New pyrazole derivatives of potential biological activity

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Dedicated to Professor Keith Smith on the occasion of his 65th anniversary

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Abstract

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (**1**) was reacted with hydrazine hydrate and thiosemicarbazide to afford the corresponding hydrazones **2** and thiosemicarbazones **4**. The latter compounds were used to obtain the pyrazole derivatives **3, 5-7**. A series of azines **8a-e** were obtained by reacting **2** with aromatic aldehydes. Potassium permanganate oxidation of **1** gave the acid **9**, which was transformed into the corresponding acid azide **11** then used to prepare diverse urea derivatives **13-18** via Curtius reaction**.**

Keywords: Pyrazoles, ureas, hydrazones, thiosemicarbazones, thiadiazolidinones, imidazolidinones

Introduction

Pyrazole derivatives are known to exhibit a wide range of biological properties, such as anti-inflammatory,[1-5] antimicrobial,[5-7] antioxidant,[6] anticancer,[8] fungicidal,[9] and antiviral activities.[8,10,11] Some pyrazole derivatives were reported to possess high affinity and selectivity towards A_{2b} adenosine receptor antagonists.[12] Particularly, aryl pyrazoles are important in medicinal and pesticidal chemistry.[13] Some aryl pyrazoles were reported to have non-nucleoside

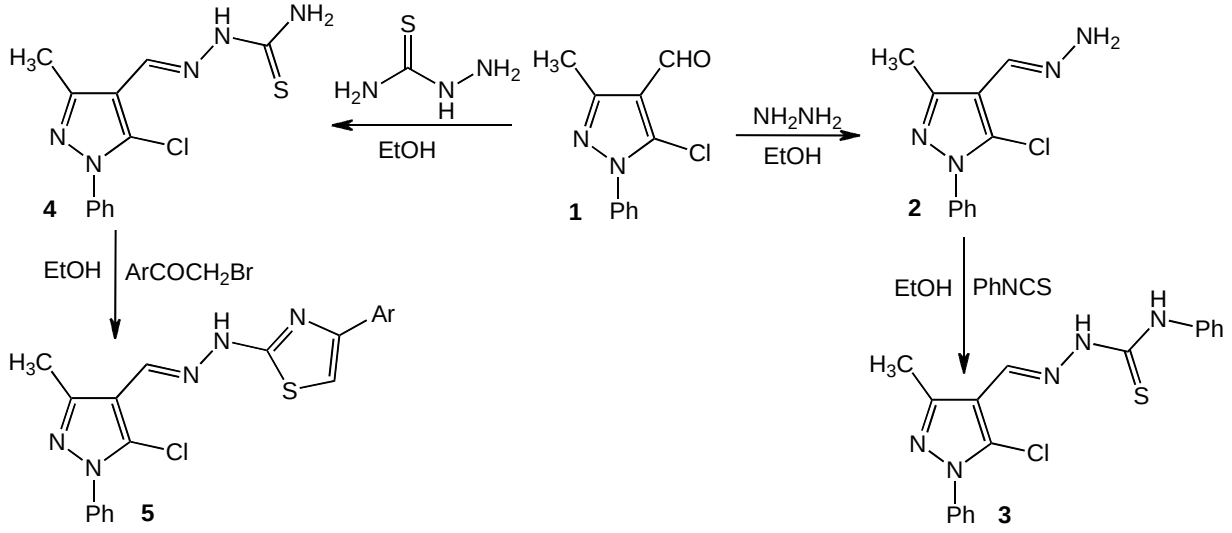
HIV-1 reverse transcriptase inhibitory activity.[11] Also, it was reported that pyrazole-4-carboxylic acid hydrazides and corresponding hydrazones possess antimicrobial activity.[14]

In the light of the above report, and in continuation to our previous work,[15-17] we report herein the synthesis of new pyrazole derivatives of potential biological activity.

Results and Discussion

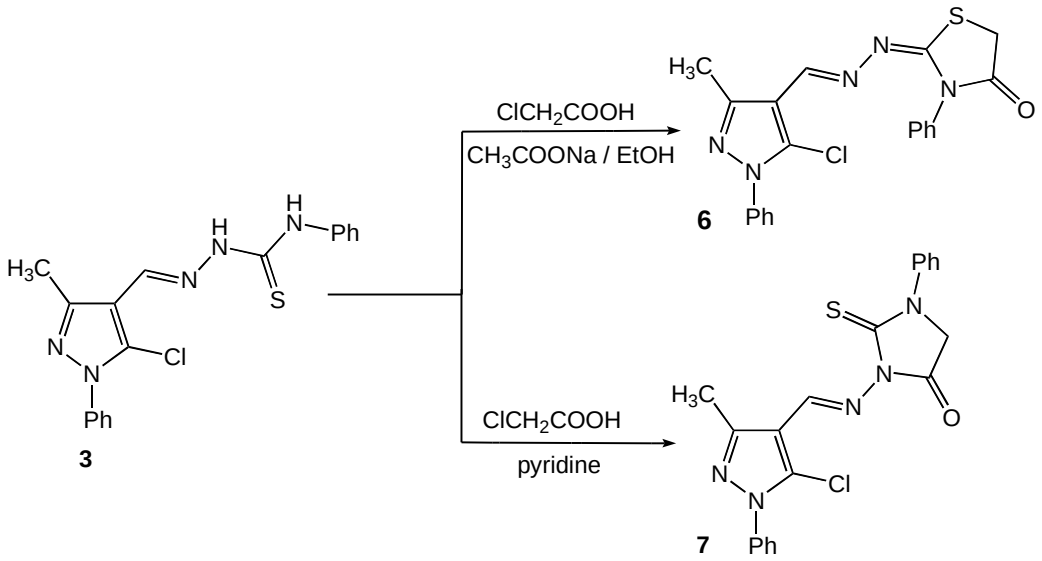
5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (**1**) was utilized as a starting material. This aldehyde could be obtained from the easily accessible 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one under Vilsmeier-Haack reaction conditions.[18] Treatment of **1** with hydrazine hydrate gave the corresponding hydrazone **2**, which was allowed to react with phenyl isothiocyanate to give the thiosemicarbazone derivative **3**.[19]

The thiazole **5** was obtained in a two-step sequence by reacting **1** with thiosemicarbazide to afford the corresponding thiosemicarbazone **4** followed by treatment with phenacyl bromide, in a similar procedure to that reported before.[20] The IR spectrum of compound **4** showed absorption bands at ν_{max} = 3400, 3270 and 3150 cm^{-1} due to ν_{NH2} and ν_{NH}. Its ^{1}H NMR spectrum showed a singlet at δ 11.44 ppm (NH), a singlet at δ 8.27 ppm (NH_2) and a singlet at δ 8.09 ppm (CH=N), while the ^{1}H NMR spectrum of **5** was characterized by a singlet at δ 6.86 ppm due to the C-5 proton of the thiazole ring, and the absence of the NH_2 signal shown by **4**. The two-hydrogen singlet in the ^{1}H NMR spectrum of **2** at δ 5.48 (NH_2) was replaced by two one-hydrogen singlets at δ 9.86 and 9.15 ppm in the ^{1}H NMR spectrum of **3** corresponding to two N-hydrogens.



