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Design, synthesis and biological evaluation of new 2,3-diarylquinoline derivatives as selective cyclooxygenase-2 inhibitors

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ABSTRACT

A new group of 2,3-diarylquinoline derivatives possessing a methylsulfonyl COX-2 pharmacophore at the *para*-position of the C-2 phenyl ring were synthesized and evaluated as selective COX-2 inhibitors. In vitro COX-1/COX-2 structure–activity relationships were determined by varying the substituents on the C-4 quinoline ring. Among the 2,3-diarylquinolines, 2-(4-(methylsulfonyl) phenyl)-3-phenylquinoline-4-carboxylic acid (**8**) exhibited the highest potency and selectivity for COX-2 inhibitory activity (COX-2 IC_{50} = 0.07 μM; selectivity index = 687.1) that was more selective than the reference drug celecoxib (COX-2 IC_{50} = 0.06 μM; selectivity index = 405). A molecular modeling study where **8** was docked in the binding site of COX-2 indicated that the *p*-$MeSO_2$ COX-2 pharmacophore group on the C-2 phenyl ring is oriented in the vicinity of the COX-2 secondary pocket (Arg^{513}, Phe^{518} and Val^{523}) and the carboxylic acid substituent can interact with Ser^{530}. The structure activity data acquired indicate that the size and nature of the C-4 quinoline substituent are important for COX-2 inhibitory activity.

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are competitive inhibitors of cyclooxygenase (COX), the enzyme that mediates the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs).[1,2] COX is a membrane-bound heme protein which exists at least in two different isoforms, a constitutive form (COX-1) and an inducible form (COX-2). The COX-1 enzyme is constitutively expressed and it is involved in the synthesis and supply of the necessary arachidonic acid metabolites for maintaining of gastric and renal functions as well as for an adequate vascular homeostasis whereas COX-2 induces inflammatory conditions.[3,4] The therapeutic anti-inflammatory action of NSAIDs is produced by inhibition of COX-2, while the undesired side effects arise from inhibition of COX-1 activity.[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 especially colon cancer[6] and neurological diseases such as Parkinson[7] and Alzheimer's[8] diseases still continues to attract investigations on development of COX-2 inhibitors. 1,2-Diarylheterocycles, and other central ring pharmacophore templates, have been extensively studied as the most important selective COX-2 inhibitors. All these tricyclic molecules possess 1,2-diaryl substitution attached to a monocyclic or bicylclic central system in conjunction with a characteristic sulfonyl group such as a *para*-SO_2NH_2 or a *para*-SO_2Me substituent on one of the phenyl rings which plays an important role on COX-2 selectivity.[9] Celecoxib and rofecoxib are two well known selective COX-2 inhibitors belong to COXIBs class.[10,11] However, the recent market removal of rofecoxib and some other COX-2 inhibitors due to their adverse cardiovascular side effects[12] clearly encourages the researchers to explore and evaluate alternative templates with COX-2 inhibitory activity. In addition, recent 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.[13] For this reason novel scaffolds with high selectivity for COX-2 inhibition need to be found and evaluated for their biological activities. Recently, we reported several investigations describing the design, synthesis and molecular modeling studies for a group of 2-phenyl-4-carboxylquinolines 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.[14] In this group, 2-(4-(methylsulfonyl) phenyl)quinoline-4-carboxylic acid (see structure **2** in Fig. 1) having lipophilic substituents at C-7 and C-8 positions exhibited higher selectivity for COX-2 inhibition than reference drug celecoxib. On the other hand, we recently introduced a new class of 2,3-diaryl-1,3-benzthiazinan-4-ones containing a bicyclic central ring as highly potent COX-2 inhibitors.[15] For example, 3-(*p*-fluorophenyl)-2-(4-methylsulfonylphenyl)-1,3-benzthiazinane-4-one (see structure **1** in Fig. 1) showed highly potency on COX-2 inhibition even more potent than

