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Synthesis, antibacterial, antifungal and antioxidant activity studies on 2-benzylthio- and 2-benzylsulfonyl-1*H*-imidazoles

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ABSTRACT

New 2-(2-methylbenzylthio)-1H-imidazole-4,5-dicarboxylic acid derivatives were prepared by the reaction of diethyl 2-mercapto-4,5-imidazole dicarboxylate, DMF, $NaHCO_3$, K_2CO_3 and alkyl or aryl halides. These on further reaction with DCM and MCPBA form 2-(2-methylbenzylsulfonyl)-1H-imidazole-4,5-dicarboxylic acid derivatives. All new compounds were tested for their biological activities.

Keywords: Diethyl 2-mercapto-4,5-imidazoledicarboxylate, 2-(2-methylbenzylthio)-1*H*-imidazole-4,5-dicarboxylic acid derivatives, 2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid derivatives, antibacterial, antifungal and antioxidant activity.

INTRODUCTION

For a long time heterocyclic have constituted one of the largest areas of research in organic chemistry. Heterocyclic compounds are of particular importance as they are associated with a wide variety of physiological activities with wide variety of heterocyclic systems known today. The nitrogen heterocyclics are of great importance as they are present in nucleic acids, vitamins, proteins and other biologically important molecular systems. Among different nitrogen heterocycles, the imidazole and benzimidazole ring systems are very important since several of its derivatives have been found to be medicinally useful. With increase in the incidence of multi drug–resistant to Gram-positive and Gram-negative bacteria it becomes imperative to continuously search for small molecules as anti-infective agents. Imidazoles and benzimidazoles fit this requirement well since they have demonstrated a diverse set of biological activities that include antibacterial, antiamoebic, antiviral, antifungal [1-4], anthelmintic [5], antiHIV [6], antihistaminic [7], antiulcer [8,9], cardiotonic [10], antihypertensive [11,12], and neuroleptic [13]. Their observed activity depends upon the functional group attached to the moiety. In order to obtain more effective chemotherapeutic agents, a variety of reports have been presented on the

synthesis and biological evaluation of new imidazoles and benzimidazoles [14]. The development of resistance to current antibacterial therapy continues to search for more effective agents.

As known not only biochemical similarity of the human cell and fungi forms a handicap for selective activity but also the easily gained resistance is the main problem encountered in developing safe and efficient antifungals. The imidazole antifungals such as clotrimazole, miconazole and ketoconazole showed good optical activity, but were only of limited value for systematic administration. But triazole derivatives are the other major chemical group of antifungal azole derivatives. The triazoles (fluconazole and itraconazole) possess a broad spectrum of antifungal activity and reduced toxicity when compared with the imidazole antifungals [15-17]. Metronidazole and related N-1 substituted 5-nitroimidazoles like ornidazole, secnidazole and tinidazole are widely used in the treatment of diseases caused by protozoa and anaerobic bacteria [18,19]. In view of the above it is worthwhile to prepare imidazole and benzimidazoles derivatives.
In organic synthesis many rate enhancement reactions has been reported in recent years [20].

MATERIALS AND METHODS

The IR spectra were recorded in KBr discs (υ_{max} in cm^{-1}) on Perkin-Elmer FT-IR spectrophotometer. The ^{1}H-NMR spectra were recorded at 300 MHz with a Bruker Avance DPX 300 instrument. Mass spectra under electron impact conditions (EI) were recorded at 70 ev ionizing voltage with a VG Prospec instrument and the presented as m/z (% rel int.). Elemental analyses (C,N,H) results were found to be in good agreement with the calculated values. Melting points were determined with Capillaries Thomas Hoover melting point apparatus and are uncorrected. TLC monitored all reactions and purity of the synthesized compounds.

