AN EFFICIENT PREPARATIVE ROUTE TO FUSED IMIDAZO[1,2-*a*]-PYRAZIN-4-ONE DERIVATIVES

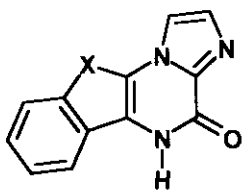
Dominique Damour, Jean-Claude Aloup, Michel Barreau, Arielle Genevois-Borella, Patrick Jimonet, Jean-Pierre Leconte, Yves Ribeill, Marc Vuilhorgne, and Serge Mignani*

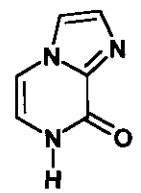
Rhône-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, 13 Quai Jules Guesde, F-94400, Vitry-sur-Seine, France

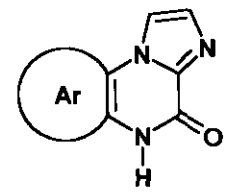
Abstract- New fused imidazo[1,2-*a*]pyrazin-4-one derivatives (**1a-f**) are easily obtained from ring closure reactions of ethyl imidazole-2-carboxylate derivatives (**4a, c, d**) or imidazole-2-carboxamide derivatives (**5b, e**).

L-Glutamate is a major excitatory amino acid neurotransmitter in the mammalian central nervous system, and the overstimulation of its postsynaptic receptors (*N*-methyl-D-aspartate, α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), kainate and metabotropic) has been shown to be linked to neurodegeneration and cell death. [1] In connection with our research project directed towards the synthesis of potent AMPA and glycine/NMDA antagonists, [2] an easy and efficient method for the synthesis of new fused pyrazin-4-one derivatives (**1a-f**) [3] was required (Figure 1).

Figure 1







1a : X = CH_2 **1d** : X = NH

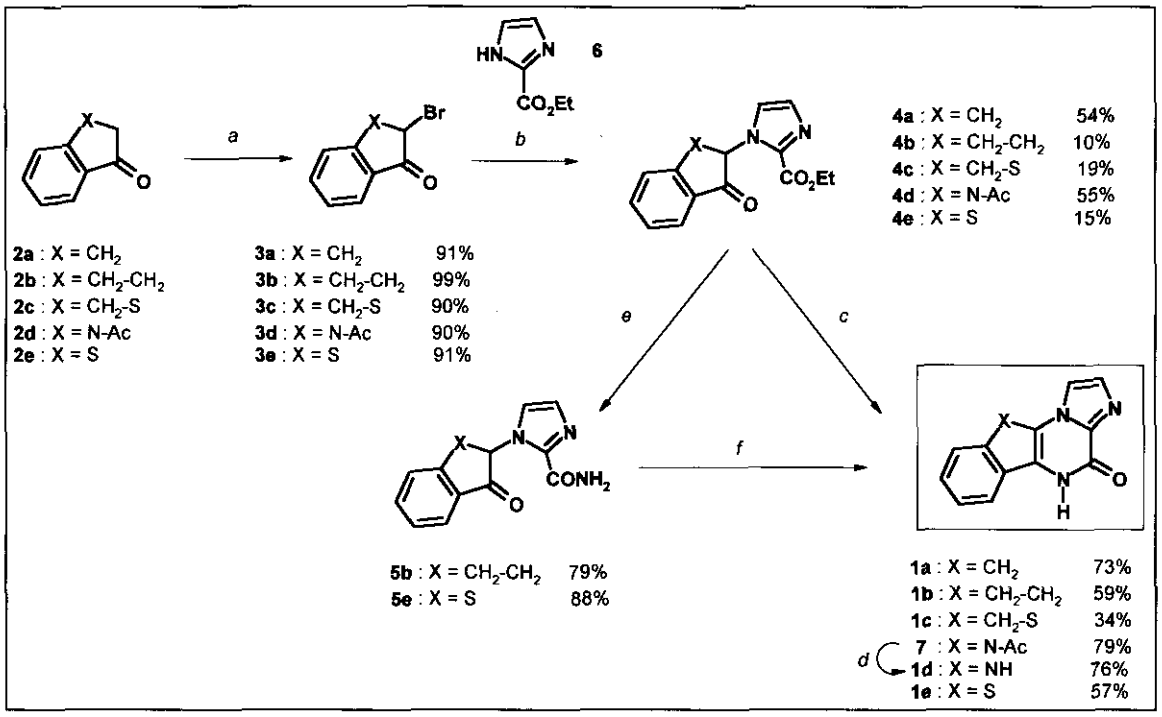
1b : X = CH_2-CH_2 **1e** : X = S **1g** **1h**

1c : X = CH_2-S **1f** : X = O

To our knowledge, only imidazo[1,2-*a*]pyrazin-8-one derivatives (**1g**), [4a] or imidazo[1,2-*a*]-pyrazin-4-one derivatives (**1h**) bearing a fused aromatic system such as a phenyl or a naphtyl, [4b] a pyrimidine, [4c] or a pyridine [4d] were described (Figure 1).

