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ORIGINAL PAPER

Synthesis, characterization, docking study and antimicrobial activity of 2-(4-benzoylphenoxy)-1-[2-(1-methyl-1*H*-indol-3-yl) methyl)-1*H*-benzo[d]imidazol-1-yl] ethanone derivatives

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Abstract
The occurrence of drug-resistant bacterial infections impulses the development of new antibacterial agents that own a mechanism of action different from traditional antibiotics. From the earlier days, benzophenone, indole and benzimidazole moieties alone are one of the most important frameworks in the discovery of innovative drugs. In this present study, we have described a detailed synthesis and structural elucidation of new benzimidazole bridged benzophenone substituted indole scaffolds **11a–k**. Further, all the newly synthesized compounds were tested for *in vitro* antimicrobial activity by disk diffusion and serial dilution method and the compounds **11b, 11e, 11f** and **11h** were revealed as potent compounds among the tested strains in the series**11a–k**. Further, compounds **11b, 11e, 11f** and **11h** were subjected for *in silico* studies and FtsZ has been recognized as a key functional protein in bacterial cell division and it is currently considered to be a potential target for the growth of novel antibacterial agents. In continuation, the results obtained from docking studies were in accordance with *in vitro* results and compounds **11b, 11e, 11f** and **11h** emerged as potent molecules in the series **11a–k**.

Introduction

Antibiotics are of our most important weapons in fighting bacterial infections and have greatly benefited the health-related quality of human life since their introduction [1]. Conversely, over the past few decades, these health benefits are at risk as many commonly used antibiotics have become less and less effective against certain diseases not only because many of them produce toxic reactions but also due to the emergence of drug resistant bacteria. In this view, it is highly essential to investigate newer drugs, with lesser resistance [2]. Over the past several years, the emergence of organisms resistant to nearly all the class of antimicrobial agents has become a serious public health concern [3]. Normally, bacteria have the genetic ability to transmit and attain resistance to drugs, which are utilized as therapeutic agents[4]. In the past two decades, there has been a significant increase in the frequency of systematic fungal infection in man. The first orally active antifungal agent that was effective against a broad array of systematic and superficial fungal infections was ketoconazole [5]. Further, a number of azole antifungal agents, viz. itraconazole, fluconazole [6], voriconazole [7], ravuconazole [8] and glucan synthesis inhibitor caspofungin [9], have been introduced to the clinic.

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In addition, benzophenone derivatives are having good pharmacological properties [10]. For instance, during the past years, extensive evidence has been accumulated to establish the efficiency of benzophenone analogs as an antimicrobial agent [11, 12]. Furthermore, benzophenone analogs (garcinol) have been isolated from the stem bark of *Garcinia huillensis* grown in Zaire and used in central-African traditional medicine and this has been shown to exhibit chemotherapeutic activity against gram-positive and gram-negative *cocci*, mycobacteria and fungi. Recently, Selvi*et al*. have reported antifungal activity of benzophenone analogs, at its lower concentration and the results displayed that chloro-substituted benzophenones have exhibited more antifungal activity [13].

Besides, metrafenone, a novel benzophenone-derived fungicide, recently registered in several countries for control of powdery mildews in different crops [14] and eyespot in cereals.

Subsequently, benzimidazoles are outstandingly successful compounds, with respect to their both inhibitory activity and encouraging selectivity ratio. The broad biochemical and pharmacological studies have verified that benzimidazole molecules are effective against various strains of microorganisms [15–21]. Benzimidazoles are considered a capable class of bioactive heterocyclic compounds with a wide range of biological activities. Specifically, this nucleus is a constituent of vitamin-B_{12} [22]. This ring system is present in numerous antioxidant [23–25], antiparasitic [26, 27], antihelmintics [28], antiproliferative [29], anti-HIV [30], anticonvulsant [31], anti-inflammatory [32–35], antihypertensive [36], antineoplastic [37, 38] and antitrichinellosis analogs. Based on the immense significance and diverse bioactivities exhibited by benzimidazoles, efforts have been made from time to time to create libraries of these compounds and screened them for potential biological activities.

Further, indole derivatives are an important class of heterocyclic compounds with a wide range of biological activities [39]. Indole is a substructural element of many natural products and is widely used as a scaffold in agricultural and medicinal chemistry. For example, indole-3-acetic acid is a key plant growth hormone [40] and tryptophan, an essential amino acid, participates in many essential biological processes [41]. Indomethacin is a nonsteroidal anti-inflammatory drug [42]. Sumatriptan, frovatriptan and zolmitriptan are used to treat acute migraine attacks and headaches [43]. Besides, the indole alkaloid reserpine is an antipsychotic and antihypertensive drug that has been used for the management of high blood pressure and for the relief of psychotic symptoms [44].

Progress in the discovery of antimicrobial agents has led to the identification of an array of compounds targeting the bacterial divisiome. Comprising of a series of highly conserved proteins responsible for cell division, membrane constriction during division and biosynthesis of peptidoglycan, this protein complex is gaining focus for the development of antibiotics. The filamentous temperature-sensitive protein Z (FtsZ) is one such target protein with proven efficacy. Several studies have validated the inhibition of this protein as a platform for the development of broad spectrum-antibiotics [45–47]. Despite its potential, small molecules with inhibitory potential against this protein are lacking in clinical trials, thereby opening newer avenues for research on molecular scaffolds with inhibitiory potential against FtsZ.

With this background (potential of benzimidazole nucleus) and in continuation of our previous work [48–53], it was thought that it would be worthwhile to design and synthesize some new benzimidazole derivatives bearing indole and benzophenone moieties and screen them for potential antimicrobial agents.

Experimental Section

All reagents were of commercial quality and were purified before use, and some of the starting materials were synthesized according to standard procedure. The organic solvents were of analytical grade and purified by standard procedure. The chemicals used for the synthesis of intermediates and end products were purchased from Sigma-Aldrich, Merck, Ranbaxy, Spectrochem and SD fine chemicals. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated silica gel-G F254 aluminum plates. Visualization of the spots on TLC plates was achieved by either exposure to iodine vapor or UV light. The completion of the reaction was checked by using TLC plates, varying the solvent proportions and by the multiple irrigations. All evaporation of solvents was carried out under reduced pressure on IKA rotary evaporator. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded on FTIR Shimadzu 8300 spectrophotometer using nujol mull or potassium bromide water. NMR spectra were recorded on a Bruker 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrophotometer, respectively, in deuterated dimethyl sulfoxide (DMSO-d_6), deuterated chloroform, and the chemical shifts were recorded in parts per million down field from tetramethylsilane. Mass spectra were obtained with a VG70-70H mass spectrometer, and important fragments are given with the relative intensities in the brackets. Microanalyses were performed by the Regional Sophisticated Instrumentation Centre, C.D.R.I, Lucknow, and the results are within 0.5% of the calculated value.

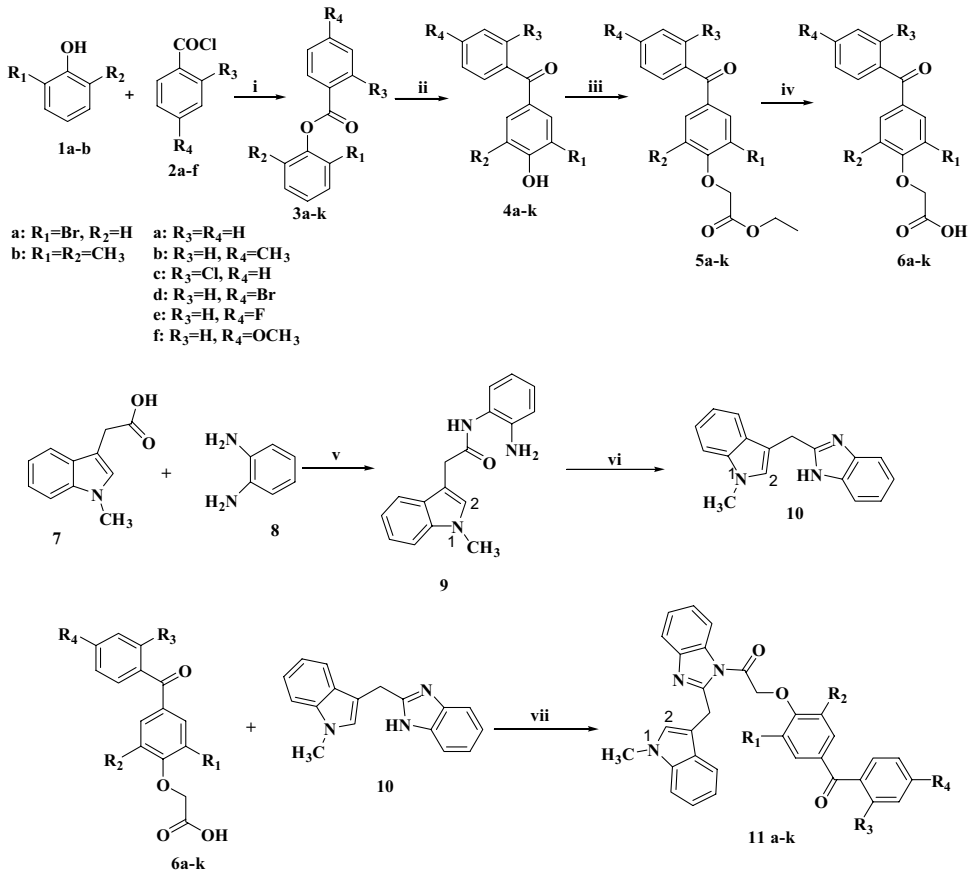
Chemistry: plan of the synthesis

Synthesis of the title compounds **10a–k** was accomplished by a synthetic procedure as shown in Scheme 1. The benzoylated products **3a–k** were synthesized by the benzoylation of substituted phenols **1a–b** under low temperature, and these on Fries rearrangement using anhydrous aluminum chloride as a catalyst under neat condition gave hydroxy benzophenones **4a–k**. Compounds **4a–k** on etherification with ethyl chloroacetate using dry acetone as a solvent gave substituted ethyl esters **5a–k**, and compounds **5a–k** on refluxing with aqueous sodium hydroxide in ethanol gave (4-benzoyl-phenoxy)-acetic acids **6a–k**. Further, N-(2-aminophenyl)-2-(1-methyl-1H-indol-3-yl) acetamide (**9**) was obtained by the reaction of 2-(1-methyl-1H-indol-3-yl)acetic acid **(7**) and 1,2-diaminobenzene (**8**) in the presence of lutidine as a base and dichloromethane as a solvent to give the compound **9**. Then this compound **9** on refluxing with neat acetic acid undergoes cyclization to give compound **10**. Finally, substituted (4-benzoyl-phenoxy)-acetic acids (**6a–k**)and2-((1-methyl-1H-indol-3-yl)methyl)-1H-benzo[d]imidazole (**10**) were treated with thionyl chloride in the presence of triethyl amine and 1,4-dioxane as solvent and the reaction mixture was refluxed to deliver the expected final products **11a–k** in a good yield.

