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Synthesis and biological evaluation of (*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-benzylidene)hydrazinyl) ethanethioate derivatives

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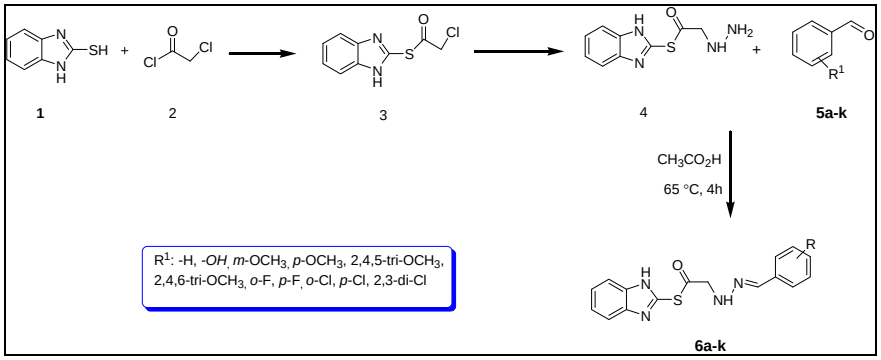
Abstract
We have developed a highly efficient approach for the preparation of *S*-1*H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate 4 in acetic acid. Product 4 was further used for the synthesis of (*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-substituted benzylidene)hydrazinyl) ethanethioate derivatives 6a-k under mild reaction condition. The synthesized compounds were further confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. All the synthesized compounds were screened for their biological activity against different strains of bacteria, fungi and antitubercular.

Keywords: Chloroacetylchloride, Hydrazine hydrate, *S*-1*H*-benzo[*d*]imidazol-2-yl 2-chloroethanethioate, *S*-1*H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate, Hydrazide.

1. Introduction
A variety of pharmacologically active and natural products are known to have such heterocycles in their basic skeleton [1, 2]. Hydrazide constitute an important class of such molecules which has attracted the attention of medicinal chemists due to their wide range of pharmacological and biological properties [3, 4].
There is always a demand for the safer antibacterial agents and research efforts are constantly being carried out to develop safer antibacterial agents. Hydrazide approach is one of the most promising scaffolds. Recently, hydrazide have gained much attention due to their diverse biological properties including antibacterial [5], anticonvulsant [6], anticancer [7], antimalarial, antituberculosis and anti-inflammatory [8] activities.
With an aim of obtaining novel hydrazide with a variety of pharmaceutical applications, we report herein the synthesis of such series together with their use in a series of heterocyclic transformations and their evaluation as antimicrobial agents [9].
From the synthetic point of view, the opportunity to prepare biologically important heterocyclic molecule in limited steps under mild reaction condition is an exciting goal for every modern organic chemists. Although a number of methods are available for the synthesis of simple substituted hydrazide typically require multistep synthesis and expensive reagents [10].
Our group has paid special attention to the synthesis of bioactive molecules using simple bench top available chemical under mild reaction conditions [11]. We have also reported antibacterial, antifungal and antitubercular activities of all synthesized compounds (Scheme 1).



Scheme 1: Synthetic representation of the present work

2. Materials and Methods

All the chemicals and reagents were used in the synthesis process of analytical grade chemicals. All commercial solvents were used after purified. The prepared compound (*E*)-*S*-1*H*-benzo[*d*]imidazol-2-yl 2-benzylidene)hydrazinyl)ethanethioate derivatives confirmed by Mass, IR, ^{1}H NMR, ^{13}C NMR and CHN analysis. Instrumental analyses ^{1}H NMR and ^{13}C NMR were performed at SAI Punjab University, Chandigarh. Mass spectra analysed on Agilent 6420 LCMS at Atul Ltd. IR spectra analysed on Perkin-Elmer 1600 FTIR spectrometer. Melting points measured using a Buchi-610 apparatus. Reactions monitoring carried out using TLC (Thin Layer Chromatography) on Merck silica gel $60F_{254}$, the solvent systems and compound spots were detected either in UV irradiation or by developing with I_2.

