Bull. Pharm. Sci., Assiut University, Vol. 27, Part 1, June 2004, pp. 141-154.

SYNTHESIS AND ANTIBACTERIAL SCREENING OF SOME 2,5,7-TRIARYL-1,2,4-TRIAZOLO[1,5-a]PYRIMIDINES

Nawal A. El-Koussi[1], Farghaly A. Omar[1], Salah A. Abdel-Aziz[1], and Mohamed F. Radwan[2]

[1]*Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Assiut University, Assiut, Egypt*
[2]*Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, El-Minia University, El-Minia, Egypt*

تم تحضير ثلاث سلاسل من مشتقات ١و٢و٤ تريازولو(١و٥ ا) بيريميدين كمضادات للبكتيريا وتم تحضير المركبات المستهدفة عن طريق تفاعل ٥ امينو -٣ (٢و٣و٤ بيريديل) ١و٢و٤تريازول مع مشتقات الشالكون فى الايثيلين جليكول. تم التأكد من الصيغة البنائية للمركبات التى تم تخليقها بواسطة استخدام الاشعة تحت الحمراء والرنين النووى المغناطيسى وطيف الكتلة بالاضافة الى استخدام التحاليل الدقية وكروماتوجرافيا الطبقة الرقيقة واجرى اختبار الفاعلية البيولوجية للمركبات المخلقة كمضدات للبكتيريا و الفطريات مقارنة بعقار الاموكسيسيلين والكلوتريمازول. وقد تبين ان سلسلة ٢ بيريديل هى الاكثر فاعلية عن مثيلاتها ٣ بيريديل و٤ بيريديل. اما فى حالة البكتيريا السالبة الجرام سيراتيا مارسينس لوحظ ان الفاعلية تزداد فى ٣ بيريديل خاصة التى تمتلك مجموعات على حلقة البنزين بها خاصية اعطاء الالكترونات. وثبت ان هذه المركبات ليس لها اى فاعلية ضد الفطريات.

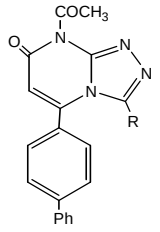
*Three novel series of 5,7-diaryl-2-(pyridyl)-1,2,4-triazolo[1,5-a]pyrimidines were prepared as antibacterial and antifungal agents. The triazolopyrimidines **(21-23)a-m** were synthesized by reaction of the respective 3-amino-5-(2-,3- or 4-pyridyl)-1,2,4-triazoles **(14-16)** with substituted chalcones analogues **(17a-m)** in ethylene glycol. As the cyclocondensation* reaction of such heterocyclic amines with α,β-*unsaturated ketones might produce isomeric triazolopyrimidines, the isolated products were identified by studying their IR, [1]H-NMR and MS. Their purity have been ascertained through TLC and elemental analyses. The antibacterial activity of the prepared compounds was screened against several bacterial species in comparison to Amoxycillin. As general features the 2-pyridyl series **(21a-m)** exhibited higher activity than the corresponding 3- or 4-pyridyl analogues **(22-23)a-m**. The 3-pyridyl derivatives **(22a-m)**, particularly those having electron-donating substituent on the phenyl nucleus, showed selective antibacterial activity against S. marcescens. The synthesized derivatives were tested for antifungal activity, in comparison to Clotrimazole but no activity has been observed.*

INTRODUCTION

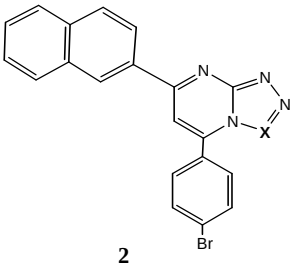
Fused heterocycles are representing major classes of the synthetic antibacterial agents. The excellent therapeutic results attained by the use of quinolones and their related structures potentiated the development of several isosteric modifications. Some of the synthesized analogues including thienopyridines; furano-pyridines; pyrazolopyridines; pyrazolo-pyrimidines,[1-3] imidazopyrimidines[4] and triazolopyrimidines[5] exhibited marked antibacterial and antifungal activities. Alternatively, substituted-1,2,4-triazolo[4,3-a]-pyrimidines **(1)** were prepared and tested for antibacterial activity, but they exhibited weak in vitro activity against both *G-postive* and *G-negative* bacteria e.g *B. subtilis* and *E. coli* respectively.[6] They showed also weak antifungal activity against *C. albican* and *A. niger*. In some cases when the compounds containing naphthyl moiety (**2**) marked activity against *Aspergillus species* was observed.

Received in 14/3/2004 & Accepted in 4/5/2004

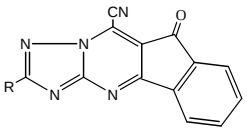
On the other hand, a number of 1,2,4-triazolo[1,5-a]pyrimidines **(3)** as well as their indeno- and thieno-fused analogues[7-8] exhibited potent antibacterial activity against *Staphylococus aureus* and *Salmonella bacilli*. Moreover, a series of 2-pyridyl-7-hydroxy-5-methyl-1,2,4-triazolo[1,5-a]pyrimidines **(4)** were reported as potential antileishmanial agents on basis of their ability to inhibit hypoxanthine-guanine-phosphoribosyl transferase enzyme.[9]



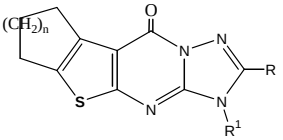
1



2



3



4

Based on these observations we planned the synthesis of several 2,5,7-triaryl-1,2,4-triazolo[1,5-a]pyrimidines to be tested for potential antibacterial and antifungal activity. The model reactions for these syntheses were in accordence with the reported preparations of 5,7-diphenyldihydro-1,2,4-triazolo[1,5-a]-pyrimidines;[10] 2,7-disubstituted-6,7-dihydro-4H-1,2,4-triazolo[1,5-a]pyrimidine-5-ones[11] as well as the through dehydrogenating the products from reacting 3-amino-1,2,4-triazoles and different chalcones.

EXPERIMENTAL

Melting points were determined on an electrothermal melting point apparatus (Stuart Scientific Co.) and were uncorrected. Elemental microanalyses were performed at the microanalytical center, Cairo University, Cairo, Egypt, and Assiut University Central Lab, Assiut, Egypt. ^{1}H-NMR spectra were determined on Varain Em-360L NMR spectrophotometer (60 MHz) (Varian USA) at the Faculty of Pharmacy, Assiut University, and on Joel, Lambda, Oxford NMR YH (400 MHz, Japan at Assiut University Central Lab using TMS as an internal standard. The chemical shifts are expressed in δ (ppm). IR spectra are recorded as KBr disks on Shimadzu IR Spectrophotometer at the Faculty of Pharmacy, Assiut University. Mass spectra were performed with JEOL JMS600, Assiut University Central Lab, Assiut, Egypt.

Synthesis of 3-amino-5-pyridyl-1,2,4-triazoles (14-16)

Method a: A mixture of the appropriate pyridinyl carboxylic acid **(5-7)** (30.75 g, 0.25 mol) and aminoguanidine sulfate (74 g, 0.6 mol) was heated at 210° for 2 hrs. After cooling, water (125 ml) was added cautiously and the mixture was warmed again until clear solution was attained. The pH of the solution was adjusted to 9.5 by addition of 20% NaOH solution and the mixture was cooled to 0° in an ice bath. The precipitated product was filtered, washed with isopropyl alcohol, then with ether, dried in vacuum, and crystallized from water.

Method b: To a stirred solution of the appropriate pyridinylhydrazide **(8-10)** (20 g, 0.12 mole), a solution of sodium hydroxide (0.01 mole) and S-methylpseudothiourea sulfate (34 g, 0.122 mole) was added. Stirring was continued at room temperature for 20 hrs. The resulting precipitate was filtered, washed several times with water then with ether and dried in vacuum. Crystallization from water afforded the corresponding pyridinylamidinohydrazides **(11-13)**. The resulting products (17.9 g, 0.1 mole) were then fused at 250° for 30 min and allowed to cool. The solidified products were crystallized from water to give the required amino triazole derivatives.

