HETEROCYCLES, Vol. 68, No. 10, 2006, pp. 2063 - 2077. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd June, 2006, Accepted, 23rd August, 2006, Published online, 25th August, 2006. COM-06-10824

SYNTHESIS OF NOVEL PYRAZOLOPYRROLIZINONES AS PROSPECTIVE ANTICANCER AGENTS

Christophe Rochais, Jana Sopkovà-de Oliveira Santos, Patrick Dallemagne, and Sylvain Rault*

CERMN, Faculty of Pharmacy, 1, rue Vaubénard, 14032 Caen Cedex, France. sylvain.rault@unicaen.fr.

Abstract – Herein we describe the access of novel pyrazolopyrrolizinones from commercial arylacetonitriles. The first step conducts to the corresponding aminoester which was first submitted to Clauson-Kaas procedure. Amidification and cyclisation afford then the first examples of the expected heterocycles. In order to improve the sequence and to obtain *N*-substituted isomers, 3-aryl-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazoles **(5)** were alkylated and conduct to two different *N*-substituted pyrazoles. These novel products were separated by chromatography and clearly identified using different analytical techniques. Application of the cyclisation procedure conducts then to the two corresponding final title products.

INTRODUCTION

In previous studies novel thienopyrrolizinones, or “tripentones” were reported by our team to be potent agents with antiproliferative activity in the nanomolar range in relation to an antitubulin action.[1] In fact, the lead compound MR 22388 (Figure 1) exhibits a nanomolar IC_{50} toward various cell lines. In order to define more precisely the SAR in this series, new modulations on this core were planned and dedicated to increase the structural diversity. Synthesis of the aza-analogs **(1)** in pyrrole series was then first described.[2] In relation with numerous references of novel biologically active compounds based on a pyrazole nucleus,[3] we then wished to explore a second new family and we describe herein the synthesis of novel diaza-analogs of MR22388 belonging to the pyrazole series **(2)**.

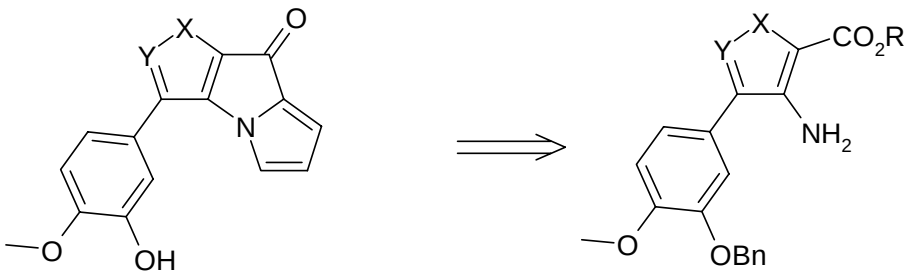
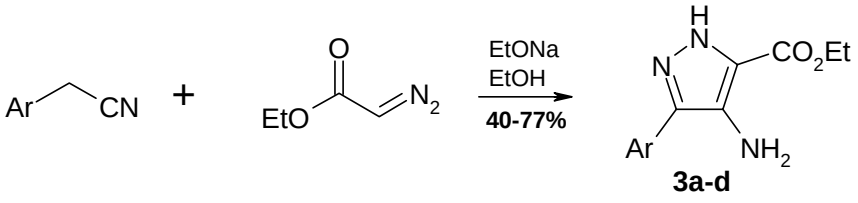


Figure 1

RESULTS AND DISCUSSION

According to the route developed in the previous series,[1,2,4] the corresponding pyrazole aminoesters **(3)** appeared as the key intermediates in the synthesis of the final "tripentones" so the first step consisted in the preparation of ethyl 4-amino-5-aryl-1*H*-pyrazole-3-carboxylates. This synthesis was first described by Tarzia[5] in one step from arylacetonitriles, and more recently by Majid[6] through an interesting ring-closure procedure from a α,β-dicarbonyl compound treated with an excess of hydrazine. Because of the accessibility of the starting material, we decided to expand the Tarzia's method in our series from commercially available arylacetonitriles (Figure 2). The isovannilic acetonitrile was however prepared in our laboratory according to previous procedure.[7] In the presence of ethyl diazoacetate in sodium ethoxide solution, selected acetonitrile afforded in one step the expected aminoesters **(3a-d)** in 40 to 77% yield.



	(Hét)Ar
a	*m,p*diOMeC$_6$H$_3$
b	*p*MeC$_6$H$_4$
c	*p*ClC$_6$H$_4$
d	*p*OMe*m*OBnC$_6$H$_3$

Figure 2

In order to achieve the synthesis of the tripentones, aminoesters **(3a-d)** were involved in a four step synthesis beginning by the synthesis of a pyrrole nucleus from the free amine through a Clauson-Kaas procedure.[8] Smoothly conditions were used for this reaction using 4-chloropyridine hydrochloride in dioxane instead of acetic acid, in the presence of 2,5-dimethoxytetrahydrofurane (2,5-DMTHF) (Figure 3).[9] The pyrroles **(4a-d)** were obtained in good to quantitative yields and afforded in refluxing pyrrolidine the corresponding carboxamides **(5a-d)**. These amides appeared as crucial intermediates toward the ring-closure procedure using Vilsmeier conditions. In refluxing phosphorus oxychloride the corresponding pyrrolidinium salts **(6a-d)** were intermediary formed, without isolation they were finally hydrolysed under alkaline conditions to afford the first examples of the ketones **(2b-d)** in moderate to low yields. In the dimethoxyphenyl series however, no traces of the tripentones **(2a)** were found.

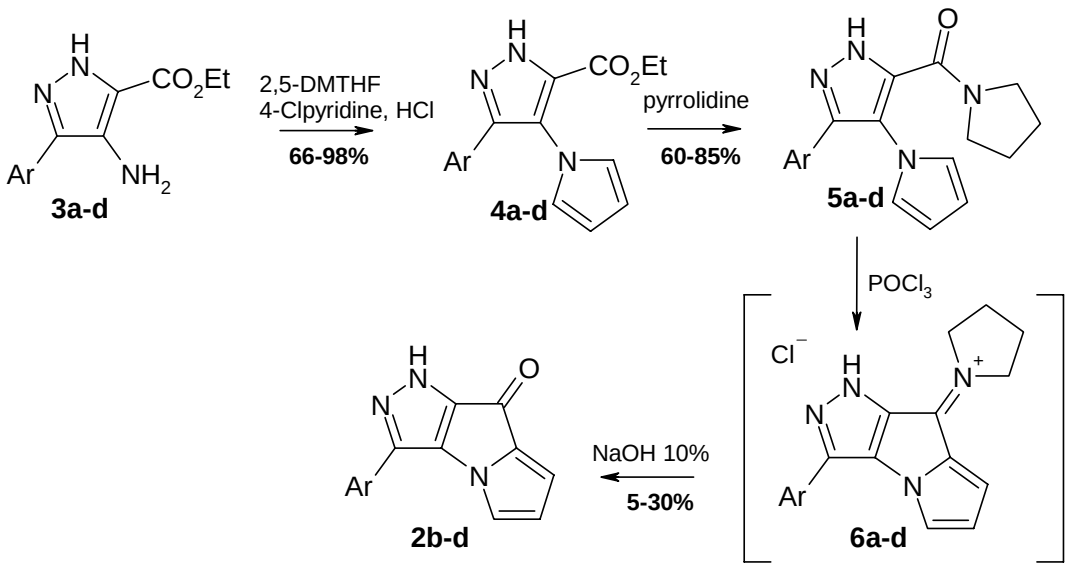


Figure 3

As already discussed in the pyrrole series, we decided to investigate influence of the *N*-substitution of the pyrazole ring on the ring-closure. So, the carboxamide **(5d)** was *N*-methylated in dimethylformamide using sodium hydride and methyl iodide. The pyrazole can exist as a mixture of two tautomers, and abstraction of the proton under treatment with NaH conduct to the delocalisation of the negative charge between the two pyrazole nitrogens (Figure 4),[10] this substitution with iodomethane takes place on N1 and N2 and resulted in a mixture of the two isomers **(7)** and **(8)**.

