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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME ISOXAZOLE BASED HETEROCYCLES

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Abstract – The versatile hitherto unreported 2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (**3**) was utilized for the synthesis of a variety of heterocycles incorporating sulfamoyl moiety. The 2-pyridone derivatives were obtained *via* reaction of cyanoacetamide with pentane-2,4-dione, arylidenes malononitrile, or terephthalaldehyde and malononitrile upon heating under reflux in the presence of a catalyst. Condensation of the cyanoacetamide **3** with salicylaldehyde furnished the corresponding chromene derivatives. Coupling of **3** with arene diazonium chlorides gave the hydrazone derivatives **13a-c**, which upon treatment with hydrazine hydrate and ethyl chloroformate furnished the corresponding pyrazole and triazine derivatives, respectively. Reaction of **3** with carbon disulfide and 1,2-dibromoethane, 1,3-dibromopropane or dimethyl sulfate afforded 2-cyano-2-(1,3-dithiolan-2-ylidene)-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (**18**), 2-cyano-2-(1,3-dithian-2-ylidene)-*N*-4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (**19**), and 2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-3,3-bis(methylthio)acryl-amide (**20**). The newly synthesized compounds were evaluated for their *in vitro* antibacterial and antifungal activities, and showed promising results.

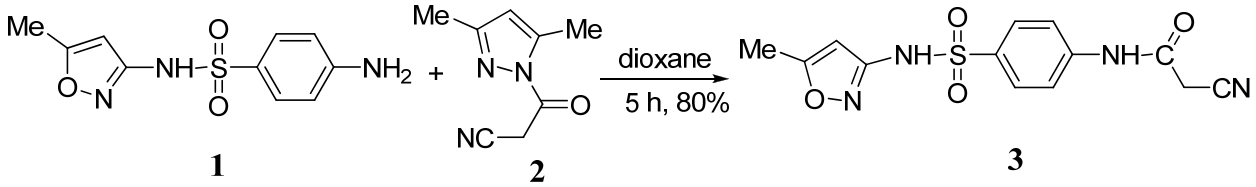
INTRODUCTION

Cyanoacetamides are highly reactive bifunctional compounds. The carbonyl and the cyano functions of these compounds are suitably situated to enable reactions with common reagents to form a variety of heterocycles. Also, the active methylene of cyanoacetamide can take part in a variety of condensation and substitution reactions. Moreover, cyanoacetamides and their related heterocyclic derivatives have attracted great attention due to their interesting biological, therapeutic value and pharmaceutical activities

such as antimicrobial,[1,2] antifungal,[3] insulin releasing,[4] carbonic anhydrase inhibitory,[5] anti-inflammatory,[6] and antitumor properties.[7] Some active sulfonamides as antibacterial are also known for their immune-modifying effects.[8,9] In addition, pyrazole derivatives have attracted much more attention due to their utilities in the field of drug discovery and agricultural research.[10-16] They are also known for their anticancer,[17-22] antipyretic,[23] anti-inflammatory,[24] antimicrobial activities,[25-27] antiviral,[28] tranquillizing,[29] antihypertensive,[30] antidepressant,[31] anti-arrhythmic,[32] anticonvulsant,[33] and antidiabetic activities.[34] Moreover, some 2-pyridones are also reported to possess antitumor,[35] antibacterial,[36] elastase inhibitors[37] and other biological activities.[38,39] In view of these observations and in continuation of our previous work directed to the synthesis of novel heterocyclic compounds of potential biological and pharmacological activities,[40-57] we report here the synthesis of some new pyridone, pyrazole and chromene derivatives incorporating sulfonamide moiety starting from 2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (**3**) as an excellent building block for the synthesis of the target compounds.

RESULTS AND DISCUSSION

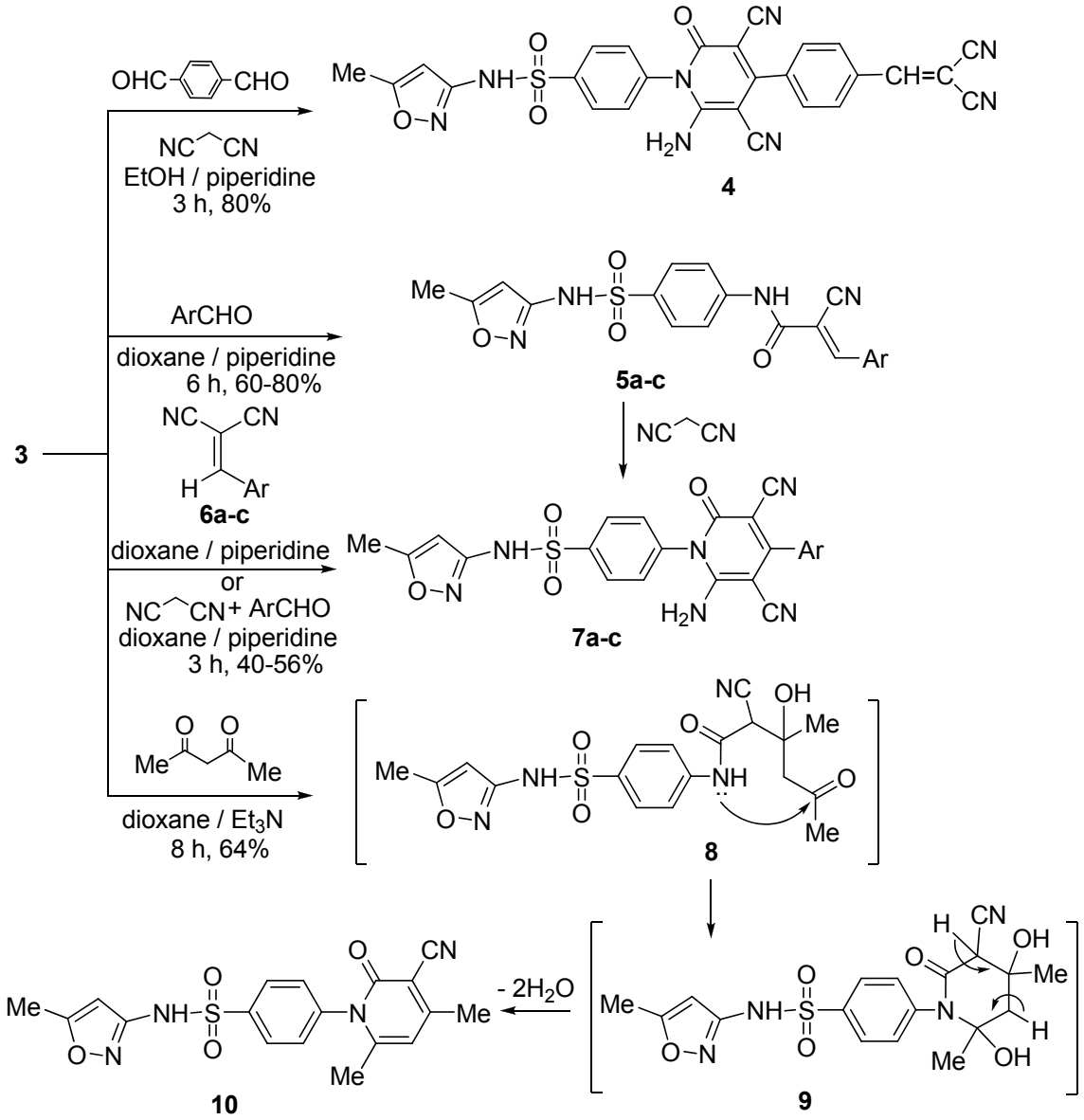
Cyanoacetamide **3** was synthesized by cyanoacetylation of 4-amino-*N*-(5-methylisoxazole-3-yl)benzene-sulfonamide (sulfamethoxazole) (**1**) with 3,5-dimethyl-1-cyanoacetylpyrazole (**2**)[58] as previously described (Scheme 1).



