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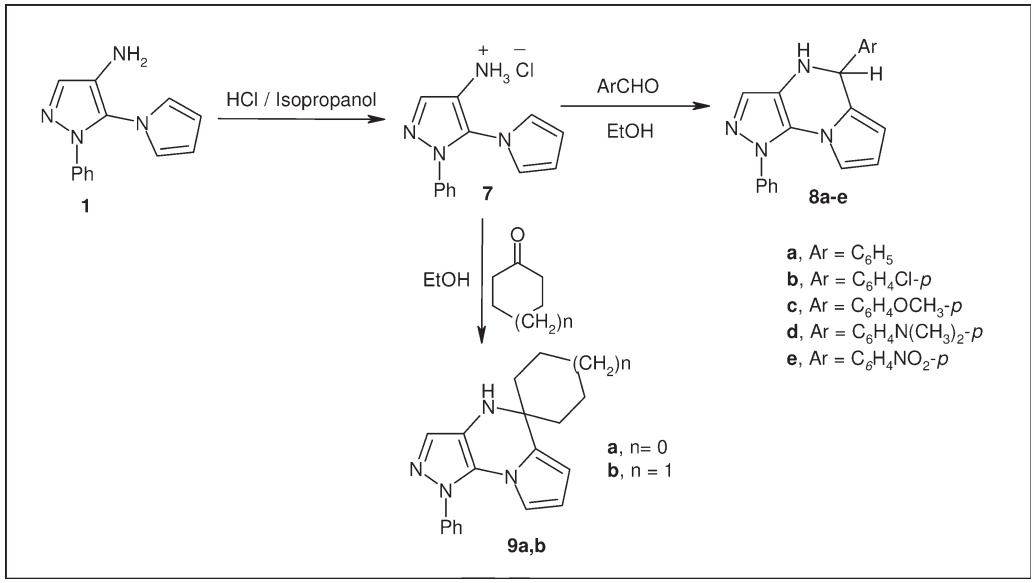

Synthesis of the title compounds was achieved using the anils **2a–e** and **5a–c** derived from the 4-aminopyrazole **1** as starting materials. These compounds were allowed to react with mercaptoacetic acid in boiling dry benzene to afford the corresponding thiazolidinones and spiro-thiazolidinones **3a–e** and **6a–c**, respectively. Pictet–Spengler reaction of the 4-aminopyrazole hydrochloride **7** with aromatic aldehydes and cyclic ketones resulted in the formation of new pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazines **8a–e** and **9a,b**, respectively. Other derivatives of pyrazolo pyrrolopyrazines **10** and **11** were obtained *via* the reaction of the amino derivative **1** with 1,1′-carbonyldiimidazol and CS_2, respectively.

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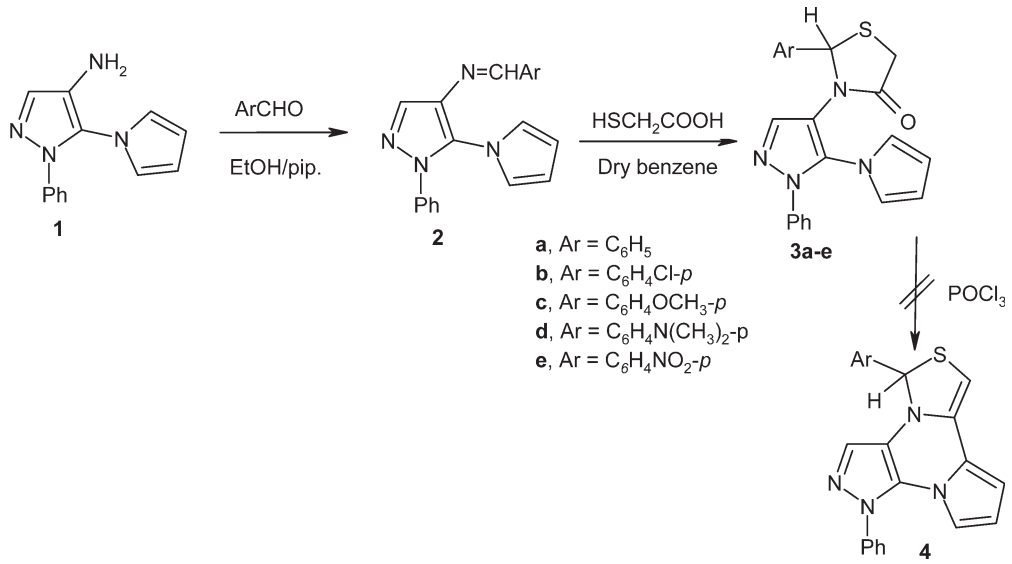
INTRODUCTION

Pyrazolo[3,4-*b*]pyrazine ring system is an interesting class of heterocycles. It has been reported that some of its derivatives are used as bone metabolism improvers [1], antiinflammatories [2], blood platelet aggregation inhibitors [2], and anticancer agents with low toxicity [3,4]. Pyrazolo[3,4-*b*]pyrazines are also used as fluorescent [5] and disperse dyes in dye chemistry [6]. In addition, they were reported to possess antiviral, antineoplastic, antifungal, and antiparasitic activities [7–10]. Furthermore, other tricyclic systems containing the pyrazole moiety, with a bridge-head nitrogen atom have been extensively studied because of their interesting biological and pharmacological activities [11,12]. On the other hand, the tricyclic system pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazine showed antimicrobial activity [13] and was reported to be a potential analog of sildenafil [14]. In continuation to our program directed toward the synthesis of new fused pyrazines [9,10,13,15–19], we report herein the synthesis of new pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazines and some new thiazolidinones derived from pyrazole.

