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Studies on Synthesis Characterisation and Antimicrobial activity of Pyrimidine based derivatives

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Abstract: - m-phenoxy benzaldehydes react with 4-methoxy acetophenone to form chalcone which is treated with thiaourea to form pyrimidine. Pyrimidine react with substituted N-1,3-benzothiazole-2-yl-2-chloro acetamide gives title compounds. The structures of all the synthesized compounds have been confirmed by elemental analysis and spectral data. The synthesized compounds have been tested for their antibacterial activity.
Keywords: Pyrimidine, Benzthiazole, Antimicrobial activity.

INTRODUCTION

Nitrogen and sulphar containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. Pyrimidine and their derivatives are considered to be important for drugs and agricultural chemicals. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities[1]. The synthesis of substituted pyrimidine and many detailed review have been appeared[2, 3].

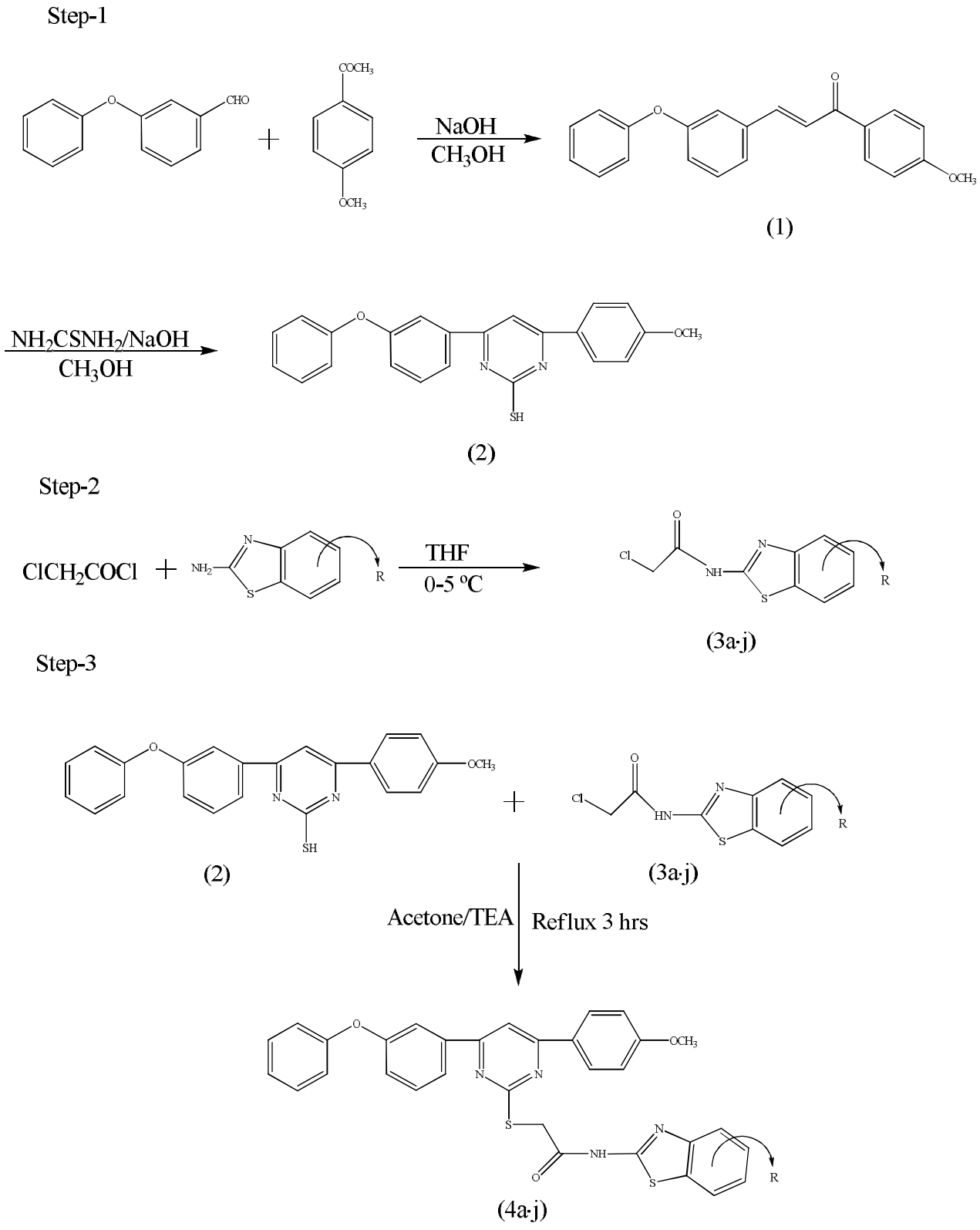
Pyrimidine derivatives possess several interesting biological activities such as antitumor[4-7], antiviral[8], antifungal, anticancer[9], antibcteria[10], antiinflammator[11-14], analgesic[15], antagonist[16-17], antifolate[18], antimicrobial[19], anti-HIV[20], atiproliferative[21], antiplatelet[22], antithrombotic[22], antifilarial[23] activites, etc.