Scheme 1

One pot reaction of the cyanoacetamide derivative **3** with terephthalaldehyde and malononitrile (1: 1: 2 molar ratio), at reflux temperature in the presence of catalytic amount of piperidine afforded the corresponding derivative **4** (Scheme 2). The mass spectrum of **4** showed a molecular ion peak at *m/z* 548 corresponding to a molecular formula $C_{27}H_{16}N_8O_4S$ with a base peak at *m/z* 235 (100%). Knoevenagel condensation of the cyanoacetamide **3** with aromatic aldehydes *viz.* benzaldehyde, *p*-anisaldehyde, and *p*-chlorobenzaldehyde, furnished the corresponding arylidene derivatives **5a-c** (Scheme 2). The IR spectrum of compound **5a**, taken as a typical example of the series prepared, revealed absorption bands at 1678, 2219, 3304 and 3194 cm^{-1} corresponding to carbonyl, nitrile and NH functions, respectively. Its ^1H NMR spectrum showed signals at δ 8.30, 10.77 and 11.35 (D_2O-exchangeable) due to CH and 2NH protons in addition to aromatic protons at δ 7.62-8.00. Its mass spectrum showed a molecular ion peak at

m/z 408. Pyridin-2(1*H*)-ones **7a-c** were obtained through the reaction of the arylidene derivatives **5a-c** with malononitrile in dioxane containing a catalytic amount of piperidine. 2-Pyridone derivatives **7a-c** were also obtained *via* one-pot reactions of the cyanoacetamide derivative **3** with malononitrile and the same aldehydes (1:1:1 molar ratio) at reflux temperature in the presence of piperidine. On the other hand, the 2-pyridone derivatives **7a-c** were also obtained *via* reaction of the cyanoacetamide **3** with arylidenemalononitrile *viz.* benzylidenemalononitrile, 2-(4-chlorobenzylidene)malononitrile, or 2-(4-methoxybenzylidene)malononitrile upon heating under reflux in the presence of piperidine as a catalyst. The spectroscopic data and elemental analyses of the obtained products were in complete agreement with the assigned structures **7a-c**.

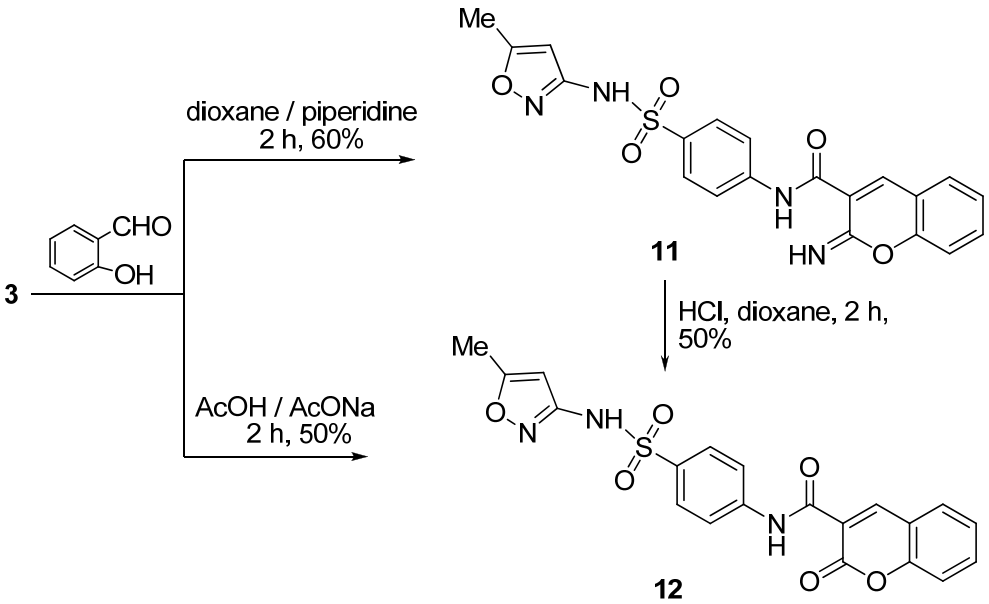


5,7: a, Ar = Ph; b, Ar = 4-$MeOC_6H_4$; c, Ar = 4-ClC_6H_4

Scheme 2

When the cyanoacetamide **3** was treated with pentane-2,4-dione, in dioxane in the presence of a catalytic amount of triethylamine, it afforded the corresponding 2-pyridinone derivative **10** (Scheme 2). It can be postulated that the reaction initially proceeds *via* a nucleophilic attack to form the Michael adduct which in turn underwent cyclization *via* elimination of two water molecules, affording the final product (Scheme 2).

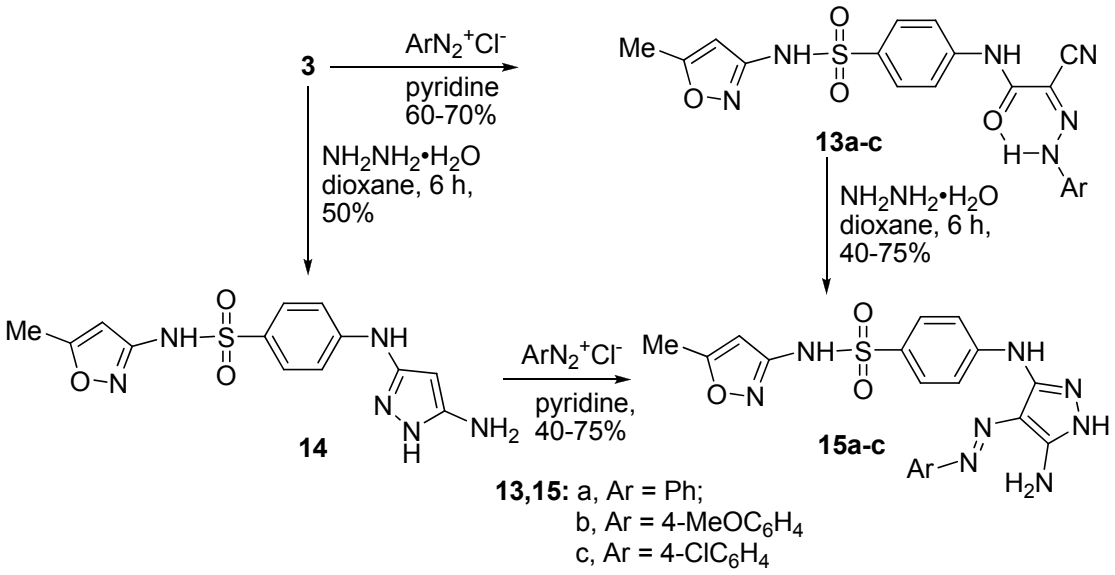
Similarly, cyclocondensation of the cyanoacetamide **3** with salicylaldehyde, in dioxane and in the presence of a catalytic amount of piperidine afforded 2-iminochromene **11** (Scheme 3). On the other hand, reaction of **3** with salicylaldehyde in the presence of AcOH/AcONa afforded chromenone **12**. The structure of compound **12** was further confirmed through its synthesis upon hydrolysis of **11** with ethanolic HCl. (Scheme 3). The IR spectrum of compound **11** revealed the disappearance of cyano absorption band and showed absorption bands at 1683, 3135, 3241 and 3301 cm^{-1} corresponding to carbonyl and three NH functions, respectively. Its ^1H NMR spectrum showed three D_2O-exchangeable signals at δ 9.29, 11.40 and 13.16 due to three NH protons, in addition to an aromatic multiplet in the region 7.31-7.91. Its mass spectrum showed a molecular ion peak at *m/z* 424 whereas the ^1H NMR spectrum of compound **12** showed two D_2O-exchangeable signal at δ 10.93 and 11.36 due to two NH protons.



