Asian Pub. Corp.

www.asianpubs.org

ARTICLE

Azaindole Derivatives as COX-2 Inhibitors: An *in silico* Approach

D. Giles✉ and V.N. Saiprabha

Asian Journal of Organic & Medicinal Chemistry

Volume: 3 Year: 2018
Issue: 2 Month: April–June
pp: 34–40
DOI: https://doi.org/10.14233/ajomc.2018.AJOMC-P111

Received: 29 April 2018
Accepted: 1 June 2018
Published: 27 June 2018

ABSTRACT

The main aim of the present work was to design novel chalcone derivatives of azaindole towards COX-2 inhibition. The compounds were designed targeting the effective binding by substitution in the phenyl ring attached to the chalcone. Most of the compounds were found to possess good affinity towards the target. All the designed compounds were within the rule of 5 as predicted by Lipinski's. Compounds with trimethoxy substitution in the phenyl ring possess good CDOCKER interaction energy. Among the 92 designed compounds substitution of methoxy, hydroxyl, amino group possess good interaction energy and hydrogen bonding.

KEYWORDS

CDOCKER, Cyclooxygenase, Docking, Inflammation.

INTRODUCTION

Cyclooxygenase (COX) metabolizes arachidonic acid to prostaglandin [1,2], which serves as the precursor for the biosynthesis of various prostaglandins, thromboxanes and prostacyclin. COX activity originates from two distinct and independently regulated isozymes [3], COX-1 and COX-2. COX-1 is a constitutive enzyme, which is responsible for the biosynthesis of prostaglandins in the gastric mucosa and in the kidney [4]. Whereas COX-2 is inducible and short-lived appears responsible for biosynthesis in inflammatory cells and the central nervous system.

Because of the pivotal role of cyclooxygenase in the inflammatory processes, non-steroidal anti-inflammatory drugs (NSAIDs) that suppress COX activities have been used clinically for the treatment of inflammatory diseases/syndromes [5]. All non-steroidal anti-inflammatory drugs inhibit the cyclooxygenase isozymes to different extents, which accounts for their anti-inflammatory. The COX-2 selective inhibition was designed to minimize gastrointestinal influx. Selective COX-2 inhibitors are a type of non-steroidal anti-inflammatory drug (NSAID) that directly targets cyclooxygenase-2 [6]. Few approved therapies exist for these acute inflammatory states, mainly due to the complex interplay of interacting inflammatory and physiological elements working at multiple levels. Also, COX-2 inhibition-derived suppressive or preventive effects against initiation/proliferation/invasion/motility/

Author affiliations:

Department of Pharmaceutical Chemistry, Acharya & B.M. Reddy College of Pharmacy, Achit Nagar Post, Bengaluru-560 107, India

✉To whom correspondence to be addressed:

E-mail: sahayagiles@yahoo.com

Available online at: http://ajomc.asianpubs.org

recurrence/metastasis of various cancers/tumours such as colon, gastric, skin, lung, liver, pancreas, breast, prostate, cervical and ovarian cancers are significant [7,8].

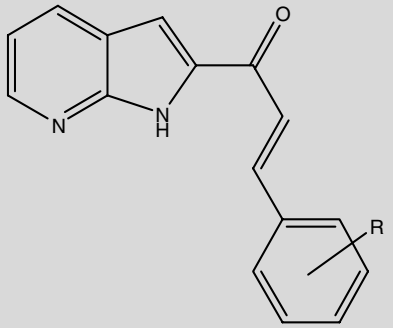
Most selective COX-2 inhibitors, including the drugs celecoxib [9,10] and rofecoxib [11], belong to the heterocyclic class of compounds. Azaindole being a heterocyclic compound which has a extensive role in inflammation [12,13], cancer [14,15], CNS activity [16]. In this study, we have designed several chalcone derivatives of azaindole for its effective binding towards COX-2.

EXPERIMENTAL

Computational studies of novelazaindole derivatives where carried out using discovery studio 3.5.