3-Amino-5-(2-pyridyl)-1,2,4-triazole (14): 12.9 g, 80%; mp 215-217°, (reported[12] m.p 223-225°); ^{1}H-NMR (d_6-DMSO, δ ppm): 6.1 (2H; brs; D_2O exchangeable; -NH_2); 7.4 (1H, m; pyr. H-6); 7.9 (2H; m; pyr. H-4 and H-5); 8.6 (1H; d; $J_{3,4}$ = 5Hz; pyr. H-3); 13.0 (1H, brs; D_2O exchangeable; -NH).

3-Amino-5-(3-pyridyl)-1,2,4-triazole (15): 14.5 g, 90%, mp 225 – 227° (reported[12] m.p: 233-235°); ^{1}H-NMR (d_6-DMSO, δ ppm): 6.2

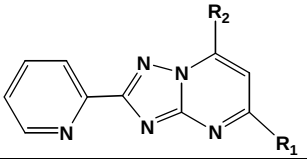
(2H, brs, D_2O exchangeable; $-NH_2$); 7.5 (1H, 3d, $J_{6,5}$= 5 Hz, $J_{6,4}$=.2 Hz, $J_{6,2}$= 2 Hz, pyr. H-6); 8.3 (1H; 2d, $J_{5,6}$= 5 Hz, $J_{5,4}$= 5 Hz, pyr. H-5); 8.7 (1H, dd, $J_{4,5}$= 5 Hz, $J_{4,6}$= 2 Hz, pyr. H-4); 9.15 (1H; s, pyr. H-2); 12.25 (1H, brs, D_2O exchangeable; -NH).

3-Amino-5-(4-pyridyl)-1,2,4-triazole (16): 15.3 g, 95%, mp 274-277° (reported[13] m.p: 279-281°); ^{1}H-NMR (d_6-DMSO, δ ppm): 6.2 (2H, brs, D_2O exchangeable, $-NH_2$); 7.85 (2H, d, J= 5 Hz, pyr. H-3, H-5); 8.7 (2H, d, J= 5 Hz; pyr. H-2, H-6); 12.3 (1H, brs, D_2O exchangeable; -NH).

General method for the synthesis of 5,7-diaryl -2-pyridyl-1,2,4-triazolo[1,5-a]pyrimidine derivatives (21-23)a-m:

The appropriate chalcone analogues **(17a-m),** (1.24 mmol) was added to a stirred solution of the proper 3-amino-5-(pyridyl)-1,2,4-triazoles **(14-16)** (200 mg, 1.24 mmol) in ethylene or propylene glycol (10 ml), and the resulting mixture was heated at 220-230° for 3 hrs. The mixture was then cooled and diluted with water (50 ml). The precipitated product was separated by filtration, washed with hot water and crystallized from the appropriate solvents. Yields, physical and elemental data are listed in Tables 1-3 and ^{1}H-NMR data are summerized in Tables 4-6.

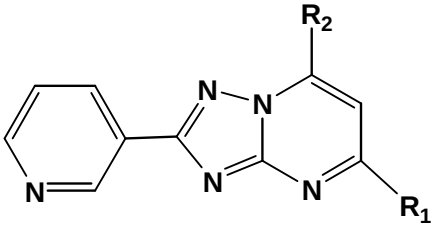
Table 1: Physical data of 5,7-diaryl-2-(2-pyridyl)-1,2,4-triazolo[1,5-a]pyrimidines **(21a-m).**



Compd No.	R_1	R_2	Yield %	M.P °/ Solvent of crys.	M.F./ M.Wt.	Microanalysis Calculated/Found		
						C%	H%	N%
21a	H	H	61	225-27 E	$C_{22}H_{15}N_5$ 349.396	75.63 75.23	4.32 4.32	20.04 19.75
21b	Cl	H	65	231-33 E	$C_{22}H_{14}ClN_5$ 383.841	68.84 68.60	3.68 3.70	18.25 18.30
21c	Br	H	50	232-35 E	$C_{22}H_{14}BrN_5$ 428.300	61.69 61.53	3.29 3.31	16.35 15.92
21d	OCH_3	H	60	208-11 E	$C_{23}H_{17}N_5O$ 379.421	72.81 72.46	4.52 4.46	18.46 18.18
21e	CH_3	H	63	219-21 E	$C_{23}H_{17}N_5$ 363.422	76.01 75.76	4.72 4.56	19.20 19.11
21f	OH	H	65	> 300 E	$C_{22}H_{15}N_5O$ 365.395	72.32 72.44	4.14 4.58	19.17 19.18
21g	NO_2	H	71	260-62 A/W	$C_{22}H_{14}N_6O_2$ 394.392	67.00 67.00	3.58 3.50	21.31 21.10
21h	H	Cl	64	231-34 E	$C_{22}H_{14}ClN_5$ 383.841	68.84 68.40	3.68 3.70	18.25 18.20
21i	H	Br	55	241-43 E	$C_{22}H_{14}BrN_5$ 428.300	61.70 61.30	3.29 3.60	16.35 16.70
21j	H	OCH_3	60	240-42 E	$C_{23}H_{17}N_5O$ 379.422	72.81 72.50	4.52 4.10	18.46 18.20
21k	H	NO_2	85	>300 A/W	$C_{22}H_{14}N_6O_2$ 394.392	66.99 66.57	3.58 3.83	21.31 20.61
21l	H	$N(CH_3)_2$	63	243-45 A/W	$C_{24}H_{20}N_6$ 392.464	73.44 73.80	5.14 4.80	21.42 21.50
21m	H	F	70	202-05 E	$C_{22}H_{14}FN_5$ 367.386	71.92 71.90	3.84 3.50	19.06 19.00

E: Ethanol A/W: Acetic acid/ water (1:1) E/W: Ethanol/ Water (2:1)

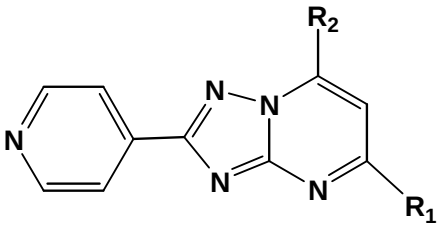
Table 2: Physical data 5,7-diaryl-2-(3-pyridyl)-1,2,4-triazolo[1,5-a]pyrimidines **(22a-m).**



Compd. No.	R_1	R_2	Yield %	M.P °/ Solvent of crys.	M.F./ M.Wt.	Microanalysis Calculated/Found		
						C%	H%	N%
22a	H	H	70	196-98 E	$C_{22}H_{15}N_5$ 349.396	75.63 75.11	4.32 4.39	20.04 19.86
22b	Cl	H	74	216-18 E	$C_{22}H_{14}ClN_5$ 383.841	68.84 69.25	3.68 3.48	18.25 18.11
22c	Br	H	62	209-11 E	$C_{22}H_{14}BrN_5$ 428.300	61.69 62.07	3.29 3.15	16.35 16.37
22d	OCH_3	H	69	200-03 E	$C_{23}H_{17}N_5O$ 379.422	72.81 72.72	4.52 4.84	18.46 18.62
22e	CH_3	H	65	192-95 E	$C_{23}H_{17}N_5$ 363.423	76.01 75.60	4.72 4.30	19.27 19.40
22f	OH	H	68	>300 E	$C_{22}H_{15}N_5O$ 374.395*	70.57 70.30	4.31 3.90	18.71 19.00
22g	NO_2	H	74	270-72 A/W	$C_{22}H_{14}N_6O_2$ 394.392	67.00 66.60	3.58 3.30	21.31 20.90
22h	H	Cl	75	234-36 E	$C_{22}H_{14}ClN_5$ 383.841	68.84 68.80	3.68 3.70	18.25 18.50
22i	H	Br	64	232-34 E	$C_{22}H_{14}BrN_5$ 428.300	61.69 61.40	3.29 3.30	16.35 16.30
22j	H	OCH_3	75	230-32 E	$C_{23}H_{17}N_5O$ 379.422	72.81 72.53	4.52 4.91	18.46 18.14
22k	H	NO_2	87	> 300 A/W	$C_{22}H_{14}N_6O_2$ 394.392	66.99 66.59	3.58 3.18	21.30 21.20
22l	H	$N(CH_3)_2$.	68	240-42 E/W	$C_{24}H_{20}N_6$ 392.464	73.45 73.22	5.14 5.03	21.41 20.94
22m	H	F	72	225 E	$C_{22}H_{14}FN_5$ 367.386	71.92 71.50	3.84 3.90	19.06 18.90

