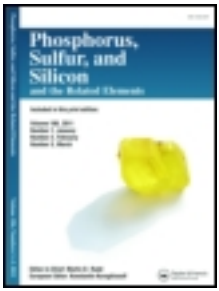

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Heteroaromatization with Sulfonamido Phenyl Ethanone, Part I: Synthesis of Novel Pyrrolo[2,3-D]Pyrimidine and Pyrrolo[3,2-E][1,2,4]Triazolo[1,5-C]Pyrimidine Derivatives Containing Dimethylsulfonamide Moiety

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Heteroaromatization with Sulfonamido Phenyl Ethanone, Part I: Synthesis of Novel Pyrrolo[2,3-D]Pyrimidine and Pyrrolo[3,2-E][1,2,4]Triazolo[1,5-C]Pyrimidine Derivatives Containing Dimethylsulfonamide Moiety

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*4-(5-Amino-4-cyano-1-p-tolyl-1H-pyrrol-3-yl)-N,N-dimethyl-benzenesulfonamide (**4**) was prepared and converted to several pyrrolo[2,3-d]pyrimidin-5-yl)-N,N-dimethyl-benzenesulfonamide derivatives (**5**,**7**,**9**, and **13**). Cyclocondensation of **13** with different electrophilic carbon reagents afforded several 4-(N,N-dimethylaminosulfonylphenyl)]pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]-pyrimidine derivatives (**14–17**,**19**, and **20**); IR, ^{1}HNMR, and mass spectra of the newly synthesized compounds were recorded. Most of the obtained compounds were screened against Gram-positive and Gram-negative bacteria and fungi, for which some of these derivatives gave promising results.*

Keywords Antimicrobial and antifungal activities; 4-(2-bromoacetyl)-N,N-dimethyl-benzenesulfonamide; 4-(N,N-dimethylaminosulfonylphenyl)]pyrrolo[3,2-e][1,2,4]triazolo-[1,5-c]pyrimidines; pyrrolo[2,3-d] pyrimidin-5-yl)-N,N-dimethyl-benzenesulfonamide

INTRODUCTION

The pyrrolo[2,3-d]pyrimidine ring system has aroused considerable interest due to its presence in several natural products. It is contained in the nucleoside antibiotics tubercidin, toyocamyin, and sangivamycin.[1] Also, sulfonamides are drugs of therapeutic importance, and they have a wide spectrum of antibacterial activities.[2–6] In continuation of our research program concerning the synthesis of fused pyrimidines[7–12] from enaminonitriles, we report here the synthesis of a variety

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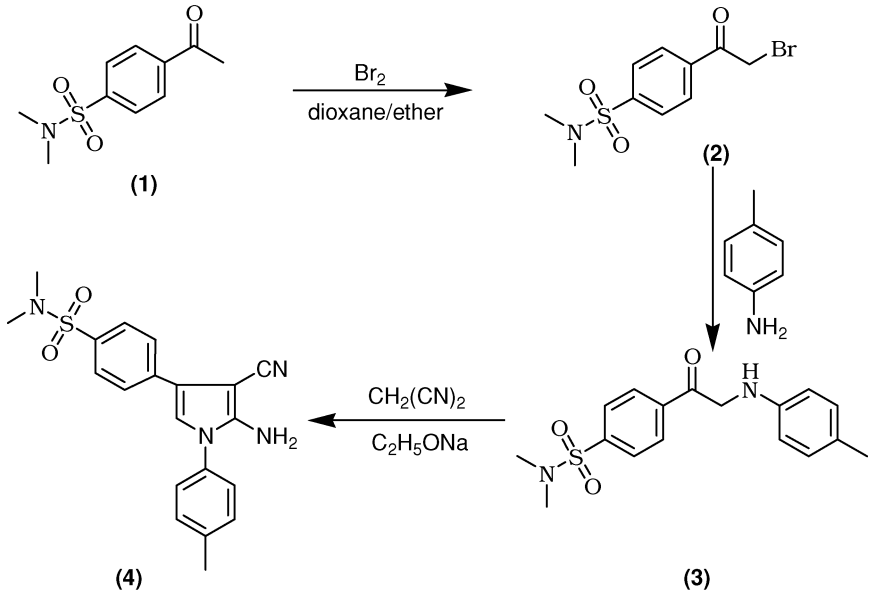
of new pyrrolo[3,2-d]pyrimidine and pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine derivatives containing sulfonamide moiety, utilizing the novel starting material 4-(5-Amino-4-cyano-1-*p*-tolyl-1H-pyrrol-3-yl)-N,N-dimethyl-benzenesulfonamide (**4**) (Table I).

RESULTS AND DISCUSSION

Bromination of 4-acetyl-N,N-dimethylbenzenesulfonamide (**1**)[13] in dioxane/ether mixture afforded 4-(2-bromoacetyl)-N,N-dimethy- lbenzenesulfonamide(**2**), which reacts with *p*-toludine in boiling ethanol to give N,N-dimethyl-4-(2-*p*-tolylaminoacetyl-benzenesulfonamide (**3**).

Compound (**3**) reacts with malononitrile in ethanolic sodium ethoxide solution to give the starting material 4-(5-amino-4-cyano-1-*p*-tolyl-1H-pyrrol-3-yl)-N,N-dimethylbenzenesulfonamide (**4**), which upon treatment with boiling formic acid to obtain N,N-dimethyl-4-(4-oxo-7-*p*-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d] pyrimidin-5-yl)benzenesulfonamide (**5**), the reaction is believed to proceed through the cyclization of aminopyrrolecarboxamide intermediate [**A**] (Scheme 1).



SCHEME 1

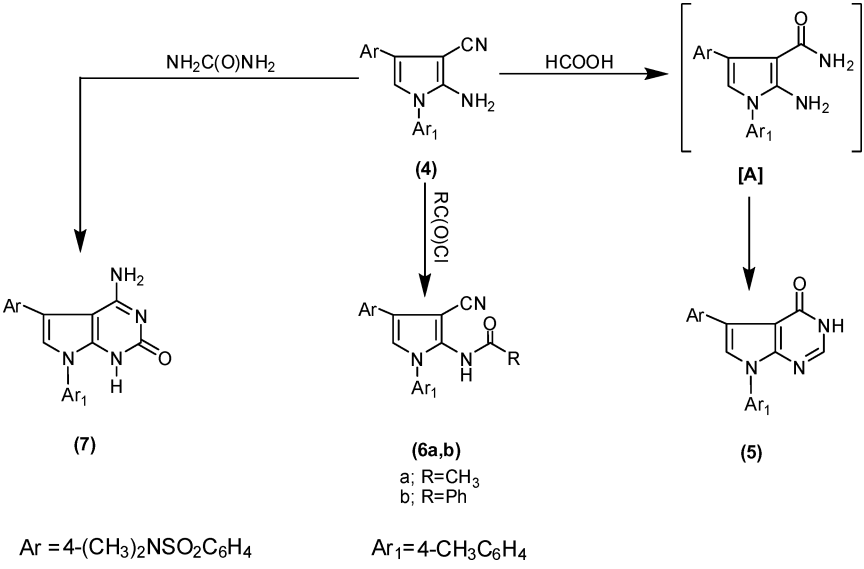
Acetylation and benzoylation of **4** afforded the corresponding acetylamino and benzoylamino pyrrolo derivatives (**6a**,**b**) respectively.