Detailed synthetic procedures

Procedure for the synthesis of phenyl benzoates (3a–k)

Benzoic acid-2-bromo phenyl ester **(3a)** was synthesized by benzoylation of 2-bromo phenol **(1a)** with benzoyl chloride (**2a**, 1:1) using 10% sodium hydroxide solution. The reaction mass was stirred for 2–3 h at 0 °C. The reaction was monitored by TLC using 4:1 n-hexane/ethyl acetate solvent mixture. After completion of the reaction, the oily product



Scheme 1 Synthesis of 2-(4-benzoylphenoxy)-1-(2-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-benzo[d]imidazol-1-yl) ethanone derivatives (11a-k)

was extracted with ether layer (3 × 30 mL). Ether layer was washed with 10% sodium hydroxide solution (3 × 50 mL) followed by water (3 × 30 mL) and then dried over anhydrous sodium sulfate and evaporated the solvent under pressure to afford a desired compound (**3a).** Compounds (**3b–k)** were synthesized analogously starting with compounds (**1a–b)** and **(2b–f)**.

Reagents and reaction conditions: (i) Aq. NaOH, stirring 0–5 °C for 2–3 h, (ii) Anhy. $AlCl_3$, neat 150–170 °C for 2–3 h, (iii) $ClCH_2COOC_2H_5/K_2CO_3$/dry acetone, reflux, for 8–14 h, (iv) Aq. NaOH/ethanol, reflux, for 5–8 h, (v) TBTU/Lutidine, dry DCM, cold stirring, (vi) acetic acid, reflux, (vii) thionyl chloride, 1,4-dioxane, triethyl amine, reflux.

2-Bromophenyl benzoate (3a): Yield 90%. Colorless viscous liquid, IR (neat): 1715 cm^{-1} (C = O). ^1H NMR (DMSO-d_6):δ 7.3–7.8 (m, 9H, Ar–H). LC–MS m/z 276.98 (M + 1), 278.98 (M + 2). Anal. calcd. for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.37; H, 3.24%.

2-Bromophenyl-4-methylbenzoate (3b): Pale yellow solid, yield 95%. IR (neat): 1720 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ2.30 (s, 3H, CH_3), 7.4–7.9 (m, 8H, Ar–H). LC–MS m/z 290.99 (M + 1), 292.99 (M + 2). Anal. calcd. for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81. Found: C, 57.72; H, 3.85%.

2-Bromophenyl-2-chlorobenzoate (3c): Pale yellow solid, yield 85%. IR (neat): 1725 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 7.4–7.9 (m, 8H, Ar–H). LC–MS m/z 310.94 (M + 1), 312.94 (M + 2), 314.94 (M + 4). Anal. calcd. for $C_{13}H_8BrClO_2$: C, 50.12; H, 2.59. Found: C, 50.15; H, 2.55%.

2-Bromophenyl-4-bromobenzoate (3d): Yellow solid, yield 80%. IR (neat): 1705 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 7.2–7.8 (m, 8H, Ar–H). LC–MS m/z 354.89 (M + 1), 356.89 (M + 2). Anal. calcd. for $C_{13}H_8Br_2O_2$: C, 43.86; H, 2.26. Found: C, 43.82; H, 2.29%.

2-Bromophenyl-4-fluorobenzoate (3e): Pale yellow solid, yield 92%. IR (neat): 1725 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 7.2–7.8 (m, 8H, Ar–H). LC–MS m/z 294.97 (M + 1), 296.97 (M + 2). Anal. calcd. for $C_{13}H_8BrFO_2$: C, 52.91; H, 2.73. Found: C, 52.95; H, 2.75%.

2,6-Dimethylphenyl benzoate (3f): White solid, yield 85%. IR (neat): 1730 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 2.33 (s, 6H, $2CH_3$), 6.9–7.6 (m, 8H, Ar–H). LC–MS m/z 227.1 (M + 1). Anal. calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.65; H, 6.22%.

2,6-Dimethylphenyl-4-methylbenzoate(3 g): White solid, yield 90%. IR (neat): 1735 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 2.2 (s, 6H, $2CH_3$), 2.3 (s, 3H, CH_3), 6.8–7.7 (m, 7H, Ar–H). LC–MS m/z 241.12 (M + 1). Anal. calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.95; H, 6.76%.

2,6-Dimethylphenyl-2-chlorobenzoate (3 h): White solid, yield 95%. IR (neat): 1733 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 2.25 (s, 6H, $2CH_3$), 6.7–7.7 (m, 7H, Ar–H). LC–MS m/z 261.06 (M + 1), 263.06 (M + 2). Anal. calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 69.15; H, 5.07%.

2,6-Dimethylphenyl-4-bromobenzoate (3i): Yield 90%. IR (neat): 1722 cm^{-1} (C = O). ^1H NMR (DMSO-d_6):δ 2.26 (s, 6H, $2CH_3$), 6.7–7.7 (m, 7H, Ar–H). LC–MS m/z 305.01 (M + 1), 307.01 (M + 2). Anal. calcd. for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29. Found: C, 59.07; H, 4.25%.

2,6-Dimethylphenyl-4-fluorobenzoate (3j): Pale brown solid, yield 85%. IR (neat): 1715 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 2.28 (s, 6H, $2CH_3$), 6.9–7.6 (m, 7H, Ar–H). LC–MS m/z 245.09 (M + 1). Anal. calcd. for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.78; H, 5.37%.

2,6-Dimethylphenyl-4-methoxybenzoate (3 k): White solid, yield 90%. IR (neat): 1718 cm^{-1} (C=O). ^1H NMR (DMSO-d_6):δ 2.24 (s, 6H, $2CH_3$), 3.80 (s, 3H, OCH_3), 6.8–7.7 (m, 7H, Ar–H). LC–MS m/z 257.11(M + 1). Anal. calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.95; H, 6.26%.

Procedure for the synthesis of 4-Hydroxy benzophenones (4a–k)

Substituted 4-hydroxy-diarylmethanone commonly known as hydroxy benzophenones **(4a–k)** was synthesized by Fries rearrangement. For instance, (3-bromo-4-hydroxyphenyl) (phenyl)methanone (**4a**) was obtained by treating compound (**3a,**0.001 mol) with anhydrous aluminum chloride (0.002 mol) as a catalyst at 150–170 °C under without solvent condition for about 2–3 h. Then the reaction mixture was cooled to room temperature and quenched with 6 N HCl in the presence of ice water. The reaction mixture was stirred for about 2–3 h, filtered the solid and recrystallized it with methanol to obtain desired compounds (**4a).** Compounds (**4b–k)** were synthesized analogously starting with (**3b–k)**.

(3-Bromo-4-hydroxyphenyl)(phenyl)methanone (4a): Pale yellow solid, yield 72%. mp 125–128 °C. IR: (KBr) 1640 (C=O),3510–3600 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 4.50 (bs, 1H, OH) 6.71–7.80 (m, 8H, Ar–H). LC–MS m/z 276.98 (M + 1), 278.98 (M + 2). Anal. calcd. for $C_{13}H_9BrO_2$: C, 56.18; H, 3.69. Found: C,55.92; H, 3.70%.

(3-Bromo-4-hydroxyphenyl)(4-methylphenyl)methanone (4b): Pale yellow solid, yield 90%. mp 120–122 °C. IR: (KBr) 1645 (C=O),3520–3610 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.30 (s, 3H, CH_3), 4.60 (bs, 1H, OH), 7.4–7.9 (m, 7H, Ar–H). LC–MS m/z 290.99 (M + 1), 292.99 (M + 2). Anal. calcd. for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81. Found: C, 57.73; H, 3.86%.

(3-Bromo-4-hydroxyphenyl)(2-chlorophenyl)methanone (4c): White solid, yield 80%. mp 121–122 °C. IR: (KBr) 1635 (C=O), 3515–3620 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 4.55 (bs, 1H, OH), 7.4–7.9 (m, 7H, Ar–H). LC–MS m/z 310.94 (M + 1), 312.94 (M + 2), 314.94 (M + 4). Anal. calcd. for $C_{13}H_8BrClO_2$: C, 50.12; H, 2.59. Found: C, 50.16; H, 2.56%.

(3-Bromo-4-hydroxyphenyl)(4-bromophenyl)methanone (4d): Pale yellow solid, yield 85%. mp 118–120 °C. IR: (KBr) 1630 (C=O),3505–3605 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 4.45 (bs, 1H, OH), 7.2–7.8 (m, 7H, Ar–H). LC–MS m/z 354.89 (M + 1), 356.89 (M + 2), 358.89 (M + 4). Anal. calcd. for $C_{13}H_8Br_2O_2$: C, 43.86; H, 2.26. Found: C, 43.82; H, 2.29%.

(3-Bromo-4-hydroxyphenyl)(4-fluorophenyl)methanone (4e): Pale yellow solid, yield 90%. mp 107–110 °C. IR: (KBr) 1625 (C=O),3530–3615 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 4.35 (bs, 1H, OH), 7.2–7.8 (m, 7H, Ar–H). LC–MS m/z 294.97 (M + 1), 296.97 (M + 2). Anal. calcd. for $C_{13}H_8BrFO_2$: C, 52.91; H, 2.73. Found: C, 52.94; H, 2.76%.

(3,5-Dimethyl-4-hydroxyphenyl)(phenyl)methanone (4f): White solid, yield 88%. mp 113–115 °C. IR: (KBr) 1635 (C=O),3540–3630 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.33 (s, 6H, $2CH_3$), 4.25 (bs, 1H, OH), 6.9–7.6 (m, 7H, Ar–H). LC–MS m/z 227.1 (M + 1). Anal. calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.66; H, 6.21%.

(3,5-Dimethyl-4-hydroxyphenyl)(4-methylphenyl)methanone (4g): White solid, yield 92%. mp 115–117 °C. IR: (KBr) 1645 (C=O), 3510–3620 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.2 (s, 6H, $2CH_3$), 2.3 (s, 3H, CH_3), 4.44 (bs, 1H, OH), 6.8–7.7 (m, 6H, Ar–H). LC–MS m/z 241.12 (M + 1). Anal. calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.96; H, 6.75%.

