Synthesis and antimicrobial activity of 2-((4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl) pyrimidin-2-yl)thio)-N-methylacetamide

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It has been possible to synthesise a brand new series of 2-((4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidin-2-yl)thio)-N-methyl acetamide 4a-h. The reaction of 1-(1H-benzo[d]imidazol-2-yl)ethanone with 2-ethylcyclopentane carbaldehyde with ethanol and KOH yields (E)-1-(1H-benzo[d]imidazol-2-yl)-3-(2-ethylcyclopentyl)prop-2-en-1-one 1a-c. All compounds have been shown to have antimicrobial action via pharmacological study and are listed here. Chloramphenicol and Amphotericin B, two conventional antibiotics, have been compared to the antibacterial and antifungal properties of the synthetic compounds. It has been discovered that Schlenter products had spectroscopic properties worth investigating.

Keywords: Benzimidazole, pyrimidine, chloramphenicol, in vitro anti-bacterial activity, anti-fungal activity

The 4- and 5-positions of the benzene and imidazole rings fuse to form benzimidazole, a bicyclic heteroaromatic chemical molecule. It is a crucial moiety in heterocyclic aromatic chemistry. The benzimidazole moiety is formed by joining two imidazole and benzophenyl rings. Many heterocycles, including benzimidazole and its substituted variants, include a nitrogen atom. Benzimidazoles have several uses in veterinary medicine, including ulcer therapy, antihelmint medication, and anthistamines.

Benzimidazole derivatives with substituted benzene rings have piqued synthetic organic chemists' interest, leading to the development of catalytic heterocyclic molecules. Benzimidazole derivatives have been studied for their fungicidal and antibacterial properties. This core is related with anticancer, antiviral, antifungal, insecticidal, and herbicidal action. Pyrimidine derivatives are vital in the pesticide business because of their high activity, low toxicity, and biocompatibility.

Results and Discussion
As seen in Scheme I, the target compounds are being synthesised as aldol condensation was used to synthesise, α,β-unsaturated ketones 1a-c from 2-acetylbenzimidazole, which were subsequently cyclised in 1 and thiourea 'PrONa + 'PrOH solution at refluxing temperature to yield substituted pyrimidine-2-thiols 2a-c. Chloroacetic acid react at 78°C in a KOH–ethanol solution to yield substituted (pyrimidin-2-yl) thioacetic acids 3a-c. Intermediate 3 then reacted with various amines under the catalysis of EDCI/HOBt to form the desired compounds (4a–h, Scheme II).

Newly synthesised 1a-c were described using the IR, 1H and 13C NMR spectra. There was an absorption band at 1760 cm⁻¹ owing to the C=O group in compound 1, whereas NH stretching bands appeared at 3400 cm⁻¹ in the IR spectra. It is also possible to synthesise substituted pyrimidine-2-thiols 2a-c by heating compound 1 with isopropanol and 'PrONa/Hcl for 6 h at RT. Charcoal acetic acid and potassium hydroxide were used in the reaction of compound 2 to produce 2-((4H-benzo[d]imidazol-2-yl)-6H-(2 ethoxycyclopentyl)pyrimidin-2-yl thio)acetic acid 3a-c. Another reaction occurs under the catalytic action of the EDCI/HOBt catalyst, which produces N-methylacetamide as a result of the reaction of different amines with EDCI/HOBt 4a-h.

Compounds were characterised using 1H and 13C NMR, FT-IR, and elemental analysis. There was an NH signal of amide bond about 8.47 ppm when R₂ was CH₃ or OCH₃ (4a, 4b, 4c, 1b, and 1c), whereas around 3.80 ppm when other protons of benzene or...
benzimidazole (4a, 4b, 4c, 1b, 1c). The benzimidazole ring’s N–H stretching vibration was detected at 3300–3430 cm$^{-1}$ in the IR spectra, whereas the amide bond’s C=O stretching vibration was detected at 1658–1760 cm$^{-1}$. The structure of the isolated compounds was confirmed using their spectral data.

**In vitro anti-microbial activity**

The antibacterial activity of extracts was evaluated using well diffusion method. For sample preparation, the substance was dissolved in DMSO (1mg/mL) and antimicrobial (antibacterial and antifungal) activity was then tested on medium.

**Anti-bacterial activity**

On gram-positive bacteria such as *Staphylococcus aureus* and on gram-negative bacteria such as *Escherichia coli*, the newly synthesised compounds were examined in vitro. The minimum inhibitory concentration (MIC, μg/mL) was defined as the lowest concentration (maximum dilution) required to stop the growth of bacteria. The MIC values of the substances tested were determined and compared with the Chloramphenicol conventional antibiotics, and the MIC values of the substances tested are listed in Table I.

