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One Pot Synthesis, Antimicrobial and *In Silico* Molecular Docking Study of 1,3-Benzoxazole-5-Sulfonamide Derivatives

Vinoda BM[1], Bodke YD[1]*, Vinuth M[1], Aruna Sindhe M[1], Venkatesh T[1] and Sandeep Telkar[2]

[1]*Department of PG Studies and Research in Industrial Chemistry, Kuvempu University, Karnataka-577 451, India*
[2]*Department of PG Studies and Research in Biotechnology, Kuvempu University, Karnataka-577 451, India*

Abstract

A series of 1,3-benzoxazole-5-sulfonamide derivatives have been synthesized *via* acetophenones, aldehydes and 2-sulfanyl-1,3-benzoxazole-5-sulfonamide using Fe(III)-montmorillonite (Fe(III)-mont) as catalyst. Catalyst is good Lewis acid and support to increase the yield of the final compounds. The structures of newly synthesized compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic methods. The antimicrobial potential of title compounds was tested against several bacterial and fungal strains. Some compounds exhibited comparable or better antimicrobial activity in comparison to the reference drugs Ciprofloxacin and Fluconozole. The selected compounds were also subjected for *in silico* molecular docking study.

Keywords: Fe(III)-Montmorillonite; Multi component reactions; Antimicrobial activity; *In silico* molecular docking study

Introduction

One pot synthesis, represent an increasingly important and attractive area of research in organic synthesis, because they provide high levels of efficiency *via* the combination of several operational steps, as well as allowing for operational steps involving the isolation of intermediates or changing of reaction conditions to be avoided. In terms of the advantages that they offer, one pot synthesis is general efficient procedures that provide high levels of atom economy and significant cost savings. One pot synthesis well attracted for easy to workup, fast reaction time and higher yield using Lewis acid as catalyst. These types of reactions are attracted particular attention because of the possibility that these reactions may comply with the green chemistry protocols. Three component reactions are the other hand have emerged as powerful tools in organic synthesis that permit to quick access to the variety of small organic molecules, helpful for medicinal chemistry [1-5]. Thus three component reactions using catalyst are projected to have a main impact and worth in the area of organic synthesis. The sulfonamides drugs have been widely used to treat microbial diseases [6]. On the other hand, due to the quick emergence of sulfonamide resistance organisms and the development of more potent drugs have limited their medical use. The sulfonamide functional group is considered as a pharmacophore which is present in a number of biologically active molecules, particularly antimicrobial agents [7-9]. Several sulfonamide derivatives have been reported as carbonic anhydrase inhibitor [10-14], anticancer [15], and anti-inflammatory agents [16]. Chemical transformation of sulfanilamide is ready to achieve more effective antibacterial activity, broad range of microorganisms affected or more prolonged action. Because of their low price they are still used in various parts of the world. These sulfonamides are still used to treat some urinary tract infections, leprosy, and in combination with other drugs, fungal diseases such as toxoplasmosis. Fe(III)-mont clay is environmentally benign catalyst suited for the 'greening' of modern synthetic chemistry, they are naturally rich, low-cost, harmless, chemically versatile, and eco-friendly [17]. We have shown that Fe(III)-mont clay is an efficient catalyst for a variety of reactions synthesis of fused heterocycles α-aminonitriles [18], 3,5-disubstituted isoxazoles [19], Diels-Alder reaction [20,21], Michael addition [22] and so on. Our efforts to synthesis of 1,3-benzoxazole-5-sulfonamide derivatives using aldehydes with acetophenones and 2-sulfanyl-1,3-benzoxazole-5-sulfonamide. These compounds are important synthetic building blocks, keeping within our premise of green chemistry and in a continuation of our studies for the development of cheap and environmentally benign methodologies for organic synthesis, we decided to examine the flexibility of Fe(III)-mont as a catalyst for the synthesis of 1,3-benzoxazole-5-sulfonamide derivatives. Following this we synthesized the organic molecules using multi-component reaction techniques in the presence of catalysts. The structure was confirmed using spectral data IR, ^{1}H NMR, ^{13}C NMR and LC-MS spectra. The newly synthesized 1,3-benzoxazole-5-sulfonamide derivatives were evaluated for their biological activity with the belief that the assimilation of more than one bio-potent nuclei into a single structure may furnish novel heterocyclic with stimulating antimicrobial activity. Based on the promising *in vitro* antimicrobial results, comparative and automated docking studies with newly synthesized compounds were performed to determine the best *in silico* conformation. The molecular docking studies were performed to considerate coordination between *in silico* studies with *in vitro* antimicrobial results considering gyrase enzyme as the target receptor. The gyrase enzyme relieves strain while double-strand DNA is being unwound by helicase [23,24]. It is an essential enzyme present in all bacteria but absent in higher eukaryotes, hence making it an attractive antibacterial target [25-28].