Moreover benzothiazole[24-26] is other important pharmacodynamic heterocyclic nuclei which when incorporated in different heterocyclic templets have been possess wide spectrum of activities.

The literature study reveals that both pyrimidine and benzthiazole are an important pharmacophor and exhibits out standing biological activities. Encourage by these observation, we synthesized a new series of pyrimidine derivatives by incorporating the benzthiazole moiety in the hope of obtaining better antimicrobial activity agent. All the synthesized compounds have been screened for their antimicrobial activities.

EXPERIMENTAL

General Procedures: Laboratory Chemicals were supplied by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was monitored by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene: ethyl acetate (7.5:2.5). The spots were observed by exposure to iodine vapour or by UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H-NMR & ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in $CDCl_3$. Elemental analysis of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer.


Step-1
NaOH
CH3OH
(1)
NH2CSNH2/NaOH
CH3OH
(2)
Step-2
ClCH2COCl
THF
0-5 ºC
(3a-j)
Step-3
(2)
(3a-j)
Acetone/TEA
Reflux 3 hrs
(4a-j)

Scheme

Step-1 :

Synthesis of 1-(4-methoxyphenyl)-3-(3-phenoxy-phenyl) prop-2-en-1-one (1) : To a solution of 3-phenoxy benzaldehyde (0.01 mol) and 4-methoxyacetophenone (0.01 mol) in ethanol (25 mL)) cooled at 5- 10 ^{0}C was added aqueous sodium hydroxide (70 %, 5mL) drop wise with constant stirring. The reaction mixture was further stirred for 2h and left over night. The reaction mixture was neutralized with concentrated hydrochloric acid, and then the solid separated was collected and crystallized from suitable solvent to get the chalcone derivatives with 80-95 % yield. mp. 178-180 ºC, IR (KBr): 1511, 1649, 2840, 2917, ^{1}H NMR ($CDCl_3$) δ ppm; 3.81 (s,3H,-OCH_3), 6.65-6.67 (d,1H,-CO-CH), 7.38-7.41 (d, 1H,=CH-Ar) 7.02-8.32 (m, 13H,Ar-H) ; ^{13}C NMR (40 MHz, DMSO-d_6): δ 54.43, 113.83, 114.50, 116.32, 118.17, 118.63, 121.54, 121.93, 128.37, 128.69, , 130.63, 131.78, 133.89, 143.48, 157.02, 159.38, 165.36, 189.14. Mass (*m/z*): 330. Anal. (%) for $C_{22}H_{18}O_3$, Calcd. C, 79.98; H,5.49; Found: C, 79.95; H, 5.83.

