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Green Approach to the Synthesis of New Indole and Benzimidazole Analogs and Their Biological Evaluation

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Abstract—To obtain new lead compounds with potent antimicrobial and antioxidant activities, new indole analogs containing various heterocyclic moieties were synthesized by a rapid, facile, eco-friendly, cost-effective, and efficient method under microwave irradiation. Their structures were determined on the basis of their spectral and elemental analysis data. The compounds were evaluated for their in vitro antimicrobial and antioxidant activities. Some of the compounds revealed good antimicrobial and antioxidant activities. The structure–activity relationship (SAR) study revealed that the most active are compounds containing a substituent at the 5-position of indole.

Keywords: green synthesis, solvent-free reaction, microwave irradiation, indole, benzimidazole, thiazolidinone, azetidinone, thioethers, antimicrobial activity, antioxidant activity

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INTRODUCTION

Green chemistry (GC) addresses our future challenges in working with chemical processes and products by using methods that can maximize the desired products and minimize by-products, simplify operations in chemical production, and use environmentally benign solvents. The concept of green chemistry has emerged in the early 1990s and is now widely used to meet the major scientific challenges concerned with protecting the human health and the environment while simultaneously achieving commercial feasibility. Nonclassical methods following the GC principles reduce or even eradicate the production of harmful substances and increase product yield. Microwave (MW)-assisted synthesis is one of the important GC techniques used during the recent years. The ability of MW-assisted reactions to rapidly synthesize organic compounds is of major benefit for library generation. Moreover, MW-assisted synthesis allows modifications of selectivity (chemo-, regio-, and stereoselectivity) and the use of solvent-free and catalyst-free conditions [1–4].

In the past few decades, the synthesis of heterocyclic compounds has played a significant role in medicinal chemistry, and many advances have been achieved in the practical aspects, including novel synthetic strategies and methods and analytical techniques. Benzimidazole derivatives are associated with various types of pharmacological properties. Benzimidazole is one of the most bioactive heterocyclic compounds that exhibit a wide range of biological activities. Specifically, benzimidazole nucleus is a constituent of vitamin B_{12} [5] and many other pharmacologically active compounds [6–9]. Some examples of clinically approved drugs are shown in Fig. 1.

It is well known that indole moiety is probably the most widely spread nitrogen heterocycle in nature and that it is very important for its medicinal and biological aspects. Indole derivatives have been found to possess pharmacological and chemotherapeutic properties such as anticancer, antidiabetic, anti-inflammatory, antimalarial, antibacterial, antifungal, antiviral, etc. [1–4, 10–15]. Thiazolidin-4-ones and azetidinones also play an important role in medicinal chemistry [2]; several analogs of these compounds have been extensively studied due to their ready accessibility, diverse chemical reactivity, and broad spectrum of biological properties.

In view of the literature reports and the wide application of benzimidazole drugs for the treatment of various diseases, herein we describe the microwave-assisted synthesis of benzimidazole derivatives containing an indole fragment in combination with thiazolidinone, triazole, azetidinone, or thioether moiety with the goal of obtaining compounds with better biological activities.

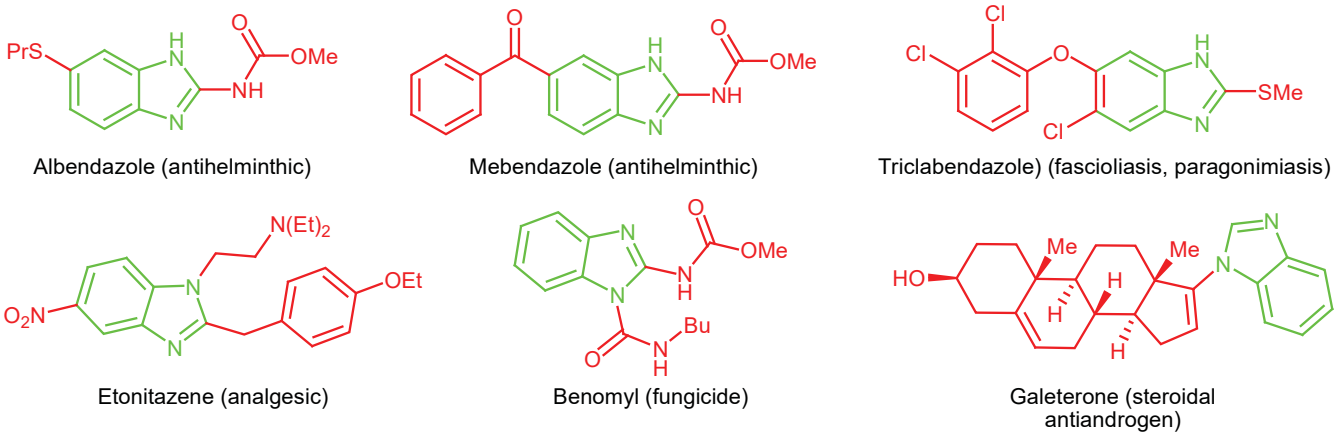


Fig. 1. Some of clinically used drugs containing a benzimidazole moiety.

RESULTS AND DISCUSSION

In the present study, we were interested in using ecofriendly reagents and methods and avoiding the use of organic solvents to meet the GC principles. The target indolyl benzimidazole analogs were synthesized in two steps as outlined in Scheme 1. In the first step, hydrazones **3a**–**3d** were prepared by reacting 2,5-substituted 1*H*-indole-3-carbaldehydes **1a**–**1d** and an equimolar amount of 2-hydrazinyl-1*H*-benzimidazole (**2**) in ethanol in the presence of glacial acetic acid. Hydrazones **3a**–**3d** were cyclized with thioglycolic acid in the presence of anhydrous zinc chloride to produce thiazolidin-4-one derivatives **4a**–**4d**. Cyclocondensation of **3a**–**3d** in acetic anhydride under reflux afforded [1,2,4]triazolo[4,3-*b*]benzimidazole derivatives **5a**–**5d**. Azetidinone derivatives **6a**–**6d** were obtained by cyclization of **3a**–**3d** with chloroacetyl chloride in 1,4-dioxane. Finally, treatment of **3a**–**3d** with 1*H*-benzimidazole-2-thiol furnished thioether derivatives **7a**–**7d**.

