International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Synthesis, Identification and Evaluation of Antimicrobial Activities of some New N-substituted 2-azetidinone, Imidazolidinone and tetrazole derivatives of 2-(methylthio) benzimidazole

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Abstract: ***New derivatives of 2-azetidinone, imidazolidine-4-one and tetrazole were obtained from the work that was conducted in this research. Firstly; reaction of 2-mercaptobenzimidazole (2-MBI) in basic conditions with methyl iodide to give 2-(methylthio) benzimidazole [1] then compound [1] was reacted with sodium hydride in DMF at (0 °C) to bring the salt of compound [1], the produced salt was reacted with chloroacetyl chloride to produce 1-(α-chloroaceto)-2- (methylthio) benzimidazole as a starting compound [2] . Thereafter, compound [2] was reacted with hydrazine hydrate to give 1-(α-hydrazideaceto)-2-(methylthio) benzimidazole [3] then reacted with a different substitution of an aromatic aldehyde in absolute ethanol to give Schiff's bases derivatives [4-8]. The reactions of compounds [4-8] were carried out through three pathways for cyclization: the first pathway involved a reaction with chloroacetyl chloride in the presence of triethyl amine to give 2-azetidinone derivatives [9-13]. While; the second pathway was cyclization with 2-aminoacetic acid to give imidazolidine-4-one derivatives [14-18]. Finally, the third pathway was conducted by a reaction with sodium azide to give tetrazole derivatives [19-23]. The new prepared compounds were identified by [FTIR, ^{1}H-NMR and ^{13}C-NMR] and their physical properties were measured. Furthermore, we have evaluated the effect of some prepared compounds on some bacterial and fungal strains.***

Keywords: 2-MBI, Schiff base, β -lactam, imidazolidine, tetrazole, anti-microbial

1. Introduction

2-Mercaptobenzimidazole exhibits a wide variety of interesting biological activities such as anti- microbial, antihistamine, neurotropic and analgesic activities (1). Alkylation of 2-Mercapto benzimidazole was previously demonstrated in literature survey (2). Schiff's bases are synthesized from aldehydes or ketones by some sort of a reversible-reaction. It occurs under base or acid catalysis or by heating. It is formed by nucleophile addition of primary aromatic amine to the carbonyl group (3). Schiff's bases have acquired an unparalleled significance in both the pharmaceutical and medicinal fields given their commonly used organic synthetic intermediates (4). 2-Azetidinones are also known as β-lactams and it is one of the most common heterocyclic rings found in antibiotics, which consists of a carbonyl group on the second position (5). Staudinger's ketene–imine is considered one of the most widely-used methods for the synthesis of azetidinones (β-lactam) (6). Imidazolines (dihydro imidazole) are important five membered heterocycles. Also, they can be classified according to the position of the double bond (7). A persuasive amount of studies have indicated that imidazolidine derivatives have strong antibacterial effects against pathogenic agents such as *Escherichia coli* and *Staphylococcus aureus* (8). Furthermore, Tetrazole is a five-membered ring that consists of a one carbon and four nitrogen atoms (9). 1,3-dipolar cycloaddition reaction, which was used initially to synthesize tetrazole ring by imine as a 1,3-dipolarphile reaction with azide group as a 1,3-dipolar molecule(10). Synthesis of tetrazole derivatives is obviously an important task in modern medicinal chemistry (11). In this research we aimed to synthesize new 1-(α-chloroaceto)-2-(methylthio)benzimidazolederivatives including β-lactam, imidazolidine-4-one and tetrazolemoieties and evaluation of its' antimicrobial activities.

2. Experimental

Materials and Methods

All chemicals used were supplied by: Merck, BDH, Fluka and sigma Aldrich chemicals companies. The melting point was recorded using Gallenkamp, electro-thermal melting point apparatus. Infrared spectra were recorded using (FTIR) 8400s Fourier transitions infrared spectrometer shimadzu, Japan, (KBr) disc in (4000-600) cm^{-1} spectral range, in the Department of Chemistry, College of Science, University of Baghdad and Research Laboratory, College of Pharmacy, University of Al- Mustansiriyah. ^{1}H-NMR spectra were recorded on near magnetic resonance Bruker, Ultra-shield (400) MHz, in the University of Ain-Shams, College of Pharmacy, Egypt. DMSO-d*6* was used as a solvent and in Central Laboratory Isfahan University, Iran. $CDCl_3$ was used as solvent.

