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Synthesis and biological evaluation of new 4-carboxyl quinoline derivatives as cyclooxygenase-2 inhibitors

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ABSTRACT

A group of 4-carboxyl quinoline derivatives possessing a methylsulfonyl COX-2 pharmacophore at the *para* position of the C-2 phenyl ring were designed and synthesized as selective COX-2 inhibitors. In vitro COX-1/COX-2 structure–activity relationships were determined by varying the substituents on the C-7 and C-8 quinoline ring. Among the 4-carboxyl quinolines, 7,8,9,10-tetrahydro-2-(4-(methyl sulfonyl)phenyl)benzo[*h*]quinoline-4-carboxylic acid (**9e**) was identified as potent and high selective COX-2 inhibitor (COX-2 IC_{50} = 0.043 μM; selectivity index > 513) that was more potent than the reference drug celecoxib (COX-2 IC_{50} = 0.060 μM; SI = 405). A molecular modeling study where **9e** was docked in the binding site of COX-2 showed that the *p*-$MeSO_2$ substituent on the C-2 phenyl ring is oriented in the vicinity of the COX-2 secondary pocket (Arg513, Phe518 and Val523) and the carboxyl group can interact with Arg120. The structure activity data acquired indicate that the presence of lipophilic substituents on the C-7 and C-8 quinoline ring is important for COX-2 inhibitory activity.

1. Introduction

The clinical use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen for the treatment of inflammation and pain is often accompanied by adverse gastrointestinal (GI) effects. Their anti-inflammatory activity is due to inhibition of cyclooxygenases (COXs), which catalyze the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs).[1,2] COX is a membrane-bound heme protein which exists at least in two isoforms, a constitutive form (COX-1) and an inducible form (COX-2). The COX-1 enzyme is responsible for maintaining homeostasis whereas COX-2 induces inflammatory conditions. Because COX-1 is involved in the maintenance of the GI tract, NSAIDs which are inhibitors of both COX-1 and COX-2 have been found to cause side effects associated with GI ulcers.[3–5] Thus it was though that more selective COX-2 inhibitors would have reduced side effects. Moreover, recent studies indicating the place of COX-2 inhibitors in cancer chemotherapy[6] and neurological diseases such as Parkinson[7] and Alzheimer's[8] diseases still continues to attract investigations on development of COX-2 inhibitors. Research attempts in the discovery of selective COX-2 inhibitors have produced many classes of compounds such as coxibs possessing desired selectivity. The coxibs (e.g., celecoxib and rofecoxib, Fig. 1)[9,10] for treating pain and inflammation associated with arthritis have been shown to be well tolerated and reduced GI side effects. All coxibs possess 1,2-diarylsubstitution on a central hetero or carbocyclic ring system with a characteristic sulfonyl group on one of the aryl rings that plays a crucial role on COX-2 selectivity.[11] The recent market withdrawal of some coxibs such as rofecoxib and valdecoxib due to their adverse cardiovascular side effects[12,13] clearly delineates the need to explore and evaluate alternative templates with COX-2 inhibitory activity. In addition, some studies have suggested that rofecoxib's adverse cardiac events may not be a class effect but rather an intrinsic chemical property related to its metabolism.[14] For this reason novel scaffolds with high selectivity for COX-2 inhibition need to be found and evaluated for their anti-inflammatory effects. Recently, we reported several investigations describing the design, synthesis and a molecular modeling study for a group of 2-phenyl-1*H*-indoles possessing a methylsulfonyl COX-2 pharmacophore at the *para*-position of phenyl ring in conjunction with an 1*H*-indole ring having different substituents at C-5 position.[15] For example, 5-methoxy-2-(4-(methylsulfonyl) phenyl)-1*H*-indole (see structure **1** in Fig. 1) exhibited high selective COX-2 inhibition (COX-2 IC_{50} = 0.080 μM; SI = 291.2). On the other hand, it is well known that the carboxyl group of NSAIDs has a key role for binding to COX enzyme through interaction with Arg120 of active site.[16] Accordingly, we now describe the synthesis

