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Original Article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF INDOLE DERIVATIVES BEARING BENZIMIDAZOLE/BENZOTHIAZOLE MOIETY

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ABSTRACT

Objective: The present work deals with the synthesis and characterization of biologically active new indole derivatives viz., 2-((1*H*-benzo[d]imidazol-2-yl)thio)-*N*-(4-(3-(1*H*-indol-3-yl)acryloyl)phenyl)acetamide 6a-d, *N*-(4-(3-(1*H*-indol-3-yl)acryloyl)phenyl)-2-((5-methoxy-1*H*-benzo[d]imidazol-2-yl)thio)acetamide 7a-d and *N*-(4-(3-(1*H*-indol-3-yl)acryloyl)phenyl)-2-(benzo[d]thiazol-2-ylthio)acetamide 8a-d.

Methods: All these newly synthesized compounds were screened for their *in vitro* antimicrobial activity by an agar plate diffusion method, antioxidant activities: like 1,1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity (RSA), ferric ions (Fe^{3+}) reducing antioxidant power (FRAP), ferrous (Fe^{2+}) metal ion chelating activity.

Results: The structures of all the newly synthesized compounds were characterized by their IR, ^{1}HNMR, mass spectral studies and elemental analysis. Compounds 6b, 7a, 7b, 8a and 8b exhibited good radical scavenging activity (RSA) at a concentration 100 µg/ml, compounds 7b, 7c, 7d and 8b displayed good ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) at a concentration 100 µg/ml, compounds 7b, 7d, 8b and 8d showed good ferrous (Fe^{2+}) ion metal chelating activity. Compounds 7d and 8d exhibited good activity against all the screened bacteria and fungi.

Conclusion: The synthesised compounds 7d having methoxy group at 5 positions of benzimidazoles ring, bromo group at 5 positions of indole ring, and 8d having bromo group at position 5 of indole ring, both the compounds have exhibited potent antimicrobial activity. Some compound**s** have shown very good antioxidant activity.

Keywords: Indole, Benzimidazole, Benzothiazole, Antimicrobial, Antioxidant

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INTRODUCTION

Many derivatives of indole were synthesized, and their biological activities were validated by *in vitro* or *in vivo* methods [1, 2]. Indoles and its biheterocycles are featured in a wide variety of biological and pharmacologically active compounds [3]. The indole derivatives are known to possess anticancer [4, 5], antioxidant [6, 7], anti-inflammatory [8, 9], antiviral [10], and antihypertensive [11] activities.

Benzimidazole is an important pharmacophore and a privileged structure in medicinal chemistry. It has been found to possess antioxidant [12], anti-inflammatory [13], diuretic [14], JAK1-selective inhibitor [15], angiotensin II receptor antagonist [16], antiviral [17], anticonvulsant [18], and antidiabetic [19] activities.

Benzothiazole is also a heterocyclic compound, with diverse biological activities and is of extreme scientific interest. This heterocycle exhibits different biologic activities such as antibacterial [20], antifungal [21], anticancer [22], antioxidant [23], and tubulin polymerization inhibitor [24] activities.

Bearing in mind the above reports of bioactive indole and benzimidazole/benzothiazole, we reported herein the synthesis of the indole and benzimidazole/benzothiazole nucleus, in anticipation to get molecules with enhanced biological activities. All the newly synthesized compounds were screened for their antioxidant activities: like 1, 1-diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity (RSA), ferric ions (Fe^{3+}) reducing antioxidant power (FRAP), ferrous (Fe^{2+}) metal ion chelating activity. They have been screened for the antibacterial and antifungal activities.

MATERIALS AND METHODS

Materials

All chemicals and solvents were of commercial reagent grade and used as received from Sigma Aldrich and Spectrochem Pvt. Ltd. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC using silica gel-G coated aluminum plates (Merck) and spots were visualized by exposing the dry plates to iodine vapors. The IR (KBr) spectra were recorded on a Perkin-Elmer spectrum one FT-IR spectrometer. The ^{1}H NMR (DMSO-d_6) spectra recorded on a Bruker NMR (400 MHz) and the chemical shifts were expressed in ppm (δ scale) downfield from TMS. Mass spectral data were recorded by electron impact method on JEOL GCMATE II GC-MS mass spectrometer. Elemental analysis was carried out using Flash EA 1112 series elemental analyzer. All the compounds gave C, H and N analysis within±0.5% of the theoretical values.

General procedure for the synthesis of *N*-(4-acetylphenyl)-2-chloroacetamide (2) was prepared by following the literature method [25]

General procedure for the synthesis of 2-(1*H*-benzo[d]imidazole-2-ylthio)*N*-(4-acetylphenyl) acetamide, *N*-(4-acetylphenyl)-2-((5-methoxy-1*H*-benzo[d]imidazol-2-yl)thio)acetamide and *N*-(4-acetylphenyl)-2-(benzo[d]thiazol-2-ylthio) acetamide (3, 4 and 5) were prepared by following the literature method [25]

N-(4-acetylphenyl)-2-chloroacetamide (2) (0.01 mol) obtained was further reacted with 2-mercatobenzimidazole, 2-mercapto-5-methoxy benzimidazole and 2-mercapto benzothiazole (0.01 mol). The reaction was stirred for 4 h at room temperature in the presence of K_2CO_3 (0.02 mol), and acetone (20 ml) was used as the reaction medium. After the completion of reaction monitored on TLC using Toluene: Acetone (8:2) as mobile phase, the product was poured into water and stirred vigorously for 1 h. The separated precipitate was collected and dried. The product was recrystallized from ethanol.

2-(1*H*-benzo [d] imidazole-2-ylthio)-*N*-(4-acetyl phenyl) acetamide (3)

Yield 86% (Ethanol); M. P 210 °C; R_f = 0.57 (Toluene: Acetone 8:2 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1409, 1650, 2850, 3110, 3285, 3400. ^{1}H

NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 2.50 (S,3H,-CH_3), 4.32 (S, 2H,-CH_2), 7.10-7.96 (m, 8H, Ar-H), 10.85 (S, 1H,-NH), 12.86 (S, 1H, benzimidazole-NH). Analysis: Calcd for $C_{17}H_{15}N_3O_2S$ (325): C, 62.75; H, 4.65; N, 12.91. Found: C, 62.74; H, 4.67; N, 12.90.

_N_-(4-acetylphenyl)-2-((5-methoxy-1_H_-benzo[d]imidazol-2-yl) thio)acetamide (4)

Yield 80% (Ethanol); M. P 152 °C; R_f = 0.69 (Toluene: Acetone 8:2 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1406, 1625, 2862, 2992, 3285, 3379. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 2.50 (S, 3H,-CH_3), 3.76 (S, 3H, OCH_3), 4.32 (S, 2H,-CH_2), 6.72-8.22 (m, 7H, Ar-H), 10.88 (S, 1H,-NH), 12.48 (S, 1H, benzimidazole-NH). Analysis: Calcd for $C_{18}H_{17}N_3O_3S$ (355): C, 60.83; H, 4.82; N, 11.82. Found: C, 60.81; H, 4.85; N, 11.81.

***N*-(4-acetylphenyl)-2-(benzo[d]thiazol-2-ylthio)acetamide (5)**

Yield 77% (Ethanol); M. P 130 °C; R_f = 0.63 (Toluene: Acetone 8:2 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1457, 1625, 2850, 2992, 3276, 3380. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 2.50 (S, 3H,-CH_3), 4.40 (S, 2H,-CH_2), 7.29-7.92 (m, 8H, Ar-H), 10.71 (S, 1H,-NH). Analysis: Calcd for $C_{17}H_{14}N_2O_2S_2$ (342): C, 59.63; H, 4.12; N, 8.18. Found: C, 59.61; H, 4.15; N, 8.19.