General Procedure:
We have been continuously working on developing new heterocyclic systems i.e. for substituted 2-(2-methylbenzylthio)-1*H*-imidazole-4,5-dicarboxylic acid derivatives (**5a-5g**) and substituted 2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid derivatives (**6a-6g**) taking advantage of simple reaction conditions. Initially we have prepared glycine ethyl ester hydrochloride (**2**) from reaction of glycine (**1**) with ethanol in the presence of $SOCl_2$ in only 75% good yield according to literature report [21-23]. The compound **2** was converted to N-formylglycine ethyl ester (**3**) in triethylamine and methylformate in good yields [24-27]. **3** on reaction with diethyl oxlate and KSCN gave intermediate product *viz*. diethyl 2-mercapto-4,5-imidazoledicarboxylate (**4**). [28-30]. Substituted 2-(2-methylbenzylthio)-1*H*-imidazole-4,5-dicarboxylic acid derivatives (**5a-5g**) were prepared by treating diethyl 2-mercapto-4,5-imidazole dicarboxylate (**4**) (1gm,1mmol) in DMF and sodium bicarbonate (1.5 mmol) at 0 ^{o}C and benzyl halides (2-methyl benzyl bromide) (1.3 mmol) were added for S-benzylation and stirred at room temperature for 1h. Then N-alkylations were carried out by refluxing the mixture for 5h by the addition of potassium carbonate (1.3 mmol) and alkyl halides (isobutyl iodide) (1.1mmol). The contents were neutralized with dilute acid and extracted with ethyl acetate to obtain the compounds **5a-5g**.

1-Isobutyl-2-(2-methylbenzylthio)-1*H*-imidazole-4,5-dicarboxylic acid (**5a**): Yield 75%, mp 257-258°C, IR spectrum, υ, cm^{-1}: 3334 (OH); 1763 (C=O); 1630 (C=C); 1564 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.75 (d, 6H); 1.9-1.95 (m, 1H); 2.35 (s, 3H); 4.1 (d, 2H); 4.4 (s, 2H); 7.12-7.30 (m, 4H); 12.85 (s, 1H). Mass spectrum, m/z: 349 $(M+1)^+$. Found, %: C, 58.62; H, 5.74; N, 8.45. $C_{17}H_{20}N_2O_4S$. Calculated, %: C, 58.60; H, 5.79; N, 8.04.

Diethyl 2-(2-methylbenzylthio)-1*H*-imidazole-4,5-dicarboxylate (**5b**)**:** Yield 73%, mp 242-244°C, IR spectrum, υ, cm^{-1}: 3243 (NH); 1736 (CO_2Et); 1619 (C=C); 1573 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32-1.40 (t, 6H); 2.4 (s, 3H); 4.4 (m, 6H); 7.1-7.3 (m, 4H); 9.6 (s, 1H). Mass spectrum, m/z: 349 $(M+1)^+$. Found, %: C, 58.62; H, 5.74; N, 8.45. $C_{17}H_{20}N_2O_4S$. Calculated, %: C, 58.60; H, 5.79; N, 8.04.

2-((1,2,3,4-Tetrahydronaphthalen-1-yl)methylthio)-1*H*-imidazole-4,5-dicarboxylic acid (**5c**)**:** Yield 85%, mp 250-252°C, IR spectrum, υ, cm^{-1}: 3215 (NH); 3410 (OH); 1760 (C=O); 1623 (C=C); 1574 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.6 (s, 1H); 1.8 (m, 3H); 2.7 (d, 2H); 3.0 (s, 1H); 3.20-3.33 (d, 1H); 3.6 (d, 1H); 7.1 (m, 3H); 7.4 (d, 1H); 12.85 (s, 1H). Mass spectrum, m/z: 331$(M+ 1)^+$. Found, %: C, 57.83; H, 4.81; N, 8.43. $C_{16}H_{14}N_2O_4S$. Calculated, %: C, 57.85; H, 4.80; N, 8.43.

Triethyl-2-(2-methylbenzylthio)-1*H*-imidazole-1,4,5-tricarboxylate (**5d**)**:** Yield 87%, mp 181-182°C, IR spectrum, υ, cm^{-1}: 1725 (CO_2Et); 1620 (C=C); 1545 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.3-1.4 (t, 9H); 2.4 (s, 3H); 4.45 (q, 6H); 4.55 (s, 2H); 7.1-7.2 (m, 3H); 7.4 (d, 1H). Mass spectrum, m/z: 421 $(M+1)^+$. Found, %: C, 57.15; H, 5.71; N, 6.66. $C_{20}H_{24}N_2O_6S$. Calculated, %: C, 57.13; H, 5.75; N, 6.66.

