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Research Article

SYNTHESIS AND EVALUATION FOR ANTIMICROBIAL ACTIVITY OF 2-SUBSTITUTED BENZIMIDAZOLE AND BENZODIAZEPINONE DERIVATIVES

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ABSTRACT

A series of 2-substituted benzimidazole and benzodiazepinone derivatives have been efficiently synthesized in high yields by the condensation of *o*-phenylenediamine with *β*-ketoesters and 1,3 diketonesby using Lewis acid $SnCl_2.2H_2O$as a catalyst under conventional as well as micro-wave method and investigated for their antimicrobial activity. The compounds such as **7e** and **E** exhibited good antibacterial activities and anti fungal activity. Compound **7e** was found to show the activity equipotent to the standard drug ciprofloxacin.

Keywords: 2-Substituted benzimidazoles, Benzodiazepinones, Antimicrobial activity.

INTRODUCTION

Benzimidazole, benzodiazepinones and their derivatives are of wide interest because of their diverse biological activity and clinical applications.[1,2]Benzimidazole ring is an important pharmacophore in modern drug discovery and synthesis of benzimidazoles resulted in the discovery of potent drug molecules such as omeprazole, lansoprazole, rabeprazole and pantoprazole.[3]Natural products also contain benzimidazole ring as pharmacophore and play a vital role in biological processes. They can act as ligands to transition metals for modeling biological systems.[4]Benzodiazepines are primarily known for their actions in thecentral nervous system. In addition to their established anxiolytic activities, 1,4-benzodiazepines also demonstrate activities as antibiotic, antimalarial, and are anti-HIV agents.[5-7] Additionally, there have been several reports of benzodiazepinesas anticancer agents.[8]The high profile applications of benzimidazoles, benzodiazepinones have prompted us to do their synthesis.

Our studies recently focused on the feasible reactions of carbonyl compounds/salicylaldehydes with 3-oxobutanoates bearing chloro/trifluorosubstituents. In this context, we studied the reactivity of salicylaldehydes with ethyl 4-chloro-3-oxobutanoate to provide 2*H*-chromenes,[9] interim thesederivatives were successfully converted to useful heterocyclic compounds.[10-12] We also studied the reactivity of various carbonyl compounds withethyl 4,4,4-trifluoro-3-oxobutanoate toprovide a series of (*E*)-*α*,*β*-unsaturated esters and ketones.[13-14]The present manuscript describes a systematic study for the preparation of 2-substituted benzimidazoles and benzodiazepinones derivatives by the condensation of *ortho*-phenylenediamines with ethyl 3-oxobutanoate tri fluoroethyl acetoacetate, 1,3 diketones.

RESULTS AND DISCUSSION

Conventional method

Initially, *o*-phenylenediamine **1a** (1 mmol) was reacted with ethyl 3-oxobutanoate **2a** (1.2 mmol) in DCM (2 mL) at room temperature for 15 h. This furnished a colorless solid (32% yield) and identified as 2-methyl-*1H*-benzo[*d*]imidazole **3a** (**Scheme 1**, table 1, entry 1). The same reaction was carried out under reflux condition afforded the desired product **3a** in 48% yield within 6 h (**Table 1**, entry 2). To see the effect of solvent we have carriedout the reaction in different solvents and the results were summarized in table 1 (entries 3-9). Polar aprotic solvents THF, CH_3CN, 1,4 dioxane, non polar solvents toluene, benzene, polar protic solvents methanol and ethanol were screened. The reaction in ethanol provided higher yield under reflux condition than did other organic solvents (entry 9), hence, ethanol was chosen as solvent for further reactions. The effect of Lewis acid catalysts such as $CuCl_2.2H_2O$,$SnCl_2.2H_2O$,$Cu(OAc)_2$, $La(OTf)_3$, CuI, $La(OTf)_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, $FeCl_3$, $AlCl_3$ and Protonic acids such as *p*-TsOH,AcOHon the reaction was further explored, and the results were summarized in table 1 (entries 10-19). To our delight, under the optimized conditions, the yield of **3a** was finally improved to 95% by using the $SnCl_2.2H_2O$ under conventional as well as micro-wave methods. Regarding the optimum quantity of catalyst, 10 mol % of $SnCl_2.2H_2O$is necessary to promote the reaction in an efficient manner (**Table 1**).

A plausible mechanism is depicted in **(Scheme 2)**, condensation of *o*-phenylenediamine and ethyl -3-oxobutanoate provides **A** (*Z*)-ethyl 3-(2-aminophenylimino)butanoate (Schiff base). Then, cyclization occurs by nucleophilic addition of amine to imine carbon provides ethyl 2-(2-methyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)acetate **B** with the elimination of ethyl acetate to give 2-methyl-1*H*-benzoimidazole **3a**.

In order to evaluate the efficiency of the methodology, varioussubstitutedethyl -3-oxobutanoates werereacted with substituted *o*-phenylenediamines having electron-withdrawing and donating substituents at various positions on the benzene ring such as nitro, benzoyl and methyl to give a series of 2-substituted benzimidazoles **3a-j** in good yields **(Scheme 3, Table 2)**. Electron withdrawing groups on the aromatic ring afforded higher yields when compared to electron-donating groups.

Microwave method

Having succeeded in the synthesis of a series 2-substituted benzimidazoles by conventional method, next we studied the microwave-assisted synthesis of 2-substituted benzimidazoles under solvent-free conditions.The present methodology shows some specific advantages such as mildness, short reaction times and enhanced selectivity under solvent free conditions. The reaction conversion was poor in 2-9 mins (20-38%). However, the conversion was improved to 97% under 180 W irradiation 15 min(**Table 3**) to give2-substituted benzimidazoles (**3a-e**)**.**

Next, the reaction between 4-nitrobenzene-1,2-diamine **1d** and ethyl 3-oxo-3-phenylpropanoate **2b** in the presence of $SnCl_2.2H_2O$ in ethanol under reflux conditions, intermediate **C**was formed**.** Due to the(-)I effect of NO_2 on benzene ring and steric hindrance of phenyl on ethyl 3-oxo-3-phenylpropanoate, cyclization was not occurred (**Scheme 4**). In progress of our work, the condensation of *o*-phenylenediamine **1a-e** with ethyl 4,4,4trifluoro-3-oxobutanoate **4**in the presence of $SnCl_2.2H_2O$ catalyst in ethanol under reflux conditions providedbenzodiazepinones**5a-c, 5e**instead of benzimidazoles**(Scheme 5, table 4,5)**.

