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Original article

Design, synthesis and evaluation of tetrahydropyran based COX-1/-2 inhibitors

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ABSTRACT

Chiral tetrahydropyrans were designed and synthesized by allylations of enantiomerically enriched β-hydroxy ketones followed by iodocyclisations and nucleophilic replacement of iodo group with $C_2H_5S^-$ and SCN−. *In vitro* COX-1/-2 inhibitory activities and the docking studies of these compounds identify some of them as moderate inhibitors of COX-1 and COX-2 enzymes.

1. Introduction

Two isoforms of enzyme cyclooxygenase viz. COX-1 and COX-2 perform key roles in arachidonic acid metabolism [1,2]. The inducible enzyme COX-2 [3] also constitutively expressed in human kidney and brain is found in inflamed and neoplastic tissues; takes part in the production of inflammatory prostaglandins, responsible for promoting cancer [4–7] and in the development of multidrug resistance [8–10] and it continues to be a target of a large number of anti-inflammatory drugs. However, higher inhibition of COX-2 shifts the arachidonic acid metabolism to lipoxygenase pathway and leads to more production of leukotrienes, responsible for cancer induction [11,12]. Moreover, COX-2 inhibitors are also responsible for nephrotoxicity and cardiovascular risks [13–17]. The prostaglandins produced from arachidonic acid through the participation of COX-1 are mainly responsible for gastrointestinal (GI) protection, induction of labor pains and blood clotting [18]. Higher inhibition of COX-1, by the use of non-selective COX-1/2 inhibitors, leads to thinning of blood. Keeping in mind the functions of these two isoforms of cyclooxygenase, the development of new molecules with optimum inhibition of both COX-1 and COX-2 seems to be desirable. Structurally, the COX-2 inhibitors consist of two aryl rings on the adjacent sp^2 hybridized carbons of an acyclic template as well as on 3-, 4-, 5-, 6-membered carbocyclic/heterocyclic moieties [19–22]. However, a few reports are available for the rational design and development of selective/non-selective COX-1 inhibitors [23–27] which might be due to the gastrointestinal ulcerations (GI) associated with COX-1 inhibition. Further investigations indicate that it is not only the inhibition of COX-1 which is responsible for GI ulcerations but the inhibition of COX-2 also [27].

Based upon the flexible and the chiral natures of COX-1 and COX-2 active sites (so is the case for every other enzyme), it was envisaged that the central template with asymmetric carbons could adapt more conveniently in the active sites of these enzymes and could prove as better inhibitors (only *S*-ibuprofen is active [28]). Moreover, non-selective COX-1/-2 inhibitors require an optimum size so that they could be accommodated in the active sites of both COX-1 and COX-2 (due to the small difference in the size of the active site cavities of COX-1 and COX-2). Keeping both these factors in mind and the reports available on the COX-2 inhibitory activities of pyran-2/4-ones [29–31], in the present investigations, chiral tetrahydropyrans (Fig. 1) with an aryl ring at C-2 and an appropriate substituent at C-6 have been synthesized. *In vitro* bio-evaluations (supported by dockings) of these molecules have identified two molecules as moderate inhibitors of COX-1 and COX-2.

2. Results and discussion

2.1. Chemistry

Considerable attention has been paid for the synthesis of substituted tetrahydropyrans, with well defined stereochemistry at

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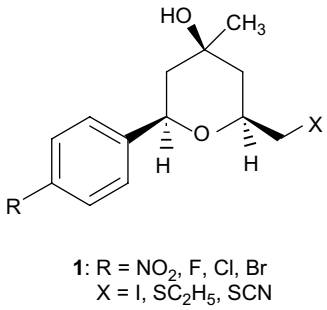


1: R = NO_2, F, Cl, Br
X = I, SC_2H_5, SCN

Fig. 1. Design of tetrahydropyrans.

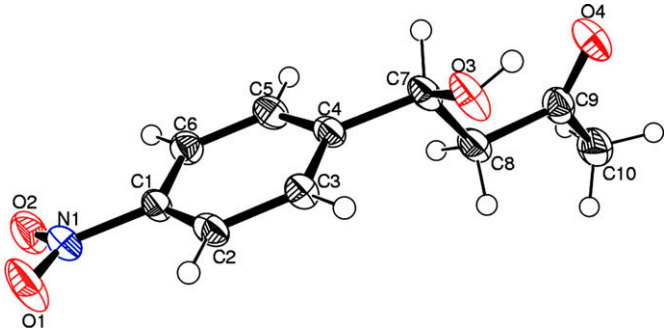


Fig. 2. ORTEP view of **2** (R = NO_2).

the ring carbons, starting from simple acyclic compounds [32–34], by ring enlargement [35], via hetero Diels–Alder reaction [36,37], olefin metathesis [38] and recently an increasing interest has been shown for the synthesis of stereo-controlled tetrahydropyrans by Prins cyclization [39–43]. Here, the stereoselective synthesis of polysubstituted tetrahydropyrans has been achieved by the allylations of enantiomerically enriched β-hydroxy ketones followed by diastereoselective iodocyclisations.

2.1.1. Enantioselective synthesis of β-hydroxy ketones

β-Hydroxy ketones have been procured stereoselectively through the reactions of appropriate aldehydes and ketones mediated by small organic molecules viz. proline and its derivatives [44–48]. Here, improved over the reported procedures for the synthesis of 4-hydroxy-4-(4-nitrophenyl)-butan-2-one (**2**, R = NO_2) [44] (entry 1, Table 1), it has been synthesized (72%, $[\alpha]_D = +44^\circ$ and 72% ee) by the reaction of 4-nitrobenzaldehyde with acetone (as solvent) using proline as catalyst (entry 3, Table 1). The reaction of 4-nitrobenzaldehyde with acetone in 1:1 mixture of DMSO and water yielded compound **2** (R = NO_2) (80%) with poor optical rotation and enantioselectivity (entry 2, Table 1). Under the reaction conditions as mentioned in entry 3 (Table 1), the treatment of other benzaldehydes (entries 4–8, Table 1) with acetone provided the corresponding β-hydroxy ketones in comparable yields and enantioselectivities as reported using DMSO/acetone as the solvent and 'proline derivatives' as the catalysts. The *R*-configuration at the chiral center of these hydroxy ketones has been confirmed from the X-ray structure of **2** (R = NO_2) (Fig. 2).

2.1.2. Allylation of β-hydroxy ketones

To the cooled solution of the reagent $In_2(allyl)_3Br_3$, generated by refluxing the mixture of allyl bromide (0.5 mmol) and indium metal (0.4 mmol) in dry THF, was added **2** (R = NO_2, 1 equiv). Stirring the reaction mixture at room temperature, after usual work up and column chromatography provided a mixture of two diastereomers **3a** and **3b** (88%, M^+ *m/z* 251) which in ^{1}H NMR spectrum clearly shows two sets of signals in the ratio 7:3 (Scheme 1). Under the same reaction conditions, the treatment of **2** (R = F, Cl, Br) with pre-generated reagent $In_2(allyl)_3Br_3$ gave the corresponding compounds **4**, **5** and **6** as a mixture of two diastereomers (**a** and **b**) in the ratio 5:4, 2:1 and 7:3, respectively (Scheme 1).

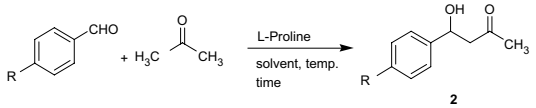
It has been observed that the diastereoselectivity of the allylated products (**3**–**6**) formed from β-hydroxy ketones (**2**) is lower as compared to the high diastereoselectivity of the allylations of α-hydroxy ketones [49]. This might be attributed to the formation of a relatively flexible six-membered transition state during the allylation of **2** (Fig. 3) in contrast to the five-membered transition state formed in the case of allylations of α-hydroxy ketones. The formation of the *syn*- and *anti*-diastereomer could be visualized through the existence of Cram's chelation models **A** and **B** (Fig. 3).

2.1.3. Diastereoselective conversion of allylated products to tetrahydropyrans

Treatment of diastereomeric mixture of **3** with iodine in dry CH_3CN using $NaHCO_3$ provided a mixture of two compounds (2:1, ^{1}H NMR spectrum) which after purification with column chromatography have been identified as compounds **7** (40%, $[\alpha]_D = +43.3^\circ$) and **8** (20%, $[\alpha]_D = +41^\circ$). Similar reactions of **4**, **5** and **6** provided compounds **9** (35%, $[\alpha]_D = +40^\circ$), **10** (30%, $[\alpha]_D = +35^\circ$); **11** (35%, $[\alpha]_D = +47^\circ$), **12** (30%, $[\alpha]_D = +48^\circ$) and **13** (32%, $[\alpha]_D = +41.2^\circ$), **14** (21%, $[\alpha]_D = +40^\circ$), respectively (Scheme 2).

