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Synthesis of Imidazo[1,2-*c*]pyrazolo [4,3-*e*]pyrimidines Derived From Indole and Related Heterocycles[#]

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Summary. The syntheses of the title heterocycles were achieved using 5-amino-1-(1-benzyl-1*H*-indol-3-ylcarbonyl)-1*H*-pyrazole-4-carbonitrile as starting material. These compounds were converted into the 4-imidazolinyl derivatives which were subjected to cyclization reactions to afford the title compounds.

Keywords. Indole; Imidazole; Pyrazole; Imidazopyrazolopyrimidine.

Introduction

Several purines are reported to possess anti-tumor activity [1]. Also a few pyrazolopyrimidines and pyrazolotriazines (purine isosteres) are known for their therapeutic importance [2, 3]. Moreover, derivatives of pyrazolopyrimidine are known for their anti-tumor and cytostatic activity [4–8]. Some pyrazolotriazolopyrimidines were reported as new A_{2A} and A_3 adenosine receptor antagonists [9]. On the other hand, it is well known that indole derivatives possess a broad-spectrum of biological activities, several of these derivatives showed potent central nervous system (CNS) activity and anti-inflammatory properties [10–14]. Indometacin, an indole derivative, posseses anti-inflammatory and analgesic activity [15, 16]. Also it has been reported that the substitution at position 1 and 3 of the indole nucleus enhances these activities [17]. Coupling of the imidazopyrazolopyrimidines with the indole moiety may result in gains of the pharmacological activity. With this in mind and in continuation to our interest in the synthesis of new fused polyheterocyclic compounds of potential pharma-

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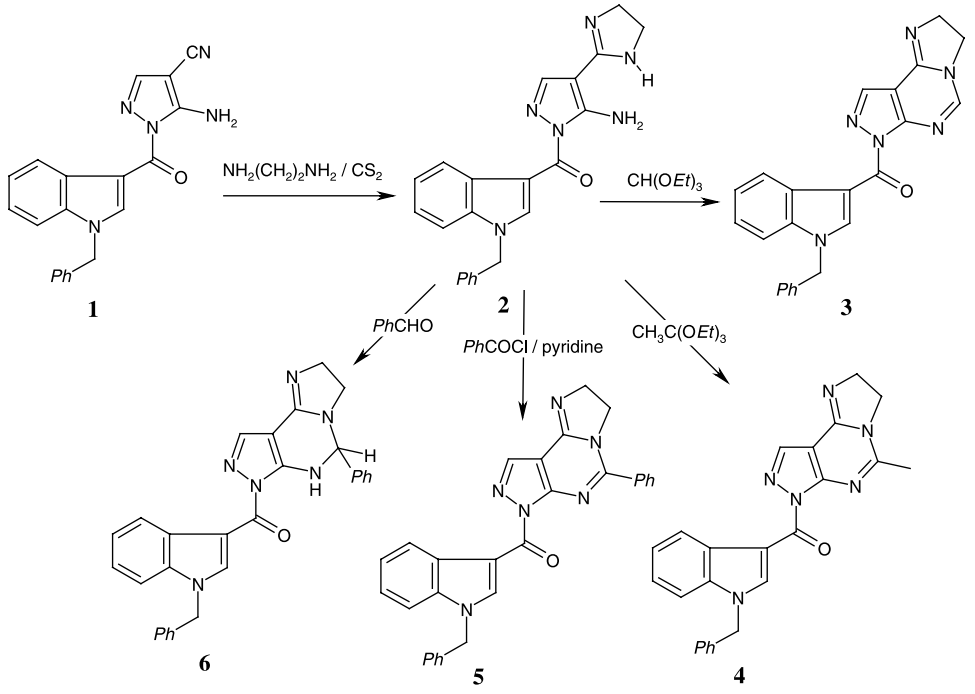
ceutical importance [8, 18, 19], we report herein the synthesis of the title compounds.

