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A high-atom economic and one-pot facile synthesis of active antimicrobial 2,4-disubstituted aryl-2*H*-pyrido / pyrimido[1,2-a]pyrimidines scafffold: a Michael addition approach

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ABSTRACT

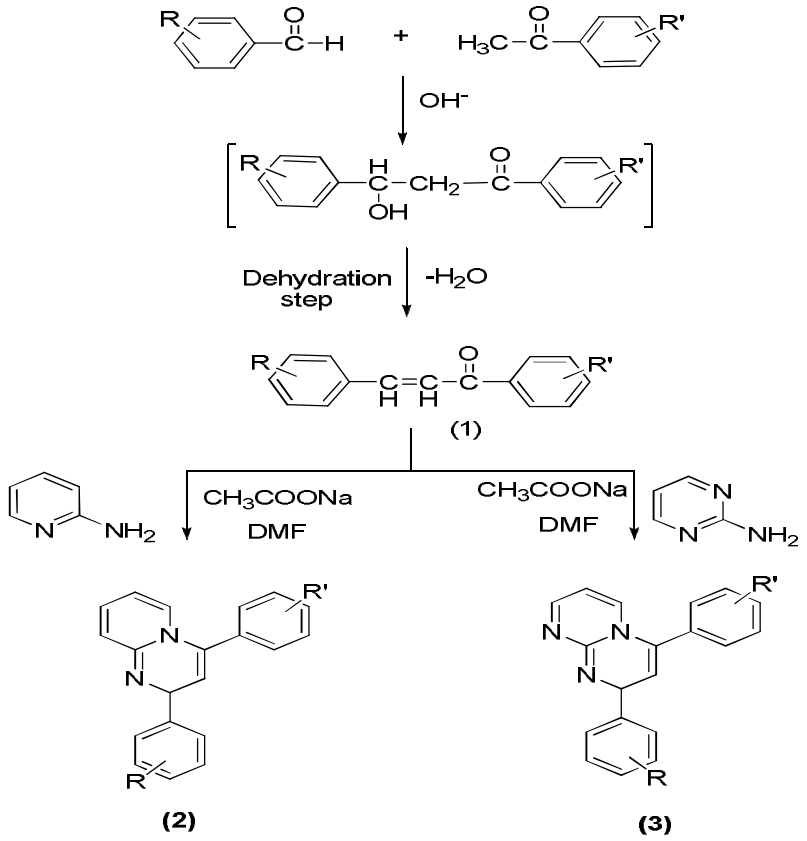
*An one–pot, efficient and high-atom economic protocol involving Michael addition between chalcone(**1a-g**) and 2-aminopyridine/2-aminopyrimidine in presence of sodium acetate and DMF for the synthesis of 2,4-disubstituted aryl-2H- pyrido/pyrimido [1,2-a] pyrimidines (**2**) and (**3**) was developed. The structures of the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR spectral data and elemental analysis. All these compounds were screened for their antibacterial and antifungal activities. The results were compared with standard drugs tested under similar conditions. Some of these compounds showed promising antimicrobial activities*

Keywords: Michael addition, Antibacterial activity, antifungal activity, Pyrido-/pyrimido-pyrimidines.

INTRODUCTION

Pyridine and pyrimidine ring systems are ubiquitous structural components of naturally occurring alkaloids, biologically active synthetic molecules and organic fine chemicals. These structural motif have been extensively used in heterocyclic chemistry from the chemical, biological and medicinal point of view [1-4] **.**The high therapeutic properties of the compounds incorporating nitrogen heterocycles have encouraged the medicinal chemists to synthesize large numbers of novel therapeutic agents [5–8]. In addition, the applications of nitrogen heterocycles as toxic agents into the cell wall of pathogenic microorganism have evoked considerable attention during the last twenty years [9–11].Several fused heterocyclic systems, incorporating a pyrimidine ring in their structures, play important roles as analgesic [12], antihypertensive [13],antiviral [14], anti-inflammatory[15], antioxidant [16], antiplatelet [17], and hepatoprotective [18] agents. Pyrimido-pyrimidines, an important class of nitrogen-containing heterocycles, occupy a unique place in medicinal chemistry owing to their wide spectrum of clinical applications [19–20].Many analogues of pyrimido[4,5-d]pyrimidine have been reported to display a substantial level of inhibitory action against the tyrosine-kinase domain of epidermal growth factor receptor [21] and have potential applications in cancer therapy [22–23]. A perusal of the literature has revealed manifold implications of pyridopyrimidines. eg., pyrido[1,2-b]pyrimidine systems show antifungal[24-26], pyrido[2,3-d]pyrimidines were found to have strong biological activities [27–28]. Therefore, it was thought of interest to design a system which combines bio-labile nuclei; pyridine and