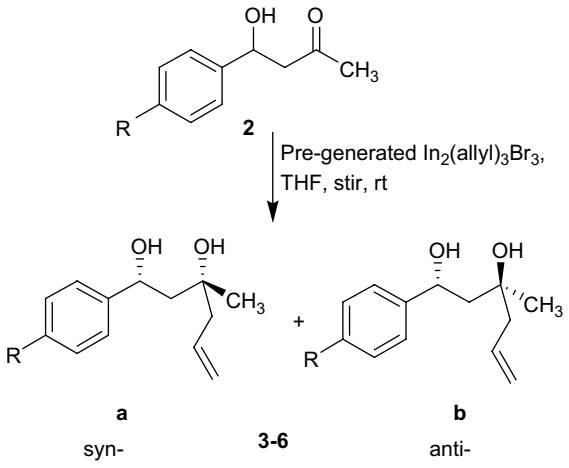
The relative stereochemistries at the various asymmetric carbons of compounds **7**–**14** have been ascertained on the basis of

Table 1
Reaction conditions, percentage yields, optical rotation and ee values for **2**



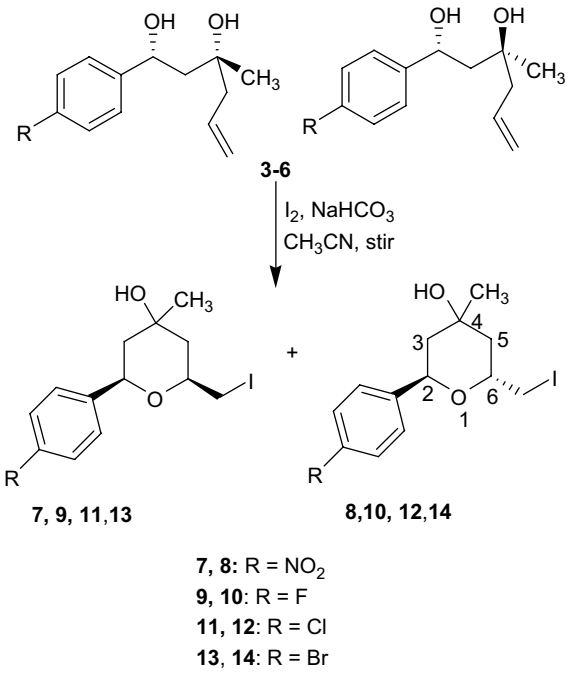
Entry	R	Solvent	Temperature (°C)	Time (h)	% Yield	$[\alpha]_D$ (°)	ee[a] %
1 [44]	NO_2	DMSO	0	8	76	+46	76
2	NO_2	DMSO/H_2O	25	6	80	+22	35
3	NO_2	Acetone	25	10	72	+44	72
4	F	Acetone	25	10	70	+49	74
5	Cl	Acetone	25	11	68	+51	77
6	Br	Acetone	25	10	75	+40.4	60
7	OCH_3	Acetone	25	15	64	+43.6	60
8	SCH_3	Acetone	25	30	55	+41.4	58

[a] Enantiomeric excess was determined by ^{1}H NMR experiments using $Eu(hfc)_3$ chiral shift reagent.



	yield	dr(a:b)
3, R = NO_2	88%	70:30
4, R = F	86%	56:44
5, R = Cl	80%	67:33
6, R = Br	70%	70:30

Scheme 1.



Scheme 2.

NOE experiments (Fig. 4) and X-ray structure of **13** (Fig. 5). The observation of NOE between 2-H and 6-H in the case of compounds **7**, **9**, **11** and **13** indicates the *syn* orientation of these hydrogens.

The X-ray structure of **13** (Fig. 5) shows the equatorial orientation of phenyl ring, CH_2I and OH groups and supports the stereochemistries observed for these compounds on the basis of NMR experiments. Compounds **15**–**22** (analogues of **7**, **9**, **11** and **13**) with stereochemistries at various asymmetric carbons as shown in Fig. 5 are used for docking studies while in the case of compounds **23**–**30** (analogues of **8**, **10**, **12** and **14**), the stereochemistry at C-6 of tetrahydropyran is reversed.

2.1.4. Replacement of iodo group with other nucleophiles

It has been found [50,51] that the groups like $CH_2SCH_2CH_3$, CH_2SCN, etc., when present at five-membered cyclic template, are suitable for interacting with the guanidine moiety of R120, an amino acid present in the active site of COX-2. In order to introduce such groups on tetrahydropyrans, equimolar quantities of **7**/**9**/**11**/**13** and C_2H_5SH/KSCN were stirred in CH_3CN using K_2CO_3 as base which provided the respective compounds **15**–**22** (Scheme 3).

Therefore, starting from β-hydroxy ketones, following a two step synthetic approach viz. allylation and iodocyclisation, polysubstituted tetrahydropyrans have been procured in moderate to high yields.

2.2. Biology

Compounds **15**–**22** (except **20**) were evaluated in duplicate at 10^{-5} M and 10^{-6} M concentrations for COX-2 inhibition and 10^{-5} M concentration for COX-1 inhibition (Table 2) using COX (ovine) inhibitor screening assay kits (Cayman Chemicals, Cat. No. 560101) with 96 well plates following the standard procedure [51]. On the basis of the results of docking studies, compounds **23**–**30** which show very poor or no interactions with the enzymes are not included in the experimental investigations. For compounds **15**–**22**, almost no difference in the COX-2 inhibitory activities between compounds **15** and **16**; **17** and **18**; **21** and **22** has been observed which indicates that $CH_2SC_2H_5$ and SCN groups may contribute equally towards the activity of these compounds. It was also found during the docking studies that the S atom of both these substituents approaches to R120 in the active site of COX-2. Compounds **17** and **18** with F on the aryl ring show considerably higher inhibition of COX-2 ($IC_{50} \sim 1\ \mu M$) as compared to other compounds with NO_2, Cl and Br substituted aryl rings. Moreover, **17** and **18** exhibit lower inhibition of COX-1 in comparison to ibuprofen (a non-selective COX-1/2 inhibitor). Therefore, in addition to the identification of **17** and **18** as suitable candidates for further refinement to develop as COX-1/2 inhibitors, these investigations also justify the design of these molecules.

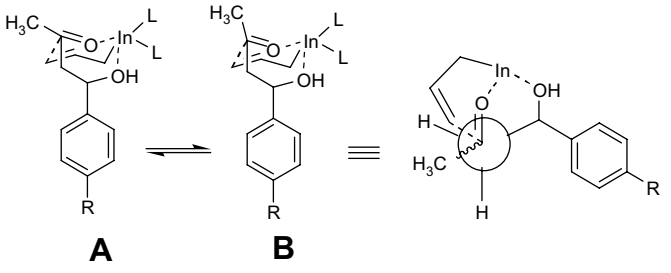
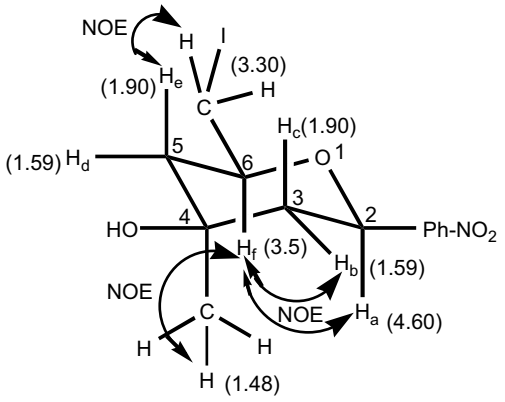


Fig. 3. Transition state during allylations of **2** and Cram's chelation model.



$J_{a\text{-}b}$ = 2.1 Hz, $J_{a\text{-}c}$ = 11.7 Hz, $J_{d\text{-}f}$ = 2.1 Hz, $J_{e\text{-}f}$ = 11.4 Hz

Fig. 4. Orientation of the groups at each carbon of **7** as depicted from ^1H decoupling and NOE experiments. ^1H chemical shifts are given in brackets.

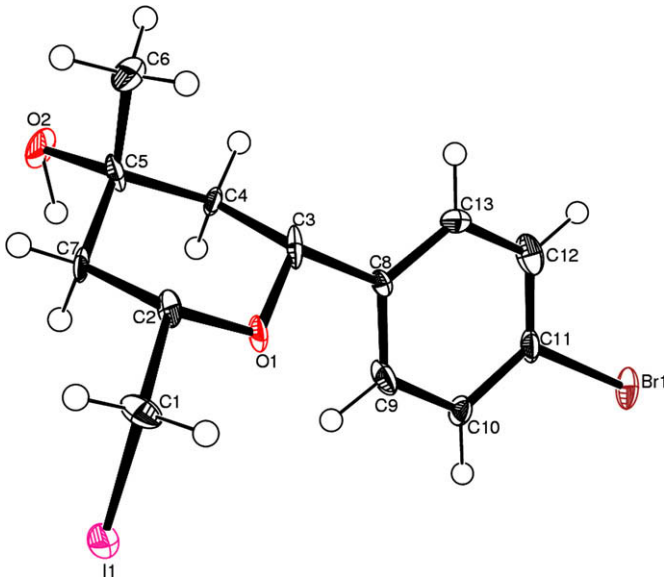


Fig. 5. ORTEP diagram of **13**.

