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Facile Syntheses and Studies of 8-Substituted-4-(4-*tert*-butylphenyl/ 4-acetamidophenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic Acids

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ABSTRACT

Two series of new 8-substituted-4-(4-*tert*-butylphenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids and 8-substituted-4-(4-acetamidophenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids have been synthesized by Michael condensation of 5-substituted-2-aminobenzenethiols with β-(4-*tert*-butylbenzoyl) acrylic acid or β-(4-acetamidobenzoyl) acrylic acid, in ethanol in acidic medium in a single step, in 58-64 % yield. The structures of the newly synthesized compounds were confirmed by their IR, ^{1}H NMR and mass spectral analyses and micro analytical data. They were screened for antimicrobial activity, against the Gram-positive bacteria, *Staphylococcus aureus*, Gram-negative bacteria, *Enterobacter cloacae* and *Escherichia coli*, with respective reference compounds, vancomycin, polymyxin B, colistin-polymyxin B and against the fungus, *Candida albicans* with reference drug fluconazole. Most of the compounds showed activity against *Staphylococcus aureus*, *Enterobacter cloacae* and fungus *Candida albicans*, while none of the compounds showed activity against *Escherichia coli*.

KEYWORDS

1,5-Benzothiazepine-2-carboxylic acids, β-Benzoyl acrylic acids, Antibacterial, Antifungal activity.

INTRODUCTION

1,5-Benzothiazepine derivatives have been reported to possess many biological activities like calcium antagonists [1], coronary vasodilators [2], antiischemics [3], antiarrhythmics [4], antihypertensives [5], blood platelet aggregation inhibitors [6] *etc*. Many clinically used drugs [7] feature the 1,5-benzothiazepine ring system, which acts as a proficient pharmacophore [8]. The presence of a carboxyl group in 1,5-benzothiazepine nucleus is thought to be important because of its usefulness in drug designing, as it can be used to obtain its further derivatives having useful bioactivity. The β-(benzoyl) acrylic acids also exhibit biological activities [9] and have been reported to inhibit phospholipase from snake venom and from procaine pancreas, they also have antibacterial activities and antiproliferative action against human cervix carcinoma. A few 1,5-benzothiazepine compounds having a free carboxylic group have been reported to possess bioactivities. The

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compound, 2-phenyl-5-carboxymethyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one has been patented as antiulcer agent [10]. The syntheses of compounds having a carboxylic function being reported, *i.e.* 8-substituted-4-(4-aryl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids, may therefore, be fruitful in leading towards compounds having useful bioactivity themselves or could be used as a tool to obtain useful products in the process of drug designing.

EXPERIMENTAL

To obtain the new series of compounds 8-substituted-4-(4-*tert*-butylphenyl)-2,3-dihydro-1,5-benzothiazpine-2-carboxylic acids (**3a-f**) and 8-substituted-4-(4-acetamidophenyl)-2,3-dihydro-1,5-benzothiazpine-2-carboxylic acids (**3g-l**), the 5-substituted-2-aminobenzenethiols [11] (**1a-f**) and α,β-unsaturated keto acids [12-15], β-(4-*tert*-butylbenzoyl) acrylic acid (**2a**) or β-(4-acetamidobenzoyl) acrylic acid, (**2b**) were reacted in equimolar quantities in acidic medium to form title compounds in 58.65-64.70 % yields.

All the melting points of the reported compounds are uncorrected. Homogeneity of the compounds was checked by TLC on glass plates coated with silica gel 'G' using benzene: ethanol: aq. ammonia (50 %) (7:2:1, upper layer) as solvent system. The IR spectra were taken in KBr pellets on Shimadzu 8201 PC spectrophotometer. NMR spectra were recorded on a Bruker DRX-300 (300 MHz FT NMR) instrument using $CDCl_3$ as solvent and TMS as internal standard. The FAB mass spectra were recorded on JEOL-SX 102/DA-6000 mass spectrometer/data system using argon/xenon (6 kV, 10 mA) as the FAB gas. The accelerating voltage was 10 kV and spectra were recorded at room temperature. *m*-Nitrobenzoyl alcohol (NBA) was used as the matrix. Microestimations for carbon, hydrogen and nitrogen were carried out in Elemental Analyzer, Carlo Erba 1108. The spectral analysis and elemental analysis of some of the compounds were carried out at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow.