Experimental

Materials and methods

All the reagents were used directly as obtained commercially. Melting points were determined in open capillary tubes and are uncorrected. Thin layer chromatography was performed on silica gel plates and the spots were visualized by exposure to UV light/ iodine vapor. IR spectra were recorded using KBr pellet (SHIMADZU)

***Corresponding author:** Bodke YD, Department of PG Studies and Research in Industrial Chemistry, Kuvempu University, Karnataka-577 451, India, Tel: +918282256228; E-mail: ydbodke@gmail.com

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instrument, ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO on a Bruker Fourier 400 MHz and 300 MHz spectrometer respectively and chemical shifts (δ) reported relative to internal standard TMS. The LC-MS was recorded using Shimadzu instrument.

Preparation of Fe(III)-mont catalyst

The raw clay Na-mont was purchased from Kunipia F, its cation exchange capacity (CEC) was about 113 meq./100 g. The approximate chemical composition of this clay mineral is given as $(Na_{0.431}K_{0.002}Ca_{0.002})(Al_{1.56}Mg_{0.305}Fe_{0.099}Ti_{0.007})^{oct}(Si_{3.949}Al_{0.051})^{tet}O_{10}(OH)_2\,nH_2O$. The 20 g raw clay was mixed with 1M solution of $FeCl_3$, the interlayer Na(I) ions are exchanged between Fe(III) ions and the reaction mixture was continuously stirred for 24 h. Clay was filtered and dried in hot air oven at 40°C and used as a catalyst [29,30].

Synthesis of 1,3-benzoxazole-5-sulfonamide derivatives using Fe(III)-mont as catalyst

To a solution of substituted acetophenones (1 mmol), aldehyde (1 mmol) and 2-sulfanyl-1,3-benzoxazole-5-sulfonamide (1 mmol) in ethanol, Fe(III)-mont (50% w/w) catalyst was added and the mixture was stirred for 5h at 80°C. After completion of the reaction, solution was poured to the ice cold water. The compound was obtained by the extraction with ethyl acetate, dried, recrystalized using ethanol as solvent.

N-[3-oxo-3-phenyl-1-(thiophen-2-yl)propyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4a): Brown color. mp: 243–244°C. IR (KBr, cm^{-1}): 1056 (S=O), 1718 (C=O), 1452 (Ar-C=C), 2454 (C-S-C), 2560 (SH), 3318 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.08 (s, 1H, NH), 2.72 (s, 1H, SH), 2.89 (d, 2H, CH_2), 4.46 (d, 1H, CH), 7.15 (m, 3H, *J* = 8.24 Hz), 7.42 (m, 3H, *J* = 8.66 Hz), 7.65 (d, 2H, *J* = 7.44 Hz) 7.92 (m, 3H, *J* = 8.12 Hz). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 27.3, 43.7, 72.6, 111.8, 117.2, 121.3, 123.6, 126.2, 126.8, 127.4, 128.4, 128.8, 129.0, 129.6, 136.6, 141.7, 154.6, 182.5. MS (CI): m/z = 444 [M+].

N-[3-(4-methylphenyl)-3-oxo-1-(thiophen-2-yl)propyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4b): Light red color. mp: 265-266°C. IR (KBr, cm^{-1}): 1050 (S=O), 1718 (C=O), 1450 (Ar-C=C), 2451 (C-S-C), 2562 (SH), 3322 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.01 (s, 1H, NH), 2.42 (s, 3H, CH_3), 2.75 (s, 1H, SH), 2.86 (d, 2H, CH_2), 4.42 (d, 1H, CH), 7.11 (m, 3H, *J* = 8.10 Hz), 7.39 (d, 2H, *J* = 8.74 Hz), 7.65 (d, 2H, *J* = 7.96 Hz) 7.92 (m, 3H, *J* = 8.44 Hz). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 29.7, 76.71, 112.73, 116.42, 121.49, 127.49, 127.25, 127.34, 127.45, 128.91, 129.03, 135.85, 137.85, 139.89, 140.88, 145.81, 153.04, 155.58, 183.78. MS (CI): m/z =458 [M+].