Synthesis of 4-(4-methoxyphenyl)-6-(3-phenoxy phenyl) pyrimidine-2-thiol (2) : A mixture of 1-(4-methoxyphenyl)-3-(3-phenoxyphenyl)prop-2-en-1-one(0.01 mole), thiourea (0.01 mol) and sodium hydroxide (0.01 mole) in methanol (25 mL) was refluxed for 8h. After the completion of reaction, the resultant mixture was cooled to room temperature. Separated compound was filtered, washed with water, dried and crystallized from methanol get title compound with 80 % yield. mp. 162-164 ºC, IR (KBr): 1177, 1625, 2846, 2928, ^{1}H NMR ($CDCl_3$) δ ppm; 8.89 (s,1H, NH), 3.81 (s,3H,-OCH_3), 7.08-8.11 (m, 14H,Ar-H) ; ^{13}C NMR (40 MHz, DMSO-d_6): δ 55.13, 113.83, 114.50, 109.76, 116.63, 118.48, 118.87, 121.54, 121.89, 128.37, 128.69, , 129.63, , 136.09, 157.80,165.64, 160.58, 164. 63, 181.14. Mass (*m/z*): 386. Anal. (%) for $C_{23}H_{18}N_2O_2S$, Calcd. C, 71.48; H 4.69; N 7.25; Found: C, 71.55; H, 4.83; N 7.43.

Step-2 :

General method for the Preparation of N-(benzo[d]thiazol-2-yl)-2-chloroacetamide (3a-j) :

In conical flask take 0.01 mole substituted benzothiazole in 25 ml benzene and stirring it for 30 min in ice-bath till temp below 0-5 ^{0}C then add drop by drop 0.01 mole chloroacetyle chloride in conical flask within 2h. After complete addition reflux it for 2h in water bath then cool it and evaporate it and collect comp. Recrystalliaztion from alcohol afforded yield 88% of yellow needles, IR (KBr): 752, 1728, 3345, ^{1}H NMR ($CDCl_3$) δ ppm 9.21 (s,1H, NH), 7.54-8.27 (m, 4H,Ar-H) ; ^{13}C NMR (40 MHz, DMSO-d_6): δ 43.67, 118.31, 121.89, 124.55, 125.32,130.67, 153.41, 165.42, 174.47. Mass (*m/z*): 226. Anal. (%) for $C_{23}H_{18}N_2O_2S$, Calcd. C, 47.69; H 3.11; N 12.36; Found: C, 47.55; H, 3.18; N 12.43.

Step-3 :

General method for synthesis of 2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)-N-(substitutedbenzo[d]thiazol-2-yl) acetamide(4a-j) : In R.B.F take 0.01 mole 4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidine-2-thiol in 25ml acetone then add 0.01 mole substituted N-(1,3-benzothiazole-2yl)-2-chloro acetamide and add 2-3 drop TEA as a catalyst and reflux it for 3h then cool it and fall out in ice precipitate come out filter it and recrystalliaztion from alcohol.

N-(6-chlorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxy phenyl)-6-(3-phenoxyphenyl) pyrimidin 2-ylthio)acetamide (4a). Yield 71%, mp. 112-115 ºC, IR (KBr): 3175, 2917, 2840, 1690, 1602, 1530, 745, 695. ^{1}H NMR ($CDCl_3$) δ ppm; 9.45 (s,1H, -NH), 3.78 (s,3H,-OCH_3), 4.67 (s,2H,-CH_2), 6.70-8.10 (m, 17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 38.82, 55.87, 107.33, 114.35, 115.14, 116.49, 118.31, 118.96, 119.37, 120.39, 121.62, 123.64, 124.28, 125.48, 126.15, 127.74, 128.21, 128.58, 129.28, 130.19, 131.38, 132.83, 136.46, 151.33, 157.70, 159.35, 160.16, 164.71, 165.86, 168.24, 172.63, 174.95. Mass (*m/z*): 610. Anal. (%) for $C_{33}H_{24}N_3O_3S_2$, Calcd. C, 64.96; H,3.96; N,6.89; Found: C, 64.95; H, 3.93; N, 6.83.

