Iranian Journal of Pharmaceutical Research (2014),13 (supplement): 61-69
Received: November 2013
Accepted: November 2013

Original Article

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_2Me 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_2Me 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_2Me 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_2Me 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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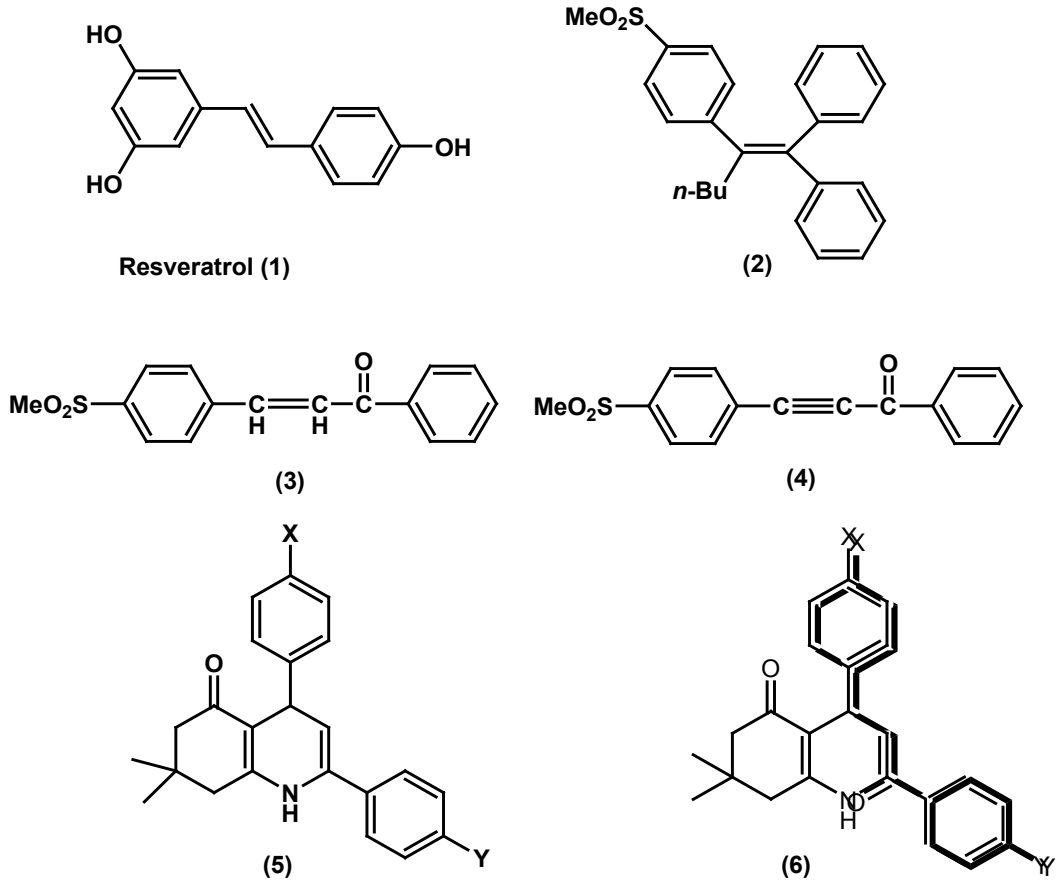