N-[3-(4-chlorophenyl)-3-oxo-1-(thiophen-2-yl)propyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4c): Brown color. mp: 276-277°C. IR (KBr, cm^{-1}): 1060 (S=O), 1720 (C=O), 1460 (Ar-C=C), 2452 (C-S-C), 2561 (SH), 3365 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.07 (s, 1H, NH), 2.52 (s, 1H, SH), 3.40 (d, 2H, CH_2), 4.12 (d, 1H, CH), 6.84 (s, 1H), 6.96 (m, 3H, *J* = 8.44 Hz), 7.26 (m, 3H, *J* = 8.24 Hz) 7.46 (t, 2H, *J* = 8.56 Hz), 7.67 (t, 1H, *J* = 8.56 Hz). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 29.1, 29.47, 40.55, 63.91, 74.98, 103.03, 110.76, 133.32, 122.03, 125.81, 128.35, 129.17, 130.78, 133.54, 137.13, 143.83, 153.69, 155.81, 163.64. MS (CI): m/z = 480 [M+2].

N-[3-(4-fluorophenyl)-3-oxo-1-(thiophen-2-yl)propyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4d): Brown color. mp: 281-282°C. IR (KBr, cm^{-1}): 1055 (S=O), 1718 (C=O), 1450 (Ar-C=C), 2450 (C-S-C), 2560 (SH), 3328 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.14 (s, 1H, NH), 2.93 (s, 1H, SH), 3.24 (d, 2H, CH_2), 4.30 (d, 1H, CH), 6.80 (d, 2H, *J* = 8.36 Hz), 6.85 (s, 1H), 7.40 (d, 2H, *J* = 8.14 Hz), 7.66 (d, 2H *J* = 8.54 Hz), 7.65 (m, 3H *J* = 8.28 Hz). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 28.2, 31.25, 44.8, 71.5, 109.7, 118.3, 122.4, 125.5, 126.5, 126.8, 127.2, 128.4, 128.5, 135.1, 136.5, 140.9, 156.5, 181.2. MS (CI): m/z =462 [M+].

N-[3-(4-nitrophenyl)-3-oxo-1-(thiophen-2-yl)propyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4e): Light red color. mp: 295-296°C. IR (KBr, cm^{-1}): 1060 (S=O), 1719 (C=O), 1450 (Ar-C=C), 2456 (C-S-C), 2568 (SH), 3320 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.13 (s, 1H, NH), 2.91 (d, 1H, CH), 3.23 (d, 2H, CH_2), 3.11 (s, 1H, SH), 6.66 (d, 2H, *J* = 8.24 Hz), 6.68 (s, 1H), 7.61 (d, 2H, *J* = 8.08 Hz), 7.71 (d, 2H), 8.30 (m, 3H *J* = 9.16 Hz). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 26.5, 40.5, 73.8, 113.6, 118.3, 122.5, 122.9, 125.6, 126.2, 127.1, 128.6, 133.6, 134.1, 136.7, 137.2, 138.6, 142.8, 155.4, 180.6. MS (CI): m/z =489 [M +].

N-[3-(4-methoxyphenyl)-3-oxo-1-(thiophen-2-yl)propyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4f): Light brown color. mp: 262-263°C. IR (KBr, cm^{-1}): 1051 (S=O), 1715 (C=O), 1453 (Ar-C=C), 2462 (C-S-C), 2556 (SH), 3328 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.38 (s, 1H, NH), 2.93 (d, 1H, CH), 3.26 (d, 2H, CH_2), 3.15 (s, 1H, SH), 3.83 (s, 3H, CH_3), 6.69 (d, 2H, *J* = 8.28 Hz), 6.72 (s, 1H), 7.58 (d, 2H, *J* = 8.06 Hz), 7.70 (d, 2H), 7.85 (m, 3H). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 29.3, 43.8, 70.2, 116.2, 118.2, 119.3, 124.5, 125.2, 126.9, 127.7, 128.6, 130.5, 132.5, 134.9, 136.5, 139.2, 145.3, 152.9, 178.2. MS (CI): m/z =475 [M +1].

N-[1-(furan-2-yl)-3-oxo-3-phenylpropyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4g): Red color. mp: 242-243°C. IR (KBr, cm^{-1}): 1040 (S=O), 1722 (C=O), 1444 (Ar-C=C), 2459 (C-S-C), 2571 (SH), 3329 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.10 (s, 1H, NH), 2.86 (d, 1H, CH), 3.25 (d, 2H, CH_2), 3.12 (s, 1H, SH), 6.71 (d, 2H, *J* = 8.30 Hz), 6.76 (s, 1H), 7.44 (d, 2H, *J* = 8.02 Hz), 7.66 (m, 3H), 7.75 (m, 3H). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 28.6, 42.6, 71.9, 115.4, 119.1, 121.2, 123.6, 127.4, 127.6, 128.4 128.8, 129.2, 132.6, 137.3, 138.8, 142.2, 154.8, 185.5. MS (CI): m/z =429 [M +1].