Preparation of 2-(methylthio) benzimidazole (1)

This compound was prepared according to the literature's procedure (12). Physical properties and (FTIR) spectral data are listed in Table (1).

Preparation of 1-(α-chloroaceto)-2-(methylthio)benzimidazole (2) (13)

Solution of compound [I] (1gm, 0.006 mole) in anhydrous dimethyl formamide (DMF) (7ml) was cooled to 0°C, and

Sodium hydride (0.14gm, 0.006 mole) in small portions was added. The solution was stirred for (30 minutes) then Chloroacetyl chloride (0.5ml, 0.006mole) was added drop wise. The mixture was stirred for 10 minutes at 0°C, and then stirred at room temperature for another (4 hours). The solvent was evaporated then poured into ice water and filtered. The precipitate was recrystallized with ethanol to give a brown powder. The physical properties and (FRIT) spectral data are listed in Table (1).

Preparation of 1-(α-hydrazideaceto)-2-(methylthio) benzimidazole (3) (14)

(80%) Hydrazine hydrae (0.3ml, 0.008 mole) was added to compound [2] (1gm, 0.004 mole), which was dissolved in absolute ethanol (10ml). The mixture was stirred for 1 hour then refluxed for (4 hours). The solvent was evaporated to give a pale brown product and recrystallized with acetone. The physical properties and (FTIR) spectral data are listed in Table (1).

Preparation of 1-[(4-substituted benzylidene) acetohydrazide]-2-(methylthio) benzimidazole (4-8) (15)

The solution of different aromatic aldehyde compounds (0.004 mole), (3-4) drops of glacial acetic acid in absolute ethanol (5ml) was stirred for (5) minutes, then the solution of compound [3] (1gm, 0.004 mole) in absolute ethanol (10ml) was added. The mixture was refluxed and stirred for (5-6) hours, then the mixture was poured into crushed ice and the precipitate was filtrated, recrystallized with suitable solvent. The physical properties and (FTIR) spectral data are listed in Table (2).

Preparation of N-aminoacetyl-4-[(4-substituted phenyl)-3-chloro-2-oxoazetidin-1-yl]-2-(methylthio) benzimidazole (9-13) (16)

The solution of Schiff base's compounds [4-8] (0.001mole) in anhydrous DMF (10ml) was added to Chloroacetyl chloride (0.086 ml, 0.001mole), triethyl amine (0.15ml, 0.001mole) solutions in anhydrous DMF (5ml) at 0-5 °C. The mixture was refluxed for (14-16) hours at 110 °C, the mixture was then cooled at room temperature and the solvent was evaporated .The product was washed with cold water and recrystallized with suitable solvent. The physical properties and (FTIR) spectral data are listed in Table (3).

Preparation of N-aminoacetyl-2-[(4-substituted phenyl)-4-oxo-imidazolidin]-2-(methylthio) benzimidazole (14-18) (17)

The solution of Schiff bases [4-8] (0.0007 mole) in absolute ethanol (10ml), 2-amino acetic acid (0.05 gm, 0.0007 mole) in absolute ethanol (5 ml) was refluxed for (18-20) hours. The mixture was cooled and the solvent was evaporated. The product was washed with cold water and filtrated, recrystallized with suitable solvent. The physical properties are listed in Table (4).

Preparation of N-aminoacetyl-2-[(4-substituted phenyl)-4, 5-dihydro-1H-tetrazole-1-yl)]-2-(methylthio) benzimidazole (19-23) (18)

The solution of Sodium azide (0.04gm, 0.0006 mole) that was dissolved in absolute ethanol (5 ml), was added to the solution of Schiff bases [4-8] (0.0006 mole) in absolute ethanol (10 ml). The mixture was refluxed for (14 hours). The solvent was evaporated and the product was washed with cold water then recrystallized with suitable solvent. The physical properties and (FTIR) spectral data are listed in Table (5).

