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A FACILE SYNTHESIS OF BENZAZOLYLSULFONYL PYRIMIDINYL ACETAMIDE DERIVATIVES WITH IONIC LIQUID UNDER ULTRASONIC IRRADIATION

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ABSTRACT

2-amino-4,6-diarylpyrimidine (1mmol) (1) and methyl 2-(benzoxazoylsulfonyl) acetate were irradiated in an ultrasonic bath at a low frequency of 35 kHz at room temperature to synthesize a variety of benzazolysulfonyl primidinyl acetamide derivatives. As a result of the antibacterial activity examined, the substances were highly potent towards Gram-positive bacteria (*S. aureus and B. subtilis*) compared to Gram-negative bacteria (*S. aureus & B. subtilis and P. aeruginosa & K. pneumoniae*), respectively. Compounds with electron-withdrawing groups 15c, 15e, 16c, and 16e showed superior antibacterial and antifungal activity against *B. subtilis and A. niger* compared to conventional medications, chloramphenicol, and ketoconazole, with MICs of 6.25 µg/ml that were comparable to those of the conventional medications.

Keywords: Ultrasonication, Ionic Liquid, Antifungal, Antimicrobial, Bacteria, Frequency.

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INTRODUCTION

Even though antimicrobial resistance is becoming a more severe risk to human health[1], many microbial infections will eventually become incurable, making it very challenging for humans to survive. To combat microbial resistance, innovative tactics that utilize and developed are required. Therefore, new antimicrobial techniques are needed to overcome immunology and stop the spread of drug resistance. Due to their various biological features, the synthesis of compounds containing benzimidazole, benzothiazole, and benzimidazole skeletons is of great interest. The derivatives of the benzimidazole nucleus have garnered significant interest for their potential antimicrobial[2–12], antitumor[13–15], antifungal[16,17], antibacterial[18–20], antihelmintic[21], anti-inflammatory[22–24], antidepressant[25], antihypertensive[26–27], and antiviral[28–29] properties. Numerous chemotherapeutic properties of benzoxazoles include antibacterial[30,31], antiviral[32], anticancer[33,34], and antioxidant properties.[35] Benzothiazole has received a lot of attention in the realm of heterocyclic compounds due to its several uses as an anticancer, antibacterial, anti-tubercular, and anti-inflammatory drug.[36–38] The pyrimidine nucleus exhibited antifungal activity and anti-inflammatory anti-hypertensive, antiviral, antidiabetic, antioxidant, and anticancer properties.[39,40] These liquids may dissolve both polar and non-polar substances and are liquid below 100 °C or even at ambient temperature.[41] Due to a combination of pharmaceutically active cations and anions that make them good and easily soluble pharmaceuticals in the human body, ionic liquids make up more than half of all medications available on the market.[42] We concentrated on the investigation of antibacterial activity as we continued our efforts to find additional active benzazole-containing compounds here.

In this study, we used the ionic liquid to create a new family of benzazolylsulfonyl pyrimidinyl acetamide derivatives and their antimicrobial activity.

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EXPERIMENTAL

Apparatus and Analysis

All the chemicals were obtained from Sigma-Aldrich. A Mel-Temp apparatus was used to determine melting points in open capillaries, without correction. A TLC analysis was performed to determine the purity of compounds by silica gel, using ethyl acetate-hexane (1:3) as eluent (silica gel H, BDH hexane, ethyl acetate, 3:1). A Bruker spectrometer functioning at 400 and 100 MHz was used to record the ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra in DMSO-d_6. Using an internal standard (TMS), all the chemical shifts are reported in δ (ppm). A Thermo Nicolet IR 200 FT-IR spectrometer was used to record the Infrared (IR) spectra, which were recorded as KBr pellets, and the wavenumbers were given in cm^{-1}. On a micro mass Q-TOF micro mass spectrometer, high-resolution mass spectra (HRMS) were captured by using electrospray ionization. The ultrasonication was done in a Bandelin sonorex RK 12 H ultrasonic bath with a 35 KHz frequency. A Perkin-Elmer 240C elemental analyzer was used for the microanalyses. TLC was used to monitor the reaction's progress using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm).

An overview of the general steps involved in the synthesis of 2-(benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-diarylpyrimidin-2-yl)acetamide (14), 2-(benzo[d]thiazol-2-ylsulfonyl)-N-(4,6-diarylpyrimidin-2-yl)acetamide (15), and 2-((1H-benzo[d]imidazol-2-yl)sulfonyl)-N-(4,6-diphenylpyrimidin-2-yl)acetamide (16).

