A Series of Quinoline-2-carboxylic Acid Derivatives: New Potent Glycine Site NMDA Receptor Antagonists

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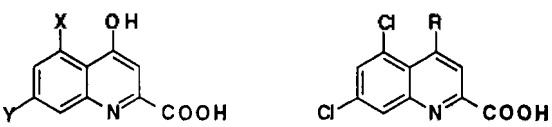
Several types of 4-substituted-quinoline-2-carboxylic acid derivatives possessing different substituents at C4-position such as sulfonyl, phosphonyl, carbonyl groups, or a flexible alkyl chain have been synthesized and evaluated for their *in vitro* antagonistic activity at the glycine site on the N-methyl-D-aspartate (NMDA) receptor. Of them, 5,7-dichloro-4-(tolylsulfonylamino)-quinoline-2-carboxylic acid **9** was found to have the best *in vitro* binding affinity with IC_{50} of 0.57 μM. On the other hand, in compounds **21** and **22** the introduction of flexible alkyl chains on C4 of the quinoline mother nuclei caused a significant decrease of the *in vitro* binding affinity. In addition, replacement of polar carboxylic acid group on C2 by neutral bioisosteres in compounds **23a-d** also seems to be disadvantageous to *in vitro* activity. In the structure-activity relationship (SAR) study of the 4-substituted quinoline-2-carboxylic acid acid derivatives, it was realized that the substitution pattern on C4 significantly influences on the binding affinity for the glycine site of NMDA receptor and the binding affinity might be increased by the introduction of a suitable electron rich substituent at C4 which has the ability of H-bonding donor.

Introduction

NMDA receptor is a cell surface protein complex that is involved in excitatory synaptic transmission.[1] Scientific evidences have implied that NMDA receptor plays a key role in neurodegeneration and related brain cell death and that its antagonists are considered as a class of potential therapeutic agents for the treatment of neurological disorders including ischemia, epilepsy.[2] They may also be useful in the prevention of chronic neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, and Parkinsonism.[3] The importance of NMDA receptor in neurodegenerative processes has been emphasized by recent progress in the understanding of the physiological functions and structural details of the subunits on the receptor.[4]

The NMDA receptor comprises a ligand gated ion channel which includes several distinct binding sites such as glutamate, glycine, phencyclidine (PCP), polyamines, and two inhibitory divalent cations, Mg^{++} and Zn^{++}, binding sites. Among them, glycine site is known to be rather pharmaceutically advantageous target because they may have a larger window between the desired and untoward effects of NMDA receptor blockage than other sites.[5] Of the earlier reported NMDA antagonists acting at the glycine site, 4-hydroxy-quinoline-2-carboxylic acid **1**, an endogenous product of the tryptophan metabolism pathway, has micromolar binding affinity for the glycine site of NMDA receptor (IC_{50}=16 μM *vs* [^{3}H]glycine).[6] Subsequently, a simple modification of **1** provided the 7-chloro- **2**,[7] 5,7-dichloro- **3**,[8] 5,7-dichloro-4-(hydroxycarbonylmethyloxy)- **4** and 5,7-dichloro-4-(hydroxycarbonylmethylamino)- derivatives **5**,[9] which were found to be more potent and selective to the glycine site. However they severely suffered from a lack of *in vivo* activity following intraperitoneal or intravenous administration. It seems likely that these compounds, which contain highly polar carboxylic acid groups, do not readily cross the blood brain barrier (BBB).



1, X = Y = H, **2**, X = H, Y = Cl, **3**, X = Cl, Y = Cl,

4, R = OCH_2CO_2H, **5**, R = $NHCH_2CO_2H$,

Figure 1.

The SAR study of the known NMDA antagonist implies that a hydroxyl group at C4 of the quinoline-2-carboxylic acids is capable to interact with a H-bonding domain on the receptor and its spatial orientation is very important for the binding activity. As a part of a program aimed at the discovery of new NMDA antagonist, we became interested in preparing a new class of quinoline-2-carboxylic acids possessing various subsituents as a H-bonding acceptor, at C4. Our efforts for the development of NMDA antagonists with improved *in vivo* activity have focused on the strategies of i) introduction of appropriate substituents onto C4-position which can provide two distinct structural features, H-bonding acceptor and hydrophobic surface and ii) replacement of the 2-carboxylic acid group in the quinoline-2-carboxylic acids. In present paper, we describe the synthesis and evaluation of newly designed quinoline-2-carboxylic acid derivatives as potential NMDA glycine site antagonists.

Experimental

General. All melting points were taken on a Thomas-Hoover melting point apparatus and were uncorrected. ^{1}H NMR spectra were obtained on Varian Gemini 200 or Varian AM-300 spectrometers. Chemical shifts were reported in

parts per million (d) relative to a tetramethylsilane as an internal standard. Mass spectra were obtained with VG 12-250 mass spectrometer. Analytical thin-layer chromatography was performed using 0.25 mm silica gel glass-backed plates. E. Merck silica gel (230-400 mesh) was used for flash chromatography. Solvents and reagents were dried and purified prior to use when deemed necessary. Reactions were carried out under nitrogen or argon atmosphere unless otherwise stated.