Results and Discussion

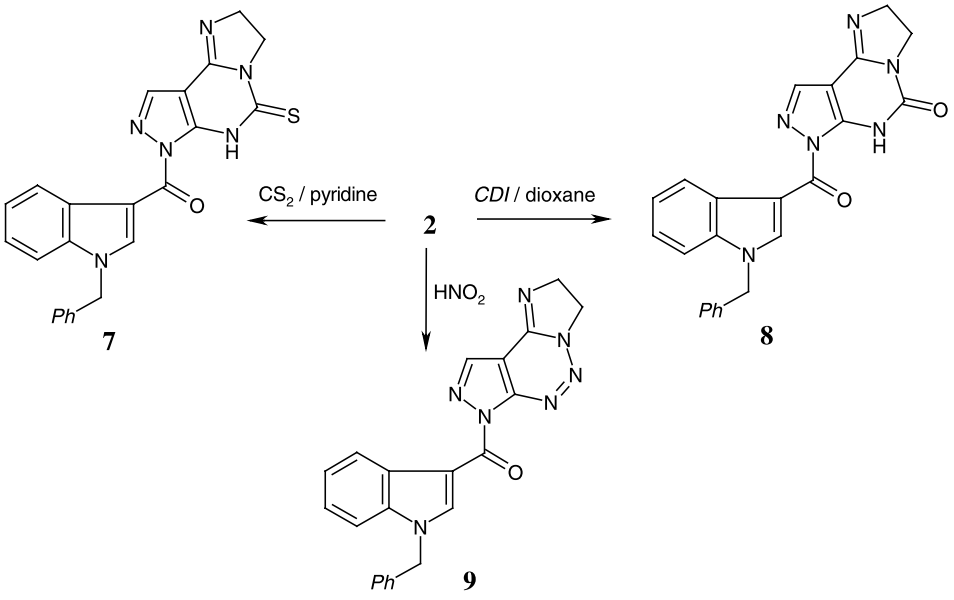
In an earlier paper [19], the synthesis of 5-amino-1-(1-benzyl-1*H*-indol-3-ylcarbonyl-1*H*-pyrazole-4-carbonitrile (**1**) has been described. The nitrile function of **1** has been easily converted into the corresponding imidazolinyl group *via* the reaction with ethylenediamine in the presence of a catalytic amount of carbon disulfide following a reported procedure [20] to yield compound **2**. The latter compound could be ring closed into the tricyclic imidazopyrazolopyrimidine in different ways. The reaction of **2** with triethyl orthoformate afforded the parent compound **3**, and the 5-methyl derivative **4** was obtained by reaction with trimethyl orthoacetate. When **2** was allowed to react with benzoyl chloride in boiling pyridine the corresponding 5-phenyl derivative **5** was formed. Interaction of **2** with benzaldehyde in a procedure similar to the one of *Ried* and *Russ* [21] afforded the corresponding imidazopyrazolopyrimidine **6** (Scheme 1).

Treatment of **2** with carbon disulfide in boiling pyridine led to the formation of the corresponding imidazopyrazolopyrimidinethione **7**, whereas its reaction with 1,1′-carbonyldiimidazole (*CDI*) in boiling dioxane gave the oxo-derivative **8**. The triazine derivative **9** could be obtained by reacting **2** with nitrous acid at room temperature (Scheme 2).