1-(2-Methylbenzyl)-2-(2-methylbenzylthio)-1*H*-imidazole-4,5-dicarboxylic acid (**5e**)**:** Yield 75%, mp 215-216°C, IR spectrum, υ, cm^{-1}: 3390 (OH); 1765 (C=O); 1640 (C=C); 1565 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.20 (s, 6H); 4.4 (s, 2H); 5.3 (s, 2H); 7.0-7.20 (m, 8H); 11.1 (s, 1H). Mass spectrum, m/z: 397 $(M+1)^+$. Found, %: C, 63.62; H, 5.08; N, 7.07. $C_{21}H_{20}N_2O_4S$. Calculated, %: C, 63.60; H, 5.02; N, 7.05.

1-Benzyl-2-(benzylthio)-1*H*-imidazole-4,5-dicarboxylic acid (**5f**)**:** Yield 79%, mp 184-185°C, IR spectrum, υ, cm^{-1}: 3365 (OH); 1745 (C=O); 1605 (C=C); 1545 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.4 (s, 2H); 5.32 (s, 2H); 7.20-7.30 (m, 10H); 11.5 (s, 1H). Mass spectrum, m/z: 369 $(M+1)^+$. Found, %: C, 61.94; H, 4.38; N, 7.60. $C_{19}H_{16}N_2O_4S$. Calculated, %: C, 61.89; H, 4.35; N, 7.55.

1-Isobutyl-2-(isobutylthio)-1*H*-imidazole-4,5-dicarboxylic acid (**5g**)**:** Yield 67%, mp 234-235°C, IR spectrum, υ, cm^{-1}: 3400 (OH); 1735 (C=O); 1620 (C=C); 1565 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.75 (d, 12H); 1.85-1.95 (m, 2H); 3.1 (d, 2H); 3.85 (d, 2H); 11.2 (s, 1H). Mass spectrum, m/z: 301 $(M+1)^+$. Found, %: C, 51.98; H, 6.71; N, 9.33. $C_{13}H_{20}N_2O_4S$. Calculated, %: C, 51.97; H, 6.69; N, 9.30.

General Procedure for the synthesis of substituted 2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid derivatives (**6a-6g**).

To an equimolar mixture of (**5a-5g**) 1 mmol, MCPBA (2 mmol) and DCM (10 ml) were added at RT and stirred for 1 hr. After it was neutralized with Na_2SO_3 solution DCM layer separated, dried and recrystallization with ethanol.

1-Isobutyl-2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid (6a): Yield 65%, mp 213-214°C, IR spectrum, υ, cm^{-1}: 3420 (OH); 1765 (C=O); 1630 (C=C); 1560 (C=N);1335, 1136 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.80 (d, 6H); 1.95-2.0 (m, 1H); 2.35 (s, 3H); 4.1 (d, 2H); 4.85 (s, 2H); 7.2-7.40 (m, 4H); 12.85 (s, 1H). Mass spectrum, m/z: 381 $(M+1)^+$. Found, %: C, 53.68; H, 5.26; N, 7.36. $C_{17}H_{20}N_2O_6S$. Calculated, %: C, 53.65; H, 5.28; N, 7.35.

Diethyl 2-(2-Methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylate (6b): Yield 80%, mp 270-271°C, IR spectrum, υ, cm^{-1}: 3243 (NH); 1730 (CO_2Et); 1610 (C=C); 1570 (C=N); 1325, 1130 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30-1.42 (t, 6H); 2.45 (s, 3H); 4.4-4.6 (m, 6H); 7.20-7.30 (m, 4H); 9.6 (s, 1H). Mass spectrum, m/z: 381 $(M+1)^+$. Found, %: C, 53.67; H, 5.30; N, 7.36. $C_{17}H_{20}N_2O_6S$. Calculated: C, 53.65; H, 5.29; N, 7.35.