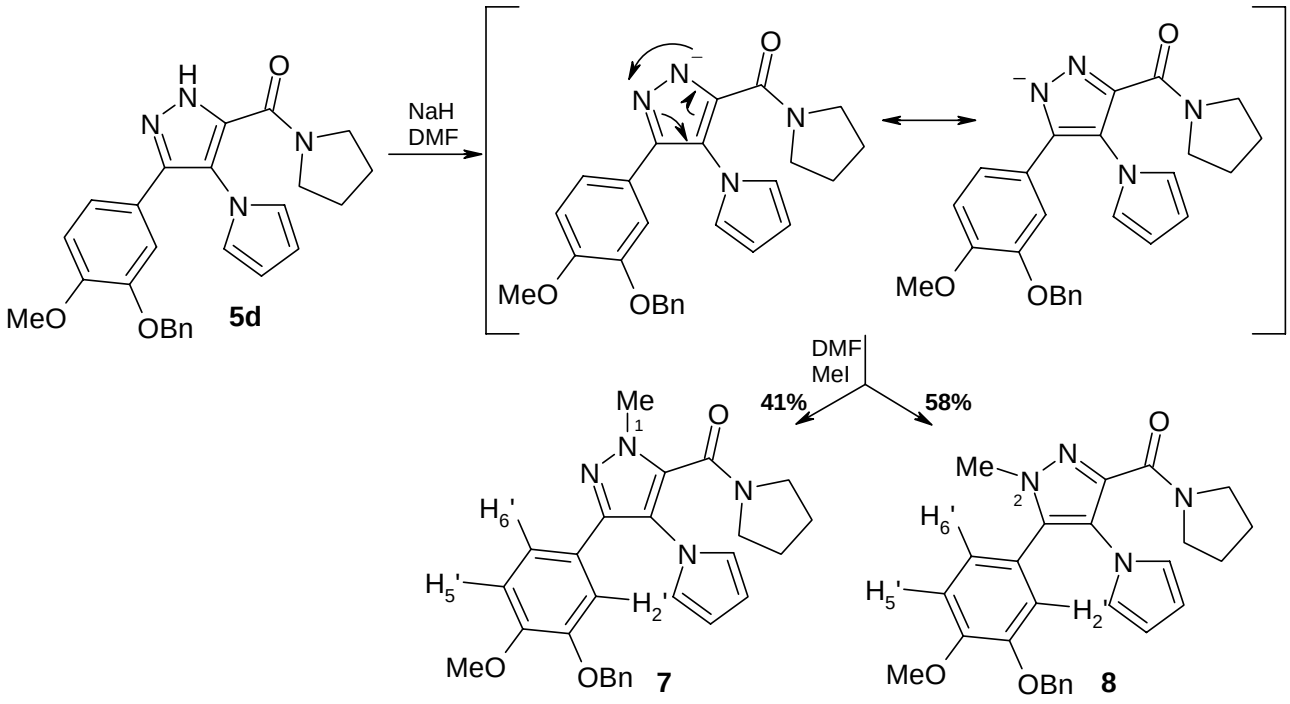


Figure 4

These two carboxamides were then separated on silica gel chromatography affording regioisomers **(7)** and **(8)** in 41 and 58% yield respectively. The determination of the two different structures was first attempted

using their ^{1}H NMR spectrum. We could indeed notice some differences between the chemical shifts of specific signals concerning the two isomers (Table 1).

Product	H_6'	H_5'	H_2'	$H_{\alpha pyrrole}$	$H_{\beta pyrrole}$	NMe	OMe
7	7.01	6.86	6.80	6.67	6.29	4.01	3.89
8	6.78	6.90	6.60	6.60	6.14	3.68	3.88

Table 1: Example of ^{1}H-NMR chemical shifts of compounds **(7)** and **(8)**.

Because of a good resolution the aromatic protons H_2', H_5' and H_6' which appeared in both products respectively as a small doublet, a doublet of doublet and a large doublet which attribution was easy. But the major difference between these two compounds was the chemical shifts of the *N*-methyl group. The electronic effect of the carbonyl on the near *N*-methyl in the case of compound **(7)** conducts to a signal at 4.01 ppm. In the case of compound **(8)** the same group appears as a singulet at 3.68 ppm. This difference was then turned to account through ^{1}H NMR-NOE experiments.[10,11] In the case of compound **(7)** specific irradiation at the resonance frequency of the N-methyl group only yielded to background noise. The same experiment performed on **8** (the more polar isomer) yielded significant peaks on the proton $H_{2'}$ and $H_{5'}$ signals, both situated on α position of the aromatic substituant. As the NOE effect is only observed over short distances (2-4 Å), compound **(8)** was assigned as the expected *N*2-methyl derivative. Structural assignment of the other members was then realize by analogy to these compound and more particularly to the specific downfield of ca 0.2 ppm in the case of $H_{6'}$ and $H_{2'}$ chemical shift.

Finally the conclusive evidence of this theoretical explanation was given by X-Ray crystallography resolution of both isomers, realized in our laboratory, presented below (Figure 5).

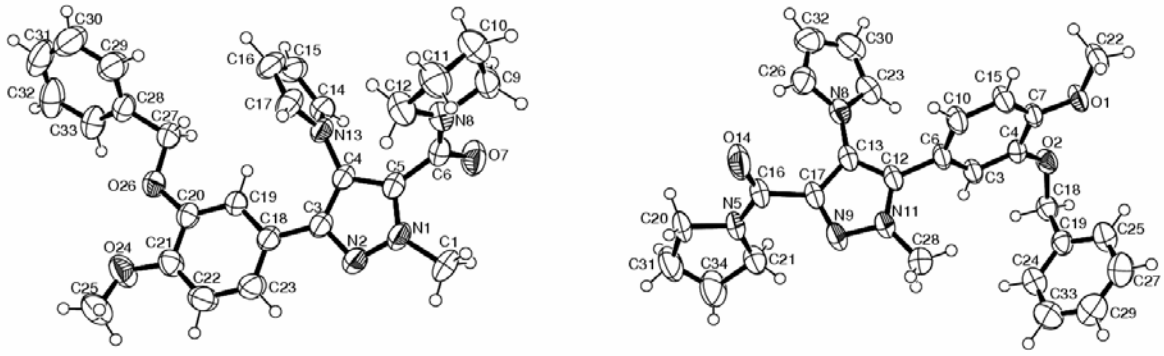


Figure 5 : X-Ray crystallography of compounds **(7)** (left) and **(8)** (right).

The carboxamides could then be separately introduced into the ring-closure reaction to afford the expected tripentones **(9)** and **(10)** (Figure 6). As already discussed, we could see an impressive enhancement of the ring-closure yields when the pyrazole moiety was substituted as well in N1 position than in N2 one with 72 and 75% yield respectively. A *O*-debenzylation reaction could be easily conducted

using an HBr solution in acetic acid media, followed by alkaline hydrolysis to afford in good yields the N-substituted isomers **(11)** and **(12)**.