2-(3,5-Dichlorophenylamino)-but-2-enedioic acid dimethyl ester (6); 5,7-dichloro-4-oxo-1,4-dihydro-quinoline-2-carboxylic acid methyl ester (7). A solution of 3,5-dichloroaniline (5.00 g, 30.8 mmol) and dimethylacetylene dicarboxylate (4.36 g, 30.8 mmol) in 150 mL of anhydrous methanol was refluxed for 14 h, and the resulting mixture was evaporated under reduced pressure to give a crude **6**, which was used for next reaction without further purification. A analytically pure sample of **6** was obtained as a yellow crystal by recrystallization from methanol or by flash column chromatography (EtOAc: *n*-hexane= 6 : 1): mp 79-80 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.54 (s, 1H, vinyl H), 6.74 (d, 2H, *J*= 2.4 Hz, ArH), 7.04 (t, 1H, *J*=2.4 Hz, ArH), 9.55 (br s, 1H, NH); MS(EI) m/e 304 [M^+], 273 [M^+-CH_3], 245, 213. The crude **6** was dissolved in 25 mL of diphenyl ether and heated at 240-250 °C for 4 h. The mixture was cooled to room temperature and excess *n*-hexane (about 500 mL) was added to precipitate a crude solid. The solids were filtered, washed with ether several times and dried *in vacuo* to provide 7.22 g (86%) of a desired quinolone **7** as a white solid. Analytical sample was prepared by recrystallization from methanol: mp 282-284 °C; ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 3H, OCH_3), 6.59 (s, 1H, ArH), 7.45 (d, 1H, *J*=2.4 Hz, ArH), 7.99 (d, 1H, *J*=2.4 Hz, ArH), 12.09 (br s, 1H, NH); MS (EI) m/e 272 [M^+], 213.

5,7-Dichloro-4-(toluene-4-sulfonylimino)-1,4-dihydro-quinoline-2-carboxylic acid methyl ester (8). A suspension of the quinolone **7** (3.00 g, 11.03 mmol) and toluenesulfonyl isocyanate (2.39 g, 12.1 mmol) in 100mL of acetonitrile was refluxed for 4 h. At refluxing temperature the reaction mixture was homogeneous. The mixture was cooled to room temperature to produce an insoluble yellow precipitate. This precipitate was washed with petroleum ether and dried *in vacuo* to provide 4.45 g (95%) of a 4-toluenesulfonylamido-2-quinolone **8** as a bright yellow solid: mp 211-213 °C; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H, $ArCH_3$), 4.02 (s, 3H, OCH_3), 7.38 (d, 2H, *J*=8.2 Hz, ArH), 7.64 (d, 1H, *J*=2.4 Hz, ArH), 7.81 (d, 2H, *J*=8.2 Hz, ArH), 7.84 (s, 1H, ArH), 8.06 (d, 1H, *J*=2.4 Hz, ArH), 12.45 (br s, 1H, NH); MS (EI) m/e 425 [M^+], 367, 272, 213.

5,7-Dichloro-4-(toluene-4-sulfonylimino)-1,4-dihydro-quinoline-2-carboxylic acid (9). A solution of a methyl ester **8** (4.00 g, 9.41 mmol) in 50 mL of methanol was treated with 50 mL of aqueous NaOH solution [containing 0.75 g (18.8 mmol) of NaOH] at ice bath temperature for 2 h. The mixture was concentrated under reduced pressure until total volume of the mixture is around 40 mL. The remaining solution was diluted with 100 mL of H_2O, washed with 150 mL of methylene chloride three times, and acidified with concentrated HCl to pH 3. The forming precipitates thus formed were filtered, washed with H_2O, and then dried in vacuo to give 3.75 g (97%) of a 4-toluenesulfonylamido-quinoline-2-carboxylic acid **9** as a slightly yellow solid: mp 181 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.46 (s, 3H, $ArCH_3$), 7.44 (d, 2H, *J*=8.2 Hz, ArH), 7.68 (d, 1H, *J*=2.4 Hz, ArH), 7.86 (s, 1H, ArH), 7.88 (d, 2H, *J*=8.2 Hz, ArH), 8.21 (d, 1H, *J*=2.4 Hz, ArH); MS (EI) m/e 411 [M^+], 367, 308, 272, 213.

5,7-Dichloro-4-(2-chloro-acetylamino)-1,4-dihydro-quinoline-2-carboxylic acid methyl ester (10). To a suspension of 5,7-dichloroquinolinic acid methyl ester **7** (0.68 g, 2.50 mmol) in 20 mL of acetonitrile was added chloroacetyl isocyanate (0.33 g, 2.75 mmol) at room temperature, and then refluxed for 12 h. The mixture was evaporated under reduced pressure to give a crude yellow solid. The solid was diluted with 50 mL of methanol and heated at reflux, and then cooled down to room temperature. After filtration of the insoluble precipitate and drying *in vacuo*, a pure 4-chloroacetylamindo-quinoline-2-carboxylate 10 was obtained in 75% (0.65 g) yield as a white solid: ^{1}H NMR (DMSO-d_6) δ 4.05 (s, 3H, OCH_3), 4.58 (s, 2H, CH_2Cl), 8.10 (d, 1H, *J*=1.8 Hz, ArH), 8.36 (d, 1H, *J*= 1.8 Hz, ArH), 8.39 (s, 1H, ArH), 10.87 (br s, 1H, NH); MS (EI) m/e 348 [M^+], 312 [M^+-Cl], 298, 272, 254.

5,7-Dichloro-4-[(2-diethoxy-phosphonyl)-acetyl-amino]-1,4-dihydro-quinoline-2-carboxylic acid methyl ester (11). A suspension of the quinoline-2-carboxylate **10** (0.31 g, 0.89 mmol) in triethyl phospite (4 mL) was refluxed for 3 h. The excess triethyl phospite was evaporated under reduced pressure to give residue as slightly brown syrups. The residue was recrystallized from a 1 : 1 mixture of ethyl ether and *n*-hexanes to give 0.36 g (92%) of a desired diethyl phosphonate **11** as a white crystal: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 6H, *J*=7.0 Hz, OCH_2CH_3), 3.17 (d, 2H, *J*=21.2 Hz, $POCH_2$), 4.08 (s, 3H, OCH_3), 4.23 (q, 4H, *J*=7.0 Hz, OCH_2), 7.66 (d, 1H, *J*=2.1 Hz, ArH), 8.26 (d, 1H, *J*=2.1 Hz, ArH), 9.09 (s, 1H, ArH), 10.30 (br s, 1H, NH); MS (EI) m/e 450 [M^+], 405 [M^+-CH_2CH_3], 357, 214.