2-((1,2,3,4-Tetrahydronaphthalen-1-yl)methylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid (6c): Yield 80%, mp 192-193°C, IR spectrum, υ, cm^{-1}: 3232 (NH); 3324 (OH); 1750 (C=O); 1635 (C=C); 1545 (C=N); 1338, 1136 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.6 (s, 1H); 1.8 (m, 3H); 2.9 (d, 2H); 3.04 (s, 1H); 3.25-3.30 (d, 1H); 3.65 (d, 1H); 7.1-7.2 (m, 3H); 7.5 (d, 1H); 12.85 (s, 1H). Mass spectrum, m/z: 365 $(M+1)^+$. Found, %: C, 52.74; H, 4.43; N, 7.69. $C_{16}H_{14}N_2O_6S$. Calculated, %: C, 52.69; H, 4.41; N, 7.60.

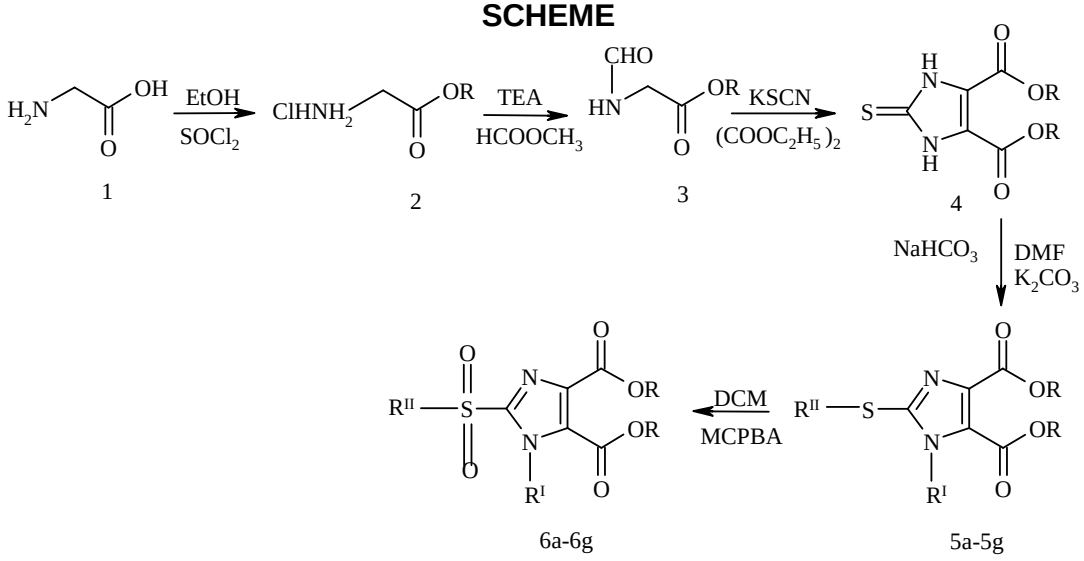
Triethyl 2-(2-methylbenzylsulfonyl)-1*H*-imidazole-1,4,5-tricarboxylate (6d): Yield 81%, mp 210-211°C, IR spectrum, υ, cm^{-1}: 1745 (CO_2Et); 1655 (C=C); 1563 (C=N); 1341, 1125 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.2-1.4 (t, 9H); 2.5 (s, 3H); 4.32-4.60 (q, 6H); 5.0 (s, 2H); 7.1-7.35 (m, 3H); 7.4 (d, 1H). Mass spectrum, m/z: 453 $(M+1)^+$. Found, %: C, 53.09; H, 5.37; N, 6.19. $C_{20}H_{24}N_2O_8S$. Calculated, %: C, 53.05; H, 5.37; N, 6.17.

