2, 3-Diaryl-5-ethylsulfanylmethyltetrahydrofurans as a new class of COX-2 inhibitors and cytotoxic agents†

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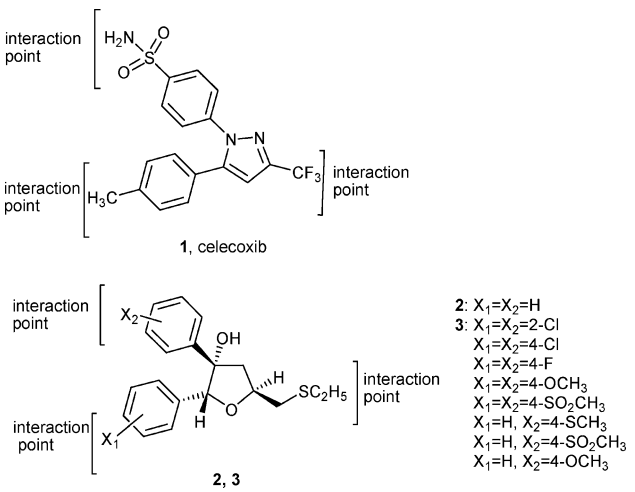
2,3-Diaryl-5-ethylsulfanylmethyltetrahydrofuran-3-ols were designed and synthesized by the allylations of benzoins followed by iodocyclization and nucleophilic replacement reactions with ethanthiol. These molecules exhibit IC_{50} for COX-2 at <10 nM concentration and exhibit average GI_{50} over all the 59 human tumor cell lines at μM concentration.

Introduction

Starting with the steroids and passing through the use of non-selective and selective non-steroids, the process of treatment of inflammation has travelled a long way. The modern era of anti-inflammatory drugs dates back to 1897 when aspirin was introduced for the treatment of inflammation, fever and pain, which was followed by the launch of many other drugs like ibuprofen, diclofenac, and indomethacin. However, the rationalization of the mechanism of inflammation in 1971, with the identification of the enzyme cyclooxygenase[1] as being responsible for the formation of prostaglandins during arachidonic acid metabolism, has focused attention on the inhibition of this enzyme for the treatment of inflammation. Moreover, the cause of undesirable side effects of inflammatory drugs was unraveled by the identification of two isoforms of enzyme cyclooxygenase *viz*. COX-1 and COX-2.[2–5] Whereas COX-1 performs desirable roles in the protection of the gastrointestinal wall, induction of labor *etc.*, the over-expression of COX-2, in response to stimuli like inflammatory cytokines, growth factors, tumor promoters, peroxisomal proliferators, hypoxia, ionizing radiations and carcinogens, is responsible for various inflammatory diseases,[6,7] promotion of cancer[8–14] and induction of multi drug resistance.[15–18] The close structural similarities between COX-1 and COX-2 have heralded the era of selective COX-2 inhibitors,[19–24] the coxibs,[25,26] which were considered to be safer than the conventional non-steroidal anti-inflammatory drugs. However, the withdrawal of rofecoxib, due to its cardiac toxicity, was a major setback to the use of selective COX-2 inhibitors for inflammatory diseases. It has been proposed that the oxidation[27] of rofecoxib is a possible contributor to its toxicity, while the diminished synthesis of prostacyclin, a vasodilator, has also been considered to be a limitation of selective COX-2 inhibitors.[28,29] Therefore, the multiple role of enzyme COX-2 and the side effects associated with the presently available drugs for blocking this enzyme demand more investigations in this field.

Based upon the common structural feature of diaryl based COX-2 inhibitors[24] most of which have three interacting sites present on a central template (pyrazole in celecoxib; **1**, Scheme 1), we have chosen tetrahydrofuran (THF) as the template (structurally similar to the template of rofecoxib but devoid of oxidation) and introduced appropriately substituted phenyl rings at its C-2, C-3 positions and ethylsulfanyl methyl group at C-5 (**3**, Scheme 1). The dockings of molecules **3** (Scheme 1) in the active site of COX-2 show that C-5 substituent interacts with R120 through S and unlike compound **2**, the presence of substituents on the phenyl rings enhances their interactions with the active site amino acid residues. The *in-vitro* COX-2 inhibition activities of **3** are significantly higher in comparison to compound **2**[30] (Scheme 1).



Scheme 1

Results and discussion

A detailed account of the synthesis of target molecules has been shown in Scheme 2. The condensation of benzaldehydes **4–9** in the presence of NaCN (benzoin condensation) provided the corresponding symmetrical benzoins **10–15**, while the unsymmetrical benzoins (**16**, **17**) have been obtained by the crossed benzoin condensation (Scheme 2). In the crossed benzoin reactions, small

