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European Journal of Medicinal Chemistry 43 (2008) 2792–2799
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
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Original article

2,3,5-Substituted tetrahydrofurans: COX-2 inhibitory activities of 5-hydroxymethyl-/carboxyl-2,3-diaryl-tetrahydro-furan-3-ols

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Received 28 August 2007; received in revised form 6 December 2007; accepted 11 December 2007
Available online 28 December 2007

Abstract

5-Hydroxymethyl-/carboxyl-2,3-diaryl-tetrahydro-furan-3-ols have been investigated for their COX-1 and COX-2 inhibitory activities. Compounds **17**, **18** and **20** have been identified as showing appreciable COX-2 inhibition and selectivity. The group present at C-5 of tetrahydrofuran and the substituents at the two phenyl rings, through their interactions with active site amino acid residues, significantly affect the activities of these molecules. The quantitative structure–activity relationship studies indicate the role of log *P*, TPSA, molecular connectivity and valence connectivity towards the activities of these molecules.

Keywords: Cyclooxygenase-2; 2,3-Diaryl-tetrahydrofurans; *In vitro* studies; COX-2 inhibitors; QSAR

1. Introduction

The establishment of the role of COX-2 (out of the two isoforms of cyclooxygenase [1,2] *viz*. COX-1 and COX-2) in causing inflammation, promotion of cancer [3–7] and activation of P-glycoprotein [3,6,8–10] (transporter protein responsible for multidrug resistance) has made this enzyme as the cellular target of a number of chemical entities for the treatment of inflammation [11–15], minimizing the growth of cancer [16–19] and reducing multidrug resistance [20–23]. While COX-2 inhibitors are primarily used as anti-inflammatory agents, their applications for the treatment of cancer and modulating multidrug resistance are still at the infancy.

Due to the multiple role of COX-2, we are aiming at the development of COX-2 inhibitors and their evaluations as anti-cancer agents also. Based upon the chiral nature and flexibility of COX-2 active site, we have designed 5-substituted 2,3-diaryl-tetrahydrofuran-3-ols which, in contrast to the reported COX-2 inhibitors [14], carry aryl rings on chiral, sp^3 hybridized C-2 and C-3 carbons of tetrahydrofuran. Preliminary investigations have identified 5-hydroxymethyl-/carboxyl-/ethylsulfanylmethyl-2,3-diphenyl-tetrahydrofuran-3-ols as highly potent and selective COX-2 inhibitors [24]. In the present contribution, tetrahydrofurans with CH_2OH (**A**, Fig. 1), COOH (**B**, Fig. 1) group at C-5 and various substituents at the two aryl rings have been investigated for their COX-1 and COX-2 inhibitory activities. Experimental data and the docking studies indicate the role of substituents at the two phenyl rings of tetrahydrofuran-3-ols in affecting the COX-1 and COX-2 inhibitory activities of these molecules. Quantitative structure–activity relationship (QSAR) studies, to some extent, specify the contributions of log *P*, total polar surface area, molecular connectivity and valence molecular connectivity for the activities of these molecules.

2. Results

2.1. Chemistry

Benzoins **1–6** on treatment with indium metal, allyl bromide in THF–H_2O (2:1) at 0 °C provided the corresponding allylic alcohols **7–12**. Treatment of **12** with oxone

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doi:10.1016/j.ejmech.2007.12.017

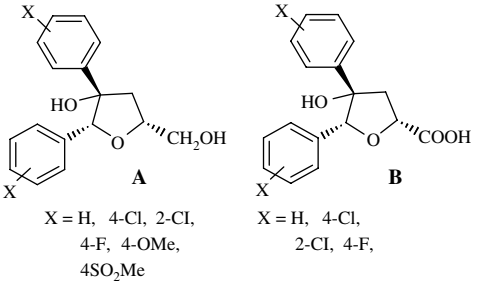
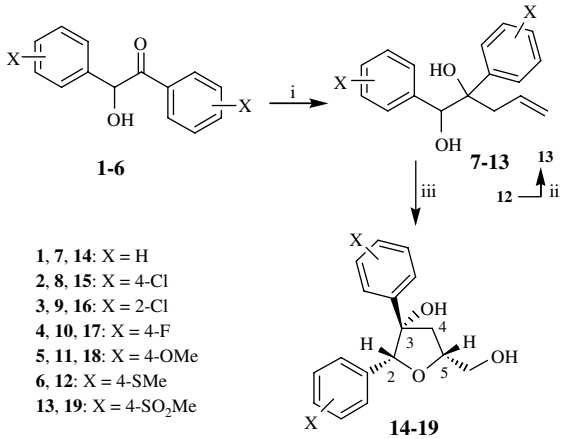


Fig. 1.

transformed its SMe group to SO_2Me in **13** (Scheme 1). The reactions of compounds **7–13** with *m*-CPBA in chloroform furnished the respective compounds **14–19**.

