

## Design, Synthesis and Biological Evaluation of 5-Oxo-1,4,5,6,7,8 Hexahydroquinoline Derivatives as Selective Cyclooxygenase-2 Inhibitors

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### Abstract

A group of regioisomeric 5-oxo-1,4,5,6,7,8 hexahydroquinoline derivatives possessing a COX-2 SO<sub>2</sub>Me pharmacophore at the *para* position of the C-2 or C-4 phenyl ring, in conjunction with a C-4 or C-2 phenyl (4-H) or substituted-phenyl ring (4-F,4-Cl,4-Br,4-OMe,4-Me, 4-NO<sub>2</sub>), were designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. These target 5-oxo-1,4,5,6,7,8 hexahydroquinolines were synthesized via a Hansch condensation reaction. In vitro COX-1/COX-2 isozyme inhibition structure-activity studies identified 7,8-dihydro-7,7-dimethyl-2-(4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)quinolin-5(1*H*,4*H*,6*H*)-one (9c) as a potent COX-2 inhibitor (IC<sub>50</sub> = 0.17 M) with a high COX-2 selectivity index (S.I. = 97.6) comparable to the reference drug celecoxib (COX-2 IC<sub>50</sub> = 0.05 mM; COX-2 S.I. = 405). A molecular modeling study where 9c was docked in active site of COX-2 showed that the *p*-SO<sub>2</sub>Me substituent on the C-2 phenyl ring is inserted into the secondary COX-2 binding site. The structure activity data acquired indicate that the position of the COX-2 SO<sub>2</sub>Me pharmacophore and type of substituent are important for COX-2 inhibitory activity.

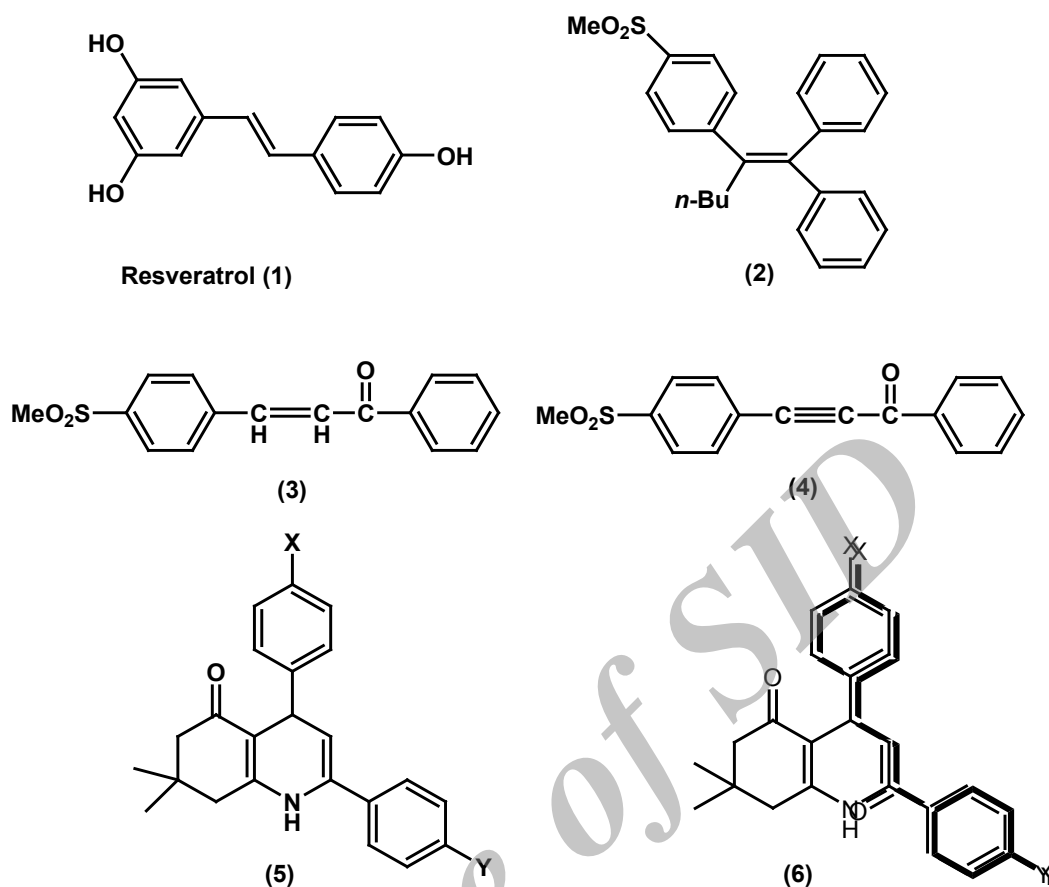
**Keywords:** 5-Oxo-1,4,5,6,7,8 hexahydroquinolines; COX-2 Inhibitors; Molecular modeling; Hansch condensation.