Scheme 3

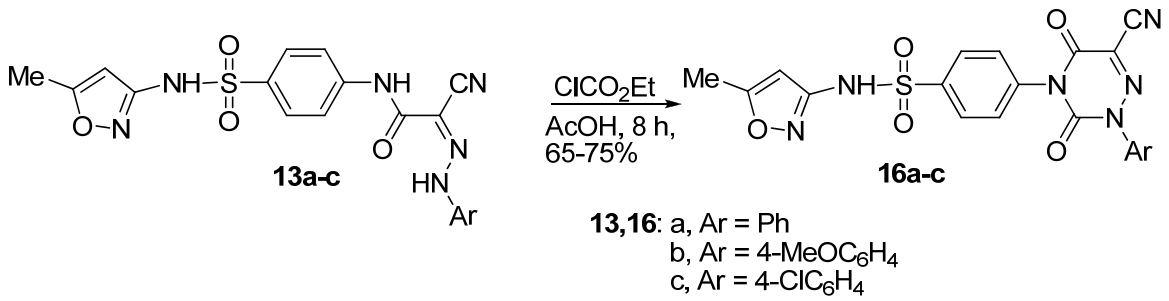
The cyanoacetamide **3** coupled smoothly with arenediazonium salts, in pyridine to afford the respective hydrazones **13a-c** (Scheme 4). The analytical and spectral data of the latter products are consistent with the proposed structures. The ^1H NMR spectrum of **13a**, taken as an example of the prepared series, displayed, besides an aromatic multiplet at 7.13-7.95 ppm, D_2O exchangeable signals at 10.23, 11.32 and 12.02 ppm corresponding to 3 NH protons. Its IR spectrum showed bands at 3382, 3243, 3080, 2217 and

1684 cm^{-1} due to 3 NH, CN and CO groups, respectively. The latter hydrazones **13a-c** underwent intramolecular cyclization upon treatment with hydrazine hydrate to give products identified as the 3-aminopyrazole derivatives **15a-c**. The IR spectra of **15a-c** showed, in each case, the absence of nitrile and carbonyl bands and revealed the appearance of three bands in the region 3460-3185 cm^{-1} due to NH_2 and NH groups as depicted in Scheme 4. Their ^1H NMR spectra displayed singlet in the region 6.05-6.07 and 9.97 and 10.82 ppm attributable to the NH_2 and 2NH protons, respectively. Compounds **15a-c** were alternatively obtained by reaction of the aminopyrazole derivative **14** with diazotized aromatic amines in pyridine. Compound **14** was prepared by the reaction of **3** with hydrazine hydrate in refluxing dioxane (Scheme 4)**.**



Scheme 4

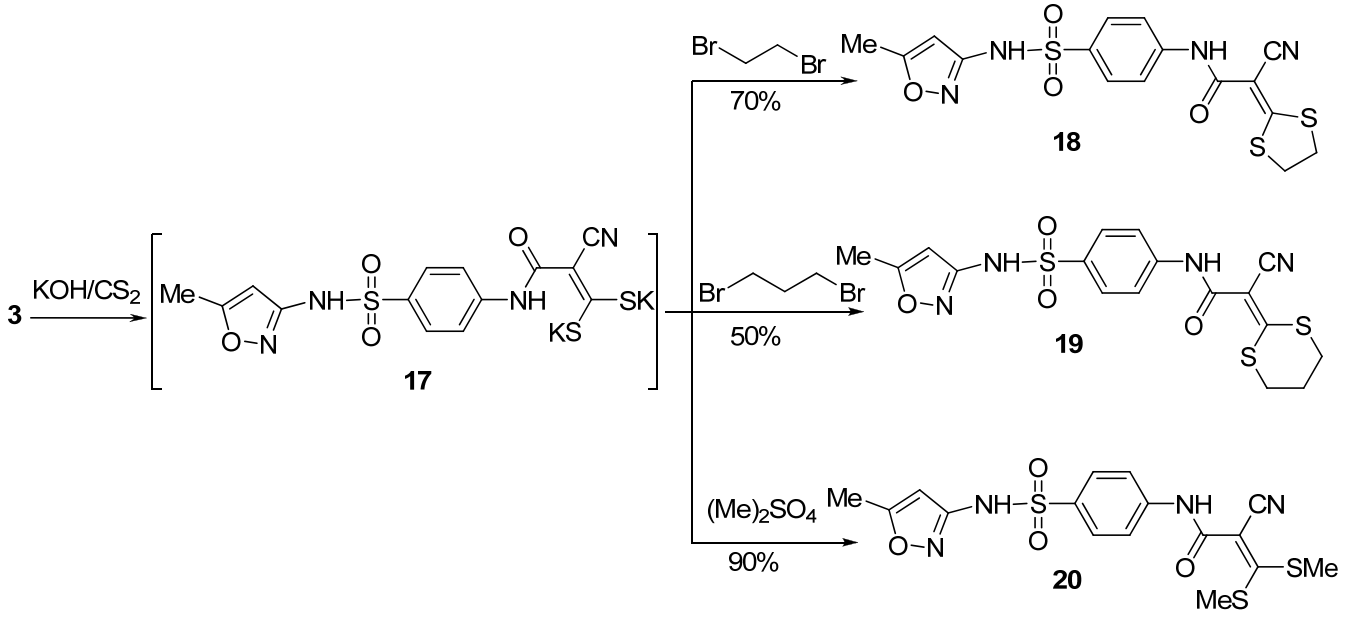
Treatment of the hydrazones **13a-c** with ethyl chloroformate in acetic acid, afforded the corresponding triazine derivatives **16a-c** (Scheme 5). The structures of compounds **16a-c** were established based on their elemental analyses and spectral data (see Experimental part).



Scheme 5

When the cyanoacetamide **3** was treated with carbon disulfide, in the presence of potassium hydroxide in DMF followed by cycloalkylation with 1,2-dibromoethane or 1,3-dibromopropane, yielded

2-cyano-2-(1,3-dithiolan-2-ylidene)-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (**18**), and 2-cyano-2-(1,3-dithian-2-ylidene)-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-acetamide (**19**), respectively in good yield (Scheme 6). Furthermore, reaction of **3** with CS_2 in the presence of KOH and dimethyl sulfate afforded 2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}-phenyl)-3,3-bis(methylthio)acrylamide (**20**) (Scheme 6). The IR spectra of compounds **18**, **19** and **20** showed, in each case, bands corresponding to NH, CH-aliphatic, C≡N and C=O groups. The ^{1}H NMR spectrum of the compound **18** showed signal at 3.95 (s, 4H, $2CH_2$-dithiolane). Its mass spectrum showed a molecular ion peak at *m/z* 422. The ^{1}H NMR spectrum of compound **19** showed signals for dithiene moiety at 2.10 (m, 2H, J = 6.80 Hz, CH_2), 3.03 (t, 2H, J = 6.6 Hz, CH_2), 3.21 (t, 2H, J = 6.6 Hz, CH_2). Its mass spectrum showed a molecular ion peak at *m/z* 436.



Scheme 6

ANTIMICROBIAL ACTIVITY

The newly synthesized compounds **4**, **5a**, **5b**, **7b**, **10**, **11**, **14**, **15a**, **15b**, **15c, 19**, and **20** were evaluated for their *in vitro* antibacterial activity against *Streptococcus pneumoniae* (RCMB-010010) (SP) and *Bacillis subtilis* (RCMB-010067) (BS) as examples of Gram-positive bacteria and *Pseudomonas aeruginosa* (RCMB-010043) (PA) and *Escherichia coli* (RCMB-010052) (EC) as examples of Gram-negative bacteria. They were also evaluated for their *in vitro* antifungal activity against *Aspergillus fumigatus* (RCMB-02568) (AF), *Syncephalastrum racemosum* (RCMB-05922) (SR), *Geotricum candidum* (RCMB-05097) (GC) and *Candida albicans* (RCMB-05036) (CA) fungal strains. Inhibition zone diameter (IZD) in mm was used as criterion for the antimicrobial activity using the diffusion technique. The fungicide amphotericin B and the antibiotic sulfamethoxazole were used as references to evaluate the

potency of the tested compounds under the same conditions. The results are depicted in Table 1. As it can be seen from the data present in Table 1, all the synthesized derivatives showed moderate to good activity against the tested microorganisms. The most active compounds were **15a,b**,**c** and **7b** which revealed strong inhibitory activity to the tested bacteria and fungi. The elevated activity of **15a,b,c** and **7b** is attributed to the presence of pharmacological pyrazole moiety in compound **15a,b,c** and pyridone ring in **7b**.

