Synthesis of Novel Quinoxaline-5-Carboxylic Acid Derivatives

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This paper describes the synthesis of several new 2,3-dimethoxy-6-methyl-7-nitro-quinoxaline-5-carboxylic acid derivatives (**13a-m**) *via* a multistep synthetic route from 5-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (**1**).

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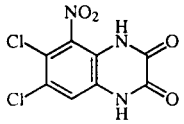
Quinoxaline-2,3-dione analogs have been reported in the literature as potent excitatory amino acid receptor antagonists [1]. The overstimulation of excitatory amino acid receptors in the mammalian central nervous system due to excessive production of L-glutamate, the major excitatory neurotransmitter in the brain, has been implicated in disease states such as Parkinson's disease [2], Alzheimer's disease [3], stroke [4], and epilepsy [5]. Earlier work by other groups in this area has shown that compounds such as ACEA-1021 which contain an electron-withdrawing nitro group at the C-5 position are potent antagonists at both the N-methyl-D-aspartate and glycine receptor [6]. However, incorporation of other electron-withdrawing groups at the C-5 position were not reported. This prompted us to develop a new synthesis of 5-substituted aminocarboxy-2,3-dimethoxy quinoxalines and the corresponding quinoxaline-2,3-diones as part of an ongoing effort in our laboratories to develop compounds for treating a variety of neurological disorders.



ACEA-1021

The synthetic route to obtain the target compounds is as depicted in the scheme starting from isatoic anhydride **1** [7] which was prepared from 2-amino-6-methylbenzoic acid. Protection of the anthranilic acid with phosgene gave **1** in near quantitative yield [8]. To avoid dinitration of **1**, the 6-position was brominated with bromine in a solution of acetic acid and trifluoroacetic acid to give **2** which was subsequently nitrated using potassium nitrate in concentrated sulfuric acid to give compound **3**. Refluxing **3** in methanol for approximately 3 hours gave the ester **4** in 55% yield. Catalytic hydrogenation under basic conditions afforded diamine **5**, which was reacted with oxalic acid in refluxing aqueous hydrochloric acid to give the quinoxaline-2,3-dione **6** [9]. Alternate attempts to form **6** by refluxing **5** with dimethyl oxalate in methanol resulted in longer reaction times with poorer yields of product. Compound **6** was nitrated with a 20% excess of potassium nitrate in concentrated sulfuric acid to give the corresponding 5-carbomethoxy-6-methyl-7-nitroquinoxaline-2,3-dione **7** in good yield (the regioselectivity of nitration was confirmed by nOe NMR). Compound **7** was saponified in refluxing aqueous sodium hydroxide to give the corresponding carboxylic acid **8**, which was our primary target compound to be coupled with a variety of amines to give the corresponding 5-substituted amides. However, employment of coupling agents such as 1,3-dicyclohexylcarbodiimide and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride under a variety of conditions resulted in mainly unreacted starting material.

Based on these results we decided to protect the quinoxaline-2,3-dione moiety of **7** by first forming the corresponding dimethoxy analog followed by conversion of the methyl ester to the acid chloride. Thus compound **12** was envisioned as a key intermediate in the synthesis of the 6-methyl-7-nitro quinoxaline-2,3-dione-5-carboxamides. In order to obtain **12** it was first necessary to convert **7** to the 2,3-dichloro intermediate **9**. Initial attempts using phosphorus oxychloride in the presence of phosphorus pentachloride under reflux gave very poor yields of **9** with significant decomposition of starting material. Other attempts using phosphorus oxychloride with *N,N*-dimethylaniline [10], triphenylphosphine/carbon tetrachloride [11], phosphorus oxychloride/pyridine [12], or heating **7** in phosphorus oxychloride in a sealed tube failed to give **9**. A moderate degree of success in forming **9** was obtained by heating **7** in phenylphosphonic dichloride [13] at 100°. However, the difficulty of removing phenylphosphonic dichloride due to its high boiling point as well as its solubility in both aqueous and organic solvents made this reagent impractical for scale-up. Dropwise addition of phosgene solution in toluene to a stirred solution of **7** in *N,N*-dimethylformamide at room temperature [14] proved to be the most efficacious method, producing **9** in 80-90% yield. It was also found that concentrating the reaction mixture, followed by trituration with methanol precipitated **9** analytically pure.