Experimental

General procedure for the synthesis of *S*-1*H*-benzo [*d*]imidazol-2-yl 2-chloroethanethioate (3)

To the stirred solution of chloroacetyl chloride (0.02mol) in 25 mL of dimethylchloride at 0-5 °C. 2-mercapto benzimidazole 1 (0.01mol) was added at same temperature. The resulting reaction mixture was stir to room temperature for 6h. Completion of reaction on TLC, the reaction mixture was cooled and poured in crushed ice and the solid mass obtainedwas filtered off, filtrate was wash with dimethyl chloride. The product was recrystallised from ethanol to afforded as S-1H-benzo[d]imidazol-2-yl 2-chloroethanethioate 3. The product was obtained as offwhite solid, mp: 180-183 °C; Anal. Calcd for: $C_9H_7ClN_2OS$ (226.68); Calculation (C, 47.69; H, 3.11; N, 12.36 %); found (C, 47.61; H, 3.09; N, 12.28 %). MS (EI) *m*/*z*: 226.68 (M^+), 227.8 (M+1).IR (KBr, cm^{-1}): ν=3268 (-NH), 1678(C=O), 1585(-NH bending), 1433(C=N cyclic ring), 761(C-S).

General procedure for the synthesis of *S*-*1H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate (4): To the stirred solution of S-1H-benzo[d]imidazol-2-yl 2-chloroethanethioate 3 (0.010mol) in 25 mL of ethanol and 3-4 drops of aceticacid was add at 25-30 °C. Hydrazine hydrate (0.015mol) in 25 mL of ethanol was added at 25-30 °C. The resulting reaction mixture was refluxed for 3h. Completion of reaction on TLC, the clear solution formed was removed under reduced pressure to obtain the solid residue. The residue was dissolved in ethyl acetate and washed with water (100 ml) to get rid of excess hydrazine. The organic layer was collected, dried over sodium sulphate and distilled under reduced pressure to get off-white solid. The product was recrystallised from ethanol to afforded as (*E*)-*S*-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(4-methylbenzylidene) hydrazinyl) ethanethioate 4. The product was obtained asoff white soild, mp: 230–232 °C; Anal. Calcd for: $C_9H_{10}N_4OS$ (222.26); Calculation (C, 48.63; H, 4.53; N, 25.21; %); found (C, 48.58; H, 4.42; N, 25.19; %). MS (EI) *m*/*z*: 222.26 (M^+), 223.8 (M+1).IR (KBr, cm^{-1}): ν= 3320 (NH_2), 3258 (-NH), 1678(C=O), 1585(-NH bending), 1497(-CH_2 bending), 1443(C=N cyclic ring), 1360 (C-N), 751(C-S).

General procedure for the synthesis of (*E*)-*S*-1*H*-benzo[*d*] imidazol-2-yl 2-(2-(benzylidene)hydrazinyl)ethanethioate 6a: To the stirred solution of S-*1H*-benzo[*d*]imidazol-2-yl 2-hydraziny lethanethioate 4 (0.010mol) in 25 mL of ethanolat 20-25 °C. Ethanolic solution of benzaldehyde 5a (0.011mol) drop wise added at same temperature. The resulting reaction mixture was stir at room temperature for 24h. Completion of reaction on TLC, the reaction mixture was cooled and poured in crushed ice and the solid mass obtainedwas filtered off, filtrate was washed with ethanol. The product was recrystallised from ethanol to afforded as (*E*)-*S*-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(benzylidene) hydrazinyl) ethanethioate 6a. The product was obtained as offwhite soild, mp: 230-232 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.65 (s, 1H, NH of benzimidazole), 8.0 (N=CH, 1H), 7.64-7.70 (m, 3H, Ar-H, NH), 7.36-7.40 (m, 4H), 7.08-7.14 (m, 3H, Ar-H), 4.59 (s, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ:33.60, 121.22, 121.37, 126.77, 127.05, 128.24, 129.17, 129.69, 129.94, 133.92, 143.63, 147.13, 149.47, 149.67, 164.06, 169.04. Anal. Calcd for: $C_{16}H_{14}N_4OS$ (310.37); Calculation (C, 61.92; H, 4.55; N, 18.03%); found (C, 61.90; H, 4.49; N, 17.93%). MS (EI) *m*/*z*: 310.37 (M^+), 311.41 (M+1).IR (KBr, cm^{-1}): ν= 3258 (-NH), 1678(C=O), 1607(C=N), 1585(-NH bending), 1497(-CH_2 bending), 1443(C=N cyclic ring), 1360 (C-N), 751(C-S).