pyrimidine fused together in a molecular framework to see their additive effect on antimicrobial power. Owing to the chemical, biological and medicinal interest, substituted pyrido /pyrimido [1,2- a] pyrimidines appear to be an attractive scaffold for exploiting chemical diversity and generating a drug like library to screen for lead candidates of drug discovery. Hetero Michael additions, *viz.*aza- Michael, thia-Michael *etc.* are the most exploited organic reactions and are the mainstay of efficient synthetic tools for the construction of druggable heterocyclic scaffolds and natural products. Construction of molecular architecture by two or more bond formation in one-step operation via Michael reaction has been one of the current interests in synthetic organic chemistry .We have explored the scope of Michael annulations for the synthesis of biologically active heterocyclic systems in our earlier investigations.[29-30]. Therefore, we thought it of interest to utilize Michael addition reaction further, for the construction of these titled scaffolds. The toxicity, side effects, and resistance of common pathogens to standard drugs play important roles in treatment failure [31–32]. Therefore, searching for new antimicrobial agents with specific activity, possibly acting through mechanism, which are distinct from those of well-known classes is of prime interest.



Scheme-1

The above facts coupled with our desire to develop efficacious antimicrobial agents and in continuation of our work on fused heterocycles with biological interest [33–35], prompted us to device an efficient, one – pot, high atom economic and convenient synthetic method of hitherto unknown and novel title compounds 2,4- diaryl pyrido / pyrimido[1,2-a]pyrimidines(**2)** and(**3)** involving Michael annulations. The antibacterial and antifungal results of newly synthesized compounds are reported in this paper.

MATERIALS AND METHODS

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 8201 PC Spectrophotometer (ν_{max} in cm^{-1}), ^1H NMR and ^{13}C NMR spectra in DMSO-d_6 on a Bruker DRX–300 (300 MHz) spectrometer using TMS as a internal reference (Chemical shifts in δ, ppm). All the reagents used were AR grade; analyses were performed on an elemental Vario EL III Carlo Erba 1108 C H N analyzer. Elemental (C, H, N) analysis data are within the acceptable limits (±0.4%) between calculated and observed values. The purity of compounds was checked by thin layer chromatography on silica gel plate using ether and ethyl acetate as solvents and iodine chamber was used as a developing chamber.

Preparation of 1,3-diaryl-2-propenones (chalcones):
These were prepared according to standard reported method [36].

2,4-Disubstituted aryl-2*H*-pyrido[1,2-a]pyrimidines. (Genaral procedure): A mixture of 1,3-diarnyl-2-propenone (0.01M), 2-aminopyridine (0.01M) and sodium acetate(0.01M) in dimethyl formamide (10mL) was refluxed for 2-3hrs. The reaction mixture was cooled and poured into crushed ice. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from appropriate solvents. The physical and characterization data of compounds thus prepared are as under.

2a. 4-(4-Fluorophenyl)-2-p-tolyl-2*H*-pyrido[1,2-a]pyrimidine : Yield: (65%), light yellow solid (EtOH); m.p 135^{0}C;IR: 3020(C-H arom), 2930 (C-H aliph), 1610(C=N), 1462(C=C)cm^{-1}; ^1H NMR (DMSO-d6): δ =6.92-7.85(m, 12H, H-arom), 5.02(d,1H, C3 proton of pyrimidine ring), 3.4(d, 1H, C2 proton of pyrimidine ring), 2.31(s, 3H, CH_3 proton);^{13}C NMR (δ ppm):21.3, 63.2, 91.7, 112.2, 115.4, 122.4, 128.0, 128.9, 131.5, 135.4, 135.7, 138.2, 158.9, 162.1 Anal.clacd for $C_{21}H_{17}FN_2$: C,79.72; H,5.42; N,8.85; Found C,78.10; H,4.79; N,8.06

