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Mono-, Di-, and Triaryl Substituted Tetrahydropyrans as Cyclooxygenase-2 and Tumor Growth Inhibitors. Synthesis and Biological Evaluation

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Rationally designed tetrahydropyrans (THPs) carrying one, two, or three aryl rings and other substituents were synthesized by the allylation of β-hydroxy ketones followed by iodocyclization. It has been observed that compounds with one aryl ring on THP are moderate inhibitors of cyclooxygenase-1 (COX-1) (IC_{50} = 0.3 μM) and cyclooxygenase-2 (IC_{50} = 0.17 μM) with poor selectivity index (SI = 2−3) for COX-2. The presence of two aryl rings enhanced their inhibitory activities for COX-2 (IC_{50} = 0.9−5.5 nM). Selectivity for COX-2 over COX-1 also increased (SI = 50−1900), while triaryl substituted THPs, along with high inhibition (IC_{50} = 0.57−4.0 nM), also exhibited excellent selectivity for COX-2 over COX-1 (SI = 3200−44000). Similar to the experimental results of increased COX-2 inhibition and selectivity with the increase in the size of the molecule, their docking in the active sites of COX-1 and COX-2 also showed same trend. Seven compounds from the category of di- and triaryl substituted THPs exhibited average GI_{50} over all the human tumor cell lines in the range 1.6−3.2 μM and showed in vitro therapeutic indices of 8−17.

Introduction

The side effects associated with the use of conventional anti-inflammatory drugs[1] and the failure of the coxibs (rofecoxib, valdecoxib, etc.) due to their cardiovascular toxicity[2−8] have drawn the attention of the scientific community to the development of a variety of new chemical entities[9,10] and their evaluation for anti-inflammatory activities. Since the pioneering work of Vane[11] on the role of cyclooxygenase in arachidonic acid metabolism for the production of inflammatory prostaglandins, three isoforms of cyclooxygenase have been identified so far. Among the three isoforms of this enzyme (COX-1,[a] COX-2, and COX-3), the structures and functions of COX-1 and COX-2[12−14] are well established while the functions of COX-3[15] (a variant of COX-1) are still uncertain though it is the target of a very usual antipyretic and analgesic drug acetaminophen.[15,16] Besides the role of COX-2 in the production of inflammatory prostaglandins, its momentous participation in the initiation/propagation of cancer[17−21] and in the development of multidrug resistance[22,23] is well explored. A number of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors have been investigated for anticancer activities,[24−28] and even celecoxib is recommended for the treatment of familial adenomatous polyposis, an inherited tendency to develop a large number of colorectal polyps that eventually become cancerous. Therefore, the overexpression of COX-2 in the cancerous cells and the potential of COX-2 inhibitors for suppressing cancer growth indicate that the cytotoxicity of COX-2 inhibitors might be associated with the inhibition of COX-2 (however, COX-2 independent pathways are also documented for the cytotoxicity of COX-2 inhibitors). As a result, the research activities are continuously focusing on the development of COX-2 inhibitors. Keeping in mind the structural similarities between the constitutive, housekeeping form of cyclooxygenase (COX-1) and the inducible, inflammatory isozyme[14] COX-2 and the desirability for selective inhibition of COX-2, the present work was planned. It is based on the facts that the enzyme COX-2 could accommodate structurally distinct inhibitors,[29] the active site of COX-2 is approximately 25% larger[30] than that of COX-1, and the molecular volume of a six membered heterocycle (e.g., tetrahydropyran) is about 20% larger than the corresponding five membered heterocycle (tetrahydrofuran (THF)). Therefore, in continuation of our earlier reports[31−33] (**1**, Chart 1) and the appreciable COX-2 inhibitory results of pyran-2-ones,[34] we have designed tetrahydropyrans bearing one, two, and three aryl rings (**2**−**4**, Chart 1). It was envisaged that aryl substituted tetrahydropyrans, otherwise retaining the substitution pattern of tetrahydrofuran-like molecules (**1**) but differing in number of aryl rings, should selectively inhibit COX-2 over COX-1. The synthesis of compounds **2**−**4** (Chart 1) was followed by their evaluations for COX-1/2 inhibitory activities, and it has been found that starting from moderate inhibition of COX-1/2 by **2**, inhibitory activities were increased with **3** while **4** along with high inhibition of COX-2 also exhibited increased selectivity for COX-2 over COX-1. The experimental results were supported by the docking of these molecules in the active sites of COX-1 and COX-2. The investigations at 59 human tumor cell lines found significant tumor growth inhibitory activities of di- and triaryltetrahydropyrans.

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[a] Abbreviations: COX, cyclooxygenase; THP, tetrahydropyran; THF, tetrahydrofuran; NOE, nuclear Overhauser effect; nM, nanomolar; GI_{50}, 50% growth inhibition; TGI, total growth inhibition; LC_{50}, 50% lethal concentration; TI, therapeutic index; SI, selectivity index.

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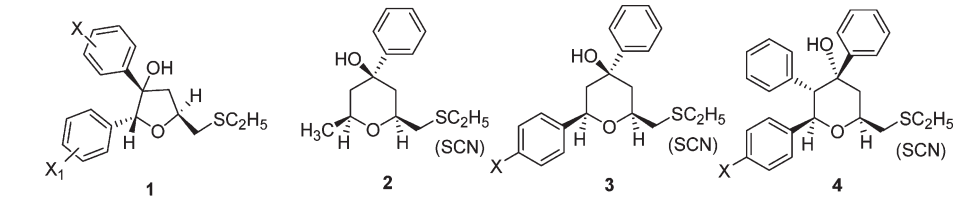
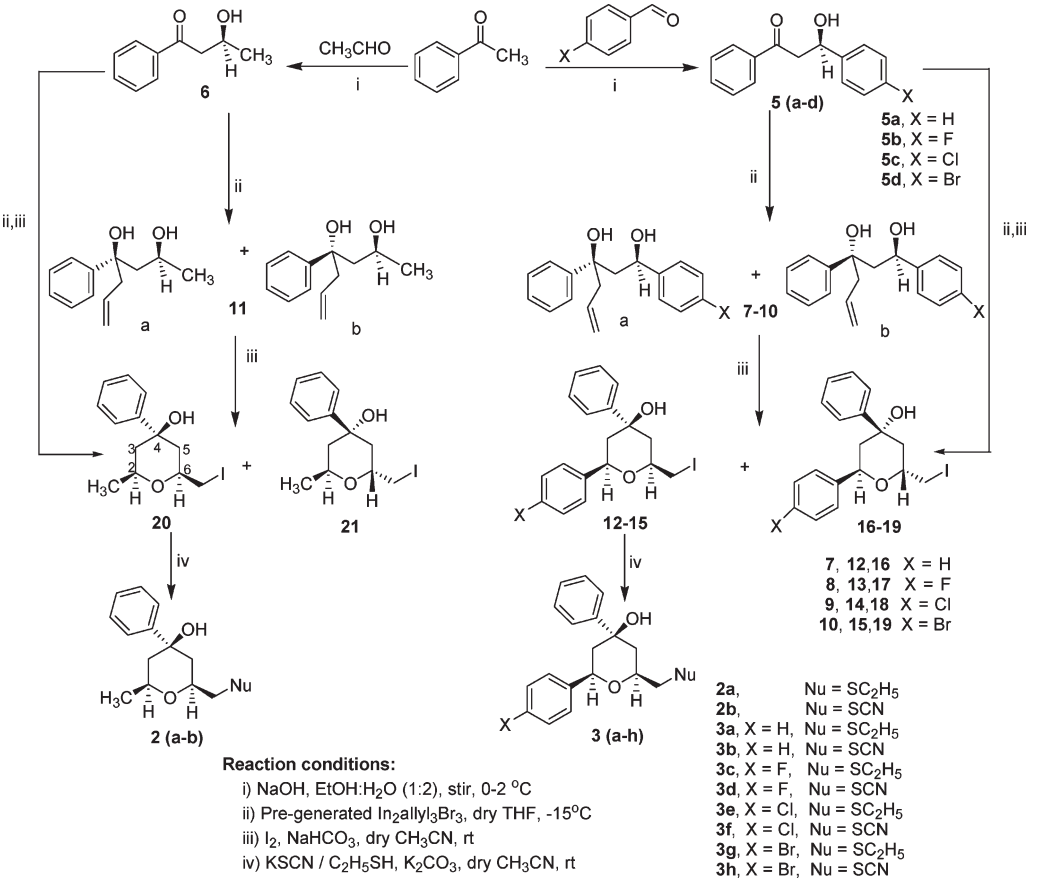
Chart 1. Design of New Molecules