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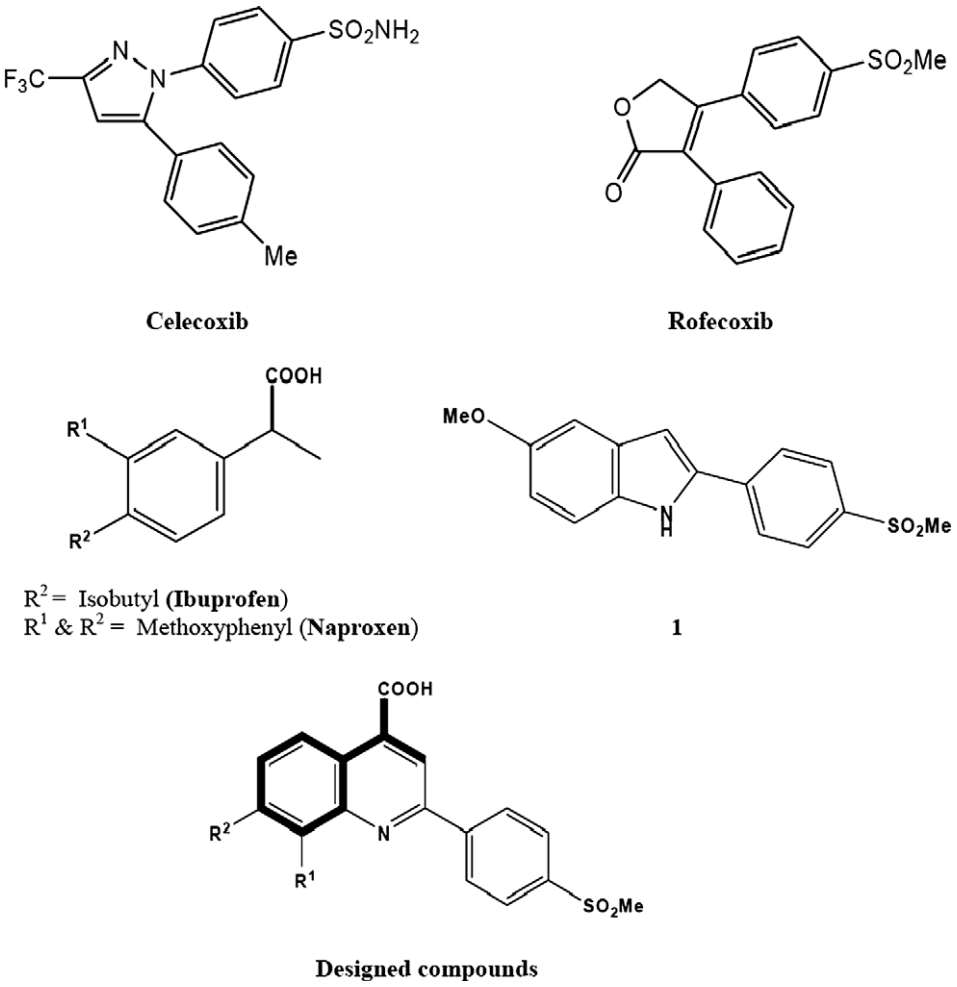


Figure 1. Some representative examples of COXIBs (celecoxib and rofecoxib), NSAIDs (ibuprofen and naproxen), 2-phenyl-1*H*-indole lead compound and our quinoline scaffolds.