### Introduction

Selective cyclooxygenase-2 (COX-2) inhibitors frequently belong to a class of diarylheterocycles that possess two vicinal rings attached to a central heterocyclic scaffold in conjunction with a COX-2 pharmacophore such as a *para*-SO<sub>2</sub>Me substituent on one of

the rings (1). Compounds having an acyclic central scaffold have also been identified that exhibit COX inhibitory activity. Accordingly, resveratrol (1) possessing *trans*-olefin system displays COX-1 selectivity (2). In contrast, it showed that the 1,1,2-tiraryl (*Z*)-olefin (2) (3), the 1,3-diphenylprop-2-en-1-one (3) (4) and the 1,3-diphenylprop-2-yn-1-one (4) (5) exhibit not only potent, but also highly selective, COX-2 inhibitory activity (see structures 1-4 in Figure 1). Recently, we reported several

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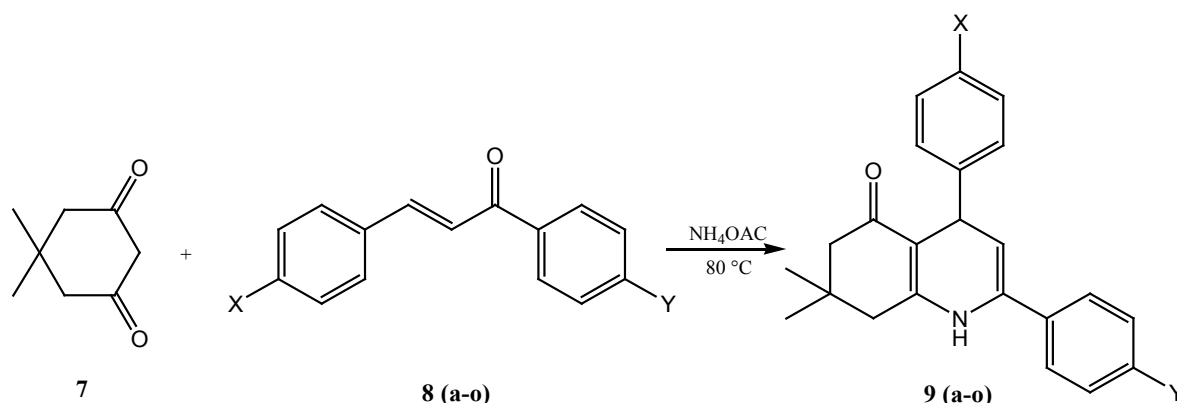
**Figure 1.** Some representative examples of a selective cyclooxygenase-1 (1), cyclooxygenase-2 (2-4) inhibitors, designed molecules (5) and overlay of our design molecules on lead compound 3 (6).

investigations describing the design, synthesis, and anti-inflammatory properties for a novel class of compounds possessing an acyclic 1, 3-diphenylprop-2-en-1-one structural template. Our results showed that the propenone moiety is a suitable scaffold (template) to design COX-2 inhibitors (4, 6, 7). As part of our ongoing program to design new types of selective COX-2 inhibitors, we now report the synthesis, some structure-activity relationships, and a molecular modeling study for a group of 5-oxo-1,4,5,6,7,8 hexahydroquinoline regioisomers possessing a COX-2 SO<sub>2</sub>Me pharmacophore at the *para*-position of one phenyl ring in conjunction with a substituent (4-F, 4-Cl, 4-Br, 4-OMe, 4-Me, 4-NO<sub>2</sub>) at the *para*-position of the other phenyl ring. In this study we utilized the 1, 3-diphenylprop-2-en-1-one moieties as a part of our designed molecules.

## Experimental

### General

All chemicals and solvents used in this study were purchased from Merck AG and Aldrich Chemical. Melting points were determined using a Thomas-Hoover capillary apparatus. Infrared spectra were acquired using a Perkin Elmer Model 550 SE spectrometer. A Bruker AM-300 NMR spectrometer was used to acquire <sup>1</sup>H NMR spectra with TMS as internal standard. 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 an MAT CH5/DF (Finnigan) mass spectrometer that was coupled on line to a Data General DS 50 data system. Electron-impact ionization was performed at an ionizing energy



Scheme 1. Synthesis of 5-oxo-1,4,5,6,7,8 hexahydroquinoline derivatives 9a-o.

of 70 eV with a source temperature of 250 °C. Elemental microanalyses, determined for C and H, were within  $\pm 0.4\%$  of theoretical values. 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 (Bruker Biosciences, USA) was used to acquire  $^1\text{H}$ NMR spectra with TMS as internal standard. Chloroform- $D$  was 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). The mass spectral measurements were performed on a 6410 Agilent LCMS triple quadrupole mass spectrometer (LCMS) with an electrospray ionization (ESI) interface.

#### Chemistry

The two sets of 5-oxo-1,4,5,6,7,8 hexahydroquinoline regioisomers in which the 4-methanesulfonyl phenyl substituent is attached to C-2 (9a-g) or to C-4 (9h-n), were synthesized in 48–97% yield using a one-pot Hansch reaction as shown in Scheme 1 (8). Accordingly, a mixture of 5, 5-dimethyl-1, 3-cyclohexandione, 1, 3-diaryl-2-propen-1-one and ammonium acetate dissolved in methanol and was refluxed for overnight. The completion of the reaction was monitored by TLC.

