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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL PYRAZOLO[1,5-*a*]PYRIMIDINE, PYRIMIDO[1,2-*a*]BENZIMIDAZOLE, TRIAZOLO[4,3-*a*]PYRIMIDINE AND PYRIDO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES INCORPORATED PHENYLSULFONYL MOIETY

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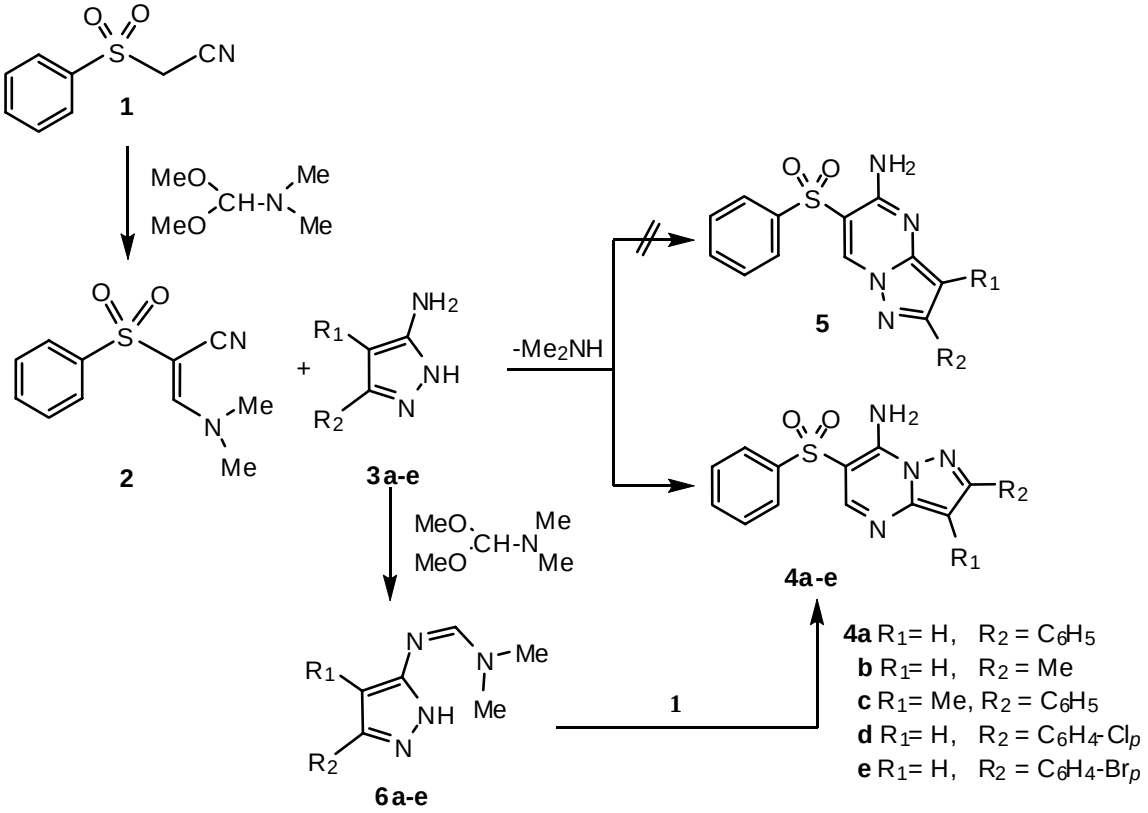
Abstract – Phenylsulfonylacetonitrile (**1**) reacts with dimethylformamide dimethyl acetal (DMF-DMA) to afford 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile (**2**). Enaminonitrile **2** reacts with 5-aminopyrazole derivatives **3a-e**, 5-amino-1,2,4-triazole (**7**) and 2-aminobenzimidazole (**11**) to afford new pyrazolo[1,5-*a*]pyrimidine, triazolo[4,3-*a*]pyrimidine and pyrimido[1,2-*a*]benzimidazole derivatives **4a-e**, **9** and **12**, respectively. Also, 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile (**2**) reacts with 2-(1*H*-benzimidazol-2-yl)acetonitrile (**13**) to give the corresponding pyrido[1,2-*a*]benzimidazole derivative **15**. Some of the newly synthesized compounds were tested *in vitro* for their antibacterial and antifungal activities, and showed promising results.