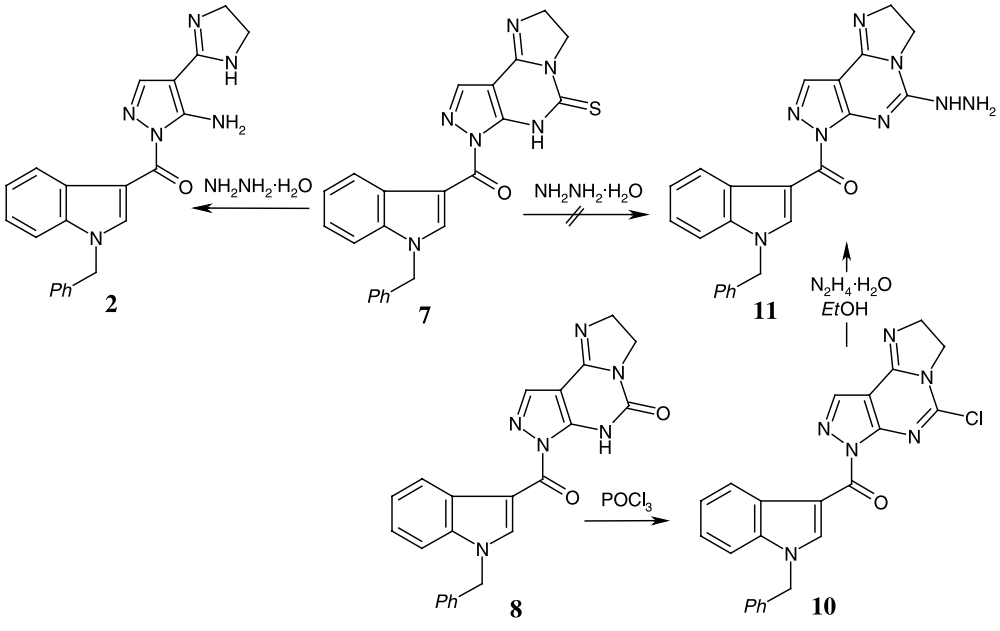
Interestingly enough, hydrazinolysis of the thione **7** with hydrazine hydrate did not afford the expected hydrazino product **11**, but led to opening of the pyrimidine



Scheme 1



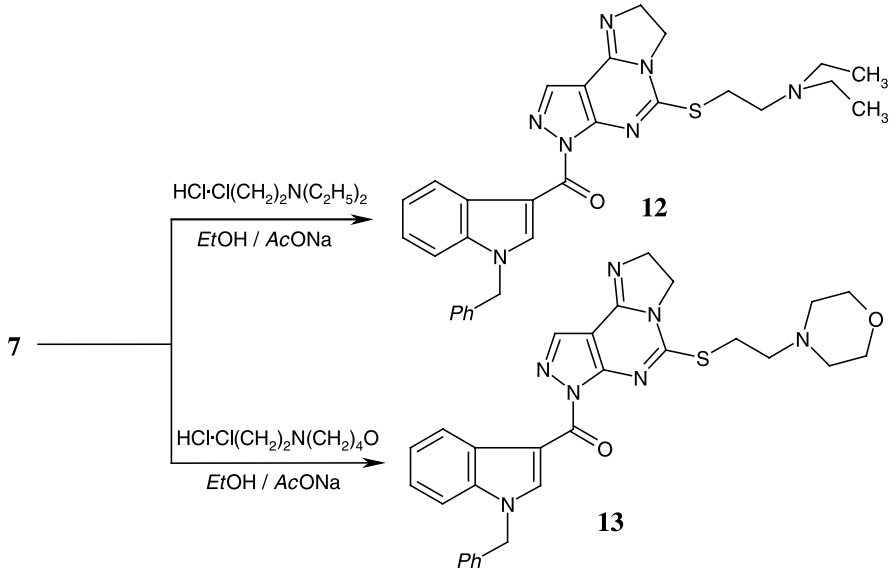
Scheme 2



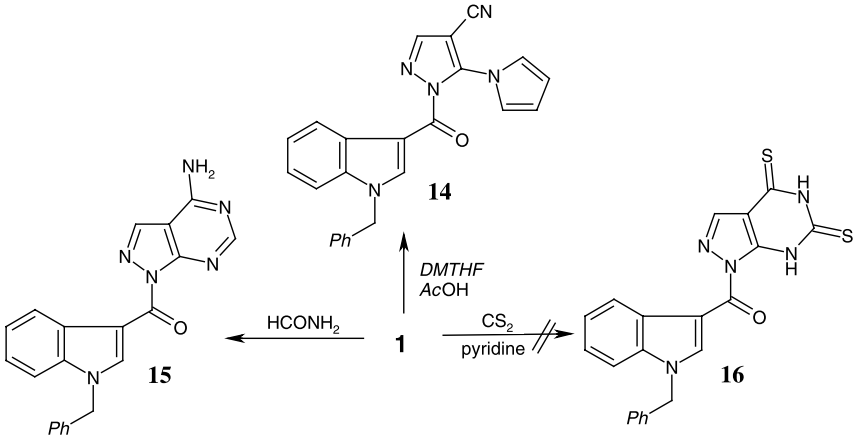
Scheme 3

ring giving back **2**. However, **11** could be prepared by treatment of **8** with phosphoryl chloride to give the corresponding 5-chloro-derivative **10**, which gave the corresponding **11** upon treatment with hydrazine hydrate (Scheme 3).