1,3-Diaryl-2-propen-1-ones (8a-n) were prepared according to our previously literature procedure (4).

#### General procedure for the synthesis of (*E*)-1,3-diaryl prop-2-en-1-ones (9a-h)

A mixture of 5, 5-dimethyl-1,3-cyclohexandione (3 mmol), 1,3-diaryl-2-propen-1-one (2 mmol), ammonium acetate (4mmol) dissolved in 15 mL methanol and was refluxed at 80 °C for overnight. The completion of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature; ethanol (10 mL) was added to dilute mixture. The mixture was poured into 80 ml ice-water, the precipitate was filtered off and washed with water, and the crude products were obtained. The crude products were purified by recrystallization from ethanol to give final products.

#### 7,8-Dihydro-7,7-dimethyl-2-(4-methylsulfonyl phenyl)-4-phenylquinolin-5-(1H,4H,6H)-one (9a)

Yield, 76 %; mp 229–231 °C; IR(KBr disk)  $\nu$  ( $\text{cm}^{-1}$ ) 1150, 1300 ( $\text{SO}_2$ ), 1400–1600 (aromatic), 1667 ( $\text{C}=\text{O}$ ), 3254 (NH);  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  1.07 (s, 3H,  $\text{CH}_3$ ), 1.15 (s, 3H,  $\text{CH}_3$ ), 2.21–2.31 (q, 2H, dihydroquinoline  $\text{H}_8$ ), 2.39–2.48 (q, 2H, dihydroquinoline  $\text{H}_6$ ,  $J=16.2$  Hz), 3.08 (s, 3H,  $\text{SO}_2\text{Me}$ ), 4.79 (d, 1H, dihydroquinoline  $\text{H}_4$ ,  $J=5.2$  Hz), 5.44 (d, 1H, dihydroquinoline  $\text{H}_3$ ,  $J=5.3$  Hz), 5.88 (s, 1H, NH), 7.17–7.20 (t, 1H, phenyl  $\text{H}_4$ ), 7.29–7.32 (t, 2H, phenyl  $\text{H}_3$  and  $\text{H}_5$ ), 7.38 (d, 2H, phenyl  $\text{H}_2$  and  $\text{H}_6$ ,  $J=7.0$  Hz), 7.64(d, 2H, methanesulfonyl phenyl  $\text{H}_2$  and  $\text{H}_6$ ,  $J=8.4$  Hz), 7.96 (d, 2H, methanesulfonyl phenyl  $\text{H}_3$  and  $\text{H}_5$ ,  $J=8.4$  Hz); Anal. Calcd. for  $\text{C}_{25}\text{H}_{27}\text{NO}_3\text{S}$ : C, 71.23; H, 6.46; N, 3.32. Found: C, 71.46; H, 6.55; N, 3.22.

7, 8-Dihydro-7, 7-dimethyl-4-(4-methylphenyl)-2-(4-methylsulfonyl) phenyl quinolin-5-(1H, 4H, 6H)-one (9b)

Yield, 51 % ; mp 250-253 °C; IR(KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1667 (C=O); 3254 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  1.08 (s, 3H, CH<sub>3</sub>), 1.15 (s, 3H, CH<sub>3</sub>), 2.22–2.47 (m, 4H, dihydroquinoline H<sub>6</sub> and H<sub>8</sub>), 2.32 (s, 3H, CH<sub>3</sub>), 3.08 (s, 3H, SO<sub>2</sub>Me), 4.76 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J=5.1$  Hz), 5.44 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J=5.2$  Hz), 5.68 (s, 1H, NH), 7.08-7.12 (m, 2H, *p*-toluoyl H<sub>3</sub> and H<sub>5</sub>), 7.25–7.27 (m, 2H, *p*-toluoyl H<sub>2</sub> and H<sub>6</sub>), 7.64 (d, 2H, methane sulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J=8.3$  Hz), 7.98 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.3$  Hz); Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>NO<sub>3</sub>S : C, 70.73; H, 6.18; N, 3.44. Found: C, 70.53; H, 6.32; N, 3.52.

7, 8-Dihydro-7, 7-dimethyl-4-(4-methoxyphenyl)-2-(4-(methylsulfonyl) phenyl) quinolin-5-(1H, 4H, 6H)-one (9c)

Yield, 56 %; mp 250-253 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1665 (C=O); 3240 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  0.98 (s, 3H, CH<sub>3</sub>), 1.06 (s, 3H, CH<sub>3</sub>), 2.10–2.13 (t, 1H, dihydroquinoline H<sub>8</sub>), 2.21 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J=16.3$  Hz), 2.41 (d, 2H, dihydroquinoline H<sub>6</sub>,  $J=16.4$  Hz), 3.01 (s, 3H, SO<sub>2</sub>Me), 3.7 (s, 3H, OCH<sub>3</sub>), 4.66 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J=5.3$  Hz), 5.32 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J=5.3$  Hz), 6.77 (d, 2H, 4-methoxyphenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.6$  Hz), 7.20-7.24 (m, 2H, 4-methoxyphenyl H<sub>2</sub> & H<sub>6</sub>), 7.64 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J=8.1$  Hz), 7.88 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.4$  Hz); Anal. Calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>4</sub>S : C, 68.62; H, 6.22; N, 3.20. Found: C, 68.89; H, 6.36; N, 3.39.