N-[1-(furan-2-yl)-3-(4-methylphenyl)-3-oxopropyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4h): Light red color. mp: 233-235°C. IR (KBr, cm^{-1}): 1046 (S=O), 1717 (C=O), 1454 (Ar-C=C), 2450 (C-S-C), 2570 (SH), 3318 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.05 (s, 1H, NH), 2.44 (s, 3H, CH_3), 2.69 (s, 1H, SH), 2.79 (d, 2H, CH_2), 4.44 (d, 1H, CH), 7.15 (m, 3H, *J* = 8.18 Hz), 7.35 (d, 2H, *J* = 8.66 Hz), 7.66 (d, 2H, *J* = 7.84 Hz) 7.96 (m, 3H, *J* = 8.48 Hz). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 30.5, 42.8, 74.5, 113.6, 119.4, 120.6, 123.5, 126.7, 126.9, 127.5, 128.9, 128.4, 130.1, 130.3, 138.9, 142.8, 151.3, 181.4. MS (CI): m/z =442 [M+].

N-[3-(4-chlorophenyl)-1-(furan-2-yl)-3-oxopropyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4i): Brown color. mp: 255-256°C. IR (KBr, cm^{-1}): 1060 (S=O), 1720 (C=O), 1462 (Ar-C=C), 2452 (C-S-C), 2558 (SH), 3331 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.16 (s, 1H, NH), 2.90 (d, 1H, CH), 3.22 (d, 2H, CH_2), 3.38 (s, 1H, SH), 6.70 (d, 2H, *J* = 8.28 Hz), 6.84 (s, 1H), 7.44 (d, 2H, *J* = 8.02 Hz), 7.69 (d, 2H), 7.85 (m, 3H). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 28.6, 42.8, 73.8, 113.5, 118.4, 122.2, 123.6, 124.3, 126.6, 127.4, 128.4, 129.4, 130.1, 130.8, 138.5, 141.7, 154.6, 182.5. MS (CI): m/z = 464 [M+2].

N-[3-(4-fluorophenyl)-1-(furan-2-yl)-3-oxopropyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4j): Brown color. mp: 286-287°C. IR (KBr, cm^{-1}): 1045 (S=O), 1718 (C=O), 1445 (Ar-C=C), 2447 (C-S-C), 2562 (SH), 3327 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.19 (s, 1H, NH), 2.96 (d, 1H, CH), 3.36 (d, 2H, CH_2), 3.20 (s, 1H, SH), 6.63

(d, 2H, *J* = 8.24 Hz), 6.66 (s, 1H), 7.51 (d, 2H, *J* = 8.08 Hz), 7.70 (d, 2H), 7.58 (m, 3H). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 29.5, 42.7, 62.5, 112.3, 117.8, 121.6, 122.7, 124.3, 126.3, 127.9, 128.5, 129.6, 130.8, 131.3, 136.8, 138.9, 142.6, 155.9, 186.7. MS (CI): m/z =446 [M+].

N-[1-(furan-2-yl)-3-(4-nitrophenyl)-3-oxopropyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4k): Light red color. mp: 272-273°C. IR (KBr, cm^{-1}): 1066 (S=O), 1718 (C=O), 1455 (Ar-C=C), 2459 (C-S-C), 2563 (SH), 3328 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.43 (s, 1H, NH), 2.84 (d, 1H, CH), 3.21 (d, 1H, CH), 3.13 (s, 1H, SH), 4.41 (d, 1H, CH), 6.66 (d, 2H, *J* = 8.26 Hz), 6.71 (s, 1H), 7.55 (d, 2H, *J* = 8.10 Hz), 7.72 (d, 2H), 8.25 (m, 3H). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 27.4, 47.7, 75.6, 112.8, 117.2, 121.3, 123.6, 126.2, 126.8, 127.4, 128.5, 129.4, 131.2, 136.3, 137.6, 138.5, 141.7, 154.6, 182.5. MS (CI): m/z =473 [M+].

N-[1-(furan-2-yl)-3-(4-methoxyphenyl)-3-oxopropyl]-2-sulfanyl-1,3-benzoxazole-5-sulfonamide (4l): Red color. mp: 261-262°C. IR (KBr, cm^{-1}): 1040 (S=O), 1724 (C=O), 1455 (Ar-C=C), 2459 (C-S-C), 2568 (SH), 3316 (NH). ^{1}H NMR (400 MHz, DMSO): δ (in ppm) 2.14 (s, 1H, NH), 2.82 (d, 1H, CH), 3.44 (d, 2H, CH_2), 3.16 (s, 1H, SH), 3.92 (s, 3H, CH_3), 6.62 (d, 2H, *J* = 8.16 Hz), 6.82 (s, 1H), 7.49 (d, 2H, *J* = 8.12 Hz), 7.68 (d, 2H), 7.85 (m, 3H). ^{13}C NMR (300 MHz, DMSO): δ (in ppm) 29.3, 40.3, 71.3, 110.7, 112.4, 116.2, 122.5, 122.6, 124.2, 127.6, 129.2, 129.5, 131.8, 136.2, 136.6, 138.5, 142.4, 152.6, 180.5. MS (CI): m/z =459 [M+1].