(3,5-Dimethyl-4-hydroxyphenyl)(2-chlorophenyl)methanone (4h): White solid, yield 90%. mp 121–122 °C. IR: (KBr) 1645 (C=O), 3525–3615 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.25 (s, 6H, $2CH_3$), 4.39 (bs, 1H, OH), 6.7–7.7 (m, 6H, Ar–H). LC–MS m/z 261.06 (M + 1), 263.06 (M + 2). Anal. calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.03. Found: C, 68.15; H, 5.06%.

(3,5-Dimethyl-4-hydroxyphenyl)(4-bromophenyl)methanone (4i): White solid, yield 95%. mp 127–128 °C. IR: (KBr) 1640 (C=O), 3515–3635 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.26 (s, 6H, $2CH_3$), 4.29 (bs, 1H, OH), 6.7–7.7 (m, 6H, Ar–H). LC–MS m/z 305.01 (M + 1), 307.01 (M + 2). Anal. calcd. for $C_{15}H_{13}BrO_2$: C, 59.04; H, 4.29. Found: C, 59.06; H, 4.24%.

(3,5-Dimethyl-4-hydroxyphenyl)(4-fluorophenyl)methanone (4j): White solid, yield 88%. mp 120–122 °C. IR: (KBr) 1605 (C=O), 3545–3630 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.28 (s, 6H, $2CH_3$), 4.22 (bs, 1H, OH), 6.9–7.6 (m, 6H, Ar–H). LC–MS m/z 245.09 (M + 1). Anal. calcd. for $C_{15}H_{13}FO_2$: C, 73.76; H, 5.36. Found: C, 73.77; H, 5.36%.

(3,5-Dimethyl-4-hydroxyphenyl)(4-methoxyphenyl) methanone (4 k): White solid, yield 95%. mp 119–121 °C. IR: (KBr) 1635 (C=O), 3510–3610 (O–H) cm^{-1}. ^1H NMR (DMSO-d_6):δ 2.24 (s, 6H, $2CH_3$), 3.85 (s, 3H, OCH_3), 4.32 (bs, 1H, OH), 6.8–7.7 (m, 6H, Ar–H). LC–MS m/z 257.11(M + 1). Anal. calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.96; H, 6.25%.

Procedure for the synthesis of (4-Benzoyl-phenoxy)-acetic acid ethyl esters (5a–k)

(4-Benzoyl-2-bromo-phenoxy)-acetic acid ethyl ester (**5a)** was obtained by refluxing a mixture of compound (**4a,** 0.013 mol), ethyl chloroacetate (0.026 mol) and anhydrous potassium carbonate (0.019 mol) in dry acetone (50 mL) for 8–9 h. The reaction mixture was cooled, and solvent was removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate and extracted with ether (3 × 50 mL). The ether layer was washed with 10% sodium hydroxide solution (3 × 50 mL) followed by water (3 × 30 mL) and then dried over anhydrous sodium sulfate and evaporated to dryness to obtain crude solid, which on recrystallization with ethanol afforded desired compound (**5a**).Similarly, compounds (**5b–k)** were synthesized analogously starting with (**4b–k)**.

(4-Benzoyl-2-bromo-phenoxy)-acetic acid ethyl ester (5a): Pale brown solid, yield 90%. mp 49–52 °C. IR (Nujol): 1664 (C=O), 1760 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.2 (t, 3H, CH_3 of ester, $J = 6.6$ Hz),4.1 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.9 (s, 2H, OCH_2), 6.9–7.7 (m, 8H, Ar–H). LC–MS m/z 363.02 (M + 1), 365.02 (M + 2). Anal. calcd. For $C_{17}H_{15}BrO_4$: C, 56.47; H, 4.04. Found: C, 56.26; H, 4.12%.

[4-(4-Methylbenzoyl-2-bromo)phenoxy]acetic acid ethyl ester (5b): Pale brown solid, yield 95%. mp 45–47 °C. IR (Nujol): 1666 (C=O), 1765 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.3 (t, 3H, CH_3 of ester, $J = 6.6$ Hz),2.33 (s, 3H, CH_3), 4.2 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.8 (s, 2H, OCH_2), 6.8–7.8 (m, 7H, Ar–H). LC–MS m/z 377.02 (M + 1), 379.02 (M + 2). Anal. calcd. For $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.54. Found: C, 57.33; H, 4.56%.

[4-(2-Chlorobenzoyl-2-bromo-)phenoxy]acetic acid ethyl ester (5c): Pale brown solid, yield 85%. mp 51–53 °C. IR (Nujol): 1662 (C=O), 1769 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.4 (t, 3H, CH_3 of ester, $J = 6.6$ Hz),4.5 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.8 (s, 2H, OCH_2), 6.8–7.8 (m, 7H, Ar–H). LC–MS m/z 396.98 (M + 1), 398.98 (M + 2), 400.98 (M + 4).Anal. calcd. For $C_{17}H_{14}BrClO_4$: C, 51.35; H, 3.55. Found: C, 51.37; H, 3.58%.

[4-(4-Bromobenzoyl-2-bromo-)phenoxy]acetic acid ethyl ester (5d): Pale yellow solid, yield 80%. mp 54–56 °C. IR (Nujol): 1668 (C=O), 1762 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.2 (t, 3H, CH_3 of ester, $J = 6.6$ Hz),4.1 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.9 (s, 2H, OCH_2), 6.6–7.7 (m, 7H, Ar–H). LC–MS m/z 440.93 (M + 1), 442.93 (M + 2), 444.93 (M + 4). Anal. calcd. For $C_{17}H_{14}Br_2O_4$: C, 46.18; H, 3.19. Found: C, 46.19; H, 3.17%.

[4-(4-Fluorobenzoyl-2-bromo)phenoxy]acetic acid ethyl ester (5e): Pale brown solid, yield 82%. mp 50–52 °C. IR (Nujol): 1662 (C=O), 1770 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.3 (t, 3H, CH_3 of ester,

$J = 6.6$ Hz),4.1 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.8 (s, 2H, OCH_2), 7.1–7.8 (m, 7H, Ar–H). LC–MS m/z 381.02 (M + 1), 383.02 (M + 2). Anal. calcd. For $C_{17}H_{14}BrFO_4$: C, 53.56; H, 3.70. Found: C, 53.58; H, 3.75%.

(4-Benzoyl-2,6-dimethylphenoxy) acetic acid ethyl ester (5f): Pale yellow solid, yield 88%. mp 55–57 °C. IR (Nujol): 1665 (C=O), 1775 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.4 (t, 3H, CH_3 of ester, $J = 6.6$ Hz), 2.34 (s, 6H, $2CH_3$), 4.2 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.7 (s, 2H, OCH_2), 6.9–7.8 (m, 7H, Ar–H). LC–MS m/z 313.14 (M + 1). Anal. calcd. For $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.09; H, 6.42%.

[4-(4-Methylbenzoyl-2,6-dimethyl)phenoxy]acetic acid ethyl ester (5g): Pale brown solid, yield 88%. mp 54–56 °C. IR (Nujol): 1666 (C=O), 1779 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.5 (t, 3H, CH_3 of ester, $J = 6.6$ Hz), 2.3 (s, 6H, $2CH_3$), 2.4 (s, 3H, CH_3), 4.5 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.9 (s, 2H, OCH_2), 6.8–7.7 (m, 6H, Ar–H). LC–MS m/z 327.15 (M + 1). Anal. calcd. For $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.64; H, 6.77%.

[4-(2-Chlorobenzoyl)-2,6-dimethylphenoxy]acetic acid ethyl ester (5h): Pale brown solid, yield 95%. mp 57–60 °C. IR (Nujol): 1665 (C=O), 1775 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.6 (t, 3H, CH_3 of ester, $J = 6.6$ Hz), 2.31 (s, 6H, $2CH_3$), 4.6 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.9 (s, 2H, OCH_2), 6.9–7.9 (m, 6H, Ar–H). LC–MS m/z 347.10 (M + 1), 349.10 (M + 2). Anal. calcd. For $C_{19}H_{19}ClO_4$: C, 65.80; H, 5.52. Found: C, 65.84; H, 5.55%.

[4-(4-Bromobenzoyl)-2,6-dimethylphenoxy]acetic acid ethyl ester (5i): Pale brown solid, yield 80%. mp 52–54 °C. IR (Nujol): 1650 (C=O), 1768 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.2 (t, 3H, CH_3 of ester, $J = 6.6$ Hz), 2.31 (s, 6H, $2CH_3$), 4.2 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.9 (s, 2H, OCH_2), 7.1–7.7 (m, 6H, Ar–H). LC–MS m/z 391.05 (M + 1), 393.05 (M + 2). Anal. calcd. For $C_{19}H_{19}BrO_4$: C, 58.33; H, 4.89. Found: C, 58.38; H, 4.86%.

[4-(4-Fluorobenzoyl)-2,6-dimethylphenoxy]acetic acid ethyl ester (5j): Pale brown solid, yield 82%. mp 58–59 °C. IR (Nujol): 1656 (C=O), 1778 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.25 (t, 3H, CH_3 of ester, $J = 6.6$ Hz), 2.36 (s, 6H, $2CH_3$), 4.25 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.8 (s, 2H, OCH_2), 7.1–7.7 (m, 6H, Ar–H). LC–MS m/z 331.13 (M + 1). Anal. calcd. For $C_{19}H_{19}FO_4$: C, 69.08; H, 5.80. Found: C, 69.05; H, 5.85%.

[4-(4-Methoxybenzoyl)-2,6-dimethylphenoxy]acetic acid ethyl ester (5k): Pale brown solid, yield 87%. mp 45–48 °C. IR (Nujol): 1645 (C=O), 1765 (ester, C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.30 (t, 3H, CH_3 of ester, $J = 6.6$ Hz), 2.35 (s, 6H, $2CH_3$), 3.71 (s, 3H, OCH_3), 4.2 (q, 2H, CH_2 of ester, $J = 6.6$ Hz), 4.8 (s, 2H, OCH_2), 7.0–7.8 (m, 6H, Ar–H). LC–MS m/z 343.15 (M + 1). Anal. calcd. For $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.18; H, 6.45%.

