6.	1	4	357.201	3.776	4
7.	1	4	357.201	3.776	4
8.	1	5	308.331	3.011	5
9.	2	4	282.269	3.007	3
10.	1	3	248.279	3.043	3
11.	1	4	312.75	3.692	4
12.	1	4	312.75	3.692	4

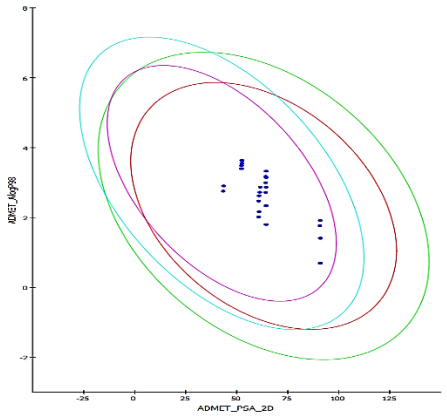

Fig. 1 ADME investigation of the designed compounds

2.3 Docking

2.3.1 Preparation of the Target Protein

The crystal structure of Raf-B (pdb: 4EHG) active site was employed as the template for molecule docking [12]. All crystallographic water molecules were removed. Hydrogen atoms were added using CHARMm

*Corresponding Author:sahayagiles@yahoo.com(D. Giles)

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force field. The site for docking was selected from the receptor cavity and protein was prepared using protein preparation tool.

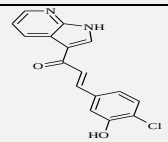
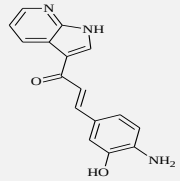
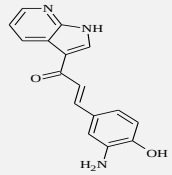
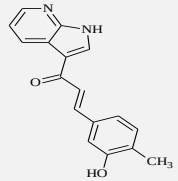
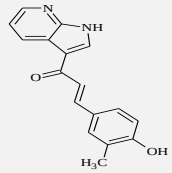
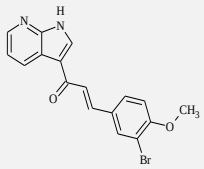
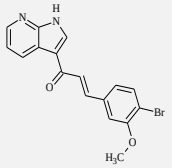
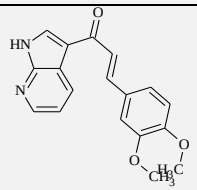
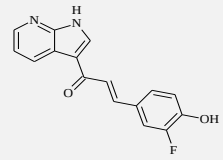
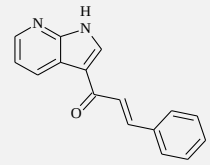
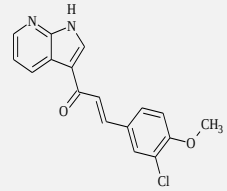
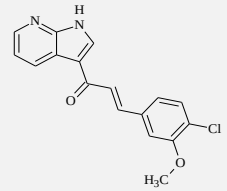
2.3.2 Ligand Preparation

Aza indole based ligand library was prepared and minimized using CHARMm force field [13]. The ligands were designed on the basis of binding group of azaindole to fit into the 1CX2 effectively. Methyl, amino, hydroxy, chloro, bromo, iodo, fluro, and nitro groups in phenyl ring were considered as mono or substituent form in chalcone. These compounds were designed on the basis of the binding affinity and the target specificity. A total of 12 compounds were designed for the docking study. All conformers were treated with the ligand minimization of the receptor ligand interaction module. Minimized ligand and protein were used for the docking studies.

2.3.3 Docking Studies

To identify the molecule binding interaction of the designed compound with the target, all the compounds were docked into the active sites of both the targets. Computational studies of novel azaindole derivatives where carried out using Discovery Studio 3.5. CDOCKER interaction energy, hydrogen bonding and the interacting amino acid involved in the binding where used to predict the effect of binding with the target. The results of docking were listed in Table 2. Docking poses were mentioned in Figs. 2 and 3.

