Synthesis, characterization and biological effects of a few novel pyrimidine derivatives

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Abstract

Pyrimidine and its derivatives are crucial in the domains of pharmaceuticals and agricultural chemicals. In recent decades, numerous pharmacological studies have been conducted on Pyrimidine and its derivatives. However, further research is essential to address the need for biological compounds. "Chalcone is an aromatic compound that serves as the central core for various biological compounds. Chalcone is produced through an aldol condensation of 4-methoxy acetophenone with m-phenoxy benzaldehydes, utilizing a catalyst that is subsequently treated with thiourea to yield Pyrimidine. The Pyrimidine, when treated with substituted N-1,3-benzothiazole-2-yl-2-chloro amide, results in a compound". Elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR), M.P. and TLC using silica gel G are employed to assess the purity of the compounds. All synthesized compounds were evaluated against four distinct strains, specifically two Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and were compared with standard antibiotics such as ampicillin, chloramphenicol, ciprofloxacin and norfloxacin. Additionally, all synthesized compounds were tested against *Candida albicans* and *Aspergillus niger*, with analyses conducted alongside standard antifungal agents nystatin and griseofulvin. This paper emphasizes the reactions, synthesis, spectral analysis, and microbial activities of pyrimidine-based benzothiazole derivatives. The methodology presented demonstrates superior results compared to previously published literature. Several of the compounds exhibited significant efficacy as antimicrobial and antifungal agents.

Keywords- Antimicrobial activity; Benzothiazole; Pyrimidine

Introduction

Nitrogen and sulfur-containing heterocyclic compounds have garnered significant attention due to their extensive applications in pharmacological activity. Pyrimidine and its derivatives are crucial in the domains of pharmaceuticals and agricultural chemicals. Pyrimidine serves as a fundamental nucleus in DNA and RNA; it is linked to numerous biological activities [1]. The synthesis of substituted pyrimidines has been extensively reviewed in the literature [2,3].

Pyrimidine and its derivatives are well-regarded in the field of inorganic synthetic chemistry. Although pyrimidine itself is not found in nature, its various derivatives are widely distributed. The derivatives of pyrimidine attract attention due to their pharmacological properties which include antitumor [4-7], antiviral [8], antifungal, anticancer [9], antibacterial [10], anti-inflammatory [11-14], analgesic [15], antagonist [16,17], antifolate [18], antimicrobial [19], anti-HIV [20], antiproliferative [21], antiplatelet [22], antithrombotic [22] and antifilarial [23] activities etc.

Furthermore, benzothiazole [24-26] serves as an essential alternative pharmacodynamic heterocyclic nucleus, which, when integrated into various heterocyclic frameworks, currently demonstrates

a broad range of activities. The review of existing literature indicates that both pyrimidine and benzothiazole represent significant pharmacophores and display remarkable biological activities. Motivated by these findings, we have synthesized a new series of pyrimidine derivatives by incorporating the benzothiazole moiety, aiming to achieve enhanced antimicrobial activity. All synthesized compounds have undergone screening for their antimicrobial properties.

Experimental

General Procedure

Laboratory chemicals were supplied by Across and Ficher Scientific Ltd. Melting points were assessed using the open tube capillary method and are inaccurate. The purity of the compounds was evaluated using thin layer chromatography (TLC) plates (silica gel G) within the solvent system of toluene: ethyl acetate (7.5:2.5). The spots were detected through exposure to iodine vapors or UV light. The IR spectra were obtained using a PerkinElmer 1720 FT-IR spectrometer (KBr pellets). The ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker Advance II 400 spectrometer utilizing TMS as the internal standard in $CDCl_3$. Elemental analysis of the newly synthesized compounds was conducted using a Carlo Erba 1108 analyzer. The synthesis of the compounds follows the Scheme 1 provided below.