Table 1. Antibacterial and antifungal activities of the synthesized compounds

Compound	Inhibition Zone Diameter (cm)							
	Gram (+ve)		Gram (-ve)		Fungi			
Standard values*	*(SP)*	*(BS)*	*(PA)*	*(EC)*	*(AF)*	*(SR)*	*(GC)*	*(CA)*
	26.6± 0.2	18.2± 0.3	13.8± 0.1	15.3± 0.3	23.7± 0.1	19.7± 0.2	28.7± 0.2	25.4± 0.1
4	12.90± 0.63	13.20± 0.58	11.8± 0.36	10.80± 0.44	18.70± 0.36	16.90± 0.27	13.40± 0.65	10.90± 0.23
5a	16.90± 0.58	18.20± 0.44	10.70± 0.34	11.90± 0.63	15.70± 0.33	13.80± 0.25	18.30± 0.34	15.20± 0.53
5b	16.30± 0.55	18.30± 0.25	11.60± 0.19	15.40± 0.39	17.30± 0.44	12.60± 0.25	19.00± 0.58	16.9± 0.25
7b	16.90± 0.58	18.20± 0.44	9.80± 0.27	11.90± 0.63	16.20± 0.36	15.00± 0.44	17.60± 0.58	14.10± 0.43
10	16.30± 0.33	19.0± 0.25	10.20± 0.31	13.50± 0.34	16.60± 0.38	13.20± 0.56	19.50± 0.16	15.80± 0.40
11	14.60± 0.58	14.30± 0.58	10.20± 0.32	9.40± 0.44	13.60± 0.25	11.70± 0.34	16.50± 0.58	13.40± 0.45
14	12.30± 0.58	12.70± 0.37	10.10± 0.39	8.50± 0.37	17.60± 0.58	15.40± 0.25	12.6± 0.38	11.30± 0.34
15a	16.70± 0.36	19.20± 0.27	13.30± 0.36	13.60± 0.36	16.80± 0.39	13.40± 0.58	19.60± 0.19	15.90± 0.44
15b	18.30± 0.25	22.60± 0.44	19.30± 0.52	17.80± 0.44	20.60± 0.58	16.70± 0.33	22.40± 0.36	17.60± 0.58
15c	23.0± 0.2	32.40± 0.3	17.30± 0.1	19.90± 0.3	23.70± 0.1	19.70± 0.20	28.70± 0.20	25.40± 0.10
19	12.10± 0.56	12.50± 0.34	11.30± 0.31	10.60± 0.41	17.40± 0.55	15.00± 0.23	12.40± 0.35	10.50± 0.11
20	16.90± 0.42	17.60± 0.31	12.90± 0.28	14.70± 0.40	13.90± 0.42	11.80± 0.31	13.70± 0.34	14.00± 0.29

Data are expressed in the form of mean ± SD. Mean zone of inhibition in mm ± standard deviation beyond well diameter; (6 mm) produced on a range of environmental and clinically pathogenic microorganism using (5 mg/mL) concentration of tested sample (100 μL was tested).

* The antifungal used: amphotericin B and the antibacterial used: sulfamethoxazole.

EXPERIMENTAL

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The IR spectra were recorded using KBr disks on a Pye Unicam SP 3-300 or a Shimadzu FTIR 8101 PC IR spectrophotometer. The NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 and 75 MHz (^{1}H and ^{13}C NMR spectra, respectively) using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts were related to that of the solvent. Mass spectra (EI) were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer. Elemental analyses were carried out at the Micro-analytical Center of Cairo University, Giza, Egypt. The biological evaluation of the products was carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt.

2-Cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (**3**). A mixture of 4-amino-*N*-(5-methylisoxazole-3-yl)benzenesulfonamide (**1**) (5.06 g, 20 mmol) and 3,5-dimetyl-1-cyanoacetylpyrazole (**2**) (3.26 g, 20 mmol) in dioxane (20 mL) was refluxed for 3 h. The reaction mixture was poured into crushed ice and the resulting precipitate was filtrated off, washed with EtOH, dried, and finally crystallized from DMF/MeOH (1:3) to give **3**. Yield (80%), mp 220-222 ºC (from DMF/MeOH); IR (KBr) $\nu_{max/}$ cm^{-1}: 3329, 3277 (2NH), 2964, 2861 (aliphatic CH), 2262 (C≡N), 1691 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 6.11 (s, 1H, isoxazole-H-4), 7.71 (d, 2H, J = 9 Hz, ArH), 7.83 (d, 2H, J = 9 Hz, ArH), 10.67 (s, 1H, D_2O-exchangeable, NH), 11.32 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 11.9, 26.9, 66.3, 95.3, 119.1, 128.1, 133.9, 142.5, 157.4, 161.8, 170.2; MS (*m/z*, %): 322 (M^++2, 2.7), 321 (M^++1, 2.9), 320 (M^+, 4.1), 256 (8.2), 238 (2.9), 223 (11.7), 186 (80.1), 159 (62.9), 132 (41.3), 97 (6.2), 82 (3.1), 68 (100). Anal. Calcd for $C_{13}H_{12}N_4O_4S$ (320.32): C, 48.74; H, 3.78; N, 17.49; S, 10.01. Found: C, 48.70; H, 3.72; N, 17.43; S, 9.88%.

6-Amino-4-(4-(2,2-dicyanovinyl)phenyl)-1-(*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (4). To a mixture of the acetamide **3** (0.01 mol), terephthalaledehyde (0.01 mol) and malononitrile (0.02 mol) in EtOH (30 mL), few drop of piperidine was added. The reaction mixture was heated under reflux for 3 h. The formed solid product while hot, was filtrated off, washed with EtOH, dried, and finally crystallized from dioxane to give **4** as white crystals. Yield (80%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3435, 3148 (NH, NH_2), 2959 (aliphatic-H), 2214 (C≡N), 1639 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.20 (s, 3H, CH_3), 6.00 (s, 1H, isoxazole-H-4), 7.39 (m, 4H, Ar-H), 7.44 (s, 1H, D_2O-exchangeable, NH), 7.74 (s, 1H, olefinic-H), 7.91 (m, 4H, ArH), 8.40 (s, 2H, D_2O-exchangeable NH_2); ^{13}C-NMR (DMSO-d_6) δ 12.2, 43.6, 66.3, 75.3, 87.8, 96.6, 112.0, 114.0, 115.4, 116.0, 127.9, 128.3, 128.7, 129.5, 135.3, 136.2, 146.9, 157.0, 159.4, 160.2, 163.9, 167.1; MS (*m/z*, %): 549 (M^++1, 78.1), 548 (M^+, 89.5), 474 (66.7), 466 (54.3), 451 (67.6), 331 (59.1), 235 (100), 215 (49.5), 153 (70.5), 77 (59.1). Anal. Calcd for $C_{27}H_{16}N_8O_4S$ (548.53): C, 59.12; H,

2.94; N, 20.43; S, 5.85. Found: C, 59.01; H, 2.90; N, 20.39; S, 5.80%.

***N*-[4-(Aminosulfonyl)phenyl]-3-aryl-2-cyanoacrylamide (5a-c).**

General Procedure: To a solution of the cyanoacetamide **3** (0.320 g, 1 mmol) and the appropriate aromatic aldehydes (1 mmol) in dioxane (20 mL), was added few drops of piperidine and the reaction mixture was refluxed for 6 h. The formed solid product was filtered off, washed with EtOH, dried, and finally recrystallized from proper solvent to give **5a-c**.