2-(2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)acetamido) benzo[d]thiazole-6-sulfonic acid (4b). Yield 70%, mp. 201-204 ºC, IR (KBr): 3172, 2919, 2845, 1687, 1606, 1533, 1354, 1163, 692. ^{1}H NMR ($CDCl_3$) δ ppm; 9.36 (s,1H, -NH), 3.86 (s,3H,-OCH_3), 4.78 (s,2H,-CH_2), 7.05-8.46 (m, 17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 38.15, 55.43, 107.42, 114.98, 115.24, 116.74, 118.21, 118.56, 119.84, 120.19, 121.84, 122.14, 123.98, 125.17, 126.32, 127.45, 128.15, 129.86, 130.21, 131.06, 136.22, 140.82, 156.83, 157.04, 159.49, 160.42, 164.53, 165.83, 168.86, 172.30, 174.39. Mass (*m/z*): 656. Anal. (%) for $C_{32}H_{24}N_5O_2S$, Calcd. C, 58.52; H,3.68; N,8.53; Found: C, 58.55; H, 3.63; N, 8.58.

N-(6-acetamidobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)acetamide (4c). Yield 69%, mp. 177-180 ºC, IR (KBr): 3176, 2986, 2922, 2842, 1697, 1665, 1612, 1538, 693. ^{1}H NMR ($CDCl_3$) δ ppm; 9.46 (s,1H, NH), 3.72 (s,3H,-OCH_3), 4.76 (s,2H,-CH_2), 6.86-8.20 (m,

17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 24.06, 38.82, 55.87, 107.13, 110.61, 114.21, 115.83, 11602, 117.16, 117.53, 118.94, 119.28, 120.26, 123.75, 124.36, 126.81, 127.64, 128.01, 128.74, 130.76, 131.42, 131.22, 136.76, 137.08, 148.11, 157.32, 159.86, 160.54, 164.65, 165.32, 168.04, 168.42, 172.14, 174.72. Mass (*m/z*): 633. Anal. (%) for $C_{34}H_{27}N_5O_4S_2$, Calcd. C, 64.44; H,4.29; N,11.05; Found: C, 64.42; H, 4.28; N, 11.03.

2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)-N-(6-methylbenzo [d]thiazol-2-yl)acetamide (4d). Yield 78%, mp. 129-132 ºC, IR (KBr): 3170, 2914, 2840, 1694, 1602, 1532, 696. ^{1}H NMR ($CDCl_3$) δ ppm; 2,34 (s,3H,-CH_3), 9.28 (s,1H,-NH), 3.78 (s,3H,-OCH_3), 4.64 (s,2H,-CH_2), 6.52-8.46 (m,17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 20.92, 38.75, 55.26, 107.42, 114.64, 115.46, 116.97, 117.42, 118.67, 119.55, 120.75, 121.13, 123.43, 124.08, 125.54, 126.53, 127.27, 128.28, 128.27, 130.71, 130.67, 131.06, 134.76, 136.84, 150.53, 157.11, 159.64, 160.76, 164.97, 165.15, 168.02, 172.33, 174.64. Mass (*m/z*): 590. Anal. (%) for $C_{33}H_{26}N_4O_3S_2$, Calcd. C, 67.10; H,4.44; N,9.48; Found: C, 67.05; H, 4.38; N, 9.43.

N-(benzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamide (4e). Yield 72%, mp. 204-207 ºC, IR (KBr): 3172, 2918, 2842, 1690, 1608, 1537, 695. ^{1}H NMR ($CDCl_3$) δ ppm; 9.38 (s,1H,- NH), 3.83 (s,3H,-OCH_3), 4.57 (s,2H,-CH_2), 7.16-8.52 (m, 18H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 37.42, 55.43, 107.48, 114.04, 115.74, 116.13, 118.26, 118.32, 119.65, 120.29, 121.18, 123.42, 124.07, 125.37, 126.73, 127.19, 128.85, 128.29, 129.53, 130.32, 131.54, 132.64, 136.20, 153.17, 157.52, 159.67, 160.01, 164.32, 165.87, 168.42, 172.79, 174.02. Mass (*m/z*): 576. Anal. (%) for $C_{32}H_{24}N_4O_3S_2$, Calcd. C, 66.65; H,4.19; N,9.72; Found: C, 66.65; H, 4.18; N, 9.78.