All these compounds are well characterised by various spectroscopic data. The observation of NOE between 2-H and 5-H indicates their *syn* orientation. X-ray crystal structure of **14** (Fig. 2) shows an almost *anti*-orientation of the two phenyl rings and *syn*-positioning of 2-H and 5-H while 3-OH and CH_2OH groups are projecting in the same direction. On the basis of NOE experiments and X-ray crystal structure, the relative configurations at the three chiral centres have been assigned (Scheme 1) and the molecules with these geometries have been used in docking studies.

Treatment of **14** with pyridinium chloro chromate (PCC) [25] in dichloromethane after usual work up provided the corresponding carboxyl derivative of tetrahydrofuran (**20**). Under the same reaction conditions, compounds **15–17** when treated with PCC gave the corresponding compounds **21–23** (Scheme 2) The appearance of an absorption peak in the region 1800 cm^{-1} in the IR spectra of compounds **21–23** in comparison to a peak at 1710 cm^{-1} in the IR spectrum of **20** indicates the presence of an ester group in compounds **21–23**. Later investigations are indicating structure **22A** for compound **22** (X-ray crystal structure will be reported separately) which probably has been formed by the *in-situ* lactonization of **22**. However, the same reactions of compounds **18** and **19** provided, respectively, an unstable compound **24** and a mixture of two products from which **25** could not be separated. The relative stereochemistries at various chiral centres of these molecules have also been defined on the basis of NOE experiments and X-ray structure of **14**.



Reaction conditions and reagents:

i) In, THF-H_2O, allyl bromide, stir

ii) Oxone, THF-H_2O, stir

iii) m-CPBA, $CHCl_3$, 0 °C, stir

Scheme 1.

2.2. Biology

In vitro COX-2 inhibiting activities of these compounds have been evaluated using 'COX (ovine) inhibitor screening assay' kit with 96-well plates (Caymen Chemicals, catalogue no. 560101). This screening assay directly measures $PGF_{2\alpha}$ produced by $SnCl_2$ reduction of COX-derived PGH_2. COX-1 and COX-2 initial activity tubes were prepared by taking 950 μl of reaction buffer, 10 μl of heme, 10 μl of COX-1 and COX-2 enzymes in respective tubes. Similarly, COX-1 and COX-2 inhibitor tubes were prepared by adding 20 μl of inhibitor (compound under test) in each tube in addition to the above ingredients. The background tubes correspond to inactivated COX-1 and COX-2 enzymes obtained after keeping the tubes containing enzymes in boiling water for 3 min. Reactions were initiated by adding 10 μl of arachidonic acid in each tube and quenched with 50 μl of 1 M HCl. PGH_2 thus formed was reduced to $PGF_{2\alpha}$ by adding 100 μl of $SnCl_2$. The prostaglandin produced in each well was quantified using broadly specific prostaglandin antiserum that binds with major prostaglandins and reading the 96-well plate at 405 nm. The wells of the 96-well plate showing low absorption at 405 nm indicate the low level of prostaglandins in these wells and hence the less activity of the enzyme. Therefore, the COX inhibitory activities of the compounds could be quantified from the absorption values of different wells of the 96-well plate. The results of these studies have been represented in terms of the percentage inhibition of COX-1 and COX-2 enzymes.

The anti-cancer activities were determined on 59 human tumor cell lines at five concentrations (10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M) following the standard procedure [26–28] at NIH. The results are given in terms of the GI_{50} values and the percentage inhibition of growth of tumor cells at some specific cell lines.

2.3. Molecular modeling and QSAR studies

For dockings, the crystal structure of COX-2 with Sc-558 as the ligand present in the active site (mouse COX, pdb ID 6COX) and COX-1 with ibuprofen in the active site (ovine COX, pdb ID 1EQG) were downloaded from protein data bank. The crystal structures of the enzymes were refined, docking procedure was validated and dockings were performed using 'dock into active site module' of BioMed Cache 7.5.0.85 following the previously described procedure [29]. Quantitative structure–activity relationship studies were carried out using 'Project Leader' module with the available descriptors in BioMed Cache 7.5.0.85.