A plausible mechanism is depicted below(**Scheme 6)**, condensation of *o*-phenylenediamine and ethyl 4,4,4-trifluoro-3-oxobutanoate provides **C**(*E*)-ethyl 3-(2-aminophenylimino)-4,4,4-trifluorobutanoate (Schiff base). Then cyclization occurs by the nucleophilic addition of amine on carbonyl carbon provides 2-ethoxy-4-(trifluoromethyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-ol **D** with the elimination of ethanol to give benzodiazipinones**5a-c, 5e**.When the4-nitrobenzene-1,2-diamine **1d** react with ethyl 4,4,4-trifluoro-3-oxobutanoate **4** in the presence of $SnCl_2.2H_2O$catalyst in ethanol under reflux conditions, intermediate **E** was formed.Due to the (-)I effect of NO_2 on benzene ring and loan pair-loan pair repulsions between fluorine and amine the cyclization was not occurred (**Scheme 7**).Further, the condensation of *o*-phenylenediamine **1a-c, 1e** with 4,4,4-trifluoro-1-phenylbutane-1,3-dione**6a** and4,4,4-trifluoro-1-(furan-3-yl)butane-1,3-dione**6b**in the presence of $SnCl_2.2H_2O$ catalyst in ethanol under reflux conditions afforded corresponding (trifluoromethyl)-1*H*-benzo[*d*]imidazoles**7a-c, 7e** in good yields**(Scheme 8, Table 6,7)**.In case of 4-nitrobenzene-1,2-diamine **1d** react with 4,4,4-trifluoro-1-phenylbutane-1,3-dione **6a**afforded compound **3i** instead of **7d**, due to the (-)I effect of NO_2 on benzene ring and loan

pair-loan pair repulsions and steric hindrance between fluorine and amine (**Scheme 9**).

o-phenylenediamines **1a-b, 1d-e** (1 mmol) was reacted with 5,5-dimethylcyclohexane-1,3-dione **8**(1.2 mmol) in the presence of $SnCl_2.2H_2O$ (10 mol %) in ethanol (2 ml) under reflux condition furnished a brown color solid Schiff bases**9a-b, 9d-e**in good yields**(Scheme 10, Table 8,9)**.

ANTIMICROBIAL ACTIVITY

The antimicrobial activity[15] of the synthesized compounds was investigated against different bacterial strains i.e, *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli,*and fungal strains *i.e, Aspergillusniger, Sclerotiumrolfsii, Macrophominaphaseolina*using agar well diffusion method. The test solutions of synthesized compounds were prepared in DMSO at concentrations of 1, 5, 10, 20 and 25 mg /ml for evaluation of minimum inhibitory concentration (MIC). Ciprofloxacin and Fluconazole were used as standard drugs for antibacterial and antifungal studies respectively by dissolving in DMSO to get a final concentration of 5µg /ml. The solvent DMSO was used as negative control. Inhibition zones were measured and the diameter was calculated in millimeters **(Table 10, 11, Figure 1, 2, 3, 4)**.

The twenty five compounds library was evaluated for its in-vitro antimicrobacterial activity. The zone of inhibition values of the synthesized compounds(**3c, 3e, 3f-j**, **7a-c, 7e,E, 9a, 9d** and **9e**) and ciprofloxacin (standard) are found to range from 5-35 mm**(Table 10, 11, Figure 1, 2, 3, 4)**.Among them **3c, 3e, 3f-j, 7a-c, 7e**were found to exhibit good activity against both Gram positive and Gram negative.

Five compounds in series **9a**, **9d**, **9e,** and **E**, showed activity against Gram +ve bacteria (*Bacillus subtills, Staphylococcus aureus*), and no activity against Gram -ve bacteria (*Pseudomonas aeruginosa, Escherichia coli*). Compound **7e** was found to show excellent activity with zone of inhibition 28, 17, 10, 11mm for the above mentioned bacterial strains, being at par the standard drug ciprofloxacin (ZI: 35 28, 25, 27mm). The establishment of structure activity relationships (SAR) for 2-substituted benzimidazole derivatives**3c**, **3e, 3f-j**, **7a-c, 7e,E,9a, 9d** and **9e** are discussed below.

Compound having phenyl substitution at 2^{nd} position on benzimidazole ring and benzoyl substitution at 5^{th}position on benzimidazole moiety **7e** displayed goodantibacterial activity (ZI: 28 mm) when compared to methyl (**3c**,ZI: 6mm) However, *2*-trifluoro and phenyl substituted derivative **7e** and **3f-j** displayed moderate activity (ZI: 10 mm) when compared to methyl **3c** and **3e**. Over all review of present studies concluded that, the electron withdrawing groups on benzeneand trifluoromethyl group at 2^{nd} position of benzimidazole group have the positive effect on the antimicrobial activity such as compound **7e(Table 10, 11, Figure 1, 2, 3, 4)**was found to be the most active antimicrobial compound amongst other in the series. These new data might be helpful in the future development of benzimidazole analogues as novel antimicrobial agent.

EXPERIMENTAL SECTION

General

Ortho-phenylenediamines and ethyl 4-chloro-3-oxobutanoate,*β*-ketoesters and 1, 3 diketones were obtained from Sigma-Aldrich, solvents were commercially available. Column Chromatography (CC): silica gel (SiO_2; 60-120 mesh). MpMettler-Temp apparatus; uncorrected. IR Spectra: Perkin-Elmer-1600FT-IR spectrometer; in KBr; *v*in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: Bruker-Avance-300 spectrometers; solvent $CDCl_3$; chemical shifts *δ* in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS-ESI: 7070H spectrometer with a direct inlet system; in *m/z* (rel. %). ESI-HR-MS: Agilent6510 Q-TOFLC/MS instrument.

Conventional method: General Procedure for the Synthesis of 2-(Chloromethyl)-1*H*-benzo[*d*]imidazole(3a-j)

$SnCl_2$ (0.1 mmol) was added to a stirred soln. of *ortho*-phenylenediamine**1**(1 mmol) and ethyl 4-chloro-3-oxobutanoate**2**(1 mmol) in EtOH (2 mL) under reflux. The mixture was stirred under reflux for 6 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was subjected to CC (hexane/AcOEt 8:2) to give the pure benzimidazoles**(3a-j).**

Microwave Method

In a model reaction, $SnCl_2.2H_2O$ (10 mol %) was added to a borosilicate test tube having *ortho*-Phenylenediamine**1** (1 mmol) and ethyl 3-oxobutanoate **2**and **4,6,8** (1 mmol) in DCM (1 mL), neutral alumina was added, and the solvent was removed under reduced pressure below 28 ^{0}C. The adsorbed solid was taken up for irradiation under 180 W. The progress of the reaction was monitored by TLC,after 15 min, the formation of 2-substituted benzimidazoles and benzodiazipines were observed.