Antimicrobial activity

The synthesized compounds were screened for antibacterial activity against four bacterial strains using agar well diffusion method [31]. Dimethylsulfoxide (DMSO) was used as solvent control. The bacterial cultures were inoculated on nutrient agar (Merck) and fungal culture was inoculated on potato dextrose agar media (20 mL). The test compounds were dissolved in DMSO to get a concentration of 1 mg/mL. 100 µL of this sample was loaded into the wells of agar plates directly. Plates inoculated with the bacteria were incubated at 37°C for 24 h and the fungal culture was incubated at 25°C for 72 h. All determinations were done in triplicates. The Ciprofloxacin and Fluconazole were used as standard drugs for antibacterial and antifungal activities, respectively. After the incubation period, the Minimum Inhibition zone at which the microorganism growth was inhibited was measured in mm.

In silico molecular docking studies

An entirely in-house developed drug discovery informatics system OSIRIS was used to perform ADMET based calculations. It is a Java based library layer that provides reusable cheminformatics functionality and was used to predict the toxicity risks and overall drug score via *in silico* [32]. The structure of synthesized molecules and the standards were drawn in ChemBioDraw tool (ChemBioOffice Ultra 14.0 suite) assigned with proper 2D orientation and structure of each was checked for structural drawing error. Energy of each molecule was minimized using ChemBio3D (ChemBioOffice Ultra 14.0 suite). The energy minimized ligand molecules were then used as input for AutoDock Vina, in order to carry out the docking simulation [33]. The protein databank (PDB) coordinate file entitled '2XCT.pdb' was used as receptor (protein) molecule which is a structure of *S. aureus* gyrase in complex with Ciprofloxacin and DNA [34]. All the water molecules were removed from the receptor and SPDBV Deep view was used to automatically rebuild the missing side chains in receptor. The Graphical User Interface program 'MGL Tools' was used to set the grid box for docking simulations. The grid was set so that it surround the region of interest (active site) in the macromolecule. In the present study, the active site was selected based on the amino acid residues of 2XCT, which are involved in binding with Ciprofloxacin. Therefore, the grid was centered at the region including the 2 amino acid residues (Arg 458 and Gly 459) and 4 nitrogenous bases from DNA that is guanine (G), adenine (A), thymine (T) or cytosine (C) as evidenced by the work of Bax et al. this surrounds the active site. The grid box volume was set to 8, 14, and 14 Å for x, y and z dimensions respectively, and the grid center was set to 3.194, 43.143 and 69.977 for x, y and z center respectively, which covered the 2 amino acid residues and 4 nitrogenous base in the considered active pocket. AutoGrid 4.0 Program, supplied with AutoDock 4.0 was used to produce grid maps [35]. The docking algorithm provided with AutoDock Vina was used to search for the best docked conformation between ligand and protein. During the docking process, a maximum of 10 conformers was considered for each ligand. All the AutoDock docking runs were performed in Corei7 Intel processor CPU with 16 GB DDR3l RAM. AutoDock Vina was compiled and run under Windows 8.0 professional operating system. LigPlot+ [36] and PyMol were used to deduce the pictorial representation of interaction between the ligands and the target protein.

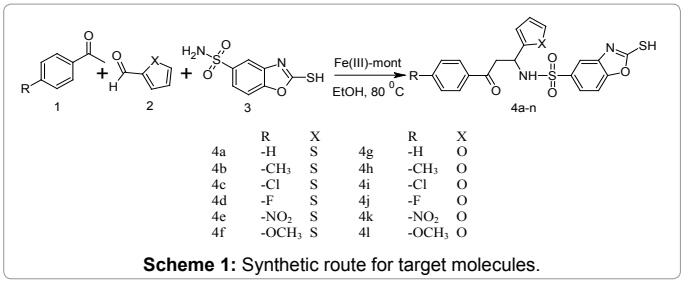
Results and Discussion

In our research work, development in the novel transformation in organic synthesis using catalyst, we have developed a route for the construction of 1,3-benzoxazole-5-sulfonamide derivatives using Fe(III)-mont is an efficient catalyst. The reaction of acetophenones, aldehydes and 2-sulfanyl-1,3-benzoxazole-5-sulfonamide was initially selected as a model transformation to optimize the reaction condition in Scheme 1. As shown in the Table 1, when the reaction was initially conducted in the absence of the catalyst, only less yields was obtained after long reaction time. The addition of the 5 w/w% of catalyst led to a considerable yield (34%) with the reaction time being reduced to 9 h. Increasing the catalyst amount from 5 to 10 and 25 w/w%, the yield (42 and 62%) was increased and the reaction time was reduced. Further increase in the catalytic amount to 50 w/w%, product yield was increased to 73%. Catalytic amount increased to 75 w/w%, however led to a reduction in the product yield (64%) and increase in the reaction