X_1 = X = H, 2-Cl, 4-Cl, 4-F, 4-OCH_3, 4-SO_2CH_3
X_1 = H, X = 4-SCH_3, 4-SO_2CH_3, 4-OCH_3

Scheme 1

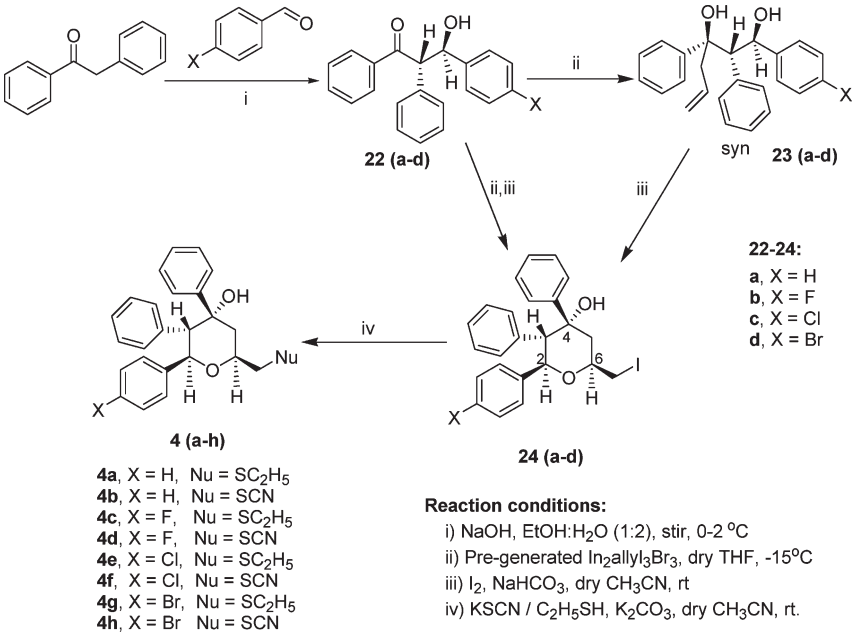


Results and Discussion

Chemistry. Because of the biological significance of THPs,[35−38] considerable attention has been paid to their syntheses starting from simple acyclic compounds,[39−41] by ring enlargement,[42,43] via hetero Diels−Alder reaction,[44−46] olefin metathesis,[47] and synthesis of stereocontrolled THPs by Prins cyclization[48−53] which involves the condensation of an allylic alcohol with an aldehyde in the presence of a Lewis acid. In the present contribution, with a target to synthesize mono-, di-, and triaryl substituted tetrahydropyrans, allylations of β-hydroxy ketones were performed to get homoallylic alcohols which after iodocyclization gave the target compounds (Scheme 1 and 2).

β-Hydroxy ketones were procured by the reactions of acetophenone with acetaldehyde/benzaldehydes in ethanol−water (1:2) in the presence of NaOH at 0−2 °C (instead of using metal enolates[54−56]) (Scheme 1). Products **5** and **6** were accompanied by the formation of traces of corresponding chalcones that were separated by column chromatography. By use of the available procedure for allylation of carbonyl compounds to get homoallylic alcohols,[57−61] the cooled, transparent solution obtained by refluxing allyl bromide (0.5 mmol) and indium metal (0.4 mmol) in dry THF was added to β-hydroxy ketone **6** (0.5 mmol). After the reaction mixture was stirred at room temperature (30 ± 2 °C) and after usual workup and column chromatography, a viscous oil (83%) was isolated and identified as a mixture of the two diastereomers **11a** and **11b** (3:1.2, ^{1}H NMR spectrum, trace a, Figure S1 and Table S1 of Supporting Information, Scheme 1). Diastereomeric ratio was calculated from the integration of signals of respective diastereomers in the region 5.5−5.6 ppm, due to olefinic hydrogen (=CH). Lowering the reaction temperature to −15 ± 1 °C slightly improved the product yield (90%) without affecting the diastereomeric ratio (3:1.2; trace b, Figure S1 of Supporting Information). A similar reaction of β-hydroxy ketone **5a** with a solution of allyl bromide and indium in dry THF at 30 ± 2 °C gave compounds **7a** and **7b** in the diastereomeric ratio 3:2 (trace c, Figure S1 of Supporting Information). However, when this reaction was performed at −15 ± 1 °C,

Scheme 2



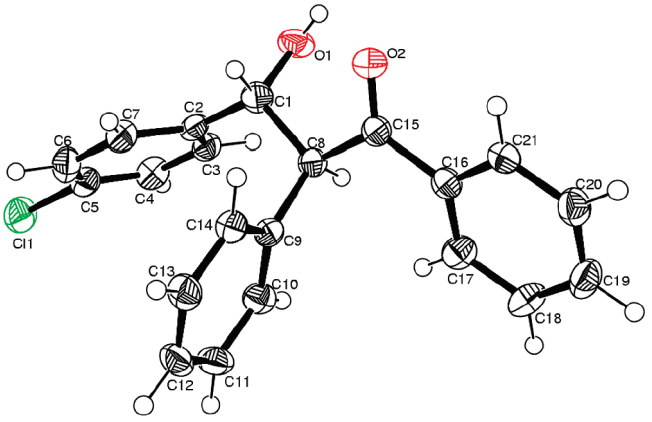


Figure 1. X-ray structures of compound **22c**.

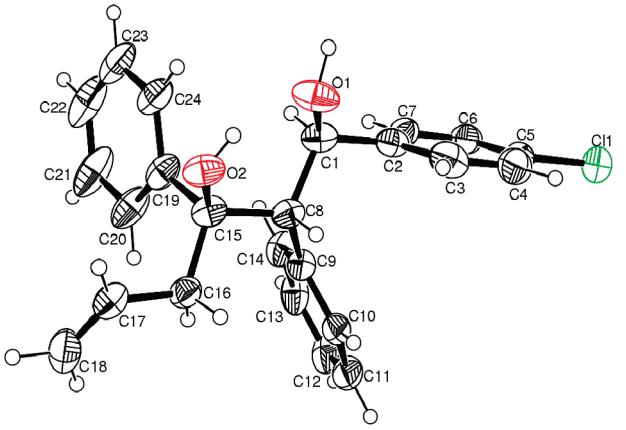


Figure 2. X-ray structure of compound **23c**.

the diastereomeric ratio of the product (**7a**/**7b**) was enhanced to 9:1 (trace d, Figure S1 and Table S1 of Supporting Information). For comparison of percentage yields and diastereomeric ratios, allylations of other β-hydroxy ketones (**5b**−**d**) were carried out at two different temperatures, namely, 30 ±2 °C and −15 ± 1 °C.

In all these reactions, when performed at −15 ± 1 °C, the diastereoselectivity of homoallylic alcohols **7**−**10** was significantly high with an improvement in their percentage yields. The stereochemistry at one asymmetric center in compounds **5** and **6** and the stereochemistry at two asymmetric centers in compounds **7**−**11** were assigned on the basis of X-ray structures of compounds **22c** (Figure 1) and **23c** (Figure 2).

Intramolecular cyclization of alkenes with OH group promoted by iodine constitutes an important synthetic approach for oxygen containing heterocycles.[62] In compounds **7**−**11**, the presence of an OH group at position ε to the double bond makes them suitable precursors of six membered oxygen containing rings. Treatment of the diastereomeric mixture of **11** with iodine in dry CH_3CN using $NaHCO_3$ provided a mixture of two diastereomers (3:1.2, from ^{1}H NMR spectrum) which, after purification with column chromatography, were obtained as viscous oils and characterized as compounds **20** (55%) and **21** (20%). Formation of **20** and **21** in the ratio 3:1.2 shows the conversion of two diastereomers of **11** (3:1.2) to corresponding THPs in a highly diastereoselective manner. The relative stereochemistry at C-2 and C-6 of **20** and **21** was ascertained on the basis of nuclear Overhauser effect (NOE) experiments where observation of NOE between CH_2I and CH_3 groups in **20** indicated their *syn* orientation, while no NOE was observed between these two groups in compound **21** pointing toward their *anti* positioning. Moreover, the relative stereochemistry at C-2, C-4, and C-6 of **20** was also supported by the X-ray structure of **24c** (Figure 3). Similarly, the iodocyclization of homoallylic alcohols **7**−**10** provided respective THPs **12**−**19** (Scheme 1, Table S2). Through an alternative route, after the allylation of β-hydroxy ketone at −15 ± 1 °C (TLC monitoring), in situ iodocylization was carried out (Scheme 1) to procure THPs **12**−**21** in the same diastereomeric ratio and yields as in the stepwise reactions. On the basis of our previous results[31−33] where the presence of SC_2H_5 and SCN groups on THF resulted in better COX-2 inhibition,

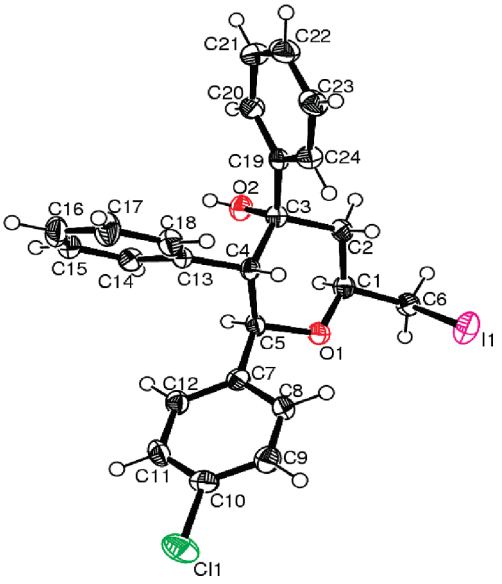


Figure 3. X-ray structure of compound **24c**.

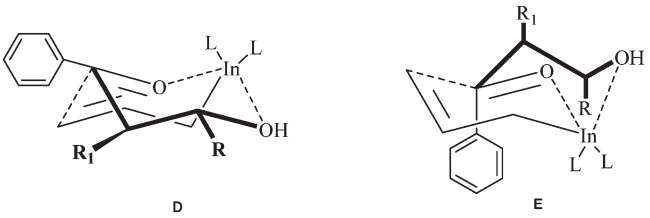


Figure 4. Schematic representation for the transition states formed during allylation of β-hydroxy ketones.

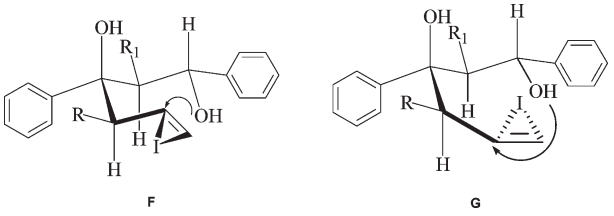


Figure 5. Transition states during iodocyclization of homoallylic alcohol.

the iodo group in the major diastereomer of THPs **12**−**15** and **20** was replaced with SC_2H_5/SCN. Treatment of these compounds (**12**−**15** and **20**) with C_2H_5SH/KSCN in acetonitrile provided compounds **2** and **3** (Scheme 1, Table S2).