2.3. Dockings of tetrahydropyrans in the active sites of COX-1 and COX-2

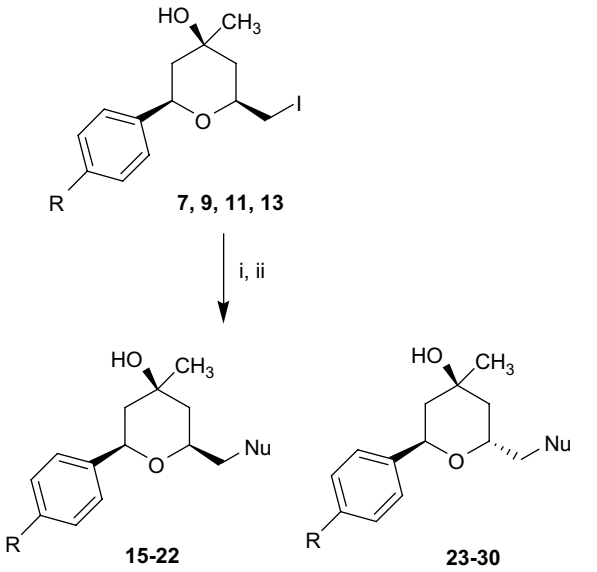
In order to get further insight into the nature of interactions between the tetrahydropyrans and the amino acids of COX-1, COX-2 active sites, the dockings of compounds **15**–**22** in the active sites of COX-1 and COX-2 were performed. For making a comparison between the dockings of two sets of diastereomers (**15**–**22** and **23**–**30**), compounds **23**–**30** were also included for docking studies. All the compounds were built with specific stereochemistry at the different asymmetric centers and energy minimized before their dockings in the active sites of COX-1 and COX-2. Crystal coordinates of COX-2 with SC-558 in the active site pocket were downloaded from protein data bank (Pdb ID 6COX) and refined as reported previously [52]. The crystal structure of COX-1 (Pdb ID 1EQG) has ibuprofen in the active site pocket. The docking program [53] was validated by docking ibuprofen in the active site of COX-1 and a close overlapping of the docked ibuprofen with the one present in the crystal structure of the enzyme was observed (Fig. 6).

Compounds **15**–**22**, like ibuprofen, aspirin and diclofenac, exhibit negative docking scores (Table 3) for COX-2 and COX-1 indicating their significant interactions with active site amino acids of these enzymes. Compounds **17** and **18**, which show best experimental results in this series of compounds, also exhibit better docking score in comparison to other compounds. Docking scores of other compounds, except **19**, follow almost parallel trend with the experimental results (inhibition of both COX-1 and COX-2 by these compounds). Interestingly, the dockings of compounds **23**–**30** in the active sites of both COX-1 and COX-2 show positive docking scores (Table 3) indicating their poor or no interactions

Table 2
In vitro percentage inhibition of COX-1 and COX-2 by compounds **15**–**22**

Compound	Percentage inhibition			IC_{50} (μM)	
	COX-2		COX-1	COX-2	COX-1
	10^{-5} M	10^{-6} M	10^{-5} M		
15	37	37	34	>10	>10
16	35	34	29	>10	>10
17	56	55	42	<1	>10
18	49	47	34	1	>10
19	34	30	34	>10	>10
20	nd	nd	nd	–	–
21	30	30	24	>10	>10
22	28	26	32	>10	>10
Ibuprofen [25]	76	87	96		
Aspirin (IC_{50}) [26]				2.4	0.35

nd – Not done.



15, **23**: R = NO_2, Nu = SC_2H_5
16, **24**: R = NO_2, Nu = SCN
17, **25**: R = F, Nu = SC_2H_5
18, **26**: R = F, Nu = SCN
19, **27**: R = Cl, Nu = SC_2H_5
20, **28**: R = Cl, Nu = SCN
21, **29**: R = Br, Nu = SC_2H_5
22, **30**: R = Br, Nu = SCN

Scheme 3. Reagents and reaction conditions: (i) C_2H_5SH, K_2CO_3, CH_3CN, stir, rt; (ii) KSCN, K_2CO_3, CH_3CN, stir, rt.

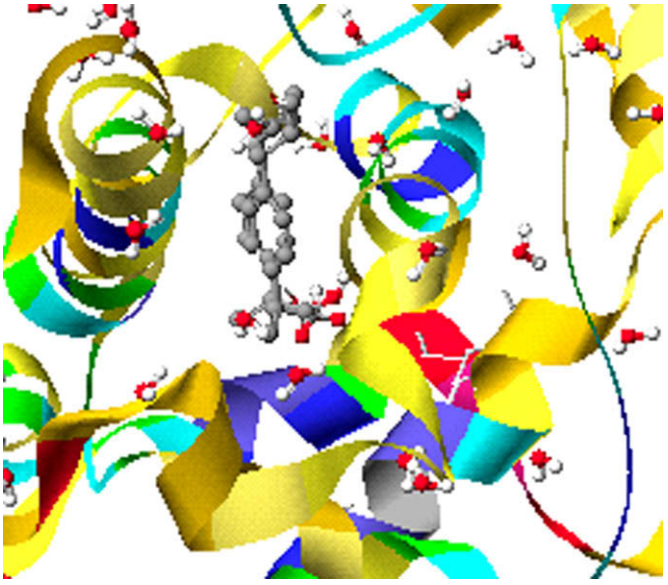


Fig. 6. A close overlapping between the two Ibuprofen molecules validates the docking programme.

Table 3
Docking scores (kcal/mol) of compounds **15**–**30** when docked in the active sites of COX-1 and COX-2

Compound	Docking score (kcal/mol)	
	COX-2	COX-1
15	−37	−20
16	−45	−30
17	−50	−24
18	−49	−33
19	−50	−25
20	−40	−26
21	−38	−3
22	−40	−26
23	103	72
24	32	100
25	64	−7.4
26	74	36
27	32	27
28	−18	6.8
29	69	43
30	89	46
Ibuprofen	−47	−21
Aspirin	−62	−60
Diclofenac	−27	−41

with these enzymes and also indicates that the stereochemistry at C-6 of tetrahydropyran significantly affects the interactions of these compounds in the active sites of COX-1 and COX-2.

During the docking of compound **15** in the active site of COX-2 (Fig. 7), the nitro group present at the phenyl ring shows H-bonding with H90 residue and the S atom present at C-6 substituent approaches R120 (the amino acid active during the metabolic phase of COX-2) at a distance of 2.7 Å.

When **15** is docked in the active site of COX-1 (Fig. 8), the C-6 substituent ($CH_2SC_2H_5$) is placed in the hydrophobic sub-pocket of COX-1 active site constituted by Y385, W387, F381 and F518 residues. The nitrophenyl group present at C-2 of **15** is oriented towards the polar sub-pocket comprising R120, V116, Y355 residues. A similar placement of molecules **16**–**22** has been observed during their dockings in the active sites of COX-1 and COX-2.

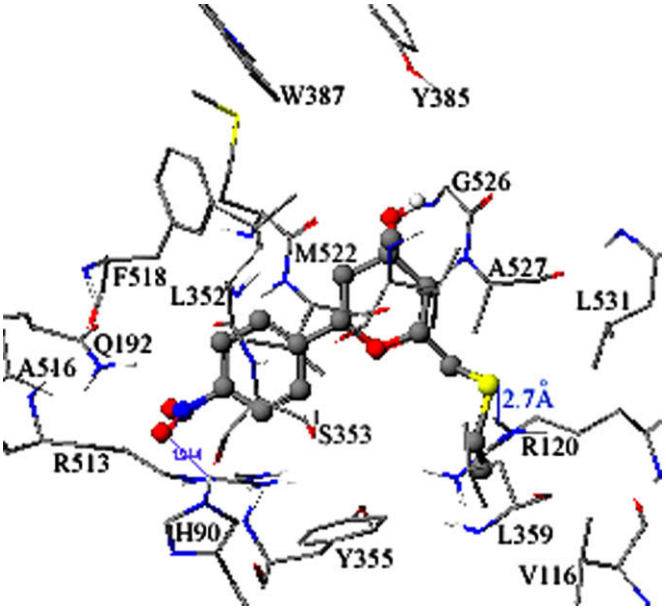


Fig. 7. Compound**15** docked in the active site of COX-2. One of the oxygens of the nitro group of **15** forms H-bond with H90 while S atom present at C-6 substituent approached R120 at a distance of 2.7 Å.

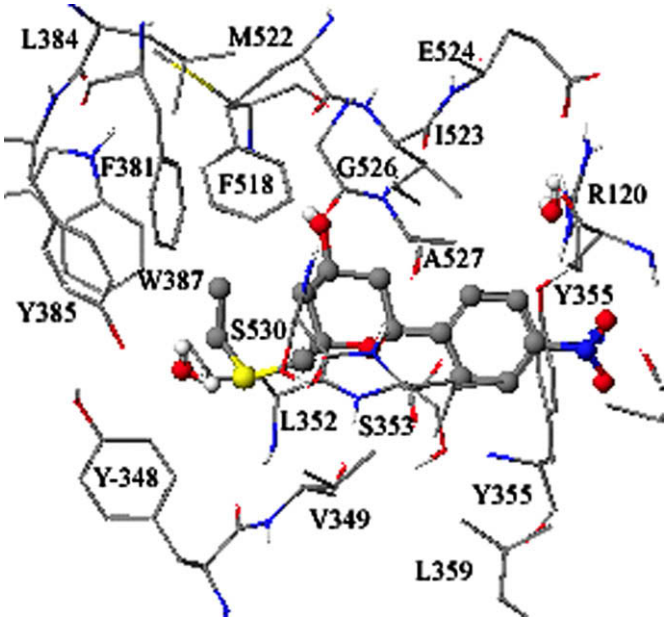


Fig. 8. Compound **15** docked in the active site of COX-1.

The optimum size and appropriate stereochemistry of these molecules allow them to enter the active sites of COX-1 as well as COX-2, thereby inhibiting both these enzymes. The close parallelism between the docking results and the experimental results could be helpful in further refinements of these molecules.