INTRODUCTION

Sulfones[1-2] are versatile class of compounds due to their applications in many pharmaceutical fields.[3-9] Thus, sulfones have attracted many authors and great efforts have been done to develop new approaches to a variety of heterocycles incorporating phenylsulfonyl moiety for biological screening. On the other hand, enamines[10] are important building blocks for the synthesis of many heterocyclic systems of great value from biological point of view. In continuation to our interest in the synthesis of new fused heterocycles with expected biological activity,[11-13] this work deals with the synthesis of the multifunctional, 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile (**2**), its utility as a reactive intermediate for the synthesis of the title compounds and to evaluate their biological activity.

RESULTS AND DISCUSSION

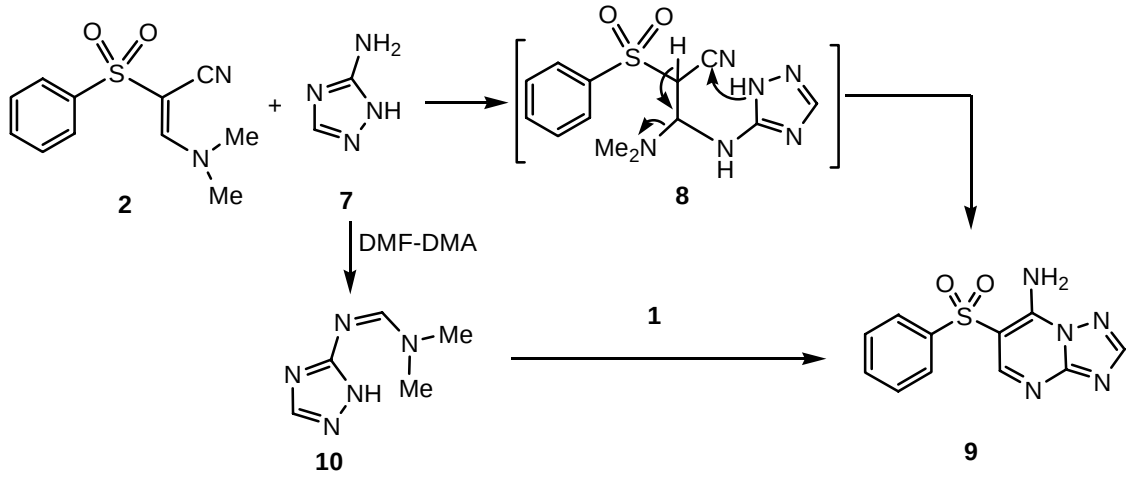
Treatment of phenylsulfonylacetonitrile (**1**) with dimethylformamide dimethyl acetal (DMF-DMA), in refluxing xylene, afforded the corresponding 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile (**2**) in an excellent yield (Scheme 1).



Scheme 1

The reactivity of compound **2** towards some heterocyclic amines as potential precursors for fused heterocyclic systems was also investigated. Thus, when enaminonitrile **2** was treated with 1*H*-5-aminopyrazole derivatives **3a-e** in refluxing ethanol, in the presence of piperidine, it afforded the corresponding 7-amino-6-(phenylsulfonyl) pyrazolo[1,5-*a*]pyrimidine derivatives **4a-e** (Scheme 1). The structures of compounds **4a-e** were established on the basis of their elemental analyses and spectral data, besides their independent synthesis *via* the reaction of 3-*N*-(*N*,*N*-dimethylaminomethylene)iminopyrazole derivatives **6a-e** with phenylsulfonylacetonitrile (**1**) which afforded products identical in all respects (mp, mixed mp, and IR spectra) with those obtained previously from the reaction of enaminonitrile **2** with 5-amino-1*H*-pyrazole derivatives **3a-e** (Scheme 1).

In a similar manner, the reaction of 1*H*-5-amino-1,2,4-triazole (**7**) with compound **2** in refluxing pyridine afforded 5-amino-6-(phenylsulfonyl) [1,2,4]triazolo[1,5-*a*]pyrimidine (**9**) (Scheme 2). The structure of compound **9** was established on the basis of its elemental analysis and spectral data as well as its independent synthesis of product **9** from the reaction of *N*,*N*-dimethyl-*N*′-(1*H*-1,2,4-triazol-5-yl)formimidamide (**10**) and phenylsulfonylacetonitrile (**1**) (Scheme 2).



