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Letters in Drug Design & Discovery, 2018, *15*, 154-159

RESEARCH ARTICLE

Synthesis and Antimicrobial Activity of Some New N-(1*H*-benzimidazol-2-yl)-2-mercaptoacetamide Derivatives

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ARTICLE HISTORY

Received: February 24, 2017
Revised: May 30, 2017
Accepted: June 06, 2017

DOI:
10.2174/1570180814666170619092147

Abstract: ***Background*:** Due to multi-drug, extended-drug, and pandrug resistance phenotypes, bacterial resistance to antibiotics and fungal infections are a general health issue. Particulary, increase of fungal infections due to secondary cause of human diseases have been observed. An extensive variety of benzimidazole derivatives have been characterized for their chemotherapeutic significance. Benzimidazole derivatives have received important attention because of pharmacological significance during current years, especially antimicrobial, anti-fungal, antitubercular, anti-oxidant, anti-Alzheimer's disease and antihypertension activities.

***Methods*:** Some *N*-(1*H*-benzimidazol-2-yl)-2-mercaptoacetamide derivatives (**2a-h**) were synthesised and evaluated for their antimicrobial activity. The title compounds were gained by reacting *N*-(1*H*-benzimidazol-2-yl)-2-chloroacetamide with some substituted 2-mercapto heterocyclic rings. The synthesised compounds were investigated for their antimicrobial activities against *C. albicans* (ATCC 24433), *C. krusei* (ATCC 6258), *C. glabrata* (ATCC90030), *C. parapsilosis* (ATCC 22019), *E. coli* (ATCC 25922), *E. coli* (ATCC 35218), *E. feacalis* (ATCC 51299), *E. feacalis* (ATCC 29212), *S. aureus* (ATCC 25923), *K. pneumoniae* (ATCC 700603), *P. aeruginosa* (ATCC 27853).

***Results*:** The compounds showed high antifungal activity when compared with standard drug ketoconazole. In addition, all compounds (MIC 100 µg/mL) showed inhibitor activity against *P. aeruginosa* at two fold concentration of chloramphenicol (MIC 50 µg/mL). Also, compounds **2a, 2c** and **2e** (MIC: 50 µg/mL) have equal effect against *E. coli* (ATCC 35218) and more effective than other compounds (MIC of chloramphenicol: 100 µg/mL).

***Conclusion*:** All compounds showed notable activity. Compounds have determined to possess higher antifungal activity than antibacterial activity. Additionally, compounds **2a** with 1-methyltetrazole, **2c** with benzothiazole and **2e** with 6-chlorobenzothiazole moieties were found as the most active compounds.

Keywords: Benzimidazole, azoles, antifungal activity, antibacterial activity, bacteria, fungi.

1. INTRODUCTION

Bacterial and fungal infections are some sort of highly prevalent diseases [1]. Bacteria and fungi are ordinarily found as commensal organisms colonizing, plentiful in nature and generally co-inhabit many natural circumference [2, 3].

Due to multi-drug, extended-drug, and pandrug resistance phenotypes, bacterial resistance to antibiotics and fungal infections are global health problems and the increase of human disease's origin fungal infections is observed [4, 5]. *Candida species* which are major group of fungal pathogens have also long been recognized as an important cause of human disease, especially, but non-exclusively, between those with compromised immunity [3, 6]. The synthesis of a new division of antibacterial and antifungal agents against drug resistant bacteria and some fungi is desperately needed now [7].

A wide variety of benzimidazole derivatives have been characterized for their chemotherapeutic significance [8]. They are signally effective compounds, both considering their inhibitory activity and their favorable selectivity ratio [7].

In particular, benzimidazole derivatives have received important attention because of pharmacological significance

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1875-628X/18 $58.00+.00

during current years, having antiviral [9], anti-fungal [10], anticancer [11], antihelmintic [12], antitubercular [13], antioxidant [14], anti-Alzheimer's disease, antihypertension [15] antitumor [16] lipase inhibition activities [17], antiprotozoal, antimalarial, antiallergic [18] properties. Also, benzimidazole derivatives have shown good effect on clinical samples from real patients with non-healing infections and comlicated courses of treatment [19]. As well, some drugs containing benzimidazole moiety like thiabendazole, flubendazole, Imet 3393, and astemizole are in medical use [20].

