Synthesis of Novel Derivatives of 1*H*-Imidazo[1,2-*b*]Pyrazole as Potential CNS-Agents

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Received November 19, 1993

As part of a preliminary study on novel 5-HT_3 ligands, tbe synthesis of a series of 1H-imidazo[1,2-*b*]-pyrazole derivatives is described. The bicyclic heteroaromatic nucleus was functionalized at positions 1, 6 and 7 to give the series of tropanyl derivatives **4a-g, 12a, 12d** (Table 1). Different synthetic approaches were utilized to obtain the desired molecules: endo and exo 6-amides **4a, 12a** and 6-ester **4b** required two independent schemes due to the opposite behavior of the intermediate imidazolide **3** towards tropine and tropanamine. The 7-congeners, ester **4c**, its tropinium salt **4e**, the endo and exo amides **4d** and **12d** were prepared from the known common precursor **8** [1], while derivatives **4f-g**, originated by functionalizing position 1, were obtained from 1*H*-imidazo[1,2-*b*]pyrazole by direct *N*-acylation. Since the structural features of these molecules seemed to meet the main rules of the S.A.R. studies published so far [2-5], they were evaluated "*in vitro*" for 5-HT_3 receptor affinity (Table 2). The biochemical data show significant activity for derivatives **4a-e, 4g**. These results are encouraging and justify further investigational work on this class of molecules.

J. Heterocyclic Chem., **31**, 737 (1994).

Drugs acting on 5-HT_3 receptors are effective in controlling emesis caused by oncolytic drugs, an event suggested to be modulated by 5-HT_3 receptors in area postrema [6]. Besides, they could play an important therapeutical role in CNS disorders such as schizophrenia and anxiety [7,8]. For these reasons an intense effort is focused on the discovery of new compounds acting on 5-HT_3 receptors.

Many S.A.R. studies [2-5] have uncovered structural features, as the aromatic nucleus, the side chain and the basic nitrogen, important for biological activity; an aromatic pharmacophore, linked to tropane by ester or amide tethers, is present in many 5-HT_3 antagonists, like MDL-72222 [9], Tropisetron [10], Granisetron [11] and Zatosetron [12]. In all these molecules biological activity is associated with the endo conformation of the tropanyl ring [4].

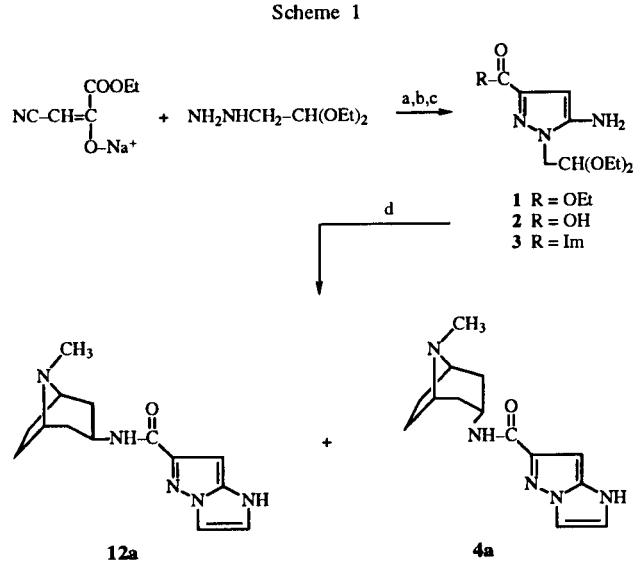
In the search for novel compounds endowed with 5-HT_3 receptor affinity we focused our attention on the aromatic nucleus: for this portion we utilized 1*H*-imidazo[1,2-*b*]pyrazole[13] to design a short series of new derivatives, namely amides and ester of 1*H*-imidazo[1,2-*b*]pyrazole-6-carboxylic acid **4a, 12a, 4b**, esters and amides of 1*H*-imidazo[1,2-*b*]pyrazole-7-carboxylic acid (**4c, 4e, 4d, 12d**), urea **4f** [14] and carbamate **4g** (see Table 1).

In particular, we describe the preparation of endo and exo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl} imidazo[1,2-*b*]pyrazole-6-carboxyamide **4a, 12a**; endo and exo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]pyrazole-7-carboxyamide **4d, 12d**; endo-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]pyrazole-6-carboxylate **4b**, endo-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]pyrazole-7-carboxylate **4c**, endo-{8,8-dimethyl-8-ammoniobicyclo[3,2,1]oct-3-yl}imidazo[1,2-*b*]pyrazole-7-carboxylate methyl sulfate **4e**; endo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}-imidazo[1,2-*b*]pyrazole-1-carboxyamide **4f** and endo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]-pyrazole-1-carboxylate **4g**.

Synthesis.

