Synthesis and Potential Central Nervous System Stimulant Activity of 5,8-Methanoquinazolines and Bornano-[1,2,4]triazines Fused with Imidazole and Pyrimidine

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Starting from 3-chloro-5,8-methanoquinazoline **1** and 3-chloro-bornano[1,2,4]triazine **7**, the novel 5,8-methanoquinazolines **5a-b** and bornano[1,2,4]triazines **10a-b** fused with imidazole and pyrimidine were prepared. None of these compounds showed any satisfactory central nervous system stimulant activities.

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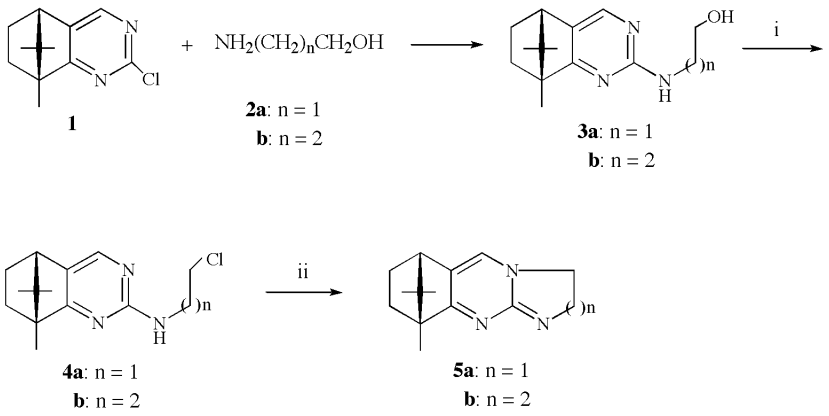
Since our findings that bornano[1,2,3]triazine showed a strong central nervous system (CNS) stimulant activity, we have been engaged in the synthesis of a series of isomeric bornano[1,2,4]triazines and 5,8-methanoquinazolines fused with five and six-membered heterocycles in order to investigate the structure activity relationship [1]. In this paper, we report the synthesis of novel 5,8-methanoquinazolines and bornano[1,2,4]triazines fused with imidazole and pyrimidine as shown in Scheme 1 and Scheme 2.

Condensation of 3-chloro-5,8-methanoquinazoline **1** with hydroxyalkylamines **2a-b** in boiling dioxane, followed by chlorination of **3a-b** with thionyl chloride gave the corresponding chloroalkylamines **4a-b**. Ring closure of **4a-b** was readily accomplished by heating in benzene in the presence of Hunig's base to yield 5,8-methanoquinazolines **5a-b** fused with imidazole and pyrimidine in good yields. In the nmr spectra of **5a-b**, the secondery amino protons observed in **4a-b** were disappeared and the mass spectra of **5a-b** clearly showed the molecular ion peaks at 229 and 243 m/z respectively.

3-Chlorobornano[1,2,4]triazine **7** prepared by chlorination of bornano[1,2,4]triazin-3-one **6** with phosphorous oxychloride was similarly condensed with **2a-b** to provide hydroxyalkylamines **8a-b** as shown in Scheme 2. The attempted chlorination of **8a-b** with thionyl chloride however failed to give unidentified products. Cyclization of **8a-b** was then achieved in one pot by methanesulfonylation in the presence of triethylamine to give the objective bornano[1,2,4]triazines **10a-b** fused with imidazole and pyrimidine *via* elimination of methanesulfonate from the mesyloxy intermediates **9a-b**. The structures of **10a-b** were also confirmed by the spectral data as **5a-b**.

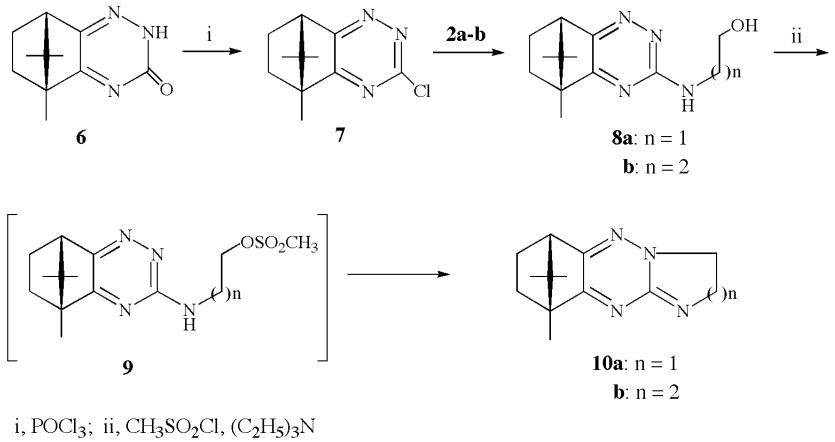
The CNS stimulant activity of synthesized compounds was evaluated using mice (ddy, strain, male, 25-30 g). The compounds were dissolved in dimethyl sulfoxide and administered intraperitonealy in a dose of 100 mg/Kg. Contrary to our expectations, none of these compounds showed any satisfactory CNS stimulant activity. Administration in a dose of up to 250 mg/Kg however was ineffective on activity. These pharmacological results