On the other hand, when **7** was allowed to react with bioactive alkylating agents, such as 4-(2-chloroethyl)morpholine hydrochloride or 2-dimethyaminopropyl chloride hydrochloride in boiling ethanol in the presence of fused sodium acetate, the S-alkylated products **12** and **13** were obtained.



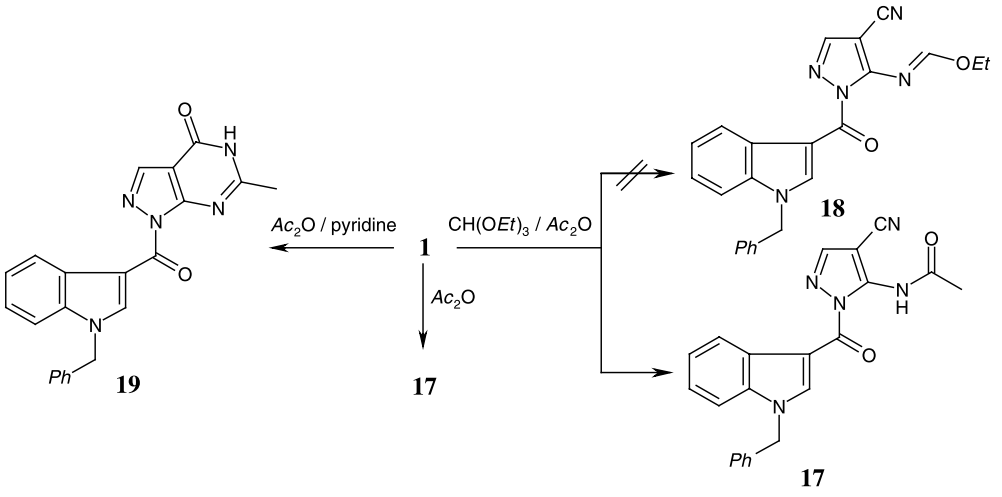
Scheme 4



Scheme 5

The interaction of **1** with 2,5-dimethoxytetrahydrofurane (*DMTHF*) afforded the pyrrolyl derivative **14**. However, reaction of **1** with formamide gave the aminopyrazolopyrimidine **15**. An attempt to prepare the pyrazolopyrimidinedithione **16** *via* the reaction of **1** with carbon disulfide in boiling pyridine was unsuccessful and **1** was recovered unchanged (Scheme 5).

Finally, acetylation of **1** was accomplished in boiling acetic anhydride to give the acetyl derivative **17**. When **1** was treated with triethyl orthformate in the presence of acetic anhydride, the product obtained was not the expected ethoxymethyleneimino derivative **18**, but the acetyl derivative **17**. On the other hand, when acetylation was carried out using acetic anhydride in boiling pyridine, the product was the pyrazolopyrimidine derivative **19** (Scheme 6).



Scheme 6

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 wafers. ^{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. 5-Amino-1-(1-benzyl-1*H*-indol-3-ylcarbonyl)-1*H*-pyrazole-4-carbonitrile (**1**) was prepared as described before [19].