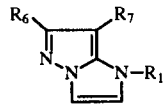
Reaction Schemes 1 and 2 were utilized to synthesize derivatives in position 6, **4a-b, 12a,** starting from ethyl cyanopyruvate sodium salt and hydrazinoacetaldehyde diethylacetal in a biphasic water/chloroform system in the presence of a stoichiometric amount of sulfuric acid,

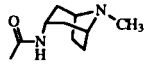
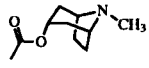
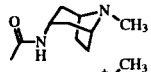
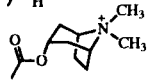
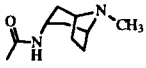
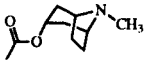
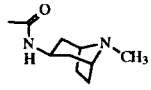
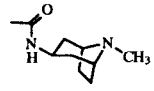
Scheme 1



(a) 20% H_2SO_4, $CHCl_3/H_2O$, 25°C (69%); (b) 4*N* NaOH, reflux, then 20% aqueous HCl to *p*H 2 (83%); (c) carbonyldiimidazole, THF, 25°C (85%); (d) 3-tropanamine, THF, reflux (95%), then $EtOH/H_2SO_4$, reflux and chromatography (38% **4a**; 22% **12a**).

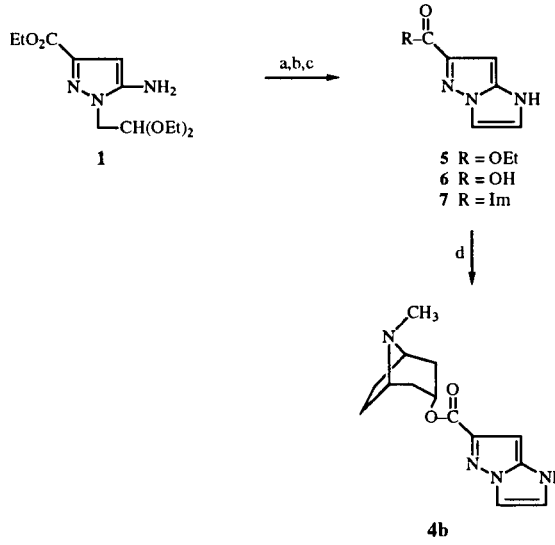
Table 1
Analytical and Spectral Data of 1*H*-Imidazo[1,2-*b*]pyrazole Derivatives



Compound	R_1	R_6	R_7	Yield %	Mp °C	Formula	Analysis Calcd./Found C	H	N	IR(KBr) C=O, C=N (cm^{-1})
4a	H		H	38	197-199	$C_{14}H_{19}N_5O$	61.54/61.68	7.02/7.05	25.64/25.68	1644,1626
4b	H		H	33	210-212	$C_{14}H_{18}N_4O_2$	61.31/61.46	6.62/6.60	20.44/20.37	1712,1598
4c	H	H		92	198-201	$C_{14}H_{18}N_4O_2$	61.31/61.49	6.62/6.63	20.44/20.39	1672,1622
4d	H	H		36	211-213	$C_{14}H_{19}N_5O$	61.54/61.62	7.02/7.01	25.64/25.49	1607,1533
4e	H	H		55	200-214	$C_{16}H_{24}N_4O_6S$	47.99/48.14	6.04/6.03	13.99/13.93	1701,1612
4f		H	H	36	126-130	$C_{14}H_{19}N_5O$	61.54/61.43	7.02/7.03	25.64/25.56	1710,1552
4g		H	H	63	130-135	$C_{14}H_{18}N_4O_2$	61.31/61.13	6.62/6.63	20.44/20.51	1739,1589
12a	H		H	22	183-185	$C_{14}H_{19}N_5O$	61.54/61.31	7.02/7.08	25.64/25.83	1636,1616
12d	H	H		24	235-236	$C_{14}H_{19}N_5O$	61.54/61.32	7.02/7.03	25.64/25.54	1670,1616

required to supply the free cyanopyruvate without salt formation of the hydrazine. The biphasic system proved to be very convenient to preserve the cyanoketone from decomposition.

Scheme 2



(a) 2.6% HCl in Et_2O, THF, 25°C (43%); (b) 4*N* NaOH, 25°C (58%); (c) carbonyldiimidazole, DMSO (quant.); (d) tropine potassium salt, CH_2Cl_2, 25°C (33%).