Some heterocyclic rings such as like triazoles, tetrazoles and benzothiazoles are known to have antibacterial and antifungal effects [8, 21-23]. Azole drugs such as Ketoconazole, Fluconazole, Voriconazole, Posoconazole, Itraconazole and Ravuconazole act inhibiting the synthesis of ergosterol, which is the primary component of the fungal cell membrane [5].

By the reasons of the above information, in this work we synthesised some new *N*-(1*H*-benzimidazol-2-yl)-2-(substituted mercapto)acetamide derivatives as potential antimicrobial agent.

2. MATERIALS AND METHODS

2.1. Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck Chemicals (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: ^{1}H NMR (nuclear magnetic resonance) Bruker DPX- 300 FT-NMR spectrometer, ^{13}C NMR, Bruker DPX 75 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA); M+1 peaks were determined by Shimadzu 8040 LC/MS/MS system (Shimadzu, Tokyo, Japan). Elemental analyses were performed on a Leco 932 CHNS analyzer (Leco, Michigan, USA).

2.1.1. General Procedure for the Synthesis of the Compounds N-(1H-benzimidazol-2-yl)-2-mercaptoacetamide (1)

1*H*-Benzimidazol-2-amine (0.04 mol, 5.33 g) and triethylamine (0.048 mol, 6.70 mL) were dissolved in THF with a constant stirring at 0–5°C, then chloroacetyl chloride (0.048 mol, 3.82 mL) was added dropwise gradually to this solution. The reaction mixture thus obtained was further agitated for 2 h at room temperature. After the solvent was vaporised to dryness, the solid was filtered and washed with water. After that, raw product was recrystallised from ethanol.

2.1.2. N-(1H-benzimidazol-2-yl)-2-(substituted mercapto) acetamide derivatives (2a-2h)

A mixture of *N*-(1*H*-benzimidazol-2-yl)-2-chloroacetamide (**1**) (2.39 mmol, 0.5 g), appropriate mercapto derivatives (3.20 mmol) and K_2CO_3 (2.39 mmol, 0.24 g) in acetone was stirred for 6 hours. At the end of the period, the solvent was vaporised and the residue was washed with water and filtered. After dryness, raw product was recrystallised from alcohol. Some chemical properties were given in Table **1**.

2.1.3. N-(1H-benzimidazol-2-yl)-2-[(1-methyl-1H-tetrazol-5-yl)thio]acetamide (2a)

m. p. 235°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.00 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.08-7.11 (m, 2H, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 12.02 (brs, 2H, NH).

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 34.17 (CH_3), 37.75 (CH_2), 114.40, 121.81, 136.04, 153.73, 167.90 (C=O). MS $[M+1]^+$: m/z 290.0819.

For $C_{11}H_{11}N_7OS$ calculated: Elemental Analysis: %C 45.67; %H 3.83; %N 33.89; found: %C 45.66; %H 3.84; %N 33.87.

2.1.4. N-(1H-benzimidazol-2-yl)-2-((4-methyl-4H-1,2,4-triazol-3-yl)thio)acetamide (2b)

m. p. 205°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 3.63 (s, 3H, CH_3), 4.17 (s. 2H, CH_2), 7.09-7.12 (m, 2H, Ar-H), 7.44-7.47 (m, 2H, Ar-H), 8.58 (s, 1H, Ar-H), 12.02 (brs, 2H, NH).

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 31.34 (NCH_3), 37.63 (CH_2), 114.54, 121.68, 121.91, 146.74, 146.96, 148.98, 168.21 (C=O). MS $[M+1]^+$: m/z 289.0863.

For $C_{12}H_{12}N_6OS$ calculated: Elemental Analysis: %C 49.99; %H 4.20; %N 29.15; found: %C 50.00; %H 4.21; %N 29.16.

2.1.5. N-(1H-benzimidazol-2-yl)-2-(benzothiazol-2-ylthio) acetamide (2c)

m. p. 236°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.49 (s, 2H, CH_2), 7.08-7.11 (m, 2H, Ar-H), 7.35 (t, 1H, J=7.50, Ar-H), 7.42-7.47 (m, 3H, Ar-H), 7.81 (d, H, J=8.46 Hz, Ar-H), 8.01, (d, H, J=7.89 Hz, Ar-H), 12.07 (s, 2H, NH)

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 37.71 (CH_2), 114.51, 121.60, 121.73, 122.32, 125.02, 126.87, 147.20 (C=N), 152.99, 166.34 (C=N), 167.91 (C=O). MS $[M+1]^+$: m/z 341.0508.