3. Conclusions

Rationally designed tetrahydropyrans, with asymmetric centers and appropriate substituents, were synthesized by the allylations of enantioselective β-hydroxy ketones followed by the iodocyclisations. The *in vitro* investigations of these molecules identify compounds **17** and **18** as moderate inhibitors of COX-1/-2 enzymes. The dockings of these molecules in the active sites of COX-1 and COX-2 indicate their significant interactions with the active site amino acid residues of these enzymes.

4. Experimental

4.1. General details

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were run on JEOL 300 MHz and 75 MHz NMR spectrometer, 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. In ^{13}C NMR spectral data, +ve, −ve terms correspond to CH_3, CH, CH_2 signals in DEPT-135 NMR spectra.

4.2. General procedure for the synthesis of β-hydroxy ketones

To the solution of 4-substituted benzaldehyde (0.4 mmol) in 10 ml acetone was added L-proline (20 mol%) and the resulting mixture was stirred at 25 °C for 8–13 h. The reaction mixture was treated with saturated ammonium chloride solution, the layers were separated and aqueous layer was extracted with ethyl acetate

(3 × 25 ml) and combined organic layers were dried over anhydrous Na_2SO_4. Ethyl acetate was distilled off and the residue was purified by column chromatography using ethyl acetate and hexane (1:2) as eluents.

4.2.1. (4R)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one (**2a**)

4-Nitrobenzaldehyde was allowed to react with acetone as described in the general procedure to give **2a** as white crystalline solid, 72% yield, mp 60 °C; ν_{max} ($CHCl_3$): 1705 (C═O), 3580 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 2.87 (d, $J = 6$ Hz, 2H, CH_2), 5.27 (t, $J = 6$ Hz, 1H, CH), 7.54 (d, $J = 6.9$ Hz, 2H, ArH), 8.20 (d, $J = 6.9$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 30.64 (+ve, CH_3), 51.39 (−ve, CH_2), 68.83 (+ve, CH), 123.70 (+ve, ArCH), 126.33 (+ve, ArCH), 147.30 (absent, ArC), 149.88 (absent, ArC), 208.56 (absent, CO); FAB mass m/z 209 (M^+); $[\alpha]_D = +44°$ (c 1, $CHCl_3$).

4.2.2. (4R)-4-(4-Fluorophenyl)-4-hydroxybutan-2-one (**2b**)

4-Fluorobenzaldehyde was allowed to react with acetone as described in the general procedure to give **2b** as white crystalline solid, 70% yield, mp 55 °C; ν_{max} ($CHCl_3$): 1700 (C═O), 3640 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H, CH_3), 2.81 (d, $J = 6$ Hz, 2H, CH_2), 5.13 (dd, $J = 8.4$ Hz, $J = 3.9$ Hz, 1H, CH), 7.02 (t, $J = 8.7$ Hz, 2H, ArH), 7.31 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 30.67 (+ve, CH_3), 51.85 (−ve, CH_2), 69.11 (+ve, CH), 115. 92, (+ve, ArCH, *ortho* to F, $J_{C-F} = 21.0$ Hz), 127.28 (+ve, ArCH, *meta* to F, $J_{C-F} = 8.02$ Hz), 138.46 (absent, ArC, *para* to F, $J_{C-F} = 1.87$ Hz), 162.14 (mid point of two peaks at 160.52 and 163.76) (absent, ArC–F, $J_{C-F} = 243.5$ Hz), 209.00 (absent, C═O); FAB mass m/z 182 (M^+); $[\alpha]_D = +49°$ (c 1, $CHCl_3$).

4.2.3. (4R)-4-(4-Chlorophenyl)-4-hydroxy-2-butanone (**2c**)

4-Chlorobenzaldehyde was allowed to react with acetone as described in the general procedure to give **2c** as white crystalline solid, 68% yield, mp 45 °C; ν_{max} ($CHCl_3$): 1715 (C═O), 3540 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H, CH_3), 2.80 (d, $J = 6$ Hz, 2H, CH_2), 5.13 (dd, $J = 8.1$ Hz, $J = 4$ Hz, 1H, CH), 7.21–7.32 (m, 4H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 30.66 (+ve, CH_3), 51.73 (−ve, CH_2), 69.05 (+ve, CH), 126.95 (+ve, ArCH), 128.56 (+ve, ArCH), 133.23 (absent, ArC), 141.22 (absent, ArC), 208.80 (absent, C═O); FAB mass m/z 198 (M^+); $[\alpha]_D = +51°$ (c 1, $CHCl_3$).

4.2.4. (4R)-4-(4-Bromophenyl)-4-hydroxybutan-2-one (**2d**)

4-Bromobenzaldehyde was allowed to react with acetone as described in the general procedure to give **2d** as white crystalline solid, 75% yield, mp 57 °C; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.66 (dd, $J = 17.1$ Hz, $J = 3.6$ Hz, 1H, 1H of CH_2), 2.78 (dd, $J = 17.1$ Hz, $J = 9.0$ Hz, 1H, 1H of CH_2), 4.07 (br, 1H, OH), 5.01 (br d, $J = 9.0$ Hz), 7.15 (d, $J = 8.1$ Hz, 2H, ArH), 7.39 (d, $J = 8.1$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 30.63 (+ve, CH_3), 51.78 (−ve, CH_2), 68.94 (+ve, CH), 120.78 (absent, ArC), 127.10 (+ve, ArCH), 131.04 (+ve, ArCH), 141.90 (absent, ArC), 206.14 (absent, C═O); FAB mass m/z 242 (M^+); $[\alpha]_D = +40.4°$ (c 1, $CHCl_3$).

4.2.5. (4R)-4-Hydroxy-4-(4-methoxyphenyl)-butan-2-one (**2e**)

4-Methoxybenzaldehyde was allowed to react with acetone as described in the general procedure to give **2e** as thick liquid, 64% yield; ν_{max} ($CHCl_3$): 1705 (C═O), 3580 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H, CH_3), 2.69 (dd, $J = 16.8$ Hz, $J = 3.6$ Hz, 1H, 1H of CH_2), 2.84 (dd, $J = 16.2$ Hz, $J = 9.0$ Hz, 1H, 1H of CH_2), 3.75 (s, 3H, OCH_3), 5.03 (dd, $J = 9.0$ Hz, $J = 3.6$ Hz, 1H, CH), 6.84 (d, $J = 6.6$ Hz, 2H, ArH), 7.21 (d, $J = 6.6$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 30.67 (+ve, CH_3), 51.92 (−ve, CH_2), 55.16 (+ve, CH_3), 69.38 (+ve, CH), 113.77 (+ve, ArCH), 126.86 (+ve, ArCH), 134.96 (absent, ArC), 158.88 (absent, ArC), 208.95 (absent, CO); FAB mass m/z 194 (M^+); $[\alpha]_D = +43.6°$ (c 1, $CHCl_3$).

4.2.6. (4R)-4-Hydroxy-4-(4-methylsulfanylphenyl)-butan-2-one (**2f**)

4-Methylsulfanylbenzaldehyde was allowed to react with acetone as described in the general procedure to give **2f** as thick liquid, 55% yield; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.73 (dd, $J = 17.1$ Hz, $J = 3.6$ Hz, 1H, 1H of CH_2), 2.84 (dd, $J = 17.1$ Hz, $J = 9.0$ Hz, 1H, 1H of CH_2), 3.55 (br, 1H, OH), 5.06 (dd, $J = 9.0$ Hz, $J = 3.6$ Hz, 1H, CH), 7.18–7.28 (m, 4H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 15.75 (+ve, CH_3), 30.71 (+ve, CH_3), 51.82 (−ve, CH_2), 69.32 (+ve, CH), 126.03 (+ve, ArCH), 126.45 (+ve, ArCH), 137.46 (absent, ArC), 139.64 (absent, ArC), 208.78 (absent, C═O); FAB mass m/z 210 (M^+); $[\alpha]_D = +41.4°$ (c 1, $CHCl_3$).

4.3. General procedure for allylation of β-hydroxy ketones

To the magnetically stirred solution of allyl bromide (0.5 mmol) in dry THF was added indium metal (0.4 mmol) and mixture was refluxed for 30 min. During this period indium was dissolved. To the cooled solution was added a solution of β-hydroxy ketone (0.5 mmol) in dry THF. The reaction mixture was stirred at room temperature for 6–10 h (TLC). The reaction mixture was treated with saturated solution of ammonium chloride and extracted with ethyl acetate (3 × 25 ml), dried over anhydrous Na_2SO_4. Removal of ethyl acetate by distillation and the purification of the residue by column chromatography using ethyl acetate and hexane as eluents (1:5) gave a mixture of two diastereomers (**a** and **b**) for compounds **3–6**. The assignments of the signals to various Hs' in the ^1H NMR experiments are based upon the decoupling, ^1H–^{13}C HETCOR, NOE experiments.