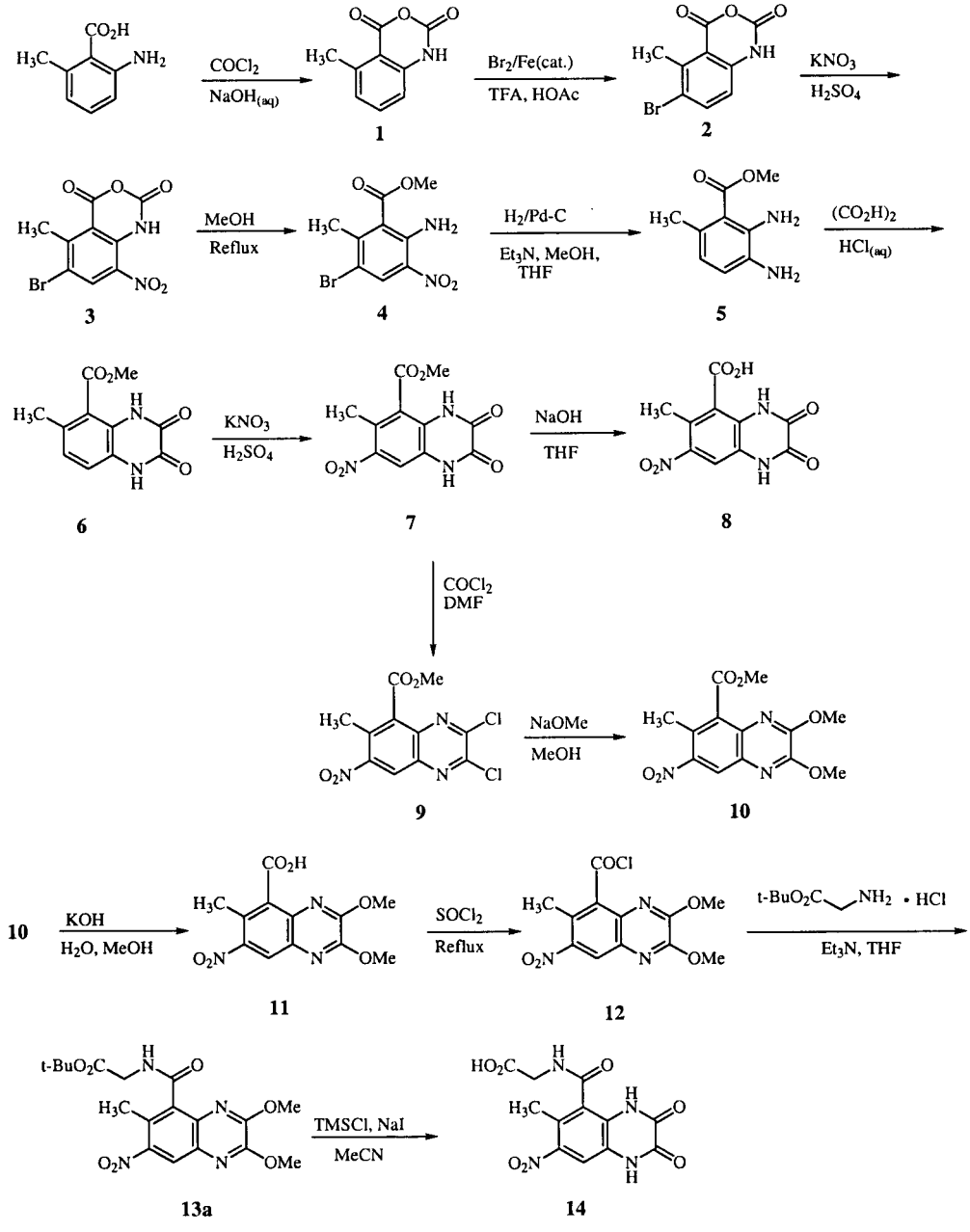
Compound **9** was converted to the 2,3-dimethoxyquinoxaline **10** by reaction with sodium methoxide in

methanol [15]. Alkaline hydrolysis of **10** at room temperature gave the carboxylic acid **11** in excellent yield after stirring for 24 hours. Attempts to increase the rate of hydrolysis by heating resulted in deprotection of the 2,3-dimethoxy quinoxaline derivative to give the carboxylic acid analog **8**.

The acid chloride **12** was formed by refluxing **11** in excess thionyl chloride for 20 hours. The best yields were obtained when the thionyl chloride was freshly distilled over triphenyl phosphite [16]. Although **12** proved to be quite labile in reacting with a variety of amines, it was also found to be relatively stable with a good shelf life. An analytically pure sample of **12** was obtained by elution through a flash column.

