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\textsubscript{2}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\textsubscript{2}), 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\textsubscript{H},4\textsubscript{H},6\textsubscript{H})-one (9c) as a potent COX-2 inhibitor (IC\textsubscript{50} = 0.17 M) with a high COX-2 selectivity index (S.I. = 97.6) comparable to the reference drug celecoxib (COX-2 IC\textsubscript{50} = 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 \textit{p}-SO\textsubscript{2}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\textsubscript{2}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 \textit{para}-SO\textsubscript{2}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 \textit{trans}-olefin system displays COX-1 selectivity (2). In contrast, it showed that the 1,1,2-tiraryl (\textit{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...
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\textsubscript{2}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\textsubscript{2}) 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.

**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).

**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 \textsuperscript{1}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...
of 70 eV with a source temperature of 250 °C. Elemental microanalyses, determined for C and H, were within ±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 1HNMR 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-cyclohexandion, 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. 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.

**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-cyclohexandion (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) υ (cm⁻¹) 1150, 1300 (SO₂), 1400-1600 (aromatic), 1667 (C=O), 3254 (NH); 1HNMR (CDCl₃, 500 MHz): δ 1.07 (s, 3H, CH₃), 1.15 (s, 3H,CH₃), 2.21–2.31 (q, 2H, dihydroquinoline H₈), 2.39-2.48 (q, 2H, dihydroquinoline H₆, J=16.2 Hz), 3.08 (s, 3H, SO₂Me), 4.79 (d, 1H, dihydroquinoline H₄, J=5.3 Hz), 5.44 (d, 1H, dihydroquinoline H₃, J=5.3 Hz), 5.88 (s, 1H, NH), 7.17–7.20 (t, 1H, phenyl H₃), 7.29–7.32 (t, 2H, phenyl H₃ and H₅), 7.38 (d, 2H, phenyl H₂ and H₆, J= 7.0 Hz), 7.64(d, 2H, methanesulfonyl phenyl H₂ and H₆, J=8.4 Hz), 7.96 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J=8.4 Hz); Anal. Calcd. for C₂₅H₂₇NO₃S: 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-methoxyphenyl)-2-(4-methylsulfonyl) phenyl quinolin-5-(1H, 4H, 6H)-one (9b)**

Yield, 51 %; mp 250-253 °C; IR (KBr disk) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1667 (C=O); 3254 (NH); 1H NMR (CDCl₃, 500 MHz): δ 1.08 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.22–2.47 (m, 4H, dihydroquinoline H₂ and H₅), 2.32 (s, 3H, CH₃), 3.08 (s, 3H, SO₂Me), 4.76 (d, 1H, dihydroquinoline H₃, J = 5.1 Hz), 5.44 (d, 1H, dihydroquinoline H₄, J = 5.2 Hz), 5.68 (s, 1H, NH), 7.08-7.12 (m, 2H, p-toluoyl H and H₂), 7.25–7.27 (m, 2H, p-toluoyl H and H₂), 7.64 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.3 Hz), 7.98 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.3 Hz); Anal. Calcd. for C₂₆H₂₅NO₃S: C, 70.53; H, 6.32; N, 3.52.