4-(trifluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ones (5a-e)

$SnCl_2$ (0.1 mmol) was added to a stirred soln.of*ortho*-phenylenediamine**1** (1 mmol) and ethyl 4,4,4 trifluoro-3-oxobutanoate**4**(1 mmol) in EtOH (2 mL) under reflux. The mixture was stirred under reflux for 6 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was subjected to CC (hexane/AcOEt8:2) to give the pure benzodiazepinones **(5a-e).**

2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (7a-e)

$SnCl_2$ (0.1 mmol) was added to a stirred soln. of *ortho*-phenylenediamine(**1,**1 mmol) and 4,4,4-trifluoro-1-phenylbutane-1,3-dione**6a**and 4,4,4-trifluoro-1-(furan-3-yl)butane-1,3-dione **6b**(1 mmol) in EtOH (2 mL) under reflux. The mixture was stirred under reflux for 8 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was subjected to CC (hexane/AcOEt8:2) to give the pure benzodiazepinones**(7a-e).**

2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (9a-e)

$SnCl_2$ (0.1 mmol) was added to a stirred soln.of*ortho*-phenylenediamine(**1,**1 mmol) and 5,5-dimethylcyclohexane-1,3-dione **8**(1 mmol) in EtOH (2 mL) under reflux. The mixture was stirred under reflux for 6 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure. The crude product was subjected to CC (hexane/AcOEt 8:2) to give the pure schiff's base **(9a-e).**

2-methyl-*1H*-benzo[*d*]Imidazole (3a)

Pale brown solid, Yield: 95%,M.P: 170-172 ^oC, FT-IR (KBr): 2920, 2677, 1450, 1386, 1271, 1027, 833, 732, cm^{-1}. ^1H NMR(300 MHz, $CDCl_3$) δ: 7.55(dd, 2H, *J* =3.2, 5.7 Hz, aromatic), 7.22 (m, 2H, aromatic), 2.65 (s, 3H, CH_3).MS-ESI: *m/z* 133 $(M+H)^+$.

2,5-dimethyl-*1H*-benzo[*d*]imidazole (3b)

Pale brown solid, Yield: 93%,M.P: 148-152 ^oC, FT-IR (KBr): 2990, 2701, 1830, 1619, 1546, 1425, 1380, 1279, 1079, 1026, 964, 896 cm^{-1}.^1H NMR(300 MHz, $CDCl_3$) δ: 7.36 (d, 1H, *J* =7.9 Hz, aromatic), 7.12 (t, 1H, *J* =7.3 Hz, aromatic), 7.02(d, 1H, *J* =7.3 Hz, aromatic), 2.60 (d, 6H, CH_3). MS-ESI: *m/z* 147 $(M+H)^+$.

2,5,6-trimethyl-1*H*-benzo[*d*]imidazole (3c)

Pale brown solid, Yield: 90%, M.P: 235 ^oC, FT-IR (KBr): 2979, 2923, 1688, 1538, 1452, 1385, 1304, 1230, 1161, 1000, 855 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 7.24 (s, 2H, aromatic), 2.54 (s, 6H, CH_3), 2.33 (s, 3H, CH_3). MS-ESI: *m/z* 161 $(M+H)^+$.

2-methyl-5-nitro-*1H*-benzo[*d*]imidazole (3d)

Pale colourless solid, Yield: 87%, M.P: 212-220 ^oC, FT-IR (KBr): 2922, 1629, 1515, 1472, 1381, 1024, 823, 736, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.26-8.54 (m, 1H, aromatic), 8.09 (dd, *J* = 8.8, 2.0 Hz, 1H, aromatic), 7.42-7.69 (m, 1H, aromatic), 2.68 (s, 3H, CH_3). MS-ESI: *m/z* 178 $(M+H)^+$.

(2-methyl-1*H*-benzo[*d*]imidazol-5-yl)(phenyl)methanone (3e)

Pale brown solid, Yield: 85%,M.P: 133-135 ^oC, FT-IR (KBr): 3432, 2926, 1649, 1621, 1546, 1305, 1025, 889 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.02 (s, 1H aromatic), 7.82-7.75 (m, 2H, aromatic), 7.72 (dd, *J* = 8.4, 1.4 Hz, 1H, aromatic), 7.58-7.51 (m, 2H, aromatic), 7.44 (t, *J* = 7.6 Hz, 2H aromatic), 2.64 (s, 1H,CH_3). MS-ESI: *m/z* 237 $(M+H)^+$.

2-phenyl-1*H*-benzo[*d*]imidazole (3f)

Pale brown solid, Yield: 94%, M.P: 288-290 ^oC, FT-IR (KBr): 3430, 2921, 2675, 1621, 1590, 1410, 1373, 1226, 1119, 970, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.24-8.17 (m, 2H, aromatic), 7.62 (dt, *J* = 6.7, 3.4 Hz, 2H, aromatic), 7.52-7.41 (m, 3H, aromatic), 7.26-7.18 (m, 2H, aromatic). MS-ESI: *m/z* 195 $(M+H)^+$.

5-methyl-2-phenyl-1*H*-benzo[*d*]imidazole (3g)

Pale brown solid, Yield: 92%, M.P: 250-253 ^oC, FT-IR (KBr): 2717, 1619, 1537, 1458, 1371, 1287, 1075, 970, 785 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.29-8.19 (m, 2H, aromatic), 7.50 (tt, *J* = 8.7, 4.4 Hz, 4H, aromatic), 7.13 (t, *J* = 7.6 Hz, 1H, aromatic), 7.02 (d, *J* = 7.2 Hz, 1H, aromatic), 2.66 (s, 3H, CH_3).MS-ESI: *m/z* 209 $(M+H)^+$.

5,6-dimethyl-2-phenyl-1*H*-benzo[*d*]imidazole (3h)

Pale brown solid, Yield: 90%, M.P: 242-247 ^oC, FT-IR (KBr): 3439, 2918, 1669, 1452, 1398, 1229, 1115, 968 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.17 (dd, *J* = 8.1, 1.4 Hz, 2H, aromatic), 7.58 (d, *J* = 2.3 Hz, 1H, NH), 7.52-7.33 (m, 5H, aromatic), 2.38 (s, 1H).MS-ESI: *m/z* 223 $(M+H)^+$.

5-nitro-2-phenyl-1*H*-benzo[*d*]imidazole (3i)

Pale brown solid, Yield: 85%, M.P: 145 ^oC, FT-IR (KBr): 3420, 2930, 1614, 1527, 1468, 1337, 1057, 950, 701 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$+DMSO) δ 8.52 (d, *J* = 51.5 Hz, 1H, aromatic), 8.18 (dd, *J* = 21.8, 6.3 Hz, 3H,

aromatic), 7.64-7.60 (m, 4H, aromatic). MS-ESI: *m/z* 240 $(M+H)^+$.

***(Z)*-ethyl 3-(2-amino-5-nitrophenylimino)-3-phenylpropanoate (C)**

Yellowish solid, Yield: 80%, M.P: 196 ^oC, FT-IR (KBr): 3476, 3346, 2926, 1655, 1606, 1574, 1479, 1296, 1183, 1086, 892 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 9.62 (s, 1H), 7.71 (dd, *J* = 8.9, 2.5 Hz, 1H, aromatic), 7.29 (ddd, *J* = 11.0, 7.7, 1.8 Hz, 6H, aromatic), 6.74 (d, *J* = 9.0 Hz, 1H, aromatic), 5.90 (s, 1H, NH_2), 5.17 (s, 1H, NH_2), 4.21 (q, *J* = 7.1 Hz, 2H, OCH_2), 1.32 (t, *J* = 7.1 Hz, 3H, CH_3). MS-ESI: *m/z* 328 $(M+H)^+$.

phenyl(2-phenyl-1*H*-benzo[*d*]imidazol-5-yl)methanone (3j)

Pale brown solid, Yield: 85%, M.P: 215-220 ^oC, FT-IR (KBr): 3242, 3057, 1641, 1455, 1314, 1284, 1127, 1081, 944, 894 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.21 (s, 2H, aromatic), 8.10 (s, 1H, aromatic), 7.80 (s, 4H, aromatic), 7.56 (dd, *J* = 23.5, 7.5 Hz, 6H, aromatic). ^{13}C NMR(75 MHz, $CDCl_3$): δ 153.20, 137.30, 130.71, 130.34, 129.19, 128.63, 128.52, 127.71, 127.01, 125.81, 123.38.MS-ESI: *m/z* 299 $(M+H)^+$.

