Monatshefte für Chemie 136, 217–227 (2005)
DOI 10.1007/s00706-004-0234-2

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Pyrazoles and Pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazines, I. Synthesis and Antimicrobial Activity

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Received May 18, 2004; accepted (revised) June 16, 2004
Published online October 8, 2004 © Springer-Verlag 2004

Summary. The synthesis of the title compounds was achieved using 1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-3-carboxylic acid azide as starting material. The latter compound was allowed to react with alcohols and amines to afford the corresponding carbamates and urea derivatives. Alkaline hydrolysis of the carbamates gave the corresponding amine, which was acylated and/or aroylated to give amide derivatives. These and the urea derivatives were subjected to cyclodehydration to give the title compounds. Antibacterial and antifungal activities were observed for several derivatives.

Keywords. Pyrazoles; Pyrrolylpyrazoles; Pyrazolopyrazines; Pyrazolopyrrolopyrazines.

Introduction

1-Phenyl-1*H*-pyrazolo[3,4-*b*]pyrazines have been reported to possess antiviral, antineoplastic, antifungal, and antiparasitic activities [1–4]. Also other compounds of related structure have been prepared for pharmacological evaluation [5]. Furthermore, some tricyclic systems containing the pyrazole moiety with a bridgehead nitrogen atom have been extensively studied owing to their interesting biological and pharmacological activities [6, 7]. In view of these findings and in continuation of our program directed towards the synthesis of new pyrazolopyrazines [3, 4] and other fused pyrazines [8–12] we report herein the synthesis and antimicrobial activities of some new pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazines and related heterocycles.

Results and Discussion

The synthesis of the acid azide **2** has been reported earlier [2, 13]. We have prepared the same azide by treating the carbohydrazide **1** with nitrous acid. Heating

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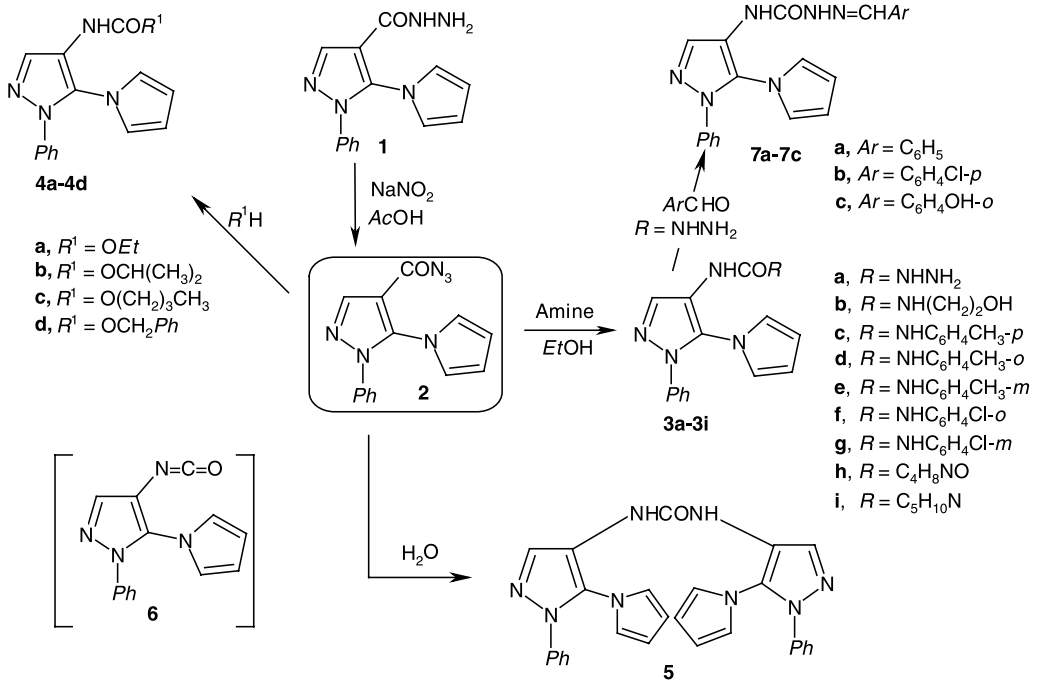
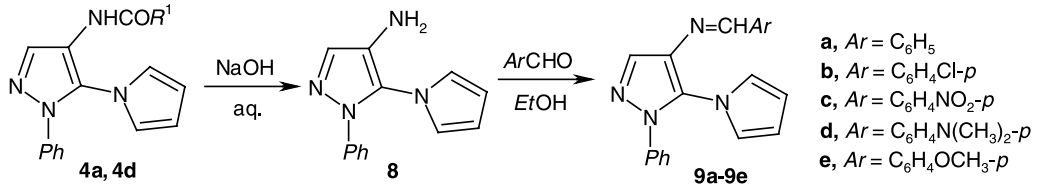