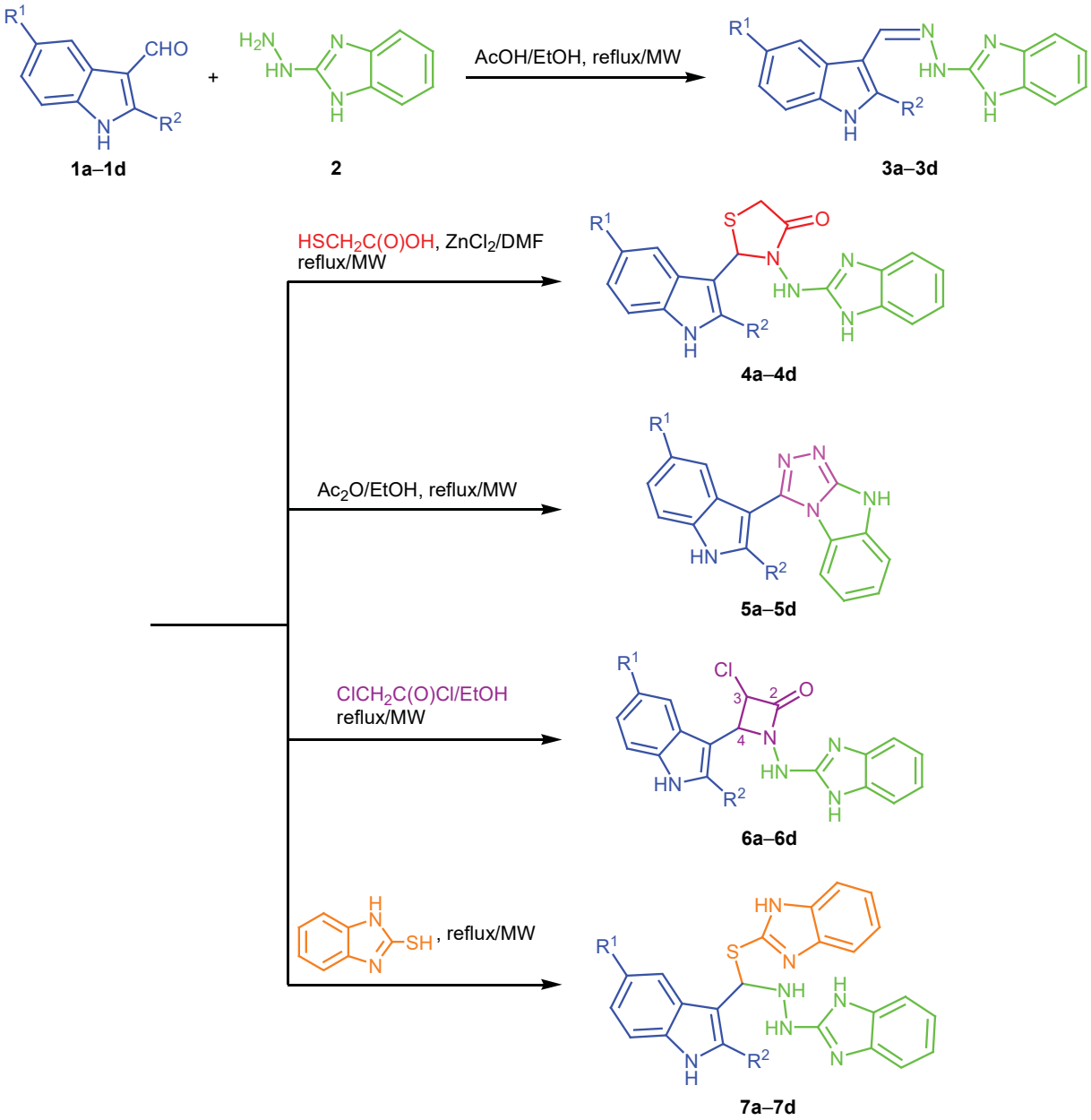
All these reactions were carried out under both conventional heating conditions and microwave irradiation. The conventional syntheses gave the corresponding products in low yields with moderate purity and suffered from many disadvantages such as the use of solvent, long reaction time, and lengthy workup process. In contrast, MW irradiation provided a rapid, economical, and environmentally benign procedure, and the target compounds were obtained in excellent yields with high purity (Table 1).

All compounds **3**–**7** are stable solids soluble in DMSO in room temperature. Their structure was confirmed by FT-IR, ^{1}H and ^{13}C NMR, and mass spectra. The IR spectrum of **3a** showed absorption peaks at 3423, 3238, and 3106 cm^{-1} due to indole, imidazole, and hydrazine N–H stretchings, respectively, a peak at 2926 cm^{-1} due to aromatic C–H bond vibrations, and a peak at 1704 cm^{-1} due to CH=N imine bond. Other peaks at 1457 and 509 cm^{-1} were assigned to C=N and C–Cl bonds, respectively. The ^{1}H NMR spectrum of **3a** showed a singlet at δ 2.06 ppm (1H, NH), a multiplet at δ 6.55–7.30 ppm (12H, H_{arom}), a singlet at δ 9.66 ppm (NH, imidazole), and a singlet at δ 10.09 ppm (NH, indole). The ^{13}C NMR spectrum of **3a** displayed signals at δ_C 112, 113, 120, 123, 126, 129, 130, 134, and 150 due to aromatic carbons, and the most deshielded imine carbon resonated at δ_C 185 ppm. The mass spectrum of **3a** contained the doublet molecular ion peak at *m*/*z* 383/385 (I_{rel} 100/33%) with the intensity ratio (3:1) corresponding to the presence of one chlorine atom in its molecule.

The IR spectrum of **4a** showed absorption bands at 3400, 3383, and 3080 cm^{-1} due to N–H stretchings and a carbonyl band at 1654 cm^{-1}. Other peaks at 1520, 602, and 498 cm^{-1} were assigned to the C=N, C–Cl, C–S–C bonds, respectively. The ^{1}H NMR spectrum of **4a** showed a singlet at δ 2.57 ppm (1H, NH), a singlet at δ 4.37 ppm (2H, CH_2) due to methylene protons of the thiazolidine ring, a singlet at δ 5.99 ppm (1H) due to the SCHN proton of thiazolidinone, a multiplet between δ 6.98–7.42 (12H, H_{arom}), and singlets at δ 8.65 and 9.89 ppm due to imidazole and indole NH protons, respectively. The ^{13}C NMR spectrum of **4a** showed signals at δ_C 107, 112, 113, 114, 115, 116, 120, 123, 121, 126, 129, 130, 134, 135, 149, and 150 ppm due to aromatic carbons and downfield signals at δ_C 154 (C^2, thiazolidine) and 185 ppm (C=O). The mass spectrum of **4a** showed the doublet molecular ion peak at *m*/*z* 459/461 (I_{rel} 45/15%).

The spectral data for the other compounds were consistent with their structure. In particular, in the ^{13}C NMR spectrum of **5a**, the most deshielded carbons

Scheme 1.



