A Platinum Open Access Journal for Organic Chemistry

Paper

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Design and synthesis of novel thiazole–benzimidazole hybrids as antimicrobial agents

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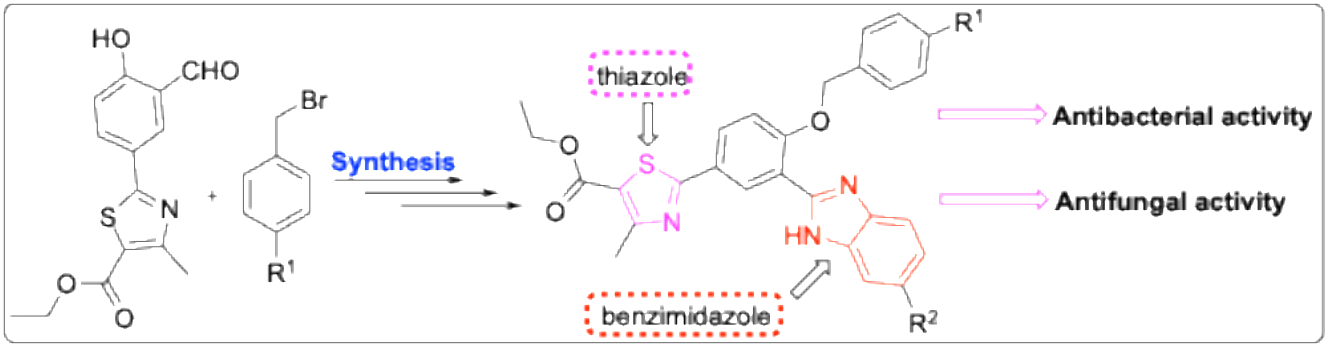
Received 11-13-2024 **Accepted** 12-09-2024 **Published on line** 12-21-2024

Abstract

A novel series of compounds, with a thiazole combined with a benzimidazole, were synthesized from an acid catalyzed condensation-cyclization reaction of ethyl 2-(4-(benzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylates and variously substituted benzene-1,2-diamines in ethanol. The new compounds were screened for their antimicrobial activities against four bacterial and two fungal strains. All products presented a noteworthy zone of inhibitions in comparison to the reference drugs viz. *Ciprofloxacin* and *Itraconazole*.



Keywords: Antimicrobial, benzimidazole, molecular hybridization, thiazole

Introduction

Antimicrobial Resistance (AMR) refers to the ability of microorganisms, such as bacteria, viruses, fungi, and parasites, to adapt and thrive in the presence of drugs that previously affected them.[1] Antimicrobial resistance (AMR) poses a substantial risk to public health, not only in underdeveloped nations but globally.[2] The emergence of antibiotic-resistant infectious illnesses portends an uncertain future in the field of healthcare. Contracting antimicrobial resistance (AMR) results in severe diseases, extended stays in hospitals, elevated healthcare expenses, increased expenditures on secondary medications, and treatment ineffectiveness.[3]

The benzimidazole nucleus is widely recognized as a preferred structure in the field of drug development.[4,5] It has been extensively utilized by multiple research groups for developing a variety of compounds with potential antibacterial properties.[6] The similarity in structure between the benzimidazole nucleus and the purine nucleus in nucleotides makes benzimidazole derivatives appealing ligands for interacting with biopolymers in biological systems.[7] The primary benzimidazole molecule found in nature is *N*-ribosyldimethylbenzimidazole, which functions as a central ligand for cobalt in vitamin B12.[8] Due to the similar structure, medicinal chemists worldwide have synthesized various benzimidazole derivatives and investigated them for a range of biological activities, including anticancer,[9] antiviral,[10] antihistamine,[11] antiparasitc,[12] antiulcer,[13] antimicrobial,[14] antihypertensive,[15] anti-inflammatory,[16] analgesic,[17] anticonvulsant,[18] antitubercular,[19] antioxidant,[20] antidepressant[21] and antidiabetic[22] activities. Omeprazole is a benzimidazole derivative that functions as a proton-pump inhibitor. It is employed in the treatment of ailments associated with gastric acid. [23] Albendazole is a benzimidazole-derived drug prescribed for the treatment of two specific forms of parasitic infections: neurocysticercosis and hydatid disease.[24] Astemizole is a second-generation antihistamine that is utilized for the treatment of allergy symptoms. It contains benzimidazole in its chemical structure.[25]

Thiazole is known for its diverse range of biological activity and medicinal properties. As a result, thiazoles have become a very desirable category of chemicals in drug discovery initiatives.[26] Thiazole compounds have consistently shown a range of interesting biological properties, such as antitubercular,[27] antioxidant,[28] anti-HIV,[29] antibacterial,[30] antiviral,[31] anticancer,[32] analgesic,[33] antidiabetic[34] and anti-inflammatory[35] effects. The thiazole and benzothiazole containing molecules are known to be potent inhibitors of carbonic anhydrase enzyme.[36,37] Regarding antimicrobial effect, the thiazole moiety is commonly used as a fundamental component in the structure of various medicines. The tetrahydrothiazole-containing antibiotics Ampicillin,[38] Amoxicillin,[39] Ceftriaxone,[40] Cefotaxime,[41] and Penicillin,[42] Sulfathiazole,[43] and antibiotics containing a thiazole nucleus, such as Abafungin,[44] Ethaboxam,[45] Ravuconazole,[46] and Myxothiazole,[47] are marketed drugs. Some of the compounds containing either a benzimidazole or thiazole nucleus are shown in Figure 1. The combination of thiazole with benzimidazole results in improved biological characteristics that have appealed to chemists.[48–51] Based on these discoveries, we were motivated to design and synthesize a new series of hybrid compounds that have thiazole and benzimidazole units (Figure 2) and evaluated their antimicrobial activities.