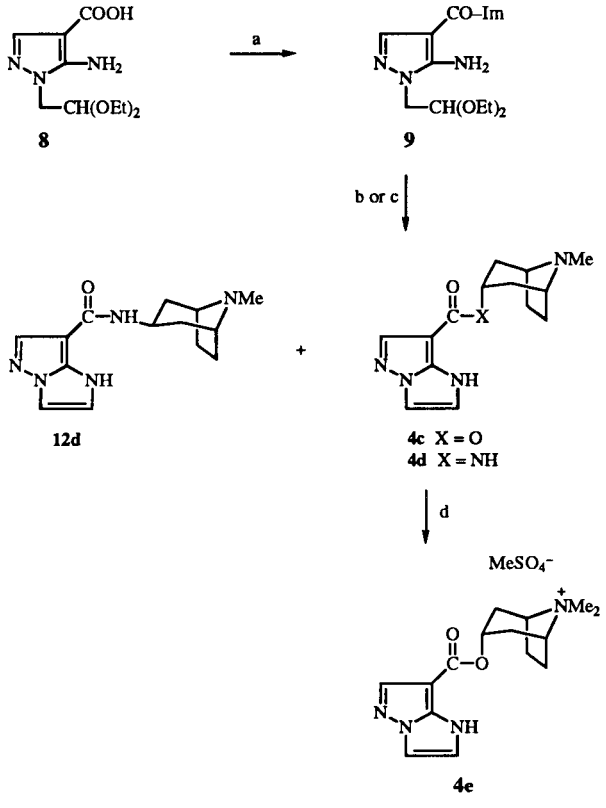
The pyrazole intermediate **1** was hydrolyzed to acid **2** (attempts to esterify acid **6** directly with dicyclohexylcarbodiimide and *N,N*-dimethylamino pyridine were unsuccessful [15]) and activated as imidazolide **3** that, unexpectedly, did not react with the tropine potassium salt [5] while it did with tropanamine to provide the desired amide **4a** and the exo isomer **12a**. The ester **4b** was obtained through the series of bicyclic intermediates **5, 6, 7** (Scheme 2), exploiting the surprising chemical stability of the latter two derivatives.

In opposition to the open ring imidazolide **3**, the bicyclic analog **7** reacted smoothly with the tropine potassium salt yielding **4b**.

For the synthesis of derivatives functionalized in position 7 an approach was conceived based on the already known carboxypyrazole **8** [1] (Scheme 3). It was independently obtained from the same starting materials, hydrazinoacetaldehyde and ethyl ethoxymethylene cyanoacetate, using different solvents (toluene instead of ethanol/water) and conditions. These differences apparently led to better overall yields (74% compared to 28%).

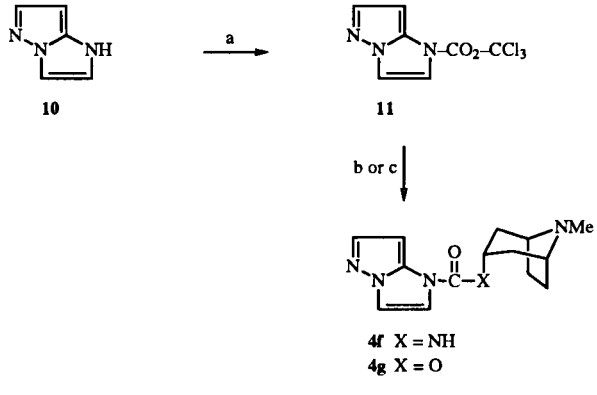
Originally, the purpose was to cyclize it to 7-carboxyimidazo[1,2-*b*]pyrazole, however this product decarboxylates in solution with extraordinary ease. Accordingly, **8**

Scheme 3



(a) Carbonyldiimidazole, THF, 25°C (89%); (b) Tropine potassium salt, CH_2Cl_2, 25°C (35%), then H_2SO_4/EtOH, 100°C (92%); (c) 3-Tropanamine, THF, 25°C (quant.), then 1*N* H_2SO_4/EtOH, reflux and chromatography (36% **4d**; 24% **12d**); (d) Me_2SO_4, 18-C-6 crown ether, K_2CO_3, benzene (55%).

Scheme 4



(a) Cl_3C-O-COCl, Et_3N, CH_2Cl_2, -15°C→25°C (quant.); (b) 3-tropanamine, CH_2Cl_2, 25°C, then chromatography (36%); (c) tropine potassium salt, CH_2Cl_2, 25°C, (63%).

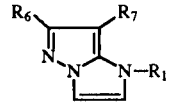
was activated as imidazolide to yield the corresponding monocyclic ester and amide that were cyclized upon treatment with 20% aqueous sulfuric acid in ethanol (trifluoroacetic acid or anhydrous hydrochloric acid in aprotic solvents can alternatively be utilized).

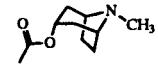
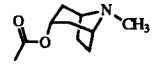
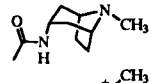
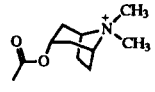
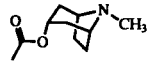
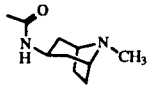
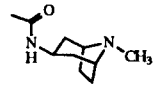
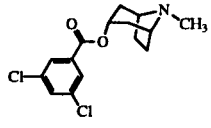
The derivatives at position 1, namely urea **4f** and carbamate **4g**, were conveniently obtained from 1*H*-imidazo-[1,2-*b*]pyrazole through the activated 1-trichloromethoxycarbonyl derivative **11** (Scheme 4). Imidazo[1,2-*b*]pyrazole (**10**) was obtained, *via* cyclization-decarboxylation in ethanol and 20% sulfuric acid, from 1-(2,2-diethoxyethyl)-4-carboxy-5-aminopyrazole (**8**) with improved overall yield (77% versus 53%) with respect to the published method [1] that involves the use of 4*N* hydrochloric acid in tetrahydrofuran.