2-amino-4,6-diarylpyrimidine (1 mmol), 1-methyl-2-(benzoxazoylsulfonyl)acetate (14/15/16) (1 mmol), and 1-NaOH (1/1) (1 mmol) were irradiated in an ultrasonic bath at a 35 kHz operating frequency of at room temperature to bmim[Br]. With TLC, the reaction process was examined. The final product was filtered out of aqueous ethanol and recrystallized.

2-(Benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-diphenylpyrimidin-2-yl)acetamide (14a) Yield 87%, m.p. 153–155 °C, IR KBr (cm^{-1}): 1324-1132 (SO_2), 1561 (C=N), 1634 (C=C), 1672 (CONH), 3264 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.29 (2H, CH_2), 7.29–7.84 (14H, m, ArH), 8.37 (1H, s, C5'-H), 10.31 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 63.8 (CH_2), 153.1 (C-2), 167.9 (C=O), 167.9 (C-2'), 164.2 (C-4'&C-6'), 107.6 (C-5'), 110.1, 117.6, 122.9, 123.8, 125.1, 127.6, 128.3, 134.9, 139.1, 149.4, HRMS (*m/z*): 493.4919 $[M+Na]^+$; Anal. Calcd. for $C_{24}H_{16}N_4O_2S$: C, 63.82; H, 3.86; N, 11.91; Found: C, 63.75; H, 3.79; N, 11.98%.

2-(Benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-di-p-tolylpyrimidin-2-yl)acetamide (14b) Yield 86%, m.p. 144–146 °C, IR KBr (cm^{-1}): 1329-1139 (SO_2), 1574 (C=N), 1649 (C=C), 1675 (CONH), 3279 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 2.36 (s, CH_3), 4.21 (2H, CH_2), 7.29–7.84 (12H, m, ArH), 8.37 (1H, s, C5'-H), 10.31 (1H, bs, NH; ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 66.4 (CH_2), 153.9 (C-2), 167.2 (C=O), 151.8 (C-2'), 165.8 (C-4'&C-6'), 109.9 (C-5'), 110.9, 118.2, 123.0, 124.2, 126.9, 128.1, 129.4, 135.7, 139.8, 150.7, HRMS (*m/z*): 521.5457 $[M+Na]^+$; Anal. Calcd. for $C_{27}H_{22}N_4O_4S$: C, 65.05; H, 4.45; N, 11.24; Found: C, 65.11; H, 4.39; N, 11.30%.

2-(Benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-bis(4-chlorophenyl)pyrimidin-2-yl)acetamide (14c) Yield 79%, m.p. 156–158 °C, IR KBr (cm^{-1}): 1327-1126 (SO_2), 1568 (C=N), 1638 (C=C), 1669 (CONH), 3264 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.32 (2H, CH_2), 7.31–7.89 (12H, m, ArH), 8.44 (1H, s, C5'-H), 10.36 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 63.7 (CH_2), 158.7 (C-2), 170.0 (C=O), 152.7 (C-2'), 166.5 (C-4'&C-6'), 114.9 (C-5'), 111.6, 119.4, 123.2, 124.7, 127.4, 128.6, 130.2, 136.4, 140.1, 152.3, HRMS (*m/z*): 562.3776 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{16}Cl_2N_4O_4S$: C, 55.67; H, 2.99; N, 10.39; Found: C, 55.62; H, 2.94; N, 10.26%.

2-(Benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-bis(4-bromophenyl)pyrimidin-2-yl)acetamide (14d) Yield 85%, m.p. 145-147–210 °C, IR KBr (cm^{-1}): 1328-1134 (SO_2), 1562 (C=N), 1629 (C=C), 1661 (CONH), 3253 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.30 (2H, CH_2), 7.32–7.87 (12H, m, ArH), 8.39 (1H, s, C5'-H), 10.33 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 68.2 (CH_2), 158.2 (C-2), 169.7 (C=O), 152.0 (C-2'), 166.1 (C-4'&C-6'), 113.2 (C-5'), 111.2, 118.8, 123.0, 124.1, 127.0, 128.1, 129.8,

135.9, 140.0, 151.7, HRMS (*m/z*): 651.2857 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{16}Br_2N_4O_4S$: C, 47.79; H, 2.57; N, 8.92; Found: C, 47.70; H, 2.51; N, 8.84%.

2-(Benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-bis(4-nitrophenyl)pyrimidin-2-yl)acetamide (14e) Yield 81%, m.p. 179–181 °C, IR KBr (cm^{-1}): 1319-1139 (SO_2), 1566 (C=N), 1633 (C=C), 1664 (CONH), 3249 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.37 (2H, CH_2), 7.35–7.94 (12H, m, ArH), 8.48 (1H, s, C5'-H), 10.38 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 69.1 (CH_2), 160.0 (C-2), 171.5 (C=O), 154.4 (C-2'), 167.3 (C-4'&C-6'), 115.3 (C-5'), 112.4, 120.6, 124.4, 125.8, 128.2, 129.8, 131.1, 137.2, 141.2, 153.4, HRMS (*m/z*): 583.4879 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{16}N_6O_8S$: C, 53.57; H, 2.88; N, 14.99; Found: C, 53.51; H, 2.75; N, 14.89%.