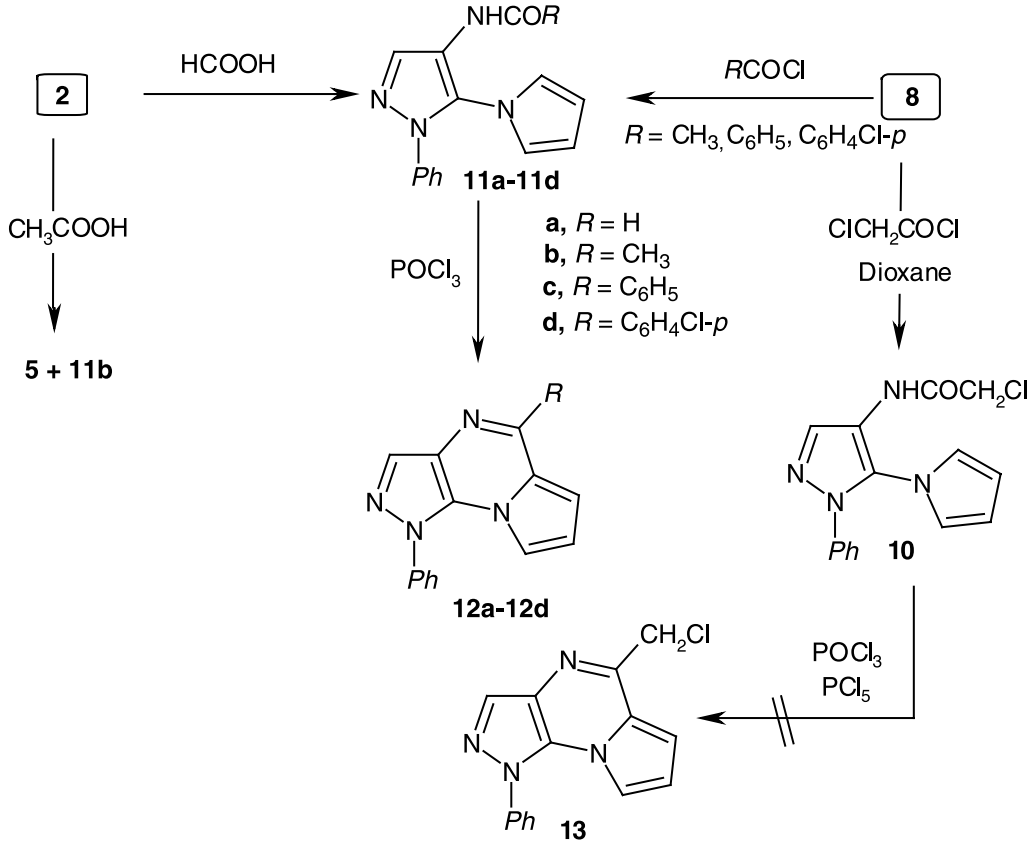
Scheme 1

this azide in boiling benzene in the presence of aliphatic or aromatic amines gave the corresponding urea derivatives **3b**–**3i**. When hydrazine hydrate was used in the former reaction the semicarbazide derivative **3a** was obtained. However, when **2** was allowed to decompose in refluxing alcohols the corresponding carbamates **4a**–**4d** resulted. The product of its decomposition in boiling water was identified as the symmetrical urea **5** (Scheme 1). It is obvious that the formation of the above-mentioned compounds **3**–**5** occurred *via* the isocyanate key intermediate **6**, which was formed *in situ* by *Curtius* rearrangement of the acid azide **2**. Several semicarbazones **7a**–**7c** were obtained from the reaction of the semicarbazide **3a** with aromatic aldehydes. On the other hand, the alkaline hydrolysis of the carbamates, *e.g.* **4a** and **4d**, led to the amine **8**, which gave the corresponding anils **9a**–**9e** through its interaction with aromatic aldehydes (Scheme 2).

The formamido derivative **11a** was obtained by reaction of **2** with formic acid (Scheme 3). It is worthy to note that when **2** was heated in boiling acetic acid, two

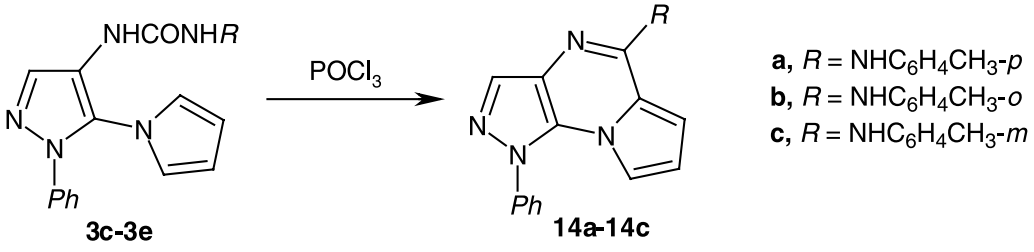


Scheme 2



Scheme 3

products were formed; the expected acetamido derivative **11b** and **5**. The formation of the latter resulted from a trace of water present in acetic acid. Alternatively, **11b**, **11c**, and **11d** were obtained by the reaction of acyl- or aroylchloride with **8** in pyridine at room temperature. The chloroacetyl derivative **10** was obtained upon treating **8** with chloroacetyl chloride in boiling dioxane. The target pyrazolo [4,3-*e*]pyrrolo[1,2-*a*]pyrazines **12a**–**12d** were obtained upon cyclodehydration of the **11a**–**11d** in boiling $POCl_3$. However, all attempts to ring close **10** into **13** using phosphoryl chloride alone or admixed with phosphorus trichoride were unsuccessful. Moreover, other pyrazine derivatives **14a**–**14c** (Scheme 4) bearing substituted



Scheme 4

anilino groups in position 5 as potential adenosine receptor antagonist candidates could be obtained by cyclodehydration reaction of **3c**–**3e** in boiling $POCl_3$.