1-(2-Methylbenzyl)-2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid (5e): Yield 73%, mp 195-197°C, IR spectrum, υ, cm^{-1}: 3390 (OH); 1760 (C=O); 1649 (C=C); 1565 (C=N); 1335, 1135 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.25 (s, 6H); 4.8 (s, 2H); 5.8 (s, 2H); 7.0-7.32 (m, 8H); 11.1 (s, 1H). Mass spectrum, m/z: 429 $(M+1)^+$. Found, %: C, 58.87; H, 4.71; N, 6.54. $C_{21}H_{20}N_2O_6S$. Calculated, %: C, 58.83; H, 4.69; N, 6.53.

1-Benzyl-2-(benzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid (6f): Yield 65%, mp 202-203°C, IR spectrum, υ, cm^{-1}: 3395 (OH); 1755 (C=O); 1630 (C=C); 1555 (C=N); 1341, 1125 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.8 (s, 2H); 5.32 (s, 2H); 7.20-7.30 (m, 10H); 11.5 (s,1H). Mass spectrum, m/z: 401 $(M+1)^+$. Found, %: C, 56.99; H, 4.03; N, 7.00. $C_{19}H_{16}N_2O_6S$. Calculated, %: C, 56.98; H, 4.02; N, 6.96.

1-Isobutyl-2-(isobutylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid (6g): Yield 77%, mp 253-254°C, IR spectrum, υ, cm^{-1}: 3392 (OH); 1735 (C=O); 1620 (C=C); 1565 (C=N); 1338, 1136 (SO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.80 (d, 12H); 1.9 (m, 1H); 2.1(m, 1H); 3.45 (d, 2H); 4.0 (d, 2H); 11.2 (s, 1H). Mass spectrum, m/z: 333 $(M+1)^+$. Found, %: C, 46.98; H, 6.07; N, 8.43. $C_{13}H_{20}N_2O_6S$. Calculated, %: C, 46.96; H, 6.08; N, 8.42.

SCHEME



1 2 3 4

6a-6g 5a-5g

	R	R^I	R^{II}
5a,6a	H	$CH_2CH(CH_3)_2$	o-Me-$CH_2C_6H_4$
5b,6b	Et	H	o-Me-$CH_2C_6H_4$
5c,6c	H	H	$C_{10}H_{11}CH_2$
5d,6d	Et	COOEt	o-Me-$CH_2C_6H_4$
5e,6e	H	o-Me-$CH_2C_6H_4$	o-Me-$CH_2C_6H_4$
5f,6f	H	$CH_2C_6H_5$	$CH_2C_6H_5$
5g,6g	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$

Antimicrobial Testing

The compound **5a-5g** and **6a-6g** were tested for in vitro antimicrobial activity at two different concentrations 100 and 200µg per disc. The antibacterial activity was screened against *Staphylococcus aureus*, *Bacillus subtilis* (Gram-positive bacteria) and *Proteus vulgaris*, *Klebsiella pneumoniae* (Gram-nagative bacteria) on nutrient agar plates at 37 ^{0}C for 24 hrs using chloramphenicol as reference during. The compounds were also evaluated for their antifungal activity against *Aspergillus niger* and *Pencillium chrysogenium* using fluconazole as standard drug. Fungi cultures were grown on potato dextrose agar (PDA) medium at 25 ^{0}C. The spore suspension was adjusted to 10^6 pores ml^{-1} at an mg ml^{-1} concentration by the Vincent and Vincent method [31].

Antioxidant Testing

The compounds **5a-5g** and **6a-6g** are tested for antioxidant property by nitric oxide [32-33] and DPPH [34] methods.

Antioxidant Testing. The compounds **5a-5g** and **6a-6g** are tested for antioxidant property by **nitric oxide** and **DPPH** methods.

Assay for Nitric Oxide (NO) Scavenging Activity. Sodium nitroprusside (5µM) in phosphate buffer pH 7.4 was incubated with 100 µM concentration of test compounds dissolved in a

suitable solvent (methanol) and tubes were incubated at 25^0C for 120 min. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals 0.5 ml of incubation solution was taken and diluted with 0.5 ml of griess reagent (1% sulfanilamide, 0.1% *N*-naphthylethylenediamine dihydrochloride and 2% *o*-phosphoric acid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthylethylenediamine dihydrochloride was read at 546 nm.