7, 8-Dihydro-4-(4-fluorophenyl)-7, 7-dimethyl-2-(4-methylsulfonyl) phenyl quinolin-5-(1H, 4H, 6H)-one (9d)

Yield, 89 % ; mp 130-133 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1669(C=O); 3390 (NH); 2.2 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J=16.1$  Hz), 2.3-2.37 (m, 2H, dihydroquinoline H<sub>6</sub> & H<sub>8</sub>), 2.45 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J=16.3$  Hz), 3.0

(s, 3H, SO<sub>2</sub>Me), 4.88 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J=5.0$  Hz), 5.1 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J=5.0$  Hz), 5.77 (s, 1H, NH), 7.10-7.22 (t, 2H, 4-fluorophenyl H<sub>3</sub> and H<sub>5</sub>), 7.40-7.42 (q, 2H, 4-fluorophenyl H<sub>2</sub> and H<sub>6</sub>), 7.58 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> & H<sub>6</sub>,  $J=8.8$  Hz), 7.9 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.2$  Hz); Anal. Calcd. for C<sub>24</sub>H<sub>24</sub>FNO<sub>3</sub>S : C, 67.74; H, 5.67; N, 3.29. Found: C, 67.94; H, 5.81; N, 3.12.

4-(4-Chlorophenyl)-7, 8-dihydro-7, 7-dimethyl-2-(4-methylsulfonyl) phenyl quinolin-5-(1H, 4H, 6H)-one (9e)

Yield, 86 %; mp 232-236 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1669(C=O); 3248 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  1.07 (s, 3H, CH<sub>3</sub>), 1.15 (s, 3H, CH<sub>3</sub>), 2.21–2.31 (q, 2H, dihydroquinoline H<sub>8</sub>), 2.33-2.47 (q, 2H, dihydroquinoline H<sub>6</sub>,  $J=16.2$  Hz), 3.08 (s, 3H, SO<sub>2</sub>Me), 4.75 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J=5.3$  Hz), 5.44 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J=5.3$  Hz), 5.78 (s, 1H, NH), 6.85 (d, 2H, 4-chlorophenyl H<sub>3</sub> and H<sub>5</sub>,  $J=9.6$  Hz), 7.29 (m, 2H, 4-chlorophenyl H<sub>2</sub> & H<sub>6</sub>), 7.65 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J=8.4$  Hz), 7.98 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.5$  Hz); Anal. Calcd. for C<sub>24</sub>H<sub>24</sub>ClNO<sub>3</sub>S : C, 65.22; H, 5.47; N, 3.17. Found: C, 65.54; H, 5.56; N, 3.42.

4-(4-Bromophenyl)-7, 8-dihydro-7, 7-dimethyl-2-(4-methylsulfonyl) phenyl quinolin-5-(1H, 4H, 6H)-one (9f)

Yield, 88 %; mp 237-240 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1661(C=O); 3198 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  0.98 (s, 3H, CH<sub>3</sub>), 1.07 (s, 3H, CH<sub>3</sub>), 2.14–2.19 (m, 2H, dihydroquinoline H<sub>8</sub>), 2.2-2.1 (q, 2H, dihydroquinoline H<sub>6</sub>), 3.02 (s, 3H, SO<sub>2</sub>Me), 4.18-4.21 (t, 1H, dihydroquinoline H<sub>4</sub>), 4.69 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J=5.3$  Hz), 5.27 (d, 1H, NH), 7.17 (d, 2H, 4-bromophenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.3$  Hz), 7.32 (d, 2H, 4-bromophenyl H<sub>2</sub> & H<sub>6</sub>,  $J=8.3$  Hz), 7.64 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J=8.3$  Hz), 7.90 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J=8.4$  Hz); Anal. Calcd. for C<sub>24</sub>H<sub>24</sub>BrNO<sub>3</sub>S : C, 59.29; H, 4.97; N, 2.88. Found: C, 59.60; H, 5.11; N, 3.02.

7, 8-Dihydro-7, 7-dimethyl-2-(4-methylsulfonyl phenyl)-4-(4-nitrophenyl) quinolin-5-(1H, 4H, 6H)-one (9g)

Yield, 97 %; mp 234-240 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1661(C=O); 3238 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  0.98 (s, 3H, CH<sub>3</sub>), 1.08 (s, 3H, CH<sub>3</sub>), 2.11-2.24 (m, 2H, dihydroquinoline H<sub>8</sub>), 2.37-2.45 (q, 2H, dihydroquinoline H<sub>6</sub>), 3.03 (s, 3H, SO<sub>2</sub>Me), 4.86 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J$ =5.1 Hz), 5.24 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J$ =5.1 Hz), 7.4 (d, 2H, 4-nitrophenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.6 Hz), 7.66 (d, 2H, 4-nitrophenyl H<sub>2</sub> & H<sub>6</sub>,  $J$ =8.4 Hz), 7.92 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.4 Hz), 8.10 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J$ =8.5 Hz); Anal. Calcd. for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>S: C, 63.70; H, 5.35; N, 6.19. Found: C, 63.81; H, 5.61; N, 6.43.