Scheme 1



i, $SOCl_2$, ii, *N*,*N*-diisopropylethylamine

Scheme 2



might reconfirm our suggestions that the presence of N-N group at C-3 position of bornano[1,2,4]triazine is probably essential for the CNS stimulant activity [2].

EXPERIMENTAL

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IRA-2 spectrometer. The ^{1}H nmr spectra were recorded with a JEOL EX-270 and JEOL JMN-LA 400 spectrometers using tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-DX 300 spectrometer.

(5*R*,8*S*)-2-(2-Hydroxyethylamino)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline (**3a**).

A mixture of (5*S*,8*R*)-2-chloro-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline **1** [3] (0.2 g, 0.9 mmole) and excess ethanolamine **2a** (2 ml) in dioxane (5 ml) was refluxed 4 hours and evaporated to dryness. The residue was washed with water and extracted with chloroform. The solvent was distilled from the extract and the residue was chromatographed on silica gel (chloroform) to give light yellow viscous oil, yield 0.17 g (75 %); ir (neat): 3450 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.69 (s, 3H, anti 9-CH_3), 1.02 (s, 3H, syn 9-CH_3), 1.19 (s, 3H, 8-CH_3), 1.22 and 1.79 (two m, 2H each, 6-CH_2 and 7-CH_2), 3.01 (d, 1H, J = 4, 5-H), 3.55 (t, 2H, J = 8, *CH*$_2$NH), 3.82 (t, 2H, J = 8, *CH*$_2$OH), 5.46 (br s, 1H, OH), 7,86 (s, 1H, 4-H); ms: m/z 247 (M$^+$).

Anal. Calcd. for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 68.21; H, 8.84; N, 17.18.

(5*R*,8*S*)-2-(3-Hydroxypropylamino)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline (**3b**).

A mixture of **1** (0.12 g, 0.54 mmole) and excess 3-amino-1-propanol **2b** (5 ml) in dioxane (5 ml) was refluxed for 3 hours and evaporated to dryness. The residue was washed with water and extracted with chloroform. The solvent was distilled from the extract and the residue was chromatographed on silica gel (chloroform) to give yellow viscous oil, yield 0.11 g (83 %); ^{1}H nmr (deuteriochloroform): δ 2.28 (m, 2H, $CH_2CH_2CH_2$), 3.65 (m, 4H, *CH*$_2$NH and *CH*$_2$OH), 5.45 (br s, 1H, OH), 7.88 (s, 1H, 4-H); ms: m/z 261 (M$^+$).

Anal. Calcd. for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 69.22; H, 9.16; N, 16.28.

(5*S*,8*R*)-2-(2-Chloroethylamino)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline (**4a**).

A mixture of **3a** (0.056 g, 0.23 mmole) and thionyl chloride (0.1 g, 0.84 mmole) in dry benzene (40 ml) was refluxed for 1 hour and evaporated to dryness to give a light yellow powder after trituration with hexane, yield 0.058 g (97 %); ^{1}H nmr (deuteriochloroform): δ 3.72 (t, 2H, J = 8, *CH*$_2$NH), 3.91 (t, 2H, J = 8, CH_2Cl), 7.66 (s, 1H, 4-H), 8.90 (br s, 1H, NH); ms: m/z 265 (M$^+$), 267 (M$^+$+2). This compound was used for the next reaction without purification.

(5*S*,8*R*)-2-(3-Chloropropylamino)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline (**4b**).

A mixture of **3b** (0.093 g, 0.36 mmole) and thionyl chloride (0.3 g, 2.5 mmoles) in dry benzene (16 ml) was refluxed for 0.5 hour and evaporated to dryness to give a light yellow amorphous powder after trituration with hexane, yield 0.096 g (96 %), ^{1}H nmr (deuteriochloroform): δ 2.30 (m, 2H, $CH_2CH_2CH_2$), 3.72 (t, 2H, J = 8, *CH*$_2$NH), 3.92 (t, 2H, J = 8, CH_2Cl), 7.85 (s, 1H, 4-H), 8.93 (s, 1H, NH); ms: m/z 279 (M$^+$), 281 (M$^+$+2). This compound was used for the next rection without purification.

