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# Synthesis and antibacterial activity of a series of 2-trifluoromethylbenzimidazole-thiazolidinone derivatives

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**Abstract**

A series of 2-phenyl-3-(2-(trifluoromethyl)-1*H*-benzoimidazol-6-yl)thiazolidin-4-one derivatives were synthesized from *p*-nitro-*o*-phenylenediamine in a three-step reaction. Their structures were elucidated by NMR and mass spectral data. The synthesized compounds showed excellent antibacterial activity ranging from 3-fold, to greater than 100-fold higher than the standard antibiotics, ciprofloxacin and levofloxacin. Compounds **3d** (2′-Br), **3j** (4′-Br), and **3l** (4′-$NO_2$) displayed a broad spectrum of activity against the strains tested (0.14–38.33 μM). The brominated derivatives **3d** and **3j** showed excellent activity against the Gram-positive bacterial strains (MBC between 0.12 and 35.46 μM), while the nitro derivative **3l** showed excellent activity against all four Gram-negative strains tested (MBC between 0.15 and 9.58 μM).

## 1 | INTRODUCTION

Bacterial infections are a significant health threat and responsible for the majority of hospital-acquired infections, leading to extensive mortality and high burden on healthcare systems. New virulent forms of bacteria have emerged, with different levels of resistance to current therapeutic treatments, such as methicillin-resistant *Staphylococcus aureus* (MRSA),[1] multidrug-resistant tuberculosis (MDR-TB),[2] extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, and *Escherichia coli*.[3] There is an urgent need for new and more effective drug development against both drug-resistant and drug-sensitive pathogens.

Recently, much attention has focused on the development of heterocyclic scaffolds for the discovery of new drugs.[4,5] Benzimidazoles are five-membered aromatic heterocyclic compounds containing two nitrogen atoms. They are structural isosteres of nucleotides and used extensively in medicinal chemistry with the core moiety being present in a number of well-established drugs such as albendazole and tiabendazole (anthelmintic), pantoprazol and omeprazole (proton pump inhibitors), bendamustine (anticancer), carbendazim and fuberidazole (antimicrobials), and telmisartan (antihypertensive).[6]

Thiazolidinones are derivatives of thiazoles containing nitrogen, sulfur, and a carbonyl group. They are considered as privileged scaffolds in medicinal chemistry because of their various biological activities such as antimicrobial,[7,8] antiinflammatory,[9] anticancer,[10,11] anti-HIV,[12] antihypertensive,[13] and antidiabetic activities.[14]

Hybrid molecules have recently been developed as new antimycobacterial agents[15] and are obtained by the amalgamation of two or more different pharmacophores. Hybrid molecules have also demonstrated good bioactivity as antimicrobial agents.[16–18] The promising activity exhibited by these molecules prompted us to explore new conjugates by combining benzimidazole and thiazolidinones to search for possible hybrid molecules with antimicrobial activity.

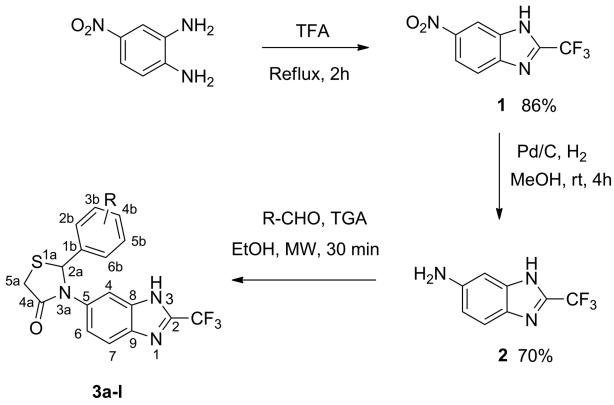
Microwave-assisted synthesis has recently been shown to have a number of advantages over conventional methods for organic reactions. It has been shown to reduce the duration of the reactions and improve the quality and yields of the products.[19] It has been popularly used for the synthesis of benzimidazole derivatives with different solvents and catalysts.[20–23] Although the benzimidazole core has been synthesized using microwave irradiation, there have been relatively few reports on the thiazolidinone moiety being synthesized under microwave conditions.[23–25]

In the present investigation, the benzimidazole-thiazolidinone hybrid molecules were synthesized using microwave synthesis and the antimicrobial activity of the compounds was determined.

## 2 | RESULTS AND DISCUSSION

### 2.1 | Chemistry

An appropriate synthetic strategy was selected for the synthesis of benzimidazole-thiazolidinone hybrids **3a-l** (Figure 1). We have successfully synthesized 12 new derivatives using microwave-assisted irradiation in the final step. The 2-trifluoromethyl benzimidazoles **2** were prepared from 4-nitro-1,2-phenyldiamine and trifluoroacetic acid. The nitro group was then reduced to the amine by catalytic (Pd/C) hydrogenation and thiazolidinones were formed using a one-pot technique by employing the Knoevenagel condensation of the amino group (of the benzimidazole), substituted benzaldehydes, and thioglycolic acid under microwave conditions. The final




| | R | Yield % | | R | Yield % |
|---|---|---|---|---|---|
| **3a** | H | 82 | **3h** | 4'-F | 83 |
| **3b** | 2'-F | 81 | **3i** | 4'-Cl | 78 |
| **3c** | 2'-Cl | 76 | **3j** | 4'-Br | 83 |
| **3d** | 2'-Br | 81 | **3k** | 4'-$CF_3$ | 82 |
| **3e** | 2'-$CF_3$ | 79 | **3l** | 4'-$NO_2$ | 78 |
| **3f** | 2'-$NO_2$ | 76 | | | |
| **3g** | 2'-$OCH_3$ | 75 | | | |

**FIGURE 1** Synthesis of substituted 2-phenyl-3-(2-(trifluoromethyl)-1*H*-benzimidazol-6-yl)thiazolidin-4-ones

benzimidazole-thiazolidinones **3a-l** were synthesized as racemic mixtures in yields of 75%–83%.

