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ARTICLE

Synthesis, Antimicrobial and β-Lactamase Enzyme Inhibition Activity of Some New Tetrazole Containing Maleamic and Phthaleamic Acid Derivatives

Bhaurao P. Sathe[1], Harshal S. Oman[2], Naziya N.M.A. Rehman[3], Prashant P. Dixit[3], Arun S. Kharat[4] and Kishan P. Haval[1,✉]

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ABSTRACT

In the present study, two series of tetrazole containing maleamic (**5a-h**) and phthaleamic acid (**5i-l**) derivatives were synthesized and evaluated for their antimicrobial and β-lactamase enzyme inhibition activities. The synthesized compounds were characterized by IR, ^{1}H NMR and ^{13}C NMR spectral techniques. Among the screened compounds, the compound **5c**, **5d, 5e, 5f, 5g** and **5h** have shown good antimicrobial activity. We further performed exploratory β-lactamase enzyme inhibitors studies on β-lactamase.

KEYWORDS

Biological activity, Antimicrobial resistance, β-Lactamase enzyme inhibitors, Tetrazoles, Maleamic acids, Phthaleamic acids.

INTRODUCTION

The increase in various infectious microbial diseases has developed a major issue of global health. This situation becomes more complex by the evolution of various microbial strains resistant to some single or combination of drugs. These resistant pathogenic bacteria produce β-lactamase enzyme that destroys β-lactam antibiotics. Within the last few years potent β-lactamase inhibitors such as clavulanic acid and sulbactam have become available for inhibiting the action of common β-lactamases. Regardless of the efficiency of some of these inhibitors *in vitro*, their attainment has not always resulted in protection of hydrolyzable β-lactam antibiotics *in vivo*. A single inhibitor is not always effective for all of the different β-lactamases that may occur in mixed infections [1-6]. Tetrazole containing moieties are most important for possessing high level of biological activities [7-14]. It includes antimicrobial as well as pharmacological activities like antiviral, antibacterial, antifungal, anti-allergic, anticonvulsant, anti-inflammatory *etc*. [15,16]. Recently, the reported new tetrazole containing derivatives as capable compounds for anticancer activity [17-20]. Owing to their wide importance, much attention is being paid to the tetrazole containing heterocyclic compounds [21-24]. The introduction of the tetrazole ring into a molecule of an organic substrate quite often leads not only to an increase in the efficiency but also to an increase in the prolongation of drug action [25,26]. Maleamic

Author affiliations:

[1]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, SubCampus, Osmanabad-413501,India
[2]Department of Biotechnology, Dr. Babasaheb Ambedkar Marathwada University, SubCampus, Osmanabad-413501, India
[3]Department of Microbiology, Dr. Babasaheb Ambedkar Marathwada University, SubCampus, Osmanabad-413501, India
[4]School of Life Sciences, Jawaharlal Nehru University, New Delhi-110067, India

✉To whom correspondence to be addressed:

E-mail: havalkp@gmail.com

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acids have been extensively used as an intermediate for preparation of many other compounds and shown variety of biological activities [27,28]. Phthaleamic acids are having wide range of applications in many fields [29-32].

In spite of many β-lactamase inhibitors have been synthesized extensively [33-38], we intend to report some new tetrazole containing maleamic acid and phthaleamic acid derivatives as potential β-lactamase enzyme inhibitors.

EXPERIMENTAL

All the chemicals used were of AR grade and purchased from SD-Fine chemicals, India. The progress of the reaction was monitored by thin-layer chromatography (petroleum ether + ethyl acetate). The IR spectra were recorded on Bruker FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 MHz and Bruker DRX-75 MHz NMR spectrometer, respectively by using $CDCl_3$ as solvent. Melting points were obtained using melting points apparatus (Model MP-96) and are uncorrected.

General procedure for the synthesis of 1,5-disubstituted tetrazole containing maleamic acid/phthaleamic acid (5a-l): The maleic/phthalic anhydride (10 mmol) was taken in 50 mL round bottom flask and 10 mL dichloromethane (DCM) was added. The solution of 1,5-disubtituted tetrazole containing amines (**4a-h**) (10 mmol) in 10 mL DCM was added to reaction mixture slowly at 0-5 °C. Then, the reaction mixture was stirred at room temperature for an appropriate time period. The progress of reaction was monitored by TLC. After completion of reaction, the solid obtained was filtered and the residue was washed with DCM. The crude product was purified by recrystallization by using ethanol to furnish the corresponding 1,5-disubstituted tetrazole containing maleamic/phthaleamic acids with 70-85 % yields.

