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Computer-Aided Design of Selective COX-2 Inhibitors: Molecular Docking of Structurally Diverse Cyclooxygenase-2 Inhibitors using FlexX Method

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Abstract

Motivation. Three-dimensional structures of pharmacologically important macromolecules offer a route to the discovery of new drugs. Understanding the macromolecule-ligand interactions and validation of method used for docking and virtual screening of chemical databases is crucial step in structure-based design. We therefore carried out molecular docking for a set of eighty two structurally diverse COX-1/COX-2 inhibitors including traditional NSAIDs and the recent developed coxibs using FlexX method to find out how good this method differentiate between the active and inactive compounds.

Method. FlexX is one of the fast flexible docking method that uses an incremental construction algorithm to place ligands into an active site. The scoring function (empirical binding free energy) of the flexX used to estimate the free binding energy of the protein-ligand complex is called F_score.

Results. Reproducibility of the experimental conformations of the bound ligands such as SC-558, indomethacin, flurbiprofen indicates the better performance of FlexX method. Good correlation between the standard FlexX score (F_score) and the COX-2 inhibitory activity (pIC_{50}) was observed. Simple linear regression analysis provided the correlation coefficient values of 0.731 and 0.670 for two classes of COX-2 inhibitors.

Conclusions. Flexible docking of eighty two structurally diverse COX-2 inhibitors have been successfully carried out. Some false positives and false negatives were observed but considering the limitations of the available docking programs, the results are encouraging. The detailed analysis of the resulted COX-2-ligand complexes may improve our knowledge in understanding the binding interactions in detail. Thus, this study will be useful for the design of novel COX-2 inhibitors based on docking and the resulted bioactive conformations of the ligands will be useful in building structure-based 3-D QSAR model.

Keywords. FlexX, cyclooxygenase-2, docking, structure-based drug design, NSAIDs

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Abbreviations and notations

NSAIDs, non-steroidal anti-inflammatory drugs
HIV, human immunodeficiency virus
PTP1B, protein tyrosine phosphate-1B
COX-2, cyclooxygenase-2
PDB, protein data bank
Rdf , receptor description file
3-D QSAR, three-dimensional quantitative structure-activity relationships

1 INTRODUCTION

The process of structure-based design started with the detailed analysis of binding site of the target protein, preferably in its complex form with a ligand. The knowledge of binding site helps to design novel drug candidates with better potency. Another approach that uses the structural information deals with the protein-based virtual screening of chemical databases whereas prior to biological screening, the potent compounds are computationally figured out from a large chemical library. Docking methods have the added advantage compared to 2-D similarity and 3-D pharmacophore search methods because it makes use of 3-D receptor structure in a quantitative way. Compound selection based on docking calculations alone and or combined with virtual screening has been carried out for targets thrombin [1] thymidylate synthase [2], dihydrofolate reductase [3], HIV protease [4], PTP1B [5] human carbonic anhydrase [6] and such study led to the identification of novel compounds with the potency between 1-100μM.

COX-2 is one of the well-known targets for the anti-inflammatory therapy. Selective inhibition of this enzyme overcomes the side effects associated with the traditional NSAIDs. The reported 3-D QSAR models [7- 10] are mainly focused to a particular class of compounds and such models may not be useful to predict structurally diverse compounds. Stewart *et al* [11] have reported a novel lead, phenothiazine for the inhibition COX-2 enzyme using combined 3-D database searching and combinatorial chemistry methodologies. The availability of several crystal structures of complexes of COX-2 with the inhibitors provides the possibility to apply structure-based design techniques for the development of specific and potent inhibitors. Therefore, we thought of exploiting the structure-based approach to design novel COX-2 inhibitors by docking studies combined with visualization of active site-ligand interactions.

2 MATERIALS AND METHODS

2.1 Preparation of ligands

All the molecular modeling and docking studies were performed on a Silicon Graphics Octane 2 workstations using Sybyl6.8 [12]. Eighty two compounds (Figure 1-3) were selected based on structural diversity and wide range of biological activity [13-24]. Major COX-2 inhibitory data was obtained from the human whole blood method [13] developed by Merck Frost Center. Known

ligands were extracted from the PDB file and converted into SYBYL mol2 format. Hydrogens were added and atom and bond types were corrected. Other molecules were sketched and subjected to systematic conformational search to find out the possible lowest energy conformation. The charges were calculated using Gasteiger Huckel method. The ligands were energy minimized using the Tripos force field. Compounds **49-82** used for CoMFA model [10] were submitted for docking. The compounds having carboxylic acids were treated as carboxylate and the formal charges were supplied.