Anti-microbial activity test (19, 20)

Some of the prepared compounds were tested clinically against two strains of bacteria (+ve) bacterial isolates as: *Streptococcus faecalis* from the (ear) and *Staphylococcus aureus* from the (wound) and two strains from clinical gram (–ve) bacterial isolates as: *Escherichia coli* from (urine) and *Klebsiella pneumonia* from the (ear) in addition to *Candida albicans* from (vagina) as fungus isolate. The bacterial suspension was spread on the surface of Mueller Hinton Agar (MHA) plates and Blood Agar Base (BAB) plates by using cotton swab, and then let it dry in room temperature. Two wells were punched in diameter (6mm). One hundred microliters of the prepared compounds in concentration (800µl and 400µl) introduced into wells. All plates were incubated at 37 °C for 18-24 hours. DMSO used as the negative controller and Ciprofloxacin was used as a standard drug for antimicrobial. The anti-microbial action of all derivatives compounds were estimated by measuring the inhibition zone (mm). The results ofantimicrobial activities are listed in table (9).

Table 1: The physical properties and the Fourier infrared values for (2-MBI-3)

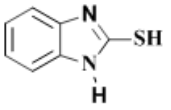
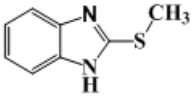
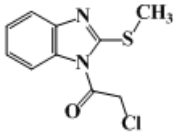
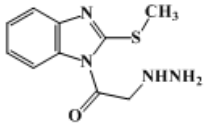
Comp. NO.	Physical properties				FTIR absorption cm^{-1}			
	Comp. structure	Melting point °C	Yield %	Color	ν(N-H)	ν(C=N)	ν(C=O)	Others
2-MBI		300-304	-	White	3155	1622	-	**ν(S-H)** 2764
1		199-200	77	Pale yellow	3220	1620	-	**ν(C-H aliph.)** 2960 2872 **ν(C-S-C)** 665
2		122-124	85	Brown	-	1616	1718	**ν (C-H aliph)** 2955 2924 2854 **ν(C-Cl)** 794
3		68-70	84	Pale brown	3227	1614	1713	**ν(NH_2)** 3473(asy.) 3416(sym.)

Table 2: The physical properties and the Fourier infrared values for (4-8)

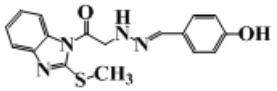
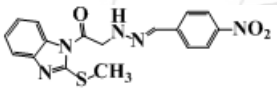
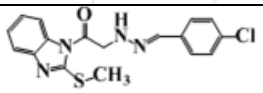
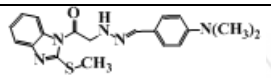
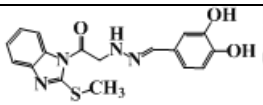
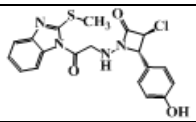
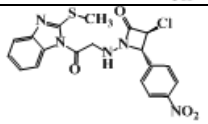
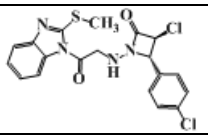
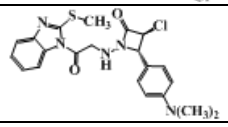
Com. NO.	Physical properties				FTIR absorption cm^{-1}			
	Comp. structure	Melting point °C	Yield %	Color	ν(N-H)	ν(C=N)	ν(C=O)	Others
4		96-98	70	Orange	3222	1620	1696	**ν(OH phenolic)** 3398
5		200-202	89	Yellow	3291	1622	1708	**ν(NO_2)** 1515 (asy.) 1352(sym.) **ν(p-NO_2)**831
6		80-82	58	Light brown	3296	1650	1700	**ν(C-Cl)** 1089 **ν(p-Cl)** 844
7		154-156	83	Deep yellow	3392	1641	1694	**ν(p-C-N(CH_3)$_2$** 813
8		130-132	48	Yellow	3195	1650	1690	**ν(OH phenolic)** 3369 3346

Table 3: The physical properties and the Fourier infrared values for (9-13)