(*E*)-*S*-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(4-ydroxybenzylidene) hydrazinyl) ethanethioate 6b: The product was obtained as off white soild, mp: 191–194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:12.54(s, 1H,-OH), 11.42 (s, 1H, NH of benzimidazole), 9.8(s, 1H, NH), 8.10(N=CH, 1H), 7.44-7.50(m, 4H, Ar-H),7.11 (m, 2H), 6.80 (s, 2H, Ar-H), 4.56(s, 1H), 4.11 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.56 115.58, 121.28, 121.43, 124.85, 124.96, 128.50, 128.84, 144.05, 147.58, 149.57, 149.83, 159.25, 159.50, 163.77, 168.71; Anal. Calcd for: $C_{16}H_{14}N_4O_2S$ (326.37); Calculation (C, 64.16; H, 3.77; N, 14.96; O, 8.55; S, 8.56%); found (C, 64.47; H, 3.51; N, 14.81%). MS (EI) *m*/*z*: 326.37 (M^+), 327.81 (M+1). IR (KBr, cm^{-1}): ν= 3405(-OH), 3207 (-NH), 1674(C=O), 1608(C=N), 1520 (-NH bending), 1497(-CH_2 bending), 1436(C=N cyclic ring), 1360 (C-N), 740(C-S).

(*E*)-*S*-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(3-methoxybenzylidene) hydrazinyl) ethanethioate 6c

The product was obtained as off white needles, mp: 196–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.65 (s, 1H, NH of benzimidazole), 8.64 (s, 1H, NH), 8.24 (N=CH, 1H), 7.56-7.47(m, 3H, Ar-H), 7.41 (s, 1H), 7.32 (s,1H), 7.16-7.19(m, 2H), 7.10 (s,1H), 4.62(s, 1H), 4.18(s, 1H), 3.91(s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.62, 55.6,115.52, 112.02, 115.52, 116.3, 121.28, 123.13, 123.23, 129.36, 138.50, 138.84, 138.92, 143.95, 159.50, 163.77, 168.74; Anal. Calcd for: $C_{17}H_{16}N_4O_2S$ (340.40); Calculation (C, 59.98; H, 4.74; N, 16.46%); found (C, 59.95; H, 4.69; N, 16.50%). MS (EI) *m*/*z*: 340.40 (M^+), 341.64 (M+1).IR (KBr, cm^{-1}): ν= 3205 (-NH), 1665 (C=O), 1604 (C=N), 1516(-NH bending), 1507(-CH_2 bending), 1439(C=N cyclic ring), 1357 (C-N), 1285(-OCH_3), 745(C-S).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(4-methoxybenzylidene) hydrazinyl) ethanethioate 6d: The product was obtained as yellow needles, mp: 286-288 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 8.61 (s, 1H, NH), 8.10 (N=CH, 1H), 7.86-7.87 (m, 2H), 7.56-7.58 (m, 2H, Ar-H),7.19-7.21 (m, 2H), 7.08-7.10 (m,2H), 4.59(s, 1H), 4.24 (s, 1H), 3.91(s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.60, 55.6, 114.52, 114.64, 115.32, 115.41, 123.13, 123.28, 126.86, 130.13, 130.32, 138.84, 138.98, 142.97, 161.84, 162.47, 168.48; Anal. Calcd for: $C_{17}H_{16}N_4O_2S$ (340.40); Calculation (C, 59.98; H, 4.74; N, 16.46%); found (C, 59.92; H, 4.65; N, 16.53%). MS (EI) *m*/*z*: 340.40 (M^+), 340.52 (M+1).IR (KBr, cm^{-1}): ν= 3185 (-NH), 3060 (-OCH_3), 1663 (C=O), 1606