(6*S*,9*R*)-9,11,11-Trimethyl-2,3,6,7,8,9-hexahydro-6,9-methanoimidazo[2,1-*b*]quinazoline (**5a**).

A mixture of **4a** (0.052 g, 0.2 mmole) and *N*,*N*-diisopropylethylamine (0.07 g, 0.54 mmole) in dry benzene (7 ml) containing chloroform (1 ml) was stirred at 50° for 22 hours and allowed to stand. The precipitates were filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (chlorofom) to give light yellow powders. Recrystallization from hexane gave light yellow crystalline powders, mp 285-286° (decomposition), yield 0.03 g (67 %); ^{1}H nmr (deuteriochlorofom): δ 0.68 (s, 3H, anti

11-CH_3), 1.03 (s, 3H, syn 11-CH_3), 1.18 (s, 3H, 9-CH_3), 3.97 and 4.54 (two t, 2H each, J = 7, 2-CH_2 and 3-CH_2), 7.93 (s, 1H, 5-H); ms: m/z 229 (M^+).

Anal. Calcd for $C_{14}H_{19}N_3$: C, 73.32; H, 8.35; N, 18.32. Found: C, 73.42; H, 8.33; N, 18.39.

(7*S*,10*R*)-10,12,12-Trimethyl-2,3,7,8,9,10-hexahydro-7,10-methano-4*H*-pyrimido[2,l-*b*]quinazoline (**5b**).

A mixture of **4b** (0.08 g, 0.29 mmole) and *N*,*N*-diisopropylethylamine (0.1 g, 0.78 mmole) in dry benzene (5 ml) containing chloroform (1 ml) was stirred at 50° for 16 hours and allowed to stand. The precipitates were filtered off and the filtrate was evaporated to dryness. The residue was chromatographed on silica gel (chloroform) to give a light yellow powder. Recrystallization from hexane gave a light yellow crystalline powder, mp 281-283° (decomposition), yield 0.06 g (86 %); ^{1}H nmr (deuteriochloroform) : δ 2.20 (m, 2H, 3-CH_2), 3.72 and 4.42 (two t, 2H each, J = 7, 2-CH_2 and 4-CH_2), 7.93 (s, 1H, 6-H); ms: m/z 243 (M^+).

Anal. Calcd. for $C_{15}H_{21}N_3$: C, 74.03; H, 8.70, N, 17.27. Found: C, 74.11, H, 8.77; N, 17.22.

(5*S*,8*R*)-5,9,9-Trimethyl-2,3,5,6,7,8-hexahydro-5,8-methano-[1,2,4]benzotriazin-3-one (**6**).

Compound **6** was prepared by the reaction of camphorquinone and semicarbazide hydrochloride according to the methods reported by M. O. Forster and A. Zimmerli , mp 166-167° (166-167° [4]), yield 33 %; ir (potassium bromide): 3260 (NH), 1690 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.21 (d, 1H, J = 4, 8-H), 10.90 (br s, 1H, NH); ms: m/z 205 (M^+), 190 (M^+-CH3), 177 (M^+-N_2).

Anal. Calcd. for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.30; H, 7.45; N, 20.40.

(5*S*,8*R*)-3-Chloro-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano[1,2,4]benzotriazine (**7**).

A solution of **6** (0.5 g, 2.4 mmoles) in phosphorous oxychloride (5 ml) was refluxed for 1.5 hours and evaporated to dryness. The residual viscous oil was dissolved in a mixture of dioxane (20 ml) and 20 % potassium hydroxide solution (10 ml). The mixture was refluxed for 1 hour and extracted with chloroform. The solvent was distilled from the extract. The residue was chromatographed on silica gel (chloroform) to give light yellow viscous oil, yield 0.48 g (90 %); ^{1}H nmr (deuteriochloroform): δ 3.00 (d, 1H, J = 3.5, 8-H); ms: m/z 223 (M^+), 225 (M^++2).

Anal. Calcd. for $C_{11}H_{14}N_3Cl$: C, 59.06; H, 6.31; N, 18.78. Found: C, 59.13; H, 6.42; N, 18.82.