Although forming thiazolidines with primary amines, aldehydes, and thioglycolic acid is common, conventional methods use harsh solvents such as DMF, dioxane, and toluene with long reaction times (16 h),[24,26] whereas microwave methods use toluene as the solvent with shorter reaction times (5–10 min).[23] We have successfully synthesized the thiazolidinones from benzimidazole precursors using the eco-friendly ethanol as solvent under microwave irradiation. This is a simple, attractive, and greener method for preparing benzimidazole-thiazolidinone hybrid molecules. The products were purified to >95% purity, monitored by the integration of their $^1$H NMR spectra.

The structures of the synthesized compounds were established by NMR spectroscopy and High Resolution Mass Spectrometry (HRMS). HRMS was particularly important because the benzimidazole carbon resonances were not observed in the $^{13}$C NMR spectra because of the degenerated tautomerism of the NH proton, resulting in the resonances becoming magnetically equivalent because of the rapid proton exchange between N1 and N3.[27] This is also responsible for the broadening of the H-4, H-6, and H-7 resonances, which should have appeared as a doublet ($J$ ~ 2 Hz), double doublet ($J$ ~ 8 and 2 Hz), and doublet ($J$ ~ 8 Hz), respectively, but appeared as broadened singlets for H-4 and H-7. H-6 appeared as a doublet (not a double doublet) in many instances and only in the case of **3l**, the *para* nitro derivative, it did appear with its correct splitting pattern, a double doublet. Compound **3l** was, therefore, used to fully interpret the $^1$H NMR spectra.

The $^1$H NMR spectrum of **3l** contained four resonances in the aromatic region of the spectrum between $\delta$ 7.30 and 8.10. The aromatic proton resonances of the *para*-substituted phenyl ring were present at $\delta$ 7.68 (H-2b/6b) and the H-3b/5b doublet appeared at $\delta$ 8.07. For the benzimidazole ring, the H-4 resonance coincided with H-2b/6b at $\delta$ 7.68. The H-7 resonance appeared as a doublet at $\delta$ 7.61 and H-6 as a doublet of doublets at $\delta$ 7.33. These resonances had coupling constants in keeping with their position on the benzimidazole ring, with $J_{H6,H7}$ = 8.8 Hz for *ortho* coupling and $J_{H6,H4}$ = 1.9 Hz for *meta* coupling. These chemical shifts for the aromatic protons of the benzimidazole ring are consistent with those reported in Nieto et al..[27]

In the thiazolidine ring, the H-2a proton was present at $\delta$ 6.64 and the diastereotopic protons H-5ai and H-5aii as a double doublet and doublet, respectively were present at $\delta$ 4.07 and $\delta$ 3.92 with $J_{H5ai,H5aii}$ = 15.8 Hz and $J_{H5ai,H2a}$ = 1.5 Hz. These coupling constants were clearly seen, even though the resonances coincided with the solvent

peak. However, in other compounds, H-5ai and H-5aii were separated from the solvent peak and were clearly observed. The large coupling constant of 15.8 Hz for $J_{H5ai,H5aii}$ is typical of geminal protons adjacent to the pi system of the carbonyl group. This is in keeping with *J* values cited in Singh et al.,[28] which quotes values of 17–18 Hz for geminal coupling in thiazolidinones.

As mentioned previously, because of the degenerate tautomerism of the NH proton, the benzimidazole carbon resonances C-4 to C-9 were not observed in the $^{13}C$ NMR spectra, however, C-2 and the $CF_3$ carbon resonances were present in almost all compounds. These occurred as two quartets, at $\delta$ 141.9 ($J$ = 40.0 Hz) and $\delta$ 119.1 ($J$ = 271.6 Hz) in **3l**. The three thiazolidinone carbon resonances were present at $\delta$ 171.5 (C-4a), 63.5 (C-2a), and 33.2 (C-5a). The nitrophenyl carbon resonances were present at $\delta$ 147.9 (C-1b), 129.0 (C-2b/6b), 124.3 (C-3b/5b), and 133.9 (C-4b).

To investigate the absence of the carbon resonances in the benzimidazole ring, we methylated one of the compounds, the 2-nitro derivative **3f**, using methyl iodide as a methylating agent. Since there are two nitrogen atoms present in the benzimidazole scaffold, a mixture of the two methylated compounds was observed upon methylation; the two methylated compounds were purified and their $^1H$ and $^{13}C$ NMR data were obtained. As expected, the carbon resonances of the benzimidazole ring were now observed in both isomers, the *N*-1 and *N*-3 methylated compounds.