7, 8-Dihydro-7, 7-dimethyl-4-(4-methylsulfonyl phenyl)-2-phenylquinolin-5-(1H, 4H, 6H)-one (9h)

Yield, 78 %; mp 205-208 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1667 (C=O); 3356 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>):  $\delta$  1.07 (s, 3H, CH<sub>3</sub>), 1.16 (s, 3H, CH<sub>3</sub>), 2.23 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J$ =16.5 Hz), 2.32 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J$ =16.5 Hz), 2.38 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J$ =16.3 Hz), 2.49 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J$ =16.3 Hz), 3.05 (s, 3H, SO<sub>2</sub>Me), 4.90 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J$ =5.0 Hz), 5.25 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J$ =5.0 Hz), 5.93 (s, 1H, NH), 7.41-7.48 (m, 5H, phenyl), 7.59 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.7 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,  $J$ =8.7 Hz); Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>NO<sub>3</sub>S: C, 70.73; H, 6.18; N, 3.44. Found: C, 71.03; H, 6.38; N, 3.59.

7, 8-Dihydro-7, 7-dimethyl-2-(4-methylphenyl)-4-(4-(methylsulfonyl phenyl) quinolin-5-(1H, 4H, 6H)-one (9i)

Yield, 48%; mp: 223-225 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1685(C=O); 3024 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  1.05 (s, 3H, CH<sub>3</sub>), 1.15 (s, 3H, CH<sub>3</sub>), 2.20 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J$ =16.1 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H<sub>6</sub> and H<sub>8</sub>), 2.40 (s, 3H, CH<sub>3</sub>), 2.45-2.48 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J$ =16.2 Hz), 3.03 (s, 3H,

SO<sub>2</sub>Me), 4.88 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J$ =5.0 Hz), 5.21 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J$ =5.0 Hz), 5.88 (s, 1H, NH), 7.32 (d, 2H, *p*-toluoyl H<sub>3</sub> and H<sub>5</sub>,  $J$ =8.0 Hz), 7.58 (d, 2H, *p*-toluoyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.3 Hz), 7.57 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.3 Hz), 7.86 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,

$J$ =8.3 Hz); Anal. Calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>3</sub>S: C, 71.23; H, 6.46; N, 3.32. Found: C, 71.54; H, 6.67; N, 3.39.

7, 8-Dihydro-2-(4-methoxyphenyl)-7, 7-dimethyl-4-(4-(methylsulfonyl phenyl) quinolin-5-(1H, 4H, 6H)-one (9j)

Yield, 53 %; mp, 226-230 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1664 (C=O); 3342 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>):  $\delta$  1.05 (s, 3H, CH<sub>3</sub>), 1.15 (s, 3H, CH<sub>3</sub>), 2.21 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J$ =16.3 Hz), 2.33 (m, 2H, dihydroquinoline H<sub>6</sub> and H<sub>8</sub>), 2.46 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J$ =16.3 Hz), 2.49 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J$ =16.3 Hz), 3.03 (s, 3H, SO<sub>2</sub>Me), 3.85 (s, 3H, OCH<sub>3</sub>), 4.87 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J$ =5.0 Hz), 5.15 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J$ =5.0 Hz), 5.88 (s, 1H, NH), 6.94 (d, 2H, 4-methoxyphenyl H<sub>3</sub> & H<sub>5</sub>,  $J$ =8.7 Hz), 7.36 (d, 2H, 4-methoxyphenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.7 Hz), 7.58 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.2 Hz), 7.86 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> & H<sub>5</sub>,  $J$ =8.2 Hz); Anal. Calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>4</sub>S: C, 68.62; H, 6.22; N, 3.20. Found: C, 68.74; H, 5.99; N, 3.31.

2-(4-Fluorophenyl)-7, 8-dihydro-7, 7-dimethyl-4-(4-(methylsulfonyl phenyl) quinolin-5-(1H, 4H, 6H)-one (9k)