For $C_{16}H_{12}N_4OS_2$ calculated: Elemental Analysis %C 56.45; %H 3.55; %N 16.46; found: %C 56.44; %H 3.54; %N 16.47.

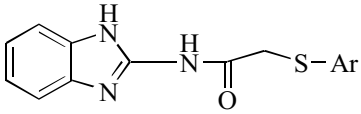
2.1.6. 2-((1H-benzimidazol-2-yl)thio)-N-(1H-benzimidazol-2-yl)acetamide (2d)

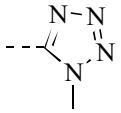
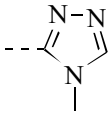
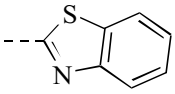
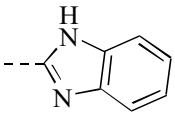
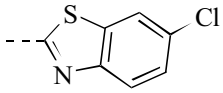
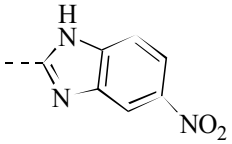
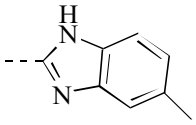
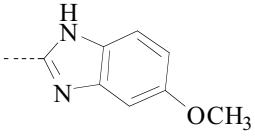
m. p. 210°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.37 (s, 2H, CH_2), 7.07-7.14 (m, 5H, Ar-H), 7.42-7.45 (m, 3H, Ar-H), 12.03 (brs, 2H, N-H), 12.60 (brs, 1H, N-H)

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 36.04 (CH_2), 119.01, 119.78, 121.62, 121.97, 123. 90, 125.94, 146.99, 149.99, 168.40 (C=O). MS $[M+1]^+$: m/z 324.0898.

For $C_{16}H_{13}N_5OS$ calculated: Elemental Analysis: %C 59.42; %H 4.05; %N 21.66; found: %C 59.40; %H 4.06; %N 21.67.

Table 1. Synthesised compounds.



C.	Ar	Melting Point (°C)	Molecular Weight	Molecular Formula	Yield (%)	Log P	DL*
2a		234.7	289.32	$C_{11}H_{11}N_7OS$	76	1.19	0.34
2b		205	288.33	$C_{12}H_{12}N_6OS$	78	0.91	0.65
2c		236	340.42	$C_{16}H_{12}N_4OS_2$	75	3.77	0.14
2d		210.4	323.37	$C_{16}H_{13}N_5OS$	74	3.15	0.10
2e		161.4	374.86	$C_{16}H_{11}ClN_4OS_2$	75	4.48	0.49
2f		189.2	368.37	$C_{16}H_{12}N_6O_3S$	79	2.74	-0.30
2g		92.8	337.40	$C_{17}H_{15}N_5OS$	78	3.55	0.14
2h		112.6	353.40	$C_{17}H_{15}N_5O_2S$	76	3.24	0.33

*DL : Drug-likeness model score. Log P and DL were calculated by http://molsoft.com/mprop/software.

2.1.7. N-(1H-benzimidazol-2-yl)-2-((6-chlorobenzothiazol-2-yl)thio)acetamide (2e)

m. p. 161°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.39 (s, 2H, CH_2), 7.09-7.12 (m, 3H, Ar-H), 7.42-7.47 (m, 3H, Ar-H), 8.03 (d, 1H, J=8.58 Hz, Ar-H), 12.11 (brs, 2H, N-H).

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 37.91 (CH_2), 114. 34, 121.01, 121.88, 123.77, 125.05, 131.69, 134.05, 135.78, 147.41, 153.89, 167.71 (C=O). MS $[M+1]^+$: m/z 375.0123.

For $C_{16}H_{11}ClN_4OS_2$ calculated: Elemental Analysis: %C 51.27; %H 2.96; %Cl 9.46; %N %14.95; found: %C 51.24; %H 2.96; %Cl 9.47; %N %14.96.

2.1.8. N-(1H-benzimidazol-2-yl)-2-((5-nitro-1H-benzimidazol-2-yl)thio)acetamide (2f)

m. p. 189°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 4.45 (s, 2H, CH_2), 7.07-7.10 (m, 2H, Ar-H), 7.41-7.44 (m, 2H, Ar-H), 7.60 (d, H, J=9.00 Hz, Ar-H), 8.02-8.06 (m, H, Ar-H), 8.29 (s, H, Ar-H), 12.24 (brs, 2H, N-H), 12.58 (brs, 1H, N-H).