Receptorial screening showed that **4a-e, 4g** have submicromolar affinity for the serotoninergic 5-HT_3 recep-

Table 2

Binding Affinity of 1*H*-Imidazo[1,2-*b*]pyrazole Derivatives



Compound	R_1	R_6	R_7	IC_{50} ± s.e. (nmol/l)
4a	H		H	259 ± 5
4b	H		H	403 ± 9
4c	H	H		217 ± 15
4d	H	H		200 ± 12
4e	H	H		103 ± 5
4f		H	H	1195 ± 58
4g		H	H	638 ± 32
12a	H		H	2921 ± 103
12d	H	H		3844 ± 142
MDL-72222				19 ± 0.5

IC_{50} values are expressed as mean ± s.e. of three different experiments; each experiment was carried out with four different final concentrations [10-10000 nmoles/ml].

tors (Table 2). The exo isomers **12a, 12d** appeared to be considerably less potent than their endo counterparts **4a, 4d**, confirming the importance of the endo stereochemistry in tropane-derived 5-HT_3 modulators [4]. The tropinium salt **4e** showed 100% higher affinity than its precursor **4c** [4].

In conclusion, this first preliminary series of compounds of general formula **4** represents a novel structural prototype potentially useful to elaborate molecules capable of modulating serotoninergic activity through 5-HT_3 receptors.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Melting points were determined on a Buchi 510 apparatus and are uncorrected. Infrared spectra were recorded with a Biorad FTS7 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on Bruker AC 200 (200 MHz) or Bruker CXP 300 (300 MHz) spectrometers (chemical shifts are expressed as parts per million downfield from internal tetramethylsilane). Merck Kieselgel-60 (70-230 mesh) was used for column chromatography. Anhydrous solvents were dried over 4A molecular sieves prior to use. Physico-chemical and analytical data of the compounds are given in Table 1. Tropanamine (mixture of 3-α and 3-β isomers) was synthesized from tropanone according to literature [16,17]. The isomeric amides, deriving from tropanamine, were separated by chromatography (analytical data of exo derivatives are also given).

Ethyl 1-(2,2-Diethoxyethyl)-5-aminopyrazole-3-carboxylate (**1**).

Hydrazinoacetaldehyde diethylacetal (14.8 g, 100 mmoles) in water (150 ml) and sulfuric acid (23 ml, 100 mmoles, 20% v/v) is added to a stirred solution of ethyl cyanopyruvate (16.3 g, 100 mmoles) in chloroform (150 ml) at room temperature. Stirring was maintained for 72 hours. The organic layer was separated, washed with saturated sodium bicarbonate, dried with sodium sulfate and concentrated. The resulting oil was chromatographed (7:3 ethyl acetate/*n*-heptane) to yield the title compound (18.7 g, 69%), mp 75°; ^1H nmr (DMSO-d_6) δ 1.20 (t, 6H), 1.40 (t, 3H), 3.70 (m, 4H), 4.10 (broad, 2H), 4.20 (d, 2H), 4.35 (q, 2H), 4.75 (t, 1H), 6.00 (s, 1H).

Anal. Calcd. for $C_{12}H_{21}N_3O_4$: C, 53.12; H, 7.81; N, 15.48. Found: C, 53.27; H, 7.79; N, 15.45.

1-(2,2-Diethoxyethyl)-5-aminopyrazole-3-carboxylic Acid (**2**).

A solution of ethyl 1-(2,2-diethoxyethyl)-5-aminopyrazole-3-carboxylate (**1**) (6.5 g, 25.8 mmoles) in 4*N* sodium hydroxide (50 ml) was heated to reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, then it was acidified to *p*H 2 with 20% v/v hydrochloric acid and extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried with sodium sulfate and concentrated to provide the crude product (4.8 g, 76%) used without further purification, mp 120°; ^1H nmr (deuteriochloroform): δ 1.15 (t, 6H), 3.45 (q, 2H), 3.69 (q, 2H), 4.20 (d, 2H), 4.72 (t, 1H), 6.00 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 166, 149, 143, 103.9, 94.4, 65.8, 51.5, 16.0.

1-(2,2-Diethoxyethyl)-3-(imidazol-1-yl)carbonyl-5-aminopyrazole (**3**).

N,N'-Carbonyldiimidazole (3.1 g, 19.3 mmoles) was added to a stirred, room temperature suspension of **2** (4.73 g, 19.3 mmoles) in dry tetrahydrofuran (60 ml). After 2 hours, the solvent was evaporated and the residue treated with water and extracted with dichloromethane (4 x 60 ml). The combined organic layers were washed with saturated sodium bicarbonate, dried with sodium sulfate and concentrated to provide the title compound (4.8 g, 85%), mp 109°; ^1H nmr (deuteriochloroform): δ 1.21 (t, 6H), 1.78 (broad, 2H), 3.50 (q, 2H), 3.53 (q, 2H), 4.22 (d, 2H), 4.62 (t, 1H), 6.26 (s, 1H), 7.09 (s, 1H), 7.94 (s, 1H), 8.93 (s, 1H).

