SYNTHESIS, REACTIONS AND ANTIMICROBIAL ACTIVITY OF SOME NEW 1,3,4-OXADIAZOLES, 1,2,4-TRIAZOLES AND 1,3,4-THIADIAZINES DERIVED FROM PYRAZOLE.

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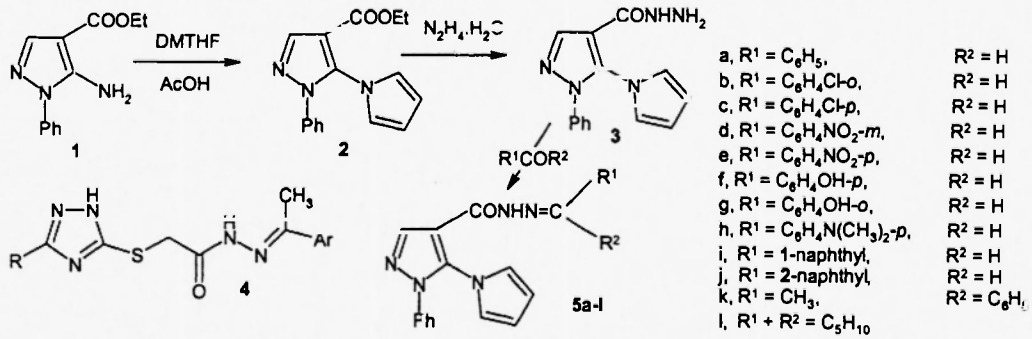
Abstract: New 1,3,4-oxadiazoles, 1,2,4-triazoles and 1,3,4-thiadiazines containing a pyrazolyl moiety **7-14** were prepared using ethyl 5-amino-1-phenyl-*1H*-pyrazole-3-carboxylate **1** as a starting material. The newly synthesized compounds were screened for their *in vitro* anti-bacterial and anti-fungal activity.

Introduction

1,2,4-triazoles have long been known to possess various biological activities such as antiviral, antibacterial, anti-inflammatory, anticonvulsant and antifungal activities.[1–9] 1,3,4-Oxadiazoles, on the other hand, are reported to have antidiabetic, anti-inflammatory and analgesic activities.[10-12] Also some arylidene hydrazides possess antimicrobial activity.[13] Keeping these aforementioned results in mind and in continuation to our interest in the synthesis of pyrazole heterocycles of potential biological activity,[14-18] we report herein the synthesis of some new oxadiazoles, triazoles and thiadiazines derived from the pyrazole.

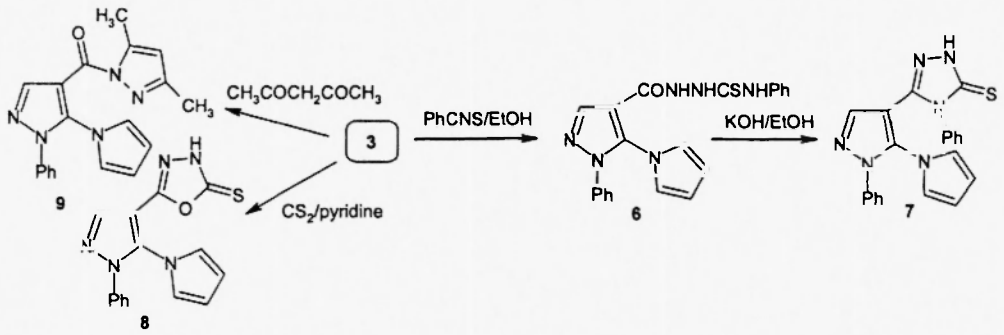
Results & Discussions

The amino group of the easily accessible ethyl 5-amino-1-phenyl-*1H*-pyrazole-3-carboxylate **1** was readily converted into the corresponding pyrrol-1-yl ester **2** *via* the interaction with dimethoxytetrahydrofuran (DMTHF) in acidic medium.[19] This latter pyrrolyl ester gave the hydrazide **3** upon treatment with hydrazine hydrate. In the light of the antibacterial and antifungal activities of the arylidene hydrazides **4**,[13] a series of arylidene derivatives **5a-l** of the hydrazide **3** was prepared by the reaction of the latter compound with different aldehydes and ketones (Scheme I).