Antibacterial and Antifungal Activities

Some of the prepared compounds were screened for the *in-vitro* antibacterial activity against four species of bacteria: *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, and *Pseudomonas aeruginosa* as well as eight fungi species: *Penicillium chrysogenum* AUMC 530-15, *Aspergillus* flavus AUMC 164-5, *Aspergillus fumigatus* AUMC 170-3, *Aspergillus* ochraceus AUMC 230-2, *Aspergillus niger* AUMC 210-1, *Curvulana lunata* AUMC 2310-1, *Fusarium solani* AUMC 2690-6, and *Trichothecium roseum* AUMC 7410-2.

In the series **3a**–**3i**, only the 3-chloro derivative **3g** was found to be active. It showed a strong activity (+++) against *B. cereus* and (++) *S. aureus*, a moderate activity (+) against *Escherichia coli* whereas all the remainder of this series showed no activity against both bacteria and fungi. On the other hand, **7d** exhibited a moderate to weak activity against four species of fungi; *P. chrysogenum*, *A. niger*, *C. lunala*, and *F. solani* with inhibition zones of 12, 8, 17, 9 mm. Also it showed activity (++) against the *Gram*-negative bacterium *B. cereus*.

Furthermore, the compound that showed a wide spectrum of activity against bacteria and fungi was found to be the methyl pyrazine derivative **12a**. Except against *T. roseum*, **12a** showed a moderate to weak activity against all the other tested fungal species *P. chrysogenum*, *A.* falvus, *A. fumigatus*, *A.* ochracus, *A. niger*, *C. lunala*, and *F. solani*, with inhibition zones 15, 8, 7, 12, 8, 12, 7 mm. Compound **12b** showed a strong activity (++) against *E. coli* and *B. cereus* and a moderate activity (+) against *S. aureus*. When the 5-methyl group of **12b** was substituted by aryls, no activity was observed.

Experimental

All melting points were determined on a *Kofler* melting point apparatus. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a Varian EM 390, 90 MHz spectrometer (*TMS* as internal reference, δ values in ppm). Mass spectra were obtained with a Shimadzu QP5050 DI 50 spectrometer. Elemental analyses were carried out using a Perkin-Elmer 240 C Micro analyzer; the results were in satisfactory agreement with the calculated values. Starting materials were commercially available. Solvents were distilled and dried before use. 1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbohydrazide (**1**) was prepared as described earlier [2].

1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazole-4-carboazide (**2**) [2]

To a suspension of 5.30 g of **1** (20 mmol) in 50 cm^3 of glacial acetic acid, a cold solution of 3.30 g of $NaNO_2$ (10 cm^3, 33%) was added dropwise with stirring at rt. After completion of the addition, stirring was continued for 1 h. The solid precipitate obtained was filtered off, washed with H_2O, dried by suction, and used in the next reaction without purification. Yield 5.22 g (95%) of yellow powder of **2**; mp (decomp) 102–104°C [2]; IR (KBr): $\bar{\nu} = 2120$ (CON_3), 1680 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 6.25$ (m, H3,4$_{pyrrole}$), 6.65 (m, H2,5$_{pyrrole}$), 7.10 (m, 2H$_{arom}$), 7.27 (m, 3H$_{arom}$), 8.10 (s, 1H$_{pyrazole}$) ppm.

Reaction of **2** *with Hydrazine Hydrate and Amines (General Procedure)*

A mixture of 0.278 g of **2** (1 mmol) and hydrazine hydrate or the appropriate amine (1 mmol) in 10 cm^3 of dry benzene was heated under reflux for 1 h. Then the reaction mixture was concentrated and the solid product formed was filtered off and recrystallized from the solvent indicated below to give **3a** or **3b**–**3i**.

4-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)semicarbazide (**3a**, $C_{14}H_{14}N_6O$)

Buff crystals; mp 194–196°C (ethanol); yield 0.24 g (85%); IR (KBr): $\bar{\nu} = 3300$, 3100 (NH and $NHNH_2$), 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.63$ (s, br, NH_2), 6.40 (m, H3,$4_{pyrrole}$), 6.60 (s, NH), 6.73 (m, H2,$5_{pyrrole}$), 7.10 (m, $2H_{arom}$), 7.23 (m, $3H_{arom}$), 8.20 (s, $1H_{pyrazole}$) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(2-hydroxyethyl)urea (**3b**, $C_{16}H_{17}N_5O_2$)

White plates; mp 142–144°C (ethanol); yield 0.25 g (80%); IR (KBr): $\bar{\nu} = 3420$–3100 (OH and NH), 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.57$ (s, NH), 3.53 (m, $2CH_2$), 5.67 (s, OH), 6.37 (m, H3,$4_{pyrrole}$), 6.72 (m, H2,$5_{pyrrole}$), 7.13 (m, $2H_{arom}$), 7.30 (m, $3H_{arom}$), 8.17 (s, $1H_{pyrazole}$), 8.32 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(p-tolyl)urea (**3c**, $C_{21}H_{19}N_5O$)

White crystals; mp 215–217°C (ethanol); yield 0.29 g (81%); IR (KBr): $\bar{\nu} = 3300$ (NH), 1650 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.23$ (s, CH_3), 6.30 (m, H3,$4_{pyrrole}$), 6.88 (m, H2,$5_{pyrrole}$), 7.03 (m, $4H_{arom}$), 7.27 (m, $5H_{arom}$), 7.80 (s, NH), 8.11 (s, $1H_{pyrazole}$), 8.67 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(o-tolyl)urea (**3d**, $C_{21}H_{19}N_5O$)