2.2 Preparation of receptor file (rdf)

The coordinates of cyclooxygenase-2 enzyme crystal structure (1CX2) were retrieved from the PDB. Any amino acid residue within 6.5Å of the inhibitor SC-558 [25] was included in the active site pocket.

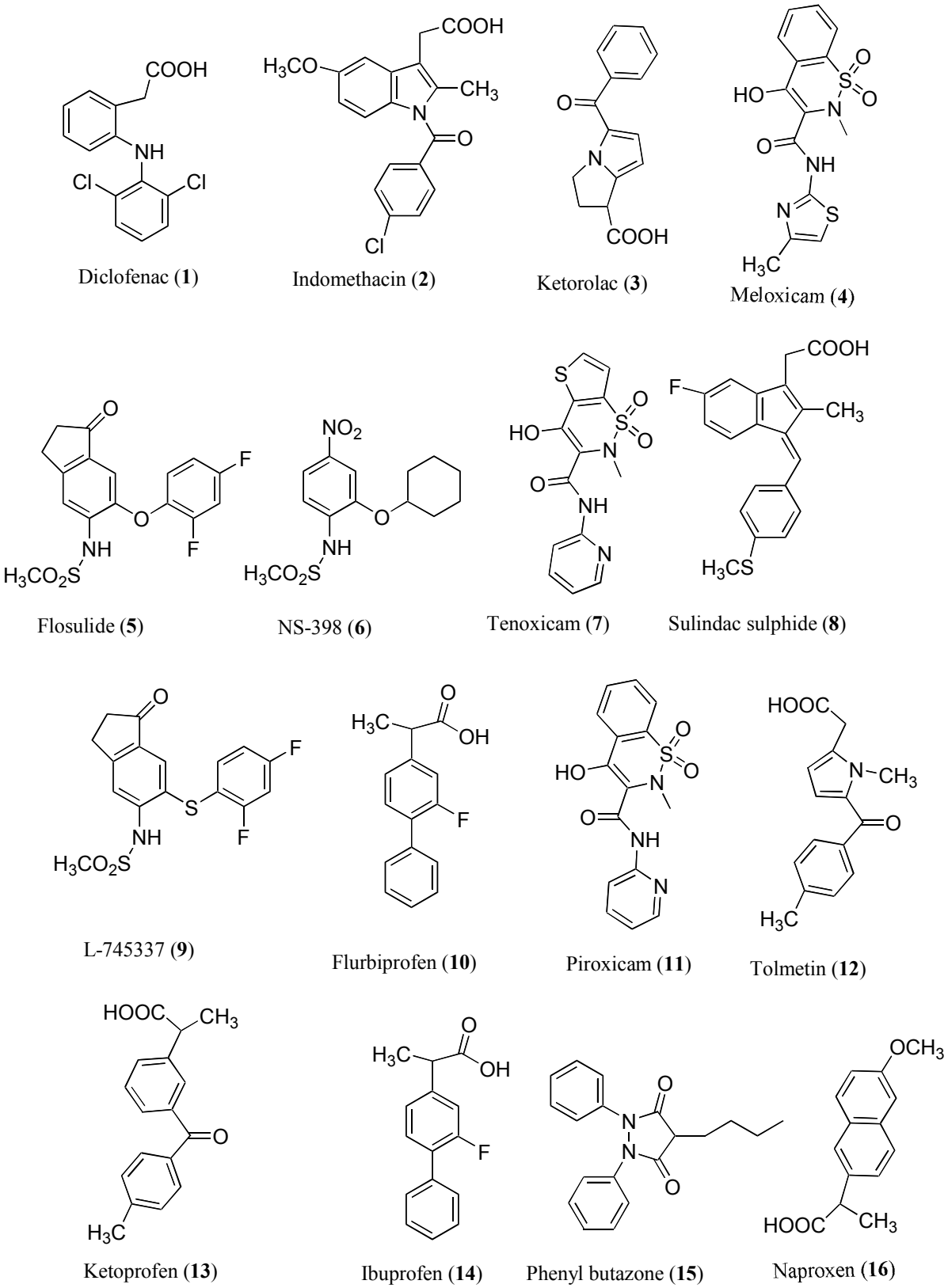
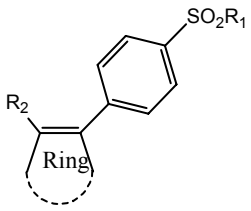
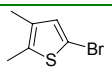
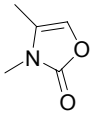
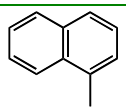
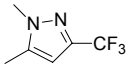
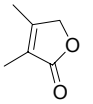
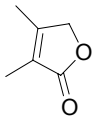
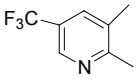
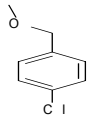
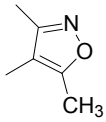
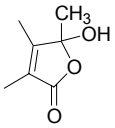
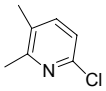
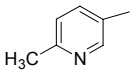
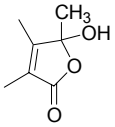
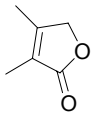
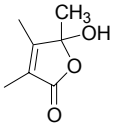
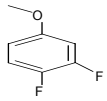
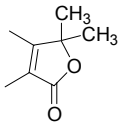
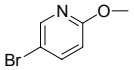
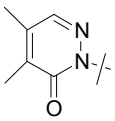
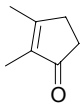
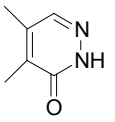
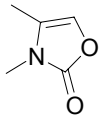
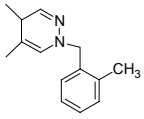
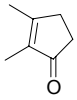
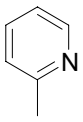
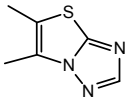
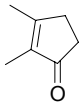
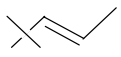
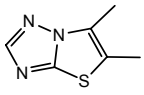
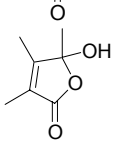
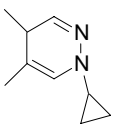
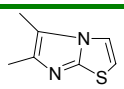
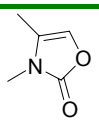
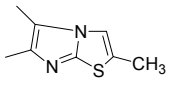
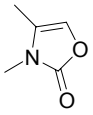
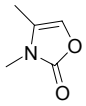
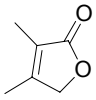
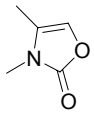
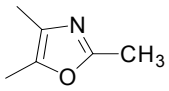