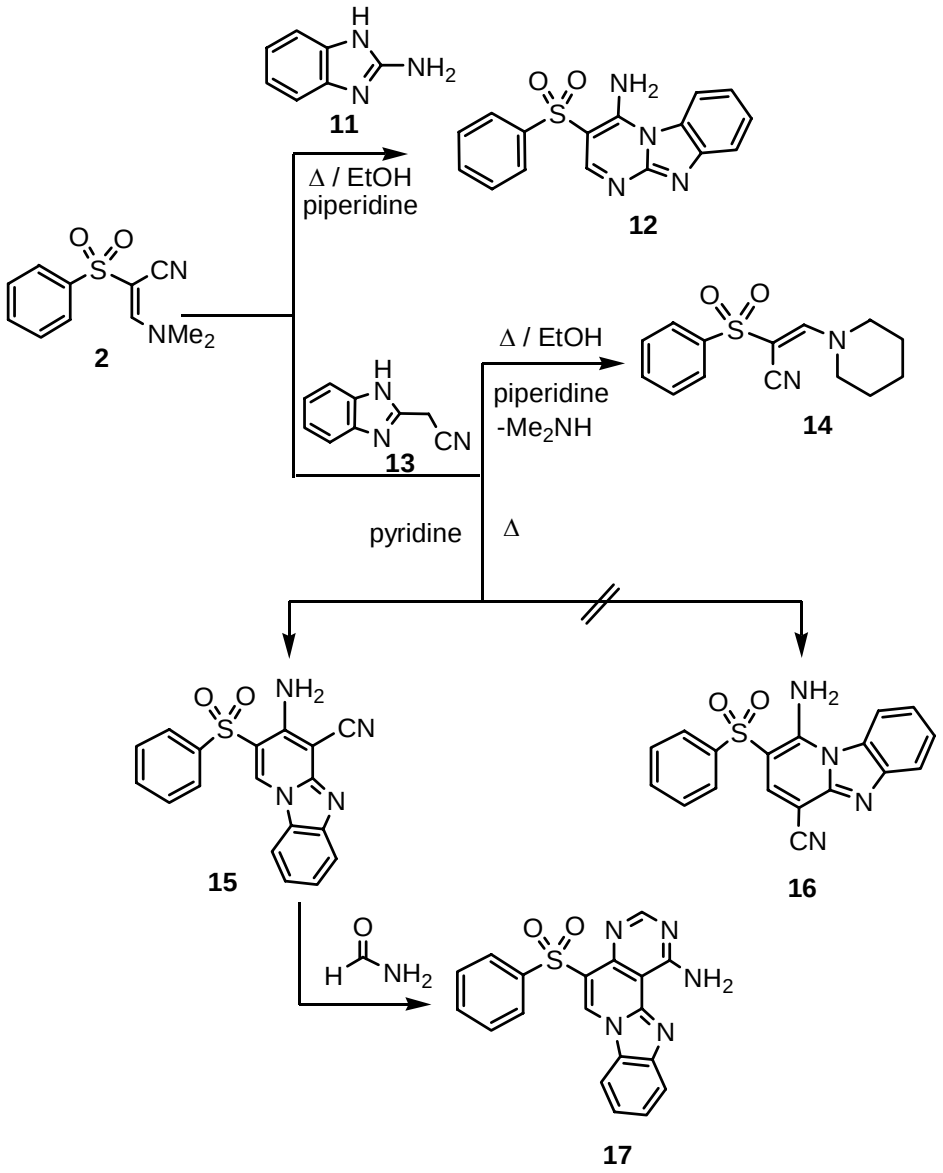
Scheme 2

The formation of compound **9** is therefore assumed to take place *via* the addition of the exocyclic amino group in compound **7** to the activated double bond in enaminonitrile **2** to give the acyclic non-isolable intermediate **8**, which undergoes cyclization and aromatization *via* the loss of dimethylamine molecule affording the final isolable product **9** as shown in Scheme 2. The presence of amino group in compound **9** was evidenced by the appearance of two absorption bands at 3421 and 3410 cm^{-1} in its IR spectrum and as a broad D_2O-exchangable signal at δ 8.83 in its ^1H NMR spectrum.