4-(3-Methyl-4-(5-methyl-1*H*-tetrazol-1-yl)phenylamino)-4-oxobut-2-enoic acid (5a): Yield: 80 %; m.p.: 156-158 °C; IR (Neat, ν_{max}, cm^{-1}): 3337, 2979, 1685, 1600, 1534, 1460, 1409, 1256, 1134, 1037, 885; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.20 (s, 3H), 2.44 (s, 3H), 5.00 (s, 1H), 6.38 (d, *J* = 12 Hz, 1H), 6.59 (d, *J* = 12 Hz, 1H), 7.19-7.80 (m, 3H), 11.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.72, 17.03, 119.28, 122.88, 124.46, 131.47, 133.90, 135.30, 138.90, 141.15, 159.57, 165.29, 167.00.

4-(3-Methoxy-4-(5-methyl-1*H*-tetrazol-1-yl)phenylamino)-4-oxobut-2-enoic acid (5b): Yield: 76 %; m.p.: 164-166 °C; IR (Neat, ν_{max}, cm^{-1}): 3313, 3072, 1711, 1646, 1597, 1542, 1401, 1334, 1241, 832, 766; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.51 (s, 3H), 3.73 (s, 3H), 5.00 (s, 1H), 6.68 (d, *J* = 12 Hz, 1H), 6.80 (d, *J* = 12 Hz, 1H), 7.60-7.75 (m, 3H), 11.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.25, 56.08, 105.04, 109.55, 111.03, 130.27, 136.96, 137.28, 139.01, 156.21, 159.58, 166.04, 167.03.

4-(4-Methyl-2-(5-methyl-1*H*-tetrazol-1-yl)phenylamino)-4-oxobut-2-enoic acid (5c): Yield: 75 %; m.p.: 165-167 °C; IR (Neat, ν_{max}, cm^{-1}): 3341, 2978, 1700, 1672, 1549, 1513, 1330, 1276, 895; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.33 (s, 3H), 2.57 (s, 3H), 6.56 (d, *J* = 12 Hz, 1H), 6.88 (d, *J* = 12 Hz, 1H), 7.26-7.83 (m, 3H), 10.13 (s, 1H), 11.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.86, 21.00, 120.64, 122.81, 124.67, 128.44, 134.09, 136.66, 138.31, 141.17, 159.67, 166.78, 168.20.

4-(4-Methyl-2-(5-methyl-1*H*-tetrazol-1-yl)phenylamino)-4-oxobut-2-enoicacid (5d): Yield: 78 %; m.p.: 217-219 °C; IR (Neat, ν_{max}, cm^{-1}): 3196, 3127, 1731, 1651, 1605, 1550, 1329, 1243, 1124, 813, 737; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.40 (s, 3H), 5.12 (s, 1H), 6.35 (d, *J* = 12 Hz, 1H), 6.51 (d, *J* = 12 Hz, 1H), 7.11-7.25 (m, 4H), 11.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.68, 122.10, 128.11, 129.68, 134.35, 136.74, 139.10, 159.77, 166.29, 166.73.

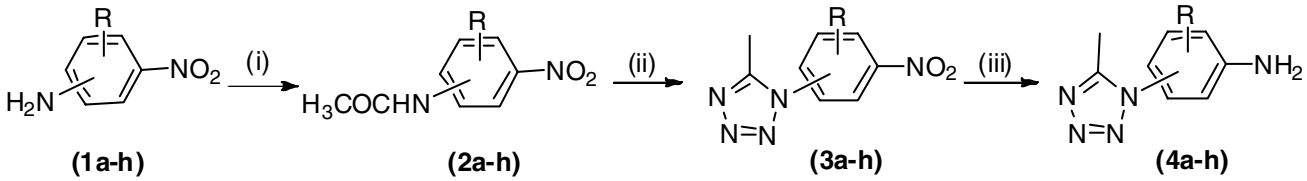
4-(4-Methyl-3-(5-methyl-1*H*-tetrazol-1-yl)phenylamino)-4-oxobut-2-enoic acid (5e): Yield: 72 %; m.p.: 188-190 °C; IR (Neat, ν_{max}, cm^{-1}): 3277, 3078, 1703, 1627, 1549, 1511, 1406, 1321, 977, 847; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.17 (s, 3H), 2.51 (s, 3H), 5.01 (s, 1H), 6.80 (d, *J* = 12 Hz, 1H), 7.30 (d, *J* = 12 Hz, 1H), 7.44-7.75 (m, 3H), 11.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 11.06, 16.57, 103.09, 119.28, 127.61, 128.85, 132.30, 135.30, 138.63, 138.80, 159.57, 166.47, 167.00.