Reduction of 1,1-diphenyl-2-picrylhydrazyl (DPPH) Free Radical (DPPH Method): The nitrogen centered stable free radical DPPH has often been used to characterize antioxidants. It is reversibly reduced and the odd electron in the DPPH free radical gives a strong absorption maximum at 517 nm, which is purple in color. This property makes it suitable for spectrophotometric studies. A radical scavenging antioxidant reacts with DPPH stable free radical and converts into1,1-diphenyl-2-picrylhydrazine. The resulting decolorization is stoichiometric with respect to the number of electrons captured. The change in the absorbance produced in this reaction has been used to measure antioxidant properties. The solutions of test compounds (100 µM) were added to DPPH (100 µM) in ethanol. The tubes were kept at an ambient temperature for 25 minutes and the absorbance was measured at 517 nm. The difference between the test and the control experiments was taken and expressed as the percentage scavenging of the DPPH radical.

Table 1. Antibacterial Activity* of the Target Compounds 5a-6g

Compound	Concentration	Zone of inhibition (mm)			
		Gram-positive bacteria		Gram-negative bacteria	
	(µg)	*S.aureus*	*B.subtilis*	*P.vulgaris*	*K.pneumoniae*
5a	100	20	22	17	19
	200	27	25	22	23
5b	100	15	18	17	19
	200	17	22	20	21
5c	100	25	23	20	23
	200	30	25	23	28
5d	100	12	11	14	13
	200	15	13	17	16
5e	100	32	27	24	26
	200	35	30	28	27
5f	100	26	26	20	21
	200	32	30	24	24
5g	100	12	13	12	14
	200	14	12	15	17
6a	100	11	12	11	11
	200	14	16	14	13
6b	100	28	31	22	21

	200	33	35	26	25
6c	100	25	24	20	21
	200	31	28	23	24
6d	100	30	31	31	35
	200	35	38	40	39
6e	100	27	24	24	23
	200	33	29	28	29
6f	100	30	28	26	22
	200	34	32	30	28
6g	100	14	12	13	14
	200	17	16	16	17
Chloram-phenicol	100	35	38	40	42
	200	39	41	44	45

* c = 100 µg / ml.; * c = 200 µg / ml.

Table 2. Antifungal Activity* of the Target Compounds 5a-6g

Compound	Concentration	Zone of Inhibition (mm)	
	(µg/ml)	***A.niger***	***P.chrysogenium***
5a	100	24	18
	200	27	26
5b	100	14	21
	200	19	29
5c	100	26	26
	200	30	29
5d	100	15	18
	200	20	23
5e	100	15	25
	200	18	28
5f	100	25	30
	200	27	32
5g	100	17	16
	200	20	20
6a	100	17	18
	200	22	22
6b	100	31	28
	200	37	34
6c	100	33	34
	200	35	36
6d	100	30	33

	200	39	40
6e	100	30	28
	200	36	34
6f	100	27	32
	200	30	40
6g	100	12	15
	200	18	20
Fluconazole	100	38	41
	200	42	44

* c = 100 µg / ml.; * c = 200 µg / ml.

Table 3: Antioxidant Activity* of the Target Compounds 5a-6g

Compound	% Inhibition at 100 µM	
	Nitric oxide method	DPPH method
5a	82.25	84.74
5b	34.33	38.12
5c	91.18	93.65
5d	29.21	27.75
5e	70.27	72.25
5f	79.10	76.80
5g	25.10	35.22
6a	24.78	26.17
6b	72.14	75.25
6c	22.18	28.61
6d	96.42	94.38
6e	31.25	29.65
6f	90.15	85.26
6g	80.65	82.45

* c = 100 µM.