TABLE I Physical and Analytical Data for the Newly Prepared Compounds

Comp.	m.p.°C (Solvent of recrystallization)	Colour (Yield%)	M.formula (M.Wt.)	Calculated / Found (%)				
				C	H	N	O	S
2	80	White (95)	$C_{10}H_{12}BrNO_3S$ (205)	39.23	3.95	4.57	15.68	10.47
	(B.)			39.21	3.94	4.55	15.67	10.45
3	150	Yellow (60)	$C_{17}H_{20}N_2O_3S$ (332)	61.42	6.06	8.43	14.44	9.65
	(Et.)			61.40	6.10	8.41	14.39	9.64
4	230	Yellow (78)	$C_{20}H_{20}N_4O_2S$ (380)	63.14	5.30	14.73	8.41	8.43
	(Et./B.)			63.12	5.28	14.71	8.40	8.42
5	270	Brown (79)	$C_{21}H_{20}N_4O_3S$ (408)	61.75	4.94	13.72	11.75	7.85
	(Et./B.)			61.72	4.92	13.70	11.73	7.84
6a	150	White (80)	$C_{22}H_{22}N_4O_3S$ (422)	62.54	5.25	13.26	11.36	7.59
	(Et./B.)			62.53	5.23	13.24	11.34	7.56
6b	243	White (70)	$C_{27}H_{24}N_4O_3S$ (484)	66.92	4.99	11.56	9.91	6.62
	(Et./B.)			66.90	4.88	11.53	9.90	6.63
7	<360	Brown (70)	$C_{21}H_{21}N_5O_3S$ (423)	59.56	5.00	16.54	11.33	7.57
	(DMF)			59.54	4.97	16.52	11.29	7.55
8	190	Brown (80)	$C_{23}H_{24}N_4O_3S$ (436)	63.28	5.54	12.83	11.00	7.35
	(Benzene)			63.26	5.52	12.81	10.89	7.34
9	240	Black (70)	$C_{21}H_{21}N_5O_2S$ (407)	61.90	5.19	17.19	7.85	7.87
	(Et./B.)			61.89	5.17	17.09	7.79	7.86
10	157	Black (82)	$C_{23}H_{25}N_5O_2S$ (435)	63.43	5.79	16.08	7.35	7.36
	(Et./B.)			63.41	5.77	16.10	7.35	7.36
12	220	Yellow (80)	$C_{22}H_{23}N_5O_2S$ (421)	62.69	5.50	16.61	7.59	7.61
	(Et./B.)			62.67	5.48	16.59	7.56	7.59
13	165	White (89)	$C_{21}H_{22}N_6O_2S$ (422)	59.70	5.25	19.89	7.57	7.59
	(Et.)			59.68	5.23	19.87	7.54	7.57
14	263	White (92)	$C_{22}H_{20}N_6O_2S$ (432)	61.10	4.66	19.43	7.40	7.41
	(Et./B.)			61.08	4.64	19.42	7.38	7.40
15a	225	White (80)	$C_{23}H_{21}ClN_6O_2S$ (480)	57.44	4.40	17.47	6.65	6.67
	(Et./B.)			57.39	4.39	17.45	6.62	6.65
15b	240	White (79)	$C_{24}H_{21}N_7O_2S$ (471)	61.13	4.49	20.79	6.79	6.80
	(Et./B.)			61.09	4.46	20.75	6.76	6.78
15c	250	Yellow (66)	$C_{24}H_{22}N_6O_3S$ (474)	60.75	4.67	17.71	10.11	6.76
	(Et./B.)			60.73	4.59	17.69	10.10	6.75
15d	253	Brown (70)	$C_{23}H_{22}N_6O_2S$ (446)	61.87	4.97	18.82	7.17	7.18
	(Et./B.)			61.85	4.85	18.81	7.16	7.09
15e	197	White (82)	$C_{26}H_{26}N_6O_4S$ (518)	60.22	5.05	16.21	12.34	6.18
	(Et./B.)			60.19	5.04	16.20	12.32	6.08
16	300	Brown (72)	$C_{22}H_{20}N_6O_2S_2$ (464)	56.88	4.34	18.09	6.89	13.80
	(D.)			56.79	4.33	18.10	6.87	13.77
17a	265	Yellow (80)	$C_{23}H_{23}N_7O_2S$ (461)	59.85	5.02	21.24	6.93	6.95
	(Et./B.)			59.82	5.01	21.23	6.91	6.93
17b	192	Brown (69)	$C_{28}H_{25}N_7O_2S$ (523)	64.23	4.81	18.73	6.11	6.12
	(Et.)			64.22	4.78	18.71	6.09	6.10
19	237	White (78)	$C_{23}H_{22}N_6O_3S$ (462)	59.73	4.79	18.17	10.38	6.93
	(Et./B.)			59.71	4.78	18.09	10.35	6.91
20	327	White (89)	$C_{28}H_{24}N_6O_2S$ (508)	66.12	4.76	16.52	6.29	6.30
	(DMF)			66.10	4.75	16.51	6.27	6.29

B., benzene; D., dioxane; DMF, dimethylformamide; Et., ethanol.

Reaction of aminopyrrole carbonitrile (**4**) with urea afforded 4-(4-amino-2-oxo-7-*p*-tolyl-2,7-dihydro-1H-pyrrolo[2,3-d] pyrimidin-5-yl)-N,N-dimethylbenzenesulfonamide (**7**) (Scheme 2).