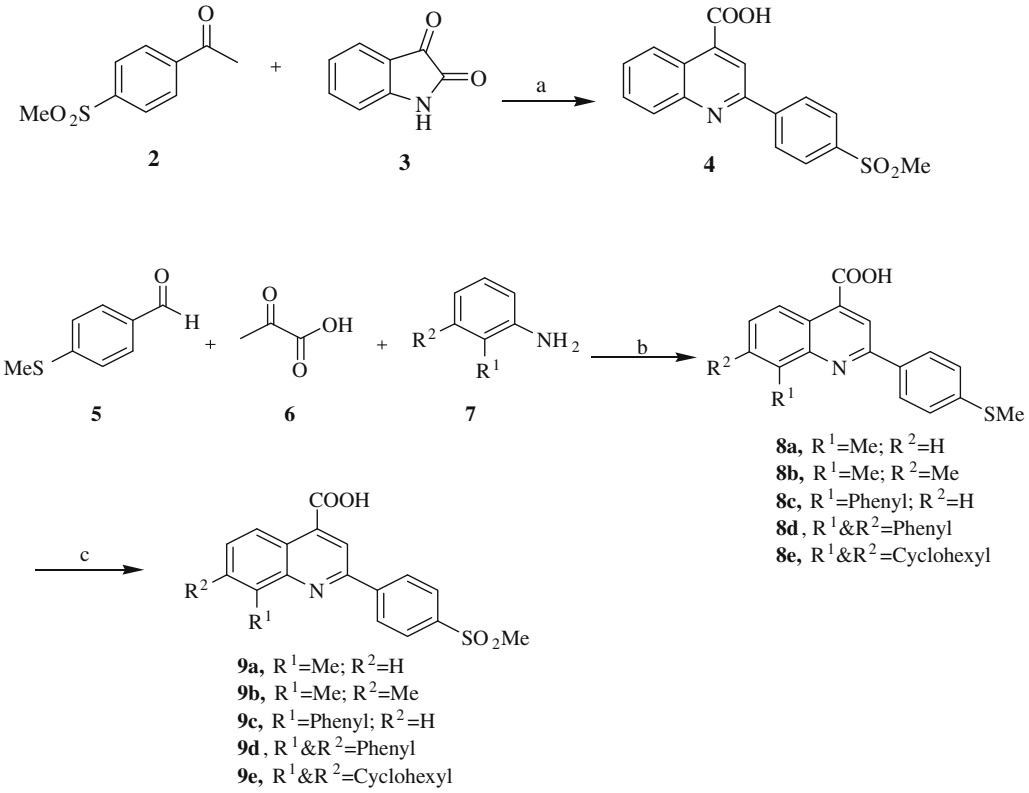
and biological evaluation of a group of 4-carboxyl quinoline derivatives possessing a methylsulfonyl COX-2 pharmacophore at the *para* position of the C-2 phenyl ring in conjunction with various substituents at C-7 and C-8 quinoline ring. In these designed compounds we utilized certain feature from NSAIDs such as aryl carboxylic acid fragment in ibuprofen and naproxen, and quinoline ring instead of 1*H*-indole ring in the our previously reported COX-2 inhibitors.

2. Chemistry

A one-step Doebner reaction was used to prepare the target 2-(4-(methylsulfonyl)phenyl)-7,8-substituted-quinoline-4-carboxylic acid derivatives **9a–e**. As illustrated in Scheme 1, 4-(methylthio) benzaldehyde **5**, pyruvic acid **6** and an appropriate amine **7** were heated in ethanol to provide 4-carboxy quinolines **8a**–**e** (16–27%)[17] and then oxidation of the methylthio substituent to a methylsulfonyl substituent was carried out using Oxone®.[18] However, the well known Doebner-type synthesis of quinolines did not yield the expected 2-(4-(methylthio)phenyl)-quinoline-4-carboxylic acid which is required for preparation of 2-(4-(methylsulfonyl)phenyl)-quinoline-4-carboxylic acid **4**. This result was agreement to similar previously reported works[19] in which aniline was used as amine in Doebner reaction. Therefore, the desired quinoline derivative **4** was prepared using Pfitzinger reaction.[20] Accordingly, 4-(methylsulfonyl)acetophenone **2**[21] was reacted with isatin **3** in alkaline ethanol to provide **4** (yield: 43%). The purity of all products was determined by thin layer chromatography using several solvent systems of different polarity. All compounds were pure and stable. The compounds were characterized by ^{1}H nuclear magnetic resonance, infrared, mass spectrometry and CHN analysis.

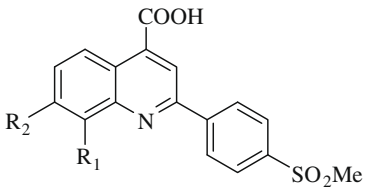
3. Results and discussion

A group of 4-carboxyl quinolines (**4**, **9a**–**e**), possessing a *para*-methylsulfonyl substituent on the C-2 phenyl ring were synthesized. In this study, the different substituents on the C-7 and C-8 quinoline ring were varied to determine the combined effects of steric and lipophilic substituent properties upon COX-1 and COX-2 inhibitory potency and selectivity. SAR data (IC_{50} values) acquired by determination of the in vitro ability of the title compounds to inhibit the COX-1 and COX-2 isozymes showed that the COX inhibition was sensitive to the lipophilic nature of substituents. As shown in Table 1, our results showed that the increase of lipophilic properties of substituents on the C-7 and C-8 quinoline ring increased COX-2 inhibitory potency and selectivity. The relative COX-2 potency, and COX-2 selectivity profiles for the 4-carboxyl quinoline derivatives, with respect to the C-7 and C-8 substituents was **9e** > **9d** > **9c** > **9b** > **9a** > **4**. Accordingly, compound **9c** showed less selectivity and potency for COX-2 isozyme compared with compounds **9d** that may be also explained by steric