General procedure for the synthesis of 2-((1_H_-benzo [d]imidazol-2-yl)thio)-_N_-(4-(3-(1_H_-indol-3-yl)acryloyl)phenyl) acetamide (6a-d)

Claisen–Schmidt condensation of an equimolar mixture of 2-(1*H*-benzo[d]imidazol-2-ylthio)-*N*-(4-acetylphenyl)acetamide (0.01 mol) and various 2,5-disubstituted indole-3-carboxaldehydes (0.01 mol) were refluxed (3–4 h) in ethanol (15–20 ml) in the presence of piperidine. The completion of the reaction was monitored by TLC. The product was poured in ice-cold water, and acetic acid was added to that solution. The product obtained was filtered and purified by ethanol.

2-((1_H_-benzo[d]imidazol-2-yl)thio)-_N_-(4-(3-(1_H_-indol-3-yl)acryloyl)phenyl)acetamide (6a)

Yield 80% (Ethanol); M. P 218 °C; R_f = 0.57 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1426, 1646, 1691, 2849, 3059, 3220, 3390, 3523; ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 4.32 (S, 2H,-CH_2), 7.31-8.13 (m, 13H, 11Ar-H, CH=CH), 9.56 (S, 1H, indole-NH), 10.95 (S, 1H,-NH), 11.93 (S, 1H, benzimidazole-NH). MS: m/z = 452 $[M]^+$. Analysis: Calcd for $C_{26}H_{20}N_4O_2S$ (452): C, 69.01; H, 4.45; N, 12.38. Found: C, 68.98; H, 4.48; N, 12.37.

2-((1_H_-benzo[d]imidazol-2-yl)thio)-_N_-(4-(3-(5-chloro-2-phenyl-1_H_-indol-3-yl)acryloyl) phenyl)acetamide (6b)

Yield 85% (Ethanol); M. P 190 °C; R_f = 0.62 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1462, 1625, 1706, 2885, 2981, 3106, 3393, 3442, 762. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 4.31 (S, 2H,-CH_2), 7.12-8.35 (m, 18H, 16Ar-H, CH=CH), 10.21 (S, 1H, indole-NH), 11.85 (S, 1H,-NH), 12.39 (S, 1H, benzimidazole-NH). MS: m/z = 562 $[M]^+$, 564 $[M+2]^+$(3:1). Analysis: Calcd for $C_{32}H_{23}ClN_4O_2S$ (562): C, 68.26; H, 4.12; N, 9.95. Found: C, 68.27; H, 4.09; N, 9.96.

2-((1_H_-benzo[d]imidazol-2-yl)thio)-_N_-(4-(3-(5-methyl-2-phenyl-1_H_-indol-3-yl)acryloyl)phenyl)acetamide (6c)

Yield 77% (Ethanol); M. P 190 °C; R_f = 0.69 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1463, 1626, 1725, 2842, 3028, 3250, 3299, 3421. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 2.41 (S, 3H,-CH_3), 4.31 (S, 2H,-CH_2), 7.11-8.03 (m, 18H, 16Ar-H, CH=CH), 9.93 (S, 1H, indole-NH), 10.85 (S, 1H,-NH), 12.28 (S, 1H, benzimidazole-NH). MS: m/z = 542 $[M]^+$. Analysis: Calcd for $C_{32}H_{26}N_4O_2S$ (542): C, 73.04; H, 4.83; N, 10.32. Found: C, 73.05; H, 4.85; N, 10.31.

2-((1_H_-benzo[d]imidazol-2-yl)thio)-_N_-(4-(3-(5-bromo-1_H_-indol-3-yl)acryloyl)phenyl) acetamide (6d)

Yield 73% (Ethanol); M. P 218 °C; R_f = 0.71 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1484, 1647, 1705, 2841, 3117, 3238, 3381, 3470, 733. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 4.31 (S, 2H,-CH_2), 7.11-8.33 (m, 14H, 12Ar-H, CH=CH), 9.92 (S, 1H, indole-NH), 10.85 (S, 1H,-NH), 12.31 (S, 1H, benzimidazole-NH). MS: m/z = 530 $[M]^+$, 532 $[M+2]^+$(1:1). Analysis: Calcd for $C_{26}H_{19}BrN_4O_2S$ (530): C, 58.76; H, 3.60; N, 10.54; Found: C, 58.74; H, 3.58; N, 10.55.

General procedure for the synthesis of _N_-(4-(3-(1_H_-indol-3-yl) acryloyl)phenyl)-2-((5-methoxy-1_H_-benzo[d]imidazol-2-yl) thio)acetamide (7a-d)

Claisen–Schmidt condensation of an equimolar mixture of *N*-(4-acetyl phenyl)-2-((5-methoxy-1*H*-benzo[d]imidazol-2-yl) thio) acetamide (0.01 mol) and various 2, 5-disubstituted indole-3-carboxaldehyde (0.01 mol) were refluxed (3–4 h) in ethanol (15–20 ml) in the presence of piperidine. The completion of the reaction was monitored by TLC. The product was poured in ice-cold water, and acetic acid was added to that solution. The product obtained was filtered and purified by ethanol.

_N_-(4-(3-(1_H_-indol-3-yl)acryloyl)phenyl)-2-((5-methoxy-1_H_-benzo[d]imidazol-2-yl)thio) acetamide (7a)

Yield 75% (Ethanol); M. P 95 °C; R_f = 0.54 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1426, 1677, 1706, 2849, 2981, 3271, 3380, 3410. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 3.98 (S, 3H,-OCH_3), 4.44 (S, 2H,-CH_2), 7.19-8.09 (m, 14H, 12Ar-H, CH=CH), 9.98 (S, 1H, indole-NH), 10.26 (S, 1H,-NH), 12.26 (S, 1H, benzimidazole-NH). MS: m/z = 482 $[M]^+$. Analysis: Calcd for $C_{27}H_{22}N_4O_3S$ (482): C, 67.20; H, 4.60; N, 11.61. Found: C, 67.21; H, 4.62; N, 11.60.

_N_-(4-(3-(5-chloro-2-phenyl-1_H_-indol-3-yl)acryloyl)phenyl)-2-((5-methoxy-1_H_-benzo[d]imidazol-2-yl)thio)acetamide (7b)

Yield 86% (Ethanol); M. P 200 °C; R_f = 0.58 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1426, 1646, 1725, 2888, 3040, 3100, 3326, 3442, 795. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 3.38 (S, 3H,-OCH_3), 4.42 (S, 2H,-CH_2), 7.11-8.01 (m, 14H, 12Ar-H, CH=CH), 9.92 (S, 1H, indole-NH), 10.76 (S, 1H,-NH), 12.27 (S, 1H, benzimidazole-NH). MS: m/z = 592 $[M]^+$, 594 $[M+2]^+$(3:1). Analysis: Calcd for $C_{33}H_{25}ClN_4O_3S$ (592): C, 66.83; H, 4.25; N, 9.45. Found: C, 66.85; H, 4.23; N, 9.43.

2-((5-methoxy-1_H_-benzo[d]imidazol-2-yl)thio)-_N_-(4-(3-(5-methyl-2-phenyl-1_H_-indol-3-yl)acryloyl)phenyl)acetamide (7c)

Yield 94 % (Ethanol); M. P 215 °C; R_f = 0.55 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1478, 1677, 1741, 2840, 2897, 3261, 3371, 3428. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 3.17 (S, 3H,-CH_3), 3.97 (S, 3H,-OCH_3), 4.44 (S, 2H,-CH_2), 7.35-8.81 (m, 17H, 15Ar-H, CH=CH), 9.94 (S, 1H, indole-NH), 10.78 (S, 1H,-NH), 12.17 (S, 1H, benzimidazole-NH). MS: m/z = 572 $[M]^+$. Analysis: Calcd for $C_{34}H_{28}N_4O_3S$ (572): C, 71.31; H, 4.93; N, 9.78. Found: C, 71.35; H, 4.91; N, 9.79.