Com. NO.	Physical properties				FTIR absorption cm^{-1}			
	Comp. structure	Melting point °C	Yield %	Color	ν(N-H)	ν(C=N)	ν(C=O)	Others
9		88-90	62	Black	3214	1631	1732 **(β-lactam)** 1690 **(amide)**	**ν(OH phenolic)** 3434 **ν(C-Cl)** 1080
10		76-78	75	Brown	3290	1623	1733(**β-lactam)** 1693 **(amide)**	**ν(NO_2)** 1519 (asy.) 1346 (sym.) **ν(C-Cl)** 1076 **ν(p-NO_2)** 852
11		112-114	76	Brown	3300	1643	1730(**β-lactam)** 1708 **(amide)**	**ν(C-Cl)** 1078 **ν(C-Cl)** 1035 **ν(p-Cl)** 844
12		174-176	67	Brown	3291	1629	1730(**β-lactam**) 1689 **(amide)**	**ν(C-Cl)** 1078

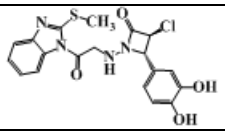
13		94-96	50	Black	3250	1606	1718(**β-lactam**) 1694 **(amide)**	**ν(OH phenolic)** 3425 **ν(C-Cl)** 1060

Table 4: The physical properties and the Fourier infrared values for (14-18)

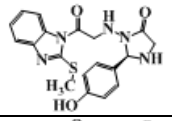
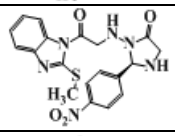
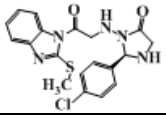
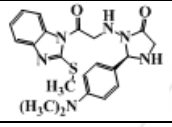
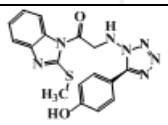
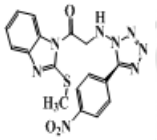
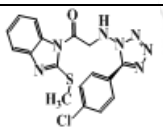
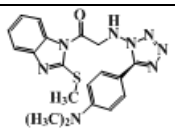
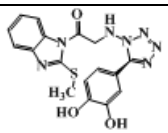
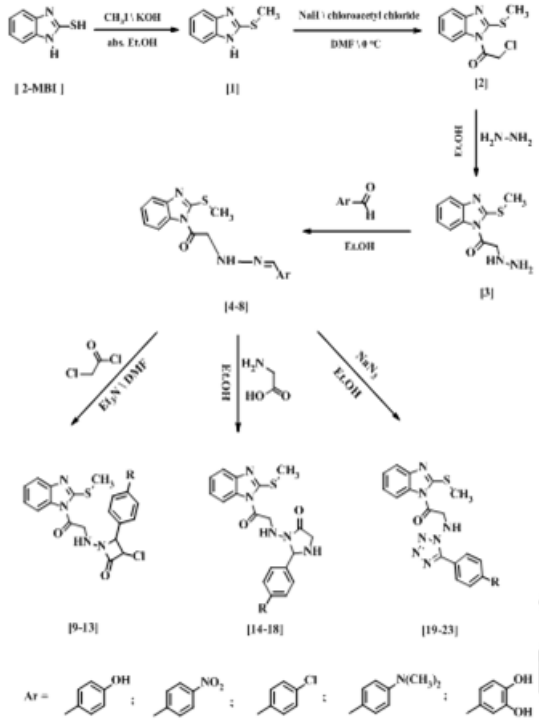
Comp. NO.	Physical properties				FTIR absorption cm^{-1}			
	Comp. structure	Melting point °C	Yield %	Color	ν(N-H)	ν(C=N)	ν(C=O)	Others
14		208-210	89	Yellow	3334 3170	1620	**(** 1700 **ring)** 1680 **(amide)**	**ν(OH phenolic)** 3444
15		174-176	88	Yellow	3345 3172	1624	**(**1708 **(ring)** 1694 **(amide)**	**ν(NO_2)** 1521 (asy.) 1342 (sym.) **ν(p-NO_2)**842
16		148-150	78	Gray	3313 3229	1613	1705 **(ring)** 1688 **(amide)**	**ν(C-Cl)** 1033
17		210-212	92	Orange	3206 3180	1612	1700 **(ring)** 1686 **(amide)**	**ν(p-C-$N(CH_3)_2$** 813

Table 5: The physical properties and the Fourier infrared values for (19-23)

