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Synthesis and antimicrobial activity of novel 2-substituted-1*H*-benzimidazole derivatives

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ABSTRACT

The reaction of chloromethyl-1-methyl-1*H*-benzimidazole (1) with ethyl 4-aminobenzoate yielded the ester 2 which upon hydrazinolysis resulted in [(1-methyl-1*H*-benzimidazol-2-ylmethyl) amino]benzohydrazide (3). Condensation of 3 with 2-nitrobenzaldhyde afforded the arylidene derivative 4 which was cyclised to thiazolidinone derivative 5. Substituted benzamide 6 and oxadiazole derivative 7 were prepared *via* reacting 3 with phthalic anhydride and benzoic acid, respectively. Reaction of 3 with 4-chlorophenyl isocyanate and ethyl isothiocyanate gave the corresponding semicarbazide 8 and thiosemicarbazide 9. The thiosemicarbazide 9 was cyclized to triazole and thiadiazole derivatives 10 and 11. Also, reacting 9 with both chloroacetic acid and maleic anhydride afforded thiazolidinone derivatives 12 and 13. The prepared compounds were evaluated for *in vitro* antimicrobial activity using ciprofloxacin and triflucan as standard references.

KEYWORDS

Benzimidazole;
Hydrazinolysis;
Thiosemicarbazide;
Triazole;
Thiadiazole;
Antimicrobial activity.

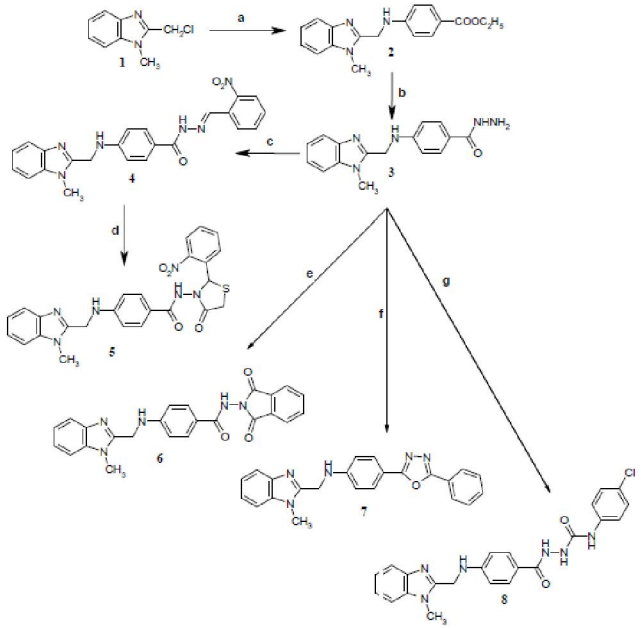
INTRODUCTION

The resistance to antimicrobial drugs is widespread, the development of new antimicrobial agents is becoming vital nowdays[1]. Despite a numerous attempts to develop new structural protype in the search for more effective antimicrobials, the benzimidazoles still remain as one of the most versatile class of compounds against microbes[2]. Literature survey shows that among the benzimidazole derivatives, 2-substituted ones are found to be pharmacologically more potent and hence the design and synthesis of 2-sustituted benzimidazoles are the potential area of research[3]. Many biochemical and pharmacological studies have confirmed that 2-sustituted benzimidazole derivatives are effective against various strains of microorganisms[4-9]. Five-membered heterocyclic compounds act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules[10]. In light of the above findings, it was considered worthwhile to prepare molecules having benzimidazole moiety linked at 2 position with another moiety containing different five-membered heterocyclic rings in an attempt to find an effective antimicrobial agent.