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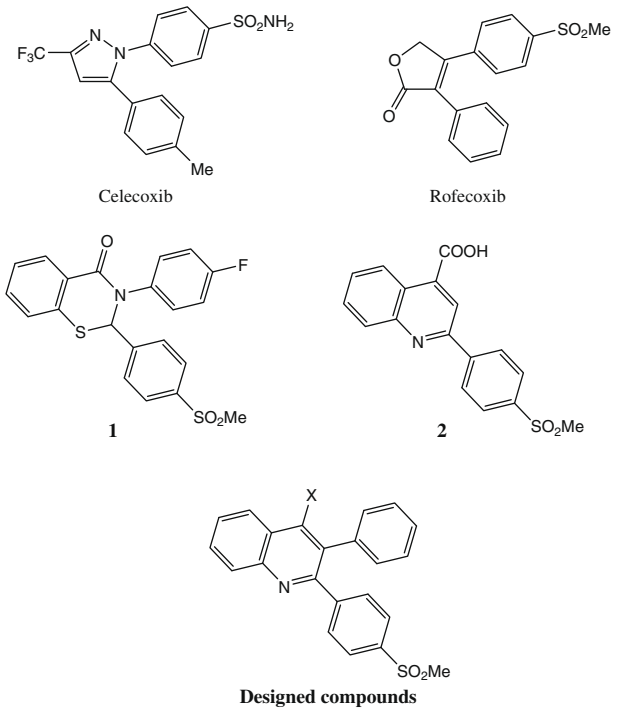


Figure 1. Some representative examples of COXIBs (celecoxib and rofecoxib), 2,3-diaryl benzthiazinan-4-one (**1**), 4-carboxyl quinoline (**2**) lead compound and our designed compounds.

celecoxib. As part of our ongoing program to design COX-2 inhibitors, we now describe the synthesis and biological evaluation of a group of 2,3-diarylquinoline derivatives possessing a methylsulfonyl COX-2 pharmacophore at the *para*-position of the C-2 phenyl ring in conjunction with various substituents at C-4 quinoline ring. In these designed compounds we utilized quinoline ring instead of benzthiazinan scaffold in our previously reported COX-2 inhibitors.

2. Chemistry

The target 2,3-diarylquinoline derivatives **4–8** were synthesized via the route outlined in Scheme 1. As illustrated in the scheme, 2-(4-(methylsulfonyl)phenyl)-1-phenylethanone[16] **3** was reacted with 2-nitrobenzaldehyde in the presence of $SnCl_2$ using microwave irradiation to provide 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline **4** (yield 10%).[17] Reaction of **3** with 2-aminoacetophenone or 2-aminobenzophenone under acidic condition through the well known Friedlander reaction gave quinolines **5** and **6** (yield: 10% and 76%, respectively).[18] Treatment of **3** with 2-aminobenzonitrile and $AlCl_3$ under argon atmosphere afforded 4-amino-2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline **7** (yield 11%).[19] The desired quinoline derivative **8** was prepared using Pfitzinger reaction.[20] Accordingly, 2-(4-(methylsulfonyl)phenyl)-1-phenylethanone **3** was reacted with isatin in alkaline ethanol to provide **8** (yield: 70%). 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

