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Molecular docking of 6-halo-2,3-disubstituted-4(3H)-quinazolinone derivatives as COX-II inhibitors

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAID's) are considered one of the most commonly prescribed drugs all over. The most recent and powerful NSAID's are COX-II inhibitors; which are clinically effective anti-inflammatory agents with less gastrointestinal and renal toxicity, yet they had serious side effects like myocardial infarction. Therefore, there is still a need to develop better therapeutically effective and tolerable COX-II inhibitors. In this study, screening of various 2,3-disubstituted-4(3H)-quinazolinones, using the Molsoft ICM 3.5; a docking software; against the COX-II enzyme is reported. Various molecular structures of ligands were docked and scored to identify structurally similar ligands to celecoxib (reference ligand) in binding interaction to COX-II binding site. The results show that 2,3-disubstituted-4(3H)-quinazolinones moiety with cyclohexyl at C-2, and aryl moiety at N-3 binds directly or indirectly to the ring system with high binding affinity. The docked ligand has orientations completely different from that of the reference drug celecoxib.

Keywords: anti-inflammatory drugs; (3H)-Quinazolin-4-ones; Molecular docking and COX-II

INTRODUCTION

The search for new, effective and safe drugs is increasingly a sophisticated process. Two pronounced characteristics marked the modern age of the drug discovery process, "competitiveness" and "high cost". Driven by the high exclusive marketing profit, competition between pharmaceutical companies is much more intensive than ever before. Also, it is a competition by innovation [1]as highlighted by the title of an article in a research management journal: "'Innovate or die' is the first rule of international industrial competition" [2]. Recent statistics shows that it would take 10-15 years, 200-350 million U.S. dollars to discover a new drug and this cost has been growing at a rate of 20% per year [3]. To help alleviate this problem, efforts have been directed to reduce the cost and time span needed for the discovery stage of a new drug. In this aspect, more and more computer approaches are now being developed to reduce the cost and cycle time for discovering a new drug. Molecular docking represents one of the growing applications in drug discovery, where molecular modeling techniques are used to predict how any macromolecules (typically a protein) interact with other molecules (may be other proteins, nucleic acids or small drug-like molecules)[4].Current COX-II inhibitors may increase the risk of serious, even fatal stomach and intestinal adverse reactions, such as ulcers, bleeding, and perforation of the stomach or intestines but to a lesser extent than other nonselective NSAIDs that block both COX-1 and COX-II. These events can occur at any time during treatment and without warning symptoms. 3H-Quinazolin-4-one moiety is found in many biologically active natural products[5-7], such as the alkaloid L-Vasicinone **1**[8], Chrysogine **2** [5]. For anti-inflammatory agents with less gastrointestinal and renal toxicity, there is now convincing evidence that highly selective COX-II inhibitors alter the

balance in the COX pathway. However,there is still a need for novel, selective, and potent COX-II inhibitors with an improved profile, compared to current COX-II inhibitors based on structural templates modification.In recent years 3*H*-quinazolin-4-one and their derivatives have drawn great attention in the field of synthetic medicinal chemistry as they were reported to possess significant pharmacological activity [9-12].It is, also, found in many FDA approved drugs such as the sedative hypnotic methaqualone **3**, the diuretic and antihypertensive quinethazone **4** and thethiazide-like diureticmetolazone **5** [13] (Fig. 1).