2b. 4-(4-Chlororophenyl)-2-(4-hydroxy phenyl)-2*H*-pyrido[1,2-a]pyrimidin-2-yl)pyrimidine : Yield: (70%), light brown solid (EtOH); m.p 140^{0}C;IR: 3010(C-H arom), 1615(C=N), 1440(C=C)cm^1; ^1H NMR (DMSO-d6): δ =6.63-7.80(m, 12H, H-arom), 5.12(d,1H, C3 proton of pyrimidine ring), 3.2(d, 1H, C2 proton of pyrimidine ring), 5.35(s, 1H, OH proton);^{13}C NMR (δ ppm): 63.2, 91.7, 112.2, 115.8, 120.4, 128.0, 128.9, 130.5, 133.4, 133.8, 134.6, 135.5, 136.3, 138.8, 155.5, 158.9 Anal.clacd for$C_{20}H_{15}ClN_2O$: C,71.75; H,4.52; N,8.37; Found C,70.08; H,4.24; N,7.78

2c. 4-(4-Chlororophenyl)-2-(4-methoxyphenyl)-2*H*-pyrido[1,2-a]pyrimidine : Yield: (72%), white solid (EtOH); m.p 143^{0}CIR: 3005(C-H arom), 1615(C=N), 1440(C=C), 950(C-O-C)cm^{-1}; ^1H NMR (DMSO-d6): δ =6.89-7.76(m, 12H, H-arom), 6.08-7.40(3H, furan ring proton) 5.07(d,1H, C3 proton of pyrimidine ring), 3.0(d, 1H, C2 proton of pyrimidine ring);^{13}C NMR (δ ppm): 61.0, 91.7, 106.7, 110.1, 112.5, 120.2, 122.4, 128.1, 129.4, 133.5,134.5, 135.6, 138.8, 142.1, 152.3, 158.4

2d. 4-(4-Methoxy phenyl)-2-(phenyl)-2*H*-pyrido[1,2-a]pyrimidine : Yield: (63%), white solid (EtOH); m.p 136^{0}C,IR: 3005(C-H arom), 2910 (C-H aliph), 1610(C=N), 1450(C=C) cm^{-1}; ^1H NMR (, DMSO-d6): δ =6.84-7.86(m, 12H, H-arom), 5.07(d,1H, C3 proton of pyrimidine ring), 3.83(3H, OCH_3 proton) 3.0(d, 1H, C2 proton of pyrimidine ring);^{13}C NMR (δ ppm): 55.8, 63.0, 91.7, 112.5, 114.2, 120.2, 122.4, 128.1, 129.4, 130.0, 133.5, 133.9, 134.5, 135.6, 138.8, 157.6, 158.9

2e. 2-(4-Fluorophenyl)-4-(phenyl)-2*H*-pyrido[1,2-a]pyrimidine : Yield: (72%), Light yellow solid (EtOH); m.p 135^{0}C;IR: 3015(C-H arom), 1610(C=N), 1450(C=C)cm^{-1}; ^1H NMR (DMSO-d6): δ =6.98-7.69(m, 13H, H-arom), 5.07(d,1H, C3 proton of pyrimidine ring), 3.0(d, 1H, C2 proton of pyrimidine ring);^{13}C NMR (δ ppm): 63.0, 91.7, 112.5, 115.6, 122.4, 127.5, 128.3, 128.9, 129.4, 130.6, 135.0, 135.5,

136.8, 138.8, 158.9, 160.8. Anal.clacd for $C_{20}H_{15}FN_2$ (302.12): C,79.54; H,5.00; N,9.27; Found C,79.20; H,4.90; N,9.03

2f. 4-(2-Chlorophenyl)- 2-phenyl-2*H*-pyrido[1,2-a]pyrimidine : Yield: (56%), colourless solid (EtOH); m.p 131^0C;IR: 3015(C-H arom), 1610(C=N), 1445(C=C) cm^{-1};^{1}H NMR (DMSO-d6): δ =7.20-7.95(m, 13H, H-arom), 5.02(d,1H, C3 proton of pyrimidine ring), 3.1(d, 1H, C2 proton of pyrimidine ring);^{13}C NMR (δ ppm): 63.0, 91.7, 112.5, 122.4, 125.5, 126.2, 126.8, 127.8, 128.2, 128.9, 129.3, 129.9, 131.3, 135.2, 135.8, 138.8, 141.3, 158.9. Anal.clacd for $C_{20}H_{15}ClN_2$ (318.09): C,75.35; H,4.74; N,8.79; Found C,75.12; H,4.50; N,8.56

