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Design, synthesis, characterization and biological evaluation of some azetidinone derivatives containing pyrimidine moiety

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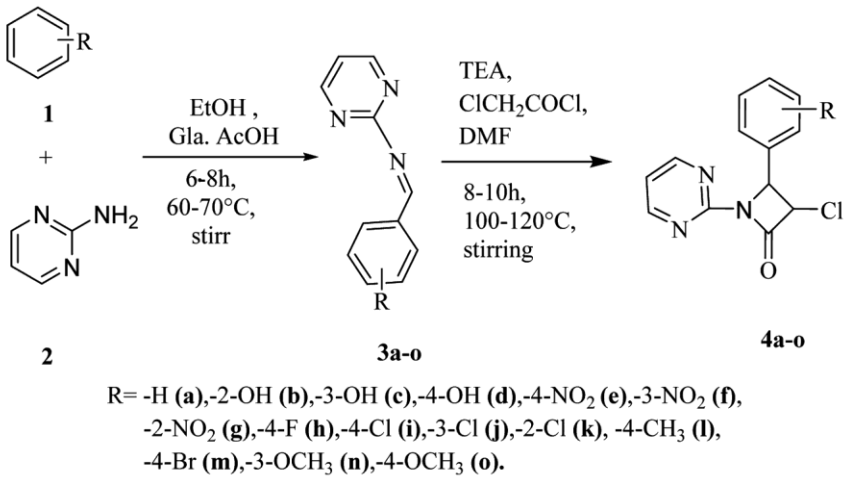
A novel family of 3-chloro-4-benzylidene-1-(pyrimidin-2-yl) azetidin-2-one **5a-o** has been developed because antimicrobial resistance (AMR) poses a significant concern to global public health and has made it exceedingly difficult to effectively manage infectious diseases that have been connected to it. The structures of the relevant compounds have been determined and verified using spectral methods. As substances are tested against gram-positive and gram-negative strains of bacteria and fungi, results must be compared to those of conventional drugs. Products with chloro substituents in both the *p*-position and the *m*-position demonstrate good activity against the fungi *Aspergillus niger* and *Fusarium javanicum*, while those with nitro, methyl, and bromo substituents in the benzene ring's *p*-position, as well as those with the nitro group at the ring's *m*-position, demonstrate excellent activitiy against bacterial strains.

Keywords: Azetidinone, Arylidene, Pyrimidine, Antimicrobial activity

It is well acknowledged that heterocyclic compounds serve as helpful pharmacophores for a number of biological processes[1,2]. Pathogenic infections caused by microbial diseases represent a serious threat to global health and have a detrimental effect on global healthcare systems. Additionally, the issue is exacerbated by growing resistance to drugs[3,4]. Azetidinone is an important pharmacophore that has been thoroughly studied as a foundational element to generate libraries of new chemical entities[5,6]. On a worldwide level, it is one of the most important therapeutic groups of antibacterials used to treat bacterial and drug-resistant infections[7-9]. Pyrimidine is one of the primary medicinal chemical moieties that may be used to create innovative drugs[10]. Depending on how the substitutions are arranged around the ring, the broad family of compounds known as pyrimidine exhibits a wide range of biological activity[11]. The synthesis of these heterocycles has garnered a lot of attention lately. The wide family of chemical compounds known as pyrimidine has many biological, industrial, and agricultural applications, including its antibacterial, analgesic, and other characteristics[12,13]. This effort involved the creation and synthesis of a variety of new hybrid compounds, including those having azetidine and pyrimidine moieties. The effectiveness of these hybrids against bacteria was then assessed.

Results and Discussion

These synthesized compounds were made using a two-step process. Benzaldehyde derivatives **1** and 2-aminopyrimidine **2** were reacted in ethanol using acetic acid as a catalyst to produce imines **3** in the first step. Chloroacetyl chloride was then used to cyclize it into azetidinone compounds **4**. In the last step, arylidene substituents (**4a-o**, Scheme 1**)** containing various electron-donating and electron-withdrawing groups were generated using an active imine group of the Schiff base. The IR spectra of compound **3a** exhibit the azomethene stretching development at 1498 cm^{-1}. The existence of various functional groups in the targeted compounds was confirmed by the IR spectra of the compound **4a**. The carbonyl group of the azetidinone ring was confirmed at 1715 cm^{-1}. The C-Cl bond at 752 cm^{-1} was used to confirm the existence of the C-Cl bond in azetidinone ring, and the ^1H NMR signal at 5.61 ppm was used to confirm the binding of the arylidene ring and β-lactam ring. The hybrid entity had aromatic protons in the range of 7.28 to 7.35 ppm. Using a chemical shift at 161.05 ppm, the carbonyl carbon of azetidinone was



R= -H **(a)**,-2-OH **(b)**,-3-OH **(c)**,-4-OH **(d)**,-4-NO_2 **(e)**,-3-NO_2 **(f)**, -2-NO_2 **(g)**,-4-F **(h)**,-4-Cl **(i)**,-3-Cl **(j)**,-2-Cl **(k)**, -4-CH_3 **(l)**, -4-Br **(m)**,-3-OCH_3 **(n)**,-4-OCH_3 **(o)**.