General procedure for the syntheses of 8-substituted-4-(4-*tert*-butylphenyl/4-acetamidophenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids (3a-l): Equimolar quantity of 2-amino-5-substituted benzenethiol (**1**, 0.001mol) and β-(4-*tert*-butylbenzoyl/4-acetamidobenzoyl) acrylic acid (**2,** 0.001 mol) were dissolved in dry ethanol (10 mL) in 100 mL round bottomed flask. After stirring, glacial acetic acid (1 mL) was added and refluxed the mixture for 2-3 h till color change became constant. Completion of reaction was checked by TLC method; then reaction mixture was concentrated under reduced pressure and cooled to give crude solid which was crystallized from dry ethanol to afford crystals of 8-substituted-4-(4-*tert*-butylphenyl/4-acetamidophenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids (**Scheme-I**).

Spectral data

Compound 3a: m.p.: 90-92 °C, R_f 0.78, yield: 60.03 %, IR (KBr, ν_{max}, cm^{-1}): 3000 (Ar C-H), 2965 (aliphatic C-H), 1690 (C=O), 3430 (O-H), 1601 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.16 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.74 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.29 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 1.43 (s, 9H, CH_3), 8.24 (s, 1H, COOH), 6.73-7.97 (7H, m, aromatic H), Anal. found (%): C, 65.22; N, 3.68; Calcd. (%) for $C_{20}H_{20}NO_2SF$ (357.4), C, 67.20, N, 3.92.

Compound 3b: m.p.: 110-112 °C, R_f 0.80, yield: 61.34 %, IR (KBr, ν_{max}, cm^{-1}): 3019 (Ar C-H), 2899 (aliphatic C-H), 1701 (C=O), 3431 (O-H), 1602 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.17 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.73 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.27 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 1.40 (s, 9H, CH_3), 8.68 (s, 1H, COOH), 6.77-7.89 (7H, m, aromatic H), Anal. found (%): C, 63.56; H, 5.34; Calcd. (%) for $C_{20}H_{20}NO_2SCl$ (373.89), C, 64.25, H, 5, 39.

Compound 3c: m.p.: 170-174 °C, R_f 0.82, yield: 58.90 %, IR (KBr, ν_{max}, cm^{-1}): 3050 (Ar C-H), 2998 (aliphatic C-H), 1680 (C=O), 3400 (O-H), 1605 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.18 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.73 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.27 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 1.41 (s, 9H, CH_3), 8.28 (s, 1H, COOH), 6.73-7.93 (7H, m, aromatic H), Anal. found (%): C, 56, 28; N, 3.20; Calcd. (%) for $C_{20}H_{20}NO_2SBr$ (373.89), C, 57.42, N, 3.35.

Compound 3d: m.p.: 110-114 °C, R_f 0.86, yield: 64.70 %), IR (KBr, ν_{max}, cm^{-1}): 3021 (Ar C-H), 2963 (aliphatic C-H), 1673 (C=O), 3399 (O-H), 1606 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.17 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.74 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.25 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 1.40 (s, 9H, CH_3), 2.26 (s, 3H, C_8-CH_3), 8.12 (s, 1H, COOH), 6.73-7.93 (7H, m, aromatic H), Anal. found (%): N, 3.88; Calcd. (%) for $C_{21}H_{23}rNO_2S$ (353.47) N, 3.96.

Compound 3e: m.p.: 80-82 °C, R_f 0.73, yield: 62.30 %, IR (KBr, ν_{max}, cm^{-1}): 3010 (Ar C-H), 2980 (aliphatic C-H), 1680 (C=O), 3345 (O-H), 1602 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.20 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.89 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.29 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 1.42 (s, 9H, CH_3), 3.85 (s, 3H, C_8-OCH_3), 8.68 (s, 1H, COOH), 6.74-7.96 (7H, m, aromatic H), Anal. found (%): C, 66, 78, H, 6.24; Calcd. (%) for $C_{21}H_{23}NO_3S$ (369.47), C, 68.27, H, 6.27.

Compound 3f: m.p.: 140-142 °C, R_f 0.87, yield: 60.00 %, IR (KBr, ν_{max}, cm^{-1}): 3010 (Ar C-H), 2895 (aliphatic C-H), 1688 (C=O), 3300 (O-H), 1600 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.20 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.77 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.28 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 1.41 (s, 9H, CH_3), [1.25 (t, 3H), 3.97 (q, 2H), C_8-OCH_2CH_3], 8.01 (s, 1H, COOH), 6.74-7.91 (7H, m, aromatic H), Anal. found (%): C, 61.00, H, 5.88, N, 3.56; Calcd. (%) for $C_{22}H_{25}NO_3S$ (383.50), C, 62.90, H, 6.57, N, 3.65.