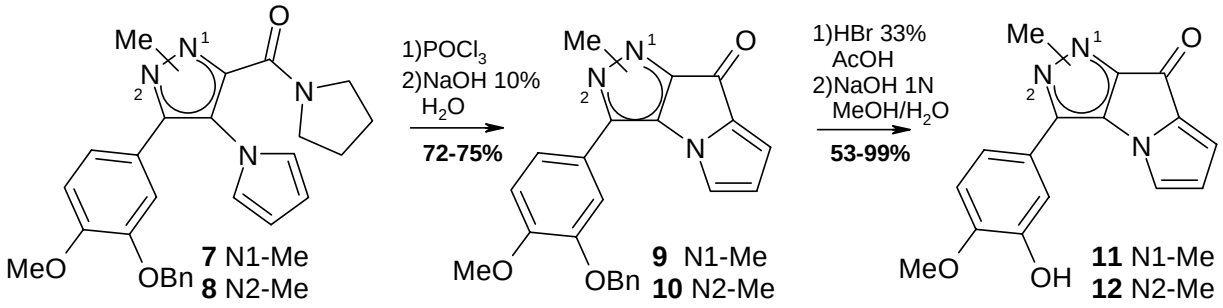


Figure 6

In front of the influence of N-protecting groups in the ring-closure reaction, we then decided to look for cleavable protecting groups in order to realize the synthesis of *N*-unsubstituted tripentones with good yields. Benzyl group was the first group to be investigated. Benzylic carboxamides **(13)** and **(14)** were easily obtained and separated from corresponding amide **(5d)**. These two compounds furnished the desired tripentones **(15)** and **(16)** which could be *O*-deprotected with HBr. However, all the classical methodologies usually employed to cleave benzyl group on nitrogen heterocycles failed. We have also noticed that Boc-protection which gave good results in pyrrolic series[2], was however inefficient in the case of pyrazole series. Only unprotected amide **(5d)** was recovered isolated after 3h in refluxing phosphorus oxychloride.

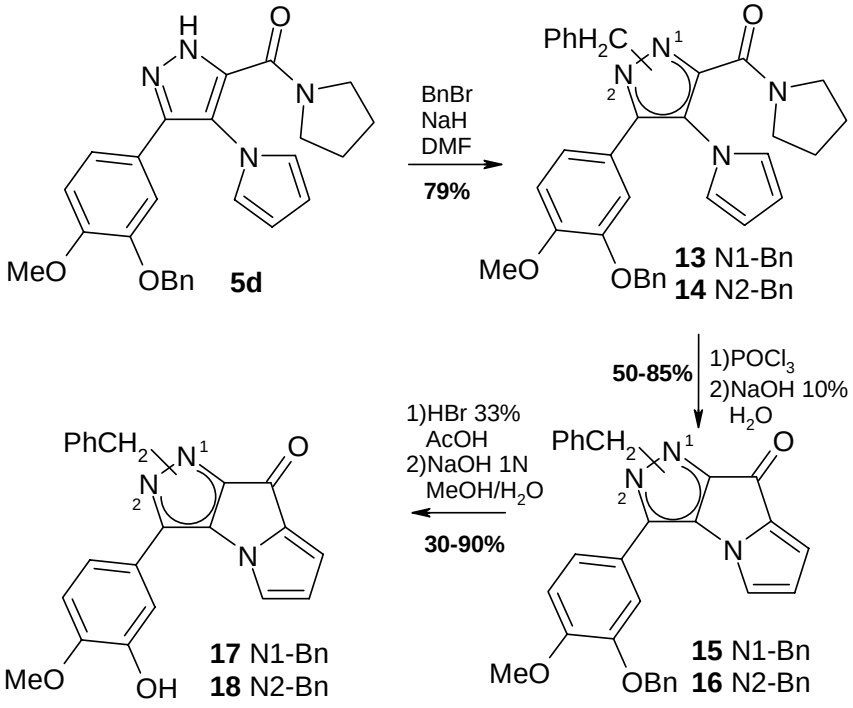


Figure 7

Numerous protecting groups were then evaluated, including silyl[11], trityl[12] and paramethoxybenzyl groups, but none allowed us to improve the yield of the synthesis of the unprotected pyrazole tripentones **(2)**.

CONCLUSION

In conclusion, we have developed an efficient synthesis of first pyrazolopyrrolizinones whose suitability as biologically active agents, particularly in the antineoplastic domain, is currently under investigation.

EXPERIMENTAL

General. Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin Elmer spectrum BX FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) were recorded on a JEOL Lambda 400 Spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as an internal standard. MS were recorded on a JEOL JMS GCMate with ionising potential of 70eV. Elemental analyses for new compounds were performed at the "Institut de Recherche en Chimie Organique Fine" (Rouen).

General synthesis of pyrazolic aminoester

Ethyl 4-amino-5-(3-benzyloxy-4-methoxyphenyl)-2*H*-pyrazole-3-carboxylate (3d)

To 3-benzyloxy-4-methoxyphenylacetonitrile (7g, 27.6 mmol) solved in 60 mL EtOH was added sodium ethoxide (2.07g, 30.4 mmol) freshly prepared. Mixture was cooled down to 0°C and ethyl diazoacetate (3.20mL, 30.4 mmol) were added. The reaction mixture was stirred over-night and diluted with 100 mL water and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$) and evaporated to give a dark solid. This residue was purified by silica gel chromatography, eluting by cyclohexane:EtOAc (1:2) to furnish aminoester **(3d)** as a orange solid (6.94 g, 62%). Mp 148°C. IR (KBr): ν = 3166 (NH), 2920, 2845, 1707(CO), 1606, 1462, 1382, 1257, 1136, 1021 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.3 (bs, 1H, NH), 7.35 (m, 6H, $H_{aromatic}$ + $H_{6'}$), 7.21 (d, $^{4}J_{H2'H6'}$ = 1.9 Hz, 1H, $H_{2'}$), 6.93 (d, $^{3}J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 5.17 (s, 2H, CH_2Ph), 4.36 (q, ^{3}J = 7.1 Hz, 2H, OCH_2), 4.0 (bs, 2H, NH_2), 3.90 (s, 3H, OCH_3), 1,38 (t, ^{3}J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.85, 149.41, 148.34, 136.94, 132.16, 128.56, 127.87, 127.40, 124.52, 120.03, 119.47, 112.42, 112.14, 111.77, 70.97, 60.71, 56.08, 14.45. MS (EI^{+}) *m/z*: 367.2. Anal. Calcd for $C_{20}H_{21}N_3O_4$: C 65.38, H 5.76, N 11.44. Found: C 65.45, H 5.36, N 11.45.

General Clauson-Kaas reaction procedure

Ethyl 3-(3,4-dimethoxyphenyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-5-carboxylate (4a)

A solution of 2,5-dimethoxytetrahydrofuran (1.07 mL, 8.20 mmol) in dioxane (50 mL) was stirred for 15 min with 4-chloropyridine hydrochloride (1.24g, 8.20 mmol). The aminoester (2g, 6.90 mmol) was added and the reaction mixture was refluxed for 4h and filtered through a small pad of Celite. The solvent was evaporated to give a brown residue that was dissolved in CH_2Cl_2 (100 mL). The solution was washed with 1N HCl (2 × 100 mL), dried ($MgSO_4$) and evaporated to give **(3a)** as a white solid (2.3 g, 98%) that was crystallized from Et_2O. Mp 168°C. IR (KBr): ν = 3256(NH), 2960, 2929, 2857, 1736(CO), 1515, 1457, 1260, 1245, 1090, 1021, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.5 (bs, 1H, NH), 6.95 (dd, $^4J_{H2'H6'}$ = 1.95 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.90 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.69 (m, 2H, $H_{\alpha pyrrole}$), 6.58 (d, $^4J_{H2'H6'}$ = 1.95 Hz, 1H, $H_{2'}$), 6.31 (m, 2H, $H_{\beta pyrrole}$), 4.24 (q, ^3J = 7.1 Hz, 2H, OCH_2), 3.86 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 1.21 (t, ^3J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.02, 149.52, 149.01, 124.34, 122.80, 122.21, 121.65, 118.68, 111.11, 110.99, 109.68, 109.03, 61.42, 55.82, 55.64, 13.91. MS (EI^+) *m/z*: 341.1. Anal. Calcd for $C_{18}H_{19}N_3O_4$: C 63.33, H 5.61, N 12.31. Found: C 63.45, H 5.63, N 12.35.