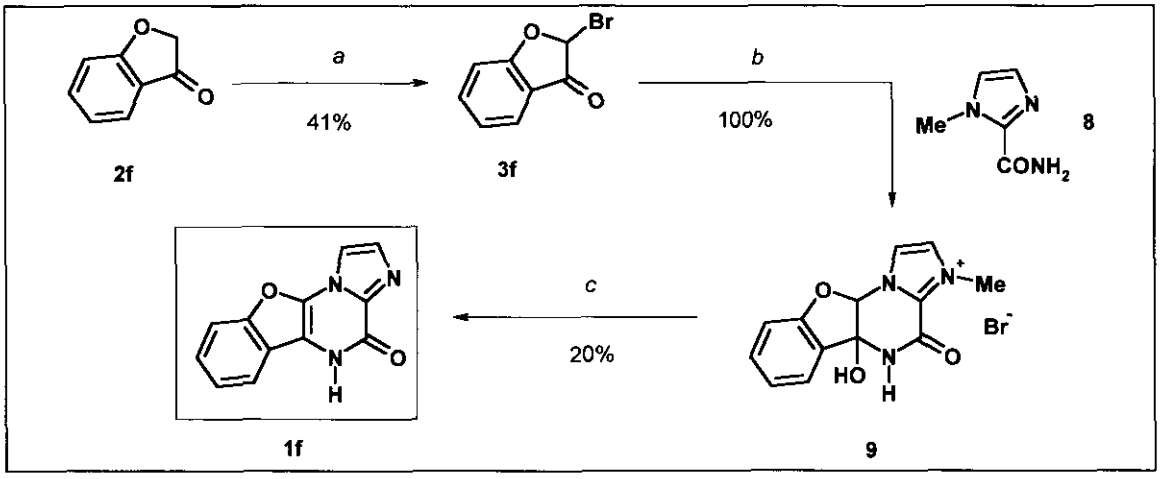
Here, we report an efficient short synthesis of new pyrazin-4-one derivatives (**1a-f**) bearing original fused moieties starting from the corresponding cyclic ketones (**2a-f**). These ketones were either commercially available (**2a-c** and **2f**) or already described in the literature (**2d** and **2e**). [6]

Scheme 1



Reaction conditions: *a)* Br_2, **3a**, **3b** and **3e:** ether, -10°C to rt, 1-2 h ; **3c:** $CHCl_3$, cat. $AlCl_3$ (3%), rt, 20 min; **3d:** dichloromethane, 5°C to rt, 2 h *b)* **4a:** K_2CO_3, acetone, reflux, 4.5 h; **4b:** NaH, DMF, rt, 1.3 h; **4c:** neat, 130°C, 10 min; **4d:** neat, 120°C, 15 min; **4e:** EtOH, reflux, 10 h *c)* NH_4Ac, AcOH, reflux, **1a:** 5 h, **1c:** 20 min, **9:** 1 h *d)* DMF, reflux, 15 min *e)* **5b:** 3N NH_3/MeOH, rt, 20 h; **5e:** 5N NH_3/MeOH, rt, 15 h *f)* **1b:** 12N HCl, MeOH, 1 h; **1e:** 10N HCl, MeOH, 10 min.

Scheme 2



Reaction conditions: *a)* Br_2, $CHCl_3$, 2 h, -10°C, *b)* MeCN, reflux, 8 h *c)* imidazole, neat, 165°C, 6 h then 175°C, 2 h.

Our synthetic approaches to these heterocycles were based on the condensation of either ethyl imidazole-2-carboxylate (**6**) [7] (Scheme 1) or the 1-methyl-1*H*-imidazole-2-carboxamide (**8**)[8] (Scheme 2) with the corresponding 2-bromo cyclic ketones (**3a-f**), [9] followed by a cyclisation affording **1a-e** and **1f** respectively. The 2-bromo cyclic ketones (**3a-f**) were prepared in moderate to high yields (41-99%) by smooth bromination of the corresponding cyclic ketones (**2a-f**) with bromine in a low-polarity, aprotic solvent such as ether, chloroform or dichloromethane.

According to Scheme 1, the synthesis of **1a-e** started on the condensation of **6** with 2-bromo cyclic ketones (**3a-e**). The reaction conditions have been optimized for each substrate. Thus, **3a,b** required basic reaction conditions, while **3c,d** reacted in neat phase at high temperature (120-130°C), and **3e** reacted in refluxing ethanol. Compounds (**4a-e**) were obtained with low to moderate yields (10-56%). The yield of the condensation reaction under basic experimental conditions is strongly dependent on both the nature of the base and the solvent used. Thus, in the condensation of **6** with **3a**, using pyridine (chloroform, reflux, 12 h), DBU (chloroform, reflux, 2 h), NaH (DMF, rt, 1.5 h) or K_2CO_3 (acetone, reflux, 4.5 h) as the base, the yields are 3%, 29%, 70% and 54% respectively. In the condensation reaction using K_2CO_3, the replacement of acetone by DMF decreased the yield to 37%.