Compound 3g: m.p.: 210-213 °C, R_f 0.58, yield: 58.65 %, IR (KBr, ν_{max}, cm^{-1}): 3020 (Ar C-H), 2977 (aliphatic C-H), 1680 (C=O), 3400 (O-H), 1599 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 2.98 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.45 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.40 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 2.13 (s, 3H, CH_3), 7.82 (s, 1H, NH), 8.02 (s, 1H, COOH), 6.46-7.92 (7H, m, aromatic H), Anal. found (%): C, 60.30, H, 3.98, Calcd. (%) for $C_{18}H_{15}N_2O_3SF$ (358), C, 60.32, H, 4.22.

Compound 3h: m.p.: 180-182 °C, R_f 0.65, yield: 59.62 %, IR (KBr, ν_{max}, cm^{-1}): 3019 (Ar C-H), 2896 (aliphatic C-H), 1687 (C=O), 3424 (O-H), 1600 (C=N); ^{1}H NMR ($CDCl_3$, *J* values in Hz): δ 3.01 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.49 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.28 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 2.23 (s, 3H, CH_3), 7.88 (s, 1H, NH), 8.01 (s, 1H, COOH), 6.52-7.98 (7H,

m, aromatic H), Anal. found (%): H, 4.00, N, 7.43 Calcd. (%) for $C_{18}H_{15}N_2O_3SCl$ (374.5), H, 4.02, N, 7.47.

Compound 3i: m.p.: 170-174 °C, R_f 0.57, yield: 59.33 %, IR (KBr, ν_{max}, cm^{-1}): 3056 (Ar C-H), 2976 (aliphatic C-H), 1705 (C=O), 3389 (O-H), 1598 (C=N); ^1H NMR ($CDCl_3$, *J* values in Hz): δ2.77 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.45 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.35 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 2.10 (s, 3H, CH_3), 7.83 (s, 1H, NH), 7.98 (s, 1H, COOH), 6.57-7.92 (7H, m, aromatic H), Anal. found (%): C, 50.57, H, 3.55, N, 6.63 Calcd. (%) for $C_{18}H_{15}N_2O_3SBr$ (419), C, 51.56, H, 3.61, N, 6.68.

Compound 3j: m.p.: 160-162 °C, R_f 0.60, yield: 60.00 %, IR (KBr, ν_{max}, cm^{-1}): 3110 (Ar C-H), 3000 (aliphatic C-H), 1689 (C=O), 3398 (O-H), 1601 (C=N); ^1H NMR ($CDCl_3$, *J* values in Hz): δ2.89 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.56 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.27 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 2.35 (s, 3H, C_8-CH_3), 2.02 (s, 3H, CH_3), 7.69 (s, 1H, NH), 8.00 (s, 1H, COOH), 6.53-7.97 (7H, m, aromatic H), Anal. found (%): C, 64.22, N, 7.86 Calcd. (%) for $C_{19}H_{18}N_2O_3S$ (354), C, 64.39, N, 7.90.

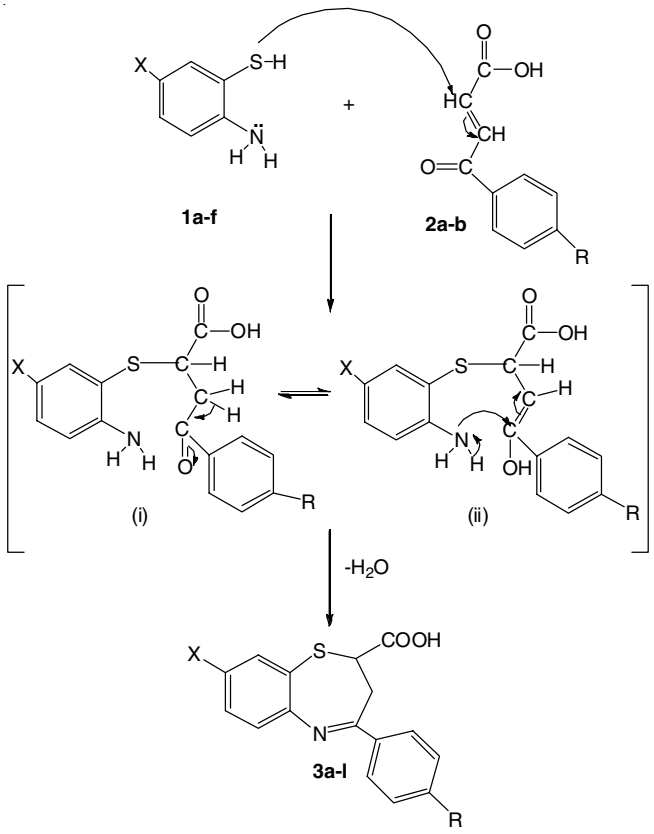
Compound 3k: m.p.: 158-160 °C, R_f 0.58, yield: 62.40 %, IR (KBr, ν_{max}, cm^{-1}): 3019 (Ar C-H), 2989 (aliphatic C-H), 1703 (C=O), 3433 (O-H), 1600 (C=N); ^1H NMR ($CDCl_3$, *J* values in Hz): δ3.00 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.61 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.28 (dd; J_{AX} = 8, J_{BX} = 7; 1H), 3.88 (s, 3H, C_8-OCH_3), 2.34 (s, 3H, CH_3), 7.82 (s, 1H, NH), 8.10 (s, 1H, COOH), 6.74-7.94 (7H, m, aromatic H), Anal. found (%): N, 7.48 Calcd. (%) for $C_{19}H_{18}N_2O_4S$ (370), N, 7.56.