Scheme 1. Reagents and conditions: (a) EtOH, 33% KOH, reflux, 48 h; (b) EtOH, reflux, 12 h; (c) oxone, THF/H_2O, 25 °C, 12 h.

Table 1
In vitro COX-1 and COX-2 enzyme inhibition assay data for 4-carboxyl quinoline derivatives **6a–f**



Compound	R^1	R^2	IC_{50}[a] (μM)		Selectivity index (SI)[b]
			COX-1	COX-2	
4	H	H	13.4	0.091	147.2
9a	Me	H	14.2	0.086	165.1
9b	Me	Me	14.5	0.075	193.3
9c	phenyl	H	14.7	0.071	207.0
9d	Phenyl		17.6	0.054	325.9
9e	Cyclohexyl		22.1	0.043	513.9
Celecoxib			24.3	0.060	405

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit and the deviation from the mean is <10% of the mean value.
[b] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).

parameter. However, among the 4-carboxyl quinoline derivatives, compound **9e** possessing an unsaturated cyclohexyl ring attached to C-7 and C-8 quinoline ring exhibited highest COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.043 μM; SI > 513) that was more potent than the reference drug celecoxib (COX-2 IC_{50} = 0.060 μM; SI = 405).

It has been reported that replacement of His513 in COX-1 by Arg513 in COX-2 plays a key role in the hydrogen-bond network of the COX-2 binding site. Access of ligands to the secondary

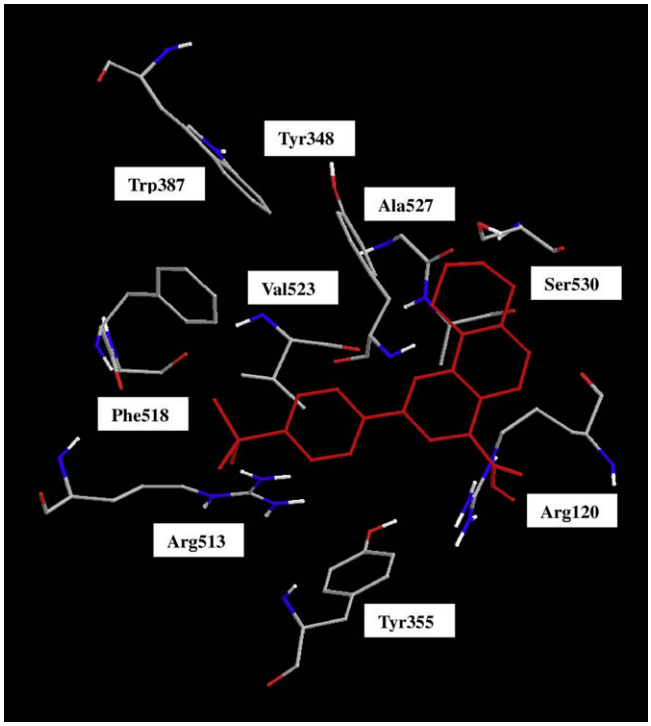


Figure 2. Docking 7,8,9,10-tetrahydro-2-(4-(methylsulfonyl) phenyl) benzo[*h*]quinoline-4-carboxylic acid (**9e**) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