Drug-likeness: Drug-likeness rules are set of guidelines for the structural properties of compounds, used for fast calculation of drug-like properties of a molecule [17]. The predicted drug-likeness properties like molecular weight, A log P, hydrogen bond donars, hydrogen bond acceptors were reported in Table-1.

TABLE-1
STRUCTURAL PROPERTIES OF DESIGNED COMPOUNDS



Ligand code	R	m.f.	m.w.	A log P	No of HB donors	No of HB acceptor
1	2-OH, 4-Cl	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
2	3-OH, 4-Cl	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
3	2-Cl, 4-OH	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
4	2-Cl, 3-OH	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
5	2-Cl, 6-OH	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
6	2-Cl, 5-OH	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
7	3-Cl, 4-OH	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
8	2-OH, 3-Cl	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
9	2-OH, 5-Cl	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
10	3-OH, 5-Cl	$C_{16}H_{11}N_2O_2Cl$	299	3.757	3	2
11	3-OH, 4-NH_2	$C_{16}H_{13}N_3O$	279	2.346	4	3
12	2-NH_2, 3-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
13	2-NH_2, 4-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
14	3-NH_2, 5-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
15	3-NH_2, 4-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
16	2-NH_2, 4-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
17	3-NH_2, 2-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
18	4-NH_2, 2-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
19	2-NH_2, 6-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
20	5-NH_2, 2-OH	$C_{16}H_{13}N_3O_2$	279	2.346	4	3
21	3-OH, 4-CH_3	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
22	2-OH, 4-CH3	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
23	3-CH_3, 4-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
24	3-CH_3, 2-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
25	5-CH_3, 2-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
26	5-CH_3, 3-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
27	2-CH_3, 4-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
28	2-CH_3, 3-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
29	6-CH_3, 2-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
30	2-CH_3, 5-OH	$C_{17}H_{14}N_2O_2$	278	3.579	3	2
31	3-I, 4-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
32	3-I, 2-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
33	5-I, 2-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
34	5-I, 3-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
35	4-I, 3-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
36	4-I, 2-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
37	2-I, 3-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
38	2-I, 4-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2

39	6-I, 2-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
40	2-I, 5-OH	$C_{16}H_{11}N_2O_2I$	390	3.671	3	2
41	4-OCH_3, 3-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
42	4-OCH_3, 2-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
43	3-OCH_3, 4-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
44	3-OCH_3, 2-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
45	5-OCH_3, 2-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
46	3-OCH_3, 5-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
47	2-OCH_3, 4-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
48	2-OCH_3, 3-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
49	2-OCH_3, 6-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
50	2-OCH_3, 5-Br	$C_{17}H_{13}N_2O_2Br$	357	4.067	3	1
51	3-OCH_3, 4-OCH_3	$C_{18}H_{16}N_2O_3$	308	3.302	4	1
52	2-OCH_3, 4-OCH_3	$C_{18}H_{16}N_2O_3$	308	3.302	4	1
53	2-OCH_3, 3-OCH_3	$C_{18}H_{16}N_2O_3$	308	3.302	4	1
54	2-OCH_3, 5-OCH_3	$C_{18}H_{16}N_2O_3$	308	3.302	4	1
55	3-OCH_3, 5-OCH_3	$C_{18}H_{16}N_2O_3$	308	3.302	4	1
56	2-OCH_3, 6-OCH_3	$C_{18}H_{16}N_2O_3$	308	3.302	4	1
57	3-OH, 4-F	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
58	3-OH, 5-F	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
59	2-F, 5-OH	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
60	2-F, 3-OH	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
61	3-F, 4-OH	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
62	2-F, 4-OH	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
63	2-OH, 5-F	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
64	2-OH, 4-F	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
65	2-OH, 3-F	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
66	2-OH, 6-F	$C_{16}H_{11}N_2O_2F$	282	3.298	3	2
67	3-OH, 4-Br	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
68	2-OH, 4-Br	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
69	3-Br, 4-OH	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
70	2-OH, 3-Br	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
71	2-OH, 5-Br	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
72	3-OH, 5-Br	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
73	2-Br, 4-OH	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
74	2-Br, 3-OH	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
75	2-OH, 6-Br	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
76	2-Br, 5-OH	$C_{16}H_{11}N_2O_2Br$	343	3.841	3	2
77	–	$C_{16}H_{12}N_2O$	248	3.335	2	1
78	2-Cl, 4-OCH_3	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
79	3-Cl, 4-OCH_3	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
80	2-OCH_3, 4-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
81	2-OCH_3, 3-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
82	2-OCH_3, 6-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
83	2-OCH_3, 5-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
84	3-OCH_3, 4-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
85	3-OCH_3, 2-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
86	5-OCH_3, 2-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
87	3-OCH_3, 5-Cl	$C_{17}H_{13}N_2O_2Cl$	313	3.983	3	1
88	3,4,5 -OCH_3	$C_{19}H_{18}N_2O_4$	338	3.286	5	1
89	3-OCH_3, 2-OH	$C_{17}H_{14}N_2O_3$	294	3.076	4	2
90	2-OH	$C_{16}H_{12}N_2O_2$	264	3.093	3	2
91	4-NO_2	$C_{16}H_{11}N_3O_3$	293	3.229	4	1
92	4-OH	$C_{16}H_{12}N_2O_2$	264	3.093	3	2