(Z)-4-((2-(5-Methyl-1*H*-tetrazol-1-yl)phenyl)amino)-4-oxobut-2-enoic acid (5h): Yield: 82 %; m.p.: 139-141 °C; IR (Neat, ν_{max}, cm^{-1}): 3340, 2985, 1700, 1672, 1613, 1548, 1513, 1406, 1330, 1276, 895; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 2.57 (s, 3H), 6.39 (d, *J* = 12 Hz, 1H), 6.46 (d, *J* = 12 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.45 (t, *J* = 8 Hz, 1H), 7.69 (t, *J* = 8 Hz, 1H), 8.39 (d, *J* = 8 Hz, 1H), 9.88 (s, 1H).

β-Lactase enzyme inhibition activity: The synthesized compounds were tested for their β-lactamase inhibitor and antibacterial property against β-lactamase trait carrying *E. coli* culture. The bacterial growth inhibition potential of the individual compound gives an idea about antibacterial activity of compound, whereas bacterial growth inhibition by the combination of compound and β-lactam antibiotics gives an idea about β-lactamase inhibitory activity of compound. The Luriea Bartani (LB) agar plates of *E. coli* cultures were prepared by pour plate method and on these plates, the compound's β-lactamase inhibitor and antibacterial were tested by combined disc diffusion assay and disc diffusion assay respectively. The 20 mg of synthesized compound was dissolved in 0.5 mL of DMSO. It was diluted to 1.0 mL stock solution by sterile distilled water. From that stock solution, 20 µL solution was placed on a plane sterile disc and β-lactam antibiotic discs. These discs were kept at 4 °C for 0.5 h for diffusion of solution. After 0.5 h, the discs of concentration as 400 µg/discs were ready to use. The obtained zone of inhibitions were compared with standard β-lactam antibiotic and β-lactam antibiotic/inhibitor, against respective classes of β-lactamase trait carrying *E. coli* culture (for Class A cefotaxime & cefotaxime/clavulanic acid, for Class B imipenam & imipenam/100 mM EDTA, for cefoxine & cefoxine/100 mM phenyl boronic acid, for Class D no such combination available). The results were interpreted according to CLSI guidelines, for combine disc diffusion assay. The zones were interpreted by consideration of extra 5 mm zone.

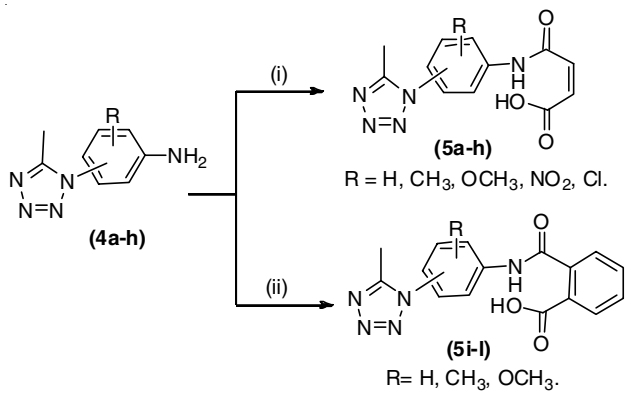
RESULTS AND DISCUSSION

In continuation with our efforts for the synthesis of biologically active target molecules [39-41], herein we have reported



Scheme-I: Reaction conditions: (i) Ac_2O, pyridine, DCM, rt; (ii) NaN_3, $TiCl_4$, CH_3CN, rt; (iii) $NaBH_4$, $Ni(OAc)_2{\cdot}4H_2O$, CH_3CN + H_2O (3:1), rt

the synthesis, β-lactamase enzyme inhibitory and antimicrobial activities of some new tetrazole containing maleamic acid and phthaleamic acid (**5a-l**) (**Schemes I** and **II**) [42-45]. The structures of synthesized compounds were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral techniques. The physical data of the synthesized compounds (**5a-l**) is summarized in Table-1.