Finally, the intramolecular ring closure reactions of the 2-*N*-substituted cyclic ketones (**4**) were carried out using ammonium acetate in glacial acetic acid leading directly to **1a**, [5b] **1c** and **7** (which is the precursor for the synthesis of **1d**). With substrates (**4b,e**), the cyclisation reaction was performed in two steps *via* the carboxamides (**5b,e**) using concentrated acidic medium (HCl) in methanol with moderate to good yields (79% and 88% respectively). The *N*-deacetylation reaction of **7** was carried out under mild reaction conditions (DMF/water/reflux) affording pure **1d** with 76% yield. The carboxamide derivatives (**5b** and **5e**) were easily obtained from the corresponding ester derivatives (**4b** and **4e**) by an ammonolysis reaction with concentrated ammonia solution in methanol with 79 and 88% yields respectively.

As shown in Scheme 2, we succeeded in the preparation of **1f** by condensation of the 1-methyl-1*H*-imidazole-2-carboxamide (**8**) with **3f** in refluxing acetonitrile giving quantitatively the cyclic derivative (**9**). This salt was demethylated and dehydrated with 20% yield by using neat imidazole at high temperature (175°C) according to a method described by Davey. [8]

In conclusion, we have developed a versatile synthetic route towards a wide variety of new fused imidazo[1,2-*a*]pyrazin-4-one derivatives (**1a-f**) from the corresponding 2-bromo cyclic ketones.

EXPERIMENTAL

Commercially available reagents were used as received from suppliers. The progress of the reactions was monitored by TLC on silica gel plates (Merck Kieselgel $60F_{254}$). Melting points were determined using a Reicher-Kofler apparatus and are uncorrected. ^{1}H NMR spectra were recorded using an AC 200 or a AC 300 Bruker spectrometers. Chemical shifts are given in ppm (δ $CDCl_3$ = 7.27 and δ DMSO = 2.5) while J coupling constants are expressed in Hz. IR spectra were recorded on a FT-IR 60SX-R Nicolet spectrophotometer. MS spectra were obtained on a Finnigan 4000 apparatus (EI; 70eV), on a VG Autospec magnetic sector mass spectrometer in LSIMS (Liquid Secondary Ion Mass Spectrometry) with a caesium gun at 35kV or on a Nermag R10-10B (DCI, reactant gas: NH_3). Elemental Analysis was performed using a Carlo Erba 1108 microanalyzer. Flash chromatography was performed on silica gel (Merck Kieselgel, 230-400 mesh).

Ethyl 1-[2-(1-oxoindanyl)]imidazole-2-carboxylate (4a)

To a mechanically stirred yellow suspension of **6** (52.3 g, 0.37 mol) in acetone (1.3 L) was added portionwise K_2CO_3 (258 g, 1.9 mol) at rt. After addition, the cream reaction mixture was heated at reflux for 0.5 h and then **3a** (110.4 g, 0.52 mol) in acetone (1.1 L) was added dropwise at the same temperature. The green-dark reaction mixture was stirred at the same temperature for 7 h, and the black reaction mixture was then allowed to reach rt. The reaction mixture was filtered, washed with acetone (5 x 150 mL) and the filtrate was evaporated to give a red solid which was recrystallised with hot acetic acid (250 mL) to yield 55.0 g (54%) of **4a** as a brown solid (mp 111°C (not recrystallized), R_f= 0.33 in dichloromethane/ethyl acetate mixture 1/1). IR (KBr) : 3125 (CH imidazole), 3000-2250 (OH acid), 1715 (C=O acid and ketone), 755 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z: 270 ($M^{+\cdot}$, 40%), 197 (35%), 130 (100%) and 68 (30%). NMR (200 MHz, $CDCl_3$) δ : 3.25 and 3.85 (2 x 1H, 2 x dd, J = 15 ; 5 and 15 ; 7, $H_{3'}$), 5.90 (1H, dd, J = 7 ; 5, $H_{2'}$), 7.00 (1H, br s, H_4), 7.30 (1H, br s, H_5), 7.50 (2H, m, $H_{4'}$ and $H_{6'}$), 7.80 (1H, br dd, J = 8 ; 8, $H_{5'}$), 8.10 (1H, br d, J = 8, $H_{7'}$).

Ethyl 1-[2-(1-oxo-1,2,3,4-tetrahydronaphthyl)]imidazole-2-carboxylate (4b)

To a stirred suspension of 80% NaH (0.6 g, 0.02 mol) in anhydrous DMF (10 mL) under a nitrogen atmosphere at rt was added a solution of **6** (2.8 g, 0.02 mol) in anhydrous DMF (30 mL). The mixture was kept 10 min, and **3b** (5.4 g, 0.024 mol) in anhydrous DMF (18 mL) was added dropwise. The reaction mixture was stirred at rt for 1.5 h, diluted with water (20 mL), poured onto water (600 mL), and extracted with chloroform (4 x 800 mL). The combined organic phases were washed with water (200 mL), dried ($MgSO_4$), evaporated to yield crude compound (**4b**) which was purified by flash chromatography using a dichloromethane/ethyl acetate mixture (70/30) as eluent to give 0.6 g (10%) of **4b** as a pale yellow solid (mp 98°C (not recrystallized), R_f= 0.33 in dichloromethane/ethyl acetate mixture 70/30). IR (KBr) : 3140 (CH imidazole), 1705 (C=O ester), 1690 (C=O ketone) and 750 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z: 284 ($M^{+\cdot}$, 30%), 211 (100%), 148 (80%), 118 (70%) and 90 (65%). NMR (200 MHz, $CDCl_3$) δ : 1.35 (3H, t, J = 7, CH_3), 2.55 (2H, m, $H_{3'}$), 3.15 (1H, ddd, J = 17 ; 3 and 3, $H_{4'}$), 3.25 (1H, ddd, J = 17 ; 8 and 8, $H_{4'}$), 4.35 (2H, q, J = 7, CH_2O), 6.25 (1H, br dd, J = 9 ; 9, $H_{2'}$), 7.05 (1H, d, J = 1, H_4), 7.30 (1H, d, J = 1, H_5), 7.40 (2H, m, $H_{7'}$ and $H_{5'}$), 7.55 (1H, ddd, J = 8 ; 8 and 1.5, $H_{6'}$), 8.05 (1H, dd, J = 8 ; 1.5, $H_{8'}$).