In the *N*-3 methylated 2-nitro derivative, the benzimidazole resonances appeared as a doublet for H-7 at $\delta$ 7.74 ($J$ = 8.8 Hz), a double doublet for H-6 at $\delta$ 7.15 ($J$ = 8.8, 1.8 Hz), and a singlet for H-4 at $\delta$ 7.65. The *N*-methyl resonance was present as a singlet at $\delta$ 3.87. The thiazolidinone resonances of H-2a and the two geminal protons of H-5a appeared at $\delta$ 6.90 as a singlet for H-2a and $\delta$ 3.92 and 3.81, two doublets with a coupling constant of 16.0 Hz. The 2-nitrophenyl proton resonances were present at $\delta$ 8.03 (d, $J$ = 8.1 Hz, H-3b), 7.44 (t, $J$ = 7.5 Hz, H-4b), and $\delta$ 7.59–7.62 (2H, m, H-5b, H-6b). The carbon resonances of the benzimidazole ring was now present at $\delta$ 106.7 (C-4), 120.1 (C-6), and 122.3 (C-7) for the protonated resonances and $\delta$ 134.9 (C-5), 136.1 (C-8), and 139.5 (C-9) for the singlet resonances. The C-2 and $CF_3$ carbon resonances appeared as quartets at $\delta$ 142.2 ($J$ = 38.3 Hz, C-2) and $\delta$ 118.8 ($J$ = 269.8 Hz). The thiazolidinone carbon resonances were present at $\delta$ 171.8 (C-4a, C=O), 60.9 (C-2a, methine), and 32.7 (C-5a, methylene). The 2-nitrophenyl carbon resonances appeared at $\delta$ 147.1 and 136.2 for the singlet carbons, C-1b and C-2b, and 134.3, 129.5, 126.9, and 125.9 for the protonated aromatic resonances C-6b, C-4b, C-5b, and C-3b, respectively. The *N*-methyl carbon resonance occurred at $\delta$ 31.0. The *N*-1 methylated 2-nitro derivative was elucidated in a similar manner. The two isomers were differentiated by NOESY data. The *N*-3 methylated compound showed a NOESY correlation to the H-4 doublet at $\delta$ 7.64, while the *N*-1 methylated compound showed a NOESY correlation to the H-7 doublet at $\delta$ 7.41.

**TABLE 1** Minimum bactericidal concentration (MBC in μM) of compounds **3a-l**

| | | Gram –ve | | | | Gram +ve | |
|---|---|---|---|---|---|---|---|
| **No.** | **R** | ***S.t.*** | ***K.p.*** | ***E.c.*** | ***P.a.*** | ***S.a.*** | **MRSA** |
| **3a** | **H** | – | – | 0.66 | – | 0.66 | – |
| **3b** | **2-F** | – | 0.32 | – | 0.16 | 0.16 | – |
| **3c** | **2-Cl** | – | 5.28 | 0.65 | 0.16 | 0.16 | – |
| **3d** | **2-Br** | – | 0.14 | 0.54 | 0.27 | 35.46 | 17.73 |
| **3e** | **2-$CF_3$** | – | 0.14 | – | 0.28 | 9.07 | – |
| **3f** | **2-$NO_2$** | 0.15 | 0.15 | 4.79 | – | 4.79 | – |
| **3 g** | **2-$OCH_3$** | – | 0.15 | 79.71 | – | 0.15 | – |
| **3 h** | **4-F** | – | 0.32 | – | 0.16 | 0.16 | – |
| **3i** | **4-Cl** | – | 0.61 | 0.61 | 0.61 | 0.30 | – |
| **3j** | **4-Br** | 17.73 | 0.14 | 0.27 | 0.55 | 0.27 | 35.46 |
| **3 k** | **4-$CF_3$** | – | 0.25 | – | – | 0.12 | – |
| **3 l** | **4-$NO_2$** | 0.15 | 0.15 | 0.15 | 9.58 | 38.33 | >250 |
| **Cip** | | 2.95 | 11.8 | 2.95 | 188.6 | 94.3 | 188.6 |
| **Lev** | | 21.6 | 21.6 | 0.34 | 345.0 | 21.6 | 86.5 |

*Note. S.t. = S. typhimurium*, *K.p. = K. pneumonia*, *E.c. = E. coli*, *P.a. = P. aeruginosa*, *S.a. = S. aureus*, Cip = Ciprofloxacin, Lev = Levofloxacin.

## 2.2 | Antimicrobial

The synthesized compounds were evaluated for their in vitro antibacterial activity against four Gram-negative bacteria, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, and *Salmonella typhimurium* and two Gram-positive bacteria, *Staphylococcus aureus* and *Staphylococcus aureus* Rosenbach (methicillin-resistant *S. aureus* (MRSA)). These are causative agents for urinary tract, gastrointestinal, and nosocomial infections as well as pneumonia and bronchitis.

Overall, the compounds demonstrated excellent activity (Table 1), when compared with the known antibiotics, ciprofloxacin and levofloxacin (Figure 2). The Gram-negative *K. pneumonia* and Gram-positive *S. aureus* were most susceptible to all the synthesized derivatives with MBC values of between 0.14–5.28 μM and 0.12–38.33 μM, respectively. Several compounds were approximately 80-fold more active than ciprofloxacin and 140-fold more active than levofloxacin against *K. pneumonia* while being approximately 600-fold more active than ciprofloxacin and 140-fold more active than levofloxacin against *S. aureus*. Compounds **3d**, **3j,** and **3l**, containing bromine and nitro groups, displayed broad-range activity against all test strains. The 2-Br (**3d**) and 4-Br (**3j**) derivatives showed excellent activity, higher than that of ciprofloxacin, against both the Gram-positive strains (*S. aureus* = 94.3 μM and MRSA = 188.6 μM). The 4-$NO_2$ (**3l**) derivative showed excellent activity against the Gram-negative strains with MBC values of 0.15 μM against *S. typhimurium*, *K. pneumonia*, and *E. coli* and 9.58 μM against *P. aeruginosa*.