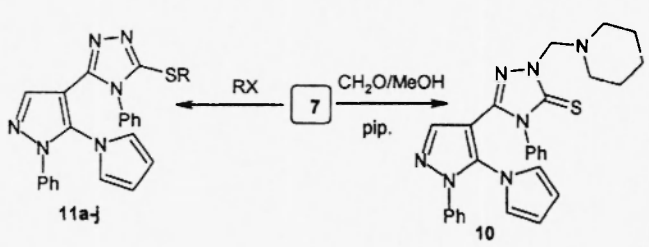
Scheme I

On one hand, when **3** was allowed to react with phenyl isothiocyanate in refluxing alcohol, the product was the semicarbazide derivative **6** which could be cyclized in alkaline medium into the triazole derivative **7**. The oxadiazole **8** was obtained when the hydrazide **3** was treated with carbon disulphide in pyridine, while its interaction with acetyl acetone led to the formation of the pyrazole derivative **9** (Scheme II).



Scheme II

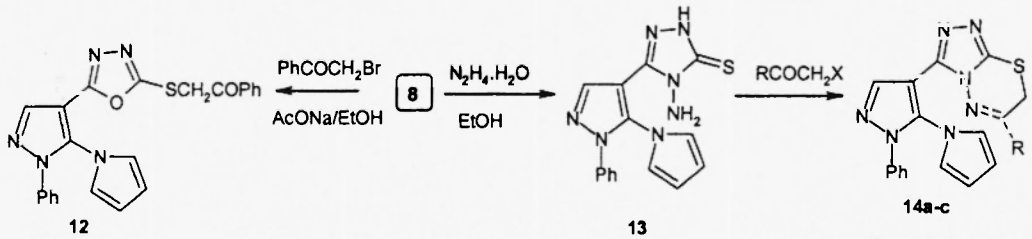
Furthermore, the Mannich reaction of compound **7** using piperidine as a base gave the Mannich base **10**, while the treatment of **7** with halo compounds (Scheme III) afforded a series of *S*-substituted mercaptotriazoles **11a-j**.



a, R = CH_2CH_3, X = I
b, R = $CH_3CHCOOCH_3$, X = Br
c, R = $CH_2COC_6H_5$, X = Br
d, R = $CH_2COC_6H_4Br$-*p*, X = Br
e, R = $CH_2COC_6H_4Cl$-*p*, X = Br
f, R = CH_2CONH_2, X = Cl
g, R = $CH_2CONHC_6H_4Cl$-p, X = Cl
h, R = $CH_2CONHC_6H_4CH_3$-*p*, X = Cl
i, R = $CH_2CONHC_6H_4OCH_3$-*p*, X = Cl
j, R = $CH_2CONHC_6H_4COCH_3$-*p*, X = Cl

Scheme III

The treatment of **8** with benzoylbromide afforded the *S*-substituted mercapto oxadiazole **12** (Scheme IV). The interaction of the oxadiazole **8** with hydrazine hydrate gave the aminotriazolethione **13**, which gave upon reaction with chloroacetone and phenacylbromides the triazolothiadiazines 14.



a, R = CH_3, X = Cl
b, R = C_6H_5, X = Br
c, R = C_6H_4Br-*p*, X = Br

Scheme IV

Antimicrobial activity

The antibacterial activity of the prepared compounds was tested against the Gram-positive strains *Staphylococcus aureus* and *Escherichia coli*, and the Gram-negative strains, *Bacillus cereus* and *Pseudomonas aeruginosa* as well as against the fungi strains *Penicillium chrysogenum* AUMC 530-15, *Aspergillus falvus* AUMC 164-5, *Aspergillus fumigatus* AUMC 170-3, *Aspergillus ochracus* AUMC 230-2, *Aspergillus niger* AUMC 210-1, *Curvulana lunala* AUMC 2310-1, *Fusarium solani* AUMC 2690-6, and *Trichothecium roseum* AUMC 7410-2.

With the exception of the phenylthiosemicarbazide derivative **6** which showed a weak activity against the bacterium *Bacillus cereus* and the fungus *Curvulana lunala*, the rest of compounds tested were totally inactive.

Experimental

Melting points were determined on a Kofler melting point apparatus and are uncorrected. 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 Microanalyzer and the results were within ±0.4% of the calculated values.

Ethyl 5-amino-1-phenyl-1*H*-pyrazole-4-carboxylate 1.

This compound was prepared by a rather simple and modified procedure, thus a mixture of ethyl ethoxymethylenecyanoacetate (17 g, 0.1 mol) and phenyl hydrazine (10 g, 0.1 mol) in ethanol (50 ml) was stirred at room temperature for 1 h. Water (20 ml) and concentrated hydrochloric acid (3 ml) were then added to the reaction mixture which was heated on boiling water bath till the red color formed disappeared. The reaction mixture was left to cool and the solid precipitate formed was recrystallized from ethanol as white crystals, m.p. 98-100 °C (lit[1]; 100 °C), yield 19.93 g, (86.5 %), IR: ν cm^{-1} 3400, 3280 and 3200 (NH_2), 1680 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.70 (s, 1H, pyrazole), 7.43 (s, 5H, phenyl), 5.16 (s, 2H, NH_2), 4.26 (q, J = 7.1 Hz, 2H, CH_2CH_3), 1.33 (t, J = 7.1 Hz, 3H, CH_2CH_3). $C_{12}H_{13}N_3O_2$ (231.25)

Ethyl 1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carboxylate 2.