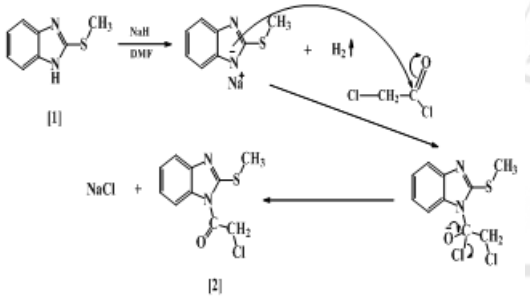
Comp. NO.	Physical properties				FTIR absorption cm^{-1}			
	Comp. structure	Melting point °C	Yield %	Color	ν(N-H)	ν(C=N)	ν(C=O)	Others
19		172-174	91	Yellow	3249	1629	1692	**ν(OH phenolic)** 3394 **ν(N=N)** 1438
20		210-214	91	Yellow	3392	1630	1705	**ν(NO_2)** 1510 (asy.) 1350 (sym.) **ν(N=N)** 1436 **ν(p-NO_2)** 833
21		184-186	41	Gray	3394	1620	1700	**ν (N=N)** 1436 **ν(C-Cl)** 1010 **ν(p-Cl)** 842
22		145-146	27	Yellow	3390	1632	1694	**ν(N=N)** 1436
23		169-170	70	Black	3200	1618	1702	**ν(OH phenolic)** 3446 **ν(N=N)** 1440

3. Result and Discussion

The steps of the synthesis 1-(α-chloroaceto)-2- (methylthio) benzimidazole, β-lactam, imidazolidine-4-one and tetrazole are shown in the scheme (1)



Compound [2] was prepared via nucelophilic acetyl substitution of compound [1] with chloroacetyl chloride as shown in mechanism (1):



FTIR spectrum of compound [2] showed the appearance of the absorption band at (1718) cm^{-1}due to ν(C=O amide) (21), (2955, 2924&2854) cm^{-1} due to ν(CH_3). The FTIR indicated the disappearance band of ν(-SH) and ν(-NH) as shown in table (1).^{1}H-NMR spectrum of compound [2] showed a singlet signal at δ= (2.90) ppm due to (S-CH_3) proton, a singlet signal at δ= (4.74) ppm due to (CH_2-Cl) proton and a signal at δ= (7.41-7.73) ppm due to the aromatic ring protons and the disappearance of the signal of (NH) proton as shown in table (6).^{13}C-NMR spectral data were listed in table (7). Also, Silver nitrate test gave (+ve) in the presence of a halide.

Compound [2] was reacted with hydrazine hydrate to give hydrazide derivative [3] (scheme 1) FTIR spectrum of compound [3] showed the appearance of the absorption band at (3473 asy.) and (3416 sym.) cm^{-1} due to ν(NH_2), (3227) cm^{-1} due to ν(NH) and (1713) cm^{-1} due to ν(C=O amide) as in table (1).^{1}H-NMR spectrum of compound [3] showed a singlet signal at δ= (2.08) ppm due to (S-CH_3) proton, a doublet signal at δ= (3.63) ppm belonged to (CH_2-NH) protons, a doublet signal at δ=(6.51) ppm for(NH_2) protons, signal at δ= (7.41-7.73) ppm due to the aromatic ring protons and signal at δ= (8.12) ppm due to (NH) proton as shown in table (6).

Compound [3] was treated with different substituted aromatic aldehydes to form Schiff's bases of the title compounds [4-8] (scheme1). FTIR spectrum of compounds [4-8] showed the disappearance band of ν(-NH_2) and appearance of the band at (1620-1650) cm^{-1} due to ν(C=N) of Schiff's bases and (3392-3195) cm^{-1} due to ν(-NH). All FTIR spectrum data of compounds [4-8] are listed in table (2).^{1}H-NMR spectrum data of compounds [4-5] showed a singlet signal at δ= (5.92-5.93) ppm due to (N=CH) proton, a singlet signal at δ= (8.33-8.88) ppm due to (-NH) proton and disappearance of the signal of (NH_2) proton as shown in table (8).