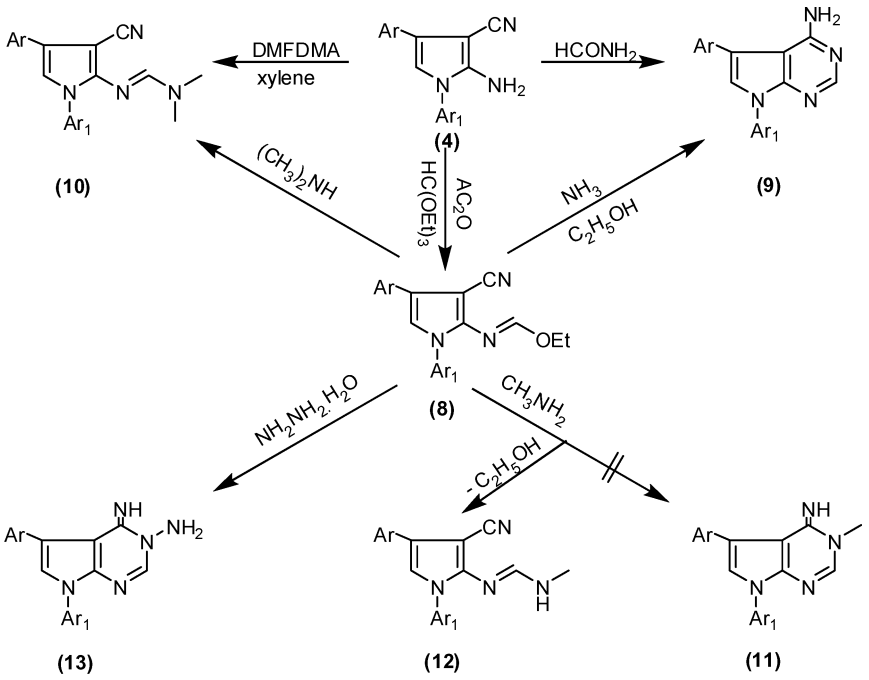


SCHEME 2

Enaminonitrile(**4**) was reacted with triethyl orthoformate in boiling acetic anhydride to give N-[3-cyano-4-(4-dimethylsulfamoylphenyl)-1-*p*-tolyl-1H-pyrrol-2-yl]formimidic acid ethyl ester (**8**), which on ammonolysis in ethanol at room temperature gave 4-(4-amino-7-*p*-tolyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N,N-dimethylbenzenesulfonamide (**9**). The structure of **9** is supported by spectral data and by an independent synthesis of the same product from the reaction of **4** with formamide (m.p., mixed m.p., and identical IR spectrum) (Scheme 3).

Interaction of **8** with dimethylamine in refluxing ethanol afforded 4-[4-cyano-5-(dimethylaminomethyleneamino)-1-*p*-tolyl-1H-pyrrol-3-yl]-N,N-dimethylbenzenesulfonamide **(10).** The latter structure is supported by spectral data and by an independent synthesis of the same product from reaction of **4** with dimethylformamide dimethylacetal in refluxing xylene (m.p., mixed m.p., and identical IR spectrum) (Scheme 3).

Interaction of (**8**) with methylamine in ethanol afforded the open chain product (**12**), instead of the expected cyclic pyrrolo pyrimidine derivative (**11**); the appearance of (CN and NH) absorption bands at



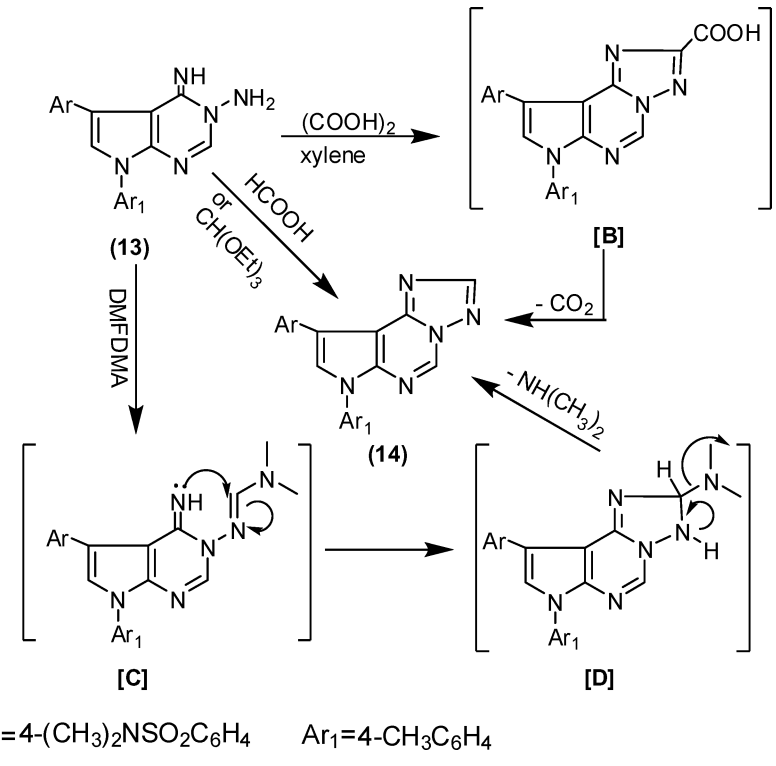
SCHEME 3

2199 and 3410 cm^{-1}, respectively, in IR spectrum of this product supported the open chain product.

Treatment of **8** with hydrazine hydrate afforded 4-(3-amino-4-imino-7-*p*-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]-pyrimidin-5-yl)-N,N-dimethylbenzenesulfonamide (**13**).

The bifunctional derivative **13** was used as starting material through cyclocondensation with electrophilic carbon reagents to give pyrrolotriazolopyrimidine derivatives. Thus, treatment of amino-imino derivative (**13**) with oxalic acid in refluxing xylene provided carboxylic acid derivative intermediate [**B**]. This compound could not be isolated, and it was decarboxylated to produce7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)] pyrrole[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**14**) (Scheme 4).