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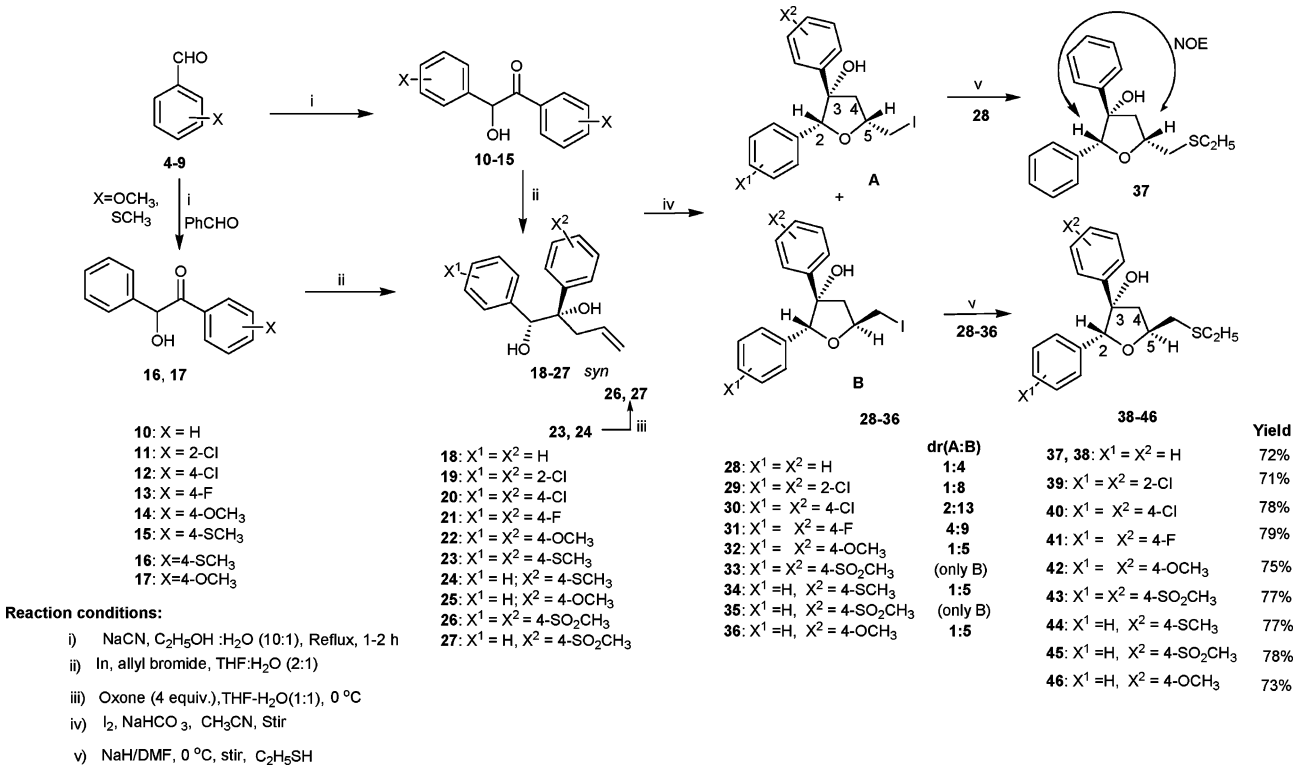
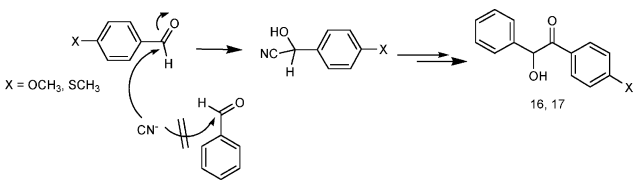
† Electronic supplementary information (ESI) available: Experimental data for compounds **24–36**, Linpinski values of compounds **38–46** and detailed growth inhibitory data for compounds **38**, **40** and **41** are given. See DOI: 10.1039/b803608j



Scheme 2

amounts of symmetrical benzoins **14**, **15** and traces of benzoin **10** are also formed which were separated by column chromatography. On the basis of the placement of the substituted/unsubstituted phenyl ring at C-2/C-3 of tetrahydrofurans **35** and **36** (coming from benzoins **16** and **17**), a plausible mechanism has been written for cross benzoin condensation (Scheme 3).



Scheme 3

A solution of benzoin **10**, allyl bromide and indium metal (suspension) (1 : 1.5 : 1) in THF–H_2O (2 : 1) on stirring at 30 ± 2 °C for 6–8 h, after usual workup provided **18** and under the same reaction conditions the substituted benzoins **11–17** furnished respective homoallylic alcohols **19–25** with diastereoselectivity >99. High diastereoselectivity at this step has been explained on the basis of Cram's chelation model.[31] Treatment of compounds **23** and **24** with oxone transformed the SCH_3 group to SO_2CH_3 in compounds **26** and **27**, respectively.

Stirring a solution of **18**, iodine, $NaHCO_3$ in CH_3CN at 0 °C gave a mixture of two diastereomers in the ratio 1 : 4 (^{1}H NMR spectrum) which were separated by column chromatography and identified as **28A** and **28B** (Scheme 2). Likewise, the iodocyclisations of homoallylic alcohols **19–22** and **24–27** resulted in the formation of respective tetrahydrofurans **29–36** (A and B) in the diastereomeric ratio shown in Scheme 2. The diastereoselective iodocyclisation of homoallylic alcohols has been explained on the basis of the formation of two transition states in this reaction.[32] In the case of tetrahydrofurans **35** and **36**, the presence of a substituted phenyl ring at C-3 of tetrahydrofuran, has been proved on the basis of HMBC and long range INEPT NMR experiments. Treatment of compounds **28A** and **28B-36B** with ethanethiol provided the corresponding compound **37–46** (Scheme 2). The relative stereochemistries at C-2 and C-5 carbons of tetrahydrofurans have been ascertained on the basis of observation of NOE between 2-H and 5-H in case of **37** and no NOE between 2-H and 5-H in case of compounds **38–46**. An energy minimised structure of **38** (Fig. 1) shows anti-orientation of the phenyl rings at C-2 and C-3 and similar geometries have been obtained after energy minimisations of compounds **39–46**.

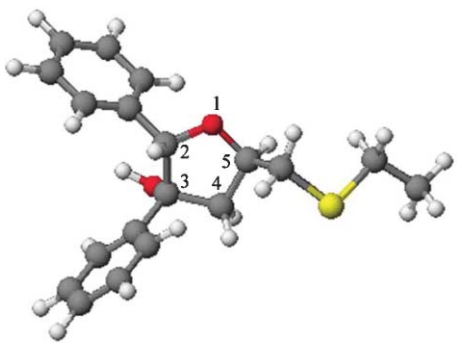


Fig. 1 Energy minimized structure of **38**. Anti-orientations of 2-H, 5-H and C-2, C-3 phenyl rings are in parallel with those observed from NOE experiments.

This particular structure of the molecules has been used during their dockings in the active site of COX-2.

Therefore, substituted/unsubstituted benzaldehydes through benzoin formation followed by diastereoselective allylation and diastereoselective iodocyclisation provided the target molecules in appreciable yields.