Ethyl 1-[2-(1-oxoisothiochromanyl)]imidazole-2-carboxylate (4c)

A mixture of **6** (2.5 g, 0.018 mol) and 3-bromoisothiochroman-4-one (**3c**) (2.2 g, 9 mmol) was mechanically stirred at 130°C for 10 min, cooled at rt, poured on dichloromethane (30 mL), and the resulting solution was washed with water (15 mL). The aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined organic phases were washed with a saturated solution of sodium hydrogen carbonate (15 mL) and then water (2 x 15 mL), dried ($MgSO_4$), filtered, evaporated, and the residue was purified by flash chromatography on silica gel using a dichloromethane/ethyl acetate mixture (80/20) as eluent to give 0.53 g (19%) of **4c** as an orange glass (R_f= 0.67 in dichloromethane/cyclohexane mixture 80/20). IR (CH_2Cl_2) : 3130 (CH imidazole) and 1710 (C=O ester and ketone) cm^{-1}. MS (EI) m/z: 302 ($M^{+\cdot}$, 45%), 256 (20%), 162 (20%), 135 (55%), 118 (80%) and 90 (100%). NMR (200 MHz, DMSO-d_6) δ : 1.30 (3H, t, J = 7, CH_3), 4.20 and 4.75 (2 x 1H, 2 x d, J = 16, $H_{1'}$), 4.30 (2H, m, CH_2O), 7.20 (1H, d, J = 1, H_4), 7.30 (1H, s, $H_{3'}$), 7.50 (3H, m, $H_{8'}$, $H_{6'}$ and H_5), 7.70 (1H, ddd J = 8 ; 8 and 1.5, $H_{7'}$), 7.90 (1H, dd, J = 8 ; 1.5, $H_{5'}$).

1-Acetyl-3-oxo-2-(2-ethoxycarbonylimidazolyl)indole (4d)

A mixture of **3d** (10.2 g, 0.04 mol) and **7** (11.2 g, 0.08 mol) was stirred with an efficient mechanical stirrer, at 120° for 15 min, cooled to rt, diluted with dichloromethane/ethyl acetate mixture (60/40), filtered, and the filtrate was evaporated to a red oil which was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (60/40) as eluent, to give 8.6 g (55%) of **4d** as a yellow solid (mp 210°C (not recrystallized), R_f = 0.25 in dichloromethane/ethyl acetate mixture 60/40). IR (KBr) : 3130 (CH imidazole), 1730 (C=O ester), 1700 (C=O ketone), 1690 (C=O) and 770 (CH 1,2 disubstituted phenyl) cm^{-1}. MS (EI) m/z: 313 ($M^{+\cdot}$, 15%), 270 (26%), 141 (50%), 132 (70%), 68 (60%) and 43 (100%). NMR (300 MHz, $CDCl_3$) δ : 1.35 (3H, t, J = 7, CH_3), 2.00 (3H, s, CH_3), 4.40 (2H, m, CH_2O), 6.80 (1H, d, J = 1, H_4), 7.10 (1H, d, J = 1, H_5), 7.20 (1H, ddd, J = 8 ; 8 and 1.5, $H_{5'}$), 7.60 (1H, br s, $H_{3'}$), 7.70 (2H, m, $H_{7'}$ and $H_{6'}$), 8.50 (1H, br d, J = 8, $H_{4'}$).

Ethyl 1-(3-oxo-2,3-dihydrobenzo[*b*]thiophen-2-yl)imidazole-2-carboxylate (4e)

To a solution of **6** (20.1 g, 0.148 mol) in ethanol (500 mL) under nitrogen atmosphere and at 50°C was added portionwise **3e** (18.0 g, 0.074 mol) with stirring. This solution was then heated to reflux. After 10 h, the heterogeneous reaction mixture was cooled to rt, filtered, and the filtrate was evaporated to a red oil which was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (80/20) as eluent to give 3.2 g (15%) of **4e** as a cream solid (mp 174°C (not recrystallized), R_f = 0.27 in dichloromethane/ethyl acetate mixture 60/40). MS (EI) m/z: 288 ($M^{+\cdot}$, 80%), 242 (100%), 216 (50%), 136 (80%) and 121(80%). NMR (200 MHz, $CDCl_3$) δ : 1.15 (3H, t, J = 7, CH_3), 4.20 (2H, q, J = 7,CH_2O), 7.03 (1H, d, J = 1, H_4), 7.18 (1H, d, J = 1, H_5), 7.45 (2H, br m, $H_{6'}$ and $H_{5'}$), 7.70 (1H, br d, $H_{7'}$), 8.00 (1H, br s, $H_{4'}$). The signal pertaining to $H_{2'}$ was not observed due to keto-enol equilibrium.