Procedure for the synthesis of (4-Benzoyl-phenoxy)-acetic acids (6a–k):

(4-Benzoyl-2-bromo-phenoxy)-acetic acid (**6a**) was synthesized from a compound (**5a,** 6.0 mmol) in ethanol (15 mL) and treated with 15 mmol of sodium hydroxide solution. The reaction mixture was refluxed for 5–6 h, cooled and acidified with 1 N hydrochloric acid. The precipitate was filtered, washed with water and finally recrystallized from methanol to afford desired compounds (**6a)** with good yield. Compounds (**6b–k)** were synthesized analogously from (**5b–k**). The characterization data of the compounds **(6a–k)** are given below. The compounds **3a–k** to **6a–k** were synthesized from the reported procedure [49].

(4-Benzoyl-2-bromo-phenoxy)-acetic acid (6a): White solid, yield 75%. mp 130–132 °C. FT-IR (KBr): 1675 (C=O), 1730 (acid C=O), 3400–3500 (acid O–H) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.86 (s, 2H, OCH_2), 6.9–7.7 (m, 8H, Ar–H), 9.0 (s, 1H, COOH). LC–MS m/z 334.9 (M + 1), 336.9 (M + 2). Anal. calcd. for $C_{15}H_{11}BrO_4$: C, 53.71; H, 3.30. Found: C, 53.68; H, 3.34%.

[4-(4-Methyl-benzoyl-2-bromo-phenoxy)]-acetic acid (6b): White solid, yield 70%. mp 125–128 °C. FT-IR (KBr): 1670 (C=O), 1735 (acid C=O), 3410–3510 (acid O–H) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.86 (s, 2H, OCH_2), 6.8–7.7 (m, 7H, Ar–H), 9.5 (s, 1H, COOH). LC–MS m/z 349 (M + 1) 351 (M + 2). Anal. calcd. for $C_{16}H_{13}BrO_4$: C, 55.71; H, 3.30. Found: C, 55.68; H, 3.35%.

[4-(2-Chloro-benzoyl-2-bromo-phenoxy)]-acetic acid (6c): White solid, yield 73%. mp 160–162 °C. FT-IR (KBr): 1665 (C=O), 1725 (acid C=O), 3405–3550 (acid O–H) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.86 (s, 2H, OCH_2), 6.7–7.7 (m, 7H, Ar–H), 9.2 (s, 1H, COOH). LC–MS m/z 368.95 (M + 1), 370.90 (M + 2), 372.90. A (M + 4). Anal. calcd. for $C_{15}H_{10}BrClO_4$: C, 48.71; H, 2.30. Found: C, 48.68; H, 2.34%.

[4-(4-Bromo-benzoyl-2-bromo-phenoxy)]-acetic acid (6d): White solid, yield 78%. mp 178–180 °C. FT-IR (KBr): 1660 (C=O), 1720 (acid C=O), 3415–3520 (acid O–H)cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.86 (s, 2H, OCH_2), 6.7–7.8 (m, 7H, Ar–H), 9.3 (s, 1H, COOH). LC–MS m/z 412.9 (M + 1), 414.9 (M + 2), 416.9 (M + 4). Anal. calcd. for $C_{15}H_{10}Br_2O_4$: C, 43.71; H, 2.30. Found: C, 43.68; H, 2.35%.

[4-(4-Fluoro-benzoyl-2-bromo-phenoxy)]-acetic acid (6e): White solid, yield 75%. mp 210–212 °C. FT-IR (KBr): 1665 (C=O), 1735 (acid C=O), 3450–3560 (acid O–H)cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.88 (s, 2H, OCH_2), 6.9–7.7 (m, 7H, Ar–H), 9.1 (s, 1H, COOH). LC–MS m/z 353 (M + 1), 355 (M + 2). Anal. calcd. for $C_{15}H_{10}BrFO_4$: C, 51.71; H, 2.85. Found: C, 51.68; H, 2.56%.

[4-(Benzoyl-2,6-dimethyl-phenoxy)]-acetic acid (6f): White solid, yield 80%. mp 121–125 °C. FT-IR (KBr): 1670 (C=O), 1735 (acid C=O), 3410–3550 (acid O–H)cm^{-1}. ^1H

NMR (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 4.9 (s, 2H, OCH_2), 7.2–7.7 (m, 7H, Ar–H), 9.5 (s, 1H, COOH). LC–MS m/z 285.2 (M + 1). Anal. calcd. for $C_{17}H_{16}O_4$: C, 71.71; H, 5.30. Found: C, 71.68; H, 5.34%.

[4-(4-Methylbenzoyl-2,6-dimethyl-phenoxy)]-acetic acid (6g): White solid, yield 85%. mp 178–180 °C. FT-IR (KBr): 1660 (C=O), 1740 (acid C=O), 3420–3560 (acid O–H) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.2 (s, 6H, $2CH_3$), 2.3 (s, 3H, CH_3), 4.9 (s, 2H, OCH_2), 7.2–7.6 (m, 6H, Ar–H), 9.2 (s, 1H, COOH). LC–MS m/z 299 (M + 1). Anal. calcd. for $C_{18}H_{18}O_4$: C, 72.71; H, 6.30. Found: C, 72.68; H, 6.33%.

[4-(2-Chlorobenzoyl-2,6-dimethyl-phenoxy)]-acetic acid (6h): White solid, yield 88%. mp 165–169 °C. FT-IR (KBr): 1660 (C=O), 1735 (acid C=O), 3460–3550 (acid O–H)cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 4.8 (s, 2H, OCH_2),, 7.25–7.65 (m, 6H, Ar–H), 9.3 (s, 1H, COOH). LC–MS m/z 319.75 (M + 1), 321. 75 (M + 2). Anal. calcd. for $C_{17}H_{15}ClO_4$: C, 64.06; H, 4.74. Found: C, 64.08; H, 4.71%.

[4-(4-Bromobenzoyl-2,6-dimethyl-phenoxy)]-acetic acid (6i): White solid, yield 74%. mp 140–145 °C. FT-IR (KBr): 1655 (C=O), 1715 (acid C=O), 3450–3510 (acid O–H) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 4.86 (s, 2H, OCH_2), 7.1–7.6 (m, 6H, Ar–H), 9.2 (s, 1H, COOH). LC–MS m/z 363.1 (M + 1), 365.1 (M + 2). Anal. calcd. for $C_{17}H_{15}BrO_4$: C, 56.71; H, 4.30. Found: C, 56.68; H, 4.34%.

[4-(4-Fluorobenzoyl-2,6-dimethyl-phenoxy)]-acetic acid (6j): White solid, yield 69%. mp 218–220 °C. FT-IR (KBr): 1660 (C=O), 1725 (acid C=O), 3470–3560 (acid O–H) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 4.85 (s, 2H, OCH_2), 7.0–7.6 (m, 6H, Ar–H), 9.4 (s, 1H, COOH). LC–MS m/z 303.1 (M + 1). Anal. calcd. for $C_{17}H_{15}FO_4$: C, 67.54; H, 5.00. Found: C, 67.68; H, 5.14%.

[4-(4-Methoxybenzoyl-2,6-dimethyl-phenoxy)]-acetic acid (6k): White solid, yield 75%. mp 201–204 °C. FT-IR (KBr): 1670 (C=O), 1730 (acid C=O), 3420–3515 (acid O–H)cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 3.72 (s, 3H, OCH_3), 4.86 (s, 2H, OCH_2), 6.7–7.7 (m, 6H, Ar–H), 9.2 (s, 1H, COOH). LC–MS m/z 315.1 (M + 1). Anal. calcd. for $C_{18}H_{18}O_5$: C, 68.71; H, 5.30. Found: C, 68.61; H, 5.35%.

Procedure for the synthesis of *N*-(2-aminophenyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (9):

To 2-(1-methyl-1*H*-indol-3-yl)acetic acid **(7,** 0.0037 mol) in dry dichloromethane (15 mL), lutidine (1.2 vol.) was added at 25–30 °C, followed by the addition of 1,2-diaminobenzene (**8**, 0.0037 mol) and the reaction mixture was stirred at 25–30 °C for 30 min. Then the reaction mixture was cooled to 0–5 °C, and *o*-(benzotriazol-1-yl)- *N*,*N*,*N*',*N*'-tetramethyl aminium tetrafluoroborate (TBTU) (0.0037 mol) was added over a period of 30 min while maintaining the temperature below 5 °C. The reaction was stirred overnight and monitored by TLC using chloroform/methanol (9:1). The reaction mixture was diluted with 20 mL of dichloromethane and treated with 1.5 N hydrochloric acid (20 mL). The organic layer was washed with water (3 × 25 mL), dried over anhydrous sodium sulfate, concentrated to a syrupy liquid and recrystallized twice from diethyl ether to afford compound **9**.

N-(2-Aminophenyl)-2-(1-methyl-1H-indol-3-yl)acetamide (9): White solid, yield 80%. mp 180–182 °C. FT-IR (KBr,): 1690 (amide C=O), 3120–3335 (NH & NH_2)cm^{-1}. ^{1}H NMR (DMSO-d_6): δ3.60 (s, 3H, N–CH_3), 3.69 (s, 2H, CH_2), 4.59 (s, 2H, NH_2), 6.3 (s, 1H, 2nd position indole ring H), 6.80–7.75 (m, 8H, Ar–H), 9.80 (s, 1H, NH). LC–MS m/z 280.1 (M + 1). Anal. calcd. for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.15; H, 6.15; N, 15.08%.

Procedure for the synthesis of 2-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-benzo[*d*]imidazole (10):

Compound **10** was synthesized via cyclization of compound **9** (0.001 mol) using acetic acid as the cyclizing agent under refluxing conditions for 5–6 h. The reaction was monitored by TLC using n-hexane/dichloromethane/acetone (5:3:2). After completion of the reaction, the reaction mixture was cooled to room temperature, poured into crushed ice and neutralized with a 10% sodium bicarbonate solution. After filtration, the solid was recrystallized from acetonitrile.

2-[(1-Methyl-1H-indol-3-yl)methyl]-1H-benzo[d]imidazole (10): White solid, yield 70%. mp 195–198 °C. FT-IR (KBr): 1650 (C=N), 3130–3210 (N–H) cm^{-1}.^{1}H NMR (DMSO-d_6): δ 3.60 (s, 3H, N–CH_3), 3.70 (s, 2H, CH_2), 6.25 (s, 1H, 2nd position indole ring H), 6.7–7.71 (m, 8H, Ar–H), 9.81 (s, 1H, NH). LC–MS m/z 262.1 (M + 1). Anal. calcd. for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.15; H, 5.75; N, 16.05%.