RESULTS AND DISCUSSION

1-Phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-ylamine (**1**) proved to be a versatile compound due to its use in the synthesis of several heterocycles [13,14]. In a preceding paper in this journal, we have reported that the reaction of **1** with aromatic aldehydes to give the corresponding arylidene derivatives **2** [13]. In this article, we would like to explore further the utility of this amino derivative in the synthesis of the title compounds. Treatment of **2** with mercaptoacetic acid in boiling dry benzene afforded the corresponding 2-aryl-3-(1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-yl) thiazolidin-4-one (**3a–e**). Attempts to cyclize the latter compounds upon heating in boiling phosphoryl chloride failed to give thiazolopyrazines **4** (Scheme 1).

Scheme 1



Interaction of the amino derivative **1** with cyclic ketones in refluxing ethanol in the presence of catalytic amount of piperidine led to the formation of the corresponding cycloalkylidene derivatives **5a–c**. When these latter compounds were reacted with mercaptoacetic acid in boiling dry benzene the corresponding cycloalkanes-spiro-2′-(3′-(1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-yl)thiazolidin-4′-one) (**6a,b**) and 1-methylpiperidine-4-spiro-2′-(3′-(1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-yl) thiazolidin-4′-one) (**6c**) were obtained (Scheme 2).

In our earlier publication [13], we reported two different synthetic pathways for the synthesis of the title compounds. These involved the Bischler–Napieralsky reaction of 4-acyl/aroylaminopyrazoles **Ia–d** or from the urea derivatives **IIIa–c** (Scheme 3).

Here we report another synthetic pathway using Pictet–Spengler reaction between the amine hydrochloride **7** and aromatic aldeydes and/or cyclic ketones in refluxing ethanol to afford the corresponding pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrazines **8a–e** and **9a–c**, respectively (Scheme 4).

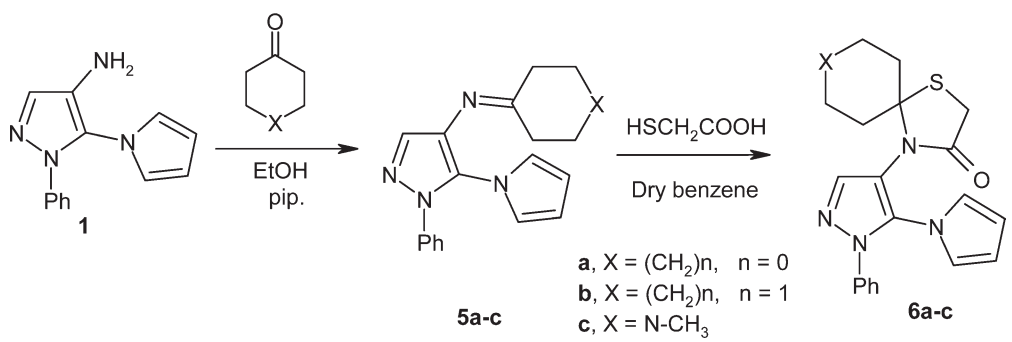
On the other hand, compound **10** was obtained by heating of the acid azide **V** in boiling toluene to form the isocyanate intermediate **VI** *via* Curtius rearrangement [20], which was cyclized concomitantly to **10** [8]. In continuation to our interest [21,22] in performing cyclization reactions using 1,1′-carbonyldiimidazole (CDI) and CS_2 instead of triphosgene and thiophosgene, respectively, we could obtain **10** and **11** by treatment of **1** with CDI in dioxane and with CS_2 in pyridine, respectively. Compound **11** could be also prepared by the interaction of pyrazinone **10** with P_2S_5 in boiling pyridine (Scheme 5).

All the compounds prepared were included in the chemical library of the University of Caen-France for their screening as anticancer, antimicrobial, and anti-inflammatory activities.