1a–1d **2** **3a–3d** **4a–4d** **5a–5d** **6a–6d** **7a–7d**

R^1 = Cl, R^2 = Ph (**a**); R^1 = Me, R^2 = Ph (**b**); R^1 = H, R^2 = Ph (**c**); R^1 = R^2 = H (**d**).

attached to three nitrogen atoms appeared at δ_C 149 and 151 ppm. The IR spectrum of **6a** showed a peak at 1684 cm^{-1} due to carbonyl group and two peaks at 730 and 704 cm^{-1} due to C–Cl stretching vibrations. The ^1H NMR spectrum of **6a** displayed signals at δ 4.59 and 5.46 ppm for protons in the azetidinone ring, and the corresponding carbon signals were observed in the ^{13}C NMR spectrum at δ_C 58 and 66 ppm together with the carbonyl carbon signal at δ_C 181 ppm. The mass spectrum of **6a** contained the molecular ion triplet at *m*/z 461/463/465 with an intensity ratio of 9:6:1, which corresponded to the presence of two chlorine atoms in its molecule. The absorption band at 689 cm^{-1} in the IR spectrum of **7a** was assigned to the C–S bond, and the CH–S fragment of **7a** gave signals at δ 4.38 and δ_C 70 ppm in the NMR spectra.

In vitro antimicrobial activity. The newly synthesized compounds were screened for their in vitro antibacterial activity against *Staphylococcus aureus* (ATCC 29513), *Pseudomonas aeruginosa* (MTCC 1688), *Escherichia coli* (MTCC 723), *Klebsiella pneumoniae* (NCTC 13368), and *Salmonella typhi*

Table 1. Synthesis of compounds **3**–**7** under conventional heating and microwave irradiation conditions

Compound no.	Conventional heating			Microwave irradiation			mp, °C
	time, min	temperature, °C	yield,[a] %	time, min	power, W	yield,[a] %	
3a	360	75–85	55	5	350	95	148–149
3b	360	75–85	50	5	350	92	202–203
3c	360	75–85	45	5	350	90	179–180
3d	360	75–85	40	5	350	85	210–211
4a	720	170–175	69	6	490	92	151–152
4b	720	170–175	66	6	490	90	205–206
4c	720	170–175	55	6	490	88	214–215
4d	720	170–175	50	6	490	80	207–208
5a	200	80–90	57	4	360	80	145–146
5b	200	80–90	55	4	360	75	181–182
5c	200	80–90	50	4	360	75	220–221
5d	200	80–90	45	4	360	70	201–202
6a	150	80–90	68	4	360	90	221–223
6b	150	80–90	65	4	360	88	205–208
6c	150	80–90	55	4	360	85	131–133
6d	150	80–90	50	4	360	78	124–126
7a	120	150–160	59	5	450	94	228–230
7b	120	150–160	55	5	450	92	178–180
7c	120	150–160	48	5	450	90	174–176
7d	120	150–160	40	5	450	88	166–168

[a] Yield refers to isolated pure compound.

(ATCC 23564) and antifungal activity against *Aspergillus oryzae* (MTCC 3567T), *Aspergillus terreus* (MTCC 1782), *Aspergillus niger* (MTCC 281), and *Aspergillus flavus* (MTCC 1973) by the cup-plate method as reported in [10, 11]. All tested compounds showed moderate to high antibacterial activity as compared to the standard drug streptomycin (Table 2). Compounds **4a**, **5a**, and **6a** showed excellent antibacterial activities against *S. aureus*. Compounds **4a** and **6a** exhibited a good activity against *P. aeruginosa*, and compound **4a** displayed a good activity against *E. coli*. On the other hand, evaluation of the antifungal activity (Table 3) revealed a significant activity of **3a** against *A. niger*, good activities of **5a** and **7a** against *A. oryzae*, and a good activity of **5a** against *A. terreus*. The other compounds were either moderately active or inactive against the bacterial and fungal strains.

The obtained result showed that derivatives **4a**, **5a**, and **7a** containing a chlorine atom at the 5-position of the indole ring are the most active against different microbial strains at a concentration of 25–100 μg/mL. The role of electron-withdrawing groups in enhancing antibacterial activity has been reported [1, 8].

Antioxidant activity. The free radical scavenging activity of compounds **3**–**7** was evaluated using DPPH assay as reported in [10, 11]. The results showed (Fig. 2) that compounds **3d**, **4d**, **5d**, **5c**, and **6d** were the most potent at concentrations of 25, 50, 75, and 100 μg/mL; compounds **5c**, **7b**, and **7c** exhibited good radical scavenging activity at those concentrations, and the other compounds were moderately active.

The reductive ability of the synthesized compounds was assessed by the ferric ion-reducing antioxidant power (FRAP) assay which implies the conversion of Fe^{3+}/ferricyanide complex to the Fe^{2+}/ferrous form [10, 11]. The results (Fig. 3) displayed excellent reducing power ability of compounds **3d** and **4d** and good reducing power of **5c**, **5d**, **6c**, **6d**, **7c**, and **7d** at concentrations of 25, 50, 75, and 100 μg/mL. The other compounds exhibited moderate reducing ability.

The total antioxidant capacity of the synthesized compounds was evaluated by the phosphomolybdenum method as described in [10, 11]. As seen from Fig. 4, compounds **4a**, **5d**, **7c**, and **7d** exhibited excellent total antioxidant capacity at 25, 50, 75, and 100 μg/mL. The other compounds were moderately active.

Table 2. In-vitro antibacterial activity[a] of compounds **3**–**7** at concentrations of 25, 50, and 100 μg/mL

Compound no.	Inhibition zone, mm, at a concentration, μg/mL														
	gram-positive			gram-negative											
	S. aureus			*P. aeruginosa*			*E. coli*			*K. pneumoniae*			*S. typhi*		
	25	50	100	25	50	100	25	50	100	25	50	100	25	50	100
3a	10	16	20	08	10	18	08	15	20	NA	09	17	12	16	18
3b	05	12	19	04	15	21	09	12	16	NA	08	15	NA	08	16
3c	NA	05	11	NA	09	15	NA	08	12	11	18	20	11	12	19
3d	08	14	22	NA	05	20	NA	08	18	NA	08	14	NA	06	10
4a	**19**	**20**	**22**	**18**	**18**	**21**	**19**	**20**	**24**	08	11	15	08	14	17
4b	07	11	12	06	10	19	08	11	18	08	09	15	08	10	14
4c	NA	04	11	NA	08	15	NA	08	14	NA	08	15	05	08	11
4d	06	10	14	NA	10	20	11	14	20	NA	08	12	NA	12	18
5a	**16**	**18**	**18**	08	11	18	05	08	14	08	09	14	08	12	16
5b	12	16	18	NA	11	18	11	16	19	NA	15	19	NA	08	10
5c	10	12	18	NA	06	11	NA	08	15	NA	10	14	11	15	19
5d	08	10	14	06	10	17	10	15	20	NA	11	13	10	14	18
6a	**19**	**20**	**20**	**18**	**18**	**20**	NA	09	14	08	10	14	08	12	16
6b	06	10	14	10	16	20	08	10	12	08	11	18	06	10	19
6c	06	12	18	05	12	19	08	12	16	NA	08	14	NA	08	15
6d	NA	10	18	NA	08	11	NA	08	11	11	14	20	NA	10	20
7a	10	14	18	08	14	22	08	11	22	05	08	14	08	11	18
7b	13	17	18	10	16	20	NA	10	20	11	16	19	NA	11	18
7c	12	14	18	08	12	19	NA	10	15	NA	08	15	NA	06	11
7d	08	10	14	NA	08	11	NA	05	11	10	15	20	06	10	17
Streptomycin	**20**	**20**	**20**	**20**	**20**	**20**	**22**	**22**	**24**	**20**	**20**	**21**	**20**	**20**	**20**

[a] "NA" stands for no activity; the data for most active compounds are shown in **bold red**.