3-[5-Amino-4-(4,5-dihydro-1H-imidazol-2-yl)-1H-pyrazol-1-ylcarbonyl]-1-benzyl-1H-indole (**2**, $C_{22}H_{20}N_6O$)

A mixture of 3.41 g **1** (10 mmol), 5 cm^3 ethylenediamine, and 0.9 cm^3 CS_2 was heated on a water bath for 8 h. After cooling the reaction mixture was diluted with an ice-H_2O mixture. The precipitate formed was filtered off, washed with H_2O, and recrystallized from ethanol to give 5.22 g (95%) **2** as yellow crystals; mp 104–106°C; IR (KBr): $\bar{\nu} = 3350$, 3250 (NH_2), 3100 (NH), 1640 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.45$ (m, $4H_{imidazole}$), 5.07 (s, $2H_{benzyl}$), 6.97 (bs, 2H, NH_2), 7.13 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.73 (s, $H2_{indole}$), 8.07 (m, $H4_{indole} + 1H_{pyrazole}$) ppm; MS: m/z (%) = 293 [$M^+ - CH_2Ph$] (2), 289 (4), 264 (12), 250 (22), 173 (3), 91 (62), 65 (6), 51 (2).

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-2,3-dihydro-7H-imidazo[1,2-c]pyrazolo[4,3-e]pyrimidine (**3**, $C_{18}H_{16}N_6O$)

A mixture of 384 mg **2** (1 mmol) and 5 cm^3 triethyl orthformate was heated under reflux for 4 h. After cooling the solvent was evaporated under reduced pressure and the residue obtained was collected and recrystallized from ethanol to give 230 mg (58%) **3** as yellow crystals; mp 125–127°C; IR (KBr): $\bar{\nu} = 2920$ (CH_{aliph}) 1640 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.41$ (m, $4H_{imidazole}$), 5.07 (s, $2H_{benzyl}$), 7.13 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.43 (s, $H4_{indole}$), 7.70 (m, $H2_{indole}$), 8.07 (m, $1H_{pyrimidine} + 1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-methyl-2,3-dihydro-7H-imidazo[1,2-c] pyrazolo[4,3-e]pyrimidine (**4**, $C_{24}H_{20}N_6O$)

A mixture of 384 mg **2** (1 mmol) and 8 cm^3 trimethyl orthoacetate was heated under reflux for 8 h. After cooling the solvent was eliminated under reduced pressure and the residue obtained was tritu-

rated with ethanol. The product formed was filtered off and recrystallized from ethanol to give 204 mg (50%) of **4** as yellow crystals; mp 113–115°C; IR (KBr): $\bar{\nu} = 2920$ (CH_{aliph}), 1650 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.45$ (s, CH_3), 3.37 (m, $4H_{imidazole}$), 5.07 (s, $2H_{benzyl}$), 7.13 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.45 (s, $H4_{indole}$), 7.75 (m, $H2_{indole}$), 8.15 (s, $1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-phenyl-2,3-dihydro-7H-imidazo[1,2-c] pyrazolo[4,3-e]pyrimidine (**5**, $C_{29}H_{22}N_6O$)

A mixture of 384 mg **2** (1 mmol) and 141 mg benzoyl chloride (1 mmol) in 10 cm^3 pyridine was heated under reflux for 4 h. After cooling, the solvent was removed *in vacuo* and the residue obtained was poured into H_2O. The solid precipitate formed was filtered off and recrystallized from ethanol to give 290 mg (62%) **5** as white crystals; mp 250–252°C; IR (KBr): $\bar{\nu} = 2900$ (CH_{aliph}), 1640 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.41$ (m, $4H_{imidazole}$), 5.07 (s, $2H_{benzyl}$), 7.13 (m, $H5,6,7_{indole} + 10H_{arom}$), 7.43 (s, $H4_{indole}$), 7.70 (m, $H2_{indole}$), 8.07 (s, $1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-phenyl-2,3,5,6-tetrahydro-7H-imidazo[1,2-c] pyrazolo[4,3-e]pyrimidine (**6**, $C_{29}H_{24}N_6O$)