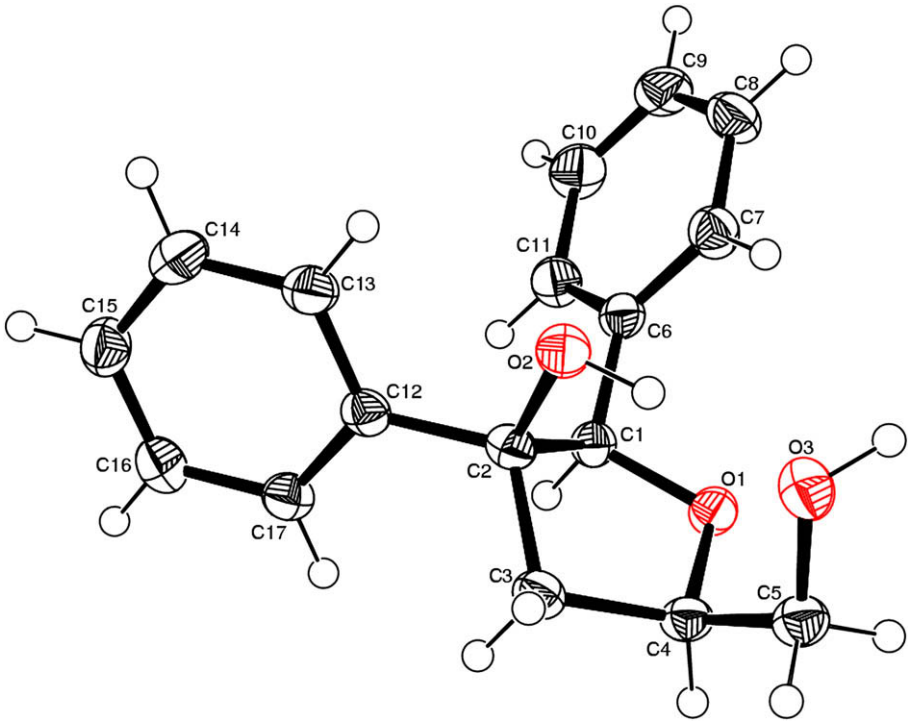
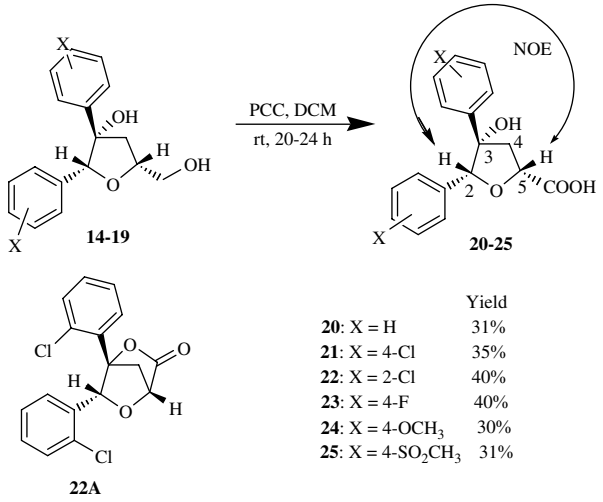


Fig. 2. The ORTEP diagram of compound **14**.

3. Discussion

The percentage inhibitions of COX-1 and COX-2 by each compound are given in Table 1. All the compounds have been evaluated in duplicates and Table 1 shows the average results. For COX-2, two concentrations of the compounds *viz*. 10^{-5} M and 10^{-6} M were used while COX-1 inhibitory activities were evaluated at 10^{-5} M concentration only. Amongst compounds **14–19** (with CH_2OH group at C-5 of tetrahydrofuran), the presence of substituents at the phenyl rings considerably affects the inhibitory activities and selectivity of these compounds for COX-2. Compounds **15** and **19** with 4-Cl and 4-SO_2Me groups at the two phenyl rings show comparable inhibitions of COX-2 (43% and 40% at 10^{-6} M) and COX-1 (56% and 55% at 10^{-5} M). Compound **16** (*o*-chlorophenyl rings) exhibits moderate inhibition of COX-2 at 10^{-6} M and 10^{-5} M concentrations (67% and 68%) and 73% inhibition of COX-1 at 10^{-5} M concentration. Compounds **17** and **18** (with *p*-fluorophenyl and *p*-methoxyphenyl rings) show significant inhibition of COX-2 at 10^{-6} M concentration (88% and 65%, respectively) and a selectivity order of >10 for COX-2 over COX-1.



	Yield
20: X = H	31%
21: X = 4-Cl	35%
22: X = 2-Cl	40%
23: X = 4-F	40%
24: X = 4-OCH_3	30%
25: X = 4-SO_2CH_3	31%

Scheme 2.

The dockings of compounds **14** (unsubstituted phenyl rings) and **17** (*p*-fluoro-substituted phenyl rings) show the difference in the interactions of two molecules in the active site of COX-2. In compound **17**, the fluorines present on C-2 and C-3 phenyl rings show significant interactions with Y385 and H90 residues, respectively. Fluorine at C-2 phenyl is at a distance of 3.0 Å from Y385 while fluorine at C-3 phenyl has approached NH of H90 at a distance of 2.36 Å (Fig. 3). The blockage of Y385 is advantageous due to the fact that tyrosyl radical initiates the cyclooxygenase reaction by abstracting the 13-pro(*S*) hydrogen of arachidonic acid (placed 2.3 Å from the phenolic oxygen on Y385) [31,32]. The oxygen of CH_2OH group of **17** lies at a distance of 2.67 Å from the H of guanidine moiety of R120, the amino acid active during the turnover phase of COX-2 in arachidonic acid metabolism. However, such interactions are not observed during the docking of compound **14** in the active site of COX-2 (Fig. 4). Instead, the CH_2OH group of **14** participates in intramolecular H-bonding with its own OH group present at C-3.