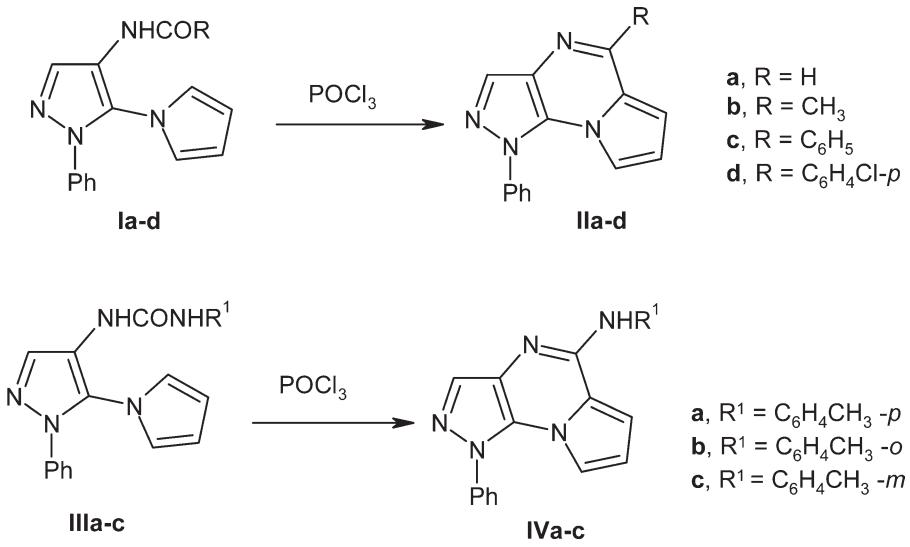
EXPERIMENTAL

Melting points were determined on a Kofler melting point apparatus and are uncorrected. Elemental analyses (C, H, N,

Scheme 2



Scheme 3



and S) were performed using a Perkin-Elmer 240 C Microanalyzer and their results were in good agreement (±0.2%) with the calculated values. IR spectra were recorded on a Pye Unicam SP3-100 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were measured on a Varian EM 390, 90 MHz—and a Jeol LA 400 MHz spectrometer [TMS as internal reference, coupling constants (*J*) were reported in Hz, δ values in ppm]. Mass spectra were recorded on a Shimadzu QP5050 DI 50 mass spectrometer. Starting materials were commercially available. Solvents were distilled and dried before use.

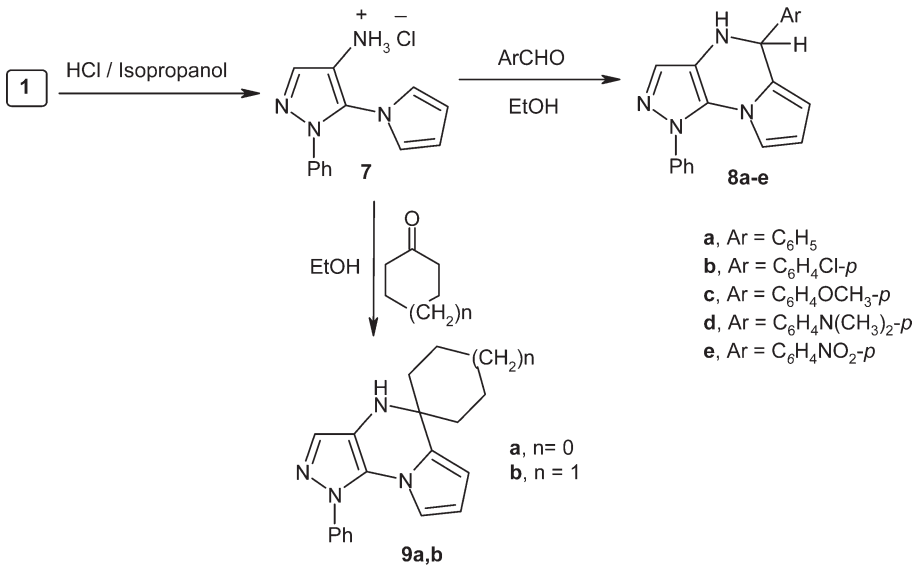
1-Phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-ylamine (1). This compound was prepared according to the previous studies [8,13] mp 140–142°C, [8] mp 144–145°C, and [13] mp 140–142°C. The IR, mass, and ^{1}H-NMR spectra of compound **1** were found to be identical with those described in refs. 8 and 13.

***N*-Arylidene-1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-ylamine (2a–e).** These compounds were prepared according to ref. 13. The IR, mass, and ^{1}H-NMR spectra of compounds **2a–e** were found to be identical with those described in ref. 13.