Scheme 1 — Synthesis of a novel family of biologically active compounds with pyrimidine based azetidinone frameworks

determined. Moreover, the signal at 134.06 ppm validated the conjunction between arylidene ring and β-lactam ring. The presence of carbon atoms on the pyrimidine was verified at 113.94,153.38, and 157.97 ppm. The mass of the produced molecule is shown by the *m/z* value of the compound **4a** at 261.07. The claimed structure was validated using the spectroscopic data described above.

Antimicrobial activity

The antimicrobial activity of recently created compounds (**4a-o**) was examined against a representative panel of bacteria, including *Escherichia coli* (*gram-negative, ATCC 25922*), *Serratia marcescens* (gram-negative, *ATCC 14756*), *Staphylococcus epidermis* (gram-positive, *ATCC 12228*), and *Streptococcus pyogens* (*gram-positive, ATCC 19615*), using chloramphenicol as the standard antibacterial drug. Nystatin was employed as the standard antifungal drug throughout the screening of antifungal activity against the two fungus species *Aspergillus Niger* (*ATCC 16404*) and *Fusarium Javanicum* (*ATCC 22403*). Following the guidelines of the Clinical and Laboratory Standards Institute[14], the minimum inhibitory concentration (MIC) of each synthesized chemical was calculated using the broth microdilution technique (CLSI) [15]. The findings of the antimicrobial evaluation revealed that compound **4e** was found to be prominent, good, and moderate to the common drugs chloramphenicol against the bacterial strains *S. marcescens*, *E. coli*, and *S. epidermis*, respectively, with MIC values of 12.5 g/mL, 25 g/mL, and 50 g/mL. Compound **4i** was shown to be excellent, prominent, and moderate to the common antibiotic chloramphenicol against the bacterial strains *S. marcescens*, *E. coli*, and *S. epidermis*, respectively, with MIC values of 25 g/mL, 12.5 g/mL, and 50 g/mL. It was discovered that the compound **4m** was moderately comparable to the common antibiotic chloramphenicol against the bacterial strains *S. marcescens* and *E. coli*. In comparison to the common antibiotic chloramphenicol, compound **4f** was shown to be effective against the bacterial strain *S. epidermis* with a MIC value of 25 g/mL. Compound **4j** was discovered to be superior to the common antibiotic chloramphenicol against the bacterial strain *S. epidermis*, with a MIC value of 12.5 g/mL. Compound **4l**, which had a MIC value of 25 g/mL, successfully cured the *S. epidermis* bacterial strain as well as the usual drug chloramphenicol. With MIC values of 200 and 1000 g/mL to the common drug nystatin, compounds **4i** and **4j** were also discovered to be moderately active against the fungi *A. Niger* and *F. Javanicum*. The aftereffects of these examinations were notable in Table 1.

Structure Activity Relationship

In this work, a few new hybrids **4a-o** have been developed and their antibacterial efficacy assessed. The results of *in vitro* antibacterial activity showed encouraging findings, as shown in Fig. 1. We have created compounds with various electron-withdrawing and electron-donating groups for evaluating their antibacterial efficacy. Antimicrobial screening of the synthesized hybrids revealed that compounds containing electron-withdrawing groups nitro (-4-NO_2, -3-NO_2), Chloro (-4-Cl,-3-Cl), Bromo (-4-Br) were found most active against gram-negative

Table 1 — *In vitro* antimicrobial activities of all products expressed as MIC [μg/mL] (**5a-o**)

Compd	Minimum inhibition concentration for bacteria (μg/mL)				Minimum inhibition concentration for fungi (μg/mL)	
	e.c.	*s.m.*	*s.e.*	*s.p.*	*a.n.*	*f.j.*
4a	1000	1400	1000	600	1500	2000
4b	1200	1000	800	1200	1000	1500
4c	1200	1400	800	1400	1000	1200
4d	2400	2400	2400	1200	1000	1200
4e	12.5	25	1200	25	2000	2500
4f	2400	1200	25	1200	1500	1500
4g	2400	2400	2400	1200	1200	1200
4h	2400	2400	2400	1200	1400	2000
4i	25	12.5	1000	50	200	1200
4j	2400	1000	12.5	1000	1200	1000
4k	1200	2000	1000	2000	600	2000
4l	1400	1200	25	25	1200	2000
4m	50	50	1000	1000	2000	2000
4n	1200	1200	1200	1000	1400	2500
4o	1200	1200	1200	1000	1200	2500
Chloramphenicol	10	10	10	10	–	–
Nystatin	–	–	–	–	200	800

e.c.= *Escherichia coli* (ATCC 25922), *s.m.*= *Serratia marcescens* (ATCC 14756), *s.e.*= *Staphylococcus epidermis* (ATCC 12228), *s.p.*= *Streptococcus pyogens* (ATCC 19615), *a.n.*= *Aspergillus niger* (ATCC 16404), *f.j.*= *Fusarium javanicum* (ATCC 22403).