Table 3. In vitro antifungal activity[a] of compounds **3**–**7** at concentrations of 25, 50, and 100 μg/mL

Compound no.	Inhibition zone, mm, at a concentration, μg/mL											
	Aspergillus oryzae			*Aspergillus terreus*			*Aspergillus niger*			*Aspergillus flavus*		
	25	50	100	25	50	100	25	50	100	25	50	100
3a	NA	08	12	NA	08	11	**14**	**12**	**14**	NA	08	11
3b	05	09	11	NA	08	12	NA	08	14	NA	08	12
3c	NA	05	09	08	09	12	NA	08	10	NA	08	11
3d	NA	06	09	NA	05	10	NA	08	10	NA	NA	08
4a	11	14	15	08	09	14	08	10	15	10	11	14
4b	10	12	14	06	10	13	08	11	14	08	09	15
4c	NA	04	10	NA	08	14	04	08	09	NA	08	12
4d	NA	06	11	NA	08	10	NA	04	09	NA	08	10
5a	**16**	**18**	**18**	**16**	**18**	**18**	08	11	14	18	11	16
5b	10	11	14	05	11	12	NA	08	08	NA	09	12
5c	NA	10	11	NA	05	09	NA	06	11	04	09	09
5d	08	11	14	NA	06	09		08	11	NA	08	09
6a	11	12	14	NA	06	08	NA	04	10	NA	04	08
6b	NA	12	14	NA	08	10	10	11	14	08	10	14
6c	NA	10	15	05	11	15	NA	10	11	08	11	15
6d	10	14	18	NA	08	10	08	11	14	NA	08	12
7a	**18**	**17**	**18**	NA	07	11	11	12	14	NA	11	13
7b	12	14	18	05	10	12	NA	12	14	10	10	16
7c	NA	10	14	10	12	14	NA	10	11	NA	09	12
7d	NA	10	14	NA	04	10	10	14	13	04	11	15
Fluconazole	**20**	**19**	**20**	**18**	**18**	**18**	**14**	**14**	**14**	**19**	**19**	**19**

[a] "NA" stands for no activity; the data for most active compounds are shown in **bold red**.

Structure–activity relationship. The obtained results suggest that halogen (Cl) substitution at the 5-position of the indole ring attached to different heterocycles favors enhanced antimicrobial activity. On the other hand, compounds having no substituent at the indole C^5 atom show good antioxidant activity. It is clear that the presence of heteroatoms like N, S, O, and halogens (Cl) provides additional binding interactions inside the active site of enzymes of microorganisms, which may contribute to the activity of the compounds.

EXPERIMENTAL

The chemicals used in this study were purchased from Merck, HiMedia, and SD Fine Chem and were used without further purification. The progress of reactions was monitored by TLC on Silica gel 60 F245 plates (Merck) using ethyl acetate–hexane (5:1 v/v) as eluent; spots were detected by exposure to a UV lamp at λ 254 nm. The melting points were measured in open capillary tubes and are uncorrected. The IR spec-

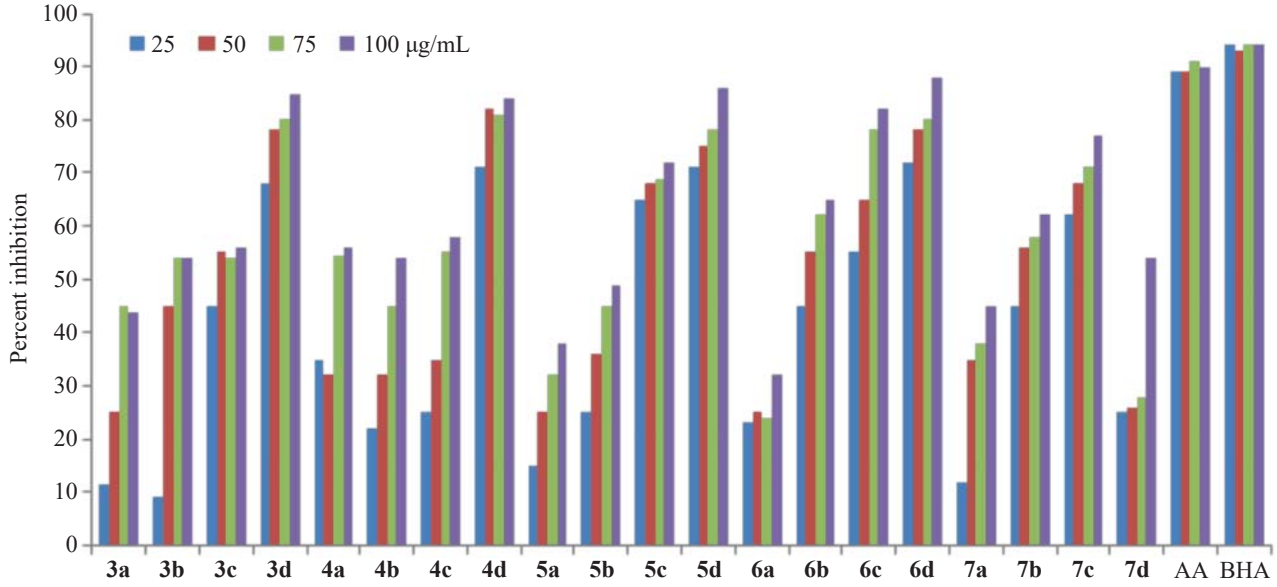


Fig. 2. DPPH free radical scavenging activity of compounds **3**–**7** at concentrations of 25, 50, 75, and 100 μg/mL in comparison to ascorbic acid (AA) and butylated hydroxyanisole (BHA).