(C=N), 1514(-NH bending), 1468(-CH_2 bending), 1439 (C=N cyclic ring), 1358 (C-N), 1285(-OCH_3), 745(C-S).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(2,4,5-trimethoxybenzylidene) hydrazinyl) ethanethioate 6e: The product was obtained as offwhite needles, mp: 196–198°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 8.86 (s, 1H, NH), 8.64 (N=CH, 1H), 7.56-7.58 (m, 2H, Ar-H),7.29 (s, 1H), 7.21-7.24 (m, 2H), 6.49 (s, 1H), 4.62 (s, 1H), 4.24 (s, 1H), 3.91(s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.69, 55.6, 56.05, 56.12, 99.04, 109.12, 110.31, 115.21, 115.21, 123.11, 123.25, 138.74, 138.97, 142.97, 144.04, 151.93, 153.34, 161.84, 168.52;Anal. Calcd for: $C_{19}H_{20}N_4O_4S$ (400.45); Calculation (C, 56.99; H, 5.03; O, 15.98; N, 13.99%); found (C, 56.95; H, 5.05; N, 13.93%). MS (EI) *m*/*z*: 400.45 (M^+), 401.52 (M+1).IR (KBr, cm^{-1}): ν= 3196 (-NH), 3067 (-OCH_3), 1676 (C=O), 1610 (C=N), 1526(-NH bending), 1489(-CH_2 bending), 1441(C=N cyclic ring), 1360 (C-N), 1255(-OCH_3), 744(C-S).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(2,4,6-trimethoxybenzylidene) hydrazinyl) ethanethioate 6f: The product was obtained as white needles, mp: 184–186°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 9.06 (s, 1H, NH), 8.59 (N=CH, 1H), 7.56-7.58 (m, 2H, Ar-H),7.21-7.24 (m, 2H), 6.19 (s,2H), 4.62 (s, 1H), 4.24 (s, 1H), 3.91(s, 9H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.58, 56.10, 56.10, 56.10, 94.04, 94.04, 102.11, 115.21, 115.29, 123.10, 123.31, 138.72, 139.02, 144.04, 159.27, 159.32, 161.84, 163.59, 168.70;Anal. Calcd for: $C_{19}H_{20}N_4O_4S$ (400.45); Calculation (C, 56.99; H, 5.03; N, 13.99%); found (C, 56.95; H, 5.00; N, 13.97%). MS (EI) *m*/*z*: 400.45 (M^+), 401.52 (M+1);IR (KBr, cm^{-1}): ν= 3198 (-NH), 3065 (-OCH_3), 1657 (C=O), 1607 (C=N), 1511(-NH bending), 1494(-CH_2 bending), 1444(C=N cyclic ring), 1343 (C-N), 1264(-OCH_3), 733(C-S).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(2-Fluorobenzylidene) hydrazinyl) ethanethioate 6g: Theproduct was obtained as offwhite needles, mp: 171-173 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 9.06 (s, 1H, NH), 8.59 (N=CH, 1H), 7.80-7.82 (s, 1H, Ar-H), 7.51-7.58 (m, 3H, Ar-H), 7.32-7.34 (s, 1H), 7.28 (s, 1H)7.21-7.24 (m, 2H), 4.62 (s, 1H), 4.24 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.68, 115.20, 116.01, 115.63, 118.13, 123.07, 123.48, 124.52, 130.75, 132.63, 138.87, 138.90, 143.57, 159.89, 165.32, 168.66; Anal. Calcd for: $C_{16}H_{13}FN_4OS$ (328.36); Calculation (C, 58.52; H, 3.99; N, 17.06%); found (C, 58.50; H, 3.97; N, 17.01%). MS (EI) *m*/*z*: 328.36 (M^+), 329.51 (M+1); IR (KBr, cm^{-1}): ν= 3181 (-NH), 1682 (C=O), 1616 (C=N), 1520(-NH bending), 1481(-CH_2 bending), 1434(C=N cyclic ring), 1348 (C-N), 1214(C-F), 747(C-S).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(4-Fluorobenzylidene) hydrazinyl) ethanethioate 6h: The product was obtained as Orange crystals, mp: 184-186 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 9.06 (s, 1H, NH), 8.59 (N=CH, 1H), 7.80-7.82 (m, 2H, Ar-H), 7.56-7.58 (m, 2H, Ar-H), 7.32-7.34 (m, 2H), 7.21-7.24 (m, 2H), 4.62 (s, 1H), 4.24 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.67, 115.19, 115.24, 115.61, 115.65, 123.10, 123.40, 129.27, 130.71, 130.74, 138.88, 138.96, 144.04, 163.59, 165.32, 168.55;Anal. Calcd for: $C_{16}H_{13}FN_4OS$ (328.36); Calculation (C, 58.52; H, 3.99; N, 17.06%); found (C, 58.53; H, 3.95; N, 17.03%). MS (EI) *m*/*z*: 328.26 (M^+), 329.56 (M+1); IR (KBr, cm^{-1}): ν= 3191 (-NH), 1678 (C=O), 1604 (C=N), 1514(-NH bending), 1472 (-CH_2 bending), 1439 (C=N cyclic ring), 1358 (C-N),751(C-S).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(2-Chlorobenzylidene) hydrazinyl) ethanethioate 6i: The product was obtained as white needles, mp: 235-236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 9.06 (s, 1H, NH), 8.59 (N=CH, 1H), 7.73-7.75 (m, 2H, Ar-H), 7.56-7.58 (m, 2H, Ar-H), 7.50-7.52 (m, 2H, Ar-H), 7.21-7.24 (m, 2H), 4.62 (s, 1H), 4.24 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.65, 115.21, 115.24, 123.11, 123.34, 128.64, 128.98, 130.75, 130.89, 136.72, 138.82, 138.88, 144.04, 163.59, 168.51;Anal. Calcd for: $C_{16}H_{13}ClN_4OS$ (344.82); Calculation (C, 69.14; H, 4.06; F, 5.47; N, 12.10; S, 9.23 %); found (C, 69.07; H, 4.18; F, 5.42; N, 12.18; S, 9.29%). MS (EI) *m*/*z*: 344.82 (M^+), 345.95 (M + 1); IR (KBr, cm^{-1}): ν= 3208 (-NH), 1672 (C=O), 1610 (C=N), 1520(-NH bending), 1473 (-CH_2 bending), 1442(C=N cyclic ring), 1344 (C-N), 745(C-S), 726 (C-Cl).