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.48; N, 23.89. Found: C, 53.07; H, 6.53; N, 23.96.

Endo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3yl}imidazo[1,2-*b*]pyrazole-6-carboxyamide (**4a**).

A suspension of imidazolide **3** (0.70 g, 2.4 mmoles) and tropanamine (0.35 g, 2.4 mmoles) in dry tetrahydrofuran (10 ml) was heated to reflux with stirring, under nitrogen, for about 3 hours. The solvent was removed and the crude product chromatographed (40:10:1 dichloromethane/methanol/32% ammonium hydroxide) to give a solid (0.840 g, 2.3 mmoles, 95%) that was dissolved in absolute ethanol (3 ml) and 1*N* sulfuric acid (8 ml). The solution was heated to reflux for about 90 minutes, cooled and basified with solid sodium bicarbonate. The solution was extracted with 3:1 chloroform/*n*-butanol (4 x 20 ml), the combined organic layers were concentrated and the resulting yellow oil was chromatographed (4:1 dichloromethane/methanol; 80:20:1; 40:10:1 dichloromethane/methanol/32% ammonium hydroxide) to provide the title compound (0.250 g, 38%) as a white solid, mp 197-199°; ir (potassium bromide): 3517 (NH), 3115, 2935, 1644 (C=O), 1626 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.60-2.20 (m, 8H), 2.25 (s, 3H), 3.15 (m, 2H), 4.00 (q, 1H), 6.05 (s, 1H), 7.31 (d, 1H), 7.58 (d, 1H), 7.65 (d, 1H), 13.2 (broad s, 1H).

Anal. Calcd. for $C_{14}H_{19}N_5O$: C, 61.54; H, 7.02; N, 25.64. Found: C, 61.68; H, 7.05; N, 25.68. The exo isomer **12a** (obtained in 22% yield) was also characterized: mp 183-185°; ir (potassium bromide): 3512 (NH), 3110, 2946, 1636 (C=O), 1616 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.70-2.00 (m, 8H), 2.50 (s, 3H), 4.20 (m, 1H), 6.05 (s, 1H), 7.30 (d, 1H), 7.55 (d, 1H), 7.90 (d, 1H), 11.30 (br s, 1H).

Anal. Calcd. for $C_{14}H_{19}N_5O$: C, 61.54; H, 7.02; N, 25.64. Found: C, 61.31; H, 7.08; N, 25.83.

Ethyl Imidazo[1,2-*b*]pyrazole-6-carboxylate (**5**).

A solution of hydrochloric acid (400 ml, 2.6% v/v) in diethyl ether was added dropwise to a stirred, room temperature solution of **1** (18 g, 66 mmoles) in dry tetrahydrofuran (350 ml), over a period of 30 minutes. Stirring was continued for additional 2 hours; the reaction mixture was filtered and the solid product washed with diethyl ether, suspended in water (250 ml) and basified with solid sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (4 x 200 ml), the combined organic layers were dried with sodium sulfate, concentrated and chromatographed (9:1 dichloromethane/methanol). The resulting

solid was recrystallized from ethyl acetate/*n*-hexane to provide the title compound (5.12 g, 43%), mp 160°; ir (potassium bromide): 1715 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.30 (t, 3H), 4.30 (q, 2H), 6.25 (s, 1H), 7.40 (d, 1H), 7.65 (d, 1H), 11.35 (broad, 1H).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.46; H, 5.14; N, 23.50.

Imidazo[1,2-*b*]pyrazole-6-carboxylic Acid (**6**).

A suspension of **5** (7.5 g, 42 mmoles) in 4*N* sodium hydroxide (70 ml) was stirred at room temperature for about 1 hour and then extracted with dichloromethane (2 x 50 ml). The aqueous layer was cooled to 30° and acidified to *p*H 4 with 20% v/v hydrochloric acid. The resulting suspension was filtered, the white solid was washed with diethyl ether and dried *in vacuo* to yield the title compound (3.7 g, 58%), mp 230° dec; ir (potassium bromide): 1670 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.20 (s, 1H), 7.35 (d, 1H), 7.65 (d, 1H), 11.40 (broad, 1H), 12.30 (broad, 1H).

Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.69; H, 3.33; N, 27.81. Found: C, 47.80; H, 3.32; N, 27.71.

Endo-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*] pyrazole-6-carboxylate (**4b**).