pocket of COX-2 and interaction of Arg513 with the bound drug is a requirement for time-dependent inhibition of COX-2.[22] The binding interactions of the most potent and selective COX-2 inhibitor compound (**9e**) within the COX-2 binding site were investigated. The most stable enzyme–ligand complex of 7,8,9,10-tetrahydro-2-(4-(methylsulfonyl) phenyl) benzo[*h*] quinoline-4-carboxylic acid possessing a $MeSO_2$ COX-2 pharmacophore at *para* position of C-2 phenyl ring within the COX-2 binding site (Fig. 2) shows that the *p*-$MeSO_2$–phenyl moiety is oriented towards the COX-2 secondary pocket (Val523, Phe518 and Arg513). One of the *O*-atoms of *p*-$MeSO_2$ substituent forms a hydrogen binding interaction with amino group of Arg513 (distance = 3.9 Å) whereas the other *O*-atom is about 5.1 Å away from N*H*$_2$ of this amino acid. In addition, a hydrogen bonding interaction may form between the nitrogen atom of quinoline ring and N*H* of Ala527 (distance < 6 Å). Also, the carboxylic group of the quinoline ring is very close to amino group of Arg120 (distance < 5 Å) which can explain the high potency of compound **9e**. These observations together with experimental results provide a good explanation for design of potent and selective COX-2 inhibitors possessing 4-carboxyl quinoline framework.

4. Conclusions

This study indicates that (i) the 4-carboxyl quinoline moiety is a suitable scaffold (template) to design COX-1/-2 inhibitors, (ii) in this class of compounds COX-1/-2 inhibition is sensitive to the lipophilic nature of the C-7 and C-8 quinoline substituents, and (iii) 7,8,9,10-tetrahydro-2-(4-(methylsulfonyl)phenyl)benzo[*h*] quinoline-4-carboxylic acid (**9e**) exhibited high COX-2 inhibitory potency and selectivity.

5. Experimental

All chemicals and solvents used in this study were purchased from Merck AG and Aldrich Chemical. Melting points were determined with a Thomas–Hoover capillary apparatus. Infrared spectra were acquired using a Perkin Elmer Model 1420 spectrometer. A Bruker FT-500 MHz instrument (Brucker Biosciences, USA) was used to acquire ^{1}H NMR spectra with TMS as internal standard. Chloroform-*d* and DMSO-d_6 were used as solvents. Coupling constant (*J*) values are estimated in hertz (Hz) and spin multiples are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Low-resolution mass spectra were acquired with a MAT CH5/DF (Finnigan) mass spectrometer that was coupled online to a Data General DS 50 data system. Electron-impact ionization was performed at an ionizing energy of 70 eV with a source temperature of 250 °C. Microanalyses, determined for C and H, were within ±0.4% of theoretical values.

5.1. Preparation of 2-(4-(methylsulfonyl)phenyl)-quinoline-4-carboxylic acid (4)

A mixture of 0.37 g (2.5 mmol) of isatin **2**, 10 ml of 33% potassium hydroxide in diluted alcohol solution, and 0.5 g (2.5 mmol) of 4-(methylsulfonyl) acetophenone **3** were stirred and heated under reflux for 48 h. After evaporation of solvent, the residue was acidified with acetic acid 10% and filtered. The precipitated product was washed with acetic acid 10%, ethanol and hexane and crystallized in methanol. Yield: 43%; cream crystalline powder; mp = 320 °C; IR (KBr): ν (cm^{-1}) 3360–2700 (OH), 1710 (C=O), 1310,1160 (SO_2); ^{1}H NMR (DMSO-d_6): δ ppm 3.26 (s, 3H, SO_2Me), 7.72 (t, 1H, quinoline H_6), 7.86 (t, 1H, quinoline H_7), 8.07 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.4 Hz), 8.16 (d, 1H, quinoline H_8, J = 8.3 Hz), 8.50 (s, 1H, quinoline H_3), 8.52 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.4 Hz), 8.63 (d, 1H, quinoline H_5, J = 8.4 Hz), 13.77 (s, 1H, COOH); MS: *m*/*z* (%) 327.6 (M^+, 100), 249.0 (80), 202.2 (30), 191.8 (20), 127.9 (10). Anal. Calcd for $C_{17}H_{13}NO_4S$: C, 62.37; H, 4.00; N, 4.28. Found: C, 62.42; H, 3.71; N, 4.39.

5.2. General procedure for preparation of 2-(4-(methylthio)phenyl)-7,8-substituted-quinoline-4-carboxylic acid (8a–e)

A solution of 4-(methylthio)benzaldehyde **5** (1.44 g, 9.45 mmol) and pyrrovic acid **6** (1.26 g, 14.3 mmol) in ethanol (5 ml) was heated for 15 min, then an appropriate amine **7** (9.45 mmol) was added and the mixture was refluxed overnight. After cooling, the produced precipitate was filtered and washed with ethanol, benzene and hexane and recrystallized in methanol (yields: 16–27%). The physical and spectral data for **8a–e** are listed below.