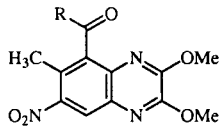
The scheme depicts a representative reaction of **12** with glycine, *tert*-butyl ester hydrochloride to give the corresponding carboxamide **13a** in good yield. Under similar conditions, **12** was reacted with a variety of amines as shown in the table and the analytical data of the amides synthesized (**13b-m**) is detailed in the experimental sec-

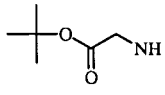
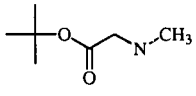
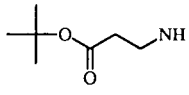
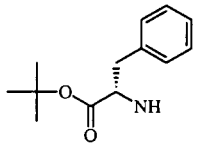
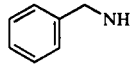
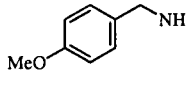
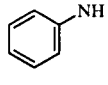
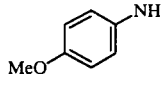
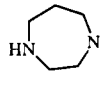
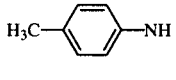
Scheme



THF = Tetrahydrofuran

Table, analogs of **13**



No.	R	Yield
13a		77%
13b		74%
13c		68%
13d		57%
13e	Me_2N	100%
13f	MeNH	76%
13g		84%
13h		47%
13i		62%
13j		66%
13k		86%
13l		87%
13m		65%

tion. Initial attempts at deprotecting the 2,3-dimethoxy groups of derivatives **13** using hydrochloric acid in 1,4-dioxane at elevated temperature resulted in deprotection of only one methoxy group with complete hydrolysis of the 5-carboxamide. Variations in both temperature and concentration of hydrochloric acid in the reaction mixture were not advantageous. Other methods involving trifluoroacetic acid in a 1:9 (v/v) mixture of water:tetrahydrofuran [17], boron tribromide-dimethyl sulfide complex [18], and 33% hydrogen bromide in acetic acid resulted in either mixtures of products or unreacted starting material. The Olah procedure of forming trimethylsilyl iodide *in situ* [19] and using the reagent to form **14** from **13** gave mixed results. Reaction times varied from 24 hours to several days and yields range from poor (~15%) to fair (35-40%) depending on starting material. Attempts to improve reaction conditions and optimize yields are in progress.

In summary we have successfully developed a novel synthesis of 2,3-dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid derivatives starting from an easily prepared isatoic anhydride intermediate.

EXPERIMENTAL

Melting points are all uncorrected and were determined in capillary tubes using a MelTemp II apparatus. The ^1H nmr spectra were recorded on a Varian 400 MHz spectrometer using tetramethylsilane as internal standard. The atmospheric pressure chemical ionization ms spectra were obtained on a Micromass platform LC mass spectrometer. Elemental analyses were carried out by Robertson Laboratories. The tlc analysis was performed on Merck silica gel 60F-254 glass plates. Flash chromatography was performed using columns packed with ICN silica 32-63, 60 A (230-400 mesh). 2-Amino-6-methyl-benzoic acid was obtained from Aldrich Chemical Company. The amines and amino acids used were obtained from commercially available sources except for sarcosine *tert*-butyl ester hydrochloride which was prepared according to literature procedure [20].

5-Methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (**1**).

To a solution of 50 g (0.33 mole) 2-amino-6-methylbenzoic acid dissolved in 500 ml water containing 33.2 g (0.83 mole) sodium hydroxide was added dropwise with vigorous stirring to 360 ml (0.73 mole) of a 20% phosgene solution in toluene over a period of 2 hours. After addition was complete the reaction mixture was stirred for an additional hour and the precipitated product was collected and washed with water, 57.2 g (98%), Rf 0.38 (1:1 hexanes:ethyl acetate); ^1H nmr (DMSO-d_6): δ 11.55 (s, 1H, NH), 7.51 (t, 1H, 7-H, J = 7.8, 7.8 Hz), 7.01 (d, 1H, 8-H, J = 7.6 Hz), 6.93 (d, 1H, 6-H, J = 7.8 Hz), 2.54 (s, 3H, CH_3); ms: m/z 178 $(M + H)^+$.

6-Bromo-5-methyl-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (**2**).

In a 3-necked 1 liter round bottom flask equipped with addition funnel, mechanical stirrer and thermometer is added 57.2 g (0.323 mole) of **1**, 1 g iron filings, 380 ml glacial acetic acid,

and 150 ml trifluoroacetic acid. The mixture is cooled to 0° with vigorous stirring and a solution of 24.99 ml (0.485 mole) bromine in 100 ml trifluoroacetic acid is added dropwise at a rate so as to maintain the temperature of the reaction below 15°. After addition was complete (approximately 1 hour) the reaction mixture was stirred at room temperature for 4 hours and poured into 2 liters cold water. The precipitated product was thoroughly washed with water upon collection, 73.41 g (89%). Some product was further purified by elution through a flash column (3:2 hexanes:ethyl acetate) to give a white, crystalline solid, mp 290-293° (dec.), Rf 0.37 (1:1 hexanes:ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 11.70 (s, 1H, NH), 7.86 (d, 1H, 7-H, J = 8.8 Hz), 6.90 (d, 1H, 8-H, J = 8.8 Hz), 2.68 (s, 3H, CH_3); ms: m/z 256 (M^+).