Entry	Fe(III)-mont (% w/w)	Time(h)	Yield (%)
1	0	13	22
2	5	9	34
3	10	7	42
4	25	6	62
5	50	5	73
6	75	6	64

[a]Reaction conditions: aldehyde (1 mmol), acetophenone (1 mmol), 2-sulfanyl-1,3-benzoxazole-5-sulfonamide (1 mmol); solvent ethonal; 80°C temperature.

Table 1: Optimization of reaction condition of 4a compound[a].



	R	X		R	X
4a	-H	S	4g	-H	O
4b	-CH_3	S	4h	-CH_3	O
4c	-Cl	S	4i	-Cl	O
4d	-F	S	4j	-F	O
4e	-NO_2	S	4k	-NO_2	O
4f	-OCH_3	S	4l	-OCH_3	O

Scheme 1: Synthetic route for target molecules.

time, hence 50 w/w% of catalyst gave a best result. Therefore 50 w/w% of catalyst is efficient to 1 mmol amount of the reaction mixture. Using the optimized conditions, several 1,3-benzoxazole-5-sulfonamide derivatives were synthesized. The results are summarized in Table 2. The structure of all products was established by spectroscopic methods FTIR, ^{1}H NMR, ^{13}C NMR and LCMS.

In vitro antimicrobial study

The newly synthesized compounds were screened for their antibacterial and antifungal activity by agar well diffusion method and the results are tabulated in Table 3. The compounds displayed moderate to good promising activity. A close investigation of the MIC values indicates that all the compounds exhibited a varied degree of MIC (21.24-96.62 µmol/L) of antibacterial and antifungal activity against all the tested strains. Furthermore, the compounds which showed good zone of inhibition were studied for minimum inhibitory concentration (MIC) to quantify the antimicrobial potency of these compounds in Table 4. The substituent's where R = Cl, F, NO_2 at the *p*-position plays a key role in varying the efficacy of antimicrobial activity. The 1,3-benzoxazole-5-sulfonamide compounds displayed good antimicrobial activity against the tested pathogens. The introduction of electron withdrawing groups Cl, F or NO_2 led to significant increase in activity compared to an electron-donating CH_3 group.

In silico molecular studies

Considering the results obtained from anti-bacterial activity, it was thought worthy to perform molecular docking studies by substantiating the *in vivo* results with *in silico* studies. The comparative docking of receptor gyrase, with compounds **4c**, **4d**, **4e** and **4k** exhibited good affinity. They established bonds with one or more amino acids in the receptor active pocket as represented in Table 5. All the docked molecules were subjected to 2D and 3D protein-ligand interaction analysis. Figure 1 represents the further extrapolation of binding conformation of the docked molecules. All the molecules that were subjected for molecular docking represented at least one H-bond. The commonly interacting residues (Figure 1) are encircled in red colour. Further, Figure 2 represents the 3D interaction of same set of molecules respectively with gyrase by using educational version of PyMol The ligands are represented in green colour, H-bonds with their respective distances are represented with cyan colour, and the interacting residues are represented in ball and stick model representation.

Entry	R	X	Catalyst	Time[b] (~h)	Yield
4a	-H	-S	Fe(III)-mont	5	70
4b	-CH_3	-S	Fe(III)-mont	5	73
4c	-Cl	-S	Fe(III)-mont	5	68
4d	-F	-S	Fe(III)-mont	5	65
4e	-NO_2	-S	Fe(III)-mont	5	71
4f	-OCH_3	-S	Fe(III)-mont	5	70
4g	-H	-O	Fe(III)-mont	5	69
4h	-CH_3	-O	Fe(III)-mont	5	71
4i	-Cl	-O	Fe(III)-mont	5	65
4j	-F	-O	Fe(III)-mont	5	64
4k	-NO_2	-O	Fe(III)-mont	5	71
4l	-OCH_3	-O	Fe(III)-mont	5	67

[a]Reaction conditions: acetophenone (1 mmol), aldehyde (1 mmol), 2-sulfanyl-1,3-benzoxazole-5-sulfonamide (1 mmol); solvent ethanol; catalyst: Fe(III)-mont (80°C)
[b]Time being ± 20 min

Table 2: One-pot synthesis of 1,3-benzoxazole-5-sulfonamide derivatives catalyzed by Fe(III)-mont[a].