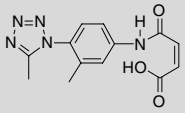
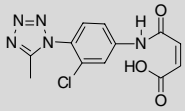
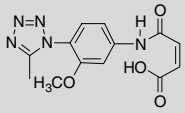
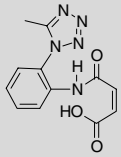
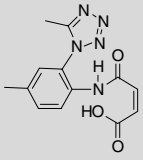
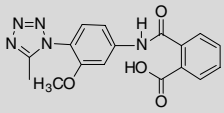
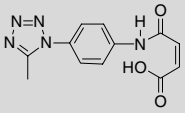
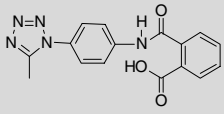
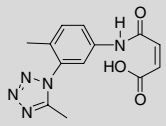
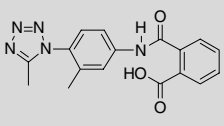
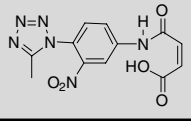
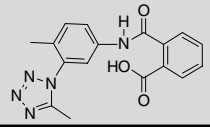


Scheme-II: Reaction conditions: (i) maleic anhydride, DCM, rt; (ii) phthalic anhydride, DCM, rt

All β-lactam antibiotics are disturbing the biosynthesis of the bacterial cell wall. The β-lactam antibiotics exhibit their bactericidal effects by inhibiting enzymes involved in cell wall synthesis. The production of β-lactamase is one of the primary mechanisms used by Gram-negative bacteria to counter β-lactam antibiotics, such as penicillin, cephalosporin, mono bactam and carbapenem. There is crucial need to develop novel β-lactamase inhibitors in response to ever-evolving β-lactamases possessing an expanded spectrum of β-lactam hydrolyzing activity.

The tetrazolic acid fragment $–CN_4H$ has similar acidity to the carboxylic acid group $–CO_2H$ (likely present in amino acids) and these two are almost isosteric, but the former is metabolically more stable. Hence, replacement of $–CO_2H$ groups by $–CN_4H$ may lead to solving number of biologically originated problems, this property that makes it possible to use tetrazole as isosteric substituents of various functional groups in the development of biologically active substances [46]. The tetrazole compounds interact with carboxylic acid group and amido group of amino acids so these compounds lead to change the structure of peptide chain and functional

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS (**5a-l**)

Entry	Compounds (**5a-l**)	Time (h)	m.p. (°C)	Yield (%)	Entry	Compounds (**5a-l**)	Time (h)	m.p. (°C)	Yield (%)
5a		8	156-158	80	**5g**		7	178-180	74
5b		7	164-166	76	**5h**		8	139-141	82
5c		6	165-167	75	**5i**		6	180-182	73
5d		8	217-219	78	**5j**		7	172-174	75
5e		7	188-190	72	**5k**		8	181-183	85
5f		6	158-160	79	**5l**		7	171-173	70

activity of proteins. In some cases researchers found that tetrazole compounds were effectively inhibiting the action of serine β-lactamase enzyme [47]. In present study, it was found that nearly all compounds shown *in vitro* β-lactamase enzyme inhibition activity against β-lactamase trait carrying organisms (Table-2). When these compounds used in combination with antibiotics that time this combination gave synergetic effect. At the same time, some of these compounds shown antibacterial activity against β-lactamase trait carrying microbes.

β-Lactamase inhibitory activities of compounds were evaluated by disc-diffusion pour plate method, against β-lactamase trait carrying culture. Antibacterial susceptibility was tested using the discs of i) compound ii) standard combination of β-lactam antibiotic & β-lactamase inhibitor iii) β-lactam antibiotic iv) β-lactam antibiotic and compound in clockwise manner. From Table-2, it was observed that the compound **5a** has shown antibacterial activity against Class A organisms. While all our compounds **5a**, **5h** and **5i** shown synergetic effect

TABLE-2
β-LACTAMASE ENZYME INHIBITION ACTIVITY OF COMPOUNDS (**5a-l**)