In-vitro COX-2 inhibiting activities of these compounds have been evaluated using a 'COX (ovine) inhibitor screening assay' kit with 96 well plates following the standard procedure. The growth inhibitory activities have been tested at 59 human tumor cell lines representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate as well as kidney, following the standard procedure of NCI, NIH, Bethesda, USA.[33–35]

All the ten compounds (**37–46**) evaluated for COX-1, COX-2 inhibitory activities (Table 1) carry a $CH_2SCH_2CH_3$ group at C-5 of tetrahydrofuran and differ from one another by the substituent at the two aryl rings. A very nice discrimination between the two diastereomers of tetrahydrofuran by COX-2 has been observed in the case of compounds **37** (2*R**, 3*S**, 5*R**) and **38** (2*R**, 3*S**, 5*S**) where compound **38** with 5*S** configuration exhibits significant inhibition of COX-2 with IC_{50} 0.25 μM while **37** shows poor inhibition of COX-2 exhibiting IC_{50} 7.56 μM. On this basis, the compounds **38–46** with 5*S** configuration were selected for investigations.

It has been observed that the compounds **39–46** exhibit high COX-2 inhibition with IC_{50} < 0.01 μM which is better than celecoxib and rofecoxib. Compounds **39–43** with *o*-chlorophenyl, *p*-chlorophenyl, *p*-fluorophenyl, *p*-methoxyphenyl and *p*-methansulfonylphenyl group, respectively, at C-2, C-3 of tetrahydrofuran show almost equal inhibition (90%, 10^{-8} M concentration) of COX-2 and poor inhibition of COX-1. Similarly, compounds **45** and **46** with a substituent at C-3 phenyl ring only, also exhibit 88% and 86% inhibition of COX-2 at 10^{-8} M concentration. Compound **44** with a SCH_3 group at C-3 phenyl shows 89% inhibition of COX-2 at 10^{-8} M concentration and 66% inhibition of COX-1 at 10^{-5} M concentration. Moreover, this class of highly selective COX-2 inhibitors, unlike rofecoxib, is devoid of air oxidation.

The docking studies[36] (docking programme was validated by performing the docking of Sc-558 in the crystal structure of COX-2, pdb ID 6COX, Fig. 2) indicate that these molecules fit in the active site of COX-2 (Fig. 3) in the same fashion as Sc-558. It is noteworthy that the sulfur atom present with the C-5 substituent of compounds **40** and **41** approaches at a distance of 2.40 Å to the NH of guanidine moiety of R120, the residue active during the metabolic phase of COX-2. The substituents present at C-2 and C-3 phenyl rings of tetrahydrofurans interact through H-bonding with W387 and H90, respectively. For compound **41**, the distance between F present at C-2 Ph and ArH of W387 is 0.987 Å.

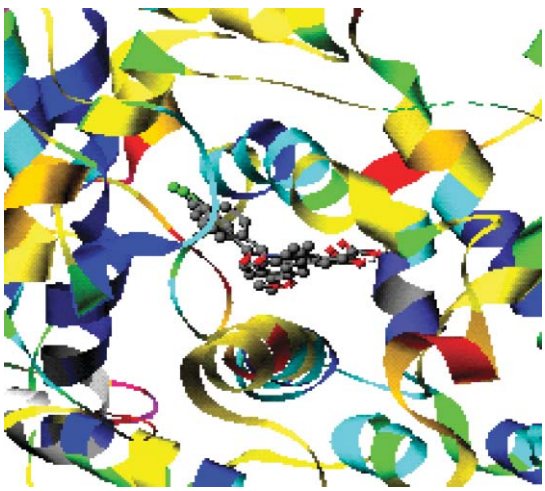


Fig. 2 Validation of docking programme. Close overlapping of docked structure of Sc-558 with its crystal structure (rms error is 0.48).

Moreover, a strong H-bond has been observed between fluorine present at C-3 Ph of compound **41** and NH of H90. Compound **43** when docked in the active site of COX-2 shows an H-bond with W387 through oxygen of SO_2Me group present at C-2 Ph.

As observed during the dockings of these compounds in COX-1, they do not enter into the active site of COX-1 and all of them exhibit a positive docking score.

The role of COX-2 in promotion of cancer has been established and many of its inhibitors like aspirin, rofecoxib, celecoxib *etc.* have been investigated for their use as cancer chemo-preventives

Table 1 *In-vitro* COX-2 inhibitory activities of tetrahydrofuran derivatives with SCH_2CH_3 group at C-5 (**37–46**)

	COX-2				COX-1			
	% Inhibition				% Inhibition			
Compound	0.01 μM	0.1 μM	1 μM (10 μM)	IC_{50} (μM)	10 μM	100 μM	IC_{50} (μM)	COX-2 selectivity[a]
37	−2	−2	−6 (68)	7.56	11.5	30	>100	>15
38	30	46	67	0.25	22	55	85	340
39	90	97	91	<0.01	22	52	93	>9300
40	89	94	97	<0.01	24.4	57	78	>7800
41	83	78	92	<0.01	−12	—	—	—
42	88	87	88	<0.01	22	54	87	>8700
43	89	85	87	<0.01	46.5	70	27	>2700
44	89	91	86	<0.01	66	80	<10	~1000
45	88	85	—	<0.01	28	63	66	>6600
46	86	89	88	<0.01	40	68	42	>4200
Celecoxib			50	0.076	65		10.75	141
Rofecoxib			75	0.5	75		>100	>200

[a] COX-2 selectivity = IC_{50}(COX-1)/IC_{50}(COX-2).

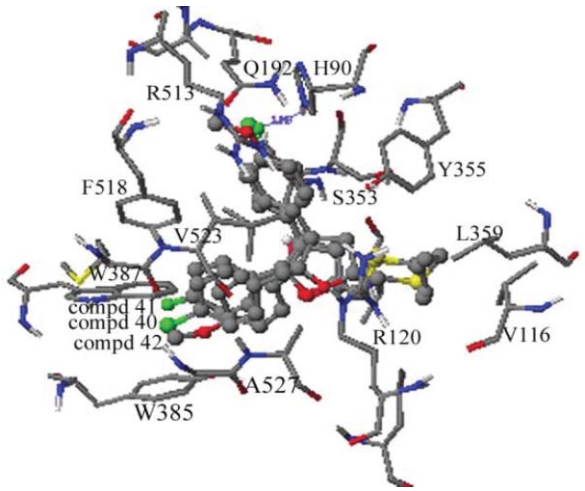


Fig. 3 Compound **40**, **41** and **42** docked in the active site of COX-2 (pdb ID 6COX). H's are omitted for clarity. 'S' of C-5 substituent approaches to the guanidine moiety of R120 at a distance of 2.40 Å for compounds **40**, **41** and 3.22 Å for compound **42**. H-bond (2.01 Å) between F present at C-3 phenyl of compound **41** and NH of H90 is visible while the corresponding substituents of compounds **40** and **42** have a distance of 2.34 Å and 2.42 Å, respectively, from NH of H90.