Anal. Calcd. for $C_9H_6BrNO_3$: C, 42.22; H, 2.36; N, 5.47; Br, 31.21. Found: C, 42.54; H, 2.34; N, 5.47; Br, 31.10.

6-Bromo-5-methyl-8-nitro-1*H*-benzo[*d*][1,3]oxazine-2,4-dione (**3**).

To a solution of 30 g (0.117 mole) of **2** in 200 ml concentrated sulfuric acid under vigorous stirring is added portionwise 14.2 g (0.14 mole) potassium nitrate. After addition was complete (approximately 5 minutes) the reaction mixture was stirred for 1.5 hours and poured into 2 liters ice water. The precipitated product was thoroughly washed with water upon collection, 22 g (62%). Some product was further purified by elution through a flash column (4:1 hexanes:ethyl acetate) to give a yellow, crystalline solid, mp 178-180°, Rf 0.58 (1:1 hexanes:ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 11.12 (br s, 1H, NH), 8.59 (s, 1H, 7-H), 2.77 (s, 3H, CH_3); ms: m/z 300 (M - H)$^+$, 302 (M + H)$^+$.

Anal. Calcd. for $C_9H_5BrN_2O_5$: C, 35.91; H, 1.67; N, 9.30; Br, 26.54. Found: C, 35.84; H, 1.64; N, 9.15; Br, 26.15.

Methyl 2-amino-5-bromo-6-methyl-3-nitrobenzoate (**4**).

A suspension of 22 g (0.073 mole) of **3** in 220 ml methanol was heated at reflux for 3 hours, after which time all solid went into solution. After overnight refrigeration, an orange, crystalline precipitate was collected and washed with methanol, 11.58 g (55%), mp 125-127°, Rf 0.59 (1:1 hexanes:ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 8.22 (s, 1H, 4-H), 7.28 (br s, 2H, NH_2), 3.86 (s, 3H, CO_2CH_3), 2.21 (s, 3H, 6-CH_3); ms: m/z 289 (M^+), 291 (M + 2H)$^+$.

Anal. Calcd. for $C_9H_9BrN_2O_4$: C, 37.39; H, 3.14; N, 9.69; Br, 27.64. Found: C, 37.42; H, 2.97; N, 9.66; Br, 27.70.

6-Methyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylic acid methyl ester (**6**).

A mixture of 10.23 g (0.0354 mole) of **4**, 5.2 ml triethylamine, and 1.5 g 20% palladium on carbon catalyst in a mixture of 100 ml methanol and 100 ml tetrahydrofuran was hydrogenated for 3.5 hours under a hydrogen pressure of 46.7 psi. The catalyst was filtered off (celite) and the filtrate was concentrated. The residue was partitioned between ethyl acetate and water and the organic layer was washed with water, dried over sodium sulfate, filtered and concentrated to give methyl 2,3-diamino-6-methylbenzoate (**5**) as a dark red oil, 6.28 g (98%), ms: m/z 181 (M + H)$^+$. The diamino compound was taken up in 120 ml 4.0 *N* aqueous hydrochloric acid and 4.77 g (0.053 mole) oxalic acid was added. The reaction mixture was heated at reflux for 1.5 hours and the quinoxaline-2,3-dione precipitated out of solution. The off-white solid was washed with water and methanol upon collection, 5.67 g (69%), mp 304-306° (dec.), Rf 0.57 (1:9 methanol:chloroform); ^{1}H nmr (DMSO-d_6): δ 11.98 (s, 1H, amide H), 11.29 (s, 1H, amide H), 7.09 (d, 1H, 8-H, J = 8.3 Hz), 6.97 (d, 1H, 7-H, J = 8.3 Hz), 3.83 (s, 3H, CO_2CH_3), 2.24 (s, 3H, 6-CH_3); ms: m/z 235 (M + H)$^+$.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.20; H, 4.34; N, 11.85.

6-Methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carboxylic acid methyl ester (**7**).

To a solution of 0.25 g (1.06 mmole) 6-methyl-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline-5-carboxylic acid methyl ester (**6**) in 4 ml concentrated sulfuric acid at room temperature is added 118 mg (1.17 mmole) potassium nitrate. The reaction mixture was stirred for 15 hours and poured over ice. The light yellow amorphous precipitate which formed was thoroughly washed with water upon collection, 250 mg (83%), mp 313-315° (dec.), Rf 0.28 (1:9 methanol:chloroform); ^{1}H nmr (DMSO-d_6): δ 12.14 (s, 1H, amide H), 11.89 (s, 1H, amide H), 7.75 (s, 1H, 8-H), 3.88 (s, 3H, CO_2CH_3), 2.29 (s, 3H, 6-CH_3); ms: m/z 280 (M + H)$^+$.