Entry	β-Lactamase type	Culture	Zone of inhibition (mm)			
			Compound	Antibiotic	Standard combinations*	Antibiotic + Compounds
5a	A	ESBL-3	–	10	–	25
		ESBL-16	–	10	–	24
	B	ESBL-5	–	29	29	29
		ESBL-17	–	37	36	35
	C	ESBL-9	16	–	18	18
		ESBL-22	–	39	39	39
	D	ESBL-10	–	–	–	–
		ESBL-28	–	–	–	–
5b	A	ESBL-3	–	16	31	–
		ESBL-16	–	–	28	10
	B	ESBL-5	–	32	32	–
		ESBL-17	–	31	34	29
	C	ESBL-9	–	–	18	–
		ESBL-22	–	–	–	–
	D	ESBL-10	–	–	–	–
		ESBL-28	–	–	10	–
5c	A	ESBL-3	–	–	25	–
		ESBL-16	–	–	22	10
	B	ESBL-5	–	25	20	29
		ESBL-17	–	27	22	23
	C	ESBL-9	–	–	18	–
		ESBL-22	11	34	33	33
	D	ESBL-10	–	–	–	–
		ESBL-28	–	–	14	–
5d	A	ESBL-3	–	–	31	12
		ESBL-16	–	–	–	–
	B	ESBL-5	–	30	24	24
		ESBL-17	–	30	27	23
	C	ESBL-9	–	–	14	–
		ESBL-22		33	32	33
	D	ESBL-10	–	–	–	–
		ESBL-28	–	–	–	–
5e	A	ESBL-3	–	–	24	–
		ESBL-16	–	–	25	–
	B	ESBL-5	–	23	18	16
		ESBL-17	–	27	12	13
	C	ESBL-9	–	–	17	–
		ESBL-22	–	–	–	–
	D	ESBL-10	–	–	–	–
		ESBL-28	–	–	–	–
5f	A	ESBL-3	–	–	19	–
		ESBL-16	–	–	22	–
	B	ESBL-5	–	26	18	28
		ESBL-17	–	22	19	22
	C	ESBL-9	–	–	19	–
		ESBL-22	–	14	14	13
	D	ESBL-10	–	–	–	–
		ESBL-28	–	–	–	–

5g	A	ESBL-3	–	9	28	–
		ESBL-16	–	–	22	–
	B	ESBL-5	–	21	21	20
		ESBL-17	–	23	25	24
	C	ESBL-9	–	–	20	–
		ESBL-22	–	21	21	12
	D	ESBL-10	–	–	–	10
		ESBL-28	–	–	–	10
5h	A	ESBL-3	–	10	28	12
		ESBL-16	–	–	24	
	B	ESBL-5	–	20	29	12
		ESBL-17	–	20	22	13
	C	ESBL-9	–	–	17	–
		ESBL-22	–	13	19	13
	D	ESBL-10	–	–	–	10
		ESBL-28	–	–	–	–
5i	A	ESBL-3	10		20	–
		ESBL-16	12		20	
	B	ESBL-5	–	25	17	22
		ESBL-17	–	21	15	21
	C	ESBL-9	–	–	17	–
		ESBL-22	–	14	18	11
	D	ESBL-10	12	–	–	–
		ESBL-28	–	–	–	–
5j	A	ESBL-3	–	10	31	–
		ESBL-16	–	–	24	–
	B	ESBL-5	–	20	20	18
		ESBL-17	–	21	21	22
	C	ESBL-9	–	–	21	–
		ESBL-22	–	22	21	15
	D	ESBL-10	–	–	–	10
		ESBL-28	–	–	–	10
5k	A	ESBL-3	–	–	24	19
		ESBL-16	–	–	22	10
	B	ESBL-5	–	24	23	23
		ESBL-17	–	20	20	19
	C	ESBL-9	–	–	16	–
		ESBL-22	–	14	23	13
	D	ESBL-3	–	–	24	19
		ESBL-16	–	–	22	10
5l	A	ESBL-3	–	–	27	–
		ESBL-16	–	–	23	–
	B	ESBL-5	–	20	22	19
		ESBL-17	–	19	19	17
	C	ESBL-9	–	–	19	–
		ESBL-22	–	12	20	15
	D	ESBL-10	–	9	–	–
		ESBL-28	–	–	–	–

*Standard β-lactam antibiotic and β-lactamase inhibitor combination for Class A: cefotaxime + clavulanic acid; Class B: imipenam + 100 mM EDTA; Class C: cefoxitin + 100 mM phenyl boronic acid; Class D: not defined.

with β-lactam antibiotics against particular β-lactamase trait carrying cultures (it means that these compounds have inhibitory activity) except compound **5f** which didn't have any effect. Two compounds **5i** and **5h** shown β-lactamase inhibitor activity against Class B, D and A, D enzyme respectively, but at the same time these two compounds also show antagonist action against Class C and Class B.