To a stirred solution of imidazolide **7**, prepared by stirring a solution of carboxylic acid **6** (1.1 g, 7.1 mmoles) and *N,N'*-carbonyldiimidazole (2.3 g, 14 mmoles) in dry dimethylsulfoxide (10 ml) for about 1 hour, a solution of tropine potassium salt (10 mmoles), prepared by stirring for 30 minutes at room temperature tropine (1.4 g, 10 mmoles) and potassium *t*-butoxide (1.12 g, 10 mmoles) in dry dimethylsulfoxide (40 ml), was added. Stirring was continued for about 20 hours, water (20 ml) was added and the mixture was extracted with ethyl acetate (3 x 30 ml) and then with 7:3 ethyl acetate/*n*-butanol (3 x 30 ml). The combined organic layers were concentrated at 40°, whereupon red coloring appeared. The crude product was chromatographed (9:1 chloroform/32% ammonium hydroxide) to provide the title compound (0.66 g, 33%) as a white solid, mp 210-212° dec; ir (potassium bromide): 3260 (NH), 3117, 2952, 1712 (C=O), 1598 (C=N), 1226 cm^{-1}; ^1H nmr(deuteriochloroform): δ 1.75-2.30 (m, 8H), 2.30 (s, 3H), 3.15 (m, 2H), 5.25 (t, 1H), 6.20 (d, 1H), 7.00 (d, 1H), 7.32 (dd, 1H).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.31; H, 6.62; N, 20.44. Found: C, 61.46; H, 6.60; N, 20.37.

1-(2,2-Diethoxyethyl)-5-aminopyrazole-4-carboxylic Acid (**8**).

Ethyl ethoxymethylene cyanoacetate (17.8 g, 105 mmoles) was added to a stirred, room temperature solution of hydrazino acetaldehyde diethylacetal (14.9 g, 101 mmoles) in toluene (130 ml), under nitrogen. Stirring was continued overnight; the resulting red solution was heated to distill off ethanol. A 4*N* solution of sodium hydroxide (210 ml) was added and, after heating for additional 90 minutes, the reaction mixture was allowed to cool to room temperature and was extracted with dichloromethane (2 x 50 ml). The aqueous layer was cooled to 5-10° with an ice-water bath and acidified to *p*H 4.5-5 with hydrochloric acid (130 ml, 20% v/v), whereupon a white precipitate appeared. The solid was collected by filtration, washed with water to *p*H 7 and dried *in vacuo* at 45° to provide the title compound (18.2 g, 74%), mp 127-128° (mp lit not reported); ir (potassium bromide): 3380-3280, 2950, 1620, 1540, 1500 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 (t, 6H), 3.50 (q, 2H), 3.70 (q, 2H), 4.10 (d, 2H), 4.70 (t, 1H), 5.50 (broad s, 2H), 7.70 (s, 1H).

Anal. Calcd. for $C_{10}H_{17}N_3O_4$: C, 49.37; H, 7.04; N, 17.27. Found: C, 49.43; H, 7.06; N, 17.22.

1-(2,2-Diethoxyethyl)-4-(imidazol-1-yl)carbonyl-5-aminopyrazole (**9**).

A mixture of **8** (12.15 g, 50 mmoles) and *N,N'*-carbonyldiimidazole (8.35 g, 50 mmoles) in dry tetrahydrofuran (200 ml) was stirred at room temperature for about 2 hours. The solvent was removed and the residue treated with water and extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with saturated sodium bicarbonate and brine, dried with sodium sulfate and concentrated. The resulting solid was triturated with *n*-hexane, filtered and dried *in vacuo* at room temperature to yield the title compound (13.2 g, 89%), mp 78°; ^1H nmr (deuteriochloroform): δ 1.17 (t, 6H), 3.41 (q, 2H), 3.66 (q, 2H), 4.00 (d, 2H), 4.65 (t, 1H), 6.11 (broad s, 2H), 7.00 (s, 1H), 7.44 (s, 1H), 7.57 (s, 1H), 8.12 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 160.3, 154.8, 139.5, 137.8, 131, 118.2, 102.2, 64.4, 52.2, 15.9.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.48; N, 23.89. Found: C, 53.06; H, 6.52; N, 23.95.

Endo-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]-pyrazole-7-carboxylate (**4c**).

A solution of tropine (0.65 g, 4.6 mmoles) and potassium *t*-butoxide (0.53 g, 4.6 mmoles) in dry dimethylsulfoxide (25 ml) was stirred at room temperature for 30 minutes. A solution of imidazolide **9** (0.46 g, 1.6 mmoles) in dry dimethylsulfoxide (15 ml) was added and the reaction mixture stirred at 120° for 2 hours. The reaction mixture was allowed to cool to room temperature, then it was treated with saturated sodium bicarbonate and extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried with sodium sulfate, concentrated and chromatographed (methanol). The resulting yellow oil (0.57 g, 1.56 mmoles, 35%) was dissolved in absolute ethanol (1 ml) and sulfuric acid (3 ml, 20% v/v) was added. The reaction mixture was heated at 100° for 15 minutes, basified with solid sodium bicarbonate, while cooling to 0° with an ice bath and extracted with *n*-butanol (3 x 10 ml). The combined organic layers were concentrated and the resulting solid was treated with chloroform and filtered to remove the inorganic salts. The filtrate was concentrated to yield the title compound (0.390 g, 92%) as a white solid, mp 198-201°; ir (potassium bromide): 3254 (NH), 3115, 2956, 1672 (C=O), 1622 (C=N), 1185 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.80 (m, 2H), 2.10 (m, 4H), 2.25 (m, 2H), 2.30 (s, 3H), 3.15 (m, 2H), 5.16 (t, 1H), 6.92 (dd, 1H), 7.46 (d, 1H), 7.95 (d, 1H).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.31; H, 6.62; N, 20.44. Found: C, 61.49; H, 6.63; N, 20.39.