Figure 1. Structures of compounds (including NSAIDs) selected for docking studies

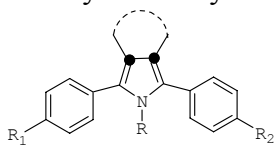


Compd.	Ring	R_1	R_2	Compd.	Ring	R_1	R_2
17		CH_3	4-F-C_6H_4	**33**		NH_2	
18		NH_2	4-CH_3-C_6H_4	**34**		CH_3	
19		CH_3	C_6H_5	**35**		CH_3	
20		NH_2	C_6H_5	**36**		CH_3	4-OH-C_6H_4
21		CH_3		**37**		CH_3	
22		SCH_3	4-OCH_3- C_6H_4	**38**		CH_3	
23		CH_3		**39**		CH_3	C_6H_5
24		CH_3	4-F-C_6H_4	**40**		CH_3	C_6H_5
25		NH_2	3,4-di-Cl-C_6H_3	**41**		CH_3	C_6H_5
26		CH_3		**42**		CH_3	3,4-di-F-C_6H_3
27		CH_3		**43**		CH_3	C_6H_5
28		CH_3	3,5-di-F-C_6H_3	**44**		CH_3	C_6H_5

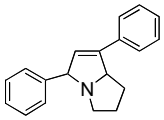
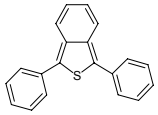
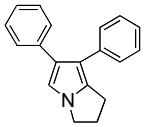
29		CH_3	3,4-di-F-C_6H_3	**45**		NH_2	4-COOH-C_6H_4
30		CH_3	3,4-di-F-C_6H_3	**46**		NH_2	3-COOH-C_6H_4
31		NH_2	4-CF_3-C_6H_4	**47**		CH_3	C_6H_5
32		NH_2	*c*-C_6H_{11}	**48**[b]		NH_2	*c*-C_6H_{11}