E: Ethanol.
A/W: Acetic acid/ water (1:1).
E/W: Ethanol/ Water (2:1).
* 0.5 molecule of water of crystallization

Table 3: Physical data of 5,7-diaryl –2-(4-pyridyl)-1,2,4-triazolo[1,5-a] pyrimidines **(23a-m).**



Compd. No.	R_1	R_2	Yield %	M.P °/ Solvent of crys.	M.F./ M.Wt.	Microanalysis Calculated/Found		
						C%	H%	N%
23a	H	H	74	232-34 E	$C_{22}H_{15}N_5$ 349.396	75.63 75.90	4.32 4.50	20.04 19.70
23b	Cl	H	75	207-09 E	$C_{22}H_{14}ClN_5$ 383.841	68.84 68.50	3.68 4.10	18.25 18.30
23c	Br	H	63	238-40 E	$C_{22}H_{14}BrN_5$ 428.300	61.69 61.73	3.29 3.27	16.35 16.25
23d	OCH_3	H	73	176-78 E	$C_{23}H_{17}N_5$ 379.422	72.81 72.94	4.52 4.46	18.46 18.45
23e	CH_3	H	66	203-05 E	$C_{23}H_{17}N_5$ 363.423	76.01 76.05	4.72 4.68	19.27 19.24
23f	OH	H	71	> 300 E	$C_{22}H_{15}N_5O$ 365.395	72.32 72.61	4.14 4.25	19.17 19.29
23g	NO_2	H	73	250-53 A/W	$C_{22}H_{14}N_6O_2$ 394.392	67.00 66.60	3.58 4.00	21.31 20.90
23h	H	Cl	76	245-47 E	$C_{22}H_{14}ClN_5$ 383.841	68.85 68.23	3.68 3.92	18.25 18.50
23i	H	Br	68	223-25 E	$C_{22}H_{14}BrN_5$ 428.300	61.70 61.30	3.29 3.10	16.35 16.30
23j	H	OCH_3	73	225-27 E	$C_{23}H_{17}N_5O$ 379.422	72.81 72.40	4.52 4.30	18.45 18.50
23k	H	NO_2	85	> 300 A/W	$C_{22}H_{14}N_6O_2$ 394.392	67.00 66.86	3.58 4.00	21.31 20.99
23l	H	$N(CH_3)_2$	58	346-48 E/W	$C_{24}H_{20}N_6$ 392.464	73.45 73.36	5.14 4.81	21.41 21.27
23m	H	F	74	215-17 E	$C_{22}H_{14}FN_5$ 367.386	71.92 71.76	3.84 4.26	19.06 19.34

E: Ethanol.
A/W: Acetic acid/ water (1:1).
E/W: Ethanol/ Water (2:1).

Table 4: ^{1}H-NMR data of 5,7-diaryl-2-(2-pyridyl)-1,2,4-triazolo[1,5-a]pyrimidine **(21a-m)**.

Comp.	^{1}H-NMR data (δ ppm; $CDCl_3$)
21a	8.8 (1H, d, J = 4.0 Hz, Pyr-H-6); 8.45 (1H, d, J = 8.0 Hz, Pyr-H-3); 8.4 -7.9 (6H, m, Ar-H, Pyr- H-5); 7.85 (1H , m, Pyr-H-4); 7.8 –7.33 (4H , m, Ar-H- 3,5); 7.26 (2H, m, Ar-H- 4).
21b	8.75 (1H, d, J = 4.6 Hz, pyr.H-6); 8.42 (1H, d, J = 8.0 Hz, pyr.H-3); 8.17 - 8.11 (4H, m, pyr.H-5, Tp.H-6, p-ClC_6H_4-H); 7.81 (1H, t, J = 8 Hz, pyr.H-4); 7.56 - 7.53 (4H, m, pyr.H-3,5, Ar-H); 7.44 (2H, d, J = 8.56 Hz, Ar-H-3,5); 7.36-7.33 (1H, m, J = 4.6 Hz, 7.5 Hz, Ar-H-4).
21c	8.77 (1H, d, J = 5.0 Hz, Pyr.H-6); 8.45 (1H, d, J = 6.6 Hz, Pyr.H-3) ; 8.14 (4H , t, J = 7.94 Hz, Pyr. H-5, Tp. H-6, p-BrC_6H_4-H-2,6); 7.85 (1H, t, Pyr. H-4); 7.64 (2H, m, J = 6.8 Hz, Ar-H); 7.58 (2H , bs, p-BrC_6H_4 -H3,5); 7.38 -7.26 (m, 1H, J = 6 Hz, Ar-H4).
21d	8.83 (1H, d, J = 5.5 Hz, Pyr.H6); 8.7 - 8.45 (1H, d, J = 8.6 Hz, Pyr.H3); 8.45 - 8.1(4H, m, Pyr.H5, Tp H6, p-$OCH_3C_6H_4$-H2,6); 7.9 (1H, m, Pyr.H4); 7.84 -7.46 (4H, m, Ar-H); 7.46 - 7.26 (1H m, , Ar-H4); 7.17 - 6.83 (2H, d, J = 4.8 Hz, Ar-H3,5); 3.9 (3H, s, OCH_3).
21e	8.72 (1H, d, J = 4.4 Hz, Pyr.H-6); 8.41 (1H, d, J = 7.8 Hz, Pyr.H-3); 8.1 - 8.0 (4H, m, Pyr.H-5, Tp.H-6, p-$CH_3C_6H_4$-H-2,6); 7.79 (1H, t, J = 7.6, 7.8 Hz , Pyr.H-4); 7.54 - 7.50(4H, m, p-$CH_3C_6H_4$-H3,5, Ar-H2,6); 7.31 (1H, t, J = 4.88 Hz, Ar-H4); 7.23 (2H, d, J = 8.0 Hz, Ar-H2,6); 2.33 (3H, s, CH_3).
21f	10.2 (1H, s, OH); 8.83 (1H, d, J = 4.0 Hz, Pyr.H-6); 8.6 (5H, m, Pyr.H-3,5, Tp H-6, p-OHC_6H_4-H2,6); 8.1 - 8.0 (1H, m, Pyr.H-4); 8.0 - 7.76 (5H, m, Ar-H); 7.34 - 7.17 (2H, d, J = 9.0 Hz,Ar-H3,5).
21g	9.0 (4H, m, Pyr.H); 8.5 (3H, s, Tp H-6, R^1H2,6); 8.2(4H, m, R^1H3,5, p-$O_2NC_6H_4$-H-2,6), 7.8 (bs, 2H, p-$O_2NC_6H_4$-H-3,5) ; 7.24 (1H, m, Ar-H-4).
21h	8.81 (1H, d, J = 4.6 Hz, Pyr.H-6); 8.5 (1H, d, J = 8.0 Hz, Pyr.H-3); 8.38 - 8.03 (4H, m, Pyr.H-5, Tp H-6, p-ClC_6H_4-H2,6); 8.03 - 7.8 (1H, m, Pyr.H-4); 7.8 - 7.53 (4H, mAr-H); 7.43 (2H, d, Ar-H-3,5); 7.3 (1H, m, Ar-H-4).
21i	8.5 (1H, d, J = 5.0 Hz, Pyr.H-6); 8.45 (1H, d, J = 6.8 Hz, Pyr.H-3); 8.33 - 8.07 (4H, m, Pyr.H-5, Tp-H-6, p-BrC_6H_4-H-2,6); 8.07 - 7.93 (1H, m, Pyr.H-4); 7.9 - 7.7 (4H, m, Ar-H); 7.33 (2H, d, Ar-H-3,5); 7.33 (1H, m, Ar-H-4).
21j	8.85 (1H, d, J = 4.6 Hz, Pyr.H-6); 8.57 (1H, d, J = 7.8 Hz, Pyr.H-3); 8.45 - 8.16 (4H, m, Pyr.H-5, Tp-H-6, p-$OCH_3C_6H_4$-H-2,6); 8.0 (1H, m, Pyr.H-4); 7.8 - 7.4 (4H, m, Ar-H); 7.4 - 7.16 (1H, m, Ar-H-4); 7.08 (2H, d, J = 4.4 Hz, Ar-H-3,5); 3.9 (3H, s, OCH_3).
21k*	9.4-8.8 (4H, m, Pyr.H-3,6, p-$O_2NC_6H_4$-H3,5); 8.77 - 8.1 (7H, m, Pyr.H-4,5, Tp- H-6, p-$O_2NC_6H_4$-H2,6); 8.0 - 7.55 (3H, m, Ar-H).
21l	8.83 (1H, d, J = 4.8, Pyr.H-6); 8.5 (1H, d, J = 8.0, Pyr.H-3); 8.44 - 8.1 (4H, m, Pyr.H-5, Tp- H-6, p-$(CH_3)_2NC_6H_4$-H); 7.95 (1H, m, Pyr.H-4); 7.82 - 7.5 (4H, m, Ar-H); 7.43 (1H, m, Ar-H-4); 7.0 -6.66 (2H, d, J = 8.0 Hz, Ar-H-3,5) ;3.15 (s, 6H, -$(CH_3)_2$N).
21m**	8.84 (1H, d, J = 4.0 Hz, Pyr.H 6); 8.73 - 8.3 (5H, m, Pyr.H-3,5, Tp- H-6, p-FC_6H_4-H-2,6); 8.0 (1H, m, Pyr.H-4); 7.61 - 7.51 (4H, m, Ar-H); 7.59 - 7.4 (2H, m, Ar-H-3,5); 7.31(1H, m, Ar-H-4).