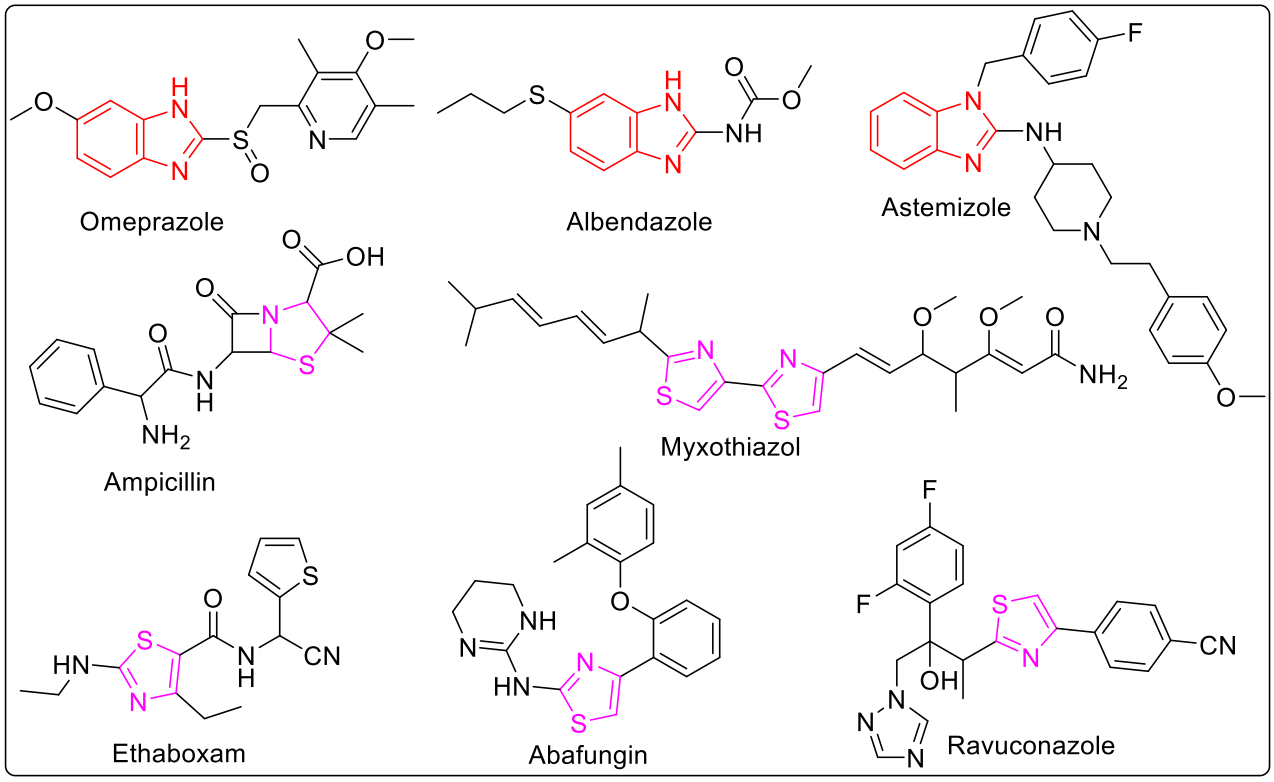


Figure 1. Marketed drugs containing benzimidazole and thiazole nuclei.

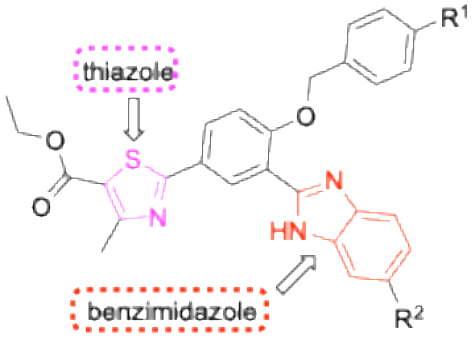


Figure 2. Design rationale of new thiazole – benzimidazole hybrids.