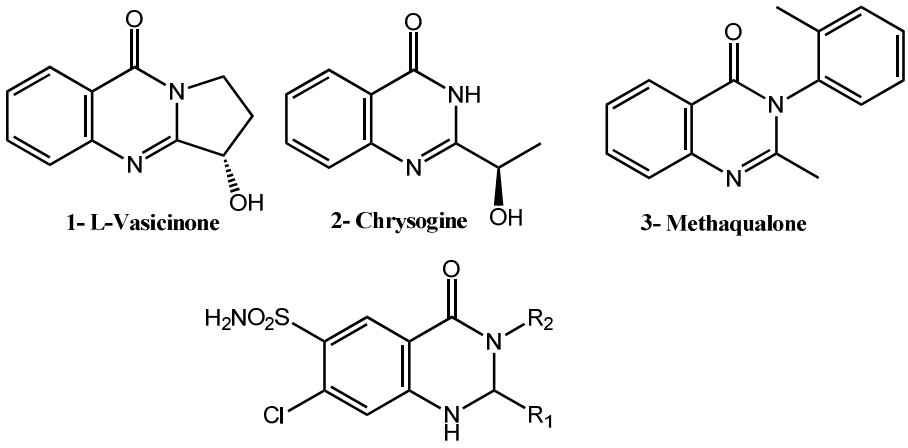


Fig. 1: FDA approved quinazoline drugs

Several other quinazoline derivatives exhibit a multitude of interesting pharmacological activities including anti-convulsant[14], anti-diabetic[15] and analgesic actions [16]. Recently, it has been reported that several quinazoline derivatives possess powerful anti-inflammatory activities with COX-II inhibition selectivity [17-19]. Based on these findings, it seemsrational to virtually screen a small library of new 2-pyridyl (3H)-quinazolin-4-one derivatives for their COX-II selectivity as potential anti-inflammatory agents using Molsoft-Pro (ICM 3.05a) docking software.

MATERIALS AND METHODS

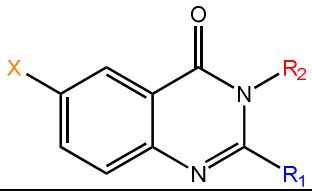
Molecular modeling studies

All docking studies were performed using 'Internal Coordinate Mechanics (Molsoft ICM 3.5-0a).

Preparation of small molecules

A set of 3H-quinazolin-4-one derivatives designed to inhibit cyclooxygenase II was compiled by us using ChemDraw. Structures were constructed using Chem 3D ultra 12.0 software, [Molecular Modeling and Analysis; Cambridge Soft Corporation, USA (2010)]. Tested compounds were then energetically minimized by using MOPAC (semi-empirical quantum mechanics), Jobtype with 100 iterations and minimum RMS gradient of 0.01, and saved as MDL MolFile (* .mol). All docking studies were carried out using Molsoft ICM 3.5-0a software. ICM docking is probably the most accurate predictive tool of binding geometry today [20,21] and generation of ligand and enzyme structures.The crystal structure of target protein cyclooxygenase (3LN1) is a COX-II complexed with celecoxib was retrieved from the Protein Data Bank (http://www.rcsb.org/pdb/welcome.do). All bound waters ligands and cofactors were removed from the protein. Docking results of all tested compounds are shown in (Table 1).

Table 1: Docking results of 6-halo substituted quinazoline derivatives against COX-II crystal structure