Prompted by the aforementioned results, compound **2** was allowed to react with 2-aminobenzimidazole (**11**), under the same experimental conditions, which afforded a white crystalline product in good yield. The structure of the obtained product was assigned as 5-amino-6-(phenylsulfonyl)pyrimido[1,2-*a*]benzimidazole (**12**) (Scheme 3).

The reaction of enaminonitrile **2** with 2-(1*H*)-benzimidazoleacetonitrile (**13**) in refluxing ethanol, in the presence of a catalytic amount of piperidine, afforded the 2-(phenylsulfonyl)-3-(piperdin-1-yl)acrylonitrile (**14**). However, when the reaction was carried out in pyridine it afforded 7-amino-6-(phenylsulfonyl)pyrido[1,2-*a*]benzimidazole-8-carbonitrile (**15**) rather than the isomeric structure **16** (Scheme 3). The IR spectrum of the product **15** revealed bands at 3459, 3308 and 2219 cm^{-1} due to the amino and nitrile functions, respectively. The ^1H NMR spectrum of the latter product revealed a broad

D_2O-exchangable signal at δ 8.63 and due to NH_2 group, a singlet at δ 8.47 due to a pyridine proton and multiplets signals in the region of 7.33-8.45 due to aromatic rings protons. An evidence for the formation of the product **15** stems from its conversion into the corresponding 4-amino-12-(phenylsulfonyl)pyrimido[5',4':3,4]pyrido[1,2-*a*]benzimidazole (**17**) upon treatment with formamide. The structure of the latter product **17** was confirmed on the basis of its elemental analysis and spectral data (see Experimental Part).



Scheme 3

EXPERIMENTAL

Melting points were measured on a Gallenkamp melting point apparatus. The IR spectra were recorded as KBr pellets on a Pye-Unicam SP 3-3oo spectrophotometer. ^{1}H NMR spectra were recorded in deuterated chloroform or dimethylsulfoxide at 300 MHz on a Varian Mercury VX NMR spectrometer using

tetramethylsilane as an internal reference, and results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Phenylsulfonylacetonitrile (**1**)[14] and aminopyrazoles **3a-e**[15-17] and their dimethylaminomethylene derivatives **6a-e**[11] were prepared according to procedures reported in the literature.

3-(Dimethylamino)-2-(phenylsulfonyl)acrylonitrile (**2**) **and** ***N,N*-dimethyl-*N'*-(1*H*-1,2,4-triazol-5-yl)formimidamide (10) .**

A mixture of phenylsulfonylacetonitrile (**1**) or 1*H*-5-amino-1,2,4-triazole (**7**) (20 mmol) and dimethylformamide dimethyl acetal (DMF-DMA) (0.23 g, 20 mmol) in dry xylene (30 mL) was refluxed for 1-3 h, then allowed to cool. The colorless precipitated product was filtered off, washed with light petroleum (bp 40-60 ˚C) and dried. Recrystallization from benzene gave the corresponding 3-(dimethylamino)-2-(phenylsulfonyl)acrylonitrile (**2**) and *N,N*-dimethyl-*N'*-(1*H*-1,2,4-triazol-5-yl)formimidamide (**10**), respectively.

3-(Dimethylamino)-2-(phenylsulfonyl)acrylonitrile (2)

85% yield; mp 110-111 ˚C; IR (KBr)υ_{max} /cm^{-1}: 2183 (C≡N); ^{1}H NMR ($CDCl_3$) δ 3.24 (6H, s, $2CH_3$), 7.59-7.85 (5H, m, ArH's), 7.66 (1H, s, alkenic-CH); ^{13}C NMR ($CDCl_3$) δ 38.51, 47.65, 82.35, 115.30, 128.32, 129.00, 132.73, 141.77, 154.21; MS (*m/z*) 236 (M^+, 33.65%). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.91; H, 5.12; N, 11.86; S, 13.57. Found: C, 55.95; H, 5.10; N, 11.91; S, 13.67.

N,N-Dimethyl-N'-(1H-1,2,4-triazol-5-yl)formimidamide (10)

89% yield; mp 180-181 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3483 (NH), 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ 2.95 (6H, s, $2CH_3$), 7.56 (1H, s, alkenic-CH), 8.36 (1H, s, triazole-CH), 12.28 (1H, s, broad NH); ^{13}C NMR ($CDCl_3$) δ 38.51, 47.65, 82.35, 115.30, 154.21. MS (*m/z*) 139 (M^+, 27.35%) Anal. Calcd for $C_5H_9N_5$: C, 43.15; H, 6.52; N, 50.33. Found: C, 43.25; H, 6.50; N, 50.33.