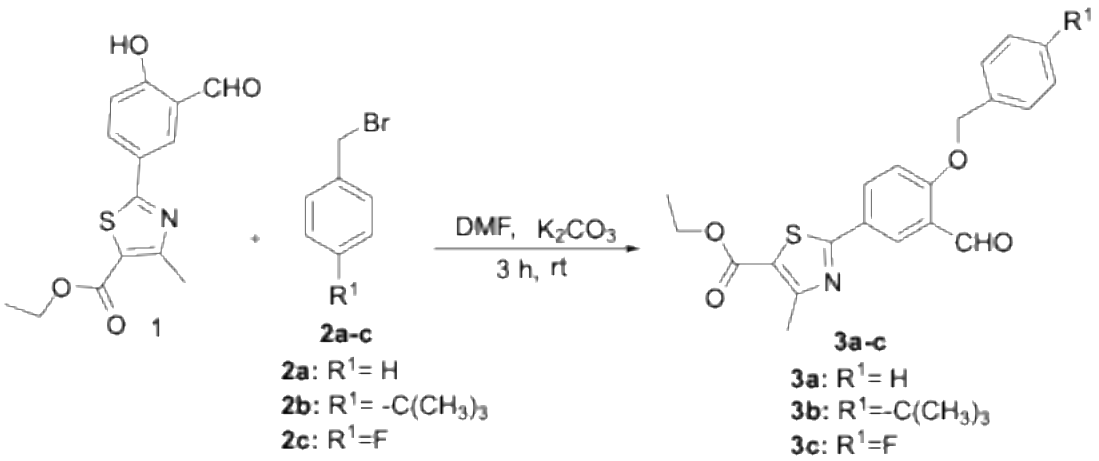
Results and Discussion

Chemistry

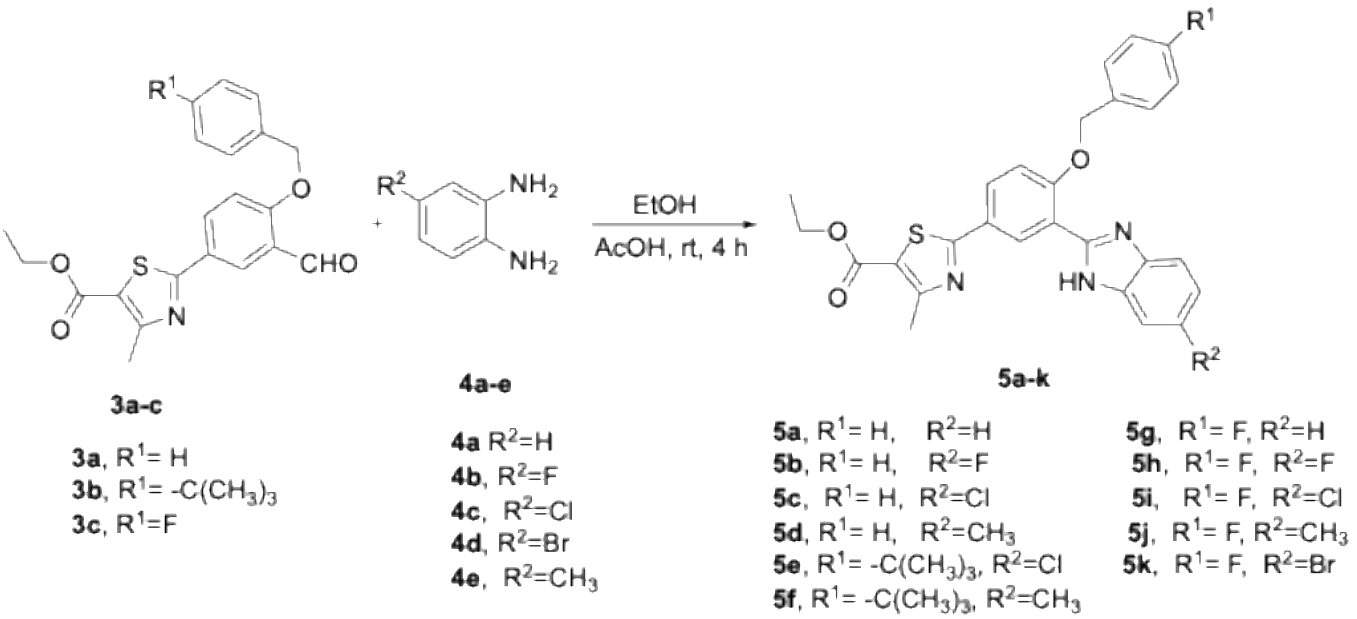
The synthesis of ethyl 2-(6-substituted-3-(1*H*-benzo[*d*]imidazol-2-yl)-4-(4-substituted benzyloxy)phenyl)-4-methylthiazole-5-carboxylate derivatives **5a-k**, are presented in Schemes 1 and 2. These hybrid heterocyclic compounds were synthesized in two steps using ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (**1**) as a starting precursor. The thiazole ester **1** was prepared by following the reported procedure.[52] The hydroxy group in the compound **1** was benzylated on reaction with substituted benzyl bromides **2a-c** in the presence of potassium carbonate to afford the corresponding ethyl 2-(4-(substitutedbenzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylates **3a-c**. These are all new compounds, their structures being

confirmed from their spectral data: thus for **3**, prominent peaks were found at 1703 cm^{-1} (COOEt), 1686 cm^{-1} (CHO) in IR; two ^{1}H NMR singlet peaks at δ 10.55 (C<u>H</u>O), 5.27 (C<u>H</u>$_2$Ar); ^{1}H NMR quartet and triplet signals at δ 4.35, 1.39 ppm (COOC<u>H</u>$_2$C<u>H</u>$_3$) and δ 188.77(<u>C</u>HO), 168.31(<u>C</u>OOC$_2$H$_5$) in ^{13}C NMR spectra.