Docking

Preparation of the target protein: The crystal structure of COX-2 (pdb: 1CX2) active site was employed as the template for molecule docking [18]. All crystallographic water molecules were removed. Hydrogen atoms were added using CHARMm force field. The site for docking was selected from the receptor cavity and protein was prepared using protein preparation tool.

Ligand preparation: Azaindole based ligand library was prepared and minimized using CHARMm force field. 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 92 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.

Docking studies: To identify the molecule binding interaction of the designed compound with the receptor all the compounds where docked into the active sites of both the targets. 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.

TABLE-2
DOCKING STUDY OF THE COMPOUNDS TOWARDS 1CX2

Ligand code	CDOCER interaction energy	Interaction ligand residue	H-bond distance (Å)	Interacting amino acid
1	-26.1565	O20	2.23901	ARG120
		N3	2.4389	TYR355
		O11	2.20546	ARG513
		OE1	2.08243	GLU524
2	-26.5813	Cl21	2.48612	LYS83
		O20	1.73729	LYS83
		N3	2.24466	TYR355
		O11	2.16385	ARG513
3	-17.7844	O11	2.32256	ARG513
4	-21.7038	N3	1.8485	TYR355
		N3	2.4098	ARG513
5	-23.0454	N3	1.84742	TYR355
		N3	2.36409	ARG513
		OE1	1.95144	GLU524
6	-24.5991	–	–	–
7	-25.7173	O11	2.36411	ARG513
		O11	2.26112	ARG513
8	-25.217	O20	2.26864	ARG120
		O11	2.22578	ARG513
		OE1	2.06845	GLU524
9	-19.6966	O20	2.19971	TYR355
10	-14.3761	N3	2.47405	ARG120
		O11	2.1765	ARG513
11	-26.4331	O20	1.77668	LYS83
		O11	2.45333	ARG513
		O11	2.21626	ARG513
12	-17.458	O11	2.40129	ARG513
13	-24.3074	O20	2.49382	ARG120
		OE1	2.32772	GLU524
		OE2	2.32606	GLU524
14	-28.2523	O20	1.76722	LYS83
		O11	2.4651	ARG513
		O11	2.17951	ARG513
15	-24.6129	O11	2.31698	ARG513
		O11	2.27848	ARG513
16	-19.6636	O11	2.27859	ARG513
17	-19.3076	O20	2.09624	TYR355
18	-24.5816	N3	2.25578	ARG513