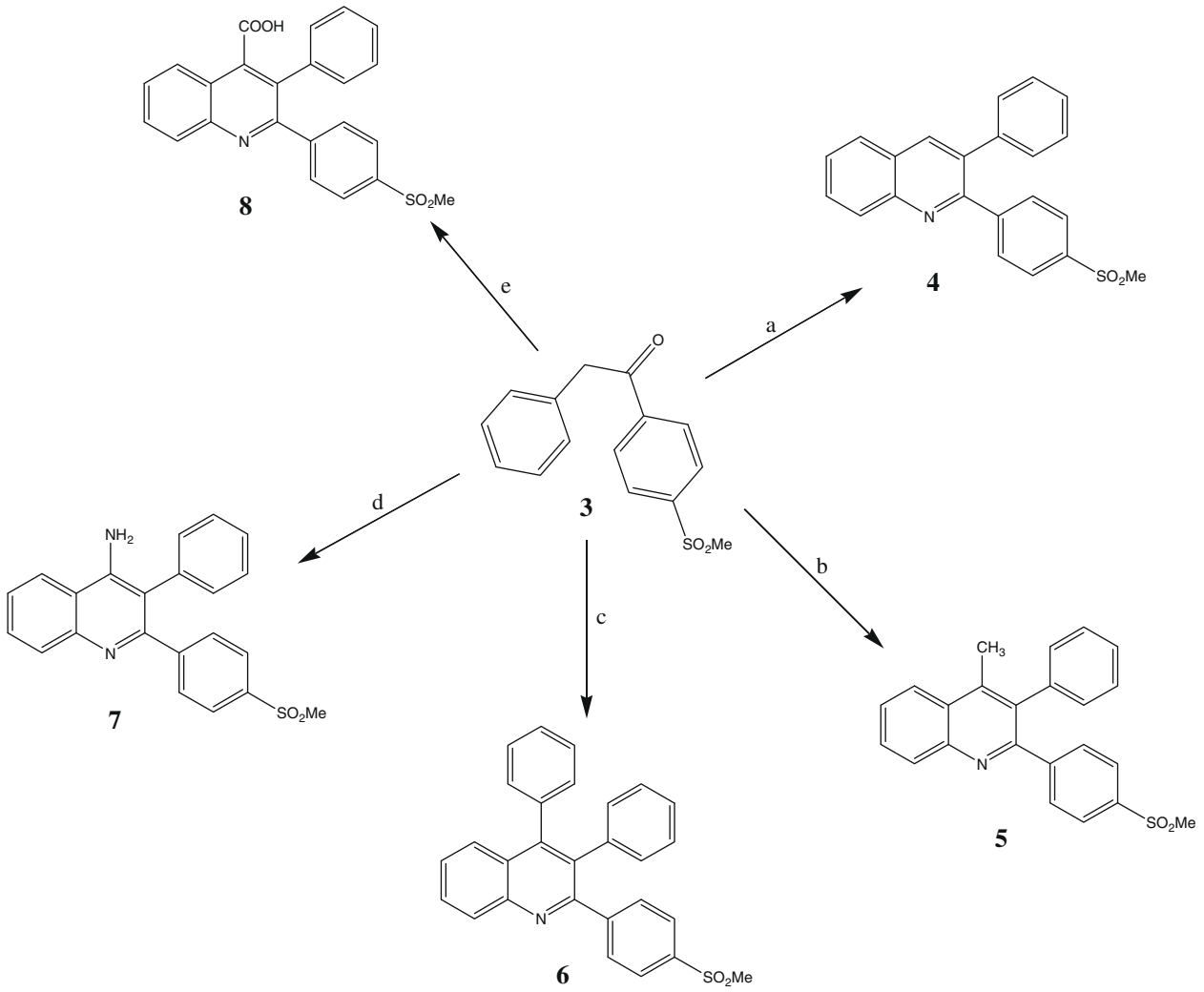
A group of 2,3-diarylquinoline derivatives having different substituents at the C-4 quinoline ring were prepared to investigate the effect of different substituents on COX-2 selectivity and potency. The ability of the 2,3-diarylquinolines **4–8** to inhibit the COX-1 and COX-2 isozymes was determined using chemiluminescent enzyme assays (see enzyme inhibition data in Table 1.) according to our previously reported method.[21] In vitro COX-1/COX-2 inhibition studies showed that all compounds **4–8** were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.07–0.13 μM range, and COX-2 selectivity indexes (SI) in the 78.5–687.1 range. The relative COX-2 potency, and COX-2 selectivity profiles for the 2,3-diarylquinoline derivatives **4–8**, with respect to the C-4 substituent (X) was COOH > H > NH_2 > Me > Ph. 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 is sensitive to the size and nature of substituent at the C-4 quinoline ring. These data showed that the type of substituent attached to C-4 of quinoline ring affected both selectivity and potency for COX-2 inhibitory activity. Accordingly, compound **6** having bulky group at the C-4 central ring showed less selectivity and potency for COX-2 isozyme compared with compounds **4** and **5** that can be explained by steric parameter. However, among the 2,3-diarylquinoline derivatives, compound **8** possessing a carboxylic acid attached to C-4 quinoline ring exhibited the highest COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.07 μM; SI = 687.1) that was more selective than the reference drug celecoxib (COX-2 IC_{50} = 0.06 μM; SI = 405). However, the replacement of carboxylic acid with amino group (**7**) decreased the selectivity for COX-2 inhibition. This effect may be explained by less ability of amino group for hydrogen binding interaction compared with the carboxylic acid substituent. The binding interactions of the most potent and selective COX-2 inhibitor compound (**8**) within the COX-2 binding site were investigated. The most stable enzyme–ligand complex of 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline-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 (Arg^{513}, Phe^{518} and Val^{523}). One of the *O*-atoms of *p*-$MeSO_2$ substituent forms a hydrogen binding interaction with amino group of Arg^{513} (distance = 4.6 Å) whereas the other *O*-atom is about 2.9 Å away from N*H* of Ser^{353}. In addition, a hydrogen bonding interaction can form between the nitrogen atom of quinoline ring and N*H* of Arg^{120} (distance = 4.9 Å). Also, the distance between the O*H* of carboxylic acid group of the quinoline ring is about 3 Å away from C=*O* of Ala^{527} whereas the *O*-atom of C=O group is close to N*H* of Ser^{530} (distance = 4.8 Å) which can explain the high potency and selectivity of compound **8**.