4.3.1. 3-Methyl-1-(4-nitrophenyl)-hex-5-ene-1,3-diols (**3a** + **3b**)

Compound **2a** was allowed to react with allyl bromide as described in the general procedure to give **3a** and **3b** as thick creamish white liquid, 88% yield; mixture of two diastereomers designated as major and minor, 7:3 (^1H NMR integration); ν_{max} ($CHCl_3$): 3720 (OH), 3780 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3H, CH_{3major}), 1.44 (s, 3H, CH_{3minor}), 1.62–1.77 (m, 2H, 1H of CH_{2major} + 1H of CH_{2minor}), 1.80–1.88 (m, 2H, 1H of CH_{2major} + 1H of CH_{2minor}), 2.25 (d, $J = 7.5$ Hz, 2H, CH_{2minor}), 2.52 (d, $J = 7.5$ Hz, 2H, CH_{2major}), 5.09–5.21 (m, 6H, 2H of $=CH_{2major}$ + 2H of $=CH_{2minor}$ + 1H of $CH{-}OH_{major}$ + 1H of $CH{-}OH_{minor}$), 5.82–5.91 (m, 2H, 1H of $=CH_{major}$ + 1H of $=CH_{minor}$), 7.48 (d, $J = 7.2$ Hz, 2H, ArH), 7.51 (d, $J = 6.6$ Hz, 2H, ArH), 8.15 (d, $J = 8.7$ Hz, 2H, ArH), 8.15 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 25.35 (+ve, CH_{3minor}), 28.87 (+ve, CH_{3major}), 29.61 (−ve, CH_{2minor}), 44.66 (−ve, CH_{2major}), 48.32 (−ve, CH_{2major}), 48.42 (−ve, CH_{2minor}), 70.66 (+ve, CH_{major}), 70.93 (+ve, CH_{minor}), 73.39 (C_{major}), 73.43 (C_{minor}), 119.34 (−ve, $=CH_{2major}$), 119.79 (−ve, $=CH_{2minor}$), 123.59 (+ve, $ArCH_{major}$), 124.13 (+ve, $ArCH_{minor}$), 126.13 (+ve, $ArCH_{major}$), 126.35 (+ve, $ArCH_{minor}$), 128.78 (+ve, $ArCH_{major}$), 130.24 (+ve, $ArCH_{minor}$), 132.61 (+ve, CH_{major}), 133.40 (+ve, CH_{minor}), 146.97 (ArC), 152.13 (ArC_{major}), 152.19 (ArC_{minor}); FAB mass m/z 251 (M^+); $[\alpha]_D = +34.3°$ (c 1, $CHCl_3$). (Found C 62.43, H 6.48, N 5.17; $C_{13}H_{17}NO_4$ requires C 62.14, H 6.82, N 5.57).

4.3.2. 1-(4-Fluorophenyl)-3-methylhex-5-ene-1,3-diols (**4a** + **4b**)

Compound **2b** was allowed to react with allyl bromide as described in the general procedure to give **4a** and **4b** as thick creamish white liquid, 86% yield; mixture of two diastereomers, 56:44 (^1H NMR integration); ν_{max} ($CHCl_3$) 3500–3560 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3H, CH_{3major}), 1.27 (s, 3H, CH_{3minor}), 1.54–1.69 (m of 8 lines, 2H, 1H of CH_{2major} + 1H of CH_{2minor}), 1.80–1.88 (m of 8 lines, 2H, IH of CH_{2major} + 1H of CH_{2minor}), 2.20 (d, $J = 7.5$ Hz, 2H, CH_{2minor}), 2.43 (d, $J = 7.2$ Hz, 2H, CH_{2major}), 4.97–5.03 (m, 2H, 1H of CH_{major} + 1H of CH_{minor}), 5.09–5.19 (m, 4H, 2H of $=CH_{2major}$ + 2H of $=CH_{2minor}$), 5.76–5.86 (m, 2H, 1H of $=CH_{major}$ + 1H of $=CH_{minor}$), 6.95–7.23 (m, 4H, ArH), 7.23–7.29 (m, 4H, ArH); ^{13}C NMR

(normal/DEPT-135) ($CDCl_3$) δ 25.35 (+ve, CH_{3minor}), 28.57 (+ve, CH_{3major}), 29.60 (−ve CH_{2minor}), 44.81 (−ve, CH_{2major}), 48.39 (−ve, CH_{2major}), 48.43 (−ve, CH_{2minor}), 70.87 (+ve, CH_{major}), 71.14 (+ve, CH_{minor}), 73.06 (C_{major}), 73.08 (C_{minor}), 115.06 (mid of two peaks at 114.92 and 115. 20) (+ve ArCH, *ortho* to F, $J_{C-F} = 21.6$ Hz), 118.59 (−ve, $=CH_{2major}$), 118.97 (−ve, $=CH_{2minor}$), 127.07 (+ve, ArCH, *meta* to F, $J_{C-F} = 8.10$ Hz), 127.21 (+ve, ArCH, *meta* to F, $J_{C-F} = 7.42$ Hz), 133.20 (+ve, $=CH_{minor}$), 133.93 (+ve, $=CH_{major}$), 140.40 (absent, ArC, *para* to F, $J_{C-F} = 3.15$ Hz), 140.48 (absent, ArC, *para* to F, $J_{C-F} = 3.07$ Hz), 161.94 (mid point of two peaks at 160.32 and 163.56) (absent, ArC–F, $J_{C-F} = 242.9$ Hz); FAB mass *m*/*z* 224 (M^+); $[\alpha]_D = +23.2^\circ$ (*c* 1, $CHCl_3$). (Found C 69.80, H 7.23; $C_{13}H_{17}FO_2$ requires C 69.62, H 7.64).

4.3.3. 1-(4-Chlorophenyl)-3-methylhex-5-ene-1,3-diols (**5a** + **5b**)

Compound **2c** was allowed to react with allyl bromide as described in the general procedure to give **5a** and **5b** as thick creamish white liquid, 80% yield; mixture of two diastereomers, 7:3 (^{1}H NMR integration); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3H, CH_{3major}), 1.17 (s, 3H, CH_{3minor}), 1.53–1.59 (m, 2H, 1H of CH_{2major} + 1H of CH_{2minor}), 1.64–1.81 (m, 2H, 1H of CH_{2major} + 1H of CH_{2minor}), 2.16 (d, $J = 7.5$ Hz, 2H, CH_{2minor}), 2.39 (d, $J = 6.9$ Hz, 2H, CH_{2major}), 4.89–5.24 (m, 6H, 2H of $=CH_{2major}$ + 2H of $=CH_{2minor}$ + 1H of CH_{major} + 1H of CH_{minor}), 5.70–5.84 (m, 2H, 1H of $=CH_{major}$ + 1H of $=CH_{minor}$), 7.15–7.25 (m, 8H, 4H of ArH_{major} + 4H of ArH_{minor}); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 25.34 (+ve, CH_{3minor}), 28.58 (+ve, CH_{3major}), 44.80 (+ve, CH_{2minor}), 48.26 (−ve, CH_{2major}), 48.34 (−ve, CH_{2major}), 48.68 (−ve, CH_{2minor}), 70.82 (+ve, CH_{major}), 71.15 (+ve, CH_{minor}), 73.09 (C_{major}), 73.11 (C_{minor}), 118.67 (−ve, $=CH_{2minor}$), 119.06 (−ve, $=CH_{2major}$), 126.83 (+ve, $ArCH_{major}$), 126.98 (+ve, $ArCH_{minor}$), 128.41 (+ve, $ArCH_{major}$), 132.79 (ArC), 133.12 (+ve, $=CH_{minor}$), 133.86 (+ve, $=CH_{major}$), 143.12 (ArC_{minor}), 143.20 (ArC_{major}); FAB mass *m*/*z* 240 (M^+); $[\alpha]_D = +34^\circ$ (*c* 1, $CHCl_3$). (Found C 64.38, H 7.15; $C_{13}H_{17}ClO_2$ requires C 64.86, H 7.12).

4.3.4. 1-(4-Bromophenyl)-3-methylhex-5-ene-1,3-diols (**6a** + **6b**)

Compound **2d** was allowed to react with allyl bromide as described in the general procedure to give **6a** and **6b** as thick creamish white liquid, 70% yield; mixture of two diastereomers, 7:3 (^{1}H NMR integration); ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3H, CH_{3major}), 1.32 (s, 3H, CH_{3minor}), 1.55–1.82 (m, 4H, CH_{2major} + CH_{2minor}), 2.18 (d, $J = 7.2$ Hz, 2H, CH_{2minor}), 2.41 (d, $J = 7.5$ Hz, 2H, CH_{2major}), 4.91–5.16 (m, 6H, 2H of $=CH_{2major}$ + 2H of $=CH_{2minor}$ + 1H of CH_{major} + 1H of CH_{minor}), 5.72–5.86 (m, 2H, 1H of $=CH_{major}$ + 1H of $=CH_{minor}$), 7.11–7.16 (d, $J = 8.4$ Hz, 4H, ArH_{major} + ArH_{minor}), 7.40 (d, $J = 8.4$ Hz, 4H, ArH_{major} + ArH_{minor}); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 25.35 (+ve, CH_{3minor}), 28.50 (+ve, CH_{3major}), 44.82 (+ve, CH_{2minor}), 48.08 (−ve, CH_{2major}), 48.17 (−ve, CH_{2minor}), 48.65 (−ve, CH_{2major}), 70.82 (+ve, CH_{major}), 71.14 (+ve, CH_{minor}), 70.70 (C_{major}), 71.07 (C_{minor}), 118.56 (−ve, $=CH_{2major}$), 118.90 (−ve, $=CH_{2minor}$), 120.78 (ArC), 131.34 (+ve, $ArCH_{major}$), 133.23 (+ve, $=CH_{minor}$), 133.96 (+ve, $=CH_{major}$), 143.59 (ArC_{minor}), 143.68 (ArC_{major}); FAB mass *m*/*z* 285 (M^+); $[\alpha]_D = +38^\circ$ (*c* 1, $CHCl_3$). (Found C 54.50, H 6.30; $C_{13}H_{17}BrO_2$ requires C 54.75, H 6.01).