19	-22.1813	O20	1.77193	TYR355
		O20	2.32524	ARG513
20	-28.1432	O20	2.24027	ARG120
		O11	2.4028	ARG513
		O11	2.17917	ARG513
		OE1	1.92597	GLU524
21	-24.8494	O11	2.3777	ARG513
		O11	2.20469	ARG513
22	-19.2525	O20	1.91088	TYR355
		O20	2.35044	ARG513
23	-20.7372	N3	2.24488	TYR355
		O11	2.13416	ARG513
24	-20.8854	N3	1.88992	TYR355
		N3	2.43124	ARG513
25	-25.3258	O20	1.77811	TYR355
		O20	2.24725	ARG513
26	-25.5792	O11	2.34961	ARG513
		O11	2.1837	ARG513
27	-18.0372	N3	1.86428	TYR355
		N3	2.34013	ARG513
28	-20.2559	O20	2.01098	LYS83
		O20	2.33154	LYS83
		O11	2.41202	ARG513
29	-18.1752	OE1	1.9205	GLU524
30	-27.2706	N3	2.39146	ARG513
31	-13.4619	N3	2.36139	LYS83
32	-28.9628	O20	2.23819	ARG120
		O20	2.43576	ARG120
		O11	2.3353	ARG513
		O11	2.18876	ARG513
		OE1	1.95583	GLU524
33	-29.8246	I21	2.41636	LYS83:
		O20	2.22272	ARG120
		O11	2.35521	ARG513
		O11	2.18846	ARG513
		OE1	1.91852	GLU524
34	-29.7312	O20	1.7441	LYS83
		O11	2.3348	ARG513
		O11	2.29718	ARG513:
35	-17.0651	O11	2.19886	TYR355
		O11	1.92531	ARG513
36	-20.9905	O11	2.23793	ARG513
37	-22.6658	N3	1.86916	TYR355
		N3	2.39976	ARG513
38	-28.9193	O20	2.11074	LYS83
		O20	2.41003	LYS83
		I21	2.4452	ARG120
		N3	2.32799	TYR355
		O11	2.11115	ARG513
39	-24.9513	N3	1.86154	TYR355
		N3	2.33082	ARG513
		OE1	1.92516	GLU524
40	-24.6784	N3	1.87495	TYR355:
		N3	2.40515	ARG513
41	-17.4841	N3	2.42531	ARG120
		N3	2.29866	ARG120
		O11	2.35619	TYR355
		O11	2.13663	ARG513
42	-23.6324	N3	1.88041	TYR355:
		N3	2.40173	ARG513
43	-29.375	O20	1.90212	LYS83
		O11	2.31849	ARG513
		O11	2.23999	ARG513
44	-18.1921	Br21	2.46141	TYR355
		O11	2.29999	ARG513
45	-26.2065	N3	1.87158	TYR355
		N3	2.37414	ARG513
46	-14.9547	–	–	–
47	-20.7212	O11	2.23224	ARG513
48	-23.9656	N3	1.87579	TYR355
		N3	2.41743	ARG513
49	-20.991	N3	1.87672	TYR355
		N3	2.32743	ARG513
50	-20.8256	O20	2.25274	ARG120
		O11	2.20635	ARG513
51	-20.5083	O11	2.37581	ARG513
52	-23.8806	O21	2.20256	TYR355
		O11	2.46007	ARG513