5,7-Dichloro-4-[(2-diethoxy-phosphonyl)-acetyl-amino]-1,4-dihydro-quinoline-2-carboxylic acid (12). To a solution of the phosphonate **11** (0.12 g, 0.27 mmol) in 15 mL of tetrahydrofuran was added 10 mL of aqueous solution containing $LiO \cdot H_2O$ (67 mg, 1.60 mmol) at ice bath temperature. The mixture was stirred for 2 h at room temperature, most of THF was evaporated under reduced pressure. The rest of the aqueous portions was diluted with 30 mL of H_2O, washed with 30 mL of methylene chloride, and then acidified by addition of 2 N HCl to pH 3 to produce a white precipitate. The precipitate was collected by filtration and dried *in vacuo* to give 0.11 g (94%) of a 4-chloroacetylamindo-quinoline-2-carboxylate **12** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 6H, *J*=7.1 Hz, OCH_2CH_3), 3.20 (d, 2H, *J*=21.3 Hz, $POCH_2$), 4.26 (quin, 4H, *J*=7.0 Hz, OCH_2), 7.70 (d, 1H, *J*=1.7 Hz, ArH), 8.11 (d, 1H, *J*=1.7 Hz, ArH), 9.14 (s, 1H, ArH), 10.36 (br s, 1H, NH); MS (EI) m/e 436 [M^+], 391 [M^+-CH_2CH_3], 346, 328, 300, 217.

4-Amino-5,7-dichloroquinoline-2-carboxylic acid methyl ester (13). To a solution of H_2SO_4 (10 mL, 90% in H_2O) was carefully added in portions the quinolinic sulfonamide 8 (0.50 g, 0.11 mol) in an ice bath, and then the mixture was stirred for 2 h. During this period, the reaction

temperature should be kept below 4 °C. The resulting mixture was slowly poured onto cracked ices over 1 h with stirring. The aqueous layer, containing insoluble solids, was basified with 8 N NaOH aqueous solution (50 mL) to pH 12. The remaining solid was filtered, washed with water (10 mL x2) and dried in vacuo to give 4-amino-quinoline **13** (0.30 g, 94%) as a slightly yellow solid: mp 130-190 °C (dec); ^{1}H NMR (DMSO-d_6) δ 3.96 (s, 3H, OCH_3), 7.46 (s, 1H, ArH), 7.55 (br s, 2H, NH), 7.71 (d, 1H, *J*=2.2 Hz, ArH), 7.96 (d, 1H, *J*=2.2 Hz, ArH); MS (EI) m/e 272 [M^++1], 212 [M^+-O_2CH_3], 184, 151.

4-Benzylamino-5,7-dichloroquinoline-2-carboxylic acid methyl ester (14). To a suspension of the 4-amino-quinoline **13** (0.20 g, 0.73 mmol) in dry dioxane (10 mL) was added pyridine (0.30 mL, 3.7 mmol) and benzyl chloride (0.43 mL, 3.7 mmol), and the mixture was heated at reflux for 4 h. The solvent was evaporated under reduced pressure and the residue was diluted with 50 mL of methylene chloride. The resulting mixture was washed with 0.5 N HCl (30 mL), H_2O (30 mL x2), and dried over $MgSO_4$. Evaporation of the organic phase afforded the crude solid materials. Recrystallization from EtOAc-hexane (1 : 1) gave pure quinolinic benzamide **14** (120 mg, 41%) as a white solid: mp 193-197 °C; ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H, OCH_3), 7.60 (m, 4H, ArH), 7.96 (d, 1H, *J*=2.0 Hz, ArH), 8.28 (d, 1H, *J*=2.0 Hz, ArH), 7.99 (m, 1H, ArH), 9.45 (s, 1H, ArH), 10.68 (br s, 1H, NH); MS (EI) m/e 375 [M^+], 343 [M^+-CH_3OH], 105.

4-Benzoylamino-5,7-dichloroquinoline-2-carcoxylic acid (15). To a solution of the quinolinic benzamide **14** (30 mg, 0.08 mmol) in THF (10 mL) was added the aqueous NaOH solution (1.3 mg, 10 mL) and stirred at room temperature for 4 h. The organic solvent was removed under reduced pressure and the remaining mixture was diluted with 20 mL of H_2O. The aqueous solution was washed with 20 mL of methylene chloride twice, and then acidified with concentrated HCl to pH 2. The precipitates were collected, washed with H_2O (5 mL x2), dried *in vacuo* to give the corresponding carboxylic acid **15** (28 mg, 98%): mp 180-210 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.72 (m, 3H, ArH), 8.07 (d, 1H, *J*=2.2 Hz, ArH), 8.35 (d, 1H, *J*=2.2 Hz, ArH), 8.14 (m, 2H, ArH), 8.44 (s, 1H, ArH), 11.13 (s, 1H, CONH); MS (EI) m/e 361 [M^+], 317 [M^+-CO_2], 282 [M^+-C_6H_5CO], 105.

4,5,7-Trichloroquinoline-2-carboxylic acid methyl ester (16). A mixture of 5,7-dichloroquinolinic acid methyl ester **7** (5.0 g, 18.4 mmol) and $POCl_3$ (20 mL) was heated at reflux for 4 h. After concentration of the mixture, the residue was recrystallization from methanol to provide 4.9 g (91%) of a 4,5,7-trichloroquinoline-2-carboxylate **16** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H, OCH_3), 7.74 (d, 1H, *J*=2.1 Hz, ArH), 8.24 (s, 1H, ArH), 8.28 (d, 1H, *J*=2.1 Hz, ArH); MS (EI) m/e 291 [M^+], 232 [M^+-OCH_3].