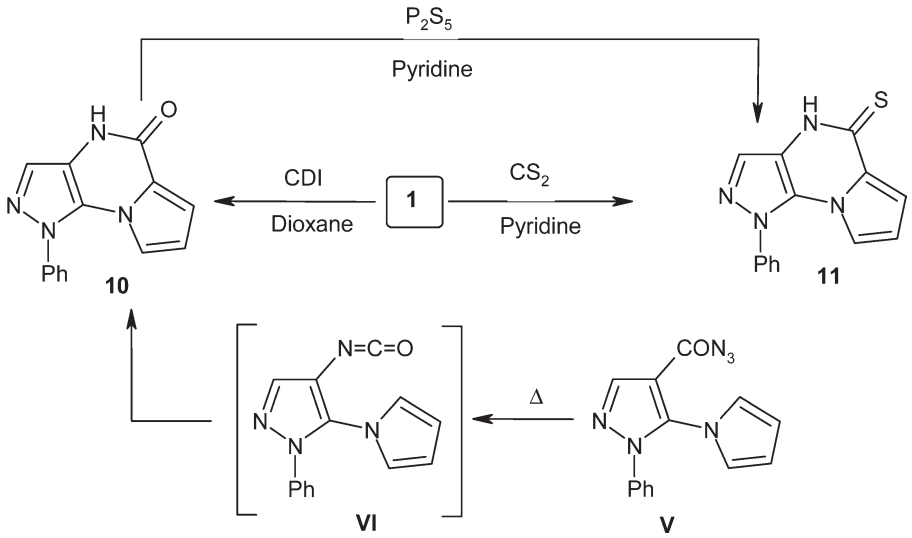
General procedure for the preparation of 2-aryl-3-(1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-yl)thiazolidin-4-one derivatives (3a–e). A mixture of compounds **2a–e** (1 mmol) and 0.184 g of mercaptoacetic acid (2 mmol) in 10 mL of dry benzene was refluxed in Dean-Stark apparatus for 48 h. Then, the solvent was evaporated and the residue was treated with 10% sodium bicarbonate solution. The precipitate formed was filtered, washed with H_2O, air dried, and recrystallized from ethanol to afford **3a–e**.

2-Phenyl-3-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl)thiazolidin-4-one (3a). This compound was obtained as buff crystals. Yield (66%); mp 115–117°C; ^{1}H-NMR (400 MHz,

Scheme 4



Scheme 5



$CDCl_3$): δ = 3.70 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.80 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 5.39 (s, 1H, thiazolidinone H), 6.22 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz,), 6.41 (t, 2H, *J* = 1.9 Hz, pyrrole H-2, H-5), 6.94 (m, 3H, ArH), 7.03 (m, 2H, ArH), 7.18 (m, 5H, ArH), 7.49 (s, 1H, pyrazole H); IR (KBr): 1680 cm^{-1} (C=O). Anal. Calcd. for $C_{22}H_{18}N_4OS$ (386.47): C, 68.37; H, 4.69; N, 14.50. Found: C, 68.27; H, 4.60; N, 14.33.

2-(4-Chlorophenyl)-3-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl)thiazolidin-4-one (3b). This compound was obtained as yellow crystals. Yield (84%); mp 78–80°C; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 3.77 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.87 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 5.41 (s, 1H, thiazolidinone H), 6.24 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz), 6.44 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.06 (m, 4H, ArH), 7.24 (m, 5H, ArH), 8.13 (s, 1H, pyrazoleH); IR (KBr): 1690 (C=O), 1640 (C=N), 1610 cm^{-1} (C=C). Anal. Calcd. for $C_{22}H_{17}N_4ClOS$ (420.92): C, 62.78; H, 4.07; N, 13.31. Found: C, 62.68; H, 4.00; N, 13.19.

2-(4-Methoxyphenyl)-3-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl)thiazolidin-4-one (3c). This compound was obtained as white crystals. Yield (72%); mp 210–212°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.70 (s, 3H, OCH_3), 3.74 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.84 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 5.76 (s, 1H, thiazolidinone H), 6.28 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz), 6.59 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 6.98 (m, 4H, ArH), 7.31 (m, 5H, ArH), 8.14 (s, 1H, pyrazole H); IR (KBr): 1700 (C=O), 1640 (C=N), 1600 cm^{-1} (C=C). Anal. Calcd. for $C_{23}H_{20}N_4O_2S$ (416.50): C, 66.33; H, 4.84; N, 13.45. Found: C, 66.39; H, 4.90; N, 13.50.

2-(4-(Dimethylaminophenyl)-3-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl)thiazolidin-4-one (3d). This compound was obtained as yellow crystals. Yield (66%); mp 133–135°C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.91 (s, 6H, $2CH_3$), 3.78 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.88 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 5.43 (s, 1H, thiazolidinone H), 6.29 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz,), 6.56 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.07 (m, 4H, ArH), 7.24 (m, 5H, ArH), 8.32 (s, 1H, pyrazole H); IR (KBr): 2900, 2850 (CH-aliphatic), 1690 (C=O), 1640 (C=N), 1600 (C=C) cm^{-1}. Anal. Calcd. for $C_{24}H_{23}N_5OS$ (429.54): C, 67.11; H, 5.40; N, 16.30. Found: C, 67.22; H, 5.34; N, 16.29.

