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

Afshin Zarghi*, Iman Sabakhi, Vigen Topuzyan, Zahra Hajimahdi and Bahram Daraie

*Department of Medicinal Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The Scientific Thecnological Centre of Organic and Pharmaceutical Chemistry NASRAAL. Mnjoyan Institute of Fine Organic Chemistry, Yerevan, Armenia. The Scientific Thecnological Centre of Organic and Pharmaceutical Chemistry NASRAAL. Mnjoyan Institute of Fine Organic Chemistry, Yerevan, Armenia. Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Department of Toxicology, School of Medicine, Tarbiat Modarres University of Medical Sciences, Tehran, Iran.

Abstract

A group of regioisomeric 5-oxo-1,4,5,6,7,8 hexahydroquinoline derivatives possessing a COX-2 SO$_2$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$_2$), 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$H$,4$H$,6$H$)-one (9c) as a potent COX-2 inhibitor (IC$_{50}$ = 0.17 M) with a high COX-2 selectivity index (S.I. = 97.6) comparable to the reference drug celecoxib (COX-2 IC$_{50}$ = 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 $p$-SO$_2$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$_2$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 para-SO$_2$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 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
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 $^1$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-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. 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-methyalsulfonyl) 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=5.2 Hz), 5.44 (d, 1H, dihydroquinoline H₃, J=5.3 Hz), 5.88 (s, 1H, NH), 7.17–7.20 (t, 1H, phenyl H₂), 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 H₆ and H₇, J=8.4 Hz), 7.96 (d, 2H, methanesulfonyl phenyl H₂ and H₇, J=8.4 Hz); Anal. Calcd. for C₂₅H₂₆NO₃S: 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); 1'H NMR (CDCl₃, 500 MHz): δ 1.08 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.22-2.47 (m, 4H, dihydroquinoline H₂ and H₆), 2.32 (s, 3H, CH₃), 3.08 (s, 3H, SO₂Me), 4.76 (d, 1H, dihydroquinoline H₄, J = 5.1 Hz), 5.44 (d, 1H, dihydroquinoline H₃, J = 5.2 Hz), 5.68 (s, 1H, NH), 7.08-7.12 (m, 2H, p-toluoyl H₁ and H₂), 7.25-7.27 (m, 2H, p-toluoyl H₁ and H₂), 7.64 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.3 Hz), 7.98 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.3 Hz); Anal. Calcd. for C₇H₆NO₂S: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.53; H, 6.32; N, 3.52.

8. **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) ν (cm⁻¹) 1150, 1300 (SO₂); 1400-1600 (aromatic); 1665 (C=O); 3240 (NH); 1'H 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 = 6.3 Hz), 2.41 (d, 2H, dihydroquinoline H₁, J = 6.4 Hz), 3.01 (s, 3H, SO₂Me), 3.7 (s, 3H, OCH₃), 4.66 (d, 1H, dihydroquinoline H₄, J = 5.3 Hz), 5.32 (d, 1H, dihydroquinoline H₂, J = 5.3 Hz), 6.77 (d, 2H, 4-methoxyphenyl H₁ and H₂, J = 8.6 Hz), 7.20-7.24 (m, 2H, 4-methoxyphenyl H₁ and H₂), 7.64 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.1 Hz), 7.88 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.4 Hz); Anal. Calcd. for C₂₅H₂₅NO₂S: C, 68.62; H, 6.22; N, 3.20. Found: C, 68.89; H, 6.36; N, 3.39.