In order to introduce three phenyl rings on THP, a similar sequence of reactions as shown in Scheme 1 was performed. Reactions of deoxybenzoin with benzaldehydes in the presence of NaOH at 0−2 °C gave a single diastereomer of β-hydroxy ketones **22a**−**d** (Scheme 2). Structures of β-hydroxy ketones were confirmed from NMR spectral data and the X-ray structure of **22c** (Figure 1). In compound **22c**, the carbonyl and hydroxyl groups are oriented in the same direction and the hydrogens at C-2 and C-3 (C-1, C-8 in the ORTEP view) are *anti* to each other. Three phenyl rings are eclipsed to one another, which might be the more stable conformation because of $\pi-\pi$ interactions.

Indium mediated allylation of β-hydroxy ketones **22a**−**d** gave diastereoselectively *syn*-homoallylic alcohols **23a**−**d** (Scheme 2, Table S1) (*syn* orientation of two OH groups was confirmed from the X-ray structure of compound **23c**, Figure 2). Iodocyclization of compounds **23a**−**d** gave 2,3,4-triaryltetrahydropyrans **24a**−**d** (Scheme 2). The stereochemistry at different asymmetric centers of compounds **24a**−**d** was assigned on the basis of the X-ray structure of compound **24c** (Figure 3). The X-ray structure of **24c** indicates equatorial orientations of the three phenyl and iodomethyl groups. The phenyl rings present at C-2 and C-4 positions and the iodomethyl group at C-6 of tetrahydropyran ring are *syn* to one another. Further treatment of compounds **24a**−**d** with C_2H_5SH and KSCN in CH_3CN gave the target compounds 4**a**−**h** (Scheme 2, Table S2).

To account for the diastereoselectivity observed at the allylation step in Schemes 1 and 2 (formation of homoallylic alcohols **5**, **6**, and **22**), transition states D and E (Figure 4) leading to the formation of *syn*- and *anti*-diols, respectively, were drawn. It seems that during allylation of **6** (corresponding to transition states D and E; R = CH_3, R_1 = H), the two transition states may contribute equally even at low temperature and result in the formation of two diastereomers. During allylation of **5a**−**d** (transition states D and E; R = Ar, R_1 = H, Figure 4) at low temperature, the presence of two phenyl rings equatorially provides more stability to transition state D and the diastereomeric ratio gets significantly improved. In allylation of β-hydroxy ketone **22a**−**d** (transition states D and E; R_1 = Ar, R = Ph, Figure 4), the presence of three equatorial phenyl rings in transition state D further increases the difference in the stability of transition states D and E and hence gave only one diastereomer. Therefore, the presence of phenyl rings (steric bulk) and low reaction temperature may be contributing toward the diastereoselectivity in the allylation of β-hydroxy ketones. High diastereoselectivity in the iodocyclization reactions may be explained on the basis of more stability of transition state F over G (Figure 5), leading to the formation of a single diastereomer in compounds **12**−**21** and **24a**−**d**.

COX-1/2 Inhibition. COX-1/2 inhibitory activities of racemic mixtures of compounds **2a**,**b**, **3a**−**h**, and **4a**−**h** were evaluated in duplicate using COX (ovine) inhibitor screening assay kits[63] (racemic mixture was used because of the non-availability of pure enantiomer at this stage and also the docking studies were indicating similar interactions of both the enantiomers in the active sites of COX-1/2). The results of the three categories of compounds, namely, **2** (with one phenyl ring), **3** (with two phenyl rings), and **4** (with three phenyl rings), are grouped in Table 1.

Compounds **2a** and **2b** showed almost equal inhibition of COX-1 and COX-2 with IC_{50} values of 0.3 and 0.1 μM, respectively. Moderate inhibition of COX-1/2 by these two compounds indicated that the size of these molecules allows them to enter the active sites of both enzymes. Also, the similar activity of **2a** and **2b** indicates that SC_2H_5 and SCN substituents may contribute equally toward the inhibition of the two enzymes. The presence of two aryl rings in THPs **3a**−**h** significantly improved the COX-2 inhibitory activities of these compounds with their IC_{50} values of 0.9−5.5 nM. However, the compounds **3g** and **3h** with Br at one of the two aryl rings exhibited slightly less COX-2 inhibitory activities (IC_{50} = 4−5.5 nM) in comparison to the analogous compounds **3a**−**f** (IC_{50} = 0.9−3.5 nM). Interesting results were observed for the COX-1/2 inhibitory activities of triaryl substituted compounds **4a**−**h**. All these compounds exhibited very poor inhibition of COX-1 (IC_{50} = 10−64 μM, Table 1, Table S3), while their COX-2 inhibitory activities (IC_{50} = 0.57−4.0 nM) were comparable or better than

Table 1. 50% Inhibitory Concentrations (IC_{50}) of Compounds **2a**,**b**, **3a**−**h**, and **4a**−**h** for COX-1 and COX-2

	IC_{50} (nM)[a]		
compd	COX-2	COX-1	selectivity index (SI)[b]
2a	175	347	1.98
2b	117	368	3.14
3a	2.07	2932	1416
3b	1.47	2788	1896
3c	2.05	1738	847
3d	3.57	488	136
3e	1.82	413	226
3f	0.9	664	737
3g	5.49	562	102
3h	4.01	209	52
4a	1.72	13880	8069
4b	1.55	63990	41283
4c	1.28	∼46990	∼36710
4d	1.11	28850	25990
4e	0.57	10700	18771
4f	0.65	28650	44076
4g	2.8	23800	8500
4h	4.03	12960	3215
celecoxib	70	33100	473
rofecoxib	500	> 100000	> 200

[a] IC_{50} values are the mean of two determinations, and the deviation from the mean in each case was 5−7%. [b] In vitro COX-2 selectivity index: (IC_{50} COX-1)/(IC_{50} COX-2).

compounds **3a**−**h**. Although COX-2 inhibitory activities of compounds **4a**−**h** were similar to those exhibited by compounds **3a**−**h**, better selectivity for COX-2 over COX-1 (**3a**−**h** SI = 50−1900; **4a**−**h** SI = 3200−44000) was observed. Compounds **4c**−**f** with F and Cl substituents at one of the three phenyl rings showed better inhibition of COX-2 in comparison to the analogues with H and Br present on the respective phenyl ring. It seems that with the increase in the number of phenyl rings on THP, the effect of $\pi-\pi$ interactions predominates over other interactions and hence the other variations in the compound (substituent at phenyl ring and C-6 of THP) have little or no effect on COX-2 inhibitory activities. The COX-2 inhibitory activity and the selectivity for COX-2 over COX-1 for all these compounds were better than the known COX-2 inhibitors celecoxib and rofecoxib. Therefore, as per the design of these molecules, based upon their size, they exhibited moderate to high COX-2 inhibitory activity as well as the selectivity for COX-2 over COX-1 and they are worth undergoing further investigations.

Docking Studies. The binding modes of a number of COX inhibitors in the active sites of COX-1/2 have been recently reviewed.[29] Here, to rationalize the experimental results and to look into the modes of interactions of these compounds in COX-1/2 active sites, the docking of both the enantiomers of tetrahydropyrans **2**, **3**, and **4** in the active sites of COX-1 and COX-2 was performed. Since both the enantiomers of compounds **2**, **3**, and **4** showed considerable interactions during docking in the active sites of COX-1 and COX-2, the interactions of one enantiomer of all the compounds (structure given in the inset) are discussed while the docking results of second enantiomer are given in the Supporting Information (Figure S2).

Compound **2a**, when docked in the active site of COX-2, placed its phenyl ring in the hydrophobic subpocket constituted by Y348, Y385, L384, and W387 (Figure 6). Docking of compound **3a** in the active site of COX-2 showed that one phenyl ring of the molecule was present in the same

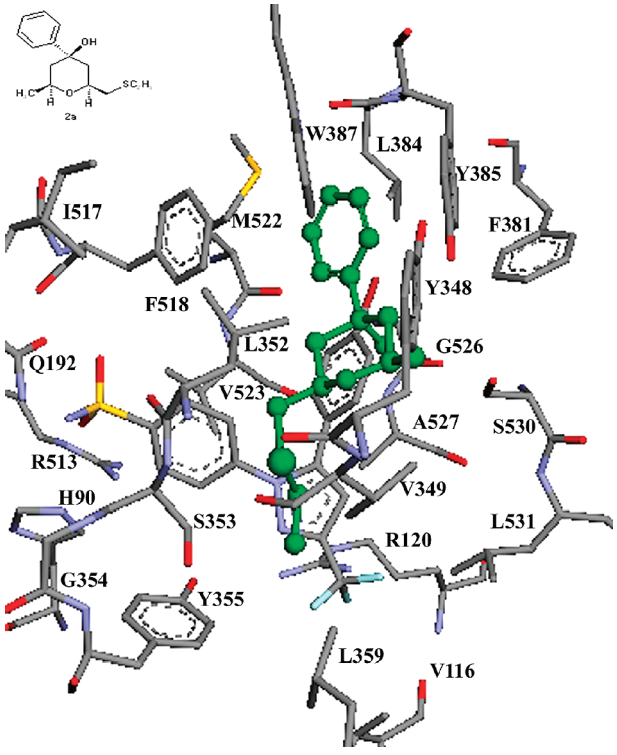


Figure 6. Compound **2a** (shown in inset) docked in the active site of COX-2. Hydrogens are omitted for clarity.

subpocket as the phenyl ring of compound **2a** while the second phenyl ring approached F518 (Figure 7). Docking of compound **2a** (same enantiomer that was docked in COX-2) in the active site of COX-1 indicated a H-bond interaction between the OH group of compound **2a** and R120 (Figure 9). However, the docking of compound **3a** in the active site of COX-1 (Figure 9) showed that this molecule does not completely enter the active site of COX-1. Docking of compounds **4** in the active sites of COX-1 and COX-2 indicated that these compounds enter the active site of COX-2 only, providing an excellent parallel between the experimental and the docking results in our hands. Docking of compound **4b** in the active site of COX-2 showed the placement of three phenyl rings alongside the active site constituted by W387, Y385, F381, Y348, and Y355. The SCN unit of compound **4b** was aligned in the same fashion as the sulfonamide group of Sc-558 (Figure 8). None of the **4** compounds entered the active site pocket of COX-1.