8. **7-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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1665 (C=O); 3240 (NH); 1H NMR (CDCl₃, 500 MHz): δ 0.98 (s, 3H, CH₃), 1.06 (s, 3H, CH₃), 2.10–2.13 (t, 1H, dihydroquinoline H₂), 2.21 (d, 1H, dihydroquinoline H₃, J = 16.3 Hz), 2.41 (d, 2H, dihydroquinoline H₅, J = 16.4 Hz), 3.01 (s, 3H, SO₂Me), 3.7 (s, 3H, OCH₃), 4.66 (d, 1H, dihydroquinoline H₁, J = 5.3 Hz), 5.32 (d, 1H, dihydroquinoline H₅, J = 5.3 Hz), 6.77 (d, 2H, 4-methoxyphenyl H and H₅, J = 8.6 Hz), 7.20-7.24 (m, 2H, 4-methoxyphenyl H and H₅), 7.64 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.1 Hz), 7.88 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.4 Hz); Anal. Calcd. for C₂₆H₂₅NO₃S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1669 (C=O); 3390 (NH); 2.2 (d, 1H, dihydroquinoline H₃, J = 16.1 Hz), 2.3-2.37 (m, 2H, dihydroquinoline H₂ and H₃), 2.45 (d, 1H, dihydroquinoline H₅, J = 16.3 Hz), 3.0 (s, 3H, SO₂Me), 4.88 (d, 1H, dihydroquinoline H₁, J = 5.0 Hz), 5.1 (d, 1H, dihydroquinoline H₅, J = 5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.22 (t, 2H, 4-fluorophenyl H and H₅), 7.40-7.42 (q, 2H, 4-fluorophenyl H and H₅), 7.58 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.8 Hz), 7.9 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.2 Hz); Anal. Calcd. for C₂₆H₂₅BrFNO₃S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1669 (C=O); 3248 (NH); 1H NMR (CDCl₃, 500 MHz): δ 1.07 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.21–2.31 (q, 2H, dihydroquinoline H₂), 2.33-2.47 (q, 2H, dihydroquinoline H₃, J = 16.2 Hz), 3.08 (s, 3H, SO₂Me), 4.75 (d, 1H, dihydroquinoline H₅, J = 5.3 Hz), 5.44 (d, 1H, dihydroquinoline H₅, J = 5.3 Hz), 5.78 (s, 1H, NH), 6.85 (d, 2H, 4-chlorophenyl H and H₅, J = 9.6 Hz), 7.29 (m, 2H, 4-chlorophenyl H and H₅), 7.65 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.4 Hz), 7.98 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.5 Hz); Anal. Calcd. for C₂₆H₂₅ClNO₃S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1661 (C=O); 3198 (NH); 1H NMR (CDCl₃, 500 MHz): δ 0.98 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 2.14-2.19 (m, 2H, dihydroquinoline H₂), 2.2-2.1 (q, 2H, dihydroquinoline H₃), 3.02 (s, 3H, SO₂Me), 4.18-4.21 (t, 1H, dihydroquinoline H₂), 4.69 (d, 1H, dihydroquinoline H₃, J = 5.3 Hz), 5.27 (d, 1H, NH), 7.17 (d, 2H, 4-bromophenyl H and H₅, J = 8.3 Hz), 7.32 (d, 2H, 4-bromophenyl H and H₅, J = 8.3 Hz), 7.64 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.3 Hz), 7.90 (d, 2H, methanesulfonyl phenyl H and H₅, J = 8.4 Hz); Anal. Calcd. for C₂₆H₂₅BrNO₃S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1661 (C=O); 3238 (NH); ¹HNMR (CDCl₃, 500 MHz): δ 0.98 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.11–2.24 (m, 2H, dihydroquinoline H₆), 2.37-2.45 (q, 2H, dihydroquinoline H₅), 3.03 (s, 3H, SO₃Me), 4.86 (d, 1H, dihydroquinoline H₇, J = 5.1 Hz), 5.24 (d, 1H, dihydroquinoline H₈, J = 5.1 Hz), 7.4 (d, 2H, 4-nitrophenyl H₆ and H₇, J = 8.6 Hz), 7.66 (d, 2H, 4-nitrophenyl H₆ and H₇, J = 8.4 Hz), 7.92 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.4 Hz), 8.10 (d, 2H, methanesulfonyl phenyl H₇ and H₆, J = 8.5 Hz); Anal. Calcd. for C₃₂H₂₆NO₈S: C, 68.74; H, 5.99; N, 3.31. Found: C, 68.81; 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1667 (C=O); 3356 (NH); ¹HNMR (CDCl₃): δ 1.07 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.23 (d, 1H, dihydroquinoline H₆, J = 16.5 Hz), 2.32 (d, 1H, dihydroquinoline H₆, J = 16.5 Hz), 2.38 (d, 1H, dihydroquinoline H₆, J = 16.3 Hz), 2.49 (d, 1H, dihydroquinoline H₆, J = 16.3 Hz), 3.05 (s, 3H, SO₃Me), 4.90 (d, 1H, dihydroquinoline H₆, J = 5.0 Hz), 5.25 (d, 1H, dihydroquinoline H₆, J = 5.0 Hz), 5.93 (s, 1H, NH), 7.41-7.48 (m, 5H, phenyl), 7.59 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.7 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.7 Hz); Anal. Calcd. for C₃₂H₂₆NO₈S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1685(C=O); 3024 (NH); ¹HNMR (CDCl₃, 500 MHz): δ 1.06 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.22 (d, 1H, dihydroquinoline H₆, J = 16.3 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H₆ and H₇), 2.40 (s, 3H, CH₃), 2.45-2.48 (d, 1H, dihydroquinoline H₆, J = 16.2 Hz), 3.03 (s, 3H, SO₃Me), 4.88 (d, 1H, dihydroquinoline H₇, J = 5.0 Hz), 5.21 (d, 1H, dihydroquinoline H₈, J = 5.0 Hz), 5.88 (s, 1H, NH), 7.32 (d, 2H, p-toluoyl H₆ and H₇, J = 8.0 Hz), 7.58 (d, 2H, p-toluoyl H₆ and H₇, J = 8.3 Hz), 7.57 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.3 Hz), 7.86 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.3 Hz); Anal. Calcd. for C₃₂H₂₆NO₈S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1664 (C=O); 3342 (NH); ¹HNMR (CDCl₃): δ 1.05 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.21 (d, 1H, dihydroquinoline H₆, J = 16.3 Hz), 2.33 (m, 2H, dihydroquinoline H₆ and H₇), 2.46 (d, 1H, dihydroquinoline H₆, J = 16.3 Hz), 2.49 (d, 1H, dihydroquinoline H₇, J = 16.3 Hz), 3.03 (s, 3H, SO₃Me), 3.85 (s, 3H, OCH₃), 4.87 (d, 1H, dihydroquinoline H₇, J = 5.0 Hz), 5.15 (d, 1H, dihydroquinoline H₈, J = 5.0 Hz), 5.88 (s, 1H, NH), 6.94 (d, 2H, 4-methoxyphenyl H₆ and H₇, J = 8.7 Hz), 7.36 (d, 2H, 4-methoxyphenyl H₆ and H₇, J = 8.7 Hz), 7.58 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.2 Hz), 7.86 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.2 Hz); Anal. Calcd. for C₃₂H₂₆NO₈S: 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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1664 (C=O); 3028 (NH); ¹HNMR (CDCl₃): δ 1.06 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.22 (d, 1H, dihydroquinoline H₆, J = 16.3 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H₆ and H₇), 2.47 (d, 1H, dihydroquinoline H₇, J = 16.3 Hz), 3.04 (s, 3H, SO₃Me), 4.88 (d, 1H, dihydroquinoline H₈, J = 5.0 Hz), 5.18 (d, 1H, dihydroquinoline H₉, J = 5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.13 (t, 2H, 4-fluorophenyl H₆ and H₇), 7.40-7.42 (q, 2H, 4-fluorophenyl H₆ and H₇), 7.58 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H₆ and H₇, J = 8.8 Hz).
$J = 8.2$ Hz); Anal. Calcd. for C$_{24}$H$_{24}$FNO$_S$: 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); $\delta$HNMR (CDCl$_3$): $\delta$ 1.07 (s, 3H, CH$_3$), 1.17 (s, 3H, CH$_3$), 2.24 (d, 1H, dihydroquinoline H$_\alpha$, $J = 16.4$ Hz), 3.05 (s, 2H, dihydroquinoline H$_\beta$ and H$_\gamma$), 2.50 (d, 1H, dihydroquinoline H$_\eta$, $J = 16.3$ Hz), 3.05 (s, 1H, SO$_2$Me), 4.88 (d, 1H, dihydroquinoline H$_\delta$, $J = 5.0$ Hz), 5.23 (d, 1H, dihydroquinoline H$_\beta$, $J = 5.0$ Hz), 5.84 (s, 1H, NH), 7.37-7.38 (m, 4H, 4-chlorophenyl), 7.58 (d, 2H, methanesulfonyl phenyl H$_\alpha$ and H$_\gamma$, $J = 8.2$ Hz), 7.88 (d, 2H, methanesulfonyl phenyl H$_\beta$ and H$_\delta$, $J = 8.2$ Hz); Anal. Calcd. for C$_{24}$H$_{24}$ClNO$_S$: C, 65.70; H, 5.47; N, 3.17. Found: C, 65.36; H, 5.69; N, 3.32