4-(trifluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one (5a)

Colourless solid, Yield: 87%, M.P: 173 ^oC, FT-IR (KBr): 3213, 3136, 2920, 2854, 1685, 1571, 1478, 1380, 1277, 1177, 1058, 954, 840 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 9.23 (s, 1H, aromatic), 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H, aromatic), 7.38 (td, *J* = 7.9, 1.4 Hz, 1H, aromatic), 7.33-7.29 (m, 1H, aromatic), 7.15 (dd, *J* = 8.0, 1.0 Hz, 1H, aromatic), 3.36 (s, 2H, CH_2). MS-ESI: *m/z* 229 $(M+H)^+$.

7-methyl-4-(trifluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one (5b)

Pale brown solid, Yield: 85%,M.P: 203-207 ^oC, FT-IR (KBr): 3219, 3137, 2998, 2910, 1676, 1582, 1464, 1424, 1378, 1275, 1173, 1048, 905, 838 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.16 (s, 1H, aromatic), 7.16 (d, *J* = 7.2 Hz, 1H, aromatic), 6.92 (d, *J* = 8.0 Hz, 1H, aromatic), 3.34 (s, 2H, CH_2), 2.43 (s, 3H, CH_3). MS-ESI: *m/z* 243 $(M+H)^+$.

7,8-dimethyl-4-(trifluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one (5c)

Pale brown solid, Yield: 83%, M.P: 248-253 ^oC, FT-IR (KBr): 3204, 3113, 2984, 1689, 1562, 1492, 1380, 1278, 1177, 1050, 922, 884 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 10.45 (s, 1H, NH), 7.65 (d, *J* = 7.0 Hz, 1H, aromatic), 6.98 (s, 1H, aromatic), 3.25 (s, 2H, CH_2), 2.28 (s, 6H, $2CH_3$).^{13}C NMR (75 MHz, $CDCl_3$): δ 163.99, 136.63, 132.82, 131.91, 127.27, 126.73, 121.41, 119.75, 36.07, 18.01, 17.49 ppm. MS-ESI: *m/z* 257 $(M+H)^+$.

***(Z)*-ethyl3-(2-amino-5-nitrophenylimino)-4,4,4-trifluorobutanoate (E)**

Yellow liquid, Yield: 76%, FT-IR (KBr): 3367, 1722, 1615, 1503, 1374, 1270, 1071, 861 cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 8.5, 2.1 Hz, 1H, aromatic), 7.36 (d, *J* = 2.0 Hz, 1H, aromatic), 6.50 (d, *J* = 8.5 Hz, 1H, aromatic), 5.61 (s, 1H, NH_2), 5.12 (s, 1H, NH_2), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.94 (s, 2H, CH_2), 1.16 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.27, 144.36, 141.20, 137.62, 119.59, 105.62, 103.42, 81.42, 61.77, 39.06, 13.62. MS-ESI: *m/z* 320 $(M+H)^+$.

7-benzoyl-4-(trifluoromethyl)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one (5e)

Pale brown solid, Yield: 73%, M.P: 198-200 ^oC, FT-IR (KBr): 3235, 2938, 1708, 1651, 1593, 1488, 1320, 1268, 1131, 1052, 936, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$+DMSO) δ: 11.06 (s, 1H, NH), 7.83 (dd, *J* = 8.2, 1.9 Hz, 1H, aromatic), 7.78 (dd, *J* = 7.6, 1.6 Hz, 2H, aromatic), 7.69-7.59 (m, 2H, aromatic), 7.59-7.45 (m, 2H, aromatic), 7.41 (s, 1H, aromatic), 3.38 (s, 2H, CH_2). MS-ESI: *m/z* 333 $(M+H)^+$.

2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (7a)

Color less solid, Yield: 82%, M.P: 195-200 ^oC, FT-IR (KBr): 2971, 2877, 2656, 1552, 1462, 1327, 1288, 1192, 1007, 980 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.73 (s, 2H, aromatic), 7.45-7.38 (m, 2H, aromatic). MS-ESI: *m/z* 186 $(M+H)^+$.

5,6-dimethyl-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole (7c)

Pale brown solid, Yield: 81%,M.P: 235 ^oC, FT-IR (KBr): 3050, 2984, 2848, 2718, 1547, 1492, 1325, 1280, 1171, 1005, 981, 852 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 9.91 (s, 1H, NH), 7.62 (s, 1H, aromatic), 7.30 (s, 1H, aromatic), 2.39 (d, *J* = 4.8 Hz, 6H, CH_3). MS-ESI: *m/z* 215 $(M+H)^+$.

phenyl(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)methanone (7e)

Brown liquid, Yield: 74%, FT-IR (KBr): 3444, 2924, 2851, 1650, 1598, 1447, 1396, 1282, 1161, 1112, 981, 891, 791, 644, 518, 447 cm^{-1}.^1H NMR (500 MHz, $CDCl_3$) δ: 8.20 (s, 1H, aromatic), 7.90 (d, *J* = 8.3 Hz, 1H, aromatic), 7.81 (d, *J* = 7.4 Hz, 2H, aromatic), 7.75 (d, *J* = 8.3 Hz, 1H, aromatic), 7.59 (t, *J* = 6.9 Hz, 1H, aromatic), 7.48 (dd, *J* = 7.2, 5.7 Hz, 2H,

aromatic).^{13}C NMR (75 MHz, $CDCl_3$): δ 197.10, 144.04, 143.40, 140.32, 137.98, 137.58, 133.75, 132.71, 130.09, 128.42, 126.48, 120.49, 116.03. MS-ESI: *m/z* 291 $(M+H)^+$.

3-(2-aminophenylamino)-5,5-dimethylcyclohex-2-enone (9a)

Pale brown solid, Yield: 78%,M.P: 155-160 ^oC, FT-IR (KBr): 3477, 3041, 2929, 2362, 1716, 1612, 1496, 1380, 1337, 1262, 1173, 1070, 981 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.11-7.06 (m, 1H, aromatic), 7.0 (dd, *J* = 7.7, 1.2 Hz, 1H, aromatic), 6.77-6.71 (m, 2H, aromatic), 6.20 (s, 1H, NH), 5.07 (s, 1H, CH), 3.73 (s, 2H, NH_2), 2.33 (s, 2H, CH_2), 2.19 (s, 2H, CH_2), 1.09 (s, 6H, $2CH_3$).^{13}C NMR (75 MHz, $CDCl_3$+DMSO): δ 195.58, 162.44, 141.97, 126.60, 122.11, 116.30, 115.03, 95.33, 49.16, 40.88, 31.55, 27.11. MS-ESI: *m/z* 231 $(M+H)^+$.