A mixture of 384 mg **2** (1 mmol), 3 cm^3 benzaldehyde (3 mmol), and 0.2 cm^3 conc. HCl in 10 cm^3 absolute ethanol was stirred at 50–60°C for 5 h. After cooling the mixture was neutralized with aqu. Na_2CO_3. The solid product formed was filtered off and recrystallized from ethanol to give 320 mg (68%) **6** as yellow crystals; mp 285–287°C; IR (KBr): $\bar{\nu} = 2930$ (CH_{aliph}) 1650 (C=O), 1610 (C=N) cm^{-1} ; ^1H NMR (*DMSO*-d_6): $\delta = 3.45$ (m, $4H_{imidazole}$), 5.12 (s, $2H_{benzyl}$), 7.16 (m, $H5,6,7_{indole} + 10H_{arom}$), 7.42 (s, $H4_{indole}$), 7.74 (m, $H2_{indole}$), 8.14 (m, $1H_{pyrimidine} + 1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-2,3,5,6-tetrahydro-7H-imidazo[1,2-c]pyrazolo [4,3-e]pyrimidin-5-thione (**7**, $C_{23}H_{18}N_6OS$)

A mixture of 384 mg **2** (1 mmol) and 2 cm^3 CS_2 in 5 cm^3 pyridine was heated under reflux on a water bath for 12 h. After cooling the solvent was removed under reduced pressure and the residue was triturated with H_2O. The solid product formed was filtered off and recrystallized from ethanol to afford 303 mg (71%) **7** as yellowish white crystals; mp 122–124°C; IR (KBr): $\bar{\nu} = 3250$ (NH), 1640 (C=O), 1610 (C=N), 1180 (C=S) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 4.16$ (m, $4H_{imidazole}$), 5.50 (s, $2H_{benzyl}$), 7.30 (m, $H5,6,7_{indole} + 5H_{arom}$), 8.23 (s, $H4_{indole} + 1H_{pyrazole}$), 8.40 (m, $H2_{indole}$), 9.52 (s, NH, exchangeable) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-2,3,5,6-tetrahydro-7H-imidazo[1,2-c]pyrazolo [4,3-e]pyrimidin-5-one (**8**, $C_{23}H_{18}N_6O_2$)

A mixture 384 mg **2** (1 mmol) and 162 mg 1,1′-carbonyldiimidazole (1 mmol) in 10 cm^3 dioxane was heated under reflux for 8 h. After cooling the solvent was removed under reduced pressure and the residue was triturated with H_2O. The solid product formed was filtered off and recrystallized from ethanol to give 307 mg (75%) **8** as white crystals; mp 175–177°C; IR (KBr): $\bar{\nu} = 3250$ (NH), 1700 (C=O), 1640 (C=O), 1620 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 3.90$ (m, $4H_{imidazole}$), 5.43 (s, $2H_{benzyl}$), 7.31 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.97 (s, $H4_{indole} + 1H_{pyrazole}$), 8.23 (m, $H2_{indole}$), 9.52 (s, NH, exchangeable) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-2,3-dihydro-7H-imidazo[1,2-c]pyrazolo[4,3-e] triazine (**9**, $C_{22}H_{17}N_7O$)