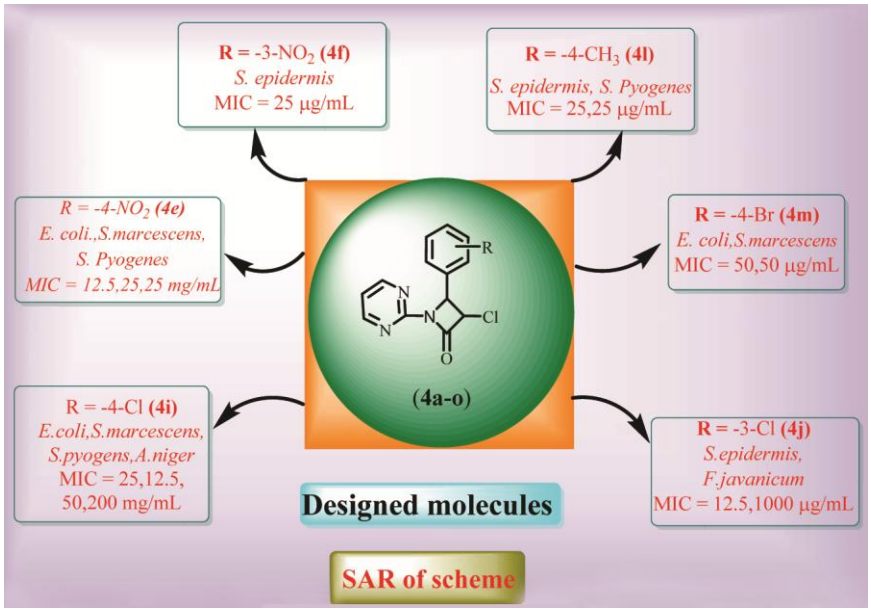


Fig. 1 — Structural presentation of the effect of various functional groups on antimicrobial activity

and gram-positive bacteria and fungal strains. The only electron-donating group methyl (-4-CH_3) is active against gram-positive bacteria *Staphylococcus epidermis*. Outcomes of the antimicrobial activity revealed that electron-withdrawing group in the fourth position and third position while the electron-donating group in the fourth position emerged as antimicrobial agents as described in Fig. 1.

Experimental Section

Preparation of 1-aryl-N-(pyrimidin-2-yl) methanimine, 3a-o

2-Aminopyrimidine **2**, several aromatic aldehydes **1**, and ethanol were mixed to homogeneity (0.01 mol each). The reaction mixture was refluxed at 60–80°C for 6–8 h after adding glacial CH_3COOH in a catalytic quantity. Once the reaction was complete, it was

checked using thin-layer chromatography (TLC), and the reaction mass was allowed to cool at ambient temperature before being poured into cold water to create the intermediate **3a-o**. Using ethanol, the product was recrystallized after drying.

1-Phenyl-N-(pyrimidin-2-yl)methanimine, 3a: Yield 58%. m.p. 174-176°C. IR (KBr): 1207 (C-N), 1498 (C=N), 3277 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.22 – 7.29 (m, 2H), 7.33 – 7.40 (m, 2H), 7.93 – 7.99 (m, 2H), 8.57 (d, *J* = 7.5 Hz, 2H), 9.07 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.41, 128.41, 129.36, 130.26, 135.31, 157.83, 163.56; 171.02; LCMS: *m/z* 184.12 $[M+H]^+$. Anal. Calcd for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.13; H, 4.93; N, 22.95%.

2-((Pyrimidin-2-ylimino)methyl)phenol, 3b: Yield 32%, m.p. 152-154°C. IR (KBr): 1210 (C-N), 1492 (C=N), 2978 (C-H), 3269 cm^{-1} (C-OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.87 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.03 (s, 1H), 11.56 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 115.36, 117.43, 119.97, 120.75, 132.60, 133.09, 158.56, 161.00, 162.89, 166.87; LCMS: *m/z* 200.07 $[M+H]^+$. Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.31; H, 4.56; N, 21.08%.