5*H*,10*H*-Imidazo[1,2-*a*]indeno[1,2-*e*]pyrazin-4-one (1a)

A brown suspension of indanone derivative (**4a**) (818 g, 3.0 mol) in acetic acid (4.9 L) was mechanically stirred at reflux for 30 min. Then, ammonium acetate (2.3 kg, 30.2 mol) was added portionwise. The mixture was maintained at reflux for five further hours, cooled to rt overnight, and the pale yellow solid was filtered and washed firstly with acetic acid/water mixture 1/1 (2 x 1 L) and finally with water (8 x 1 L) to give 1.7 kg of a solid which was dried under vacuum at 80°C to afford 491g (73%) of **1a** an ochre solid (mp > 260°C (not recrystallized), R_f= 0.33 in ethyl acetate/ methanol mixture 80/20). IR (KBr) : 3250 - 2600 (NH), 1680 (C=O) and 750 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z: 223 ($M^{+\cdot}$, 100%), 194 (60%), 169 (15%), 129 (25%) and 105 (25%). NMR (300 MHz, DMSO-d_6) δ : 4.00 (2H, s, H_{10}), 7.30 and 7.40 (2 x 1H, 2ddd, J = 8 ; 8 and 1.5, H_7 and H_8), 7.60 (2H, m, H_9 and H_2), 7.80 (1H, dd, J = 8 and 1.5, H_6), 7.90 (1H, d, J = 1, H_1), 12.20 (1H, br s, H_5). Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82; O, 7.17. Found: C, 70.3; H, 4.1; N, 18.3; O, 7.4.

5*H*,10*H*-[2]Benzothiopyrano[4,3-*e*]imidazo[1,2-*a*]pyrazin-4-one (1c)

A solution of **4c** (0.94 g, 3 mmol), ammonium acetate (27 g, 0.35 mol) in glacial acetic acid (30 mL) was heated at reflux for 20 min. After cooling, water (20 mL) was added, and the residue was filtered, washed with water (2 x 20 mL) and dried under vacuum to give a brown solid wich was crystallised from hot DMF to afford 0.26 g (34%) of pure **1c** as a cream solid (mp > 260°C (not recrystallized), R_f= 0.40 in dichloromethane/ methanol mixture 90/10). IR (KBr) : 3250 - 2600 (NH), 1675 (C=O) and 765 (CH imidazole) cm^{-1}. MS (EI) m/z: 255 ($M^{+\cdot}$,

100%), 226 (15%), 194 (10%), 161 (50%), 117 (15%) and 95 (10%). NMR (300 MHz, DMSO-d_6) δ : 4.20 (2H, s, H_{10}), 7.43 (3H, m, H_7 ; H_8 and H_9), 7.58 (1H, d, J = 1.3, H_2), 7.76 (1H, br d, J = 8, H_6), 7.90 (1H, d, J = 1.3, H_1), 11.80 (1H, br s, H_5).

10-Acetyl-5*H*-imidazo[1,2-*a*]indolo[3,2-*e*]pyrazin-4-one (7)

To a stirred solution of **4d** (8.4 g, 0.027 mol) in acetic acid (300 mL) was added portionwise ammonium acetate (206 g, 2.6 mol) at rt. The pale yellow reaction mixture was then heated at reflux for 1 h, cooled to rt. After addition of water (50 mL), the precipitate was filtered off, washed with water (2 x 50 mL), acetone (20 mL), dried under vacuum to give 5.6 g (79%) of **7** as a cream solid (mp > 260°C (not recrystallized), R_f = 0.45 in dichloromethane/methanol mixture 80/20). IR (KBr) : 3250 - 2600 (NH), 1710 (C=O acetyl), 1660 (C=O) and 755 (CH 1,2-disubstituted phenyl) cm^{-1}. NMR (200 MHz, DMSO-d_6) δ : 1.90 (3H, s, CH_3), 7.20 and 7.30 (2 x 1H, 2 x dd, J = 8 ; 8, H_7 and H_8), 7.55 (1H, br d, J = 8, H_9), 7.65 (1H, br s, H_2), 7.92 (1H, br d, J = 8, H_6), 8.10 (1H, br s, H_1), 12.20 (1H, br s, H_5).