Endo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]-pyrazole-7-carboxyamide (**4d**).

A suspension of imidazolide **9** (0.70g, 2.4mmoles) and tropanamine (0.35g, 2.4 mmoles) in dry tetrahydrofuran (10 ml) was heated to reflux for about 3 hours. The solvent was removed and the resulting yellow oil (0.9 g, 2.4 mmoles) was dissolved in absolute ethanol (4 ml); 1 *N* sulfuric acid (7.5 ml) was added and the reaction mixture heated to reflux for about 1 hour, basified with solid sodium bicarbonate, while cooling to 0° and extracted with *n*-butanol (3 x 15 ml). The combined organic lay-

ers were concentrated and the resulting white solid was chromatographed (40:10:1 dichloromethane/methanol/32% ammonium hydroxide) to provide the title compound (0.240 g, 36%) as a white solid, mp 211-213°; ir (potassium bromide): 3482, 3301, 3052, 2831, 1607 (C=O), 1533 (C=N) cm^{-1}; ^1H nmr (DMSOd_6/deuteriochloroform): δ 1.50-2.15 (m, 8H), 2.22 (s, 3H), 3.15 (m, 2H), 3.88 (m, 1H), 7.13 (broad s, 1H), 7.18 (dd, 1H), 7.51 (d, 1H), 8.02 (d, 1H).

Anal. Calcd. for $C_{14}H_{19}N_5O$: C, 61.54; H, 7.02; N, 25.64. Found: C, 61.62; H, 7.01; N, 25.49.

The exo isomer **12d**, obtained from the column in 24% yield, had the following analytical data, mp 235-236°; ir (potassium bromide): 3530, 3296, 3111, 2935, 1670 (C=O), 1616 (C=N) cm^{-1}; ^1H nmr (DMSO-d_6/deuteriochloroform): δ 1.40-2.10 (m, 8H), 2.22 (s, 3H), 3.15 (m, 2H), 4.10 (m, 1H), 7.20 (dd, 1 H), 7.45 (d, 1H), 7.55 (d, 1H), 8.00 (d, 1H), 11. 75 (br s, 1H).

Anal. Calcd. for $C_{14}H_{19}N_5O$: C, 61.54; H, 7.02; N, 25.64. Found: C, 61.32; H, 7.03; N, 25.54.

Endo-{8,8-dimethyl-8-ammoniobicyclo[3.2.1]oct-3-yl}imidazo-[1,2-*b*]pyrazole-7-carboxylate Methyl Sulfate (**4e**).

Ester **4c** (600 mg, 2.2 mmoles), potassium carbonate (318 mg, 2.3 mmoles) and a catalytic amount of 18-C-6 crown ether in benzene (20 ml) were refluxed for 30 minutes to obtain complete dissolution of the ester. A solution of dimethylsulfate (0.22 ml, 2.2 mmoles) in benzene (10 ml) was added dropwise and after 10 minutes the reaction mixture was filtered, cooled, the precipitate was filtered and washed with benzene and then with diethyl ether. There was obtained 480 mg (55% yield) of white product, mp 200-214°; ir (potassium bromide): 3125, 2827, 1701 (C=O), 1612 (C=N), 1225 cm^{-1}; ^1H nmr (DMSO-d_6/deuteriochloroform): δ 2.00 (m, 2H), 2.35 (m, 4H), 2.55 (m, 2H), 3.05 (s, 3H), 3.15 (s, 3H), 3.85 (m, 2H), 3.98 (s, 3H), 5.10 (t, 1H), 7.31(dd, 1H), 7.75 (d, 1H), 7.95 (d, 1H).

Anal. Calcd. for $C_{16}H_{24}N_4O_6S$: C, 47.99 H, 6.04; N, 13.99. Found: C, 48.14; H, 6.03; N, 13.93.

1*H*-Imidazo[1,2-*b*]pyrazole (**10**).

A mixture of **8** (18.3 g, 75.2 mmoles) and sulfuric acid (130 ml, 20% v/v) in absolute ethanol (20 ml) was heated to 75° for about 75 minutes. The cooled suspension was poured onto ice and the resulting solution was basified by adding solid sodium bicarbonate and then filtered. The filtrate was extracted with ethyl acetate (3 x 100 ml) and the combined organic layers dried with sodium sulfate and concentrated at 40°. The crude yellow solid was recrystallized from water to provide the title compound (6.2 g, 77%), mp 144-146° (mp lit not reported); ^1H nmr (DMSO-d_6): δ 5.75 (dd, 1H), 6.90 (dd, 1H), 7.35 (d, 1H), 7.70 (d, 1H), 11.46 (broad, 1H).