5,7-Dichloro-4-(diethoxyphosphoryl)-quinoline-2-carboxylic acid methyl ester (17). A mixture of 4,5,7-trichloroquinoline-2-carboxylate **16** (0.50 g, 1.72 mmol) and triethyl phosphite (2 mL) was refluxed for 12 h. The mixture was evaporated under reduced pressure to give a slightly brown colored residue. The residue was directly purified by flash column chromatography (EtOAc: *n*-hexane=2 : 1) to give 0.41 g (63%) of a desired phosphonate **17** as a white solid and 0.11 g of a recovered starting chloride **16**: ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 6H, OCH_2CH_3), 4.10 (s, 3H, OCH_3), 4.30 (m, 4H, $POCH_2$), 7.86 (d, 1H, *J*=2.2 Hz, ArH), 8.32 (t, 1H, *J*=2.2 Hz, ArH), 8.87 (d, 1H, *J*=17.5 Hz, ArH); MS (EI) m/e 392 [M^+], 300, 241.

5,7-Dichloro-4-(diethoxyphosphoryl)-quinoline-2-carboxylic acid (18). To a solution of the phosphonate **17** (0.20 g, 0.53 mmol) in 15 mL of tetrahydrofuran was added 15 mL of aqueous solution containing $LiO \cdot H_2O$ (89 mg, 2.12 mmol) at ice bath temperature. The mixture was stirred for 2 h at room temperature, and most of THF was evaporated under reduced pressure. The remaining solution was diluted with 40 mL of H_2O, washed with 40 mL of methylene chloride, and then acidified with 2 N HCl to pH 3 to give a white precipitate. The precipitate was collected by filtration and dried *in vacuo* to give 0.18 g (97%) of a quinolinyl-4-phosphonic acid **18** as a white solid: ^{1}H NMR (DMSO-d_6) δ 1.28 (m, 3H, $POCH_2CH_3$), 4.02 (m, 2H, $POCH_2$), 8.11 (d, 1H, *J*=2.8 Hz, ArH), 8.34 (t, 1H, *J*=2.8 Hz, ArH), 8.84 (t, 1H, *J*=1.98 Hz, ArH); MS (EI) m/e 350 [M^+], 298, 241.

4-[(3-Bromopropyl)-(toluene-4-solfonyl)-amino]-5,7-dichloroquinoline-2-carboxylic acid methyl ester (19b). To a suspension of a quinolinic sulfonamide **8** (0.42 g, 1.0 mmol) and K_2CO_3 (0.55 g, 4.0 mmol) in acetonitrile (30 mL) was added 1,3-dibromopropane (4.0 mL, 30 mmol) and the mixture was heated at reflux for 3 h. The remaining insoluble solid was filtered off and the filtrate was evaporated to afford brown colored residues. Purification of the residue by flash column chromatography (EtOAc : hexane=1 : 6) gave the desired bromide **19b** (0.33 g, 60%) as a pale yellow crystal: mp 189-190 °C; ^{1}H NMR ($CDCl_3$) δ 2.04-2.29 (m, 2H, CH_2), 2.48 (s, 3H, $ArCH_3$), 3.36-3.98 (m, 2H, CH_2Br), 3.37 (m, 2H, SO_2NCH_2), 4.05 (s, 3H, OCH_3), 7.33 (d, 2H, *J*=8.0 Hz, ArH), 7.50 (d, 2H, *J*=8.8 Hz, ArH), 7.52 (s, 1H, ArH), 7.78 (d, 1H, *J*=2.0 Hz, ArH), 8.23 (d, 1H, *J*=2.0 Hz, ArH); MS (EI) m/e 546 [M^+], 513 [M^+-CH_3OH], 482 [M^+-SO_2], 391 [M^+-$SO_2C_6H_4CH_3$], 331, 251, 155.

4-[(3-Bromoethyl)-(toluene-4-solfonyl)-amino]-5,7-dichloroquinoline-2-carboxylic acid methyl ester (19a). ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, $ArCH_3$), 3.42-3.71 (m, 2H, CH_2Br), 3.87 (m, 1H, NCH_2), 4.04 (s, 3H, OCH_3), 4.15 (m, 1H, NCH_2), 7.32 (d, 2H, *J*=8.4 Hz, ArH), 7.50 (d, 2H, *J*=8.4 Hz, ArH), 7.58 (s, 1H, ArH), 7.76 (d, 1H, *J*=2.2 Hz, ArH), 8.29 (d, 1H, *J*=2.2 Hz, ArH); MS (EI) m/e 532 [M^+], 501 [M^+-OCH_3], 472, 440 [M^+-$PhCH_3$], 376.

4-{[3-(4-Benzyl-piperazine-1-yl)-propyl]-(toluene-4-sulfonyl)-amino}-5,7-dichloroquinoline-2-carboxylic acid methyl ester (20b). To a solution of the bromide **19b** (0.30 g, 0.55 mmol) in acetonitrile (20 mL) was added 4-benzylpiperazine (0.11 mL, 0.66 mmol) and K_2CO_3 (0.30 g, 1.16 mmol). The resulting mixture was refluxed for 5 h and then cooled to room temperature. The solution was diluted in CH_2Cl_2 (20 mL), washed with brine (20 mL x2) and water (30 mL x2), and dried over $MgSO_4$. The organic phase was concentrated in vacuo to give a desired *N*-substituted piperazine **20b** (0.34 g, 97%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.55-1.86 (m, 2H, CH_2), 2.29 (m, 8H, NCH_2), 2.46 (s, 3H, $ArCH_3$), 2.88 (m, 1H, SO_2NCH_2), 3.45 (s, 2H, $PhCH_2$), 3.48 (m, 1H, SO_2NCH_2), 4.03 (s, 3H, OCH_3),

7.27 (s, 5H, ArH), 7.31 (d, 2H, *J*=8.2 Hz, ArH), 7.49 (d, 2H, *J*=8.2 Hz, ArH), 7.50 (s, 1H, ArH), 7.76 (d, 1H, *J*=2.2 Hz, ArH), 8.28 (d, 1H, *J*=2.2 Hz, ArH); MS (EI) m/e 486 [M^+-$SO_2C_6H_4CH_3$], 297, 283, 251, 91.