Among the studied compounds, the compound (E)-1-(1H-benzo[d]imidazol-2-yl)-3-(2-ethylcyclopentyl) prop-2-en-1-one 1a showed 10 mm in *E. coli* and 20 mm in *Staphylococcus* $^{[27]}$, while the compound (E)-1-(1H-benzo[d]imidazol-2-yl)-3-(2-methylcyclopentyl) prop-2-en-1-one 1b showed 12 mm in *E. coli* and 23 mm in *Staphylococcus*, and in the compound 4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl) pyrimidine-2-thiol 2 was found in *E. coli* at 15 mm and *Staphylococcus* at 22 mm $^{[28,29]}$, and in the combination 2-(4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidin-2-yl)thio)N-methylacetamide 4a was found in *E. coli* at 05 mm and *Staphylococcus* $^{[30,31]}$ at 18 mm. The compounds 1c, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h were found to be moderate to compatible.

**Anti fungal activity**

The novel compounds were evaluated against *Aspergillus fumigatus*. Each compound's antifungal activity was compared to that of Amphotericin B. The MIC (μg/mL) values of the substances tested were computed and compared to controls. The test compounds were active against fungi. The inhibition zones were measured in millimetres (mm), and the results are shown in Table I. The mixture (4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidin-2-yl)thio)N-methylacetamide 4a showed 10 mm in *E. coli* and 20 mm in *Staphylococcus*, while the compound (E)-1-(1H-benzo[d]imidazol-2-yl)-3-(2-methylcyclopentyl) prop-2-en-1-one 1b showed 12 mm in *E. coli* and 23 mm in *Staphylococcus*, and in the compound 4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl) pyrimidine-2-thiol 2 was found in *E. coli* at 15 mm and *Staphylococcus* at 22 mm, and in the combination 2-(4-(1H-benzo[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidin-2-yl)thio)N-methylacetamide 4a was found in *E. coli* at 05 mm and *Staphylococcus* at 18 mm. The compounds 1c, 2b, 2c, 3a, 3b, 3c, 4a, 4b, 4c, 4d, 4e, 4f, 4g, 4h were found to be moderate to compatible (Figure 1).

**Experimental Section**

The melting points were determined using Electrothermal 9002 melting point equipment. The FTS-6000 BIO-RAD equipment captured IR spectra. $^1$H and $^{13}$C NMR spectra in deuterated CDCl$_3$ and
DMSO-d₆ were obtained on a Bruker AC-300. All chemical shifts were recorded in ppm, and coupling constants (J) in Hertz (Hz). Micromass LCT (ESI technique, positive mode) spectrometers were used for mass spectra (HRES-MS). All reactions were monitored using TLC on aluminium sheets of SDS silica gel 60 F254,0.2 mm.

**General procedure for synthetic pathway to (E)-1-(1H-benzo[d]imidazol-2-yl)-3-(2-ethylcyclopentyl) prop-2-en-1-one, 1a-c**

Compounds 1a–c were synthesised using 2-acetylbenzimidazole and substituted carbaldehydes. 2-Acetylbenzimidazole (10mmol) reacted with substituted carbaldehydes (10mmol) and anhydrous potassium hydroxide 2g was added with ethanol. The precipitated material was recovered by filtering, then washed with cold water, dried, and crystallised from ethanol to produce 1a-c (Table II).

Yellow solid. Yield 78%. m.p.182-186°C. IR (KBr): 3300–3400, 1658–1760 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 1.06 (t, 3H-CH₃), 1.45 (m, 4H, Ar-H), 1.71 (m, 5H, Ar-H), 1.88 (s, 1H, Ar-H), 6.44 (d, J=11.7Hz,2H, Ar-H), 7.24 (d, J=4.6Hz,2H, Ar-H), 7.57 (d, J=0.6Hz,2H, Ar-H), 7.85 (s, 1H-NH); ¹³C NMR (125 MHz, DMSO-d₆): δ 12.11, 24.53, 25.11, 31.45, 32.07, 45.96, 50.91, 115.12, 118.49, 123.47, 125.76, 137.59, 138.78, 148.13, 178.88; MS: (M+H): m/z 268.4. Found: 268.11. Anal. Calcd for C₁₉H₂₅N₂O: C, 76.09; H, 7.59; N, 10.44. Found: C, 76.51; H, 7.49; N, 10.37%.