Anal. Calcd. for $C_{11}H_9N_3O_6$: C, 47.32; H, 3.13; N, 14.64. Found: C, 46.44; H, 3.25; N, 15.05.

6-Methyl-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-5-carboxylic acid (**8**).

A solution of 50 mg (0.18 mmole) of **7** in 1 ml (1.0 mmole) 1.0 *N* aqueous sodium hydroxide solution was heated at 40° with vigorous stirring for 92 hours. The reaction mixture was acidified with 1.0 *N* aqueous hydrochloric acid and the precipitated product which formed was recrystallized from water, 36 mg (75%), mp 338-340° (dec.); ^{1}H nmr (DMSO-d_6): δ 12.19 (s, 1H, amide H), 11.64 (br s, 1H, amide H), 7.77 (s, 1H, 8-H), 2.43 (s, 3H, 6-CH_3); ms: m/z 266 (M + H)$^+$.

Anal. Calcd. for $C_{10}H_7N_3O_6$ (1.30 moles water): C, 41.62; H, 3.35; N, 14.56. Found: C, 41.40; H, 3.34; N, 14.39.

2,3-Dichloro-6-methyl-7-nitroquinoxaline-5-carboxylic acid methyl ester (**9**).

To a suspension of 5.85 g (0.021 mole) of **7** in 60 ml anhydrous *N,N*-dimethylformamide under an atmosphere of nitrogen is added dropwise 34.03 ml (0.068 mole) of a 20% phosgene solution in toluene. During the course of addition a mild exotherm resulted and all undissolved material went into solution. After addition was complete (approximately 10 minutes) the reaction mixture was stirred at room temperature for 22 hours and concentrated. The residue was triturated with methanol and an off-white crystalline solid precipitated, 5.98 g (90%), mp 155-157°, Rf 0.66 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.48 (s, 1H, 8-H), 4.05 (s, 3H, CO_2CH_3), 2.59 (s, 3H, 6-CH_3); ms: m/z 317 (M + H)$^+$, 315 (M - H)$^+$.

Anal. Calcd. for $C_{11}H_7Cl_2N_3O_4$: C, 41.80; H, 2.23; N, 13.29; Cl, 22.43. Found: C, 41.74; H, 2.04; N, 13.23; Cl, 22.15.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid methyl ester (**10**).

To a solution of 119 mg (5.19 mmole) sodium metal (washed with hexane) dissolved in 15 ml anhydrous methanol under an atmosphere of nitrogen at room temperature is added portionwise 655 mg (2.07 mmole) of **9** (caution: exothermic). After

addition was complete (approximately 3 minutes) the reaction mixture was stirred for 10 minutes and quenched with water. The off-white amorphous precipitate was washed with water and methanol upon collection, 554 mg (87%), mp 174-176°, Rf 0.57 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.39 (s, 1H, 8-H), 4.16 (s, 3H, OCH_3), 4.14 (s, 3H, OCH_3), 4.04 (s, 3H, CO_2CH_3), 2.60 (s, 3H, 6-CH_3); ms: m/z 308 $(M + H)^+$.

Anal. Calcd. for $C_{13}H_{13}N_3O_6$: C, 50.82; H, 4.26; N, 13.68. Found: C, 50.65; H, 4.20; N, 13.39.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid (**11**).

To a suspension of 1.61 g (5.24 mmole) of **10** in 20 ml tetrahydrofuran is added a solution of 0.86 g (13.09 mmole) potassium hydroxide (85%) in 20 ml water. After stirring at room temperature for 20 hours all solid went into solution. The reaction was allowed to continue for an additional 7 hours and was then cooled to 0° (ice water bath). Acidification with aqueous 1.0 *N* hydrochloric acid produced a white, amorphous precipitate which was recrystallized from ethyl acetate to give 1.47 g (95%) product, mp 258-260°, Rf 0.24 (1:1 hexanes:ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 12.37 (br s, 1H, CO_2H), 8.09 (s, 1H, 8-H), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.34 (s, 3H, 6-CH_3); ms: m/z 294 $(M + H)^+$.

Anal. Calcd. for $C_{12}H_{11}N_3O_6$: C, 49.15; H, 3.78; N, 14.33. Found: C, 49.19; H, 3.53; N, 14.28.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carbonyl chloride (**12**).