Reaction of enaminonitrile 2 with heterocyclic amines

General procedure

A mixture of the enaminonitrile **2** (10 mmol) and the appropriate heterocyclic amine (aminopyrazole derivatives **3a-e**, 1*H*-5-amino-1,2,4-triazole (**7**), or 2-aminobenzimidazole (**11**)) (10 mmol), EtOH (30 mL) and few drops of piperidine was refluxed for 8 h, then left to cool to rt. The precipitated product was filtered off, washed with EtOH and dried. Recrystallization from DMF-EtOH afforded the corresponding pyrazolo[1,5-*a*]pyrimidine, triazolo[1,5-*a*]pyimidine, and pyrimido[1,2-*a*]benzimidazole derivatives **4a-e**, **9,** and **12**, respectively.

7-Amino-2-phenyl-6-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidine (4a)

(71% yield); mp 242-243 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3402, 3301 (NH_2); ^{1}H NMR (DMSO-d_6) δ 7.46-7.69 (10H, m, ArH's), 8.08 (1H, s, pyrazole-CH), 8.11 (1H, s, pyrimidine-CH) 8.54 (2H, br, D_2O-

exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 94.48, 100.64, 126.52, 128.75, 128.89, 129.45, 130.55, 132.65, 134.12, 142.07, 145.84, 148.82, 149.63, 156.14; MS (*m/z*) 350 (M^+, 31.96%). Anal. Calcd for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99; S, 9.15. Found: C, 61.73; H, 4.00; N, 15.79; S, 9.12.

7-Amino-2-methyl-6-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidine (4b)

(76% yield); mp 215-216 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3404, 3302 (NH_2); ^1H NMR (DMSO-d_6) δ 2.39 (3H, s, CH_3), 7.52-7.67 (5H, m, ArH's), 8.00 (1H, s, pyrazole-CH), 8.11 (1H, s, pyrimidine-CH) 8.48 (2H, br, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 14.48, 97.48, 99.64, 126.52, 129.75, 133.69, 142.27, 145.74, 148.52, 149.43, 156.34; MS (*m/z*) 288 (M^+, 22.99%). Anal. Calcd for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43; S, 11.12. Found: C, 54.21; H, 4.16; N, 19.44; S, 11.23.

7-Amino-3-methyl-2-phenyl-6-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidine (4c)

(66% yield); mp 268-270 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3382, 3306 (NH_2); ^1H NMR (DMSO-d_6) δ 2.39 (3H, s, CH_3), 7.46-7.67 (10H, m, ArH's), 8.11 (1H, s, pyrimidine-CH) 8.48 (2H, br, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 14.49, 96.48, 100.68, 126.56, 128.55, 128.99, 129.85, 130.95, 132.85, 134.52 142.17, 145.64, 148.72, 149.53, 156.44; MS (*m/z*) 364 (M^+, 31.21%). Anal. Calcd for $C_{19}H_{16}N_4O_2S$: C, 62.62; H, 4.43; N, 15.37; S, 8.80. Found: C, 62.42; H, 4.40; N, 15.57; S, 8.760.

7-Amino-2-(4-chlorophenyl)-6-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidine (4d)

(66% yield); mp 240-241 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3417, 3318 (NH_2); ^1H NMR (DMSO-d_6) δ 7.46-7.69 (10H, m, ArH's), 8.18 (1H, s, pyrazole-CH), 8.11 (1H, s, pyrimidine-CH) 8.54 (2H, br, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 94.66, 100.66, 126.42, 128.07, 128.78, 129.55, 130.68, 133.55, 134.09, 142.03, 145.83, 148.81, 149.91, 155.12; MS (*m/z*) 384 (M^+, 37.45%). Anal. Calcd for $C_{18}H_{13}ClN_4O_2S$: C, 56.18; H, 3.40; Cl, 9.21; N, 14.56; S, 8.33. Found: C, 56.20; H, 3.43; Cl, 9.31; N, 14.36; S, 8.23.