5.2.1. 8-Methyl-2-(4-(methylthio)phenyl)quinoline-4-carboxylic acid (8a)

Yield: 16%; cream crystalline powder; mp = 217–219 °C; IR (KBr): ν (cm^{-1}) 3300–2400 (OH), 1700 (C=O); ^{1}H NMR (DMSO-d_6): δ ppm 2.52 (s, 3H, SCH_3), 2.79 (s, 3H, CH_3), 7.40 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.5 Hz), 7.51 (m, 1H, quinoline H_6), 7.65 (d, 1H, quinoline H_7, J = 6.9 Hz), 8.25 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.5 Hz), 8.38 (m, 2H, quinoline H_3 and H_5), 13.95 (s, 1H, COOH); Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.62; H, 4.54; N, 4.32.

5.2.2. 7,8-Dimethyl-2-(4-(methylthio)phenyl)quinoline-4-carboxylic acid (8b)

Yield: 27%; pale yellow crystalline powder; mp = 269–270 °C; IR (KBr): ν (cm^{-1}) 3220–2360 (OH), 1700 (C=O); ^{1}H NMR (DMSO-d_6): δ ppm 2.44 (s, 3H, C7–CH_3), 2.51 (s, 3H, SCH_3), 2.73 (s, 3H, C8–CH_3), 7.38 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.5 Hz), 7.43 (d, 1H, quinoline H_6, J = 8.7 Hz), 8.23 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.5 Hz), 8.30 (m, 2H, quinoline H_3 and H_5), 13.79 (s, 1H, COOH); Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33. Found: C, 70.22; H, 5.66; N, 4.11.

5.2.3. 2-(4-(Methylthio)phenyl)-8-phenyl-quinoline-4-carboxylic acid (8c)

Yield: 16%; yellow crystalline powder; mp = 259–260 °C; IR (KBr): ν (cm^{-1}) 3345–2500 (OH), 1700 (C=O); ^{1}H NMR (DMSO-d_6): δ ppm 2.49 (s, 3H, SCH_3), 7.34 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.4 Hz), 7.42 (t, 1H, quinoline H_6, J = 7.4), 7.50 (d, 2H, phenyl H_2 and H_6, J = 7.5 Hz), 7.72 (m, 3H, phenyl H_3–H_5), 7.82 (d, 1H, quinoline H_7, J = 6.8, CH_2), 8.10 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.4 Hz), 8.42 (s, 1H, quinoline H_3), 8.56 (d, 1H, quinoline H_5, J = 8.2 Hz), 13.96 (s, 1H, COOH); Anal. Calcd for $C_{23}H_{17}NO_2S$: C, 74.37; H, 4.61; N, 3.77. Found: C, 74.65; H, 4.27; N, 3.61.

5.2.4. 2-(4-(Methylthio)phenyl)benzo[*h*]quinoline-4-carboxylic acid (8d)

Yield: 17%; orange crystalline powder; mp: 275–276 °C; IR (KBr): ν (cm^{-1}) 3300–2800 (OH), 1700 (C=O), ^{1}H NMR (DMSO-d_6): δ ppm 2.54 (s, 3H, SCH_3), 7.44 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.5 Hz), 7.76-7.79 (m, 2H, benzoquinoline H_8 and H_9), 7.99 (d, 1H, benzoquinoline H_7, J = 9.2 Hz), 8.02 (d, 1H, benzoquinoline H_6, J = 8.9 Hz), 8.37 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.5 Hz), 8.47 (d, 1H, benzoquinoline H_{10}, J = 9.1 Hz), 8.5 (s, 1H, benzoquinoline H_3), 9.34 (d, 1H, benzoquinoline H_5, J = 9.2 Hz), 13.98 (s, 1H, COOH); Anal. Calcd for $C_{21}H_{15}NO_2S$: C, 73.02; H, 4.38; N, 4.05. Found: C, 73.36; H, 4.71; N, 3.81.