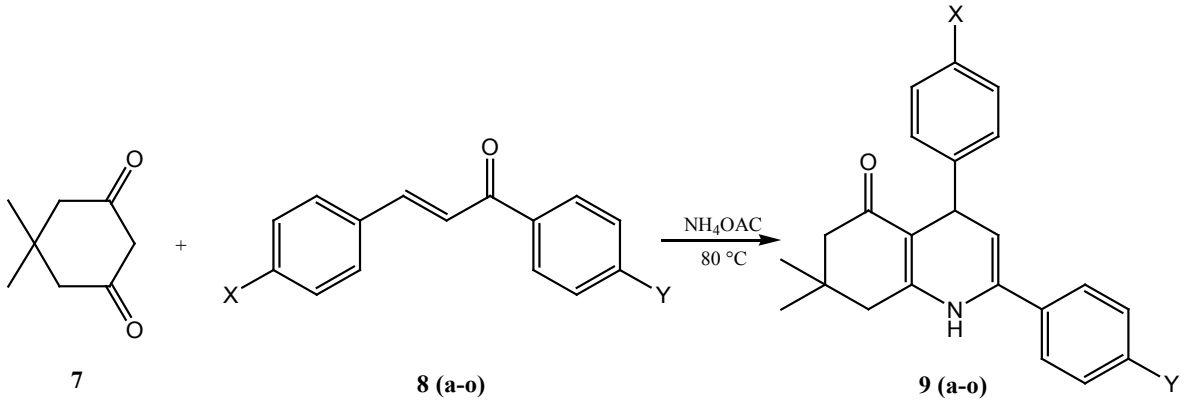
Figure 1. Some representative examples of a selective cyclooxygenase-1 (1), cyclooxygenase-2 (2-4) inhibitors, designed molecules (5) and overlay of our design molecules on lead compound 3 (6).

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_2Me 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_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.