Zone of inhibition							
Compound	***E. c.***	***P. a.***	***S. p.***	***B. s.***	***P. m.***	***C. a.***	***T. r.***
4a	14 ± 0.2	13 ± 0.2	17 ± 0.1	15 ± 0.1	11 ± 0.1	13 ± 0.1	10 ± 0.1
4b	17 ± 0.2	17 ± 0.2	15 ± 0.2	17 ± 0.2	14 ± 0.2	17 ± 0.2	15 ± 0.2
4c	20 ± 0.1	21 ± 0.1	22 ± 0.1	20 ± 0.2	17 ± 0.1	18 ± 0.1	18 ± 0.1
4d	20 ± 0.2	22 ± 0.1	22 ± 0.1	22 ± 0.1	16 ± 0.1	16 ± 0.1	22 ± 0.1
4e	21 ± 0.1	22 ± 0.2	23 ± 0.1	20 ± 0.2	18 ± 0.1	19 ± 0.1	17 ± 0.1
4f	15 ± 0.1	17 ± 0.1	19 ± 0.2	13 ± 0.1	14 ± 0.2	16 ± 0.2	17 ± 0.2
4g	13 ± 0.2	14 ± 0.2	14 ± 0.1	16 ± 0.1	14 ± 0.1	15 ± 0.1	12 ± 0.1
4h	14 ± 0.1	17 ± 0.1	12 ± 0.2	14 ± 0.2	16 ± 0.2	17 ± 0.2	13 ± 0.2
4i	20 ± 0.2	20 ± 0.1	20 ± 0.1	20 ± 0.1	17 ± 0.1	15 ± 0.1	14 ± 0.1
4j	17 ± 0.2	19 ± 0.1	22 ± 0.1	19 ± 0.1	16 ± 0.1	18 ± 0.1	19 ± 0.1
4k	20 ± 0.2	22 ± 0.1	23 ± 0.2	20 ± 0.2	19 ± 0.2	20 ± 0.2	20 ± 0.2
4l	16 ± 0.1	18 ± 0.2	16 ± 0.2	17 ± 0.2	17 ± 0.2	15 ± 0.2	17 ± 0.2
Stnd[a]	26 ± 0.2	28 ± 0.1	27 ± 0.1	27 ± 0.2	–	–	–
Stnd[b]	–	–	–	–	21 ± 0.1	22 ± 0.1	20 ± 0.2

Each value is expressed as mean ± SD of three replicates for zone of inhibition; Stnd[a]: Ciprofloxacin, Stnd[b]: Fluconazole; *E. c: Escherichia coli, P. a: Pseudomonas aeruginosa, S. p: Streptococcus pneumoniae, B. s: Bacillus subtilis* [a] *P. m: Phytophthora meadii, C. a: Candida albicans, T. r: Trichophyton rubrum*

Table 3: Antimicrobial activity data of synthesized compounds.

Minimum inhibition concentration (µmol/L)							
Compound	***E. c.***	***P. a.***	***S. p.***	***B. s.***	***P. m.***	***C. a.***	***T. r.***
4a	64.24	36.45	33.65	36.65	39.56	55.48	48.65
4b	46.45	38.65	31.97	53.65	62.85	63.91	71.85
4c	28.46	27.94	25.25	28.62	33.25	30.14	33.12
4d	29.56	29.53	31.62	28.48	53.58	69.62	52.86
4e	21.51	21.32	22.15	24.06	32.71	30.44	41.65
4f	56.13	63.15	43.98	33.15	37.79	49.53	43.56
4g	96.62	85.65	64.84	83.12	75.32	63.62	69.56
4h	28.64	31.53	26.45	38.74	89.36	44.85	69.43
4i	32.22	31.16	30.48	55.42	63.63	69.55	77.27
4j	29.28	26.34	23.83	21.89	72.24	76.35	71.49
4k	21.45	26.26	39.54	21.24	45.29	29.46	22.68
4l	32.53	26.87	28.33	32.25	44.76	45.23	48.29
Stnd[a]	6.53	5.23	6.21	5.36	–	–	–
Stnd[b]	–	–	–	–	11.25	9.36	12.35

Stnd[a]: Ciprafloxin, Stnd[b]: Fluconazole; *E. c: Escherichia coli, P. a: Pseudomonas aeruginosa, S. p: Streptococcus pneumoniae, B. s: Bacillus subtilis, P. m: Phytophthora meadii, C. a: Candida albicans, T. r: Trichophyton rubrum*

Table 4: Minimum inhibition concentration (MIC) values of 4a-l compounds.