Ethyl 3-(4-methylphenyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-5-carboxylate (4b)

From Ethyl 4-amino-5-(4-methylphenyl)-2*H*-pyrazole-3-carboxylate **(3b)** (0.7g); beige solid **(4b)** (0.56g, 66%). Mp 142°C. IR (KBr): ν = 3243(NH), 2998, 2956, 2927, 1726(CO), 1457, 1329, 1194, 1180, 1087, 1020, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.6 (bs, 1H, NH), 7.11 (m, 4H, $H_{aromatic}$), 6.66 (m, 2H, $H_{\alpha pyrrole}$), 6.29 (m, 2H, $H_{\beta pyrrole}$), 4.23 (q, ^3J = 7.1 Hz, 2H, OCH_2), 2.31 (s, 3H, CH_3), 1.17 (t, ^3J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.69, 144.89, 139.26, 129.75, 128.36, 126.36, 126.02, 122.94, 122.71, 109.69, 61.58, 21.49, 14.10. MS (EI^+) *m/z*: 295.3. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C 69.14, H 5.80, N 14.23. Found: C 68.82, H 5.36, N 11.05.

Ethyl 3-(4-chlorophenyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-5-carboxylate (4c)

From Ethyl 4-amino-5-(4-chlorophenyl)-2*H*-pyrazole-3-carboxylate **(3c)** (0.8g); beige solid **(4c)** (0.75g, 79%). Mp 114°C. IR (KBr): ν = 3436(NH), 2985, 2956, 2905, 1727(CO), 1597, 1374, 1214, 1086, 864, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.5 (bs, 1H, NH), 7.20 (d, ^3J = 8.5 Hz, 2H, $H_{aromatic}$), 7.10 (d, ^3J = 8.5 Hz, 2H, $H_{aromatic}$), 6.60 (m, 2H, $H_{\alpha pyrrole}$), 6.25 (m, 2H, $H_{\beta pyrrole}$), 4.22 (q, ^3J = 7.1 Hz, 2H, OCH_2), 1.16 (t, ^3J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.36, 145.05, 135.08, 129.51, 129.20, 127.89, 127.84, 123.07, 122.77, 110.03, 61.81, 14.05. MS (EI^+) *m/z*: 315.2. Anal. Calcd for $C_{16}H_{14}N_3O_2Cl$: C 60.86, H 4.47, N 13.31. Found: C 61.23, H 4.36, N 13.63.

Ethyl 3-(3-benzyloxy4-methoxyphenyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-5-carboxylate (4d)

From Ethyl 4-amino-5-(3-benzyloxy-4-methoxyphenyl)-2*H*-pyrazole-3-carboxylate **(3d)** (6.8g); beige solid **(4d)** (6.38g, 83%). Mp 182°C. IR (KBr): ν = 3245(NH), 2956, 2931, 2833, 1736(CO), 1513, 1257, 1237, 1204, 1086, 1021, 737, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.5 (bs, 1H, NH), 7.30 (m, 5H, H_{phenyl}), 6.94 (dd, $^4J_{H2'H6'}$ = 1.95 Hz, $^3J_{H5'H6'}$ = 8.5 Hz, 1H, $H_{6'}$), 6.80 (d, $^3J_{H5'H6'}$ = 8.5 Hz, 1H, $H_{5'}$), 6.67

(m, 2H, $H_{\alpha pyrrole}$), 6.65 (d, $^4J_{H2'H6'}$ = 1.95 Hz, 1H, $H_{2'}$), 6.32 (m, 2H, $H_{\beta pyrrole}$), 4.87 (s, 2H, CH_2Ph), 4.24 (q, ^3J = 7.1 Hz, 2H, OCH_2), 3.84 (s, 3H, OCH_3), 1.19 (t, ^3J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.61, 150.09, 148.24, 136.78, 128.53, 128.42, 127.82, 127.46, 122.85, 122.09, 121.40, 119.20, 111.68, 111.45, 111.26, 109.64, 70.43, 61.33, 55.92, 13.90. MS (EI^+) *m/z*: 417.2. Anal. Calcd for $C_{24}H_{23}N_3O_4$: C 69.05, H 5.55, N 10.07. Found: C 68.68, H 5.32, N 10.33.

General amidification reaction procedure:

3-(3,4-Dimethoxyphenyl)-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (5a)

A solution of **(4a)** (1g, 2.93 mmol) in pyrrolidine (30 mL) was refluxed for 24 h. After the mixture was cooled and evaporated, the yellow oil was dissolved in CH_2Cl_2 (200 mL) and the solution was washed with 1N HCl (2 × 100 mL), dried ($CaCl_2$) and evaporated to give a brown oil. This residue was purified by silica gel chromatography, eluting by cyclohexane:AcOEt (1:2) to furnish carboxamide **(5a)** as a yellow solid (990 mg, 56%). Mp 210°C. IR (KBr): ν = 3435(NH), 3007, 2954, 1600(CO), 1582, 1498, 1236, 1228, 1133, 1021, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.7 (bs, 1H, NH), 6.85 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.82 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.72 (m, 2H, $H_{\alpha pyrrole}$), 6.62 (s, 1H, $H_{2'}$), 6.27 (m, 2H, $H_{\beta pyrrole}$), 3.87 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.59 (m, 2H, $H_{\alpha pyrrolidine}$), 2.98 (m, 2H, $H_{\alpha pyrrolidine}$), 1.83 (m, 2H, $H_{\beta pyrrolidine}$), 1.75 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.22, 149.55, 149.20, 122.79, 122.39, 119.72, 119.31, 111.37, 110.44, 110.39, 109.78, 109.74, 56.10, 55.92, 47.47, 46.75, 26.33, 24.21. MS (EI^+) *m/z*: 366.2. Anal. Calcd for $C_{20}H_{22}N_4O_3$: C 65.56, H 6.05, N 15.29. Found: C 65.45, H 6.24, N 15.47.

3-(4-Methylphenyl)-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (5b)

From **(4b)** (0.5g); orange solid **(5b)** (0.46g, 85%). Mp 180°C. IR (KBr): ν = 3190(NH), 2956, 2923, 2875, 1609(CO), 1588, 1465, 1450, 1321, 823, 722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.5 (bs, 1H, NH), 7.12 (m, 4H, $H_{aromatic}$), 6.68 (m, 2H, $H_{\alpha pyrrole}$), 6.25 (m, 2H, $H_{\beta pyrrole}$), 3.56 (m, 2H, $H_{\alpha pyrrolidine}$), 2.96 (m, 2H, $H_{\alpha pyrrolidine}$), 2.33 (s, 3H, CH_3), 1.78 (m, 4H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.79, 138.85, 138.16, 129.65, 129.33, 126.73, 122.48, 119.76, 110.14, 109.17, 47.28, 46.47, 26.18, 24.14, 21.48. MS (EI^+) *m/z*: 320.1. Anal. Calcd for $C_{19}H_{20}N_4O$: C 71.23, H 6.29, N 17.49. Found: C 71.45, H 6.65, N 17.45.