5*H*, 10*H*-Imidazo[1,2-*a*]indolo[3,2-*e*]pyrazin-4-one (1d)

A solution of **7** (2 g, 7.5 mmol) in DMF (200 mL) was refluxed for 15 min. The hot reaction mixture was then treated with charcoal, and filtered through Celite. The filtrate was diluted with water (50 mL), poured onto crushed ice to afford 1.28 g (76%) of pure **1d** as a white solid (mp > 260°C (not recrystallized), R_f = 0.45 in dichloromethane/methanol mixture 80/20). IR (KBr) : 3250 - 2600 (NH), 1660 (C=O) and 760 (CH imidazole and 1,2-disubstituted phenyl) cm^{-1}. MS (DCI/NH_3) m/z: 225 ($M+H^+$, 100%). NMR (300 MHz, DMSO-d_6) δ : 7.20 and 7.30 (2 x 1H, 2 x ddd, J = 8; 8 and 1.5, H_7 and H_8), 7.50 (1H, br d, J = 8, H_9), 7.65 (1H, J = 1, H_2), 7.95 (1H, br d, J = 8, H_6), 8.10 (1H, d, J = 1, H_1), 12.20 (1H, br s, H_5). Anal. Calcd for $C_{12}H_8N_4O$: C, 64.27; H, 3.60; N, 24.99; O, 7.14. Found: C, 64.2; H, 3.7; N, 25.2; O, 7.5.

1-[2-(1-Oxo-1,2,3,4-tetrahydronaphthyl)]imidazole-2-carboxamide (5b)

A solution of **4b** (0.6 g, 0.0021 mol) in solution of 3N ammonia in methanol (40 mL) was stirred at rt for 20 h, then concentrated under reduced pressure. The residue was then triturated with isopropyl ether (10 mL), filtered, washed with isopropyl ether (2 x 4 mL) and dried under reduced pressure to afford 0.42 g (79%) of **5b** as a pale brown solid (mp 250°C (not recrystallized), R_f= 0.32 in ethyl acetate/dichloromethane mixture 60/40). IR (KBr) : 3325 and 3160 (NH), 1705 (C=O ketone), 1685 (C=O) and 750 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z: 255 ($M^{+\cdot}$, 20%), 237 (20%), 211 (100%), 144 (30%), 115 (40%) and 90 (45%). NMR (200 MHz, DMSO-d_6) δ : 2.80 and 3.20 (2 x 2H, 2 x m, $H_{3'}$ and $H_{4'}$), 6.30 (1H, br d, $H_{2'}$), 6.95 (1H, d, J = 1, H_4), 7.30 (4H, m, H_5, $CONH_2$, $H_{7'}$ and $H_{5'}$), 7.50 (1H, ddd, J = 8 ; 8 and 1.5, $H_{6'}$), 7.70 (1H, br s, $CONH_2$), 7.9 (1H, dd, J = 8 ; 1.5, $H_{8'}$).

5*H*-10,11-Dihydrobenzo[*f*]imidazo[1,2-*a*]quinoxalin-4-one (1b)

To a stirred solution of **5b** (0.3 g, 0.0012 mol) in methanol (55 mL) at reflux was added dropwise 12N HCl (6 mL). The reaction mixture was stirred and heated at the same temperature for 1 h, and then cooled at 5°C for 15 h. The precipitate was filtered off, washed with cold methanol (1 mL) and dried under reduced pressure to give 0.16 g (59%) of **1b** as a white solid (mp > 260°C (not recrystallized), R_f= 0.38 in dichloromethane/methanol mixture 90/10). IR (KBr) : 3250 - 2600 (NH), 1665 and 1650 (C=O), 765 (CH imidazole) and 750 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (DCI/NH_3) m/z: 238 ($M+H^+$, 100%). NMR (300 MHz,

DMSO-d_6) δ : 3.05 (4H, m, H_{10} and H_{11}), 7.30 (3H, m, H_7, H_8 and H_9), 7.60 (1H, d, J = 1, H_2), 7.9 (1H, dd, J = 8 and 1.5, H_6), 8.05 (1H, d, J = 1, H_1), 11.60 (1H, br s, H_5).

1-(3-Oxo-2,3-dihydrobenzo[*b*]thiophene-2-yl)imidazole-2-carboxamide (5e)

A solution of **4e** (1.92g, 6.7 mmol) in 5N ammonia in methanol (130 mL) was stirred for 15 h at rt, and then concentrated *in vacuo* to afford 1.66 g of a yellow solid. This solid was triturated with diisopropyl ether (30 mL), filtered off, washed with diisopropyl ether (2 x 10 mL), and dried under vacuum to give 1.5 g (88%) of **5e** as a yellow solid (mp 180°C (not recrystallized), R_f = 0.54 in dichloromethane/methanol mixture 90/10). IR (KBr) : 3325 and 3200 (NH), 3000 - 2000 (OH enol), 1685 (C=O), 1600 (C=C enol) and 750 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z: 259 ($M^{+\cdot}$, 45%), 242 (100%), 214 (15%) and 44 (10%). NMR (200 MHz, DMSO-d_6) δ : 7.20 (1H, d, J = 1, H_4), 7.40 (3H, m, $H_{6'}$, $H_{5'}$ and $CONH_2$), 7.50 (1H, d, J = 1, H_5), 7.90 (3H, m, $H_{4'}$, $H_{7'}$ and $CONH_2$), 10.20 (1H, very br s, OH). The signal pertaining to $H_{2'}$ was not observed due to enol formation.