_N_-(4-(3-(5-bromo-1_H_-indol-3-yl)acryloyl)phenyl)-2-((5-methoxy-1_H_-benzo[d]imidazol-2-yl)thio)acetamide (7d)

Yield 74% (Ethanol); M. P 165 °C; R_f = 0.59 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1425, 1677, 1741, 2831, 2983, 3115, 3371, 3456, 768. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 3.87 (S, 3H,-OCH_3), 4.48 (S, 2H,-CH_2), 7.12-8.05 (m, 13H, 11Ar-H, CH=CH), 10.12 (S, 1H, indole-NH), 11.16 (S, 1H,-NH), 12.37 (S, 1H, benzimidazole-NH). MS: m/z = 560 $[M]^+$, 562 $[M+2]^+$(1:1). Analysis: Calcd for $C_{27}H_{21}BrN_4O_3S$ (560): C, 57.76; H, 3.77; N, 9.98. Found: C, 57.80; H, 3.78; N, 9.99.

General Procedure for the synthesis of _N_-(4-(3-(1_H_-indol-3-yl)acryloyl)phenyl)-2-(benzo[d]thiazol-2-ylthio)acetamide (8a-d)

Claisen–Schmidt condensation of an equimolar mixture of *N*-(4-acetylphenyl)-2-(benzo[d]thiazol-2-ylthio)acetamide (0.01 mol) and various 2,5-disubstituted indole-3-carboxaldehydes (0.01 mol) were refluxed (3–4 h) in ethanol (15–20 ml) in the presence of piperidine. The completion of the reaction was monitored by TLC. The product was poured in ice-cold water, and acetic acid was added to that solution. The product obtained was filtered and purified by ethanol.

_N_-(4-(3-(1_H_-indol-3-yl)acryloyl)phenyl)-2-(benzo[d]thiazol-2-ylthio)acetamide (8a)

Yield 80% (Ethanol); M. P 150 °C; R_f = 0.57 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1463, 1647, 1707, 2862, 2961, 3191, 3390. ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 4.31 (S, 2H,-CH_2), 7.20-7.99 (m, 14H, 12Ar-H, CH=CH), 9.95 (S, 1H, indole-NH), 10.88 (S, 1H,-NH). MS: m/z = 469 $[M]^+$. Analysis: Calcd for $C_{26}H_{19}N_3O_2S_2$ (469): C, 66.50; H, 4.08; N, 8.95. Found: C, 66.54; H, 4.07; N, 8.93.

2-(benzo[d]thiazol-2-ylthio)-*N*-(4-(3-(5-chloro-2-phenyl-1*H*-indol-3-yl)acryloyl)phenyl) acetamide (8b)

Yield 92% (Ethanol); M. P 220 °C; R_f = 0.59 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1453, 1624, 1741, 2885, 2977, 3251, 3362, 753. ^1H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 4.33 (S, 2H,-CH_2), 7.36-8.19 (m, 18H, 16Ar-H, CH=CH), 10.5 (S, 1H, indole-NH), 11.79 (S, 1H,-NH). MS: m/z = 579 $[M]^+$, 581 $[M+2]^+$(3:1). Analysis: Calcd for $C_{32}H_{22}ClN_3O_2S_2$ (579): C, 66.25; H, 3.82; N, 7.24. Found: C, 66.28; H, 3.81; N, 7.25.

2-(benzo[d]thiazol-2-ylthio)-*N*-(4-(3-(5-methyl-2-phenyl-1*H*-indol-3-yl)acryloyl)phenyl) acetamide (8c)

Yield 84% (Ethanol); M. P 155 °C; R_f = 0.7 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1461, 1648, 1725, 2873, 2997, 3225, 3378. ^1H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 2.40 (S, 3H,-CH_3), 4.32 (S, 2H,-CH_2), 7.21-7.82 (m, 18H, 16Ar-H, CH=CH), 9.88 (S, 1H, indole-NH), 11.37 (S, 1H,-NH). MS: m/z = 559 $[M]^+$. Analysis: Calcd for $C_{33}H_{25}N_3O_2S_2$ (559): C, 70.82; H, 4.50; N, 7.51. Found: C, 70.85; H, 4.49; N, 7.53

2-(benzo[d]thiazol-2-ylthio)-*N*-(4-(3-(5-bromo-1*H*-indol-3-yl)acryloyl)phenyl)acetamide (8d)

Yield 75% (Ethanol); M. P 230 °C; R_f = 0.72 (ethyl acetate/hexane 7:3 v/v) IR (KBr) (λ_{max} in cm^{-1}): 1432, 1644, 1761, 2843, 2917, 3213, 3320, 749. ^1H NMR (DMSO-d_6+$CDCl_3$) δ(ppm): 4.30 (S, 2H,-CH_2), 7.36-8.19 (m, 14H, 12Ar-H, CH=CH), 10.21 (S, 1H, indole-NH), 11.52 (S, 1H,-NH). MS: m/z = 547 $[M]^+$, 549 $[M+2]^+$(1:1). Analysis: Calcd for $C_{26}H_{18}BrN_3O_2S_2$ (547): C, 56.94; H, 3.31; N, 7.66. Found: C, 56.97; H, 3.30; N, 7.68.

Table 1: Physical constant of all the synthesized compounds 3, 4, 5 and 6-8 (a-d)

S. No.	Sample code	R	R^1	M. For.	M. Wt.	M. Pt. °C
1	3	-	-	$C_{17}H_{15}N_3O_2S$	325	210
2	4	-	-	$C_{18}H_{17}N_3O_3S$	355	152
3	5	-	-	$C_{17}H_{14}N_2O_2S_2$	342	130
4	6a	H	H	$C_{26}H_{20}N_4O_2S$	452	218
5	6b	Ph	Cl	$C_{32}H_{23}ClN_4O_2S$	562	190
6	6c	Ph	CH_3	$C_{32}H_{26}N_4O_2S$	542	190
7	6d	H	Br	$C_{26}H_{19}BrN_4O_2S$	530	218
8	7a	H	H	$C_{27}H_{22}N_4O_3S$	482	95
9	7b	Ph	Cl	$C_{33}H_{25}ClN_4O_3S$	592	200
10	7c	Ph	CH_3	$C_{34}H_{28}N_4O_3S$	572	215
11	7d	H	Br	$C_{27}H_{21}BrN_4O_3S$	560	165
12	8a	H	H	$C_{26}H_{19}N_3O_2S_2$	469	150
13	8b	Ph	Cl	$C_{32}H_{22}ClN_3O_2S_2$	579	220
14	8c	Ph	CH_3	$C_{33}H_{25}N_3O_2S_2$	559	155
15	8d	H	Br	$C_{26}H_{18}BrN_3O_2S_2$	547	230

M. for.-Molecular formula, M. wt.-Molecular weight, M. pt.-Melting point.

Biological activities

Antibacterial and antifungal assay

The newly synthesized compounds were screened against bacterial and fungicidal activities by an agar plate diffusion method and potato dextrose agar (PDA) diffusion method respectively [29]. All the compounds were screened for their antibacterial activity against *Escherichia coli* (MTCC-723), *Staphylococcus aureus* (ATCC-29513), and *Pseudomonas aeruginosa* (MTCC-1688), as well as antifungal activity against *Aspergillus niger* (MTCC-281), *Aspergillus flavus* (MTCC-1973), and *Aspergillus oryzae* (MTCC-3567^T). DMSO was used as a vehicle to get the desired concentration of compounds to test upon microbial strains. Streptomycin and fluconazole were used as standards for antibacterial and antifungal activities respectively. The experiment was done in triplicate, and average values were calculated. The results of antibacterial and antifungal are summarized in (table 2) and (table 3) respectively.