2-(4-Nitrophenyl)-3-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl)thiazolidin-4-one (3e). This compound was obtained as yellow crystals. Yield (55%); mp 137–139°C; ^{1}H-NMR (90 MHz, DMSO-d_6): δ = 3.74 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.84 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 5.46 (s, 1H, thiazolidinone H), 6.30 (t, 2H, *J* = 1.9 Hz, pyrrole H-3, H-4), 6.58 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.10 (m, 4H, ArH), 7.28 (m, 5H, ArH), 8.36 (s, 1H, pyrazoleH); IR (KBr): 1700 (C=O), 1610 (C=N), 1600 cm^{-1} (C=C). Anal. Calcd. for $C_{24}H_{23}N_5OS$ (431.47): C, 67.11; H, 5.40; N, 16.30. Found: C, 67.22; H, 5.34; N, 16.29.

General procedure for synthesis of *N*-cycloalkylidene-1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-ylamine derivatives (5a–c). A mixture of **1** (224 mg, 1 mmol) and the appropriate cyclo alkyl ketones (1 mmol) in absolute ethanol (10 mL) was heated under reflux in the presence of two drops of piperidine for 3 h, and then the reaction mixture was concentrated. After cooling, the solid product formed was collected by filtration and recrystallized from ethyl acetate to give the corresponding derivatives **5a–c**.

***N*-Cyclopentylidene-1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-ylamine (5a).** This compound was obtained as pale yellow crystals. Yield (59%); mp 118–120°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.69 (m, 4H, cyclopentane H), 1.77 (m, 4H, cyclopentane H), 6.19 (m, 2H, pyrrole H-3, H-4), 6.85 (m, 2H, pyrrole H-2, H-5), 7.15 (m, 2H, ArH), 7.32 (m, 3H, ArH), 8.43 (s, 1H, pyrazole H); IR (KBr): 1630 cm^{-1} (C=N). Anal. calcd. for $C_{18}H_{18}N_4$ (290.36): C, 74.46; H, 6.25; N, 19.30. Found: C, 74.51; H, 6.21; N, 19.31.

***N*-Cyclohexylidene-1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-ylamine (5b).** This compound was obtained as yellow crystals. Yield (69%); mp 250–252°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.26 (m, 4H, cyclohexane H), 1.78 (m, 6H, cyclohexane H), 6.23 (m, 2H, pyrrole H-3, H-4), 6.89 (m, 2H, pyrrole H-2, H-5), 7.21 (m, 2H, ArH), 7.42 (m, 3H, ArH), 8.24 (s, 1H, pyrazole H). IR (KBr): 1640 cm^{-1} (C=N). Anal. Calcd. for $C_{19}H_{20}N_4$ (304.39): C, 74.97; H, 6.62; N, 18.41. Found: C, 75.00; H, 6.60; N, 18.35.

N-(1-Methylpiperidin-4-ylidene)-1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-ylamine (5c). This compound was obtained as yellow crystals. Yield (70%); mp 246–248°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.56 (m, 4H, piperidine H), 1.88 (m, 4H, piperidine H), 2.30 (s, 3H, CH_3), 6.25 (m, 2H, pyrrole H-3, H-4), 6.87 (m, 2H, pyrrole H-2, H-5), 7.19 (m, 2H, ArH), 7.37 (m, 3H, ArH), 8.19 (s, 1H, pyrazole H); IR (KBr): 1640 cm^{-1} (C=N). Anal. Calcd. for $C_{19}H_{21}N_5$ (319.40): C, 71.45; H, 6.63; N, 21.93. Found: C, 71.51; H, 6.60; N, 21.99.

General procedure for the preparation of cycloalkanespiro-2′-(3′-(1-phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazole-4-yl)thiazolidin-4′-one) derivatives (6a,b). A mixture of compounds **5a,b** (1 mmol) and mercaptoacetic acid (184 mg, 2 mmol) in 10 mL of dry benzene was refluxed in Dean-Stark apparatus for 48 h. Then, the solvent was evaporated and the residue obtained was treated with 10% sodium bicarbonate solution. The precipitate formed was filtered, washed with H_2O, air dried, and recrystallized from methanol to give **6a,b**.

Cyclopentanespiro-2′-(3′-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl) thiazolidin-4′-one) (6a). This compound was obtained as buff crystals. Yield (66%); mp 188–190°C; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.56 (m, 4H, cyclopentane H), 1.88 (m, 4H, cyclopentane H), 3.72 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.82 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 6.24 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz,), 6.56 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.06 (m, 3H, ArH), 7.23 (m, 2H, ArH), 7.78 (s, 1H, pyrazole H); IR (KBr): 1680 cm^{-1} (C=O). Anal. Calcd. for $C_{20}H_{20}N_4OS$ (364.47): C, 65.91; H, 6.60; N, 15.37. Found: C, 65.95; H, 5.53; N, 15.39.

Cyclohexanespiro-2′-(3′-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl) thiazolidin-4′-one) (6b). This compound was obtained as pale yellow crystals. Yield (69%); mp 214–216°C; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.30 (m, 4H-cyclohexane H), 1.79 (m, 6H-cyclohexane H), 3.74 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 3.84 (d, 1H, thiazolidinone H, *J* = 15.8 Hz), 6.18 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz), 6.47 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.10 (m, 3H, ArH), 7.26 (m, 2H, ArH), 7.85 (s, 1H, pyrazole H); IR (KBr): 1670 cm^{-1} (C=O). Anal. Calcd. for $C_{21}H_{22}N_4OS$ (378.15): C, 66.64; H, 5.86; N, 14.80. Found: C, 66.56; H, 5.90; N, 14.75.