2-(4-Chlorophenyl)-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); 1654 (C=O); 3300 (NH); $\delta$HNMR (CDCl$_3$): $\delta$ 1.06 (s, 3H, CH$_3$), 1.16 (s, 3H, CH$_3$), 2.23 (d, 1H, dihydroquinoline H$_\alpha$, $J = 16.4$ Hz), 2.29-2.38 (m, 2H, dihydroquinoline H$_\beta$ and H$_\gamma$), 2.47 (d, 1H, dihydroquinoline H$_\delta$, $J = 16.4$ Hz), 3.04 (s, 1H, SO$_2$Me), 4.87 (d, 1H, dihydroquinoline H$_\delta$, $J = 5.1$ Hz), 5.23 (d, 1H, dihydroquinoline H$_\delta$, $J = 4.9$ Hz), 5.81 (s, 1H, NH), 7.31 (d, 2H, methanesulfonyl phenyl H$_\alpha$ and H$_\gamma$, $J = 8.8$ Hz), 7.54-7.57 (m, 4H, 4-bromophenyl), 7.87 (d, 2H, methanesulfonyl phenyl H$_\alpha$ and H$_\gamma$, $J = 8.2$ Hz); Anal. Calcd. for C$_{26}$H$_{26}$BrNO$_S$: C, 59.26; H, 4.97; N, 2.88. Found: C, 59.39; H, 5.12; N, 3.01.