(5*S*,8*R*)-3-(2-Hydroxyethylamino)-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano[1,2,4]benzotriazine (**8a**).

A mixture of **7** (0.08 g, 0.36 mmole) and **2a** (1 ml) in dioxane (5 ml) was refluxed for 1.5 hours and evaporated to dryness. The residue was chromatographed on silica gel (chloroform) to give light yellow viscous oil, yield 0.064 g (72 %); ^{1}H nmr (deuteriochloroform): δ 0.65 (s, 3H, anti 9-CH_3), 1.04 (s, 3H, syn 9-CH_3), 1.21 (s, 3H, 8-CH_3), 3.61 (t, 2H, J = 8, *CH_2*NH), 3.90 (t, 2H, J = 8, *CH_2*OH), 7.97 (s, 1H, NH); ms: m/z 248 (M^+).

Anal. Calcd. for $C_{13}H_{20}N_4O$: C, 62.88; H, 8.11; N, 22.56. Found: C, 63.00; H, 8.21; N, 22.48.

(5*S*,8*R*)-3-(3-Hydroxypropylamino)-5,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano[1,2,4]benzotriazine (**8b**).

A mixture of **7** (0.06 g, 0.27 mmole) and **2b** (0.08 g) in dioxane (5 ml) was refluxed for 1.5 hours and evaporated to dryness. The residue was chromatographed on silica gel (chloroform) to give yellow viscous oil, yield 0.05 g (72 %); ^{1}H nmr (deuteriochloroform): δ 2.23 (m, 2H, CH_2*CH_2*CH_2), 3.68 (t, 2H, J = 8, *CH_2*NH), 3.94 (t, 2H, J = 8, *CH_2*OH), 5.39 (br s, 1H, OH); ms: m/z 262 (M^+).

Anal. Calcd. for $C_{14}H_{22}N_4O$: C, 64.09; H, 8.45; N, 21.36. Found: C, 64.29; H, 8.61; N, 21.11.

(6*S*,9*R*)-9,11,11-Trimethyl-2,3,6,7,8,9-hexahydro-6,9-methanoimidazo[1,2-*b*][1,2,4]benzotriazine (**10a**).

To a mixture of **8a** (0.05 g, 0.2 mmole) and triethylamine (0.07 g, 0.7 mmole) in dry tetrahydrofuran (5 ml) was added dropwise a solution of methanesulfonyl chloride (0.04 g, 0.35 mmole) in dry tetrahydrofuran (3 ml) during 10 minutes at 0°. The mixture was stirred for an additional 3 hours and evaporated to dryness. The residue was washed with 3 % sodium bicarbonate solution and extracted with ethyl acetate. The solvent was distilled from the extract to give light yellow powders. Recrystallization from ether-chloroform (1:1) gave light yellow plates, mp 95-97°, yield 0.03 g (65 %); ^{1}H nmr (deuteriochloroform): δ 0.83 (s, 3H, anti 11-CH_3), 1.01 (s, 3H, syn 11-CH_3), 1.14 (s, 3H, 9-CH_3), 3.90 and 4.05 (two t, 2H each, J = 7, 2-CH_2 and 3-CH_2); ms: m/z 230 (M^+).

Anal. Calcd. for $C_{13}H_{18}N_4$: C, 67.80; H, 7.88; N, 24.33. Found: C, 67.91; H, 7.92; N, 24.24.

(7*S*,10*R*)-10,12,12-Trimethyl-2,3,7,8,9,10-hexahydro-7,10-methano-4*H*-pyrimido[1,2-*b*][1,2,4]benzotriazine (**10b**).

This compound was prepared from **8b** and methanesulfonyl chloride according to the methods described in the preparation of **10a**. Recrystallization from ether-chloroform (1:1) gave colorless needles, mp 260-263° (sublime), yield 47 %; ^{1}H nmr (deuteriochloroform): δ 2.25 (m, 2H, 3-CH_2), 3.77 and 4.31 (two t, 2H each, J = 7, 2-CH_2 and 4-CH_2); ms: m/z 244 (M^+).

Anal. Calcd. for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.74; H, 8.31; N, 22.86.

REFERENCES AND NOTES

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[3] S. Nagai, T. Ueda, S. Sugiura and J. Sakakibara, *J. Heterocyclic Chem.*, **35**, 325, (1998).

[4] M. O. Forster and A. Zimmerli, *J. Chem. Soc.*, **97**, 2156 (1910). The spectral data of **6** have not been described.