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 39.67 (CH_2), 110.70, 111.83, 113.95, 121.68, 139.91, 142.58, 144.35 (C-N), 147.15, 156.41, 168.19 (C=O). MS $[M+1]^+$: m/z 369.0746.

For $C_{16}H_{12}N_6O_3S$ calculated: Elemental Analysis: %C 52.17; %H 3.28; %N 22.81; found: %C 52.19; %H 3.28; %N 22.80.

2.1.9. N-(1H-benzimidazol-2-yl)-2-((5-methyl-1H-benzimidazol-2-yl)thio)acetamide (2g)

m. p. 92°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 2.36 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 7.03-7.13 (m, 5H, Ar-H), 7.22 (m, H, Ar-H), 7.44-7.45 (m, H, Ar-H), 12.20 (brs, 2H, N-H), 12.55 (brs, 1H, N-H).

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 21.64 (CH_3), 38.55 (CH_2), 111.77, 114.33, 121.89, 123.16, 130.98, 147.43, 148.91, 168.51 (C=O). MS $[M+1]^+$: m/z 338.1056.

For $C_{17}H_{15}N_5OS$ calculated: Elemental Analysis: %C 60.52; %H 4.48; %N 20.76; found: %C 60.50; %H 4.49; %N 20.77.

2.1.10. N-(1H-benzimidazol-2-yl)-2-((6-methoxy-1H-benzimidazol-2-yl)thio)acetamide (2h)

m. p. 112°C, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 3.78 (s, 3H, OCH_3), 4.06 (s, 2H, CH_2), 6.98 (d, H, J=1.98 Hz, Ar-H), 7.07-7.10 (m, 2H, Ar-H), 7.26-36 (m, 3H, Ar-H), 7.43-7.45 (m, H, Ar-H), 12.22 (brs, 1H, N-H), 12.41 (brs, 2H, N-H).

^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 38.55 (CH_2), 55.87 (O-CH_3), 103.20, 111.65, 114.53, 114.95, 119.43, 121.64, 122.31, 132.30, 136.51, 140.19, 147.19, 155.81, 168.53 (C=O). MS $[M+1]^+$: m/z 354.1004.

For $C_{17}H_{15}N_5O_2S$ calculated: Elemental Analysis: %C 57.78; %H 4.28; %N 19.82; found: %C 57.76; %H 4.27; %N 19.83.

2.2. Antimicrobial Assay

Microbiological study was designed to compare MICs obtained by the CLSI reference M07–A9 broth microdilution method for antibacterial activity [24]. Anticandidal activity test was performed according to EUCAST definitive method EDef 7.1 for Candida species [25]. Four fungi and seven bacteria are on the point of being eleven strains were investigated by the microdilution method for compounds **2a-h** as shown in Table **2**. Sabouraud dextrose agar (SDB) for *Candida* and Mueller Hinton broth (MHB) for bacteria were used as the feedlot. After overnight incubation, the optical density (OD) values of the developing microorganisms were read at 630 nm for the candidates and at 540 nm for the bacterial strains. Compounds dissolved in DMSO were diluted with distilled water to a concentration of 200 μg/mL until 0.78 μg/ml with the twofold serial dilution method. As a positive control, ketokonazole was used for the fungi and chloramphenicol was used for the bacteria. And also only chemical and medium containing wells containing microorganisms were used as a negative control. After 24 hours of incubation, the resorcinol indicator was used as a final concentration of 20 μg/mL for each well. The concentration of the well prior to the colorless or pink-looking well was determined as the minumum inhibitor concentration (MIC). The concentration in the previous well which appears colorless or pink, was determined as the MIC concentration of the compounds.