A mixture of 500 mg (1.70 mmole) of **11** in 25 ml thionyl chloride (twice distilled over triphenyl phosphite) was heated at reflux for 20 hours. The reaction mixture was concentrated to an off-white solid which was purified by elution through a flash column (4:1 hexanes:ethyl acetate), 510 mg (96%), mp 162-164°, Rf 0.68 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.35 (s, 1H, 8-H), 4.15 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 2.55 (s, 3H, 6-CH_3); ms: m/z 312 $(M + H)^+$.

Anal. Calcd. for $C_{12}H_{10}ClN_3O_5$: C, 46.24; H, 3.23; N, 13.48. Found: C, 46.38; H, 3.32; N, 13.28.

{[1-(2,3-Dimethoxy-6-methyl-7-nitroquinoxalin-5-yl)-methanoyl]-amino}-acetic acid *tert*-butyl ester (**13a**). (General procedure for synthesis of compounds **13b-m**).

To a cooled (0°) mixture of 104 mg (0.67 mmole) glycine *tert*-butyl ester hydrochloride and 0.26 ml (1.69 mmole) triethylamine in 3 ml anhydrous tetrahydrofuran under an atmosphere of nitrogen is added dropwise a solution of 200 mg (0.64 mmole) of **12** in 7 ml anhydrous tetrahydrofuran. After addition was complete (approximately 5 minutes) the reaction mixture was stirred at room temperature for 24 hours, filtered, and concentrated. The residue was taken up in ethyl acetate and the organic solution was washed with water, saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated. The crude product was purified by elution through a flash column (silica gel 60, 230-400 mesh, 3:2 hexanes:ethyl acetate) to give a yellow oil which crystallized on standing, 200 mg (77%), mp 125-126°, Rf 0.44 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.32 (s, 1H, 8-H), 6.32 (br s, 1H, amide NH), 4.14 (d, 2H, CH_2, J = 5.1 Hz), 4.09 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 2.54 (s, 3H, 6-CH_3), 1.47 (s, 9H, *tert*-butyl protons); ms: m/z 407 $(M + H)^+$.

Anal. Calcd. for $C_{18}H_{22}N_4O_7$: C, 53.20; H, 5.46; N, 13.79. Found: C, 53.24; H, 5.45; N, 13.55.

{[1-(2,3-Dimethoxy-6-methyl-7-nitroquinoxalin-5-yl)-methanoyl]-methyl-amino}-acetic acid, *tert*-butyl ester (**13b**).

Prepared from 200 mg (0.64 mmole) of **12** and 122 mg (0.67 mmole) sarcosine *tert*-butyl ester hydrochloride. Reaction was continued for 24 hours and the crude product was eluted through a flash column (4:1 hexanes:ethyl acetate), 200 mg (74%), mp 102-105°, Rf 0.53 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.29 (s, 1H, 8-H), 4.27 (br s, 2H, CH_2), 4.02 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.35 (br s, 3H, NCH_3), 2.54 (s, 3H, 6-CH_3), 1.41 (s, 9H, *tert*-butyl protons); ms: m/z 421 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{24}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.51; H, 5.76; N, 13.35.

3-{[1-(2,3-Dimethoxy-6-methyl-7-nitroquinoxalin-5-yl)-methanoyl]-amino}-propionic acid, *tert*-butyl ester (**13c**).

Prepared from 250 mg (0.80 mmole) of **12** and 153 mg (0.80 mmole) β-alanine *tert*-butyl ester hydrochloride. Reaction was continued for 2.5 hours and the crude product was eluted through a flash column (3:2 hexanes:ethyl acetate), 230 mg (68%), mp 140-142°, Rf 0.47 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.31 (s, 1H, 8-H), 6.37 (br s, 1H, NH), 4.08 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 3.74 (q, 2H, methylene protons, J = 6.1, 6.1, 6.1 Hz), 2.57 (t, 2H, methylene protons, J = 6.3, 6.1 Hz), 2.55 (s, 3H, 6-CH_3), 1.42 (s, 9H, *tert*-butyl protons); ms: m/z 421 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{24}N_4O_7$: C, 54.28; H, 5.75; N, 13.33. Found: C, 54.25; H, 5.69; N, 13.00.

(*S*)-2-{[1-(2,3-Dimethoxy-6-methyl-7-nitroquinoxalin-5-yl)-methanoyl]-amino}-3-phenylpropionic acid, *tert*-butyl ester (**13d**).