3-(2-amino-5-nitrophenylamino)-5,5-dimethylcyclohex-2-enone (9d)

Yellow solid, Yield: 73%,M.P: 201-203 ^oC, FT-IR (KBr): 3431, 3330, 3241, 2960, 2935, 1637, 1570, 1487, 1374, 1249, 1150, 1089, 829 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ: 8.00-7.90 (m, 2H), 7.87 (s, 1H, NH), 6.86-6.79 (m, 1H), 5.66 (s, 2H, NH_2), 4.97 (s, 1H, CH), 2.38 (s, 2H, CH_2), 2.17 (s, 2H, CH_2), 1.12 (s, 6H, $2CH_3$). MS-ESI: *m/z* 276 $(M+H)^+$.

3-(2-amino-5-benzoylphenylamino)-5,5-dimethylcyclohex-2-enone (9e)

Pale yellowish solid, Yield: 68%,M.P: 201-203 ^oC, FT-IR (KBr): 3339, 3222, 3008, 2959, 2935, 1574, 1446, 1369, 1285,1126, 1075, 911, 890 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.76-7.72 (m, 2H), 7.72-7.68 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.50-7.43 (m, 2H), 6.77-6.73 (m, 1H), 6.19 (s, 1H, NH), 5.05 (s, 1H, CH), 4.37 (s, 2H, NH_2), 2.36 (s, 2H, CH_2), 2.28 (d, *J* = 3.4 Hz, 1H, CH_2), 2.22 (d, *J* = 4.0 Hz, 1H, CH_2), 1.10 (s, 6H, $2CH_3$). MS-ESI: *m/z* 335 $(M+H)^+$.

CONCLUSION

We developed a method for the preparation of 2-substituted benzimidazoles and benzodiazepinones by the condensation of *o*-phenylenediaminewith*β*-ketoesters and 1,3-diketonesby using Lewis acid $SnCl_2.2H_2O$as a catalystunder conventional as well as micro-wave methods and evaluated for their antimicrobial activity against ciprofloxacin (for antibacterial activity) and fluconazole (for antifungal activity). The compound **7e(phenyl(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-5-yl)methanone)** was found to be the most active antimicrobial compound amongst other in the series.

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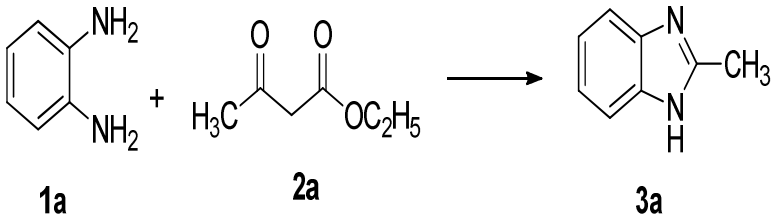
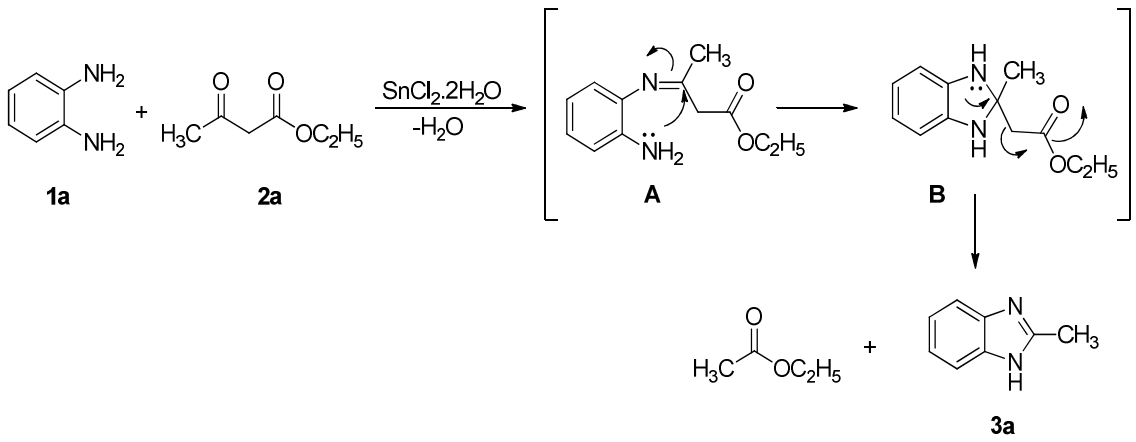


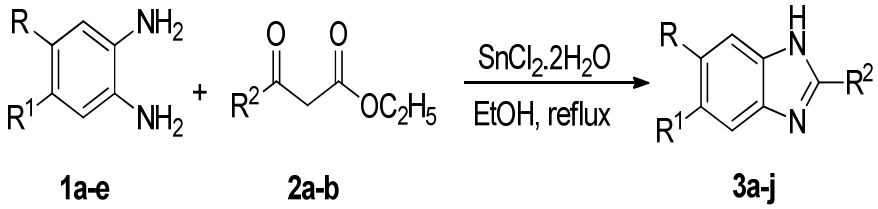
1a **2a** **3a**

(Scheme 1)

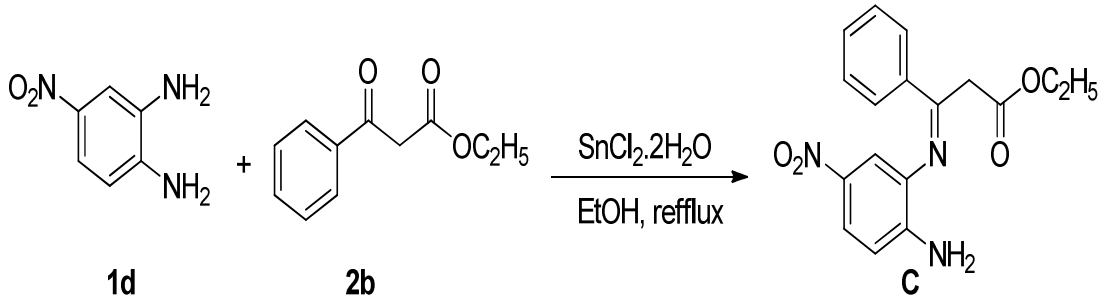
Plausible mechanism



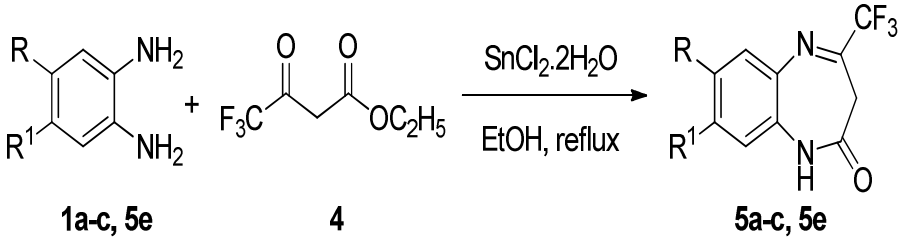
(Scheme 2)