4.4. Iodine mediated cyclization of **3**–**6**

To the ice cold solution of diastereomeric mixtures of **3**–**6** (0.5 mmol) in dry CH_3CN was added sodium hydrogen carbonate (0.6 mmol) and the resulting suspension was stirred for 10 min at 0 °C. Iodine (0.7 mmol) was added to the above reaction mixture and stirring was continued for 12–17 h (TLC monitoring). The reaction mixture was diluted with water and extracted with ethyl acetate (3 × 25 ml). The organic layer was washed with saturated aqueous sodium thiosulphate and dried over anhydrous sodium sulphate. Removal of the solvent and purification of the residue by column chromatography using ethyl acetate and hexane as eluents provided the two diastereomers of tetrahydropyrans. The numbering of the six atoms of tetrahydropyran is as per Fig. 4.

4.4.1. (2R,4S,6S)-2-Iodomethyl-4-methyl-6-(4-nitrophenyl)-tetrahydropyran-4-ol (**7**)

Compound **3a** + **3b** was allowed to undergo iodocyclisation as described in the general procedure to give **7** and **8** as thick liquids which were separated by column chromatography. 40% yield; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3H, CH_3), 1.51–1.62 (m, 2H, H-3 + H-5), 1.90–1.99 (m, 2H, H-3 + H-5), 3.30 (dd, $J = 14.1$ Hz, $J = 6.0$ Hz, 1H, 1H of CH_2I), 3.35 (dd, $J = 14.1$ Hz, $J = 4.5$ Hz, 1H, 1H of CH_2I), 3.54 (m of 16 lines, 1H, H-6), 4.69 (dd, $J = 11.7$ Hz, $J = 2.1$ Hz, 1H, H-2), 7.56 (d, $J = 9.0$ Hz, 2H, ArH), 8.23 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 8.92 (−ve, CH_2I), 26.06 (+ve, CH_3), 45.4 (−ve, CH_2), 47.5 (−ve, CH_2), 69.23 (C-4), 74.42 (+ve, C-2), 75.9 (+ve, C-6), 123.69 (+ve, ArCH), 126.45 (+ve, ArCH), 147.60 (absent, ArC), 149.00 (absent, ArC); In the decoupling NMR experiments, irradiation of signal at δ 3.54 changes the multiplicity of the multiplets at δ 1.51–1.62 and 1.90–1.99 indicating the presence of two H-5 protons in each one of these multiplets. Similarly, the irradiation of dd at δ 4.69 changes the multiplicity of both the multiplets at δ 1.51–1.62 and 1.90–1.99 which shows the presence of two C-3 protons one each in the two multiplets. These two decoupling experiments indicate the non-equivalence of the protons present at C-3 and C-5 of tetrahydropyran (axial and equatorial protons). This observation has also been confirmed from the ^{1}H–^{13}C HETCOR experiment in which the C-3 and C-5 carbons show correlations with both the multiplets present at δ 1.51–1.62 and 1.90–1.99 in ^{1}H NMR spectrum. NOE experiments: the irradiation of proton at δ 4.69 (H-2) shows NOE effect on the signal at δ 3.54 (H-6); irradiation of signal at δ 3.54 shows NOE effect on CH_3 at δ 1.48, the multiplet signal at δ 1.51–1.62, CH_2I protons at δ 3.30 and H-2 signal at δ 4.60 indicating the placement of H-6, one H-5, one H-3, H-2 and CH_3 protons *syn* to one another; FAB mass *m*/*z* 378 (M^+); $[\alpha]_D = +43.3^\circ$ (*c* 1, $CHCl_3$). (Found C 41.59, H 4.47, N 3.83; $C_{13}H_{16}INO_4$ requires C 41.40, H 4.28, N 3.71).

4.4.2. (2R,4S,6R)-2-Iodomethyl-4-methyl-6-(4-nitrophenyl)-tetrahydropyran-4-ol (**8**)

20% Yield; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3H, CH_3), 1.51–1.62 (m, 2H, H-3 + H-5), 1.79–1.88 (m, 2H, H-3 + H-5), 3.27–3.39 (m, 2H, CH_2I), 4.95 (m, 1H, H-6), 4.97 (dd, $J = 11.4$ Hz, $J = 2.4$ Hz, 1H, H-2), 7.61 (d, $J = 8.7$ Hz, 2H, ArH), 8.17 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 14.75 (−ve, CH_2I), 27.01 (+ve, CH_3), 42.99 (−ve, CH_2), 46.09 (−ve, CH_2), 68.61 (C-4), 74.14 (+ve, C-2), 77.02 (+ve, C-6), 123.35 (+ve, ArCH), 126.33 (+ve, ArCH), 146.60 (absent, ArC), 149.76 (absent, ArC); FAB mass *m*/*z* 378 (M^+); $[\alpha]_D = +41^\circ$ (*c* 1, $CHCl_3$). (Found C 41.78, H 4.25, N 3.90; $C_{13}H_{16}INO_4$ requires C 41.40, H 4.28, N 3.71).

4.4.3. (2R,4S,6S)-2-(4-Fluorophenyl)-6-iodomethyl-4-methyltetrahydropyran-4-ol (**9**)

Compound **4a** + **4b** was allowed to undergo iodocyclisation as described in the general procedure to give **9** and **10** as thick liquids which were separated by column chromatography. 35% yield; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 3H, CH_3), 1.51–1.59 (m, 2H, H-3 + H-5), 1.70–1.98 (m, 2H, H-3 + H-5), 3.30 (m, 2H, CH_2–I), 3.82 (m, 16 lines, 1H, H-6), 4.83 (dd, $J = 11.7$ Hz, $J = 1.8$ Hz, 1H, H-2), 7.01–7.07 (m, 2H, ArH), 7.34–7.37 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 10.41 (−ve, CH_2I), 31.42 (+ve, CH_3), 43.75 (−ve, CH_2), 45.83 (−ve, CH_2), 68.48 (C-4), 71.98 (+ve, C-2), 74.20 (+ve, C-6), 114.84 (mid of two peaks at 114.87 and 115.01, +ve, ArCH, *ortho* to F, $J_{C-F} = 21.6$ Hz), 127.41 (+ve, ArCH, *meta* to F, $J_{C-F} = 8.10$ Hz), 138.05 (absent, ArC, *para* to F, $J_{C-F} = 3.15$ Hz), 161.93 (mid point of two peaks at 160.31 and 163.55) (absent, ArC–F, $J_{C-F} = 243.0$ Hz); FAB

mass *m*/*z* 350 (M^+); $[\alpha]_D = +40^\circ$ (*c* 1, $CHCl_3$). (Found C 44.98, H 4.32; $C_{13}H_{16}IFO_2$ requires C 44.59, H 4.61).

4.4.4. (2R,4S,6R)-2-(4-Fluorophenyl)-6-iodomethyl-4-methyltetrahydropyran-4-ol (**10**)

30% Yield; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3H, CH_3), 1.52–1.67 (m, 2H, H-3 + H-5), 1.80–1.94 (m, 2H, H-3 + H-5), 3.22–3.31 (dd, $J = 14.1$ Hz, $J = 6.0$ Hz, 1H, 1H of CH_2I), 3.42–3.50 (m of 16 lines, 1H, H-6), 4.42 (dd, $J = 11.4$ Hz, $J = 2.1$ Hz, 1H, H-2), 7.56 (d, $J = 9.0$ Hz, 2H, ArH), 8.23 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 9.82 (−ve, CH_2I), 25.97 (+ve, CH_3), 45.34 (−ve, CH_2), 47.46 (−ve, CH_2), 69.23 (C-4), 74.42 (+ve, C-2), 75.9 (+ve, C-6), 115.16 (+ve, $J_{C-F} = 21.0$ Hz, ArCH), 127.38 (+ve, $J_{C-F} = 8.0$ Hz, ArCH), 137.33 (+ve, $J_{C-F} = 3.0$ Hz, ArC), 161.94 (absent, $J_{C-F} = 243$ Hz, ArC); FAB mass *m*/*z* 350 (M^+); $[\alpha]_D = +35^\circ$ (*c* 1, $CHCl_3$). (Found C 44.76, H 4.66; $C_{13}H_{16}IFO_2$ requires C 44.59, H 4.61).

4.4.5. (2R,4S,6S)-2-(4-Chlorophenyl)-6-iodomethyl-4-methyltetrahydropyran-4-ol (**11**)

Compound **5a** + **5b** was allowed to undergo iodocyclisation as described in the general procedure to give **11** and **12** as thick liquids which were separated by column chromatography. 35% yield; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3H, CH_3), 1.53 (m, 2H, CH_2), 1.72–1.87 (m, 2H, CH_2), 3.24 (m, 2H, CH_2–I), 3.43 (m, 1H, H-6), 4.42 (dd, $J = 11.7$ Hz, $J = 2.1$ Hz, 1H, H-2), 7.20–7.31 (m, 4H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 9.68 (−ve, CH_2I), 25.97 (+ve, CH_3), 45.34 (−ve, CH_2), 47.42 (−ve, CH_2), 69.12 (C-4), 74.15 (+ve, C-2), 76.21 (+ve, C-6), 126.95 (+ve, ArCH), 127.19 (+ve, ArCH), 128.47 (+ve, ArCH), 132.76 (ArC), 140.0 (ArC); FAB mass *m*/*z* 366 (M^+); $[\alpha]_D = +47^\circ$ (*c* 1, $CHCl_3$). (Found C 42.35, H 4.38; $C_{13}H_{16}IClO_2$ requires C 42.59, H 4.40).