RESULTS AND DISCUSSION

The ^{1}H-NMR spectrum of benzyl methylene protons of **5a** showed a singlet at δ 4.4 ppm and they were downfield shifted to δ 4.85 ppm (**6a**) indicating the oxidation of the sulfur to SO_2 with MCPBA**.**

The results of the compounds of preliminary antimicrobial testing are shown in Tables-1 and 2. The results revealed that the inhibitory activity against Gram-positive bacteria was higher than Gram-negative bacteria. The imidazole derivatives **5b, 5d, 5g, 6a** and **6g** were displayed least activity. The compounds **5a, 5c, 5e, 5f, 6b, 6c**, **6d, 6e,** and **6f** showed excellent activity against

Gram-positive bacteria (inhibitory zone>25mm) and good activity against Gram negative bacteria (inhibitory zone>20mm). All the test compounds **5a, 5c, 5f, 6b, 6c, 6d, 6e** and **6f** excellent activity and compounds **5b, 5d, 5e, 5g, 6a** and **6g** exhibited moderate activity when compared to that of standard drug fluconazole at the same concentration as the test drugs against *Aspergillus niger*. Compounds **5c, 5e, 5f, 6b, 6c, 6d, 6e** and **6f** excellent activity and compounds **5a, 5b, 5d, 5g, 6a,** and **6g** exhibited moderate activity when compared to that of standard drug fluconazole at the same concentration as the test drugs against *Pencillium chrysogenium* (Table 1 & 2). The compounds **5a,5c,5e,5f,6b,6d,6f** and **6g** exhibited high antioxidant property in both nitric oxide and DPPH methods at 100 µM concentration (Table 3).

CONCLUSION

The synthesis of target novel compound substituted 2-(2-methylbenzylthio)-1*H*-imidazole-4,5-carboxylic acid derivatives (**5a-5g**) and substituted 2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid derivatives (**6a-6g**) was achieved according to the steps indicated. These reactions are simple, easily carried under normal reaction conditions. The prepared thio and sulfonyl compounds are novel and are unknown. All the newly synthesized substituted 2-(2-methylbenzylthio)-1*H*-imidazole-4,5-carboxylic acid derivatives (**5a-5g**) and substituted 2-(2-methylbenzylsulfonyl)-1*H*-imidazole-4,5-dicarboxylic acid derivatives (**6a-6g**) found to exhibit significant activity by testing for antibacterial against *S.aureus, B.subtilis, P.vulgaris and K.pneumoniae*; antifungal activity against *A.niger, P.chrysogenium* and antioxidant activity.

REFERENCES

[1] B. C. Bishop, E. T. J. Chelton, A. S. Jones, *Biochem. Pharmacol.*, **1964,** 13, 751.
[2] N. Bhari, M. Shailendra, G. Garza, D. E. Cruz-Vega, K. Garza, F. Saleem. Naqvi, M. R. Maura, A. Azam, *Bioorg. Med. Chem. Lett.*, **2002**, 12, 8.
[3] R. V. Devivar, E. Kawashima, G. R. Revankar, J. Breitenbach, E. Kreske, J. Drach, L. Townsend, *J. Med. Chem.*, **1994**, 37, 2942.
[4] D. J. Sheehan, C. A. Hitchcock, C. M. Sibley, *Clin. Microbiol. Rev.*, **1999**, 12, 40.
[5] A. G. Saimo, A. C. Cremieux, J. M. Hay, A. Meulemans, M. D. Giovanangeli, B. Delaitre, F. P. Coulaud, *Lancet*., **1983**, 17, 652.
[6] A. Chimirri, S. Grasso, A. M. Monforte, P. Monforte, and M. Zappala, *Il Farmaco.*, **1991**, 46, 925.
[7] J. Benavides, H. Schoemaker, C. Dana, Y. Claustre, M. Delahaye, M. Prouteau, P. Manoury, J. V. Allen, B. Scatton, S. Z. Langer, S. Arbilla, *Arzneim.-Forsch.*, **1995**, 45, 551.
[8] K. Ishihara, T. Ichikawa, Y. Komuro, S. Ohara, K. Hotta, *Arzneim.- Forsch. Drug Res.*, **1994**, 44, 827.
[9] D. Y. Graham, A. Mccullough, M. Sklar, J. S. Sontag, W. M. Roufail, R. Stone, R. H. Bishop, N. Gitlin, A. J. Cagliola, R. S. Berman, and T. Humphries, *Digestive Diseases and Sciences*, **1990**, 35, 66.
[10] G. Piazzesi, L. Morano, J. C. Ruegg, *Arzneim.-Forsch. Drug Res.*, **1987**, 37, 1141.
[11] I. Wiedemann, H. Peil, H. Justus, S. Adamus, V. Brantl, H. Lohmann, *Arzneim.- Forsch. Drug Res.*, **1985**, 35, 964.
[12] K. Kubo, Y. Kohara, E. Imamiya, Y. Sugiura, Y. Inada, Y. Furukawa, K. Nishikawa, T. Naka, *J. Med. Chem.*, **1993**, 36, 2182.