Step-1

Synthesis of 1-(4-methoxyphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one

The mixture of 4-methoxyacetophenone (0.01 mol.) and 3-phenoxy benzaldehyde (0.01 mol.) in 25 ml of ethyl alcohol. After cooling to between 5 and 10 °C, aqueous sodium hydroxide (70%, 5 millilitres) was added dropwise while being constantly stirred. After two more hours of stirring, the reaction mixture was left overnight. After neutralising the mixture with concentrated hydrochloric acid, the separated solid was collected and crystallised from an appropriate solvent to yield 85–90% chalcone derivatives. mp. 178–180 °C, IR (KBr): 1511, 1649, 2840, 2917; ^{1}H NMR ($CDCl_3$) δ ppm; 3.82 (s, 3H, -OCH_3), 6.63-6.65 (d, 1H, -CO-CH_3), 7.38-7.41 (d, 1H, =CH-Ar) and 7.02-8.32 (m, 13H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): δ 54.43, 113.83, 114.50, 116.32, 118.17, 118.63, 121.54, 121.90, 128.37, 128.69, 130.63, 131.78, 133.89, 143.48, 157.02, 159.38, 165.36, 189.14. Mass (*m/z*): 333. Anal. (%) for $C_{22}H_{18}O_3$, Calcd. C, 79.95; H, 5.45; Found: C, 79.93; H, 5.80.

Synthesis of 4-(4-methoxyphenyl)-6-(3-phenoxy phenyl) pyrimidine-2-thiol

For eight hours, a combination of 1-(4-methoxyphenyl)-3-(3-phenoxyphenyl) prop-2-en-1-one (0.01 mol), thiourea (0.01 mol), and sodium hydroxide (0.01 mol) in 25 ml of methyl alcohol was refluxed. The resulting mixture cooled to room temperature when the process was finished. The chemical had an 82% yield after being separated, filtered, cleaned with water, dried, and crystallised with methyl alcohol. mp. 160-162 °C, IR (KBr): 1175, 1625, 2846, 2928, ^{1}H NMR ($CDCl_3$) δ ppm; 8.83 (s, 1H, NH), 3.81 (s,

3H, -OCH_3), 7.08-8.11 (m, 14H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): δ 55.13, 113.83, 14.50, 109.76, 116.63, 118.48, 118.87, 121.54, 121.89, 128.37, 128.69, 129.63, 160.58, 164.63, 181.14; Mass (*m/z*): 386; Anal. (%) for $C_{23}H_{18}N_2O_2S$, Calcd. C, 71.46; H 4.67; N 7.23; Found: C, 71.53; H, 4.81; N 7.41.

Step-2

General method for the preparation of N-(benzo[d]thiazol-2-yl)-2-chloroacetamide (3aej)

Add 0.01 mol of substituted benzothiazole to 25 ml of benzene in a conical flask, mix for 30 minutes in an ice bath until the temperature drops below 0.5 °C and then add 0.01 mol of chloroacetyl chloride drop by drop at intervals of two hours. Once the addition is finished, reflux it in a water bath for two hours before cooling, evaporating, and collecting the compound. IR (KBr): 752, 1728, 3345; ^{1}H NMR ($CDCl_3$) δ ppm 9.20 (s, 1H, NH), 7.53-8.26 (m, 4H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): δ 43.67, 118.31, 121.89, 125.32, 130.67, 153.41, 165.42 and 174.47. Mass (*m/z*): 226. Anal. (%) for $C_{23}H_{18}N_2O_2S$, cald.: C, 47.67; H, 3.10; N 12.34; found: C, 47.53; H, 3.16; N 12.41.