3-(4-Chlorophenyl)-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (5c)

From **(4c)** (0.7g); orange solid **(5c)** (0.51g, 67%). Mp 230°C. IR (KBr): ν = 3172(NH), 2970, 2923, 2880, 1611(CO), 1587, 1465, 1087, 1018, 831, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 11.4 (bs, 1H, NH), 7.19 (d, ^3J = 8.2 Hz, 2H, $H_{aromatic}$), 7.08 (d, ^3J = 8.2 Hz, 2H, $H_{aromatic}$), 6.50 (m, 2H, $H_{\alpha pyrrole}$), 6.18 (m, 2H, $H_{\beta pyrrole}$), 3.47 (m, 2H, $H_{\alpha pyrrolidine}$), 2.67 (m, 2H, $H_{\alpha pyrrolidine}$), 1.71 (m, 2H, $H_{\beta pyrrolidine}$), 1.59 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.70, 141.59, 134.62, 129.05, 128.62, 128.49, 128.25,

122.26, 111.04, 110.64, 46.99, 46.69, 26.16, 24.04. MS (EI^+) *m/z*: 340.1. Anal. Calcd for $C_{18}H_{17}N_4OCl$: C 63.44, H 5.03, N 16.44. Found: C 63.45, H 5.36, N 16.40.

3-(3-Benzyloxy-4-methoxyphenyl)-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (5d)

From **(4d)** (5g); orange solid **(5d)** (3.34g, 63%). Mp 182°C. IR (KBr): ν = 3173(NH), 2956, 2931, 2833, 1613(CO), 1455, 1254, 1014, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.5 (bs, 1H, NH), 7.30 (m, 5H, H_{phenyl}), 6.92 (dd, $^4J_{H2'H6'}$ = 1.7 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.80 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.68 (m, 3H, $H_{\alpha pyrrole}$ + $H_{2'}$), 6.27 (m, 2H, $H_{\beta pyrrole}$), 4.90 (s, 2H, CH_2Ph), 3.84 (s, 3H, OCH_3), 3.57 (m, 2H, $H_{\alpha pyrrolidine}$), 3.01 (m, 2H, $H_{\alpha pyrrolidine}$), 1.80 (m, 2H, $H_{\beta pyrrolidine}$), 1.72 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.08, 149.86, 148.18, 128.45, 128.24, 127.82, 127.76, 127.46, 122.53, 121.91, 119.51, 119.41, 111.74, 111.69, 110.13, 110.10, 70.49, 55.93, 47.20, 46.41, 26.02, 23.93. MS (EI^+) *m/z*: 442.4. Anal. Calcd for $C_{26}H_{26}N_4O_3$: C 70.57, H 5.92, N 12.66. Found: C 70.34, H 5.46, N 12.49.

Ring-closure reaction procedure:

3-(4-Methylphenyl)pyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (2b)

A solution of the carboxamide **(5b)** (400 mg, 1.25 mmol) in phosphorous oxychloride (20 mL) was stirred at 70°C for 3 h. After cooling, the reaction mixture was concentrated to give the intermediary iminium salt which was slowly added to an 10% aqueous NaOH (100 mL) and heated at 80°C for 3 h. After cooling, the resulting suspension was extracted with AcOEt (2 × 50 mL) and the combined organic layers were washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to give a dark red solid. This residue was purified by silica gel chromatography, eluting by cyclohexane:AcOEt (1:1) to furnish pyrazolopyrrolizinone **(2b)** as a red solid (10 mg, 2%). Mp 212°C. IR (KBr): ν = 3206, 2958, 2924, 2855, 1682(CO), 1626, 1600, 1469, 1366, 1262, 1161, 1062, 1012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.3 (bs, 1H, NH), 7.48 (d, ^3J = 8.1 Hz, 2H, $H_{aromatic}$), 7.35 (d, ^3J = 8.1 Hz, 2H, $H_{aromatic}$), 7.00 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H5H6}$ = 2.4 Hz, 1H, H_5), 6.81 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_7), 6.22 (dd, $^3J_{H5H6}$ = 2.4 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.43, 139.43, 132.22, 129.48, 127.32, 126.69, 123.33, 123.23, 116.71, 114.22, 114.13, 111.38, 21.35. MS (EI^+) *m/z*: 249.1. Anal. Calcd for $C_{15}H_{11}N_3O$: C 72.28, H 4.45, N 16.86. Found: C 72.43, H 4.36, N 16.85.

3-(4-Chlorophenyl)pyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (2c)

From **(5c)** (300mg); red solid **(2c)** (100mg, 42%). Mp 252°C. IR (KBr): ν = 3185(NH), 3106, 2927, 1686(CO), 1463, 1401, 1366, 1162, 1060, 825, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 13.7 (bs, 1H, NH), 7.51 (m, 4H, $H_{aromatic}$), 6.96 (d, $^3J_{H5H6}$ = 2.0 Hz, 1H, H_5), 6.79 (d, $^3J_{H6H7}$ = 3.8 Hz, 1H, H_7), 6.21 (dd, $^3J_{H5H6}$ = 2.0 Hz, $^3J_{H6H7}$ = 3.8 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.98, 143.41, 136.99, 129.25, 127.13, 126.28, 126.10, 123.70, 120.23, 114.19, 114.13, 113.57. MS (EI^+) *m/z*: 269.1. Anal. Calcd for $C_{14}H_8N_3OCl$: C 62.35, H 2.99, N 15.58. Found: C 62.48, H 3.18, N 15.70.

3-(3-Benzyloxy-4-methoxyphenyl)pyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (2d)

From **(5d)** (400mg); red solid **(2c)** (20mg, 6%). Mp 214°C. IR (KBr): ν = 3108(NH), 2923, 2852, 1704(CO), 1602, 1467, 1454, 1260, 1225, 1070, 1018 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.5 (bs, 1H, NH), 7.40, (m, 5H, $H_{aromatic}$), 7.15 (dd, $^4J_{H2'H6'}$ = 2.0 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 7.03 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.99 (d, $^4J_{H2'H6'}$ = 2.0 Hz, 1H, $H_{2'}$), 6.73 (d, $^3J_{H6H7}$ = 3.7 Hz, 1H, H_7), 6.27 (d, $^3J_{H5H6}$ = 2.2 Hz, 1H, H_5), 6.04 (dd, $^3J_{H5H6}$ = 2.2 Hz, $^3J_{H6H7}$ = 3.7 Hz, 1H, H_6), 5.28 (s, 2H, CH_2Ph), 3.98 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.26, 150.85, 148.72, 137.13, 136.61, 129.06, 128.23, 127.93, 127.56, 116.84, 120.71, 119.90, 119.64, 114.98, 114.22, 112.46, 112.09, 112.20, 71.01, 56.29. MS (EI^+) *m/z*: 371.1. Anal. Calcd for $C_{22}H_{17}N_3O_3$: C 71.15, H 4.61, N 11.31. Found: C 70.78, H 4.81, N 11.52.