RESULTS AND DISCUSSION

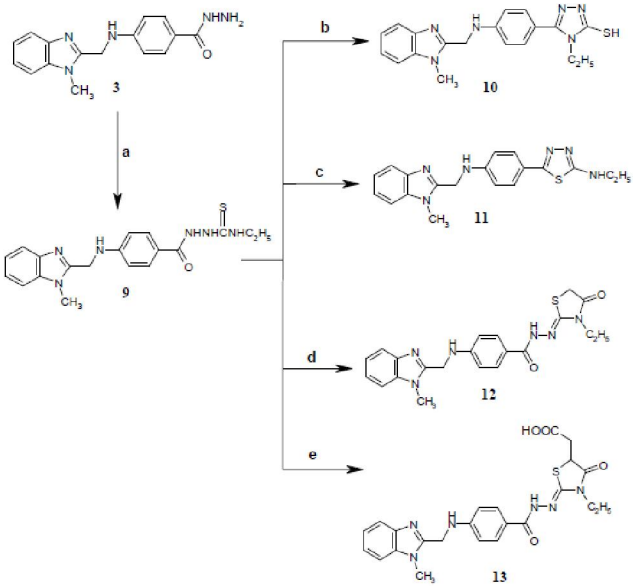
Reaction of chloromethyl-1-methyl-1*H*-benzimida-

zole (1) with ethyl 4-aminobenzoate under reflux in absolute ethanol according to reported methods of analogous reactions[11,12] furnished ethyl 4-[(1-methyl-1*H*-benzimida-zol-2-ylmethyl)amino]benzoate (2) in 70% yield. Hydrazinolysis of 2 in ethanol was not successful and no reaction occurred, while refluxing the ester 2 with hydrazine without using any solvents afforded the key acid hydrazide (3, 84%). Reaction of 3 with 2-nitrobenzaldhyde in *n*-propyl alcohol containing few drops of glacial acetic acid at reflux for 6 hours afforded the corresponding hydrazone derivative (4, 72%). Cylization of compound 4 with mercaptoacetic acid yielded the 4-thiazolidinone derivative (5, 64%). In addition, the acid hydrazide 3 was allowed to react with phthalic anhydride to afford *N*-(1,3-dioxoisoindolin-2-yl)-4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]benzamide (6) in 66% yield. Furthermore, the acid hydrazide 3 was reacted with benzoic acid in phosphorus oxychloride and the formed diacylhydrazide was simultaneously dehydrated to produce the target oxadiazole 7 in high yield (82%). Also the target semicarbazide 8 was obtained by the reaction of the acid hydrazide 3 with 4-chlorophenyl isocyanate in dioxane in 55% yield (Scheme 1).



Scheme 1 : Reagents and conditions: (a) ethyl 4-aminobenzoate, NaI, ethanol, reflux, 12 h; (b) hydrazine hydrate, reflux, 2 h; (c) 2-nitrobenzaldehyde, n-propyl alcohol, acetic acid, reflux, 6 h; (d) mercaptoacetic acid, dry benzene, reflux, 6 h; (e) phthalic anhydride, acetic acid, reflux, 3 h; (f) benzoic acid, $POCl_3$, reflux, 4 h; (g) 4-chlorophenyl isocyanate, dioxane, reflux, 4 h

When the acid hydrazide 3 was heated under reflux for 24 hours with ethy isothiocyanate in *n*-propyl alcohol in the presence of catalytic amount of triethylamine, 2-{4-[(1-methyl-1*H*-benzimidazol-2-ylmethyl)amino]benzoyl}*N*-ethylhydrazine carbothioamide (9) was obtained in 82% yield. Cyclization of the thiosemicarbazide 9 in mixture of piperidine and water afforded [1,2,4]triazole derivative (10, 56%) while, [1,3,4]thiadiazole derivative 11 was obtained *via* cyclization of 9 in concentrated sulphuric acid. On the other hand, reaction of 9 with chloroacetic acid in the presence of sodium acetate gave 1,3-thiazolidin-4-one (12, 74%), while the 4-oxo-1,3-thiazolidine acetic acid derivative 13 was prepared in 95% yield through condensation of the thiosemicarbazide 9 with maleic anhydride (Scheme 2).



Scheme 2 : Reagents and conditions: (a) ethyl isothiocyanate, triethylamine, n-propyl alcohol, reflux, 24 h; (b) piperidine, H_2O, reflux, 6 h; (c) conc. H_2SO_4, 10 minutes; (d) chloroacetic acid, sodium acetate, DMF, reflux, 6 h; (e) maleic anhydride, DMF, reflux, 4 h

The synthesized compounds were screened for their *in vitro* antimicrobial testing against two Gram-positive bacterium (*Staphylococus aureus* and *Bacillus subtilis*), two Gram-negative bacterium (*Escherichia coli* and *Pseudomonas aeruginosa*) and against a fungus (*Candida albicans*). The results revealed that all compounds showed weak antimicrobial activity, except compound 7 showed moderate activity against *Candida albicans* and compound 13 showed moderate activity against *Bacillus subtilis*.