In comparison to compound **20**, compounds **21–23** exhibit better COX-2 inhibition at 10^{-5} M concentration but

Table 1
In vitro percentage inhibition and IC_{50} values for COX-1 and COX-2 enzymes

Compound	% Inhibition			IC_{50} (μM)		COX-2 selectivity[a]	Anti-cancer activity GI_{50}
	COX-2		COX-1	COX-2	COX-1		
	1 μM	10 μM	10 μM				
14	28	77	2.8	5.1	>10	>1.96	nd
15	43	68	56	3	<10	<3.3	1.99×10^{-5} M
16	67	68	73	<1	<10	–	2.20×10^{-5} M
17	88	82	22	<1	>10	>10	9.50×10^{-5} M
18	65	67	22	<1	>10	>10	9.33×10^{-5} M
19	40	57	55	6.5	<10	<1.5	1.0×10^{-4} M
20	68	69	−1.15	<1	>10	>10	nd
21	30	94	55	3.8	<10	<2.6	nd
22	37	82	34	3.5	>10	>2.8	72%[c]
23	37	90	30	3.2	>10	>3.1	60%[d]
Rofecoxib[b]	75	100	75	0.3	40	~133	15%[e]
Celecoxib[a]	50	100	65	1.2	14	~10	4.7×10^{-5} M[f]

[a] Cox-2 selectivity = IC_{50}(COX-1)/IC_{50}(COX-2).
[b] Reported [30], nd: not determined.
[c] Inhibition of tumor cells at NCI-H522 cell line.
[d] Inhibition of tumor cells at SN 12C cell line.
[e] Rofecoxib exhibits 15% inhibition (at 10^{-6} M concentration) of tumor cells at PC3 cell line of prostate cancer.
[f] GI_{50} at PC3 cell line of prostate cancer.

a decrease in their activity has been observed at 10^{-6} M concentration. The dockings of compounds **20**–**23** in the active site of COX-2 indicate that the aryl-substituted compounds (**21**–**23**) fit in the active site of COX-2 in the same fashion as compound **20** (Fig. 5) and interact with R120 through H-bonding between carboxylate group and guanidine moiety (Fig. 5).

However, during the dockings of these compounds (**14**–**23**) in the active site of COX-1, it has been observed that none of them enters in the active site of COX-1 (all have positive docking score) except compound **16** in which the C-3 phenyl ring enters in the active site cavity of COX-1 and the chlorine present on this phenyl ring approaches Y385 at a distance of 3.07 Å. In contrast to other compounds, **16** gave a −ve docking score when docked in the active site of COX-1 (−40 kcal/mol while it is −66 kcal/mol for COX-2). This behaviour of **16** is also evident from the experimental data where it shows 73% inhibition of COX-1 at 10^{-5} M concentration.

Therefore, the nature of the substituent at C-2 and C-3 phenyl rings of tetrahydrofuran-3-ols considerably affects the efficacy of these compounds for COX-2 inhibition and also their selectivity for COX-2 over COX-1. Out of the 10 compounds for which the results are presented here, compounds **16**–**18** and **20** exhibit considerable inhibition of COX-2 which is better than the COX-2 inhibitory activity of celecoxib and comparable to that of rofecoxib. However, the reluctance of these molecules to air oxidation provides an advantage over

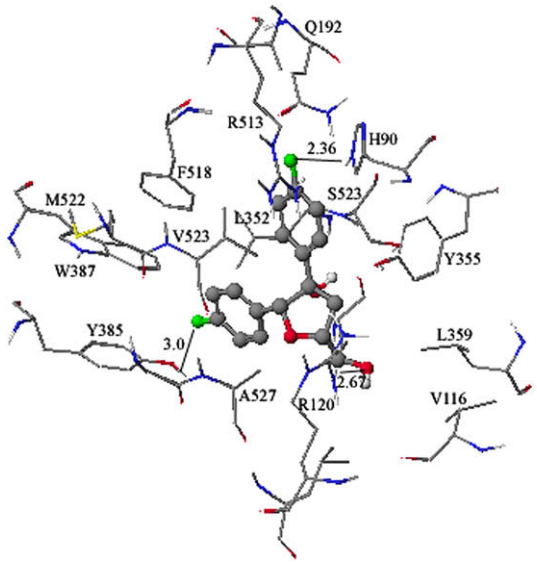


Fig. 3. Compound **17** docked in the active site of COX-2. Hydrogens are omitted for clarity. Distances of **17** from R120 (2.67 Å), Y385 (3.0 Å) and H90 (2.36 Å) are visible.

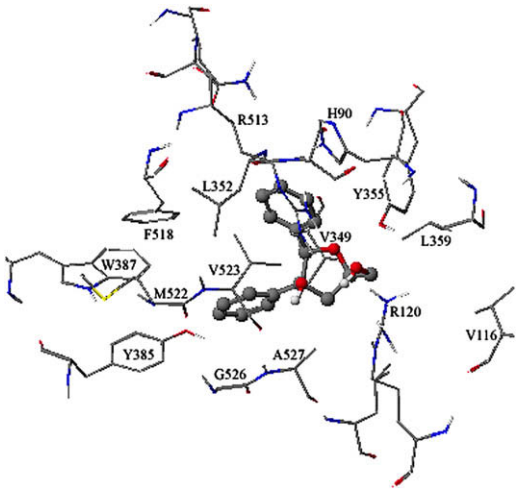


Fig. 4. Compound **14** docked in the active site of COX-2. Hydrogens are omitted for clarity.