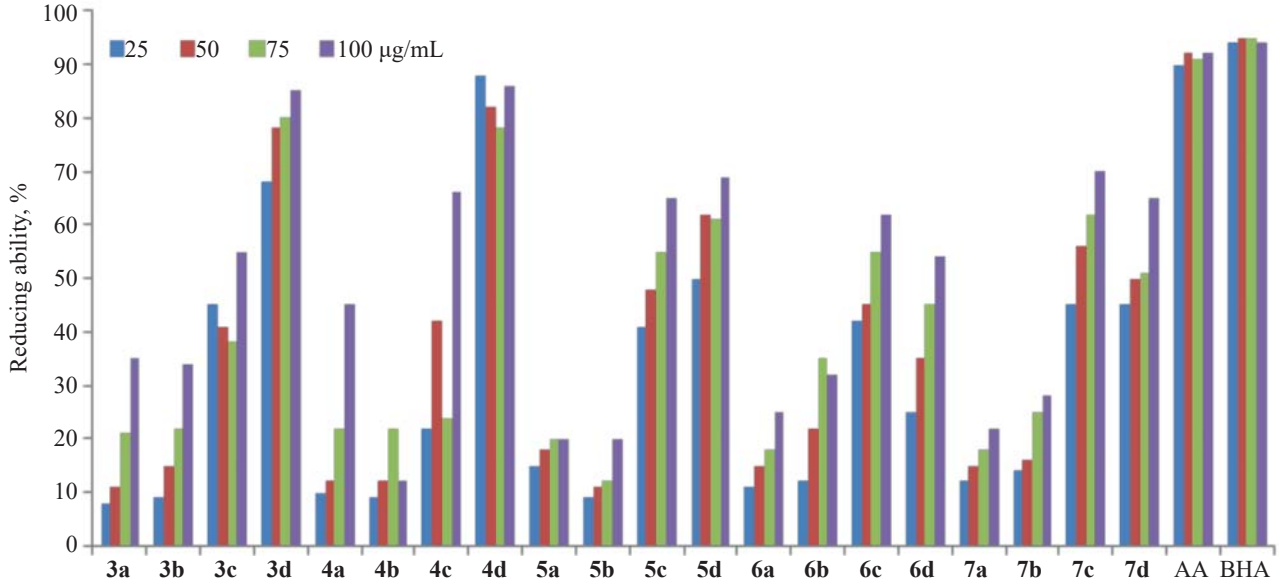


Fig. 3. Ferric ion reducing antioxidant power activity of compounds **3**–**7** at concentrations of 25, 50, 75, and 100 μg/mL in comparison to ascorbic acid (AA) and butylated hydroxyanisole (BHA).

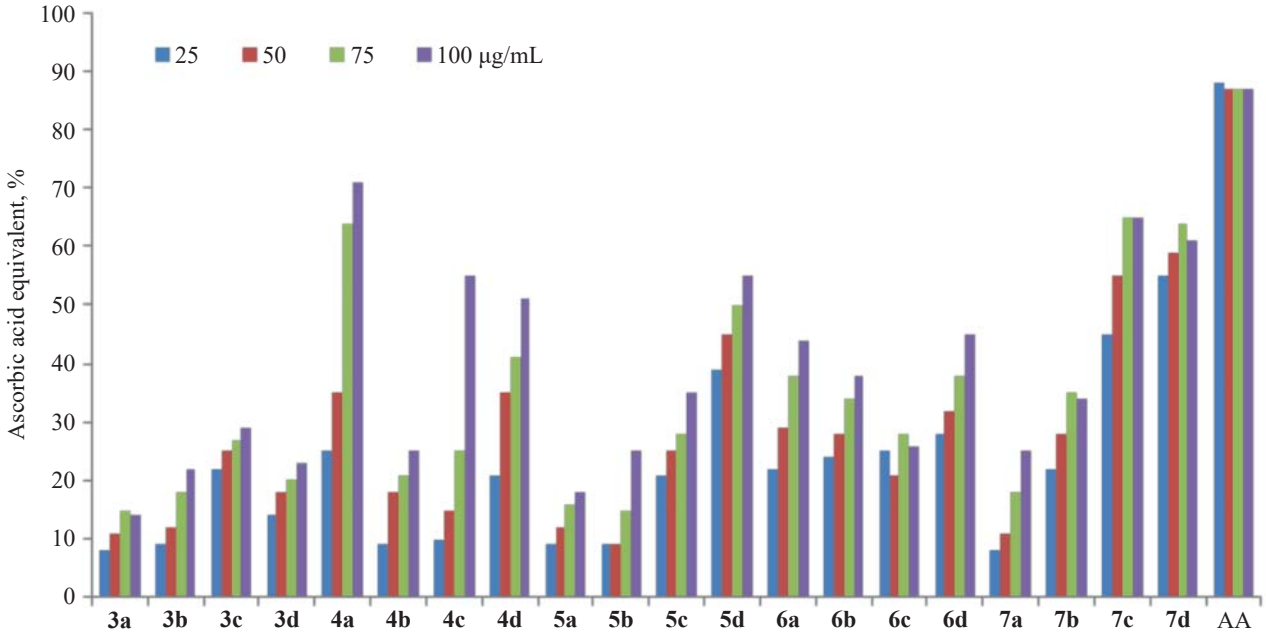


Fig. 4. Total antioxidant capacity of compounds **3**–**7** at concentrations of 25, 50, 75, and 100 μg/mL in comparison to ascorbic acid (AA).

tra were recorded in KBr on a Perkin Elmer FT-IR spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, using tetramethylsilane as internal standard. The mass spectra were run on a Shimadzu LCMS 2010A instrument. Microwave-assisted reactions were carried out in an ONIDA 20STP21 multimode microwave oven (800 W).

2,5-Substituted indole-3-carbaldehydes **1a–1d** were prepared by the Bischler method, followed by Vilsmeier–Haack formylation [16]; 1*H*-benzimidazole-2-thiol and 2-hydrazinyl-1*H*-benzimidazole (**2**) were prepared as reported in [17].

Hydrazones 3a–3d (*general procedure***).** *a*. *Conventional method*. A mixture of 1*H*-indole-3-carbaldehyde **1a**–**1d** (0.01 mol), 2-hydrazinyl-1*H*-benzimidazole (**2**), and 4–5 drops of glacial acetic acid in methanol (35 mL) was refluxed on a water bath for 5–6 h, following the reported procedure [2]. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and poured into ice water. The resulting solid was filtered off, washed with a solution of sodium hydrogen sulfate and then with cold water, dried, and recrystallized from ethanol.

b. *Microwave-assisted synthesis*. An open borosil glass tube was charged with a mixture of aldehyde **1a**–**1d** (0.01 mol) and 2-hydrazinyl-1*H*-benzimidazole (**2**) (0.01 mol) in hot methanol (5 mL) containing 4–5 drops of glacial acetic acid, and the mixture was irradiated in a MW oven at 90–100°C for 4–5 min according to the reported method [2]. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and poured into ice water, and the resulting solid was filtered off, washed with a solution of sodium hydrogen sulfate and then with cold water, dried, and recrystallized from ethanol.