along with other cytotoxic drugs.[9] Due to the high COX-2 inhibitory activities of tetrahydrofurans discussed above, some of the molecules (**38**, **40** and **41**; picked by NIH from a list of ten compounds) were subjected to 59 human tumor cell lines for screening their growth inhibitory activities (Table 2). The average GI_{50} of compound **38** over all the 59 human tumor cell lines is 5.49×10^{-5} M. It exhibits $GI_{50} < 1.00 \times 10^{-8}$ M for the SR cell line of leukemia showing 51% and 60% growth inhibitions of tumor cells at 10^{-7} M and 10^{-8} M concentrations, respectively. Compounds **40** and **41** show significant growth inhibitory activities with average GI_{50} over all the 59 cancer cell lines as 1.73×10^{-5} M and 1.31×10^{-5} M, respectively. Compound **41** exhibits GI_{50} 3.65×10^{-8} M and $< 1.00 \times 10^{-8}$ M at CCRF-CEM and SR cell lines of leukemia, respectively. Moreover, the growth inhibitory activities of compounds **40** and **41** at the PC3 cell line of prostate cancer are better than those reported for celecoxib[37] (Table 2). High LC_{50} values of compounds **38**, **40** and **41** indicate the poor toxicity of these compounds.

Therefore, the model proposed for tetrahydrofuran based COX-2 inhibitors, with three interacting sites, has proved well and the molecules show better COX-2 inhibitory activities than that of celecoxib and rofecoxib. The high COX-2 inhibition and significant growth inhibitory activities of these molecules at various cancer cell lines indicate that they could be used as lead molecules for their development into anti-inflammatory and anticancer agents. All these molecules follow Lipinski's rule of five[38] (electronic supplementary information).†

Conclusions

In parallel with the structural features of celecoxib and rofecoxib, 2,3-diaryl-5-ethylsulfanylmethyl tetrahydrofurans were designed. The benzoins, obtained from substituted/unsubstituted benzaldehydes, undergo indium mediated diastereoselective allylation followed by iodocyclisation and nucleophilic replacement of the iodo group with ethanthiol to furnish the target molecules. These molecules exhibit IC_{50} for COX-2 in the nM range and a high selectivity for COX-2 over COX-1. Compounds **40** and **41** also show considerable growth inhibitory activities at various cancer cell lines.

Experimental

General

Melting points were determined in capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were run on a JEOL JNM AL 300 MHz and 75 MHz NMR spectrometer, respectively, using $CDCl_3$ as solvent. Chemical shifts are given in ppm with TMS as an internal reference. *J* values are given in Hertz. Chromatography was performed with silica 100–200 mesh and reactions were monitored by thin layer chromatography (TLC) with silica plates coated with silica gel HF-254. The bioassay kit was purchased from Cayman Chemical. Experimental procedure and spectroscopic data of benzoins (**10–17**) and allylated products (**18–23**, **26**) (Scheme 2) has already been reported[39] and that for compounds **24**, **25**, **27–36** has been given as supplementary data in the ESI.†

(2*R**, 3*S**, 5*R**)-5-Ethylsulfanylmethyl-2,3-diphenyl-tetrahydrofuran-3-ol (37)

To the ice cold solution of NaH (0.12 g, 5.5 mmol) in DMF (2–3 ml) was added ethanethiol (0.34 g, 5.5 mmol) and stirred for 2 min, followed by the addition of ice cold solution of **28A** (2.24 g, 5 mmol). On completion of reaction (20–30 min, TLC monitoring), the reaction mixture was extracted with diethylether. The organic layer was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was column chromatographed (silica gel 100–200) using ethyl acetate, hexane as eluents to isolate **37** as thick liquid. Yield 72%; (Found: C, 72.63; H, 7.19. $C_{19}H_{22}O_2S$ requires C, 72.57; H, 7.05%). ν_{max} ($CHCl_3$/cm^{-1}): 3600 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.34 (3H, t, $J = 7.5$ Hz, CH_3), 2.17 (1H, bs, exchanges with D_2O), 2.38 (1H, dd, $^2J = 14.1$ Hz, $^3J = 4.8$ Hz, H-4), 2.76 (2H, q, $J = 7.5$ Hz, SCH_2), 2.83 1H, (dd,

Table 2 Comparison of growth inhibitory activities (GI_{50}) of compounds **38**, **40**, **41** with celecoxib[a]

Compound	Average GI_{50} over all the 59 tumor cell lines	Activity at PC3 cancer cell line, $GI_{50}/\mu M$	Average LC_{50} over all the cell lines
38	5.49×10^{-5} M	44.5	9.5×10^{-5} M
40	1.73×10^{-5} M	20.0	7.2×10^{-5} M
41	1.31×10^{-5} M	16.2	6.6×10^{-5}M
Celecoxib	—	47.0	

[a] Rofecoxib exhibits 15% inhibition (at 10^{-6} M concentration) of tumor cells of PC3 cell line of prostate cancer.[37]

^2J = 14.1 Hz, ^3J = 9.0 Hz, H-4), 2.97 (1H, dd, ^2J = 13.8 Hz, ^2J = 4.8 Hz, 5-CH_2), 3.09 (1H, dd, ^1J = 13.8 Hz, ^2J = 5.4 Hz, 5-CH_2), 4.65 (1H, dq, ^2J = 9.9 Hz, ^3J = 4.8 Hz, H-5), 5.11 (1H, s, H-2), 6.98–7.43 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$, Me_4Si): 14.95 (+ve, CH_3), 27.48 (−ve, SCH_2), 37.11(−ve, 5-CH_2), 48.17 (−ve, C-4), 77.19 (+ve, C-5), 82.04 (ab, C-3), 90.38 (+ve, C-2), 125.40 (+ve, CH), 126.65 (+ve, CH), 127.02 (+ve, CH), 127.93 (+ve, CH), 127.96 (+ve, CH), 128.21 (+ve, CH), 135.09 (ab, C), 142.01 (ab, C). NOE experiments: irrradiation of singlet at δ 5.18 (H-2) shows positive NOE with signals at δ 4.65 (H-5), and 6.94, 7.43 (ArH) and irradiation of dq at δ 4. 65 (H-5) shows positive NOE with dd at δ 2.83 (5.46%); *m/z* (FAB) 313 (M^+-1).