Yellowish buff needles; mp 225–227°C (ethanol); yield 0.25 g (70%); IR (KBr): $\bar{\nu} = 3300$ (NH), 1640 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.22$ (s, CH_3), 6.33 (m, H3,$4_{pyrrole}$), 6.91 (m, H2,$5_{pyrrole}$), 7.07 (m, $4H_{arom}$), 7.30 (m, $5H_{arom}$), 7.80 (s, NH), 8.17 (s, $1H_{pyrazole}$), 8.33 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(m-tolyl)urea (**3e**, $C_{21}H_{19}N_5O$)

White crystals; mp 198–200°C (ethanol:$H_2O = 3:1$); yield 0.27 g (76%); IR (KBr): $\bar{\nu} = 3320$ and 3250 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.28$ (s, CH_3), 6.30 (m, H3,$4_{pyrrole}$), 6.88 (m, H2,$5_{pyrrole}$), 7.17 (m, $9H_{arom}$), 7.87 (s, NH), 8.17 (s, $1H_{pyrazole}$), 8.80 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(2-chlorophenyl)urea (**3f**, $C_{20}H_{16}N_5OCl$)

Yellowish buff crystals; mp 214–116°C (ethanol); yield 0.30 g (80%); IR (KBr): $\bar{\nu} = 3350$ and 3280 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.30$ (m, H3,$4_{pyrrole}$), 6.90 (m, H2,$5_{pyrrole}$), 7.03 (m, $4H_{arom}$), 7.33 (m, $5H_{arom}$), 8.20 (s, $1H_{pyrazole}$), 8.60 (s, NH), 8.77 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(3-chlorophenyl)urea (**3g**, $C_{20}H_{16}N_5OCl$)

Buff fluffy crystals; mp 105–108°C (ethanol); yield 0.32 g (85%); IR (KBr): $\bar{\nu} = 3350$ and 3280 (NH), 1640 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.27$ (m, H3,$4_{pyrrole}$), 6.86 (m, H2,$5_{pyrrole}$), 6.96 (m, $4H_{arom}$), 7.23 (m, $5H_{arom}$), 7.93 (s, NH), 8.07 (s, $1H_{pyrazole}$), 9.00 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(morpholin-4-yl)urea (**3h**, $C_{18}H_{19}N_5O_2$)

Buff crystals; mp 150–152°C (ethanol); yield 0.26 g (77%); IR (KBr): $\bar{\nu} = 3450$ (NH), 1620 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.47$ (m, $4CH_2$), 6.30 (m, H3,$4_{pyrrole}$), 6.67 (m, H2,$5_{pyrrole}$), 7.13 (m, $2H_{arom}$), 7.33 (m, $3H_{arom}$), 7.87 (s, $1H_{pyrazole}$), 9.30 (s, NH) ppm.

1-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-3-(piperidin-1-yl)urea (**3i**, $C_{19}H_{21}N_5O$)

White crystals; mp 142–144°C (ethanol); yield 0.30 g (90%); IR (KBr): $\bar{\nu} = 3450$ (NH), 1620 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.40$ (m, $3CH_2$), 3.37 (m, $2CH_2$), 6.27 (m, H3,$4_{pyrrole}$), 6.67 (m, H2,$5_{pyrrole}$), 7.17 (m, $2H_{arom}$), 7.33 (m, $3H_{arom}$), 7.87 (s, $1H_{pyrazole}$), 9.28 (s, NH) ppm.

Alkyl N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)carbamates (General Procedure)

A solution of 0.556 g of **2** (2 mmol) in 5 cm^3 of ethanol, 2-propanol, *n*-butanol, or benzyl alcohol was heated under reflux for 2 h. The reaction mixture was concentrated and allowed to cool. The residue obtained was triturated with ethanol. The solid product formed was filtered off and recrystallized from the same alcohol used to give **4a**–**4d**.

Ethyl N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)carbamate (**4a**)

Fluffy buff crystals; mp 126–128°C (ethanol, Ref. [2] 134–135°C); yield 0.55 g (93%, Ref. [2] 85%); IR (KBr): $\bar{\nu} = 3250$ (NH), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.26$ (t, $J = 7.5$ Hz, $CH_2C\underline{H}_3$), 4.16 (q, $J = 7.5$ Hz, $C\underline{H}_2CH_3$), 6.23 (s, NH), 6.30 (m, H3,$4_{pyrrole}$), 6.63 (m, H2,$5_{pyrrole}$), 7.11 (m, $2H_{arom}$), 7.23 (m, $3H_{arom}$), 8.03 (s, $1H_{pyrazole}$) ppm.

Prop-2-yl N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)carbamate (**4b**, $C_{17}H_{18}N_4O_2$)

Buff crystals; mp 120–122°C (isopropanol); yield 0.40 g (65%); IR (KBr): $\bar{\nu} = 3250$ (NH), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.27$ (m, $2CH_3$), 4.87 (m, $COOC\underline{H}$), 6.03 (s, NH), 6.27 (m, H3,$4_{pyrrole}$), 6.60 (m, H2,$5_{pyrrole}$), 6.97 (m, $2H_{arom}$), 7.17 (m, $3H_{arom}$), 8.00 (s, $1H_{pyrazole}$) ppm.