Table 3 Docking study of Raf-B inhibitors

S.No.	Compound	C-docker interaction energy	Interacting amino acids	H-bond distance	Part of the ligand involved
1.		-17.5549	LYS483	1.78335	O11
2.		-28.8484	LYS483 THR529	1.86755 2.05177	O11 H31
3.		-7.0387	LYS483 LYS483	1.93547 1.81029	O11 O11
4.		-37.791	-	-	-
5.		-40.2868	CYS532 GLN530	2.86284 2.57379	N3 H34
6.		-36.2798	CYS532 GLN530	2.96635 2.42229	N3 H35
7.		-33.9054	LYS483	2.04414	O11
8.		-34.2681	LYS483	1.75269	O11
9.		-26.1049	LYS483	1.84323	O11
10.		-27.8466	LYS483	2.4758	O11
11.		-22.3591	LYS483	1.69613	O11
12.		-15.1297	LYS483	1.72599	O11

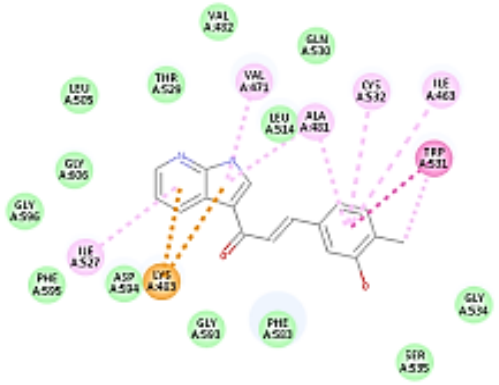


Fig. 2 Binding of compound 4 with Raf B

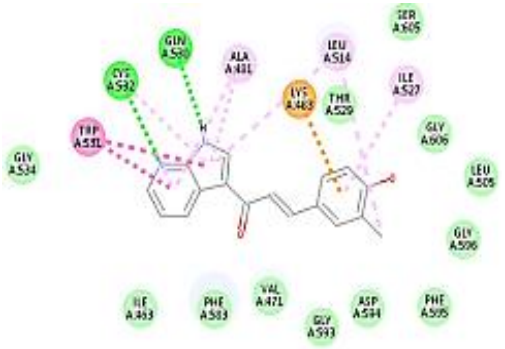


Fig. 3 Binding of compound 3 with Raf B

3. Results and Discussion

In this research work, we have designed 12 compounds for its possible Raf-B inhibition. All the minimized ligands were carried out for their

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ADME studies. All the compounds were well in accordance to the ADME parameters. It suggest that the compounds does not have any problem with the ADME. All the designed compounds also follow Lipinski Rule 5. Docking study was carried out for the designed compounds. It's effect of substitution in 3,4-substitution in phenyl ring when compared to that of the non-substituent.

Amino, chloro, hydroxy, methyl, methoxy, bromo, fluro were the substituent's studied in this research work. It was observed that presence of methyl and hydroxyl group as substituent at 3,4-position possess good CDOCKER interaction energy of -40.2868 toward the Raf-B target when compared to that of other substituents with two hydrogen bonding with the target. Reduction in the CDOCKER interaction energy of -37.791was found while interchanging the position. The compounds does not form hydrogen bonds with the target. CDOCKER interaction energy of unsubstituted phenyl group in the chalcone was found to be -27.8466 with one hydrogen bond of distance 2.4758. CDOCKER interaction energy of bromo and methoxy group as substituent in 3,4- position was found to be -36.2798 and -33.9054 respectively. The 3-bromo-4-methoxy group as substitutent was found to possess high interaction energy and two hydrogen bonds when compared to that of 4-bormo-3-methoxy group. 3-methoxy-4-chloro as substituent in phenyl ring of chalcone possess less CDOCKER interaction energy when compare to that of 3-chloro-4-methoxy group. Both interact with same amino acid LYS483 with one hydrogen bond each. Presence of dimethoxy group as substituent in phenyl ring possess good CDOCKER interaction energy of -34.2681. It forms one hydrogen bond with LYS483 with a bond length of 1.75269. High CDOCKER interaction energy difference was found with for compound with chloro and amino group as substitutent at 3,4th position in phenyl ring. Presence of 3-hydroxy-4-amino group as substituent possess good CDOCKER interaction energy of -28.8484 with two hydrogen bonds while the interaction reduces to -7.0387 on change of position of as 3-amino-4-hydroxyl group. Moderate CDOCKER interaction energy of -17.5549 was observed for compound with 3-hyroxy-4-chloro as substitution. Presence of 3-fluro-4-hydroxy group possesses good CDOCKER interaction energy of -26.1049 with one hydrogen bond with LYS483.

4. Conclusion

Twelve chalcone derivatives of 7-azaindole were designed for its Raf-B inhibition. The effect of substitution at 3,4-position was studied. It was found that all the designed compounds follow Lipinski's rule 5 and does not have any problem with ADME. Docking study reveals that all the compounds docked effectively towards the Raf-B target. Among all the designed compounds, substitution at 3-methyl-4-hydroxy group as substitution possesses good CDOCKER interaction energy when compared to that of other compounds. 4-methyl-3-hydroxyl group also possess good interaction energy. All the reports suggests that the presence of methyl and hydroxyl group as substitution at 4 and 3-position increases binding with Raf-B.

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