Procedure for the synthesis of 2-(4-benzoylphenoxy)-1-[2-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-benzo[*d*]imidazol-1-yl]ethanones(11a-k)

2-(4-Benzoyl-2-bromo-phenoxy)-1-(2-((1-methyl-1H-indol-3-yl)methyl)-1H-benzoimidazol-1-ylethanone **(11a)** was synthesized by the reaction of compound (**10,** 0.001 mol) with 2-(4-benzoyl-2-bromo-phenoxy) acetic acid (**6a,** 0.001 mol)in 1,4-dioxane and then thionyl chloride (0.002 mol) and triethyl amine (15 mL) were added. The reaction mixture was refluxed for 5 h, and the completion of the reaction was monitored by TLC using n-hexane/dichloromethane/acetone (5:3:2). After completion of the reaction, the mixture was quenched with ice cold water and washed with distilled water and dried. Obtained solid was further purified by recrystallization by using methanol to achievecompound **11a** in a pure state.

2-(4-Benzoyl-2-bromo-phenoxy)-1-[2-(1-methyl-1H-indol-3-yl)methyl-1H-benzo [d]imidazol-1-yl]ethanone (11a): White solid, yield 85%. mp 230–232 °C. FT-IR (KBr): 1675 (C=O),1680 (C=N), 1730 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.60 (s, 3H, N–CH_3), δ 3.69 (s, 2H, CH_2), 5.05 (s, 2H, OCH_2), 6.35 (s, 1H, 2nd position indole ring H), 6.9–7.71 (m, 16H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 31.3, 38.0, 73.1, 101.4, 111.9, 115.3, 116.2, 118.1, 123.0, 124.1, 126.9, 128.5, 130.3, 130.8, 132.5, 134.2, 134.8, 138.9, 139.0, 139.7, 140.7, 140.8, 141.5, 142.4, 160.7, 196.3, 200.0. LC–MS m/z 578.46 (M + 1), 580.46 (M + 2). Anal. calcd. for $C_{32}H_{24}BrN_3O_3$: C, 66.44; H, 4.18; N, 7.26. Found: C, 66.40; H, 4.15; N, 7.22%.

[2–4-(4-Methyl-benzoyl-2-bromo-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl-1H-benzo [d]imidazol-1-yl] ethanone (11b): White solid, yield 70%. mp 175–178 °C. FT-IR (KBr): 1675 (C=O), 1685 (C=N), 1730 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.60 (s, 3H, N–CH_3), 3.69 (s, 2H, CH_2), 5.05 (s, 2H, OCH_2), 6.25 (s, 1H, 2nd position indole ring H), 6.9–7.75 (m, 15H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 24.3, 31.5, 36.0, 73.6, 102.4, 112.8, 115.2, 116.7, 119.1, 123.6, 124.8, 126.6, 128.4, 130.8, 131.0, 134.6, 135.2, 136.7, 138.3, 140.4, 141.1, 141.8, 159.4, 159.9, 160.2, 161.0, 195.3, 201.0. LC–MS m/z 592.1 (M + 1), 594.1 (M + 2). Anal. calcd. for $C_{33}H_{26}BrN_3O_3$: C, 66.90; H, 4.42; N, 7.09. Found: C, 66.80; H, 4.45; N, 7.12%.

[2-[4-(2-Chloro-benzoyl]-2-bromo-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl-1H-benzo [d]imidazol-1-yl] ethanone (11c): White solid, yield 73%. mp 160–162 °C. FT-IR (KBr): 1665 (C=O),1675 (C=N), 1735 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.60 (s, 3H, N-CH_3), 3.68 (s, 2H, CH_2), 5.01 (s, 2H, OCH_2), 6.3 (s, 1H, 2nd position indole ring H), 6.95–7.70 (m, 15H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 32.4, 39.0, 76.1, 102.8, 112.6, 115.4, 116.5, 116.9, 120.1, 123.2, 125.5, 127.8, 128.5, 130.5, 131.5, 132.9, 134.3, 134.8, 135.9, 136.5, 137.5, 139.6, 140.3, 141.1, 142.1, 162.7, 171.2, 196.3, 204.0. LC–MS m/z 612.1 (M + 1), 614.1 (M + 2), 616.1 (M + 4). Anal. calcd. for $C_{32}H_{23}BrClN_3O_3$: C, 66.71; H, 3.72; N, 6.86. Found: C, 66.80; H, 3.80; N, 6.90%.

[2-(4–4-Bromo-benzoyl-2-bromo-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H-benzo [d]imidazol-1-yl]ethanone (11d): White solid, yield 78%. mp 178–180 °C. FT-IR (KBr): 1670 (C=O), 1685 (C=N),1740 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.60 (s, 3H, N-CH_3), 3.65 (s, 2H, CH_2), 5.05 (s, 2H, OCH_2), 6.3 (s, 1H, 2nd position indole ring H), 6.85–7.75 (m, 15H, Ar–H).^{13}C NMR (DMSO-d_6):δ 32.3, 37.0, 72.1, 103.4, 113.9, 114.2, 115.2, 116.7, 119.1, 121.0, 123.1, 128.9, 139.3, 130.1, 130.3, 131.3, 131.5, 134.1, 134.6, 134.8, 138.7, 139.9, 140.4, 143.5, 163.7, 194.3, 201.5. LC–MS m/z 656.0 (M + 1), 658.0 (M + 2), 660.0 (M + 4). Anal. calcd. for $C_{32}H_{23}Br_2N_3O_3$: C, 58.47; H, 3.53; N, 6.39. Found: C, 58.45; H, 3.58; N, 6.41%.

[2-(4–4-Fluoro-benzoyl-2-bromo-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H-benzo [d]imidazol-1-yl] ethanone (11e): White solid, yield 75%. mp 210–212 °C. FT-IR (KBr): 1660 (C=O),1670 (C=N),1725 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.45 (s, 3H, N-CH_3), 3.60 (s, 2H, CH_2), 5.15 (s, 2H, OCH_2), 6.4 (s, 1H, 2nd position indole ring H), 6.90–7.75 (m, 15H, Ar–H).^{13}C NMR (DMSO-d_6):δ 30.3, 35.0, 75.1, 100.4, 109.9, 114.2, 115.2, 117.7, 119.1, 122.0, 123.1, 125.9, 129.3, 130.1, 130.5, 131.8, 134.5, 134.7, 134.9, 137.3, 138.9, 149.7, 143.5, 161.7, 163.6, 198.3, 201.3. LC–MS m/z 596.1 (M + 1), 598.1 (M + 2). Anal. calcd. for $C_{32}H_{23}BrFN_3O_3$: C, 64.44; H, 3.89; N, 7.05. Found: C, 64.42; H, 3.92; N, 7.10%.

2-(4-Benzoyl-2,6-dimethyl-phenoxy)-1-(2-[(1-methyl-1H-indol-3-yl)methyl)-1H-benzo [d]imidazol-1-yl]ethanone (11f): White solid, yield 80%. mp 121–125 °C. FT-IR (KBr): 1675 (C=O),1675 (C=N),1740 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.30 (s, 6H, $2CH_3$), 3.67 (s, 3H, N–CH_3), 3.65 (s, 2H, CH_2), 5.25 (s, 2H, OCH_2), 6.3 (s, 1H, 2nd position indole ring H), 6.9–7.75 (m, 15H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 17.7, 32.3, 40.0, 71.4, 98.4, 111.2, 114.7, 120.1, 121.0, 123.1, 125.9, 126.5, 128.3, 129.8, 130.8, 131.5, 135.9, 137.5, 138.7, 139.7, 140.3, 144.5, 161.3, 167.5, 194.3, 204.0. LC–MS m/z 528.2 (M + 1). Anal. calcd. for $C_{34}H_{29}N_3O_3$: C, 77.40; H, 5.54; N, 7.96 Found: C, 77.45; H, 5.59; N, 8.01%.

[2-(4–4-Methylbenzoyl-2,6-dimethyl-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H-benzo [d]imidazol-1-yl]ethanone (11g): White solid, yield 85%. mp 178–180 °C. FT-IR (KBr): 1655 (C=O),1685 (C=N),1725 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.2 (s, 6H, $2CH_3$),2.3 (s, 3H, CH_3),3.50 (s, 3H, N-CH_3), 3.69 (s, 2H, CH_2), 5.25 (s, 2H, OCH_2), 6.25 (s, 1H, 2nd position indole ring H), 6.9–7.75 (m, 15H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 16.7, 25.3, 32.3, 39.0, 78.4, 103.4, 111.2, 112.7, 116.1, 120.0, 122.1, 123.9, 126.5, 127.7, 129.9, 130.5, 130.7, 131.5, 131.7, 135.7, 137.9, 139.7, 141.3, 142.3, 165.4, 195.3, 201.8. LC–MS m/z 542.2 (M + 1). Anal. calcd. for $C_{35}H_{31}N_3O_3$: C, 77.61; H, 5.77; N, 7.76. Found: C, 77.65; H, 5.78; N, 7.74%.

[2-(4–2-Chlorobenzoyl-2,6-dimethyl-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H-benzo [d]imidazol-1-yl]ethanone (11h): White solid, yield 88%. mp 165–169 °C. FT-IR (KBr): 1660 (C=O), 1685 (C=N),1740 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.25 (s, 6H, $2CH_3$), 3.55 (s, 3H, N-CH_3), 3.55 (s, 2H, CH_2), 5.15 (s, 2H, OCH_2), 6.3 (s, 1H, 2nd position indole ring H), 6.8–7.65 (m, 14H, Ar–H).^{13}C NMR (DMSO-d_6):δ 16.7, 32.3, 36.0, 75.4, 97.4, 111.2, 114.7, 114.1, 120.0, 121.1, 123.8, 126.5, 127.9, 129.7, 130.2, 131.9, 132.2, 133.4, 134.0, 135.9, 138.5, 139.7, 140.9, 143.5, 158.4, 193.3, 206.1. LC–MS m/z 562.1 (M + 1), 564.1 (M + 2). Anal.

calcd. for $C_{34}H_{28}ClN_3O_3$: C, 72.66; H, 5.02; N, 7.48. Found: C, 72.45.68; H, 5.06; N, 7.52%.

[2-(4–4-Bromobenzoyl-2,6-dimethyl-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H -benzo [d]imidazol-1-yl]ethanone (11i): White solid, yield 74%. mp 190–195 °C. FT-IR (KBr): 1675 (C=O), 1680 (C=N),1730 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.30 (s, 6H, $2CH_3$), 3.58 (s, 3H, N-CH_3), 3.59 (s, 2H, CH_2), 5.25 (s, 2H, OCH_2), 6.25 (s, 1H, 2nd position indole ring H), 6.95–7.75 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 19.1, 32.1, 40.0, 71.4, 103.4, 114.2, 117.7, 118.1, 122.0, 123.1, 124.8, 125.5, 129.7, 130.8, 131.1, 131.5, 132.1,134.5, 137.8, 138.1, 139.7, 140.5, 141.1, 162.4, 195.3, 198.0. LC–MS m/z 606.1. (M + 1), 608.1 (M + 2). Anal. calcd. for $C_{34}H_{28}BrN_3O_3$: C, 67.33; H, 4.65; N, 6.93. Found: C, 67.38; H, 4.68; N, 6.98%.