3. RESULTS AND DISCUSSION

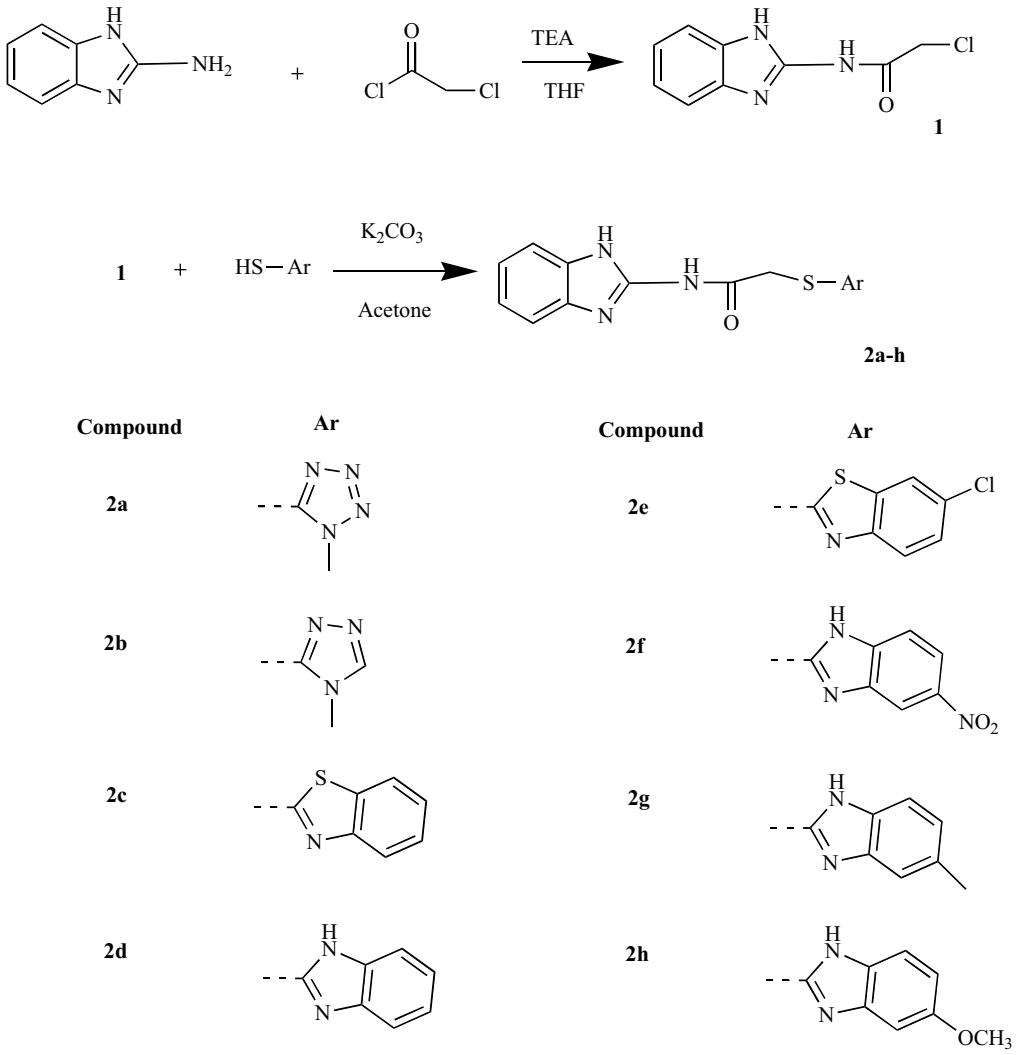
3.1. Chemistry

In this work, we synthesized eight different compounds, which contain *N*-(1*H*-benzimidazol-2-yl)-2-mercaptoacetamide moiety. The synthesis reaction was carried out *via* two steps. In the first step, 1*H*-benzimidazol-2-amine was acetylated with chloroacetyl chloride. Then, the obtained intermediate (1) 2-mercaptoaryl derivatives to gain resulting products *N*-(1*H*-benzimidazol-2-yl)-2-(substituted mercapto)acetamide derivatives (**2a-2h**) as shown in Scheme (**1**). All synthesized compounds were fully characterized by analytical and spectral data.

Table 2. Antimicrobial activity of the combounds (μg/mL).

-	A	B	C	D	E	F	G	H	I	J	K
2a	50	50	50	50	100	50	100	100	100	50	100
2b	50	50	50	50	100	100	100	100	100	50	100
2c	50	50	50	50	50	50	100	100	100	50	100
2d	50	50	50	50	100	100	100	100	100	50	100
2e	50	50	50	50	100	50	100	100	100	50	100
2f	50	50	50	50	100	100	100	100	100	50	100
2g	50	50	50	50	100	100	100	100	100	50	100
2h	50	50	50	50	100	100	100	100	100	50	100
Ref-1	25	50	50	50	-	-	-	-	-	-	-
Ref-2	-	-	-	-	12.5	12.5	25	25	25	12.5	50

Reference 1: Ketoconazole, Reference 2: Chloramphenicol.
A: C. *albicans* (ATCC 24433), **B**: C. *krusei* (ATCC 6258), **C**: C. *glabrata* (ATCC90030), **D**: C. *parasilopsiss* (ATCC 22019), **E**: E. *coli* (ATCC 25922), **F**: E. *coli* (ATCC 35218), **G**: E. *feacalis* (ATCC 51299), **H**: E. *feacalis* (ATCC 29212), **I**: S. *aureus* (ATCC 22019), **J**: K. *pneumoniae* ATCC 700603), **K**: P. *aeruginosa* (ATCC 27853).