7-Amino-2-(4-bromophenyl)-6-(phenylsulfonyl)pyrazolo[1,5-a]pyrimidine (4e)

(71% yield); mp 269-270 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3456, 3344 (NH_2); ^1H NMR (DMSO-d_6) δ 7.46-7.69 (10H, m, ArH's), 8.18 (1H, s, pyrazole-CH), 8.11 (1H, s, pyrimidine-CH) 8.54 (2H, br, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 94.28, 100.34, 126.24, 128.35, 128.59, 129.05, 130.35, 132.45, 134.10, 141.58, 145.74, 148.72, 149.43, 155.74; MS (*m/z*) 427 (M^+, 41.75%). Anal. Calcd for $C_{18}H_{13}BrN_4O_2S$: C, 50.36; H, 3.05; Br, 18.61; N, 13.05; S, 7.47. Found: C, 50.16; H, 3.15; Br, 18.41; N, 13.25; S, 7.67.

7-Amino-6-(phenylsulfonyl) [1,2,4]triazolo[1,5-a]pyrimidine (9)

(88% yield); mp 297 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3421, 3410 (NH_2); ^1H NMR (DMSO-d_6) δ 7.59-8.15 (5H, m, ArH's), 7.61 (1H, s, pyrimidine-CH), 8.58 (1H, s, triazole-CH), 8.83 (2H, br, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 103.27, 126.77, 129.54, 133.78, 141.35, 146.90, 154.11, 155.83, 156.04;

MS (*m/z*) 275 (M^+, 26.55%). Anal. Calcd for $C_{11}H_9N_5O_2S$: C, 47.99; H, 3.30; N, 25.44; S, 11.65. Found: C, 47.79; H, 3.40; N, 25.24; S, 11.35.

5-Amino-6-(phenylsulfonyl]pyrimido[1,2-a]benzimidazole (12)

(58% yield); mp > 300 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3421, 3212 (NH_2); ^{1}H NMR (DMSO-d_6) δ 7.35-8.45 (9 H, m, ArH's), 8.51 (1H, s, pyrimidine-CH), 8.64 (2H, br, D_2O-exchangeable, NH_2); MS (*m/z*) 324 (M^+, 23.87%). Anal. Calcd for $C_{16}H_{12}N_4O_2S$: C, 59.25; H, 3.73; N, 17.27; S, 9.89. Found: C, 59.37; H, 3.62; N, 17.20; S, 9.74.

2-(Phenylsulfonyl)-3-(piperidin-1-yl)acrylonitrile(14)

(58% yield); mp > 300 ˚C; IR (KBr) υ_{max} /cm^{-1}: 2212 (C≡N); ^{1}H NMR (DMSO-d_6) δ 1.60-1.62 (6H, m), 3.56-3.72 (4H, m), 7.66 (1H, s, alkenic-CH), 7.59-7.85 (5H, m, ArH's); MS (*m/z*) 276 (M^+, 19.54%). Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14; S, 11.60 . Found: C, 60.95; H, 5.74; N, 10.12; S, 11.80 .

Reaction of phenylsulfonylacetonitrile (1) with dimethylaminomethylene derivatives of heterocyclic amines and enaminonitrile 2 with (1*H*)-2-benzimidazol-2-ylacetonitrile 13

A mixture of phenylsulfonylacetonitrile (**1**) or the enaminonitrile **2** (2 mmol) and dimethylaminomethylene derivatives of heterocyclic amines **6a-e**, **10**, or (1*H*)-2-benzimidazol-2-ylacetonitrile **13** (2 mmol) in pyridine (30 mL) was heated under reflux for 4-8h, and then allowed to cool to rt. The pyridine is evaporated and the precipitated products were filtered off, washed with water, dried and finally recrystallized from DMF to give the corresponding pyrazolo[1,5-*a*]pyrimidine, triazolo[4,3-a]pyrimidine, and pyrido[1,2-*a*]benzimidazole derivatives **4a-e, 9, and 15**, respectively.