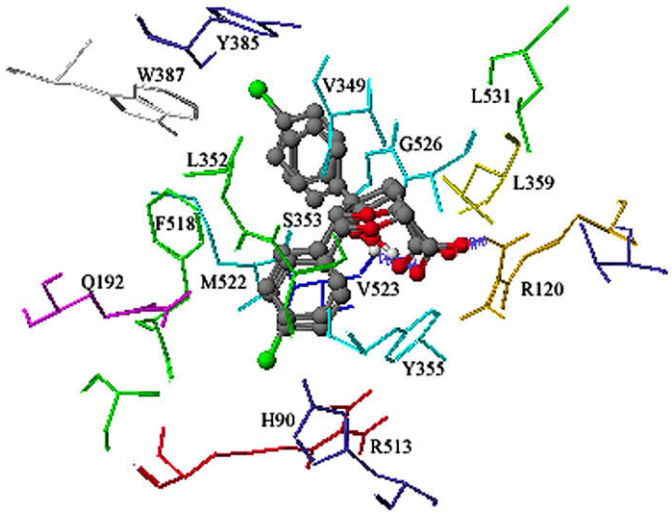


Fig. 5. Compounds **20** and **23** docked in the active site of COX-2. A close overlapping has been observed in the docking of two compounds.

rofecoxib which has been demonstrated to show toxicity due to its oxidation to maleic anhydride derivative [33].

Significant anti-cancer activities of compounds **15**–**19** have been observed at some specific cell lines of 59 human tumor cell line panels [34]. Amongst compounds **21**–**23**, compounds **22** and **23** show, respectively, 82% and 90% inhibition of COX-2 at 10^{-5} M concentration and exhibit 72% and 60% growth inhibitions of tumor cells at NCI-H522 (Non Small Cell Lung Cancer) and SN 12C (Breast Cancer) cell lines, respectively, at 10^{-5} M concentrations (Table 1). Remarkably, the anti-cancer activities of these compounds are better than those reported for rofecoxib and comparable to that of celecoxib.

The COX-2 inhibitory activities of these compounds have been correlated with various physico-chemical properties. A number of descriptors *viz*. partition coefficient (log *P*), total polar surface area (TPSA), polarizability, dipole moment, connectivity index of 0th, 1st and 2nd order, valence connectivity index of 0th, 1st and 2nd order, shape index of order 1, 2 and 3, solvent accessibility surface area (Table 2) and their combinations were taken into consideration for quantitative structure–activity relationship studies [35]. Out of these properties, not a single one shows linear relationship with the COX-2 inhibitory activities.

Taking log *P* and TPSA as the descriptors, an unpredictive equation with low statistical parameters both as fitting (r^2) and cross validation (r^2_{CV}), was obtained for the activity of these compounds. Combining TPSA, connectivity index and valence connectivity index of 0th order, Eq. (1) was obtained for the activity of these compounds.

$$C = -1.01\text{TPSA} + 15.30\chi^0 - 4.78\psi^0 - 71.29 \quad (1)$$

$r^2_{CV} = 0.28$, $r^2 = 0.55$, χ^0 = connectivity index (0th order), ψ^0 = valence connectivity index (0th order).

The predictiveness of the equation gets decreased when the dipole moment or polarizability parameters were introduced. However, introducing log *P* in Eq. (1), a reliable model for the activities of these compounds (Eq. (2)) was obtained.

$$C = -11.78 \log P - 1.37\ \text{TPSA} + 13.93\chi^0 - 3.28\psi^0 - 12.47 \quad (2)$$

$r^2_{CV} = 0.43$, $r^2 = 0.61$.

The activities of compounds predicted from Eq. (2) show close resemblance with the experimental activities (particularly the compounds carrying CH_2OH group at C-5 of tetrahydrofuran, **14**–**19**) except in the case of compound **20** (Fig. 6). Irrespective of trying a number of other combinations with the available descriptors (Table 2), no further improvement in the model was observed. These studies indicate the partial dependency of the COX-2 inhibitory activities of these molecules on lipophilicity, total polar surface area, molecular connectivity and valance molecular connectivity of the molecules.

4. Conclusion

The results of these investigations indicate that

(i) 2,3-Diaryltetrahydrofuran-3-ols with CH_2OH group at C-5 (**15**–**19**) exhibit better COX-2 inhibitory activities than compounds **21**–**23**.