Antioxidant activity assay

1, 1-Diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity (RSA)

The free radical scavenging activity (RSA) of all the compounds at concentrations of 25, 50, 75 and 100 µg/ml were carried out in the presence of freshly prepared solution of stable free radical DPPH (0.04% w/v) following Hatano's method[26],using 2-tert-butyl-4-methoxyphenol (butylated hydroxy anisole, BHA), 2-(1,1-dimethyl ethyl)-1,4-benzenediol (2-*tert*-butyl hydroquinone, TBHQ) and ascorbic acid (AA) as standards. All the test analyses were performed on three replicates, and the results were averaged. The results in percentage were expressed as the ratio of absorption decrease of DPPH in the presence of test compounds and absorption of DPPH in the absence of test compounds at λ 517 nm on ELICO SL 171 Mini Spec, spectrophotometer. The percentage scavenging activity of the DPPH free radical was measured using the following equation:

$$\% \text{ of DPPH RSA} = \frac{\text{Absorbance of Control} - \text{Absorbance of Sample}}{\text{Absorbance of Control}} \times 100$$

The results are shown in fig. 1 to 4.

Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP)

The Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of the synthesized compounds were determined according to the literature method [27]. Different concentrations of samples (25, 50, 75 and 100 µg/ml) in DMSO (1 ml) were mixed with phosphate buffer (2.5 ml, 0.2 mol, pH=6.6) and potassium ferricyanide (2.5 ml, 1%). The mixture was incubated at 50^0C for 20 min. After which a portion of trichloroacetic acid (2.5 ml, 10%) was added to the mixture and centrifuged for 10 min, at 1000 Xg. The upper layer of solution (2.5 ml) was mixed with distilled water (2.5 ml) and ferric chloride (0.5 ml, 0.1 %). Then absorbance at λ 700 nm was measured in a spectrophotometer. The higher absorbance of the reaction mixture indicated greater reducing power. The results are shown in fig. 5 to 8.

Ferrous (Fe^{2+}) metal ion chelating activity

The chelating activity of ferrous ion of synthesized compounds was estimated by following reported method [28]. The test samples (25, 50, 75 and 100 µg/ml) in ethanolic solution (0.4 ml) were added to a solution of $FeCl_2$ (0.05 ml, 2 mmol). The reaction was initiated by the addition of ferrozine (0.2 ml, 5 mmol) and the total volume was adjusted to 4 ml with ethanol. Ferozine reacted with the divalent iron, form stable magenta complex species that were very soluble in water. The mixture was shaken vigorously and kept at room temperature for 10 min. Then the absorbance of the solution was measured spectrophotometrically at λ 562 nm. All test analyses were run in triplicate and averaged. The percentage of inhibition of the ferrozine Fe^{2+} complex formation was calculated using the following formula:

$$\% \text{ of ferrousion chelating} = \frac{\text{Absorbance of Control} - \text{Absorbance of Sample}}{\text{Absorbance of Control}} \times [10]^{\circ}$$

The control contains $FeCl_2$ and ferrozine, complex formation molecule. The results are shown in fig. 9 to 12.

RESULTS AND DISCUSSION

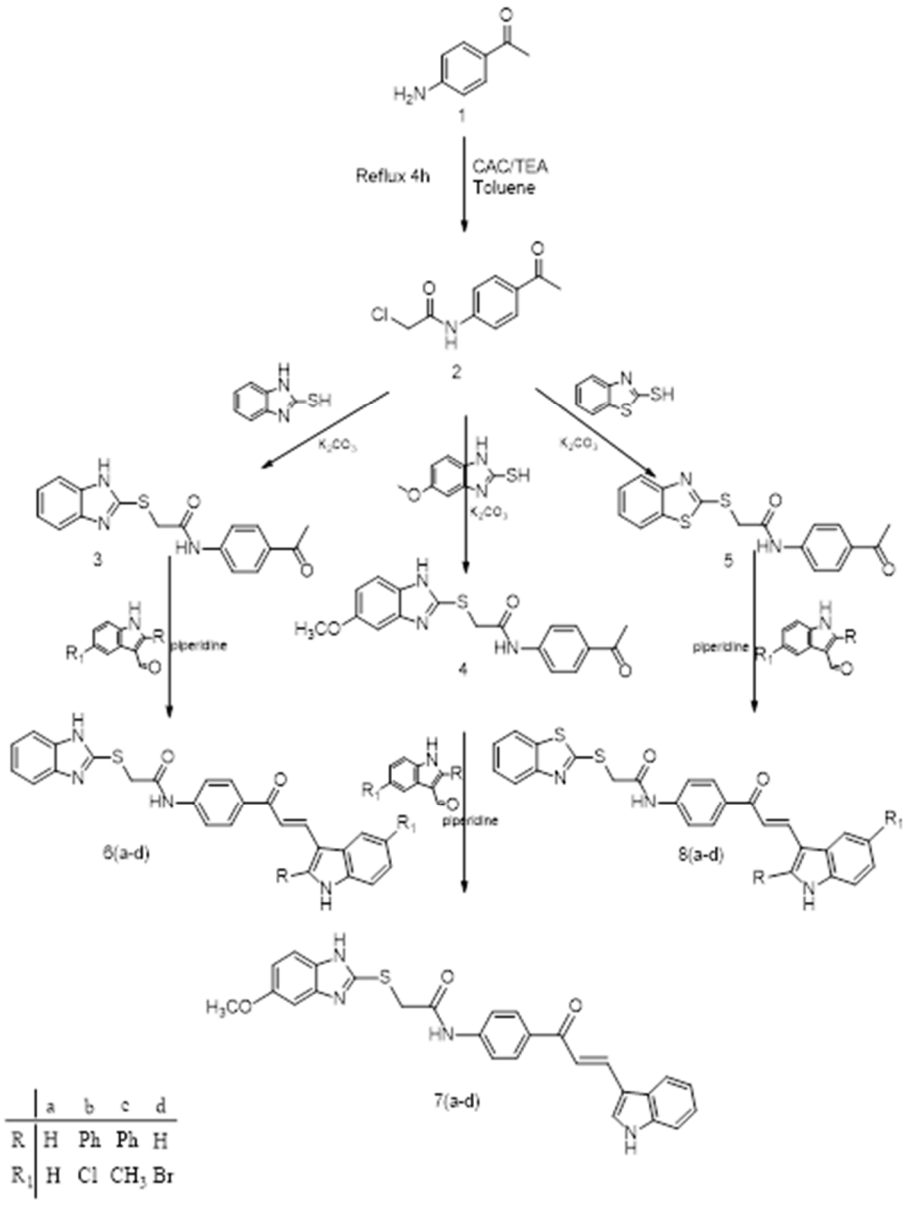
Chemistry

In the present investigation, 4-aminoacetophenone (1) was reacted with chloroacetylchloride to form an intermediate *N*-(4-acetylphenyl)-2-chloroacetamide (2), which on reaction with 2-mercatobenzimidazole, 2-mercapto-5-methoxy benzimidazole and 2-mercapto benzothiazole, resulted in the formation of 2-(1*H*-benzo[d]imidazole-2-ylthio)*N*-(4-acetylphenyl)acetamide (3), *N*-(4-acetylphenyl)-2-((5-methoxy-1*H*-benzo[d]imidazol-2-yl)thio)acetamide (4) and *N*-(4-acetylphenyl)-2-(benzo[d]thiazol-2-ylthio)acetamide (5) respectively by following the literature method [25].

Compound 3, 4 and 5 on Claisen–Schmidt condensation with various 2,5-disubstituted indole-3-carboxaldehydes were refluxed in ethanol in the presence of piperidine to yield the products 2-((1*H*-benzo[d]imidazol-2-yl)thio)-*N*-(4-(3-(1*H*-indol-3-yl)acryloyl) phenyl)acetamide 6a-d, *N*-(4-(3-(1*H*-indol-3-yl)acryloyl) phenyl)-2-((5-methoxy-1*H*-benzo[d]imidazol-2-yl)thio)acetamide 7a-d and *N*-(4-(3-(1*H*-indol-3-yl)acryloyl)phenyl)-2-(benzo [d] thiazol-2-ylthio) acetamide 8a-d respectively as presented in scheme-1.