The structure of **14** was confirmed on the basis of elemental and spectral data. When **13** was treated with formic acid, triethyl orthoformate or DMF–DMA afforded a product, which was found to be identical in



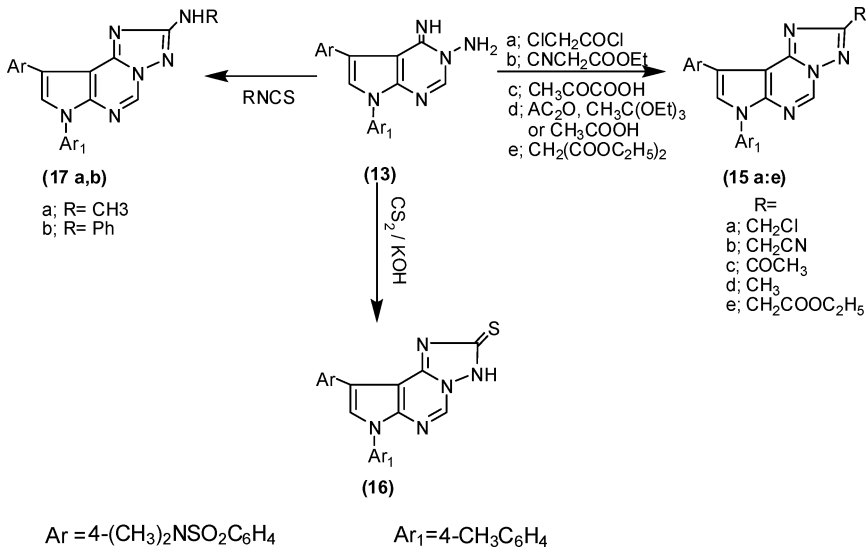
SCHEME 4

all respects (m.p., mixed m.p., and spectral data) with compound (**14**) previously obtained from **13** and oxalic acid. The formation of the latter compound from reaction of **13** with DMF-DMA could be explained via formation of intermediate [**C**], intramolecular cyclization to intermediate [**D**], followed by elimination of dimethylamine (Scheme 4).

Reaction of **13** with chloroacetyl chloride and ethyl cyanoacetate yielded the corresponding 2-chloromethyl and 2-cyanomethyl derivatives(**15a**,**b**) respectively, while when reacted with pyruvic acid in refluxing butanol, 2-acetyl derivative (**15c**) was obtained (Scheme 5).

Refluxing of a mixture of **13** and acetic anhydride produced 2-methyl derivative (**15d**). The structure of the latter product was supported by spectral data and independent synthesis of the same product from reaction of **13** with triethyl orthoacetate or acetic acid (Scheme 5).

In addition, cyclocondensation of **13** with diethylmalonate yielded 2-ethoxycarbonylmethyl derivative (**15e**).

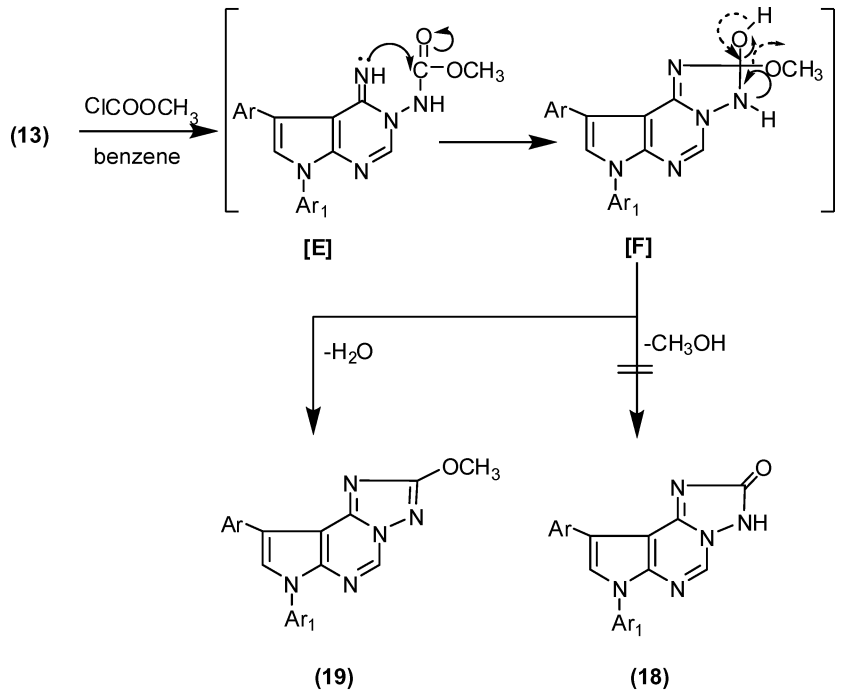


SCHEME 5

Interaction of **13** with CS_2 in the presence of KOH afforded the 2-thione derivative (**16**), while when reacted with methyl isothiocyanate and phenyl isothiocyanate afforded 2-methylamino and 2-phenylamino derivatives (**17a**,**b**) respectively (Scheme 5).

When aminoimino (**13**) reacted with equimolar ratio of methylchloro formate in refluxing dry benzene, the 2-methoxytriazolopyrimidine derivative (**19**) was obtained in excellent yield rather than the expected 2-oxotriazolopyrimidine derivative (**18**). The formation of (**19**) could be explained by the formation of methylester intermediate [**E**], which undergoes spontaneous intramolecular cyclization to give intermediate [**F**] followed by elimination of water rather than ethanol molecule under the reaction conditions (Scheme 6).

Aminoimino (**13**) reacted with benzaldehyde in refluxing dioxane to give 2-phenyltriazolopyrimidine derivative (**20**). The formation of the latter structure could be explained by the formation of benzylidineamino intermediate [**G**], which undergoes spontaneous intramolecular cyclization to non-isolable intermediate [**H**], followed by aromatization. The structure of **20** was confirmed on the basis of elemental analysis and spectral data; further confirmation was obtained by the synthesis of the same product through reaction of **13** with benzoyl chloride.



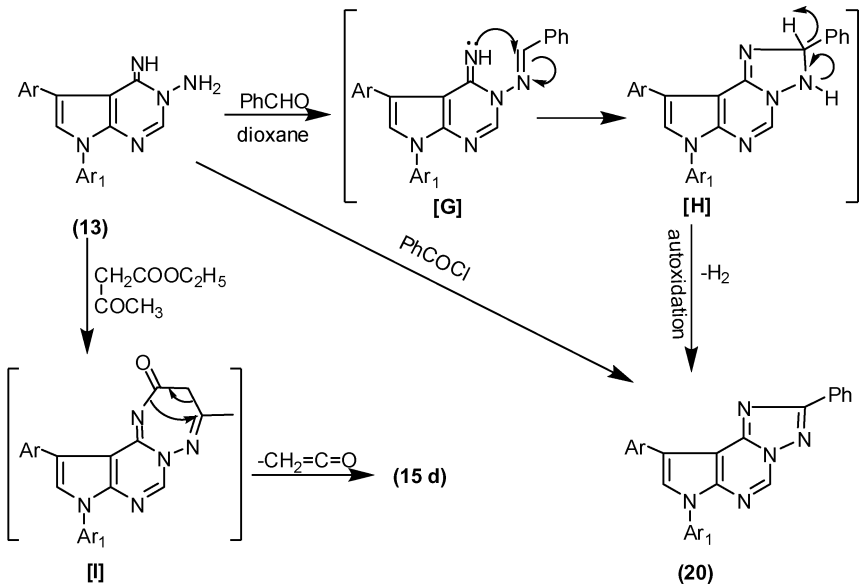
Ar = 4-$(CH_3)_2NSO_2C_6H_4$ Ar_1=4-$CH_3C_6H_4$

SCHEME 6

Finally, treatment of **13** with ethyl acetoacetate in refluxing ethanol afforded a single product, which analyzed correctly for $[C_{23}H_{22}N_6O_2S]$, which was identified as previously prepared compound (**15d**). This reaction may proceed through the formation of diazepine intermediate [**I**], which rearranged to the more stable triazolopyrimidine derivative (**15d**) through elimination of ketene (Scheme 7).