Conclusion

We have demonstrated an efficient and very simple procedure for one pot synthesis of 1,3-benzoxazole-5-sulfonamide derivatives by the reaction of acetophenones with aldehydes and 2-sulfanyl-1,3-benzoxazole-5-sulfonamide in ethanol as solvent using Fe(III)-mont catalyst, which are low cost, nontoxic, and easily available catalyst. The synthesized compounds have shown significant antimicrobial activities and *in silico* molecular docking study.

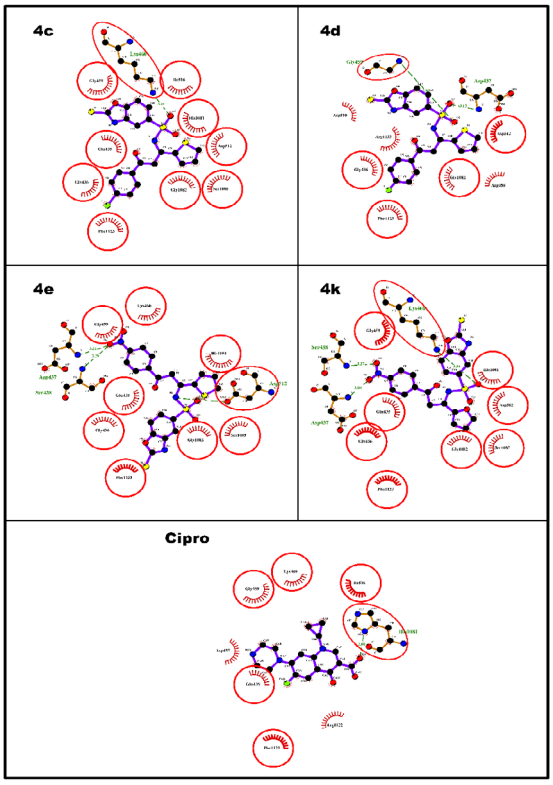


Figure 1: 2D representation of the interaction of **4c**, **4d**, **4e**, **4k** and Ciprofloxacin with gyrase (2XCT).

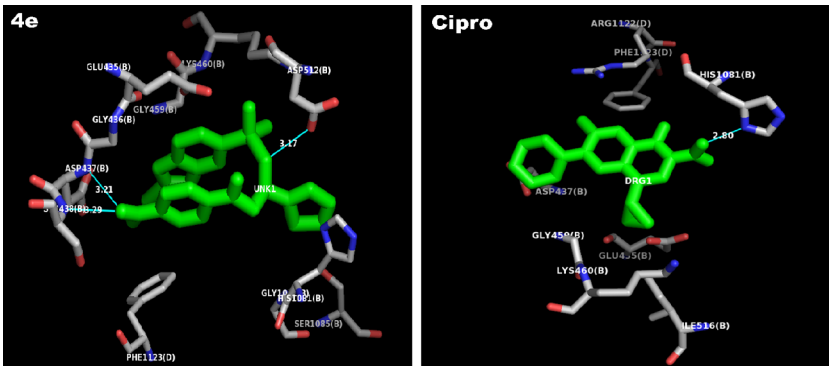


Figure 2: 3D representation of the interaction of **4e** and Ciprofloxacin with gyrase (2XCT).

Ligand	Affinity (KCal/mol)	H-bonds	H-bond length (Å)	H-bond between	Hydrophobic interactions
4c	-5.9	1	3.21	4c:O3 :: Lys460	Gly459, Ile516, Glu435, Gly436, Asp512, His1081, Gly1082, Ser1085
4d	-5.7	2	2.96	4d:O2 :: Gly459	Asp512, Asp510, Phe1123, Arg458, Arg1122, Gly436, Gly1082
			3.13	4d:O3 :: Asp437	
4e	-6.6	3	3.17	4e:N2 :: Asp512:OD2	Gly459, Glu435, Lys460, His1081, Ser1085, Gly1082, Gly436, Phe1123
			3.21	4e:O2 :: Asp437:N	
			3.29	4e:O2 :: Ser438:N	
4k	-6.2	3	3.34	4k:O5 :: Lys460:NZ	Asp512, His1082, Ser1085, Gly1082, Glu435, Gly436, Phe1123, Gly459
			3.08	4k:O2 :: Asp437:N	
			3.27	4k:O3 :: Ser438:N	
Ciprofl-oxacin	-5.4	1	2.80	Cipro:OAT :: His1081:ND1	Glu435, Asp437, Gly459, Lys460, Ile516, Arg1122, Phe1123

Table 5: Representing the binding affinity (kcal/mol), details of H-bond formation, hydrophobic interactions of the synthesized molecules (**4c, 4d, 4e** and **4k**) and the standard Ciprofloxacin.

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