CONCLUSION

A series of 2-substituted benzimidazole derivatives have been synthesized successfully in appreciable yields from the hydrazide, and thiosemicarbazide precursors. The synthesized 2-substituted benzimidazoles may serve as useful synthons in bioorganic and medicinal chemistry applications.

EXPERIMENTAL

Instrumentation, analysis and starting material

Melting points were determined on a Griffin apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu 435 Spectrometer, using KBr discs and values were represented in cm^{-1}. ^1H NMR spectra were measured on a Varian Gemini 200 MHz spectrometer in DMSO-d_6 with TMS as the internal standard. Mass spectra were run on Hewlett Packard 5988 spectrometer. Microanalyses were performed for C, H, N (Micro Analytical Centre, Cairo University, Egypt) and were within ± 0.4% of theoretical values. Progress of the reactions was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel MERCK 60 F 254 that was visualized by UV lamp. 2-chloromethyl-1-methyl-1*H*-benzimidazole (1) was prepared according to a reported procedure[13].

Ethyl 4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino] benzoate (2)

A mixture of 2-chloromethyl-1-methyl-1*H*-benzimidazole (1) (1.81 gm, 0.01 mol), ethyl 4-aminobenzoate (1.65 gm, 0.01 mol) and sodium iodide (0.2 gm) in absolute ethanol (20 ml) was heated under reflux for 12 h. The solid separated on cooling was filtered, washed with ethanol and neutralized with sodium carbonate solution (20%). The formed precipitate was collected by filtration, washed with water and crystallized from aqueous ethanol (70%) to afford 2.17 gm of 2 (70% yield); mp 260-262°; IR: 3361 (NH), 1688 (C=O ester), 1600 (C=N); ^1H NMR (DMSO-d_6) δ1.25 (t, J = 6.6 Hz, 3H, CH_2-CH_3); 3.82 (s, 3H, N-CH_3); 4.21 (q, J = 6.6 Hz, 2H, CH_2-CH_3); 4.65 (s, 2H, CH_2-NH); 6.8-7.7 (m, 9H, 8ArH and NH (D_2O exchangeable); EIMS 310 (M + 1). Anal. Calcd for $C_{18}H_{19}N_2O_3$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.50; H, 6.00; N, 13.53.

[(1-Methyl-1H-benzimidazol-2-ylmethyl)amino] benzo-hydrazide (3)

A mixture of 2 (3.1 gm, 0.01 mol) and excess hydrazine hydrate (99.9%) was heated under reflux while continuous stirring for 2 h. The reaction mixture was allowed to cool to room temperature; the separated white solid was filtered, dried and crystallized from *n*-propyl alcohol to yield 2.48 gm of 3 (84% yield); mp 246-247°; IR: 3350, 3200 (NH_2, NH), 1640 (C=O hydrazide), 1600 (C=N); ^1H NMR (DMSO-d_6) δ3.82 (s, 3H, N-CH_3); 4.31 (s, 2H, NH_2, D_2O exchangeable); 4.62 (s, 2H, CH_2-NH); 6.7-7.6 (m, 8H, ArH); 9.30 (s, 2H, 2NH, D_2O exchangeable); EIMS 296 (M + 1). Anal. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 65.26; H, 5.64; N, 23.71.

4-[(1-methyl-1H-benzimidazol-2-ylmethyl)amino]-N'-2-nitrobenzylidene benzohydrazide (4)

A mixture of the acid hydrazide 3 (1.48 gm, 0.005 mol) and 2-nitrobenzaldhyde (0.755 gm, 0.005 mol) in *n*-propyl alcohol (15 ml) containing 3 drops of glacial acetic acid was heated under reflux for 6 h. The solvent was evaporated under reduced pressure and the product obtained was crystallized from water – acetic acid mixture to afford 1.54 gm of 4 (72% yield); mp 172-174°; IR: 3430, 3200 (2 NH), 1645 (amidic C=O), 1610 (C=N); ^1H NMR (DMSO-d_6) δ 3.83 (s, 3H, N-CH_3); 4.66 (s, 2H, CH_2-NH); 6.86 (d, J = 7.2 Hz, 2H, phenylene C3-H and C5-H); 7.00 (s, 1H, CH_2-NH, D_2O exchangeable); 7.18-8.39 (m, 10H, ArH); 8.48 (s, 1H, N=CH azomethine); 11.8 (s, 1H, O=C-NH, D_2O exchangeable); EIMS 428 (M^+). Anal. Calcd for $C_{23}H_{20}N_6O_3$: C, 64.48; H, 4.71; N, 19.61. Found: C, 64.70; H, 4.75; N, 19.51.