A suspension of compound 1 (6.9 g, 0.03 mol) and 2,5-dimethyltetrahydrofuran (DMTHF) (3.96 g, 0.033 mol) in acetic acid (30 ml) was heated at 80 °C for 1 h. After cooling the reaction mixture was poured into ice-water mixture and neutralized with sodium bicarbonate. The solid product formed was filtered off and recrystallized from ethanol as white crystals, m.p. 108-110 °C (lit[1]; 113 °C), yield 8.3 g, (97 %). IR: ν cm^{-1} 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ 8.08 (s, 1H, pyrazole), 7.23 (m, 3H, phenyl), 7.05 (m, 2H, phenyl), 6.63 (m, 2H, Hα pyrrole), 6.20 (m, 2H, Hβ pyrrole), 4.20 (q, J = 7.1 Hz, 2H, CH_2CH_3), 1.23 (t, J = 7.1 Hz, 3H, CH_2CH_3). $C_{16}H_{15}N_3O_2$ (281.32)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbohydrazide 3.

To a solution of **2** (5 g, 0.018 mol) in ethanol (20 ml) was added hydrazine hydrate (80%, 5 ml, 0.1 mol) and the reaction mixture was heated under reflux for 6 h, then it was allowed to cool. The solid product was collected and recrystallized from methanol as white crystals, m.p. 197-200 °C, yield 3.7 g, (76 %). IR: ν cm^{-1} 3300, 3100 (NH, NH_2), 1640 (C=O). ^{1}H NMR (DMSO-d_6): δ 9.20 (s, 1H, NH), 8.17 (s, 1H, pyrazole), 7.32 (m, 3H, phenyl), 7.05 (m, 2H, phenyl), 6.80 (m, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole), 4.33 (s, 2H, NH_2). $C_{14}H_{13}N_5O$ (267.29)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(arylidene)-hydrazide 5a-l.

General procedure: an equimolar mixture (0.002 mol) of **3** and the appropriate aldehyde in ethanol (20 ml) was heated under reflux for 2 h. After cooling, the precipitate was filtered off and recrystallized from the appropriate solvent.

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(benzylidene)-hydrazide 5a.

White crystals from ethanol, m.p. 227-229 °C, yield 0.55 g, (78 %). IR: ν cm^{-1} 3200 (NH), 1650 (C=O). ^{1}H NMR (DMSO-d_6): δ 11.38 (s, 1H, NH), 8.37 (s, 1H, pyrazole), 7.47 (s, 1H, N=CH), 7.44 (m, 10H, phenyl), 6.86 (s, 2H, Hα pyrrole), 6.17 (m, 2H, Hβ pyrrole). $C_{21}H_{17}N_5O$ (355.40)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(2-chlorobenzylidene)-hydrazide 5b.

White powder from ethanol, m.p. 227-229 °C, yield 0.51g, (66 %). IR: ν cm^{-1} 3250 (NH), 1640 (C=O). ^{1}H NMR (DMSO-d_6): δ 12.10 (s, 1H, NH), 8.70 (s, 1H, N=CH), 8.37 (s, 1H, pyrazole), 7.90 (m, 2H, phenyl), 7.40 (m, 5H, phenyl), 7.13 (m, 2H, phenyl), 6.87 (m, 2H, Hα pyrrole), 6.17 (m, 2H, Hβ pyrrole). MS: (*m/z*) 390.7 (M^+, 62 %), 388.7 (M^{-1}, 76 %). $C_{21}H_{16}N_5ClO$ (389.85)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(4-chlorobenzylidene)-hydrazide 5c.

White crystals from ethanol, m.p. 224-225 °C, yield 0.62 g, (80 %). IR: ν cm^{-1} 3180 (NH), 1645 (C=O). ^{1}H NMR (DMSO-d_6): δ 11.53 (s, 1H, NH), 8.32 (s, 1H, pyrazole), 7.38 (m, 9H, phenyl), 7.30 (s, 1H, N=CH), 6.83 (s, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole). $C_{21}H_{16}N_5ClO$ (389.85)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(3-nitrobenzylidene)-hydrazide 5d.