Therefore, in parallel with the experimental results, docking of compounds **2a**,**b**, **3a**−**h**, and **4a**−**h** in the active sites of COX-1 and COX-2 indicated that (i) all three sets of compounds enter the active site of COX-2, (ii) the presence of an additional phenyl ring in **3a**−**h** and **4a**−**h** results in better interactions of these compounds with the amino acid residues of COX-2, (iii) **2a**,**b** also enter the active site of COX-1, (iv) **3a**−**h** partially enter the active site of COX-1, and (v) **4a**−**h** do not enter the active site of COX-1. The energies of the ligand−enzyme complexes ($E_{interaction}$) as given by the docking program also indicate the extent of interactions between the ligand and the active site amino acids. Compounds **2a**,**b** exhibited similar $E_{interaction}$ with COX-1 and COX-2 (Table S4), while compounds **3a**,**h** have higher $E_{interaction}$ for COX-2 than for COX-1. Docking of compounds **4a**−**h** in the active site of COX-2 also showed similar $E_{interaction}$ as observed during the docking

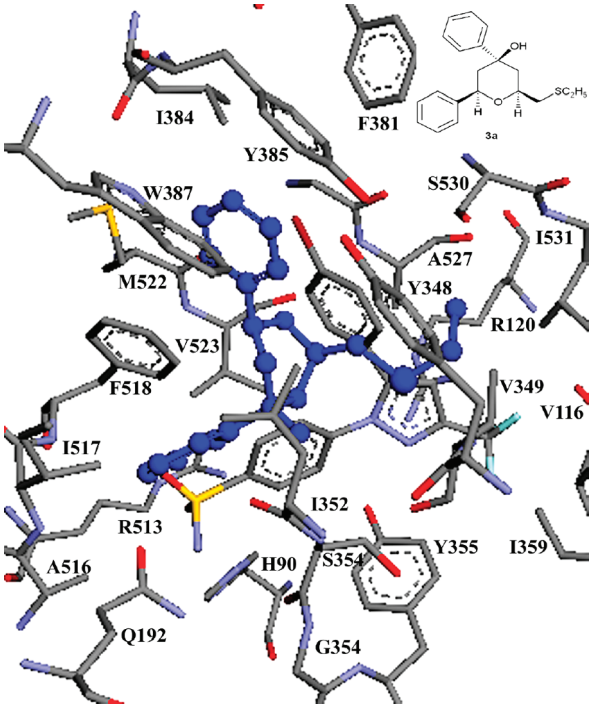


Figure 7. Compound **3a** (shown in inset) docked in the active site of COX-2. Hydrogens are omitted for clarity.

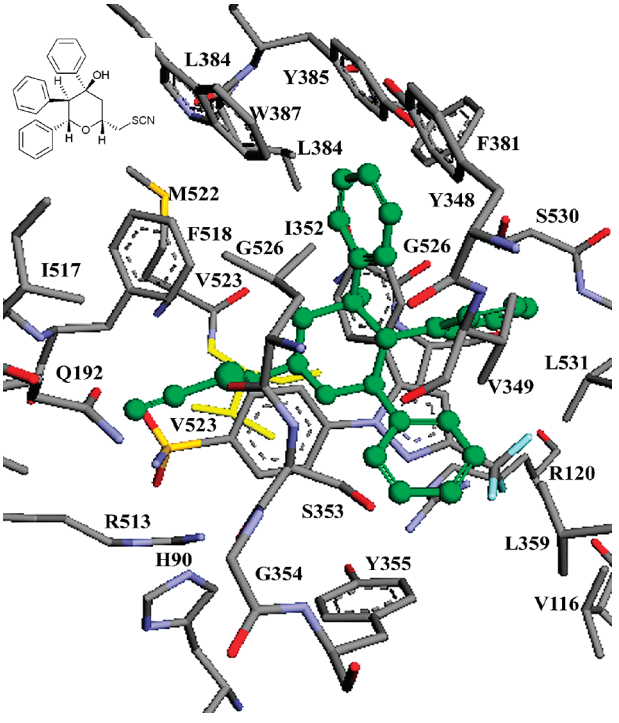


Figure 8. Compound **4a** (shown in the inset) docked in the active site of COX-2. Hydrogens are omitted for clarity.

of compounds **3a**−**h** in the active site of COX-2. However, the docking of compounds **4a**−**h** in the active site of COX-1 did not give $E_{interaction}$ values, as these compounds do not enter the active site of this enzyme.

Tumor Growth Inhibitory Activities. The momentous role of COX-2 in the propagation of cancer and investigation of various COX-2 inhibitors for reducing the cancer propagation led us to scrutinize these compounds for their anticancer

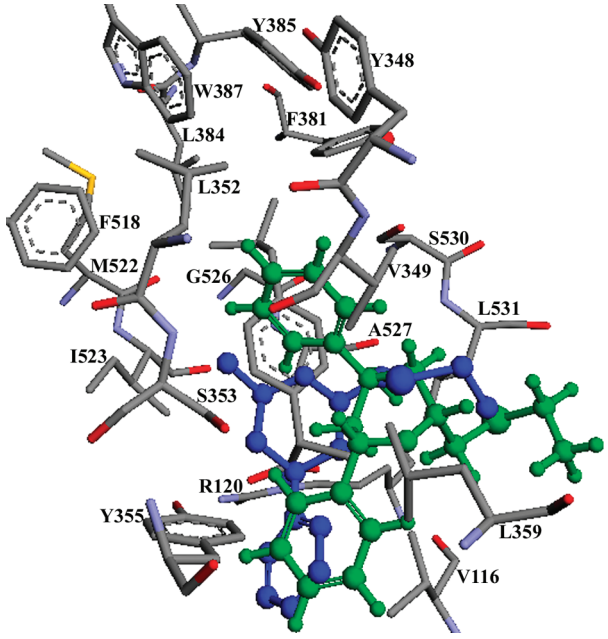


Figure 9. Compounds **2a** (blue) and **3a** (green) docked in the active site of COX-1.

Table 2. Average GI_{50} (μM) over All the Cell Lines of Compounds **3c**, **3d**, **3f**, and **4c**−**f** and Their Comparison with Tetrahydrofuran Based Molecules

compd	average GI_{50} (μM)	average LC_{50} (μM)	in vitro TI[a]
3c	1.9	15.5	8.15
3d	1.9	20.4	10.7
3f	2.2	26.9	12.2
4c	1.9	31.6	16.6
4d	3.2	43.6	13.6
4e	1.7	17.8	10.4
4f	1.6	13.1	8.1
12[64]	19.9	95.4	4.7
13[64]	22.0	95.4	4.3
38[33]	54.9	95	1.7
40[33]	17.3	72	4.1
41[33]	13.1	66	5.0
celecoxib[b]	17.5	63.3	3.61

[a] Therapeutic index = LC_{50}/GI_{50}. [b] NCI database (www.dtp.nci.nih.gov), NSC 719627.

activity. Compounds **3c**−**f** and **4c**−**f** from the di- and triaryltetrahydropyran series (with appreciable COX-2 inhibitory activities) were tested at NCI, Bethesda, MD, for tumor growth inhibition at 59 human tumor cell lines corresponding to leukemia, melanoma, and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney. Compounds were initially tested at the entire 59 cell line panel at 10^{-5} M. All the compounds except **3e** were passed to further testing at 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} M. The results of these studies are given as 50% growth inhibition concentrations (GI_{50}), total growth inhibition (TGI), and 50% lethal concentrations (LC_{50}) (Table S5). All the compounds exhibit 50% inhibition of tumor growth in all the cell lines at micromolar concentration. As in the case of COX-2 inhibitory activities, the SCN and SC_2H_5 groups seem to contribute equally toward the tumor growth inhibitory activities of these compounds which is evident from the similar average GI_{50} of compounds **3c**, **3d**, **4e**, and **4f** (Table 2). Some of the compounds were observed to show

specificity for certain cell lines. Compound **3d** showed a GI_{50} of 0.67 μM for MOLT-4 and 0.57 μM for SR cell lines of leukemia. Compound **3f** exhibited a GI_{50} of 0.06 μM for SK-MEL-5, and compound **4d** exhibited a GI_{50} 0.34 μM for SR and 0.89 μM for IGROV1 cell lines corresponding to leukemia and ovarian cancer. Compound **4f** was also specific toward MOLT-4, HCT-116, and OVCAR-3 cell lines with respective GI_{50} of 0.89, 0.57, and 0.77 μM (Table S5). Higher LC_{50} values of all the compounds indicate their low toxicity profile, and all of them had in vitro therapeutic indices (TI) of about 8−17, tolerable for diseases like cancer. In comparison to the COX-2 inhibitory and tumor growth inhibitory results of THFs[33,64] and celecoxib, THP based molecules showed better inhibition of COX-2 as well as tumor growth at various cell lines and also better in vitro TI. The average GI_{50} values of THF and THP based molecules have been compared in Table 2. Therefore, the increase in COX-2 inhibition activity of THPs over THFs, accompanied by an increase in tumor growth inhibition (Table 2), along with the literature reports (expression of COX-2 in the cancer cells[65] and COX-2 inhibitors as anticancer agents), indicates that the cytotoxicity of these compounds may be due to COX-2 inhibition. Certainly more experiments are needed to prove that the growth of tumor cells by these compounds is influenced by arachidonic acid pathway, and at this stage, the COX-2 independent modes of action could not be ruled out. To enhance the COX-2 and tumor growth inhibitory profile and to improve the druglike properties, the modifications of the compounds like introduction of OH, COOH, OSO_2CH_3 in place of SCN/SC_2H_5 or the replacement of THP ring with dioxane are under consideration.