Table 2
Various physico-chemical properties of compounds **14**–**23**

Compound	log *P*	TPSA (Å^2)	Dipole moment (Debye)	Polarizability	Connectivity index			Valence connectivity			Shape index order			Solvent accessibility surface area
					0th	1st	2nd	0th	1st	2nd	1	2	3	
14	2.502	49.69	2.476	31.07	14.00	9.73	8.55	11.14	6.83	5.22	14.91	6.40	2.97	286.63
15	3.538	49.69	2.608	35.48	15.74	10.55	9.62	13.25	7.79	6.38	16.84	6.85	3.44	321.88
16	3.538	49.69	2.091	35.17	15.74	10.52	9.80	13.25	7.78	6.26	16.84	6.85	3.16	307.24
17	2.781	49.69	2.676	31.42	15.74	10.52	9.80	11.74	7.02	5.50	16.84	6.85	3.44	300.74
18	1.996	68.15	3.480	36.91	17.15	11.60	10.14	13.80	7.87	5.95	18.78	8.13	3.90	343.24
19	0.792	117.97	6.057	39.52	20.74	12.94	13.71	17.07	12.32	11.11	22.68	8.26	4.85	400.49
20	2.611	66.76	6.369	31.30	14.87	10.11	9.28	11.34	6.82	5.24	15.87	6.63	3.20	289.73
21	3.647	66.76	6.194	35.73	16.61	10.93	10.35	13.45	7.78	6.40	17.81	7.08	3.66	329.01
22	3.647	66.76	4.173	35.33	16.61	10.89	10.53	13.45	7.77	6.28	17.81	7.08	3.38	309.21
23	2.890	66.76	6.319	31.65	16.61	10.89	10.53	11.94	7.02	5.53	17.81	7.08	3.66	306.07

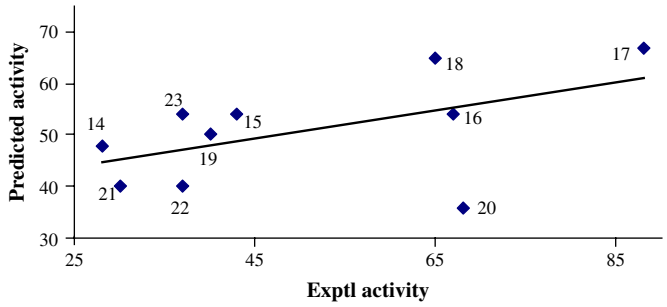


Fig. 6. Graph between the activities (% inhibition of COX-2) of compounds **14–23** predicted from Eq. (2) and experimental activities.

(ii) Among all these compounds, **17**, **18** and **20** show best COX-2 inhibition and selectivity.
(iii) The results of the docking studies are in parallel with the experimental data for COX-2 and COX-1 inhibitions.
(iv) QSAR studies indicate that the COX-2 inhibitory activities of these compounds depend upon various parameters out of which log *P*, TPSA and connectivity indices are the major ones.

5. Experimental

5.1. General details

Melting points were determined in capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on JEOL 300 MHz and 75 MHz NMR spectrometers, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in parts per million with TMS as an internal reference. *J* values are given in hertz. Chromatography was performed with silica 100–200 mesh and reactions were monitored by thin layer chromatography (TLC) with silica plates coated with silica gel HF-254. The experimental data for compounds **14–19** have already been reported [34].

5.2. Synthesis of compounds *20–25*

The solution of pyridinium chloro chromate (PCC) (2 mmol) in dry DCM (5 ml) was added to the solution of hydroxylmethyl tetrahydrofuran derivatives **14–19** (0.5 mmol) in dry DCM and stirred for 20–24 h at 30 ± 1 °C (TLC monitoring). The reaction mixture was washed with dry diethyl ether. The organic layer was concentrated and column chromatographed (silica gel 100–200) to isolate the products **20–25**.

5.2.1. (2R*,3S*,5R*)-4-Hydroxy-4,5-diphenyl-tetrahydro-furan-2-carboxylic acid *20*

Compound **14** was allowed to react with PCC as described in the general procedure to give **20** as white solid, 31% yield; mp 126 °C; ν_{max} ($CHCl_3$) 3580 (OH), 1710 (C=O) cm^{-1}; ^{1}H ($CDCl_3$) δ 1.59 (br s, 1H, OH, exchangeable with D_2O), 2.46 (d, $J = 11.1$ Hz, 1H, 4-H), 3.02 (dd, $^{2}J = 11.1$ Hz, $^{3}J = 2.1$ Hz, 1H, 4-H), 4.90 (d, $J = 2.1$ Hz, 1H, 5-H), 5.27 (s, 1H, 2-H), 6.91 (d, $J = 6.6$ Hz, 2H, ArH), 7.07–7.45 (m, 8H, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$) δ 45.53 (−ve, C-4), 78.12 (+ve, C-5), 85.65 (+ve, C-2), 92.11 (ab, C-3), 125.47 (+ve, ArCH), 126.95 (+ve, ArCH), 127.89 (+ve, ArCH), 128.36 (+ve, ArCH), 128.61 (+ve, ArCH), 128.97 (+ve, ArCH), 132.04 (ab, ArC), 133.57 (ab, ArC), 171.60 (ab, C=O). Decoupling of doublet at δ 4.90 converts double doublet at δ 3.02 into a doublet and doublet at δ 2.46 remains unaffected. Decoupling of double doublet at δ 3.02 converts doublets at δ 2.46 and 4.90 into singlets. Decoupling clearly shows that 5-H couples with only one of the two 4-H protons. NOE experiments: irradiation of singlet at δ 5.27 (2-H) shows NOE with signals at δ 4.90 (5-H), 3.02 (4-H) and 6.91, 7.06–7.45 (ArH) and irradiation of doublet at δ 4.90 (5-H) shows NOE with dd at δ 3.02 (4-H); FAB mass *m/z* 267 ($M^+ - OH$); (found C, 72.13; H, 5.97; $C_{17}H_{16}O_4$ requires C, 71.82; H, 5.67).