Scheme 1

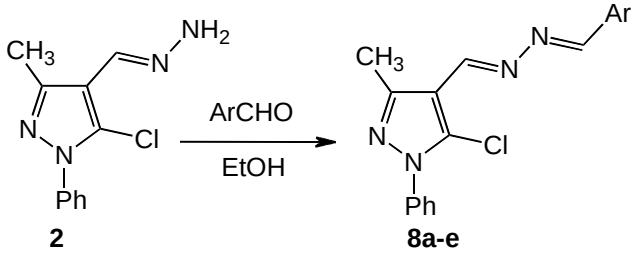
Two products were obtained when the thiosemicarbazone **3** was reacted with chloroacetic acid under different conditions. Thus, when the reaction was carried out in boiling ethanol in presence of sodium acetate, the corresponding thiazolidinone derivative **6** was produced, while the reaction yielded the thioxoimidazolidinone **7** when it was carried out in refluxing pyridine (Scheme 2). This is in accordance with earlier reports.[21]



Scheme 2

The structure of the thiazolidinone **6** was supported by its IR spectrum which showed the characteristic band of $\nu_{C=O}$ of the thiazolidinone ring at ν_{max} = 1720 cm^{-1}. Its ^{1}H NMR spectrum showed a singlet for two protons at δ 3.71 ppm for the CH_2 group of thiazolidinone. The IR spectrum of thioxoimidazolidinone **7** showed characteristic IR bands at 1720 cm^{-1} ($\nu_{C=O}$) and 1290 cm^{-1} ($\nu_{C=S}$) and in the ^{1}H NMR spectrum there was a singlet at δ 3.96 ppm for the CH_2 protons.

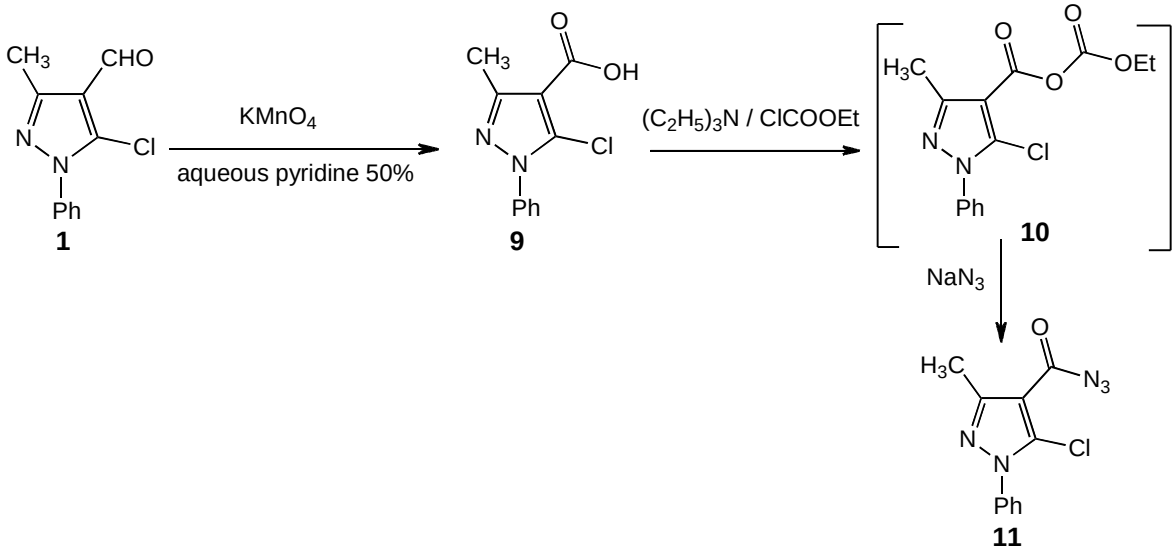
Reaction of the hydrazone **2** with aromatic aldehydes in ethanol under reflux gave the corresponding hydrazones **8a-e** (Scheme 3).



8	Ar
a	C_6H_5
b	4-$O_2NC_6H_4$
c	4-$(CH_3)_2NC_6H_4$
d	4-$CH_3OC_6H_4$
e	5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl

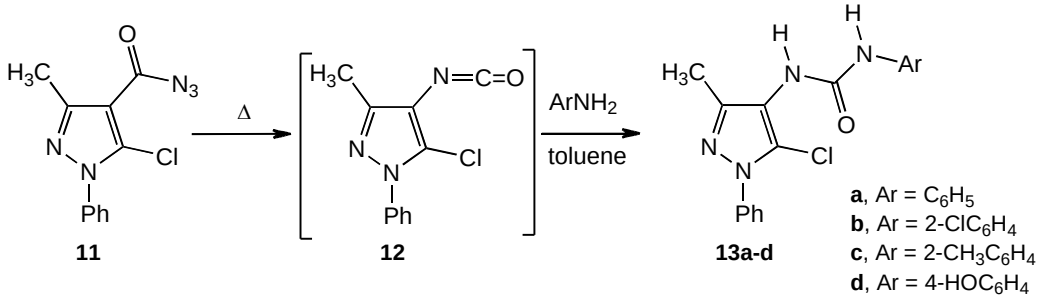
Scheme 3

Certain pyrazolylurea derivatives have been reported as p38 MAP Kinase inhibitors.[22,23] This encouraged us to synthesize a number of different unknown pyrazolylurea derivatives. The key intermediate for this objective is the 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid azide (**11**), which was prepared in a two-step sequence starting from the pyrazolecarboxaldehyde **1**. Thus, **1** was first oxidized by $KMnO_4$ to the corresponding acid **9**[18, 24] followed by a direct conversion into its acid azide **11**, by treating a solution of **9** in acetone successively with TEA then with ethyl chloroformate to give the mixed anhydride **10** which was then reacted with NaN_3 to give **11** (Scheme 4). The IR spectrum of compound **11** showed the two characteristic absorption bands of an acyl azide at ν_{max} = 2150 and 1680 cm^{-1}.