53	-25.2588	O20	2.24958	LYS83
		O20	2.48603	LYS83
		N3	1.87305	TYR355
		N3	2.45311	ARG513
54	-26.592	N3	1.87759	TYR355
		N3	2.4371	ARG513
55	-31.2811	O21	2.06818	LYS83
		O11	2.17413	ARG513
56	-20.2781	O21	2.33948	ARG120
		O11	2.45043	ARG513
57	-27.6366	O20	1.75456	LYS83
		O11	2.4502	ARG513
		O11	2.18984	ARG513
58	-16.2895	O11	2.27137	ARG513
59	-20.9455	O11	2.14811	ARG513
60	-16.0375	F21	2.10875	TYR355
61	-23.8339	O11	2.3423	ARG513
		O11	2.22535	ARG513
62	-19.9932	O11	2.14438	ARG513
63	-28.0164	F21	1.99492	LYS83
		O20	2.24407	ARG120
		O11	2.38719	ARG513
		O11	2.19542	ARG513
		OE1	1.92751	GLU524
		OE2	2.39927	GLU524
64	-20.7424	N3	1.88542	TYR355
		N3	2.47133	ARG513
65	-16.0076	O20	1.91644	TYR355
		O20	2.25393	ARG513
66	-22.9274	O20	2.16685	ARG120
		O11	2.10545	ARG513
		OE1	2.02703	GLU524
67	-26.9755	O20	1.79692	LYS83
		N3	2.19285	TYR355
		O11	2.14247	ARG513
68	-28.0518	O20	2.24979	ARG120
		O11	2.27774	ARG513
		O11	2.25869	ARG513
		OE1	1.94135	GLU524
		OE2	2.38056	GLU524
69	-26.0053	O20	2.2059	LYS83
		O20	2.27106	LYS83
		N3	2.38137	TYR355
		O11	2.1867	ARG513
70	-17.9909	N3	2.3909	LYS83
		O20	2.04478	TYR355
71	-20.4925	O20	2.14934	TYR355
72	-11.2637	-	-	-
73	-20.4404	O20	2.04869	LYS83
		O11	2.35478	ARG513
		O20	2.04869	LYS83
		O11	2.35478	ARG513
74	-17.6344	O11	2.30725	ARG513
		O11	2.30725	ARG513
75	-13.2746	N3	2.26735	ARG120
		N3	2.37271	ARG120
		O11	1.98175	TYR355
		O11	2.18334	ARG513
76	-19.5948	O11	2.28495	ARG513
		O11	2.28495	ARG513
77	-14.9674	O11	2.05964	ARG513
		O11	2.05964	ARG513
78	-20.0151	Cl21	2.43407	TYR355
		O11	2.35932	ARG513
		Cl21	2.43407	TYR355
		O11	2.35932	ARG513
80	-27.1269	O20	2.20744	ARG120
		O11	2.47948	ARG513
		O11	2.13912	ARG513
81	-19.7436	O11	2.40874	ARG513
		O11	2.40874	ARG513
82	-17.9339	O20	2.3398	ARG120
		O11	2.47283	ARG513
		O20	2.3398	ARG120
		O11	2.47283	ARG513
83	-21.8291	O20	2.22223	TYR355
		O20	2.22223	TYR355
84	-25.3127	O20	1.80689	LYS83
		N3	2.49615	TYR355
		O11	2.14702	ARG513
85	-21.7884	N3	1.87172	TYR355
		N3	2.39969	ARG513
86	-25.4565	N3	1.86571	TYR355
		N3	2.38508	ARG513
87	-21.8636	O11	2.10104	ARG513
88	-35.9675	O24	1.8015	LYS83
		O11	2.36899	ARG513
		O11	2.25047	ARG513
89	-22.7231	O20	2.31919	ARG120
		O11	2.03392	ARG513
		OE1	1.98727	GLU524
		O20	2.31919	ARG120
		O11	2.03392	ARG513
		OE1	1.98727	GLU524
90	-25.7324	O20	2.23668	ARG120
		O11	2.40473	ARG513
		O11	2.22358	ARG513
		OE1	1.93878	GLU524
91	-14.8911	N3	2.48489	LYS83
		N3	2.48489	LYS83
92	-23.933	N3	2.48489	LYS83
		O11	2.3723	ARG513
		O11	2.21936	ARG513