N-(6-methoxybenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin -2-ylthio)acetamide (4f). Yield 80%, mp. 140-143 ºC, IR (KBr): 3176, 2913, 2838, 1696, 1604, 1534, 692. ^{1}H NMR ($CDCl_3$) δ ppm; 9.48 (s,1H, NH), 3.83 (s,3H,-OCH_3), 4.68 (s,2H,-CH_2), 6.86-8.14 (m, 17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 39.43, 54.11, 57.93, 104. 43, 107.33, 111.64, 114.49, 115.14, 116.49, 118.31, 118.96, 119.37, 120.39, 123.64, 124.28, 126.15, 127.74, 128.21, 128.58, 130.19, 131.38, 132.83, 136.46, 145.33,156.26, 157.70, 159.35, 160.16, 164.71, 165.86, 168.15, 172.41, 174.05. Mass (*m/z*): 606. Anal. (%) for $C_{33}H_{26}N_4O_4S_2$, Calcd. C, 65.33; H,4.32; N,9.23; Found: C, 65.35; H, 4.38; N, 9.28.

2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)-N-(6-nitrobenzo[d]thiazol -2-yl)acetamide (4g). Yield 81%, mp.131-134 ºC, IR (KBr): 3178, 2911, 2846, 1686, 1617, 1603, 1532, 1373, 696. ^{1}H NMR ($CDCl_3$) δ ppm; 9.26 (s,1H, NH), 3.74 (s,3H,-OCH_3), 4.46 (s,2H,-CH_2), 7.14-8.64 (m, 17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 37.02, 56.36, 106.32, 114.22, 115.87, 116.41, 118.05, 119.77, 120.31, 121.14, 122.06, 123.74, 124.97, 125.53, 126.84, 127.09, 128.61, 128.72, 129.04, 130.11, 131.75, 132.79, 136.94, 147.18, 157.36, 159.66, 160.17, 164.87, 165.21, 168.76, 172.32, 174.29. Mass (*m/z*): 621. Anal. (%) for $C_{32}H_{22}N_5O_5S_2$, Calcd. C, 61.82; H,3.73; N,11.27; Found: C, 61.82; H, 3.78; N, 11.23.

N-(4,6-dichlorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)acetamide (4h). Yield 75%, mp. 182-185 ºC, IR (KBr): 3172, 2920, 2842, 1692, 1603, 1530, 743, 692. ^{1}H NMR ($CDCl_3$) δ ppm; 9.32 (s,1H, NH), 3.66 (s,3H,-OCH_3), 4.58 (s,2H,-CH_2), 6.64-8.12 (m, 16H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 39.74, 54.32, 107.64, 114.87, 115.32, 116.76, 118.01, 119.76, 120.14, 121.54, 123.98, 124.21, 125.55, 126.27, 126.19, 127.88, 128.36, 128.92, 130.05, 131.36, 132.57, 136.32, 143.76, 145.38, 151.28, 157.89, 159.43, 160.21, 164.24, 165.85, 168.14, 172.52, 174.71. Mass (*m/z*): 644. Anal. (%) for $C_{32}H_{22}N_4O_3S_2Cl_2$, Calcd. C, 59.33; H,3.43; N,8.68; Found: C, 59.29; H, 3.48; N, 8.64.

N-(4,6-dinitrobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin -2-ylthio)acetamide (4i). Yield 79%, mp. 167-170 ºC, IR (KBr): 3175,2917, 2843, 1689, 1614, 1601, 1530, 1368, 695. ^{1}H NMR ($CDCl_3$) δ ppm; 9.46 (s,1H, NH), 3.64 (s,3H,-OCH_3), 4.63 (s,2H,-CH_2), 6.78-8.26 (m, 16H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 38.82, 53.43, 107.83, 114.50, 115.99, 116.32, 118.73, 118.63, 119.77, 120.82, 121.54, 123.32, 124.27, 125.28, 126.19, 127.38, 128.37, 128.69, 129.14, 130.63, 131.78, 132.89, 136.17, 143.48, 151.47, 157.02, 159.38, 160.48, 164.88, 165.36, 168.02, 172.81, 174.14. Mass (*m/z*): 666. Anal. (%) for $C_{32}H_{22}N_6O_7S_2$, Calcd. C, 57.65; H,3.33; N,12.62; Found: C, 57.65; H, 3.38; N, 12.63.