Butyl N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)carbamate (**4c**, $C_{18}H_{20}N_4O_2$)

Buff needles; mp 94–96°C (*n*-butanol); yield 0.50 g (77%); IR (KBr): $\bar{\nu} = 3280$ (NH), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.97$ (t, $J = 7.0$ Hz, CH_3), 1.45 (m, $2CH_2$), 4.12 (t, $J = 6.9$ Hz, $COOC\underline{H}_2$), 6.17 (s, NH), 6.30 (m, H3,$4_{pyrrole}$), 6.63 (m, H2,$5_{pyrrole}$), 7.03 (m, $2H_{arom}$), 7.20 (m, $3H_{arom}$), 8.03 (s, $1H_{pyrazole}$) ppm.

Benzyl N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)carbamate (**4d**, $C_{21}H_{18}N_4O_2$)

Buff crystals; mp 133–135°C (ethanol); yield 0.54 g (75%); IR (KBr): $\bar{\nu} = 3280$ (NH), 1700 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 5.13$ (m, CH_2), 6.17 (s, NH), 6.27 (m, H3,$4_{pyrrole}$), 6.57 (m, 2H, H2,$5_{pyrrole}$), 7.00 (m, $2H_{arom}$), 7.16 (m, $3H_{arom}$), 7.30 (m, $5H_{arom}$), 8.03 (s, $1H_{pyrazole}$) ppm.

1,3-Bis-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)urea (**5**, $C_{27}H_{22}N_8O$)

A suspension of 0.55 g of **2** (2 mmol) in 20 cm^3 of H_2O was refluxed for 3 h. After cooling, the product formed was filtered off and recrystallized from ethanol:dioxane (1:1) to afford 0.40 g (84%) of **5** as buff crystals; mp 255–257°C; IR (KBr): $\bar{\nu} = 3380$, 3100 (NH), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 6.30$ (m, H3,$4_{pyrrole}$), 6.87 (m, H2,$5_{pyrrole}$), 7.03 (m, $2H_{arom}$), 7.30 (m, $3H_{arom}$), 8.13 (s,

$1H_{pyrazole}$), 8.22 (s, 1H, NH) ppm; MS: m/z (%) = 474 [M^+] (96), 369 (56), 301 (36), 224 (21), 169 (51), 128 (28), 111 (25), 104 (100), 103 (57), 79 (40), 67 (30), 62 (19), 51 (42).

1-Arylidene-4-(1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)semicarbazide (General Procedure)

A mixture of 0.282 g of **3a** (1 mmol) and the appropriate aromatic aldehyde (1 mmol) in 10 cm^3 of absolute ethanol was heated under reflux for 4 h. The reaction mixture was concentrated and left to cool. After cooling, the solid product formed was filtered off and recrystallized from the solvent indicated to give **7a**–**7c**.

1-Benzylidene-4-(1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)semicarbazide (**7a**, $C_{21}H_{18}N_6O$)

Yellow needles; mp 223–225°C (ethanol); yield 0.28 g (75%); IR (KBr): $\bar{\nu}$ = 3350 (NH), 3250 (NH), 1650 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.17 (m, H3,$4_{pyrrole}$), 6.83 (m, H2,$5_{pyrrole}$), 7.40 (m, $10H_{arom}$), 8.30 (s, NH), 8.37 (s, $2H_{pyrazole}$ + N=CH), 11.63 (s, NH) ppm.

1-(4-Chlorobenzylidene)-4-(1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)semicarbazide
(**7b**, $C_{21}H_{17}N_6OCl$)

Buff crystals; mp 218–220°C (methanol); yield 0.34 g (84%); IR (KBr): $\bar{\nu}$ = 3300 (NH), 3180 (NH), 1640 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.16 (m, H3,$4_{pyrrole}$), 6.86 (m, H2,$5_{pyrrole}$), 7.52 (m, $9H_{arom}$), 8.30 (s, NH), 8.34 (s, $1H_{pyrazole}$), 8.72 (s, N=CH), 11.63 (s, NH) ppm.

1-(2-Hydroxybenzylidene)-4-(1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)semicarbazide
(**7c**, $C_{21}H_{17}N_6O_2$)

White crystals; mp 213–215°C (ethanol); yield 0.35 g (91%); IR (KBr): $\bar{\nu}$ = 3300 (NH), 3100 (NH), 1670 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.05 (m, H3,$4_{pyrrole}$), 6.90 (m, H2,$5_{pyrrole}$ + $2H_{arom}$), 7.20 (m, $2H_{arom}$), 7.38 (m, $5H_{arom}$), 8.32 (s, NH), 8.38 (s, $1H_{pyrazole}$), 8.53 (s, N=CH), 11.03 (s, OH), 11.66 (s, NH) ppm.

1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (**8**, $C_{13}H_{12}N_4$)

A mixture of **4a** or **4d** (1 mmol) and 15 cm^3 of aqueous ethanolic NaOH (20%) was heated under reflux for 48 h. The solvent was evaporated and the residue was triturated with H_2O. The solid product obtained was filtered off and recrystallized from ethanol to afford 0.17 g (75%) or 0.204 g (90%) of **8** as yellow crystals; mp 140–142°C (Ref. [2] 144–145°C).