Yellow crystals from ethanol, m.p. 203-205 °C, yield 0.65 g, (85 %). IR: ν cm^{-1} 3300 (NH), 1660 (C=O). ^{1}H NMR (DMSO-d_6): δ 11.80 (s, 1H, NH), 8.35 (s, 1H, pyrazole), 7.94 (m, 4H, phenyl), 7.73 (s, 1H, N=CH), 7.35 (m, 3H, phenyl), 7.13 (m, 2H, phenyl), 6.83 (m, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole). $C_{21}H_{16}N_6O_3$ (400.40)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(4-nitrobenzylidene)-hydrazide 5e.

White crystals from ethanol, m.p. 225-227 °C, yield 0.56 g, (70 %). IR: ν cm^{-1} 3180 (NH), 1645 (C=O). ^{1}H NMR (CF_3COOD): δ 8.86 (s, 1H, pyrazole), 8.10 (m, 4H, phenyl), 7.40 (m, 6H, phenyl + N=CH), 6.90 (m, 2H, Hα pyrrole), 6.53 (m, 2H, Hβ pyrrole). $C_{21}H_{16}N_6O_3$ (400.40)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(4-hydroxybenzylidene)-hydrazide 5f.

White crystals from ethanol, m.p. 303-305 °C, yield 0.56 g, (76 %). IR: ν cm^{-1} 3300-3100 (OH and NH), 1640 (C=O). ^{1}H NMR (DMSO-d_6): δ 11.17 (s, 1H, NH), 8.27 (s, 1H, pyrazole), 8.10 (s, 1H, OH), 7.43 (m, 2H, phenyl), 7.33 (m, 3H, phenyl), 7.30 (s, 1H, N=CH), 7.08 (m, 2H, phenyl), 6.78 (m, 4H, phenyl + Hα pyrrole), 6.10 (m, 2H, Hβ pyrrole). MS: (*m/z*) 371 (M^+, 100 %). $C_{21}H_{17}N_5O_2$ (371.40)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(2-hydroxybenzylidene)-hydrazide 5g.

White crystals from dioxane, m.p. 211-13 °C, yield 0.50 g, (68 %). IR: ν cm^{-1} 3400 (OH) 3300 (NH), 1640 (C=O). ^{1}H NMR (CF_3COOD): δ 8.85 (s, 1H, pyrazole), 8.80 (s, 1H, N=CH), 7.77 (m, 2H, phenyl), 7.50 (m, 2H, phenyl), 7.33 (m, 5H, phenyl), 6.98 (m, 2H, Hα pyrrole), 6.45 (m, 2H, Hβ pyrrole). $C_{21}H_{17}N_5O_2$ (371.40)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(4-*N*,*N*-dimethylaminobenzylidene)-hydrazide 5h.

Fluffy yellow crystals from ethanol, mp 221-23 °C, yield 0.62 g, (78 %). IR: ν cm^{-1} 3180 (NH), 1640 (C=O), 1610 (C=N). ^{1}H NMR (CF_3COOD): δ 8.90 (s, 1H, pyrazole), 7.90 (m, 4H, phenyl), 7.50 (m, 6H, phenyl + N=CH), 6.73 (m, 2H, Hα pyrrole), 6.38 (m, 2H, Hβ pyrrole), 3.50 (s, 6H, $2CH_3$). $C_{23}H_{22}N_6O$ (398.47)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(1-naphthylidene)-hydrazide 5i.

White crystals from ethanol, mp 198-200 °C, yield 0.58 g, (72 %). IR: ν cm^{-1} 3300 (NH), 1640 (C=O). ^{1}H NMR (DMSO-d_6): δ 11.97 (s, 1H, NH), 8.90 (s, 1H, pyrazole), 8.40 (s, 1H, N=CH), 7.93 (m, 4H, phenyl), 7.60 (m, 3H, phenyl), 7.37 (m, 3H, phenyl), 7.13 (m, 2H, phenyl), 6.87 (m, 2H, Hα pyrrole), 6.02 (m, 2H, Hβ pyrrole). MS: (*m/z*) 405.7 (M^+, 96 %), 404.7 (M^{-1}, 100 %). $C_{25}H_{19}N_5O$ (405.46)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(2-naphthylidene)-hydrazide 5j.

White crystals from ethanol, mp 232-34 °C, yield 0.57 g, (70 %). IR: ν cm^{-1} 3200 (NH), 1645 (C=O). ^{1}H NMR (DMSO-d_6): δ 11.90 (s, 1H, NH), 8.40 (s, 2H, pyrazole + N=CH), 7.97 (m, 5H, phenyl), 7.43 (m, 5H, phenyl), 7.13 (m, 2H, phenyl), 6.86 (m, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole). $C_{25}H_{19}N_5O$ (405.46)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(1-phenylethylidene)-hydrazide 5k.