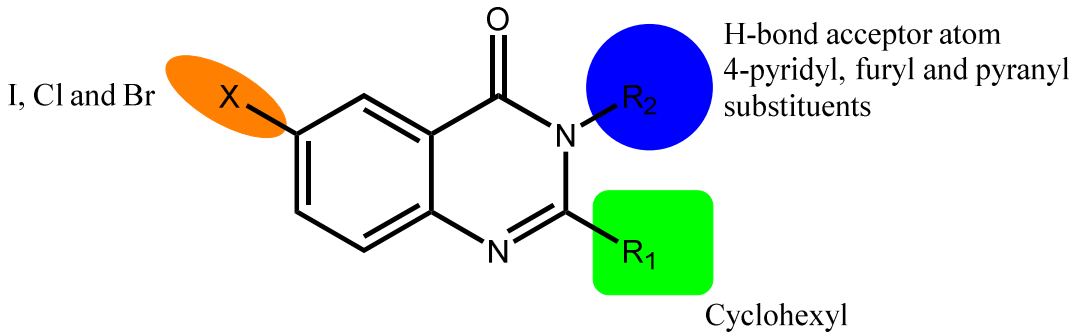


Cpd. No.	R_1	R_2	X	Docking score (Kcal/mol)	No. of Hydrogen bonds	Amino acid residues forming hydrogen bonds in A^0
Ligand (Celecoxib)				-102.24	6	R499 hh11 - m M o2 :2.56 F504 hn -- m M o1 :2.61 Q178 oe1 -- m M h6 :2.09 L338 o -- m M h5 : 2.52 L338 o -- m M h6 : 2.26 S339 o -- m M h5 :2.10
1.	Me	phenyl	Cl	-58.27	0	------
2.	Me	phenyl	Br	-58.18	0	------
3.	Me	phenyl	I	-64.17	1	T192 hg1 - m M n1 : 2.22
4.	Me	4-Pyridyl	Cl	-60.47	1	S516 hg - m M o1 :2.60
5.	Me	4-Pyridyl	Br	-62.42	0	------
6.	Me	4-Pyridyl	I	-61.01	0	------
7.	Me	2-Furyl	Cl	-64.95	1	T192 hg1 - m M n1:2.16
8.	Me	2-Furyl	Br	-62.52	0	------
9.	Me	2-Furyl	I	-62.27	1	T192 hg1 - m M n1 : 2.26
10.	Me	2-Theinyl	Cl	-57.19	0	------
11.	Me	2-Theinyl	Br	-65.69	1	T192 hg1 - m M n1 : 2.21
12.	Me	2-Theinyl	I	-62.94	1	Y371 hh -- m M n3 : 2.41
13.	Me	4H-pyran-2-yl	Cl	-64.91	1	T192 hg1 - m M n1:2.30
14.	Me	4H-pyran-2-yl	Br	-59.53	0	------
15.	Me	4H-pyran-2-yl	I	-63.87	0	------
16.	Et	phenyl	Cl	-65.24	0	------
17.	Et	phenyl	Br	-64.53	1	S516 hg -- m M o1 : 2.60
18.	Et	phenyl	I	-69.57	0	------
19.	Et	4-Pyridyl	Cl	-64.76	1	Y341 hh - m M o1: 2.64
20.	Et	4-Pyridyl	Br	-69.89	0	------
21.	Et	4-Pyridyl	I	-61.70	0	------
22.	Et	2-Furyl	Cl	-69.33	1	S516 hg -- m M o1 :2.61
23.	Et	2-Furyl	Br	-61.93	1	S516 hg -- m M o1 : 2.72
24.	Et	2-Furyl	I	-66.98	0	------
25.	Et	2-Theinyl	Cl	-68.04	0	------
26.	Et	2-Theinyl	Br	-69.33	0	------
27.	Et	2-Theinyl	I	-68.33	0	------
28.	Et	4H-pyran-2-yl	Cl	-64.37	1	S516 hg -- m M o1 :2.53
29.	Et	4H-pyran-2-yl	Br	-69.28	0	------
30.	Et	4H-pyran-2-yl	I	-70.25	1	Q447 he22 -m M o1 :2.72
31.	n-Pr	phenyl	Cl	-63.50	1	Y341 hh - m M o1 :2.64
32.	n-Pr	phenyl	Br	-72.81	0	------
33.	n-Pr	phenyl	I	-64.49	0	------
34.	n-Pr	4-Pyridyl	Cl	-66.96	1	S516 hg - m M n3: 1.78
35.	n-Pr	4-Pyridyl	Br	-66.53	1	S516 hg -- m M n3 :1.58
36.	n-Pr	4-Pyridyl	I	-68.28	0	------
37.	n-Pr	2-Furyl	Cl	-70.33	0	------
38.	n-Pr	2-Furyl	Br	-59.68	0	------
39.	n-Pr	2-Furyl	I	-70.25	1	Q447 he22 - m M o1:2.72
40.	n-Pr	2-Theinyl	Cl	-68.13	0	------
41.	n-Pr	2-Theinyl	Br	-70.20	0	------
42.	n-Pr	2-Theinyl	I	-61.48	1	Y341 hh -- m M o1 : 2.77
43.	n-Pr	4H-pyran-2-yl	Cl	-62.67	0	------
44.	n-Pr	4H-pyran-2-yl	Br	-68.09	0	------
45.	n-Pr	4H-pyran-2-yl	I	-71.43	1	R29 hh11 -m M n3: 2.07
46.	t-bu	phenyl	Cl	-60.10	0	------
47.	t-bu	phenyl	Br	-59.61	0	------
48.	t-bu	phenyl	I	-70.28	0	------
49.	t-bu	4-Pyridyl	Cl	-64.83	0	------