Scheme 1. Synthesis of the compounds (**2a-2h**).

The ^{1}H-NMR spectra of compounds showed signals at δ 4.06-4.49 ppm (CH_2) for methylene proton. The broad single peak seen at δ 12.02-12.60 ppm indicated the benzimidazole N-H proton. The appearance of a pair of singlet, doublets, triplets and/or multiples at δ 6.98-8.58 ppm was due to the aromatic protons of the phenyl ring. The ^{13}C-NMR spectra of compounds showed signals at δ 36.04-38.55 ppm for methylene carbon (CH_2) at δ 103.20-156.41 ppm for aromatic carbon and at δ 167.71-168.53 for carbonyl (C=O) carbon. M+1 peaks in LC-MS/MS spectra were in agreement with the calculated molecular weight of the target compounds (**2a-2h**). Elemental analysis results for C, H, and N elements were acceptable with calculated values of the compounds.

3.2. Antimicrobial Activity

Antimicrobial activity was investigated by finding MIC values of the synthesised compounds were tested for their antimicrobial activities against *C. albicans* (ATCC 24433), *C. krusei* (ATCC 6258), *C. glabrata* (ATCC90030), *C. parapsilosis* (ATCC 22019), *E. coli* (ATCC 25922), *E. coli* (ATCC 35218), *E. feacalis* (ATCC 51299), *E. feacalis* (ATCC 29212), *S. aureus* (ATCC 25923), *K. pneumoniae* (ATCC 700603), *P. aeruginosa* (ATCC 27853) in Table **2**.

The compounds showed high antifungal activity when compared with standard drug ketoconazole. Especially, all compounds exhibited equipotency antifungal effect to ketoconazole against *C. krusei*, *C. glabrata* and C. *parasilopsis*. Therewithal all compounds have activity against *C. albicans* as much as half of ketoconazole efficiency.

On the other hand, all compounds (MIC 100 µg/mL) showed inhibitor activity against *P. aeruginosa* at two fold concentration of chloramphenicol (MIC 50 µg/mL). Also, compounds **2a**, **2c** and **2e** (MIC: 50 µg/mL) have equal effect against *E. coli* (ATCC 35218) and more effective than other compounds (MIC of chloramphenicol: 100 µg/mL). Based on this, tetrazole and benzothiazole containing compounds are two times more effective against *E. coli* (ATCC 35218). At the same time, compound **2c** bearing benzothiazole moiety (MIC: 50 µg/mL) was determined qua most active compound against *E. coli* (ATCC 25922). Among all microorganisms, *K. pneumoniae* was found as the most susceptible strain to tested compounds. But, when we compared

the effect of all compounds on gram positive bacteria and gram negative bacteria, in general, the effect on gram-positive bacteria is higher than the effect on gram-negative bacteria. However, all compounds are less effective than chloramphenicol against bacteria.

Log P and druglikeness model score were calculated by using Molsoft software and Molecular Properties and Drug-likeness Toolkit [26]. Log P values which indicate partition coefficient were found between 0.91-4.48. These values are in the appropritae range according to Lipinski rule of five. Druglikeness scores were found to be 0.34, 0.14 and 0.49 for the most active compounds **2a, 2c** and **2e**. Although there is no clear deduction, these scores are in accordance with the activity potential of the compounds.

CONCLUSION

In this work, we have synthesized novel *N*-(1*H*-benzimidazol-2-yl)-2-(substituted mercapto)acetamide derivatives (**2a-2h**) and evaluated their antimicrobial activity against seven bacteria and four fungi species. In general, compounds have determined to possess higher antifungal activity, except *C. albicans*, all compounds showed same potency with standard drug against three *Candida* strains. Therewithal, all compounds exhibited half potency of chloramphenicol against *P. aeruginosa.* Additionally, compounds **2a** with 1-methyltetrazole, **2c** with benzothiazole and **2e** with 6-chlorobenzothiazole moieties were found as the most active compounds.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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