Yield, 89 %; mp, 226-230 °C; IR (KBr disk)  $\nu$  (cm<sup>-1</sup>) 1150, 1300 (SO<sub>2</sub>); 1400-1600 (aromatic); 1664 (C=O); 3028 (NH); <sup>1</sup>HNMR (CDCl<sub>3</sub>):  $\delta$  1.06 (s, 3H, CH<sub>3</sub>), 1.16 (s, 3H, CH<sub>3</sub>), 2.22 (d, 1H, dihydroquinoline H<sub>8</sub>,  $J$ =16.3 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H<sub>6</sub> and H<sub>8</sub>), 2.47 (d, 1H, dihydroquinoline H<sub>6</sub>,  $J$ =16.3 Hz), 3.04 (s, 3H, SO<sub>2</sub>Me), 4.88 (d, 1H, dihydroquinoline H<sub>4</sub>,  $J$ =5.0 Hz), 5.18 (d, 1H, dihydroquinoline H<sub>3</sub>,  $J$ =5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.13 (t, 2H, 4-fluorophenyl H<sub>3</sub> and H<sub>5</sub>), 7.40-7.42 (q, 2H, 4-fluorophenyl H<sub>2</sub> and H<sub>6</sub>), 7.58 (d, 2H, methanesulfonyl phenyl H<sub>2</sub> and H<sub>6</sub>,  $J$ =8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H<sub>3</sub> and H<sub>5</sub>,

$J=8.2$  Hz); Anal. Calcd. for  $C_{24}H_{24}FNO_3S$  : C, 67.74; H, 5.68; N, 3.29. Found: C, 67.88; H, 5.75; N, 3.46.

*2-(4-Chlorophenyl)-7, 8-dihydro-7, 7-dimethyl-4-(4-(methylsulfonyl) phenyl) quinolin-5(1H, 4H, 6H)-one (9i)*

Yield, 82 %; mp 226-230 °C; IR (KBr disk)  $\nu$  ( $cm^{-1}$ ) 1150, 1300 ( $SO_2$ ); 1400-1600 (aromatic); 1654 (C=O); 3342 (NH);  $^1H$ NMR ( $CDCl_3$ ):  $\delta$  1.07 (s, 3H,  $CH_3$ ), 1.17 (s, 3H,  $CH_3$ ), 2.24 (d, 1H, dihydroquinoline  $H_8$ ,  $J=16.4$  Hz), 2.30-2.35 (m, 2H, dihydroquinoline  $H_6$  and  $H_8$ ), 2.50 (d, 1H, dihydroquinoline  $H_6$ ,  $J=16.3$  Hz), 3.05 (s, 3H,  $SO_2Me$ ), 4.88 (d, 1H, dihydroquinoline  $H_4$ ,  $J=5.0$  Hz), 5.23 (d, 1H, dihydroquinoline  $H_3$ ,  $J=5.0$  Hz), 5.84 (s, 1H, NH), 7.37-7.38 (m, 4H, 4-chlorophenyl), 7.58 (d, 2H, methanesulfonyl phenyl  $H_2$  and  $H_6$ ,  $J=8.2$  Hz), 7.88 (d, 2H, methanesulfonyl phenyl  $H_3$  and  $H_5$ ,  $J=8.2$  Hz); Anal. Calcd. for  $C_{24}H_{24}ClNO_3S$ : C, 65.22; H, 5.47; N, 3.17. Found: C, 65.36; H, 5.69; N, 3.32

*2-(4-Bromophenyl)-7, 8-dihydro-7, 7-dimethyl-4-(4-(methylsulfonyl) phenyl) quinolin-5(1H, 4H, 6H)-one (9m)*

Yield, 87 %; mp 226-230 °C; IR (KBr disk)  $\nu$  ( $cm^{-1}$ ) 1150, 1300 ( $SO_2$ ); 1400-1600 (aromatic); 1664 (C=O); 3355 (NH);  $^1H$ NMR ( $CDCl_3$ ):  $\delta$  1.06 (s, 3H,  $CH_3$ ), 1.16 (s, 3H,  $CH_3$ ), 2.23 (d, 1H, dihydroquinoline  $H_8$ ,  $J=16.4$  Hz), 2.29-2.38 (m, 2H, dihydroquinoline  $H_6$  and  $H_8$ ), 2.47 (d, 1H, dihydroquinoline  $H_6$ ,  $J=16.4$  Hz), 3.04 (s, 3H,  $SO_2Me$ ), 4.87 (d, 1H, dihydroquinoline  $H_4$ ,  $J=5.1$  Hz), 5.23 (d, 1H, dihydroquinoline  $H_3$ ,  $J=4.9$  Hz), 5.81 (s, 1H, NH), 7.31 (d, 2H, methanesulfonyl phenyl  $H_2$  and  $H_6$ ,  $J=8.8$  Hz), 7.54-7.57 (m, 4H, 4-bromophenyl), 7.87 (d, 2H, methanesulfonyl phenyl  $H_3$  and  $H_5$ ,  $J=8.2$  Hz); Anal. Calcd. for  $C_{24}H_{24}BrNO_3S$ : C, 59.26; H, 4.97; N, 2.88. Found: C, 59.39; H, 5.12; N, 3.01.