2-Cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-3-phenylacrylamide (5a). Yield (80%), mp 282-284 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3304, 3194 (2NH), 2892, 2838 (aliphatic CH), 2219 (C≡N), 1678 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 6.13 (s, 1H, isoxazole-H-4), 7.62 (d, 2H, *J* = 9 Hz, ArH), 7.84-7.86 (m, 5H, ArH), 8.00 (d, 2H, *J* = 9 Hz, ArH), 8.30 (s, 1H, olefinic-H), 10.77 (s, 1H, D_2O-exchangeable, NH), 11.35 (s, 1H, D_2O-exchangeable, NH). MS (*m/z*, %): 410(M^++2, 5.5), 409 (M^++1, 5.5), 408 (M^+, 7.3), 326 (4.6), 311 (3.2), 236 (4.0), 171 (5.5), 156 (96.3), 128 (100), 101 (39.1), 77 (77.0). Anal. Calcd for $C_{20}H_{16}N_4O_4S$ (408.43): C, 58.81; H, 3.95; N, 13.72; S, 7.85. Found: C, 58.78; H, 3.88; N, 13.70; S, 7.80%.

2-Cyano-3-(4-methoxyphenyl)-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acrylamide (5b).[59] Yield (80%), mp 260-262 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3322, 3091 (2NH), 2993, 2843 (aliphatic CH), 2215 (C≡N), 1685 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.14 (s, 1H, isoxazole-H-4), 7.19 (d, 2H, *J* = 9 Hz, ArH), 7.85-7.89 (m, 4H, ArH), 8.04 (d, 2H, *J* = 9 Hz, ArH), 8.23 (s, 1H, olefinic-H), 10.64 (s, 1H, D_2O-exchangeable, NH), 11.35 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 439 (M^++1, 4.7), 438 (M^+, 6.2), 412 (6.2), 341 (4.2), 304 (10.6), 279 (6.7), 206 (4.1), 186 (100), 158 (26.5), 97 (14.3); Anal. Calcd for $C_{21}H_{18}N_4O_5S$ (438.45): C, 57.53; H, 4.14; N, 12.78; S, 7.31. Found: C, 57.50; H, 4.09; N, 12.72; S, 7.28%.

3-(4-Chlorophenyl)-2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acrylamide (5c). Yield (60%), mp 275-277 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3300, 3087 (2NH), 2988, 2898 (aliphatic CH), 2220 (C≡N), 1682 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 6.14 (s, 1H, isoxazole-H-4), 7.80 (d, 2H, ArH), 7.84 (d, 2H, Ar-H), 7.88 (d, 2H, *J* = 9 Hz, ArH), 7.95 (d, 2H, *J* = 9 Hz, ArH), 9.93 (s, 1H, olefinic-H), 10.76 (s, 1H, D_2O-exchangeable, NH), 11.34 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 444 (M^++2, 4.8), 443 (M^++1, 5.8), 442 (M^+, 6.3), 363 (15.4), 345 (9.5), 308 (36.9), 281 (21.9), 254 (5.7), 237 (4.1), 206 (8.8), 190 (100), 161 (45.0), 97 (13.4); Anal. Calcd for $C_{20}H_{15}ClN_4O_4S$ (442.87): C, 54.24; H, 3.41; Cl, 8.01; N, 12.65; S, 7.24. Found: C, 54.20; H, 3.36; Cl, 8.00; N, 12.62; S, 7.20%.

Synthesis of the pyridones 7a–c.

Method A: A mixture of **5** (10 mmol) and malononitrile (0.66 g, 10 mmol) in dioxane (30 mL)

containing piperidine (0.5 mL) was heated under reflux for 3 h, then left to cool. The solid product was filtered off, washed with EtOH, dried, and finally recrystallized from the proper solvent to give **7a-c**.

Method B: Equimolar amounts of **3** (10 mmol) and the appropriate 2-(arylidene)malononitrile (10 mmol) in dioxane (30 mL) was added piperidine (0.5 mL) and the reaction mixture was heated under reflux for 3 h, then left to cool. The solid product was filtered off, washed with EtOH, dried, and finally recrystallized from the proper solvent to give **7a-c**.

Method C: A mixture of **3** (10 mmol), the appropriate aromatic aldehyde (10 mmol), piperidine (0.85 mmol), and malononitrile (0.66 g, 10 mmol) in dioxane (30 mL) was heated under reflux for 3 h, then left to cool. The solid product was filtered off, washed with EtOH, dried, and finally recrystallized from the proper solvent to give **7a-c**.

4-(6-Amino-3,5-dicyano-2-oxo-4-phenylpyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7a). Yield (54%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3362, 3316, 3217 (NH, NH_2), 2970, 2889 (aliphatic CH), 2217 (C≡ N), 1629 (C=O); ^{1}HNMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 4.31 (br., 2H, D_2O-exchangeable, NH_2), 6.22 (s, 1H, isoxazole-H-4), 7.51-7.57 (m, 5H, ArH), 7.67 (d, 2H, *J* = 9 Hz, ArH), 8.06 (d, 2H, *J* = 9 Hz, ArH), 11.60 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 12.0, 66.3, 75.5, 87.9, 95.4, 116.0, 127.8, 128.6, 128.8, 130.0, 130.3, 134.5, 138.0, 141.1, 156.8, 157.4, 159.3, 161.5, 170.3; MS (*m/z*, %): 473 (M^++1, 42.3), 472 (M^+, 69.2), 397 (54.6), 390 (66.9), 373 (46.2), 283 (68.5), 235 (50.0), 175 (60.0), 157 (43.9), 80 (100). Anal. Calcd for $C_{23}H_{16}N_6O_4S$ (472.47): C, 58.47; H, 3.41; N, 17.79; S, 6.79. Found: C, 58.42; H, 3.38; N, 17.75; S, 6.74%.

4-[6-Amino-4-(4-methoxyphenyl)-3,5-dicyano-2-oxopyridin-1(2*H*)-yl]-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7b). Yield (56%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3324, 3280, 3191 (NH, NH_2), 2985, 2846 (aliphatic CH), 2215 (C≡N), 1688 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.9 (br., 2H, NH_2), 6.23 (s, 1H, isoxazole-H-4), 7.14 (d, 2H, Ar-H), 7.51 (d, 2H, Ar-H), 7.67 (d, 2H, ArH), 8.05 (d, 2H, ArH), 11.75 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 503 (M^++1, 10.1), 502 (M^+, 16.3), 419 (11.0), 404 (7.7), 267 (14.9), 186 (100), 158 (27.2), 106 (11.0), 97 (15.8). Anal. Calcd for $C_{24}H_{18}N_6O_5S$ (502.50): C, 57.36; H, 3.61; N, 16.72; S, 6.38. Found: C, 57.33; H, 3.58; N, 16.70; S, 6.36%.

4-4-[6-Amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxopyridin-1(2*H*)-yl]-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7c). Yield (40%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3324, 3204, 3093 (NH, NH_2), 2993, 2892 (aliphatic CH), 2220 (C≡N), 1654 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 4.31 (br., 2H, D_2O-exchangeable, NH_2), 6.22 (s, 1H, isoxazole-H-4), 7.57 (d, 2H, *J* = 9 Hz, ArH), 7.58-7.74 (m, 4H, ArH), 8.06 (d, 2H, *J* = 9 Hz, ArH), 11.60 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 507 (M^++1, 69.3), 506 (M^+, 94.7), 409 (76.3), 295 (73.7), 264 (59.7), 221 (47.4), 157 (57.9), 137 (100), 111 (45.6). Anal. Calcd for $C_{23}H_{15}ClN_6O_4S$ (506.92): C, 54.49; H, 2.98; Cl, 6.99; N, 16.58; S,

6.33. Found: C, 54.45; H, 2.93; Cl, 6.94; N, 16.56; S, 6.30%.

4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (10).