The physical data of the compounds were presented in table-1. The structures of the compounds were confirmed by IR, ^{1}H NMR, mass spectral studies and elemental data. The IR spectrum of 6a exhibited absorption band at 3523 cm^{-1}, 3390 cm^{-1} and 3220 $cm^{-1}$for NH stretching frequency of indole, benzimidazole and amide respectively. The absorption band at 1691 $cm^{-1}$and 1646 cm^{-1}corresponds to C=O stretching of carbonyl and amide. In the ^{1}HNMR spectrum, the compound 6a showed a singlet peaks at 11.93, 10.95 and 9.56 ppm ascribed to NH protons of benzimidazole, amide and indole respectively.

In addition to this, eleven aromatic protons and two protons of CH=CH resonated as a multiplet in the region 7.31-8.13 ppm. The singlet at 4.32 ppm is due to the two protons of a methylene group. Further, the mass spectrum of 6a showed a molecular ion peak M^+at m/z 452, which confirms its molecular weight and is in good agreement with nitrogen rule.



Scheme 1: Synthesis of compounds 3, 4, 5 and 6-8 (a-d)

Table 2: Antibacterial activity, size of inhibition zone (mm) formed at different concentrations (1000, 500, 250 and 125 µg/ml) of synthesized compounds 3, 4, 5 and 6-8 (a-d)

Compound	Zone of inhibition in mm											
	Staphylococcus aureus				*Escherichia coli*				*Pseudomonas aeruginosa*			
	1000	500	250	125	1000	500	250	125	1000	500	250	125
3	9.33±0.47	8.66±0.47	8.00±0.81	7.66±0.94	10.33±0.47	11.66±0.94	9.66±0.47	7.66±0.47	8±0.81	07.33±0.47	07.33±0.47	07.33±0.94
4	10.33±0.47	8.66±0.47	10.66±0.47	10.33±0.47	11.33±1.24	10.33±0.47	10.66±0.47	9.33±0.47	10.33±1.24	10.66±1.24	10.66±0.47	9.33±0.47
5	10.66±0.47	8.00±0.81	9.66±0.47	7.66±0.94	10.33±0.47	9.66±0.47	7.66±0.47	8±0.81	8.66±0.47	8.00±0.81	07.33±0.94	9.33±0.47
6a	10.33±1.24	10.66±0.47	10.66±0.47	10.33±0.47	11.33±1.24	11.66±0.94	10.66±0.47	9.33±0.47	9.33±0.47	07.33±0.94	9.66±0.47	9.66±0.47
6b	12.33±0.47	11.66±0.47	12.66±0.47	12.66±0.47	12.66±0.47	12.66±0.47	11.66±0.47	12±0.81	12±0.81	11.66±0.47	11.66±0.47	12.66±0.47
6c	12±0.81	11.66±0.47	10.33±0.47	9.66±0.47	10.66±0.47	11.66±0.47	11.66±0.47	12.33±0.47	10.66±0.47	12.33±0.47	12.33±0.47	10.66±0.47
6d	12.33±0.47	13.33±0.94	14.33±0.47	13.33±0.94	12.66±0.47	12.66±0.47	12.33±0.47	13.33±0.94	14.33±0.47	12.33±0.47	13.33±0.94	12.33±0.47
7a	12.33±0.47	11.66±0.47	10.66±0.47	12.33±0.47	10.66±0.47	11.66±0.47	12±0.81	12.33±0.47	10.66±0.47	12.66±0.47	10.66±0.47	11.66±0.47
7b	12.66±0.47	11.66±0.47	13.33±0.94	13.33±0.94	10.66±0.47	12.66±0.47	12±0.81	12.66±0.47	11.66±0.47	12.33±0.47	13.33±0.94	12.33±0.47
7c	12.33±0.47	10.66±0.47	10.66±0.47	12±0.81	11.66±0.47	10.66±0.47	12.33±0.47	12.66±0.47	11.66±0.47	11.66±0.47	10.66±0.47	10.66±0.47
7d	14.33±0.47	15.33±0.47	15.66±0.47	15.33±0.47	15.66±0.47	14.66±1.24	14.33±0.47	14.66±1.24	15.33±0.47	15.66±0.47	15.66±0.47	15.33±0.47
8a	15.33±0.47	12.66±0.47	13.33±0.94	13.33±0.94	13.33±0.94	13.33±0.94	10.66±0.47	12.33±0.47	13.33±0.94	13.33±0.94	12.66±0.47	12.66±0.47
8b	14.33±0.47	13.33±0.94	12.33±0.47	12.66±0.47	12.33±0.47	14.33±0.47	14.33±0.47	12.33±0.47	12±0.81	11.66±0.47	12.66±0.47	14.33±0.47
8c	10.66±0.47	9.33±0.47	10.66±0.47	10.66±0.47	11.33±1.24	10.33±0.47	9.33±0.47	10.66±0.47	11.66±0.47	10.66±0.47	10.66±0.47	12.33±0.47
8d	15.33±0.47	15.66±0.47	15.33±0.47	16.66±1.24	16.66±1.24	16.66±1.24	15±0.81	15.33±0.47	14.66±1.24	14.66±0.47	14.66±0.47	14.33±0.47
Streptomycin	15.66±0.47	16.33±0.47	15.66±0.47	16.66±0.94	17±0.81	15±0.81	15.33±0.47	15.66±0.47	14.33±0.47	15.33±0.47	15.66±0.47	14.66±0.47

Note: Values are expressed as mean±SD (n=3)

Table 3: Antifungal activity, size of inhibition zone (mm) formed at different concentrations (1000, 500, 250 and 125 µg/ml) of synthesized compounds 3, 4, 5 and 6-8 (a-d)