The activity of the compounds was enhanced by the substitution on the phenyl ring of the thiazolidine. Compound **3a**, with an unsubstituted phenyl ring, was only active against *E. coli* and *S. aureus* and lower than other compounds with substituents on the phenyl ring. It did not seem to make too much of a difference whether the substituents were at the 2- or the 4- position, however, slightly better activity was seen in substituents at the 4-position. For example, the 2-$NO_2$ derivative **3f**, had lower activity than that of the 4-$NO_2$ derivative **3l**, against *E. coli* and was not active against *P. aeruginosa*. However, it was more active than the 4-$NO_2$ derivative **3l**, against *S. aureus*. The activities of the 2-Cl (**3c**) and 4-Cl (**3i**), and 2-F (**3b**) and 4-F (**3h**) compounds were very similar, as were the 2-Br (**3d**) and 4-Br (**3j**) compounds, however, the 4-Br compound **3j** was additionally active against *S. typhimurium*, whereas the 2-Br (**3d**) derivative was not.

Similar benzimidazoles with a phenyl group at C-2, instead of a trifluoromethyl group, also showed good antimicrobial activity, comparable with that of ciprofloxacin[29] and 2,3-disubstituted thiazolidinone-benzimidazole hybrids with a methylthio group instead of the trifluromethyl group at C-2 and a thiazolidinone group attached to a thiosemicarbazone at N-1, showed a broad-spectrum antibacterial activity, similar to ampicillin.[16] 2-Mercaptobenzimidazole-4-phenylthiazolidinone derivatives, with a thiol group at C-2 instead of a trifluoromethyl group showed up to four-fold better activity against strain-specific bacteria than that of ciprofloxacin.[26] Our results have shown better activity to those previously reported, with a broader spectrum, and have further shown the potential of the trifluoromethyl group to be a useful moiety to tag onto C-2 of benzimidazoles to produce small molecules with good antibacterial activity.

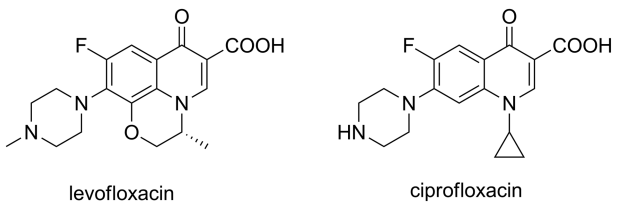



**FIGURE 2** Structures of the standard antibiotics levofloxacin and ciprofloxacin

## 3 | CONCLUSION

A series of new benzimidazole-thiazolidinone hybrids were synthesized by a simple and attractive method using 4-nitro-1,2-phenyldiamine, trifluoroacetic acid, thioglycolic acid, and a series of benzaldehydes. Microwave synthesis using ethanol as the solvent was successfully employed to synthesize the thiazolidinones in the final step with good yields in a more eco-friendly method. This is a rapid method of adding a thiazolidinone moiety to a core structure with a free amino group, providing an avenue to increase its bioactivity. The synthesized compounds showed excellent antibacterial activity against a series of Gram-positive and Gram-negative bacterial strains. Among them, the bromo and nitro derivatives **3d**, **3j**, and **3l** showed a broad spectrum of activity, being active against all of the strains tested with MBC values between 0.14 and 38.33 μM. These compounds are good hits that can be developed into lead compounds for new antibiotics.

## 4 | EXPERIMENTAL

### 4.1 | General

All reagents and chemicals were purchased from Sigma Aldrich (Germany) and used without purification. Reactions were monitored using thin layer chromatography (silica gel 60-$F_{254}$ aluminum-coated plates) and visualized under UV light. Column chromatography was carried out using silica gel (60–120 mesh) as the stationary phase and

varying ratios of organic solvents as the mobile phase. Melting points were obtained using a Stuart Smart Scientific melting point instrument and were uncorrected. Microwave reactions were performed using a CEM Discover, Explorer-12 Hybrid microwave. $^{1}H$, $^{13}C$, and 2D NMR analysis was acquired on a Bruker Avance 400 MHz spectrometer using tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in ppm in DMSO-$d_6$ ($\delta$ 2.50 for $^{1}H$ and 39.51 for $^{13}C$ NMR) or $CD_3OD$ ($\delta$ 3.35 for $^{1}H$ and 49.15 for $^{13}C$ NMR). Coupling constants ($J$) are reported in hertz (Hz). High resolution mass spectrometry (HRMS) was recorded with a Bruker micro TOF-Q II ESI instrument. All column chromatography was performed using silica gel (60–120 mesh).

## 4.2 | Synthesis

### 4.2.1 | General procedure for the synthesis of 2-phenyl-3-(2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)thiazolidin-4-ones

4-Nitro-1,2-phenyldiamine (1.00 g, 0.65 mol) was stirred at room temperature in trifluoroacetic acid (10 mL) for 2 h. The reaction was monitored to completion by TLC, after which, the trifluoroacetic acid was evaporated under pressure. The crude 6-nitro-2-trifluoromethylbenzimidazole was dissolved in ethyl acetate (15 mL), basified with sodium hydrogen carbonate (pH 8.5), and partitioned with water (15 mL). The organic layer was evaporated under reduced pressure to yield 6-nitro-2-trifluoromethyl-benzimidazole **1** as a pale white solid (86% yield). Pd/C (10%) was then added to **1** (0.5 g, 2.2 mmol) dissolved in methanol and the mixture was stirred at room temperature for 4 h under hydrogen atmosphere. On completion, the Pd was filtered off under vacuum using celite 545 and the filtrate reduced under pressure and purified by column chromatography using ethyl acetate and hexane (30:70) to yield 2-trifluoromethylbenzimidazol-6-amine **2** as a brown solid (70% yield).