To a mixture of the cyanoacetamide **3** (1.60 g, 5 mmol) and pentane-2,4-dione (0.50 g, 5 mmol) in dioxane (20 mL), triethylamine (0.5 mL) was added and the reaction mixture was refluxed for 8 h. On cooling, the separated solid was filtered, washed with EtOH, dried, and finally crystallized from DMF to afford the corresponding sulfonamide (**10**). Yield (64%), mp 295-297 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3082 (NH), 2983, 2870 (aliphatic CH), 2217 (C≡N), 1651 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.20 (s, 1H, isoxazole-H-4), 6.48 (s, 1H, pyridine-H), 7.63 (d, 2H, *J* = 9 Hz, ArH), 8.03 (d, 2H, *J* = 9 Hz, ArH), 11.60 (s, 1H, D_2O-exchangeable, NH); ^{13}C-NMR (DMSO-d_6) δ 12.0, 20.6, 21.3, 95.4, 100.0, 109.1, 115.5, 128.0, 129.4, 140.2, 141.3, 151.4, 157.3, 160.0, 160.2, 170.5; MS (*m/z*, %): 384 (M^+, 13.2), 321 (15.5), 288 (17.2), 239 (15.5), 222 (18.9), 148 (20.8), 97 (19.6), 79 (100). Anal. Calcd for $C_{18}H_{16}N_4O_4S$ (384.41): C, 56.24; H, 4.20; N, 14.57; S, 8.34. Found: C, 56.20; H, 4.16; N, 14.52; S, 8.30%.

2-Imino-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-2*H*-chromene-3-carboxamide (11).

A mixture of equimolar amounts of the cyanoacetamide **3** (1.60 g, 5 mmol) and salicylaldehyde (0.61 g, 5 mmol) in dioxane (25 mL) containing a catalytic amount of piperidine was heated under reflux for 2 h, then left to cool. The solid product formed was filtrated off, washed with EtOH, dried, and finally crystallized from dioxane to give **11**. Yield (60%), mp 255-257 ºC (from dioxane); IR (KBr) ν_{max}: 3301, 3241, 3135 (3NH), 2926, 2888 (aliphatic CH), 1683 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 6.13 (s, 1H, isoxazole-H-4), 7.31 (d, 2H, Ar-H), 7.60 (s, 2H, Ar-H), 7.62 (s, 1H, CH), 7.80-7.91 (m, 3H, Ar-H), 8.56 (s, 1H, CH), 9.29 (br., 1H, D_2O-exchangeable, NH), 11.40 (br., 1H, D_2O-exchangeable, NH), 13.16 (br., 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 425 (M^++1, 8.4), 424 (M^+, 17.9), 343 (4.8), 328 (4.4), 279 (19.8), 253 (4.8), 236 (4.4), 187 (5.4), 172 (100), 145 (54.2), 97 (6.3), 83 (11.2). Anal. Calcd for $C_{20}H_{16}N_4O_5S$ (424.43): C, 56.60; H, 3.80; N, 13.20; S, 7.56. Found: C, 56.57; H, 3.78; N, 13.18; S, 7.53%.

***N*-(4-{[(5-Methylisoxazol-3-yl)amino]sulfonyl}phenyl)-2-oxo-2*H*-chromene-3-carboxamide (12).**[60]

Method A: To a solution of **3** (1.60 g, 5 mmol) in acetic acid (30 mL) containing 0.5 g of fused sodium acetate, salicylaldehyde (0.61 g, 5 mmol) was added. The mixture was heated under reflux for 2 h. After cooling, the formed product was filtrated off, washed with EtOH, dried, and finally crystallized from DMF to give **12**.

Method B: The iminochromene derivatives **11** (1.06 g, 2.5 mmol) was dissolved in dioxane (40 mL) and treated with HCl (5 mL). The reaction mixture was heated under reflux for 2 h, left to cool. The obtained solid product was filtered off, washed with cold water, dried, and finally crystallized from dioxane. Yield

(50%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3212, 3127 (2NH), 2960, 2867 (aliphatic CH), 1708 (C=O), 1669 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 6.13 (s, 1H, isoxazole-H-4), 7.56 (d, 2H, *J* = 9 Hz, ArH), 7.75-7.91 (m, 4H, ArH), 8.02 (d, 2H, *J* = 9 Hz, ArH), 8.90 (s, 1H, CH), 10.93 (s, 1H, D_2O-exchangeable, NH), 11.36 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 11.9, 66.3, 95.3, 116.2, 118.3, 119.6, 125.2, 128.1, 130.3, 134.2, 134.4, 142.0, 147.7, 153.9, 157.4, 160.1, 160.5, 170.2; MS (*m/z*, %): 426 (M^++1, 6.7), 425 (M^+, 14.5), 353 (11.0), 328 (11.8), 278 (9.5), 253 (9.7), 188 (14.8), 173 (100), 145 (11.8), 101 (37.1), 82 (10.5). Anal. Calcd for $C_{20}H_{15}N_3O_6S$ (425.41): C, 56.47; H, 3.55; N, 9.88; S, 7.54. Found: C, 56.43; H, 3.51; N, 9.85; S, 7.50%.

Coupling of 2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (3) with arenediazonium salts. Formation of the hydrazones 13a-c.

General procedure*:* To a cold solution of the cyanoacetamide **3** (1.60 g, 5 mmol) in pyridine (20 mL), was added the appropriate diazonium salt of the appropriate aromatic amine (aniline, 4-methoxyaniline and 4-chloroaniline) (5 mmol), prepared according to literature procedures.[61] The addition was carried out portionwise with stirring at 0-5 ^{o}C over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4 h then kept in an ice chest for 12 h and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried and finally recrystallized from the proper solvent to afford the corresponding hydrazones **13a-c**.

2-Cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-2-(phenylhydrazono)acetamide (13a). Yield (60%), mp 272-274 ^{o}C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3382, 3243, 3080 (3NH), 2992, 2890 (aliphatic CH), 2217 (C≡N), 1684 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 6.14 (s, 1H, isoxazole-H-4), 7.13-7.43 (m, 5H, ArH), 7.82 (d, 2H, *J* = 9 Hz, ArH), 7.95 (d, 2H, *J* = 9 Hz, ArH), 10.23 (s, 1H, D_2O-exchangeable, NH), 11.32 (s, 1H, D_2O-exchangeable, NH), 12.02 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 425 (M^++1, 6.0), 424 (M^+, 9.5), 326 (10.12), 290 (30.9), 279 (14.9), 252 (2.2), 187 (3.1), 172 (19.1), 97 (14.6), 92 (96.2), 77 (100). Anal. Calcd for $C_{19}H_{16}N_6O_4S$ (424.43): C, 53.77; H, 3.80; N, 19.80; S, 7.55. Found: C, 53.75; H, 3.79; N, 19.78; S, 7.50%.

2-Cyano-2-[(4-methoxyphenyl)hydrazono]-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-acetamide (13b). Yield (70%), mp 283-295 ^{o}C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3375, 3240, 3084 (3NH), 2993, 2896 (aliphatic CH), 2212 (C≡N), 1680 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.14 (s, 1H, isoxazole-H-4), 6.99 (d, 2H, *J* = 7.8 Hz, ArH), 7.68 (d, 2H, *J* = 7.8 Hz, ArH), 7.84 (d, 2H, *J* = 9 Hz, ArH), 7.95 (d, 2H, *J* = 9 Hz, ArH), 10.16 (s, 1H, D_2O-exchangeable, NH), 11.32 (s, 1H, D_2O-exchangeable, NH), 11.98 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 455 (M^++1, 7.1), 454 (M^+, 11.8), 372 (2.6), 357 (1.2), 319 (5.1), 292 (16.1), 217 (1.2), 201 (4.2), 155 (24.4), 135 (21.9), 122 (100), 107 (72.6), 97 (20.9). Anal. Calcd for $C_{20}H_{18}N_6O_5S$ (454.46): C, 52.86; H, 3.99; N, 18.49; S, 7.06. Found: C, 52.83; H, 3.96; N, 18.45; S, 7.05%.