Antimicrobial and Antifungal Activities

The results of antimicrobial screening (Table II) show that compounds (**2**, **7**, **13**, **15c**, **16**, **17a**,**b**, **19**, **20**) are highly active compounds against Gram-positive (*B. subtilis*, *S. aureus*, *S. maxima*), Gram-negative (*K. pneumonia*, *Salmonella*, *P. aeruginosa*), and antifungal activity [unicellular fungi (*C. abicans*) and filamentous fungi (*Rhizopus*, *A. fumigatus*)]. While the compounds (**3**, **4**, **10**, **14**, **15a**,**b**,**e**) showed moderate activity, and the remaining compounds (**5**, **6a**,**b**, **8**, **9**, **12**, **15d**) showed



Ar = 4-$(CH_3)_2NSO_2C_6H_4$ Ar_1 = 4-$CH_3C_6H_4$

SCHEME 7

weak activity. It seems that most activity was exhibited with pyrrolotriazolopyrimidine derivatives.

EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were recorded on FT-IR 5300 spectrometer and Perkin Elmer spectrum RXIFT-IR system (ν, cm^{-1}). The ^{1}HNMR spectra were recorded at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University and Al-Azhar University.

4-(2-Bromoacetyl)-N,N-dimethylbenzenesulfonamide (2)

To a stirring solution of 4-acetyl-N,N-dimethylbenzenesulfon-amide (**1**; 0.01 mol) in dioxane/ether mixture (30 mL), the bromine (0.01 mol) was added dropwise with constant stirring after complete addition the

TABLE II Antimicrobial Activity and Antifungal Activity; Inhibition Zone Diameter (mm)

	Gram-Positive			Gram-Negative			Unicellular Fungi	Filamentous Fungi	
Compd. No.	B. Subtilis (NCTC-1040)	S. Aureus (NCTC-7447)	S. maxima (ATCC-33910)	K. Pneumonia (NCIMB-9111)	Salmonella	(P. aeruginosa) (ATCC-10145)	(C. Abicans) (IMRU-3669)	Rhizopus	A. Fumigatus
2	21	23	21	20	20	22	20	24	24
3	19	17	18	16	18	19	19	18	17
4	18	16	17	18	19	17	19	17	19
5	15	14	17	13	17	15	13	17	17
6a	13	13	12	14	12	14	12	16	17
6b	17	15	15	17	16	15	13	16	16
7	22	20	20	21	20	23	20	21	22
8	15	13	15	14	17	17	15	17	16
9	13	12	17	17	12	15	15	14	16
10	17	18	18	18	19	19	18	18	17
12	14	13	17	13	15	12	16	12	13
13	21	20	22	23	22	24	24	20	20
14	17	18	19	18	18	17	17	18	18
15a	19	18	18	17	17	19	18	17	16
15b	18	17	18	19	19	17	18	17	18
Ampicillin (AMD) 25 mg Calforan 30 mg.	26	25	27	27	26	25	24	25	25
15c	22	20	20	22	22	23	21	20	24
15d	12	14	15	17	14	13	12	17	15
15e	18	19	17	17	18	19	19	17	17
16	21	20	21	22	23	24	24	20	21
17a	20	21	22	23	24	25	20	21	22
17b	20	21	20	22	24	23	21	20	21
19	22	21	20	22	24	22	20	21	22
20	21	20	20	21	22	23	23	20	21
Ampicillin (AMD) 25 mg Calforan 30 mg.	26	25	27	27	26	25	24	25	25

24–20 mm: highly active.
19–18 mm: moderately active.
17–12 mm: weakly active.

reaction was left for 1h, then the reaction was poured in cold water (100 mL). The separated solid was filtered off and recrystallized to give **(2)** (Table I). IR (film) $\upsilon = 3062$ (CH-arom.), 2922 (CH-aliph.), 1658 (C=O), 1334, 1158 $cm^{-1}(SO_2)$.

N,N-Dimethyl-4-(2-*p*-tolylaminoacetyl)benzenesulfonamide (3)

A mixture of phenacyl bromide derivative (**2**; 0.01 mol) and *p*-toludine (0.01 mol) in ethanol (50 mL) was refluxed for 1. The obtained product was collected and recrystallized to give **(3)** (Table I). IR (film) $\upsilon = 3410$ (NH), 3061 (CH-arom.), 2917 (CH-aliph.) 1690 (CO), 1342, 1160 $cm^{-1}(SO_2)$. ^{1}H-NMR ($CDCl_3$): $\delta = 2.47$ (s, 3H, CH_3), 2.79 (s, 6H, $N(CH_3)_2$), 4.30 (s, 2H, CH_2), 7.37 and 7.56 (dd, 4H, AB-ArH), 7.91 and 8.49 (dd, 4H, AB-ArH), 9.05 ppm (s, 1H, NH).

4-(5-Amino-4-cyano-1-*p*-tolyl-1H-pyrrol-3-yl)-N,N-dimethylbenzenesulfonamide (4)

To a solution of phenacyl bromide derivative (**2**; 0.01 mol) in absolute ethanol (30 mL) malonitrile (0.01 mol) was added. The mixture was then heated under reflux while stirring, and sodium ethoxide (0.9 g in 20 mL ethanol) was added dropwise. Heating was continued for 3 h. The solid product that separated out after cooling was filtered off, washed with cold ethanol, dried, and recrystallized to give **(4)** (Table I). IR (film) $\upsilon = 3418$, 3310 (NH_2), 3130 (CH-arom.), 2917 (CH-aliph.), 2204 (CN), 1338, 1164 $cm^{-1}(SO_2)$. MS: m/z (%) =380 (100; M^+), 272 (59.3; M^+-$SO_2N(CH_3)_2$), 155 (11.2), 91 (11.2).