Compound **2** (0.2 g, 1.0 mmol) and substituted benzaldehydes (1.5 mmol) were dissolved in ethanol (3 mL) and thioglycolic acid (0.2 mL, 3.0 mmol) and glacial acetic acid (3–5 drops) was added dropwise to the mixture. The mixture then underwent microwave irradiation for 30 min at 110°C. The reaction was then basified using sodium bicarbonate until just alkaline and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate, 7:3) to yield cream solids **3a-l** in yields between 75% and 83%.

Note: C-4, C-6, and C-7 for all compounds were not present in the $^{13}C$ NMR spectra because of the degenerate tautomerism of the NH proton, resulting in the resonances becoming magnetically equivalent because of rapid proton exchange between N1 and N3.[27] This is also responsible for the broadening of the $^{1}H$ resonances for H-4, H-6, and H-7 resulting in the theoretical splitting patterns being absent. HRMS confirmed the structures of all compounds.

### 4.2.2 | 2-Phenyl-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl)thiazolidin-4-one (3a)

Cream solid; 82% yield; mp 117°C–118°C; IR (KBr) $\upsilon_{max}$:1631 $cm^{-1}$ (C=O); $^{1}H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 13.99 (1H, s, H-NH), 7.70 (1H, bs, H-4), 7.60 (1H, bs, H-7), 7.41 (2H, d, $J$ = 7.5 Hz, H-2b/6b), 7.32 (1H, bs, H-6), 7.25 (2H, t, $J$ = 7.5 Hz, H-3b/5b), 7.20 (1H, t, $J$ = 7.5 Hz, H-4b), 6.55 (1H, s, H-2a), 4.05 (1H, d, $J$ = 15.6 Hz, 5ai), 3.92 (1H, d, $J$ = 15.6 Hz, 5aii); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz)$\delta$ 170.7 (C-4a), 140.9 (q, $J$ = 39.1 Hz, C-2), 139.9 (C-1b), 128.6 (C-3b/5b), 128.5 (C-4b), 127.2 (C-2b/6b), 118.9 (q, $J$ = 270.7, $CF_3$), 64.0 (C-2a), 32.7 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{11}N_3OF_3S$ [M-H]: 362.0575. Found 362.0583.

### 4.2.3 | 2-(2-Fluorophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3b)

Cream solid; 81% yield; mp 200°C–202°C; IR (KBr) $\upsilon_{max}$:1631 $cm^{-1}$ (C=O); $^{1}H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.69 (2H, bs, H-4,7), 7.49 (1H, t, $J$ = 8.0 Hz, H-6b), 7.35 (1H, d, $J$ = 8.0 Hz, H-6), 7.26 (1H, m, H-4b), 7.10 (2H, m, H-3b/5b), 6.74 (1H, s, H-2a), 4.03 (1H, d, $J$ = 15.6 Hz, H-5ai), 3.93 (1H, d, $J$ = 15.6 Hz, H-5aii); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz)$\delta$ 170.6 (C-4a), 159.9 (d, $J$ = 245.8 Hz, C-2b), 141.2 (q, $J$ = 39.3 Hz, C-2), 130.8 (d, $J$ = 8.5 Hz, C-4b), 129.3 (d, $J$ = 2.7 Hz, C-6b), 126.9 (d, $J$ = 10.8, 1b), 124.9 (d, $J$ = 3.2 Hz, C-5b), 118.9 (q, $J$ = 271.7 Hz, $CF_3$), 115.9 (d, $J$ = 20.8 Hz, C-3b), 58.9 (d, $J$ = 2.9 Hz, C-2a), 32.8 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_3OF_4S$ [M-H]: 380.0481. Found 380.0484.

### 4.2.4 | 2-(2-Chlorophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3c)

Cream solid; 76% yield; mp 162°C–163°C; IR (KBr) $\upsilon_{max}$:1630 $cm^{-1}$ (C=O); $^{1}H$ NMR (DMSO-$d_6$, 400 MHz) $\delta$ 14.02 (NH), 7.82 (1H, bs, H-4), 7.72 (1H, bs, H-7), 7.59

(1H, bs, H-3b), 7.43 (1H, bs, H-6), 7.36 (1H, d, $J = 7.8$ Hz, H-6b), 7.29–7.21 (2H, m, H-4b, H-5b), 6.87 (1H, s, H-2a), 4.03 (1H, d, $J = 15.5$ Hz, H-5ai), 3.94 (1H, d, $J = 15.5$ Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz)$\delta$ 170.8 (C-4a), 141.5 (q, $J = 38.9$ Hz, C-2), 136.7 (C-2b), 131.6 (C-1b), 130.0* (2C, C-3b, 5b), 127.7* (2C, C-4b, C-6b), 118.8 (q, $J = 270.7$ Hz, $CF_3$), 61.9 (C-2a), 32.62 (C-5a); * assignments may be interchanged; HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_3OF_3SCl$ [M-H]: 396.0185. Found 396.0174.

### 4.2.5 | 2-(2-Bromophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3d)

Cream solid; 81% yield; mp 191°C–192°C; IR (KBr) $\upsilon_{max}$: 1679 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.75 (1H, bs, H-4), 7.65 (1H, bs, H-6b), 7.59 (1H, bs, H-7), 7.53 (1H, d, $J = 7.8$ Hz, H-3b), 7.42 (1H, d, $J = 8.4$ Hz, H-6), 7.32 (1H, t, $J = 7.8$ Hz, H-5b), 7.15 (1H, dt, $J = 7.8$, 1.6 Hz, H-4b), 6.79 (1H, s, H-2a), 4.02 (1H, dd, $J = 15.6$, 1.3 Hz, H-5ai), 3.93 (1H, d, $J = 15.6$ Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz)$\delta$ 170.9 (C-4a), 141.3 (q, $J = 39.4$ Hz, C-2), 140.9 (C-2b), 130.3 (C-3b), 128.3 (2C, C-5b, C-6b), 121.7 (C-1b), 118.8 (q, $J = 270.1$ Hz, $CF_3$), 63.5 (C-2a), 31.3 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_3OF_3SBr$ [M-H]: 439.9680. Found 439.9683.