Pyr.: pyridyl; Tp.: triazolopyrimidine; *Solvent: TFA; **Solvent: d_6-DMSO

Table 5: ^{1}H-NMR data of 5,7-diaryl-2-(3-pyridyl)-1,2,4-triazolo[1,5-a] pyrimidine **(22a-m)**.

Comp.	^{1}H-NMR (δ ppm; $CDCl_3$)
22a	9.53 (1H, s, Pyr.H-2); 8.83 - 8.5 (2H, m, Pyr.H-6,4); 8.4 - 8.0 (2H, m, Pyr.H-5, Tp.H-6); 7.9 - 7.36 (8H, m, Ar- H); 7.22 – 7.18 2H, (m, Ar-H-4).
22b	9.58 (1H, s, Pyr.H-2); 8.7 (1H, d, J = 3.0 Hz, Pyr.H-6); 8.5 (1H, d, J = 2.0 Hz,Pyr.H-4); 8.3 - 8.1 (4H, m, pyr. H-5, Tp.H-6, p-ClC_6H_4-H-2,6); 7.7 - 7.63 (4H, m, Ar-H); 7.43 (2H, m, p-ClC_6H_4-H3,5); 7.3 (1H, d, J = 8.0 Hz, Ar-H4).
22c	9.56 (1H, s, Pyr.H-2); 8.7 (1H, d, J = 3.0 Hz, Pyr.H-6); 8.56 (1H, d, J = 2.0 Hz, Pyr.H-4); 8.3 - 8.0 (4H, m, pyr. H-5, TP H-6, p-BrC_6H_4-H-2,6); 7.7 - 7.63 (4H, m, Ar-H); 7.43 (2H, m, Ar-H-3,5); 7.3 (1H, d, J = 6.0 Hz , Ar-H4).
22d	9.55 (1H, s, Pyr.H-2); 8.7 (1H, d, J = 2.8 Hz, pyr.H-6); 8.5 (1H, d, J = 2.0 Hz, pyr.H-4); 8.4 - 8.0 (4H, m, Pyr.H-5, Tp-H-6, p-$OCH_3C_6H_4$-H2,6); 79 - 7.5 (4H, m, Ar-H); 7.5 - 7.2 (1H, m, Ar-H-4); 6.82 (2H, d, J = 8.6 Hz, Ar-H-3,5); 3.9 (3H, s, OCH_3).
22e	9.56 (1H, s, Pyr.H-2); 8.68 (1H, d, J = 2.8 Hz, pyr.H-6); 8.6 (1H, d, J = 8.0 Hz, Pyr.H-4); 8.2 - 8.1(4H, m, Pyr.H-5, Tp-H-6, p-$CH_3C_6H_4$-H2,6); 7.62 (4H, m, Ar-H); 7.41 - 7.38 (1H, m, Ar-H-4); 7.31 (2H, d, J = 8.3 Hz, Ar-H-3,5); 2.41(3H, s, CH_3)
22f**	10.21(1H, s, OH); 9.34 (1H, s, Pyr.H-2); 8.7 (1H, d, J = 3.88, Pyr.H-6); 8.48 (1H, d, J = 7.65, Pyr.H-4); 8.33 -8.31 (2H, m, Pyr.H-5, Tp-H-6); 8.28 (2H, d, p-OHC_6H_4-H2,6); 7.67(4H, d, J = 5.12, Ar-H); 7.57 - 7.44 (1H, m, Ar-H-4); 6.95 - 6.93(2H, d, Ar-H-3,5)
22g	9.9 (1H, s, Pyr.H-2); 9.54 (1H, d, J = 8.0, Pyr.H-6); 9.15 (1H, d, J = 6.4, Pyr.H-4); 8.54 (4H, m, Pyr.H-4, Tp- H-6, p-$O_2NC_6H_4$-H-2,6); 8.28 (4H, m, Ar-H) ; 7.88 (2H, d, Ar-H-3,5); 7.54 (1H, m, Ar-H-4).
22h	9.6(1H, s, Pyr.H-2); 8.8 (1H, d, J = 3.4, Pyr.H-6); 8.63 (1H, d, J = 2.8, Pyr.H-4); 8.5 - 8.1 (4H, m, Pyr.H-5, Tp- H-6, p-ClC_6H_4-H-2,6); 7.9 - 7.5(4H, m, p-ClC_6H_4-H-3,5, Ar-H-2,6); 7.43 (2H, m, Ar-H3,5); 7.35 (1H, m, Ar-H-4).
22i	9.58 (1H, s, Pyr.H-2); 8.7 (1H, d, J = 3.4, Pyr.H-6); 8.6 (1H, d, J = 2.8, Pyr.H-4); 8.4 - 8.03(4H, m, Pyr.H-5, Tp H-6 , p-BrC_6H_4-H2,6); 7.9 - 7.4 (4H, m, p-BrC_6H_4-H3,5, Ar-H-2,6); 7.35 (2H, m, Ar-H-3,5); 7.28 (1H, m, Ar-H-4).
22j	9.63 (1H, s, Pyr.H-2); 8.75(1H, d, J = 4.0, Pyr.H-6); 8.6 (1H, d, J = 2.0, Pyr.H-4); 8.5 - 8.1(4H, m, Pyr.H-5, Tp-H-6, p-$OCH_3C_6H_4$-H-2,6); 7.8 - 7.35 (4H, m, Ar-H); 7.3 (1H, m, Ar-H-4); 7.2 - 7.0 (2H, d, J = 9.0, Ar-H3,5); 3.9 (3H, s, OCH_3).
22k*	10 (1H, s, Pyr.H-2); 9.62 (1H, d, J = 8.0 Hz, Pyr.H-6); 9.25 - 9.15 (1H, d, J = 6.8 Hz, Pyr.H-4); 8.75 - 8.25 (8H, m, Ar-H); 8.1 - 7.5 (3H, m, Ar-H).
22l	9.7 (1H, s, Pyr.H-2); 8.9 -8. 55 (2H, m, Pyr.H-4,6); 8.4 - 8.1 (4H, m, Pyr.H-5, Tp- H-6, Ar-H); 7.85 - 7.35(4H, m, Ar-H); 7.3 (1H, m, Ar-H-4); 7.0 - 6.7 (2H, d, J = 9.0 Hz, AR-H-3,5); 3.2 (6H, s, n(CH_3)$_2$).
22m	9.45 (1H, s, Pyr.H-2); 8.59 (1H, d, J = 8.0 Hz, Pyr.H-6); 8.5 (1H, d, J = 6.8 Hz, Pyr.H-4); 8.18 - 8.13 (4H, m, Pyr.H-5, Tp- H-6, Ar-H); 7.52 - 7.4 (4H, m, Ar-H); 7.33 - 7.3(2H, m, Ar-H-3,5); 7.26 - 7.18 (1H , m, Ar-H-4).