N-Arylidene-1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (General Procedure)

A mixture of 0.224 g of **8** (1 mmol) and the appropriate aromatic aldehyde (1 mmol) in 10 cm^3 of absolute ethanol was heated under reflux in presence of two drops of piperidine for 3 h, then the reaction mixture was concentrated. After cooling, the solid product formed was collected by filtration and recrystallized from the proper solvent to give the corresponding derivatives **9a**–**9e**.

N-Benzylidene-1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (**9a**, $C_{20}H_{16}N_4$)

Pale yellow crystals; mp 171–173°C (ethanol); yield 0.17 g (55%); IR (KBr): $\bar{\nu}$ = 1610 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): δ = 6.27 (m, H3,$4_{pyrrole}$), 6.85 (m, H2,$5_{pyrrole}$), 7.13 (m, $3H_{arom}$), 7.40 (m, $5H_{arom}$), 7.73 (m, $2H_{arom}$), 8.23 (s, $1H_{pyrazole}$), 8.77 (s, N=CH) ppm.

N-(4-Chlorobenzylidene)-1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (**9b**, $C_{20}H_{15}N_4Cl$)

Yellowish white crystals; mp 176–178°C (benzene:dioxane = 2:1); yield 0.21 g (61%); IR (KBr): $\bar{\nu} = 1620$ (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.27$ (m, H3,$4_{pyrrole}$), 6.90 (m, H2,$5_{pyrrole}$), 7.17 (m, $2H_{arom}$), 7.40 (m, $3H_{arom}$), 7.56 (d, $J = 8.9$ Hz, $2H_{arom}$), 7.83 (d, $J = 8.9$ Hz, $2H_{arom}$), 8.26 (s, $1H_{pyrazole}$), 8.83 (s, N=CH) ppm.

N-(4-Nitrobenzylidene)-1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (**9c**, $C_{20}H_{15}N_4Cl$)

Yellow crystals; mp 192–194°C (ethanol); yield 0.12 g (34%); IR (KBr): $\bar{\nu} = 1610$ (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.30$ (m, H3,$4_{pyrrole}$), 6.90 (m, H2,$5_{pyrrole}$), 7.16 (m, $2H_{arom}$), 7.43 (m, $3H_{arom}$), 8.03 (d, $J = 9$ Hz, $2H_{arom}$), 8.35 (s, $1H_{pyrazole}$), 8.36 (d, $J = 9$ Hz, $2H_{arom}$), 9.01 (s, N=CH) ppm.

N-[4-(Dimethylamino)benzylidene]-1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (**9d**, $C_{22}H_{21}N_5$)

Yellow needles; mp 182–184°C (ethanol); yield 0.153 g (43%); IR (KBr): $\bar{\nu} = 1600$ (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.03$ (s, $2CH_3$), 6.30 (m, H3,$4_{pyrrole}$), 6.67 (d, $2H_{arom}$), 6.73 (m, H2,$5_{pyrrole}$), 7.23 (m, $5H_{arom}$), 7.67 (m, $2H_{arom}$), 7.87 (s, $1H_{pyrazole}$), 8.36 (s, N=CH) ppm.

N-(4-Methoxybenzylidene)-1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-ylamine (**9e**, $C_{21}H_{18}N_4O$)

Yellow crystals; mp 147–150°C (benzene:ethanol = 1:1); yield 0.25 g (73%); IR (KBr): $\bar{\nu} = 1610$ (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.83$ (s, CH_3), 6.30 (m, H3,$4_{pyrrole}$), 6.76 (m, H2,$5_{pyrrole}$), 6.91 (d, $2H_{arom}$), 7.25 (m, $5H_{arom}$), 7.73 (m, $2H_{arom}$), 7.90 (s, $1H_{pyrazole}$), 8.43 (s, N=CH) ppm.

2-Chloro-N-(1-phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)acetamide (**10**, $C_{15}H_{13}N_4OCl$)

To a solution of 0.44 g of **8** (2 mmol) in 10 cm^3 of dry dioxane, 0.225 g of chloroacetyl chloride (2 mmol) were added dropwise, and the reaction mixture was refluxed for 4 h. After cooling, the reaction mixture was poured into ice-H_2O and the solid product formed was collected by filtration and recrystallized from ethanol to give 0.13 g (22%) of **10** as bright white flakes; mp 180–182°C; IR (KBr): $\bar{\nu} = 3250$ (NH), 1650 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 4.26$ (s, $C\underline{H}_2Cl$), 6.30 (m, H3,$4_{pyrrole}$), 6.80 (m, H2,$5_{pyrrole}$), 7.00 (m, $2H_{arom}$), 7.30 (m, $3H_{arom}$), 8.06 (s, $1H_{pyrazole}$), 9.80 (s, NH) ppm.

N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)formamide (**11a**, $C_{14}H_{12}N_4O$)

A mixture of 0.56 g of **2** (2 mmol) and 5 cm^3 of formic acid was heated under reflux for 3 h. After cooling the reaction mixture was poured into ice-H_2O, the solid precipitate formed was collected by filtration and recrystallized from ethanol into buff crystals. Yield 0.38 g (76%, Ref. [2] 96%); mp 200–202°C (Ref. [2] 209–210°C); IR (KBr): $\bar{\nu} = 3200$ (NH), 1640 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.28$ (m, H3,$4_{pyrrole}$), 6.86 (m, H2,$5_{pyrrole}$), 7.08 (m, $2H_{arom}$), 7.33 (m, $3H_{arom}$), 8.20 (s, $2H_{pyrazole} + C\underline{H}O$), 9.80 (s, NH) ppm; MS: m/z (%) = 253 [$M^+ + 1$] (31), 252 [M^+] (100), 235 (7), 224 (30), 223 (20), 196 (22), 170 (11), 169 (30), 104 (12), 77 (46), 68 (11), 51 (12).