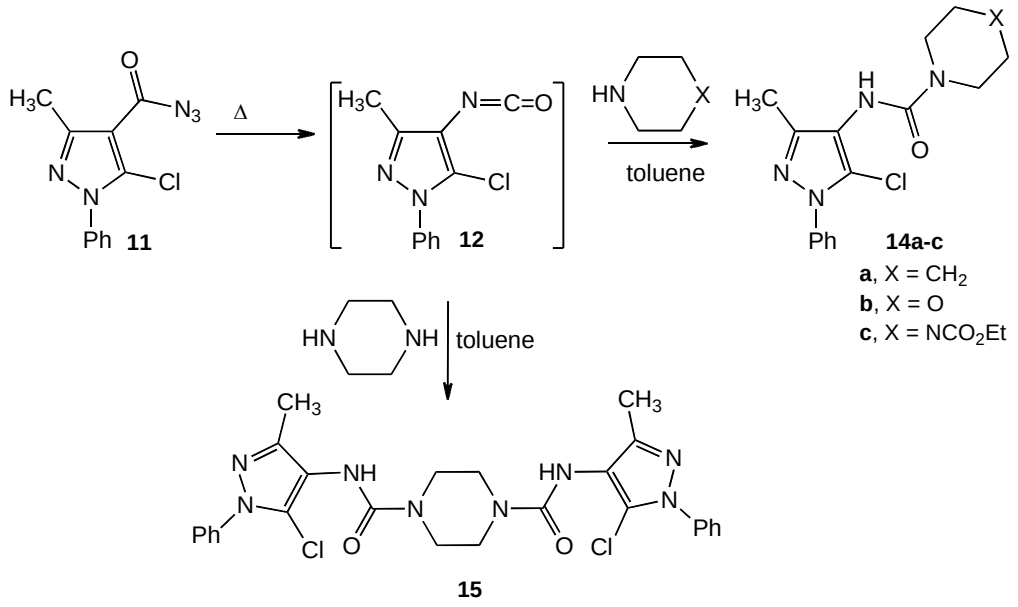


Scheme 4

Compound **11** was reacted with several primary aromatic amines in refluxing toluene to give the corresponding disubstituted ureas **13a-d** (Scheme 5). The transformation involved a Curtius rearrangement of **11** leading to the *in situ* formation of the isocyanate **12** which reacted subsequently with the amines giving the ureas **13a-d**.

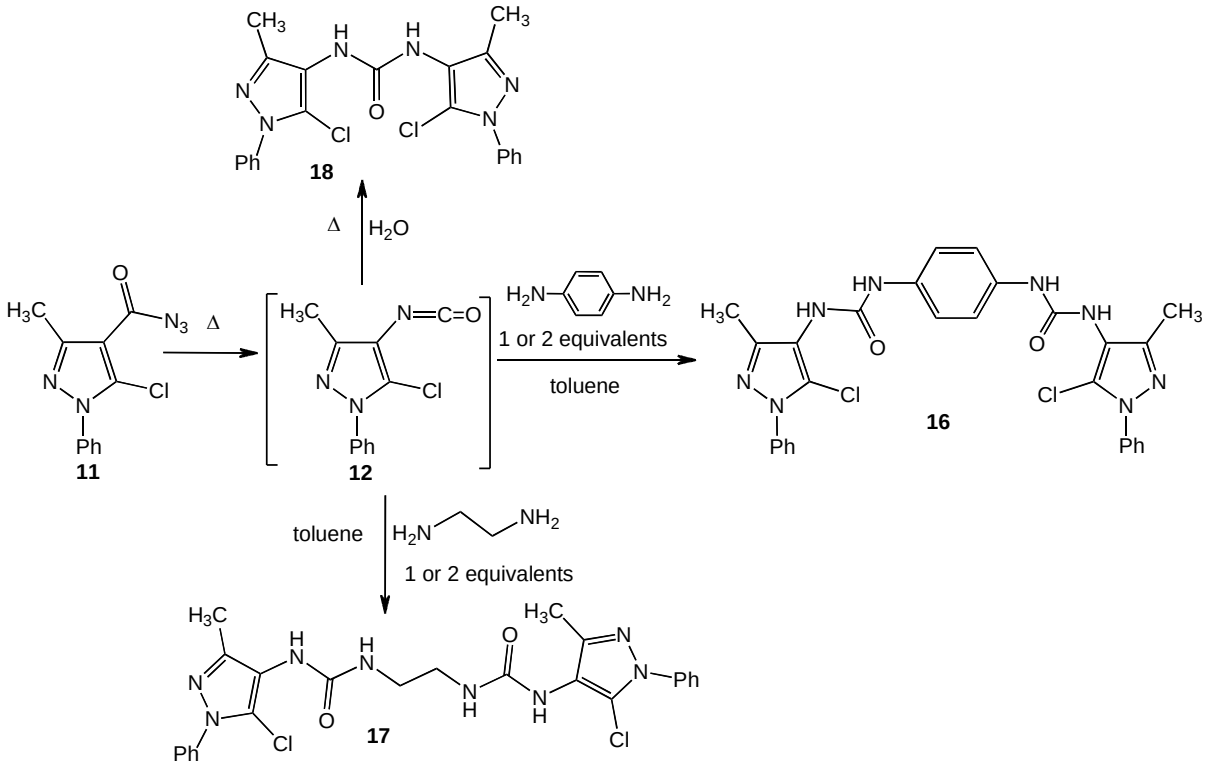


Scheme 5



Scheme 6

Similarly, treatment of **11** with secondary amines *viz* piperidine, morpholine and ethyl piperazine-1-carboxylate, in boiling toluene, led to the formation of the corresponding trisubstituted ureas **14a-c**, while its reaction with piperazine itself gave the corresponding bis urea derivative **15** whether one or two equivalents of the acid azide were used (Scheme 6).



Scheme 7

Also, when the above reaction was applied to other diamines such as phenylene-1,4-diamine or ethylenediamine, the bis ureas **16** and **17** were obtained whether one or two equivalents of amine were used. The symmetric disubstituted urea **18** was obtained when the acid azide **11** was heated in boiling water (Scheme 7).

The IR spectra of the ureas **13-18** showed υ_{NH} bands in the range ν_{max} = 3300-3250 cm^{-1} and $\nu_{C=O}$ bands in the range ν_{max} =1640-1635 cm^{-1} with the disappearance of ν_{CON3} band (ν_{max} = 2150 and 1680 cm^{-1}) of the starting acid azide. The ^{1}H NMR and ^{13}C-NMR spectra of all the ureas are given in the Experimental Section.