*7, 8-Dihydro-7, 7-dimethyl-4-(4-(methylsulfonyl) phenyl)-2-(4-nitrophenyl) quinolin-5(1H, 4H, 6H)-one (9n)*

Yield, 93 %; mp 226-230 °C; IR (KBr disk)  $\nu$  ( $cm^{-1}$ ) 1150, 1300 ( $SO_2$ ); 1400-1600 (aromatic); 1664 (C=O); 3300 (NH);  $^1H$ NMR ( $CDCl_3$ , 500 MHz):  $\delta$  1.07 (s, 3H,  $CH_3$ ), 1.17 (s, 3H,  $CH_3$ ), 2.20-2.24 (t, 1H, dihydroquinoline  $H_8$ ), 2.33

(d, 1H, dihydroquinoline  $H_8$ ,  $J=16.3$  Hz), 2.42 (d, 1H, dihydroquinoline  $H_6$ ,  $J=16.4$  Hz), 2.52 (d, 1H, dihydroquinoline  $H_6$ ,  $J=16.4$  Hz), 3.05 (s, 3H,  $SO_2Me$ ), 4.91 (d, 1H, dihydroquinoline  $H_4$ ,  $J=5.1$  Hz), 5.39 (d, 1H, dihydroquinoline  $H_3$ ,  $J=5.0$  Hz), 5.98 (s, 1H, NH), 7.57 (d, 2H, 4-nitrophenyl  $H_2$  and  $H_6$ ,  $J=8.3$  Hz), 7.61 (d, 2H, 4-nitrophenyl  $H_3$  and  $H_5$ ,  $J=8.8$  Hz), 7.87 (d, 2H, methanesulfonyl phenyl  $H_2$  and  $H_6$ ,  $J=8.3$  Hz), 8.28 (d, 2H, methanesulfonyl phenyl  $H_3$  and  $H_5$ ,  $J=8.81$  Hz); Anal. Calcd. for  $C_{24}H_{24}N_2O_5S$ : C, 63.70; H, 5.35; N, 6.19. Found: C, 63.94; H, 5.57; N, 6.41.

#### Molecular modeling and biological evaluation

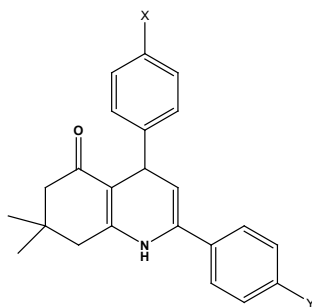
Docking studies were performed using Autodock software Version 3.0. The coordinates of the X-ray crystal structure of the selective COX-2 inhibitor SC-558 bound to the murine COX-2 enzyme was obtained from the RCSB Protein Data Bank (1cx2) and hydrogens were added. The ligand molecules were constructed 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 aim of docking is to search for suitable binding configuration between the ligands and the rigid protein. These docked structures were very similar to the minimized structures provided initially. The quality of the docked structures was determined by measuring the intermolecular energy of the ligand-enzyme assembly (9).

#### In-vitro cyclooxygenase (COX) inhibition assays

The assay was performed using an enzyme chemiluminescent kit (Cayman chemical, MI, USA) according to our previously reported method (10).

### Results and Discussion

A group of 5-oxo-1,4,5,6,7,8 hexahydroquinolines possessing a  $MeSO_2$  group at the *para*-position of the C-2 phenyl ring containing different substituents (4-F, 4-Cl, 4-Br,

**Table 1.** *In-vitro* COX-1 and COX-2 enzyme inhibition data for compounds 9a-o.

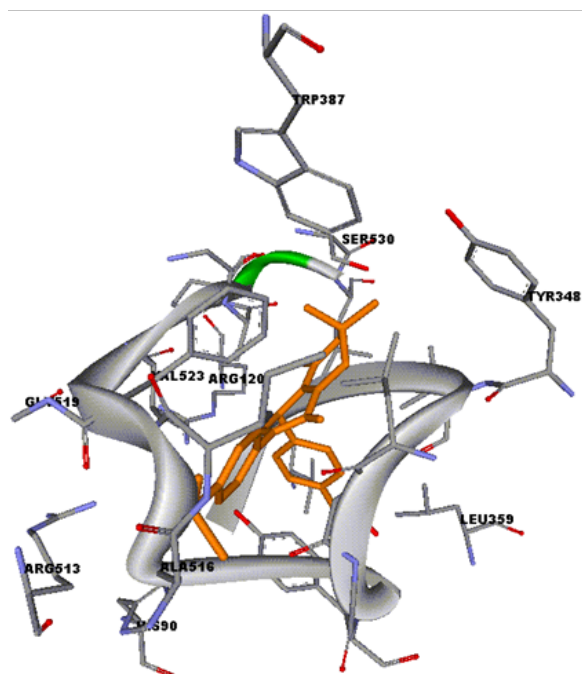
Compound	X	Y	IC <sub>50</sub> (M) <sup>a</sup>		COX-2 S.I. <sup>b</sup>
			COX-1	COX-2	
9a	H	SO <sub>2</sub> Me	2.6	0.8	3.3
9b	Me	SO <sub>2</sub> Me	2.5	0.45	5.6
9c	OMe	SO <sub>2</sub> Me	16.6	0.17	97.6
9d	F	SO <sub>2</sub> Me	12.9	0.3	43
9e	Cl	SO <sub>2</sub> Me	18.7	4.9	3.8
9f	Br	SO <sub>2</sub> Me	20.9	10.1	2.1
9g	NO <sub>2</sub>	SO <sub>2</sub> Me	17.6	16.6	1.1
9h	SO <sub>2</sub> Me	H	3.6	1.16	3.1
9i	SO <sub>2</sub> Me	Me	2.9	1.30	2.2
9j	SO <sub>2</sub> Me	OMe	18.7	0.3	62.3
9k	SO <sub>2</sub> Me	F	14.2	1.0	14.2
9l	SO <sub>2</sub> Me	Cl	21.6	6.9	3.1
9m	SO <sub>2</sub> Me	Br	17.9	13.2	1.3
9n	SO <sub>2</sub> Me	NO <sub>2</sub>	18.6	24.9	0.7
Celecoxib			24.3	0.06	405