(2*R, 3*S**, 5*S**)-5-Ethylsulfanylmethyl-2,3-diphenyl-tetrahydrofuran-3-ol (38)**

According to the preparation of **37**, **38** was obtained from **28B** as thick liquid. Yield 72%; (Found: C, 72.36; H, 6.89. $C_{19}H_{22}O_2S$ requires C, 72.57; H, 7.05%). ν_{max} ($CHCl_3$/cm^{-1}): 3620 (OH). δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.31 (3H, t, J = 7.5 Hz, CH_3), 2.46 (1H, bs, exchanges with D_2O), 2.55 (2H, d, J = 7.8 Hz, H-4), 2.69 (2H, q, J = 7.5 Hz, SCH_2), 2.96 (2H, q, J = 2.4 Hz, 5-CH_2), 4.86 (1H, m, H-5), 5.43 (1H, s, H-2), 7.02–7.44 (10H, m, ArH); δ_C (75 MHz, $CDCl_3$, Me_4Si): 14.98 (+ve, CH_3), 27.09 (−ve, SCH_2), 37.19 (−ve, 5-CH_2), 47.92 (−ve, C-4), 78.44 (+ve, C-5), 83.25 (ab, C-3), 89.53 (+ve, C-2), 125.30 (+ve, CH), 125.87 (+ve, CH), 126.60 (+ve, CH), 127.26 (+ve, CH), 128.28 (+ve, CH), 128.35 (+ve, CH), 135.48 (ab, C), 141.66 (ab, C). NOE experiments: irradiation of singlet at δ 5.43 (H-2) shows positive NOE with signals at δ 7.03 (19.8%), 7.38 (11.86%) (ArH) and shows no positive NOE with multiplet at δ 4.86 (H-5); *m/z* (FAB) 313 (M^+-1).

(2*R, 3*S**, 5*S**)-2,3-Bis-(2-chlorophenyl)-5-ethylsulfanyl-methyltetrahydrofuran-3-ol (39)**

To the ice cold solution of NaH (0.12 g, 5.5 mmol) in DMF (2–3 ml) was added ethanethiol (0.34 g, 5.5 mmol) and stirred for 2 min, followed by the addition of ice cold solution of **29B** (2.24 g, 5 mmol). On completion of reaction (20–30 min, TLC monitoring), the reaction mixture was extracted with diethylether. The organic layer was dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was column chromatographed (silica gel 100–200) using ethyl acetate, hexane as eluents to isolate **39** as thick liquid. Yield 71%; (Found: C, 59.41; H, 5.13; S, 8.21. $C_{19}H_{20}Cl_2O_2S$ requires C, 59.53; H, 5.26; S, 8.37%). ν_{max} ($CHCl_3$)/cm^{-1}): 3450 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.30 (3H, t, J = 7.5 Hz, CH_3), 1.99 (1H, d, J = 1.8 Hz, OH, exchanges with D_2O), 2.34 (1H, dd, ^2J = 12.9 Hz, ^3J = 6.0 Hz, 4-H), 2.68 (2H, dq, ^2J = 7.5 Hz, ^3J = 0.9 Hz, SCH_2), 2.90 (1H, dd, ^2J = 13.2 Hz, ^3J = 6.3 Hz, CH_2S), 3.02 (1H, dd, ^2J = 13.2 Hz, ^3J = 6.0 Hz, CH_2S), 3.27 (1H, ddd, ^2J = 12.9 Hz, ^3J = 9.6 Hz, ^4J = 1.8 Hz, 4-H, converted into dd on D_2O exchange), 4.84 (1H, ddd, ^3J = 12.0 Hz, ^3J = 9.9 Hz, ^3J = 6.0 Hz, 5-H), 6.47 (1H, s, 2-H), 7.17–7.22 (4H, m, ArH), 7.29–7.39 (2H, m, ArH), 7.51–7.54 (1H, m, ArH), 7.69 (1H, dd, ^3J = 7.5 Hz, ^3J = 1.5 Hz, ArH). Decoupling of triplet at δ 1.30 converts dq at δ 2.68 into a doublet with J = 0.9 Hz. Decoupling of double doublet at δ 2.34 converts ddd at δ 3.27 into a dd ^3J = 9.3 Hz, ^3J = 1.8 Hz; δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 14.87 (+ve, CH_3), 26.76 (−ve, SCH_2), 36.79 (−ve, CH_2S), 44.77 (−ve, C-4), 79.33 (+ve, C-5), 82.29 (+ve, C-2), 82.95 (ab, C-3), 126.73 (+ve, ArCH), 126.85 (+ve, ArCH), 128.08 (+ve, ArCH), 128.91 (+ve, ArCH), 129.31 (+ve, ArCH), 129.64 (+ve, ArCH), 129.93 (+ve, ArCH), 131.38 (+ve, ArCH), 131.57 (ab, ArC), 133.04 (ab, ArC), 134.34 (ab, ArC), 138.28 (ab, ArC); *m/z* (FAB) 364.9 (M^+-H_2O), 364.9 (M^+-OH).