Pyr.: pyridyl; Tp.: triazolopyrimidine; *Solvent: TFA; **Solvent: d_6-DMSO

Table 6: ^{1}H-NMR data of 5,7-diaryl-2-(4-pyridyl)-1,2,4-triazolo[1,5-a] pyrimidines **(23a-m)**.

Comp.	^{1}H-NMR (δ ppm in $CDCl_3$)
23a	8.5 (2H, d, J = 5.0 Hz, pyr. H-2,6); 8.5 - 8.0 (7H, m, Pyr.H-3,5,Tp H-6, Ar-H- 2,6); 7.8 - 7.5 (4H, m, Ar- H-3,5); 7.32 (m, 2H, Ar-H-4).
23b	8.75 (2H, d, J = 4.8 Hz, pyr. H-2,6); 8.5 - 8.0 (5H, m, pyr.H-3,5,Tp H-6, p-ClC_6H_4-H-3,5);7.9 - 7.6 (4H, m, Ar-H); 7.5 (2H, m, Ar-H);7.32 (1H, m, Ar-H-4).
23c	8.75 (2H, d, J = 4.0 Hz, pyr.H-2,6); 8.5 - 8.0 (5H, m, pyr.H-3,5,Tp H-6, p-BrC_6H_4-H 3,5);7.9 - 7.6 (4H, m, Ar-H); 7.5 (2H, m, p-BrC_6H_4-H-3,5);7.32 (m, 1H, Ar-H-4).
23d	8.78 (2H, d, J = 8.0 Hz, Pyr.H-2,6); 8.43 - 8.06 (5H, m, Pyr.H-3,5,Tp H-6, p-$OCH_3C_6H_4$H-2,6); 7.93 - 7.55 (4H, m, Ar-H); 7.35 (m, 1H, Ar-H-4); 7.25 - 6.9 (2H, d, J = 10.0 Hz, Ar-H-3,5); 3.9 (3H, s, OCH_3).
23e	8.68 (2H, d, J = 4.02 Hz, Pyr.H-2,6); 8.17 - 8.14 (3H, m, Pyr.H-3,5,Tp H-6); 8.07 (2H, d, J = 7.8 Hz, p-CH_3C_6H-H-2,6); 7.6 (4H, m, Ar-H); 7.28 (1H, d, J = 8.0 Hz, Ar- H-4); 7.24 (2H, d, J = 7.8 Hz, Ar-H-3,5); 2.22 (3H, s, CH_3).
23f	10.2 (1H, s, OH); 8.83 (2H, d, J = 4.0 Hz, Pyr.H-2,6); 8.4 (4H, m, Pyr.H-3,5, p-OHC_6H_4-H); 8.03 (1H, s, Tp H-6); 7.76 (5H, m, Ar-H); 7.05 (2H, d, J = 8.0 Hz, Ar-H-3,5).
23g*	9.04 (4H, m, pyr. H-2,6, p-$O_2NC_6H_4$-H-3,5); 8.54 (3H, m, Pyr.H-3,5 ,Tp H-6); 8.18 (4H, m, Ar-H); 7.82 (3H, m, Ar-H).
23h	8.9 (2H, d, J = 5.0 Hz, Pyr.H-2,6); 8.65 - 8.2 (5H, m, Pyr.H-3,5,Tp H-6, p-ClC_6H_4-H-3,5); 7.9 - 7.6(4H, m, Ar-H); 7.58 (2H, m, Ar-H-3,5); 7.35 (1H, m, Ar-H-4).
23i	8.86 (2H, d, J = 4.8 Hz, Pyr.H-2,6); 8.7 - 8.2 (5H, m, Pyr.H3,5,Tp H6, p-BrC_6H_4-H 3,5); 8.0 - 7.65(4H, m, Ar-H); 7.55 (2H, m, Ar-H); 7.33 (1H, m, Ar- H-4).
23j	8.76(2H, d, J = 3.8 Hz, Pyr.H-2,6); 8.5 - 8.0 (5H, m, Pyr.H-3,5,Tp H-6, p-$OCH_3C_6H_4$H-2,6); 7.8 - 7.35 (4H, m, Ar-H); 7.23(1H, m, Ar-H-4); 7.1(2H, d, J = 5.0 Hz, Ar-H-3,5);3.95(3H, s, OCH_3).
23k*	9.43 - 9.0 (4H, m, Pyr.H-2,6, p-$O_2NC_6H_4$-H-3,5); 8.8 - 8.2 (7H, m, Pyr.H-3,5,Tp H-6, p-$O_2NC_6H_4$-H-2,6); 8.1 - 7.59 (3H, m, Ar-H).
23l	8.86 (2H, d, J = 4.6 Hz, Pyr.H-2,6); 8.5 - 8.1 (5H, m, Pyr.H-3,5,Tp H-6, p-$(CH_3)_2NC_6H_4$-H); 7.8 - 7.46 (4H, m, Ar-H); 7.33 (1H, m, Ar-H-4); 7.0- 6.72 (2H, d, J = 9.6 Hz, Ar-H-3,5); 3.2(6H, s, -$(CH_3)_2$N).
23m	8.71 (2H, d, J = 5.88 Hz, Pyr.H-2,6); 8.24 - 8.2(3H, m, Pyr.H-3,5,Tp H-6); 8.17 -8.15 (2H, d, J = 6.12,Hz, Ar-H-2,6); 7.61 - 7.51 (4H, m, Ar-H); 7.49 - 7.47(2H, m, Ar- H-3,5); 7.32 (1H, m, Ar-H-4).

TFA; pyr: pyridyl; Tp.: triazolopyrimidine.

General method for synthesis of 5,7-diaryl-4,7-dihydro–2-(3-pyridyl)-1,2,4-triazolo-[1,5-a]pyrimidines (19a,c)

Mixture of 3-amino-5-(3-pyridyl)-[1,2,4]triazole **(15)** (400 mg, 2.48 mmol) and appropriate amount of the chalcone analogue **(17a)** or **(17c)** (2.48 mmole) was heated in an oil bath at 250° for 3 min, the products were cooled and crystallized from ethanol.

5,7-Diphenyl-2-(3-pyridyl)-4,7-Dihydro-1,2,4-triazolo[1,5-a]pyrimidine (19a): Yield 81%; m.p 238-40° (ethanol); Elemental analysis (%calc./found): $C_{22}H_{17}N_5$ (351.41), C 75.19/74.88, H 4.88/5.02, N 19.93/19.81; IR,ν cm^{-1} (KBr): 3470, 1651, 1592, 1547, 1420, 1073, 833, 753, 703. ^{1}H-NMR (d_6-DMSO, δ ppm): 9.6 (1H, s, NH); 9.3(1H, s, pyr. H-2); 8.8-8.5 (2H, m, pyr. H-6,4); 8.2-7.8 (11H, m, pyr. H-5, Ar-H), 6.7 (1H, d, J= 5 Hz, Tp. H-6); 5.4 (1H, d, J= 5 Hz, Tp. H-5). Ms: molecular ion peak at m/z 351; 53% and the base peak at m/z 274.08; 100%.