4-{[2-(4-Benzyl-piperazine-1-yl-ethyl)]-(toluene-4-sulfonyl)-amino}-5,7-dichloroquinoline-2-carboxylic acid methyl ester (20a). The *N*-substituted piperazine **20a** was prepared from the quinolinic sulfonamide **8** (0.25 g, 0.47 mmol) as described for **20b**, using 4-benzylpiperazine (92 mg, 0.52 mmol). After work up and purification by flash column chromatography (30% EtOAc in hexane), a pure *N*-substituted piperazine **20a** was obtained in a 44% yield as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 4H, NCH_2), 2.19 (m, 4H, NCH_2), 2.47 (s, 3H, ArH), 2.59 (m, 2H, CH_2), 3.27 (s, 2H, ArH), 3.59 (m, 1H, CH_2), 3.96 (m, 1H, CH_2), 4.04 (s, 3H, OCH_3), 7.23 (m, 5H, ArH), 7.31 (d, 2H, *J*=8.0 Hz, ArH), 7.51 (d, 2H, *J*=8.0 Hz, ArH), 7.53 (s, 1H, ArH), 7.77 (d, 1H, *J*=2.0 Hz, ArH), 8.28 (d, 1H, *J*=2.0 Hz, ArH).

4-{[3-(4-Benzyl-piperazine-1-yl)-propyl]-(toluene-4-sulfonyl)-amino}-5,7-dichloro-quinoline-2-carboxylic acid (21b). To a solution of the methyl ester **20b** (0.30 g, 0.47 mmol) in MeOH (20 mL) was added aqueous 0.1 N NaOH solution (20 mL, 2.00 mmol) and the resulting mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure until 20 mL of total volume, washed with 20 mL of methylene chloride, and then acidified with concentrated HCl to pH 1. The resulting precipitate were collected, washed with water (5 mL x3), and dried *in vacuo* to give the carboxylic acid **21b** (42 mg, 13%) as a white solid: mp 141-144 °C; ^{1}H NMR (CD_3OD) δ 1.91-2.11 (m, 1H, CH_2), 3.24 (s, 3H, $ArCH_3$), 3.38(m, 8H, NCH_2), 3.52 (m, 2H, CH_2), 3.49 (m, 1H, CH_2), 3.75 (s, 2H, $PhCH_2$), 3.81 (m, 1H, CH_2), 7.30 (m, 9H, ArH), 7.52 (s, 1H, ArH), 8.13 (d, 1H, *J*=2.0 Hz, ArH), 7.72 (d, 1H, *J*=2.0 Hz, ArH); MS (EI) m/e 471 [M^+-$SO_2C_6H_4CH_3$], 430, 296, 272, 203, 189.

4-{[2-(4-Benzyl-piperazine-1-yl-ethyl)]-(toluene-4-sulfonyl)-amino}-5,7-dichloroquinoline-2-carboxylic acid (21a). The methyl ester **20a** (0.13 g, 2.10 mmol) was treated with 0.4 N NaOH aqueous solution (21 mL, 0.84 mmol), under the same conditions as described for **21b** to give the corresponding acid **21a** (65 mg, 51%) as a white solid: mp 152-169 °C (dec); ^{1}H NMR (CD_3OD) δ 2.32 (s, 3H, ArH), 2.78 (m, 12H, CH_2, NCH_2, ArCH), 3.75 (s, 3H, NCH_2, CH_2), 3.96 (s, 1H, CH_2), 7.37 (m, 12H, ArH), 3.14 (br s, 1H, COOH); MS (EI) m/e 302 [M^+-benzylpiperazine, $CH_3C_6H_4$, CO_2], 283, 224, 179.

5,7-Dichloro-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethoxy]-quinoline-2-carboxylic acid (22a). A suspension of 5,7-dichloroquinolinic acid methyl ester **7** (0.5 g, 1.84 mmol), N-(2-bromoethyl)-phthalimide (0.93 g, 3.68 mmol) and anhydrous K_2CO_3 (1.0 g, 7.36 mmol) in 25 mL of dry N,N-dimethylformamide was refluxed overnight. The mixture was poured into 100 mL of 1 N HCl and extracted with 150 mL of methylene chloride three times. The combined organic phase was washed with H_2O (200 mL x2) and the brine solution (150 mL), dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give a crude methyl 4-(2-phththalimidoethyl)-quinoline-2-carboxylate. The above methyl carboxylate was dissolved in 20 mL of methanol and then saponified by treatment with 20 mL of aqueous NaOH solution [0.49 g, 12.3 mmol] at room temperature for 2 h. The mixture was diluted with 150 mL of H_2O, extracted with methylene chloride (200 mL x2). The aqueous phase was acidified by addition of concentrated HCl to pH 3. The white precipitates was filtered, washed with H_2O, and dried *in vacuo* to provide 0.46 g (59% yield from the quinolinic acid methyl ester) of the desired carboxylic acid **22a** as a white solid: ^{1}H NMR (DMSO-d_6) δ 3.85 (q, 2H, *J*=5.2 Hz, OCH_2), 4.53 (t, 2H, *J*= 5.2 Hz, NCH_2), 7.50-7.70 (m, 4H, ArH), 7.87 (d, 1H, *J*=1.7, 7.2 Hz, ArH), 7.91 (d, 1H, *J*=2.0 Hz, ArH), 8.18 (s, 1H, ArH); MS (EI) m/e 432 [M^++1], 387 [M^+-CO_2], 301, 267, 257, 228.