(2*R, 3*S**, 5*S**)-2,3-Bis-(4-chlorophenyl)-5-ethylsulfanyl-methyltetrahydrofuran-3-ol (40)**

According to the preparation of **39**, **40** was obtained from **30B** as thick liquid. Yield 78%; (Found: C, 59.41; H, 5.13; S, 8.21. $C_{19}H_{20}Cl_2O_2S$ requires C, 59.53; H, 5.26; S, 8.37%). ν_{max} ($CHCl_3$)/cm^{-1}: 3450 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.30 (3H, t, J = 7.5 Hz, CH_3), 1.69 (1H, bs, OH, exchanges with D_2O), 2.52 (2H, d, J = 8.1 Hz, 4-H), 2.68 (2H, q, J = 7.5 Hz, SCH_2), 2.90 (1H, dd, ^2J = 13.8 Hz, ^3J = 4.8 Hz, CH_2S), 2.98 (1H, dd, ^2J = 13.5 Hz, ^3J = 5.7 Hz, CH_2S), 4.79–4.88 (1H, m, 5-H), 5.31 (1H, s, 2-H), 6.96 (2H, d, J = 8.4 Hz, ArH), 7.22 (2H, d, J = 8.4 Hz, ArH) 7.35 (4H, m, ArH); Decoupling of triplet at δ 1.30 converts *q* at δ 2.68 into singlet. Decoupling of doublet at δ 2.52 converts multiplet at δ 4.79–4.88 into a double doublet; δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 14.97 (+ve, CH_3), 27.18 (−ve, SCH_2), 37.17 (−ve, CH_2S), 47.73 (−ve, C-4), 78.29 (+ve, C-5), 82.93 (ab, C-3), 88.85 (+ve, C-2), 126.79 (+ve, ArCH), 127.95 (+ve, ArCH), 128.48 (+ve, ArCH), 128.60 (+ve, ArCH), 133.36 (ab, ArC), 133.81 (ab, ArC), 134.14 (ab, ArC), 139.91 (ab, ArC); In ^{1}H-^{13}C HETCOR spectrum, carbon signal at δ 14.97 shows correlation with signal at δ 1.30 in ^{1}H spectrum, carbon signal at δ 27.18 shows correlation with quartet at δ 2.68 in ^{1}H NMR spectrum which assigns it to be CH_2 of the SC_2H_5 group, carbon signal at δ 37.17 shows correlation with two double doublets at δ 2.90 and 2.98 in ^{1}H NMR spectrum, carbon signal at δ 47.73 shows correlation with doublet at δ 2.52 in ^{1}H NMR spectrum, carbon signal at δ 78.29 shows correlation with multiplet at δ 4.79–4.88 in ^{1}H NMR spectrum, carbon signal at δ 88.85 shows correlation with signal at δ 5.31 in ^{1}H NMR spectrum and therefore confirm the assignments of hydrogens and carbons in this compound; NOE experiments: irradiation of singlet at δ 5.31 (2-H) shows NOE with signals at δ 7.35, 6.96 (ArHs), 2.68 (SCH_2), 2.52 (4-Hs) and no NOE has been observed with the signal at δ 4.79–4.88 (5-H); *m/z* (FAB) 382.9 (M^+).

(2*R, 3*S**, 5*S**)-2,3-Bis-(4-fluorophenyl)-5-ethylsulfanyl-methyl tetrahydrofuran-3-ol (41)**

According to the preparation of **39**, **41** was obtained from **31B** as thick liquid. Yield 79%; (Found: C, 65.02; H, 5.53; S, 9.09. $C_{19}H_{20}F_2O_2S$ requires C, 65.12; H, 5.75; S, 9.15%). ν_{max} ($CHCl_3$)/cm^{-1}: 3431 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.30 (3H, t, J = 7.5 Hz, CH_3), 1.73 (1H, bs, OH, exchanges with D_2O), 2.53 (2H, d, J = 7.5 Hz, 4-H), 2.68 (2H, q, J = 7.2 Hz, SCH_2), 2.92 (1H, dd, ^2J = 13.5 Hz, ^3J = 4.8 Hz, CH_2S), 2.98 (1H, dd, ^2J = 13.5 Hz, ^3J = 5.7 Hz, CH_2S), 4.79–4.88 (1H, m, 5-H), 5.33 (1H, s, 2-H), 6.89–7.09 (6H, m, ArH), 7.38 (2H, two doublets, ^3J = 5.4 Hz, ^3J = 5.1 Hz, ArH); δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 14.97 (+ve, CH_3), 27.16 (−ve, SCH_2), 37.23 (−ve, CH_2S), 47.70 (−ve, C-4), 78.15 (+ve, C-5), 82.81 (ab, C-3), 88.87 (+ve, C-2), 115.20 (+ve, d, $J_{C\text{-}F(ortho)}$ = 21.00 Hz, ArCH), 115.24 (+ve, d, $J_{C\text{-}F(ortho)}$ = 21.07 Hz, ArCH), 127.05 (+ve, d, $J_{C\text{-}F(meta)}$ = 8.02 Hz, ArCH),

128.34 (+ve, d, $J_{C\text{-}F(meta)} = 8.02$ Hz, ArCH), 131.03 (ab, d, $J_{C\text{-}F(para)} = 3.15$ Hz, C), 137.19 (ab, d, $J_{C\text{-}F(para)} = 3.08$ Hz, ArC), 162.02 (ab, d, $J_{C\text{-}F} = 244.2$ Hz, ArC), 162.63 (ab, d, $J_{C\text{-}F} = 244.8$ Hz, ArC); *m/z* [MALDI (TOF)] 373 ($M^+ + Na^+$), 389 ($M^+ + K^+$).