5-(4-bromophenyl)-7-phenyl-2-(3-pyridyl)-4,7-Dihydro-1,2,4-triazolo[1,5-a] pyrimidine (19c): Yield: 85%; mp. 240-43° (ethanol); Elemental analysis (%calc./found): $C_{22}H_{16}BrN_5$

(430.31), C 61.35/61.00, H 3.75/3.93, N 16.27/16.29; IR,ν cm^{-1} (KBr): 3480, 1647, 1593, 1557, 1410, 758, 692. ^{1}H-NMR (d_6-DMSO, δ ppm): 10.1 (1H, s, NH); 9.4 (1H, s, pyr. H-2); 8.5-8.3 (2H, m, pyr. H-6,4); 8.0-7.8 (11H, m, pyr. H-5, Ar-H), 6.7 (1H, d, J = 5 Hz, Tp. H-6); 5.4 (1H, d, J = 5 Hz, Tp.H-5)

Antibacterial and antifungal Screening

The synthesized compounds were screened *in vitro* for their antibacterial activity against the following bacterial strains: *Bacillus cereus; Staphyloccus aureus; Micrococcus roseus; Streptomyces spp.; Escherichia coli; Serratia marscens*; and *Peudomonus aeroginosa*. The tested fungi are: *Aspergillus flavus; Aspergillus fumigatus; Aspergillus niger; Fusarium oxysporum; Fusarium solani; Candida albicans; Scopulariopsis brivicalis; Chrysosporium tropicum; Geotrichum candidum; Trichoderma harzianum; Microsporium nanum,* and *Trichophyton rubrum*.

Method: The synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) and were tested at a concentration of 1% (w/v). Amoxycillin and Clotrimazole solutions (1%) were used as reference drugs for bacteria and fungi respectively.

Cultures were grown on nutrient agar medium containing peptone 5 g/l, beef extract 3g/l and NaCl 3g/l. The mixture was incubated at 121° and 1.5 atm for 20 min, distributed in sterile plates (20 ml per plate) and allowed to solidify. The tested bacterial or fungal species were firstly grown for 48 hrs, then 1 ml of each suspension was poured on the solidified agar medium and thoroughly distributed on the agar surface. Cups were made in the solidified agar (6/plate) with the aid of sterile cork borer. Aliquots of 0.1 ml of the solutions of the tested compound as well as the reference drugs were pipetted into the appropriate cup. The last cup was used as control for the solvent. The plates were left for one hr at room temperature to attain prediffusion. After 24 hrs of incubation at 37° for bacteria and 48 hrs of incubation at 30° for fungi, the diameters of inhibition zones (mm) were measured. The results are summerized in Table 7.

Table 7: The antibacterial activity for substituted 1,2,4-triazolo[1,5-a] pyrimidine **(21-23)a-m**, measured by inhibition zone test (mm).

No.	*S. aureus*	*B. cereus*	*M. roseus*	*S. spp.*	*S. marscens*	No.	*S. aureus*	*R. cereus*	*M. roseus*	*S. spp*	*S. marscens*
21a	-	12	15	16	8	**22g**	-	-	-	-	9
21b	13	8	20	14	-	**22h**	-	-	-	-	7
21c	12	10	10	13	8	**22i**	-	-	-	-	10
21d	15	7	-	-	-	**22j**	-	-	-	-	7
21e	13	-	-	14	8	**22k**	14	-	-	-	-
21f	20	8	-	-	-	**22L**	-	-	-	-	10
21g	13	-	10	8	-	**23a**	-	7	-	-	7
21h	12	7	10	12	9	**23b**	-	7	12	12	7
21i	-	8	-	-	-	**23d**	-	-	-	-	10
21k	-	8	12	10	-	**23h**	-	10	8	10	-
21L	12	7	10	-	-	**23i**	10	-	8	7	-
21m	-	9	12	14	-	**23j**	-	8	-	-	-
22a	-	-	-	-	8	**23k**	-	8	-	-	-
22b	-	-	-	-	7	**23L**	-	-	-	-	8
22c	-	-	-	-	8	**23m**	10	10	15	10	-
22d	-	-	-	-	10	Amox.	35	18	35	35	30
22e	-	-	-	7	10					-	

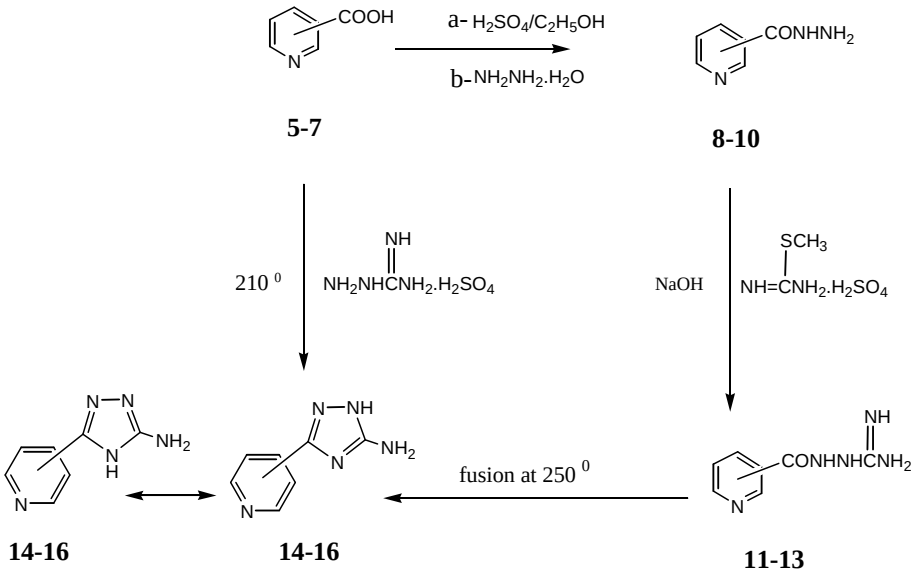
No activity against *E. coli, P aeroginosa*.

RESULTS AND DISCUSSION

Chemistry

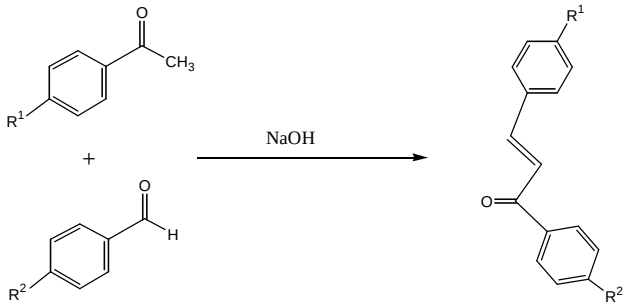
The synthesis of the starting intermediates 3-amino-5-pyridyl-1,2,4-triazoles (**14-16)** as well as the 1,3-disubstituted-2-propene-1-one (chalcone analogues) **(17a-m)** has been accomplished analogously to reported methods as depicted in scheme **1a;b.**

The amines **(14-16)** were prepared either directly by fusion of the respective pyridinylcarboxylic acids **(5-7**) and aminoguanidine sulfate at 210°[12] or by treatment of proper pyridinylhydrazides **(8-10)** with S-methyl-pseudothiourea sulfate in presence of sodium hydroxide[13] to afford the corresponding pyridinyl amidinohydrazides **(11-13)**. The latter was then cyclized by fusion at 230° to the respective 3-amino-5-pyridyl-1,2,4-triazoles **(14-16)**, scheme 1a**.** The structures of these starting amines were confirmed by comparison with the reported physical constants[12,13] as well as the recorded ^{1}H-NMR data.