Conclusions

The presence of aryl rings and reaction temperature significantly control the diastereoselectivity of the product during the allylation of β-hydroxy ketones. The homoallylic alcohols also underwent highly diastereoselective iodocyclization to provide mono-, di-, and triaryl substituted THPs. Bioevaluations on COX-1/2 enzymes indicated that with the increase in the volume of the THP molecule, the COX-2 inhibitory activity and the selectivity for COX-2 over COX-1 increase. The compounds of triaryltetrahydropyran series exhibit IC_{50} for COX-2 in the range 0.57−4.0 nM, and their selectivity for COX-2 over COX-1 is better than that of celecoxib and rofecoxib. Results of the docking studies showed remarkable correlation with the experimental results. Compounds **3c**, **3d**, **3f**, **4c**−**f** showed considerable inhibition of tumor growth at various human cancer cell lines with their GI_{50} in the range 1.6−3.2 μM. Therefore, a new class of compounds with significant in vitro inhibition of COX-2 and tumor growth on all 59 human tumor cell lines has been introduced.

Experimental Section

General Note. Melting points were determined in capillaries and were uncorrected. ^{1}H and ^{13}C NMR spectra were run on JEOL JNM AL 300 and 75 MHz NMR spectrometers, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in ppm with TMS as an internal reference. Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constants (J) (hertz), integration. In ^{13}C/DEPT-135 data, +ve signs correspond to signals due to CH_3, CH groups while −ve signs symbolize signals of CH_2 groups and signals of quaternary carbon are absent (ab) in DEPT-135 spectra. Column chromatography was performed with silica 100−200 mesh, and reactions were monitored by thin layer chromatography (TLC) with silica plates precoated with silica gel HF-254. IR and UV spectral data were recorded on FTIR 8400S Shimadzu and BioTek PowerWave XS instruments, respectively. The mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC mass spectrometer having direct analysis in real time (DART) source. The purity of the compounds was assessed on the basis of elemental analysis, and the results were greater than 95% (Thermoelectron FLASH EA1112 CHN analyzer). Synthesis and experimental data for β-hydroxy ketones (procedure A), allylation of β-hydroxy ketones (procedure B), and the iodocyclized products (procedure C) are given in the Supporting Information.

General Procedure for the Reaction of Compounds 12−15, 20, and 24a−d with Ethanthiol/KSCN (Procedure D). A solution of compounds **12**−**15**, **20**, **24a**−**d** (0.5 mmol), ethanthiol/KSCN (0.6 mmol), K_2CO_3 (0.6 mmol) in dry CH_3CN (10 mL) was stirred at room temperature. On completion of reaction (3−4 h, TLC monitoring), the reaction mixture was filtered and filtrate was concentrated under vacuum. The crude residue obtained was purified by column chromatography using hexane and ethyl acetate (3:1) to give pure compounds **2a**, **2b**, **3a**−**h**, and **4a**−**h**.

(2*S,4*R**,6*S**)-2-((Ethylthio)methyl)tetrahydro-6-methyl-4-phenyl-2*H*-pyran-4-ol (2a).** By use of procedure D, the reaction of **20** with ethanthiol gave **2a** in 92% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 221 (19060). IR ($CHCl_3$, cm^{-1}): 3413 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20−1.27 (m, 6H, 2 × CH_3), 1.85−1.98 (m, 5H, 2H of C-3 + 2H of C-5 + 1H of OH), 2.57−2.68 (m, 2H, S-CH_2), 2.70−2.86 (m, 2H, CH_2), 3.30−3.33 (m, 1H, CH), 4.21−4.26 (m, 1H, CH), 7.22−7.41 (m, 5H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.7 (+ve, CH_3), 21.5 (+ve, CH_3), 26.8 (−ve, S-CH_2), 36.9 (−ve, CH_2−S), 42.8 (−ve, CH_2), 45.5 (−ve, CH_2), 69.1 (+ve, CH), 72.1 (ab, C-4), 72.9 (+ve, CH), 124.2 (+ve, ArCH), 127.0 (+ve, ArCH), 127.1 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 147.9 (ab, ArC). FAB-MS m/z 266 [M$^+$]. Anal. ($C_{15}H_{22}O_2S$) C, H, S.

(2*S,4*R**,6*S**)-Tetrahydro-2-methyl-4-phenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (2b).** By use of procedure D, the reaction of **20** with KSCN gave **2b** in 87% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 218 (14660). IR ($CHCl_3$, cm^{-1}): 3438 (OH), 2155 (CN). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, J = 6.3 Hz, 3H, CH_3), 1.67−1.72 (m, 4H, 2H of C-3 + 2H of C-5), 2.30 (br s, 1H, OH), 2.96−3.07 (m, 2H, CH_2), 4.01−4.15 (m, 1H, CH), 4.13−4.15 (m, 1H, CH), 7.23−7.45 (m, 5H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 21.2 (+ve, CH_3), 39.2 (−ve, CH_2), 42.2 (−ve, CH_2), 45.2 (−ve, CH_2), 64.6 (+ve, CH), 69.5 (+ve, CH), 71.2 (ab, C-4), 112.9 (ab, C≡N), 124.2 (+ve, ArCH), 127.3 (+ve, ArCH), 127.5 (+ve, ArCH), 128.4 (+ve, ArCH), 147.3 (ab, ArC). FAB-MS m/z 263 [M$^+$]. Anal. ($C_{19}H_{19}NO_2S$) C, H, S, N.

(2*S,4*R**,6*R**)-2-((Ethylthio)methyl)tetrahydro-4,6-diphenyl-2*H*-pyran-4-ol (3a).** By use of procedure D, the reaction of **12** with ethanthiol gave **3a** in 94% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 218 (12270). IR ($CHCl_3$, cm^{-1}): 3512 (OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.5 Hz, 3H, CH_3), 1.88−2.14 (m, 4H, 2H of C-3 + 2H of C-5), 2.07−2.70 (m, 2H, S-CH_2), 2.80−2.96 (m, 3H, 2H of CH_2S, 1H of OH), 4.19−4.27 (m, 1H, CH), 4.95−5.01 (dd, J_1 = 8.4 Hz, J_2 = 3.9 Hz, 1H, CH), 7.23−7.25 (m, 3H, ArH), 7.29−7.32 (2 H, m, ArH), 7.35−7.48 (m, 5H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.7 (+ve, CH_3), 26.9 (−ve, S-CH_2), 36.9 (−ve, CH_2−S), 42.8 (−ve, CH_2), 45.7 (−ve, CH_2), 71.5 (ab, C-4), 72.1 (+ve, CH), 73.6 (+ve, CH), 124.3 (+ve, ArCH), 125.7 (+ve, ArCH), 127.2 (+ve, ArCH), 127.4 (+ve, ArCH), 128.2 (+ve, ArCH), 128.4 (+ve, ArCH), 142.5 (ab, ArC), 147.3 (ab, ArC). FAB-MS m/z 328 [M$^+$]. Anal. ($C_{20}H_{24}O_2S$) C, H, S.

(2*R,4*R**,6*S**)-Tetrahydro-2,4-diphenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (3b).** By use of procedure D, the reaction of **12** with

KSCN gave **3b** in 89% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 217 (8020). IR ($CHCl_3$, cm^{-1}): 3465 (OH) 2156 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 1.86−2.17 (m, 4H, 2H of C-3 + 2H of C-5), 2.18 (br s, 1H, OH), 3.07−3.24 (m, 2H, CH_2), 4.36−4.41 (m, 1H, CH), 5.0 (dd, J_1 = 8.4 Hz, J_2 = 3.9 Hz, 1H, CH), 7.21−7.47 (m, 10H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 39.3 (−ve, CH_2), 41.9 (−ve, CH_2), 45.5 (−ve, CH_2), 71.6 (ab, C-4), 72.0 (+ve, CH), 75.1 (+ve, CH), 113.1 (ab, C≡N), 124.2 (+ve, ArCH), 125.6 (+ve, ArCH), 127.5 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 141.6 (ab, ArC), 146.9 (ab, ArC). FAB-MS *m*/*z* 325 [M^+]. Anal. ($C_{19}H_{19}NO_2S$) C, H, S, N.