[a]SO_2R_1 replaced by SCH_3 [b]3-H of the sulphonyl phenyl ring is substituted by F

Figure 2. Structures of Compounds (1,2-Diaryl heterocyclic class) Selected for Docking Studies



Cd	Ring	R	R_1	R_2	Cd	Ring	R	R_1	R_2
49		H	H	H	**66**		H	F	F
50		H	H	H	**67**		H	H	H
51		CH_3	H	H	**68**		H	H	H
52		NH_2	H	H	**69**		H	H	H
53		NHMs	H	H	**70**		H	F	F
54		CH_2CO OH	H	H	**71**		H	F	F
55		H	F	F	**72**		H	F	CH_3SO_2

56		H	CH_3S	CH_3S	**73**		H	CH_3SO_2	CH_3SO_2
57		H	CH_3	CH_3	**74**		H	H	H
58		H	OCH_3	OCH_3	**75**		H	F	F
59		H	Cl	Cl	**76**		H	H	H
60		H	F	Imidazol-1-yl	**77**		H	4-F 3-NHAc	4-F 3-NHAc
61		H	Imidazol-1-yl	Imidazol-1-yl	**78**		H	4-F 3-$NHCH_3$	4-F 3-$NHCH_3$
62		H	H	H	**79**		H	-	-
63		H	H	H	**80**				
64		CH_3	H	H	**81**				
65		H	H	H	**82**				

[a] replacement of phenyl with pyridine

Figure 3. Structures of 1,3-Diaryl Heterocyclic Compounds

2.3 Molecular Docking

2.3.1 Details of FlexX method

The physicochemical model behind FlexX [26] can be divided into three parts: the conformational space of the ligand, the model of protein-ligand interactions, and the scoring function. To each acyclic single bond, a set of low-energy torsion angles is assigned using the MIMUMBA torsion angle database. Generated conformations are only tested for intramolecular clashes, and there is no conformational energy term in the scoring function. The scoring function [27] of FlexX is the function developed by Böhm for the de novo design program LUDI with some minor changes.

$$\Delta G = \Delta G_0 + \Delta g_{rot} \times N_{rot} \quad (1)$$

$+ \Delta G_{hb} \sum f(\Delta R, \Delta\alpha)$ (2)

neutral H-bonds

$+ \Delta G_{io} \sum f(\Delta R, \Delta\alpha)$ (3)

ionic int.

$+ \Delta G_{aro} \sum f(\Delta R \Delta\alpha)$ (4)

aro. Int.

$+ \Delta G_{lipo} \sum f(\Delta R)$ (5)

lipo.cont.

The scoring function can be divided into three parts. The first part (1) consists of a fixed term ΔG_0 and a term $\Delta g_{rot} \times N_{rot}$ taking into account the loss of entropy during ligand binding. The second part (2-4) contains the contributions for matched interaction groups like hydrogen bonds, salt bridges and charged hydrogen bonds and aromatic interactions. Each of these terms consists of a fixed contribution per interaction multiplied by a penalty function $f(\Delta R, \Delta\alpha)$. The penalty functions are piecewise linear functions scaling the contribution of an interaction with respect to its geometry. The third part (5) rates the atom-atom contacts between protein and ligand such as hydrophobic contacts and forbiddingly close contacts (clashes). The second and third parts of the scoring function are called match score and contact score, respectively.

The selected compounds were docked into the COX-2 active site using the default FlexX parameter settings. The results of top ranked scoring conformation were analyzed and used in the correlation of COX-2 inhibitory activity.

Table 1. Compounds Assayed by Human whole blood method, COX-2 potency and FlexX Docking scores

Entry	Compound	IC_{50} (μM) COX-2	pIC_{50}	FlexX Score COX-2
	Class 1 Highly potent molecules ($IC_{50} \leq 1.0\mu M$)			
1.	Diclofenac (**1**)	0.05	7.30	-25.80
2.	Indomethacin (**2**)	0.46	6.34	-20.50
3.	Ketorolac (**3**)	0.86	6.06	-28.70
4.	Meloxicam (**4**)	0.7	6.12	-20.20
5.	Flosulide (**5**)	0.7	6.12	-21.60
6.	NS-398 (**6**)	0.47	6.33	-10.60