RESULTS AND DISCUSSION

Most of the compounds process good molecule properties. The CDOCKER interaction energy of the compound ranges from -35.9675 to -11.2637. Trisubstituted methoxy group derivative possess good CDOCKER interaction energy with -35.9675 with 3 hydrogen bonding with various amino acids like LYS83, ARG513 and LYS83. The distance of hydrogen bonds ranges from 1.8015 to 2.3689. As the hydrogen bond length is very less, it was expected to have good interaction with 1CX2. Compound 72 possess weak interaction with the target and possess least CDOCKER interaction energy with -11.2637. Most of the designed compounds were found to possess good interaction with 1CX2 (Figs. 1 and 2). Substitution of methoxy group in the phenyl ring possesses good interaction with the target when compared to other derivatives. Di, tri substitution was found to possess good binding affinity and hydrogen bonding. It was observed that presence of hydroxyl group in the structure possess good interaction hydrogen bonding if it was adjacent to chloro, methoxy and bromo. At the same time substitution of hydroxyl at 3rd position and bromo at 5th position loss binding was observed. Maximum interaction energy was found with substitution at 2-hydroxy and 3-hydroxy group. It could be due to restricted rotation towards of the phenyl ring which was adjacent to the carbonyl group. Compounds

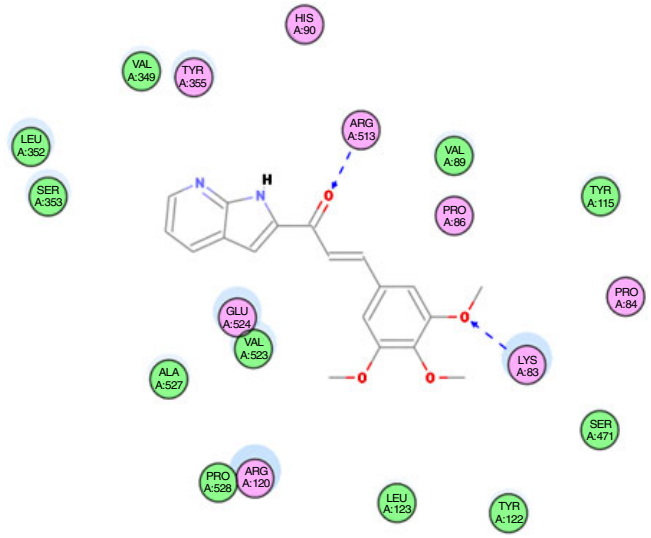


Fig. 1. Binding mode of compound **88** with 1CX2

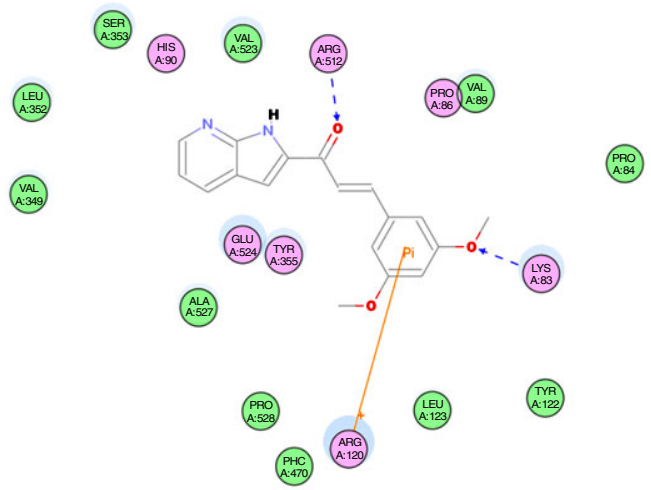


Fig. 2. Binding mode of compound **55** with 1CX2

with electron withdrawing group as substituent at 3-position was found to bind with ARG513 which was very much important for the pharmacological activity.

Presence of $–NH_2$ group at 2,3-position with OH group at 3,4- and 5-position possess good interaction with the amino acids similar to that of the standard. The different isomeric forms generated by the –OH and $–NH_2$ group were responsible for the effective interaction.

Most of the designed compounds bind with ARG513, TYR355, ARG120, LYS83, LYS83 and GLU524 with good hydrogen bonding. As per the previous literatures binding with these specific amino acids were expected to produce good pharmacological activity. Hence these designed compounds could act as good COX-2 inhibitors for its anti-inflammatory.

Conclusion

According to docking studies, we observed that the azaindole derivatives with trimethoxy group as substitution in phenyl ring possess good CDOCKER interaction energy towards COX-2. On the basis of this report, it is concluded that more research is required to prove its efficiency and specificity.