2-{2-[(5-Chloro-2-phenyl-1*H*-indol-3-yl)methylidene]hydrazinyl}-1*H*-benzimidazole (3a). Yield 95%, dark yellow powder, mp 148–149°C. IR spectrum, ν, cm^{-1}: 3423 (NH, indole), 3238 (NH, imidazole), 3106 (NH), 2926 (C–H_{arom}), 1704 (HC=N), 1457(C=N), 509 (C–Cl). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.06 s (1H, NH), 6.55–7.30 m (12H, H_{arom}), 8.15 s (1H, HC=N), 9.66 s (1H, NH, imidazole), 10.09 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 112, 113, 120, 123, 126, 129, 130, 134, 150 (C_{arom}); 185.5 (HC=N). Mass spectrum: *m*/z 383/385 (I_{rel} 100/33%) $[M]^+$.

2-{2-[(5-Methyl-2-phenyl-1*H*-indol-3-yl)methylidene]hydrazinyl}-1*H*-benzimidazole (3b). Yield 92%, light purple crystals, mp 202–203°C. IR spectrum, ν, cm^{-1}: 3422 (NH, indole), 3200 (NH, imidazole), 3046 (NH), 2849–2904 (CH_3), 1753 (HC=N), 1435 (C=N, imidazole). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.64 s (3H, CH_3), 2.19 s (1H, NH), 6.98–7.71 m

(12H, H_{arom}), 8.29 s (1H, HC=N), 8.68 s (1H, NH, imidazole), 10.00 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.29 (CH_3); 110, 111, 115, 118, 119, 120, 122, 123, 124, 126, 127, 128, 129, 131, 133, 134, 137, 142 (C_{arom}); 153 (HC=N). Mass spectrum: *m*/*z* 365 $[M]^+$.

2-{2-[(2-Phenyl-1*H*-indol-3-yl)methylidene]hydrazinyl}-1*H*-benzimidazole (3c). Yield 90%, light purple crystals, mp 179–180°C. IR spectrum, ν, cm^{-1}: 3243 (NH, indole), 3106 (NH, imidazole), 3016 (NH), 2915 (C–H_{arom}), 1720 (HC=N), 1457(C=N, imidazole). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.02 s (1H, NH), 7.22–7.43 m (13H, H_{arom}), 7.98 s (1H, HC=N), 9.06 s (1H, NH, imidazole), 10.06 s (1H, NH, indole). Mass spectrrum: *m*/*z* 351 $[M]^+$.

2-{2-[(1*H*-Indol-3-yl)methylidene]hydrazinyl}-1*H*-benzimidazole (3d). Yield 85%, dark brown crystals, mp 210–211°C. IR spectrum, ν, cm^{-1}: 3408 (NH, indole), 3286 (NH, imidazole), 3178 (NH), 1758 (HC=N), 1567 (C=N, imidazole). ^1H NMR spectrum ($CDCl_3$), δ ppm: 2.16 s (1H, NH), 6.94–7.40 m (9H, H_{arom}), 7.96 s (1H, HC=N), 9.17 s (1H, NH, imidazole), 10.37 s (1H, NH, indole). Mass spectrum: *m*/*z* 275 $[M]^+$.

Thiazolidin-4-one derivatives 4a–4d (*general procedure*). *a*. *Conventional method*. A mixture of hydrazone **3a**–**3d** (0.01 mol), thioglycolic acid (0.7 mL, 0.01 mol), and a pinch of anhydrous zinc chloride in dry DMF (15 mL) was refluxed for 10–12 h [2]. After completion of the reaction (TLC), the mixture was cooled and neutralized with a 10% aqueous solution of sodium hydrogen carbonate. The solid product was filtered off, washed with water, dried, and recrystallized from ethanol.

b. *Microwave-assisted synthesis*. An open borosil glass tube was charged with a mixture of **3a**–**3d** (0.01 mol), thioglycolic acid (0.7 mL, 0.01 mol), 50 mg of anhydrous zinc chloride, and DMF (5 mL), and the mixture was subjected to MW irradiation at 160–170°C for 5–6 min [2]. After completion of the reaction (TLC), the mixture was cooled and neutralized with a 10% aqueous solution of sodium hydrogen carbonate. The solid product was filtered off, washed with water, dried, and recrystallized from ethanol.

3-[(1*H*-Benzimidazol-2-yl)amino]-2-(5-chloro-2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4a). Yield 92%, dark yellow crystals, mp 151–152°C. IR spectrum, ν, cm^{-1}: 3440 (NH, indole), 3383 (NH, imidazole), 3080 (NH), 1654 (C=O), 1520 (C=N), 602 (C–Cl), and 498 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.57 s 1H (NH), 4.37 s (2H, CH_2), 5.99 s (1H, SCHN), 6.98–7.42 m (12H, H_{arom}), 8.65 s (1H, NH, imidazole), 9.89 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 38.04 and 40.09 (CH_2, SCHN); 107, 112, 113, 114, 115, 116, 120, 123, 121, 126, 129, 130, 134, 135, 149, 150 (CCl), 185.5 (C=O). Mass spectrum: *m*/*z* 459/461 $[M]^+$.

3-[(1*H*-Benzimidazol-2-yl)amino]-2-(5-methyl-2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4b). Yield 90%, light gray powder, mp 205–206°C. IR spectrum, ν, cm^{-1}: 3413 (NH, indole), 3218 (NH, imidazole), 3171 (NH), 2849–2920 (CH_3), 1698 (C=O), 1435 (C=N), 547 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (3H, CH_3), 2.48 s (1H, NH), 4.37 s (2H, CH_2), 5.89 s (1H, SCHN), 6.97–7.80 m (12H, H_{arom}), 8.64 s (1H, NH, imidazole), 10.27 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.30 (CH_3); 38.04 and 40.10 (CH_2, SCHN); 111, 113, 120, 125, 126, 128, 129, 131, 134 (C_{arom}); 149 (C=O). Mass spectrum: *m*/*z* 439 $[M]^+$.

3-[(1*H*-Benzimidazol-2-yl)amino]-2-(2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4c). Yield 88%, white shining crystals, mp 214–215°C. IR spectrum, ν, cm^{-1}: 3411 (NH, indole), 3393 (NH, imidazole), 3000 (NH), 1600 (C=O), 1531 (C=N), 747 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.16 s (1H, NH), 4.31 s (2H, CH_2), 6.19 s (1H, SCHN), 6.94–7.39 m (13H, H_{arom}), 7.98 s (1H, NH, imidazole), 10.38 s (1H, NH, indole). Mass spectrum: *m*/*z* 425 $[M]^+$.

3-[(1*H*-Benzimidazol-2-yl)amino]-2-(1*H*-indol-3-yl)thiazolidin-4-one (4d). Yield 80%, dark brown powder, mp 207–208°C. IR spectrum, ν, cm^{-1}: 3485 (NH, indole), 3192 (NH, imidazole), 3133 (NH), 1634 (C=O), 1567 (C=N), 715 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.62 s (1H, NH), 4.36 s (2H, CH_2), 6.19 s (1H, SCHN), 7.22–7.43 m (9H, H_{arom}), 7.98 s (1H, NH, imidazole), 10.59 s (1H, NH, indole). Mass spectrum: *m*/*z* = 349 $[M]^+$.