Anal. Calcd. for $C_5H_5N_3$: C, 56.07; H, 4.71; N, 39.23. Found: C, 55.97; H, 4.72; N, 39.36.

1-Trichloromethoxycarbonylimidazo[1,2-*b*]pyrazole (**11**).

Trichloromethyl chloroformate (1.4 ml, 11.7 mmoles), diluted in dry dichloromethane (10 ml), was added dropwise to a stirred solution of **10** (1 g, 9.3 mmoles) and triethylamine (1.6 ml, 11.7 mmoles) in dry dichloromethane (50 ml) cooled to -15° with an ice-salt bath, over a period of 30 minutes. The reaction mixture was allowed to warm to room temperature and stirring was continued for additional 4 hours. The solvent was removed and the crude product was used without further purification.

Endo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]-pyrazole-1-carboxyamide (**4f**).

A mixture of **11** (2.5 g, 9.3 mmoles) and tropanamine (1.63 g, 11.7 mmoles) in dry dichloromethane (50 ml) was stirred at room temperature for 1 hour and then filtered. The crude product was chromatographed (40:10:1 dichloromethane/methanol/32% ammonium hydroxide) to provide an oil which crystallized on standing. The resulting solid was triturated with diethyl ether, filtered and washed with petroleum ether to yield the title compound as a white solid (0.9 g, 36%), mp 126-130°; ir (potassium bromide): 3365 (NH), 3096, 2946, 1710 (C=O), 1660, 1552 (C=N) cm^{-1}; ^1H nmr (DMSOd_6): δ 1.70-2.10 (m, 8H), 2.11 (s, 3H), 3.00 (m, 2H), 3.75 (m, 1H), 6.00 (dd, 1H), 7.45 (d, 1H), 7.60 (dd, 1H), 7.70 (d, 1H), 7.75 (dd, 1H).

Anal. Calcd. for $C_{14}H_{19}N_5O$: C, 61.54; H, 7.02; N, 25.64. Found: C, 61.43; H, 7.03; N,25.56.

The exo isomer could not be isolated.

Endo-*N*-{8-methyl-8-azabicyclo[3.2.1]oct-3-yl}imidazo[1,2-*b*]-pyrazole-1-carboxylate (**4g**).

A solution of tropine (1.62 g, 11.2 mmoles) and potassium *t*-butoxide (1.26 g, 11.2 mmoles) in dry dimethylsulfoxide (50 ml) was stirred at room temperature for about 30 minutes. A solution of **11** (2.5 g, 9.3 mmoles) in dry dichloromethane (50 ml) was added dropwise to the solution after the removal of *t*-butanol. The reaction mixture was stirred at room temperature for 20 hours. After washing with water, charcoal was added and the solution was filtered, dried with sodium sulfate and concentrated. The resulting solid was chromatographed (9:1 dichloromethane/methanol) to yield the title compound as a light brown solid (1.6 g, 63%), mp 130-135°; ir (potassium bromide): 2950, 1739 (C=O), 1589 (C=N), 1190 (C-O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.85-2.45 (m, 8H), 2.32 (s, 3H), 3.23 (m, 2H), 5.22 (t, 1H), 6.15 (d, 1H), 7.20 (broad s, 1H), 7.32 (d, 1H), 7.65 (dd, 1H); ^{13}C nmr (deuteriochloroform) δ 156, 145, 116.5, 114, 87, 73.5, 61, 41, 37.5, 26.5.

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.31; H, 6.62; N, 20.44. Found: C, 61.13; H, 6.63; N, 20.51.

Binding Method.

The enthorinal cortex of male Sprague Dawley rats was dissected and the pooled tissue homogenized in 10 volumes of HEPES buffer (50 m*M*, *p*H 7.4) and centrifuged at 50.000 g for 10 minutes. The supernatant was discarded, the pellet resuspended in 10 volumes of HEPES buffer, incubated at 37° for 10 minutes and centrifuged as before. The final pellet was resuspended in 66 volumes of HEPES buffer.

Assay tubes containing 500 µl of 3H-GR65630 (87Ci/mmole, final concentration 0.26 n*M*) in HEPES buffer, 10 µl of competing drugs or their vehicles and 500 µl of the tissue preparation were incubated at 37° for 30 minutes. The incubation was terminated by rapid vacuum filtration through Whatman GF/B filters which were immediately washed with 5 x 2.5 ml of HEPES buffer. Radioactivity was assayed by liquid scintillation counting. The K_i values were calculated as described elsewhere [18] and MDL-72222 [9] was utilized as reference standard.

Acknowledgment.

The authors wish to thank S. Magnetti for chemical prep-

arations, A. Depaoli, N. Colombo and staff for spectral and analytical assays; L. Sfriso and A. Ghiglieri for biochemical determinations.

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