3-((Pyrimidin-2-ylimino)methyl)phenol, 3c: Yield 35%, solid, white, m.p. 155-157°C. IR (KBr): 1211 (C-N), 1495 (C=N), 2982 (C-H), 3270 cm^{-1} (C-OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.88 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.42 (m, 2H), 7.62 (d, *J* = 7.8 Hz, 1H), 8.59 (d, *J* = 7.5 Hz, 2H), 9.01 (s, 1H), 9.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.84, 115.27, 115.33, 124.73, 129.75, 136.28, 157.90, 158.05, 163.90, 170.11; LCMS: *m/z* 200.13 $[M+H]^+$. Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.30; H, 4.57; N, 21.07%.

4-((Pyrimidin-2-ylimino)methyl)phenol, 3d: Yield 31%, solid, white, m.p. 153-155°C. IR (KBr): 1207 (C-N), 1498 (C=N), 3277 (C-H), 3267 cm^{-1} (C-OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.85 – 6.90 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.69 – 7.75 (m, 2H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.08 (s, 1H), 9.22 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.84, 116.34, 128.99, 131.63, 156.78, 158.05, 163.89, 171.35; LCMS: *m/z* 200.16 $[M+H]^+$. Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.33; H, 4.58; N, 21.06%.

1-(4-Nitrophenyl)-N-(pyrimidin-2-yl)methanimine, 3e: Yield 42%, solid, white, m.p. 156-158°C. IR (KBr): 1207 (C-N), 1330 (C-NO_2), 1492 (C=N), 3281 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 – 7.41 (m, 1H), 8.17 – 8.23 (m, 2H), 8.29 – 8.35 (m, 2H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.11 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.58, 124.07, 129.21, 139.69, 148.53, 157.93, 162.70, 170.83; LCMS: *m/z* 229.14 $[M+H]^+$. Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.88; H, 3.51; N, 24.57%.

1-(3-Nitrophenyl)-N-(pyrimidin-2-yl)methanimine, 3f: Yield 62%, solid, white, m.p. 156-158°C. IR (KBr): 1208 (C-N), 1333 (C-NO_2), 1495 (C=N), 3282 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 – 7.41 (m, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 8.53 (t, *J* = 1.6 Hz, 1H), 8.59 (d, *J* = 7.5 Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.80, 122.87, 123.67, 129.17, 133.20, 136.22, 145.90, 158.15, 162.94, 171.13; LCMS: *m/z* 229.21 $[M+H]^+$. Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.87; H, 3.52; N, 24.56%.

1-(2-Nitrophenyl)-N-(pyrimidin-2-yl)methanimine, 3g: Yield 78%, solid, pale yellow, m.p. 187-189°C. IR (KBr): 1205 (C-N), 1337 (C-NO_2), 1497 (C=N), 3285 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 – 7.41 (m, 1H), 7.60 – 7.68 (m, 2H), 8.12 – 8.22 (m, 2H), 8.59 (d, *J* = 7.5 Hz, 2H), 8.85 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.80, 124.30, 129.60, 129.86, 130.30, 130.45, 147.92, 158.15, 162.56, 165.64; LCMS: *m/z* 229.08 $[M+H]^+$. Anal. Calcd for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 57.88; H, 3.54; N, 24.59%.

1-(4-Fluorophenyl)-N-(pyrimidin-2-yl)methani mine, 3h: Yield 52%, solid, dirty white, m.p. 162-164°C. IR (KBr): 1209 (C-N), 1276 (C-F), 1494 (C=N), 3267 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.15 – 7.22 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.92 – 7.99 (m, 2H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.08 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.84, 115.19, 115.35, 131.23, 131.30, 132.54, 132.57, 158.05, 159.31,

161.32, 164.05, 171.23; LCMS: *m/z* 202.05 $[M+H]^+$. Anal. Calcd for $C_{11}H_8F N_3$: C, 65.67; H, 4.01; N, 20.88. Found: C, 65.68; H, 4.02; N, 24.89%.

1-(4-Chlorophenyl)-N-(pyrimidin-2-yl)methanimine, 3i: Yield 72%, solid, white, m.p. 182-184°C. IR (KBr): δ 765 (C-Cl), 1269 (C-N), 1491 (C=N), 3273 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.37 (t, *J* = 7.5 Hz, 1H), 7.63 – 7.68 (m, 2H), 7.89 – 7.95 (m, 2H), 8.63 (d, *J* = 7.5 Hz, 2H), 9.09 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.68, 128.99, 130.46, 134.53, 135.95, 158.02, 164.05, 171.12; LCMS: *m/z* 219.11 $[M+2H]^+$. Anal. Calcd for $C_{11}H_8Cl N_3$: C, 60.70; H, 3.70; N, 19.31. Found: C, 60.72; H, 3.71; N, 19.33%.