White crystals from ethanol, mp 178-80 °C, yield 0.59 g, (80 %). IR: ν cm^{-1} 3340 (NH), ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H, pyrazole), 7.70 (m, 2H, phenyl), 7.30 (m, 6H, phenyl), 7.12 (m, 2H, phenyl), 6.80 (m, 2H, Hα pyrrole), 6.40 (m, 2H, Hβ pyrrole), 1.80 (s, 3H, CH_3). MS: (*m/z*) 369.7 (M^+, 81%), 370.7 (M^{+1}, 81%). $C_{22}H_{19}N_5O$ (369.43)

1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-carbo-(cyclohexylidene)-hydrazide 5l.

White crystals from ethanol, mp 180-82 °C, yield 0.61 g, (88 %). IR: ν cm^{-1} 3350 (NH), 1660 (C=O). ^1H NMR ($CDCl_3$): δ 8.33 (s, 1H, pyrazole), 7.30 (m, 3H, phenyl), 7.10 (m, 2H, phenyl), 6.80 (m, 2H, Hα pyrrole), 6.43 (m, 2H, Hβ pyrrole), 2.33 (m, 4H, $2CH_2$), 1.67 (m, 6H, $3CH_2$). MS: (*m/z*) (M^+) 347. $C_{20}H_{21}N_5O$ (347.42)

1-(1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-oyl)-4-phenylthiosemicarbazide 6.

A mixture of 3 (2 g, 0.0074 mol) and phenyl isothiocyanate (1 g, 0.0074 mol) in ethanol (20 ml) was heated under reflux for 4h. After cooling, the solid product formed, was collected and recrystallized from ethanol as white needles, m.p. 146-48 °C, yield 2.97 g, (99 %). IR: ν cm^{-1} 3400, 3200 (NH), 1645 (C=O), 1210 (C=S). ^1H NMR ($CDCl_3$): δ 9.10 (s, 1H, NH), 8.66 (s, 2H, 2NH), 8.08 (s, 1H, pyrazole), 7.17 (m, 10 H, phenyl), 6.73 (m, 2H, Hα pyrrole), 6.30 (m, 2H, Hβ pyrrole). $C_{21}H_{18}N_6OS$ (402.48)

4-Phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazole-3 (2*H*)-thione 7.

A suspension of 3 (2.57 g, 0.00638 mol) in ethanolic potassium hydroxide (25 ml, *2N*) was heated under reflux for 1 h. After cooling, the reaction mixture was acidified with diluted HCl. The solid product obtained was collected and recrystallized from ethanol as white needles, m.p. 230-33 °C, yield 2.40 g, (98 %). IR: ν cm^{-1} 3100 (NH), 1210 (C=S). ^1H NMR (DMSO-d_6): δ 14.00 (s, 1H, NH), 8.30 (s, 1H, pyrazole), 7.17 (m, 10 H, phenyl), 6.67 (m, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole). $C_{21}H_{16}N_6S$ (384.46)

5-(1-Phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl]-[1,3,4]oxadiazole-2 (3*H*)-thione 8.

A solution of 3 (1 g, 0.0035 mol) and carbon disulfide (1ml) in pyridine (20 ml) was heated under reflux for 5 h. After cooling, the reaction mixture was diluted with water, the solid product obtained, was filtered off and recrystallized from ethanol as pale yellow crystals, m.p.194-96 °C, yield 0.87 g, (80 %). IR: ν cm^{-1} 3100 (NH), 1630 (C=N). ^1H NMR (DMSO-d_6): δ 8.32 (s, 1H, pyrazole), 7.21 (m, 5H, phenyl), 6.86 (m, 2H, Hα pyrrole), 6.20 (m, 2H, Hβ pyrrole), 5.33 (sb, 1H, NH). $C_{15}H_{11}N_5OS$ (309.35)

(3,5-Dimethylpyrazol-1-yl)-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl) methanone 9.

A mixture of 3 (0.53 g, 0.002 mol) and acetyl acetone (0.2 g, 0.002 mol) in ethanol (20 ml) was heated under reflux for 4 h. After cooling, the solid product formed, was collected and recrystallized from ethanol as yellow needles, m.p. 146-48 °C, yield 0.59 g, (89.8 %). IR: ν cm^{-1} 1690 (C=O). ^1H NMR ($CDCl_3$): δ 8.53 (s, 1H, pyrazole), 7.30 (m, 3H, phenyl), 7.13 (m, 2H, phenyl), 6.73 (m, 2H, Hα pyrrole), 6.27 (m, 2H, Hβ pyrrole), 5.97 (s, 1H, pyrazolyl), 2.57 (s, 3H, CH_3), 2.27 (s, 3H, CH_3). $C_{19}H_{17}N_5O$ (331.38)

4-Phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-2-piperidin-1-ylmethyl-2,3-dihydro-[1,2,4]triazole-3-thione 10.