On other hand, The Schiff's bases [4-8] were reacted with different reagents by three various methods to give different cyclic compounds. First method; Schiff's bases [4-8] were reacted with chloroacetyl chloride in the presence of triethyl amine in diethyl formamide to produce 2-azetidinone compounds [9-13] by ketene-imine Staudinger reaction (scheme1). FTIR spectrum of compounds [9-13] showed the appearance of the absorption band at (1035-1080) cm^{-1} due to (C-Cl azetidine ring), (3300-3214) cm^{-1} for (-NH). All FTIR spectrum data of compounds [9-13] are listed in table (3). ^{1}H-NMR spectrum of compound [11-12] showed a singlet signal at δ= (3.42-3.48) ppm due to (CH azetidine ring) proton, a singlet signal at δ= (4.21-4.28) ppm due to (CH-Cl azetidine ring) proton and a singlet signal at δ= (8.32-8.83) ppm due to (-NH) proton and the disappearance of the signal of (N=CH) proton of Schiff's bases as shown in table (8).

While in the second method, Schiff's bases [4-8] were reacted with 2-amino acetic acid in absolute ethanol to give imidazolidine-4-one compounds [14-18]. FTIR spectrum of compound [14-18] showed the appearance of the absorption bands at (1718-1700) cm^{-1} due to (C=O imidazolidine ring). All FTIR spectrums of compounds [14-18] are listed in table (4). ^{1}H-NMR spectrum of compound [14-15] showed a doublet signal at δ= (3.45-3.66) ppm due to (CH imidazolidine ring) proton, a singlet signal at δ= (8.74) ppm due to (NH imidazolidine ring) proton and the disappearance of the signal of (N=CH) proton of Schiff's bases as shown in table (8).

Finally, the third method of Schiff's bases [4-8] cyclization with sodium azide in absolute ethanol to give tetrazole compounds [19-23]. FTIR spectrum data of compounds [19-23] showed the appearance of the absorption bands at (1440-1436) cm^{-1} due to (N=N tetrazole ring). All FTIR spectrum of compounds [19-23] are listed in table (5). ^{1}H-NMR spectrum of compound [19-20] showed the disappearance of the signal of (N=CH) proton of Schiff's bases as shown in table (8).

Table 6: ^{1}HNMR spectral data (δ ppm) of compounds [1-3]

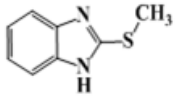
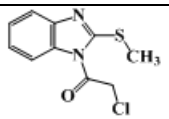
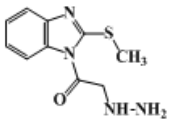
Com.NO.	Structure	^{1}HNMR spectral data (δ ppm)
1		2.70 (s,3H,-CH_3); 7.09-7.43 (m,4H,Ar-H); 12.5 (s,H,-NH).
2		2.90 (s,3H,S-$\underline{CH_3}$); 4.74 (s,2H,-CH_2-Cl); 7.41-7.73 (m,4H, Ar-H)
3		2.08 (s,3H,-S-CH_3); 3.63 (d,2H,-$\underline{CH_2}$-NH); 6.51 (d,H,-$\underline{NH_2}$); 7.41-7.73 (m,4H,Ar-H); 8.12 (m,H,-NH)

Table 7: ^{13}CNMR spectral data (δ ppm) of compounds [2]

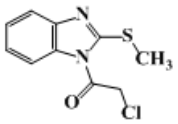
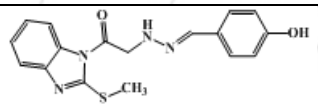
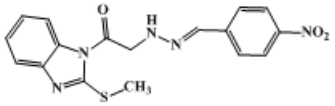
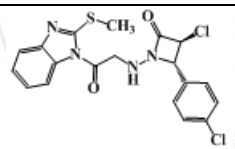
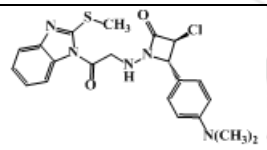
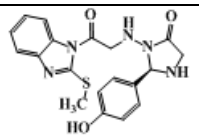
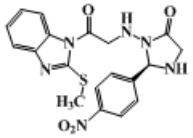
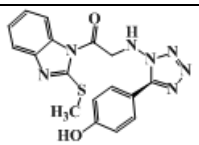
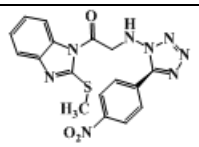
Com. NO.	Structure	^{13}CNMR spectral data (δ ppm)
2		40.81 (S-CH_3); 79 (CH_2); 113.11-139.39 (Ar); 156.33 (N=C-N); 173.60(O=C-N)

Table 8: ^{1}HNMR spectral data (δ ppm) of compounds [4,5,11,12,14,15,19,20]