[13] P. A. J. Janssen, F. T. N. Allewijn, *Arzneim.-Forsch./Drug Res.*, **1968**, 18, 279.
[14] H. Nakano, T. Inoue, N. Kawasaki, H. Miyataka, H. Matsumoto, T. Taguchi, N. Inagaki, H. Nagai, T. Satoh, *Bioorg. Med. Chem*., **2000**, 8, 373.
[15] R. A. Fromtling, *Clin. Microbiol. Rev*. **1988**, 1, 187.
[16] F. C. Odds, A. B. Abbott, *J. Antimicrob. Chemother*., **1984**, 14**, 1**05.
[17] S. Shadomy, S. C. White, H. P. Yu, *J. Infect. Dis.*, **1985**, 152**,** 1249.
[18] D. Demir-Erol, U. Calıs, R. Demirdamar, N. Yulug, M. Ertan, *J. Pharm. Sci*.,**1995**, 84 (4), 462.
[19] S. C. Bhatia, V. D. Shanbhag, Electron-capture gas chromatographic assays of 5-nitroimidazole class of antimicrobials in blood, *J. Chromatogr*., **1984,** 305, 325.
[20] W. K. Anderson, R. H. Mach, *J. Med. Chem.*, **1987**, 30, 2109.
[21] M. Waki, J. Meienhofe, *J. Org. Chem.*, **1977**, 42, 2019.
[22] L. B. Cavalieri, J. F. Tinker, A. Bendich, *J. Am. Chem. Soc.*, **1949**, 71, 533.
[23] W. K. Anderson, M. J. Halat, A. C. Rick, *J. Med. Chem.*, **1980**, 21, 87.
[24] R. G. Jones, *J. Am. Chem. Soc.*, **1949**, 71, 644.
[25] R. G. Jones, E. C. Kornfeld, K. C. Mc Laughlin, R. C. Anderson, *J. Am. Chem.Soc.*, **1949**, 71, 4000.
[26] E. F. Godefroi, P. A. J. Jannssen, C. A. M. Vander Eycken, A. H. M. T. Van Heertum, C. J. E. Viemergeera, *J. Med. Chem.*, **1965,** 8, 220.
[27] L. I. Krimen, *Org. Synthesis.*, **1975**, 50, 1.
[28] W. K. Anderson, D. Bhattacharjee, D. Michael Houston, *J. Med. Chem.*, **1989**, 32,119.
[29] Y. M. Loksha, M. A. El-Badawi, A. A. El-Barbary, E. B. Pedersen, C. Nielsen,*Arch. Pharm.*, **2003**, 175, 336.
[30] Y. M. Loksha, A. A. El-Barbary, M. A. El-Badawi, C. Nielsen, E. B. Pedersen, *Bioorganic & Medicinal Chemistry*., **2005**, 13, 4209.
[31] J. C. Vincent H. W. Vincent, *Proc. Soc. Exp. Biol. Med*., **1944**, 55, 162.
[32] A. Shirwaiker, K. Rajendran, C. Dinesh kumar, *Indian J. Exp. Biol*., **2004**, 42, 803.
[33] B. H. Babu, B. S. Shailesh, J. Paddikala, *Fitotherapia*, **2001,** 72, 272.
[34] K. Kato, S. Terao, N. Shimamoto, M. Hirata, *J. Med. Chem.* **1988**, 31, 793.