A mixture of compound 7 (0.384 g, 0.001 mol), formaldehyde (1ml, 37 %), and piperidine (0.085 g, 0.001 mol) in methanol (20 ml) was stirred at rt for 3 h. The resulting precipitate was filtered off and recrystallized from ethanol to give white crystals, m.p. 165-67 °C, yield 0.38 g, (79 %). IR: ν cm^{-1} 1618 (C=N), 1120 (C=S). ^1H NMR (DMSO-d_6): δ 8.40 (s, 1H, pyrazole), 7.43 (m, 2H, phenyl), 7.20 (m, 8H, phenyl), 6.50 (m, 2H, Hα pyrrole), 6.20 (m, 2H, Hβ pyrrole), 5.16 (s, 2H, CH_2), 2.73 (m, 4H, pip.), 1.53 (m, 6H, pip.). $C_{27}H_{27}N_7S$ (481.63)

3-Substituted thio-4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazole 11a-i.

General procedure:

To a suspension of triazolethione 7 (0.384 g, 0.001 mol) and dry sodium acetate (0.5 g, 0.006 mol) in ethanol (10 ml), the alkylating agent (0.001 mol) was added and the reaction mixture was refluxed for 2h. After cooling, the precipitate formed was collected and recrystallized from the appropriate solvent.

3-Ethylthio-4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazole 11a.

This compound was prepared *via* the general procedure by using ethyl iodide (0.155 g, 0.001 mol) as white crystals from ethanol, m.p. 188-90 °C, yield 0.30 g, (73 %). IR: ν cm^{-1} 1610 (C=N). ^1H NMR ($CDCl_3$): δ 7.57 (s, 1H, pyrazole), 7.27 (m, 6H, phenyl), 6.93 (m, 4H, phenyl), 6.33 (m, 2H, Hα pyrrole), 6.06 (m, 2H, Hβ pyrrole), 2.23 (q, J = 6.90 Hz, 2H, CH_2CH_3), 1.44 (t, J = 6.75 Hz 3H, CH_2CH_3). $C_{23}H_{20}N_6S$ (412.52)

Methyl [2-methyl-2-(4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazol-3-ylthio] propionate 11b.

This compound was obtained using methylbromopropionate (0.167 g, 0.001 mol) as white crystals from ethanol, m.p. 167-69 °C, yield 0.35 g, (75 %). IR: ν cm^{-1} 1740 (C=O). ^1H NMR ($CDCl_3$): δ 7.52 (s, 1H, pyrazole), 7.25 (m, 6H, phenyl), 6.93 (m, 4H, phenyl), 6.33 (m, 2H, Hα pyrrole), 6.06 (m, 2H, Hβ pyrrole), 4.48 (q, J = 7.0 Hz, 1H, $CHCH_3$), 3.67 (s, 3H, $COOCH_3$), 1.60 (d, J = 7.2 Hz, 3H, $CHCH_3$). $C_{25}H_{22}N_6O_2S$ (470.56)

3-Phenacylthio-4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazole 11c.

This compound was obtained using phenacyl bromide (0.199 g, 0.001 mol) as white fluffy crystals from ethanol, m.p. 220-22 °C, yield 0.42 g, (84 %). IR: ν cm^{-1} 1660 (C=O). ^1H NMR (CF_3CO_2D): δ 8.03 (s, 1H, pyrazole), 7.40 (m, 15H, phenyl), 6.38 (m, 4H, pyrrole), 4.93 (s, 2H, CH_2). $C_{29}H_{22}N_6OS$ (502.60)

3-(4-Bromophenacylthio)-4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazole 11d.

This compound was obtained using 4-bromophenacyl bromide (0.272 g, 0.001 mol) as buff crystals from methanol, m.p. 230-32 °C, yield 0.45 g, (75 %). IR: ν cm^{-1} 1670 (C=O). ^1H NMR (CF_3CO_2D): δ 8.08 (s, 1H, pyrazole), 7.55 (m, 14H, phenyl), 6.35 (m, 4H, pyrrole), 5.00 (s, 2H, CH_2). $C_{29}H_{21}N_6BrOS$ (581.50)

3-(4-Chlorophenacylthio)-4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazole 11e.

This compound was obtained using 4-chlorophenacyl bromide (0.232 g, 0.001 mol) as buff crystals from ethanol/dioxane (2:1), m.p. 240-42 °C, yield 0.43 g, (80 %). IR: ν cm^{-1} 1670 (C=O). ^1H NMR (CF_3CO_2D): δ 8.03 (s, 1H, pyrazole), 7.35 (m, 14H, phenyl), 6.32 (m, 4H, pyrrole), 4.98 (s, 2H, CH_2). MS: (*m/z*) 537.32 (M^+, 49%). $C_{29}H_{21}N_6ClOS$ (537.05)

2-[4-Phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazol-3-ylthio]acetamide 11f.