N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)acetamide (**11b**, $C_{15}H_{14}N_4O$)

Method A: A mixture of 0.44 g of **8** (2 mmol) and 0.16 g of acetyl chloride (2 mmol) in 10 cm^3 of pyridine was stirred at rt for 2 h. Then, the reaction mixture was poured into ice-H_2O and the solid

product formed was filtered off and recrystallized from ethanol to give 0.34 g (79%) of **11b** as bright white flakes; mp 202–204°C; IR (KBr): $\bar{\nu} = 3200$ (NH), 1640 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.00$ (s, CH_3), 6.23 (m, H3,$4_{pyrrole}$), 6.78 (m, H2,$5_{pyrrole}$), 7.03 (m, $2H_{arom}$), 7.30 (m, $3H_{arom}$), 8.03 (s, $1H_{pyrazole}$), 9.40 (s, NH) ppm.

Method B: A mixture of 0.50 g of **2** (1.8 mmol) and 10 cm^3 of acetic acid in presence of 0.5 g of fused NaO*Ac* was heated under reflux for 3 h. After cooling the reaction mixture was poured into ice-H_2O, the solid product formed was filtered off and recrystallized from ethanol to afford 0.13 g of **11b** (27%).

N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)benzamide (**11c**, $C_{20}H_{16}N_4O$)

To a well stirred cooled suspension of 0.44 g of **8** (2 mmol) in 10 cm^3 of pyridine, 0.28 g of benzoyl chloride (2 mmol) were added dropwise with stirring. The reaction mixture was stirred at rt for 2 h and the solid precipitate obtained was filtered off and recrystallized from ethanol to give 0.50 g (76%) of **11c** as white crystals; mp 128–130°C; IR (KBr): $\bar{\nu} = 3220$ (NH), 1640 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 6.23$ (m, H3,$4_{pyrrole}$), 6.70 (m, H2,$5_{pyrrole}$), 7.22 (m, $5H_{arom}$), 7.46 (m, $3H_{arom}$), 7.80 (m, $2H_{arom}$), 8.41 (s, $1H_{pyrazole}$), 9.96 (s, NH) ppm; MS: m/z (%) = 328 [M^+] (37), 224 (10), 223 (11), 222 (9), 195 (10), 152 (12), 132 (9), 106 (12), 105 (100), 104 (12), 77 (52), 75 (11), 67 (18), 51 (15), 50 (10).

N-(1-Phenyl-5-(pyrrol-1-yl)-1H-pyrazol-4-yl)-4-chlorobenzamide (**11d**, $C_{20}H_{15}N_4OCl$)

A mixture of 0.44 g of **8** (2 mmol) and 0.35 g of 4-chlorobenzoyl chloride (2 mmol) in 10 cm^3 of pyridine was stirred at rt for 2 h. The reaction mixture was then poured into ice-H_2O and the solid product formed was collected by filtration and recrystallized from ethanol to give 0.72 g (99%) of **11d** as fluffy white crystals; mp 172–174°C; IR (KBr): $\bar{\nu} = 3320$ (NH), 1632 (C=O), 1590 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.21$ (m, H3,$4_{pyrrole}$), 6.81 (m, H2,$5_{pyrrole}$), 7.02 (m, $2H_{arom}$), 7.32 (m, $3H_{arom}$), 7.56 (d, $J = 8.52$ Hz, $2H_{arom}$), 7.87 (d, $J = 8.52$ Hz, $2H_{arom}$), 7.99 (s, $1H_{pyrazole}$), 9.98 (s, NH) ppm; MS: m/z (%) = 362 [M^+] (100), 345 (23), 223 (84), 169 (40), 141 (56), 139 (100), 113 (16), 111 (47), 103 (12), 77 (52), 46 (10), 45 (23).

1-Phenyl-5-substitued-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazines (General Procedure)

A mixture of **11a**–**11d** (1 mmol) in 5 cm^3 of phosphoryl chloride was heated under gentle reflux for 3 h. After cooling the reaction mixture was poured into ice-H_2O and neutralized with NaOH solution (20%). The solid precipitate formed was collected by filtration and recrystallized from the proper solvent.

1-Phenyl-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**12a**)

This compound was prepared according to the general procedure and the analytical data are in accordance with that of the reported procedure [2].

1-Phenyl-5-methyl-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**12b**, $C_{15}H_{12}N_4$)

Buff needles; mp 120–122°C (petroleum ether (40–60): benzene = 1:1); yield: 0.15 g (60%); IR (KBr): $\bar{\nu} = 1600$ (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.37$ (s, CH_3), 6.67 (m, $1H_{pyrrole}$), 6.90 (m, $1H_{pyrrole}$), 6.96 (m, $1H_{pyrrole}$), 7.53 (m, $5H_{arom}$), 8.10 (s, $1H_{pyrazole}$) ppm; MS: m/z (%) = 249 [$M^+ + 1$] (25), 248 [M^+] (100), 247 [$M^+ - 1$] (23), 220 (11), 144 (7), 118 (7), 92 (10), 77 (18), 51 (15).