[1,2,4]Triazolo[4,3-*b*]benzimidazoles 5a–5d. *a*. *Conventional method*. A mixture of compound **3a**–**3d** (0.01 mol) and acetic anhydride (10 mL) was refluxed for about 3–4 h, following the reported procedure [18]. After completion of the reaction (TLC), the mixture was cooled to room temperature and poured into ice water. The solid product was filtered off, washed thoroughly with cold water, dried, and recrystallized from 1,4-dioxane.

b. *Microwave-assisted synthesis*. An open borosil glass tube was charged with a mixture of **3a**–**3d** (0.01 mol) and acetic anhydride (10 mL), and the mix-

ture was irradiated in a MW oven at 140–150°C for 2–4 min. After completion of the reaction (TLC), the mixture was cooled to room temperature and poured into ice water, and the solid product was filtered off, washed thoroughly with cold water, dried, and recrystallized from 1,4-dioxane.

3-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-9*H*-[1,2,4]-triazolo[4,3-*b*]benzimidazole (5a). Yield 80%, dark brown powder, mp 145–146°C. IR spectrum, ν, cm^{-1}: 3459 (NH, indole), 3369 (NH, imidazole), 1443 (C=N), 591 (C–Cl). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.86–7.50 m (12H, H_{arom}), 8.40 s (1H, NH, imidazole), 10.02 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 112, 113, 116, 117, 118, 121, 123, 126, 129, 130, 131, 134, 135 (C_{arom}); 149, 151 (C^3, C^5, triazole). Mass spectrum: *m*/*z* 383/385 $[M]^+$.

3-(5-Methyl-2-phenyl-1*H*-indol-3-yl)-9*H*-[1,2,4]-triazolo[4,3-*b*]benzimidazole (5b). Yield 75%, light purple powder, mp 181–182°C. IR spectrum, ν, cm^{-1}: 3422 (NH, indole), 3382 (NH, imidazole), 2849–2950 (CH_3), 1523 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 s (3H, CH_3), 6.84–7.49 m (12H, H_{arom}), 8.54 s (1H, NH, imidazole), 9.98 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21.54 (CH_3); 111, 113, 120, 125, 126, 128, 129, 130, 131, 134 (C_{arom}); 148 (CH, triazole). Mass spectrum: *m*/*z* 363 $[M]^+$.

3-(2-Phenyl-1*H*-indol-3-yl)-9*H*-[1,2,4]triazolo-[4,3-*b*]benzimidazole (5c). Yield 75%, light brown shining crystals, mp 220–221°C. IR spectrum, ν, cm^{-1}: 3448 (NH, indole), 3242 (NH, imidazole), 3022 (C–H_{arom}), 1535 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 6.93–7.85 m (13H, H_{arom}), 8.15 s (1H, NH, imidazole), 9.12 s (1H, NH, indole). Mass spectrum: *m*/*z* 349 $[M]^+$.

3-(1*H*-Indol-3-yl)-9*H*-[1,2,4]triazolo[4,3-*b*]benzimidazole (5d). Yield 70%, dark brown powder, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3348 (NH, indole), 3286 (NH, imidazole), 3152 (C–H_{arom}), 1680 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.23–7.99 m (9H, H_{arom}), 8.00 s (1H, NH, imidazole), 9.01 s (1H, NH, indole). Mass spectrum: *m*/*z* 273 $[M]^+$.

Azitidin-2-one derivatives 6a–6d (*general procedure***).** *a*. *Conventional method*. A few drops of triethylamine and chloroacetyl chloride (0.01 mol) were added with stirring at room temperature over a period of about 15 min to a mixture of compound **3a**–**3d** (0.01 mol) and anhydrous benzene (30 mL). The mixture was refluxed for 2–3 h on a water bath, following the reported procedure [19], and the precipitate of triethylamine hydrochloride was filtered off and washed several times with benzene. The filtrate was combined with the washings and concentrated under reduced pressure, and the residue was washed with petroleum ether (bp 40–60°C) to remove unreacted initial compound **3**, dried, and recrystallized from 1,4-dioxane.

b. *Microwave-assisted synthesis*. A few drops of triethylamine and chloroacetyl chloride (0.01 mol) were added with stirring at room temperature over a period of about 15 min to a mixture of compound **3a**–**3d** (0.01 mol) and anhydrous benzene (5 mL). The mixture was transferred into an open borosil glass tube and irradiated in a MW oven at 100–110°C for 2–4 min, the precipitate of triethylamine hydrochloride was filtered off and washed several times with benzene, the filtrate was combined with the washings and concentrated under reduced pressure, and the residue was washed with petroleum ether (bp 40–60°C) to remove unreacted initial compound **3**, dried, and recrystallized from 1,4-dioxane.

1-[(1*H*-Benzimidazol-2-yl)amino]-3-chloro-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)azetidin-2-one (6a). Yield 90%, light brown crystals, mp 221–223°C. IR spectrum, ν, cm^{-1}: 3312 (NH, indole), 3201 (NH, imidazole), 3060 (NH), 2926 (C–H), 1684 (C=O), 1637 (C=N), 730 (C^3–Cl), 704 ($C^{5'}$–Cl). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.62 s (1H, NH), 4.59 d (1H, 4-H), 5.46 d (1H, 3-H), 6.17–7.98 m (12H, H_{arom}), 9.35 s (1H, NH, imidazole), 9.85 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 58 (C^4), 66 (C^3); 108, 109, 121, 122, 124, 125, 126, 128, 129, 131, 132, 133, 134, 135, 136, 137, 138, 145, 147, 149, 164 (C_{arom}); 181 (C=O). Mass spectrum: *m*/*z* 461/463/465 (intensity ratio 9:6:1) $[M]^+$.

1-[(1*H*-Benzimidazol-2-yl)amino]-3-chloro-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)azetidin-2-one (6b). Yield 88%, light yellow crystals, mp 205–208°C. IR spectrum, ν, cm^{-1}: 3311 (NH, indole), 3250 (NH, imidazole), 3174 (NH), 2952 (C–H), 2830–2890 (CH_3), 1661 (C=O), 1544 (C=N), 726 (C–Cl). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.78 s (3H, CH_3), 2.17 s (1H, NH), 4.58 d (1H, 4-H), 5.43 d (1H, 3-H), 6.94–7.98 m (12H, H_{arom}), 8.88 s (1H, NH, imidazole), 10.51 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21 (CH_3), 60 (C^4), 66 (C^3); 114, 116, 118, 119, 123, 127, 128, 130, 131, 134, 135, 144, 149, 152 (C_{arom}); 180 (C=O). Mass spectrum: *m*/z 441/443 (3:1) $[M]^+$.