5,7-Dichloro-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyloxy]-quinoline-2-carboxylic acid (22b). 5,7-Dichloro-4-(2-phththalimidopropyl)-quinoline-2-carboxylic acid **22b** was prepared by the same condition as described above, except using N-(2-bromopropyl)-phthalimide (0.97 g, 3.68 mmol) instead of N-(2-bromoethyl)-phthalimide. After saponification of the corresponding methyl ester, a pure carboxylic acid **22b** was obtained as a white solid in a 69% (0.56 g) yield: ^{1}H NMR (DMSO-d_6) δ 2.20 (m, 2H, CH_2), 3.59 (m, 2H, OCH_2), 4.45 (m, 2H, NCH_2), 7.47-7.68 (m, 4H, ArH), 7.84 (d, 1H, *J*=1.5 Hz, ArH), 7.89 (s, 1H, ArH), 8.16 (s, 1H, ArH); MS (EI) m/e 445 [M^+], 271, 257, 241.

N-Glycine-5,7-dichloro-4-toluenesulfonylamidoquinolinic amide (23a). The N-glycine-2-quinolinic amide **23a** was prepared by the similar procedure used for compounds **23b-d** and by consequent base hydrolysis. To a solution of a carboxylic acid **9** (0.3 g, 0.73 mmol), glycine ethyl ester hydrochloride (0.11 g, 0.80 mmol), triethylamine (0.87 mmol) and 1-hydroxybenzotriazole hydrate (0.11 g, 0.80 mmol) in DMF (30 mL) was added dicyclohexyl carbodiimide (0.18 g, 0.87 mmol). The reaction mixture was stirred for 12 h at room temperature, was poured into 150 mL of H_2O, extracted with 150 mL of methylene chloride three times. The combined organic phase was washed with 1 N HCl solution, H_2O and brine, and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc : Hex =4 : 1) to give (0.31 g, 86%) of a desired ethyl ester as a white solid. The above ethyl ester (0.31 g, 0.61 mmol) was dissolved in 20 mL of THF and was treated with 20 mL of aqueous LiOH solution [containing 51.2 mg (1.22 mmol) of $LiO \cdot H_2O$] at ice bath temperature for 2 h. The mixture was concentrated under reduced pressure until total volume is about 20 mL. The remaining solution was diluted with 100 mL of H_2O, washed with 100 mL of methylene chloride, and acidified with concentrated HCl at pH 3. The insoluble precipitates was filtered, washed with H_2O, and then dried *in vacuo* to give 0.28 g (99%) of a N-glycine-2-quinolinic amide **23a** as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, $ArCH_3$), 3.56 (br s, 1H, NH), 4.08 (2H, d, *J*=6 Hz), 7.46 (2H, d, *J*=8 Hz, ArH), 7.84 (d, 1H, *J*=2 Hz, ArH), 7.86 (d, 1H, *J*=2 Hz, ArH), 7.88 (2H, d, *J*=8 Hz, ArH), 8.21 (s, 1H, ArH), 9.56 (br s, 1H, COOH), 12.98 (br s, 1H, NH); MS (EI) m/e 468 [M^+], 424 [M^+-CO_2], 377 [M^+-$ArCH_3$], 367, 267, 213.

5,7-Dichloro-4-(toluene-4-sulfonylimino)-1,4-di-

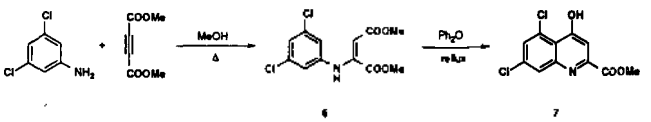
hydro-quinolinic amides (23b-d). To a solution of the carboxylic acid **9** (0.3 g, 0.73 mmol) in DMF (10 mL) was added a solution of appropriate amines (0. 80 mmol) and 1-hydroxybenzotriazole hydrate (0.11 g, 0.80 mmol) in DMF (10 mL), and then dicyclohexylcarbodiimide (0.18 g, 0.87 mmol) at room temperature. After stirring for 24 h at room temperature, the mixture was diluted with 150 mL of methylene chloride and washed with H_2O and a brine solution. The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give a crude product. The corresponding pure quinolinic amides **23b-d** were obtained by a flash column chromatography or recrystallization.

5,7-Dichloro-4-(toluene-4-sulfonylimino)-1,4-dihydro-quinoline-2-carboxylic acid (thiazol-2-yl) amide (23b). ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H, $ArCH_3$), 3.65 (br s, 1H, NH), 7.40 (d, 1H, *J*=5 Hz, thiazole CH), 7.46 (d, 2H, *J*=8 Hz, ArH), 7.74 (d, 1H, *J*=5 Hz, thiazole CH), 7.75 (d, 1H, *J*=2 Hz, ArH), 7.94 (d, 2H, *J*=8 Hz, ArH), 8.18 (s, 1H, ArH), 8.26 (d, 1H, *J*=2 Hz, ArH); MS (EI) m/e 493 [M$^+$], 367, 339, 303.

5,7-Dichloro-4-(toluene-4-sulfonylimino)-1,4-dihydro-quinoline-2-carboxylic acid (2H-triazol-5-yl) amide (23c). ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H, $ArCH_3$), 3.55 (br s, 1H, NH), 7.48 (d, 2H, *J*=8 Hz, ArH), 7.52 (s, 1H, triazoleCH), 7.88 (d, 2H, *J*=8 Hz, ArH), 7.92 (s, 1H, ArH), 7.98 (d, 1H, *J*=2 Hz, ArH), 8.26 (d, 1H, *J*=2 Hz, ArH), 8.36 (br s, 1H, NH), 9.98 (br s, 1H, NH); MS (EI) m/e 477 [M$^+$], 367, 303.

5,7-Dichloro-4-(toluene-4-sulfonylimino)-1,4-dihydro-quinoline-2-carboxylic acid (2H-tetrazol-5-yl) amide (23d). ^{1}H NMR (DMSO-d_6) δ 2.45 (s, 3H, $ArCH_3$), 3.56 (br s, 1H, NH), 7.48 (d, 2H, *J*=8 Hz, ArH), 7.88 (d, 2H, *J*=8 Hz, ArH), 7.96 (s, 1H, ArH), 7.97 (d, 1H, *J*=2 Hz, ArH), 8.24 (d, 1H, *J*=2 Hz, ArH); MS (EI) m/e 478 [M$^+$], 367, 303.