3-(3-Benzyloxy-4-methoxyphenyl)-1-methylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (9)

From **(7)** (250mg); red solid **(9)** (150mg, 72%). Mp 180°C. IR (KBr): ν = 2959, 2927, 2837, 1690(CO), 1501, 1445, 1255, 1017, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 5H, H_{arom}), 7.26 (dd, $^4J_{H2'H6'}$ = 1.9 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 7.17 (d, $^4J_{H2'H6'}$ = 1.9 Hz, 1H, $H_{2'}$), 6.99 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.68 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_7), 6.44 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H5H6}$ = 2.4 Hz, 1H, H_5), 5.95 (dd, $^3J_{H5H6}$ = 2.4 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 5.25 (s, 2H, OCH_2), 3.96 (s, 3H, CH_3), 3.94 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.37, 150.10, 148.45, 138.77, 136.86, 136.24, 134.77, 133.26, 128.77, 127.96, 127.02, 123.56, 122.16, 119.83, 115.99, 113.07, 112.14, 112.07, 70.89, 56.13, 37.94. MS (EI^+) *m/z*: 385.2. Anal. Calcd for $C_{23}H_{19}N_3O_3$: C 71.68, H 4.97, N 10.90. Found: C 72.05, H 4.68, N 11.15.

3-(3-Benzyloxy-4-methoxyphenyl)-2-methylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (10)

From **(8)** (230mg); red solid **(10)** (160mg, 75%). Mp 205°C. IR (KBr): ν = 2959, 2928, 2835, 1693(CO), 1514, 1464, 1255, 1019, 821 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 6H, H_{arom} + $H_{6'}$), 7.04 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.87 (d, $^4J_{H2'H6'}$ = 1.5 Hz, 1H, $H_{2'}$), 6.68 (d, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_7), 6.23 (d, $^3J_{H5H6}$ = 2.7 Hz, 1H, H_5), 6.01 (dd, $^3J_{H5H6}$ = 2.7 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 5.27 (s, 2H, OCH_2Ph), 4.00 (s, 3H, OCH_3), 3.66 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.71, 150.77, 148.13, 138.28, 136.52, 131.40, 128.90, 126.97, 126.82, 124.44, 122.08, 119.53, 119.26, 114.46, 114.07, 113.99, 113.66, 112.13, 70.84, 56.14, 38.19. MS (EI^+) *m/z*: 385.2. Anal. Calcd for $C_{23}H_{19}N_3O_3$: C 71.68, H 4.97, N 10.90. Found: C 71.87, H 4.99, N 10.92.

3-(3-Benzyloxy-4-methoxyphenyl)-1-benzylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (15)

From **(14)** (140mg); red solid **(15)** (110mg, 85%). Mp 146°C. IR (KBr): ν = 2925, 2847, 1696(CO), 1442, 1361, 1271, 1248, 1217, 1018, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 11H, H_{arom} + $H_{6'}$), 7.16 (d, $^4J_{H2'H6'}$ = 2.0 Hz, 1H, $H_{2'}$), 6.98 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.65 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_7), 6.41 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H5H6}$ = 2.4 Hz, 1H, H_5), 5.93 (dd, $^3J_{H5H6}$ = 2.4 Hz, $^3J_{H6H7}$ =

3.9 Hz, 1H, H_6), 5.31 (s, 2H, CH_2Ph), 5.25 (s, 2H, CH_2Ph), 3.94 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.90, 150.00, 148.29, 138.07, 137.02, 136.82, 135.48, 135.01, 131.09, 130.14, 128.76, 128.40, 127.94, 126.95, 123.52, 122.13, 119.89, 115.99, 113.06, 112.18, 111.92, 109.92, 70.83, 56.09, 55.19. MS (EI^+) *m/z*: 461.2. Anal. Calcd for $C_{29}H_{23}N_3O_3$: C 75.47, H 5.02, N 9.10. Found: C 75.65, H 5.32, N 8.75.

3-(3-Benzyloxy-4-methoxyphenyl)-2-benzylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (16)

From **(14)** (100mg); red solid **(16)** (40mg, 50%). Mp 194°C. IR (KBr): ν = 3036, 2935, 2847, 1697(CO), 1522, 1458, 1256, 1203, 1021, 742, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 8H, H_{arom}), 7.05 (m, 2H, H_{arom}), 6.97 (d, $^3J_{H5'H6'}$ = 8.2 Hz, 1H, $H_{5'}$), 6.92 (dd, $^4J_{H2'H6'}$ = 1.9 Hz , $^3J_{H5'H6'}$ = 8.2 Hz, 1H, $H_{6'}$), 6.76 (d, $^4J_{H2'H6'}$ = 1.9 Hz, 1H, $H_{2'}$), 6.70 (d, $^3J_{H6H7}$ = 3.5 Hz, 1H, H_7), 6.27 (d, $^3J_{H5H6}$ = 2.5 Hz, 1H, H_5), 6.02 (dd, $^3J_{H5H6}$ = 2.5 Hz, $^3J_{H6H7}$ = 3.4 Hz, 1H, H_6), 5.16 (s, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph), 3.97 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.66, 150.60, 148.09, 147.99, 136.65, 136.38, 136.22, 131.50, 128.69, 128.64, 127.98, 127.83, 127.23, 126.99, 126.95, 126.80, 121.99, 119.43, 119.07, 113.99, 113.66, 111.87, 70.34, 55.96, 54.14. MS (EI^+) *m/z*: 461.2. Anal. Calcd for $C_{29}H_{23}N_3O_3$: C 75.47, H 5.02, N 9.10. Found: C 75.35, H 4.98, N 9.25.

Alkylation procedure :

3-(3-Benzyloxy-4-methoxyphenyl)-1-methyl-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (7) and 5-(3-Benzyloxy-4-methoxyphenyl)-1-methyl-3-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (8)

To a cooled solution of **(5d)** (750mg, 1.69 mmol) in DMF (7mL) was successively added NaH (88mg, 2.03 mmol) and MeI (97μL, 2.03 mmol). The reaction mixture was stirred at rt for 12h and diluted with water (100mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$) and evaporated to give an off-white solid. This residue was purified by silica gel chromatography, eluting by cyclohexane:AcOEt (2:1) to furnish amide **(7)** as a white solid (320mg, 41%). Mp 118°C. IR (KBr): ν = 3120, 2927, 1631(CO), 1454, 1260, 1015, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H, H_{phenyl}), 7.01 (dd, $^4J_{H2'H6'}$ = 1.9 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.86 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.80 (d, $^4J_{H2'H6'}$ = 1.9 Hz, 1H, $H_{2'}$), 6,67 (m, 2H, $H_{\alpha pyrrole}$), 6.29 (m, 2H, $H_{\beta pyrrole}$), 4.97 (s, 2H, OCH_2Ph), 4.01 (s, 3H, NCH_3), 3.89 (s, 3H, OCH_3), 3.57 (m, 2H, $H_{\alpha pyrrolidine}$), 2.84 (m, 2H, $H_{\alpha pyrrolidine}$), 1.84 (m, 2H, $H_{\beta pyrrolidine}$), 1.72 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.05, 149.72, 148.22, 144.13, 137.19, 133.77, 128.60, 127.93, 127.65, 123.77, 122.11, 119.93, 119.76, 112.27, 111.85, 110.28, 70.69, 56.12, 47.20, 45.96, 38.69, 25.87, 24.16. MS (EI^+) *m/z*: 456.2. Anal. Calcd for $C_{27}H_{28}N_4O_3$: C 71.03, H 6.18, N 12.27. Found: C 70.85, H 6.38, N 12.35; and amide **(8)** as a white solid (450mg, 58%). Mp 146°C. IR (KBr): ν = 3189, 2925, 2869, 1623(CO), 1455, 1251, 1105, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 5H, H_{phenyl}), 6.90 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.78 (dd,

$^4J_{H2'H6'}$ = 1.9 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.60 (m, 2H, $H_{\alpha pyrrole}$), 6.53 (d, $^4J_{H2'H6'}$ = 1.9 Hz, 1H, $H_{2'}$), 6.14 (m, 2H, $H_{\beta pyrrole}$), 5.00 (s, 2H, OCH_2Ph), 3.88 (s, 3H, OCH_3), 3.68 (s, 3H, NCH_3), 3.58 (m, 2H, $H_{\alpha pyrrolidine}$), 3.24 (m, 2H, $H_{\alpha pyrrolidine}$), 1.80 (m, 4H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.76, 150.37, 148.02, 141.13, 137.65, 136.69, 128.63, 127.96, 127.20, 122.42, 122.37, 120.97, 119.66, 114.90, 111.64, 109.18, 70.93, 55.94, 47.73, 45.88, 38.08, 25.96, 24.14. MS (EI^+) *m/z*: 456.2. Anal. Calcd for $C_{27}H_{28}N_4O_3$: C 71.03, H 6.18, N 12.27. Found: C 71.04, H 6.25, N 12.35.