1-[(1*H*-Benzimidazol-2-yl)amino]-3-chloro-4-(2-phenyl-1*H*-indol-3-yl)azetidin-2-one (6c). Yield 85%,

light yellow crystals, mp 131–133°C. IR spectrum, ν, cm^{-1}: 3309 (NH, indole), 3051 (NH, imidazole), 3000 (NH), 1700 (C=O), 1655 (C=N), 721 (C–Cl). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.00 s (1H, NH), 3.58 d (1H, 4-H), 4.31 d (1H, 3-H), 6.17–7.98 m (13H, H_{arom}), 9.88 s (1H, NH, imidazole), 10.16 s (1H, NH, indole). Mass spectrum: *m*/*z* 427/429 (3:1) $[M]^+$.

1-[(1*H*-Benzimidazol-2-yl)amino]-3-chloro-4-(1*H*-indol-3-yl)azetidin-2-one (6d). Yield 78%, light yellow crystals, mp 124–126°C. IR spectrum, ν, cm^{-1}: 3433 (NH, indole), 3119 (NH, imidazole), 3042 (NH), 3005 (C–H_{arom}), 2816–2953 (C–H), 1649 (C=O), 1621 (C=N), 754 (C–Cl). ^1H NMR spectrum ($CDCl_3$), δ_C, ppm: 2.62 s (1H, NH), 3.59 d (1H, 4-H), 4.36 d (1H, C^3), 7.22–7.98 m (8H, H_{arom}), 9.22 s (1H, NH, imidazole), 10.59 s (1H, NH, indole). Mass spectrum: *m*/*z* 351/353 (3:1) $[M]^+$.

Thioethers 7a–7d (*general procedure*). *a. Conventional method*. A mixture of compound **3a**–**3d** (0.01 mol) and 1*H*-benzimidazole-2-thiol (0.01 mol) was heated at 150–160°C in an oil bath for 1–2 h according to the reported procedure [20]. After completion of the reaction (TLC), the mixture was cooled to room temperature, and the solid product was filtered off, washed with cold ethanol, and recrystallized from 1,4-dioxane.

b. Microwave-assisted synthesis. An open borosil glass tube was charged with a mixture of compound **3a**–**3d** (0.01 mol) and 1*H*-benzimidazole-2-thiol (0.01 mol), and the mixture was irradiated in a MW oven at 150–160°C for 2–4 min. After completion of the reaction (TLC), the mixture was cooled to room temperature, and the solid product was filtered off, washed with cold ethanol, and recrystallized from 1,4-dioxane.

2-({[2-(1*H*-Benzimidazol-2-yl)hydrazinyl](5-chloro-2-phenyl-1*H*-indol-3-yl)methyl}sulfanyl)-1*H*-benzimidazole (7a). Yield 94%, light brown crystals, mp 228–230°C. IR spectrum, ν, cm^{-1}: 3429 (NH, indole), 3295 (NH, imidazole), 2959 (NH), 1661 and 1608 (C=N), 745 (C–Cl), 689 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.19 s and 2.64 s (1H each, NHNH), 4.38 s (1H, CH), 6.98–8.28 m (16H, H_{arom}), 8.29 s (1H, NH, imidazole), 8.60 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 70 (CHS); 112, 113, 119, 122, 123, 124, 125, 126, 127, 128, 130, 132, 134, 135, 136, 147, 149, 166, 170 (C_{arom}). Mass spectrum: *m*/*z* 535/537 (3:1) $[M]^+$.

2-({[2-(1*H*-Benzimidazol-2-yl)hydrazinyl](5-methyl-2-phenyl-1*H*-indol-3-yl)methyl}sulfanyl)-1*H*-benzimidazole (7b). Yield 92%, dark gray crystals, mp 178–180°C. IR spectrum, ν, cm^{-1}: 3264 (NH, indole), 3179 (NH, imidazole), 3058 (NH), 2882–2964 (CH_3), 1694 and 1613 (C=N), 685 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.62 s (3H, CH_3), 2.19 s and 2.64 s (1H each, NHNH), 4.37 s (1H, CHS), 6.86–8.23 m (16H, H_{arom}), 8.25 s (1H, NH, imidazole), 8.40 s (1H, NH, indole). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 21 (CH_3), 66 (CHS); 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 134, 135, 136, 145, 148, 166, 178 (C_{arom}). Mass spectrum: *m*/*z* 515 $[M]^+$.

2-({[2-(1*H*-Benzimidazol-2-yl)hydrazinyl](2-phenyl-1*H*-indol-3-yl)methyl}sulfanyl)-1*H*-benzimidazole (7c). Yield 90%, dark gray crystals, mp 174–176°C. IR spectrum, ν, cm^{-1}: 3392 (NH, indole), 3271 and 3183 (NH, imidazole), 3061 (NH), 2965 (CHS), 1694 and 1610 (C=N), 686 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.19 s and 2.64 s (1H each, NHNH), 4.37 s (1H, CH), 6.98–8.26 m (17H, H_{arom}), 8.28 s (1H, NH, imidazole), 8.65 s (1H, NH, indole). Mass spectrum: *m*/*z* 501 $[M]^+$.

2-({[2-(1*H*-Benzimidazol-2-yl)hydrazinyl](2-phenyl-1*H*-indol-3-yl)methyl}sulfanyl)-1*H*-benzimidazole (7d). Yield 88%, dark brown crystals, mp 166–168°C. IR spectrum, ν, cm^{-1}: 3364 (NH, indole), 3176 (NH, imidazole), 3059 (NH), 1610 and 1540 (C=N), 688 (C–S–C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.06 s and 2.52 s (1H each, NHNH), 4.30 s (1H, CHS), 6.55–7.97 m (13H, H_{arom}), 8.15 s (1H, NH, imidazole), 9.12 s (1H, NH, indole). Mass spectrum: *m*/*z* 425 $[M]^+$.

Biological evaluations. The antimicrobial and antioxidant activities of compounds **3**–**7** in vitro were assayed by the cup-plate method as reported in [10, 11]. The detailed procedures are given in Supplementary Materials.

CONCLUSIONS

A rapid, convenient, and environmentally friendly microwave-assisted procedure has been developed for the synthesis of new biologically active thiazolidin-4-one, triazole, azitidine-2-one, and thioether derivatives bearing indole and benzimidazole scaffolds. Five of the twenty synthesized compounds exhibited considerable antimicrobial activity comparable to the activity of reference drugs, and some of the compounds showed excellent antioxidant activity. Thus, the synthesized compounds may be promising candidates for new antimicrobial drugs and further investigations in the field of medicinal chemistry.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest

SUPPLEMENTARY INFORMATION

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