2g. 2-(2-Fluorophenyl)-4-phenyl-2*H*-pyrido[1,2-a]pyrimidine : Yield: (56%), yellow solid (EtOH); m.p 137^0C; IR: 3015(C-H arom), 1610(C=N), 1445(C=C) cm^{-1}.^{1}H NMR (, DMSO-d6): δ =7.14-7.96(m, 13H, H-arom), 5.02(d,1H, C3 proton of pyrimidine ring) 3.1(d, 1H, C2 proton of pyrimidine ring)'^{13}C NMR (δ ppm): 63.0, 91.7, 112.5, 115.4, 121.9, 122.4, 124.1, 125.5, 126.2, 127.7, 128.2, 128.9, 129.5, 135.7, 138.6, 141.5, 156.8, 158.9. Anal.clacd for $C_{20}H_{15}FN_2$ (302.12): C,79.45; H,5.00; N,9.27; Found C,79.07; H,4.86; N,9.05

2,4-Disubstituted aryl-(2*H*)-pyrimido[1,2-a]pyrimidines.(General procedure): A mixture of 1,3-diaryl-2-propenone (0.01M), 2-aminopyrimidine (0.01M) and sodium acetate (0.01M) in DMF (20mL) was refluxed for about 2-3 hrs. The resulting mixture was cooled and poured in to cold water. The precipitate thus obtained was filtered, washed, dried and recrystallized from appropriate solvents. The physical and characterization data of compounds thus prepared are as under

3a. 4-(4-Chloro phenyl)-2-(p-tolyl)-2*H*-pyrimido[1,2-a]pyrimidine: Yield: (69%), brown solid (aq ethanol); m.p.167^0C; IR: 3020(C-H arom), 2900 (C-H aliph), 1605(C=N), 1450(C=C) cm^{-1}, ^{1}H NMR (DMSO-d6): δ =7.01-8.0(m,11H, H-arom), 5.0(d,1H, C3 proton of pyrimidine ring), 3.22(d, 1H, C2 proton of pyrimidine ring), 2.32(s, 3H, CH_3 proton);^{13}C NMR (δ ppm): 21.4, 61.0, 91.1, 102.2, 125.4, 128.4, 126.8, 129.1, 131.1, 131.6, 135.3, 137.5, 138.6, 139.3, 153.6, 163.8 Anal. Calcd. for $C_{20}H_{16}ClN_3$: C,71,96; H4.83; N,12.59; Found C,71.60; H,5.0; N,12.34.

3b. 4-(4-Chlorophenyl)-2-(2-hydroxyl phenyl)-2*H*-pyrimido[1,2-a]pyrimidine: Yield: (79%), white solid (aq ethanol); m.p.180^0C; IR: 3020(C-H arom), 2915 (C-H aliph), 1605(C=N), 1465(C=C) cm^{-1} ^{1}H NMR (DMSO-d6): δ =7.0-8.0(m,11H, H-arom), 5.12(d,1H, C3 proton of pyrimidine ring), 3.20(d, 1H, C2 proton of pyrimidine ring), 4.12(s, 3H, OCH_3 proton);^{13}C NMR (δ ppm): 55.6,91.0, 102.6, 125.1, 128.5, 126.5, 129.2, 131.5, 131.7, 135.7, 137.6, 138.2, 139.1, 153.5, 163.5 Anal. Calcd. for $C_{19}H_{14}ClN_30$: C,67.97, H4.20; N,10.56; Found C,67.63; H,4.12; N,10.54.