5.2.5. 7,8,9,10-Tetrahydro-2-(4-(methylthio)phenyl)benzo[*h*]quinoline-4-carboxylic acid (8e)

Yield: 27%; cream crystalline powder; mp = 249–251 °C; IR (KBr): ν (cm^{-1}) 3320–2850 (OH), 1695 (C=O), ^{1}H NMR (DMSO-d_6): δ ppm 1.79–1.86 (m, 4H, CH_2), 2.5 (s, 3H, SCH_3), 2.85 (m, 2H, CH_2), 3.28 (m, 2H, CH_2), 7.31 (d, 1H, tetrahydrobenzoquinoline H_6, J = 8.8 Hz), 7.36–7.38 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.5 Hz), 8.21 (d, 2H, 4-methylthiophenyl H_2 and H_6, J = 8.5 Hz), 8.27 (d, 1H, tetrahydrobenzoquinoline H_5, J = 8.8 Hz), 8.31 (s, 1H, tetrahydrobenzoquinoline H_3), 13.78 (s, 1H, COOH); Anal. Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01. Found: C, 72.40; H, 5.75; N, 3.84.

5.3. General procedure for preparation of 2-(4-(methylsulfonyl)phenyl)-7,8-substituted-quinoline-4-carboxylic acid (9a–e)

One gram of 2-(4-(methylthio)phenyl)-7,8-substituted quinoline-4-carboxylic acid **8a–e** dissolved in 10 ml of THF and 5 g oxone in THF/water (20 ml) was added. The mixture was stirred at room temperature overnight. After evaporation of THF, the residue was extracted with ethyl acetate and dried with sodium sulfate and then evaporated, the product was recrystallized in ethanol (yields: 40–89%). The physical and spectral data for **9a–e** are listed below.

5.3.1. 8-Methyl-2-(4-(methylsulfonyl)phenyl)quinoline-4-carboxylic acid (9a)

Yield: 69%; cream crystalline powder; mp = 262 °C; IR (KBr): ν (cm^{-1}) 3370–2480 (OH), 1690 (C=O), 1300, 1150 (SO_2); ^{1}H NMR (DMSO-d_6): δ ppm 2.80 (s, 3H, CH_3), 3.26 (s, 3H, SO_2Me), 7.58 (t, 1H, quinoline H_6), 7.71 (d, 1H, quinoline H_7, J = 6.8 Hz), 8.07 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.5 Hz), 8.43 (d, 1H, quinoline H_5, J = 8.5 Hz), 8.49 (s, 1H, quinoline H_3), 8.54 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.5 Hz), 13.96 (s, 1H, COOH); MS: m/z (%) 341.6 (M^+, 100), 261.9 (30), 217.0 (20); Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10. Found: C, 63.62; H, 4.70; N, 4.31.

5.3.2. 7,8-Dimethyl-2-(4-(methylsulfonyl)phenyl)quinoline-4-carboxylic acid (9b)

Yield: 83%; cream crystalline powder; mp = 266–267 °C; IR (KBr): ν (cm^{-1}) 3220–2370 (OH), 1700 (C=O), 1300, 1140 (SO_2); ^{1}H NMR (DMSO-d_6): δ ppm 2.76 (s, 3H, quinoline, C7–CH_3), 3.26 (s, 6H, SO_2Me and C8–CH_3), 7.51 (d, 1H, quinoline H_6, J = 8.7 Hz), 8.06 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.5 Hz), 8.33 (d, 1H, quinoline H_5, J = 8.8 Hz), 8.42 (s, 1H, quinoline H_3), 8.53 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.5 Hz), 13.95 (s, 1H, COOH); MS: m/z (%) 355.7 (M^+, 100), 277.1 (20), 230.9 (20); Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.52; H, 4.50; N, 4.21.

5.3.3. 2-(4-(Methylsulfonyl)phenyl)-8-phenyl-quinoline-4-carboxylic acid (9c)