(Scheme 3)

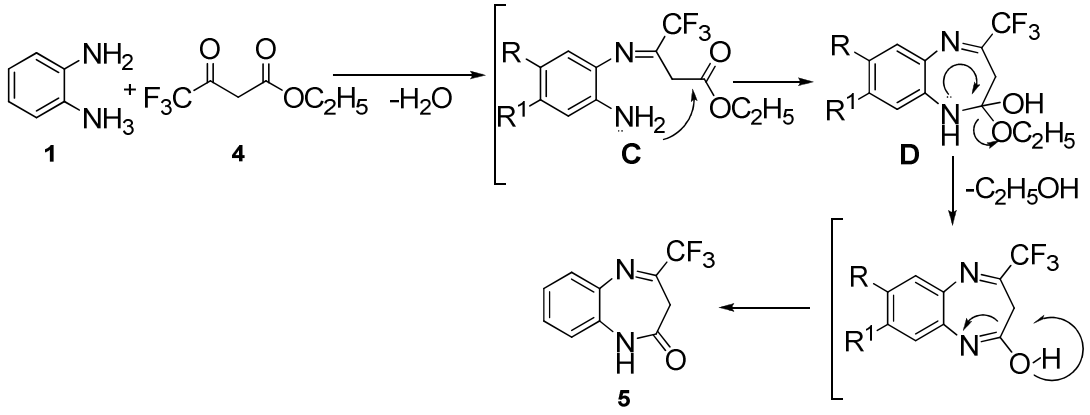


(Scheme 4)

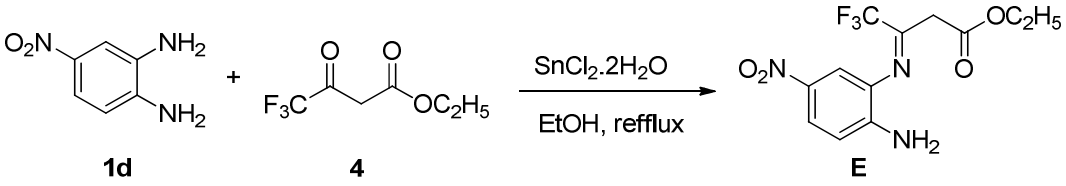


(Scheme 5)

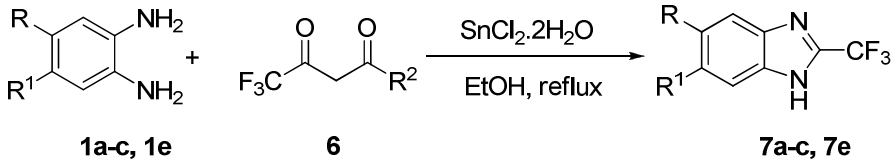
Plausible mechanism



(Scheme 6)

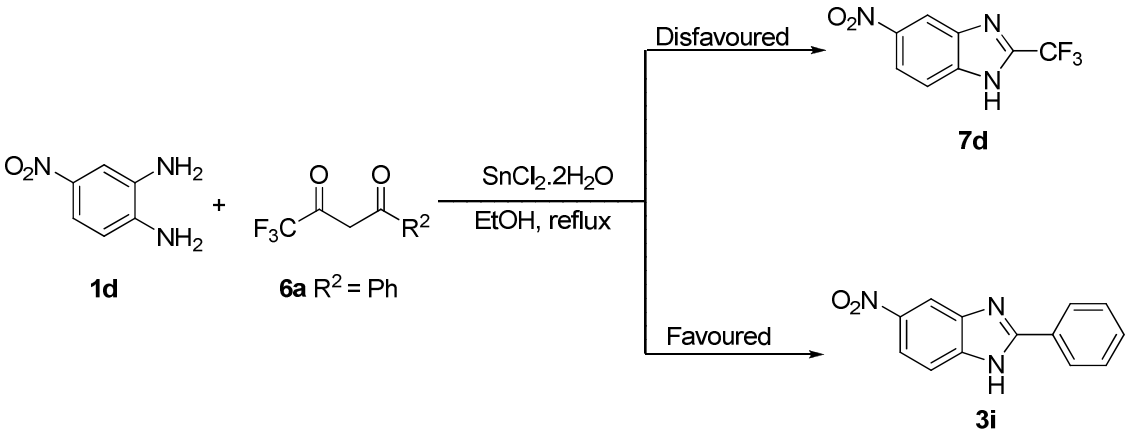


(Scheme 7)

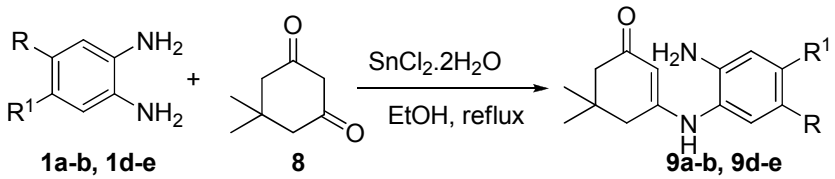


6a R^2 = Ph
6b R^2 = Furyl

(Scheme 8)



(Scheme 9)



1a-b, 1d-e **8** **9a-b, 9d-e**

(Scheme 10)

Table 1: Optimization of reaction conditions

Entry	Catalyst (10 mol %)	Solvent	Time (h)	Yield (%)[c]3a
1[a]	--	DCM	15	32
2[b]	--	DCM	6	48
3[b]	--	THF	6	52
4[b]	--	CH_3CN	6	57
5[b]	--	1,4-Dioxane	7	51
6[b]	--	Toluene	7	42
7[b]	--	Benzene	6	40
8[b]	--	CH_3OH	6	59
9[b]	--	C_2H_5OH	6	66
10[b]	$CuCl_2$	C_2H_5OH	7	71
11[b]	**$SnCl_2.2H_2O$**	**C_2H_5OH**	**6**	**95**
12[b]	$Cu(OAc)_2$	C_2H_5OH	7	68
13[b]	$La(OTf)_3$	C_2H_5OH	7	72
14[b]	CuI	C_2H_5OH	6	73
15[b]	$Bi(OTf)_3$	C_2H_5OH	7	75
16[b]	$FeCl_3$	C_2H_5OH	8	67
17[b]	$AlCl_3$	C_2H_5OH	8	59
18[b]	*p*-TsOH	C_2H_5OH	6	85
19[b]	AcOH	C_2H_5OH	7	64

[a]Room temperature, [b]reflux, [c]Isolated yield.

