Synthesis and Central Nervous System Stimulant Activity of 5,8-Methanoquinazolines Fused with Imidazole, Thiadiazole, Pyrimidine and 1,3,5-Triazine

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5,8-Methanoquinazolines fused with imidazoles **4a-4b**, thiadiazoles **5-6**, pyrimidines **7**, **9**, **11** and **12**, and 1,3,5-triazine **13** were prepared starting from (5*R*,8*S*)-2-amino-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazoline **3**. Most compounds possessed central nervous system stimulant activities.

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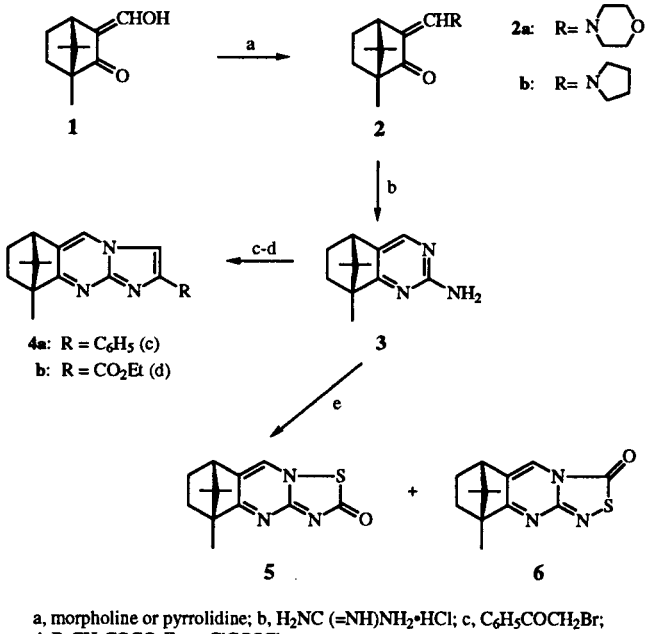
Since our discovery that camphor-1,2,3-triazine displayed a strong central nervous system (CNS) stimulant activity [1], we have been engaged in the synthesis of isomeric camphor-1,2,4-triazines fused with five and six-membered heterocycles in order to investigate the structure-activity relationships [2]. In a previous paper we reported that the presence of a N-N group at the C-3 position of camphor-1,2,4-triazine is essential for CNS stimulant activity [3]. In continuation of our studies on the structure-activity relationships, we report now the synthesis of structurally isomeric 5,6,7,8-tetrahydro-5,8-methanoquinazolines fused with five-membered **4-6** and six-membered heterocycles **7**, **9**, **11-12** and **13** as shown in Scheme 1 and Scheme 2, respectively.

It has already been reported that our key intermediate **3** has been prepared by reaction of (1*R*)-3-hydroxymethylenecamphor **1** with guanidine carbonate [4]. However, attempted synthesis according to the literature method failed to give **3**. The unreactivity of **1** was then circumvented by activating **1** to the enaminoketones **2a** and **2b**. When the enaminoketones were allowed to react with guanidine hydrochloride, only pyrrolidino derivative **2b** successfully underwent cyclization to give 2-aminoquinazoline **3**. The ^{1}H nmr spectrum of **3** showed amino protons (δ 4.92 ppm) and a pyrimidine proton (δ 7.89 ppm) which were consistent with the structure **3**. Cyclocondensation of **3** with 2-bromoacetophenone or ethyl bromopyruvate readily provided imidazo-[2,1-*b*]quinazolines **4a** and **4b**, the imidazole protons of which appeared at δ 7.67 ppm and δ 8.00 ppm in ^{1}H nmr spectrum. Treatment of **3** with chlorocarbonylsulfenyl chloride at 0° produced an inseparable mixture of two compounds. From ^{1}H nmr spectrum, we confirmed two structures to be [1,2,4]thiadiazolo[3,2-*b*]quinazoline **5** and [1,2,4]thiadiazolo[3,4-*b*]quinazoline **6**.