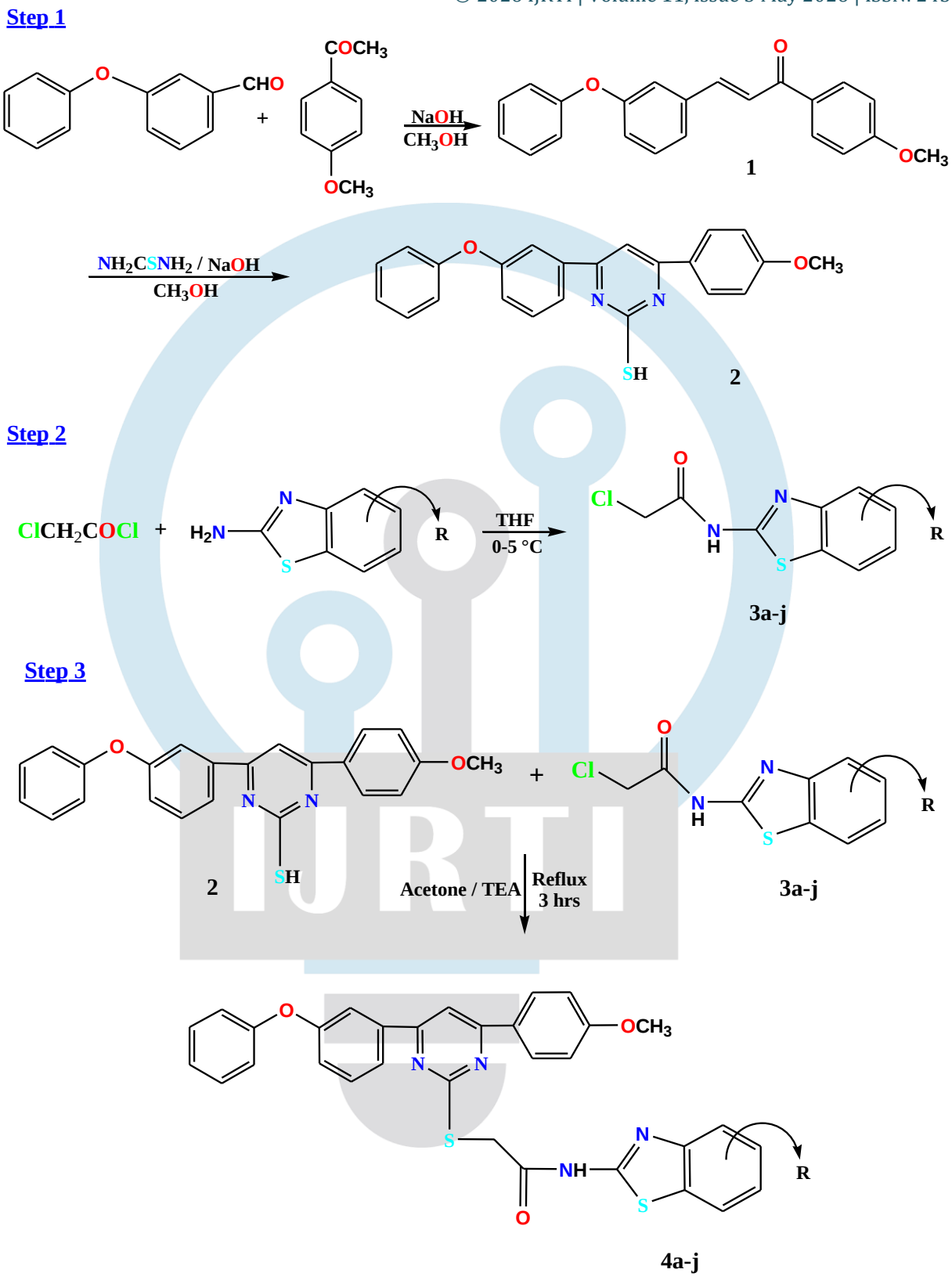
Step-3

General method for synthesis of 2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio)-N-(substituted benzo[d]thiazol-2-yl) acetamide(4aej)

In R.B.F., take 0.01 mol of 4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidine-2-thiol in 25 millilitres of acetone, add 0.01 mol of substituted N-(1,3-benzothiazole-2yl)-2-chloro acetamide, add 2 drops of TEA as a catalyst and reflux for three hours, cool, precipitate, filter and recrystallise from alcohol.

N-(6-chlorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxy phenyl)-6-(3-phenoxyphenyl) pyrimidin 2-ylthio)acetamide (4a)

Yield 70%, mp. 110-113 °C, IR (KBr): 3175, 2917, 2840, 1690, 1602, 1530, 745, 695. ^{1}H NMR ($CDCl_3$) δ ppm; 9.44 (s, 1H, -NH), 3.78 (s, 3H, -OCH_3), 4.65 (s, 2H, -CH_2), 6.70-8.10 (m, 17H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): 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, 130.18, 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, 3.91; N, 6.83.



Scheme 1 Reaction scheme of synthesized compounds

2-(2-(4-(4-Methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)acetamido)benzo[d]thiazole-6-sulfonic acid (4b)

Yield 69%, mp. 201-204 °C, IR (KBr): 3172, 2917, 2845, 1687, 1605, 1533, 1354, 1163, 692. ^{1}H NMR ($CDCl_3$) δ ppm; 9.35 (s, 1H, -NH), 3.85 (s, 3H, -OCH_3), 4.76 (s, 2H,-CH_2), 7.03-8.43 (m, 17H, Ar-

H); ^{13}C NMR (40 MHz, DMSO-d6): 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, 58.50; H, 3.66; N, 8.53; Found: C, 58.55; H, 3.64; N, 8.58.