2-[(4-Chlorophenyl)hydrazono]-2-cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-acetamide (13c). Yield (70%), mp 290-292 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3384, 3258, 3079 (3NH), 2981, 2887 (aliphatic CH), 2216 (C≡N), 1686 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 6.13 (s, 1H isoxazole-H-4), 7.46 (d, 2H, *J* = 8.7 Hz, ArH), 7.74 (d, 2H, *J* = 8.7 Hz, ArH), 7.85 (d, 2H, *J* = 9 Hz, ArH), 7.94 (d, 2H, *J* = 9 Hz, ArH), 10.27 (s, 1H, D_2O-exchangeable, NH), 11.32 (s, 1H, D_2O-exchangeable, NH), 12.15 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 459 (M^++1, 23.0), 458 (M^+, 11.6), 360 (10.4), 325 (7.2), 303 (0.3), 296 (33.8), 279 (20.1), 205 (10.6), 155 (20.8), 140 (19.9), 126 (66.4), 111 (100), 97 (30.3). Anal. Calcd for $C_{19}H_{15}ClN_6O_4S$ (458.87): C, 49.73; H, 3.29; Cl, 7.73; N, 18.31; S, 6.99. Found: C, 49.71; H, 3.27; Cl, 7.70; N, 18.30; S, 6.96%.

4-[(5-Amino-1*H*-pyrazol-3-yl)amino]-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (14). To a solution of the compound **3** (1.60 g, 5 mmol) in dioxane (20 mL), hydrazine hydrate (80%, 1.0 mL) was added and the reaction mixture was refluxed for 6 h and then allowed to cool. The solid product was filtered, washed with EtOH and dried. Recrystallized from dioxane afforded **14**. Yield (50%), mp 245-246 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3476, 3372, 3266 (NH, NH_2), 1629 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.03 (s, 3H, CH_3), 4.15 (br., 2H, D_2O-exchangeable, NH_2), 5.77 (s, 1H, isoxazole-H-4), 6.30 (s, 1H, CH), 6.60 (d, 2H, *J* = 9 Hz, ArH), 6.85 (s, 1H, D_2O-exchangeable, NH), 7.48 (d, 2H, *J* = 9 Hz, ArH), 7.84 (s, 1H, D_2O-exchangeable, NH), 10.45 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 335 (M^++1, 3.9), 334 (M^+, 5.3), 272 (5.5), 253 (4.6), 236 (4.1), 172 (67.4), 156 (58.4), 108 (69.8), 92 (85.4), 80 (40.6), 65 (100). Anal. Calcd for $C_{13}H_{14}N_6O_3S$ (334.35): C, 46.70; H, 4.22; N, 25.14; S, 9.59. Found: C, 46.67; H, 4.20; N, 25.10; S, 9.55%.

Synthesis of aminopyrazole derivatives 15a-c.

Method A: To a solution of the appropriate hydrazone **13** (5 mmol) in dioxane (20 mL) was added hydrazine hydrate (5 mmol). The reaction mixture was refluxed for 6 h, and then left to cool. The solid product was collected, washed with EtOH, dried and finally recrystallized from dioxane to afford the corresponding 4-arylazopyrazole derivatives **15a-c**, respectively.

Method B: To a stirred cold solution of the pyrazole derivative **14** (1.67 g, 5 mmol) in pyridine (30 mL) was added the appropriate arenediazonium chloride[61] (5 mmol) portionwise over a period of 30 min at 0-5 °C. After complete addition, the reaction mixture was stirred for further 3 h at 0-5 °C. The solid product was collected, washed with water, dried, and finally recrystallization from dioxane afforded the corresponding aminopyrazoles **15a-c**.

4-({5-Amino-4-[phenyldiazenyl]-1*H*-pyrazol-3-yl}amino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (15a). Yield (40%), mp 248-250 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3431, 3367 (NH, NH_2), 2921 (aliphatic CH); ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 6.05 (s, 2H, D_2O-exchangeabl, NH_2), 6.14

(s, 1H, isoxazole-H-4), 6.59 (d, 2H, ArH), 7.18 (d, 2H, *J* = 9 Hz, ArH), 7.47 (d, 3H, ArH), 7.84 (d, 2H, *J* = 9 Hz, ArH), 7.92 (s, 1H, D_2O-exchangeable, NH), 10.20 (s, 1H, D_2O-exchangeable, NH), 10.82 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 439 (M^++1, 27.9), 438 (M^+, 37.6), 424 (39.3), 356 (58.1), 333 (38.2), 314 (50.6), 251 (40.9), 238 (29.0), 203 (53.8), 186 (29.6), 105 (33.9), 92 (100), 77 (59.7). Anal. Calcd for $C_{19}H_{18}N_8O_3S$ (438.46): C, 52.05; H, 4.14; N, 25.56; S, 7.31. Found: C, 52.00; H, 4.10; N, 25.53; S, 7.30%.

4-({5-Amino-4-[(4-methoxyphenyl)diazenyl]-1*H*-pyrazol-3-yl}amino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (15b). Yield (72%), mp 234-236 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3345, 3219 (NH, NH_2), 2970, 2857 (aliphatic CH); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 3.39 (s, 3H, OCH_3), 6.05 (s, 2H, D_2O-exchangeable, NH_2), 6.13 (s, 1H, isoxazole-H-4), 7.09 (d, 2H, *J* = 7.8 Hz, ArH), 7.37 (d, 2H, *J* = 9 Hz, ArH), 7.51 (d, 2H, *J* = 7.8 Hz, ArH), 7.87 (d, 2H, *J* = 9 Hz, ArH), 7.93 (s, 1H, D_2O-exchangeable, NH), 9.97 (s, 1H, D_2O-exchangeable, NH), 10.40 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 469 (M^++1, 12.2), 468 (M^+, 10.6), 458 (10.8), 437 (10.2), 368 (16.9), 255 (13.3), 206 (10.8), 156 (34.1), 135 (10.2), 119 (43.7), 108 (58.8), 92 (100). Anal. Calcd for $C_{20}H_{20}N_8O_4S$ (468.49): C, 51.27; H, 4.30; N, 23.92; S, 6.84. Found: C, 51.24; H, 4.28; N, 23.90; S, 6.82%.

4-({5-Amino-4-[(4-chlorophenyl)diazenyl]-1*H*-pyrazol-3-yl}amino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (15c). Yield (75%), mp 250-252 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3460, 3369, 3185 (NH, NH_2), 2922, 2856 (aliphatic CH); ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 5.83 (s, 1H, isoxazole-H-4), 6.07 (s, 2H, D_2O-exchangeable, NH_2), 6.59 (d, 2H, *J* = 8.7 Hz, ArH), 7.47 (d, 2H, *J* = 9 Hz, ArH), 7.59 (d, 2H, *J* = 8.7 Hz, ArH), 7.84 (d, 2H, *J* = 9 Hz, ArH), 7.95 (s, 1H, D_2O-exchangeable, NH), 10.52 (s, 2H, D_2O-exchangeable, 2NH); MS (*m/z*, %): 473 (M^++1, 47.5), 472 (M^+, 71.3), 440 (72.9), 292 (60.7), 237 (100), 219 (59.8), 152 (50.8), 111 (46.7), 98 (47.5), 82 (60.7). Anal. Calcd for $C_{19}H_{17}ClN_8O_3S$ (472.90): C, 48.26; H, 3.62; Cl, 7.50; N, 23.69; S, 6.78. Found: C, 48.24; H, 3.60; Cl, 7.48; N, 23.66; S, 6.76%.

Reaction of hydrazones 13a-c with ethyl chloroformate. Formation of the triazine derivatives 16a-c. To a solution of the hydrazone **13a-c** (1 mmol) in acetic acid (20 mL), ethyl chloroformate (1 mmol) was added and the reaction mixture was refluxed for 8 h, then left to cool. The solid product was filtered off, washed with EtOH, dried, and finally recrystallized from dioxane afforded the corresponding triazine derivatives **16a-c**.