The synthesis of a novel series of the target hybrid heterocycles having thiazole and benzimidazole scaffolds **5a-k** was achieved using the thiazole based substituted benzaldehydes **3a**-**c** and substituted benzene-1,2-diamines **4a**-**e** as precursors in acid-catalyzed cyclocondensation reactions. Initially, the aldehyde **3a** was treated with *ortho*-phenylene diamine **4a** in the presence of a few drops of acetic acid. The final hybrid compound **5a** was isolated a standard work-up and purification. The N<u>H</u> of benzimidazole ring and benzyl C<u>H</u>$_2$ protons and protons of methyl group resonated as singlet signals at δ 10.54, 5.35, 2.79 ppm with integration 1:2:3 ratio in its ^{1}H NMR spectrum and the quartet, triplet signals at δ 4.36 and 1.40 ppm for the ethyl group of an ester moiety along with the remaining protons signals in the aromatic region. In the ^{13}CMR spectrum the disappearance of a carbon peak at δ 188.12 ppm due to CHO group, and the appearance of the signal at δ 152.61 ppm due to benzimidazole C-2 carbon located, between two nitrogen atoms indicated the formation of the product **5a**. The ethyl ester group carbons resonated at δ 168.65, 61.41 and 14.60 ppm (<u>C</u>OO<u>C</u>H$_2$<u>C</u>H$_3$), while the benzyl carbon is resonated at δ 70.15 ppm. The compound also showed a protonated molecular ion peak at *m/z* 470.35 in its ESI-MS spectrum. A group of thiazole-based benzimidazoles **5a-k** were made by reacting the ethyl 2-(4-(benzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylates **3a-c** with substituted benzene-1,2-diamines **4a-e** using the protocol shown in Scheme 2.



Scheme 1. Synthesis of ethyl 2-(4-(substitutedbenzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylates **3a-c.**



Scheme 2. Synthesis of thiazole based benzimidazole hybrid compounds **5a-k.**

Antimicrobial Activity

The newly developed thiazole - benzimidazole hybrids were examined for their antimicrobial activity in vitro against two gram positive bacteria (*S.aureus, B.Substilis*), two gram negative bacteria (*E.coli, P.aeruginosa*), and two fungal strains (*C.albicans, A.niger*) using the agar disc fusion method. Ciprofloxacin and Itraconazoles were employed as standard reference drugs and presented all of their zone of inhibitions in Figure 3 and **4**. Interestingly, these compounds had shown moderate to high activity against all of the bacterial and fungal strains. The compounds **5d** (R^1 = H, R^2 = CH_3) and **5e** (R^1 = $C(CH_3)_3$, R^2 = Cl) exhibited higher levels of activity compared to the reference compounds against both bacterial and fungal strains. Compound **5b** (R^1 = H, R^2 = F) exhibited greater action against the bacterial strain *B.substillis*. The compounds **5a** (R^1 = H, R^2 = H) and **5h** (R^1 = F, R^2 = F) exhibited the highest level of activity against the fungal strain *C.albicans*. The effectiveness of the other compounds ranged from adequate to modest. The activity of these molecules may be attributed to the presence of thiazole and benzimidazole in their structural constituents.

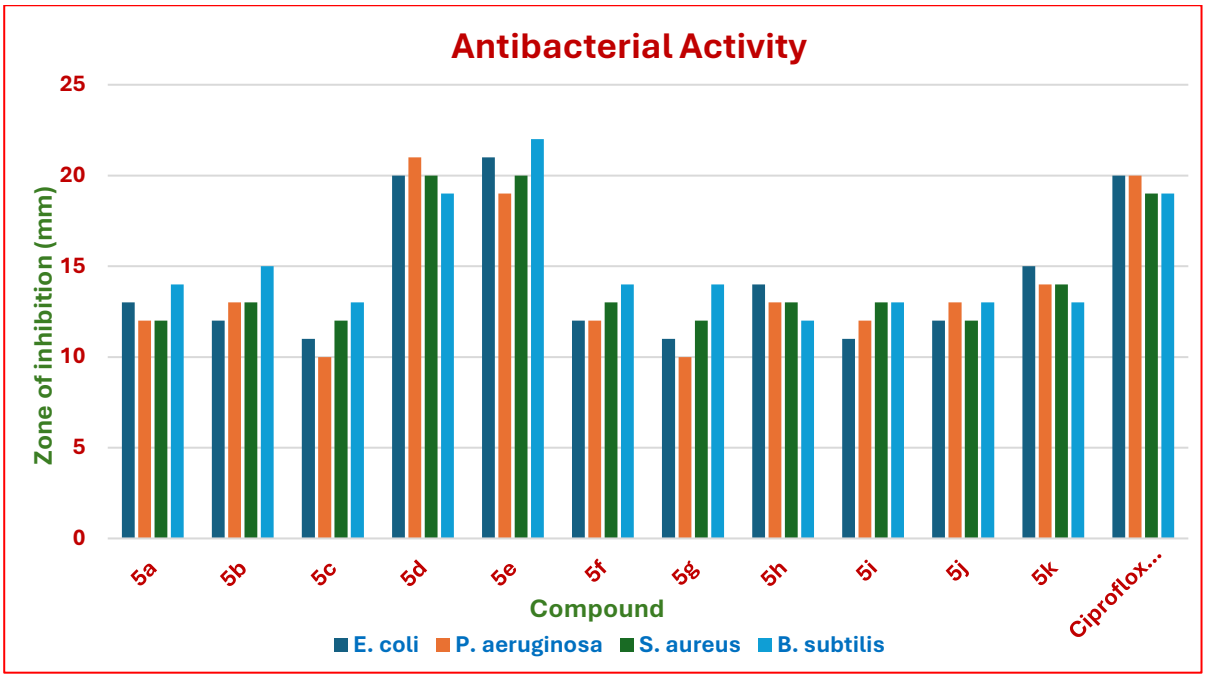


Figure 3. Zone of inhibition of thiazole – benzimidazole hybrids against bacteria.