This compound was obtained as white fluffy crystals from ethanol/dioxane (1:1) starting with chloroacetamide (0.093 g, 0.001 mol), m.p. 253-55 °C, yield 0.37 g, (84 %). IR: ν cm^{-1} 3450, 3350 (NH_2), 1675 (C=O). ^1H NMR (DMSO-d_6): δ 7.52 (s, 1H, pyrazole), 7.50 (m, 3H, phenyl), 7.30 (m, 5H, phenyl), 7.05 (m, 2H, phenyl), 6.62 (m, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole), 3.92 (s, 2H, CH_2). MS: (*m/z*) 441 (M^+, 79 %). $C_{23}H_{19}N_7OS$ (441.52)

***N*-(4-Chlorophenyl)-2-[4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazol-3-ylthio] acetamide 11g.**

This compound was obtained as white crystals from ethanol/dioxane (1:1) starting with *N*-(4-chlorophenyl)-2-chloroacetamide (0.204 g, 0.001 mol), m.p. 247-49 °C, yield 0.40 g, (72 %). IR: ν cm^{-1} 3240 (NH), 1680 (C=O). ^1H NMR (DMSO-d_6): δ 10.48 (s, 1H, NH), 7.63 (s, 1H, pyrazole), 7.50 (m, 5H, phenyl), 7.32 (m, 7H, phenyl), 7.03 (m, 2H, phenyl), 6.60 (m, 2H, Hα pyrrole), 6.12 (m, 2H, Hβ pyrrole), 4.15 (s, 2H, CH_2). $C_{29}H_{22}N_7ClOS$ (552.06)

***N*-(*p*-Tolyl)-2-[4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazol-3-ylthio]acetamide 11h.**

This compound was obtained as white needles from ethanol starting with *N*-(*p*-tolyl)-2-chloroacetamide (0.183 g, 0.001 mol), m.p. 228-30 °C, yield 0.43 g, (81 %). IR: ν cm^{-1} 3250 (NH), 1680 (C=O), 1620 (C=N). ^1H NMR (DMSO-d_6): δ 10.25 (s, 1H, NH), 7.31 (m, 15H, phenyl and 1H pyrazole), 6.48 (m, 2H, Hα pyrrole), 6.17 (s, 2H, H β pyrrole), 4.15 (s, 2H, CH_2), 2.30 (s, 3H, CH_3). $C_{30}H_{25}N_7OS$ (531.64)

***N*-(*p*-Anisyl)-2-[4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazol-3-ylthio]acetamide 11i.**

This compound was obtained as white fine crystals from ethanol starting with *N*-(4-methoxyphenyl)-2-chloroacetamide (0.199 g, 0.001 mol), m.p. 228-30 °C, yield 0.40 g, (73 %). IR: ν cm^{-1} 3250 (NH), 3030 (CH arom.), 1670 (C=O), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 10.43 (s, 1H, NH), 7.52 (s, 1H, pyrazole), 7.17 (m, 14H, phenyl), 6.31 (m, 2H, Hα pyrrole), 6.11 (m, 2H, Hβ pyrrole), 3.96 (s, 3H, OCH_3), 3.76 (s, 2H, CH_2). $C_{30}H_{25}N_7O_2S$ (547.64)

N-(4-Acetylphenyl)-2-(4-phenyl-4*H*-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)-[1,2,4]triazol-3-ylthio) acetamide 11i.

This compound was obtained as buff needles from ethanol starting with *N*-(4-acetylphenyl)-2-chloroacetamide (0.211 g, 0.001 mol), m.p. 245-47 °C, yield 0.52 g, (93 %). IR: ν cm^{-1} 3250 (NH), 3040 (CH arom.), 2900 (CH aliph.), 1670 (C=O), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 10.40 (s, 1H, NH), 7.49 (m, 15H, phenyl + pyrazole), 6.57 (m, 2H, Hα pyrrole), 6.13 (m, 2H, Hβ pyrrole), 4.20 (s, 2H, CH_2), 2.57 (s, 3H, $COCH_3$). $C_{31}H_{25}N_7O_2S$ (559.65)

3-Phenacylthio-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-yl)-[1,3,4]oxadiazole 12.