Table 2: Synthesis of 2-substituted benzimidazole derivatives

Entry	Reactant 1	R	R^1	R^2	Time (h)	Product 3	Yield(%)[a]
1	**1a**	H	H	CH_3	6	**3a**	95
2	**1b**	H	CH_3	CH_3	6	**3b**	92
3	**1c**	CH_3	CH_3	CH_3	6	**3c**	90
4	**1d**	H	NO_2	CH_3	8	**3d**	87
5	**1e**	H	CO Ph	CH_3	8	**3e**	85
6	**1a**	H	H	Ph	6	**3f**	94
7	**1b**	H	CH_3	Ph	6	**3g**	92
8	**1c**	CH_3	CH_3	Ph	7	**3h**	90
9	**1d**	H	NO_2	Ph	8	**3i**	85
10	**1e**	H	CO Ph	Ph	7	**3j**	85

[a]Yields of isolated products

Table 3: Microwave-assisted synthesis of 2-substituted benzimidazole derivatives

Entry	Reactant 1	R	R^1	R^2	Power (W)	Time (min)	Compound	Yield (%)
1	**1a**	H	H	CH_3	180	5	**3a**	97
2	**1b**	H	CH_3	CH_3	180	10	**3b**	96
3	**1c**	CH_3	CH_3	CH_3	180	15	**3c**	95
4	**1d**	H	NO_2	CH_3	180	15	**3d**	95
5	**1e**	H	COPh	CH_3	180	10	**3e**	95
6	**1a**	H	H	Ph	180	15	**3f**	95
7	**1b**	H	CH_3	Ph	180	15	**3g**	92
8	**1c**	CH_3	CH_3	Ph	180	15	**3h**	85
9	**1d**	H	NO_2	Ph	180	15	**3i**	80
10	**1e**	H	COPh	Ph	180	10	**3j**	92

Table 4: Synthesis of benzodiazepinone derivatives

Entry	Reactant 1	R	R^1	Time (h)	Product 5	Yield(%)[a]
1	**1a**	H	H	6	**5a**	87
2	**1b**	H	CH_3	6	**5b**	85
3	**1c**	CH_3	CH_3	7	**5c**	83
4	**1e**	H	COPh	8	**5e**	73

[a]Yields of isolated products

Table 5: Microwave-assisted Synthesis of benzodiazepinone derivatives

Entry	reactant	R	R^1	Power (W)	Time (min)	product	Yield (%)
1	**1a**	H	H	180	10	**5a**	85
2	**1b**	H	CH_3	180	15	**5b**	86
3	**1c**	CH_3	CH_3	180	15	**5d**	10
4	**1e**	H	COPh	180	15	**5e**	65

Table 6: Synthesis of 2-substituted benzimidazole derivatives[a]

Entry	Reactant 1	Reactant 6	R	R^1	Time (h)	product 7	Yield(%)[a]
1	1a	6a/6b	H	H	8	7a	87
2	1b	6a/6b	H	CH_3	6	7b	85
3	1c	6a/6b	CH_3	CH_3	6	7c	83
4	1e	6a/6b	H	COPh	7	7e	73

[a]Yields of isolated products

Table 7: Microwave-assisted Synthesis of 2-substituted benzimidazole derivatives

Entry	Reactant 1	Reactant6	R	R^1	Power (W)	Time (min)	Product	Yield (%)
1	**1a**	**6a/6b**	H	H	180	10	**7a**	83
2	**1b**	**6a/6b**	H	CH_3	180	15	**7b**	84
3	**1c**	**6a/6b**	CH_3	CH_3	180	15	**7c**	92
5	**1e**	**6a/6b**	H	COPh	180	15	**7e**	55

Table 8: Synthesis of 3-(2-amino-5-methylphenylamino)-5,5-dimethylcyclohex-2-enone derivatives

Entry	Reactant1	Reactant8	R	R^1	Time (h)	Product9	Yield (%)[a]
1	**1a**	**8**	H	H	6	**9a**	87
2	**1b**	**8**	H	CH_3	6	**9b**	85
3	**1d**	**8**	H	NO_2	7	**9d**	76
4	**1e**	**8**	H	COPh	7	**9e**	73

[a]Yields of isolated products

Table 9: Microwave-assisted Synthesis of 3-(2-amino-5-methylphenylamino) -5,5-dimethylcyclohex-2-enone derivatives

Entry	Reactant1	Reactant8	R	R^1	Power (W)	Time (min)	Product	Yield (%)
1	**1a**	**8**	H	H	180	10	**9a**	82
2	**1b**	**8**	H	CH_3	180	15	**9b**	85
3	**1d**	**9**	H	NO_2	180	15	**9d**	90
4	**1e**	**8**	H	COPh	180	15	**9e**	60

Table 10: Zone of inhibition of 2-substituted benzimidazoles against Bacteria

S.no	Sample code	Gram +ve				Gram -ve			
		Bacillus		*Staphylococus*		*Pseudomonas*		*E.coli*	
		MIC (mg)	mm	MIC (mg)	mm	MIC (mg)	mm	MIC (mg)	mm
1	**3c**	20	5.4±0.5	-	-	-	-	-	-
2	**3e**	20	6±1	5	4.8±0.7	20	5.3±0.5	20	8±1
3	**3f**	20	5±1	25	5.4±0.5	25	6±1	25	5.3±0.5
4	**3g**	20	7±1	5	5.3±0.5	25	5.3±0.5	20	7±1
5	**3h**	1	8±1	1	7±1	20	6±1	20	6±1
6	**3i**	1	7±1	1	6±1	25	6±1	25	5.6±1.1
7	**3j**	1	6±1	1	5.3±0.5	25	7±1	25	7±1
8	**7a**	5	5.3±0.5	25	8±1	20	7±1	10	7±1
9	**7b**	25	7±0.7	25	6±1	20	5±1	25	5±1
10	**7c**	20	6.3±1.5	25	6±1	25	7±1	25	6±1
11	**7e**	1	28±1	1	17±1	20	10±1	20	11±1
12	**E**	1	16±1	1	11±1	-	-	-	-
13	**9a**	25	6.4±0.5	20	5.6±0.5	-	-	-	-
14	**9d**	25	9±1	20	8±1	-	-	-	-
15	**9e**	25	10±1	25	8±1	-	-	-	-
16	**Cipro**	1	35±1	1	28±2	1	25±1	1	27±1
17	**Control**	-	-	-	-	-	-	-	-

Table 11: Zone of inhibition of 2-substituted benzimidazoles against Fungi

S.no	Sample code	Fungi					
		Aspergillusniger		*Sclerotiumrolfsii*		*Macrophominaphaseolina*	
		MIC (mg)	mm	MIC (mg)	mm	MIC (mg)	mm
1	3e	10	15±0.5	10	-	10	-
2	3f	5	-	5	-	5	6±0.5
3	3g	5	-	5	-	5	8±1
4	3h	5	7±1	5	-	5	10±0.5
5	7a	20	10±1	20	-	20	14±1
6	7b	20	-	20	-	20	15±1
7	7e	1	21±1	1	8±1	1	20±1
8	E	1	18±1	1	20±1	1	22±1
9	9a	15	-	10	-	15	11±1
10	9d	15	-	10	-	15	13±1
11	Flu	1	26±0.5	1	25±1	20	27±1