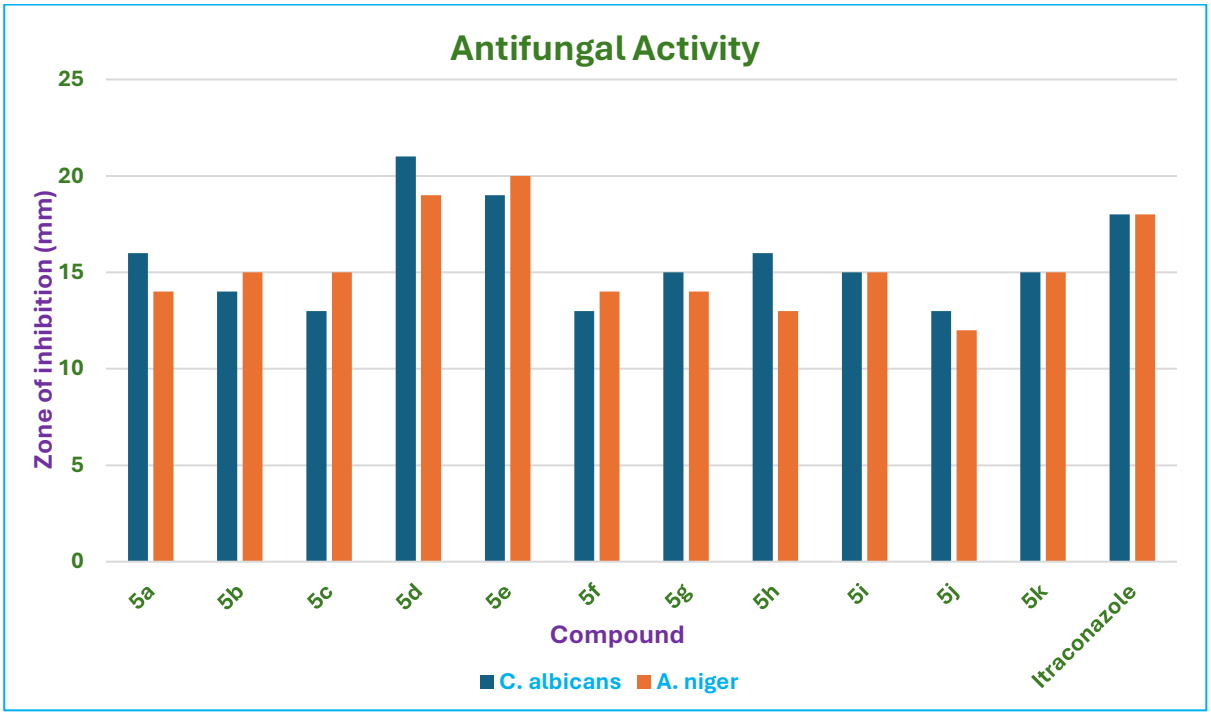


Figure 4. Zone of inhibition of thiazole – benzimidazole hybrids against fungus.

Conclusions

A novel series of thiazole combined benzimidazole derivatives **5a-k** were synthesized from an acid catalyzed condensation-cyclization reaction of ethyl 2-(4-(benzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylates

3a, **3b**, **3c** and variously substituted benzene-1,2-diamines (**4a-e**) in ethanol. Compounds **3a**-**c** were in turn obtained from dehydrobromination of corresponding phenol **1** with (bromomethyl)benzenes **2a-c**. Evaluating the antimicrobial activities of new compounds against two gram positive bacteria (*S.aureus, B.Substilis*), two gram negative bacteria (*E.coli, P.aeruginosa*), and two fungal strains (*C.albicans, A.niger*). All of the molecules presented a noteworthy zone of inhibitions in comparison to the reference drugs viz. Ciprofloxacin and Itraconazole. Compounds **5d** and **5e** presented outstanding activity against all bacterial and fungal strains. Hence, these could be further investigated in the process of discovery and development of new antimicrobial drugs.

Experimental Section

General. All the reagents and solvents purchased from Sigma-Aldrich, these were used directly without further purification. Melting points (°C) were recorded by Labtronics digital melting point apparatus (Panchkula, India). IR spectra were recorded on Bruker-27 in ATR method. The ^{1}H NMR & ^{13}C NMR spectra recorded using TMS as an internal reference in $CDCl_3$ solvent were captured on JEOL JNM-ECZ500R/S1 instrument at 400 MHz and 100 MHz, respectively. Mass spectrometry analyses were carried out on a Jeol SX-102 spectrometer (Tokyo, Japan). TLC plates, aluminum sheets pre-coated with silica gel 60 F_{254} were used to predict the progress of the reaction.