2-(Benzo[d]thiazol-2-ylsulfonyl)-N-(4,6-diphenylpyrimidin-2-yl)acetamide (15a) Yield 80%, m.p. 159-161°C, IR KBr (cm^{-1}): 1329-1130 (SO_2), 1564 (C=N), 1639 (C=C), 1659 (CONH), 3266 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.23 (2H, CH_2), 7.21–7.76 (14H, m, ArH), 8.29 (1H, s, C5'-H), 10.22 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 65.6 (CH_2), 154.8 (C-2), 168.0 (C=O), 152.1 (C-2'), 165.4 (C-4'&C-6'), 109.8 (C-5'), 120.7, 121.4, 123.9, 125.5, 126.0, 127.8, 128.9, 134.2, 137.9, 151.6, HRMS (*m/z*): 509.5530 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{18}N_4O_3S_2$: C, 61.71; H, 3.73; N, 11.52; Found: C, 61.67; H, 3.79; N, 11.52%.

2-(benzo[d]thiazol-2-ylsulfonyl)-N-(4,6-di-p-tolylpyrimidin-2-yl)acetamide (15b) Yield 84%, m.p. 155–157 °C, IR KBr (cm^{-1}): 1325-1121 (SO_2), 1569 (C=N), 1648 (C=C), 1670 (CONH), 3272 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 2.31 (s, CH_3), 4.19 (2H, CH_2), 7.19–7.72 (12H, m, ArH), 8.31 (1H, s, C5'-H), 10.27 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 69.4 (CH_2), 156.1 (C-2), 168.6 (C=O), 153.3 (C-2'), 166.2 (C-4'&C-6'), 110.9 (C-5'), 121.0, 122.6, 124.8, 127.2, 127.9, 128.8, 130.2, 136.1, 139.6, 152.9, HRMS (*m/z*): 537.6086 $[M+Na]^+$; Anal. Calcd. for $C_{27}H_{22}N_4O_3S_2$: C, 63.02; H, 4.31; N, 10.89; Found: C, 63.10; H, 4.37; N, 10.85%.

2-(benzo[d]thiazol-2-ylsulfonyl)-N-(4,6-bis(4-chlorophenyl)pyrimidin-2-yl)acetamide (15c) Yield 81%, m.p. 150–152 °C, IR KBr (cm^{-1}): 1340-1145 (SO_2), 1561 (C=N), 1634 (C=C), 1661 (CONH), 3265 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.28 (2H, CH_2), 7.24–7.80 (12H, m, ArH), 8.37 (1H, s, C5'-H), 10.30 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 71.8 (CH_2), 159.1 (C-2), 173.3 (C=O), 156.0 (C-2'), 169.3 (C-4'&C-6'), 116.6 (C-5'), 123.1, 122.8, 125.8, 127.0, 128.4, 128.9, 129.7, 135.6, 139.2, 154.3, HRMS (*m/z*): 578.4382 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{16}Cl_2N_4O_3S_2$: C, 54.06; H, 2.90; N, 10.09; Found: C, 54.12; H, 2.84; N, 10.02%.

2-(benzo[d]thiazol-2-ylsulfonyl)-N-(4,6-bis(4-bromophenyl)pyrimidin-2-yl)acetamide (15d) Yield 79%, m.p. 161–163 °C, IR KBr (cm^{-1}): 1333-1128 (SO_2), 1548 (C=N), 1629 (C=C), 1656 (CONH), 3242 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.24 (2H, CH_2), 7.23–7.77 (12H, m, ArH), 8.39 (1H, s, C5'-H), 10.29 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 70.1 (CH_2), 158.6 (C-2), 172.1 (C=O), 155.7 (C-2'), 168.0 (C-4'&C-6'), 115.4 (C-5'), 122.4, 121.7, 124.6, 126.5, 128.0, 128.2, 129.1, 134.0, 138.3, 153.1; HRMS (*m/z*): 667.3458 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{16}Br_2N_4O_3S_2$: C, 46.60; H, 2.50; N, 8.70; Found: C, 46.51; H, 2.46; N, 8.63%.