1-Methylpiperidine-4-spiro-2′-(3′-(1-phenyl-5-(1H-pyrrol-1-yl)-1H-pyrazol-4-yl) thiazolidin-4′-one) (6c). A mixture of **5c** (319 mg, 1 mmol) and mercaptoacetic acid (184 mg, 2 mmol) in 10 mL of dry benzene was refluxed in Dean-Stark apparatus for 48 h. Then, the solvent was evaporated, and the residue was treated with 10% sodium bicarbonate solution. The precipitate formed was filtered, washed with H_2O, air dried, and recrystallized from ethanol to give **6c** as buff crystals. Yield: 0.30 g (76%); mp 178–180°C; ^{1}H-NMR (90 MHz, $CDCl_3$): δ = 1.48 (m, 4H-piperidine), 1.88 (m, 4H, piperidine H), 2.35 (s, 3H, CH_3), 6.28 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz), 6.62 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.11 (m, 3H, ArH), 7.33 (m, 2H, ArH), 7.80 (s, 1H, pyrazole H); IR (KBr): 1680 cm^{-1} (C=O). Anal. Calcd. for $C_{21}H_{23}N_5OS$ (393.51): C, 64.10; H, 5.89; N, 17.80. Found: C, 64.02; H, 5.85; N, 17.82.

1-Phenyl-5-(1*H*-pyrrol-1-yl)-1*H*-pyrazol-4-ylammonium chloride (7). A mixture of **1** (224 mg, 1 mmol) and 5 mL of 10*N* of HCl in 10 mL of 2-propanol was heated under reflux for 1 h. The reaction mixture was concentrated and left to cool. The solvent was removed under reduced pressure, and the residue obtained was triturated with ethanol. The solid product formed was filtered off, dried, and recrystallized from 2-propanol to afford **7** as white crystals. Yield: 0.240 g (92%); mp 201–202°C (ref. 15, 203°C, 88%); ^{1}H-NMR (90 MHz, DMSO-d_6): δ = 3.46 (bs, $^+NH_3$), 6.30 (t, 2H, pyrrole H-3, H-4, *J* = 1.9 Hz), 6.87 (t, 2H, pyrrole H-2, H-5, *J* = 1.9 Hz), 7.08 (m, 2H, ArH), 7.30 (m, 3H, ArH), 8.13 (s, 1H, pyrazole H); IR (KBr): 3400–3300 ($^+NH_3$), 1620 cm^{-1} (C=N). Anal. Calcd. for $C_{13}H_{13}ClN_4$ (260.72): C, 59.89; H, 5.03; N, 21.49. Found: C, 59.90; H, 5.10; N, 21.53.

General procedure for preparation of 1-phenyl-5-substitued-4,5-dihydro-1*H*-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazines (8a–e). A mixture of **7** (260 mg, 1 mmol) and the appropriate aromatic aldehyde (1 mmol) in absolute ethanol (10 mL) was heated under reflux for 3 h. The solvent was then evaporated to dryness. The solid precipitate formed was collected by filtration and recrystallized from anhydrous ethanol to give the corresponding derivatives **8a–e**.

1,5-Diphenyl-4,5-dihydro-1H-pyrazolo[4,3-e]pyrrolo[1,2-a]-pyrazine (8a). This compound was obtained as pale brown crystals. Yield (48%); mp 175–177°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.85 (s, 1H, pyrazine H), 6.43 (m, 1H, pyrrole H), 6.60 (m, 1H, pyrrole H), 6.87 (m, 1H, pyrrole H), 7.54 (m, 3H, ArH), 7.64 (m, 5H, ArH), 7.87 (m, 2H, ArH), 8.37(s, 1H, pyrazole H), 9.53 (s, 1H, NH); IR (KBr): 3300 (NH), 1600 cm^{-1} (C=N); MS: *m/z* (%) = 312 [M$^+$] (4), 311 [M − 1] (29), 310 (100), 309 (18), 308 (2), 305 (3), 284 (7), 282 (7), 179 (13), 155 (11), 77 (12). Anal. Calcd. for $C_{20}H_{16}N_4$ (312.37): C, 76.90; H, 5.16; N, 17.94. Found: C, 77.01; H, 5.15; N, 17.90.