1-(3-Chlorophenyl)-N-(pyrimidin-2-yl)methanimine, 3j: Yield 63%, solid, white, m.p. 177-179°C. IR (KBr): 767 (C-Cl), 1267 (C-N), 1493 (C=N), 3275 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.37 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.53 (m, 2H), 7.84 – 7.93 (m, 2H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.08 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.68, 128.16, 129.11, 129.78, 130.87, 134.11, 136.49, 158.02, 164.07, 170.46; LCMS: *m/z* 219.17 $[M+2H]^+$. Anal. Calcd for $C_{11}H_8Cl N_3$: C, 60.70; H, 3.70; N, 19.31. Found: C, 60.73; H, 3.72; N, 19.32%.

1-(2-Chlorophenyl)-N-(pyrimidin-2-yl)methanimine, 3k: Yield 48%, solid, white, m.p. 164-166°C. IR (KBr): 769 (C-Cl), 1265 (C-N), 1491 (C=N), 3276 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.33 – 7.42 (m, 3H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.91 (d, *J* = 6.9 Hz, 1H), 8.59 (d, *J* = 7.5 Hz, 2H), 8.94 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.68, 127.97, 128.96, 130.20, 131.08, 133.61, 135.51, 158.02, 163.27, 163.69; LCMS: *m/z* 219.14 $[M+2H]^+$. Anal. Calcd for $C_{11}H_8Cl N_3$: C, 60.70; H, 3.70; N, 19.31. Found: C, 60.71; H, 3.73; N, 19.34%.

N-(Pyrimidin-2-yl)-1-(*p*-tolyl)methanimine, 3l: Yield 32%, solid, white, m.p. 164-166°C. IR (KBr): 1265 (C-N), 1491 (C=N), 2928 (C-CH_3), 3282 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.31 (d, *J* = 0.9 Hz, 3H), 7.13 – 7.19 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.79 – 7.85 (m, 2H), 8.63 (d, *J* = 7.5 Hz, 2H), 9.10 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.90, 114.85, 128.85, 129.64, 133.19, 140.22, 158.05, 163.89, 171.29; LCMS: *m/z* 198.23 $[M+H]^+$. Anal. Calcd for $C_{12}H_{11} N_3$: C, 73.07; H, 5.62; N, 21.30. Found: C, 73.08; H, 5.63; N, 21.32%.

1-(4-Bromophenyl)-N-(pyrimidin-2-yl)methanimine, 3m: Yield 32%, solid, white, m.p. 153-155°C. IR (KBr): 769 (C-Br), 1255 (C-N), 1496 (C=N), 3277 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.34 – 7.41 (m, 1H), 7.62 – 7.68 (m, 2H), 7.83 – 7.89 (m, 2H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.11 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 114.64, 123.98, 130.19, 131.43, 134.63, 158.06, 163.12, 171.23; LCMS: *m/z* 264.18 $[M+2H]^+$. Anal. Calcd for $C_{11}H_8Br N_3$: C, 50.41; H, 3.08; N, 16.03. Found: C, 50.42; H, 3.07; N, 16.05%.

1-(3-Methoxyphenyl)-N-(pyrimidin-2-yl)methanimine, 3n: Yield 51%, solid, white, m.p. 141-143°C. IR (KBr): 1260 (C-N), 1392 (C=N), 2867 (C-OCH_3), 3268 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.81 (s, 3H), 6.90 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 8.57 (d, *J* = 7.5 Hz, 2H), 9.05 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.08, 113.17, 114.68, 115.77, 125.83, 128.36, 136.24, 158.13, 159.32, 164.24, 170.32; LCMS: *m/z* 214.17 $[M+H]^+$. Anal. Calcd for $C_{12}H_{11} N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.58; H, 5.21; N, 19.73%.

1-(4-Methoxyphenyl)-N-(pyrimidin-2-yl)methanimine, 3o: Yield 57%, solid, white, m.p. 154-156°C. IR (KBr): 1261 (C-N), 1396 (C=N), 2866 (C-OCH_3), 3269 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.79 (s, 3H), 6.91 – 7.09 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.75 – 8.03 (m, 2H), 8.62 (d, *J* = 7.5 Hz, 2H), 9.10 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.39, 113.81, 114.97, 129.78, 130.65, 158.42, 159.14, 164.34, 171.45; LCMS: *m/z* 214.24 $[M+H]^+$. Anal. Calcd for $C_{12}H_{11} N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.56; H, 5.21; N, 19.72%.

Preparation of 3-chloro-4-aryl-1-(pyrimidin-2-yl)azetidin-2-one, 4a-o

In the presence of trimethyl amine (0.01 mol), 2-chloroacetyl chloride (0.01 mol) was added to Schiff base (**3a-o**, 0.01 mol), using dimethyl formamide as a solvent. The reaction mass was then refluxed for 8–10 h using a reflux condenser at 100–120°C. The reaction mixture was poured into ice-cold water when it had finished. A product

(**4a-o**) was produced by filtering the precipitate off, washing it with water, drying it, and recrystallizing it from ethanol.