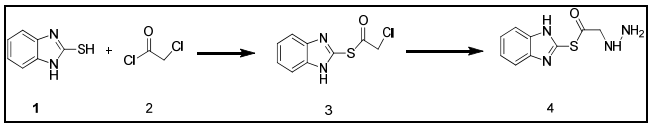
(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(4-chloro benzylidene) hydrazinyl) ethanethioate 6j: The product was obtained as yellow needles, mp: 273–275 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 9.06 (s, 1H, NH), 8.59 (N=CH, 1H), 7.73-7.75 (m, 2H, Ar-H), 7.56-7.58 (m, 2H, Ar-H), 7.50-7.52 (m, 2H, Ar-H), 7.21-7.24 (m, 2H), 4.62 (s, 1H), 4.24 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.61, 115.21, 115.33, 123.12, 123.25, 128.84, 128.96, 130.75, 131.08, 136.72, 138.79, 138.82, 144.04, 163.59, 168.49;Anal. Calcd for: $C_{16}H_{13}ClN_4OS$ (344.82); Calculation (C, 55.73; H, 3.80; N, 16.25%); found (C, 55.70; H, 3.85; N, 16.19%). MS (EI) *m*/*z*: 344.82 (M^+), 345.92 (M+1); IR (KBr, cm^{-1}): ν= 3208 (-NH), 1675(C=O), 1608 (C=N), 1516(-NH bending), 1475 (-CH_2 bending), 1442 (C=N cyclic ring), 1344 (C-N), 749 (C-S), 735 (C-Cl).