5: 2-pyridyl; **6**: 3-pyridyl; **7**: 4-pyridyl

Scheme 1a



(17) a-m

	R^1	R^2		R^1	R^2		R^1	R^2
a	H	H	f	OH	H	k	H	NO_2
b	Cl	H	g	NO_2	H	l	H	$HN(CH_3)_2$
c	Br	H	h	H	Cl	m	H	F
d	CH_3O	H	i	H	Br			
e	CH_3	H	j	H	CH_3O			

Scheme 1b

The spectra revealed the presence of two D_2O exchangeable broad singlets at δ = 6.2 ppm and 12.3-13.0 ppm due to the exocyclic NH_2 and the ring NH respectively. Their chemical shift values were slightly shifted to lower field relative to reported data of the unsubstitued analogue[14] due to the presence of pyridyl substituent at C-5 of the ring. The characteristic peaks of the pyridyl moiety in each of the respective amines **(14-16)** has been identified. In case of 3-amino-5-(2-pyridyl)-1,2,4-triazoles **(14)**, the ^{1}H-NMR spectrum showed two multiplets at δ values= 7.4 ppm (H-6) and 8.0 ppm (H-4 and H-5), whereas the peak due to H-3 appeared as doublet at δ= 8.7 ppm. The spectrum of the 3-pyridyl analogue **(15)** illustrated 4 different peaks of the pyridyl moiety. three overlapped doublets at δ= 7.5 ppm that could be attributed to H-6, which would be affected by H-5 in ortho position in addition to long range coupling with H-4 and H-2. A second peak at δ 8.3 ppm appeared as pair of doublets was assigned to H-5 and a similar one at δ 8.7 ppm was due to H-4. The most downfield shifted singlet at δ= 9.2 ppm should be distinctive for H-2. The protons of the 4-pyridyl derivative **(16)** appeared as two symmetrical doublets at δ= 7.85 and 8.7 ppm for H-3; H-5 and H-2, H-6 respectively.

The α,β-unsaturated carbonyl derivative **(17a-m)** were prepared by reaction of the appropriate aldehydes with acetophenone derivatives in presence of NaOH.[15-17]

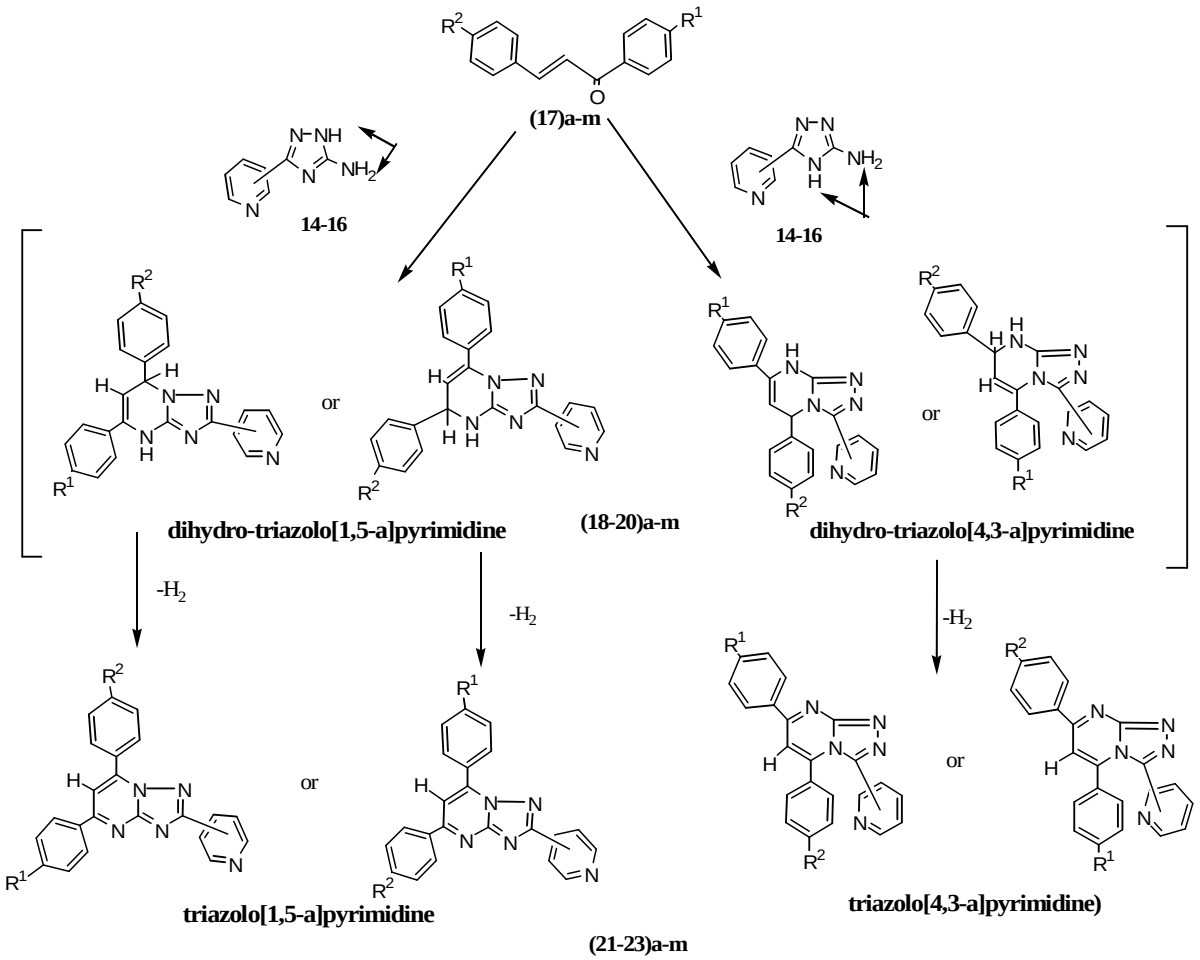
For the synthesis of the target compounds **(21-23)a-m** the reactions outlined in scheme 2 were applied. Thus equimolar amounts of 3-amino-5-(2-,3-, or 4-pyridyl)-1,2,4-triazoles **(14-16)** and the appropriate chalcone derivative **(17a-m)** were reacted in ethylene glycol at 220-230° to produce the 5,7-diaryl-2-pyridyl-1,2,4-triazolopyrimidines **(21-23)a-m** in good yields. Alternatively, fusion of the starting amine with the respective chalcone at 260° resulted also in formation of the same products but in fairly lower yields than the aforementioned method**.** The physical constants, yields and elemental analyses data of the synthesized compounds are summerized in Tables 1-3

As illustrated in Scheme 2, the cyclocondensation of the 3-amino-5-pyridyl-1,2,4-triazoles **(14-16)** with the α,β-unsaturated ketones **(17a-m)** was ambiguous leading oftenly to a mixture of isomeric 1,2,4-triazolopyrimidines. Wheather the initial attack of the chalcone **(17)** proceeded at the NH of the ring or at the exocyclic amino group,should remain an open question. However, depending on the regioselectivity of the ring closure reactions, the prepared compounds could possess up to four different isomers[18] and might exist as dihydro intermediates **(18-20)a-m**; scheme 2; which upon elimination of hydrogen;would lead to the more stable 5,7-diaryl-2-pyridyl-1,2,4-triazolopyrimidines **(21-23)a-m**.

The formation of dihydropyrimidine intermediates **(18-20)a-m** during the cyclo-condensation reaction has been detected throughout the fusion of the amines with chalcone analogues. As representative examples, the 4,7-dihydro-5,7-diphenyl-2-(3-pyridyl)-1,2,4-triazolo[1,5-a]pyrimidine **(19a)** as well as 5-(4-bromophenyl) analogue **(19c)** were isolated after 3-5 minutes of the fusion of the aminotriazole derivative **(15)** and the chalcones **(17a)** and **(17c)** respectively. The physical constants and elemental analyses of the two isolated dihydro-intermediates **(19a)** and **(19c)** are summerized in experimental section. Their structures were ascertained by comparison with the unsaturated 5,7-diphenyl-2-(3-pyridyl)-1,2,4-triazolo[1,5-a]pyrimidine **(22a)** and **(22c)** on basis of the elemental analyses, ^{1}H-NMR and MS.

The ^{1}H-NMR spectra of the dihydroproduct **(19a)** is characterized by the presence of the signals of H-6 and H-7 protons as a pair of doublets at δ= 6.7 and 5.4 ppm, respectively. This pattern was not observed in the spectra of the corresponding aromatic derivatives **(22a)**. In addition a signal at δ= 9.6 ppm characteristic for the NH proton has been observed. The mass spectrum of 4,7-dihydro-5,7-diphenyl-2-(3-pyridyl)-1,2,4-triazolo[1,5-a] pyrimidine **(19a)** revealed the molecular ion peak at m/z 351; 53% and the base peak at m/z 274; 100%.