3-Chloro-4-phenyl-1-(pyrimidin-2-yl)azetidin-2-one, 4a: Yield 53%. m.p. 178-180°C. IR (KBr): 752 (C-Cl), 1069 (C-N), 1590 (C=N), 1715 (C=O), 3028 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.35 (d, *J* = 7.0 Hz, 1H), 5.61 (d, *J* = 7.0 Hz, 1H), 7.17 – 7.28 (m, 2H), 7.28 – 7.35 (m, 4H), 8.49 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.16, 63.28, 113.94, 126.45, 127.38, 128.19, 134.06, 153.38, 157.97, 161.05; LCMS: *m/z* 261.07 $[M+2H]^+$. Anal. Calcd for $C_{13}H_{10}Cl\,N_3O$: C, 60.13; H, 3.88; N, 16.18. Found: C, 60.14; H, 3.89; N, 19.72%.

3-Chloro-4-(2-hydroxyphenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4b: Yield 42%, m.p. 161-163°C. IR (KBr): 755(C-Cl), 1065 (C-N), 1597 (C=N), 1719 (C=O), 3026 (C-H),3265 cm^{-1} (C-OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.49 (d, *J* = 7.0 Hz, 1H), 5.72 (d, *J* = 6.9 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.19 – 7.27 (m, 2H), 8.53 (d, *J* = 7.6 Hz, 2H), 9.35 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.16, 63.28, 113.94, 126.45, 127.38, 128.19, 134.06, 153.38, 157.97, 161.05; LCMS: *m/z* 277.21 $[M+2H]^+$. Anal. Calcd for $C_{13}H_{10}Cl\,N_3O_2$: C, 56.64; H, 3.66; N, 15.24. Found: C, 56.66; H, 3.67; N, 15.26%.

3-Chloro-4-(3-hydroxyphenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4c: Yield 35%, solid, white, m.p. 155-157°C. IR (KBr): 753 (C-Cl), 1064 (C-N), 1599 (C=N), 1718 (C=O), 3027 (C-H), 3268 cm^{-1} (C-OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.48 (d, *J* = 7.1 Hz, 1H), 5.54 – 5.60 (m, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 6.87 – 6.92 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 8.50 (d, *J* = 7.5 Hz, 2H), 9.23 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.37, 63.59, 114.06, 114.32, 115.07, 119.99, 129.48, 134.74, 153.38, 157.82, 157.97, 160.74; LCMS: *m/z* 277.05 $[M+2H]^+$. Anal. Calcd for $C_{13}H_{10}Cl\,N_3O_2$: C, 56.64; H, 3.66; N, 15.24. Found: C, 56.65; H, 3.66; N, 15.27%.

3-Chloro-4-(4-hydroxyphenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4d: Yield 52%, solid, white, m.p. 173-175°C. IR (KBr): 750 (C-Cl), 1064 (C-N), 1622 (C=N), 1714 (C=O), 3051 (C-H), 3261 cm^{-1} (C-OH); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.47 (d, *J* = 7.0 Hz, 1H), 5.63 – 5.68 (m, 1H), 6.71 – 6.77 (m, 2H), 7.17 – 7.23 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 8.50 (d, *J* = 7.5 Hz, 2H), 8.99 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.34, 63.24, 114.06, 115.08, 127.82, 128.12, 153.38, 157.06, 157.97, 160.74; LCMS: *m/z* 277.08 $[M+2H]^+$. Anal. Calcd for $C_{13}H_{10}Cl\,N_3O_2$: C, 56.64; H, 3.66; N, 15.24. Found: C, 56.63; H, 3.67; N, 15.23%.

3-Chloro-4-(4-nitrophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4e: Yield 74%, solid, white, m.p. 146-148°C. IR (KBr): 767 (C-Cl), 1068 (C-N), 1590 (C-NO_2), 1626 (C=N), 1711 (C=O), 3054 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.47 (d, *J* = 7.0 Hz, 1H), 5.63 (d, *J* = 6.8 Hz, 1H), 7.17 – 7.23 (m, 1H), 7.52 – 7.58 (m, 2H), 8.15 – 8.21 (m, 2H), 8.51 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.05, 63.13, 113.74, 123.46, 127.18, 137.56, 147.31, 153.38, 157.97, 160.97; LCMS: *m/z* 306.16 $[M+2H]^+$. Anal. Calcd for $C_{13}H_9Cl\,N_4O_3$: C, 51.25; H, 2.98; N, 18.39. Found: C, 51.27; H, 2.96; N, 18.37%.