### 4.2.6 | 3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl)-2-(2-(trifluoromethyl) phenyl)thiazolidin-4-one (3e)

Cream solid; 79% yield; mp 194°C–196°C; IR (KBr) $\upsilon_{max}$: 1667 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.96 (1H, d, $J = 7.8$ Hz, H-6b), 7.71 (1H, bs, H-4), 7.65 (2H, m, H-4b, H-6), 7.57 (1H, d, $J = 7.8$ Hz, H-3b), 7.40 (2H, m, H-5b, H-7), 6.74 (1H, s, H-2a), 4.07 (1H, d, $J = 15.5$ Hz, H-5ai), 3.95 (1H, d, $J = 15.5$ Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz)$\delta$ 171.0 (C-4a), 141.6 (q, $J = 39.5$ Hz, C-2), 138.4 (C-1b), 133.5 (C-4b), 129.2 (C-5b), 129.0 (C-6b), 125.6 (q, $J = 45.6$ Hz, C-2b), 125.4 (q, $J = 5.7$ Hz, C-3b), 118.8 (q, $J = 270.3$ Hz, $CF_3$), 59.8 (C-2a), 32.6 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{18}H_{10}N_3OF_6S$ [M-H]: 430.0449. Found 430.0445.

### 4.2.7 | 2-(2-Nitrophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3f)

Cream solid; 76% yield; mp 149°C–150°C; IR (KBr) $\upsilon_{max}$:1667 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.94 (1H, dd, $J = 8.0$, 1.2 Hz, H-3b), 7.88 (1H, dd, $J = 8.0$, 1.2 Hz, H-6b), 7.83 (1H, bs, H-4), 7.71 (1H, dt, $J = 8.0$, 1.2 Hz, H-5b), 7.64 (1H, d, $J = 8.8$ Hz, H-7), 7.50 (1H, dd, $J = 8.8$, 1.5 Hz, H-6), 7.47 (1H, dt, $J = 8.0$, 1.2 Hz, H-4b), 6.85 (1H, s, H-2a), 4.05 (1H, dd, $J = 15.8$, 1.5 Hz, H-5ai), 3.88 (1H, d, $J = 15.8$ Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz)$\delta$ 171.0 (C-4a), 147.2 (C-2b), 141.1 (q, $J = 39.3$ Hz, C-2), 135.2 (C-1b), 134.4 (C-5b), 129.5 (C-4b), 128.1 (C-6b), 124.8 (C-3b), 59.6 (C-2a), 31.9 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_4O_3F_3S$ [M-H]: 407.0426. Found 407.0420.

### 4.2.8 | 2-(2-Methoxyphenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3g)

Cream solid; 75% yield; mp 170°C–172°C; IR (KBr) $\upsilon_{max}$: 1676 cm$^{-1}$ (C=O); $^1$H NMR ($CD_3OD$, 400 MHz) $\delta$ 7.97 (1H, d, $J = 7.4$ Hz, H-6), 7.63 (1H, d, $J = 8.6$ Hz, H-3b), 7.20 (1H, dt, $J = 8.0$, 1.5 Hz, H-5b), 7.02–6.96 (3H, m, H-4b, H-4, H-7), 6.78 (1H, d, $J = 8.0$ Hz, H-6b), 6.24 (1H, bs, H-2a), 3.40 (1H, d, $J = 16.0$ Hz, H-5ai), 3.38 (3H, s, $OCH_3$), 2.81 (1H, d, $J = 16.0$ Hz, H-5aii); $^{13}$C NMR ($CD_3OD$-$d_4$, 100 MHz) $\delta$ 173.8 (C-4a), 158.4 (C-2b), 130.4 (C-3b), 129.6 (C-5b), 121.0 (C-4b), 111.6 (C-6b), 55.6 ($OCH_3$), 31.9 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{18}H_{13}N_3O_2F_3S$ [M-H]: 392.0681. Found 392.0674.

### 4.2.9 | 2-(4-Fluorophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3h)

Cream solid; 83% yield; mp 212°C–213°C; IR (KBr) $\upsilon_{max}$: 1632 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.62 (2H, bs, H-4, H-7), 7.47 (2H, dd, $J = 8.8$, 5.4 Hz, H-2b/6b), 7.29 (1H, d, $J = 8.6$ Hz, H-6), 7.07 (2H, t, $J = 8.8$ Hz, H-3b/5b), 6.55 (1H, s, H-2a), 4.04 (1H, d, $J = 15.6$ Hz, H-5ai), 3.92 (1H, d, $J = 15.6$ Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz)$\delta$ 170.7 (C-4a), 162.1 (d, $J = 243.7$ Hz, C-4b), 141.1 (q, $J = 39.9$, C-2), 136.1 (d, $J = 2.8$ Hz, C-1b), 129.5 (d, $J = 9.2$ Hz, C-2b/6b), 118.8 (q, $J = 271.2$ Hz, $CF_3$), 115.5 (d, $J = 21.1$ Hz, C-3b/5b), 63.4 (C-2a), 32.8 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_3OF_4S$ [M-H]: 380.0481. Found 380.0484.