5.2.2. (2R*,3S*,5R*)-4,5-Bis-(4-chloro-phenyl)-4-hydroxy-tetrahydro-furan-2-carboxylic acid *21*

Compound **15** was allowed to react with PCC as described in the general procedure to give **21** as white solid, 35% yield; mp 80 °C; ν_{max} ($CHCl_3$) 3450 (OH), 1801(C=O) cm^{-1}; ^{1}H ($CDCl_3$) δ 1.59 (br s, 1H, OH, exchanges with D_2O), 2.45 (dd, $^{2}J = 11.1$ Hz, $^{3}J = 0.3$ Hz, 1H, 4-H), 2.98 (dd, $^{2}J = 11.1$ Hz, $^{3}J = 2.4$ Hz, 1H, 4-H), 4.89 (d, $J = 1.8$ Hz, 1H, 5-H), 5.20 (s, 1H, 2-H), 6.83 (d, $J = 8.1$ Hz, 2H, ArH), 7.12 (d, $J = 9.0$ Hz, 2H, ArH), 7.22 (d, $J = 8.4$ Hz, 2H, ArH), 7.37 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$) δ 45.31 (−ve, C-4), 78.10 (+ve, C-5), 85.04 (+ve, C-2), 91.36 (ab, C-3), 126.85 (+ve, ArCH), 128.22 (+ve, ArCH), 128.26 (+ve, ArCH), 129.05 (+ve, ArCH), 130.27 (ab, ArC), 131.82 (ab, ArC), 134.47 (ab, ArC), 135.22 (ab, ArC), 170.96 (ab, C=O); MALDI (TOF) *m/z* 335.59 ($M^+ - OH$); (found C, 57.69; H, 3.91; $C_{17}H_{14}Cl_2O_4$ requires C, 57.81; H 4.00).

5.2.3. (2R*,3S*,5R*)-4,5-Bis-(2-chloro-phenyl)-4-hydroxy-tetrahydro-furan-2-carboxylic acid *22*

Compound **16** was allowed to react with PCC as described in the general procedure to give **22** as white solid, 40% yield; mp 168 °C; ν_{max} ($CHCl_3$) 3431, 3418 (OH), 1797 (C=O) cm^{-1}; ^{1}H ($CDCl_3$) δ 1.60 (br s, 1H, OH, exchangeable with D_2O), 2.47 (d, $J = 11.4$ Hz, 1H, 4-H), 3.84 (dd, $^{2}J = 11.4$ Hz, $^{3}J = 2.4$ Hz, 1H, 4-H), 4.86 (d, $J = 2.4$ Hz, 1H, 5-H), 6.24 (s, 1H, 2-H), 7.08–7.21 (m, 4H, ArH), 7.28–7.39 (m, 4H, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$) δ 44.75 (−ve, C-4), 77.73 (+ve, C-5), 78.84 (+ve, C-2), 91.68 (ab, C-3), 126.69 (+ve, ArCH), 127.00 (+ve, ArCH), 129.11 (+ve, ArCH), 129.21 (+ve, ArCH), 129.37 (+ve, ArCH), 129.49 (+ve, ArCH), 129.72 (ab, ArC), 130.12 (+ve, ArCH), 130.49 (+ve, ArCH), 131.56 (ab, ArC), 133.42 (ab, ArC), 170.83 (ab, C=O). Decoupling of doublet at δ 4.86 converts double doublet at δ 3.84 into a doublet and doublet at δ 2.47 remains unaffected. Decoupling of double doublet at δ 3.84 converts doublets at δ 2.47 and δ 4.86 into singlets. Here also the decoupling experiments show that 5-H couples with only one of the

two 4-H protons; FAB mass *m/z* 336 ($M^+ - OH$); (found C, 57.72; H, 3.89; $C_{17}H_{14}Cl_2O_4$ requires C, 57.81; H 4.00).