Compound	Zone of inhibition in mm											
	Aspergillus nizer				*Aspergillus flavus*				*Aspergillus oryzae*			
	1000	500	250	125	1000	500	250	125	1000	500	250	125
3	12.33±0.47	10.33±1.24	7.66±0.94	6.66±0.94	9.33±0.47	9.66±0.47	9.33±0.47	7.66±0.94	9.33±0.47	9.33±0.47	8±0.81	7.66±0.94
4	10.66±0.47	9.33±0.47	7.66±0.94	7.66±0.94	9.33±0.47	9.33±0.47	7±0.81	6.66±0.94	8±0.81	7.66±0.94	9.33±0.47	6.33±0.94
5	9.33±0.47	9.33±0.47	7.66±0.94	6.66±0.94	7.66±0.94	7.66±0.94	7.66±0.94	6.33±0.94	9.33±0.47	7.66±0.94	6.66±0.94	6.66±0.94
6a	13.33±0.94	10.33±1.24	9.33±0.47	9.33±0.47	9.66±0.47	12.66±0.47	9.66±0.47	12.33±0.47	10.33±1.24	10.66±0.47	9.33±0.47	12.33±0.47
6b	14.33±0.47	14.33±0.47	13.33±0.94	12.66±0.47	14.33±0.91	13.33±0.94	14.33±0.91	14.33±0.47	14.33±0.47	14.33±0.47	14.33±0.47	14.33±0.47
6c	13.33±0.94	13.33±0.94	12.33±0.47	12.33±0.47	12.33±0.47	10.33±1.24	12.66±0.47	12.33±0.47	13.33±0.94	12.66±0.47	10.66±0.47	10.33±0.47
6d	10.66±0.47	12.66±0.47	10.66±0.47	13.66±0.94	10.66±0.47	12.66±0.47	12.66±0.91	13.33±0.94	13.33±0.94	12.66±0.47	12.33±0.47	13.33±0.47
7a	14.33±0.47	12.33±0.47	13.33±0.94	13.33±0.94	13.33±0.94	12.33±0.47	10.66±0.47	12.33±0.47	12.66±0.47	10.33±1.24	10.33±0.47	13.33±0.94
7b	13.33±0.94	12.66±0.47	10.66±0.47	12.66±0.91	12.66±0.47	12.33±0.47	10.66±0.91	14.33±0.47	13.33±0.47	10.66±0.47	10.66±0.47	12.33±0.47
7c	12.33±0.47	10.33±1.24	10.66±0.47	12.33±0.47	12.33±0.47	12.66±0.47	10.33±0.47	13.33±0.94	13.33±0.94	12.33±0.47	9.33±0.47	12.66±0.47
7d	15.66±0.47	14.66±0.47	13.33±0.94	13.33±0.94	14.66±0.47	14.33±0.47	14.33±0.91	14.33±0.47	15.66±0.47	15.66±0.47	14.33±0.47	14.33±0.47
8a	14.66±0.47	13.33±0.94	12.33±0.47	12.33±0.47	13.33±0.94	12.66±0.47	13.33±0.94	12.33±0.47	14.33±0.47	14.33±0.47	12.33±0.47	12.66±0.47
8b	13.33±0.94	10.33±0.47	10.33±1.24	13.33±0.94	10.66±0.47	12.66±0.47	13.33±0.47	12.33±0.47	13.33±0.94	13.33±0.94	9.66±0.47	12.66±0.47
8c	12.33±0.47	12.66±0.47	12.66±0.47	12.33±0.47	12.66±0.47	12.66±0.47	13.33±0.94	13.33±0.94	13.33±0.94	14.33±0.47	14.33±0.47	14.66±0.47
8d	14.66±0.47	14.33±0.47	14.33±0.47	14.33±0.47	15.66±0.47	14.33±0.47	14.66±0.47	14.33±0.47	15.66±0.47	15.33±0.47	15.33±0.47	14.66±0.47
Fluconazole	15.66±0.47	15.33±0.94	14.66±0.47	14.66±0.91	16.33±0.47	15±0.81	15.33±0.47	14.33±0.47	16.66±0.94	15.66±0.47	15.66±0.47	15.66±0.47

Note: Values are expressed as mean±SD (n=3)

Antimicrobial activity

The analysis of antibacterial screening (table 2) revealed that all compounds tested, have moderate to high antibacterial activity as compared to the standard drug streptomycin. These results are better in comparison with the earlier reported ones, this might be because of the presence of benzimidazole ring and amide group in addition to the indole ring [7]. The molecules 6d (the molecule having bromo substitution at 5th position of indole ring), 8b (chloro substitution at 5th position of indole ring) and 8d (Bromo substitution at 5th position of indole ring) showed excellent antibacterial activity against the tested microorganism *S. aureus* (ATCC-29513). The compounds 7d (bromo substitution at 5th position of indole ring and methoxy substitution at 5th position of benzimidazole ring) and 8d (bromo substitution at 5th position of indole ring) have exhibited good activity against *E. coli* (MTCC-723). Whereas, the compounds 6d (bromo substitution at 5th position of indole ring), 7d (bromo substitution at 5th position of indole ring and methoxy substitution at 5th position of benzimidazole ring), 8a (the molecule possesses indole and benzothiazole rings) and 8d (bromo substitution at 5th position of indole ring) displayed good activity against *P. aeruginosa* (MTCC-1688).

On the other hand, the antifungal activity results (table 3) discovered that, the compounds 6b (the molecule having chloro substitution at 5th position of indole ring), 7d (bromo substitution at 5th position of indole ring and methoxy substitution at 5th position of benzimidazole ring) and 8d (bromo substitution at 5th position of indole ring) have revealed profound activity against *A. niger* (MTCC-281), *A. flavus* (MTCC-1782) and *A. oryzae* (MTCC-3567T).

The rest of the compounds were found to exhibit moderate activity against the bacterial or fungal strains.

Antioxidant activities

1, 1-Diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity (RSA)

In vitro method of scavenging of the stable DPPH radical is extensively used to evaluate the antioxidant activity in less time than other methods. DPPH is a stable free radical that can accept hydrogen radical or an electron and must thus be converted to a stable diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517 nm. When this electron becomes paired off, the absorption decreases stoichiometrically with respect to the number of electrons or hydrogen atoms taken up. The DPPH antioxidant assay measures the hydrogen donating capacity of the molecules under study. When the free-radical DPPH is reduced by the sample, its colour changes from violet to yellow. The results (fig. 1 to 4) suggested that compounds 6b, 8a and 8b showed promising RSA at all concentrations. Compounds 3, 6b, 8a, 8b and 8c were found to enhance the RSA 52.07, 62.13, 57.39, 56.80 and 56.80 % respectively at conc. 25 µg/ml. Compounds 6b, 8a, 8b and 8c showed good activity i. e; 65.38, 61.24, 61.83 and 62.42% respectively at conc. 50 µg/ml and 68.34, 70.71, 67.15 and 64.79 % respectively at conc. 75 µg/ml. Compound 5, 6b, 7a, 7b, 8a and 8b showed promising activity i. e; 71.00, 72.18, 70.71, 73.66, 73.96 and 72.78 % respectively at conc. 100 µg/ml. Among all the synthesized compounds, compound 6b exhibited the highest activity at all the concentrations this may be due to the presence of chlorine substituent at 5th position of the indole ring. The rest of the compounds were found to enhance the RSA to a lesser extent. However, none of the compounds exhibited better RSA than the standard.

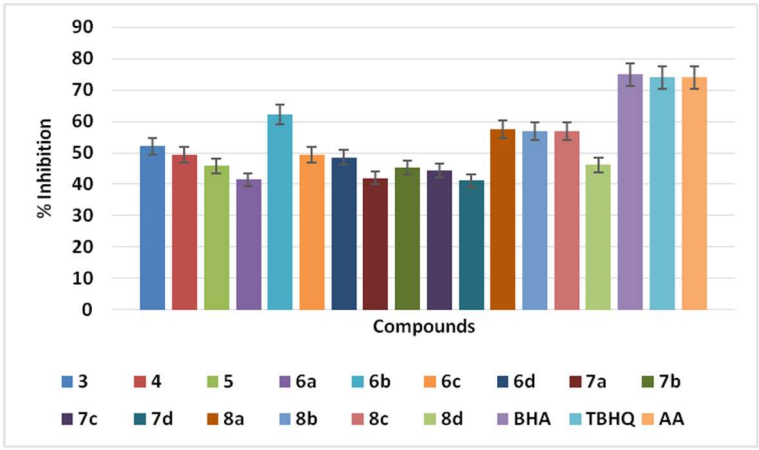


Fig. 1: DPPH radical scavenging activity of synthesized compounds at conc. 25 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

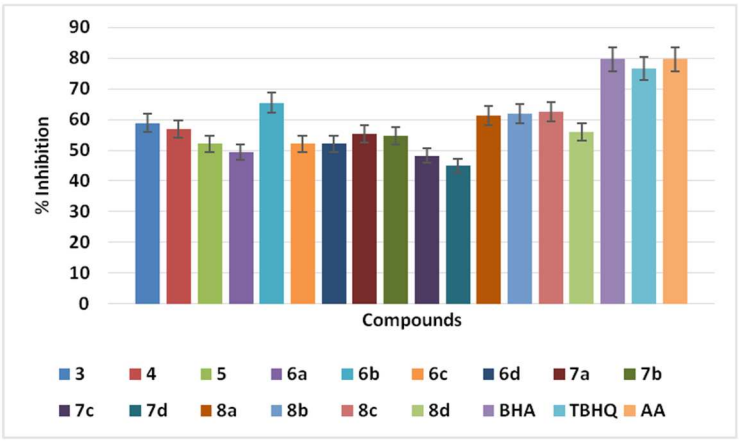


Fig. 2: DPPH radical scavenging activity of synthesized compounds at conc. 50 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