Prepared from 200 mg (0.64 mmole) 2,3-dimethoxy-6-methyl-7-nitro-quinoxaline-5-carbonyl chloride (**12**) and 173 mg (0.67 mmole) L-phenylalanine, *tert*-butyl ester hydrochloride. Reaction was continued for 24 hours and the crude product was eluted through a flash column (4:1 hexanes:ethyl acetate), 180 mg (57%), mp 86-88°, Rf 0.49 (7:3 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.32 (s, 1H, 8-H), 7.22 (m, 5H, Ar-H), 6.39 (d, 1H, amide NH, J = 6.6 Hz), 4.88 (q, 1H, CH, J = 6.1, 6.8, 6.1 Hz), 4.07 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.23 (d, 2H, CH_2, J = 5.9 Hz), 2.56 (s, 3H, 6-CH_3), 1.37 (s, 9H, *tert*-butyl protons); ms: m/z 497 $(M + H)^+$.

Anal. Calcd. for $C_{25}H_{28}N_4O_7$: C, 60.48; H, 5.68; N, 11.28. Found: C, 59.73; H, 5.53; N, 11.28.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid dimethylamide (**13e**).

Prepared from 250 mg (0.80 mmole) of **12** and an excess of a solution of gaseous dimethylamine bubbled into anhydrous tetrahydrofuran. Reaction was continued for 19 hours and the crude product was eluted through a flash column (7:3 hexanes:ethyl acetate), 260 mg (100%), mp 138-141°, Rf 0.50 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.29 (s, 1H, 8-H), 4.03 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.28 (s, 6H, $N(CH_3)_2$), 2.54 (s, 3H, 6-CH_3); ms: m/z 321 $(M + H)^+$.

Anal. Calcd. for $C_{14}H_{16}N_4O_5$: C, 52.50; H, 5.03; N, 17.49. Found: C, 52.54; H, 5.01; N, 17.30.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid methylamide (**13f**).

Prepared from 250 mg (0.80 mmole) of **12** and an excess of a solution of gaseous monomethylamine bubbled into anhydrous tetrahydrofuran. Reaction was continued for 17 hours and the crude product was eluted through a flash column (11:9 hexanes:ethyl acetate), 190 mg (76%), mp 205-206°, Rf 0.31 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.32 (s, 1H, 8-H), 5.83 (br s, 1H, NH), 4.07 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 3.07 (d, 3H, amide CH_3, J = 5.1 Hz), 2.56 (s, 3H, 6-CH_3); ms: m/z 307 $(M + 1)^+$.

Anal. Calcd. for $C_{13}H_{14}N_4O_5$: C, 50.98; H, 4.61; N, 18.29. Found: C, 51.12; H, 4.72; N, 18.25.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid benzylamide (**13g**).

Prepared from 250 mg (0.80 mmole) of **12** and 90 μl (0.84 mmole) benzylamine. Reaction was continued for 24 hours and the crude product was eluted through a flash column (7:3 hexanes:ethyl acetate), 260 mg (84%), mp 171-173°, Rf 0.51 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.32 (s, 1H, 8-H), 7.32 (m, 5H, Ar-H), 6.12 (br s, 1H, amide NH), 4.68 (d, 2H, CH_2, J = 5.6 Hz), 4.06 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 2.56 (s, 3H, 6-CH_3); ms: m/z 383 $(M + 1)^+$.

Anal. Calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.63; H, 4.94; N, 14.56.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid, 4-methoxybenzylamide (**13h**).

Prepared from 250 mg (0.80 mmole) of **12** and 0.11 ml (0.84 mmole) 4-methoxybenzylamine. Reaction was continued for 16 hours and the crude product was recrystallized from hexanes:ethyl acetate to give yellow needles, 156 mg (47%), mp 187-189°, Rf 0.42 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.32 (s, 1H, 8-H), 7.28 (d, 2H, 4-methoxyphenyl ring protons, J = 8.5 Hz), 6.85 (d, 2H, 4-methoxyphenyl ring protons, J = 8.5 Hz), 6.07 (br t, 1H, amide NH, J = 5.4, 5.6 Hz), 4.61 (d, 2H, CH_2, J = 5.6 Hz), 4.05 (s, 3H, quinoxaline OCH_3), 3.97 (s, 3H, quinoxaline OCH_3), 3.76 (s, 3H, 4-OCH_3 (phenyl ring)), 2.56 (s, 3H, 6-CH_3); ms: m/z 413 $(M + 1)^+$.

Anal. Calcd. for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.55; H, 4.85; N, 13.47.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid phenylamide (**13i**).

Prepared from 250 mg (0.80 mmole) of **12** and 80 μl (0.84 mmole) aniline. Reaction was continued for 40 hours and the crude product was eluted through a flash column (3:2 hexanes:ethyl acetate), 180 mg (62%), mp 238-240°, Rf 0.43 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.34 (s, 1H, 8-H), 7.81 (d, 2H, 2-H and 6-H of phenyl ring, J = 8.8 Hz), 7.69 (s, 1H, amide NH), 7.35 (t, 2H, 3-H and 5-H of phenyl ring, J = 7.6, 8.5 Hz), 7.11 (t, 1H, 4-H of phenyl ring, J = 6.3, 7.3 Hz), 4.17 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 2.58 (s, 3H, 6-CH_3); ms: m/z 369 $(M + H)^+$.