4.4.6. (2R,4S,6R)-2-(4-Chlorophenyl)-6-iodomethyl-4-methyltetrahydropyran-4-ol (**12**)

30% Yield; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H, CH_3), 1.54 (m, 2H, CH_2), 1.71–1.87 (m, 2H, CH_2), 3.23 (m, 2H, CH_2–I), 3.77 (m, 1H, H-6), 4.76 (dd, $J = 11.2$ Hz, $J = 2.4$ Hz, 1H, H-2), 7.20–7.28 (m, 2H, ArH), 7.31–7.45 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 9.77 (−ve, CH_2I), 25.97 (+ve, CH_3), 45.31 (−ve, CH_2), 47.42 (−ve, CH_2), 69.0 (C-4), 74.13 (+ve, C-2), 76.09 (+ve, C-6), 126.96 (+ve, ArCH), 127.18 (+ve, ArCH), 128.39 (ArC), 140.0 (ArC); FAB mass *m*/*z* 366 (M^+); $[\alpha]_D = +48^\circ$ (*c* 1, $CHCl_3$). (Found C 42.65, H 4.56; $C_{13}H_{16}IClO_2$ requires C 42.59, H 4.40).

4.4.7. (2R,4S,6S)-2-(4-Bromophenyl)-6-iodomethyltetrahydropyran-4-ol (**13**)

Compound **6a** + **6b** was allowed to undergo iodocyclisation as described in the general procedure to give **13** as solid and **14** as thick liquid which were separated by column chromatography. 32% yield; mp 68 °C; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H, CH_3), 1.53–1.62 (m, 2H, H-3 + H-5), 1.69–1.99 (m, 2H, H-3 + H-5), 3.27 (m, 2H, CH_2I), 3.82 (m, 16 lines, 1H, H-6), 4.93 (dd, $J = 11.4$ Hz, $J = 3.6$ Hz, 1H, H-2), 7.25 (d, $J = 8.1$ Hz, 2H, ArH), 7.44 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) δ 10.33 (−ve, CH_2I), 31.44 (+ve, CH_3), 43.71 (−ve, CH_2), 45.78 (−ve, CH_2), 68.67 (C-4), 72.00 (+ve, C-2), 74.24 (+ve, C-6), 121.04 (absent, ArC), 127.52 (+ve, ArCH), 131.44 (+ve, ArCH), 141.40 (absent, ArC); FAB mass *m*/*z* 411 (M^+); $[\alpha]_D = +41.2^\circ$ (*c* 1, $CHCl_3$). (Found C 37.62, H 4.35; $C_{13}H_{16}IBrO_2$ requires C 37.98, H 3.92).

4.4.8. (2R,4S,6R)-2-(4-Bromophenyl)-6-iodomethyltetrahydropyran-4-ol (**14**)

21% Yield; ^1H NMR ($CDCl_3$) δ 1.44 (s, 3H, CH_3), 1.50–1.63 (m, 2H, H-3 + H-5), 1.70–2.04 (m, 2H, H-3 + H-5), 3.23 (m, 2H, CH_2I), 3.64 (m, 16 lines, 1H, H-6), 4.93 (dd, $J = 14.1$ Hz, $J = 11.7$ Hz, 1H, H-2), 7.25 (d, $J = 7.2$ Hz, 2H, ArH), 7.46 (d, $J = 8.4$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) δ 9.40 (−ve, CH_2I), 25.97 (+ve, CH_3), 45.27 (−ve, CH_2), 47.40 (−ve, CH_2), 69.31 (C-4), 72.27 (+ve, C-2), 74.25 (+ve, C-6), 121.36 (absent, ArC), 127.49 (+ve, ArCH), 131.43 (+ve, ArCH), 141.40 (absent, ArC); FAB mass *m*/*z* 411 (M^+); $[\alpha]_D = +40^\circ$ (*c* 1, $CHCl_3$). (Found C 37.80, H 4.05; $C_{13}H_{16}IBrO_2$ requires C 37.98, H 3.92).

4.5. Reactions of **7**, **9**, **11**, **13** with C_2H_5SH and KSCN

A solution of **7**/**9**/**11**/**13** (0.5 mmol), ethanthiol/KSCN (0.5 mmol), K_2CO_3 (0.7 mmol) in CH_3CN (20 ml) was stirred at room temperature for 2 h. The reaction mixture after filtration and evaporation of the solvent was column chromatographed to get pure compounds **15**–**22**.

4.5.1. 2-Ethylsulfanylmethyl-4-methyl-6-(4-nitrophenyl)-tetrahyropyran-4-ol (**15**)

Compound **7** was allowed to react with ethanthiol as described in the general procedure to give **15** as thick liquid, 65% yield; ^1H NMR ($CDCl_3$) δ 1.27 (t, $J = 3.1$ Hz, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.51–1.65 (m, 2H, H-3 + H-5), 1.79–2.13 (m, 2H, H-3 + H-5), 2.58–2.69 (m, 2H, SCH_2), 2.75–2.82 (m, 2H of CH_2), 4.1 (m, 1H, H-6), 4.69 (dd, $J = 11.7$ Hz, $J = 2.1$ Hz, 1H, H-2), 7.52 (d, $J = 8.4$ Hz, 1H, ArH), 7.70 (d, $J = 8.1$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 26.38 (−ve, S–CH_2), 31.28 (+ve, CH_3), 31.38 (+ve, CH_3), 39.16 (−ve, CH_2–S), 43.83 (−ve, CH_2), 45.73 (−ve, CH_2), 68.45 (C-4), 71.94 (+ve, C-2), 73.91 (+ve, C-6), 123.31 (+ve, ArCH), 123.51 (+ve, ArCH), 126.38 (+ve, ArCH), 126.84 (+ve, ArCH), 149.45 (absent, ArC), 149.99 (absent, ArC); FAB mass *m*/*z* 311 (M^+); $[\alpha]_D = +36.72^\circ$ (*c* 1, $CHCl_3$). (Found C 58.11, H 6.77, N 4.66; $C_{15}H_{21}NO_4S$ requires C 57.86, H 6.80, N 4.50).

4.5.2. 4-Methyl-2-(4-nitrophenyl)-6-thiocyanatomethyltrtrahydropyran-4-ol (**16**)

Compound **7** was allowed to react with KSCN as described in the general procedure to give **16** as thick liquid; 80% yield; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3H, CH_3), 1.50-1.65 (m, 2H, H-3 + H-5), 1.72-1.91 (m, 2H, H-3 + H-5), 3.19 (m, 2H, CH_2), 4.28 (m, 1H, H-6), 4.98 (dd, $J = 11.7$ Hz, $J = 2.1$ Hz, 1H, H-2), 7.53 (d, $J = 8.7$ Hz, 2H, ArH), 8.20 (d, $J = 8.7$ Hz, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 31.18 (+ve, CH_3), 39.09 (−ve, CH_2S), 42.08 (−ve, CH_2), 45.69 (−ve, CH_2), 68.65 (C-4), 71.69 (+ve, C-2), 74.23 (+ve, C-6), 112.86 (absent, C≡N), 123.43 (+ve, ArCH), 123.53 (+ve, ArCH), 126.22 (+ve, ArCH), 126.68 (+ve, ArCH), 147.12 (absent, ArC), 149.32 (absent, ArC); FAB mass *m*/*z* 308 (M^+); $[\alpha]_D = +35.62^\circ$ (*c* 1, $CHCl_3$). (Found C 54.49, H 5.40, N 9.17; $C_{14}H_{16}N_2O_4S$ requires C 54.53, H 5.29, N 9.08).

4.5.3. 2-Ethylsulfanylmethyl-6-(4-fluorophenyl)-4-methyltetrahyropyran-4-ol (**17**)

Compound **9** was allowed to react with ethanthiol as described in the general procedure to give **17** as thick liquid; 78% yield; ^1H NMR ($CDCl_3$) δ 1.24 (t, $J = 6.6$ Hz, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.49–1.55 (m, 2H, H-3 + H-5), 1.79–1.81 (m, 2H, H-3 + H-5), 2.59–2.58 (m, 2H, SCH_2), 2.75–2.82 (m, 2H of CH_2), 3.28(m, 1H, H-6), 4.79 (dd, $J = 11.7$ Hz, $J = 1.8$ Hz, 1H, H-2), 6.69–7.07 (m, ArH), 7.30–7.49 (m, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 26.95 (−ve, S–CH_2), 31.46 (+ve, CH_3), 36.92 (+ve, CH_3), 39.60 (−ve, CH_2–S), 43.74 (−ve, CH_2), 45.83 (−ve, CH_2), 68.46 (C-4), 71.99 (+ve, C-2), 73.43 (+ve, C-6), 115.04 (+ve, $J_{C-F} = 21.0$ Hz, ArCH), 127.50 (+ve, $J_{C-F} = 8.0$ Hz, ArCH), 137.52 (+ve, $J_{C-F} = 3.0$ Hz, ArC), 161.91 (absent, $J_{C-F} = 243$ Hz, ArC); FAB mass *m*/*z* 284 (M^+); $[\alpha]_D = +39.72^\circ$ (*c* 1, $CHCl_3$). (Found C 63.11, H 7.28, S 11.16; $C_{15}H_{21}FO_2S$ requires C 63.35, H 7.44 S 11.28).