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 ^1H 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 ±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}HNMR 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-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 (SO_2), 1400-1600 (aromatic), 1667 (C=O), 3254 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 3H, CH_3), 1.15 (s, 3H,CH_3), 2.21–2.31 (q, 2H, dihydroquinoline H_8), 2.39-2.48 (q, 2H, dihydroquinoline H_6, *J*=16.2 Hz), 3.08 (s, 3H, SO_2Me), 4.79 (d, 1H, dihydroquinoline H_4, *J*=5.2 Hz), 5.44 (d, 1H, dihydroquinoline H_3, *J*=5.3 Hz), 5.88 (s, 1H, NH), 7.17–7.20 (t, 1H, phenyl H_4), 7.29–7.32 (t, 2H, phenyl H_3 and H_5), 7.38 (d, 2H, phenyl H_2 and H_6, *J*= 7.0 Hz), 7.64(d, 2H, methanesulfonyl phenyl H_2 and H_6, *J*=8.4 Hz), 7.96 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J*=8.4 Hz); Anal. Calcd. for $C_{25}H_{27}NO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1667 (C=O); 3254 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.08 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.22–2.47 (m, 4H, dihydroquinoline H_6 and H_8), 2.32 (s, 3H, CH_3), 3.08 (s, 3H, SO_2Me), 4.76 (d, 1H, dihydroquinoline H_4, *J*= 5.1 Hz), 5.44 (d, 1H, dihydroquinoline H_3, *J*=5.2 Hz), 5.68 (s, 1H, NH), 7.08-7.12 (m ,2H, *p*-toluoyl H_3 and H_5) , 7.25–7.27 (m, 2H, *p*-toluoyl H_2 and H_6), 7.64 (d, 2H, methane sulfonyl phenyl H_2 and H_6, *J*=8.3 Hz), 7.98 (d, 2H, methanesulfonyl phenyl $H_3$and H_5, *J*= 8.3 Hz); Anal. Calcd. for $C_{24}H_{25}NO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1665 (C=O); 3240 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 0.98 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.10–2.13 (t, 1H, dihydroquinoline H_8), 2.21 (d, 1H, dihydroquinoline H_8, *J*=16.3 Hz), 2.41 (d, 2H, dihydroquinoline H_6, *J*=16.4 Hz), 3.01 (s, 3H, SO_2Me), 3.7 (s, 3H, OCH_3), 4.66 (d, 1H, dihydroquinoline H_4, *J*= 5.3 Hz), 5.32 (d, 1H , dihydroquinoline H_3, *J*= 5.3 Hz) , 6.77 (d, 2H, 4-methoxyphenyl H_3 and H_5, *J*= 8.6 Hz), 7.20-7.24 (m, 2H, 4-methoxyphenyl H_2 & H_6), 7.64 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J*=8.1 Hz), 7.88 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J*=8.4 Hz); Anal. Calcd. for $C_{25}H_{27}NO_4S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1669(C=O); 3390 (NH); 2.2 (d, 1H, dihydroquinoline H_8, *J*= 16.1 Hz), 2.3-2.37 (m, 2H, dihydroquinoline H_6 & H_8), 2.45 (d, 1H, dihydroquinoline H_6, *J*=16.3 Hz), 3.0 (s, 3H, SO_2Me), 4.88 (d, 1H, dihydroquinoline H_4, *J*= 5.0 Hz), 5.1 (d, 1H, dihydroquinoline H_3, *J*= 5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.22 (t, 2H, 4-fluorophenyl H_3 and H_5), 7.40-7.42 (q, 2H, 4-fluorophenyl H_2 and H_6), 7.58 (d, 2H, methanesulfonyl phenyl H_2 & H_6, *J*=8.8 Hz), 7.9 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J*=8.2 Hz); Anal. Calcd. for $C_{24}H_{24}FNO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1669(C=O); 3248 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.07 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.21–2.31 (q, 2H, dihydroquinoline H_8), 2.33-2.47 (q, 2H, dihydroquinoline H_6 , *J*=16.2 Hz), 3.08 (s, 3H, SO_2Me) , 4.75 (d, 1H, dihydroquinoline H_4, *J*=5.3 Hz), 5.44 (d, 1H, dihydroquinoline H_3, *J*=5.3 Hz), 5.78 (s, 1H, NH), 6.85 (d, 2H, 4-cholorophenyl H_3 and H_5, *J*= 9.6 Hz),7.29 (m, 2H, 4-cholorophenyl H_2 & H_6) 7.65 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J*=8.4 Hz), 7.98 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J*=8.5 Hz); Anal. Calcd. for $C_{24}H_{24}ClNO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1661(C=O); 3198 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 0.98 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.14–2.19 (m, 2H, dihydroquinoline H_8), 2.2-2.1 (q, 2H, dihydroquinoline H_6), 3.02 (s, 3H, SO_2Me), 4.18-4.21 (t, 1H, dihydroquinoline H_4), 4.69 (d, 1H, dihydroquinoline H_3, *J*=5.3 Hz), 5.27 (d, 1H, NH), 7.17 (d, 2H, 4-bromophenyl H_3 and H_5, *J*= 8.3 Hz), 7.32 (d, 2H, 4-bromophenyl H_2 & H_6, *J*= 8.3 Hz), 7.64 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J*=8.3 Hz), 7.90 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J*=8.4 Hz); Anal. Calcd. for $C_{24}H_{24}BrNO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1661(C=O); 3238 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 0.98 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.11–2.24 (m, 2H, dihydroquinoline H_8) , 2.37-2.45 (q, 2H, dihydroquinoline H_6), 3.03 (s, 3H , SO_2Me), 4.86 (d, 1H, dihydroquinoline H_4, *J*= 5.1 Hz) , 5.24 (d, 1H, dihydroquinoline H_3, *J*= 5.1 Hz), 7.4 (d, 2H, 4-nitrophenyl H_2 and H_6, *J*= 8.6 Hz), 7.66 (d, 2H, 4-nitrophenyl H_2 & H_6, *J*= 8.4 Hz), 7.92 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J*=8.4 Hz), 8.10 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J*=8.5 Hz); Anal. Calcd. for $C_{24}H_{24}N_2OS_5$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1667 (C=O); 3356 (NH); ^{1}HNMR ($CDCl_3$): δ 1.07 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 2.23 (d, 1H, dihydroquinoline H_8, *J*= 16.5 Hz), 2.32 (d, 1H, dihydroquinoline H_8, *J*=16.5 Hz), 2.38 (d, 1H, dihydroquinoline H_6, *J*=16.3 Hz), 2.49 (d, 1H, dihydroquinoline H_6, *J*= 16.3 Hz), 3.05 (s, 3H, SO_2Me), 4.90 (d, 1H, dihydroquinoline H_4, *J*= 5.0 Hz), 5.25 (d, 1H, dihydroquinoline H_3, *J*= 5.0 Hz), 5.93 (s, 1H, NH), 7.41-7.48 (m, 5H, phenyl), 7.59 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J* = 8.7 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J* = 8.7 Hz); Anal. Calcd. for $C_{24}H_{25}NO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1685(C=O); 3024 (NH) ;^{1}HNMR ($CDCl_3$, 500 MHz): δ 1.05 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.20 (d, 1H, dihydroquinoline H_8, *J*=16.1 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H_6 and H_8), 2.40 (s, 3H, CH_3), 2.45-2.48 (d, 1H, dihydroquinoline H_6, *J*= 16.2 Hz), 3.03 (s, 3H, SO_2Me), 4.88 (d, 1H, dihydroquinoline H_4, *J*= 5.0 Hz), 5.21 (d, 1H, dihydroquinoline H_3, *J*= 5.0 Hz), 5.88 (s, 1H, NH), 7.32 (d, 2H, *p*-toluoyl H_3 and H_5, *J* =8.0 Hz), 7.58 (d, 2H, *p*-toluoyl H_2 and H_6, *J*=8.3 Hz), 7.57 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J* =8.3 Hz), 7.86 (d, 2H, methanesulfonyl phenyl H_3 and H_5, *J* =8.3 Hz); Anal. Calcd. for $C_{25}H_{27}NO_3S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1664 (C=O); 3342 (NH); ^{1}HNMR ($CDCl_3$): δ 1.05 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.21 (d, 1H, dihydroquinoline H_8, *J*=16.3 Hz), 2.33 (m, 2H, dihydroquinoline H_6 and H_8), 2.46 (d, 1H, dihydroquinoline H_6, *J*=16.3 Hz), 2.49 (d, 1H, dihydroquinoline H_6, *J*=16.3 Hz), 3.03 (s, 3H, SO_2Me), 3.85 (s, 3H, OCH_3), 4.87 (d, 1H, dihydroquinoline H_4 , *J*= 5.0 Hz), 5.15 (d, 1H, dihydroquinoline H_3, *J*= 5.0 Hz), 5.88 (s, 1H, NH), 6.94 (d, 2H, 4-methoxyphenyl H_3 & H_5, *J*=8.7 Hz), 7.36 (d, 2H, 4-methoxyphenyl H_2 and H_6, *J*=8.7 Hz), 7.58 (d, 2H, methanesulfonyl phenyl H_2 and H_6 , *J* =8.2 Hz), 7.86 (d, 2H, methanesulfonyl phenyl H_3 & H_5, *J* =8.2 Hz); Anal. Calcd. for $C_{25}H_{27}NO_4S$: 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1664 (C=O); 3028 (NH); ^{1}HNMR ($CDCl_3$): δ 1.06 (s, 3H, CH_3), 1.16 (s, 3H,CH_3), 2.22 (d, 1H, dihydroquinoline H_8, *J*= 16.3 Hz), 2.29-2.37 (m, 2H, dihydroquinoline H_6 and H_8), 2.47 (d, 1H, dihydroquinoline H_6, *J*=16.3 Hz), 3.04 (s, 3H, SO_2Me), 4.88 (d, 1H, dihydroquinoline H_4, *J*= 5.0 Hz), 5.18 (d, 1H, dihydroquinoline H_3, *J*= 5.0 Hz), 5.77 (s, 1H, NH), 7.10-7.13 (t, 2H, 4-fluorophenyl H_3 and H_5), 7.40-7.42 (q, 2H, 4-fluorophenyl H_2 and H_6), 7.58 (d, 2H, methanesulfonyl phenyl H_2 and H_6, *J*=8.8 Hz), 7.87 (d, 2H, methanesulfonyl phenyl H_3 and H_5,