50.	t-bu	4-Pyridyl	Br	-68.20	0	------
51.	t-bu	4-Pyridyl	I	-71.30	0	------
52.	t-bu	2-Furyl	Cl	-68.89	0	------
53.	t-bu	2-Furyl	Br	-68.18	0	------
54.	t-bu	2-Furyl	I	-66.13	0	------
55.	t-bu	2-Theinyl	Cl	-66.06	1	Q447 he22 m M o2: 2.58
56.	t-bu	2-Theinyl	Br	-68.89	1	R29 hh11 -m M n3 : 2.11
57.	t-bu	2-Theinyl	I	-60.96	0	------
58.	t-bu	4H-pyran-2-yl	Cl	-59.51	0	------
59.	t-bu	4H-pyran-2-yl	Br	-66.51	1	Y341 hh - m M o1 : 2.28
60.	t-bu	4H-pyran-2-yl	I	-68.10	0	------
61.	Cyclohexyl	phenyl	Cl	-75.00	0	------
62.	Cyclohexyl	phenyl	Br	-81.07	0	------
63.	Cyclohexyl	phenyl	I	-76.05	0	------
64.	Cyclohexyl	4-Pyridyl	Cl	-77.31	0	------
65.	Cyclohexyl	4-Pyridyl	Br	-76.33	0	------
66.	Cyclohexyl	4-Pyridyl	I	-78.67	0	------
67.	Cyclohexyl	2-Furyl	Cl	-80.44	0	------
68.	Cyclohexyl	2-Furyl	Br	-71.68	0	------
69.	Cyclohexyl	2-Furyl	I	-74.12	0	------
70.	Cyclohexyl	2-Theinyl	Cl	-79.52	0	------
71.	Cyclohexyl	2-Theinyl	Br	-80.60	0	------
72.	Cyclohexyl	2-Theinyl	I	-68.00	0	------
73.	Cyclohexyl	4H-pyran-2-yl	Cl	-75.95	0	------
74.	Cyclohexyl	4H-pyran-2-yl	Br	-63.72	0	------
75.	Cyclohexyl	4H-pyran-2-yl	I	-79.13	0	------

RESULTS AND DISCUSSION

The aim of the flexible docking calculations is prediction of correct binding geometry for each binder. The scoring functions and hydrogen bonds formedwith the surrounding amino acids of the receptor COX-II are used to predict tested compounds binding modes. Celecoxib was used as reference drug for binding mode towards COX-II binding site. In the aspect a set of 75compounds of 2,3-disubstituted-4(3H)-quinazolinone derivatives of the general structure (Fig.2) was chosen for docking study against crystal structure of COX-II PDB id (3LN1). Celecoxib, the reference drug, showed binding energy of -102.24 Kcal/mol forming six hydrogen bonds with COX-II amino acid residues. On the other hand, docking results of all tested compounds towards COX-II crystal structure reveal moderate to high affinity ranging from -58.53 to -81.07 Kcal/ mol.



X= Cl, Br; R1=CH3, Ethyl, Isopropyl, t-Bu and cyclohexyl
R2= phenyl, 4-pyridyl, thiophyl, furyl and pyranyl
Fig. 2: General structure of tested compounds

The tested compounds were divided into three major groups according to their halogen substituent in position 6 of the quinazoline ring where group 1 are compoundsthat are 6-chloro substituted, and group 2 are 6- bromo substituted quinazoline ring compounds, and group 3 are 6-iodo substituted quinazoline compounds(Table 1). All tested compounds in all group A, B and C showed moderate to high affinity towards COX-II with zero or one hydrogen bond at the receptor's binding site.The poses of the highest binding derivatives **23, 24, 46, 49,72** and **75** to the binding site of COX-II are shown below (Fig 3).