3-(3-Benzyloxy-4-methoxyphenyl)-1-benzyl-5-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (13) and 5-(3-Benzyloxy-4-methoxyphenyl)-1-benzyl-3-(pyrrolidin-1-ylcarbonyl)-4-(1*H*-pyrrol-1-yl)-1*H*-pyrazole (14)

To a cooled solution of **5d** (250mg, 0.57 mmol) in DMF (7mL) was successively added NaH (30mg, 0.68 mmol) and benzyl bromide (81µL, 0.68 mmol). The reaction mixture was stirred at rt for 12h and diluted with water (100mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($MgSO_4$) and evaporated to give an off-white solid. This residue was purified by silica gel chromatography, eluting by cyclohexane:EtOAc (3:2) to furnish amide **(13)** as a yellow solid (140mg, 46%). Mp 152°C. IR (KBr): ν = 2964, 2929, 2876, 1633(CO), 1455, 1436, 1259, 1220, 1133, 1025, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 10H, H_{arom}), 7.04 (dd, $^4J_{H2'H6'}$ = 2.0 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.84 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6,82 (d, $^4J_{H2'H6'}$ = 2.0 Hz, 1H, $H_{2'}$), 6.63 (m, 2H, $H_{\alpha pyrrole}$), 6.23 (m, 2H, $H_{\beta pyrrole}$), 5.47 (s, 2H, NCH_2Ph), 4.96 (s, 2H, OCH_2Ph), 3.87 (s, 3H, OCH_3), 3.31 (m, 2H, $H_{\alpha pyrrolidine}$), 2.38 (m, 2H, $H_{\alpha pyrrolidine}$), 1.63 (m, 2H, $H_{\beta pyrrolidine}$), 1.29 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.00, 149.53, 148.02, 143.55, 137.03, 136.61, 133.39, 128.56, 128.42, 128.22, 128.07, 127.75, 127.49, 123.65, 121.90, 120.14, 119.81, 112.15, 111. 63, 109.96, 70.56, 55.94, 55.19, 46.72, 45.33, 25.14, 23.87. MS (EI^+) *m/z*: 532.2. Anal. Calcd for $C_{33}H_{32}N_4O_3$: C 74.41, H 6.06, N 10.52. Found: C 74.35, H 5.97, N 10.76.; and amide **(14)** as a yellow solid (100mg, 34%). Mp 142°C. IR (KBr): ν = 2961, 2920, 2869, 1631(CO), 1526, 1449, 1251, 1136, 1016, 759, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 8H, H_{arom}), 7.04 (m, 2H, H_{arom}), 6.90 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.65 (dd, $^4J_{H2'H6'}$ = 2.0 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.64 (m, 2H, $H_{\alpha pyrrole}$), 6.46 (d, $^4J_{H2'H6'}$ = 2.0 Hz, 1H, $H_{2'}$), 6.12 (m, 2H, $H_{\beta pyrrole}$), 5.20 (s, 2H, NCH_2Ph), 4.81 (s, 2H, OCH_2Ph), 3.87 (s, 3H, OCH_3), 3.59 (m, 2H, $H_{\alpha pyrrolidine}$), 3.35 (m, 2H, $H_{\alpha pyrrolidine}$), 1.84 (m, 2H, $H_{\beta pyrrolidine}$), 1.61 (m, 2H, $H_{\beta pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.99, 150.63, 148.11, 141.60, 137.00, 135.17, 128.91, 128.73, 128.09, 127.39, 127.38, 127.09, 124.49, 122.74, 114.89, 113.15, 111.76, 109.25, 109.21, 109.19, 70.78, 56.05, 53.77, 48.14, 46.16, 27.28, 26.21. MS (EI^+) *m/z*: 532.2. Anal. Calcd for $C_{33}H_{32}N_4O_3$: C 74.41, H 6.06, N 10.52. Found: C 74.33, H 6.24, N 10.52.

***O*-Deprotection procedure :**

3-(3-Hydroxy-4-methoxyphenyl)-1-methylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (11)

A solution of the tripentone **(9)** (50mg, 0.13 mmol) in a 33% solution of HBr in AcOH (10 mL) was stirred at rt for 1 h. 50mL of ice-water mixture were then added and the mixture stirred for 1h. The resulting suspension was extracted with AcOEt (2 × 50 mL) and the combined organic layers were washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated. The resulting product was solved in a mixture of MeOH (10mL) and 1N NaOH (10mL) and stirred at rt for 1h. The reaction mixture was then concentrated under vacuum, acidified using 1N HCl and extracted with AcOEt (2 × 50 mL). The combined organic layers were washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to give a dark red solid. This residue was purified by silica gel chromatography, eluting by cyclohexane:AcOEt (1:1) to furnish pyrazolopyrrolizinone **(11)** as a red solid (40 mg, 99%). Mp 130°C. IR (KBr): ν = 3392(OH), 3118, 2935, 1683(CO), 1487, 1436, 1261, 1133, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (dd, $^4J_{H5H7}$ = 1.6 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_7), 6.85 (d, $^4J_{H2'H6'}$ = 2.1 Hz, 1H, $H_{2'}$), 6.84 (dd, $^4J_{H5H7}$ = 1.6 Hz, $^3J_{H5H6}$ = 2.7 Hz, 1H, H_5), 6.69 (d, $^3J_{H5'H6'}$ = 8.5 Hz, 1H, $H_{5'}$), 6.60 (dd, $^4J_{H2'H6'}$ = 2.1 Hz, $^3J_{H5'H6'}$ = 8.5 Hz, 1H, $H_{6'}$), 6.30 (dd, $^3J_{H5H6}$ = 2.7 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 5.0 (bl, $1H_{deutérable}$, OH), 3.96 (s, 3H, CH_3), 3,83 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.64, 146.95, 146.12, 145.88, 130.40, 128.91, 125.18, 124.75, 120.12, 118.79, 117.71, 113.26, 110.97, 109.29, 55.81, 39.47. MS (EI^+) *m/z*: 295.3. Anal. Calcd for $C_{16}H_{13}N_3O_3$: C 65.08, H 4.44, N 14.23. Found: C 65.24, H 4.65, N 14.01.