N-(6-fluorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)acetamide (4j). Yield 70%, mp. 186-189 ºC, IR (KBr): 3177, 2909, 2846, 1698, 1612, 1532, 1254,

687. ^{1}H NMR ($CDCl_3$) δ ppm; 9.41 (s,1H, NH), 3.70 (s,3H,-OCH_3), 4.52 (s,2H,-CH_2), 7.06-8.36 (m, 17H,Ar-H); ^{13}C NMR (40 MHz, DMSO-d_6): δ 38.23, 52.47, 105.33, 107.16, 114.59, 115.24, 116.65, 113.98, 118.04, 119.76, 120.13, 123.76, 124.34, 125.14, 126.54, 127.31, 128.56, 128.72, 130.08, 131.43, 132.17, 136.32, 148.87, 157.70, 158.21, 159.39, 160.72, 164.14, 165.64, 168.03, 172.29, 174.83. Mass (*m/z*): 570. Anal. (%) for $C_{30}H_{23}N_4O_3S_2F$, Calcd. C, 63.14; H, 4.06; N, 9.82; Found: C, 63.12; H, 4.08; N, 9.83.

BIOLOGICAL ACTIVITY

Minimum inhibitory concentration (MIC) of all the synthesized compounds was determined against four different strains, viz two Gram positive bacteria (*S. aureus & S. pyogenes* and two Gram negative bacteria (*E. coli & P. aeruginosa*) compared with standard drugs ampicillin, chloramphenicol, ciprofloxacin, & norfloxacin by broth dilution method.[27] Antifungal activities against *C. albicans*, and *A. niger* organisms were compared with standard drugs nystatin and greseofulvin by same method. We have synthesized N-(substituted[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)acetamide.
which showed some of them to have excellent activity against Gram positive and Gram negative bacteria.

ANTIBACTERIAL ACTIVITY

From screening results, compounds **4f** possesses very good activity against gram +ve and gram –ve bacteria compared with standard drugs. In detail the compounds **4b, 4d** and **4e** have good activity against E. coli and *S.Aureus*. Compound **4c** &**4h** against *P.aeruginosa* and Compound **4b** against *S. pyogenus* have found good activity. The remaining compounds displayed moderate to poor activities against all four bacterial species.

ANTIFUNGAL ACTIVITY

Antifungal screening data showed that Compound **4b** & **4h** show highly promising activity against *C. albicans*. Compound **4g** possessed excellent activity against *A.niger*. The remaining compounds of the series exhibited only moderate to poor activity.

CONCLUSIONS

Our present investigation is centered on the studies of reactions, synthesis, spectral analysis and biological activities of Pyrimidine based benzthiazole derivatives. The procedure proved more profitable than those previously reported in the literature. Some compounds were found effective as antibacterial and antifungal agents.

Table 1. Antimicrobial activity of compounds 4a-4i

Comp.	Minimal Bactericidal Concentration ug /ml				Minimal Fungicidal Concentration ug/ml	
	Grame -ve		Grame +ve			
	E.Coli	***P. aeruginosa***	***S.aureus***	***S. pyogenus***	***C.albicans***	***A.niger***
4a	**100**	250	200	250	500	1000
4b	**62.5**	200	**100**	**100**	**200**	250
4c	250	**100**	200	250	500	500
4d	**50**	200	**100**	250	**250**	500
4e	200	500	250	500	500	1000
4f	**25**	**50**	**100**	**50**	500	250
4g	500	500	250	500	**250**	**200**
4e	**50**	**100**	**100**	125	500	500
4h	500	500	250	250	**200**	**250**
4i	**100**	250	500	200	500	**250**
Ampicillin	100	100	250	100	-	-
Chloramphenicol	50	50	50	50	-	-
Ciprofloxacin	25	25	50	50	-	-
Norfloxacin	10	10	10	10	-	-
Nystatin	-	-	-	-	100	100
Greseofulvin	-	-	-	-	500	100

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