Experimental Section

General. Melting points were measured on Stuart melting point apparatus (Bibby Scientific) SMP3. The IR spectra were recorded on a Shimadzu 470 IR-Spectrophotometer using KBr wafer technique. The ^{1}H NMR spectra were recorded on a Bruker ARX 200 spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C) at the Faculty of Pharmacy, University of Aix Marseille, France, and on a Jeol LA 400 MHz (400 MHz for ^{1}H, 100 MHz for the ^{13}C) at Assiut university, ^{1}H and ^{13}C NMR chemical shifts (δ) were reported in parts per million (ppm) and were referenced to the solvent peak; $CDCl_3$ (7.26 ppm for ^{1}H and 76.90 ppm for ^{13}C) and DMSO-d_6 (2.50 ppm for ^{1}H and 39.70 ppm for ^{13}C). Multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained with a Jeol JMS-600 mass spectrometer (Assiut University). Elemental analyses were carried out using a Perkin-Elmer 240C Microanalyzer at the Microanalytical Laboratory, Faculty of Science, Assiut University, and the results were in an acceptable range (± 0.4%).

The starting materials, 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde (**1**)[18] and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid (**9**)[18,24] were previously reported.

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxaldehyde hydrazone (**2**)**.** To a suspension of **1** (440 mg, 2 mmol) in methanol (10 mL), hydrazine hydrate (0.5 mL, 10 mmmol) was added. The reaction mixture was stirred at room temperature for 30 min., then it was heated under reflux for 4 h and left to stand overnight at rt. The solid precipitate formed was filtered off and recrystallized from petroleum ether/ethyl acetate (2:1) to afford **2** as buff crystals (240 mg, 52%), mp 96-98 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H, CH_3), 5.48 (s, 2H, NH_2), 7.36-7.41 (m, 3H, ArH), 7.46-7.55 (m, 2H, ArH), 7.75 (s, 1H, N=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.44 ($\underline{C}H_3$), 113.58 (C), 124.83 (2$\underline{C}$H), 128.14 ($\underline{C}$H), 129.00 (2$\underline{C}$H), 135.31 ($\underline{C}$-Cl), 137.95 (C), 148.66 ($\underline{C}$H=N), 153.36 ($\underline{C}$-CH_3); IR (KBr, cm^{-1}): ν_{max} 3370, 3200 (NH_2), 3050 (CH arom.), 2910 (CH aliph.), 1620 (C=N), 1600 (C=C). Anal. Calcd for $C_{11}H_{11}ClN_4$ (234.69): C, 56.30; H, 4.72; N, 23.87. Found: C, 56.37; H, 4.65; N, 23.78%.

***N*^{1}-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-*N*^{4}-phenylthiosemicarbazone (3)**[19]. A mixture of hydrazone **2** (235 mg, 1 mmol) and phenyl isothiocyanate (1 mg, 1 mmol) in absolute ethanol (10 mL) was heated under reflux for 6 h. The mixture was then cooled and the solid product obtained was filtered of and recrystallized from ethanol to give **3** (230 mg, 62%) as pale buff crystals, mp 178-180 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H, CH_3), 7.22-7.26 (m, 2H, ArH), 7.38-7.56 (m, 6H, ArH), 7.69-7.71 (m, 2H, ArH), 7.94 (s, 1H, N=CH), 9.15 (s, 1H, NH), 9.86 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.82 (CH_3), 112.44 (C), 123.70 (2CH), 124.88 (2CH), 125.98 (CH), 128.44 (C), 128.83 (2CH), 129.18 (2CH), 134.95 (C-Cl), 137.33 (C), 137.45 (C), 137.83 (CH=N), 148.95 (C-CH_3), 175.12 (C=S); IR (KBr, cm^{-1}): ν_{max} 3300, 3150 (NH), 3050, (CH arom.), 2990 (CH aliph.), 1590 (C=N), 1550 (C=C). Anal. Calcd for $C_{18}H_{16}ClN_5S$ (369.88): C, 58.45; H, 4.36; N, 18.93. Found: C, 58.36; H, 4.29; N, 18.87%.

***N*^{1}-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)thiosemicarbazone (4).** To a solution of **1** (220 mg, 1 mmol) in ethanol (10 mL), thiosemicarbazide (91 mg, 1 mmol) in water (3 mL) was added. The reaction mixture was heated under reflux for 2 h. The solid precipitate formed was filtered off and recrystallized from ethanol/chloroform (2:1) to give **4** (240 mg, 83%) as pale buff crystals, mp 250-252 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.46 (s, 3H, CH_3), 7.56-7.29 (m, 5H, ArH), 8.09 (s, 2H, NH_2), 8.27 (s, 1H, N=CH), 11.44 (s, 1H, NH); IR (KBr, cm^{-1}): ν_{max} 3150, 3270, 3400 (NH, NH_2), 3000 (CH arom.), 2910 (CH aliph.), 1590 (C=N). Anal. Calcd for $C_{12}H_{12}ClN_5S$ (293.78): C, 49.06; H, 4.12; N, 23.84**.** Found: C, 49.15; H, 4.05; N, 23.77%.

(2-(2-((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazino)-4-phenyl-1,3-thiazole (**5**). A mixture of thiosemicarbazone **4** (290 mg, 1 mmol) and phenacyl bromide (199 mg, 1 mmol) in dioxane (10 mL) was heated under reflux for 6 h. The reaction mixture was left to stand overnight at rt. The solid product formed was collected by filtration and recrystallized from ethanol to afford **5** (320 mg, 82%) as buff crystals, mp 120-122 ºC . ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3H, CH_3), 6.86 (s, 1H, CH thiazole), 7.37-7.41 (m, 2H, ArH), 7.50-7.54 (m, 6H, ArH),7.56 (s, 1H, N=CH), 7.81-7.85 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.79 (CH_3), 103.13 (CH-S), 113.35 (C), 124.72 (2CH), 126.02 (CH), 126.77 (2CH), 128.22 (C), 128.90 (2CH), 129.00 (2CH), 134.33 (C), 134.43 (C-Cl), 137.73 (C), 144.63 (CH=N), 149.02 (C-CH_3), 150.63 (C), 170.43 (N=C-S); IR (KBr, cm^{-1}): ν_{max} 3040 (CH arom.), 2990, 2900 (CH aliph.), 1640 (C=N). Anal. Calcd for $C_{20}H_{16}ClN_5S$ (393.89): C, 60.98; H, 4.09; N, 17.78. Found: C, 60.88; H, 4.11; N, 17.67%.