To a solution of 384 mg **2** (1 mmol) in 10 cm^3 glacial acetic acid, a cold solution of 3.30 g $NaNO_2$ (10 cm^3, 33%, 4.7 mmol) was added dropwise with stirring at rt. After completion stirring was continued for 1 h. The solid product obtained was filtered off, washed with H_2O, dried, and recrystallized from ethanol to give 230 mg (58%) **9** as buff crystals; mp 138–140°C; IR (KBr): $\bar{\nu} = 1640$ (C=O), 1610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.17$ (t, $J = 9.00$ Hz, $2H_{imidazole}$), 4.93 (t, $J = 9.00$ Hz, $2H_{imidazole}$), 5.27 (s, $2H_{benzyl}$), 7.17 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.78 (m, $H2,4_{indole}$), 8.63 (s, $1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-chloro-2,3-dihydro-7H-imidazo[1,2-c] pyrazolo[4,3-e]pyrimidine (**10**, $C_{23}H_{17}ClN_6O$)
A mixture of 410 mg **8** (0.5 mmol) and 10 cm^3 of $POCl_3$ was heated under reflux for 1 h. After cooling the solvent was removed under reduced pressure and the residue obtained was poured into an ice-H_2O mixture. The reaction mixture was neutralized with NH_4OH and the solid precipitate formed was filtered off and recrystallized from ethanol to give 368 mg (86%) **10** as buff crystals; mp 128–130°C; IR (KBr): $\bar{\nu} = 2950$ (CH_{aliph}), 1640 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.67$ (m, $4H_{imidazole}$), 5.20 (s, $2H_{benzyl}$), 7.13 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.50 (m, $H4_{indole}$), 7.80 (s, $H2_{indole}$), 8.10 (s, $1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-2,3-dihydro-5-hydrazino-7H-imidazo[1,2-c] pyrazolo[4,3-e]pyrimidine (**11**, $C_{23}H_{20}N_8O$)
A mixture of 428 mg **10** (1 mmol) and 5 cm^3 $NH_2NH_2 \cdot H_2O$ (100 mmol) was heated under reflux for 3 h. After cooling the solvent was removed under reduced pressure and the precipitate obtained was triturated with 50 cm^3 H_2O. The solid product formed was filtered off and recrystallized from ethanol to afford 300 mg (71%) **11** as buff crystals; mp 145–147°C; IR (KBr): $\bar{\nu} = 3350, 3250, 3150$ ($NHNH_2$), 2980 (CH_{aliph}), 1680 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 4.23$ (m, $NH_2 + 4H_{imidazole}$), 5.50 (s, $2H_{benzyl}$), 6.47 (sb, NH), 7.37 (m, $H5,6,7_{indole} + 5H_{arom}$), 8.17 (m, $H2,4_{indole}$), 8.28 (s, $1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-(2-diethylaminoethylthio)-2,3-dihydro-7H-imidazo[1,2-c]pyrazolo[4,3-e]pyrimidine (**12**, $C_{29}H_{31}N_7OS$)
A mixture of 213 mg **7** (0.5 mmol), 400 mg fused sodium acetate (5 mmol), and 172 mg 2-diethylaminoethyl chloride hydrochloride (1 mmol) in 10 cm^3 ethanol was heated under reflux for 7 h. After cooling the solvent was eliminated *in vacuo* and the solid product obtained was washed with H_2O, filtered off, and recrystallized from ethanol to give 210 mg (80%) **12** as yellow crystals; mp 100–102°C; IR (KBr): $\bar{\nu} = 2950$ (CH_{aliph}), 1640 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.23$ (s, $N(CH_2C\underline{H}_3)_2$), 3.63 (m, $4H_{imidazole} + S(C\underline{H}_2)_2N + N(C\underline{H}_2CH_3)_2$), 5.23 (s, $2H_{benzyl}$), 7.17 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.53 (s, $H4_{indole}$), 7.90 (m, $H2_{indole}$), 8.13 (s, $1H_{pyrazole}$) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-(2-morpholinoethylthio)-2,3-dihydro-7H-imidazo[1,2-c]pyrazolo[4,3-e]pyrimidine (**13**, $C_{29}H_{29}N_7O_2S$)
A mixture of 213 mg **7** (0.5 mmol), 400 mg fused sodium acetate (5 mmol), and 188 mg 4-(2-chloroethyl)morpholine hydrochloride (1 mmol) in 10 cm^3 ethanol was heated under reflux for 8 h. After cooling the solvent was eliminated *in vacuo* and the solid product obtained was washed with H_2O, filtered off, and recrystallized from ethanol to give 220 mg (81%) **13** as yellow crystals; mp 95–97°C; IR (KBr): $\bar{\nu} = 2950$ (CH_{aliph}), 1640 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.47$ (t, unresolved $N(CH_2)_2$), 3.27 (m, $SCH_2C\underline{H}_2N$), 3.63 (m, $O(CH_2)_2 + SC\underline{H}_2CH_2N + 4H_{imidazole}$), 5.20 (s, $2H_{benzyl}$), 7.17 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.83 (m, $H2,4_{indole}$), 8.13 (s, $1H_{pyrazole}$) ppm.