7.	Dup-697 (**17**)	0.06	7.22	-20.30
8.	Celecoxib (**18**)	1.0	6.00	-24.10
9.	Rofecoxib (**19**)	0.5	6.30	-21.60
10.	Valdecoxib (**20**)	0.89	6.05	-24.87
11.	Etoricoxib (**21**)	1.0	6.00	-14.68
12.	**22**	0.19	6.72	-22.92
13.	**23**	0.03	7.52	-14.50
14.	**24**	0.08	7.10	-28.54
15.	**25**	0.40	6.40	-28.10
16.	**60**	0.08	7.10	-12.20
17.	**75**	0.12	6.92	-12.88
	Class II Moderately potent molecules (IC_{50}>1-30μM)			
18	**26**	9.08	5.01	-13.90
19	**27**	5.2	5.28	-9.88
20	**28**	13.4	4.87	-14.14
21	**29**	2.2	5.66	-17.56
22	**30**	17.5	4.76	-13.25
23	Tenoxicam (**7**)	14.22	4.85	-19.67
24	Sulidac sulphide (**8**)	10.43	4.98	-11.77
25	L-745337 (**9**)	9.7	5.01	-13.58
26	**31**	2.0	5.70	-28.00
27	**32**	18.9	4.72	-16.20
28	**33**	4.7	5.33	-22.90
29	Flurbiprofen (**10**)	6.46	5.19	-25.70
30	Piroxicam (**11**)	8.99	5.05	-20.00
31	Tolmetin (**12**)	7.09	5.15	-19.10
32	Ketoprofen (**13**)	1.08	5.97	-26.80
	Class III Inactive molecules ((IC_{50}>30μM)			
33	Ibuprofen (**14**)	>30	4.52	-8.84
34	Phenylbutazone (**15**)	>30	4.52	-12.15
35	Naproxen (**16**)	73.74	4.13	-19.65
36	**34**	>33	4.48	-16.01
37	**35**	>33	4.48	-23.65
38	**36**	>33	4.48	-15.47
39	**37**	>33	4.48	-13.20
40	**38**	>33	4.48	-11.97
41	**39**	>33	4.48	-6.85
42	**40**	>33	4.48	-15.29
43	**41**	>33	4.48	-13.41
44	**42**	>30	4.48	-15.62
45	**43**	>30	4.48	-13.53
46	**44**	>33	4.48	-15.20
47	**45**	59%[a]	4.00	-31.00
48	**46**	100	4.00	-32.00

49	**47**	inactive	-	-23.25
50	JTE-522 (**48**)	>33	4.48	-19.68

[a] at 100μM

Table 2. Compounds Assayed by Mouse macrophage method, COX-2 potency and FlexX Docking scores

S.No.	Compound	IC_{50} (nM) COX-2	pIC_{50}	FlexX Score COX-2
51.	**49**	1.5	8.82	-27.20
52	**50**	3.3	8.48	-24.80
53	**51**	>1000	6.00	-21.40
54	**52**	1.8	8.74	-20.30
55	**53**	500	6.30	-12.10
56	**54**	>100	7.00	-18.20
57	**55**	1.7	8.77	-27.20
58	**56**	500	6.30	-11.20
59	**57**	16.7	7.78	-12.00
60	**58**	21.3	7.67	-16.40
61	**59**	5.0	8.30	-21.00
62	**60**	42.0	7.38	-17.20
63	**61**	>100	7.00	-20.30
64	**62**	3.1	8.51	-27.50
65	**63**	14.5	7.84	-22.10
66	**64**	>1000	6.00	-5.90
67	**65**	0.7	9.15	-27.50
68	**66**	2.9	8.54	-26.00
69	**67**	>100	7.00	-11.10
70	**68**	>100	7.00	-16.70
71	**69**	2.6	8.58	-15.70
72	**71**	4.5	8.35	-18.80
73	**72**	700	6.15	-15.10
74	**73**	>10000	5.00	-14.50
75	**74**	1.6	8.79	-11.50

76	**76**	35.6	7.45	-14.50
77	**77**	>100	7.00	-30.70
78	**78**	>100	7.00	-19.60
79	**79**	>100	7.00	-17.80
80	**80**	50.0	7.30	-25.90
81	**81**	10.9	7.96	-16.20
82	**82**	28.7	7.54	-13.50