2-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylenehydrazono)-3-phenylthiazolidin-4-one (6). A mixture of **3** (370 mg, 1 mmol), monochloroacetic acid (95 mg, 1 mmol) and sodium acetate (80 mg, 1 mmol) in absolute ethanol (10 ml) was heated under reflux for 20 h. After cooling, the reaction mixture was poured onto crushed ice, the separated solid precipitate was filtered off, dried and recrystallized from 1,4-dioxane to give **6** (270 mg, 66%) as colorless crystals, mp 236-238 ºC. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 3.71 (s, 2H, CH_2 thiazolidinone), 7.01-7.36 (m, 10H, ArH), 8.42 (s, 1H, N=CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.07 (CH_3), 30.90 (CH_2), 113.61 (C), 124.85 (2CH), 127.11 (CH), 128.00 (CH), 128.47 (2CH), 129.04 (2CH), 129.37 (2CH), 134.46 (C-Cl), 137.20 (C), 137.58 (C), 150.19 (CH=N), 150.53

(C-CH_3), 163.81 (C), 171.81 (C=O); IR (KBr, cm^{-1}): ν_{max} 3050, (CH arom.), 2990, 2900, 2820 (CH aliph.), 1720 (C=O). Anal. Calcd for $C_{20}H_{16}ClN_5OS$ (409.89): C, 58.60; H, 3.93; N, 17.09. Found: C, 58.49; H, 3.87; N, 17.17%.

3-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyleneamino)-1-phenyl-2-thioxo-imidazolidin-4-one (7). A mixture of **3** (0.370 mg, 1 mmol) and monochloroacetic acid (95 mg, 1 mmol) in pyridine (10 mL) heated under reflux for overnight. After cooling, the resulting mixture was poured onto crushed ice, the solid product formed was filtered off, air dried and recrystallized from ethanol/chloroform (2:1) to give **7** (310 mg, 76%) as brown crystals, mp 228-230 ºC. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 7.41-7.57 (m, 10H, ArH), 8.33 (s, 1H, N=CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.92 (CH_3), 63.25 (CH_2), 113.53 (C), 124.98 (2CH), 126.23 (CH), 127.76 (CH), 128.55 (2CH), 129.13 (2CH), 129.41 (2CH), 134.28 (C-Cl), 137.72 (C), 150.35 (C), 155.19 (CH=N), 156.00 (C-CH_3), 172.30 (C=O), 184.07 (C=S); IR (KBr**,** cm^{-1}): ν_{max} 3070, (CH arom.), 2990, 2900 (CH aliph.), 1720 (C=O), 1290 (C=S). Anal. Calcd for $C_{20}H_{16}ClN_5OS$ (409.89): C, 58.60; H, 3.93; N, 17.09. Found: C, 58.49; H, 3.84; N, 17.18%.

General procedure for the synthesis of *N*-((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)- *N′*-(arylidene)hydrazine (8a-e). A mixture of the hydrazone **2** (240 mg, 1 mmol) and appropriate aromatic aldehydes (1 mmol) in ethanol (10 mL) was heated under reflux for 3 h. After cooling, the solid precipitate formed was collected by filtration and recrystallized from an appropriate solvent to afford **8a-e**.

***N*-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-*N′*-benzylidenehydrazine (8a).** Yellow crystals (ethanol) (250 mg, 78%), mp 142-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H, CH_3), 7.42-7.58 (m, 8H, ArH), 7.83-7.86 (m, 2H, ArH), 8.67 (s, 1H, N=CH),), 8.69 (s, 1H, N=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.85 (CH_3), 113.46 (C), 124.93 (2CH), 128.53 (CH), 128.44 (2CH), 128.75 (2CH), 129.08 (2CH), 131.17 (CH), 134.13 (C-Cl), 137.65 (C), 150.34 (C), 153.35 (C-CH_3), 154.02 (CH=N), 161.54 (CH=N); IR (KBr, cm^{-1}): ν_{max} 3040, (CH arom.), 2980, 2900 (CH aliph.), 1640 (C=N). Anal. Calcd for $C_{18}H_{15}ClN_4$(322.80): C, 66.98; H, 4.68; 10.98; N, 17.36. Found: C, 66.87; H, 4.55; 10.84; N, 17.2%.

***N*-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-*N′*-(4-nitrobenzylidene) hydrazine (8b).** Yellow fluffy crystals (ethanol/chloroform, 2:1)(340 mg, 93%), mp 188-190 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H, CH_3), 7.43-7.47 (m, 1H, ArH), 7.49-7.54 (m, 2H, ArH), 7.57-7.59 (m, 2H, ArH), 8.01 (d, *J*=8.8 H_Z ,2H, ArH), 8.31 (d, *J*=8.8 H_Z ,2H, ArH), 8.71 (s, 1H, N=CH),), 8.72 (s, 1H, N=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.93 (CH_3), 113.23 (C), 124.01 (2CH), 124.95 (2CH), 128.73 (CH), 128.98 (2CH), 129.18 (2CH), 130.33 (C-Cl), 137.54 (C), 140.10 (C), 149.04 (C-CH_3), 150.58 (CH=N), 155.83 (C-NO_2), 158.79 (CH=N); IR (KBr, cm^{-1}): ν_{max} 3040 (CH arom.), 2980, 2900 (CH aliph.)1620 (C=N). Anal. Calcd for $C_{18}H_{14}ClN_5O_2$ (367.80): C, 58.78; H, 3.84; N, 19.04. Found: C, 58.66; H, 3.72; N, 19.17%.

***N*-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-*N*'-(4-dimethylamino-benzylidene)hydrazine (8c).** Yellow crystals (ethanol) (230 mg, 62%), mp 142-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H, CH_3), 3.05 (s, 6H, N($\underline{C}H_3$)$_2$), 6.71-6.74 (m, 2H, ArH), 7.40-7.59 (m, 5H, ArH), 7.69-7.73 (m, 2H, ArH), 8.59 (s, 1H, N=$\underline{C}H$),), 8.67 (s, 1H, N=$\underline{C}H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.80 ($\underline{C}H_3$), 40.11 (2$\underline{C}H_3$), 113.81 (C), 124.91 (2$\underline{C}$H), 111.64 (2$\underline{C}$H), 128.50 ($\underline{C}$H), 130.10 (2$\underline{C}$H), 129.88 (2$\underline{C}$H), 137.67 ($\underline{C}$-Cl), 150.14 (C), 150.29 (C), 151.90 ($\underline{C}$-CH_3), 152.28 ($\underline{C}$H=N), 153.35 ($\underline{C}$-N(CH_3)$_2$), 162.13 ($\underline{C}$H=N); IR (KBr, cm^{-1}): ν_{max} 3050 (CH arom.), 2910, 2800 (CH aliph.)1620 (C=N). Anal. Calcd for $C_{20}H_{20}ClN_5$ (365.87**)**: C, 65.66; H, 5.51; N, 19.14. Found: C, 65.69; H, 5.46; N, 19.02%.