General procedure for the synthesis of ethyl 2-(4-(substitutedbenzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylates (3a-c). The ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (**1**) was prepared according to the reported procedure.[53] A solution containing the compound **1** (0.01 mol), appropriate substituted bromomethyl benzene (**2a-c)** (0.01 mol) and potassium carbonate (0.04 mol) in DMF (12ml) was stirred at rt for 3 h. After complete consumption of the reactants, the reaction mixture was poured into ice cold water, the obtained solid product was filtered off and dried. The residue was purified by column chromatography using silica gel (60-120 mesh) and ethyl acetate: pet ether solvent mixture as eluent to give the corresponding product **3a-c.**

Ethyl 2-(4-(benzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylate (3a). Yield: 85%; mp: 120 °C. IR (ATR, ν_{max}, cm^{-1}): 1703 (CO), 1686 (CHO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.55 (s, 1H), 8.38 (d, *J* 2.4 Hz, 1H), 8.20 (dd, *J* 8.8, 2.4 Hz, 1H), 7.55 – 7.32 (m, 5H), 7.14 (d, *J* 8.8 Hz, 1H), 5.27 (s, 2H), 4.35 (q, *J* 7.1 Hz, 2H), 2.76 (s, 3H), 1.39 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.8, 168.3, 162.6, 162.2, 161.1, 135.4, 133.8, 128.9, 128.6, 127.4, 127.3, 126.4, 125.3, 121.7, 113.7, 70.9, 61.3, 17.5, 14.3; ESI-MS: *m/z* 382.57 $[M+H]^+$.

Ethyl 2-(4-((4-(tert-butyl)benzyl)oxy)-3-formylphenyl)-4-methylthiazole-5-carboxylate (3b). Yield: 80%; mp: 125°C. IR (ATR, ν_{max}, cm^{-1}):1691 (CO) , 1672 (CHO); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (s, 1H), 8.36 (d, *J* 2.4 Hz, 1H), 8.19 (dd, *J* 8.8, 2.4 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.38 (d, *J* 8.4 Hz, 2H), 7.15 (d, *J* 8.8 Hz, 1H), 5.23 (s, 2H), 4.35 (q, *J* 7.1 Hz, 2H), 2.76 (s, 3H), 1.38 (t, *J* 7.1 Hz, 3H), 1.34 (s, 9H);^{13}C NMR (126 MHz, $CDCl_3$): δ 188.8, 168.3, 162.7, 162.2, 161.0, 151.7, 133.7, 132.4, 131.3, 127.3, 127.2, 126.2, 125.8, 125.3, 121.7, 113.7, 70.8, 61.3, 34.7, 31.3, 17.5, 14.3. ESI-MS: *m/z* 438.66 $[M+H]^+$.

Ethyl 2-(4-((4-fluorobenzyl)oxy)-3-formylphenyl)-4-methylthiazole-5-carboxylate (3c). Yield: 90%; mp: 138 °C. IR (ATR, ν_{max}, cm^{-1}):1716 (CO) , 1677 (CHO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.37 (d, *J* 2.4 Hz, 1H), 8.20 (dd, *J* 8.8, 2.4 Hz, 1H), 7.43 (dd, *J* 8.5, 5.4 Hz, 2H), 7.12 (dd, *J* 9.6, 4.8 Hz, 3H), 5.22 (s, 2H), 4.35 (q, *J* 7.1 Hz, 2H), 2.76 (s, 3H), 1.39 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.7, 168.3, 164.1, 162.4, 161.2, 133.9, 131.3, 129.5, 129.4, 127.5, 126.6, 125.4, 121.9, 116.1, 113.7, 70.3, 61.4, 17.6, 14.5.; ESI-MS*: m/z* 400.57 $[M+H]^+$.

General procedure for the synthesis of ethyl 2-(6-substituted-3-(1*H*-benzo[*d*]imidazol-2-yl)-4-(4-substitutedbenzyloxy)phenyl)-4-methylthiazole-5-carboxylates (5a-k). A solution containing the appropriate ethyl 2-(4-(4-substitutedbenzyloxy)-3-formylphenyl)-4-methylthiazole-5-carboxylate **(3a-c)** (0.001 mol), appropriate substituted benzene-1,2-diamine (**4a-e)** (0.001 mol) and catalytic amount of acetic acid in ethanol (8 ml) was stirred at rt. After 4 h, the reaction mixture was poured into ice cold water, the separated solid was filtered and purified by column chromatography using ethyl acetate and pet ether solvent mixture to give the corresponding hybrid compounds **5a-k**.

Ethyl 2-(3-(1*H*-benzo[*d*]imidazol-2-yl)-4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylate (5a). Yield: 84%; mp: 170 cC. IR (ATR, ν_{max}, cm^{-1}): 3286 (N-H), 1764 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.54 (s, 1H), 9.14 (d, *J* 2.3 Hz, 1H), 8.09 (dd, *J* 8.7, 2.4 Hz,1H), 7.59 – 7.44 (m, 5H), 7.29 – 7.14 (m, 5H), 5.35 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.79 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.6, 161.8, 160.7, 157.9, 152.6, 148.4, 136.9, 129.4, 128.9, 128.7, 128.2, 127.4, 125.9, 122.8, 121.2, 120.0, 118.1, 114.9, 70.1, 61.4, 17.7, 14.6. ESI-MS: *m/z* 470.35 $[M+H]^+$.