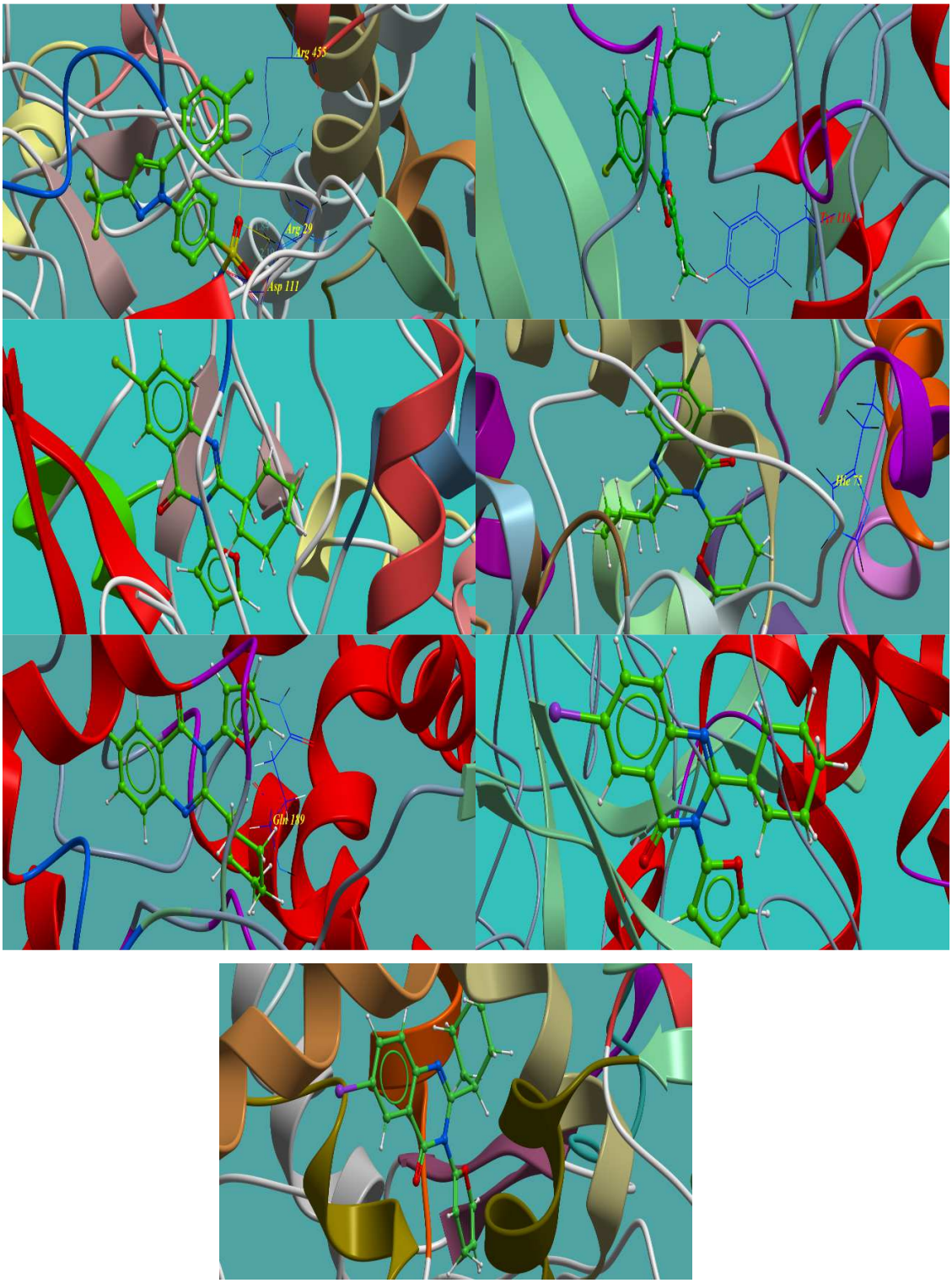


Fig. 2: Binding mode of the Compounds celecoxib,23, 24, 46, 49, 72 and 75 in greeninto binding site of COX-II

The type of halogen substituent at position 6 of the quinazoline ring did not affect the binding energy as chloro, bromo andiodo substituents showed similar binding energy values to the COX-II receptor. The binding energy of tested compounds increased substantially when the alkyl group at position 2 of the quinazoline ring was cyclohexyl

ring compared to methyl, ethyl, isopropyl and t-Bu.The type of aryl substituents at position 3 of the quinazoline ring showed little or no effect on the binding energy value.Hydrogen bonding between the tested ligands and COX-II appears only in case of the presence of hydrogen acceptor atom on the substituent like in case of 4-pyridyl, furyl and pyranyl substituents (Fig. 2).The ligands that showed hydrogen bonding with amino acid residues of COX-II have in many cases bind to the amino acid Ser-516 which indicates that this particular amino acid plays an important role in binding the quinazoline derivatives with hydrogen acceptor atom to theCOX-II binding site. The highest binding energy ligands were those containing cyclohexyl substituents in position 2 of the quinazoline ring (Table 1).Since most of the tested compounds showed moderate to high affinity towards COX-II receptor compared to the reference drug celecoxib, it is obvious that the tested quinazoline derivatives bind to COX-II in completely different pattern. The lack of hydrogen bonding formation groups in most of the tested compounds appears to be the major reason for the moderate binding energies to the COX-II binding site, which suggests that adding substituents with hydrogen bonding formation ability might increase the binding energies and, therefore, might increase the biological activity of 2,3-disubstituted-4(3H)-quinazolinone as potential anti-inflammatory agents.

CONCLUSION

By combining the results from this preliminary study with the literature data of anti-inflammatory activity of 2,3-disubstituted quinazolin-4-one derivatives, we can conclude that these compounds are considered potential drug candidates for its expected anti-inflammatory activity. The presence of cyclo aliphatic substituents in position 2 of the quinazoline ring is important to enhance the anti-inflammatory activity.Also, the presence of polar groups or hydrogen bonding acceptor on the aryl substituents in positions 3 of the quinazoline ring is important to enhance the binding affinity of ligands to the binding site of COX-II.

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