(2*S,4*R**,6*R**)-2-((Ethylthio)methyl)-6-(4-fluorophenyl)tetrahydro-4-phenyl-2*H*-pyran-4-ol (3c).** By use of procedure D, the reaction of **13** with ethanthiol gave **3c** in 92% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 217 (9930). IR ($CHCl_3$, cm^{-1}): 3433 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, J = 7.8 Hz, 3H, CH_3), 1.83−1.96 (m, 4H, 2H of C-3 + 2H of C-5), 2.03−2.67 (m, 2H, S-CH_2), 2.77−2.83 (m, 3H, 2H of CH_2S, 1H of OH), 4.19−4.22 (m, 1H, CH), 4.94 (dd, J_1 = 8.4 Hz, J_2 = 3.9 Hz, 1H, CH), 6.89−6.99 (m, 3H, ArH), 7.20−7.46 (m, 6H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.8 (+ve, CH_3), 26.9 (−ve, S-CH_2), 36.9 (−ve, CH_2-S), 42.7 (−ve, CH_2), 45.9 (−ve, CH_2), 72.3 (ab, C-4), 73.6 (+ve, CH), 74.5 (+ve, CH), 115.0 (+ve, J_{C-F} = 21.6 Hz, ortho to C−F, ArCH), 124.3 (+ve, ArCH), 125.2 (+ve, ArCH), 126.7 (+ve, ArCH), 126.8 (+ve, J_{C-F} = 13.6 Hz, meta to C−F, ArCH), 127.2 (+ve, ArCH), 127.4 (+ve, ArCH),128.2 (+ve, ArCH), 128.6 (+ve, ArCH), 136.3 (ab, J_{C-F} = 3 Hz, para to C−F, ArC), 145.5 (ab, ArC), 162.2 (ab, J_{C-F} = 243.2 Hz, ArC-F). FAB-MS *m*/*z* 346 [M^+]. Anal. ($C_{20}H_{23}FO_2S$) C, H, S.

(2*R,4*R**,6*S**)-2-(4-Fluorophenyl)tetrahydro-4-phenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (3d).** By use of procedure D, the reaction of **13** with KSCN gave **3d** in 90% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 219 (6820). IR ($CHCl_3$, cm^{-1}): 3434(OH), 2164 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 1.72−1.93 (m, 4H, 2H of C-3 + 2H of C-5), 2.30 (br s, 1H, OH), 2.98−3.12 (m, 2H, CH_2), 4.26−4.29 (m, 1H, CH), 4.91 (dd, J_1 = 8.4 Hz, J_2 = 3.9 Hz, 1H, CH), 6.86−6.94 (m, 2H, ArH), 7.11−7.37 (m, 7H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 38.6 (−ve, CH_2), 41.3 (−ve, CH_2), 44.9 (−ve, CH_2), 71.1 (ab, C-4), 71.4 (+ve, CH), 73.9 (+ve, CH), 112.4 (ab, C≡N), 115.2 (+ve, J_{C-F} = 21.6 Hz, ortho to C−F, ArCH), 123.6 (+ve, ArCH), 126.6 (+ve, ArCH), 126.8 (+ve, ArCH), 127.3 (+ve, J_{C-F} = 8 Hz, meta to F, ArCH), 127.9 (+ve, ArCH), 136.8 (+ve, ArCH), 142.2 (ab, J_{C-F} = 4.2 Hz, para to F, ArC), 147.3 (ab, ArC), 162.2 (ab, J_{C-F} = 243.2 Hz, ArC-F). FAB-MS *m*/*z* 343 [M^+]. Anal. ($C_{19}H_{18}FNO_2S$) C, H, S, N.

(2*R,4*R**,6*S**)-2-(4-Chlorophenyl)-6-((ethylthio)methyl)tetrahydro-4-phenyl-2*H*-pyran-4-ol (3e).** By use of procedure D, the reaction of **14** with ethanthiol gave **3e** in 93% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 220 (12580). IR ($CHCl_3$, cm^{-1}): 3485 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, J = 7.5 Hz, 3H, CH_3), 1.88−2.06 (m, 4H, 2H of C-3 + 2H of C-5), 2.60−2.67 (m, 2H, S-CH_2), 2.71−2.89 (m, 3H, 2H of CH_2S, 1H of OH), 4.22−4.29 (m, 1H, CH), 5.01 (dd, J_1 = 8.3 Hz, J_2 = 3.9 Hz, 1H, CH), 7.22−7.51 (m, 9H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.8 (+ve, CH_3), 27.1 (−ve, S-CH_2), 37.1 (−ve, CH_2−S), 42.9 (−ve, CH_2), 46.1 (−ve, CH_2), 72.5 (ab, C-4), 73.7 (+ve, CH), 75.2 (+ve, CH), 124.3 (+ve, ArCH), 125.8 (+ve, ArCH), 127.3 (+ve, ArCH), 128.5 (+ve, ArCH), 128.9 (+ve, ArCH), 130.9 (+ve, ArCH), 132.3 (ab, ArC), 142.5 (ab, ArC), 147.7 (ab, ArC). FAB-MS *m*/*z* 362 [M^+] (73%), 364 [M^+] (23%). Anal. ($C_{20}H_{23}ClO_2S$) C, H, S.

(2*R,4*R**,6*S**)-2-(4-Chlorophenyl)tetrahydro-4-phenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (3f).** By use of procedure D, the reaction of **14** with KSCN gave **3f** in 92% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 221 (15700). IR ($CHCl_3$, cm^{-1}): 3457 (OH) 2170 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 1.97−2.03 (m, 4H, 2H of C-3 + 2H of C-5), 3.17−3.34 (m, 2H, CH_2), 4.42−4.51 (m, 1H, 1H of CH), 5.07 (dd, J_1 = 9.8 Hz, J_2 = 3 Hz, 1H, CH), 7.31−7.56 (m, 9H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 38.6 (−ve, CH_2), 41.3 (−ve, CH_2), 44.9 (−ve, CH_2), 71.1 (+ve, CH), 71.4 (ab, C-4), 73.9 (+ve, CH), 112.3 (ab, C≡N), 123.5 (+ve, ArCH), 126.4 (+ve, ArCH), 126.9 (+ve, ArCH), 127.8 (+ve, ArCH), 127.9 (+ve, ArCH), 132.4 (ab, ArC), 139.5 (ab, ArC), 146.1 (ab, ArC). FAB-MS *m*/*z* 359 [M^+] (73%), 361 [M^+] (23%). Anal. ($C_{19}H_{18}ClNO_2S$) C, H, S, N.

(2*R,4*R**,6*S**)-2-(4-Bromophenyl)-6-((ethylthio)methyl)tetrahydro-4-phenyl-2*H*-pyran-4-ol (3g).** By use of procedure D, the reaction of **15** with ethanthiol gave **3g** in 92% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 219 (14200). IR ($CHCl_3$, cm^{-1}): 3462 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.8 Hz, 3H, CH_3), 1.90−2.08 (m, 4H, 2H of C-3 + 2H of C-5), 2.59−2.64 (m, 2H, S-CH_2), 2.70−2.86 (m, 3H, 2H of CH_2S, 1H of OH), 4.23−4.27 (m, 1H, CH), 5.01 (dd, J_1 = 8.2 Hz, J_2 = 3.9 Hz, 1H, CH), 7.22−7.50 (m, 9H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.8 (+ve, CH_3), 27.1 (−ve, S-CH_2), 37.1 (−ve, CH_2−S), 42.9 (−ve, CH_2), 46.1 (−ve, CH_2), 72.5 (ab, C-4), 73.6 (+ve, CH), 75.1 (+ve, CH), 119.8 (ab, ArC), 124.3 (+ve, ArCH), 124.5 (+ve, ArCH), 124.8 (+ve, ArCH), 125.8 (+ve, ArCH), 126.8 (+ve, ArCH), 127.3 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 142.5(ab, ArC), 147.7 (ab, ArC). FAB-MS *m*/*z* 406 [M^+] (96%), 408 [M^+] (98%). Anal. ($C_{20}H_{23}BrO_2S$) C, H, S.

(2*R,4*R**,6*S**)-2-(4-Bromophenyl)tetrahydro-4-phenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (3h).** By use of procedure D, the reaction of **15** with KSCN gave **3h** in 90% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 218 (14400). IR ($CHCl_3$, cm^{-1}): 3489 (OH) 2158 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 1.81−1.98 (m, 4H, 2H of C-3 + 2H of C-5), 3.02−3.19 (m, 2H, CH_2), 4.30−4.36 (m, 1H, CH), 4.95 (dd, J_1 = 10.8 Hz, J_2 = 3 Hz, 1H, CH), 7.17−7.41 (m, 9H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 40.1 (−ve, CH_2), 42.7 (−ve, CH_2), 46.3 (−ve, CH_2), 72.5 (+ve, CH), 72.8 (ab, C-4), 75.3 (+ve, CH), 113.7 (ab, C≡N), 121.1 (ab, ArC), 124.9 (+ve, ArCH), 127.8 (+ve, ArCH), 128.4 (+ve, ArCH), 129.2 (+ve, ArCH), 129.4 (+ve, ArCH), 133.8 (+ve, ArCH), 140.9 (ab, ArC), 147.5 (ab, ArC). FAB-MS *m*/*z* 403 [M^+] (97%), 405 [M^+] (100%). Anal. ($C_{19}H_{18}BrNO_2S$) C, H, S, N.

(2*R,3*S**,4*R**,6*S**)-6-((Ethylthio)methyl)tetrahydro-2,3,4-triphenyl-2*H*-pyran-4-ol (4a).** By use of procedure D, the reaction of **24a** with ethanthiol gave **4a** in 95% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 219 (13890). IR ($CHCl_3$, cm^{-1}): 3467 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J = 7.5 Hz, 3H, CH_3), 1.92−2.13 (m, 3H, 2H of C-5 + 1H of OH), 2.41−2.46 (m, 2H, S-CH_2), 2.56−2.58 (m, 1H, CH_2S) 2.67−2.74 (m, 1H, CH_2S), 3.11 (d, J = 9.9 Hz, 1H, CH), 4.25−4.34 (m, 1H, CH), 5.12 (d, J = 10.5 Hz, 1H, CH), 6.78−6.99 (m, 5H, ArH), 7.01−7.11 (m, 10H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.8 (+ve, CH_3), 27.1 (−ve, S-CH_2), 36.9 (−ve, CH_2−S), 44.3 (−ve, CH), 58.1 (+ve, CH), 73.6 (+ve, CH), 75.1 (ab, C-4), 78.9 (+ve, CH), 124.5 (+ve, ArCH), 126.7 (+ve, ArCH), 126.8 (+ve, ArCH), 127.8 (+ve, ArCH), 128.0 (+ve, ArCH), 128.9 (+ve, ArCH), 129.8 (+ve, ArCH), 132.9 (+ve, ArCH), 136.1 (ab, ArC), 139.3 (ab, ArC). FAB-MS *m*/*z* 404 [M^+]. Anal. ($C_{26}H_{28}O_2S$) C, H, S.