3-Chloro-4-(3-nitrophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4f: Yield 63%, solid, white, m.p. 159-161°C. IR (KBr): 768 (C-Cl), 1066 (C-N), 1592 (C-NO_2), 1627 (C=N), 1713 (C=O), 3055 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.31 – 5.36 (m, 1H), 5.48 (d, *J* = 7.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.63 – 7.69 (m, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.13 (t, *J* = 1.5 Hz, 1H), 8.58 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.62, 63.59, 114.26, 122.75, 122.91, 129.90, 131.65, 134.69, 149.13, 153.89, 158.48, 161.48; LCMS: *m/z* 306.19 $[M+2H]^+$. Anal. Calcd for $C_{13}H_9Cl\,N_4O_3$: C, 51.25; H, 2.98; N, 18.39. Found: C, 51.26; H, 2.97; N, 18.36%.

3-Chloro-4-(2-nitrophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4g: Yield 57%, solid, white, m.p. 169-171°C. IR (KBr): 763 (C-Cl), 1065 (C-N), 1594 (C-NO_2), 1623 (C=N), 1715 (C=O), 3053 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.47 (d, *J* = 7.0 Hz, 1H), 5.54 (d, *J* = 7.1 Hz, 1H), 6.95 – 7.02 (m, 1H), 7.51 – 7.65 (m, 3H), 8.17 (d, *J* = 7.2 Hz, 1H), 8.59 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 61.40, 61.52, 113.74, 124.12, 127.71, 128.28, 128.81, 130.84, 147.49, 152.66, 157.97, 160.89; LCMS: *m/z* 306.12 $[M+2H]^+$. Anal. Calcd for $C_{13}H_9Cl\,N_4O_3$: C, 51.25; H, 2.98; N, 18.39. Found: C, 51.29; H, 2.99; N, 18.35%.

3-Chloro-4-(4-fluorophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4h: Yield 47%, solid, white, m.p. 176-178°C. IR (KBr): 763 (C-Cl),1126 (C-F) 1182 (C-N), 1612 (C=N), 1760 (C=O), 3011 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.47 (d, J = 7.0 Hz, 1H), 5.63 – 5.68 (m, 1H), 7.04 – 7.12 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.34 – 7.41 (m, 2H), 8.50 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.45, 63.34, 114.35, 115.44, 115.60, 128.00, 128.06, 131.50, 131.52, 153.67, 158.26, 161.04, 161.25, 163.27; LCMS: *m/z* 279.09 $[M+2H]^+$. Anal. Calcd for $C_{13}H_9ClF\,N_3O$: C, 56.23; H,3.27; N, 15.13. Found: C, 56.24; H, 3.25; N, 15.16%.

3-Chloro-4-(4-chlorophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4i: Yield 68%, solid, white, m.p. 182-184°C. IR (KBr): 759 (C-Cl), 1086 (C-N), 1637 (C=N), 1706 (C=O), 3066 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.47 (d, J = 6.9 Hz, 1H), 5.65 (d, J = 6.9 Hz, 1H), 7.15 – 7.22 (m, 1H), 7.32 – 7.40 (m, 4H), 8.50 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.12, 62.73, 114.06, 127.93, 128.30, 130.89, 132.92, 153.38, 157.97, 160.81; LCMS: *m/z* 296.08 $[M+4H]^+$. Anal. Calcd for $C_{13}H_9Cl_2\,N_3O$: C, 53.09; H,3.08; N, 14.29. Found: C, 53.07; H, 3.09; N, 14.27%.

3-Chloro-4-(3-chlorophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4j: Yield 56%, solid, white, m.p. 165-167°C. IR (KBr): 757 (C-Cl), 1087 (C-N), 1634 (C=N), 1704 (C=O), 3065 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.48 (d, J = 7.0 Hz, 1H), 5.63 – 5.68 (m, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.32 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.60 (q, J = 1.3 Hz, 1H), 8.50 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 63.12, 64.27, 114.79, 126.89, 128.67, 129.01, 130.43, 134.37, 135.75, 154.11, 158.70, 161.55; LCMS: *m/z* 296.14 $[M+4H]^+$. Anal. Calcd for $C_{13}H_9Cl_2\,N_3O$: C, 53.09; H,3.08; N, 14.29. Found: C, 53.06; H, 3.07; N, 14.26%; LCMS: *m/z* 296.14 $[M+4H]^+$. Anal. Calcd for $C_{13}H_9Cl_2\,N_3O$: C, 53.09; H,3.08; N, 14.29. Found: C, 53.08; H, 3.07; N, 14.25%.

3-Chloro-4-(2-chlorophenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4k: Yield 39%, solid, white, m.p. 155-157°C. IR (KBr): 758 (C-Cl), 1089 (C-N), 1639 (C=N), 1709 (C=O), 3067 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.52 (d, J = 7.0 Hz, 1H), 5.71 – 5.76 (m, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.23 – 7.34 (m, 2H), 7.31 – 7.41 (m, 2H), 8.52 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 61.17, 62.62, 114.79, 128.34, 128.77, 129.95, 130.12, 133.62, 135.29, 153.86, 158.70, 161.77; LCMS: *m/z* 296.05 $[M+4H]^+$. Anal. Calcd for $C_{13}H_9Cl_2\,N_3O$: C, 53.09; H,3.08; N, 14.29. Found: C, 53.07; H, 3.06; N, 14.28%.