Compound 3l: m.p.: 220-224 °C, R_f 0.53, yield: 58.60 %, IR (KBr, ν_{max}, cm^{-1}): 3019 (Ar C-H), 2878 (aliphatic C-H), 1687 (C=O), 3421 (O-H), 1599 (C=N); ^1H NMR ($CDCl_3$, *J* values in Hz): δ 3.04 (dd; J_{AB} = 16, J_{AX} = 8; 1H), 3.60 (dd; J_{AB} = 16, J_{BX} = 7; 1H), 4.30 (dd; J_{AX} = 8, J_{BX} = 7; 1H), [1.25 (t 3H), 4.08 (q, 2H) C_8-OCH_2CH_3], 2.13 (s, 3H, CH_3), 7.79 (s, 1H, NH), 8.01 (s, 1H, COOH), 6.62-7.90 (7H, m, aromatic H), Anal. found (%): H, 5.22 Calcd. (%) for $C_{20}H_{20}N_2O_4S$ (384), H, 5.24.

RESULTS AND DISCUSSION

The carbonyl carbon atom of the β-benzoyl acrylic acid is rendered electron deficient due to the occurrence of unsaturation in conjugation with a keto group. The labile C_2-C_3 electrons therefore shift towards C-3, making C-2 an electron deficient centre, thus resulting in the generation of a carbocation. The nucleophilic addition of sulphhydryl electrons to C-2 followed by simultaneous dehydrative cyclization results in the formation of 8-substituted-4-(4-*tert*-butylphenyl/4-acetamidophenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids (**3a-l**, **Scheme-I**). The structures of the final products were assigned on the basis of elemental and spectral analysis comprising IR, ^1H NMR and mass spectra.

In the IR spectra of compounds **3a-l,** a sharp absorption signal was observed at 1705-1673 cm^{-1} due to C=O stretching vibrations of carboxylic group. A broad absorption signal observed in the region 3433-3300 cm^{-1} may be due to the O-H stretching vibrations and the sharp absorption signals observed at 1421-1384 cm^{-1} indicate the presence of δ C-O-H in-plane bending. In addition to these absorptions, a broad intense absorption in the region 1606-1598 cm^{-1} in all the spectra showed the presence of C=N, as has been characterized [16] in 1,5-benzodiazepines. Absorption at 2998-2878 cm^{-1} and at around 3110-3000 cm^{-1} may be assigned to aliphatic and aromatic C-H stretching vibration, respectively. The spectra of compounds **3g-l** showed absorption at 1654-1635 cm^{-1} indicating the presence of carbonyl group of acetamido group (amide-I band) and absorption at 770-668 cm^{-1} due to δ N-H out-of-plane vibration.



Comp.	X	R	Comp.	X	R
3a	F	$C(CH_3)_3$	**3g**	F	$NHCOCH_3$
3b	Cl	$C(CH_3)_3$	**3h**	Cl	$NHCOCH_3$
3c	Br	$C(CH_3)_3$	**3i**	Br	$NHCOCH_3$
3d	CH_3	$C(CH_3)_3$	**3j**	CH_3	$NHCOCH_3$
3e	OCH_3	$C(CH_3)_3$	**3k**	OCH_3	$NHCOCH_3$
3f	OC_2H_5	$C(CH_3)_3$	**3l**	OC_2H_5	$NHCOCH_3$