5*H*-[1]Benzothieno[3,2-*e*]imidazo[1,2-*a*]pyrazin-4-one (1e)

A solution of **5e** (1.0 g, 3.8 mmol) in 10N aq. HCl solution (50 mL) was stirred at rt for 10 min, and the precipate was filtered off , washed successively with water (10 mL) and acetone (5 mL), and dried under vacuum to give 0.61 g (57%) of **1e** as an ochre solid (mp 320°C (*decomp, not recrystallized*), R_f= 0.38 in dichloromethane/methanol mixture 90/10). IR (KBr) : 3200 - 2200 (NH and NH^+ salified imidazole), 1705 (C=O) 1540 (ring breathing of salified imidazole), 765 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z : 241 ($M^{+\cdot}$, 15 %), 135 (50 %), 91 (45 %), 44 (100 %). NMR (300 MHz, DMSO-d_6) δ : 7.50 and 7.57 (2 x 1H, 2 x br dd, J = 8 ; 8, H_7 and H_8), 7.80 (1H, br s, H_4), 8.15 (1H, br d, J = 8, H_9), 8.35 (1H, br s, H_5), 8.40 (1H, br d, J = 8, H_6), 12.90 (1H, br s, H_5).

5a-Hydroxy-3-methyl-4-oxo-5a,10a-dihydro-5*H*-benzofuro[3,2-e]imidazo[1,2-a]pyrazinium bromide (9)

To a solution of **3f** (2.5 g, 0.02 mol) in anhydrous acetonitrile (30 mL) under nitrogen atmosphere and at reflux was added dropwise **3f** (6 g, 0.025 mol) in anhydrous acetonitrile (20 mL) with stirring. After 8 h, the reaction mixture was cooled to rt, the resulting solid was filtered off, washed with acetone (2 x 50 mL) and ether (50 mL) successively, and dried under vacuum to afford 6.7 g (100%) of **9** as a pale yellow solid (mp> 260°C (not recrystallized), R_f = 0.05 in dichloromethane/methanol mixture 80/20). IR (KBr) : 3425 (OH alkohol), 3130 and 3050 (NH), 1700 and 1690 (C=O), 1540 (ring breathing imidazolium), 1220 (C-O ether) and 760 (CH 1,2-disubstituted phenyl) cm^{-1}. MS (LSIMS/glycerol) m/z: 258 (M^+, 100%). NMR (200 MHz, DMSO-d_6) δ : 4.15 (3H, s, CH_3), 6.75 (1H, s, H_{10a}), 7.1 (1H, br d, J = 8, H_9), 7.20 and 7.45 (2 x 1H, 2 x br dd, J = 8 ; 8, H_7 and H_8), 7.60 (1H, br d, J= 8, H_6), 8.15 (1H, d, J = 1.3, H_1), 8.25 (1H, d, J = 1.3, H_2), 10.60 (1H, br s, H_5).

5*H*-Benzofuro[3,2-*e*]imidazo[1,2-*a*]pyrazin-4-one (1f)

A mixture of **9** (6 g, 0.018 mol) and imidazole (30 g, 0.43 mol) was stirred and successively heated at 155°C for 4 h, at 165°C for 6 h and then 175°C for 2 h. The reaction mixture was cooled at 100°C, and water (50 mL) was added with **caution**. This solution was pourred into water (250 mL), cooled at rt, and the filtrate was concentrated to about 50 mL to afford a brown solid which was filtered off and then recrystallized from acetic acid in presence of charcoal. The solid was washed with ethanol (2 x 100 mL) and ether (50 mL) to give 0.8 g

(20%) of pure **1f** as a white solid (mp > 260°C (not recrystallized), R_f = 0.41 in dichloromethane/methanol mixture 90/10). IR (KBr) : 3250 - 2600 (NH), 1680 (C=O) and 755 (CH imidazole and 1,2-disubstituted phenyl) cm^{-1}. MS (EI) m/z: 225 ($M^{+\cdot}$, 100%), 169 (10%) and 95 (80%). NMR (300 MHz, DMSO-d_6) δ : 7.40 (2H, m, H_7 and H_8), 7.60 (1H, d, J = 1, H_2), 7.70 (1H, br d, J = 8, H_9), 7.90 (1H, br d, J = 8, H_6), 8.20 (1H, d, J = 1, H_1), 12.20 (1H, br s, H_5). Anal. Calcd for $C_{12}H_7N_3O_2$: C, 64.00; H, 3.03; N, 18.66; O, 14.21. Found: C, 63.8; H, 3.4; N, 18.5; O, 14.4.

ACKNOWLEDGEMENT

We wish to thank M^s A. Bouet, M^s R. Kerphirique and M^r P. Ganil for technical assistance.