7. **8-Dihydro-4-(3-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 H₄, J = 16.1 Hz), 2.3-2.37 (m, 2H, dihydroquinoline H₁ and H₂), 2.45 (d, 1H, dihydroquinoline H₄, J = 16.3 Hz), 3.0 (s, 3H, SO₂Me), 4.88 (d, 1H, dihydroquinoline H₅, J = 5.0 Hz), 5.1 (d, 1H, dihydroquinoline H₆, J = 5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.22 (t, 2H, 4-fluorophenyl H₁ and H₂), 7.40-7.42 (q, 2H, 4-fluorophenyl H₁ and H₂), 7.58 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.8 Hz), 7.9 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.2 Hz); Anal. Calcd. for C₂₅H₂₅FNO₂S: 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); 1'H 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 H₁, J = 6.2 Hz), 3.08 (s, 3H, SO₂Me), 4.75 (d, 1H, dihydroquinoline H₆, J = 5.3 Hz), 5.44 (d, 1H, dihydroquinoline H₃, J = 5.3 Hz), 5.78 (s, 1H, NH), 6.85 (d, 2H, 4-chlorophenyl H₁ and H₂, J = 9.6 Hz); 7.29 (m, 2H, 4-chlorophenyl H₁ and H₂), 7.65 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.4 Hz), 7.98 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.5 Hz); Anal. Calcd. for C₂₅H₂₃ClNO₂S: 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); 1'H NMR (CDCl₃, 500 MHz): δ 0.98 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 2.14-2.19 (m, 2H, dihydroquinoline H₂), 2.2-2.21 (q, 2H, dihydroquinoline H₁), 3.02 (s, 3H, SO₂Me), 4.18-4.21 (t, 1H, dihydroquinoline H₄), 4.69 (d, 1H, dihydroquinoline H₃, J = 5.3 Hz), 5.27 (d, 1H, NH), 7.17 (d, 2H, 4-bromophenyl H₁ and H₂, J = 8.3 Hz), 7.32 (d, 2H, 4-bromophenyl H₁ and H₂, J = 8.3 Hz), 7.64 (d, 2H, methanesulfonyl phenyl H₁ and H₂, J = 8.3 Hz), 7.90 (d, 2H, methanesulfonyl phenyl H₂ and H₆, J = 8.4 Hz); Anal. Calcd. for C₂₅H₂₁BrNO₂S: 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); 3000-1600 (aromatic); 1662 (C=O); 3328 (NH); 1HNMR (CDCl₃, 500 MHz): δ 0.98 (s, 3H, CH₃), 1.08 (s, 3H, CH₃), 2.11-2.24 (m, 2H, dihydroquinoline H₂), 2.37-2.45 (q, 2H, dihydroquinoline H₃), 3.03 (s, 3H, SO₂Me), 4.86 (d, 1H, dihydroquinoline H₁₀, J = 5.1 Hz), 5.24 (d, 1H, dihydroquinoline H₉, J = 5.1 Hz), 7.4 (d, 2H, 4-nitrophenyl H, and H, J = 8.6 Hz), 7.66 (d, 2H, 4-nitrophenyl H, and H, J = 8.4 Hz), 7.92 (d, 2H, methanesulfonyl phenyl H₂, and H, J = 8.4 Hz), 8.10 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.7 Hz); Anal. Calcd. for C₃₈H₃₇NO₂S: C, 71.23; H, 6.46; N, 3.32. Found: C, 71.54; H, 6.67; N, 3.39.

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

Yield, 53%; mp 220-240 °C; IR (KBr disk) ν (cm⁻¹) 1150, 1300 (SO₂); 3000-1600 (aromatic); 1664 (C=O); 3342 (NH); 1HNMR (CDCl₃, 500 MHz): δ 1.05 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.21 (d, 1H, dihydroquinoline H₉, J = 16.5 Hz), 2.38 (d, 1H, dihydroquinoline H₉, J = 16.5 Hz), 2.49 (d, 1H, dihydroquinoline H₉, J = 16.3 Hz), 3.05 (s, 3H, SO₂Me), 4.90 (d, 1H, dihydroquinoline H₁₀, J = 5.0 Hz), 5.25 (d, 1H, dihydroquinoline H₁₀, J = 5.0 Hz), 5.93 (s, 1H, NH), 7.41-7.48 (m, 5H, phenyl), 7.59 (d, 2H, methanesulfonyl phenyl H₂, and H, J = 8.7 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.7 Hz); Anal. Calcd. for C₃₈H₃₇NO₂S: C, 70.70; 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 (9i)

Yield, 53%; mp 220-240 °C; IR (KBr disk) ν (cm⁻¹) 1150, 1300 (SO₂); 3000-1600 (aromatic); 1664 (C=O); 3342 (NH); 1HNMR (CDCl₃, 500 MHz): δ 1.05 (s, 3H, CH₃), 1.15 (s, 3H, CH₃), 2.21 (d, 1H, dihydroquinoline H₉, J = 16.3 Hz), 2.33 (m, 2H, dihydroquinoline H, and H, J = 6.3 Hz), 2.46 (d, 1H, dihydroquinoline H, J = 16.3 Hz), 2.49 (d, 1H, dihydroquinoline H, J = 16.3 Hz), 3.03 (s, 3H, SO₂Me), 3.85 (s, 3H, OCH₃), 4.87 (d, 1H, dihydroquinoline H, J = 5.0 Hz), 5.15 (d, 1H, dihydroquinoline H, J = 5.0 Hz), 5.88 (s, 1H, NH), 6.94 (d, 2H, 4-methoxyphenyl H, and H, J = 8.7 Hz), 7.36 (d, 2H, 4-methoxyphenyl H, and H, J = 8.7 Hz), 7.58 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.2 Hz); Anal. Calcd. for C₃₈H₃₇NO₂S: 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 (9j)