1-(1-Benzyl-1H-indol-3-ylcarbonyl)-5-(pyrrol-1-yl)-1H-pyrazole-4-carbonitrile (**14**, $C_{24}H_{17}N_5O$)
A mixture of 341 mg **1** (1 mmol) and 145 mg *DMTHF* (1.1 mmol) in 10 cm^3 glacial acetic acid was heated at 80°C for 1 h. After cooling the reaction mixture was poured into an ice-H_2O mixture and neutralized with Na_2CO_3. The solid product formed was filtered off and recrystallized from ethanol to afford 384 mg (98%) **14** as brown crystals; mp 100–102°C; IR (KBr): $\bar{\nu} = 2920$ (CH_{aliph}), 2220 (C≡N), 1640 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 5.27$ (s, $2H_{benzyl}$), 6.30 (m, $H3,4_{pyrrole}$), 7.20 (m, $H2,5_{pyrrole}$, $H5,6,7_{indole}$, $1H_{pyrazole} + 5H_{arom}$), 7.83 (s, $H2_{indole}$), 8.13 (s, $H4_{indole}$) ppm.

4-Amino -7-(1-benzyl-1H-indol-3-ylcarbonyl)pyrazolo[3,4-d]pyrimidine (**15**, $C_{21}H_{16}N_6O$)
A mixture of 341 mg **1** (1 mmol) and 10 cm^3 formamide was heated under reflux for 4 h. After cooling the solvent was removed under reduced pressure and the residue obtained was triturated with H_2O. The solid product formed was filtered off and recrystallized from ethanol to afford 162 mg (44%) **15** as grey

crystals; mp 166–168°C; IR (KBr): $\bar{\nu} = 3400$, 3200 (NH_2), 2900 (CH_{aliph}), 1630 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 5.50$ (s, $2H_{benzyl}$), 6.40 (s, NH_2), 7.40 (m, $H4,5,6,7_{indole} + 5H_{arom}$), 8.27 (s, $H2_{indole}$), 8.27 (s, $H2_{indole} + 1H_{pyrazole}$), 8.23 (s, $1H_{pyrimidine}$) ppm.

5-Acetylamino-1-(1-benzyl-1H-indol-3-ylcarbonyl)-1H-pyrazole-4-carbonitrile (**17**, $C_{22}H_{17}N_5O_2$)
A mixture of 341 mg **1** (1 mmol) and 10 cm^3 acetic anhydride was heated under reflux for 2 h. After cooling the solvent was removed under reduced pressure and the residue obtained was poured into an ice-H_2O mixture. The solid product obtained was filtered off and recrystallized from ethanol to afford 349 mg (91%) **19** as brownish red crystals; mp 178–180°C; IR (KBr): $\bar{\nu} = 3250$ (NH), 2950 (CH_{aliph}), 2220 (C≡N), 1680 and 1640 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.07$ (s, $COC\underline{H}_3$), 5.47 (s, $2H_{benzyl}$), 7.23 (m, $H5,6,7_{indole} + 5H_{arom}$), 7.93 (s, $H4_{indole}$), 8.17 (s, $H2_{indole}$), 8.30 (s, $1H_{pyrazole}$), 10.20 (s, NH) ppm.

7-(1-Benzyl-1H-indol-3-ylcarbonyl)-2-methyl-3,4-dihydropyrazolo[3,4-d]pyrimidin-4-one
(**19**, $C_{22}H_{17}N_5O_2$)
A mixture of 341 mg **1** (1 mmol) and 5 cm^3 acetic anhydride in 10 cm^3 pyridine was heated under reflux for 4 h. After cooling the solvent was removed under reduced pressure and the residue obtained was poured into an ice-H_2O mixture. The solid product obtained was filtered off dried, and recrystallized from ethanol to afford 200 mg (52%) **17** as buff crystals; mp 192–194°C; IR (KBr): $\bar{\nu} = 3150$ (NH), 2950 (CH_{aliph}), 1660 and 1630 (C=O), 1600 (C=N) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.88$ (s, CH_3), 5.53 (s, $2H_{benzyl}$), 7.40 (m, $H5,6,7_{indole} + 5H_{arom}$), 8.10 (s, $H4_{indole}$), 8.30 (s, $H2_{indole}$), 9.10 (s, $1H_{pyrazole}$), 11.20 (s, NH) ppm.

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