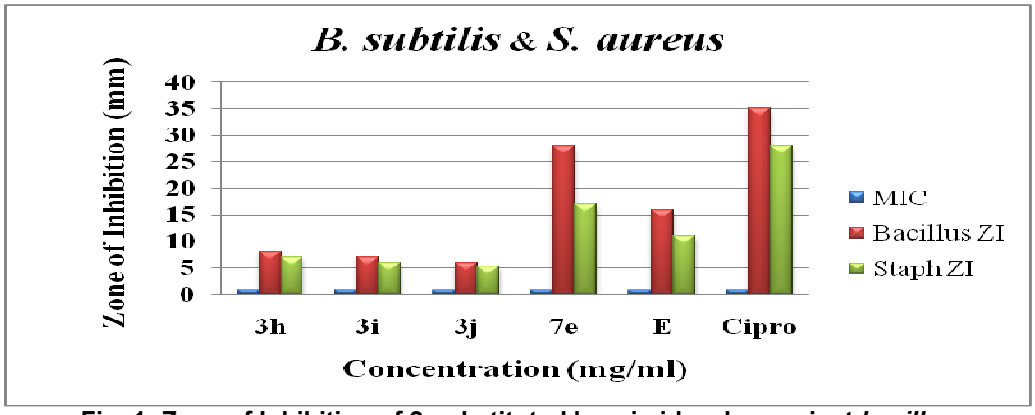


Fig. 1: Zone of Inhibition of 2-substituted benzimidazoles against *bacillus subtilis* & *Staphylococusaureus* by Agar Well Diffusion Assay

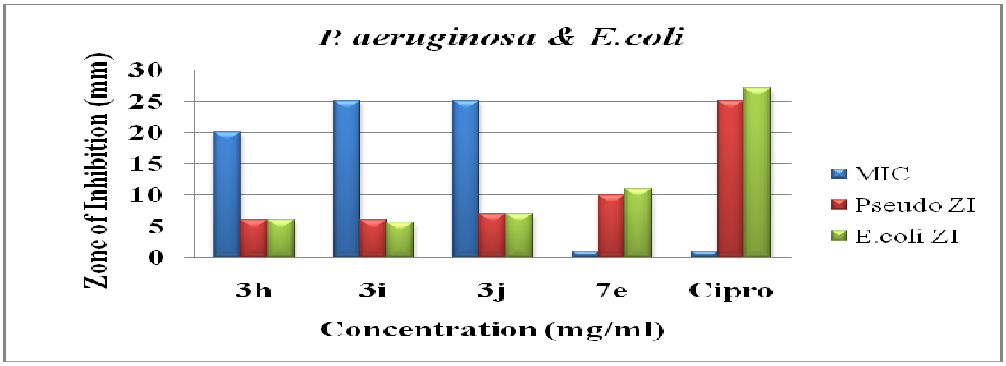


Fig. 2: Zone of Inhibition of 2-substituted benzimidazoles against *Pseudomonas aeruginosa* & *Escherichia coli* by Agar Well Diffusion Assay

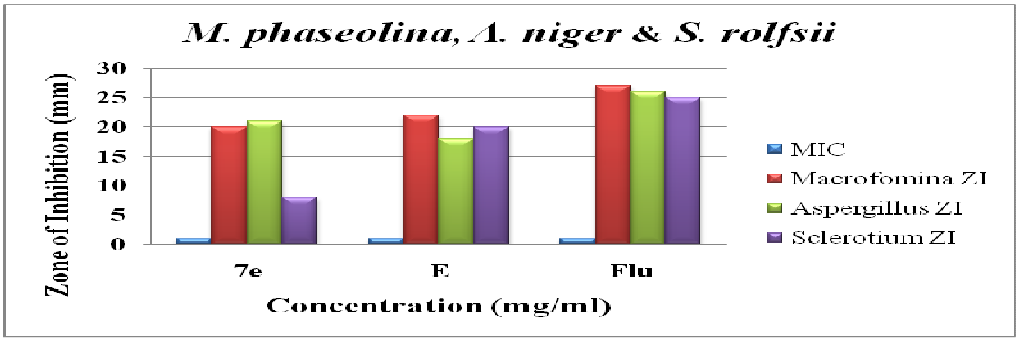


Fig. 3: Zone of inhibitionof 2-substituted benzimidazoles against *Macrophomina phaseolina, Aspergillusniger*and*Sclerotiumrolfsii* by Agar Well Diffusion Assay

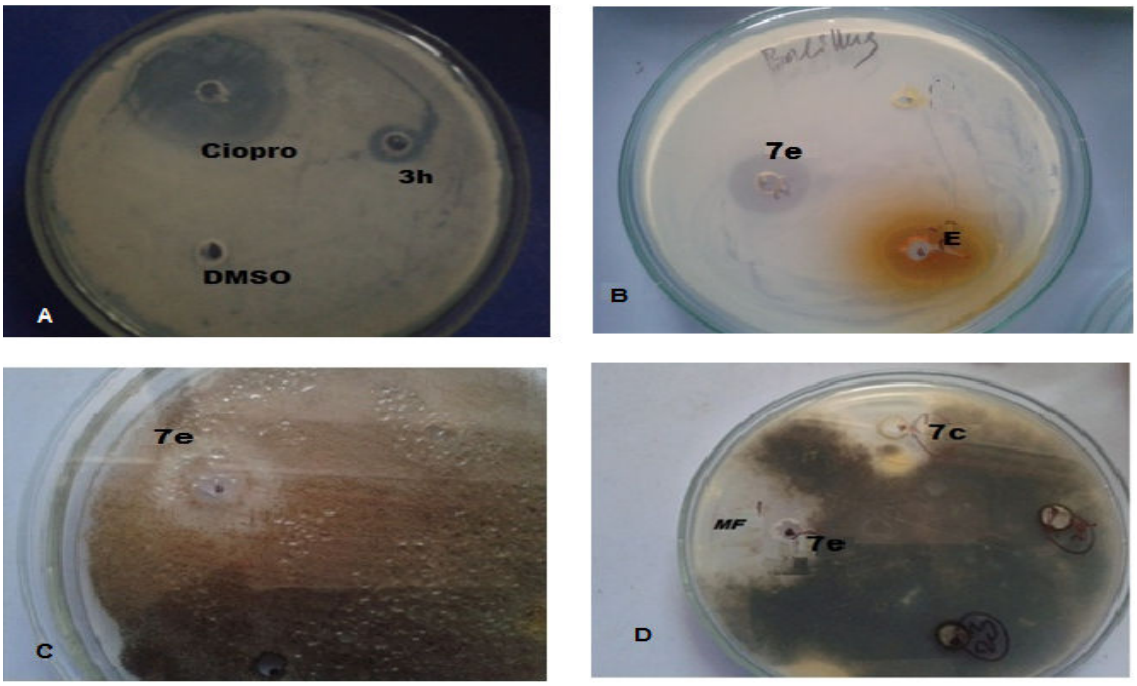


Fig. 4: Agar well diffusion assay showing inhibition zones. A) ciprofloxacin, compound3h and DMSOagainst *bacillus subtilis,* B) Compound 7e and E against *bacillus subtills,* C) compound 7e against *Aspergillusniger,* D) compound 7c and 7e against*Macrophominaphaseolina*

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