Com. No.	Structure	^{1}HNMR spectral data (δ ppm)
4		2.24 (s,3H,-CH_3); 2.82 (d,2H,-CH_2); 5.92 (s,H,-N=CH); 7.21-7.87 (m,8H,Ar-H); 8.88 (s,H,-NH-N); 9.99 (s,2H,-OH)
5		2.18 (s,3H,-CH_3); 3.53 (d,2H,-CH_2); 5.93 (s,H,-N=CH); 7.44-8.08 (m,8H,Ar-H) 8.33 (t,H,-NH-N)
11		2.78 (s,3H,-CH_3); 3.13 (s,2H,-CH_2); 3.42 (s,1H,-CH azetidine ring); 4.21 (s,1H,-CH-Cl); 7.06-7.29 (m,8H,Ar-H); 8.32 (s,1H,-NH)
12		1.53 (s,6H,-N-CH_3) ; 2.73 (s,3H,-S-CH_3) ; 3.17 (d,2H,-CH_2); 3.48 (s,H,-CH azetidine ring); 4.28 (s,-CH-Cl); 7.29-7.77 (m,8H,Ar-H); 8.83 (s,H,-NH)
14		2.13 (s,3H,-CH_3); 2.77 (s,4H,-CH_2); 2.84 (s,-CH_2imidazolidine ring); 3.45 (s,H,-CH imidazolidine ring); 7.24-7.81 (m,8H,Ar-H); 8.31 (s,H,-NH); 8.74 (s,H,-NH imidazolidine ring); 9.72 (s,H,-OH)
15		2.12 (s,3H,-CH_3); 2.85 (s,4H,-CH_2 and -CH_2imidazolidine ring); 3.66 (s,H,-CH imidazolidine ring); 6.91-7.82 (m,8H,Ar-H); 8.31 (s,H,-NH); 8.74 (s,H,-NH imidazolidine ring)
19		2.10 (s,3H,-CH_3); 3.06 (d,2H,-CH_2); 6.76-7.76 (m,8H,Ar-H); 8.74 (s,H,-NH); 10.03 (s,H,-OH)

20		2.80 (s,3H,-CH_3); 3.54 (d,2H,-CH_2); 6.94-7.77 (m,8H,Ar-H); 9.17 (t,H,-NH)

Anti-microbial activity's test:

Table 9 shows the inhibition zones in (mm) of the mentioned derivatives. In comparison with a standard drug (Ciprofloxacin). The antimicrobial activity's test showed that those compounds were specific for *Escherichia coli* bacteria while some of the compounds showed no activity for *Klebsiella pneumonia*, however, in *Streptococcus faecalis* bacterial showed a weak activity. Some of the prepared compounds showed high activity for *Staphylococcus aureus* bacteria and *Candida albicans* fungi.

Table 9: Anti-microbial activity of select compounds

Sample code and stand.	Conc (µg/ml)	Zone of inhibition (mm)				
		Gram positive		Gram negative		Fungal
		Strept.	Stap.	E-Coli	Klebs.	Candida
9	800	10	18	12	-	10
	400	10	14	6	-	12
10	800	8	10	4	-	-
	400	6	14	6	-	8
11	800	8	6	12	6	8
	400	6	22	6	12	6
12	800	10	10	4	8	16
	400	10	14	6	14	6
13	800	8	12	4	-	12
	400	10	12	-	-	6
14	800	14	12	4	14	10
	400	10	8	8	-	4
15	800	8	6	12	8	24
	400	6	10	6	14	-
16	800	6	6	-	10	8
	400	6	14	6	20	14
17	800	6	-	-	8	4
	400	6	8	-	8	4
18	800	6	-	4	8	14
	400	6	12	16	18	16
19	800	8	6	8	-	12
	400	6	-	12	6	14
20	800	6	-	20	6	14
	400	6	12	22	14	12
21	800	16	16	8	-	6
	400	10	10	4	-	4
22	800	8	8	6	-	-
	400	-	-	4	-	-
23	800	16	16	4	14	14
	400	12	12	6	16	12
Ciprofloxacin	10	40	16	-	30	12
DMSO	-	-	-	-	-	-

Zone of inhibition: (-) no inhibition; (3-6) weak; (7-10) moderate; (11-15) strong

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