4. Conclusions

This study indicates that (i) the bicyclic quinoline ring 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 size and nature of the C-4 quinoline substituent, and (iii) 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline-4-carboxylic acid (**8**) exhibited high COX-2 inhibitory potency and selectivity.

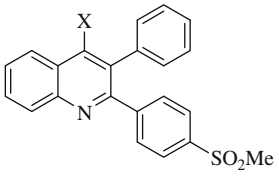
5. Experimental section

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}HNMR 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),



Scheme 1. Reagents and conditions: (a) 2-nitrobenzaldehyde, $SnCl_2{\cdot}2H_2O$, MW (180 W), 10 min; (b) 2-aminoacetophenone, H_2SO_4, CH_3COOH, reflux; (c) 2-aminobenzophenone, H_2SO_4, CH_3COOH, reflux; (d) 2-aminobenzonitrile, $AlCl_3$, 1,2-dichloroethane, reflux; (e) isatin, KOH, EtOH, reflux.

Table 1
In vitro COX-1 and COX-2 enzyme inhibition assay data for 2,3-diarylquinoline derivatives **4**–**8**



Compound	X	IC_{50}[a] (μM)		Selectivity index[b] (SI)
		COX-1	COX-2	
4	H	33.5	0.11	304.5
5	Me	13.3	0.11	121.3
6	Ph	10.2	0.13	78.5
7	NH_2	14.4	0.08	180.0
8	COOH	48.1	0.07	687.1
Celecoxib	—	24.3	0.06	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}).

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. A 6410Agilent LC–MS triple quadrupole mass spectrometer (LC–MS) with an electrospray ionization (ESI) interface was also used for molecular weight measurement. Microanalyses, determined for C, H, and N were within ±0.4% of theoretical values.

5.1. Synthesis of 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline (4)

2-Nitrobenzaldehyde (0.3 g, 1.82 mmol) and 2-(4-(methylsulfonyl)phenyl)-1-phenylethanone (0.5 g, 1.82 mmol) were uniformly mixed with $SnCl_2$, $2H_2O$ (1.5 g, 4.35 mmol) the resulting mixture was then irradiated with microwaves (MW) for 10 min while the power was set on 180 W. The reaction mixture was cooled at room temperature and treated with 10% $NaHCO_3$ solution, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to obtain the crude product, which was further purified by plate chromatography using chloroform as mobile phase. Yield: 10% (70 mg); white crystalline powder; mp: 135–136 °C; IR (KBr): ν (cm^{-1}) 1310, 1150 (SO_2), ^{1}HNMR ($CDCl_3$): δ (ppm) 3.02 (s, 3H, SO_2Me), 7.21–7.24 (m, 2H, phenyl H_2 and H_6), 7.32–7.34 (m, 3H, phenyl H_3–H_5), 7.61 (t, 1H, quinoline H_7, J = 7.5 Hz), 7.67 (d, 2H, 4-methylsulfonylphenyl H_2

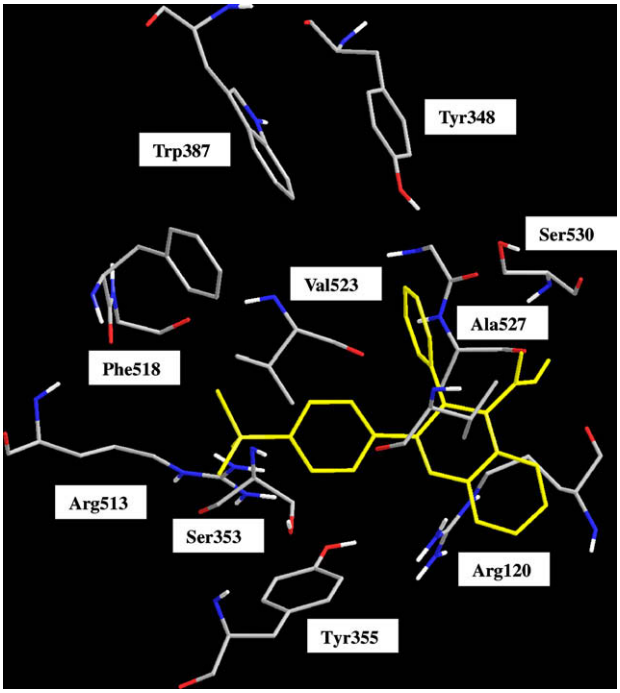


Figure 2. Docking 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline-4-carboxylic acid (**8**) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