[2-(4–4-Fluorobenzoyl-2,6-dimethyl-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H -benzo [d]imidazol-1-yl]ethanone (11j): White solid, yield 69%. mp 218–220 °C. FT-IR (KBr): 1680 (C=O),1675 (C=N),1745 (N–C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.25 (s, 6H, $2CH_3$), 3.55 (s, 3H, N–CH_3), 3.69 (s, 2H, CH_2), 5.25 (s, 2H, OCH_2), 6.2 (s, 1H, 2nd position indole ring H), 6.85–7.75 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 16.4, 36.3, 37.0, 73.1, 98.4, 112.2, 114.7, 116.1, 119.0, 120.1, 122.9, 124.5, 128.7, 129.9, 130.9, 132.3, 133.2, 135.9, 139.7, 140.9, 141.5, 160.4, 161.6, 165.6, 193.3, 205.1. LC–MS m/z 546.2 (M + 1). Anal. calcd. for $C_{34}H_{28}FN_3O_3$: C, 74.85; H, 5.17; N, 7.70. Found: C, 74.88; H, 5.19; N, 7.75%.

[2-(4–4-Methoxybenzoyl-2,6-dimethyl-phenoxy)]-1-[2-(1-methyl-1H-indol-3-yl)methyl)-1H-benzo [d]imidazol-1-yl]ethanone (11k): White solid, yield 75%. mp 201–204 °C. FT-IR (KBr): 1675 (C=O), 1680 (C=N),1730 (N–C=O)cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.25 (s, 6H, $2CH_3$), 3.65 (s, 3H, N-CH_3), 3.69 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.02 (s, 2H, OCH_2), 6.3 (s, 1H, 2nd position indole ring H), 6.75–7.76 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6):δ 16.1, 33.1, 40.0, 58.8, 76.4, 102.4, 113.2, 114.7, 114.9, 116.1, 120.0, 123.1, 123.1, 125.8, 126.3, 126.8, 128.1, 129.7, 131.1, 131.5, 135.3, 140.7, 143.5, 158.4, 161.3, 195.3, 204.0. LC–MS m/z 558.2 (M + 1). Anal. calcd. for $C_{35}H_{31}N_3O_4$: C, 75.38; H, 5.60; N, 7.54. Found: C, 75.40; H, 5.63; N, 7.56%.

Biology

Antimicrobial activity

Compounds (**6a–l**) were tested for their antimicrobial activity by disk diffusion assay and minimum inhibitory concentration (MIC) methods. Ampicillin and ciprofloxacin (Sigma) were used as positive control against bacteria. Ketoconazole and fluconazole (Himedia, Mumbai) were used as positive control against fungi.

Tested microbes

The following gram-positive bacteria were used for the experiments: *S.aureus*, *S.aureus* (*MRSA*), *M.luteus* and *E.erogenes*. The gram-negative bacteria included *K.pneumonia*, *S.typhimurium*, *P.Vulgaris* and *S.Paratyphi-B*. In addition, fungi *C.albicans, B.cinerea, C.Krusei and M.pachydermatis* were also used for the experiments. All cultures were obtained from the Department of Microbiology, Manasagangotri, Mysuru.

Preparation of inoculums

Bacterial inoculums were prepared by growing cells in Mueller Hinton Broth (MHA, Himedia Mumbai) for 24 h at 37 °C. These cell suspensions were diluted with sterile MHB to provide initial cell counts of about 104 CFU/mL. The filamentous fungi were grown on sabouraud dextrose agar (SDA) slants at 28 °C for 10 days, and the spores were collected using sterile doubled distilled water and homogenized.

Disk diffusion assay

Antibacterial activity was carried out using a disk diffusion method [54]. Petri plates were prepared with 20 mL of sterile (MHA). The test cultures were swabbed on the top of the solidified media and allowed to dry for 10 min. The tests were conducted at 1000 µg/disc. The loaded discs were placed on the surface of the medium and left for 30 min at room temperature for compound diffusion. Negative control was prepared using respective solvent. Streptomycin (10 µg/disc) was used as positive control. The plates were incubated for 24 h at 37 °C for bacteria and 48 h at 27 °C for fungi. A zone of inhibition was recorded in millimeters, and the experiment was repeated thrice.

Minimum inhibitory concentration (MIC)

MIC study of synthesized compounds (**11a–k**) was performed according to the standard reference method [55] for bacteria and filamentous fungi by serial dilution method (compounds were dissolved in DMSO). An inoculum of 100 µL from each well was inoculated. The antifungal agents ketoconazole, fluconazole for fungi and streptomycin and ciprofloxacin for bacteria were included in the assays as positive controls. For fungi, the plates were incubated for 48–72 h at 28 °C, and for bacteria, the plates were incubated for 24 h at 37 °C. The MIC for fungi was defined as the lowest extract concentration, showing no visible fungal growth

after incubation time. Further, 5 mL of testing broth was placed on the sterile MHA plates for bacteria and incubated at respective temperatures. The MIC for bacteria was determined as the lowest concentration of the compound inhibiting the visual growth of the test cultures on the agar plate.

Docking studies

The molecular interaction between protein and ligand can virtually be studied by subjecting the input files for molecular docking study. The docking operations can be performed by several algorithms, of which SURFLEX DOCK being such a program as available with SYBYL-X 2.1.1 software package (Tripos Inc., USA). The algorithm can readily be applied to rigid to flexible type docking. The input files as PDB file of protein and virtually sketched files of synthesized compounds showing best biological activity were either collected from online server or drawn by using Chemdraw 15.0., and all other necessary calculations were performed as per default protocol [56]. Preamble to docking protocol, all the required input files were prepared, hydrogen atoms were added, water was removed, ionization state of C-terminal and N-terminal was fixed and finally energy minimized by steepest descent method applying Gasteiger–Marsili charges and MMFF94s forcefield to the protein file with 100 iterations of conjugate gradient method with 1.0 kcal/mol as the convergence criteria fixing to 0.5 dielectric constant, whereas ligand files were converted to 3D forms and energy minimized by applying Gasteiger–Huckel charges. The Geom mode of Surflex dock allows the ligand files to flexibly interact with rigid protein files. The binding site of the protein file was abstracted from co-crystal ligand bound information and protomol generation program uses such information to find suitable cavity for docking. The adopted docking protocol was validated using a comparison of the binding modes of co-crystalized ligand of the target protein FtsZ (PDB: 3VOB) before and after the docking study. Highlighting feature of Geom mode is generation of 20 conformers for each ligand which interacts to the protein individually in order to identify the most stable conformer having best binding pose and binding energy. The respective ligand poses and docking scores in terms of Total score, Crash score and Polar score were obtained and represented accordingly.

Result and discussion

Chemistry

Synthesis of the title compounds **10a–k** was accomplished by a synthetic procedure as shown in Scheme 1. All the synthesized compounds were established by IR, NMR and mass spectral data. The benzoylated products **3a–k** were synthesized by the benzoylation of substituted phenols **1a–b** with substituted benzoyl chlorides **2a–f** under low temperature and confirmed by the appearance of the carbonyl stretching band (1705–1735 cm^{-1}) for the ester group in the IR spectra and the disappearance of broad singlet of the OH proton of substituted phenols **1a–b** in proton NMR spectra. Fries rearrangement of compounds **3a–k** using anhydrous aluminum chloride as a catalyst under neat condition gave hydroxy benzophenones **4a–k**, which were established by the disappearance of carbonyl stretching of compounds **3a–k** and appearance of OH stretching bands around 3505-3635 cm^{-1} in IR spectra also by the appearance of broad singlet for OH proton around4.22–4.6 ppm and decrease in one aromatic proton in proton NMR spectra. Compounds **4a-k** on etherification with ethyl chloroacetate using dry acetone as a solvent gave substituted (4-benzoyl-phenoxy)-acetic acid ethyl esters**5a-k**, which were confirmed by the disappearance of the OH stretching of compounds **4a-k** and appearance of carbonyl stretching band around 1760-1779 cm^{-1} for the ester group in the IR absorption spectra. The proton NMR observations revealed that broad singlet for the OH proton of compounds **4a-k** was disappeared and a triplet and quartet for CH_3(1.2–1.6 ppm) and CH_2(4.1–4.6 ppm) protons were appeared, respectively. The compounds **5a–k** on refluxing with aqueous sodium hydroxide in ethanol gave (4-benzoyl-phenoxy)-acetic acids **6a–k**, which was clearly evident with the appearance of carbonyl (1715–1740 cm^{-1}) and OH (3400–3560 cm^{-1}) groups stretching bands of carboxylic group in the IR spectra. In proton NMR, the appearance of COOH proton (9.0–9.5 ppm) and disappearance of triplet and quartet peaks for CH_3 and CH_2 protons, respectively, of compounds **5a-k** has confirmed the formation of the products **6a-k.** Besides, N-(2-aminophenyl)-2-(1-methyl-1*H*-indol-3-yl)acetamide (**9**) was obtained by the reaction of 2-(1-methyl-1*H*-indol-3-yl)acetic acid (**7**) and 1,2-diamino benzene (**8**) in the presence of lutidine as a base and dichloromethane as a solvent. This compound **9** was established by the disappearance of O–H stretching of compound **7**and NH_2 stretching of compound **8** in the IR spectrum. Besides, an appearance of NH (9.8 ppm) proton and the disappearance of one -COOH proton and NH_2 proton of compound **7** and **8**, respectively, in the NMR spectrum was also observed. Compound **9** on refluxing with acetic acid undergoes cyclization to give 2-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-benzo[d]imidazole (**10)** which was confirmed by the appearance of C = N stretching at 1680 cm^{-1} and disappearance of NH_2 stretching band in the IR spectrum. Further, in NMR spectrum of compound **10** there is a disappearance of NH_2 proton of compound **8**. Finally, substituted (4-benzoyl-phenoxy)-acetic acids (**6a–k)**, on treatment with 2-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-benzo[d]imidazole (**10**) in the presence of lutidine and TBTU as a coupling reagent, delivered the

expected final products 2-(4-benzoylphenoxy)-1-(2-((1-methyl-1*H*-indol-3-yl)methyl)-1*H*-benzo [d]imidazol-1-yl) ethanones (**11a–k)** in a good yield (75–85%). This was supported by the disappearance of NH proton of compound **10**and COOH proton of compound **9** and also by the increase in number of aromatic protons in NMR spectra and by appearance of amide carbonyl stretching around 1725-1745 cm^{-1} in the IR spectra.