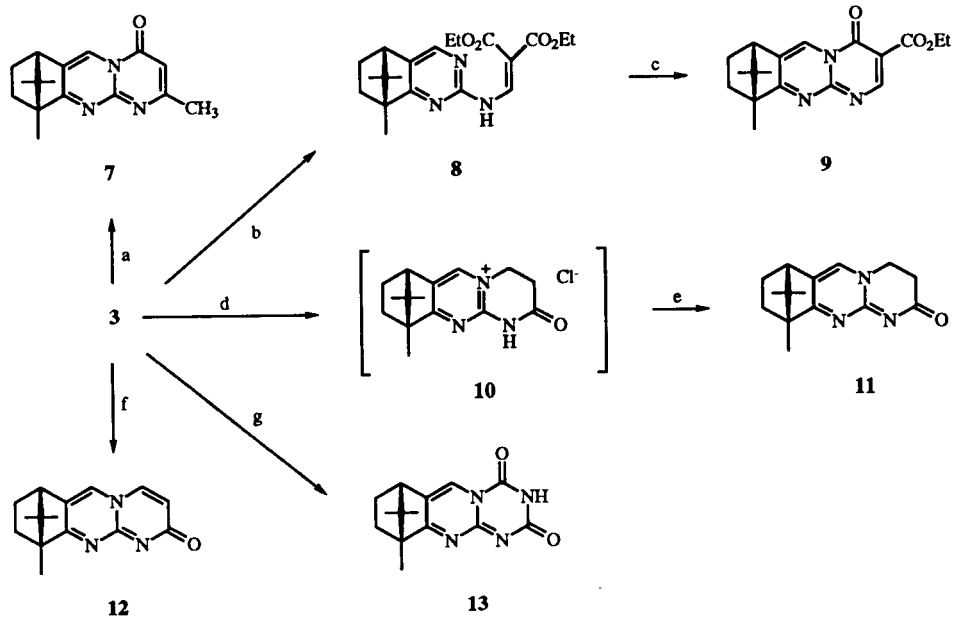
Compounds **7**, **9** and **11-13** in which the six-membered rings are annelated to the quinazoline ring were prepared as summarized in Scheme 2. Compound **3** and ethyl acetoacetate were cyclocondensed in boiling acetic acid to give 2-methylpyrimido[2,1-*b*]quinazoline **7**. The 3-ethoxycarbonyl analogue **9** was also obtained in two steps. Condensation of **3** with diethyl ethoxymethylenemalonate yielded diethyl aminomethylenemalonate **8** which, on heating at 190° in Dowtherm A, cyclized to give **9**. The structure of **7** and **9** were confirmed by ^{1}H nmr spectrum in which the C-6 protons were both shifted downfield due to the anisotropy of the adjacent C-4 carbonyl groups. The quinazolinium chloride **10** obtained

Scheme 1



a, morpholine or pyrrolidine; b, H_2NC (=NH)NH_2•HCl; c, $C_6H_5COCH_2Br$; d, $BrCH_2COCO_2Et$; e, ClCOSCl

Scheme 2



a, $CH_3COCH_2CO_2Et$; b, $EtOCH{=}C(CO_2Et)_2$; c, Dowtherm A; d, $ClCH_2CH_2COCl$, Et_3N; e, 10% K_2CO_3; methyl propiolate; g, ClCONCO

from reaction with 3-chloropropionyl chloride was readily converted to the free base **11** on treatment with 10% potassium carbonate solution. The preparation of dihydro analog **12** was accomplished by a prolonged heating of **3** with methyl propiolate in ethanol. The mass spectra of **11** and **12** clearly showed the molecular ion peaks.

The bifunctional electrophilic reagent, *N*-(chlorocarbonyl)isocyanate was reacted with **3**, followed by treatment with triethylamine to provide [1,3,5]triazino[2,1-*b*]-quinazoline-2,4-(3*H*)-dione **13**. The ^1H nmr spectrum showed a characteristic deuterium oxide exchangeable broad proton signal centered at δ 9.42, confirming the 1,3,5-triazinedione structure.