3-Chloro-1-(pyrimidin-2-yl)-4-(*p*-tolyl)azetidin-2-one, 4l: Yield 28%, solid, white, m.p. 185-187°C. IR (KBr): 755 (C-Cl), 1087 (C-N), 1624 (C=N), 1721 (C=O), 2984 (C-CH_3), 3044 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.33 (d, J = 0.8 Hz, 3H), 5.47 (d, J = 6.9 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 7.05 – 7.15 (m, 4H), 7.23 (t, J = 7.5 Hz, 1H), 8.50 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.53, 61.94, 63.14, 113.84, 126.46, 128.77, 131.93, 137.11, 153.16, 157.75, 160.52; LCMS: *m/z* 275.07 $[M+2H]^+$. Anal. Calcd for $C_{14}H_{12}Cl\,N_3O$: C, 61.43; H, 4.42; N, 15.35. Found: C, 61.42; H, 4.41; N, 15.34%.

4-(4-Bromophenyl)-3-chloro-1-(pyrimidin-2-yl)azetidin-2-one, 4m: Yield 48%, solid, white, m.p. 195-197°C. IR (KBr): 771 (C-Cl),896 (C-Br), 1060 (C-N), 1628 (C=N), 1729(C=O), 3055 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.37 (d, J = 7.0 Hz, 1H), 5.66 (d, J = 6.9 Hz, 1H), 7.15 – 7.22 (m, 1H), 7.23 – 7.29 (m, 2H), 7.43 – 7.49 (m, 2H), 8.48 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 62.11, 63.22, 114.03, 122.25, 127.92, 130.98, 133.12, 153.38, 157.96, 160.97; LCMS: *m/z* 338.21 $[M+4H]^+$. Anal. Calcd for $C_{13}H_9ClBr\,N_3O$: C, 46.12; H, 2.68; N, 12.41. Found: C, 46.14; H, 2.69; N, 12.42%.

3-Chloro-4-(3-methoxyphenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4n: Yield 43%, solid, white, m.p. 151-153°C. IR (KBr): 755 (C-Cl), 1087 (C-N), 1624 (C=N), 1698 (C=O), 2935 (C-OCH_3), 3054 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.79 (s, 3H), 5.48 (d, J = 7.0 Hz, 1H), 5.57 – 5.62 (m, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 1.9 Hz, 1H), 7.10 – 7.15 (m, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 8.51 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.81, 62.89, 64.27, 112.87, 114.45, 114.59, 122.51, 129.26, 135.22, 154.11, 158.70, 160.52, 161.55; LCMS: *m/z* 291.12 $[M+2H]^+$. Anal. Calcd for $C_{14}H_{12}Cl\,N_3O_2$: C, 58.04; H, 4.18; N, 14.50. Found: C, 58.05; H, 4.16; N, 14.51%.

3-Chloro-4-(4-methoxyphenyl)-1-(pyrimidin-2-yl)azetidin-2-one, 4o: Yield 43%, solid, white, m.p. 154-156°C. IR (KBr): 755 (C-Cl), 1087 (C-N), 1624 (C=N), 1693 (C=O), 2931 (C-OCH_3), 3054 cm^{-1} (C-H); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.76 (s, 2H), 5.46 (d, J = 7.0 Hz, 1H), 5.62 – 5.67 (m, 1H), 6.87 – 6.93 (m, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.21 – 7.26 (m, 2H), 8.50 (d, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 55.10, 62.13, 63.09, 113.38, 113.72, 127.32, 129.01, 153.38, 157.97, 159.08, 160.81; LCMS: *m/z* 291.07 $[M+2H]^+$. Anal. Calcd for $C_{14}H_{12}ClN_3O_2$: C, 58.04; H, 4.18; N, 14.50. Found: C, 58.07; H, 4.17; N, 14.49%.

Conclusion

In our most recent research, we used a multicomponent reaction to create a whole new family of antibacterial compounds. These substances have an azetidinone core structure made up of pyrimidine and a number of aromatic aldehydes. Azetidinone hybrids **4a-o** were produced by cyclizing Schiff bases, which was the primary step. The synthesized hybrids included a variety of functional groups with substituents integrated with electron-donating and electron-withdrawing groups to boost their antibacterial activity. The compounds **4e** and **4i** were revealed to be the most effective antibacterial substitutes by the *in vitro* examination due to their significant activity compared to the conventional antibiotic chloramphenicol against *E. coli*, *S. marcescens*, and *S. epidermis*. Additionally, when the **4i** and **4j** substituents were employed, nystatin was particularly effective against *A. niger* and *F. Javanicum*, respectively.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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