Biological Evaluation: [^{3}H]-Glycine Binding Assay. Synaptic membranes for receptor binding studies were prepared by the modified methods of Foster and Fagg.[13] [^{3}H]-Glycine binding assays were performed as described by Baron *et al.*[14] For saturation binding analysis of [^{3}H]-Glycine, synaptic membranes (100 mg of membrane protein) were incubated at 4 °C for 30 min in 13×100 mm borosilicated glass tube in a final volume of 0.5 mL reaction mixture containing 50 mM Tris-acetate buffer, pH 7.1, and 5-500 nM [^{3}H]-Glycine. For drug displacement analysis, various concentrations of testing compounds were incubated as described above, in a reaction mixture containing synaptic membranes (100 mg of membrane protein), 50 nM of [^{3}H]-Glycine and 50 mM Tris-acetate buffer, pH 7.1. After incubation, the reaction was terminated by the addition of 2.5 mL of ice-cold 50 mM Tris-acetate buffer, pH 7.1, and the bound radioactivity was separated using a Brandel cell harvester (Brandel M-12R) by rapid filtration through Whatman GF/B glass fiber filter which was presoaked in 0.3% polyethylenimine in the assay buffer. The filters were washed twice with 2.5 mL of cold buffer within 10 sec. The trapped radioactivity on the filter was measured by a liquid scintillation counter (Beckman LS 6000TA) using 3 mL Luma gel at a counting efficiency of 50-55%. Non-specific binding was determined in the presence of 1 mM glycine.



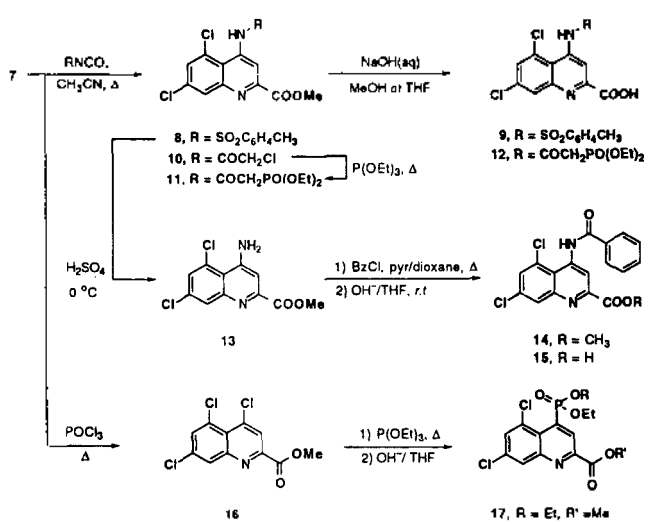
Scheme 1.

All testing compounds were dissolved in dimethylsulfoxide (DMSO), and serially diluted to various concentrations for binding assays.

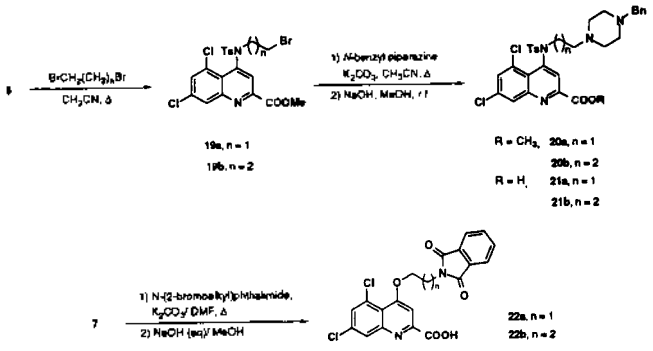
Results and Discussion

The primary synthetic goal for the envisaged antagonists was the preparation of the intermediate, the quinolinic methyl ester **7**. We were able to prepare the ester **7** readily by using the method of Cornard and Limpach.[10] This involved the reaction of 2,4-dichloroaniline with dimethyl acetylenedicarboxylate and subsequent thermal cyclization of the adduct **6**. Although alternative synthetic approaches starting from the corresponding anthranilic acid ester are known,[11] these tend to give low yields and are not of general synthetic use.

Modification at C4 position of the quinolinic acid backbone. Modification of the ester **7** was initiated by introducing either a sulfonylamino or an acylamino groups at the C4 position, instead of a hydroxyl group. Treatment of **7** with *p*-tolylsulfonyl isocyanate in refluxing acetonitrile gave the N-tosyl derivative **8** in 95% yield[12] and the subsequent basic hydrolysis gave the acid **9**. Reaction of **7** with chloroacetyl isocyanate also readily provided the corresponding 4-chloroacetylamino-quinolinic methyl ester **10** in 92% yield. The resulting methyl ester **10** was treated with triethylphospite and then hydrolyzed in basic condition to afford the quinolinic acid **12**. In contrast, treatment of **7** with benzoyl isocyanate did not give the desired product under the same reaction conditions. Alternative synthesis was began with acidic hydrolysis of the 4-tolylsulfonylamido compound **8** to produce 4-amino-quinolinic acid methyl ester **13**. Benzoylation of **13** in refluxing dioxane in



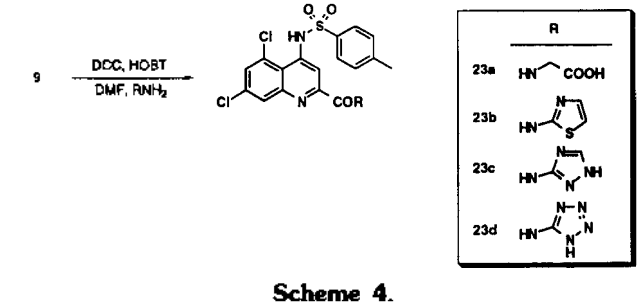
Scheme 2.