***N*-((5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-*N*'-(4-methoxybenzylidene)-hydrazine (8d).**Yellow crystals (ethanol) (280 mg, 80%), mp 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (s, 3H, CH_3), 3.87 (s, 3H, O$\underline{C}H_3$), 6.97 (d, *J*=8.8 Hz, 2H, ArH), 7.43-7.45 (m, 1H, ArH), 7.48-7.52 (m, 2H, ArH), 7.57-7.58 (m, 2H, ArH), 7.79 (d, *J*=8.8 Hz, 2H, ArH), 8.63 (s, 1H, N=$\underline{C}H$),), 8.68 (s, 1H, N=$\underline{C}H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.84 ($\underline{C}H_3$), 55.38 (O$\underline{C}H_3$), 113.58 (C), 114.25 (2$\underline{C}$H), 124.93 (2$\underline{C}$H), 126.84 (CH), 128.49 ($\underline{C}$H), 129.08 (2$\underline{C}$H), 130.15 (2$\underline{C}$H), 132.42 ($\underline{C}$-Cl), 137.68 (C), 150.25 ($\underline{C}$-CH_3), 153.23 ($\underline{C}$H=N), 162.02 ($\underline{C}$-OCH_3), 161.23 ($\underline{C}$H=N); IR (KBr, cm^{-1}): ν_{max} 2910, 2810 (CH aliph.)1620 (C=N). Anal. Calcd for $C_{19}H_{17}ClN_4O$ (352.83): C, 64.68; H, 4.86; N, 15.88. Found: C, 64.59; H, 4.77; N, 15.94%.

***N*,*N*'-Bis-((5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine (8e).** Brown crystals (chloroform) (390 mg, 89%), mp 226-228 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.48 (s, 6H, 2CH_3), 7.36-7.42 (m, 6H, ArH), 7.47-7.56 (m, 4H, ArH), 7.87 (s, 2H, 2N=$\underline{C}H$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.87 (2$\underline{C}H_3$), 116.57 (2C), 124.67 (4$\underline{C}$H), 126.14 (2CH), 129.50 (4$\underline{C}$H), 134.12 (2$\underline{C}$-Cl), 137.50 (2C), 152.13 (2$\underline{C}$-CH_3), 161.20 (2$\underline{C}$H=N); IR (KBr, cm^{-1}): ν_{max} 3050 (CH arom.), 2900 (aliph. CH), 1620 (C=N). Anal. Calcd for $C_{22}H_{18}Cl_2N_6$ (437.33): C, 60.42; H, 4.15; N, 19.22. Found: C, 60.34; H, 4.09; N, 19.30%.

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid (9)[18,24]**.** A mixture of carboxaldehyde **1** (440 mg, 2 mmol) and potassium permanganate (320 mg, 2 mmol) in aqueous pyridine (10 mL, 50%) was stirred at room temperature for 3 h. The products of the reaction were filtered off and the filtrate acidified with HCl. The reslting solid was collected, washed with water and recrystallized from ethanol to give **9** (360 mg, 76%) as colorless needles, mp 218-220 ºC (lit.[24] mp 217-219 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.39 (s, 3H, CH_3), 7.52-7.56 (m, 5H, ArH), 12.92 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.42 ($\underline{C}H_3$), 110.02 (C), 125.69 (2$\underline{C}$H), 129.13 (CH), 129.24 (2$\underline{C}$H), 130.46 ($\underline{C}$-Cl), 137.14 (C), 151.27 ($\underline{C}$-CH_3), 163.05 ($\underline{C}$=O); IR (KBr, cm^{-1}): ν_{max} 3070-2550 (OH), 1680 (C=O). Anal. Calcd for $C_{11}H_9ClN_2O_2$ (236.66)**:** C, 55.83; H, 3.83; N, 11.84. Found**:** C, 55.68; H, 3.77; N, 11.86%.

5-Chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxylic acid azide (11). A solution of triethylamine (1200 mg, 12 mmol) in acetone (10 mL) was added to the acid **9** (2370 mg, 10 mmol) in acetone (95 mL) and water (5 mL) at 0 °C. After stirring for 30 min. at that temperature ethyl chloroformate (1300 mg, 12 mmol) was added and stirring was continued for 1 h further, then of sodium azide (910 mg, 14 mmol) in cold water (10 mL) was added and the

stirring was further continued for 1.5 h. The reaction mixture was then diluted with ice-cold water (70 mL) and the solid formed was filtered off and air dried to give **11**, which was used without further purification **(**1480 mg, 57%) as colorless crystals, mp 72-74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H, CH_3), 7.47-7.57 (m, 5H, ArH); IR (KBr, cm^{-1}): ν_{max} 2150 (CON_3), 2910 (CH aliph.), 1680 (C=O). Anal. Calcd for $C_{11}H_8ClN_5O$ (261.67): Calcd C, 50.49; H, 3.08; N, 26.76. Found. C, 50.39; H, 3.17; N, 26.69%.

General procedure for the synthesis of urea derivatives (13-15). A mixture of acid azide **3** (260 mg, 1 mmol) and amine (1 mmol) (aniline, 2-chloroaniline, *o*-toluidine, 4-aminophenol, ethyl piperazine-1-carboxylate, ethylenediamine, piperidine, morpholine) in toluene (10 mL) was heated under reflux for 1 h. After cooling, the solid precipitate formed was collected and recrystallized to afford **13-15**.

***N*^{1}-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*^{3}-phenylurea (13a).** Colorless crystals (EtOH) (240 mg, 75%), mp 208-210 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.17 (s, 3H, CH_3), 7.23-7.27 (m, 2H, ArH), 7.44-7.46 (m, 4H, ArH), 7.55-7.56 (m, 4H, ArH), 7.82 (s, 1H, NH), 8.81 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.99 (CH_3), 117.21 (C), 118.27 (2CH), 121.77 (CH), 124.31 (2CH), 128.02 (CH), 128.68 (2CH), 129.22 (2CH), 132.94 (C-Cl), 138.06 (C), 139.82 (C), 146.86 (C-CH_3), 153.36 (C=O); IR (KBr, cm^{-1}) ν_{max} 3300 (NH), 3030 (CH arom.), 2910 (CH aliph.), 1640 (C=O). Anal. Calcd for $C_{17}H_{15}ClN_4O$ (326.79): C, 62.48; H, 4.63; N, 17.14. Found: C, 62.33; H, 4.49; N, 17.05%.