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 hydrogen 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,
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4-OMe, 4-Me, 4-NO2) 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 (IC50 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 SO2Me 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 MeSO2 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, IC50 = 0.17 M, S.I. = 97.6; 9j, IC50 = 0.30 M, S.I. = 62.3). In contrast introduction of large groups such as Cl, Br or NO2 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(1H,4H,

| Compound | X   | Y    | IC50 (M)a | COX-1 | COX-2 | S.I. b |
|----------|-----|------|-----------|-------|-------|-------|
| 9a       | H   | SO2Me| 2.6       | 0.8   | 3.3   |
| 9b       | Me  | SO2Me| 2.5       | 0.45  | 5.6   |
| 9c       | OMe | SO2Me| 16.6      | 0.17  | 97.6  |
| 9d       | F   | SO2Me| 12.9      | 0.3   | 43    |
| 9e       | Cl  | SO2Me| 18.7      | 4.9   | 3.8   |
| 9f       | Br  | SO2Me| 20.9      | 10.1  | 2.1   |
| 9g       | NO2 | SO2Me| 17.6      | 16.6  | 1.1   |
| 9h       | SO2Me| H  | 3.6       | 1.16  | 3.1   |
| 9i       | SO2Me| Me | 2.9       | 1.30  | 2.2   |
| 9j       | SO2Me| OMe| 18.7      | 0.3   | 62.3  |
| 9k       | SO2Me| F  | 14.2      | 1.0   | 14.2  |
| 9l       | SO2Me| Cl | 21.6      | 6.9   | 3.1   |
| 9m       | SO2Me| Br | 17.9      | 13.2  | 1.3   |
| 9n       | SO2Me| NO2| 18.6      | 24.9  | 0.7   |
| Celecoxib|     |     | 24.3      | 0.06  | 405   |

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.

In-vitro COX-2 selectivity index (COX-1 IC50/ COX-2 IC50).
Figure 2. 7, 8-Dihydro-2-(4-methoxyphenyl)-7,7-dimethyl-4-(4-(methylsulfonyl)phenyl)quinolin-5(1H, 4H,6H)-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.

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(1H,4H,6H)-one (9c) is not only a potent, but also a selective COX-2 inhibitor.

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