1-Phenyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazolo[4,3-e]-pyrrolo[1,2-a]pyrazine (8b). This compound was obtained as pale yellow crystals. Yield (59%); mp 187–189°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.28 (m, 1H, pyrazine H), 6.88 (m, 1H, pyrrole H), 7.00 (m, 1H, pyrrole H), 7.07 (m, 1H, pyrrole H), 7.62 (d, 2H, ArH, *J* = 8.5 Hz), 7.68 (m, 3H, ArH), 7.72 (m, 2H, ArH), 7.94 (d, 2H, ArH, *J* = 8.5 Hz), 8.39 (s, 1H, pyrazole H), 8.56 (s, 1H, NH, D_2O exchangeable); IR (KBr): 3400 (NH), 1610 cm^{-1} (C=N); MS: *m/z* (%) = 348 (2), 347 (10), 346 [M$^+$] (37), 345 (27), 344 (100), 343 (12), 310 (8), 308 (2), 179 (15), 155 (7), 77 (16). Anal. Calcd. for $C_{20}H_{15}ClN_4$ (346.81): C, 69.26; H, 4.36; N, 16.15. Found: C, 69.20; H, 4.31; N, 16.15.

1-Phenyl-5-(4-methoxyphenyl)-4,5-dihydro-1-H-pyrazolo[4,3-e]-pyrrolo[1,2-a]pyrazine (8c). This compound was obtained as greenish yellow crystals. Yield (58%); mp 128–130°C; ^{1}H-NMR (90 MHz, DMSO-d_6): δ = 3.78 (s, 3H, OCH_3), 6.17 (m, 1H, pyrazine H), 6.72 (m, 1H, pyrrole H), 7.08 (m, 1H, pyrrole H), 7.16 (m, 1H, pyrrole H), 7.58 (d, 2H, ArH, *J* = 8.5 Hz), 7.65 (m, 3H, ArH), 7.76 (m, 2H, ArH), 7.90 (d, 2H, ArH, *J* = 8.5 Hz), 8.35 (s, 1H, pyrazole H), 8.60 (s, 1H, NH, D_2O exchangeable); IR (KBr): 3350 (NH), 1600 cm^{-1} (C=N). Anal. Calcd. for $C_{21}H_{18}N_4O$ (342.39): C, 73.67; H, 5.30; N, 16.36. Found: C, 73.74; H, 5.33; N, 16.30.

1-Phenyl-5-(4-dimethyaminoyphenyl)-4,5-dihydro-1H-pyrazolo[4,3-e]pyrrolo [1,2-a]pyrazine (8d). This compound was obtained as yellow crystals. Yield (70%); mp 256–258°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 2.97 (s, 6H, $2CH_3$), 6.24 (m, 2H, pyrazine H + pyrrole H), 6.73 (m, 2H, ArH), 6.85 (m, 2H, pyrrole H), 7.10 (d, 2H, ArH, *J* = 8.5 Hz), 7.35 (m, 3H, ArH), 7.57 (d, 2H, ArH, *J* = 8.5 Hz), 8.12 (s, 1H, pyrazole H), 8.56 (s, 1H, NH, D_2O exchangeable); IR (KBr): 3300 (NH), 1600 cm^{-1} (C=N). MS: *m/z* (%) = 357 (M + 2) (9), 356 (M + 1)

(40), 355 (M^+) (100), 354 (M − 1) (15), 327 (7), 311 (14), 310 (43), 208 (9), 179 (10), 177 (14), 169 (38), 159 (15), 155 (5), 77 (35). Anal. Calcd. for $C_{22}H_{21}N_5$ (355.44): C, 74.34; H, 5.96; N, 19.70. Found: C, 74.45; H, 5.99; N, 19.64.

1-Phenyl-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazolo[4,3-e]-pyrrolo[1,2-a]pyrazine (8e). This compound was obtained as yellow crystals. Yield (57%); mp 256–258°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.69 (s, 1H, pyrazine H), 5.75 (m, 1H, pyrrole H), 6.12 (m, 1H, pyrrole H), 6.33 (m, 1H, pyrrole H), 7.53 (m, 5H, ArH), 7.68 (d, 2H, ArH, J = 8.5 Hz), 8.21 (d, 2H, ArH, J = 8.5 Hz), 8.41 (s, 1H, pyrazole H), 8.57 (s, 1H, NH, D_2O exchangeable); IR (KBr): 3350 (NH), 1620, 1600 cm^{-1} (C=N); MS: m/z (%) = 358 (M + 1) (12), 357(M^+) (48), 356 (M − 1) (35), 355 (M − 2) (100), 354 (5), 310 (7), 309 (14), 308 (6), 282 (7), 236 (17), 235 (76), 179 (8), 178 (5), 177 (4), 167 (11), 155 (6), 149 (34), 77 (19). Anal. Calcd. for $C_{20}H_{15}N_5O_2$ (357.37): C, 67.22; H, 4.23; N, 19.60. Found: C, 67.18; H, 4.21; N, 19.65.

General procedure for preparation of 1-phenyl-5-cycloalkanespiro-4,5-dihydro-1*H*-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazines (9a,b). A mixture of **7** (260 mg, 1 mmol) and the appropriate cyclic ketones (1 mmol) in 10 mL of absolute ethanol was heated under reflux for 4 h. The reaction mixture was concentrated, and the solid product obtained on cooling was collected by filtration and recrystallized from ethanol to give the corresponding derivatives **9a,b**.