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-Cholorophenyl)-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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1654 (C=O); 3342 (NH); ^{1}HNMR ($CDCl_3$): δ 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1664 (C=O); 3355 (NH); ^{1}HNMR ($CDCl_3$): δ 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, hydroquinoline 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) υ (cm^{-1}) 1150, 1300 (SO_2); 1400-1600 (aromatic); 1664 (C=O); 3300 (NH); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 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*= 5.1Hz), 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, methane sulfonyl 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 intermolcular energy of the ligand-enzyme assembly (9).

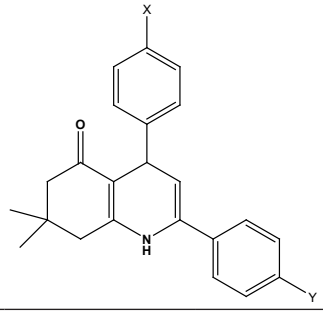
In-vitro cyclooxygenase (COX) inhibition assays

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_{50} (M)[a]		COX-2 S.I.[b]
			COX-1	COX-2	
9a	H	SO_2Me	2.6	0.8	3.3
9b	Me	SO_2Me	2.5	0.45	5.6
9c	OMe	SO_2Me	16.6	0.17	97.6
9d	F	SO_2Me	12.9	0.3	43
9e	Cl	SO_2Me	18.7	4.9	3.8
9f	Br	SO_2Me	20.9	10.1	2.1
9g	NO_2	SO_2Me	17.6	16.6	1.1
9h	SO_2Me	H	3.6	1.16	3.1
9i	SO_2Me	Me	2.9	1.30	2.2
9j	SO_2Me	OMe	18.7	0.3	62.3
9k	SO_2Me	F	14.2	1.0	14.2
9l	SO_2Me	Cl	21.6	6.9	3.1
9m	SO_2Me	Br	17.9	13.2	1.3
9n	SO_2Me	NO_2	18.6	24.9	0.7
Celecoxib			24.3	0.06	405

[a]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.
[b]*In-vit*ro COX-2 selectivity index (COX-1 IC_{50}/ COX-2 IC_{50}).

4-OMe, 4-Me, 4-NO_2) 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_{50} 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_2Me 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 $MeSO_2$ 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_{50} = 0.17 M, S.I. = 3.3; 9j, IC_{50} = 0.30 M, S.I. = 62.3). In contrast introduction of large groups such as Cl, Br or NO_2 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*,

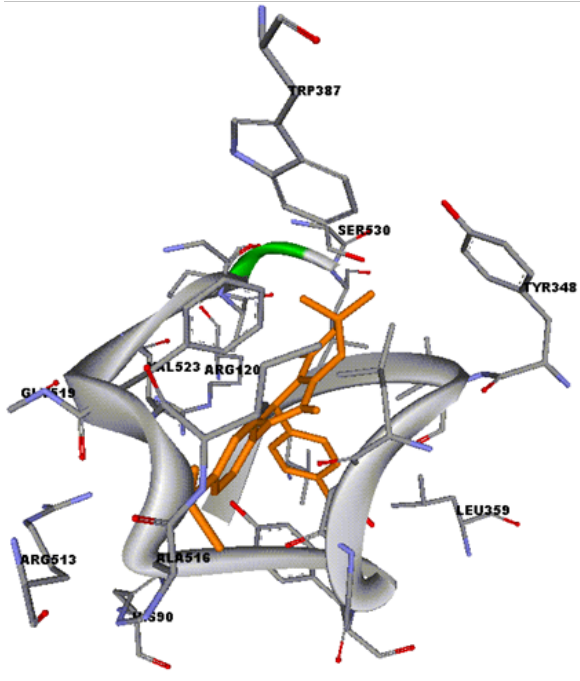


Figure 2. 7, 8-Dihydro-2-(4-methoxyphenyl)-7,7-dimethyl-4-(4-(methylsulfonyl)phenyl)quinolin-5(1*H*, 4*H*,6*H*)-one (9c) (orange) docked in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

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_2Me 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_2Me moiety forms a *H*-bond with the NH_2 of Arg^{513} (distance = 3.1 Å), whereas the other *O*-atom is closer to the N*H* of His^{90} (distance = 3.0 Å). In addition, the N-*H* of the central ring is near to C=*O* of Val^{349}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 N*H* of Arg^{120} (distance < 3Å) and can form *H*-bond with the N*H* of Arg^{120}. 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.

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.

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