Scheme-I

The ^1H NMR spectra of all the compounds **3a-l** showed multiplet absorption signal in the region δ 6.46-7.98, corresponding to the aromatic protons and a broad signal in the region δ 7.98-8.68 corresponding to one proton; which may be assigned to the carboxylic proton. The double doublet signals corresponding to the methylene and methine protons at C-3 and C-2, respectively, were found, to occur in the ABX pattern; each of the three double doublets integrating for one proton. The two methylene protons couple with each other and give rise to a doublet with the *geminal* coupling constant of 15-16 Hz. Each of the two methylene protons also couple with the methine proton, therefore the doublet signal again splits, this time with a vicinal coupling constant of 7-9 Hz, thus resulting in the formation of two almost similar doublets, the one which comes upfield, at δ 2.77-3.20 is assigned to H_A, which is axial, while

the other double doublet at δ 3.45-3.89 may be assigned to H_B. The methine proton signal at δ 4.25-4.40, assigned to H_X, is also obtained as a double doublet due to the vicinal protons and as it possesses two vicinal protons, the different values of coupling constant for AX and BX protons may arise due to the axial and equatorial conformations of H_A and H_B.

Also, peaks were observed at δ 1.40-1.43 (s, 9H) and 2.02-2.34 (s, 3H) due to methyl protons of $C(CH_3)$ and NH-CO-CH_3 present in compounds **3a-f** and **3g-l** respectively; signal observed at δ 7.69-7.88 may be due to NH in **3g-l**.

The mass spectrum of **3b** showed cluster of isotopic molecular ion peaks, *m/z* at 372, 374, 376 and **3h** showed *m/z* at 374, 376, 378; **3c** showed, *m/z* at 418, 420, 422 while **3i** showed a cluster of signals at 419, 421, 423 which correspond to their respective molecular mass, *m/z*, M^+, $[M+2]^+$ and $[M+4]^+$. The cluster of molecular ion peaks in mass spectra of compounds **3b** and **3h;** and **3c** and **3i** confirmed the presence of chlorine and bromine in the respective compounds.

Antimicrobial activity: All the synthesized compounds were screened for relative antibacterial activity against the Gram-positive bacteria, *Staphylococcus aureus* and the Gram-negative bacteria, *Enterobacter cloacae, Escherichia coli* and antifungal activity against the fungus, *Candida albicans* by using Paper Disc method [15] at the concentration of 200 µg/disc. The results have been compared with reference compounds vancomycin (*S. aureus*), polymyxin-B (*E. cloacae)* colistin-polymyxin-B (*E. coli*) for evaluating antibacterial activity and fluconazole for antifungal activity. Zones of inhibition, exhibited by the reference and test compounds were measured and relative activities were calculated as activity index (Table-1).

TABLE-1
ANTIMICROBIAL ACTIVITY OF COMPOUNDS **3a-l**

Compd. No.	X	Bacteria		Fungus
		S. aureus	*E. cloacae*	*C. albicans*
3a	F	–	13 (1.08)	23 (0.92)
3b	Cl	19 (1.11)	10 (0.83)	–
3c	Br	–	15 (1.25)	14 (0.56)
3d	CH_3	–	12.5 (1.04)	–
3e	OCH_3	–	16 (1.33)	12 (0.48)
3f	OC_2H_5	–	13 (1.08)	–
3g	F	15 (0.88)	–	15 (0.60)
3h	Cl	13 (0.76)	–	14 (0.56)
3i	Br	12 (0.70)	13 (1.17)	13 (0.52)
3j	CH_3	14 (0.82)	–	15 (0.60)
3k	OCH_3	11(0.64)	15 (1.36)	11 (0.44)
3l	OC_2H_5	13 (0.76)	–	14 (0.56)

Zones of inhibition are given in mm, Values in parentheses represent activity index.
Zone of inhibition of vancomycin for *Staphylococcus aureus* is 15-21 mm, of polymyxin B for *Enterobacter cloacae* is 11 mm, of colistin-polymyxin B for *Enterobacter cloacae* is 11-12 mm, of fluconazole for *Candida albicans* is 25 mm.
Concentrations of test and reference compounds were 200 µg/disc.

Most of the compounds showed higher activity than the reference compound against the bacteria *Enterobacter cloacae*, while none of the compounds showed antibacterial activity against *E. coli*. Against the fungus, *Candida albicans*, most of the compounds exhibited lower activity (activity index ≥ 1) than the reference compound, in a duration of 40 h incubation.

Conclusion

All the newly synthesized compounds had a bulky substituent which may have affected the stability of the compounds as is reflected in the almost similar percentage yields of the products. The compounds showed higher antibacterial activity against *Enterobacter cloacae* at the concentration of 200 µg/disc, while none was shown against *Escherichia coli.* Compounds **3g-l** showed moderate activity against *Candida albicans.*

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