***2*-(benzo[d]thiazol-2-ylsulfonyl)-N-(4,6-bis(4-nitrophenyl)pyrimidin-2-yl)acetamide (15e)** Yield 78%, m.p. 180–182 °C, IR KBr (cm^{-1}): 1324-1140 (SO_2), 1564 (C=N), 1620 (C=C), 1652 (CONH), 3251 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.30 (2H, CH_2), 7.29-7.97 (12H, m, ArH), 8.42 (1H, s, C5'-H), 10.34 (1H, bs, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 72.2 (CH_2), 159.8 (C-2), 176.7 (C=O), 157.4 (C-2'), 170.4 (C-4'&C-6'), 117.8 (C-5'), 123.4, 123.7, 126.4, 127.6, 129.2, 129.8, 130.4, 137.2, 140.0, 155.9; HRMS (*m/z*): 599.5467 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{16}Br_2N_4O_3S_2$: C, 52.08; H, 2.80; N, 14.58; Found: C, 52.15; H, 2.71; N, 14.65%.

2-((1H-benzo[d]imidazol-2-yl)sulfonyl)-N-(4,6-diphenylpyrimidin-2-yl)acetamide (16a) Yield 84%, m.p. 144–146 °C, IR KBr (cm^{-1}): 1339-1135 (SO_2), 1551 (C=N), 1629 (C=C), 1669 (CONH), 3266 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.33 (2H, CH_2), 7.30–7.91 (14H, m, ArH), 8.41 (1H, s, C5'-H), 10.34 (1H, bs, NH), 12.10 (1H, bs, Benzimidazole NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 64.6

(CH_2), 140.9 (C-2), 168.4 (C=O), 148.7 (C-2'), 162.9 (C-4'&C-6'), 109.1 (C-5'), 113.0, 121.9, 125.9, 126.0, 127.1, 131.3, 135.2; HRMS (*m/z*): 492.5076 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{19}N_5O_3S$: C, 63.95; H, 4.08; N, 14.92; Found: C, 63.88; H, 4.17; N, 14.98%.

2-((1H-benzo[d]imidazol-2-yl)sulfonyl)-N-(4,6-di-p-tolylpyrimidin-2-yl)acetamide (16b) Yield 88%, m.p. 139–141 °C, IR KBr (cm^{-1}): 1342-1126 (SO_2), 1561 (C=N), 1640 (C=C), 1677 (CONH), 3275 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.26 (2H, CH_2), 7.26–7.87 (12H, m, ArH), 8.39 (1H, s, C5'-H), 10.29 (1H, bs, NH), 12.00 (1H, bs, Benzimidazole NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 65.7 (CH_2), 142.7 (C-2), 169.2 (C=O), 150.6 (C-2'), 163.7 (C-4'&C-6'), 110.3 (C-5'), 113.2, 122.7, 126.4, 126.9, 127.8, 132.7, 136.7; HRMS (*m/z*): 520.5636 $[M+Na]^+$; Anal. Calcd. for $C_{27}H_{23}N_5O_3S$: C, 65.18; H, 4.66; N, 14.08; Found: C, 65.25; H, 4.58; N, 14.16%.

2-((1H-benzo[d]imidazol-2-yl)sulfonyl)-N-(4,6-bis(4-chlorophenyl)pyrimidin-2-yl)acetamide (16c) Yield 76%, m.p. 151–153°C, IR KBr (cm^{-1}): 1334-1130 (SO_2), 1567 (C=N), 1635 (C=C), 1661 (CONH), 3263 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.39 (2H, CH_2), 7.38–8.01 (12H, m, ArH), 8.47 (1H, s, C5'-H), 10.39 (1H, bs, NH), 12.28 (1H, bs, Benzimidazole NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 69.9 (CH_2), 145.4 (C-2), 172.0 (C=O), 154.1 (C-2'), 166.4 (C-4'&C-6'), 111.5 (C-5'), 115.8, 123.1, 127.0, 127.8, 129.6, 134.2, 138.9; HRMS (*m/z*): 561.3919 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{17}Cl_2N_5O_3S$: C, 55.17; H, 3.18; N, 13.01; Found: C, 58.64; H, 3.11; N, 13.12%.

2-((1H-benzo[d]imidazol-2-yl)sulfonyl)-N-(4,6-bis(4-bromophenyl)pyrimidin-2-yl)acetamide (16d) Yield 80%, m.p. 139–142°C, IR KBr (cm^{-1}): 1340-1135 (SO_2), 1555 (C=N), 1629 (C=C), 1658 (CONH), 3257 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.37 (2H, CH_2), 7.34–7.98 (12H, m, ArH), 8.43 (1H, s, C5'-H), 10.34 (1H, bs, NH), 12.25 (1H, bs, Benzimidazole NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 68.7 (CH_2), 144.0 (C-2), 170.6 (C=O), 153.7 (C-2'), 165.8 (C-4'&C-6'), 113.9 (C-5'), 114.3, 122.8, 126.5, 127.1, 129.0, 133.6, 137.3; HRMS (*m/z*): 650.3020 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{17}Br_2N_5O_3S$: C, 47.87; H, 2.73; N, 11.16; Found: C, 47.80; H, 2.73; N, 11.11%.