(*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(2,3-Dichloro benzylidene) hydrazinyl) ethanethioate 6k: The product was obtained as yellow needles, mp: 277–280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ:11.61 (s, 1H, NH of benzimidazole), 9.06 (s, 1H, NH), 8.59 (N=CH, 1H), 7.67-7.65 (s, 1H, Ar-H), 7.46-7.48 (s, 1H, Ar-H), 7.50-7.52 (m, 2H, Ar-H), 7.21-7.24 (m, 2H), 4.62 (s, 1H), 4.24 (s, 1H); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 33.67, 115.22, 115.41, 123.12, 123.24, 125.10, 128.84, 130.75, 132.53, 134.72, 138.81, 138.85, 142.61, 144.04, 163.59, 168.59;Anal. Calcd for: $C_{16}H_{12}Cl_2N_4OS$ (379.26); Calculation (C, 64.16; H, 3.77; N, 14.96%); found (C, 64.07; H, 3.51; N, 14.87%). MS (EI) *m*/*z*: 374.50 (M^+), 375.5 (M+1); IR (KBr, cm^{-1}): ν= 3196 (-NH), 1669 (C=O), 1608 (C=N), 1518(-NH bending), 1471(-CH_2 bending), 1442(C=N cyclic ring), 1360 (C-N), 751(C-S), 726 (C-Cl).

3. Result and Discussion

Chemistry

The intermediate S-*1H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate 4 was prepared in two steps (Scheme 2). Intermediate 3 is prepared by 1*H*-benzo[*d*]imidazole-2-thiol 1 condensation with chloroacetyl chloride. Intermediate 3 afforded the compound 4 by using hydrazine hydrate in the presence of acetic acid in 75% yield.



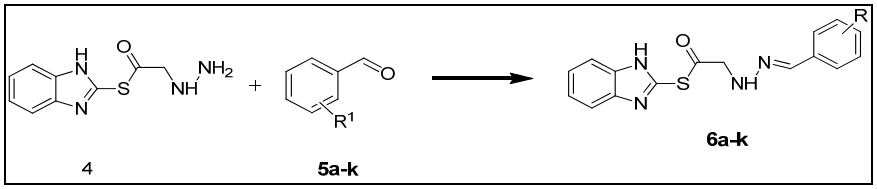
Scheme 2: Synthetic scheme for the preperation of *S-1H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate 4

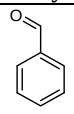
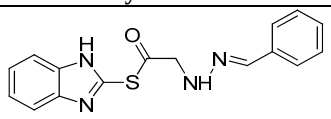
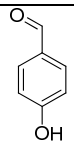
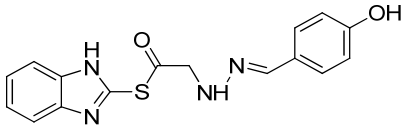
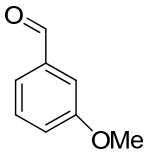
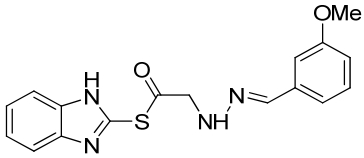
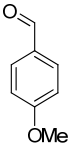
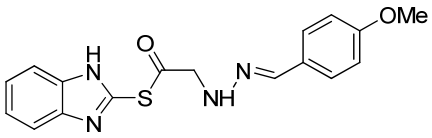
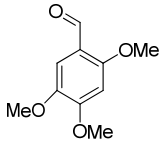
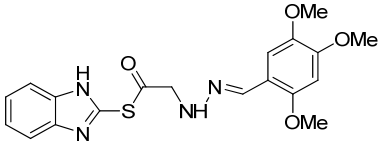
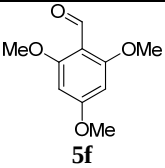
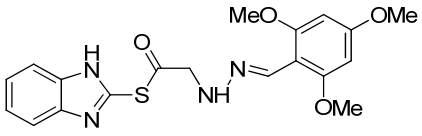
Scope of the reaction was studies for the synthesis of hydrazide derivatives of S-*1H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate 6a-k (Table 1, entries 1-11). The products of the reaction were fully characterized by ^{1}H, ^{13}C NMR, Mass, Elemental analysis and IR. The synthesized compounds were characterized on the basis of the spectral and analytical studies.