The CNS stimulant activity of compounds **1-13** 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. All compounds except **8** and **11** showed effective CNS stimulation. Among them, **13** showed the most potent activity and caused a death of animals by strong seisure immediately after the administration. The activity of **13** was comparable to pentylenetetrazole. A clear difference in activity was not observed between 5,8-methanoquinazolines annelated to five-membered and six-membered heterocycles. It is also remarkable to note that 2-aminoquinazoline **3** itself has an activity whereas isomeric 2-aminocamphor-1,2,4-triazine showed no behavioral stimulant activity.

In conclusion, we have prepared new 5,8-methanoquinazolines fused with imidazole, thiadiazole, isothiazole, pyrimidine and 1,3,5-triazine, most of which showed CNS stimulant activity.

EXPERIMENTAL

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

(1*R*,4*S*)-1,7,7-Trimethyl-3-morpholinomethylenebicyclo-[2.2.1]heptan-2-one **2a**.

A mixture of 0.1 g (0.56 mmole) of **1** and 0.056 g (0.65 mmole) of morpholine in 5 ml of dry benzene was stirred at room temperature for 21 hours and evaporated to dryness. The residue was recrystallized from hexane to give a white crystalline powder, mp 105-106°, yield 0.085 g (61%); ^1H nmr (deuteriochloroform): δ 3.35 and 3.71 (two m, 4H each, morpholine protons), 6.92 (s, 1H, =CH); ms: m/z 249 (M^+).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.11; H, 9.55; N, 5.79.

(1*R*,4*S*)-1,7,7-Trimethyl-3-pyrrolidinomethylenebicyclo-[2.2.1]heptan-2-one **2b**.

A mixture of 5 g (0.028 mole) of **1** and 2.23 g (0.031 mole) of pyrrolidine in 50 ml of dry benzene was stirred at room temperature for 3 hours and evaporated to dryness. The residue was chromatographed on silica gel eluting with chloroform. The eluate was collected and distilled off. The residue was recrystallized from hexane to give colorless needles, mp 76-78°, yield

5 g (77%); ^{1}H nmr (deuteriochloroform): δ 1.90 and 3.34 (two m, 4H each, pyrrolidine methylenes), 7.24 (s, 1H, =CH); ms: m/z 233 (M^+).

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.21; H, 9.94; N, 6.00. Found: C, 77.41; H, 10.09; N, 5.86.

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

A mixture of 3 g (0.013 mole) of **2b**, 2.46 g (0.026 mole) of guanidine hydrochloride in 77 ml of absolute ethanol containing 0.6 g (0.026 mole) of sodium was refluxed for 42 hours. A solution of 0.58 g (6.1 mmoles) of guanidine hydrochloride in 10 ml of absolute ethanol containing 0.14 g (6.1 mmoles) of sodium was then added to the reaction mixture. The mixture was refluxed for an additional 25 hours. To the reaction mixture was added again a solution of 0.1 g (1 mmole) of guanidine hydochloride in 12 ml of absolute ethanol containing 0.39 g (0.017 mole) of sodium. The resulting mixture was refluxed for 25 hours and evaporated to dryness. The residue was dissolved in 50 ml of water and extracted with chloroform. The extract was evaporated to dryness and the residue was recrystallized from ethyl acetate to give colorless needles, mp 192-195°, yield 1.2 g (46%); ^{1}H nmr (deuteriochloroform): δ 4.92 (br s, 2H, NH_2), 7.89 (s, 1H, 4-H); ms: m/z 203 (M^+).

Anal. Calcd. for $C_{12}H_{17}N_3$: C, 70.91; H, 8.43; N, 20.67. Found: C, 70.76; H, 8.39; N, 20.71.

(6*S*,9*R*)-2-Phenyl-9,11,11-trimethyl-6,7,8,9-tetrahydro-6,9-methanoimidazo[2,1-*b*]quinazoline **4a**.

A mixture of 15 mg (0.074 mmole) of **3** and 20 mg (0.1 mmole) of 2-bromoacetophenone in 1.5 ml of ethanol was refluxed for 10 hours and evaporated to dryness. The residue was washed with 5% sodium bicarbonate solution and extracted with ethyl acetate. The solvent from the extract was distilled and the residue was recrystallized from hexane to give light yellow crystals, mp >300°, yield 20 mg (89%); ^{1}H nmr (deuteriochloroform): δ 7.39 (m, 3H, 3, 4 and 5-H of phenyl), 7.67 (s, 1H, 3-H), 8.00 (m, 2H, 2 and 6-H of phenyl), 8.03 (s, 1H, 5-H); ms: m/z 303 (M^+).