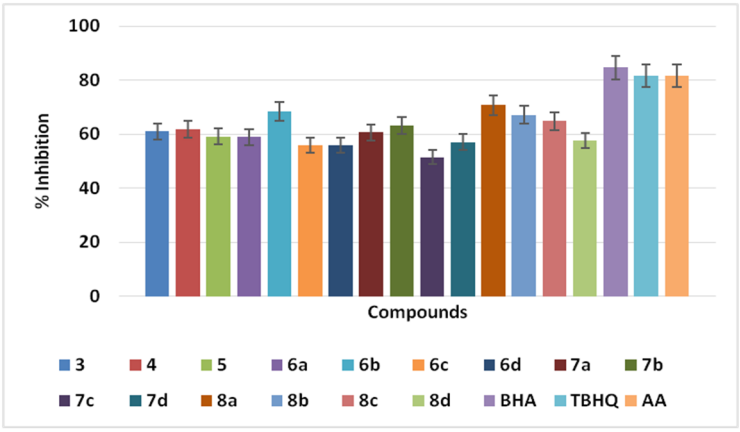


Fig. 3: DPPH radical scavenging activity of synthesized compounds at conc. 75 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01-significant compared to the standard group

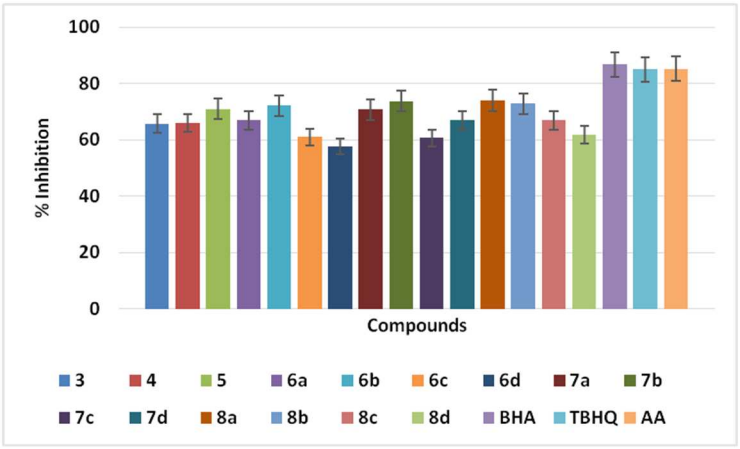


Fig. 4: DPPH radical scavenging activity of synthesized compounds at conc. 100 µg/ml. The graph represents the mean±SEM, (n=3), P<0.01-significant compared to the standard group

Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP)

The FRAP results (fig. 5 to 8) suggested that, the compounds 7a-d and 8b-d showed good absorbance 0.893, 0.911, 0.894, 0.894, 0.874, 0.851, and 0.831 nm at concentration 100 µg/ml, indicating that these compounds have good ferric ions (Fe^{3+}) reducing antioxidant power at concentrations of 100 µg/ml. In other words, these compounds showed the ability of electron donor to scavenge free radicals. Among the synthesized compounds 7a-d have exhibited highest ferric ions (Fe^{3+}) reducing antioxidant power at concentration 100 µg/ml. This may be due to the presence of methoxy substituent at 5-position of benzimidazole ring. The rest of the compounds showed lower absorbance as related to the standards. The higher the absorbance of the compounds indicated greater reducing power.

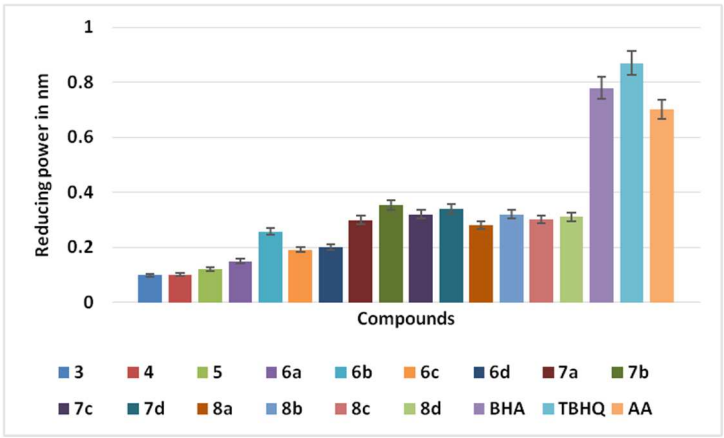


Fig. 5: Reducing power activity of synthesized compounds at conc. 25 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01-significant compared to the standard group

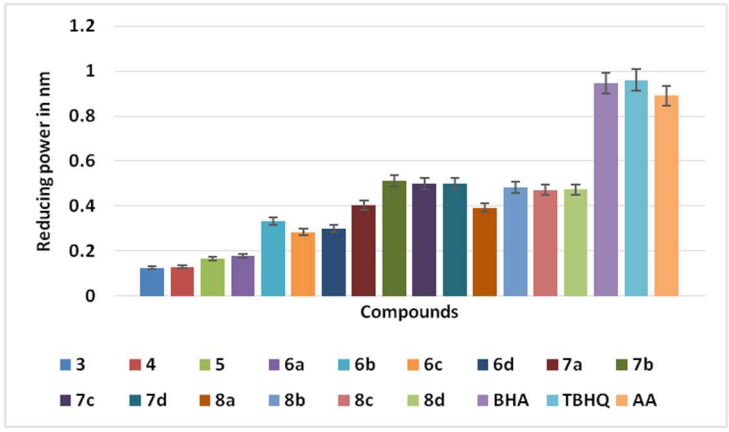


Fig. 6: Reducing power activity of synthesized compounds at conc. 50 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

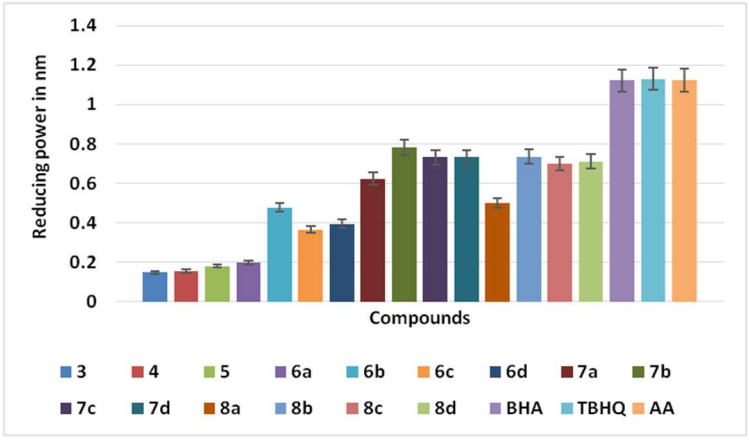


Fig. 7: Reducing power activity of synthesized compounds at conc. 75 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

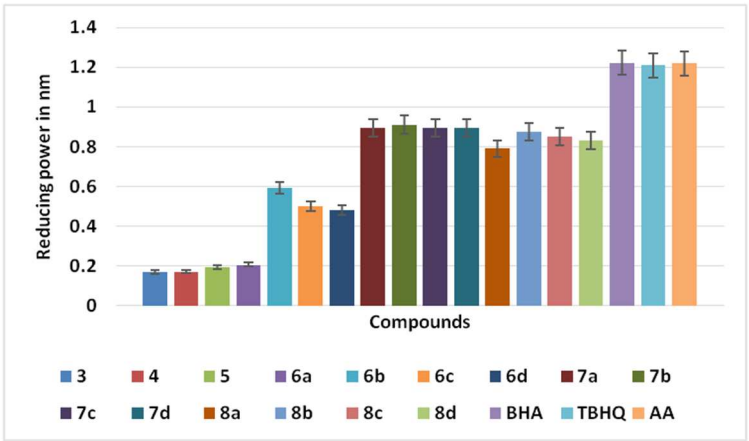


Fig. 8: Reducing power activity of synthesized compounds at conc. 100 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