Yield, 89%; mp 220-240 °C; IR (KBr disk) ν (cm⁻¹) 1150, 1300 (SO₂); 3000-1600 (aromatic); 1664 (C=O); 3342 (NH); 1HNMR (CDCl₃, 500 MHz): δ 1.06 (s, 3H, CH₃), 1.16 (s, 3H, CH₃), 2.22 (d, 1H, dihydroquinoline H, J = 16.3 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H, and H, J = 6.3 Hz), 2.47 (d, 1H, dihydroquinoline H, J = 16.3 Hz), 3.04 (s, 3H, SO₂Me), 4.88 (d, 1H, dihydroquinoline H, J = 5.0 Hz), 5.18 (d, 1H, dihydroquinoline H, J = 5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.13 (t, 2H, 4-fluorophenyl H, and H), 7.40-7.42 (q, 2H, 4-fluorophenyl H, and H), 7.58 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.8 Hz), 7.58 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H, and H, J = 8.8 Hz).
\[ J = 8.2 \text{ Hz}; \] 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); \(^1\)H NMR (CDCl\(_3\)) : \( \delta \) 1.07 (s, 3H, CH\(_3\)), 1.17 (s, 3H, CH\(_3\)), 2.24 (d, 2H, dihydroquinoline H\(_1\), \( J = 16.3 \) Hz), 3.05 (s, 3H, SO\(_2\)Me), 4.88 (d, 1H, dihydroquinoline H\(_3\), \( J = 5.0 \) Hz), 5.23 (d, 1H, dihydroquinoline H\(_5\), \( J = 5.0 \) Hz), 5.84 (s, 1H, NH), 7.37-7.38 (m, 4H, 4-chlorophenyl), 7.58 (d, 2H, methanesulfonyl phenyl H\(_2\) and H\(_3\), \( J = 8.2 \) Hz), 7.88 (d, 2H, methanesulfonyl phenyl H\(_2\) and H\(_3\), \( J = 8.2 \) Hz); Anal. Calcd. for C\(_{24}\)H\(_{24}\)CINO\_S: 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); \(^1\)H NMR (CDCl\(_3\)) : \( \delta \) 1.06 (s, 3H, CH\(_3\)), 1.16 (s, 3H, CH\(_3\)), 2.23 (d, 1H, dihydroquinoline H\(_1\), \( J = 16.4 \) Hz), 2.29-2.38 (m, 2H, dihydroquinoline H\(_1\) and H\(_3\)), 2.47 (d, 1H, hydroquinoline H\(_5\), \( J = 16.4 \) Hz), 3.04 (s, 3H, SO\(_2\)Me), 4.87 (d, 1H, dihydroquinoline H\(_5\), \( J = 5.1 \) Hz), 5.23 (d, 1H, dihydroquinoline H\(_5\), \( J = 4.9 \) Hz), 5.81 (s, 1H, NH), 7.31 (d, 2H, methanesulfonyl phenyl H\(_2\) and H\(_3\), \( J = 8.8 \) Hz), 7.54-7.57 (m, 4H, 4-bromophenyl), 7.87 (d, 2H, methanesulfonyl phenyl H\(_2\) and H\(_3\), \( J = 8.2 \) Hz); Anal. Calcd. for C\(_{24}\)H\(_{22}\)BrNO\_S: 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); \(^1\)H 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\(_5\)), 2.33 (d, 1H, dihydroquinoline H\(_5\), \( J = 16.3 \) Hz), 2.42 (d, 1H, dihydroquinoline H\(_5\), \( J = 16.4 \) Hz), 2.52 (d, 1H, dihydroquinoline H\(_5\), \( J = 16.4 \) Hz), 3.05 (s, 3H, SO\(_2\)Me), 4.91 (d, 1H, dihydroquinoline H\(_5\), \( J = 5.1 \) Hz), 5.39 (d, 1H, dihydroquinoline H\(_5\), \( J = 5.0 \) Hz), 5.98 (s, 1H, NH), 7.57 (d, 2H, 4-nitrophenyl H\(_2\) and H\(_3\), \( J = 8.3 \) Hz), 7.61 (d, 2H, 4-nitrophenyl H\(_2\) and H\(_3\), \( J = 8.8 \) Hz), 7.87 (d, 2H, methanesulfonyl phenyl H\(_2\) and H\(_3\), \( J = 8.3 \) Hz), 8.28 (d, 2H, methanesulfonyl phenyl H\(_2\) and H\(_3\), \( J = 8.1 \) Hz); Anal. Calcd. for C\(_{24}\)H\(_{24}\)N\(_2\)O\(_2\): C, 63.70; H, 5.35; N, 6.19. Found: C, 63.94; H, 5.57; N, 6.41.

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, 4-Br, 4-Br).
Design, Synthesis and Biological Evaluation of 5-Oxo-1,4,5,6,7,8-

67

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,

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

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

*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.

bIn-vitro COX-2 selectivity index (COX-1 IC₅₀/COX-2 IC₅₀).
6H)-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-SO₂Me substituent on the C-2 phenyl ring is well oriented into secondary pocket present in COX-2. One of the O-atoms of the SO₂Me moiety forms a H-bond with the NH₂ of Arg⁵¹³ (distance = 3.1 Å), whereas the other O-atom is closer to the NH of His⁹⁰ (distance = 3.0 Å). In addition, the N-H of the central ring is near to C=O of Val³⁹⁸ 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 Arg¹²⁰ (distance < 3 Å) and can form H-bond with the NH of Arg¹²⁰. 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-1-2-(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.

Acknowledgments

We like to thank Deputy of Research, School of Pharmacy, Shahid Beheshti University of Medical Sciences for financial support of this work as part of PhD thesis of Iman Sabakhi.

References


This article is available online at http://www.ijpr.ir