Yield: 40%; yellow crystalline powder; mp = 272–273 °C; IR (KBr): ν (cm^{-1}) 3250–2380 (OH), 1680 (C=O), 1300, 1140 (SO_2), ^{1}H NMR (DMSO-d_6): δ ppm 3.23 (s, 3H, SO_2Me), 7.43–7.50 (m, 3H, phenyl H_3–H_5), 7.72 (d, 2H, phenyl H_2 and H_6, J = 7.5 Hz), 7.78 (t, 1H, quinoline H_6), 7.88 (d, 1H, quinoline H_7, J = 7.1 Hz), 8.01 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz), 8.39 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.4 Hz), 8.45 (s, 1H, quinoline H_3), 8.61 (d, 1H, quinoline H_5, J = 8.4 Hz), 14.08 (s, 1H, COOH); MS m/z (%): 403.3 (M^+, 100), 323.1 (60), 278.1(20), 201.9 (10), 139.3 (10), 83.5 (20); Anal. Calcd for $C_{23}H_{17}NO_4S$: C, 68.47; H, 4.25; N, 3.47. Found: C, 68.66; H, 4.30; N, 3.21.

5.3.4. 2-(4-(Methylsulfonyl)phenyl)benzo[*h*]quinoline-4-carboxylic acid (9d)

Yield: 64%; yellow crystalline powder; mp: 270–271 °C; IR (KBr): ν (cm^{-1}) 3330–2500 (OH), 1725 (C=O), 1310, 1150 (SO_2); ^{1}H NMR (DMSO-d_6): δ ppm 3.32 (s, 3H, SO_2Me), 7.83–7.86 (m, 2H, benzoquinoline H_8 and H_9), 8.09 (d, 2H, benzoquinoline H_7 and H_{10}, J = 9.1 Hz), 8.15 (d, 2H, 4-methyltsulfonylphenyl H_2 and H_6, J = 8.5 Hz), 8.55 (d, 1H, benzoquinoline H_6, J = 9.2 Hz), 8.67 (s, 1H, benzoquinoline H_3), 8.71 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.5 Hz), 9.40 (d, 1H, benzoquinoline H_5, J = 7.9 Hz), 14.05 (s, 1H, COOH); MS m/z (%): 377.8 (M^+, 100), 298.9 (50), 253.8 (25), 242.0 (20), 152.0 (10); Anal. Calcd for $C_{21}H_{15}NO_4S$: C, 66.83; H, 4.01; N, 3.71. Found: C, 66.56; H, 4.31; N, 3.82.

5.3.5. 7,8,9,10-Tetrahydro-2-(4-(methylsulfonyl)phenyl)benzo[*h*]quinoline-4-carboxylic acid (9e)

Yield: 89%; cream crystalline powder; mp = 277–278 °C; IR (KBr): ν (cm^{-1}) 3230–2670 (OH), 1715 (C=O), 1300, 1140 (SO_2); ^{1}H NMR (DMSO-d_6): δ ppm 1.80–1.87 (m, 4H, CH_2), 2.87 (m, 2H, CH_2), 3.25 (s, 3H, SO_2 Me), 3.30 (m, 2H, CH_2), 7.37 (d, 1H, tetrahydrobenzoquinoline H_6, J = 8.8 Hz), 8.05 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.3 Hz), 8.32 (d, 1H, tetrahydrobenzoquinoline H_5, J = 8.7 Hz), 8.42 (s, 1H, tetrahydrobenzoquinoline H_3) 8.51 (d, 2H, 4-methylsulfonylphenyl H_3 and H_5, J = 8.3 Hz), 13.77 (s, 1H, COOH); MS m/z (%): 382.1 (M^+, 100), 366.9 (20), 302 (20), 287.5 (20), 229.2 (10); Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67. Found: C, 66.42; H, 4.75; N, 3.54.

6. Molecular modeling (docking) studies

Docking studies were performed using AUTODOCK software Version 3.0.5. The coordinates of the X-ray crystal structure of the selective COX-2 inhibitor SC-558 bound to the murine COX-2 enzyme was obtained from the RCSB Protein Data Bank (1cx2) and hydrogens were added. The ligand molecules were constructed using the Builder module and were energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The energy minimized ligands were superimposed on SC-558 in the PDB file 1cx2 after which SC-558 was deleted. The purpose of docking is to search for favorable binding configuration between the small flexible ligands and the rigid protein. Protein residues with atoms greater than 7.5 Å from the docking box were removed for efficiency. These docked structures were very similar to the minimized structures obtained initially. The quality of the docked structures was evaluated by measuring the intermolecular energy of the ligand–enzyme assembly.[23,24]

7. In vitro cyclooxygenase (COX) inhibition assays

The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using chemiluminescent enzyme assays kit (Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[25]

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