(E)-1-(1H-Benz[d]imidazol-2-yl)-3-(2-methylcyclopentyl) prop-2-en-1-one, 1b: Yellow solid. Yield 72%. m.p.194-198°C. IR (KBr): 3300–3400, 1658–1760 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 1.19 (t, 3H-CH₃), 1.45 (m, 4H, Ar-H), 1.71 (m, 4H, Ar-H), 6.45 (d, 3H, Ar-H), 6.65 (s, 1H, Ar-H), 7.23 (d, J=6.2Hz,2H, Ar-H), 7.86 (s, 1H-NH); ¹³C NMR (125 MHz, DMSO-d₆): δ 18.60, 24.32, 31.10, 34.65, 40.10, 52.66, 115.12, 118.49, 123.62, 125.42, 137.59, 138.78, 148.70, 178.88; MS: (M+H): m/z 254.3. Found: 254.11. Anal. Calcd for C₁₉H₂₇N₂O: C, 75.56; H, 7.13; N, 11.01. Found: C, 76.51; H, 7.49; N, 10.37%.

(E)-1-(1H-Benz[d]imidazol-2-yl)-3-(2-methoxycyclopentyl) prop-2-en-1-one, 1c: Yellow solid. Yield 73%. m.p.192-195°C. IR (KBr): 3300–3400, 1658–1760 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 1.45 (q, 4H, Ar-CH₂), 1.67 (m, 3H, Ar-CH₂), 2.18 (q, 3H, Ar-H), 3.31 (s, 1H, Ar-H), 3.38 (s, 1H, Ar-H), 6.40 (d, J=10.2Hz, 2H, Ar-H), 6.48 (d, J=6.4Hz, 2H, Ar-H), 7.44 (s, 1H, Ar-H) 7.63 (s, 1H, Ar-H); ¹³C NMR (125 MHz, DMSO-d₆): δ 24.57, 29.17, 31.87, 50.86, 57.02, 86.02, 115.12, 118.49, 123.32, 123.62, 124.62, 137.69, 138.78, 146.67, 178.88; MS: (M+H): m/z 270.3. Found: 270.31. Anal. Calcd for C₁₆H₁₈N₂O₂: C, 70.09; H, 6.71; N, 10.36. Found: C, 70.12; H, 6.75; N, 10.39%.

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<th>Mol. Formula</th>
<th>Yield (%)</th>
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<td>C₂₆H₂₆CIN₅O₅S</td>
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4-(1H-Benz[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidine-2-thiol, 2a-c

With caution, the potassium was placed into 20 mL 1PrOH and heated to 80°C until the sodium was depleted. Add thiourea (0.34 g, 4.5 mmol) and compound 1 (4.5 mmol), and the residue was dissolved in water (H2O, 40 mL). The precipitate was filtered, washed, and dried to yield yellow solid substituted pyrimidine-2-thiol. 2a. m.p. 192-195°C, 2b, m.p. 164–166°C; 2c, m.p. 175–177°C.

Yellow solid. Yield 72%. IR (KBr): 3300–3400 cm−1; 1H NMR (200 MHz, DMSO-d6): δ 0.98 (t, 3H, CH3), 1.12 (d, J=8.2Hz, 2H-CH2), 1.13 (s, 1H, Ar-CH), 1.64 (dd, J=15.5Hz, 3.8Hz, 4H, Ar-H), 1.91 (d, J=18.4Hz, 2H, Ar-H) 2.44 (s, 1H, Ar-H), 3.47 (s, 1H-CH), 7.31 (d, J=7.1Hz, 2H, Ar-H), 7.58 (m, 3H, Ar-H), 7.85 (m, 1H-NH); 13C NMR (50 MHz, DMSO-d6): δ 12.11, 12.13, 12.48, 123.48, 137.60, 148.09, 151.53, 166.10, 170.99, 174.82; MS: (M+H)+: m/z 324.4. Found: 324.8. Anal. Calcd for C18H18N2S: C, 63.77; H, 6.37; N, 17.39.

2-((4-(1H-Benz[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidine-2-thio)-N-methylacetic acid, 3a-c

Sodium hydroxide (0.27 g, 6.6 mmol) and intermediate 2 (3.3 mmol) to ethanol (15 mL) (0.32 g, 3.3 mmol). To add water, the reaction mixture was refluxed for 5 hours, then cooled to RT. Substituted (pyrimidin-2-yl)thio)acetic acid 3 was obtained by suction filtering the solution and washing it with H2O(20 mL). 3a, m.p. 223–225°C; 3b, m.p. 192–196°C; 3c, m.p. 175–179°C.

Yellow solid. Yield 72%. IR (KBr): 3300–3400 cm−1; 1H NMR (200 MHz, DMSO-d6): δ 1.12 (t, 3H-CH3), 1.28 (d, J=18.8Hz, 2H-CH2), 1.63 (dd, J=18.6, 3.7Hz, 4H, Ar-H), 1.92 (d, J=15.5Hz, 2H-CH2), 2.69 (s, 1H, Ar-H), 3.99 (m, 4H, Ar-H) 7.31 (d, J=7.1Hz, 2H, Ar-H) 7.50 (s, 1H, Ar-H) 7.58 (s, 1H-NH) 7.64 (d, J=7.9Hz, Ar-H); 13C NMR (50 MHz, DMSO-d6): δ 12.11, 24.70, 32.45, 33.04, 34.64, 49.14, 114.43, 115.12, 118.49, 123.48, 137.60, 148.09, 151.53, 166.10, 170.99, 174.82; MS: (M+H)+: m/z 492.0. Found: 492.8. Anal. Calcd for C26H25N3O5S; C, 63.77; H, 6.37; N, 14.23. Found: C, 63.83; H, 6.25; N, 14.39.