and H_6, J = 8.5 Hz), 7.78 (t, 1H, quinoline H_6, J = 8.3 Hz), 7.86 (d, 2H, 4-methylthiophenyl H_3 and H_5, J = 8.5 Hz), 7.91 (d, 1H, quinoline H_5, J = 8.1 Hz), 8.20 (d, 1H, quinoline H_8, J = 8.1 Hz), 8.24 (s, 1H, quinoline H_4); MS *m/z* (%): 359.2 (M^+, 15), 283.2 (70), 205.1 (10), 180.1 (60), 165.0 (75), 77.1 (100); Anal. Calcd for $C_{22}H_{17}NO_2S$: C, 62.37; H, 4.00; N, 4.28. Found: C, 62.42; H, 3.71; N, 4.39.

5.2. Synthesis of 4-methyl-2-(4-methylsulfonyl)phenyl)-3-phenylquinoline (5)

A suspension of 2-aminoacetophenone (0.5 g, 3.70 mmol) and 2-(4-(methylsulfonyl)phenyl)-1-phenylethanone (0.7 g, 2.55 mmol) and 0.01 ml concentrated sulfuric acid in 5 ml of glacial acetic acid was refluxed for 4 h, the reaction mixture was then cooled and poured slowly with stirring into an ice-cold solution of 5 ml concentrated ammonium hydroxide in 15 ml of water. The resultant suspension was allowed to stand in an ice bath until the initially oily precipitate had hardened; the crude product was collected and then purified by plate chromatography using chloroform–ethyl acetate (95:5 v/v). Yield: 10% (95 mg); cream crystalline powder; mp: 129–130 °C; IR (KBr): ν (cm^{-1}) 1310, 1160 (SO_2), ^{1}HNMR ($CDCl_3$): δ (ppm) 2.57 (s, 3H, Me), 2.97 (s, 3H, SO_2Me), 7.09–7.11 (m, 2H, phenyl H_2 and H_6), 7.27–7.32 (m, 3H, phenyl H_3–H_5), 7.52 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.2 Hz), 7.65 (t, 1H, quinoline H_6, J = 7.5 Hz), 7.64–7.67 (m, 3H, 4-methylsulfonylphenyl H_3 and H_5 and quinoline H_7), 8.11 (d, 1H, quinoline H_5, J = 8.4 Hz), 8.18 (d, 1H, quinoline H_8, J = 8.4 Hz); MS *m/z* (%): 373.2 (M^+, 10), 372.1 (100), 293.2 (45), 278.2 (15), 145.7 (25), 78.9 (18); Anal. Calcd for $C_{23}H_{19}NO_2S$: C, 62.37; H, 4.00; N, 4.28. Found: C, 62.42; H, 3.71; N, 4.39.

5.3. Synthesis of 3,4-diphenyl-2-(4-methylsulfonyl)phenyl)-quinoline (6)

A solution of 2-aminobenzophenone 0.72 g, 3.65 mmol) and 2-(4-(methylsulfonyl)phenyl)-1-phenyl ethanone (1 g, 3.65 mmol) and 0.04 ml concentrated sulfuric acid in 5 ml of glacial acetic acid was refluxed for 3 h, the reaction mixture was then cooled and poured slowly with stirring into an ice-cold solution of 6 ml concentrated ammonium hydroxide in 15 ml of water. The resultant suspension was allowed to stand in an ice bath until the initially oily precipitate had hardened. The crude product was collected, washed with water and recrystallized from ethanol and washed with hexane. Yield: 76% (1.2 g); pale yellow crystalline powder; mp: 235–236 °C; IR (KBr): ν (cm^{-1}) 1310, 1155 (SO_2), ^{1}HNMR ($CDCl_3$): δ (ppm) 3.04 (s, 3H, SO_2Me), 6.91–6.93 (m, 2H, 4-phenyquinoline H_2 and H_6), 7.05–7.09 (m, 3H, 4-phenylquinoline H_3–H_5), 7.17–7.19 (m, 2H, 3-phenylquinoline H_2 and H_6), 7.32–7.34 (m, 3H, 3-phenylquinoline H_3–H_5), 7.56 (t, 1H, quinoline H_6), 7.63–7.67 (m, 3H, 4-methylsulfonyl phenyl H_2 and H_6 and quinoline H_5), 7.80–7.85 (m, 3H, 4-methylsulfonyl-phenyl H_3 and H_5 and quinoline H_7), 8.28 (d, 1H, quinoline H_8, J = 8.4 Hz); LC–MS (ESI) *m/z* : 436.2 (M+1) (100); Anal. Calcd for $C_{28}H_{21}NO_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.62; H, 4.54; N, 4.32.