(±) 4-[(1-Methyl-1H-benzimidazol-2-ylmethyl) amino] N-)2-(2-nitrophenyl)-4-oxo-thiazolidin-3-yl)benzamide (5)

A mixture of the azomethine derivative 4 (4.28 gm, 0.01 mol) and mercaptoacetic acid (0.921 gm, 0.01 mol) in dry benzene (100 ml) was heated under reflux using a water separator until the theoretical amount of water was collected (6 h). The solvent was then evaporated under reduced pressure and the residue was crystallized from ethanol – acetic acid mixture to afford 3.21

gm of 5 (64% yield); mp 131-133°; IR: 3400, 3300 (2 NH), 1705 (C=O exocyclic), 1650 (amidic C=O), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.65-4.01 (m, 5H, N-CH_3 and CH_2 of thiazolidinone ring); 4.62 (s, 2H, CH_2-NH); 6.21 (s, 1H, CH of thiazolidinone ring); 6.75 (d, J = 7.2 Hz, 2H, phenylene C3-H and C5-H); 6.97 (s, 1H, CH_2-NH, D_2O exchangeable); 7.22-8.03 (m, 10H, ArH); 10.38 (s, 1H, O =C-NH, D_2O exchangeable); EIMS 502 (M^+). Anal. Calcd for $C_{25}H_{22}N_6O_4S$: C, 59.75; H, 4.41; N, 16.72. Found: C, 59.75; H, 4.12; N, 16.52.

N-(1,3-Dioxoisoindolin-2-yl)-4-[(1-methyl-1H-benzimid-azol-2-ylmethyl)amino]benzamide (6)

A mixture of the acid hydrazide 3 (2.95 gm, 0.01 mol) and phthalic anhydride (1.47 gm, 0.01 mol) in glacial acetic acid (10 ml) was heated under reflux for 3 h. After cooling, the solution was poured into ice-cold water while stirring. The formed precipitate was filtered, dried and crystallized from acetic acid/water to give 2.8 gm of 6 (66% yield); mp 303-305°; IR: 3350, 3310 (2NH), 1740, 1725 (2C=O of anhydride moiety), 1650 (amidic C=O), 1605 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.83 (s, 3H, N-CH_3); 4.66 (s, 2H, CH_2-NH); 6.87 (d, J = 7.2 Hz, 2H, phenylene C3-H and C5-H); 7.11 (s, 1H, CH_2-NH, D_2O exchangeable); 7.18-7.96 (m, 10H, ArH); 10.38 (s, 1H, O=C-NH, D_2O exchangeable); EIMS 426 (M + 1). Anal. Calcd for $C_{24}H_{19}N_5O_3$: C, 67.67; H, 4.50; N, 16.46. Found: C, 68.02; H, 4.36; N, 16.45.

4-(5-Phenyl[1,3,4]oxadiazol-2-yl)N-(1-methyl-1H-benzimidazol-2-ylmethyl)aniline (7)

A mixture of acid hydrazide 3 (0.59 gm, 0.002 mole) and benzoic acid (0.244 gm, 0.002 mole) in phosphorus oxychloride (10 ml) was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto crushed ice and neutralized with sodium carbonate solution (20%). The formed precipitate was filtered, washed with water, dried and crystallized from ethanol/water to give 0.47 gm of 7 (82% yield); mp 123-124°; IR: 3375 (NH), 1650 (C=N), 1270 (C–O–C); ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H, N-CH_3); 4.71 (s, 2H, CH_2-NH); 7.17-8.09 (m, 14H, ArH & NH (D_2O exchangeable); EIMS 382 (M + 1). Anal. Calcd for $C_{23}H_{19}N_5O$: C, 72.42; H, 5.02; N, 18.36. Found: C, 72.30; H, 5.20; N, 18.41.