Biology

As per the literature, the biological activities of indole, benzimidazole, benzophenone and their derivatives have been recognized for a long time. Based on this in the present investigation, the combination of above three molecules was chosen for the synthesis of novel molecules as antimicrobial agents. The title compounds were designed to achieve a wide range of potential microbial inhibitors by replacing the hydrogen at various positions of the benzophenone ring with different groups. All the synthesized compounds **11a–k** were evaluated for antimicrobial activity by disk diffusion method and compared with the activity of the standard drugs (ampicillin, ciprofloxacin, ketoconazole and fluconazole). The synthesized analog was tested for *in vitro* antibacterial activity against gram-positive (*S.aureus*, *S.aureus* (*MRSA*), *M.luteus* and *E.erogenes)* and gram-negative (*K.pneumonia*, *S.typhimurium*, *P.Vulgaris* and *S.Paratyphi-B)* bacteria. Also, these compounds were tested with fungal strains like *C.albicans, B.cinerea, C.Krusei* and *M.pachydermatis.*

The antibacterial results displayed that compounds **11b** with a methyl group at the para position of benzoyl ring and bromo group at the ortho position of the phenoxy ring, **11e** with fluoro group at para position of benzoyl ring and a bromo group at the ortho position of the phenoxy ring, **11f** with two methyl groups at the ortho positions of phenoxy ring, and **11h** with a chloro group at the ortho position of benzoyl ring and two methyl groups at ortho positions of phenoxy ring were found to be more active towards all the tested strains. Consequently, these compounds were subjected to MIC assay by broth dilution method. In this screening compounds, **11b** and **11f** were shown the least MIC value against gram-negative bacteria and compounds **11f** and **11h** shown the least MIC value against gram-positive bacteria. Incontrast, compounds **11c** with a chloro group at the ortho position of benzoyl ring and bromo group at the ortho position of the phenoxy ring, **11d** with a bromo group at para position of benzoyl ring and another bromo group at the ortho position of the phenoxy ring, **11i** with two methyl groups at the ortho positions of phenoxy ring and abromo group at the para position of benzoyl ring, **11j** with two methyl groups at the ortho positions of phenoxy ring and a fluoro group at the para position of benzoyl ring and **11k** with two methyl groups at the ortho positions of phenoxy ring and a methoxy group at the para position of benzoyl ring exhibited weak activity towards most of the bacterial strains. Moreover, compounds **11a** with a bromo group at the ortho position of the phenoxy ring and **11g** with two methyl groups at the ortho positions of phenoxy ring and a third methyl group at the para position of the benzoyl ring displayed moderate antibacterial activity towards most of the strains.

Interestingly, in antifungal assay the same compounds **11b**, **11e, 11f** and **11h** exhibited broad activity with MIC values in the range 15.62–250 µg/mL against *C.albicans*, *B.cinerea*, *C.Krusei* and *M.pachydermatis* fungal strains. On the contrary, the MIC values for the remaining compounds are 250 µg/ mL and above. The enhanced activity of the compounds **11b**, **11e**, **11f** and **11h** is due to various substituents at different positions of the benzophenone ring. On the other hand, compounds **11d**, **11g**, **11j** and **11k** displayed very weak antifungal activity**.** The structural activity relationship revealed that the synthesized compounds with electron withdrawing groups at the ortho position of the phenoxy and benzoyl ring were more bioactive while the compounds with electron-donating groups at the ortho position of the phenoxy ring were also more bioactive than other compounds in the series (Tables 1, 2).

Docking studies

A molecular docking study fundamentally defines the binding modes of ligand interaction at the active site of the receptor [56]. In our study, the four compounds with notable antibacterial activity were subjected for docking studies against FtsZ protein and the results are shown in Table 3. The inhibition of FtsZ (filamentous temperature-sensitive protein Z) protein prevents the formation of divisome, and hence, it is proven to be a striking target for antibiotic research [57]. Present docking study tries to provide with an insight to the protein binding of biologically active potent ligands, and the rationale of selecting only four ligands for docking study was based on antibacterial biological activity data which then subjected to bind the active site of FtsZ protein. The best binding pose for docked ligands was identified and visualized based on binding affinities. The binding interactions of protein with the compounds revealed that almost all the compounds were interacting similarly to the identified binding site and valine 297, leucine 200, isoleucine 226, isoleucine 228, threonine 265, valine 307 and methionine 226 (Fig. 1–4), with different H-bond and hydrophobic interactions showing distances ranging between 2.117 and 3.786 Å, docking result included with several scores as Total score, Crash score and Polar score, where Total score being representing the binding affinities. The docking outcome provides

Table 1 *In vitro* antibacterial and antifungal activity of compounds 11a-k

Compounds	Zone of inhibition in mm											
	Gram-positive bacteria				Gram-negative bacteria				Fungi			
	S.a	S.a-M	M.l	E.e	K.p	S.t	P.v	Sp.B	C.a	B.c	C.k	M.p
11a	16	12	14	15	10	15	12	11	14	10	16	23
11b	23	17	21	18	16	23	19	11	22	9	15	12
11c	9	11	11	12	12	9	9	8	12	10	13	16
11d	10	9	11	9	9	11	8	8	10	8	14	12
11e	23	20	15	25	22	13	18	24	22	13	17	21
11f	22	14	17	19	15	24	18	9	21	10	15	12
11g	17	13	16	14	15	17	10	11	12	8	13	8
11h	22	11	21	20	15	24	17	13	20	13	11	23
11i	11	8	12	9	11	10	9	8	12	10	16	13
11j	11	9	10	9	12	11	13	9	9	10	8	8
11k	10	8	11	10	11	12	11	10	9	9	9	10
Streptomycin	24	21	23	26	23	25	19	25	–	–	–	–
Ketoconazole	–	–	–	–	–	–	–	–	23	14	18	24

Gram-positive bacteria—S.a *S. aureus*, S.aM *S. aureus* (MRSA), M.l *M. luteus*, E.e *E. erogenes*
Gram-negative bacteria—K.p *K. pneumonia*, S.t *S. typhimurium*, P.v *P. vulgaris*, Sp.B *S. Paratyphi*–B
Fungi—C.a *C. albicans*, B.c *B. cinerea*, C.k *C. krusei*, M.p *M. pachydermatis*

Table 2 MIC (μg/mL) of potent compounds against tested bacteria and fungi

Compounds	Minimum inhibitory concentration (μg/ mL)											
	Gram-positive bacteria				Gram-negative bacteria				Fungi			
	S.a	S.aM	M.l	E.e	K.p	S.t	P.v	Sp.B	C.a	B.c	C.k	M.p
11b	15.62	31.25	15.62	62.5	125	62.5	125	500	62.5	15.62	250	125
11e	31.25	62.5	31.25	250	250	31.25	62.5	250	125	62.5	250	250
11f	15.62	250	31.25	15.62	15.62	15.62	15.62	125	31.5	125	31.5	500
11 h	15.62	125	62.5	62.5	550	31.25	125	500	15.62	15.62	250	250
Streptomycin	6.25	> 100	6.25	25	6.25	30	ni	6.25	-	-	-	-
Ciprofloxacin	< 0.78	> 100	< 0.78	> 100	< 0.78	> 100	6.25	< 0.78	-	-	-	-
Ketoconazole	–	–	–	–	–	–	–	–	25	25	15	15
Fluconazole	–	–	–	–	–	–	–	–	> 100	ni	12.5	12.5

Gram-positive bacteria—S.a *S. aureus*, S.aM *S. aureus* (MRSA), M.l *M. luteus*, E.e *E. erogenes*
Gram-negative bacteria—K.p *K. pneumonia*, S.t *S. typhimurium*, P.v *P. vulgaris*, Sp.B *S. Paratyphi*–B
Fungi—C.a *C. albicans*, B.c *B. cinerea*, C.k *C. krusei*, M.p *M. pachydermatis*
ni no inhibition

Table 3 Docking scores of compounds with respect to FtsZ protein

Sl. No	Compounds	Total score	Crash score	Polar score
1	**11b**	9.5396	– 2.5956	0
2	**11e**	8.9102	– 1.564	1.1547
3	**11f**	8.1618	– 1.5306	0
4	**11h**	6.4529	– 2.4048	0.0159

*Crash score: revealing the inappropriate penetration into the binding site

^Polar score: reports the polar region of the ligands

understanding of ligand interaction and offers a support to the hypothesis.

Binding pose with the maximum binding affinity for docked conformation of compounds 11b, 11e, 11f and 11h is shown in Fig. 1–4. Figure 1–4 reveals that various interactions in terms of hydrogen bonding, π—donor hydrogen bonding, π—alkyl and π–π interactions are mainly responsible for anchoring of the compounds 11b, 11e, 11f and 11h in the active site of FtsZ protein. Compound 11f interacts with FtsZ protein with the docking score of 9.5396 and the

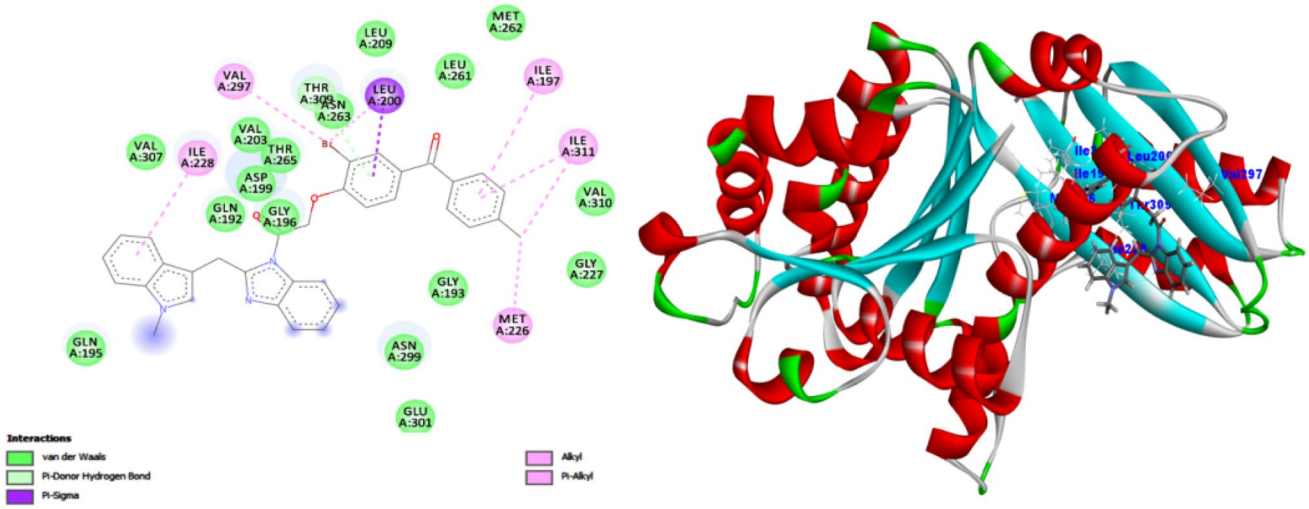


Fig. 1 Binding pose of compound 11b with FtsZ protein (2D) and (3D) after docking studies

π-electrons of benzophenone phenyl ring interacts with Leu-261 by π-sigma interactions. Meanwhile, the same Leu-261 interacts with the halogen/bromine which is present at the ortho/2nd position of the phenyl ring. Further, the benzoyl ring π-electrons interact with Ile-197 and Ile-311. Simultaneously, the methyl group present at para position in the benzoyl ring interacts with Ile-311and Met-226. In the same vicinity, the π-electrons of indole benzene ring having pi-alkyl interacts with Ile-228 (Fig. 1).