N-(6-Acetamidobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio) acetamide (4c)

Yield 68%, mp. 177-180 °C, IR (KBr): 3176, 2986, 2922, 2842, 1697, 1665, 1612, 1538, 693. ^{1}H NMR ($CDCl_3$) δ ppm; 9.45 (s, 1H, NH), 3.70 (s, 3H, -OCH_3), 4.75 (s, 2H, -CH_2), 6.85-8.20 (m, 17H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): 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, 136.74, 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, 64.43; H, 4.28; N, 11.04; Found: C, 64.40; H, 4.26; N, 11.02.

2-(4-(4-Methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)-N-(6-methylbenzo [d]thiazol-2-yl) acetamide (4d)

Yield 79%, mp. 128-130 °C, IR (KBr): 3170, 2914, 2840, 1694, 1602, 1532, 696. ^{1}H NMR ($CDCl_3$) δ ppm; 2.32 (s, 3H, -CH_3), 9.26 (s, 1H, -NH), 3.76 (s, 3H, -OCH_3), 4.62 (s, 2H, -CH_2), 6.50-8.44 (m, 17H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): δ 20.90, 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, 131.04, 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*): 589. Anal. (%) for $C_{33}H_{26}N_4O_3S_2$, Calcd. C, 67.08; H, 4.42; N, 9.46; Found: C, 67.04; H, 4.37; N, 9.42.

N-(Benzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamide (4e)

Yield 70%, mp. 203-205 °C, IR (KBr): 3170, 2916, 2840, 1690, 1608, 1537, 695. ^{1}H NMR ($CDCl_3$) δ ppm; 9.36 (s, 1H, -NH), 3.82 (s, 3H, -OCH_3), 4.56 (s, 2H, -CH_2), 7.15-8.51 (m, 18H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): 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, 130.30, 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*): 575. Anal. (%) for $C_{32}H_{24}N_4O_3S_2$, Calcd. C, 66.64; H, 4.19; N, 9.71; Found: C, 66.64; H, 4.11; N, 9.76.

N-(6-Methoxybenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamide (4f)

Yield 82%, mp. 140-142 °C, IR (KBr): 3176, 2913, 2838, 1696, 1604, 1534, 692. ^{1}H NMR ($CDCl_3$) δ ppm; 9.49 (s, 1H, NH), 3.82 (s, 3H, -OCH_3), 4.67 (s, 2H, -CH_2), 6.85-8.15 (m, 17H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): 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*): 605. Anal. (%) for $C_{33}H_{26}N_4O_4S_2$, Calcd. C, 65.31; H, 4.30; N, 9.21; Found: C, 65.33; H, 4.36; N, 9.26.

2-(4-(4-Methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)-N-(6-nitrobenzo[d]thiazol-2-yl) acetamide (4g)

Yield 80%, mp.130-133 °C, IR (KBr): 3178, 2911, 2846, 1686, 1615, 1603, 1532, 1373, 696. ^{1}H NMR ($CDCl_3$) δ ppm; 9.25 (s, 1H, NH), 3.75 (s, 3H, -OCH_3), 4.46 (s, 2H, -CH_2), 7.14-8.64 (m, 17H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): 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, 131.73, 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, 61.80; H, 3.71; N, 11.25; Found: C, 61.82; H, 3.76; N, 11.21.

N-(4,6-Dichlorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl) pyrimidin-2-ylthio) acetamide (4h)

Yield 73%, mp. 180-183 °C, IR (KBr): 3172, 2920, 2842, 1692, 1603, 1530, 743, 692. ^{1}H NMR ($CDCl_3$) δ ppm; 9.30 (s, 1H, NH), 3.64 (s, 3H, -OCH_3), 4.58 (s, 2H, -CH_2), 6.62-8.12 (m, 16H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): δ 39.72, 54.30, 107.62, 114.87, 115.30, 116.74, 118.01, 119.74, 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, 160.22, 164.24, 165.85, 168.14, 172.52, 174.72. Mass (*m/z*): 642. Anal. (%) for $C_{32}H_{22}N_4O_3S_2Cl_2$, Calcd. C, 59.31; H, 3.41; N, 8.66; Found: C, 59.27; H, 3.46; N, 8.62.