The structure of the target compounds **(21-23)a-m** was determined by spectroscopic methods. The IR spectra were characterized by some general features such as strong absorption band within the frequency values ranging from 1590-1610 cm^{-1}, that resulting from the C-N stretching vibrations of triazolopyrimidine nucleus. In addition there were some other



Scheme 2

characteristic bands of variable intensities at 1530; 1510; 1420 cm^{-1} due to the bending vibrations of the C-N bonds and also weak to moderate bands at 1375; 1115; 1075 cm^{-1} of the C-C stretching and bending vibrations of the aryl and triazolopyrimidine skeleton. Specific bands of the respective substituents on the phenyl moieties of the synthesized compounds such as those at ν values ranging from 3270-3290 cm^{-1} due to hydroxyl groups and at ν values= 810; 760 and 690 cm^{-1} of the p-substituted phenyl nucleus were also observed. In case of the dihydro triazolopyrimidine derivatives **(19a)** and **(19c)** a strong sharp peak at ν= 3470 cm^{-1} appeared indicating the stretching vibrations of the NH group.

The ^{1}H-NMR spectra illustrated a single set of signals for each compound that might indicate the existence of only one isomer either of the 1,2,4-triazolo[1,5-a]pyrimidine or 1,2,4-triazolo[4,3-a]pyrimidine series. This observation could be supported on basis of the reported thermal as well as acidic rearrangement of triazolo[4,3-a]pyrimidines to the corresponding triazolo[1,5-a]pyrimidine analogues.[19] Consequently, it could be assumed that the intermediates **(18–20)a-m** as well as the final products **(21 –23)a-m** would be existing as [1,5-a] isomeric form.

The characteristic signals in ^{1}H-NMR spectra of the synthesized compounds are listed in Tables 4-6. The signals characteristic for 2-pyridyl moiety **(21a-m**; Table 4**)** are observed at chemical shifts, δ-values: 7.8 (1H, t, J= 8Hz, H-4); 8.45 (1H, d, J= 8.0, H-3); 8.8 (1H, d, J= 4.6 Hz,H-6). The signal of H-5 is not differentiated from the multiplet of the other aromatic protons of the 5- and 7- diaryl

substituents within the range of 8.4-7.9. In case of 3-pyridyl series **(22a-m**; Table 5**)**, the signal of the 3-pyridyl nucleus appeared at δ-values: 8.55 (1H, d, H-4); 8.7 (1H, d, H-6) 9.6 (1H, s, H-2). The 4-pyridyl moiety in the third series **(23a-m**; Table 6**)**, showed the two characteristic AB system at chemical shift 8.5 (2H, d, H-2,6) and that of H-3 and H-5 incorporated within the multiplet of other aromatic protons. The characteristically differentiated signals for other moieties are observed in ^{1}H-NMR spectra of compounds **(21-23)d** at δ = 3.9 (3H, s, OCH_3); compounds **(21-23)e** at δ = 2.33 (3H, s, CH_3); **(21-23)f** at δ = 10.2 (1H, s, OH); and compounds **(21-23)l** at δ = 3.15 (6H, s, CH_3).

Biological evaluation

The synthesized compounds were tested against seven bacterial strains and twelve fungal species. The method described by Kwon-Chungand and Bennet[20] was adopted where the tested compounds were allowed to diffuse readily from wells into the medium inoculated with the microorganism. Amoxycillin was used as a reference for comparison of the antibacterial activity and clotrimazole was used in case of antifungal screening.

The results presented in Table 7 revealed that, the tested compounds exhibited lower antibacterial activity than the reference drug. most derivatives having 2-pyridyl moiety **(21a-m**) were more effective against *G-positive* bacteria such as *B. cereus, M. roseus, Streptomyces spp*, and *S.aureus* than the corresponding analouges of the 3-pyridyl **(22a-m)** and 4-pyridyl **(23a-m)**. The most active compounds within this series were compounds **(21a-c and h)** bearing phenyl, p-chlorophenyl, p-bromophenyl at C-5 and p-chlorophenyl at C-7 of the triazolopyrimidine nucleus. On the other hand the p-hydroxyphenyl derivative **(21f)** showed good activity against *S. aureus* although it had a week or no activity against the remaining organism.

Some of the tested 3-pyridyl series **(22a-m)**, specially those having electron donating substituents on the phenyl nucleus, exhibited antibacterial activity against *S. marscens*. The 4-pyridyl analogues (**23a-m)** exhibited scattered weak activity against some *G-positive* and *G-negative* bacteria, so that no general pattern could be observed. The most active compounds were (**23b**, **h**, **i**, and **m)**, which contain p-chlorophenyl at C-5, p-chlorophenyl, p-bromophenyl, and p-flourophenyl at C-7. None of the tested compounds showed any activity against the Gram negative (*E. coli and P. aeroginosa*). All of the tested fungi were found to be not sensitive for any of the tested compound.

REFERENCES

1- N. Nakanishi, T. Kojima, T. Fujimoto and S. Mitsuhashi, Prog. Drug Res., 38, 19 (1992).

2- P. W. Mark and B. C. James, Ann. Rep. Med. Chem., 2**0**, 145 (1985).

3- L. Doub, Ann. Rep. Med. Chem., 4, 109 (1969).

4- G. R. Revankar, R. T. Matthews and R. K. Robins., J. Med. Chem., 18, 1253 (1975).

5- A.M. Abdelal, M. M. Gineinah and M. M. S. Kheira, Med. Chem. Res., 9, 277 (1999).

6- M. A. E. Shaban, A. Z. Nasr and A. E. A. Morgan, Pharmazie, 55, 87 (2000).

7- A.A. Hassan, N. K. Mohamed, A. A. Aly and A. F. E. Mourad, Pharmazie, 52, 23 (1997).

8- M. A. El-Sherbeny, M. B. El-Ashmawy, H. I. El-Subbbagh, A. A. El-Emam and F. A. Badria, Eur. J. Med. Chem.**,** 30, 445 (1995).

9- V. J. Ram., Indian J. of Chem.**,** 27B**,** 825 (1988).

10- M. S. Desenko, V. V. Lipson, O. V. Shishkin, S. A. Komykhov, V. D. Orlov, E. E. Lakin and V. P. Kuzentsov, J. Heterocyclic Chem., 36, 205 (1999).

11- A.A. Abdel-Hafez, H. A. El-sherief, J. Michiko, K. Masahiko, S. Kimiyasu, K. Takuya, O. Toru, N. Norio and M. Hattori, Arzneim-Forsch Drug Res., 52, 833 (2002).

12- C. A. Lipinski, J. Med. Chem.**,** 26, 1 (1983).

13- C. A. Lipinski, J. L. LaMattina and L. A. Hohnke, J. Med. Chem.**,** 28, 1628 (1985).

14- T. Hirata, Li-M. H. Twanmo, B. H. Wood, A. Golden and J. S. Driscoll, J. Het. Chem., 9, 99 (1972).

15- D. N. Dhar, Chemistry of Chalcones and Related Compounds, Wiley; New York (1981).

16- D. G. Batt, R. Goodman, D. G. Jones, J. S. Kerr, L. R. Mantegna, C. McAllister, R. C. Newton, S. Nurnberg, P. K.Welch and M. B. Covington, J. Med. Chem.**,** 36, 1434 (1993).

17- C. K. Bradsher, F. C. Brown, W. B. Blue, J. Am. Chem. Soc.**,** 71, 3570 (1959).

18- J. Reiter, L. Pongo, and P. Dydrtsak, Tetrahedron**,** 43, 2497 (1987).

19- E. S. H. El-Ashry and N. Rashed, Advanced Het. Chem., Katritzky A. R. (Ed.), 72, 127 (1999).

20- K. J. Kwon-Chung and J. E. Bennett, Medical Mycology, 1st ed, Lea and Febeiger Philadelphia, (1992).