5.2.4. (2R,3S*,5R*)-4,5-Bis-(4-fluoro-phenyl)-4-hydroxy-tetrahydro-furan-2-carboxylic acid **23***

Compound **17** was allowed to react with PCC as described in the general procedure to give compound **23** as white solid, 40% yield; mp 135 °C; ν_{max} ($CHCl_3$) 3481, 3418 (OH), 1805 (C=O) cm^{-1}; ^1H ($CDCl_3$) δ 1.59 (br s, 1H, OH, exchangeable with D_2O), 2.46 (d, $J = 11.1$ Hz, 1H, 4-H), 3.00 (dd, $^2J = 11.1$ Hz, $^3J = 2.4$ Hz, 1H, 4-H), 4.89 (d, $J = 1.8$ Hz, 1H, 5-H), 5.20 (s, 1H, 2-H), 6.85–6.90 (m, 2H, ArH), 6.91–6.97 (m, 2H, ArH), 7.03–7.10 (m, 2H, ArH), 7.11–7.17 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz, $CDCl_3$) δ 45.21 (−ve, C-4), 78.06 (+ve, C-5), 85.14 (+ve, C-2), 91.42 (ab, C-3), 115.03 (+ve, d, $J_{C-F(ortho)} = 21.00$ Hz, ArCH), 115.83 (+ve, d, $J_{C-F(ortho)} = 21.68$ Hz, ArCH), 127.42 (+ve, d, $J_{C-F(meta)} = 8.02$ Hz, ArCH), 127.71 (ab, d, $J_{C-F(para)} = 3.68$ Hz, ArC), 128.72 (+ve, d, $J_{C-F(meta)} = 8.02$ Hz, ArCH), 129.04 (ab, d, $J_{C-F(para)} = 3.08$ Hz, ArC), 162.80 (ab, d, $J_{C-F} = 245.4$ Hz, ArC), 162.94 (ab, d, $J_{C-F} = 246.6$ Hz, ArC), 171.21 (ab, C=O); FAB mass *m/z* 303 ($M^+ - OH$); (found C, 63.70; H, 4.29; $C_{17}H_{14}F_2O_4$ requires C, 63.75; H 4.41).

5.2.5. (2R,3S*,5R*)-4-Hydroxy-4,5-bis-(4-methoxy-phenyl)-tetrahydro-furan-2-carboxylic acid **24***

Compound **18** was allowed to react with PCC as described in the general procedure to give **24** as thick liquid, 30% yield; ^1H ($CDCl_3$) δ 1.26 (br s, 1H, OH, exchangeable with D_2O), 2.42 (d, $J = 11.1$ Hz, 1H, 4-H), 2.96 (dd, $^2J = 11.1$ Hz, $^3J = 2.4$ Hz, 1H, 4-H), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.83 (d, $J = 1.8$ Hz, 1H, 5-H), 5.15 (s, 1H, 2-H), 6.78 (d, $J = 8.7$ Hz, 2H, ArH), 6.84–6.89 (m, 4H, ArH), 7.07 (d, $J = 9.0$ Hz, 2H, ArH). MALDI (TOF) *m/z* 327.71 ($M^+ - OH$).

5.2.6. (2R,3S*,5R*)-4-Hydroxy-4,5-bis-(4-methane-sulfonyl-phenyl)-tetrahydro-furan-2-carboxylic acid **25***

Compound **19** was allowed to react with PCC as described in the general procedure to give **25** as yellowish solid, 31% yield (based upon ^1H NMR integration); mp 180–85 °C; ν_{max} ($CHCl_3$) 3407 (OH), 1800 (C=O), 1307 (S=O) cm^{-1}; ^1H ($CDCl_3$) δ 1.81 (br s, 1H, OH, exchangeable with D_2O), 2.53 (d, $^1J = 11.1$ Hz, 1H, 4-H), 3.04 (s, 3H, SO_2CH_3), 3.05 (dd, $^2J = 11.1$ Hz, $^3J = 1.8$ Hz, 1H, 4-H), 3.09 (s, 3H, SO_2CH_3), 5.01 (d, $J = 1.8$ Hz, 1H, 5-H), 5.44 (s, 1H, 2-H), 7.08 (d, $J = 8.4$ Hz, 2H, ArH), 7.48 (d, $J = 8.7$ Hz, 2H, ArH), 7.81 (d, $J = 8.4$ Hz, 2H, ArH), 8.00 (d, $J = 8.4$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) (75 MHz, $CDCl_3$) δ 44.34 (+ve, CH_3), 44.34 (+ve, CH_3), 46.06 (−ve, C-4), 77.42 (+ve, C-5), 78.32 (ab, C-3), 84.78 (+ve, C-2), 118.23 (ab, ArC), 126.42 (+ve, ArCH), 127.31 (+ve, ArCH), 127.61 (+ve, ArCH), 128.19 (+ve, ArCH), 131.61 (ab, ArC), 139.55 (ab, ArC), 188.82 (ab, C=O); MALDI (TOF) *m/z* 477.8 ($M^+ - 1 + K^+$). From the ^1H and ^{13}C NMR spectra, which show the signals due to two components, the signals of compound **25** were identified on the basis of the comparative chemical shifts in compounds **20**–**24**.

Acknowledgements

We thank DST, New Delhi, CSIR, New Delhi and UGC, New Delhi for financial assistance. Anu thanks CSIR, New Delhi for Senior Research Fellowship. We also thank Dr. V.L. Narayanan and his group at NIH, Bethesda, USA, for anti-cancer screening. Authors are also thankful to the referees for their encouraging comments, helpful in the revision of the article.

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