5.4. Synthesis of 4-amino-2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline (7)

A solution of 2-(4-(methylsulfonyl)phenyl)-1-phenylethanone (1 g, 3.72 mmol) in dry 1,2-dichloroethane (5 ml) was added dropwise to a suspension of $AlCl_3$ (0.48 g, 3.72 mmol) and 2-aminobenzonitrile (0.43 g, 3.72 mmol) in dry 1,2-dichloroethane under argon atmosphere. The temperature was kept at 0–5 °C for 30 min then the reaction mixture was heated under reflux for 24 h. A mixture of THF (40 ml) and cold water (20 ml) was added to the mixture and then rendered basic (pH 8) and the mixture was stirred at room temperature for 30 min. The organic solvents were evaporated at reduced pressure, the produced oily liquid was purified by column chromatography (hexane/ethyl acetate 1:1 v/v), the product was recrystallized in methanol. Yield:11% (155 mg); pale yellow crystalline powder; mp: 256 °C; IR (KBr): ν (cm^{-1}) 3485, 3390 (NH_2), 1300, 1145 (SO_2); ^{1}HNMR (DMSO-d_6): δ (ppm) 3.12 (s, 3H, SO_2Me), 6.15 (s, 2H, NH_2), 7.16 (d, 2H, phenyl H_2 and H_6, J = 7.2 Hz), 7.28 (t, 1H, phenyl H_4, J = 7.3 Hz), 7.33 (t, 2H, phenyl H_3 and H_5, J = 7.4 Hz), 7.43–7.46 (m, 3H, 4-methyl sulfonylphenyl H_2 and H_6 and quinoline H_6), 7.63–7.68 (m, 3H, 4-methylsulfonyl-phenyl H_3 and H_5 and quinoline H_7), 7.80 (d, 1H, quinoline H_5, J = 8.4 Hz), 8.28 (d, 1H, quinoline H_8, J = 8.4 Hz); LC–MS (ESI) *m/z* : 375.8 (M+1) (100); Anal. Calcd for $C_{22}H_{18}N_2O_2S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.62; H, 4.54; N, 4.32.

5.5. Synthesis of 2-(4-(methylsulfonyl)phenyl)-3-phenylquinoline-4-carboxylic acid (8)

Isatin (0.7 g, 4.32 mmol) was added in 25 ml ethanol and heated, then 14.2 mmol of 33% potassium hydroxide was added to the solution and heated for 15 min. After this time, 2-(4-(methyl sulfonylphenyl)-1-phenylethanone (1.3 g, 4.74 mmol) was added and refluxed for 48 h. After evaporation of ethanol, the precipitate was acidified with acetic acid 10% and washed with ethanol and hexane. Yield: 70% (1.3 g); white crystalline powder; mp: 310–311 °C; IR (KBr): ν (cm^{-1}) 3100–2700 (OH), 1730 (C=O), 1320, 1155 (SO_2); ^{1}HNMR (DMSO-d_6): δ (ppm) 3.21 (s, 3H, SO_2Me), 7.25–7.29 (m, 2H, phenyl H_2 and H_6), 7.31–7.36 (m, 3H, phenyl H_3–H_5), 7.59 (d, 2H, 4-methylsulfonylphenyl H_2 and H_6, J = 8.4 Hz), 7.78–7.81 (m, 3H, 4-methylsulfonylphenyl H_3 and H_5 and quinoline H_7), 7.91–7.94 (m, 2H, quinoline H_6 and H_8), 8.18 (d, 1H, quinoline H_5, J = 8.3 Hz), 13.93 (s, 1H, COOH); LC–MS (ESI) *m/z* : 404.2 (M+1), 425.1 (M+23); Anal. Calcd for $C_{23}H_{17}NO_4S$: C, 69.88; H, 4.89; N, 4.53. Found: C, 69.62; H, 4.54; N, 4.32.

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.[22,23]

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.[21]

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