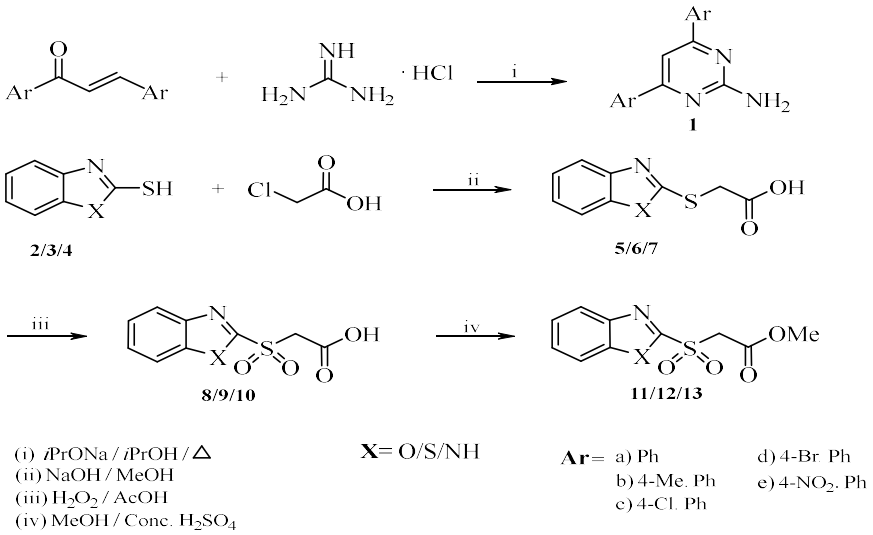
2-((1H-benzo[d]imidazol-2-yl)sulfonyl)-N-(4,6-bis(4-nitrophenyl)pyrimidin-2-yl)acetamide (16e) Yield 78%, m.p. 196–198 °C, IR KBr (cm^{-1}): 1329-1124 (SO_2), 1548 (C=N), 1618 (C=C), 1649 (CONH), 3244 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm: 4.41 (2H, CH_2), 7.40–8.07 (12H, m, ArH), 8.51 (1H, s, C5'-H), 10.40 (1H, bs, NH), 12.36 (1H, bs, Benzimidazole NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 70.3 (CH_2), 147.2 (C-2), 173.4 (C=O), 155.2 (C-2'), 168.2 (C-4'&C-6'), 114.2 (C-5'), 116.4, 124.4, 129.6, 129.9, 130.4, 136.8, 140.2; HRMS (*m/z*): 582.5028 $[M+Na]^+$; Anal. Calcd. for $C_{25}H_{17}N_7O_7S$: C, 53.67; H, 3.06; N, 17.52; Found: C, 53.59; H, 3.13; N, 17.63%.

RESULTS AND DISCUSSION

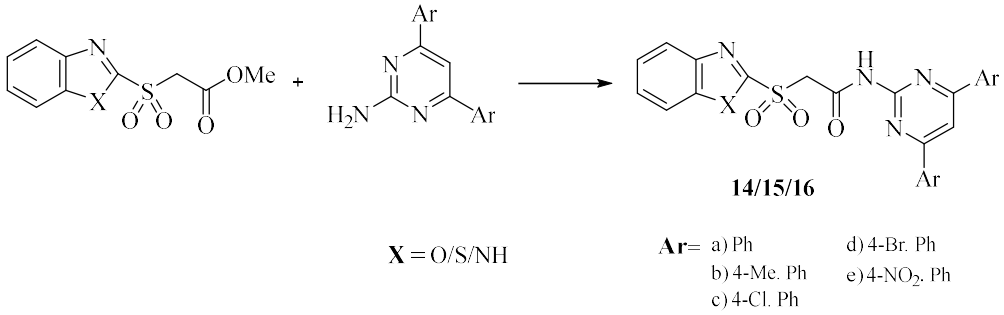
Chalcone and guanidine hydrochloride was reacted in the presence of sodium isopropoxide in isopropanol to produce 2-amino-4,6-diarylpyrimidine (1).[43] The treatment of 2-aminophenol/2-aminothiophenol/o-phenylenediamine with carbon disulfide in the presence of potassium hydroxide in ethanol produced benzoxazole-2-thiol (2), benzothiazole-2-thiol (3), and 1H-benzimidazole-2-thiol (4).[44] In the same way as compounds 3 and 4 created 2-(benzothiazol-2-ylthio)acetic acid (6) and 2-(1H-benzimidazol-2-ylthio)acetic acid (7), compound 2's reaction with chloroacetic acid in the presence of NaOH in methanol produced 2-(benzoxazol-2-ylthio) acetic acid (5).[45] Two-(benzoxazol-2-yl-sulfonyl)acetic acid (8), two-(benzothiazol-2-yl-sulfonyl)acetic acid (9), and two-(1H-benzimidazol-2-yl)acetic acid (10) were produced by oxidizing the aforementioned intermediates 5, 6, and 7 with hydrogen peroxide.[46] Methyl 2-(benzoxazol-2-ylsulfonyl)acetate (11), methyl 2-(benzothiazol-2-ylsulfonyl)acetate (12), and methyl 2-(1H-benzimidazol-2-ylsulfonyl)acetate (13) were generated by the compounds 8, 9, and 10 when they were esterified with methanol in the presence of concentrated H_2SO_4 (Scheme-1).