Anal. Calcd. for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.01; H, 7.09; N, 13.61.

Ethyl (6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methanoimidazo[2,1-*b*]quinazoline-2-carboxylate **4b**.

A mixture of 40 mg (0.197 mmole) of **3** and 130 mg (0.667 mmole) of ethyl bromopyruvate in 2 ml of dry tetrahydrofuran was stirred at room temperature for 22 hours and then under reflux for 3 hours. The reaction mixture was washed with 5% sodium bicarbonate solution and extracted with chloroform. The extract was distilled off and the residue was recrystallized from ethyl acetate to give colorless plates, mp 228-230°, yield 42 mg (71%); ^{1}H nmr (deuteriochloroform): δ 8.00 and 8.01 (each s, 2H, 3 and 5-H); ms: m/z 299 (M^+).

Anal. Calcd. for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.41; H, 7.22: N, 14.25.

(6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methano-2*H*-[1,2,4]thiadiazolo[3,2-*b*]quinazolin-2-one **5** and (6*S*,9*R*)-9,11,11-Trimethyl-6,7,8,9-tetrahydro-6,9-methano-3*H*-[1,2,4]thiadiazolo[3,4-*b*]quinazolin-3-one **6**.

To a solution of 0.1 g (0.493 mmole) of **3** in 3 ml of dry tetrahydrofuran was added dropwise at 0° under argon a solution of 0.4 ml of chlorocarbonylsulfenyl chloride in 3 ml of dry tetrahydrofuran. The mixture was stirred at room temperature for 19 hours. The precipitate was collected, washed with ether and recrystallized from ethyl acetate to give an inseparable mixture of **5** and **6** (1:1) as colorless crystals, mp 168-170°, yield 94 mg (73%); ir (potassium bromide): 1710 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.28 (s, 1H, pyrimidine proton of **5**), 8.48 (s, 1H, pyrimidine proton of **6**); ms: m/z 229 (M^+-S).

Anal. Calcd. for $C_{13}H_{15}N_3OS$: C, 59.75; H, 5.79; N, 16.08. Found: C, 59.66; H, 5.83; N, 16.16.

(7*S*,10*R*)-2,10,12,12-Tetramethyl-7,8,9,10-tetrahydro-7,10-methanopyrimido[2,1-*b*]quinazolin-4-one **7.**

A mixture of 40 mg (0.2 mmole) of **3** and 120 mg (0.89 mmole) of ethyl acetoacetate in 20 ml of acetic acid was refluxed for 6 hours and evaporated to dryness. The residue was mixed with 5 ml of 5% sodium bicarbonate solution and extracted with chloroform. The solvent from the extract was distilled to give a viscous oil which was triturated with hexane to give a white solid. Recrystallization from ether gave colorless needles, mp 147-149°, yield 28 mg (53%); ^{1}H nmr (deuteriochloroform): δ 2.48 (s, 1H, 2-CH_3), 6.32 (s, 1H, 3-H), 8.87 (s, 1H, 6-H); ms: m/z 269 (M^+).

Anal. Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60. Found: C, 71.26; H, 7.03; N, 15.78.

Diethyl [(5*S*,8*R*)-8,9,9-Trimethyl-5,6,7,8-tetrahydro-5,8-methanoquinazolin-2-yl]aminomethylenemalonate **8**.

A mixture of 0.1 g (0.49 mmole) of **3** and 0.13 g (0.63 mmole) of diethyl ethoxymethylenemalonate in 20 ml of dry dimethylformamide was refluxed for 22 hours and evaporated to dryness. The residue was recrystallized from ether to give light yellow crystalline powders, mp 131-133°, yield 82 mg (44%); ^{1}H nmr (deuteriochloroform): δ 8.11 (s, 1H, 4-H), 9.17 (d, 1H, =CH; changeable to singlet on deuterium oxide addition), 10.95 (d, 1H, NH); ms: m/z 373 (M^+).