3-(3-Hydroxy-4-methoxyphenyl)-2-methylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (12)

From **(10)** (70mg); red solid **(12)** (30mg, 53%). Mp 126°C. IR (KBr): ν = 3240(OH), 3115, 2943, 2840, 1698(CO), 1489, 1457, 1276, 1224, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, $^4J_{H5H7}$ = 1.6 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_7), 6.79 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.75 (m, 2H, H_5 + $H_{2'}$), 6.62 (dd, $^4J_{H2'H6'}$ = 2.1 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.17 (dd, $^3J_{H5H6}$ = 2.7 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 3.87 (s, 3H, CH_3), 3.85 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.26, 147.19, 145.66, 138.94, 135.90, 131.79, 124.53, 123.33, 121.36, 120.99, 120.15, 115.2, 110.75, 109.39, 55.88, 37.91. MS (EI^+) *m/z*: 295.2. Anal. Calcd for $C_{16}H_{13}N_3O_3$: C 65.08, H 4.44, N 14.23. Found: C 65.09, H 4.46, N 14.42.

3-(3-Hydroxy-4-methoxyphenyl)-1-benzylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (17)

From **(15)** (100mg); red solid **(17)** (30mg, 30%). Mp 178°C. IR (KBr): ν = 3448(OH), 2963, 2926, 2855, 1686(CO), 1457, 1435, 1269, 1123, 1021, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 2H, H_{arom}), 7.30 (m, 4H, H_{arom} + $H_{2'}$), 7.17 (dd, $^4J_{H2'H6'}$ = 1.9 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 7.00 (d, $^3J_{H5H6}$ = 2.4 Hz, 1H, H_5), 6.90 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.68 (d, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_5), 6.04 (dd, $^3J_{H5H6}$ = 2.4 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 5.7 (bs, 1H, OH), 5.30 (s, 2H, NCH_2Ph), 3.92 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.35, 147.03, 146.16, 138.20, 136.44, 135.61, 135.11, 131.01, 128.89, 128.56, 128.53, 124.38, 122.40, 118.68, 116.16, 113.08, 112.96, 111.01, 56.15, 55.35. MS (EI^+) *m/z*: 371.2. Anal. Calcd for $C_{22}H_{17}N_3O_3$: C 71.15, H 4.61, N 11.31. Found: C 71.05, H 4.72, N 11.46.

3-(3-Hydroxy-4-methoxyphenyl)-2-benzylpyrazolo[3,4-*b*]pyrrolizin-8(1*H*)-one (18)

From **(16)** (40mg); red solid **(18)** (30mg, 30%). Mp 178°C. IR (KBr): ν = 3448(OH), 2963, 2926, 2855, 1686(CO), 1457, 1435, 1269, 1123, 1021, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 3H, H_{arom}), 7.11 (m, 2H, H_{arom}), 6.95 (d, $^4J_{H2'H6'}$ = 2.2 Hz, 1H, $H_{2'}$), 6.93 (d, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{5'}$), 6.85 (dd, $^4J_{H2'H6'}$ = 2.2 Hz, $^3J_{H5'H6'}$ = 8.3 Hz, 1H, $H_{6'}$), 6.73 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H5H7}$ = 3.6 Hz, 1H, H_7), 6.67 (dd, $^4J_{H5H7}$ = 0.7 Hz, $^3J_{H6H5}$ = 2.4 Hz, 1H, H_5), 6.10 (dd, $^3J_{H5H6}$ = 2.4 Hz, $^3J_{H6H7}$ = 3.9 Hz, 1H, H_6), 5.8 (bs, 1H, OH), 5.28 (s, 2H, NCH_2Ph), 3.96 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.38, 148.18, 146.81, 137.35, 136.83, 129.24, 129.09, 128.49, 127.75, 127.65, 127.52, 121.62, 120.58, 120.16, 115.45, 114.69, 114.24, 111.62, 56.59, 54.79. MS (EI^+) *m/z*: 371.2. Anal. Calcd for $C_{22}H_{17}N_3O_3$: C 71.15, H 4.61, N 11.31. Found: C 71.35, H 4.83, N 11.52.

X-Ray Crystallography. Suitable crystals of the title compounds were obtained by slow evaporation from methylene chloride/methanol (v/v) at room temperature, and they were mounted on a glass fiber. Diffraction data were collected on an Enraf-Nonius CAD4 diffractometer with Mo Kα radiation (λ) 0.710 73 Å) at room temperature. Data were measured using θ-2θ scan. The data treatment, polarization and decay corrections, was carried out with JANA98 program.[14] The crystal structure was solved by direct methods using the SHELX97 package.[15] All nonhydrogen atoms were refined anisotropically.

ACKNOWLEDGEMENTS

We thank the Société de Chimie Thérapeutique and Les Laboratoires Servier for a doctoral grant to Ch. R. and Mr. Dat for the NMR experiment.

REFERENCES

1. V. Lisowski, S. Leonce, L. Kraus-Berthier, J. Sopkova-de Oliveira Santos, A. Pierré, G. Atassi, D.-H. Caignard, P. Renard, and S. Rault, *J. Med. Chem.*, 2004, **47**, 1448.
2. C. Rochais, V. Lisowski, P. Dallemagne, and S. Rault, *Tetrahedron Lett.*, 2004, **45**, 6353.
3. V. Lisowski, D.N. Vu, X. Feng, and S. Rault, *Synthesis*, 2002, **6**, 753.
4. For recent examples see: a) M. Liu, Z. Xin, J. E. Clampit, S. Wang, R. J. Gum, D. L. Haasch, J. M. Trevillyan, C. Abad-Zapatero, E. H. Fry, H. L. Sham, and G. Liu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2590. b) F. Chimenti, A. Bolasco, F. Manna, D. Secci, P. Chimenti, A. Granese, B. O. Befani, P. Turini, R. Cirilli, T. F. La, S. Alcaro, F. Ortuso, T. Langer, and F. L. Torre, *Current Medicinal Chemistry*, 2006, **13**, 1411. c) G. Murineddu, S. Ruiu, G. Loriga, I. Manca, P. Lazzari, R. Reali, L. Pani, L. Toma, and G. A. Pinna, *J. Med. Chem.*, 2005, **48**, 7351.

5. G. Tarzia, G. Panzone, A. De Paoli, P. Schiatti, and D. Selva, *Il Farmaco – Ed. Sc.*, 1984, **39**, 618.
6. T. Majid, C. R. Hopkins, B. Pedgrift, and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 2137.
7. V. Lisowski, C. Enguehard, J. C. Lancelot, D.-H. Caignard, S. Lambel, S. Leonce, A. Pierré, G. Atassi, P. Renard, and S. Rault, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2205.
8. N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, 1952, **6**, 667.
9. I. Cardinaud, A. Gueiffier, J. C. Debouzy, J. C. Milhavet, and J. P. Chapat, *Heterocycles*, 1993, **36**, 2513.
10. J. Ichikawa, M. Kobayashi, Y. Noda, N. Yokota, K. Amano, and T. Minami, *J. Org. Chem.*, 1996, **61**, 2763.
11. D. S. Fischer, G. M. Allan, C. Bubert, N. Vicker, A. Smith, H. J. Tutill, A. Purohit, L. Wood, G. Packham, M. F. Mahon, M. J. Reed, and B.V. L. Potter, *J. Med. Chem.*, 2005, **48**, 5749.
12. N. Fugina, W. Holzer, and M. Wasicky, *Heterocycles*, 1992, **34**, 303.
13. F. Gellibert, A. C. de Gouville, J. Woolven, N. Mathews, V. L. Nguyen, C. Bertho-Ruault, A. Patikis, E. T. Grygielko, N. J. Laping, and S. Huet, *J. Med. Chem.*, 2006, **49**, 2210.
14. V. Petricek and M. Dusek, *JANA98*; Institute of Physics, Academy of Sciences of the Czech Republic: Praha. Czech Republic, 1998.
15. G. M. Sheldrick, *Acta Crystallogr*., 1990, **A46**, 467.