3c. 4-(4-Chloro phenyl)-2-(p-tolyloxy)-2*H*-pyrimido[1,2-a]pyrimidine: Yield: (76%), brown solid (aq ethanol); m.p.167^0C; IR: 3025(C-H arom), 2910 (C-H aliph), 1605(C=N), 1455(C=C) cm^{-1} ^{1}H NMR (DMSO-d6): δ =7.0-8.0(m,11H, H-arom), 5.0(d,1H, C3 proton of pyrimidine ring), 3.22(d, 1H, C2 proton of pyrimidine ring), 2.32(s, 3H, CH_3 proton);^{13}C NMR (δ ppm): 21.4, 61.0, 91.1, 102.2, 125.4, 128.4, 126.8, 129.1, 131.1, 131.6, 135.3, 137.5, 138.6, 139.3, 153.6, 163.8 Anal. Calcd. for $C_{20}H_{16}ClN_3O$: C,69,96; H4.53; N,12.19; Found C,70.20; H,4.49; N,12.0.

3d. 2-(4-Methoxyphenyl)-4-(phenyl)-2*H*-pyrimido[1,2-a]pyrimidine: Yield: (70%), yellow solid (EtOH); m.p 149^0C;IR: 3015(C-H arom), 2950 (C-H aliph), 1605(C=N), 1445(C=C)cm^{-1};^{1}H NMR (DMSO-d6): δ =7.01-8.1(m,12H, H-arom), 5.0(d,1H, C3 proton of pyrimidine ring), 3.75(s, 3H, OCH_3 proton), 3.2(d, 1H, C2 proton of pyrimidine ring), ^{13}C NMR (δ ppm): 55.6, 60.7, 91.4, 102.5, 114.2, 127.4, 128.4, 129.3, 130.7, 134.1, 135.1, 136.3, 138.6, 139.3, 153.4, 157.9, 164.8; Anal. calcd. for $C_{20}H_{17}N_3O$: C,76.17; H,5.43; N,13.32; Found C,76.01; H,5.48; N,13.19

3e. 2-(4-Chlorophenyl)-4-(phenyl)-2*H*-pyrimido[1,2-a]pyrimidine : Yield: (71%), brown solid (EtOH); m.p 143^{0}C**;**IR: 3025(C-H arom), 1605(C=N), 1445(C=C)cm^{-1}.^{1}H NMR (DMSO-d6): δ =7.21-8.02(m,12H, H-arom), 5.11(d,1H, C3 proton of pyrimidine ring), 3.19(d, 1H, C2 proton of pyrimidine ring)**;** ^{13}C NMR (δ ppm): 60.4, 91.2, 102.3, 120.6, 125.2, 125.9, 128.4, 129.3, 133.7, 134.6, 135.5, 138.6, 141.3, 153.4, 164.8 ;Anal. calcd. for $C_{19}H_{14}ClN_3$; C,71.36; H,4.41; N,13.14; Found C,71.20; H,4.27; N,13.01

3f. 2-(4-Chlorophenyl)-4 (2-Chlorophenyl)-2*H*-pyrimido[1,2-a]pyrimidine : Yield: (70%), light brown solid (EtOH); m.p 153^{0}C;IR: 3035(C-H arom), 1615(C=N), 1450(C=C)cm^{-1}.^{1}H NMR (DMSO-d6): δ =7.19-8.04(m,11H, H-arom), 5.16(d,1H, C3 proton of pyrimidine ring), 3.23(d, 1H, C2 proton of pyrimidine ring); ^{13}C NMR (δ ppm): 60.7, 91.5, 102.6, 120.5, 128.2, 130.9, 131.7, 133.7, 134.6, 135.5, 138.8, 139.6, 153.7, 163.8. Anal. calcd. for $C_{19}H_{13}Cl_2N_3$; C,64.42; H,3.70; N,11.86; Found C,64.0 ; H,4.0; N,11.21.

3g. 4-phenyl-2-(p-tolyl-2*H*-pyrimido[1,2-a]pyrimidine : Yield: (80%), light brown solid (EtOH); m.p 150 ^{0}C;IR: 3025(C-H arom), 2920 (C-H aliph), 1605(C=N), 1452(C=C)cm^{-1};^{1}H NMR (DMSO-d6): δ =7.01-8.0(m,12H, H-arom), 5.04(d,1H, C3 proton of pyrimidine ring), 3.2(d, 1H, C2 proton of pyrimidine ring), 2.35(s, 3H, CH_3 proton);^{13}C NMR (δ ppm): 21.7, 61.2, 91.5, 102.0, 127.4, 128.4, 129.3, 130.1, 134.1, 135.2, 136.3, 137.5, 138.6, 139.3, 153.6, 163.8 Anal. Calcd. for $C_{20}H_{17}N_3$: C,80.24; H,5.72; N,14.04; Found C,80.01; H,5.60; N,13.90.