A mixture of 8 (0.16 g, 0.52 mmol), phenacylbromide (0.10 g, 0.5 mmol) and sodium acetate (0.5 g, 6 mmol) in ethanol (10 ml) was heated under reflux for 2 h. After cooling, the solid fluffy product was collected by filtration and recrystallized from ethanol as colorless crystals, m.p. 185-87 °C, yield 0.15 g, (35 %). IR: ν cm^{-1} 3050 (CH arom.), 1675 (C=O), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 8.33 (s, 1H, pyrazole), 7.57 (m, 10H, phenyl), 6.92 (m, 2H, Hα pyrrole), 6.17 (m, 2H, Hβ pyrrole), 5.00 (s, 2H, CH_2). $C_{23}H_{17}N_5O_2S$ (427.49)

4-Amino-5-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazol-4-yl)[1,2,4]triazole-3-thiol 13.

A mixture of **8** (0.50 g, 0.0016 mol) and hydrazine hydrate (2 ml) in ethanol (10 ml) was heated under reflux for 12 h. After concentration, the solid product formed, was collected by filtration and recrystallized from ethanol as white needles, m.p. 233-35 °C, yield 0.42 g, (80 %). IR: ν cm^{-1} 3300, 3120 (NH, NH_2), 2610 (SH). ^{1}H NMR (DMSO-d_6): δ 8.43 (s, 1H, pyrazole), 7.36 (m, 3H, phenyl), 7.17 (m, 2H, phenyl), 6.83 (m, 2H, Hα pyrrole), 6.17 (m, 2H, Hβ pyrrole), 5.70 (s, 2H, NH_2). MS: (*m/z*) 323.9 (M^+, 100 %), 322.79 (M^{-1}, 58 %) and 324.91 (M^{+2}, 24 %). $C_{15}H_{13}N_7S$ (323.38)

6-Substitued-3-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 14a-c.

General procedure:

A mixture of the triazole **13** (0.32 g, 0.001 mol), sodium acetate (0,5 g, 6 mmol) and the selected halo compound (0.001 mol) in ethanol (10 ml) was heated under reflux for 4 h. The precipitate formed was filtered off and recrystallized from proper solvent.

6-Methyl-3-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-yl)-7*H*-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazine 14a.

This compound was obtained using chloroacetone (0.096 g, 0.001 mol) as fluffy crystals from ethanol, m.p. 203-205 °C, yield 0.26 g, (68 %). IR: ν cm^{-1} 3050 (CH arom.), 2950 (CH aliph.). ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H, pyrazole), 7.23 (m, 5H, phenyl), 6.63 (m, 2H, Hα pyrrole), 6.15 (m, 2H, Hβ pyrrole), 3.30 (s, 2H, CH_2), 2.13 (s, 3H, CH_3). MS: (*m/z*) 361.98 (M^+, 46 %), 360.98 (M^{-1}, 100 %). $C_{18}H_{15}N_7S$ (361.43)

6-Phenyl-3-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 14b.

This compound was obtained using phenacylbromide (0.199 g, 0.001 mol) as pale yellow crystals from ethanol, m.p. 193-95 °C, yield 0.31 g, (74 %). IR: ν cm^{-1} 1610 (C=N). ^{1}H NMR (CF_3COOD): δ 8.80 (s, 1H, pyrazole), 7.52 (m, 10H, phenyl), 6.60 (m, 2H, Hα pyrrole), 6.17 (m, 2H, Hβ pyrrole), 4.30 (s, 2H, CH_2). MS: (*m/z*) 423.49 (M^+, 60 %). $C_{23}H_{17}N_7S$ (423.50)

6-(4-Bromophenyl)-3-(1-phenyl-5-(pyrrol-1-yl)-1*H*-pyrazole-4-yl)-7*H*-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 14c.

This compound was obtained using *p*-bromophenacylbromide (0.27 g, 0.001 mol) as yellow needles from ethanol, m.p. 228-30 °C, yield 0.31 g, (62 %). IR: ν cm^{-1} 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H, pyrazole), 7.97 (d, J = 9

Hz, 2H, phenyl), 7.77 (d, J = 9 Hz, 2H, phenyl), 7.37 (m, 3H, phenyl), 7.17 (m, 2H, phenyl), 6.83 (m, 2H, Hα pyrrole), 6.07 (m, 2H, Hβ pyrrole), 4.30 (s, 2H, CH_2). $C_{23}H_{16}BrN_7S$ (502.40)

Biological Screening

In vitro evaluation of antibacterial and antifungal activities:

Tested compounds and the control antibiotic were dissolved in DMSO and sterile distilled water, respectively for the preparation of stock solutions. Further dilutions were made in sterile distilled water. The *in vitro* anti-microbial activities of the tested compounds were carried out using the filter paper disc diffusion method.[20] Filter paper discs (5 mm) saturated with the solution of each tested compound (20 mg / 2 ml of 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 hours at 37 °C for the bacteria and at 28 °C for the fungi. Discs saturated with DMSO were used as control and Clotrimazole was used as an anti-fungal reference and Cloxacillin as an anti-bacterial reference.

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