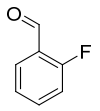
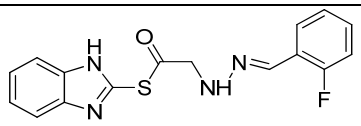
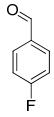
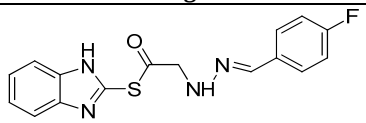
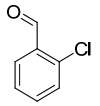
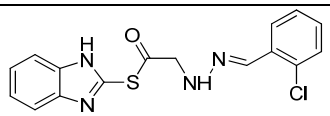
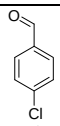
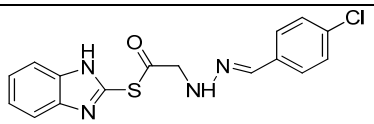
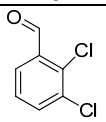
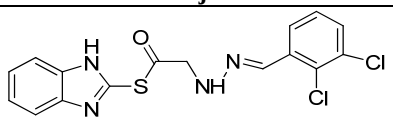
The IR spectra of compounds 6a-k are observed a broad band in the region 3271-3180 cm^{-1}due to the N-H group. The N-H bending vibrations are observed as a sharp medium to strong band at 1540-1500 cm^{-1}. The C-S linkage of the compounds caused a weak and sharp absorption band at 800-740 cm^{-1} in all the compounds. The C=O group is observed as a strong and sharp band at1700-1650 cm^{-1}in all compounds. The C-H (aliphatic and aromatic), C=C stretching vibrations are observed at their usual positions. Similarly, all these compounds were purified by column chromatography and characterized on the basis of spectral studies.

^{1}H NMR spectra exhibited multiplets in the region at δ7.64-7.08 ppm for ten protons of aromatic ring, one proton of CH=N group are shown singlet in the region at δ 8.0 ppm, one proton of -NH group of side chain are shown singlet in the region at δ7.70 ppm one proton of -NH group of benzimidazole are shown singlet in the region at δ 11.65 ppm and Two protons present in $–CH_2$ are found to resonate as doublets at δ 4.59 ppm and δ 4.92 ppm in compound 6a.^{13}C NMR spectra exhibited multiplets in the region at δ 121.22-164.06 ppm for 13 carbons of aromatic ring, one carbon of C=O group are observed at δ 169.04 ppm, one carbon of CH=N group are observed at δ 143.63 ppm and two carbons present of CH_2 group at δ 33.60-34.22 ppm of compound 6a.

Table 1: Synthesis of (*E*)-S-1*H*-benzo[*d*]imidazol-2-yl 2-(2-(benzylidene) hydrazinyl) ethanethioate 6a–k



Entry	Aldehyde	Hydrazide[a]	Yields[b]
1	 **5a**	 **6a**	75%
2	 **5b**	 **6b**	80%
3	 **5c**	 **6c**	74%
4	 **5d**	 **6d**	70%
5	 **5e**	 **6e**	76%
6	 **5f**	 **6f**	73%

7	 **5g**	 **6g**	71%
8	 **5h**	 **6h**	78%
9	 **5i**	 **5i**	75%
10	 **5j**	 **6j**	68%
11	 **5k**	 **6k**	69%

[a]All the reaction were carried out using 0.01 mol of *S*-1*H*-benzo[*d*]imidazol-2-yl 2-hydrazinylethanethioate 4 and 0.011 mol ofaldehyde 5 in 25 mL of ethanol and 2-4 drops of aceticacid at refluxed for 4h.[b]Isolated yields.

The IR spectra of compounds 6a-k are observed a broad band in the region 3271-3180 cm^{-1}due to the N-H group. The N-H bending vibrations are observed as a sharp medium to strong band at 1540-1500 cm^{-1}. The C-S linkage of the compounds caused a weak and sharp absorption band at 800-740 cm^{-1} in all the compounds. The C=O group is observed as a strong and sharp band at 1700-1650 cm^{-1}in all compounds. The C-H (aliphatic and aromatic), C=C stretching vibrations are observed at their usual positions. Similarly, all these compounds were purified by column chromatography and characterized on the basis of spectral studies.