### 4.2.10 | 2-(4-Chlorophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3i)

Cream solid; 78% yield; mp 188°C–190°C; IR (KBr) $\upsilon_{max}$: 1656 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 14.00 (1H, bs, NH), 7.71 (1H, bs, H-4), 7.58 (1H, bs, H-

7), 7.46 (2H, d, $J$ = 8.4 Hz, H-2b/6b), 7.31 (1H, bs, H-6*), 7.30 (2H, d, $J$ = 8.4 Hz, 3b/5b*), 6.58 (1H, s, H-2a), 4.06 (1H, d, $J$ = 15.7 Hz, H-5ai), 3.93 (1H, d, $J$ = 15.7 Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 170.5 (C-4a), 141.2 (q, $J$ = 39.8 Hz, C-2), 139.0 (C-1b), 132.9 (C-4b), 129.2 (C-2b/6b), 128.6 (C-3b/5b), 118.8 (q, $J$ = 270.2 Hz, $CF_3$), 63.1 (C-2a), 32.7 (C-5a); *overlapping resonances; HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_3OF_3SCl$ [M-H]: 396.0185. Found 396.0179.

### 4.2.11 | 2-(4-Bromophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3j)

Cream solid; 83% yield; mp 200°C–201°C; IR (KBr) $\upsilon_{max}$:1634 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.64 (2H, bs, H-4, H-7), 7.45 (2H, d, $J$ = 8.5 Hz, H-3b/5b), 7.40 (2H, d, $J$ = 8.5 Hz, H-2b/6b), 7.31 (1H, d, $J$ = 8.8 Hz, H-6), 6.56 (1H, s, H-2a), 4.06 (1H, dd, $J$ = 15.7, 1.4 Hz, H-5ai), 3.93 (1H, d, $J$ = 15.7 Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 170.6 (C-4a), 141.2 (q, $J$ = 39.5 Hz, C-2), 139.5 (C-1b), 131.5 (C-3b/5b), 129.5 (C-2b/6b), 121.6 (C-4b), 118.8 (q, $J$ = 271.2 Hz, C-$CF_3$), 63.2 (C-2a), 37.7 (C-5a); HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_3OF_3SBr$ [M-H]: 439.9680. Found 439.9682.

### 4.2.12 | 3-(2-(Trifluoromethyl)-1H-benzimidazol-5-yl)-2-(4-(trifluoromethyl) phenyl)thiazolidin-4-one (3k)

Cream solid; 82% yield; mp 183°C–184°C; IR (KBr) $\upsilon_{max}$: 1637 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 7.71 (1H, s, H-4), 7.67 (3H, d, $J$ = 8.3 Hz, H-2b/6b, H-7*), 7.61 (2H, d, $J$ = 8.3 Hz, H-3b/5b), 7.35 (1H, d, $J$ = 8.7 Hz, H-6), 6.68 (1H, s, H-2a), 4.10 (1H, d, $J$ = 15.6 Hz, H-5ai), 3.95 (1H, d, $J$ = 15.6 Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 170.8 (C-4a), 144.9 (C-1b), 141.4 (q, $J$ = 40.0 Hz, C-2), 128.9 (q, $J$ = 31.3 Hz, C-4b), 128.0 (C-2b/6b), 125.7 (d, $J$ = 3.7 Hz, C-3b/5b), 124.7 (q, $J$ = 270.4 Hz, Ph$\underline{C}F_3$), 118.8 (q, $J$ = 270.4 Hz, $CF_3$), 63.2 (C-2a), 32.7 (C-5a); *H-7 is underneath the H-2b/6b resonance; HR-ESI(−)-MS. *Anal*. Calcd. for $C_{18}H_{10}N_3OF_6S$ [M-H]: 430.0449. Found 430.0448.

### 4.2.13 | 2-(4-Nitrophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl) thiazolidin-4-one (3l)

Cream solid; 78% yield; mp 153°C–154°C; IR (KBr) $\upsilon_{max}$: 1671 cm$^{-1}$ (C=O); $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 8.07 (2H, d, $J$ = 8.8 Hz, H-3b/5b), 7.68 (3H, d, $J$ = 8.8, H-2b/6b, H-4*), 7.61 (1H, d, $J$ = 8.8 Hz, H-7), 7.33 (1H, dd, $J$ = 8.8, 1.9 Hz, H-6), 6.64 (1H, s, H-2a), 4.07 (1H, dd, $J$ = 15.8, 1.5 Hz, H-5ai), 3.92 (1H, d, $J$ = 15.8 Hz, H-5aii); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 171.5 (C-4a), 147.9 (C-1b), 141.9 (q, $J$ = 40.0 Hz, C-2), 133.9 (C-4b), 129.0 (C-2b/6b), 124.3 (C-3b/5b), 119.1 (q, $J$ = 271.6 Hz, $CF_3$), 63.5 (C-2a), 33.2 (C-5a); *H-4 overlaps with H-2b/6b; HR-ESI(−)-MS. *Anal*. Calcd. for $C_{17}H_{10}N_4O_3F_3S$ [M-H]: 407.0426. Found 407.0431.