2-{4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]benzoyl} N-(4-chlorophenyl) hydrazine carboxamide (8)

A mixture of acid hydrazide 3 (2.95 gm, 0.01 mol) and 4-chlorophenylisocyanate (1.534 gm, 0.01 mol) in dioxane (20 ml) was heated under reflux for 4 h. The obtained solid was filtered, washed with dioxane (10 ml), dried and crystallized from aqueous ethanol (70%) to give 2.47 gm of 8 (55% yield); mp 263-264°; IR: 3400-3100 (4NH), 1700, 1650 (2 C=O), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H, N-CH_3); 4.66 (s, 2H, CH_2-NH); 6.82-7.76 (m, 12H, ArH), 8.08 (s, 1H, CH_2-NH-phenylene, D_2O exchangeable); 8.85-8.92 (s, 2H, NH–NH, D_2O exchangeable); 9.87 (s, 1H, O=C–NH–Ar, D_2O exchangeable); EIMS 446 (M - 2). Anal. Calcd for $C_{23}H_{21}ClN_6O_2$: C, 61.54; H, 4.72; N, 18.72. Found: C, 61.43; H, 4.41; N, 18.85.

2-{4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]benzoyl}N-ethylhydrazinecarbothioamide(9)

A mixture of the acid hydrazide 3 (2.95 gm, 0.01 mol) and ethylisothiocyanate (0.911 gm, 0.01 mol) in *n*-propyl alcohol (20 ml) was heated under reflux for 24 h in presence of three drops of triethylamine. After cooling, the precipitated product was filtered and crystallized from ethanol/water to give 3.14 gm of 9 (82% yield); mp 252-254°; IR: 3400-3100 (4NH), 1670 (amidic C=O), 1610 (C=N), 1217, 1191 (C=S); ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J = 6.6 Hz, 3H, CH_2CH_3); 3.46 (q, J = 6.6 Hz, 2H, CH_2CH_3); 3.82 (s, 3H, N-CH_3); 4.65(s, 2H, CH_2-NH); 6.79 (d, J = 7.2 Hz, 2H, phenylene C3-H and C5-H); 6.91 (s, 1H, CH_2-NH-phenylene, D_2O exchangeable); 7.14-7.71 (m, 6H, ArH); 7.93 (s, 1H, S=C–NH– CH_2CH_3, D_2O exchangeable); 9.08 (s, 1H, NH–NH–C=S, D_2O exchangeable); 9.87 (s, 1H, O=C–NH, D_2O exchangeable); EIMS 382 (M^+). Anal. Calcd for $C_{19}H_{22}N_6OS$: C, 59.66; H, 5.80; N, 21.96. Found: C, 59.50; H, 5.71; N, 21.96.

4-Ethyl-5-{4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]phenyl}-4H-[1,2,4]triazole-3-thiol (10)

A mixture of ethylthiosemicarbazide derivative 9 (1.91 gm, 0.005 mol) was heated under reflux for 6 h

in a mixture of piperidine (2 ml) and water (5 ml). The reaction mixture was poured into ice-cold water and the mixture was adjusted to pH 7 with acetic acid (20%). The solid obtained was filtered, dried and crystallized from chloroform to give 1.02 gm of 10 (56% yield); mp 275-277°; IR: 3310 (NH), 2570 (SH), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.17 (t, J = 6.6 Hz, 3H, CH_2CH_3); 3.83 (s, 3H, N-CH_3); 4.10 (q, J = 6.6 Hz, 2H, CH_2CH_3); 4.62 (s, 2H, CH_2-NH); 6.89 (d, J = 7.2 Hz, 2H, phenylene C3-H and C5-H); 7.17 (s, 2H, NH&SH, D_2O exchangeable); 7.36-7.61 (m, 6H, ArH); EIMS 364 (M^+). Anal. Calcd for $C_{19}H_{20}N_6S$: C, 62.61; H, 5.53; N, 23.06. Found: C, 62.39; H, 5.85; N, 23.11.