Ethyl 2-(4-(benzyloxy)-3-(6-fluoro-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-4-methylthiazole-5-carboxylate (5b). Yield: 82%; mp: 178 °C. IR (ATR, ν_{max}, cm^{-1}): 3286 (N-H), 1764 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.54 (s, 1H), 9.09 (d, *J* 2.1 Hz, 1H), 8.09 (dd, *J* 8.7, 2.3 Hz, 1H), 7.60 – 7.46 (m, 7H), 7.19 (d, *J* 8.8 Hz, 2H), 5.35 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.6, 162.3, 161.1, 157.6, 157.1, 152.5, 135.3, 129.3, 129.2, 128.9, 127.9, 127.4, 124.9, 121.7, 120.2, 118.8, 117.1, 116.3, 113.4, 107.6, 103.1, 71.8, 61.2, 17.5, 14.4; ESI-MS*: m/z* 488.30 $[M+H]^+$.

Ethyl 2-(4-(benzyloxy)-3-(6-chloro-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-4-methylthiazole-5-carboxylate (5c). Yield: 90%; mp: 180 °C. IR (ATR, ν_{max}, cm^{-1}): 3413 (N-H), 1711 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 9.09 (d, *J* 2.3 Hz, 1H), 8.09 (dd, *J* 8.7, 2.3 Hz, 1H), 7.76 (d, *J* 2.5 Hz, 1H), 7.50 (d, *J* 8.1 Hz, 5H), 7.18 (d, *J* 8.8 Hz, 3H), 5.34 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H).; ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.5, 162.3, 161.0, 157.6, 151.3, 149.8, 135.2, 129.59, 129.3, 128.8, 127.9, 127.3, 126.8, 125.9, 124.9, 123.36, 121.7, 120.3, 119.2, 118.5, 113.3, 71.7, 61.3, 17.5, 14.4; ESI-MS: *m/z* 504.30 $[M+H]^+$.

Ethyl 2-(4-(benzyloxy)-3-(6-methyl-1H-benzo[d]imidazol-2-yl)phenyl)-4-methylthiazole-5-carboxylate: (5d). Yield: 92%; mp: 172 °C. IR (ATR, ν_{max}, cm^{-1}): 3413 (N-H), 1711 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.41 (s, 1H), 9.11 (d, *J* 2.3 Hz, 1H), 8.07 (dd, *J* 8.7, 2.4 Hz, 1H), 7.67 (d, *J* 3.8 Hz, 1H), 7.54 – 7.44 (m, 5H), 7.14 (t, *J* 21.3 Hz, 3H), 5.33 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 2.47 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H).; ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.8, 162.4, 161.0, 157.6, 152.8, 148.3, 135.4, 133.8, 132.3, 129.2, 129.1, 129.0, 128.8, 127.9, 127.3, 124.4, 121.6, 119.1, 116.4, 113.3, 110.6, 71.7, 61.2, 21.8, 17.5, 14.4; ESI-MS: *m/z* 484.16 $[M+H]^+$.

Ethyl 2-(4-((4-(tert-butyl)benzyl)oxy)-3-(6-chloro-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-4-methylthiazole-5-carboxylate (5e). Yield: 86%; mp: 174 °C. IR (ATR, ν_{max}, cm^{-1}):3428 (N-H) 1712 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.54 (s, 1H), 9.08 (d, *J* 2.3 Hz, 1H), 8.09 (dd, *J* 8.7, 2.3 Hz, 1H), 7.48 (dd, *J* 12.4, 8.3 Hz, 5H), 7.19 (d, *J* 8.7 Hz, 3H), 5.31 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.47 – 1.32 (m, 12H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.5, 162.3, 161.0, 157.8, 152.4, 149.6, 132.2, 129.5, 128.8, 127.7, 127.2, 126.2, 123.4, 121.6, 120.1, 119.2, 118.5, 116.3, 114.6, 113.5, 111.6, 71.8, 61.2, 34.8, 31.3, 17.5, 14.4; ESI-MS: *m/z* 560.40 $[M+H]^+$.

Ethyl 2-(4-((4-(tert-butyl)benzyl)oxy)-3-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-4-methylthiazole-5-carboxylate (5f). Yield: 90%; mp: 182 °C. IR (ATR, ν_{max}, cm^{-1}): 3398 (N-H), 1713 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.44 (s, 1H), 9.11 (d, *J* 2.3 Hz, 1H), 8.08 (dd, *J* 8.7, 2.3 Hz, 1H), 7.67 (d, *J* 5.4 Hz, 1H), 7.48 (dd, *J* 5.9, 8.3 Hz, 4H), 7.22 – 7.01 (m, 3H), 5.32 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 2.47 (s, 3H), 1.42 – 1.37 (m, 12H).; ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.8, 162.4, 161.0, 157.7, 152.3, 148.3, 134.7, 132.9, 132.4, 131.5, 129.0, 128.8, 127.7, 127.2, 126.1, 124.4, 121.6, 119.2, 117.8, 115.9, 113.5, 71.6, 61.2, 34.8, 31.4, 21.8, 17.5, 14.4; ESI-MS: *m/z* 540.45 $[M+H]^+$.