Similarly, compound 11e has a docking score of 8.9102. The formation of conventional hydrogen bond with Thr-265 amino acid and oxygen of benzophenone C=O is clearly visible, whereas Val-307 having alkyl group interacts with this compound through the bromine present at 2nd position of phenyl ring. In the same path, Leu-302 having a π-alkyl group interacts with the π-electrons of benzoyl ring; in addition the same benzoyl ring having a π-lone pair interacts with Glu-301 amino acid. In continuation, compound 11e correspondingly interacts with Ile-228, Leu-200 and Val-297 amino acids with benzimidazole and indole by alkyl, π-sigma and π-alkyl groups, respectively (Fig. 2).

Likewise, compound **11f** having a total docking score of 8.1618 interacts or forming a bond with FtsZ protein by carbon-hydrogen bonding, π-lone pair and π-alkyl interaction with Val-203—indole and benzimidazole ring systems, Asp-199—phenyl ring of benzophenone and Ile-228—benzoyl ring, Leu -200—benzene ring of indole and Val—297 -imidazole ring of benzimidazole, respectively (**Fig. 3**).

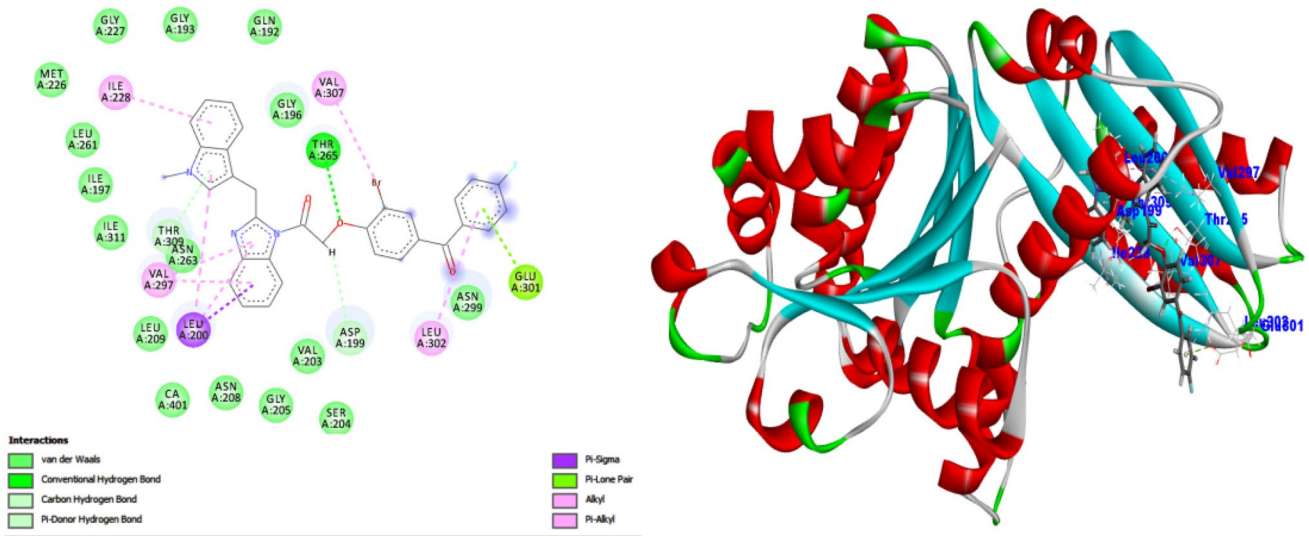


Fig. 2 Binding pose of compound 11e with FtsZ protein (2D) and (3D) after docking studies

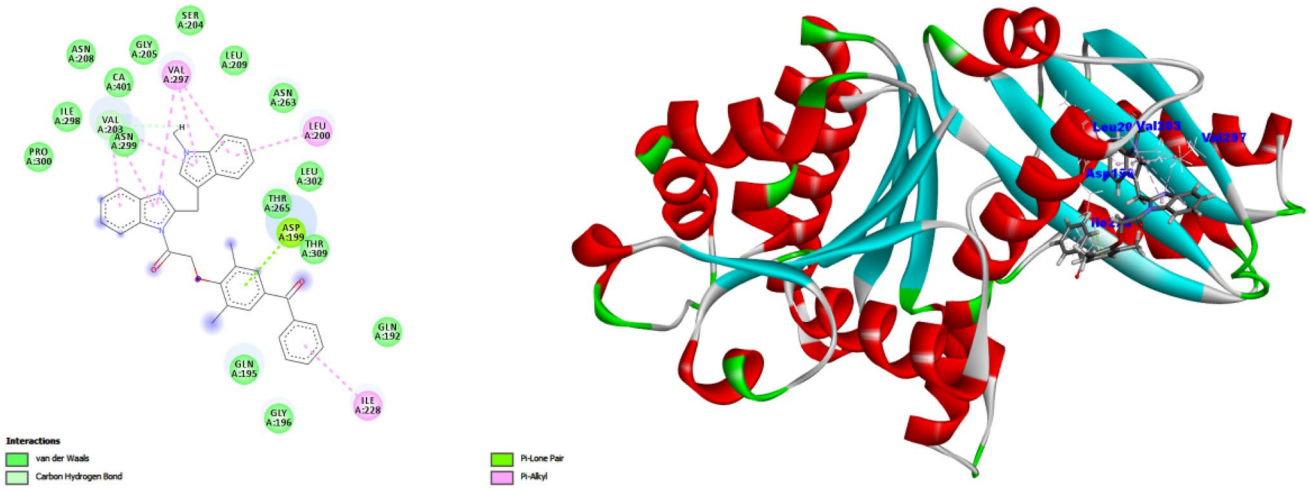


Fig. 3 Binding pose of compound 11f with FtsZ protein (2D) and (3D) after docking studies

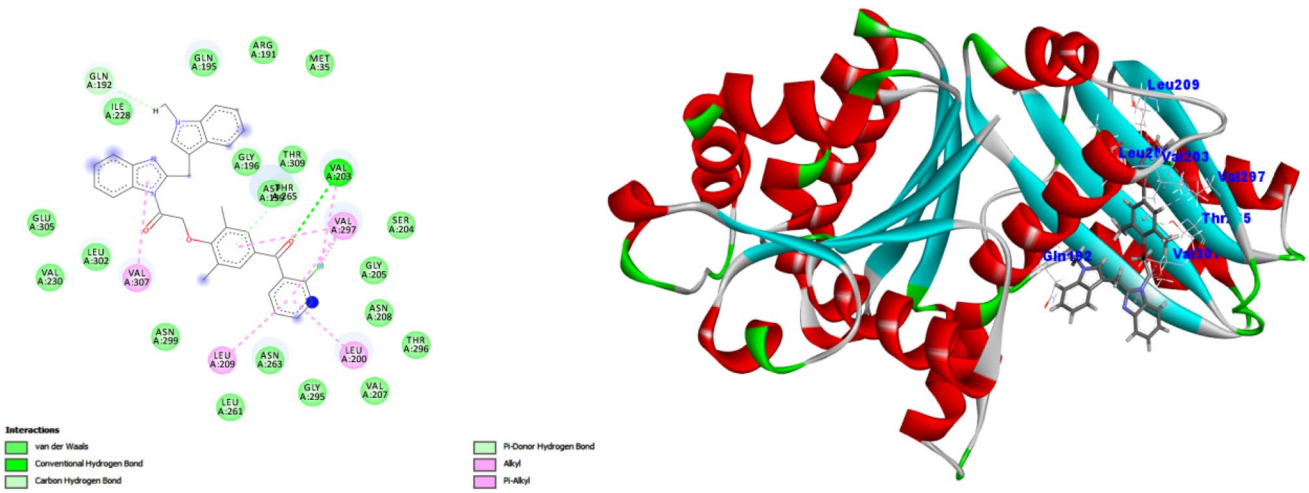


Fig. 4 Binding pose of compound 11 h with FtsZ protein (2D) and (3D) after docking studies

Finally compound 11 h, scoring 6.4529 in docking with FtsZ protein, forms a conventional hydrogen bond between benzophenone oxygen—Val -203, carbon hydrogen bond formation with Gln—192 and hydrogen of indole N–H. Further, compound 11 h has an alkyl interaction between Val—307—imidazole, and Leu—209, Val—297, Leu—200 with the benzoyl ring system. Similarly, Val—297 having a π-alkyl group interacts with the phenyl ring of benzophenone ring system (Fig. 4).

Conclusion

In conclusion, the synthesis of various indole and benzimidazole containing benzophenone derivatives was achieved by multi step synthesis. All the synthesized compounds **11a–k** were subjected for the antimicrobial activity and compared with the activity of standard drugs. In the series of **11a–k**, the compounds **11b, 11e, 11f** and **11h**

were publicized as potent compounds among the tested strains. Further, results obtained from docking studies were accordance with *in vitro* results. Finally, the structural activity relationalship revealed that substitution of electron withdrawing and donating groups in the proper position and the combination of two heterocyclic moieties, with benzophenone nucleus leads to the enhanced bioactivity of the synthesized compounds.

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Compliance with ethical standards

Conflict of interest Authors declare that we don't have any conflict of interest with respect to this research work.

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