(2*R,3*S**,4*R**,6*S**)-Tetrahydro-2,3,4-triphenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (4b).** By use of procedure D, the reaction of **24a** with KSCN gave **4b** in 92% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 221 (17840). IR ($CHCl_3$, cm^{-1}): 3454 (OH) 2157 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 2.03−2.39 (m, 3H, 2H of C-5 + OH), 3.18 (d, J = 11.4 Hz, 1H, CH), 3.22−3.33 (m, 2H, CH_2), 4.62−4.66 (m, 1H, CH), 5.32 (d, J = 10.8 Hz, 1H, CH), 6.90−6.97 (m, 3H, ArH), 7.00−7.28 (m, 12H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 39.0 (−ve, CH_2), 43.5 (−ve, C-5), 57.7 (+ve, CH), 71.8 (+ve, CH), 74.9 (ab, C-4), 79.1 (+ve, CH), 112.7 (ab, C≡N), 124.4 (+ve, ArCH), 124.5 (+ve, ArCH), 126.7(+ve, ArCH), 126.9 (+ve, ArCH), 127.8 (+ve, ArCH), 128.0 (+ve, ArCH), 128.2 (+ve, ArCH), 129.7 (+ve, ArCH), 138.5 (+ve, ArCH), 138.7 (ab, ArC). 139.1 (ab, ArC), FAB-MS *m*/*z* 401 [M^+]. Anal. ($C_{25}H_{23}NO_2S$) C, H, S, N.

(2*R,3*S**,4*R**,6*S**)-6-((Ethylthio)methyl)-2-(4-fluorophenyl)-tetrahydro-3,4-diphenyl-2*H*-pyran-4-ol (4c).** By use of procedure D, the reaction of **24b** with ethanthiol gave **4c** in 94% yield as a

colorless viscous oil. UV (EtOH): λ_{max} (ε) 219 (14570). IR ($CHCl_3$, cm^{-1}): 3474 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.5 Hz, 3H, CH_3), 1.99−2.19 (m, 2H, CH_2), 2.49−2.60 (m, 3H, 2H of S-CH_2 + 1H of CH_2S), 2.74−2.79 (m, 1H, CH_2S), 3.16 (d, J = 10.8 Hz, 1H, CH), 4.30−4.40 (m, 1H, CH), 5.19 (d, J = 10.5 Hz, 1H, CH), 6.66−6.88 (m, 5H, ArH), 7.04−7.16 (m, 9H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.7 (+ve, CH_3), 26.9 (−ve, S-CH_2), 36.8 (−ve, CH_2-S), 44.2 (+ve, C-5), 58.2 (+ve, CH), 73.5 (+ve, CH), 76.6 (ab, C-4), 78.9 (+ve, CH), 114.68 (+ve, J_{C-F} = 21 Hz, ortho to C−F, ArCH), 124.4 (+ve, ArCH), 126.65 (+ve, J_{C-F} = 14.2 Hz, meta to C−F, ArCH), 127.6 (+ve, ArCH), 127.9 (+ve, ArCH), 128.9 (+ve, ArCH), 129.1 (+ve, ArCH), 129.7 (+ve, ArCH), 136.2 (ab, ArC), 136.32 (ab, J_{C-F} = 3.1 Hz, para to C−F, ArC), 145.84 (ab, ArC), 162.74 (ab, J_{C-F} = 243.5 Hz, ArC-F). FAB-MS m/z 422 [M^+]. Anal. ($C_{26}H_{27}FO_2S$) C, H, S.

(2*R,3*S**,4*R**,6*S**)-2-(4-Fluorophenyl)tetrahydro-3,4-diphenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (4d).** By use of procedure D, the reaction of **24b** with KSCN gave **4d** in 90% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 219 (14350). IR ($CHCl_3$, cm^{-1}): 3495 (OH), 2159 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 1.99−2.04 (m, 1H, 1H of C-5), 2.31−2.36 (m, 2H, 1H of C-5 + OH), 3.14 (dd, J_1 = 11 Hz, J_2 = 6.9 Hz, 1H, 1H of CH_2), 3.24−3.32 (m, 2H, 1H of CH_2 + 1H of C-3), 4.62−4.66 (m, 1H, CH), 5.33 (d, J = 10.8 Hz, 1H, CH), 6.77−6.99 (m, 8H, ArH), 7.17−7.26 (m, 6H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 39.1 (−ve, CH_2), 43.4 (−ve, CH_2), 57.8 (+ve, C-3), 71.6 (+ve, CH), 74.9 (ab, C-4), 78.9 (+ve, CH), 112.8 (ab, C≡N), 114.3 (+ve, J_{C-F} = 21 Hz, ortho to C−F, ArCH), 124.4 (+ve, ArCH), 124.5 (+ve, ArCH), 126.53 (+ve, J_{C-F} = 16.6 Hz, meta to C−F, ArCH), 127.1 (+ve, ArCH), 127.8 (+ve, ArCH), 127.9 (+ve, ArCH), 128.1 (+ve, ArCH), 128.2 (+ve, ArCH), 129.1 (+ve, ArCH), 129.6 (+ve, ArCH), 135.7 (ab, ArC), 136.1 (ab, J_{C-F} = 3.1 Hz, para to C−F, ArC), 145.1 (ab, ArC), 161.9 (ab, J_{C-F} = 244.2 Hz, ArC-F). FAB-MS m/z 419 [M^+]. Anal. ($C_{25}H_{22}FNO_2S$) C, H, S, N.

(2*R,3*S**,4*R**,6*S**)-2-(4-Chlorophenyl)-6-((ethylthio)methyl)-tetrahydro-3,4-diphenyl-2*H*-pyran-4-ol (4e).** By use of procedure D, the reaction of **24c** with ethanthiol gave **4e** in 95% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 222 (20410). IR ($CHCl_3$, cm^{-1}): 3498 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, J = 7.5 Hz, 3H, CH_3), 1.99−2.18 (m, 3H, 2H of C-5 + 1H of OH), 2.49−2.60 (m, 3H, 2H of S-CH_2 + 1H of CH_2S), 2.63−2.78 (m, 1H, CH_2S), 3.15 (d, J = 10.8 Hz, 1H, CH), 4.32−4.40 (m, 1H, CH), 5.17 (d, J = 10.5 Hz, 1H, CH), 6.71−7.16 (m, 14H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.8 (+ve, CH_3), 27.1 (−ve, S-CH_2), 36.8 (−ve, CH_2-S), 44.2 (−ve, CH_2), 58.1 (+ve, CH), 73.5 (+ve, CH), 75.0 (ab, C-4), 78.9 (+ve, CH), 124.5 (+ve, ArCH), 126.6 (+ve, ArCH), 126.7 (+ve, ArCH), 127.7 (+ve, ArCH), 127.9 (+ve, ArCH), 128.1 (+ve, ArCH), 128.8 (+ve, ArCH), 129.7 (+ve, ArCH), 132.8 (ab, ArC), 136.1 (ab, ArC), 139.3 (ab, ArC), 145.8 (ab, ArC). FAB-MS m/z 438 [M^+] (75%), 440 [M^+] (24%). Anal. ($C_{26}H_{27}ClO_2S$) C, H, S.

(2*R,3*S**,4*R**,6*S**)-2-(4-Chlorophenyl)tetrahydro-3,4-diphenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (4f).** By use of procedure D, the reaction of **24c** with KSCN gave **4f** in 92% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 221 (18070). IR ($CHCl_3$, cm^{-1}): 3494 (OH), 2155 (CN). ^1H NMR (300 MHz, $CDCl_3$): δ 2.03−2.06 (m, 1H, 1H of C-5), 2.20 (br s, 1H, OH), 2.30−2.39 (1H, m, 1H of C-5), 3.21 (dd, J_1 = 13.2 Hz, J_2 = 6.9 Hz, 1H, 1H of CH_2), 3.27−3.33 (m, 2H, 1H of CH_2 + 1H of C-3), 4.61−4.66 (m, 1H, CH), 5.32 (d, J = 10.5 Hz, 1H, CH), 6.61−6.63 (m, 2H, ArH), 6.99−7.28 (m, 12H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 39.1 (−ve, CH_2), 43.5 (−ve, CH_2), 57.6 (+ve, CH), 71.7 (+ve, CH), 74.9 (ab, C-4), 79.1 (+ve, CH), 112.7 (ab, C≡N), 124.4 (+ve, ArCH), 124.5 (+ve, ArCH), 126.9 (+ve, ArCH), 127.1 (+ve, ArCH), 127.8 (+ve, ArCH), 128.2 (+ve, ArCH), 129.1 (+ve, ArCH), 129.7 (+ve, ArCH), 133.3 (ab, ArC), 138.4 (ab, ArC), 145.1 (ab, ArC). FAB-MS m/z 435 [M^+] (74%), 437 [M^+] (23%). Anal. ($C_{25}H_{22}ClNO_2S$) C, H, S, N.