N,N-Dimethyl-4-(4-oxo-7-*p*-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)benzenesulfonamide (5)

A mixture of (**4**; 0.01 mol) and formic acid (30 mL) was refluxed for 5 h. The solvent was concentrated until dry. After cooling, the solid product that formed was collected and recrystallized to give **(5)** (Table I). IR (film) $\upsilon = 3400$ (NH), 3142 (CH-arom.), 2848 (CH-aliph.), 1658 (CO), 1334, 1166 $cm^{-1}(SO_2)$. MS: m/z (%) = 408 (70.5; M^+), 316 (15.9), 301 (100; M^+-$SO_2N(CH_3)_2$), 272 (4.9), 172 (13.8), 91 (15.5).

N-[3-Cyano-4-(4-dimethylsulfamoylphenyl)-1-*p*-tolyl-1H-pyrrol-2-yl]acetamide (6a)

A mixture of (**4**; 0.01 mol) and acetyl chloride (30 mL) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was collected by filtration and recrystallized to give **(6a)** (Table I). IR

(film) υ = 3426 (NH), 3093 (CH-arom.), 2928 (CH-aliph.), 2226 (CN) 1728 (CO), 1336, 1162 $cm^{-1}(SO_2)$. MS: m/z (%) =422 (76.5; M^+), 380 (100; M^+-CH_2 =C=O), 272 (26.4), 91 (20.1), 44 (29.4).

N-[3-Cyano-4-(4-dimethylsulfamoyl-phenyl)-1-*p*-tolyl-1H-pyrrol-2-yl]benzamide (6b)

A mixture of (**4**; 0.01 mol) and benzoylchloride (10 mL) was refluxed for 2 h. Then it was allowed to cool and was treated with petroleum ether (60–80 °C) (50 mL), whereby petroleum ether was decanted, and the solid product was separated, collected by filtration, washed with petroleum ether (60–80°C) several times, dried, and recrystallized to give **(6b)** (Table I). IR (film) υ = 3282 (NH), 3118 (CH-arom.), 2922 (CH-aliph.), 2228 (CN) 1664 (CO) , 1336, 1158 $cm^{-1}(SO_2)$. MS: m/z (%) =484 (9.9; M^+), 407 (16.2), 299 (7.9), 271 (2.6), 105 (100; C_6H_5CO), 77 (23.8), 44 (5.4).

4-(4-Amino-2-oxo-7-*p*-tolyl-2,7-dihydro-1H-pyrrolo[2,3-d] pyrimidin-5-yl)-N,N-dimethylbenzenesulfonamide (7)

A mixture of (**4**; 0.01 mol) and urea (0.02 mol) was heated at 160 °C for 20 min, and the heating was continued for another 1 h at 200 °C until the mixture became solid. The resulting solid was dissolved in a hot dilute sodium hydroxide solution, and the boiling basic was allowed to stand approximately 10 min and then filtered off. Further purification was accomplished by the reprecipitation froma hot solution with acetic acid. The separated solid was filtered off and recrystallized to give **(7)** (Table I). IR (film) υ = 3466, 3340 (NH_2), 3410 (NH), 3054 (CH-arom.), 2782 (CH-aliph.), 1726 (CO), 1335, 1155 $cm^{-1}(SO_2)$. MS: m/z (%) = 423 (0.24; M^+), 408 (0.77), 354 (0.58), 301 (0.75), 129 (100), 70 (9.4), 44 (52.8).

N-[3-Cyano-4-(4-dimethylsulfamoyl-phenyl)-1-*p*-tolyl-1H-pyrrol-2-yl]formimidic Acid Ethyl Ester (8)

A mixture of (**4**; 0.01 mol) and triethylorthoformate (0.01 mol) in acetic anhydride (25 mL) was heated under reflux for 6 h. The reaction mixture was concentrated until dry. The solid that was obtained was collected by filtration and recrystallized to give **(8)** (Table I). IR (film) υ = 3092 (CH-arom.), 2932 (CH-aliph.), 2208 (CN), 1336, 1166 $cm^{-1}(SO_2)$. ^{1}H-NMR ($CDCl_3$): δ =1.29 (t, 3H, $OCH_2\underline{CH_3}$), 2.40 (s, 3H, CH_3), 2.72 (s, 6H, $N(CH_3)_2$), 4.24 (q, 2H, $O\underline{CH_2}CH_3$), 6.98 (s, 1H, CH-pyrrole) 7.28

and 7.0 (dd, 4H, AB-ArH), 7.79 and 7.80 (dd, 4H, AB-ArH), 8.37 ppm (s, 1H, $\underline{CH}OC_2H_5$).

4-(4-Amino-7-*p*-tolyl-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N,N-dimethylbenzenesulfonamide (9)

Procedure A

A mixture of (**4**; 0.01 mol) and formamide (10 mL) was heated under reflux for 8 h. The solvent was removed under vacuum, and the solid obtained was recrystallized to give **(9)** (Table I).

Procedure B

Compound (**8**; 0.01 mol) was treated with methanolic ammonia (100 mlL) at room temperature for 3 h. The separated solid was collected and recrystallized. M.p. and mixed m.p determined with authentic sample gave no depression. IR (film) $\upsilon = 3484$, 3306 (NH_2), 3116 (CH-arom.), 2917 (CH-aliph.), 1340, 1162 cm^{-1}(SO_2). MS: m/z (%) =407 (100; M^+), 299 (66.1), 172 (10.6), 105 (13.8) 91 (12.1), 44 (63.9).

4-[4-Cyano-5-(dimethylaminomethyleneamino)-1-*p*-tolyl-1H-pyrrol-3-yl]-N,N-dimethylbenzenesulfonamide (10)

Procedure A

A mixture of (**4**; 0.01 mol) and N,N-dimethylformamide dimethylacetal (0.01 mol) in xylene (20 mL) was refluxed for 2 h. The solvent was removed under reduced pressure, and the residue was collected and recrystallized to give **(10)** (Table I).

Procedure B

A solution of (**8**; 0.01 mol) and dimethylamine (0.01 mol) in ethanol (50 mL) was stirred for 45 min. The solid that was obtained was filtered off and recrystallized. M.p. and mixed m.p determined with authentic sample gave no depression. IR (film) $\upsilon = 3135$ (CH-arom.), 2876 (CH-aliph.) 2207 (CN), 1335, 1163 cm^{-1}(SO_2). ^{1}H-NMR ($CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 2.73 (s, 6H, $SO_2N(CH_3)_2$), 2.95 and 3.09 (2s, 6H, $N(CH_3)_2$), 6.86 (s, 1H, CH-pyrrole), 7.25 and 7.38 (dd, 4H, AB-ArH), 7.78 and 7.80 (dd, 4H, AB-ArH), 8.20 ppm (s, 1H, N=$\underline{CH}$).