N-Ethyl-5-{4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]phenyl}-[1,3,4] thiadiazol-2-amine (11)

The ethylthiosemicarbazide derivative 9 (1.23 gm, 0.0034 mol) was stirred for 10 minutes in 10 ml ice cold concentrated sulfuric acid, then left for another 10 minutes at room temperature. The resulting solution was poured slowly into ice-cold water and made alkaline to pH 8 with aqueous ammonia (30%). The precipitated product was filtered, washed with water and crystallized from absolute ethanol to give 1.14 gm of 11 (92% yield); mp 151-153°; IR: 3395, 3350 (2NH), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ1.32 (t, J = 6.6 Hz, 3H, CH_2CH_3); 3.39 (q, J = 6.6 Hz, 2H, CH_2CH_3); 3.82 (s, 3H, N-CH_3); 4.59(s, 2H, CH_2-NH); 5.23(s, 2H, 2NH, D_2O exchangeable); 6.78 (d, J = 7.2 Hz, 2H, phenylene C3-H and C5-H); 7.28-7.78 (m, 6H, ArH); EIMS 364 (M^+). Anal. Calcd for $C_{19}H_{20}N_6S$: C, 62.61; H, 5.53; N, 23.06. Found: C, 62.30; H, 5.50; N, 22.97.

N'-(3-Ethyl)- 4-oxo-thiazolidin-2-ylidene)4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]benzohydrazide (12)

A mixture of the ethylthiosemicarbazide derivative 9 (3.82 gm, 0.01 mol), chloroacetic acid (0.95 gm, 0.01 mole) and anhydrous sodium acetate (0.5 gm) in DMF (20 ml) was heated under reflux while stirring for 6 h. After cooling, the solution was poured into ice-cold water. The obtained solid was filtered, washed with water, dried and crystallized from aqueous ethanol (70%) to give 3.13 gm of 12 (74% yield); mp 92-95°; IR: (3400, 3330) (2NH), 1675, 1640 (C=O exocyclic and amidic C=O), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.31 (t, J = 6.6 Hz, 3H, CH_2CH_3); 3.45 (q, J = 6.6 Hz, 2H, CH_2CH_3); 3.82 (s, 3H, N-CH_3); 4.41-4.80 (m, 4H, CH_2-NH and CH_2 of thiazolidinone ring); 5.21(s, 2H, 2NH, D_2O exchangeable); 6.78-7.76 (m, 8H, ArH); EIMS 423 (M + 1). Anal. Calcd for $C_{21}H_{22}N_6O_2S$: C, 59.70; H, 5.25; N, 19.89. Found: C, 59.78; H, 5.30; N, 19.90.

3-Ethyl-2-{4-[(1-methyl-1H-benzimidazol-2-ylmethyl) amino]benzoyl}hydrazono-4-oxo-thiazolidin-5-acetic acid (13)

A mixture of the ethylthiosemicarbazide derivative 9 (3.82 gm, 0.01 mol) and maleic anhydride (0.98 gm, 0.01 mole) in DMF (20 ml) was heated under reflux while stirring for 4 h. After cooling, the solution was poured into ice-cold water. The obtained solid was filtered, washed with water, dried and crystallized from aqueous ethanol (70%) to yield 4.57 gm of 13 (95% yield); mp 192°(dec.); IR: 3550-3100 (broad band of 2NH and OH groups), 1725, 1705, 1650 (C=O of COOH group, C=O exocyclic and amidic C=O), 1610 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.27 (t, J = 6.6 Hz, 3H, CH_2CH_3); 2.91 (d, J = 6.9 Hz, 2H, CH_2-COOH); 3.63 (s,1H, CH_2-NH, D_2O exchangeable); 3.84 (s, 3H, N-CH_3); 4.02 (q, J = 6.6 Hz, 2H, CH_2CH_3); 4.67 (s, 2H, CH_2-NH); 4.99 (t, J = 6.9 Hz, 1H, CH of thiazolidinone ring); 6.69-7.78 (m, 8H, ArH); 9.02 (s, 1H, O=C-NH, D_2O exchangeable), 11.07 (s, 1H, COOH group); EIMS 480 (M^+). Anal. Calcd for $C_{23}H_{24}N_6O_4S$: C, 57.49; H, 5.03; N, 17.49. Found: C, 57.50; H, 5.29; N, 17.48.

Antimicrobial screening

MIC (the lowest concentration of the compound that prevents the growth of visible colonies) was determined using agar dilution technique according to a reported procedure[14].

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