(2*R,3*S**,4*R**,6*S**)-2-(4-Bromophenyl)-6-((ethylthio)methyl)-tetrahydro-3,4-diphenyl-2*H*-pyran-4-ol) (4g).** By use of procedure D, the reaction of **24d** with ethanthiol gave **4g** in 94% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 222 (19810). IR ($CHCl_3$, cm^{-1}): 3439 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.6 Hz, 3H, CH_3), 2.10−2.16 (m, 3H, 2H of C-5 + 1H of S-CH_2), 2.26−2.34 (m, 1H, S-CH_2), 2.57−2.91 (m, 2H, CH_2S), 3.26 (d, J = 10.8 Hz, 1H, CH), 4.17−4.23 (m, 1H, CH), 5.32 (d, J = 10.5 Hz, 1H, CH), 6.61−6.63 (m, 2H, ArH), 6.99−7.26 (m, 12H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 14.8 (+ve, CH_3), 27.1 (−ve, S-CH_2), 36.9 (−ve, CH_2−S), 44.9 (−ve, CH_2), 57.8 (+ve, CH), 73.6 (+ve, CH), 75.1 (ab, C-4), 78.8 (+ve, CH), 121.2 (ab, ArC), 124.4 (+ve, ArCH), 124.5 (+ve, ArCH), 126.9 (+ve, ArCH), 127.9 (+ve, ArCH), 128.1 (+ve, ArCH), 128.9 (+ve, ArCH), 129.7 (+ve, ArCH), 135.8 (+ve, ArCH), 138.9 (ab, ArC), 145.4 (ab, ArC). FAB-MS m/z 482 [M^+] (100%), 484 [M^+] (100%). Anal. ($C_{26}H_{27}BrO_2S$) C, H, S.

(2*R,3*S**,4*R**,6*S**)-2-(4-Bromophenyl)tetrahydro-3,4-diphenyl-6-(thiocyanatomethyl)-2*H*-pyran-4-ol (4h).** By use of procedure D, the reaction of **24d** with KSCN gave **4h** in 90% yield as a colorless viscous oil. UV (EtOH): λ_{max} (ε) 220 (16280). IR ($CHCl_3$, cm^{-1}): 3470 (OH) 2154 (SCN). ^1H NMR (300 MHz, $CDCl_3$): δ 2.04−2.07 (m, 1H, 1H of C-5), 2.14 (br s, 1H, OH), 2.19−2.33 (m, 1H, 1H of C-5), 3.19−3.22 (m, 1H, 1H of CH_2), 3.23−3.32 (m, 2H, 1H of CH_2 + 1H of C-3), 4.63−4.69 (m, 1H, CH), 5.31 (d, 1H, J = 10.8 Hz, CH), 6.80−6.82 (m, 2H, ArH), 6.99−7.27 (m, 12H, ArH). ^{13}C NMR (normal/DEPT-135, $CDCl_3$): δ 37.7 (−ve, CH_2), 42.0 (−ve, CH_2), 56.0 (+ve, CH), 71.0 (+ve, CH), 73.5 (ab, C-4), 77.6 (+ve, CH), 111.2 (ab, C≡N), 120.9 (ab, ArC), 125.2 (+ve, ArCH), 125.7 (+ve, ArCH), 126.4 (+ve, ArCH), 126.6 (+ve, ArCH), 126.7 (+ve, ArCH), 127.74 (+ve, ArCH), 128.2 (+ve, ArCH), 131.6 (+ve, ArCH), 134.15 (ab, ArC), 137.6 (ab, ArC), 139.2 (ab, ArC). FAB-MS m/z 479 [M^+] (98%), 481 [M^+] (97%). Anal. ($C_{25}H_{22}BrNO_2S$) C, H, S, N.

X-ray Crystal Data Collection for 22c, 23c, and 24c. X-ray crystal data were measured by using $\theta-2\theta$ scan mode. The structure was solved by using direct method SHELX-97. For **22c** (CCDC no. 745039), crystals were developed after dissolving the compound in a mixture of $CHCl_3$/hexane (3:1). Molecular formula $C_{21}H_{17}ClO_2$; space group $P\bar{1}$; cell lengths a = 6.3885 Å, b = 11.386 Å, c = 12.656 Å; cell angles α = 67.04°, β = 79.987°, γ = 84.850°; V = 834.503 $Å^3$; Z = 2; Z' = 0; R-factor = 8.5. For **23c** (CCDC no. 745041), crystals were developed from $CHCl_3$/benzene (3:2). Molecular formula $C_{24}H_{23}ClO_2$; space group $Pbca$; cell lengths a = 12.18 Å, b = 8.514 Å, c = 39.144 Å; cell angles α = 90.00°, β = 90.00°, γ = 90.00°; cell volume 4061.25 $Å^3$; Z = 8; Z' = 0; R-factor = 7.65. For **24c** (CCDC no. 745040), crystals were developed from CH_3CN/hexane (3:1). Molecular formula $C_{24}H_{22}ClIO_2$; space group $P21/c$; cell lengths a = 15.367 Å, b = 13.9365 Å, c = 9.7027 Å; cell angles α = 90.00°, β = 93.568°, γ = 90.00°; cell volume 2073.92 $Å^3$; Z = 4; Z' = 0; R-factor = 3.82.

In Vitro COX-1 and COX-2 Inhibitory Activities. In vitro COX-1 and COX-2 inhibitory activities of tetrahydropyrans were evaluated using "COX (ovine) inhibitor screening assay" kits with 96-well plates (catalog no. 560101, Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions. This screening assay directly measures PGF_{2a} produced by $SnCl_2$ reduction of COX-derived PGH_2. COX-1 and COX-2 initial activity tubes were prepared taking 950 μL of reaction buffer (0.1 M Tris-HCl, pH 8.0, containing 5 mM EDTA and 2 mM phenol), 10 μL of heme, 10 μL of COX-1 and COX-2 enzymes into respective tubes. Similarly, COX-1 and COX-2 inhibitor tubes were prepared by adding 20 μL of inhibitor (compound under test with final concentrations of 100, 10, 1, 0.1, 0.01, and 0.001 μM) in each tube in addition to the above ingredients, making a final volume of 1 mL. 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. After incubation of the tubes at 37 °C for 20 min, reactions were initiated by adding 10 μL of arachidonic acid in each tube and again incubating at 37 °C for 2 min. The reaction was quenched with 50 μL of 1 M HCl. PGH_2 thus formed was reduced to PGF_{2a} by adding 100 μL of $SnCl_2$. The prostaglandin produced in each well was quantified using broadly specific prostaglandin antiserum. The PGs and PG-acetylcholinesterase (AChe) conjugate (PG tracer) have a competition for a limited amount of PG antiserum. Because the concentration of the PG tracer is held constant while the concentration of PG varies, the amount of PG tracer that is able to bind to the PG antiserum will be inversely proportional to the concentration of PG in the well. This rabbit antiserum-PG (either free or tracer) complex binds to a mouse monoclonal antirabbit antibody that has been previously attached to the well. The plate is washed to remove any unbound reagents, and then Ellman's reagent (which contains the substrate to AChe) is added to the well. The product of this enzymatic reaction has a distinct yellow color and absorbs strongly at 420 nm. The intensity of this color, determined spectrophotometrically, is proportional to the amount of PG tracer bound to well, which is inversely proportional to the amount of free PG present in the well during the incubation.

The wells of the 96-well plate showing low absorbance at 420 nm indicate the higher level of prostaglandins in these wells and hence less inhibition of the enzyme. Therefore, the COX inhibitory activities of the compounds could be quantified from the absorbance values of different wells of the 96-well plates. The concentrations of the test compound causing 50% inhibition (IC_{50}) were determined using a dose−response inhibition curve (duplicate determinations) with GraphPad PRISM.

Screening for Tumor Growth Inhibitory Activities. The compounds were tested for anticancer activities by the screening unit of NCI at NIH, Bethesda, MD, following their standard procedure (www.dtp.nci.nih.gov). Compounds were first screened at 10^{-5} M on all 59 cancer cell lines and, on the basis of the initial activity, were tested at 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} M. The percentage growth of tumor cells was calculated at each cell line for each concentration of the compound. The results are expressed as growth inhibition of 50% (GI_{50}) which is the concentration of the compound causing 50% reduction in the net protein increase (as measured by SRB staining) in control cells during drug incubation.

Docking Procedure. The crystal coordinates of COX-1 (ovine) and COX-2 (murine) were downloaded from the Protein Data Bank with PDB codes 1EQG (ibuprofen in the active site) and 6COX (Sc-558 in the active site), respectively. Compounds were built using the builder Toolkit of the software package ArgusLab, version 4.0.1,[66] and SYBYL, version 7.1,[67] and energy-minimized using semiempirical quantum mechanical method PM3. In the molecule tree view, the monomeric structure of the enzyme was selected and the active site was defined as 15 Å around the ligand (ibuprofen/Sc558). The molecule to be docked in the active site of the enzyme was pasted in the work space carrying the structure of the enzyme. The docking program implements an efficient grid based docking algorithm that approximates an exhaustive search within the free volume of the binding site cavity. The conformational space was explored by the geometry optimization of the flexible ligand (rings are treated as rigid) in combination with the incremental construction of the ligand torsions. Thus, docking occurred between the flexible ligand parts of the compound and enzyme. The ligand orientation was determined by a shape scoring function based on Ascore, and the final positions were ranked by lowest interaction energy values (Table S4). The $E_{interaction}$ is the sum of the energies involved in H-bond interactions, hydrophobic interactions, and van der Waal's interactions. H-Bond and hydrophobic interactions between the compound and enzyme were explored by measuring the distances between the various groups of the ligand and the amino acid residues.

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Supporting Information Available: Experimental data for β-hydroxy ketones, homoallylic alcohols, and iodocyclized compounds; results from combustion analysis; calculation for percentage inhibition; percentage COX-1/2 inhibition; docking score; ^1H and ^{13}C NMR spectra of all the compounds; ^1H NMR spectra of diastereomers obtained at different reaction temperatures; docking structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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