***N*^{1}-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*^{3}-(2-chlorophenyl)urea (13b)**. Pale blue crystals (EtOH) (280 mg, 78%), mp 206-208 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.16 (s, 3H, CH_3), 7.02 (m, 1H, ArH), 7.28 (m, 1H, ArH), 7.44-7.46 (m, 1H, ArH), 7.50-7.52 (m, 5H, ArH), 8.11-8.13 (m, 1H, ArH), 8.50 (s, 1H, NH) 8.62 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.09 (CH_3), 117.00 (C), 121.21 (CH), 121.94 (CH), 124.35 (2CH), 127.60 (CH), 128.09 (C-Cl), 128.29 (CH), 129.24 (2CH), 129.50 (CH), 130.35 (C-Cl), 136.05 (C), 137.98 (C), 146.55 (C-CH_3), 152.94 (C=O); IR(KBr, cm^{-1}) ν_{max} 3300 (NH), 3050 (CH arom.), 2910 (CH aliph.)1640 (C=O). Anal. Calcd for $C_{17}H_{14}Cl_2N_4O$ (361.23): C, 56.53; H, 3.91; N, 15.51. Found: C, 56.44; H, 3.85; N, 15.43%.

***N*^{1}-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*^{3}-(2-methylphenyl)urea (13c).** Colorless crystals (EtOH) (300 mg, 88%), mp 234-236 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.19 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 6.92-6.96 (m, 1H, ArH), 7.1-7.17 (m, 1H, ArH), 7.45-7.46 (m, 1H, ArH), 7.52-7.56 (m, 5H, ArH), 7.75-7.77 (m, 1H, ArH), 8.04 (s, 1H, NH), 8.16 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.10 (CH_3), 117.46 (C), 121.14 (CH), 122.61 (CH), 122.89 (CH), 124.32 (2CH), 126.13 (CH), 128.01 (CH), 129.21 (2CH), 130.18 (C-Cl), 131.41 (C-CH_3), 137.50 (C), 138.06 (C), 146.72 (C-CH_3), 153.54 (C=O); IR(KBr, cm^{-1}) ν_{max} 3300 (NH), 3050 (CH arom.), 2910 (CH aliph.)1620 (C=O). Anal. Calcd for $C_{18}H_{17}ClN_4O$ (361.23): C, 63.44; H, 5.03; N, 16.44. Found: C, 63.37; H, 5.11; N, 16.36%.

***N*^{1}-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-*N*^{3}-(4-hydroxyphenyl)urea (13d).** Colorless crystals (EtOH) (320 mg, 94%), mp 286-288 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.16 (s, 3H, CH_3), 6.66 (d, *J*=8.8 Hz, 2H, ArH), 7.21 (d, *J*=8.8 Hz, 2H, ArH), 7.45- 7.57 (m, 5H, ArH), 7.67 (s, 1H, NH), 8.45 (s, 1H, NH), 9.05 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.00 ($\underline{C}H_3$), 117.46 (C), 115.09 (2$\underline{C}$H), 120.52 (2$\underline{C}$H), 124.29 (2$\underline{C}$H), 128.02 ($\underline{C}$H), 129.21 (2$\underline{C}$H), 122.89 ($\underline{C}$-Cl), 131.23 (C), 138.01 (C), 146.93 ($\underline{C}$-CH_3), 152.46 ($\underline{C}$=O), 153.71 ($\underline{C}$-OH); IR (KBr, cm^{-1}) ν_{max} 3250 (NH), 1635 (C=O). Anal. Calcd for $C_{17}H_{15}ClN_4O_2$ (342.79): C, 59.57; H, 4.41; N, 16.34. Found: C, 59.44; H, 4.34; N, 16.27%.

5-Chloro-3-methyl-1-phenyl-1*H*-4-(piperidinocarbonylamino)pyrazole (14a). Colorless crystals (petroleum ether/ethyl acetate, 2:1) (110 mg, 34%), mp 82-84 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 3.46 -3.51 (m, 6H, 3CH_2), 3.76-3.77 (m, 4H, 2CH_2), 5.75 (s, 1H, NH), 7.38-7.39 (m, 1H, ArH), 7.48-7.44 (m, 2H, ArH), 7.55-7.53 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12. 22 ($\underline{C}H_3$), 25.60 ($\underline{C}H_2$), 44.45 (2$\underline{C}H_2$), 66.44 (2$\underline{C}H_2$), 116.69 (C), 123.42($\underline{C}$-Cl), 124.57 (2$\underline{C}$H), 127.98 ($\underline{C}$H), 128.98 (2$\underline{C}$H), 138.39 (C), 147.31 ($\underline{C}$-CH_3), 155.63 ($\underline{C}$=O); IR (KBr, cm^{-1}) ν_{max} 3300 (NH), 3050 (CH arom.), 2970-2850 (CH aliph.) 1635 (C=O). Anal. Calcd for $C_{16}H_{19}ClN_4O$ (318.81): C, 60.28; H, 6.01; N, 17.57. Found: C, 60.19; H, 6.09; N, 17.49%.

5-Chloro-3-methyl-1-phenyl-1*H*-4-(morpholinocarbonylamino)pyrazole (14b). Colorless crystals (petroleum ether/ ethylacetate, 2:1) (200 mg, 63%), mp 152-154 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H, CH_3), 3.49 (t, *J*=4.88 Hz, 4H, N-$(CH_2)_2$), 3.75 (t, *J*=4.88 Hz, 4H, O$(CH_2)_2$), 5.81 (s, 1H, NH), 7.29-7.27 (m, 1H, ArH), 7.45-7.55 (m, 2H, ArH), 7.66-7.68 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.19 ($\underline{C}H_3$), 44.40 (2$\underline{C}H_2$), 66.40 (2$\underline{C}H_2$), 116.70 (C), 124.12 ($\underline{C}$-Cl), 124.52 (2$\underline{C}$H), 127.98 ($\underline{C}$H), 129.00 (2$\underline{C}$H), 138.34 (C), 147.31 ($\underline{C}$-CH_3), 155.67 ($\underline{C}$=O); IR (KBr, cm^{-1}) ν_{max} 3300 (NH), 2950-2850 (CH aliph). Anal. Calcd for $C_{15}H_{17}ClN_4O_2$ (320.78): C, 56.17; H, 5.34; N, 17.47. Found: C, 56.10; H, 5.27; N, 17.39%.