REFERENCES AND NOTES

1. For reviews, see: D.W. Choi and S.M. Rothman, *Annual Rev.,* 1990, **13**, 171; B.S. Meldrum 'Excitatory Amino Acid Antagonists', eds by B.S. Meldrum, 1991; H.F. Bradford, *Progress in Neurobiology,* 1995, **47**, 477; C.F. Bigge and S.S. Nikam, *Exp. Opin. Ther. Patents,* 1997, **7**, 1099 and references cited therein.
2. J-C. Aloup, F. Audiau, M. Barreau, D. Damour, A. Genevois-Borella, P. Jimonet, S. Mignani, and Y. Ribeil, *Patent Applications,* WO 94/9407893 (*Chem. Abstr.,* 1994, **121**, 1111); WO 95/26351 (*Chem. Abstr.,* 1995, **124**, 1268); WO 96/31511 (*Chem. Abstr.,* 1997, **126**, 907), WO 96/02544 (*Chem. Abstr.,* 1996, **125**, 1190); WO 97/10246 (*Chem. Abstr.,* 1997, **126**, 674).
3. S. Mignani and J-C. Aloup, *French Patent Applications,* FR 2707645 (*Chem. Abstr.,* 1995, **122**, 1068); J-C. Aloup, F. Audiau, M. Barreau, D. Damour, A. Genevois-Borella, P. Jimonet, S. Mignani, and Y. Ribeill, *Patent Applications,* WO 95/26352 (*Chem. Abstr.,* 1996, **124**, 1268).
4. a) M. Doise, D. Blondeau, and H. Sliwa, *Heterocycles,* 1992, **34**, 2065. b) J. Ohmori, M. S. Shimizu-Sasamata, M. Okada, and S. Sakamoto, *J. Med. Chem.,* 1997, **40**, 2053; H-J. Treiber, W. Lubisch, B. Behl, and H-P. Hofmann, *Patent Applications,* WO 97/34896 (*Chem. Abstr.,* 1997, **127**, 587), *German Patent Applications,* DE 4329970 (*Chem. Abstr.,* 1995, **123**, 931), *German Patent Applications,* DE 4310523 (*Chem. Abstr.,* 1994, **121**, 427); S. Ceccarelli, S. Zanarella, M. Altobelli, and A. D'Alessandro, *Patent Applications,* WO 97/19079 (*Chem. Abstr.,* 1997, **127**, 647); V. Colotta, D. Catarzi, F. Varano, F. Nelani, G. Filacchioni, L. Cecchi, A. Galli, and C. Costagli, *Farmaco,* 1996, **51**, 223; L. Jeppesen, *Patent Applications,* WO 95/21842 (*Chem. Abstr.,* 1996, **124**, 939); D. Catarzi, L. Cecchi, V. Colotta, F. Melani, G. Filacchioni, C. Martini, L. Giusti, and A. Lucacchini, *J. Med. Chem.,* 1994, **37**, 2846; S. Sakamoto, J. Ohmori, M. Sasamata, M. Okada, and K. Hidaka, *Patent Applications,* WO 93/20077 (*Chem. Abstr.,* 1994, **120**, 1088); P. Albaugh and A. J. Hutchinson, *US Patent Applications,* US 5182386 (*Chem. Abstr.,* 1993, **119**, 937); L. McQuaid, C. Mitch, P. Ornstein, D. Schoepp, and E. Smith, *US Patent Applications,* US 5153196 (*Chem. Abstr.,* 1993, **118**, 1007). c) D. D. Davey and J. W. Lampe, *European Patent Applications,* EP 429149 (*Chem. Abstr.,* 1991, **115**, 934 d) D. D. Davey, P. W. Erhardt, E. H. Cantor, and S. S. Greenberg, *J. Med. Chem.,* 1991, **34**, 2671; D. D. Davey, *European Patent Applications,* EP 400583 (*Chem. Abstr.,* 1991, **114**, 799).
5. a) J-C. Aloup, F. Audiau, D. Damour, A. Genevois-Borella, P. Jimonet, and S. Mignani, *Patent Applications,* WO 94/07893 (*Chem. Abstr.,* 1994, **121**, 1111) b) This 2-step

synthetic pathway represents an convenient procedure for the large scale preparation of **1a** from **3a**. Previously, we described the synthesis of **1a** starting from **3a** in 2-step synthesis or 3-step synthesis with 33 and 70% overall yields respectively in gram scale (see: ref 5a).

6. **2d:** D. Raileanu, O. Constantinescu-Simon, and E. Mosanu, *Rev. Roum. Chim.,* 1967, 12, 105; **2e:** G. Wagner and B. Eppner, *Pharmazie,* 1979, **34**, 527.
7. E. Galeazzi, A. Guzman, J.L. Nava, Y. Liu, M.L. Maddox, and J.M. Muchowski, *J. Org. Chem.,* 1995, **60**, 1090.
8. D.D. Davey, *J. Org. Chem.,* 1987, **52**, 4379.
9. **3a:** A.D. Allen, M. Fujio, N. Mohammed, T.T. Tidwell, and Y. Tsuji, *J. Org. Chem.,* 1997, **62**, 246; **3b:** J.N. Srivastava, P. Kumar, S.N. Thakur, S.N. Sahay, and L.K. Srivastava, *J. Indian Chem. Soc.,* 1990, **67**, 210; **3c:** R. Lesser and A. Mehrländer, *Ber.,* 1923, **56**, 1642; **3d:** V.S. Velezheva, A.I. Mel'man, Y.I. Smushkevich, V.I. Pol'shakov, and O.S. Anisimova, *Khim. Farm. Zh.,* 1990, **24**, 46; **3e:** Z.I. Mirosshnichenko and M.A. Al'perovich, *J. Gen. Chem. USSR,* 1962, **32**, 1218; **3f:** K. Fries and W. Pfaffendorf, *Ber.,* 1912, **45**, 160.

Received, 29th June, 1998