N-(4,6-Dinitrobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamide (4i)

Yield 79%, mp. 167-171 °C, IR (KBr): 3175, 2917, 2843, 1689, 1614, 1601, 1530, 1368, 695. ^{1}H NMR ($CDCl_3$) δ ppm; 9.44 (s, 1H, NH), 3.62 (s, 3H, -OCH_3), 4.61 (s, 2H, -CH_2), 6.76-8.24 (m, 16H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): 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, 132.87, 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, 57.63; H, 3.33; N, 12.60; Found: C, 57.63; H, 3.38; N, 12.61.

N-(6-Fluorobenzo[d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio) acetamide (4j)

Yield 68%, mp. 185-188 °C, IR (KBr): 3176, 2910, 2846, 1696, 1612, 1530, 1254, 685. ^{1}H NMR ($CDCl_3$) δ ppm; 9.40 (s, 1H, NH), 3.71 (s, 3H, -OCH_3), 4.50 (s, 2H, -CH_2), 7.05-8.35 (m, 17H, Ar-H); ^{13}C NMR (40 MHz, DMSO-d6): δ 38.22, 52.45, 105.32, 105.16, 114.58, 115.22, 116.65, 113.96, 118.03, 119.75, 120.12, 123.75, 124.34, 125.14, 126.54, 127.31, 128.56, 128.72, 130.06, 131.42, 132.17, 136.32, 148.85, 157.70, 158.20, 159.38, 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, 63.12; H, 4.04; N, 9.80; Found: C, 63.10; H, 4.06; N, 9.81.

Biological activity

The Minimum Inhibitory Concentration (MIC) for all synthesized compounds was evaluated against four distinct strains, specifically two Gram-positive bacteria (Staphylococcus aureus and Streptococcus pyogenes) and two Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa), utilizing standard pharmaceuticals including ampicillin, chloramphenicol, ciprofloxacin, and norfloxacin through various dilution techniques. Antifungal efficacy against Candida albicans and Aspergillus niger was assessed with established antifungal agents nystatin and griseofulvin employing the same methodological approach. We have synthesized N-(substituted [d]thiazol-2-yl)-2-(4-(4-methoxyphenyl)-6-(3-phenoxyphenyl)pyrimidin-2-ylthio)acetamide, which exhibited remarkable activity against both Gram-positive and Gram-negative bacteria, as presented in Table 1.

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

Compounds	Minimal bactericidal concentration ug/ml				Minimal fungicidal concentration ug/ml	
	Gram -ve		Gram +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**
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

- The characters in red and bold show the antimicrobial activity of the synthesized compounds like **4f** possesses excellent activity against gram +ve and gram -ve bacteria compared with standard drugs.
- The compounds **4b**, **4d** and **4e** have sensible activity against *E. coli* and *S. aureus*.
- Compound **4c** and **4h** against *P. aeruginosa* and
- Compound **4b** against *S. pyogenes* have found sensible activity.
- The remaining compounds displayed average to poor activities against all four bacterial species.
- The antifungal screening of the synthesized Compounds **4b** and **4h** show extremely promising against *C. albicans*.
- Compound **4g** possessed excellent activity against *A. niger*.
- The rest of the compounds of the series exhibited average to poor activity.

Antimicrobial activity

Based on the screening outcomes, compound 4f exhibits remarkable efficacy against both Gram-positive and Gram-negative bacteria in comparison to established pharmaceuticals. More specifically, compounds 4b, 4d, and 4e demonstrate significant activity against Escherichia coli and Staphylococcus aureus. Additionally, compounds 4c and 4h show noteworthy activity against Pseudomonas aeruginosa, while compound 4b reveals considerable effectiveness against Streptococcus pyogenes. The other

compounds displayed levels of activity ranging from moderate to suboptimal against the four bacterial species examined (as illustrated in Table 1).

Antifungal activity

The results of the antifungal screening demonstrated that compounds 4b and 4h exhibit highly promising activity against *C. albicans.* Compound 4g displayed exceptional activity against *A. niger*. The remaining compounds in the series showed activity ranging from average to poor, as illustrated in Table 1.

Conclusions

Our current research concentrates on the reactions, synthesis, spectral analysis, and microbial activities of pyrimidine-based benzothiazole derivatives. The method has demonstrated to be significantly more advantageous than those previously documented in the literature. Several of the compounds exhibited effectiveness as antimicrobial and antifungal agents.

Conflicts of interest

All authors have none to declare.

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