ACKNOWLEDGEMENTS

The authors are thankful to Rajiv Gandhi University of Health Science Karnataka, Bengaluru, India for the financial support. The authors are also thankful to The Chairman and The Principal of Acharya & BM Reddy College of Pharmacy, Bangalore, India for providing research facilities to carry out the work.

REFERENCES

1. S. Basu, Novel Cyclooxygenase?Catalyzed Bioactive Prostaglandin F2? from Physiology to New Principles in Inflammation, *Med. Res. Rev.*, **27**, 435 (2007); https://doi.org/10.1002/med.20098.
2. N.R. Ferreri, S.J. An and J.C. McGiff, Cyclooxygenase-2 Expression and Function in the Medullary Thick Ascending Limb, *Am. J. Physiol.*, **277**, F360 (1999).
3. E.M. Martin and S.L. Jones, Inhibition of Microsomal Prostaglandin E-Synthase-1 (mPGES-1) Selectively Suppresses PGE_2 in an *in vitro* Equine Inflammation Model, *Vet. Immunol. Immunopathol.*, **192**, 33 (2017); https://doi.org/10.1016/j.vetimm.2017.09.008.
4. Y.R. Tran Dinh, A. Jomaa, J. Callebert, A.M. Reynier-Rebuffel, A. Tedgui, A. Savarit and R. Sercombe, Overexpression of Cyclooxygenase-2 in Rabbit Basilar Artery Endothelial Cells after Subarachnoid Hemorrhage, *Neurosurgery*, **48**, 626 (2001); https://doi.org/10.1097/00006123-200103000-00037.
5. A.M. Mohassab, H.A. Hassan, D. Abdelhamid, M. Abdel-Aziz, K.N. Dalby and T.S. Kaoud, Novel Quinoline Incorporating 1,2,4-Triazole/Oxime Hybrids: Synthesis, Molecular Docking, Anti-inflammatory, COX Inhibition, Ulceroginicity and Histopathological Investigations, *Bioorg. Chem.*, **75**, 242 (2017); https://doi.org/10.1016/j.bioorg.2017.09.018.
6. H. Schroder, Nitric Oxide and Aspirin: A New Mediator for an Old Drug, *Am. J. Ther.*, **16**, 17 (2009); https://doi.org/10.1097/MJT.0b013e318164bd60.
7. S.E. Kassab, M.A. Khedr, H.I. Ali and M.M. Abdalla, Discovery of New Indomethacin-Based Analogs with Potentially Selective Cyclooxygenase-2 Inhibition and Observed Diminishing to PGE2 Activities, *Eur. J. Med. Chem.*, **141**, 306 (2017); https://doi.org/10.1016/j.ejmech.2017.09.056.
8. S. Hayashi, N. Ueno, A. Murase and J. Takada, Design, Synthesis and Structure-Activity Relationship Studies of Novel and Diverse Cyclooxygenase-2 Inhibitors as Anti-Inflammatory Drugs, *J. Enzyme Inhib. Med. Chem.*, **29**, 846 (2014); https://doi.org/10.3109/14756366.2013.864650.
9. L. Dhondt, M. Devreese, S. Croubels, S. De Baere, R. Haesendonck, T. Goessens, R. Gehring, P. De Backer and G. Antonissen, Comparative Population Pharmacokinetics and Absolute Oral Bioavailability of COX-2 Selective Inhibitors Celecoxib, Mavacoxib and Meloxicam in Cockatiels (*Nymphicus hollandicus*), *Sci. Rep.*, **7**, 12043 (2017); https://doi.org/10.1038/s41598-017-12159-z.
10. B. Zhang, K. Jin, T. Jiang, L. Wang, S. Shen, Z. Luo, Y. Tuo, X. Liu, Y. Hu and Z. Pang, Celecoxib Normalizes the Tumor Microenvironment and Enhances Small Nanotherapeutics Delivery to A549 Tumors in Nude Mice, *Sci. Rep.*, **7**, 10071 (2017); https://doi.org/10.1038/s41598-017-09520-7.
11. A. Aghazadeh-Habashi, W. Asghar and F. Jamali, Drug-Disease Interaction: Effect of Inflammation and Nonsteroidal Anti-Inflammatory Drugs on Cytochrome P450 Metabolites of Arachidonic Acid, *J. Pharm. Sci.*, **107**, 756 (2017); https://doi.org/10.1016/j.xphs.2017.09.020.
12. D. Riether, C. Harcken, H. Razavi, D. Kuzmich, T. Gilmore, J. Bentzien, E.J. Pack Jr., D. Souza, R.M. Nelson, A. Kukulka, T.N. Fadra, L. Zuvela-Jelaska, J. Pelletier, R. Dinallo, M. Panzenbeck, C. Torcellini, G.H. Nabozny and D.S. Thomson, Nonsteroidal Dissociated Glucocorticoid Agonists Containing Azaindoles As Steroid A-Ring Mimetics, *J. Med. Chem.*, **53**, 6681 (2010); https://doi.org/10.1021/jm100751q.