According to the significance of green methodology, the reactivity of ionic liquids and to reduce reaction time acetamide bond is synthesized from heterocycles having ester and amine functionality where 1a and 11 were executed in the presence of ionic liquid with imidazole ring-1-butyl-3-methylimidazolium bromide ([bmim]Br) in sodium hydroxide under ultrasound irradiation (35kHz) resulted in the formation of 2-(benzo[*d*]oxazol-2-ylsulfonyl)-*N*-(4,6-diphenylpyrimidin-2-yl)acetamide (14a). In connection to this, we

adopted the synthesis of substituted benzoazolylsulfonyl diarylpyrimidinyl acetamides where the reaction of 1 with 11 yielded 2-(benzo[d]oxazol-2-ylsulfonyl)-N-(4,6-diarylpyrimidin-2-yl)acetamide (14), 1 with 12 and 13 afforded 2-(benzo[*d*]thiazol-2-ylsulfonyl)-*N*-(4,6-diarylpyrimidin-2-yl)acetamide (15) and 2-((1H-benzo[*d*]imidazol-2-yl)sulfonyl)-*N*-(4,6-diarylpyrimidin-2-yl)acetamide (16) the products obtained in good to excellent yield (up to 87%) (Scheme-2).



Scheme-1: Synthetic Route of Target Compounds



Scheme-2: Synthetic Route of Target Compounds

Antibacterial Activity

The antibacterial activity of compounds 14–16 was examined in a three-well plate assay using three different concentrations of 25, 50, and 100 μg/ml. The results of the antibacterial sensitivity tests revealed that all substances examined were more sensitive to Gram +ve bacteria (*S. aureus and B. subtilis*) than Gram -ve bacteria (*P. aeruginosa and K. pneumoniae*) (Table-1 and Fig.-1). Chloramphenicol, an antibacterial medication, serves as a standard. The benzothiazolylsulfonyl pyrimidines (15) exhibited greater activity than benzoxazolylsulfonyl pyrimidines (14) and benzimidazolylsulfonyl pyrimidines (16). Additionally, compound 16 displayed more activity than compound 14. The activity is increased due to the presence of electron-withdrawing substituents presence on the ring.

When compared to electron-donating (methyl) and unsubstituted compounds, benzazolylsulfonyl pyrimidines 14–16 with electron-withdrawing (chloro, bromo, nitro) on the aromatic ring demonstrated superior antibacterial activity. 15c 2-(benzo[*d*]thiazol-2-ylsulfonyl)-*N*-(4,6-bis(4-chlorophenyl)pyrimidin-2-yl)acetamide, 15e 2-(benzo[*d*]thiazol-2-ylsulfonyl)-*N*-(4,6-bis(4-nitrophenyl)pyrimidin-2-yl)acetamide, 16c 2-((1H-benzo[*d*]imidazol-2-yl)sulfonyl)-N-(4,6-bis(4-chlorophenyl)pyrimidin-2-yl)acetamide and 16e 2-((1H-benzo[*d*]imidazol-2-yl)sulfonyl)-N-(4,6-bis(4-nitrophenyl)pyrimidin-2-yl)acetamide showed admirable activity against *B. subtilis* than the standard drug.

Table-1: The in Vitro Antibacterial Activity of Compounds (14-16)