(2*R, 3*S**, 5*S**)-5-Ethylsulfanylmethyl-2,3-bis-(4-methoxyphenyl)-tetrahydrofuran-3-ol (42)**

According to the preparation of **39**, **42** was obtained from **32B** as thick liquid. Yield 75%; (Found: C, 67.23; H, 6.97; S, 8.44. $C_{21}H_{26}O_4S$ requires C, 67.35; H, 7.00; S, 8.56%). ν_{max} ($CHCl_3$)/cm^{-1}: 3458 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.29 (3H, t, $J = 7.5$ Hz, CH_3), 1.76 (1H, bs, OH, exchanges with D_2O), 2.47 (1H, dd, $^2J = 12.9$ Hz, $^3J = 9.0$ Hz, 4-H), 2.53 (1H, dd, $^2J = 12.9$ Hz, $^3J = 6.3$ Hz, 4-H), 2.68 (2H, q, $J = 7.5$ Hz, SCH_2), 2.91 (1H, dd, $^2J = 13.8$ Hz, $^3J = 5.4$ Hz, CH_2S), 2.96 (1H, dd, $^2J = 13.5$ Hz, $^3J = 5.7$ Hz, CH_2S), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.76–4.85 (1H, m, 5-H), 5.31 (1H, s, 2-H), 6.78 (2H, d, $J = 9.0$ Hz, ArH), 6.88 (2H, d, $J = 9.0$ Hz, ArH), 6.98 (2H, d, $J = 8.4$ Hz, ArH), 7.32 (2H, d, $J = 8.7$ Hz, ArH); δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 14.95 (+ve, CH_3), 27.01 (−ve, SCH_2), 37.22 (−ve, CH_2S), 47.54 (−ve, C-4), 55.11 (+ve, OCH_3), 55.17 (+ve, OCH_3), 78.01 (+ve, C-5), 82.68 (ab, C-3), 89.03 (+ve, C-2), 113.56 (+ve, ArCH), 113.58 (+ve, ArCH), 126.46 (+ve, ArCH), 127.36 (ab, ArC), 127.87 (+ve, ArCH), 133.74 (ab, ArC), 158.58 (ab, ArC), 159.38 (ab, ArC); *m.z* (FAB) 357 (M^+-OH).

(2*R, 3*S**, 5*S**)-5-Ethylsulfanylmethyl-2,3-bis-(4-methanesulfonylphenyl)-tetrahydrofuran-3-ol (43)**

According to the preparation of **39**, **43** was obtained from **33B** as white solid, mp 123 °C. Yield 77%; (Found: C, 53.44; H, 6.02; S, 20.26. $C_{21}H_{26}O_6S_3$ requires C, 53.59; H, 5.57; S, 20.44%). ν_{max} ($CHCl_3$)/cm^{-1}: 3400 (OH), 1300 (S=O); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.31 (3H, t, $J = 7.5$ Hz, CH_3), 1.77 (1H, bs, OH, exchanges with D_2O), 2.58 (1H, dd, $^2J = 13.2$ Hz, $^3J = 6.3$ Hz, 4-H), 2.67 (1H, dd, $^2J = 13.2$ Hz, $^3J = 9.9$ Hz, 4-H), 2.69 (2H, q, $J = 7.5$ Hz, SCH_2), 2.93 (1H, dd, $^2J = 13.5$ Hz, $^3J = 4.5$ Hz, CH_2S), 3.02 (4H, m, 3H of SO_2CH_3 + 1H of CH_2S), 3.09 (3H, s, SO_2CH_3), 4.92–5.44 (1H, m, 5-H), 5.44 (1H, s, 2-H), 7.21 (2H, d, $J = 8.4$ Hz, ArH), 7.68 (2H, d, $J = 8.4$ Hz, ArH), 7.79 (2H, d, $J = 8.1$ Hz, ArH), 7.94 (2H, d, $J = 8.7$ Hz, ArH); δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 14.97 (+ve, CH_3), 27.27 (−ve, SCH_2), 37.03 (−ve, CH_2S), 44.32 (+ve, SO_2CH_3), 44.39 (+ve, SO_2CH_3), 48.21 (−ve, C-4), 78.48 (+ve, C-5), 83.45 (ab, C-3), 88.94 (+ve, C-2), 126.55 (+ve, ArCH), 127.10 (+ve, ArCH), 127.59 (+ve, ArCH), 127.65 (+ve, ArCH), 139.67 (ab, ArC), 140.08 (ab, ArC), 142.01 (ab, ArC), 147.54 (ab, ArC); *m/z* (FAB) 493.1 ($M^+ + Na^+$), 509.1 ($M^+ + K^+$).

(2*R, 3*S**, 5*S**)-5-Ethylsulfanylmethyl-3-(4-methylsulfanyl-phenyl)-2-phenyltetrahydrofuran-3-ol (44)**

According to the preparation of **39**, **44** was obtained from **34B** as thick liquid. Yield 77%; (Found: C, 66.58; H, 6.69; S, 17.66. $C_{20}H_{24}O_2S_2$ requires C, 66.63; H, 6.71; S, 17.79%). ν_{max} ($CHCl_3$)/cm^{-1}: 3415 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.29 (3H, t, $J = 7.2$ Hz, CH_3), 1.79 (1H, bs, OH, exchanges with D_2O), 2.48 (3H, s, SCH_3), 2.50 (2H, dd, $^2J = 14.1$ Hz, $^3J = 7.2$ Hz, 4-H), 2.68 (2H, q, $J = 7.2$ Hz, SCH_2), 2.93 (1H, d, $J = 2.7$ Hz, CH_2S), 2.95 (1H, d, $J = 3.6$ Hz, CH_2S), 4.79–4.88 (1H, m, 5-H), 5.37 (1H, s, 2-H), 7.03–7.06 (2H, m, ArH), 7.21–7.25 (5H, m, ArH), 7.33 (2H, d, $J = 8.7$ Hz, ArH); δ_C (75 MHz, $CDCl_3$, Me_4Si): 14.94 (+ve, CH_3), 15.54 (+ve, SCH_3), 27.04 (−ve, SCH_2), 37.13 (−ve, CH_2S), 47.79 (−ve, C-4), 78.29 (+ve, C-5), 82.96 (ab, C-3), 89.29 (+ve, C-2), 125.83 (+ve, ArCH), 126.16 (+ve, ArCH), 126.56 (+ve, ArCH), 128.17 (+ve, ArCH), 128.22 (+ve, ArCH), 135.43 (ab, ArC), 137.34 (ab, ArC), 138.49 (ab, ArC); *m/z* [MALDI (TOF)] 383.69 ($M^+ + Na^+$), 399.69 ($M^+ + K^+$).