4.5.4. 2-(4-Fluorophenyl)-4-methyl-6-thiocyanatomethyltetrahydropyran-4-ol (**18**)

Compound **9** was allowed to react with KSCN as described in the general procedure to give **18** as thick liquid; 71% yield; ^1H NMR

($CDCl_3$) δ 1.44 (s, 3H, CH_3), 1.54–1.68 (m, 2H, H-3 + H-5), 1.78–1.92 (m, 2H, H-3 + H-5), 3.15 (m, 2H, CH_2S), 3.83 (m, 1H, H-6), 4.98 (dd, $J = 11.7$ Hz, $J = 2.1$ Hz, 1H, H-2), 6.99–7.05 (m, 2H, ArH), 7.28–7.33 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 25.83 (+ve, CH_3), 39.11 (−ve, CH_2S), 43.96 (−ve, CH_2), 47.38 (−ve, CH_2), 69.06 (C-4), 73.41 (+ve, C-2), 76.57 (+ve, C-6), 112.66 (absent, C≡N), 115.18 (mid of two peaks at 115.04 and 115.33, +ve, ArCH, *ortho* to F, $J_{C-F} = 21.6$ Hz), 127.40 (+ve, ArCH, *meta* to F, $J_{C-F} = 8.02$ Hz), 136.89 (absent, ArC, *para* to F, $J_{C-F} = 3.15$ Hz), 162.11 (mid point of two peaks at 160.49 and 163.74, absent, ArC) (absent, ArC–F, $J_{C-F} = 243.0$ Hz); FAB mass *m*/*z* 281 (M^+); $[\alpha]_D = +37.84^\circ$ (*c* 1, $CHCl_3$). (Found C 59.60, H 5.70, N 4.98, S 11.20; $C_{14}H_{16}FNO_2S$ requires C 59.77, H 5.73, N 4.92, S 11.40).

4.5.5. 2-(4-Chlorophenyl)-6-ethylsulfanylmethyl-4-methyltetrahyropyran-4-ol (**19**)

Compound **11** was allowed to react with ethanthiol as described in the general procedure to give **19** as thick liquid; 71% yield; ^1H NMR ($CDCl_3$) δ 1.26 (t, $J = 5.8$ Hz, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.49 (m, 2H, H-3 + H-5), 1.72–1.81 (m, 2H, H-3 + H-5), 2.56–2.59 (m, 2H, SCH_2), 2.61–2.76 (m, 2H of CH_2), 3.27 (m, 1H, H-6), 4.79 (dd, $J = 10.5$ Hz, $J = 2.4$ Hz, 1H, H-2), 7.28–7.30 (m, 4H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 26.97 (−ve, S–CH_2), 31.38 (+ve, CH_3), 31.57 (+ve, CH_3), 39.49 (−ve, CH_2–S), 43.24 (−ve, CH_2), 45.77 (−ve, CH_2), 68.63 (C-4), 72.02 (+ve, C-2), 74.19 (+ve, C-6), 127.00 (+ve, ArCH), 128.47 (+ve, ArCH), 132.76 (ArC), 140.8 (ArC); FAB mass *m*/*z* 300 (M^+); $[\alpha]_D = +41.26^\circ$ (*c* 1, $CHCl_3$). (Found C 59.90, H 7.14, S 10.70; $C_{15}H_{21}ClO_2S$ requires C 59.88, H 7.04, S 10.66).

4.5.6. 2-(4-Chlorophenyl)-4-methyl-6-thiocyanatomethyltetrahydropyran-4-ol (**20**)

Compound **11** was allowed to react with KSCN as described in the general procedure to give **20** as thick liquid; 67% yield; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3H, CH_3), 1.53–1.67 (m, 2H, H-3 + H-5), 1.77–2.02 (m, 2H, H-3 + H-5), 3.14 (m, 2H, CH_2), 4.18 (m, 1H, H-6), 4.78 (dd, $J = 11.4$ Hz, $J = 1.8$ Hz, 1H, H-2), 7.23 (m, 2H, ArH), 7.39 (m, 2H, ArH); ^{13}C NMR (normal) ($CDCl_3$) δ 31.33 (+ve, CH_3), 39.11 (CH_2S), 42.45 (CH_2), 45.57 (CH_2), 68.09 (C-4), 71.95 (C-2), 76.57 (+ve, C-6), 112.86 (C≡N), 127.26 (ArCH), 127.62 (ArCH), 131.14 (ArCH), 131.18 (ArCH), 139.76 (ArC), 140.85 (ArC); FAB mass *m*/*z* 298 (M^+); $[\alpha]_D = +36.61^\circ$ (*c* 1, $CHCl_3$). (Found C 56.40, H 5.41, N 4.69, S 10.72; $C_{14}H_{16}ClNO_2S$ requires C 56.46, H 5.42, N 4.70, S 10.77).

4.5.7. 2-(4-Bromophenyl)-6-ethylsulfanylmethyl-4-methyltetrahyropyran-4-ol (**21**)

Compound **13** was allowed to react with ethanthiol as described in the general procedure to give **21** as thick liquid; 80%; ^1H NMR ($CDCl_3$) δ 1.23 (t, $J = 7.3$ Hz, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.50 (m, 2H, H-3 + H-5), 1.77–1.89 (m, 2H, H-3 + H-5), 2.43–2.59 (m, 2H, S–CH_2), 2.61–2.78 (m, 2H of CH_2), 3.25 (m, 1H, H-6), 4.37 (dd, $J = 11.7$ Hz, $J = 1.8$ Hz, 1H, H-2), 7.30 (m, 2H, ArH), 7.43 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 25.87 (+ve, CH_3), 25.96 (+ve, CH_3), 37.09 (−ve, S–CH_2), 44.86 (−ve, CH_2–S), 45.36 (−ve, CH_2), 47.41 (−ve, CH_2), 69.03 (C-4), 74.17 (+ve, C-2), 76.15 (+ve, C-6), 127.48 (+ve, ArCH), 127.51 (+ve, ArCH), 131.33 (+ve, ArCH), 131.39 (+ve, ArCH), 140.62 (absent, ArC), 141.98 (absent, ArC); FAB mass *m*/*z* 345 (M^+); $[\alpha]_D = +38.6^\circ$ (*c* 1, $CHCl_3$). (Found C 52.10, H 5.09, S 9.28; $C_{15}H_{21}BrO_2S$ requires C 52.18, H 5.13, S 9.29).

4.5.8. 2-(4-Bromophenyl)-4-methyl-6-thiocyanatomethylterahydropyran-4-ol (**22**)

Compound **13** was allowed to react with KSCN as described in the general procedure to give **22** as thick liquid; 78%; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3H, CH_3), 1.52–1.69 (m, 2H, H-3 + H-5), 1.76–2.03 (m, 2H, H-3 + H-5), 3.13 (m, 2H, CH_2), 4.19 (m, 1H, H-6), 4.79 (dd, $J = 11.5$ Hz, $J = 2.4$ Hz, 1H, H-2), 7.27 (m, 2H, ArH), 7.45 (m, 2H, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ 31.20 (+ve, CH_3), 39.31 (−ve, CH_2S), 42.17 (−ve, CH_2), 45.68 (−ve, CH_2), 67.76 (C-4), 71.58 (+ve, C-2), 74.44 (+ve, C-6), 112.82 (absent, C≡N), 127.44 (+ve, ArCH), 127.80 (+ve, ArCH), 131.34 (+ve, ArCH), 131.39 (+ve, ArCH), 139.78 (absent, ArC), 140.88 (absent, ArC); FAB mass *m*/*z* 342 (M^+); $[\alpha]_D = +37.62^\circ$ (*c* 1, $CHCl_3$). (Found C 50.55, H 5.01, N 3.90, S 8.92; $C_{14}H_{16}BrNO_2S$ requires C 49.13, H 4.71, N 4.09, S 9.37).

4.6. X-ray crystal data for **2a** and **13**

X-ray crystal data was measured by using θ–2θ scan mode. The structure was solved by using direct method SHELX-97. For **2a**, molecular formula $C_{10}H_{11}NO_4$; space group $P2_1$, $a = 7.1698$ Å, $b = 5.6136$ Å, $c = 12.6297$ Å; $\alpha = 90.00^\circ$, $\beta = 103.042^\circ$, $\gamma = 90.00^\circ$; $V = 495.213$ Å^3; $Z = 2$, $Z' = 0$, *R*-factor = 3.7. For **13**, molecular formula $C_{13}H_{14}BrIO_2$; space group $P2_1$, $a = 6.0080$ Å, $b = 8.0672$ Å, $c = 14.788$ Å; $\alpha = 90.00^\circ$, $\beta = 101.72^\circ$, $\gamma = 90.00^\circ$; $V = 701.799$ Å^3; $Z = 2$, $Z' = 0$; *R*-factor = 3.81.

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