Scheme 3.

the presence of pyridine followed by basic hydrolysis afforded the desired 4-benzoylamido-quinolinic acid **15** in 40% yield. Alternatively, the hydroxyl group at C4 of the ester **7** was transformed into a phosphonate group by treatment with $POCl_3$ and subsequent heating in excess $P(OEt)_3$, producing 4-(diethoxyphosphoryl)-quinolinic methyl ester **17** as the sole product in 61% yield. Subsequently, the desired 4-(ethoxyphosphoryl)-quinolinic acid **18** was obtained by basic hydrolysis of **17** in aqueous THF. In addition, the alkylation of sulfonylamido anion of **8** with dibromoalkanes in the presence of K_2CO_3 was followed by substitution of the resulting bromide **19a, b** with N-benzylpiperazine. Subsequent basic hydrolysis of **20a, b** provided the corresponding 4-(N-alkyl substituted tolylsulfonylamido)-quinolinic acid **21a, b** in 42% and 49% yields from **8**, respectively. Accordingly, 4-alkoxy quinolinic acid **22a** and **22b** were also synthesized as follows. The O-alkylation of the methyl ester **7** was conducted by refluxing with N-(ω-bromoalkyl)phthalimides in DMF and consequent basic hydrolysis provided the target compounds, 4-alkoxy quinolinic acids **22a** and **22b** in 59% and 69% isolated yields, respectively.

Modification at C2 position of the quinolinic acid back-bone. In order to investigation the structural effects on blood brain barrier (BBB) penetration during drug delivery, replacement of a polar carboxylic acid functionality at C2 with several neutral carboxylate bioisosteres was carried out. The N-tosylated acid **9** was coupled with the appropriate amines by the DCC-HOBT method to afford the N-azole amides **23b-d**. N-quinolinic glycine **23a** could also be prepared by the above-mentioned DCC coupling of the acid **9** with glycine ethyl ester and the subsequent basic hydrolysis in THF-H_2O. In these derivatives, the C2 position of quinoline-backbone was reoccupied by various bioisosteres of a carboxylic acid group which presumably interact



Scheme 4.

Table 1. Biological data of the quinolinic acid derivatives

Compound No.	[^{3}H]-Gly Binding	
	% Inhibition*	IC_{50} (μM)
3	89	0.42**
9	90	0.57
12	64	13.5
15	22	>100
18	23	>100
21a	29	>100
21b	18	>100
22a	23	>100
22b	63	51.5
23a	38	77.4
23b	22	>100
23d	48	>100

*Percent inhibition was determined by [^{3}H]glycine replacement assays at 100 μM of testing compound. **For a comparison with the others, IC_{50} value of **3** as a reference was redetermined under our assay conditions.

with a coulombic binding domain at the receptor active site.

The synthesized compounds were evaluated for their ability to compete with [^{3}H]glycine for strychnine-insenstive binding sites.[13] IC_{50} values reported, representing the concentration of compound required to reduce the glycine binding by 50%, were mean values from two or more experiments. As indicated in Table 1, *in vitro* binding activity was found to be quite sensitive to the nature of the substituents at C4 and C2 of the quinolinic mother nucleus. For example, the flexible and bulky substituent at C4 of compounds **21** and **22** deteriorate *in vitro* activity, while rather small and rigid ones of compound **9** and **12** are preferable to maintain a high activity. The replacement of a polar carboxylic acid group at C2 by the neutral bioisosteres of compounds **23a-d** also seems to be disadvantageous to their *in vitro* activity. However it is expected that compounds **23a-d** may exhibit improved *in vivo* activity due to removal of a negatively charged carboxylate group, as demonstrated in the precedent results from Moore's Lab.[15] Further studies on the biological properties of these compounds including *in vivo* assay and the details of the structure-activity relationship of these derivatives are under investigation.

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Structure and Reactivity in the Reaction of Diazoindanes and Diazoindanones with Triphenylphosphine: The Formation of Mono-, and Bisphosphazines and Hydrazone-Compounds

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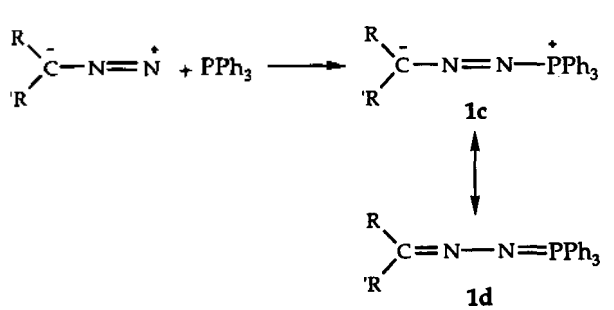
The reactions of diazoindanes and diazoindanones with triphenylphosphine have been studied in acetonitrile. The diazoindanes and diazoindanones react with triphenylphosphine to give triphenylphosphazine. The reaction of 1,3-bis(diazo)indan-2-one with a tenfold excess of triphenylphosphine in dry acetonitrile gave the 1,3-bis (phosphazino)indan-2-one, however in acetonitrile containing below of 1% water, the 1,3-bis(hydrazono)indan-2-one was produced by hydrolysis. The phosphazine compound could be easily converted into bishydrazone by recrystallization, due to small amounts of water in the solvent. The reactivity of triphenylphosphine toward diazoindanes and diazoindanones depends on the structure of the diazo compounds.

Introduction

Diazoalkanes provide a useful source of a wide variety of reactive intermediates such as, carbocations, radicals, carbenes and organometallic species.[1-5] Generally the reactivity of diazoalkanes towards nucleophiles increases with increasing contribution of limiting electron structures, **1a** and **1b**.[6]

1a **1b**

Even though triphenylphosphine is more weak nucleophile than amine, it forms stable addition complexes through the reaction of diazoalkanes unlike amines.[7] This unique reaction results in the ability of phosphorus to stabilize the phosphazine which is formed by π-acceptance into its empty *d* orbitals.[8]



1c **1d**

In general diazo compounds react with triphenylphosphine to give the adduct (**1d**), which is formed easily in a