4-4-Cyano-5-[(N-methylformimidoyl)amino]-1-*p*-tolyl-1H-pyrrol-3-yl-N,N-dimethylbenzenesulfonamide (12)

To a solution of (**8**; 0.01 mol) in absolute ethanol (50 mL), methyl amine (0.01 mol) was added. The reaction mixture was stirred for 1 h. the solid that was obtained was filtered off and recrystallized to give **(12)**

(Table I). IR (film) $\upsilon = 3410$ (NH) 3130 (CH-arom.), 2924 (CH-aliph.), 2199 (CN), 1335, 1159 $cm^{-1}(SO_2)$. ^{1}H-NMR (DMSO): $\delta = 2.36$ (s, 3H, CH_3), 2.64 (s, 6H, $N(CH_3)_2$), 2.75 (d, 3H, $NH\underline{CH}_3$), 3.50 (d, 1H, $\underline{NH}CH_3$), 7.28 and 7.46 (dd, 4H, AB-ArH) 7.44 (s, 1H, CH-pyrrole), 7.76 and 7.93 (dd, 4H, AB-ArH), 8.18 ppm (d, 1H, $\underline{CH}NH$).

4-(3-Amino-4-imino-7-*p*-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]-pyrimidin-5-yl)-N,N-dimethylbenzenesulfonamide (13)

To a stirred solution of (**8**; 0.01 mol) in ethanol (50 mL), hydrazine hydrate (0.02 mol) was added. Stirring was continued for 7 h at room temperature. The solid product was isolated by filtration and recrystallized to give **(13)** (Table I). IR (film) $\upsilon = 3408$, 3338 (NH_2), 3286 (NH), 3130 (CH-arom.), 2920 (CH-aliph.), 1338, 1162 $cm^{-1}(SO_2)$. MS: m/z (%) = 422 (70.1; M^+), 300 (32.3), 229 (11.7), 91 (17.2).

7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)]pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (14)

Procedure A

A mixture of (**13**; 0.01 mol) and oxalic acid (0.01 mol) in xylene (20 mL) was refluxed for 8 h. The precipitate product was filtered off and recrystallized to give (**14**) (Table I).

Procedure B

A mixture of (**13**; 0.01 mol) and formic acid (0.01 mol) was refluxed for 6 h. The obtained solid was filtered off and recrystallized to give (**14**).

Procedure C

A mixture of (**13**; 0.01 mol) and triethylorthoformate (0.01 mol) in benzene (50 mL) was refluxed for 5 h. The obtained solid was filtered off and recrystallized to give (**14**).

Procedure D

Compound (**13**; 0.01 mol) reacted with N,N-dimethylformamide dimethylacetal (0.01 mol) according to procedure (C) to give **(14)**. M.p. and mixed m.p determined with authentic sample gave no depression. IR (film) $\upsilon = 3072$ (CH-arom.), 2924 (CH-aliph.), 1332, 1156 $cm^{-1}(SO_2)$. MS: m/z (%) = 432 (15.8; M^+), 325 (100), 184 (13.3), 118 (15.2), 91 (27.5), 65 (16.3).

2-Chloromethyl-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonyl phenyl)]pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15a)

A mixture of (**13**; 0.01 mol) and chloroacetylchloride (0.01 mol) in benzene (50 mL) was refluxed for 6 h. The product obtained was filtered off and recrystallized to give (**15a**) (Table I). IR (film) $\upsilon = 3082$ (CH-arom.), 2924 (CH-aliph.), 1338, 1156 $cm^{-1}(SO_2)$. ^{1}H-NMR ($CDCl_3$): $\delta = 2.47$ (s, 3H, CH_3), 2.78 (s, 6H, $N(CH_3)_2$), 4.87 (s, 2H, CH_2), 7.38 and 7.56 (dd, 4H, AB-ArH) 7.81 (s, 1H, CH-pyrrole), 7.87 and 8.44 (dd, 4H, AB-ArH), 9.09 ppm (s, 1H, CH-pyrimidine).

2-Cyanomethyl-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonyl phenyl)]pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15b)

A mixture of (**13**; 0.01 mol) and ethylcyanoacetate (0.01 mol) in ethanol (50 mL) was refluxed for 5 h. The solid obtained was collected by filtration and recrystallized to give (**15b**) (Table I). IR (film) $\upsilon = 3134$ (CH-arom.), 2966 (CH-aliph.) 2966 (CN), 1336, 1162 $cm^{-1}(SO_2)$. MS: m/z (%) = 471 (10.9; M^+), 406 (0.4), 364 (21.9), 299 (0.5), 78 (100).

2-Acetyl-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)]-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15c)

A mixture of (**13**; 0.01 mol) and pyruvic acid (0.01 mol) in butanol (50 mL) was refluxed for 7 h. The solid obtained after concentration of the reaction mixture was filtered off and recrystallized to give (**15c**) (Table I). IR (film) $\upsilon = 3135$ (CH-arom.), 2928 (CH-aliph.) 1650 (CO), 1338, 1160 $cm^{-1}(SO_2)$. MS: m/z (%) = 472 (4.8; M^+-2), 408 (100), 367 (32.1), 325 (27.0), 300 (32.8), 299 (54.0), 91 (18.2).

2-Metyl-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)]-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15d)

Procedure A

A mixture of (**13**; 0.01 mol) and acetic anhydride (20 mL) was refluxed for 5 h. The solvent was removed under vacuum. The solid obtained was recrystallized to give (**15d**) (Table I).

Procedure B

Compound (**15d**) prepared from (**13**; 0.01 mol) and triethylorthoacetate (15 mL) according to procedure A to give (**15d**).

Procedure C

A mixture of (**13**; 0.01 mol) and acetic acid (20 mL) was refluxed for 6 h. The solid obtained was filtered off and recrystallized to give (**15d**).

Procedure D

The reaction of (**13**; 0.01 mol) with ethyl acetoacetate (0.01 mol) was carried out as in the reaction of (**13**) with ethyl cyanoacetate to give (**15d**). M.p. and mixed m.p determined with authentic sample gave no depression. IR (film) $\upsilon = 3070$ (CH-arom.), 2924 (CH-aliph.), 1334, 1156 $cm^{-1}(SO_2)$. ^{1}H-NMR ($CDCl_3$): $\delta = 2.47$ (s, 3H, CH_3), 2.67 (s, 3H, CH_3-triazole), 2.79 (s, 6H, $N(CH_3)_2$), 7.37 and 7.56 (dd, 4H, AB-ArH) 7.77 (s, 1H, CH-pyrrole), 7.91 and 8.49 (dd, 4H, AB-ArH), 9.04 ppm (s, 1H, CH-pyrimidine). MS: m/z (%) = 446(39.1; M^+), 339 (100), 297 (14.8).