RESULTS AND DISCUSSION

The newly designed compounds have been synthesized as given in Scheme 1. The chalcones **1** were used as valuable intermediates for the preparation of the title compounds. In fact, these compounds with an α,β-unsaturated ketonic (-CH=CH-CO-) function in their structure served as activated alkenes, used as a component of Michael addition. These chalcones when condensed with 2-aminopyridine/2-aminopyrimidine in presence of sodium acetate furnished the final products **2a-g** and **3a-g** via the spontaneous cyclodehydration of Michael adducts which have not been isolated .The structures of the final products have been confirmed by elemental and spectral (IR, ^{1}HNMR & ^{13} CNMR) data. The IR: spectrum of **2a** gave peaks at 3020(C-H arom), 2915 (C-H aliph), 1605(C=N), 1465(C=C) cm^{-1}; ^{1}H NMR (DMSO-d6): δ =7.0-8.0(m,11H, H-arom), 5.12(d,1H, C3 proton of pyrimidine ring), 3.20(d, 1H, C2 proton of pyrimidine ring), 4.12(s, 3H, OCH_3 proton); while^{13}C NMR gave signals at 55.6,91.0, 102.6, 125.1, 128.5, 126.5, 129.2, 131.5, 131.7, 135.7, 137.6, 138.2, 139.1, 153.5, 163.5ppm .Similar pattern of spectral results were also obtained for 2,4-disubstituted aryl-2*H*-pyrimido[1,2-a]pyrimidines (**3a-g**).

The results of antibacterial testing revealed that all tested compounds showed moderate to good antibacterial activity .Compound **2f** and **2c**, belong to pyrido-pyrimidine scaffold showed promising activity against, *E.coli* and *P.aeruginosa* while three compounds *viz*: **3c, 3e** and **3f** belonging to pyrimido-pyrimidines scaffold ,showed more promising activity on these bacterial strains. The activity of compound **3f** is nearly comparable with the standard drug ciprofloxacin. The screening data of antifungal activity of this series of **c**ompounds show moderate activity. The compounds **2c** and **2f,** belong to pyrido-pyrimidines and compounds **3c** and **3f** belonging to pyrimido-pyrimidine scaffold possess notable activity on the both tested fungi. The most active compound is **2f**, which inhibit 80 % of fungal growth. The data of antimicrobial activity also revealed that compounds having polar substituent like, chloro and methoxy, imparts much toward antimicrobial power in this series of compounds. The results of the antifungal and antibacterial studies are listed in Table-1 and Table-2 respectively.

APPLICATIONS

In order to see the applicability of these newly synthesized compounds, we have tested them on biological screen. These compounds have been evaluated for their following two type of activity.

Antifungal screening: The newly synthesized compounds were screened for their antifungal activity against two species of fungi *viz. Aspergilus Flavus* and *Candida albicans* in DMSO by poisoned food technique [37]. The desired amount of the test material was taken in pre sterilized, cold petriplates having 0.5 ml of acetate and 9.5 ml of the molten medium, the petriplates were moved in round fashion to get a homogenous mixture of the contents. In the control set, 9.5 ml of the medium, 0.5 ml of acetone and distilled water equal in amount to the test material were taken; when the medium solidified one mycelial disc of the inoculums was aseptically inoculated upside down in the centre of each assay plate which were then incubated. The visual colony diameter of the test fungi in each assay was noted in mutually perpendicular direction at intervals of 24 hours up to 168 hours (i.e 7 days). The diameter of the inoculated fungal disc was subtracted from the apparent colony diameter to represent the mycelial growth. On the basis of growth recorded on 7th day of incubation, the fungicidal activity of test compounds was calculated in terms of present inhibition using the following formula.

$$\% \text{ inhibition of mycelial growth} = \frac{dc\text{-}dt}{dc} \times 100$$

dc = Average diameter growth of the colony in control set on 7th day of incubation.
dt = Average diameter growth of the colony in treatment set on 7th day of incubation.

A commercial drug, Dithane M-45 was also tested under similar conditions to compare the results of tested compounds. The data for the antifungal studies are listed in table -1.