The *in vitro* antimicrobial activity of all synthesized compounds was assessed by using agar well diffusion method with some modifications [48,49]. For screening of antibacterial activity, both Gram-positive and Gram-negative bacterial pathogens were used, while for antifungal activity potent fungal pathogens were used. *Staphylococcus aureus* ATCC 6538, *Bacillus cereus* ATCC 14579, *Bacillus megaterium* ATCC 2326, *Bacillus subtilis* ATCC 6633 were Gram-positive pathogens used in this study. *Escherichia coli* ATCC 8739, *Salmonella typhi* ATCC 9207, *Shigella boydii* ATCC 12034, *Enterobacter aerogenes* ATCC 13048, *Pseudomonas aeruginosa* ATCC 9027, *Salmonella abony* NCTC 6017 were the Gram-negative pathogens used in this study. Antifungal activity of synthesized compounds was determined against *Aspergillus niger* ATCC 16404, *Saccharomyces cereviseae* ATCC 9763 and *Candida albicans*

TABLE-3
ANTIMICROBIAL ASSAY OF SYNTHESIZED COMPOUNDS (**5a-l**)

Pathogens	Compounds												Standard
	5a	**5b**	**5c**	**5d**	**5e**	**5f**	**5g**	**5h**	**5i**	**5j**	**5k**	**5l**	
S. aureus	10	–	14	14	10	15	08	08	15	–	–	–	32
B.cereus	–	–	12	11	10	15	13	13	10	–	–	–	33
B. megaterium	–	–	11	12	09	13	14	11	10	–	–	–	34
B. subtilis	–	–	12	11	10	11	13	12	08	–	–	–	34
E. coli	–	–	12	13	08	13	14	13	08	–	–	–	34
S. typhi	–	–	12	08	12	13	15	10	–	–	–	–	34
S. boydii	–	–	13	11	09	11	12	10	–	–	–	–	31
E. aerogenes	–	–	13	11	10	12	10	13	–	–	–	–	33
P. aeruginosa	–		09	13	08	12	10	11	–	–	–	–	30
S. abony	–	–	10	10	08	10	12	12	–	–	–	–	30
A. niger	–	–	13	12	15	10	14	12	–	–	–	–	30
S. cerevisiae	–	–	10	13	12	–	12	–	–	–	–	–	30
C. albicans	–	–	10	–	12	–	13	–	–	–	–	–	28

TABLE-4
MIC VALUES OF MOST POTENT COMPOUNDS

Pathogens	Compounds						Standard
	5c	**5d**	**5e**	**5f**	**5g**	**5h**	
S. aureus	320 ± 2.7	312 ± 1.4	390 ± 3.3	295 ± 2.8	428 ± 0.6	400 ± 3.3	5 ± 1.4 (Tetracycline)
S. typhi	420 ± 2.8	573 ± 3.3	380 ± 3.3	320 ± 2.8	261 ± 1.6	460 ± 2.8	3.0 ± 1.5 (Tetracycline)
A. niger	500 ± 3.3	516 ± 4.4	420 ± 2.8	550 ± 0.0	472 ± 1.4	510 ± 3.3	18 ± 1.4 (Fluconazole

ATCC 10231 fungal pathogens. Fluconazole and tetracycline were used as antifungal and antibacterial standard reference compounds respectively. The diameter of the zone of inhibition is given in millimetre. Compound **5c**, **5e** and **5g** have shown good antibacterial and antifungal activity. Compound **5d**, **5f** and **5h** have shown significant antibacterial activity but these compounds didn't show activity against fungal pathogens. Compound **5a** has shown activity against only Gram-positive bacterial pathogens (Table-3).

The MIC was determined for the six most potent antimicrobial compounds **5c**, **5d**, **5e, 5f, 5g** and **5h**. The MIC was determined against *S. aureus* ATCC 6538, *S. typhi* ATCC 9207 and *A. niger* ATCC 16404 (Table-4). The MIC was determined by following the method and guidelines of the Clinical and Laboratory Standard Institute (CLSI). All experiments were performed in triplicates. The results are expressed as mean ± SD in µg/mL.

Conclusion

In this study, the synthesis, antimicrobial and β-lactamase inhibitory activities of 1,5-disubstituted tetrazole containing maleamic/phthaleamic acid derivatives are reported. The 1,5-disubstituted tetrazole containing maleamic acid derivatives have shown better antimicrobial activities as compared to phthaleamic acid derivatives. Few of the synthesized compounds have shown very good antimicrobial and β-lactamase inhibitor activities.

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