13. J. Yi and H. Fang, Theoretical Investigation on the Water-Assisted Excited-State Proton Transfer of 7-Azaindole Derivatives: Substituent Effect, *J. Mol. Model.*, **23**, 312 (2017); https://doi.org/10.1007/s00894-017-3487-5.
14. C. Barberis, N. Moorcroft, J. Pribish, E. Tserlin, A. Gross, M. Czekaj, M. Barrague, P. Erdman, T. Majid, J. Batchelor, M. Levit, A. Hebert, L. Shen, S. Moreno-Mazza and A. Wang, Discovery of N-substituted 7-Azaindoles as Pan-PIM Kinase Inhibitors – Lead Series Identification-Part II, *Bioorg. Med. Chem. Lett.*, **27**, 4735 (2017); https://doi.org/10.1016/j.bmcl.2017.08.068.
15. C. Yang, X. Zhang, Y. Wang, Y. Yang, X. Liu, M. Deng, Y. Jia, Y. Ling, L. Meng and Y. Zhou, Discovery of a Novel Series of 7-Azaindole Scaffold Derivatives as PI3K Inhibitors with Potent Activity, *ACS Med. Chem. Lett.*, **8**, 875 (2017); https://doi.org/10.1021/acsmedchemlett.7b00222.
16. G.M. Giblin, A. Billinton, M. Briggs, A.J. Brown, I.P. Chessell, N.M. Clayton, A.J. Eatherton, P. Goldsmith, C. Haslam, M.R. Johnson, W.L. Mitchell, A. Naylor, A. Perboni, B.P. Slingsby and A.W. Wilson, Discovery of 1-[4-(3-Chlorophenylamino)-1-methyl-1*H*-pyrrolo[3,2-c]-pyridin-7-yl]-1-morpholin-4-ylmethanone (GSK554418A), A Brain Penetrant 5-Azaindole CB2 Agonist for the Treatment of Chronic Pain, *J. Med. Chem.*, **52**, 5785 (2009); https://doi.org/10.1021/jm9009857.
17. G.S. Hassan, S.M. Abou-Seri, G. Kamel and M.M. Ali, Celecoxib Analogs Bearing Benzofuran Moiety as Cyclooxygenase-2 Inhibitors: Design, Synthesis and Evaluation as Potential Anti-inflammatory Agents, *Eur. J. Med. Chem.*, **76**, 482 (2014); https://doi.org/10.1016/j.ejmech.2014.02.033.
18. A. Manikandan, S. Ravichandran, K.I. Sathiyanarayanan and A. Sivakumar, Efficacy of Phenyl Quinoline Phenol Derivatives as COX-2 Inhibitors; An Approach to Emergent the Small Molecules as the Anti-inflammatory and Analgesic Therapeutics, *Inflammopharmacology*, **25**, 621 (2017); https://doi.org/10.1007/s10787-017-0342-3.