2-Ethoxy carbonyl methyl-7-*p*-tolyl-9-[4-(N,N-dimethylamino-sulfonylphenyl)]pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (15e)

A mixture of (**13**; 0.01 mol) and diethylmalonate (0.01 mol) in ethanol (50 mL) was refluxed for 5 h. The solid obtained was collected by filteration and recrystallized to give (**15e**) (Table I). IR (film) $\upsilon = 3142$ (CH-arom.), 2950 (CH-aliph.) 1742 (CO), 1336, 1158 $cm^{-1}(SO_2)$. MS: m/z (%) = 518 (3.6; M^+), 505 (40.2), 398 (24.0), 339 (100), 91 (14.8).

2-thioxo-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)]-2,3-dihydropyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (16)

A mixture of (**13**; 0.01 mol), 30 mL of ethanol, 0.3 g of KOH, and 3 mL of CS_2 were refluxed for 5 h. After removal of ethanol, water was added, and the alkaline solution was filtered. The clear filtrate was acidified with acetic acid, and the formed precipitate was collected and recrystallized to give (**16**) (Table I). IR (film) $\upsilon = 3432$ (NH), 3060 (CH-arom.), 2926 (CH-aliph.), 1332, 1156 $cm^{-1}(SO_2)$. MS: m/z (%) = 464 (5.7; M^+), 408 (48.1), 354 (100), 301 (89.7), 229 (10.1), 199 (28.3), 91 (32.4), 44 (46.5).

2-Methylamino-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonyl-phenyl)]pyrrolo[3,2-e][1,2,4]triazolo[1,5-c] pyrimidine (17a)

A mixture of (**13**; 0.01 mol) in ethanol (30 mL) was treated with methyl isothiocyanate (0.012 mol) and refluxed for 3 h. The obtained product was filtered off and recrystallized to give **(17a)** (Table I). IR (film) $\upsilon =$

3404 (NH), 3060 (CH-arom.), 2916 (CH-aliph.), 1334, 1160 $cm^{-1}(SO_2)$. ^{1}H-NMR ($CDCl_3$): $\delta = 2.45$ (s, 3H, CH_3), 2.76 (s, 6H, $N(CH_3)_2$), 3.07 (d, 3H, NH-$\underline{CH_3}$), 4.73 (d, 1H, $\underline{NH}$-CH_3), 7.35 and 7.54 (dd, 4H, AB-ArH), 7.69 (s, 1H, CH-pyrrole), 7.83 and 8.38 (dd, 4H, AB-ArH), 8.87 ppm (s, 1H, CH-pyrimidine). MS: m/z (%) =461 (86.2; M^+), 407 (35.7), 354 (100), 270 (10.6), 229 (2.4), 199 (21.9), 91 (10.9).

2-Phenylamino-7-*p*-tolyl-9-N,N-[4-(N,N-dimethylaminosulfonyl- phenyl)] pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (17b)

Compound **(17b)** was prepared from (**13**; 0.01 mol) and phenyl isothiocyanate (0.012 mol) according to the preparation of **(17a)** (Table I). IR (film) $\upsilon = 3304$ (NH), 3050 (CH-arom.), 2964 (CH-aliph.), 1338, 1158 $cm^{-1}(SO_2)$. MS: m/z (%) = 423 (93.3; M^+), 417 (75.1), 208 (17.0), 91 (27.2).

2-Methoxy-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)]-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (19)

Compound **(19)** was prepared from the reaction of (**13**; 0.01 mol) and methyl chloroformate (0.01 mol) according to the procedure used for preparing **(15a)**. IR (film) $\upsilon = 3055$ (CH-arom.), 2926 (CH-aliph.), 1332, 1162 $cm^{-1}(SO_2)$. ^{1}H-NMR ($CDCl_3$): $\delta = 2.43$ (s, 3H, CH_3), 2.67 (s, 6H, $N(CH_3)_2$), 3.98 (s, 3H, O-CH_3), 7.37 and 7.83 (dd, 4H, AB-ArH), 7.68 (s, 1H, CH-pyrrole), 8.46 and 9.20 (dd, 4H, AB-ArH), 9.53 ppm (s, 1H, CH-pyrimidine). MS: m/z (%) = 463 (4.0; M^+), 357 (10.5), 341 (100), 298 (11.0).

2-Phenyl-7-*p*-tolyl-9-[4-(N,N-dimethylaminosulfonylphenyl)]-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (20)

Procedure A

A mixture of (**13**; 0.01 mol) and benzaldehyde (0.012 mol) in dioxane (20 mL) and few drops of piperidine was refluxed for 5 h. The mixture was then cooled, and the separated solid was filtered off and recrystallized to give **(20)** (Table I).

Procedure B

A mixture of (**13**; 0.01 mol) and benzoylchloride (10 mL) was refluxed for 3 h. The reaction mixture was then diluted with cold NaOH solution, and the solid obtained was washed with water and recrystallized to give

(20) (Table I). M.p. and mixed m.p determined with authentic sample gave no depression. IR (film) $v = 3074$ (CH-arom.), 2918 (CH-aliph.), 1338, 1160 $cm^{-1}(SO_2)$. MS: m/z (%) = 508 (32.9; M^+), 401 (100), 297 (19.8), 118 (41.4), 91 (50.0).

Antimicrobial and Antifungal Screening

The prepared compounds were evaluated for their antimicrobial activity using the agar diffusion technique.[14,15] A mg/mL solution in DMF was used. The test organisms were Gram-positive *Bacillus subtilis* (NCTC-1040), *Staphylococcus aureus* (NCTC-7447), and *Sarcina maxima* (ATCC-33910); Gram-negative *Klebsiella pneumonia* (NCIMB-9111), *Salmonella*, and *Pseudomonas aeruginosa* (ATCC-10145); and for antifungal activity, unicellular fungi *Candida abicans* (IMRU-3669), filamentous fungi *Rhizopus* and *Asperigillus fumigatus*. DMF showed no inhibition zones. The reference antibiotics were Ampicillin (AMD) and Calforan. The inhibition zones (IZ) of these compounds are listed in (Table II).

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