2-((4-(1H-Benz[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidine-2-thio)-N-(methoxy-2-nitrophenyl)acetamide, 4a-b

White solid. Yield 71%. IR (KBr): 3400, 1760 cm−1; 1H NMR (200 MHz, DMSO-d6): δ 0.98 (t, 3H, CH3), 1.12 (d, J=8.2Hz, 2H-CH2), 1.13 (s, 1H, Ar-CH), 1.64 (dd, J=15.5Hz, 3.8Hz, 4H, Ar-H), 1.91 (d, J=18.4Hz, 2H, Ar-H) 2.44 (s, 1H, Ar-H), 3.47 (s, 1H-CH), 13C NMR (50 MHz, DMSO-d6): δ 12.11, 24.71, 33.12, 46.33, 49.13,114.33, 115.12, 118.49, 123.48, 137.60, 148.09, 151.52, 166.10, 170.90, 174.81; MS: (M+H)+: m/z 492.0. Found: 492.8. Anal. Calcd for C26H23ClN2OS; C, 63.47; H, 5.33; N, 14.23. Found: C, 63.83; H, 6.25; N, 14.39.

2-((4-(1H-Benz[d]imidazol-2-yl)-6-(2-ethylcyclopentyl)pyrimidine-2-thio)-N-(4-methoxy-2-chlorophenyl)acetamide, 4c

White solid. Yield 74%. IR (KBr): 3400, 1760 cm−1; 1H NMR (200 MHz, DMSO-d6): δ 0.99 (t, 3H, CH3), 1.19 (m, 5H-CH2) 1.32 (s, 1H, Ar-H), 1.63 (dd, J=19.0, 5.6Hz, 4H, CH2), 1.91 (d, J=16.1Hz, 2H-CH2), 2.69 (s, 1H, Ar-H), 3.80 (m, 3H-CH3), 3.96 (m, 2H-CH2), 7.33 (t, J=6.0Hz, 3H, Ar-CH), 7.88 (m, 3H, Ar-H), 7.94 (s, 1H, Ar-H); 13C NMR (50 MHz,
**2-((4-(1H-Benz[d][imidazol-2-yl]-6-(2-ethylcyclopentyl)pyrimidin-2-yl(thio))-N-(4-nitrophenoxy)acetamide, 4g:** White solid. Yield 78%. IR (KBr): 3400, 1760 cm⁻¹; ¹H NMR (200 MHz, DMSO-d₆): δ 0.98 (t, 3H, J=6.5Hz –CH₃), 1.69 (m, 5H, Ar-CH₂), 2.69 (q, J=8.9Hz, Ar-H), 3.96 (s, 2H-CH₂), 7.12 (m, 5H, Ar-H), 8.12 (s, 2H, Ar-H), 8.55 (m, 7H, Ar-CH), 9.27 (s, 1H-NH) ¹³C NMR (50 MHz, DMSO-d₆): δ 12.11, 24.86, 32.58, 46.33, 49.13, 114.43, 115.12, 118.49, 120.78, 123.47, 136.36, 137.96, 148.09, 151.52, 153.55, 162.59, 166.10, 168.72, 174.81; MS: (M+: m/z 502.8. Found: 502.80. Anal. Caled for C₂₃H₂₆N₇O₃S: C, 62.13; H, 5.21; N, 16.33. Found: C, 62.83; H, 5.55; N, 16.39%.

**Conclusion**

Our approach for producing 2-(4-(1H-benzo[d][imidazol-2-yl]-6-(2-ethylcyclopentyl)pyrimidin-2-ethyl)acetamide 4a-h and its derivatives was exceedingly efficient. The compounds collected had good yields and were antimicrobial tested. This transformation demonstrates the process's maximum efficiency under moderate conditions, short response times, and operational simplicity. This agreement may be extended to a variety of substrates.

**Supplementary Information**

Supplementary information is available in the website [http://nopr.niscair.res.in/handle/123456789/58776](http://nopr.niscair.res.in/handle/123456789/58776).
Compliance with Ethical Standards
It is not intended to include any of the authors’ investigations with animals or human beings in this publication.

Conflict of Interests
Authors affirm to no conflicts of interest.

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References