Table-1: Antifungal activity data of 2,4-diaryl-2H-pyrido/pyrimido[1,2-a]pyrimidines

Comp. No	R	R'	Percent Mycelial Inhibition (Compound dose in ppm)					
			A. Flavus			*C. Albicans*		
			10	100	500	10	100	500
9a	4-CH_3	4-F	28	40	57	30	39	55
9b	2-OH	4-Cl	33	45	66	32	51	68
9c	4-OCH_3	4-Cl	35	48	75	36	57	79
9d	4-OCH_3	H	30	42	58	27	45	55
9e	4-F	H	26	40	51	27	47	52
9f	H	2-Cl	38	50	72	39	64	75
9g	2-F	H	25	39	50	27	50	59
10a	4-CH_3	4-Cl	32	47	67	31	59	73
10b	2-OH	4-Cl	28	40	56	30	51	60
10c	4-OCH_3	4-Cl	35	50	75	36	63	76
10d	4-OCH_3	H	29	40	58	27	42	55
10e	4-Cl	H	30	43	68	32	59	70

10f	4-Cl	2-Cl	38	50	80	39	65	79
10g	4-CH_3	H	25	39	50	27	50	59
Dithane M-45			50	60	100	50	76	100

Antibacterial studies: The newly synthesized heterocyclic compounds were screened in vitro for their antibacterial activity against *Escherichia coli* as example of gram-negative bacteria and *Bacillus subtilis* as example of gram-positive bacteria by the disc diffusion method [38]. The bacterial strains were sub cultured in broth agar and incubated for 18hr at 37^0C and then freshly prepared bacterial cells were spread onto nutrient agar plate in a laminar flow cabinet. Sterilized paper disks (6.0 mm in diameter) were placed on the nutrient agar plates. 5 Mg of each test compounds were dissolved in 1 mL of dimethylsulfoxide (DMSO)separately to prepare stock solution. From stock solution, different concentrations 10, 100, and 500ppm of each compound were prepared. Thus, proper amounts of the different concentrations of compounds were pipetted on the blank disks, which were placed on the plates. The plates were incubated at 37^0C for 24hr. DMSO was used as a solvent control to ensure that solvent had no effect on bacterial growth. Ciprofloxacin was designated in our experiment as a control drug. The results of antibacterial activity data is given in table -2.

Table-2: Antibacterial activity data of 2,4-diaryl-2*H*-pyrido/pyrimido[1,2-a]pyrimidines

Comp. No	**R**	**R'**	**Percent Mycelial Inhibition (Compound dose in ppm)**					
			E. coli			***P. aeruginosa***		
			10	**100**	**500**	**10**	**100**	**500**
9a	4-CH_3	4-F	28	40	57	30	39	55
9b	2-OH	4-Cl	33	45	66	32	51	68
9c	4-OCH_3	4-Cl	39	48	76	37	60	75
9d	4-OCH_3	H	30	42	58	27	45	55
9e	4-F	H	26	40	51	27	47	52
9f	H	2-Cl	36	50	72	39	64	75
9g	2-F	H	25	39	50	27	50	59
10a	4-CH_3	4-Cl	39	49	70	38	60	74
10b	2-OH	4-Cl	36	43	62	34	59	65
10c	4-OCH_3	4-Cl	41	51	78	40	65	77
10d	4-OCH_3	H	34	45	69	33	43	70
10e	4-Cl	H	39	49	73	37	62	77
10f	4-Cl	2-Cl	43	53	83	44	70	86
10g	4-CH_3	H	31	43	61	29	52	61
Ciprofloxacin			50	60	100	50	76	100

CONCLUSIONS

We have developed an efficient ,high atom economic and one-pot synthetic protocol for novel 2,4-disubstitutedphenyl pyrido/pyrimido[1,2-a]pyrimidine scaffold (**2**) and (**3**) to evaluate their antimicrobial properties. The results of antimicrobial screening suggest that their activity is dependent on the nature of substituent on aryl ring. Polar substituent, e.g. Cl , -OH and -OCH_3 imparts much towards antimicrobial power of this series of compounds. This work is important, since it offers the possibility to find new compounds being more efficacious drugs against bacteria and fungi; for them, a thorough investigation regarding the structure-activity relationship, toxicity, and their biological effects is essential. This could be helpful in designing more potent antimicrobial agents for therapeutic use.

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