1,5-Diphenyl-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**12c**, $C_{20}H_{14}N_4$)

Yellowish brown crystals; mp 175–177°C (ethanol); yield 0.10 g (32%); IR (KBr): $\bar{\nu} = 1600$ (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.90$ (m, $1H_{pyrrole}$), 7.03 (m, $2H_{pyrrole}$), 7.53 (m, $3H_{arom}$), 7.67 (m, $5H_{arom}$), 7.90 (m, $2H_{arom}$), 8.37 (s, $1H_{pyrazole}$) ppm; MS: m/z (%) = 311 [$M^+ + 1$] (45), 310 [M^+] (100), 309 [$M^+ - 1$] (33), 283 (5), 282 (11), 188 (17), 154 (13), 127 (5), 77 (20), 51 (11).

1-Phenyl-5-(4-chlorophenyl)-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**12d**, $C_{20}H_{13}N_4Cl$)

White crystals; mp 187–189°C (ethanol); yield 0.34 g (99%); IR (KBr): $\bar{\nu} = 1592$ (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 6.90$ (m, $1H_{pyrrole}$), 7.01 (m, $1H_{pyrrole}$), 7.07 (m, $1H_{pyrrole}$), 7.62 (d, $J = 8.52$ Hz, $2H_{arom}$), 7.69 (m, $3H_{arom}$), 7.71 (m, $2H_{arom}$), 7.94 (d, $J = 8.52$ Hz, $2H_{arom}$), 8.39 (s, $1H_{pyrazole}$) ppm; MS: m/z (%) = 343 [$M^+ - 1$] (100), 342 (10), 316 (76), 307 (37), 290 (27), 280 (38), 178 (87), 171 (29), 76 (66), 51 (35).

1-Phenyl-5-substitued-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (General Procedure)

A mixture of **3c–3e** (1 mmol) in 5 cm^3 of phosphoryl chloride was heated under reflux for 2 h. After cooling the reaction mixture was poured into ice-H_2O and neutralized with NH_4OH. The solid white precipitate formed was collected by filtration and recrystallized from the proper solvent to give the corresponding compounds **14a–14c**.

1-Phenyl-5-(p-tolylamino)-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**14a**, $C_{21}H_{17}N_5$)

White crystals; mp 220–222°C (ethanol); yield: 0.30 g (88%); IR (KBr): $\bar{\nu} = 3425$ (NH), 1629 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.36$ (s, CH_3), 6.84 (m, $1H_{pyrrole}$), 6.98 (m, $1H_{pyrrole}$), 7.41 (d, $J = 8.32$ Hz, $2H_{p\text{-tolyl}}$), 7.64 (d, $J = 8.32$ Hz, $2H_{p\text{-tolyl}}$), 7.74 (m, $5H_{arom}$), 7.98 (m, $1H_{pyrrole}$), 8.01 (s, $1H_{pyrazole}$), 10.82 (s, NH, exchangeable) ppm.

1-Phenyl-5-(o-tolylamino)-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**14b**, $C_{21}H_{17}N_5$)

Colorless needles; mp 212–215°C (ethanol); yield 0.32 g (94%); IR (KBr): $\bar{\nu} = 3340$ (NH), 1595 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.23$ (s, CH_3), 6.71 (m, $1H_{pyrrole}$), 6.86 (m, $1H_{pyrrole}$), 7.13 (m, $1H_{pyrrole}$), 7.26 (m, $4H_{o\text{-tolyl}}$), 7.54 (m, $3H_{arom}$), 7.60 (m, $2H_{arom}$), 7.79 (s, $1H_{pyrazole}$), 8.53 (s, NH, exchangeable) ppm.

1-Phenyl-5-(m-tolylamino)-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine (**14c**, $C_{21}H_{17}N_5$)

White crystals; mp 222–224°C (ethanol); yield 0.28 g (82%); IR (KBr): $\bar{\nu} = 3420$ (NH), 1630 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 6.80 (m, $1H_{pyrrole}$), 6.94 (m, $1H_{pyrrole}$), 7.03 (m, $1H_{pyrrole}$), 7.29 (m, $4H_{m\text{-tolyl}}$), 7.65 (m, $5H_{arom}$), 7.98 (s, $1H_{pyrazole}$), 10.12 (s, NH, exchangeable) ppm.

Antibacterial and Antifungal Assay

The tested compounds and the control antibiotic were dissolved in *DMSO* as stock solutions, and dilutions were made using sterile distilled H_2O. The *in vitro* anti-microbial activities of the tested compounds were carried out using the filter paper disc diffusion method [14]. Filter paper discs (5 mm) saturated with the solution of each tested compound (20 mg/2 cm^3 *DMSO*) were placed on the surface of the media (Nutrient agar for bacteria and Dextrose Agar for the fungi). The inhibition zones were

measured in mm at the end of an incubation period of 48 h at 37°C for the bacteria and at 28°C for the fungi. Discs saturated with *DMSO* were used as control; Clotrimazole was used as an anti-fungal and Cloxacillin as an anti-bacterial reference. Both control (+++) in the test (inhibition zones >25 mm).

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