Anal. Calcd. for $C_{18}H_{16}N_4O_5$: C, 58.69; H, 4.38; N, 15.21. Found: C, 58.62; H, 4.52; N, 15.06.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid 4-methoxyphenylamide (**13j**).

Prepared from 250 mg (0.80 mmole) of **12** and 207 mg (1.68 mmole) 4-anisidine. Reaction was continued for 24 hours and the crude product was eluted through a flash column (3:2 hexanes:ethyl acetate), 210 mg (66%), mp 206-208°, Rf 0.41 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.33 (s, 1H, 8-H), 7.71 (d, 2H, Ar-H, J = 9.0 Hz), 7.60 (s, 1H, amide NH), 6.88 (d, 2H, Ar-H, J = 8.8 Hz), 4.16 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.57 (s, 3H, 6-CH_3); ms: m/z 399 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{18}N_4O_6$: C, 57.29; H, 4.55; N, 14.06. Found: C, 57.23; H, 4.73; N, 14.01.

1-(2,3-Dimethoxy-6-methyl-7-nitroquinoxalin-5-yl)-1-piperazin-1-yl methanone (**13k**).

Prepared from 250 mg (0.80 mmole) of **12** and 138 mg (1.60 mmole) piperazine. Reaction was continued for 2 hours and the crude product was eluted through a flash column (8% methanol in chloroform): 250 mg (86%), mp 150-152°, Rf 0.23 (1:9 methanol:chloroform); ^{1}H nmr (deuteriochloroform): δ 8.30 (s, 1H, 8-H), 4.05 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 3.81 (t, 4H, piperazinyl-H, J = 4.9, 5.1 Hz), 2.96 (t, 4H, piperazinyl-H, J = 5.1, 4.9 Hz), 2.54 (s, 3H, 6-CH_3), 1.84 (br s, 1H, NH); ms: m/z 362 $(M + H)^+$.

Anal. Calcd. for $C_{16}H_{19}N_5O_5$: C, 53.18; H, 5.30; N, 19.38. Found: C, 53.08; H, 5.22; N, 18.82.

1-[1,4]Diazepan-1-yl-(2,3-dimethoxy-6-methyl-7-nitroquinoxalin-5-yl)methanone (**13l**).

Prepared from 250 mg (0.80 mmole) of **12** and 160 mg (1.60 mmole) homopiperazine. Reaction was continued for 30 hours and the crude product was eluted through a flash column (8% methanol in chloroform), 260 mg (87%), mp 141-143°, Rf 0.24 (1:9 methanol:chloroform); ^{1}H nmr (deuteriochloroform): δ 8.29 (s, 1H, 8-H), 4.03 (s, 3H, OCH_3), 3.93 (br s, 7H, OCH_3 and azepinyl protons), 3.02 (br s, 2H, azepinyl CH_2), 2.82 (t, 2H, azepinyl CH_2, J = 5.4, 5.6 Hz), 2.54 (s, 3H, 6-CH_3), 1.88 (t, 2H, azepinyl CH_2, J = 5.6, 5.4 Hz), 1.79 (br s, 1H, NH); ms: m/z 376 $(M + H)^+$.

Anal. Calcd. for $C_{17}H_{21}N_5O_5$: C, 54.39; H, 5.64; N, 18.66. Found: C, 54.07; H, 5.57; N, 18.24.

2,3-Dimethoxy-6-methyl-7-nitroquinoxaline-5-carboxylic acid, *p*-tolylamide (**13m**).

Prepared from 250 mg (0.80 mmole) of **12** and 180 mg (1.68 mmole) *p*-toluidine. Reaction was carried out in refluxing tetrahydrofuran for 50 hours and the crude product was eluted through a flash column (7:3 hexanes:ethyl acetate), 200 mg (65%), mp 214-215°, Rf 0.50 (1:1 hexanes:ethyl acetate); ^{1}H nmr (deuteriochloroform): δ 8.33 (s, 1H, 8-H), 7.69 (d, 2H, toluidyl protons, J = 8.3 Hz), 7.65 (s, 1H, amide NH), 7.15 (d, 2H, toluidyl protons, J = 8.3 Hz), 4.17 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 2.58 (s, 3H, 6-CH_3), 2.32 (s, 3H, toluidyl CH_3); ms: m/z 383 $(M + H)^+$.

Anal. Calcd. for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.97; H, 4.68; N, 14.71.

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