Ethyl 4-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-ylcarbamoyl)piperazine-1-carboxylate (14c). Colorless crystals (ethanol) (382 mg, 98%), mp 198-200 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J*=7.17 Hz, 3H, $CH_2C\underline{H}_3$), 2.24 (s, 3H, CH_3), 3.49-3.52 (m, 8H, 4CH_2), 4.16 (q, *J*=7.17 H_Z , 2H, $C\underline{H}_2CH_3$), 6.06 (s, 1H, NH), 7.36-7.39 (m, 1H, ArH), 7.44-7.47 (m, 2H, ArH), 7.52-7.54 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12. 15 ($\underline{C}H_3$), 14.61 ($CH_2\underline{C}H_3$), 61.68 ($\underline{C}H_2CH_3$), 43.98 ($\underline{C}H_2$), 43.20 (2$\underline{C}H_2$), 66.44 (2$\underline{C}H_2$), 116.70 (C), 123.47 ($\underline{C}$-Cl), 124.50 (2$\underline{C}$H), 127.96 ($\underline{C}$H), 128.96 (2$\underline{C}$H), 138.32 (C), 147.29 ($\underline{C}$-CH_3), 155.40 ($\underline{C}$=O), 155.49 ($\underline{C}$OO); IR (KBr, cm^{-1}) ν_{max} 3220 (NH), 2998, 2900 (CH aliph.), 1690 (C=O ester), 1630 (C=O). Anal. Calcd for $C_{18}H_{22}ClN_5O_3$ (391.85): C, 55.17; H, 5.66; N, 17.87. Found: C, 55.29; H, 5.79; N, 18.10%.

***N*^{1},*N*^{4}-Bis-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)piperazine-1,4-dicarboxamide (15).** Colorless crystals (petroleum ethanol) (200 mg, 36%), mp 288-290 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.12 (s, 6H, 2CH_3), 3.34 (s, 8H, 4CH_2), 7.44-7.47 (m, 6H, ArH), 7.54-7.55 (m, 4H, ArH), 8.12 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.86 (2$\underline{C}H_3$), 43.61 (4$\underline{C}H_2$), 118.20 (2C-Cl), 123.04 (2$\underline{C}$-NH), 124.22 (4$\underline{C}$H), 127.94 (2$\underline{C}$H), 129.26 (4$\underline{C}$H), 138.10 (2C), 147.19 (2$\underline{C}$-CH_3) 155.54 (2C=O); IR (KBr, cm^{-1}) ν_{max} 3220 (NH), 3080 (CH arom.) 2950-2850 (CH

aliph.)1635 (C=O). Anal. Calcd for $C_{26}H_{26}Cl_2N_8O_2$ (553.44): C, 56.42; H, 4.74; N, 20.25. Found: C, 56.39; H, 4.67; N, 20.32%.

1,4-Di(3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ureido)benzene (16). A mixture of acid azide **11** (260 mg, 1 mmol) and *p*-phenylene-1,4-diamine (110 mg, 1 mmol) in toluene (10 mL) was heated under reflux for 3h. After cooling, the solid precipitate was collected by filtration and recrystallized from ethanol to give **16** (320 mg, 56%) as colorless crystals, mp 324 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.17 (s, 6H, 2CH_3), 7.34 (m, 4H, ArH), 7.46 -7.56 (m, 10H, ArH), 7.75 (s, 2H, 2NH), 8.66 (s, 2H, 2NH); IR (KBr, cm^{-1}): ν_{max} 3300 (NH), 3050 (CH arom.), 1640 (C=O). Anal. Calcd for $C_{28}H_{24}Cl_2N_8O_2$ (575.45): C, 58.44; H, 4.20; N, 19.47. Found: C, 58.32; H, 4.11; N, 19.35%.

1,4-Di(3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ureido)ethane (17). A mixture of acid azide **11** (260 mg, 1 mmol) and ethylenediamine (60 mg, 1 mmol) in toluene (10 mL) was heated under reflux for 2 h. After cooling, the precipitate was collected by filtration and recrystallized from (ethanol/chloroform, 2:1) to give **17** (160 mg, 30%) as colorless crystals, mp 294-296 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.15 (s, 3H, CH_3), 3.33 (s, 4H, 2CH_2), 6.33 (s, 2H, 2NH), 7.43-7.45 (m, 2H, ArH), 7.50-7.53 (m, 8H, ArH), 7.66 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.92 (2$\underline{C}H_3$), 40.12 (2$\underline{C}H_2$), 117.74 (2$\underline{C}$-Cl), 123.04 (2$\underline{C}$-NH), 124.28 (4$\underline{C}$H), 127.93 (2$\underline{C}$H), 129.17 (4$\underline{C}$H), 138.13 (2C), 146.92 (2$\underline{C}$-CH_3),156.31 (2C=O); IR (KBr, cm^{-1}): ν_{max} 3300 (NH), 3050, 3100 (CH arom.), 2950, 2900 (CH aliph.), 1637 (C=O). Anal. Calcd for $C_{24}H_{24}Cl_2N_8O_2$ (527.41): C, 54.66; H, 4.59; N, 21.25. Found**:** C, 54.54; H, 4.45; N, 21.16%.

***N*^{1},*N*^{3}-Bis(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)urea (18).** A mixture of acid azide **11** (260 mg, 1.1 mmol) in water (10 ml) was heated under reflux for 2 h. After cooling, the solid product was collected and recrystallized from ethanol to give **18** (190 mg, 43%) as colorless crystals, mp 258-260 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.18 (s, 6H, 2CH_3), 7.43-7.47 (m, 2H, ArH), 7.52-7.58 (m, 8H, ArH), 7.96 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 11.86 (2$\underline{C}H_3$), 117.38 (2C-Cl), 123.24 (2$\underline{C}$-NH), 124.34 (4$\underline{C}$H), 128.04 (2$\underline{C}$H), 129.21 (4$\underline{C}$H), 138.09 (2C), 147.19 (2$\underline{C}$-CH_3) 153.51 (C=O); IR (KBr, cm^{-1}): ν_{max} 3300 (NH), 3050 (CH arom.), 1640 (C=O), 1610 (C=C). Anal. Calcd for $C_{21}H_{18}Cl_2N_6O$ (441.31): C, 57.15; H, 4.11; N, 19.04. Found: C, 57.08; H, 4.04; N, 19.07%.

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