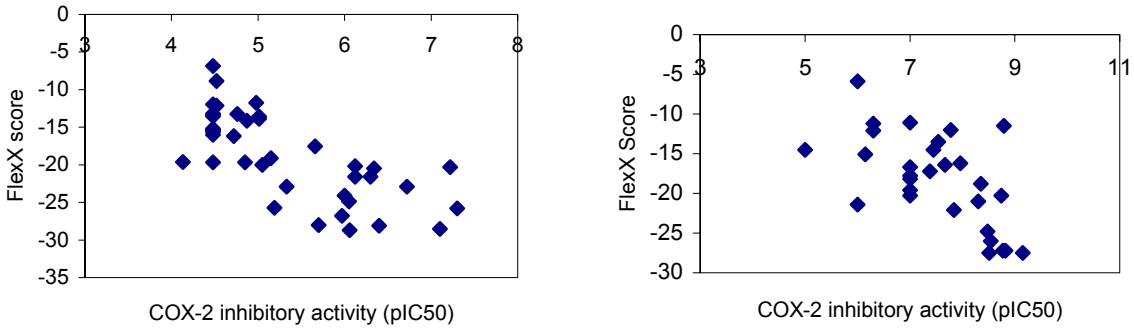


Figure 4. FlexX score Vs COX-2 Inhibitory Activity (pIC_{50})

a. Molecules from human whole blood assay b Molecules from mouse macrophage assay

4 RESULTS AND DISCUSSION

Reproducibility of the experimental conformations of the bound ligands such as SC-558, indomethacin and flurbiprofen was observed from docking. As previously observed by Plount-Price *et al* [28] we found that FlexX docks the sulphonyl amino group of SC-558 in a way that can make hydrogen bonding with Arg513 and His90. However in the crystal structure complex (1CX2.pdb) bad N-N contact was observed between sulphonyl amino group and nitrogen of His90. The carboxylate group of active NSAIDs was oriented towards the guanidine group of Arg120. The top scoring docked conformation was selected and the non-hydrogen atoms were aligned to the experimental conformation of the ligand. The low rms deviations (<1.74Å) between the theoretical and experimental conformations observed for the ligands studied indicated the better performance of FlexX method.

a. Compounds tested by human whole blood assay

The resulted FlexX scores and the COX-2 inhibitory activities were shown in Table 1 and 2. We

found more negative scores (Table 1) for the potent molecules, indicating the better binding of the ligands into the active site. Molecules NS-698 (**6**), etoricoxib (**21**), **23**, **60** and **75** were found to be false negatives. However, the docking scores were found to be less negative in case of moderately potent and inactive molecules. We observed some false positives (**35**, **45**, **46**, and **47**) from the set of inactive molecules. FlexX assigned good scores to these inhibitors as these compounds form more than one hydrogen bond with the protein. These observations are in confirmatory with the virtual screening studies reported by Martin *et al* [29]. The resulted FlexX docking score was correlated with the COX-2 inhibitory property (Figure 4). The linear regression analysis was performed for the molecules that are assayed by human whole blood method. After removing the false positives and false negatives the following regression equation was obtained for 40 molecules.

COX-2 inhibitory activity (pIC_{50}) = 3.181-(0.114 x FlexX score)

The r^2 value was found to be 0.534 and R-value was 0.731 with the standard error of 0.619.

b. Compounds tested by in vitro mouse macrophage assay

Another class of compounds selected for the docking studies is the non sulphonyl analogues (Figure 3). After removing the false positives (**77**, **80**) and false negative (**74**) the following regression equation was obtained for 29 molecules of 1,3-diaryl isoindole.

COX-2 inhibitory activity (pIC_{50}) = 5.233-(0.119 x FlexX score)

The r^2 value was found to be 0.449 and R-value was 0.670 with the standard error of 0.775. The calculated correlation coefficient values indicate a good correlation between the FlexX score and COX-2 inhibitory activity.

4 CONCLUSIONS

We have successfully carried out flexible docking for eighty two structurally diverse COX-2 inhibitors. The obtained FlexX docking score was correlated with the biological activities. Some false positives and false negatives were observed but considering the limitations of the available docking program, the results are encouraging. The detailed analysis of the resulted COX-2-ligand complexes may improve our knowledge in understanding the binding interactions in detail. Thus this study will be useful for the design of novel COX-2 inhibitors based on docking and the resulted bioactive conformations of ligands will be useful in building structure-based 3-D QSAR model.

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