1-Phenyl-1H,4H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine-5-spirocyclopentane. This compound was obtained as buff crystals. Yield (62%); mp 252–254°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.60 (m, 4H, cyclopentane H), 1.95 (m, 4H, cyclopentane H), 6.00 (m, 1H, pyrrole H), 6.18 (m, 1H, pyrrole H), 6.87 (m, 1H, pyrrole H), 6.98 (m, 3H, ArH), 7.28 (m, 2H, ArH), 8.14 (s, 1H, pyrazole H), 8.27 (s, 1H, NH) IR (KBr): 3300 (NH), 1620 cm^{-1} (C=N). Anal. Calcd. for $C_{18}H_{18}N_4$ (290.36): C, 74.46; H, 6.25; N, 19.30. Found: C, 74.51; H, 6.24; N, 119.28.

1-Phenyl-1H,4H-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine-5-spirocyclopentane. This compound was obtained as buff crystals. Yield (42%); mp 248–250°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.20 (m, 4H, cyclohexane H), 1.76 (m, 6H, cyclohexane H), 6.05 (m, 1H, pyrrole H), 6.28 (m, 1H, pyrrole H), 6.89 (m, 1H, pyrrole H), 7.00 (m, 3H, ArH), 7.29 (m, 2H, ArH), 8.12 (s, 1H, pyrazole H), 8.29 (s, 1H, NH); IR (KBr): 3220 (NH), 1620 cm^{-1} (C=N). Anal. Calcd. for $C_{19}H_{20}N_4$ (304.39): C, 74.97; H, 6.62; N, 18.41. Found: C, 75.02; H, 6.55; N, 18.31.

1-Phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazin-5-one (10). A mixture of **1** (224 mg, 1 mmol) and (162 mg, 1 mmol) of CDI in 10 mL of dioxane was heated under reflux for 6 h. The solvent was removed under reduced pressure, and the residue obtained was triturated with water. The solid product formed was filtered off, dried, and recrystallized from ethanol to afford **10** as white crystals. Yield: 0.210 g (84%); mp 296–298°C (ref. 9, 297–298°C, 53%); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.36 (m, 1H, pyrrole H), 6.68 (m, 1H, pyrrole H), 6.94 (m, 1H, pyrrole H), 7.22 (m, 3H, ArH), 7.78 (m, 2H, ArH), 8.18 (s, 1H, pyrazole H), 11.50 (s, 1H, NH); IR (KBr): 3380 (NH), 1690 (C=O), 1620 cm^{-1} (C=N); MS: m/z (%) = 250 [M^+] (75), 223 (100), 206 (15), 195 (66), 180 (19), 168 (91), 130 (24), 128 (20), 93 (19), 87 (20), 78 (18), 76 (92), 66 (49). Anal. Calcd. for $C_{14}H_{10}N_4O$ (250.26): C, 67.19; H, 4.03; N, 22.39. Found: C, 67.26; H, 4.09; N, 22.42.

1-Phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-e]pyrrolo[1,2-a]pyrazine-5-thione (11). ***Method A.*** A mixture of **1** (224 mg, 1 mmol) and 3 mL of CS_2 in 10 mL of dry pyridine was heated under reflux for 8 h. The solvent was removed under reduced pressure, and the residue formed was diluted with water. The solid product obtained was filtered off, dried, and recrystallized from ethanol to give **11** as buff crystals. Yield: 0.156 g (58%); mp 206–208°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.32 (m, 1H, pyrrole H), 6.63 (m, 1H, pyrrole H), 6.98 (m, 1H, pyrrole H), 7.20 (m, 3H, ArH), 7.71 (m, 2H, ArH), 8.15 (s, 1H, pyrazole H), 11.80 (s, 1H, NH); IR (KBr): 3200 (NH), 1620 (C=N), 1170 cm^{-1} (C=S); MS: m/z (%) = 266 [M^+] (57), 265 (7), 255 (11), 250 (10), 249 (51), 238 (39), 223 (57), 210 (13), 210 (13), 206 (34), 196 (40), 195 (33), 193 (52), 180 (36), 168 (45), 130 (35), 128 (28), 93 (20), 78 (12), 76 (100), 67 (66). Anal. Calcd. for $C_{14}H_{10}N_4S$ (266.32): C, 63.14; H, 3.78; N, 21.04. Found: C, 63.15; H, 3.72; N, 21.11.

Method B. A mixture of **1** (224 mg, 1 mmol) and P_2S_5 (442 mg, 2 mmol) in 10 mL of dry pyridine was heated under reflux for 4 h. The solvent was removed under reduced pressure, and the residue formed was diluted with water. The solid product obtained was filtered off, dried, and recrystallized from ethanol to give **11** as buff crystals. Yield 0.136 g (51%); mp 206–208°C.

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