### 4.2.14 | Methylation of 2-(2-nitrophenyl)-3-(2-(trifluoromethyl)-1H-benzimidazol-5-yl)thiazolidin-4-one (3f)

2-(2-Nitrophenyl)-3-(2-(trifluoromethyl)-1*H*-benzimidazol-5-yl)thiazolidin-4-one **3f** (142 mg, 0.336 mmol) and potassium carbonate (193 mg, 1.40 mmol) were added to dimethylformamide (5 mL) and stirred at room temperature for 45 min. Thereafter, iodomethane (0.2 mL) in dimethylformamide (0.5 mL) was added dropwise to the reaction mixture, which was stirred at room temperature for 15 h. The reaction mixture was poured into an ice slurry, where a white precipitate formed. The precipitate was filtered, washed with water, and air dried to afford a mixture of the *N*-1 and *N*-3 methylated compounds in 72% yield. They were separated by column chromatography on silica gel (hexane:ethyl acetate, 8:2) to yield pure cream solids of *N*-1 methyl derivative (27 mg) and *N*-3 methyl derivative (9 mg) in yields of 19% and 6%, respectively. An amount of 55 mg (39%) remained as a mixture of the two *N*-methylated derivatives.

### 4.2.15 | N-1 methylated derivative of 3f: 3-(1-methyl-2-(trifluoromethyl)-1H-benzo[d] imidazol-5-yl)-2-(2-nitrophenyl)thiazolidin-4-one

Cream solid; $^1$H NMR ($CDCl_3$, 600 MHz) $\delta$ 8.03 (1H, d, $J$ = 8.1 Hz, H-3b), 7.74 (1H, d, $J$ = 8.8 Hz, H-7), 7.65 (d, $J$ = 1.8 Hz, H-4), 7.59–7.62 (2H, m, H-5b, H-6b), 7.44 (1H, t, $J$ = 7.5 Hz, H-4b), 7.15 (1H, dd, $J$ = 8.8, 1.8 Hz, H-6), 6.90 (1H, s, H-2a), 3.92 (1H, d, $J$ = 16.0 Hz, H-5ai), 3.87 (3H, s, N-$CH_3$), 3.81 (1H, d, $J$ = 16.0 Hz, H-5aii); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 171.8 (C-4), 147.1 (C-1b), 142.2 (q, $J$ = 38.3 Hz, C-2), 139.5 (C-9), 136.2 (C-2b), 136.1 (C-8), 134.9 (C-5), 134.3 (C-6b), 129.5 (C-4b), 126.9 (C-5b), 125.9 (C-3b), 122.3 (C-7), 120.0 (C-6), 118.8 (q, $J$ = 269.8 Hz, $\underline{C}F_3$), 106.7 (C-4), 60.9 (C-2a), 32.7 (C-5a), 31.0 (N-$\underline{C}H_3$).

#### 4.2.16 | N-3 methylated derivative of 3f: 3-(1-methyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)-2-(2-nitrophenyl)thiazolidin-4-one

Cream solid; $^{1}$H NMR ($CDCl_3$, 600 MHz) $\delta$ 8.04 (1H, d, $J$ = 8.2 Hz, H-3b), 7.62–7.63 (2H, m*, H-5b, H-6b), 7.60 (1H, d, $J$ = 1.8 Hz, H-4), 7.56 (1H, dd, $J$ = 8.9, 1.8 Hz, H-6), 7.44 (1H, m, H-4b), 7.41 (1H, d, $J$ = 8.9 Hz, H-7), 6.78 (1H, d, $J$ = 1.0 Hz, H-2a), 3.92 (1H, dd, $J$ = 16.1, 1.0 Hz, H-5ai), 3.88 (3H, s, N-$CH_3$), 3.80 (1H, d, $J$ = 16.1 Hz, H-5aii); $^{13}$C NMR ($CDCl_3$, 150 MHz) $\delta$ 171.9 (C-4a), 146.9 (C-1b), 141.0 (C-5), 136.4 (C-8), 134.4 (C-5b), 133.6 (C-9), 129.4 (C-4b), 126.9 (C-6b), 125.9 (C-3b), 122.8 (C-6), 117.9 (C-4), 111.0 (C-7), 61.2 (C-2a), 32.4 (C-5a), 31.0 (N-$\underline{C}H_3$). *This resonance appears as a doublet but two separate resonances, H-5b and H-6, overlap in this region. The C-2 and $\underline{C}F_3$ resonances were not detected.

### 4.3 | Antibacterial assays

The antibacterial activity of the synthesized compounds was tested against two Gram-positive bacteria, *Staphylococcus aureus* ATCC 25923 and *Staphylococcus aureus* Rosenbach ATCC BAA-1683 (methicillin-resistant *S. aureus*), and four Gram-negative bacteria, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumonia* ATCC 31488, *Escherichia coli* ATCC 25922, and *Salmonella typhimurium* ATCC 14026.

Sterilized Mueller-Hinton agar plates were lawn inoculated with different bacterial strains. Stock solutions of each test compound (1 mg $mL^{-1}$ in DMSO) were prepared and 5 μL of each compound was placed onto the plates and incubated at 37°C for 24 h, after which, the compounds that inhibited bacterial growth were further tested using the minimum bactericidal concentration (MBC) assay.

### 4.4 | Minimum bactericidal concentration assay

All compounds showing any activity in the initial disk diffusion screening assay were tested for their antibacterial activity by the MBC assay. They were dissolved in DMSO and a two-fold serial dilution was carried out to give a range from 1000 μg $mL^{-1}$ to 0.03 μg $mL^{-1}$. Mueller-Hinton agar plates lawn inoculated with the different bacterial strains were impregnated with 5 μL of each concentration of compound and incubated for 24 h at 37°C. Ciprofloxacin and levofloxacin were used as positive controls, while DMSO was used as a negative control. The lowest concentration that inhibited the growth of bacteria was taken to be the MBC value. The assay was performed in triplicate and an average of the readings was taken.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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