Ferrous (Fe^{2+}) metal ion chelating activity

Ferrous (Fe^{2+}) metal ion chelating activity results (fig. 9 to 12) revealed that synthesized compounds obstructed the formation of ferrous and ferrozine complex. Compounds 6b, 7b, 7d, 8b and 8d exhibited (69.75, 75.00, 74.38, 78.08 and 75.61%) good metal chelating activity at concentration of 100 µg/ml. Compound 7c and 8c also showed the highest (69.44 and 73.76 %) metal chelating activity at concentration 100 µg/ml. This may be due to the presence of a chlorine/bromine atom at 5-position of the indole ring and methoxy substituent 5-position of benzimidazole ring. The highest metal chelating activity of these compounds indicates that these compounds are able to capture ferrous ion before ferrozine. This might be the reason for the higher metal chelating activity. The rest of the compounds showed reasonable to less activity when compared with the standard drugs.

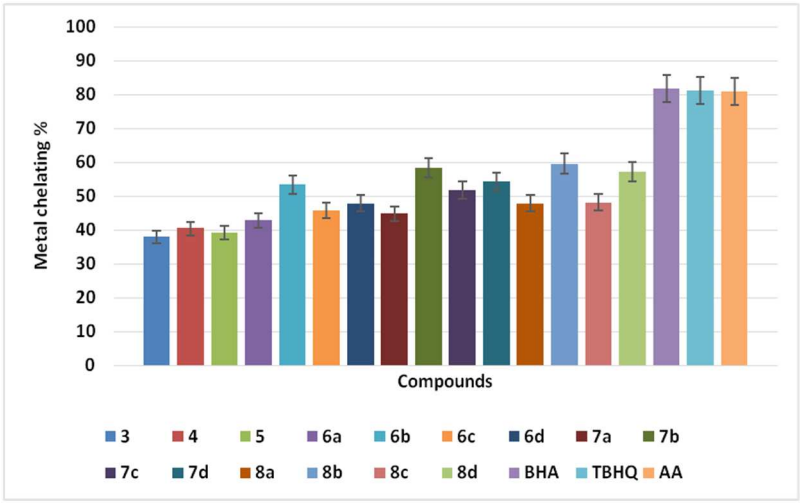


Fig. 9: Metal chelating activity of synthesized compounds at conc. 25 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

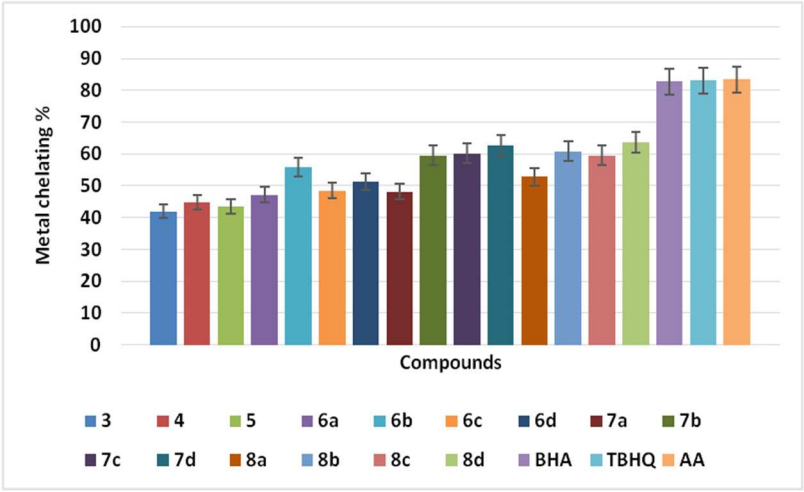


Fig. 10: Metal chelating activity of synthesized compounds at conc. 50 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

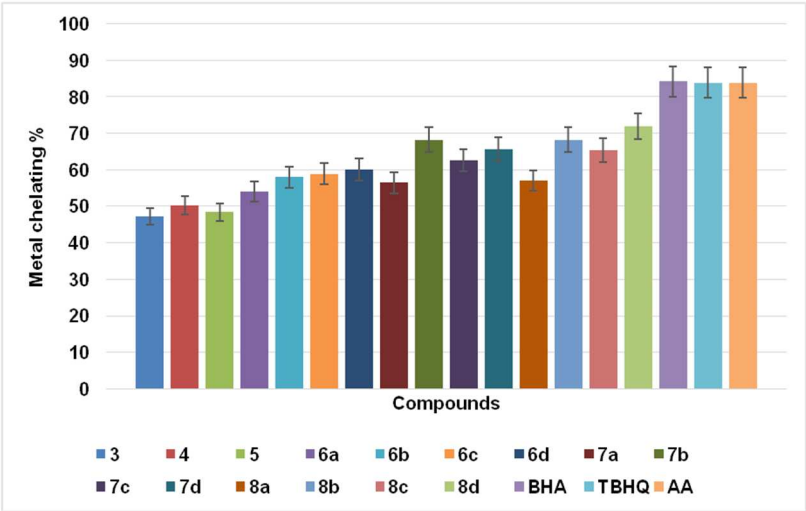


Fig. 11: Metal chelating activity of synthesized compounds at conc. 75 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

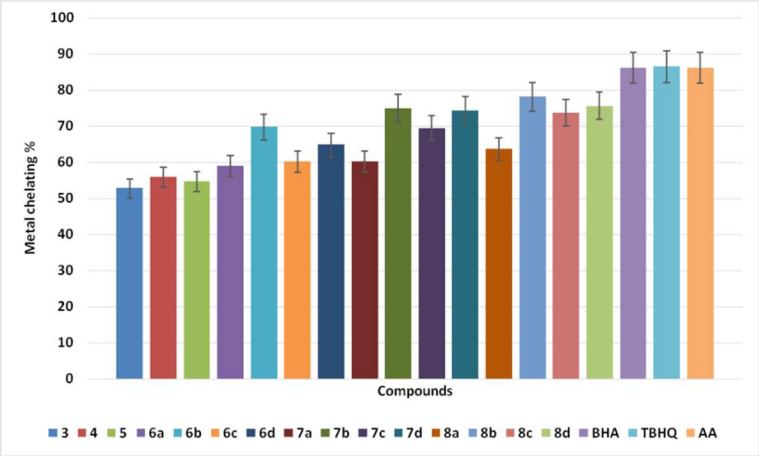


Fig. 12: Metal chelating activity of synthesized compounds at conc. 100 µg/ml, The graph represents the mean±SEM, (n=3), P<0.01- significant compared to the standard group

CONCLUSION

The title compound of indole derivatives attached with benzimidazole/benzothiazole were synthesised and characterized by spectral and analytical data. All the compounds were subjected for antimicrobial, antifungal and antioxidant screening. We found that compounds 6b, 6d, 7a, 7d, 8a-b and 8d are active towards antibacterial and antifungal strains. Compounds 6b, 7a-d and 8a-d, showed potent antioxidant activity compared to the standard. These studies may promote further expansion of the indole derivatives bearing benzimidazole/benzothiazole moieties, which may lead to compounds with potent antioxidant and antimicrobial activities. Based on these results, selected novel compounds are being screened *in vivo* which will be reported in due course.

AUTHORS CONTRIBUTION

J. S. Biradar the corresponding author made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data.

Author carried out the experimental part, conducting the pharmacological evaluation, drafting the article and revising it critically for important intellectual content.

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CONFLICT OF INTERESTS

Declared none

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