(2*R, 3*S**, 5*S**)-5-Ethylsulfanylmethyl-3-(4-methanesulfonyl-phenyl)-2-phenyltetrahydrofuran-3-ol (45)**

According to the preparation of **39**, **45** was obtained from **35B** as white solid, mp 115 °C. Yield 78%; (Found: C, 61.26; H, 6.04; S, 16.22. $C_{20}H_{24}O_4S_2$ requires C, 61.20; H, 6.16; S, 16.34%). ν_{max} ($CHCl_3$)/cm^{-1}: 3500 (OH), 1320 (S=O); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.31 (3H, t, $J = 7.5$ Hz, CH_3), 1.61 (1H, bs, OH, exchanges with D_2O), 2.58 (2H, dd, $^2J = 9.3$ Hz, $^3J = 6.6$ Hz, 4-H), 2.70 (2H, q, $J = 7.2$ Hz, SCH_2), 2.93 (1H, dd, $^2J = 13.8$ Hz, $^3J = 4.2$ Hz, CH_2S), 3.03 (1H, dd, $^2J = 13.5$ Hz, $^3J = 6.0$ Hz, CH_2S), 3.09 (3H, s, SO_2CH_3), 4.87–4.92 (1H, m, 5-H), 5.46 (1H, s, 2-H), 6.98–7.01 (2H, m, ArH), 7.24–7.01 (3H, m, ArH), 7.68 (2H, d, $J = 8.7$ Hz, ArH), 7.95 (2H, d, $J = 8.7$ Hz, ArH); Decoupling of multiplet at δ 4.87–4.92 converts dd's at δ 2.93, 3.03 and 2.58 into doublets and can be assigned as 5-H; δ_C (75.4 MHz, $CDCl_3$, Me_4Si): 14.97 (+ve, CH_3), 27.18 (−ve, SCH_2), 37.05 (−ve, CH_2S), 44.43 (+ve, SO_2CH_3), 48.01 (−ve, C-4), 78.47 (+ve, C-5), 83.07 (ab, C-3), 89.60 (+ve, C-2), 126.33 (+ve, ArCH), 126.58 (+ve, ArCH), 127.41 (+ve, ArCH), 128.53 (+ve, ArCH), 128.59 (+ve, ArCH), 134.76 (ab, ArC), 139.34 (ab, ArC), 148.45 (ab, ArC); *m/z* (FAB) 392.9 (M^++1), 375 (M^+-OH).

(2*R, 3*S**, 5*S**)-5-Ethylsulfanylmethyl-3-(4-methoxyphenyl)-tetrahydrofuran-3-ol (46)**

According to the preparation of **39**, **46** was obtained from **36B** as thick liquid. Yield 73%; (Found: C, 69.58; H, 6.99; S, 9.17. $C_{20}H_{24}O_3S$ requires C, 69.73; H, 7.02; S, 9.31%). ν_{max} ($CHCl_3$)/cm^{-1}: 3448 (OH); δ_H (300 MHz, $CDCl_3$, Me_4Si): 1.29 (3H, t, $J = 7.5$ Hz, CH_3), 1.75 (1H, bs, OH, exchanges with D_2O), 2.50 (2H, d, $J = 6.9$ Hz, 4-H), 2.68 (2H, q, $J = 7.5$ Hz, SCH_2), 2.88–2.99 (2H, two double doublets, $^2J = 13.8$ Hz, $^3J = 6.0$ Hz, $^3J = 5.1$ Hz, CH_2S), 3.81 (3H, s, OCH_3), 4.78–4.87 (1H, m, 5-H), 5.36 (1H, s, 2-H), 6.88 (2H, d, $J = 9.0$ Hz, ArH), 7.03–7.06 (2H, m, ArH), 7.22–7.25 (3H, m, ArH), 7.32 (2H, d, $J = 9.0$ Hz, ArH); δ_C (75 MHz, $CDCl_3$, Me_4Si): 14.95 (+ve, CH_3), 27.02 (−ve, SCH_2), 37.19 (−ve, CH_2S), 47.77 (−ve, C-4), 55.17 (+ve, OCH_3), 78.21 (+ve, C-5), 82.91 (ab, C-3), 89.26 (+ve, C-2), 113.59 (+ve, ArCH), 126.46 (+ve, ArCH), 126.64 (+ve, ArCH), 128.07 (+ve, ArCH), 128.15 (+ve, ArCH), 133.62 (ab, ArC), 133.65 (ab, ArC), 158.62 (ab, ArC); *m/z* (FAB) 327 (M^+-OH).

***In-vitro* COX-1, COX-2 inhibitory activities**

In-vitro COX-1, COX-2 inhibiting activities of these compounds have been evaluated using 'COX (ovine) inhibitor screening assay' kit with 96 well plates. Both ovine COX-1 and COX-2 enzymes were included. This screening assay directly measures $PGF_{2\alpha}$ produced by $SnCl_2$ reduction of COX-derived PGH_2. COX-1, COX-2 initial activity tubes were prepared taking 950 µl of reaction

buffer, 10 μl of heme, 10 μl of COX-1 and COX-2 enzymes in respective tubes. Similarly, COX-1, COX-2 inhibitor tubes were prepared by adding 20 μl of inhibitor (compound under test) in each tube in addition to the above ingredients. The background tubes correspond to inactivated COX-1 and COX-2 enzymes obtained after keeping the tubes containing enzymes in boiling water for 3 min. Reactions were initiated by adding 10 μl of arachidonic acid in each tube and quenched with 50 μl of 1M HCl. PGH_2 thus formed was reduced to $PGF_{2\alpha}$ by adding 100 μl of $SnCl_2$. The prostaglandin produced in each well was quantified using broadly specific prostaglandin antiserum that binds with major prostaglandins and reading the 96 well plate at 405 nm. The wells of the 96 well plate showing low absorption at 405 nm indicate the low level of prostaglandins in these wells and hence less activity of the enzyme. Therefore, the COX inhibitory activities of the compounds could be quantified from the absorption values of different wells of the 96 well plate. The results of these studies have been represented in terms of the percentage inhibition of COX-1 and COX-2 enzymes.

In-vitro growth inhibitory activities

The detailed evaluations for growth inhibitory activities at 59 human tumor cell lines were carried out by screening unit of NCI at NIH Bethesda, USA. The compounds were evaluated at five concentrations *viz*. 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M 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, total growth inhibition (TGI) and LC_{50} indicating the net loss of cells following treatment.

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