^{1}H NMR spectra exhibited multiplets in the region at δ7.64-7.08 ppm for ten protons of aromatic ring, one proton of CH=N group are shown singlet in the region at δ 8.0 ppm, one proton of -NH group of side chain are shown singlet in the region at δ7.70 ppm one proton of -NH group of benzimidazole are shown singlet in the region at δ 11.65 ppm and Two protons present in $–CH_2$ are found to resonate as doublets at δ 4.59 ppm and δ 4.92 ppm in compound 6a.^{13}C NMR spectra exhibited multiplets in the region at δ 121.22-164.06 ppm for 13 carbons of aromatic ring, one carbon of C=O group are observed at δ 169.04 ppm, one carbon of CH=N group are observed at δ 143.63 ppm and two carbons present of CH_2 group at δ 33.60-34.22 ppm of compound 6a.

4. Biological activity

Antibacterial activity

The minimum inhibitory concentration (MIC) of the tested compounds 6a-k is shown in (Table 2, Figure-II). Most of the compounds tested, exhibited considerable activities against four bacterial species, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcus pyogenes. Hydrazidecompounds 6d exhibited excellent at 62.5 µg/mL; 6a, 6e, 6f and 6k exhibited a good activity at 100-125 µg/mL against Escherichia coli as compared to Ampicillin (MIC=100 µg/mL). Compound 6a exhibited excellent activity against Pseudomonas aeruginosa at 100 µg/mL; 6c, 6d, 6e, 6f and 6k exhibited good activity as compared to Ampicillin (MIC= 100 µg/mL).

Table 2: Antimicrobial activity data of synthesized compounds

Entry	*E. Coli* MTCC 443	*P. Aeruginosa* MTCC 1688	*S. Aureus* MTCC 96	*S. Pyogenus* MTCC 442
6a	100	125	500	200
6b	125	200	200	250
6c	200	125	200	250
6d	62.5	100	250	500
6e	125	125	200	125
6f	125	125	200	250
6g	200	200	125	100
6h	250	250	200	250
6i	200	250	125	125
6k	125	125	100	100
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Standard deviation	± 5	± 5	± 5	± 5
Control (DMSO)	-	-	-	-

Compounds 6g, 6i and 6k exhibited very good activity at 100–125 µg/mL; 6b, 6c, 6d, 6e, 6f and 6k exhibited good activity at 200–250 µg/mL against Staphylococcus aureus as compared to Ampicillin (MIC= 250 µg/mL). Compounds 6e, 6g, 6i and 6k exhibited good activity against Streptococcus pyogenes at 100 µg/mL as compared to Ampicillin (MIC= 100 µg/mL).

Table 3: Antifungal activity (MIC) of synthesis compounds

Compound No.	*C. Albicans* MTCC 227	*A. Niger* MTCC 282	*A. Clavatus* MTCC 1323
6a	>1000	500	500
6b	>1000	500	500
6c	250	1000	1000
6d	1000	>1000	>1000
6e	500	500	500
6f	1000	>1000	>1000
6g	500	>1000	>1000
6h	>1000	>1000	>1000
6i	500	>1000	>1000
6j	250	500	500
6k	250	500	500
Griseofulvin	500	100	100
Control (DMSO)	-	-	-

Antifungal activity

The minimum inhibitory concentration (MIC) of the tested compounds 6a-k is shown in (Table 3, Figure III). Compounds 6c, 6e, 6g, 6i, 6j and 6k exhibited very good activity at 250-500 µg/mL against Candida albicansas compared to Griseofulvin (MIC= 500 µg/mL); their MIC values were in the range between (100–500 µg/mL).

All the screened compounds were less active against Aspergillusniger and Aspergillus clavatus. The other compounds tested showed less activity against the fungal species.

5. Conclusion

In conclusion, we have described a simple approach for the synthesis of hydrazide derivatives of benzimidazole 6a-k. Synthesized compounds were screened for antibacterial, antifungal and anti tubercular activity. Compounds 6d, 6e, 6f and 6k were possessed excellent activity comparable to ampicillin for different four species. Compounds 6c, 6j and 6k showed good activity of 250 µg/ml comparable to griseofulvin. Compounds bearing fluoro, chloro, methoxy and methyl derivatives are more effective to inhibit the both bacterial and fungal species. Present work will be useful for understanding antimicrobial activity of hydrazide derivatives of benzimidazole.

6. Acknowledgements

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