Compound No.	Zone of inhibition (mm)											
	Gram-positive bacteria						Gram-negative bacteria					
	S. aureus			*B. subtilis*			*P. aeruginosa*			*K. pneumoniae*		
	25 μg/ml	50 μg/ml	100 μg/ml	25 μg/ml	50 μg/ml	100 μg/ml	25 μg/ml	50 μg/ml	100 μg/ml	25 μg/ml	50 μg/ml	100 μg/ml
14a	-	8±1.3	10±1.1	6±1.6	9±1.7	11±1.3	-	6±1.2	9±1.6	-	9±1.4	11±1.7
14b	-	10±1.2	11±1.6	-	11±1.8	14±2.0	-	-	11±1.5	-	8±1.9	10±1.2
14c	11±1.4	13±1.8	15±1.6	13±1.3	16±1.5	17±1.2	-	9±2.0	11±1.6	9±1.5	10±1.6	14±1.9
14d	9±1.6	12±1.3	14±1.9	10±1.4	13±1.6	15±1.9	-	8±1.5	9±1.4	-	10±1.2	13±1.7
14e	17±1.4	22±1.9	25±1.3	19±1.6	24±1.3	30±1.8	15±1.4	14±1.7	19±2.2	20±1.2	23±1.6	25±1.1
15a	19±1.2	21±18	23±1.3	17±2.3	22±1.8	27±1.7	11±1.8	13±1.6	14±1.1	17±1.8	20±1.4	22±1.5
15b	-	14±1.5	18±1.9	12±1.2	17±1.4	21±2.0	-	10±1.3	13±1.5	-	-	17±1.8
15c	28±1.5	31±1.7	32±1.3	35±1.6	41±1.1	43±1.1	19±1.5	20±1.7	23±1.9	26±1.8	29±1.5	32±1.1
15d	22±1.6	25±1.3	29±1.2	31±1.9	32±1.8	36±1.5	17±2.1	18±1.6	21±1.3	24±1.9	27±1.5	30±1.2
15e	27±1.2	31±1.4	32±1.4	38±1.3	43±1.1	44±1.4	21±1.5	24±1.4	25±1.9	30±1.7	34±1.4	36±1.6
16a	12±1.4	14±1.3	19±1.7	14±1.2	17±2.0	19±1.2	9±1.5	10±1.7	14±1.2	6±1.6	10±1.7	13±1.8
16b	-	11±1.5	16±1.2	12±1.9	14±1.1	15±1.2	-	9±1.6	13±1.5	-	8±1.9	11±1.6
16c	20±1.2	23±1.9	24±1.6	33±1.5	35±1.2	39±1.3	17±1.2	19±1.6	21±1.2	24±1.6	29±1.8	31±1.3
16d	18±1.4	21±1.3	25±1.5	27±1.7	29±1.6	31±2.0	16±1.6	18±1.2	19±2.1	23±1.3	24±1.5	26±1.6
16e	23±1.6	26±2.0	30±1.4	35±1.3	38±1.6	40±1.1	19±1.9	22±1.3	25±1.8	27±1.6	29±1.8	34±1.5
Chloramphenicol	30±1.8	33±1.6	35±2.5	32±1.9	34±3.0	38±2.4	25±2.1	27±1.2	30±1.7	38±2.1	40±1.2	42±1.7
Control (DMSO)	-	-	-	-	-	-	-	-	-	-	-	-

(-) No activity; (±) Standard deviation.

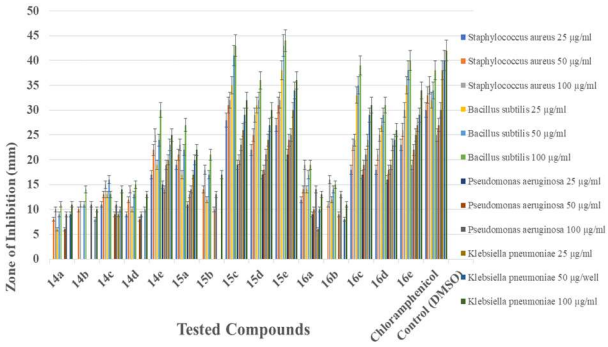


Fig.-1: Inhibition of Bacterial Growth by Compounds 14-16

Antifungal Activity

The antifungal properties of compounds 14-16 were evaluated on *A. niger* and P. chryogenum and the findings are shown in Fig.-2 and Table-2. There was a higher level of activity for compound 16 than compound 15 while the least activity for compound 14 was observed. It was observed that the electron-withdrawing substituents displayed higher inhibitory activity in all series and that the activity grew as the electronegativity of the substituent increased. There was a much greater activity of (16e) and (15e) against *A. niger* than the standard drug, Ketoconazole.

Table-2: The in Vitro Antifungal Activity of Compounds (14-16)

Compound	Zone of inhibition (mm)					
	A. Niger			*P. chrysogenum*		
	25 μg/ml	50 μg/ml	100 μg/ml	25 μg/ml	50 μg/ml	100 μg/ml
14a	-	9±1.7	13±1.2	-	7±1.8	12±1.9
14b	-	8±1.2	15±2.0	-	9±1.4	13±1.6
14c	14±1.6	16±2.0	21±1.8	15±1.6	17±1.9	18±1.4
14d	10±1.3	11±1.7	14±1.4	10±1.3	12±1.4	14±1.2
14e	20±1.2	22±1.4	24±1.7	13±1.9	16±2.0	19±1.5
15a	21±1.5	25±1.9	26±2.1	16±2.0	17±1.7	21±2.0
15b	-	12±1.5	15±1.9	-	11±1.2	14±1.7
15c	29±1.2	30±1.4	34±1.6	22±2.3	24±1.8	28±1.4
15d	24±1.5	26±1.7	29±1.8	20±2.0	22±1.1	24±1.6
15e	32±1.3	37±1.1	40±1.4	26±1.5	28±1.8	33±2.2