Ethyl 2-(3-(1H-benzo[d]imidazol-2-yl)-4-((4-fluorobenzyl)oxy)phenyl)-4-methylthiazole-5-carboxylate (5g). Yield: 91%; mp: 171 °C. IR (ATR, ν_{max}, cm^{-1}): 3398 (N-H), 1713 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.44 (s, 1H), 9.13 (d, *J* 2.3 Hz, 1H), 8.08 (dd, *J* 8.7, 2.4 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.26-7.15 (m, 7H), 5.31 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.6, 162.3, 162.1, 161.0, 157.5, 152.1, 142.8, 131.2, 129.9, 129.2, 127.4, 123.2, 122.7, 121.7, 119.0, 116.3, 113.3, 110.8, 71.0, 61.2, 17.5, 14.4; ESI-MS: *m/z* 488.30 $[M+H]^+$.

Ethyl 2-(3-(6-fluoro-1*H*-benzo[*d*]imidazol-2-yl)-4-((4-fluorobenzyl)oxy)phenyl)-4-methyl thiazole-5-carboxylate (5h). Yield: 85%; mp: 182 °C. IR (ATR, ν_{max}, cm^{-1}): 3432 (N-H), 1703 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.45 (s, 1H), 9.08 (s, 1H), 8.07 (dd, *J* 8.7, 2.3 Hz, 1H), 7.50 (dd, *J* 8.5, 5.2 Hz, 3H), 7.24 – 7.10 (m, 5H), 5.30 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): 168.5, 164.4, 162.3, 161.1, 157.4, 156.0, 151.7, 140.1, 137.8, 131.0, 130.0, 129.3, 129.0, 128.8, 127.6, 118.8, 116.4, 116.2, 113.4, 109.4, 102.5, 71.1, 61.2, 17.5, 14.4. ESI-MS: *m/z* 506.35 $[M+H]^+$.

Ethyl 2-(3-(6-chloro-1*H*-benzo[*d*]imidazol-2-yl)-4-((4-fluorobenzyl)oxy)phenyl)-4-methylthiazole-5-carboxylate (5i). Yield: 86%; mp: 179 °C. IR (ATR, ν_{max}, cm^{-1}):3432 (N-H), 1703 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.41 (s, 1H), 9.08 (d, *J* 2.3 Hz, 1H), 8.08 (dd, *J* 8.7, 2.4 Hz, 1H), 7.57 – 7.44 (m, 2H), 7.22 – 7.12 (m, 6H), 5.30 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.4, 162.3, 161.9, 161.1, 157.5, 152.1, 131.0, 130.0, 129.9, 129.5, 129.0, 127.5, 123.5, 123.2, 121.8, 120.3, 118.6, 116.5, 116.2, 115.4, 113.4, 71.1, 61.3, 17.5, 14.4; ESI-MS: *m/z* 522.35 $[M+H]^+$.

Ethyl 2-(4-((4-fluorobenzyl)oxy)-3-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)phenyl)-4-methylthiazole-5-carboxylate (5j). Yield: 94%; mp: 168 °C. IR (ATR, ν_{max}, cm^{-1}): 3432 (N-H), 1703 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.32 (s, 1H), 9.09 (d, *J* 2.3 Hz, 1H), 8.05 (dd, *J* 8.7, 2.3 Hz, 1H), 7.49 (dd, *J* 8.5, 5.3 Hz, 3H), 7.23 – 7.11 (m, 5H), 5.28 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 2.48 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 168.7, 164.3, 162.3, 161.8, 161.0, 157.4, 148.2, 141.5, 139.7, 133.0, 131.2, 130.0, 129.9, 129.0, 128.9, 127.4, 124.5, 121.7, 119.2, 116.3, 116.1, 70.9, 61.2, 21.7, 17.5, 14.4; ESI-MS: *m/z* 502.35 $[M+H]^+$.

Ethyl 2-(3-(6-bromo-1*H*-benzo[*d*]imidazol-2-yl)-4-((4-fluorobenzyl)oxy)phenyl)-4-methylthiazole-5-carboxylate (5k). Yield: 90%; mp: 177 °C. IR (ATR, ν_{max}, cm^{-1}):3432 (N-H), 1703 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.42 (s, 1H), 9.07 (d, *J* 2.3 Hz, 1H), 8.07 (dd, *J* 8.7, 2.4 Hz, 1H), 7.59 – 7.30 (m, 4H), 7.25 – 7.07 (m, 4H), 5.28 (s, 2H), 4.36 (q, *J* 7.1 Hz, 2H), 2.78 (s, 3H), 1.40 (t, *J* 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 170.1, 162.3, 161.7, 161.1, 157.5, 153.2, 141.5, 140.2, 133.2, 130.0, 129.9, 129.6, 129.0, 127.5, 126.6, 126.0, 121.8, 118.5, 116.4, 115.7, 113.4, 71.1, 61.3, 17.5, 14.4; ESI-MS: *m/z* 566.30 $[M+H]^+$.

Acknowledgements

The authors express their gratitude to the Head of the Department of Chemistry for providing laboratory facilities at Osmania University and CFRD Osmania University for providing analytical support. Also, the management of Geetanjali College of Engineering and Technology and the Head of the F.E. Department for supporting the research work.

Supplementary Material

Copies of all ^{1}H and ^{13}C NMR spectra of all products are available in the Supplementary material.

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