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.19; H, 6.60; N, 12.79.

Ethyl (7*S*,10*R*)-4-Oxo-10,12,12-trimethyl-7,8,9,10-tetrahydro-7,10-methanopyrimido[2,1-*b*]quinazoline-3-carboxylate **9**.

A solution of 98 mg (0.26 mmole) of **8** in 10 ml of Dowtherm A (Fluka) was stirred at 190° for 130 hours. After cooling, the reaction mixture was diluted with 50 ml of hexane and allowed to stand in a refrigerator. The precipitate was collected and recrystallized from ethyl acetate to give brown crystals, mp 208-210°, yield 39 mg (45%); ^{1}H nmr (deuteriochloroform): δ 9.09 and 9.13 (each s, 2H, 2 and 6-H); ms: m/z 327 (M^+).

Anal. Calcd. for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.11; H, 6.40; N, 12.72.

(7*S*,10*R*)-10,12,12-Trimethyl-2,3,7,8,9,10-hexahydro-7,10-methano-4*H*-pyrimido[2,1-*b*]quinazolin-2-one **11**.

A mixture of 0.1 g (0.5 mmole) of **3** and 0.35 g (2.76 mmoles) of 3-chloropropionyl chloride in 20 ml of dry benzene was refluxed for 5 hours and evaporated to dryness to give crude (7*S*,10*R*)-2-oxo-10,12,12-trimethyl-2,3,7,8,9,10-hexahydro-7,10-methano-4*H*-pyrimido[2,1-*b*]quinazolinium chloride **10** as a light yellow powder. To a solution of **10** in 5 ml of water was added 5 ml of 10% potassium carbonate solution, and the mixture was extracted with chloroform. The extract was distilled off to give a white powder. Recrystallization from ethyl acetate

gave **11** as colorless crystals, mp 291-293°, yield 44 mg (35%); ^{1}H nmr (deuteriochloroform): δ 2.66 (m, 2H, 3-CH_2), 4.22 (m, 2H, 4-CH_2), 7.58 (s, 1H, 6-H); ms: m/z 257 (M^+).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.08; H, 7.52; N, 16.41.

(7*S*,10*R*)-10,12,12-Trimethyl-7,8,9,10-tetrahydro-7,10-methanopyrimido[2,1-*b*]quinazolin-2-one **12**.

A mixture of 0.1 g (0.49 mmole) of **3** and 0.07 g (0.83 mmole) of methyl propiolate in 6 ml of ethanol was refluxed for 24 hours. After cooling, the precipitate was collected, washed with ether and recrystallized from ethanol to give colorless needles, mp>300°, yield 73 mg (58%); ^{1}H nmr (deuteriochloroform): δ 6.53 (d, 1H, 3-H), 8.08 (s, 1H, 6H), 8.14 (d, 1H, 4-H); ms: m/z 255 (M^+).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.49; H, 6.79; N, 16.59.

(7*S*,10*R*)-10,12,12-Trimethyl-7,8,9,10-tetrahydro-7,10-methano-[1,3,5]triazino[2,1-*b*]quinazoline-2,4-(3*H*)-dione **13**.

To a stirred solution of 0.1 g (0.49 mmole) of **3** in 10 ml of dry dichloromethane was added dropwise at 0° a solution of 0.1 g (0.95 mmole) of *N*-(chlorocarbonyl)isocyanate in 5 ml of dry dichloromethane. After stirred at room temperature for 30 minutes, 0.2 ml of triethylamine was added by syringe. The reaction mixture was stirred for an additional 4 hours and evaporated to dryness. The residue was mixed with water and extracted with chloroform. The extract was distilled off to give a white solid. Recrystallization from ethyl acetate-hexane gave colorless crystals, mp 196-198°, yield 0.11 g (80%); ^{1}H nmr (deuteriochloroform): δ 8.31 (s, 1H, 6-H), 9.42 (br s, 1H, NH); ms: m/z 272 (M^+).

Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.66; H, 5.99; N, 20.71.

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