4-(6-Cyano-3,5-dioxo-2-phenyl-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (16a). Yield (70%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3383 (NH), 2992, 2894 (aliphatic CH), 2219 (C≡N), 1682 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, CH_3), 6.14 (s, 1H, isoxazole-H-4), 7.18 (s, 1H, ArH), 7.43 (d, 2H, *J* = 9 Hz, ArH), 7.73 (s, 2H, ArH), 7.85 (s, 2H, ArH),

8.06 (d, 2H, *J* = 9 Hz, ArH), 10.23 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 450 (M^+, 38.0), 416 (52.8), 368 (42.9), 355 (44.8), 337 (33.1), 284 (47.9), 268 (50.3), 213 (60.1), 136 (45.4), 77 (86.5), 65 (100). Anal. Calcd for $C_{20}H_{14}N_6O_5S$ (450.42): C, 53.33; H, 3.13; N, 18.66; S, 7.12. Found: C, 53.31; H, 3.11; N, 18.63; S, 7.09%.

4-[6-Cyano-2-(4-methoxyphenyl)-3,5-dioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl]-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (16b). Yield (75%), mp 292-294 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1} 3381 (NH), 2991, 2896 (aliphatic CH), 2214 (C≡ N), 1682 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.23 (s, 1H, isoxazole-H-4), 7.14 (d, 2H, *J* = 9 Hz, ArH), 7.51 (d, 2H, *J* = 8.7 Hz, ArH), 7.67 (d, 2H, *J* = 8.7 Hz, ArH), 8.05 (d, 2H, *J* = 9 Hz, ArH), 11.60 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 481 (M^++1, 23.7), 480 (M^+, 18.1), 457 (16.7), 397 (19.0), 375 (16.9), 307 (18.4), 240 (16.7), 237 (16.1), 215 (20.8), 133 (20.5), 111 (18.1), 107 (16.9), 97 (60.6), 92 (16.1), 80 (100). Anal. Calcd for $C_{21}H_{16}N_6O_6S$ (480.45): C, 52.50; H, 3.36; N, 17.49; S, 6.67. Found: C, 52.48; H, 3.33; N, 17.46; S, 6.65%.

4-[2-(4-Chlorophenyl)-6-cyano-3,5-dioxo-2,5-dihydro-1,2,4-triazin-4(3*H*)-yl]-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (16c). Yield (65%), mp > 300 ºC (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3427 (NH), 2927 (aliphatic CH), 2197 (C≡N), 1628 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 6.02 (s, 1H, isoxazole-H-4), 7.74-7.77 (m, 4H, ArH), 7.82 (d, 2H, ArH), 8.25 (s, 2H, ArH), 10.65 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 485 (M^++1, 5.2), 484 (M^+, 83.2), 450 (61.1), 402 (66.3), 373 (61.1), 347 (57.9), 278 (82.1), 249 (80.0), 237 (54.7), 138 (90.5), 110 (65.3), 98 (100). Anal. Calcd for $C_{20}H_{13}ClN_6O_5S$ (484.87): C, 49.54; H, 2.70; Cl, 7.31; N, 17.33; S, 6.61. Found: C, 49.51; H, 2.68; Cl, 7.29; N, 17.31; S, 6.59%.

Synthesis of compounds 18, 19 and 20.

***General procedure*:**

To a stirred suspension of finely powdered potassium hydroxide (0.26 g, 5 mmol) in dry DMF (20 mL) cyanoacetamide **3** (1.60 g, 5 mmole) was added. The resulting mixture was cooled at 10 °C in an ice bath, then carbon disulfide (5 mmol) was added slowly over the course of 10 min. After complete addition, stirring was continued for additional 2 h, then dibromoethane or dibromopropane or dimethyl sulfate (5 mmol) was added to the mixture while cooling (~15 °C) and stirring for 1 h. then poured into crushed ice, the resulting precipitate was filtrated off, dried, and finally crystallized from the proper solvent to give **18-20**.

2-Cyano-2-(1,3-dithiolan-2-ylidene)-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (18). Yield (70%), mp 200-202 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3327, 3277 (2NH), 2962 (aliphatic CH), 2190 (C≡N), 1692 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, CH_3), 3.95 (s, 4H, $2CH_2$), 6.11 (s, 1H,

isoxazole-H-4), 7.72 (d, 2H, *J* = 9 Hz), 7.84 (d, 2H, *J* = 9 Hz), 10.69 (s, 1H, D_2O-exchangeable, NH), 11.32 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 11.9, 29.9, 95.3, 112.5, 115.5, 119.0, 128.1, 133.8, 142.5, 153.2, 157.4, 161.8, 170.2; MS (*m/z*, %): 422 (M^+, 35.7), 353 (54.1), 338 (44.3), 326 (33.5), 284 (36.8), 252 (37.8), 238 (35.1), 186 (100), 169 (28.1), Anal. Calcd for $C_{16}H_{14}N_4O_4S_3$ (422.50): C, 45.48; H, 3.34; N, 13.26; S, 22.77. Found: C, 45.46; H, 3.31; N, 13.24; S, 22.75%.

2-Cyano-2-(1,3-dithian-2-ylidene)-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)acetamide (19). Yield (50%), mp 205-207 °C (from dioxane); IR (KBr) ν_{max}/cm^{-1}: 3324, 3277 (2NH), 2960 (aliphatic CH), 2208 (C≡N), 1691 (C=O); ^1H NMR (DMSO-d_6) δ 2.10 (m, 2H, *J* = 6.80 Hz, CH_2), 2.29 (s, 3H, CH_3), 3.03 (t, 2H, *J* = 6.6 Hz, CH_2), 3.21 (t, 2H, *J* = 6.6 Hz, CH_2), 6.11 (s, 1H, isoxazole-H-4), 7.74 (d, 2H, *J* = 9 Hz, ArH), 7.83 (d, 2H, *J* = 9 Hz, ArH), 10.68 (s, 1H, D_2O-exchangeable, NH), 11.32 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 436 (M^+, 9.4), 356 (8.4), 335 (12.3), 280 (11.8), 255 (17.2), 253 (8.4), 238 (13.1), 200 (16.2), 186 (98.7), 155 (16.5), 97 (15.4), 68 (100). Anal. Calcd for $C_{17}H_{16}N_4O_4S_3$ (436.53): C, 46.77; H, 3.69; N, 12.83; S, 22.04. Found: C, 46.75; H, 3.66; N, 12.80; S, 22.00%.

2-Cyano-*N*-(4-{[(5-methylisoxazol-3-yl)amino]sulfonyl}phenyl)-3,3-bis(methylthio)acrylamide (20). Yield (90%), mp 180-182 °C (from EtOH); IR (KBr) ν_{max}/cm^{-1}: 3325, 3275 (2NH), 2969 (aliphatic CH), 2186 (C≡N), 1640 (C=O); ^1H NMR (DMSO-d_6) δ 2.29 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.14 (s, 1H, isoxazole-H-4), 7.80 (d, 2H, *J* = 9 Hz, ArH), 7.95 (d, 2H, *J* = 9 Hz, ArH), 10.68 (s, 1H, D_2O-exchangeable, NH), 11.34 (s, 1H, D_2O-exchangeable, NH); MS (*m/z*, %): 425 (M^++1, 28.5), 424 (M^+, 42.5), 392 (41.9), 342 (38.3), 327 (30.1), 236 (40.4), 186 (33.7), 171 (41.9), 144 (27.9), 99 (34.2), 82 (49.2), 64 (100). Anal. Calcd for $C_{16}H_{16}N_4O_4S_3$ (424.52): C, 45.27; H, 3.80; N, 13.20; S, 22.66. Found: C, 45.25; H, 3.78; N, 13.17; S, 22.64%.

Antimicrobial Evaluation

The antibacterial and antifungal activity assays were carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt. Using the diffusion plate method.[62-64] A bottomless cylinder containing a measured quantity (1 mL, mg/mL) of the sample is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or fungal medium, which has been heavily seeded with a spore suspension of the test organism. After incubation (24 h for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as measure of the inhibitory power of the sample against the particular test organism. The solvent used was DMSO and the concentration of the sample used is 100 μg/mL. The results of antimicrobial activity are summarized in Table 1.

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