16a	21±1.7	23±1.9	26±1.5	19±1.6	21±1.7	24±1.5
16b	-	15±1.3	19±1.9	-	13±1.3	17±1.6
16c	30±1.6	31±1.9	34±2.2	26±1.7	27±1.5	30±1.4
16d	28±1.8	29±1.7	32±1.6	25±1.8	26±2.3	29±1.9
16e	36±1.4	39±1.5	42±1.2	27±1.4	30±2.1	23±1.8
Ketoconazole	31±2.7	33±2.1	36±2.0	35±1.9	36±2.2	38±2.4
Control (DMSO)	-	-	-	-	-	-

(-) No activity; (±) Standard deviation.

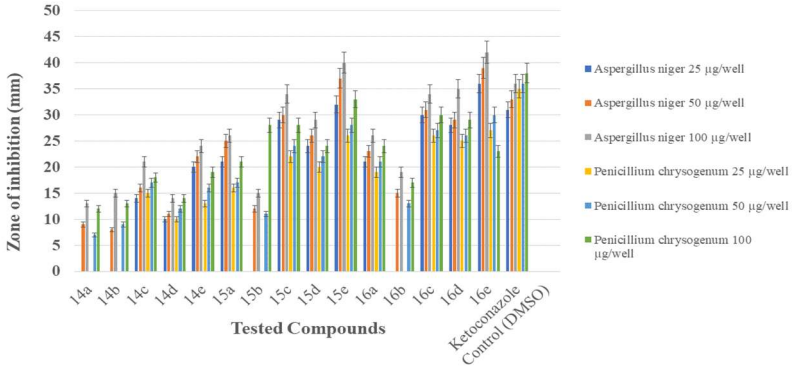


Fig.-2: Inhibition of Fungal Growth by Compounds[14-16]

MIC, MBC, and MFC of Compounds

As shown in Table-3, compounds that showed higher antimicrobial activity were further evaluated for minimum inhibitory concentrations (MIC), minimum bactericidal concentrations (MBC), and minimum fungicidal concentrations (MFC). There is a minimum inhibitory concentration (MIC) of an antimicrobial in which microorganisms cannot grow or reproduce. An MBC/MFC refers to the minimized dosage of antibiotic needed to kill a certain bacteria/fungus, which requires further procedures once the MIC is established. If the MBC/MFC is not more than four times the MIC, the antimicrobials are typically considered to be bactericidal/fungicidal.[46] The compounds 15c, 15e, 16c, and 16e exhibited low MIC against *B. subtilis* and MBC is 2×MIC. The compounds 16e and 15e also showed low MIC against *A. niger* and MFC is 2×MIC.

Table-3: An Analysis of Compounds MIC, MBC, and MFC[14-16]

Compd.No.	*B. subtilis*	The concentration of minimum inhibitory activity				
		MIC (MBC / MFC) µg/ml				
		S. aureus	*K. pneumoniae*	*P. aeruginosa*	*P. chrysogenum*	*A. niger*
15c	6.25(12.5)	25(100)	200(-)	50(200)	200(-)	25(100)
15e	6.25(12.5)	25(100)	100(>200)	50(200)	200(-)	6.25(12.5)
16c	25(100)	100(>200)	200(-)	100(>200)	200(-)	12.5(50)
16e	6.25(12.5)	50(200)	200(-)	100(>200)	100(>200)	6.25(12.5)
Chloramphenicol	6.25	6.25	12.5	6.25	-	-
Ketoconazole	-	-	-	-	6.25	12.5

(-) No activity.

CONCLUSION

Ionic liquids have remarkable properties and applications in the synthesis of heteroaromatic compounds; here in this, a new class of benzazolylsulfonyl pyrimidinyl acetamide was synthesized from 2-amino-4,6-diarylpyrimidine and methyl 2-(benzoxazoylsulfonyl)acetate under ultrasonication. The compounds evaluated for antimicrobial activity among all the compounds with electron-withdrawing groups 15c, 15e, 16c, and 16e showed excellent antibacterial and antifungal activity towards *B. Subtilis* and *A. niger* than standard antibiotics Chloramphenicol and Ketoconazole, A MIC of 6.25 μg/ml was found to be equal to standard drugs.

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CONFLICT OF INTERESTS

No authors have disclosed any conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing and editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below.

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