7-Amino-6-(phenylsulfonyl)pyrido[1,2-a]benzimidazole-8-carbonitrile (15)

(68% yield); mp > 300 ˚C; IR (KBr) υ_{max} /cm^{-1}: 3459, 3308 (NH_2), 2219 (C≡N); ^{1}H NMR (DMSO-d_6) δ 7.35-8.45 (9H, m, ArH's), 8.47 (1H, s, pyridine-CH), 8.638 (2H, br, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 101.41, 115.08, 115.84, 119.12, 120.67, 121.97, 128.05, 128.89, 129.58, 133.71, 138.72, 141.48, 150.74, 154.61, 155.43, 156.94; MS (*m/z*) 348 (M^+, 46.24%). Anal. Calcd for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08; S, 9.20. Found: C, 62.19; H, 3.36; N, 16.17; S, 9.33.

Reaction of 7-amino-6-(phenylsulfonyl)pyrido[1,2-*a*]benzimidazole-8-carbonitrile (15) with formamide.

A mixture of 7-amino-6-(phenylsulfonyl)pyrido[1,2-*a*]benzimidazole-8-carbonitrile (**15**) and excess formaide was heated under reflux for 6h, and then allowed to cool. The excess formamide is was distilled off under reduced pressure and the precipitated products were filtered off, washed with EtOH, dried and finally recrystallized from EtOH/DMF to give the corresponding 4-amino-12-(phenylsulfonyl)pyrimido[5',4':3,4]pyrido[1,2-*a*]benzimidazole (**17**).

4-Amino-12-(phenylsulfonyl)pyrimido[5',4':3,4]pyrido[1,2-a]benzimidazole (17)

75% yield; mp 210-211 ˚C; IR (KBr)υ_{max} /cm^{-1}: 3460, 3312 (NH_2); ^{1}H NMR (DMSO-d_6) δ 7.24-8.18 (9H, m, ArH's), 8.51 (1H, s, pyridine-CH), 8.61 (2H, br, D_2O-exchangeable, NH_2), 8.95 (1H, s, pyrimidine-CH); ^{13}C NMR (DMSO-d_6) δ 97.85, 104.17, 118.72, 118.72, 125.93, 121.97, 126.66, 129.31, 129.33, 129.72, 132.53, 138.10, 142.75, 153.11, 155.15, 158.10, 168.98; MS (*m/z*) 375 (M^+, 36.24%). Anal. Calcd for $C_{19}H_{13}N_5O_2S$: C, 60.79; H, 3.49; N, 18.66; S, 8.54. Found: C, 60.75; H, 3.46; N, 18.69; S, 8.51.

BIOLOGICAL ACTIVITY

The antibacterial and antifungal activity were carried out in the Microbiology Division of Microanalytical Center of Cairo university, using the diffusion plate method[18-20] a bottomless cylinder containing a measured quantity (1ml, mg/mL) of the sample is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or fungal medium (Dox's medium) which has been heavily seeded with the spore suspention of the test organism.

Table 1. Antibacterial and Antifungal Activities of the Synthesized Compounds

COMPOUNDS NO.	Inhibition Zone Diameter (IZD) (mm/mg Compound Tested)				
	Gram (-)		Gram (+)		Fungus
	(EC) anaerobic	(PA)	(SA)	(SF)	(CA)
CONTROL	0.0	0.0	0.0	0.0	0.0
2	14 ++	13 ++	14 ++	14 ++	15 ++
4a	15 ++	15 ++	14 ++	15 ++	13 ++
4b	16 ++	18 ++	15 ++	15 ++	14 ++
4c	16 ++	16 ++	18 ++	17 ++	12 ++
4d	14 ++	14 ++	15 ++	14 ++	13 ++
4e	15 ++	14 ++	14 ++	14 ++	15 ++
9	18 ++	14 ++	14 ++	15 ++	13 ++
12	16 ++	15 ++	16 ++	18 ++	12 ++
15	15 ++	15 ++	14 +	15 ++	12 ++
Amphotericin B	--	--	--	--	**18 ++**
Tetracycline	**26 +++**	**30 +++**	**22 ++**	**26 +++**	--

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 (Table 1).

Most of the compounds were tested *in vitro* against gram negative bacteria [Escherichia coli anaerobic (EC) and Pseudomonae aeruginosa (PA)], gram positive bacteria [Staphylococcus aureus (SA), and Streptococcus faecalis (SF)] and antifungal activity against Candida albicans (CA). The reference antibiotic *Tetracycline* and *Amphotricine* were used as references to evaluate the potency of the tested compounds under the same condition.

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