<sup>a</sup>Values are mean values of two determinations acquired using an ovine COX-1/COX-2 assay kit, where the deviation from the mean is < 10% of the mean value.

<sup>b</sup>*In-vitro* COX-2 selectivity index (COX-1 IC<sub>50</sub> / COX-2 IC<sub>50</sub>).

4-OMe, 4-Me, 4-NO<sub>2</sub>) at the *para*-position of the C-4 phenyl ring (9a-g), and the corresponding regioisomers (9h-n), were prepared to study the effect of these substituents on COX-2 selectivity and potency. SAR data (IC<sub>50</sub> M values) obtained by determination of the *in vitro* ability of the synthesized compounds to inhibit the COX-1 and COX-2 isozymes showed that the position of the COX-2 SO<sub>2</sub>Me pharmacophore and the nature of the *para*-substituents on the C-2 or C-4 phenyl ring were important on COX-2 inhibitory potency and selectivity. *In vitro* COX-1/COX-2 inhibition studies showed that compounds having a MeSO<sub>2</sub> group at the *para*-position of the C-2 phenyl ring (9a-g) were more selective COX-2 inhibitors compared to their corresponding regioisomers (9h-n). These results also indicated

that incorporation of a methoxy (OMe) substituent at the *para*-position of the C-2 or C-4 phenyl ring increased the potency and COX-2 selectivity. Accordingly, compounds 9c and 9j showed the best activity among the synthesized compounds (9c, IC<sub>50</sub> = 0.17 M, S.I. = 3.3; 9j, IC<sub>50</sub> = 0.30 M, S.I. = 62.3). In contrast introduction of large groups such as Cl, Br or NO<sub>2</sub> at the same position of C-2 phenyl (9e-g) and C-4 phenyl (9l-n) decreased COX-2 inhibitory potency and selectivity. However, the two regioisomers having an unsubstituted C-2 phenyl (9a), or C-4 phenyl (9h), ring were approximately equipotent inhibitors of COX-2 and showed similar selectivity. Our results indicated that 7, 8-dihydro-7,7-dimethyl-2-(4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)quinolin-5(1*H*,4*H*,



**Figure 2.** 7, 8-Dihydro-2-(4-methoxyphenyl)-7,7-dimethyl-4-(4-(methylsulfonyl)phenyl)quinolin-5(1*H*, 4*H*,6*H*)-one (9c) (orange) docked in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

6*H*)-one (9c), showed the optimal combination of COX-2 inhibitory potency and selectivity. A molecular modeling study of the most selective COX-2 inhibitor compound 9c docked in the COX-2 active site (Figure 2) shows that it binds in the primary binding-site such that the *p*-SO<sub>2</sub>Me substituent on the C-2 phenyl ring is well oriented into secondary pocket present in COX-2. One of the *O*-atoms of the SO<sub>2</sub>Me moiety forms a *H*-bond with the NH<sub>2</sub> of Arg<sup>513</sup> (distance = 3.1 Å), whereas the other *O*-atom is closer to the NH of His<sup>90</sup> (distance = 3.0 Å). In addition, the N-*H* of the central ring is near to C=O of Val<sup>349</sup> and can form hydrogen bonding interaction with this amino acid. (Distance = 3.9 Å). Moreover, the carbonyl group of 5-oxo-1, 4, 5,6,7,8 hexahydroquinolines is close to NH of Arg<sup>120</sup> (distance < 3Å) and can form *H*-bond with the NH of Arg<sup>120</sup>. These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity exhibited by 9c.

## Conclusions

A new class of 5-oxo-1, 4, 5,6,7,8 hexahydroquinolines that are readily accessible via a simple Hansch reaction, was designed for evaluation as COX-2 inhibitors. In vitro enzyme inhibition structure-activity studies indicated that (i) the hexahydroquinoline moiety present in a 2,4-diaryl-5-oxo-1,4,5,6,7,8 hexahydroquinoline structure is a suitable scaffold (template) to design COX-2 inhibitors, and (ii) 7,8-dihydro-7,7-dimethyl-2-(4-methoxyphenyl)-4-(4-(methylsulfonyl)phenyl)quinolin-5(1*H*,4*H*,6*H*)-one (9c) is not only a potent, but also a selective COX-2 inhibitor.

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