Facile Synthesis and Studies of 1,5-Benzothiazepine-2-carboxylic Acids

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Abstract: A series of 8-substituted-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids were synthesized by one-pot reactions of six 5-substituted-2-amino benzenethiols, the substitutes being fluoro, chloro, bromo, methyl, methoxy and ethoxy; and substituted β -benzoyl acrylic acid in ethanol utilizing glacial acetic acid as catalyst in 59-85% yields. The structures of compounds were characterized by FT-IR, NMR, and elemental analysis. Antimicrobial activities of these compounds were determined by using paper disc method against the gram-positive and gram-negative bacteria, Staphylococcus aureus and Escherichia coli respectively; and against the fungus, Candida albicans.

Index Terms: β-benzoyl acrylic acid, 1,5-benzothiazepine-2-carboxylic acids, Staphylococcus aureus, Escherichia coli, Candida albicans

INTRODUCTION

The 1, 5-benzothiazepines are important nitrogen and sulfur containing seven membered heterocyclic compounds which exhibit a number of pharmacological activities such as anti-HIV, calcium (II) channel antagonist [1], anticancer [2] and antimicrobial [3]. The findings have stimulated interest to develop new methodologies for the synthesis of newer 1,5-benzothiazepines.

The first 1,5- benzothiazepine molecule is diltiazem used clinically, followed by clentiazem for their cardiovascular activity [4]. The presence of a carboxyl group in 1,5-benzothiazepine nucleus is important because of its usefulness in drug designing, as it can be used to obtain its further derivatives having useful bioactivity themselves. A few 1,5-benzothiazepine compounds having a free carboxylic group have been reported to possess bioactivities [5-6]. The synthesis of 2-carboxy-2,3-dihydro-4-phenyl/p-tolyl/p-chlorophenyl/2,4-dihydroxyphenyl-1,5-benzothiazepines, having no substituents at position-8, have been reported [7] earlier.

Also, β-(benzoyl) acrylic acids have been reported [8-9] to inhibit phospholipase from snake venom and from procaine pancreas, they also have antibacterial activities [10-11] and anti-proliferative [12] action against human cervix carcinoma.

In this study, the syntheses of a new series of 8-substituted-1,5-benzothiazepine-2-carboxylic acids, having disubstituted aryl group at position-4, along with their antimicrobial studies, are being reported.

MATERIAL AND METHODS

The 8-substituted - 4 - (3, 4 - dimethylphenyl) - 2,3 – dihydro - 1,5-benzothiazpine-2-carboxylic acids were synthesized by the reactions of 5-substituted-2-aminobenzenethiols with β-(3,4-dimethylbenzoyl) acrylic acid [13] in acidic medium.

General method for the preparation of 8-Substituted-4-(3,4- dimethylphenyl)-2,3-dihydro-1,5-benzothiazpine-2-carboxylic acids, 3a-f:

Equimolar quantities of β-keto acid, β-(3,4-dimethylbenzoyl) acrylic acids (2) and 5-substituted-2-aminobenzenethiols (1a-f) were dissolved in dry ethanol and mixed together. Glacial acetic acid (1ml) was added to this reaction mixture which was refluxed for 3-4 hrs. The reaction mixture was concentrated under reduced pressure. The crude solid thus obtained was crystallized from dry ethanol to afford six new compounds, 8-substituted-4-(2,3-dimethylphenyl)-2,3-dihydro-1,5-benzothiazpine-2-carboxylic acids (3a-f).

The reactions were monitored by TLC using solvent system benzene: ethanol: aq ammonia (50%) (7:2:1) on silica gel 'G' coated glass plates. All the melting points are uncorrected. 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 mass spectra were recorded on a Jeol-AccuTOF JMS-T100LC Mass spectrometer having a DART source. Dry helium was used with 4 LPM flow rate. Micro estimation for carbon hydrogen, nitrogen and sulfur were carried out in elemental analyzer, at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow.

Antimicrobial Activity

All the synthesized compounds (3a-f) were screened for relative antibacterial activity against the gram-positive bacteria, *Staphylococcus aureus* and the gram-negative bacteria, *Escherichia coli* and antifungal activity against the fungus, *Candida albicans* by using Paper Disc Method [14]. The results have been compared with reference compounds Vancomycin (*S.a*), 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.

RESULT AND DISCUSSION

In the studies of reactions of 2-amino-benzenethiol with α,β-unsaturated acids, it has been reported [15-16] that the syntheses of 8-substituted-4-aryl-2,3-dihydro-1,5-benzothiazepines 2-carboxylic acid were attained by single step reaction. The reactions have been reported to be initiated by nucleophilic attack of the sulphhydryl electrons of 5-substituted-2-aminobenzenethiols at the activated β-carbon atom of the α,β-unsaturated- β-keto acids, to give Michael adduct type intermediates in the first step, which then

undergoes dehydrative cyclization to give cyclized seven membered heterocyclic products in the second step. The flow chart of the progress of reaction is given in scheme-I.

IR SPECTRAL STUDIES

The IR spectra of 8-substituted -4-(3,4-dimethylphenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids (3a-f), showed strong absorptions at 1690-1678 cm^{-1}, which may be assigned to carbonyl stretching frequency. The appearance of this band at low frequency indicated that the carbonyl group is having conjugation with unsaturation. A very broad absorption in the region 3425-3383 cm^{-1} due to O-H stretching vibrations and also a broad intense absorption in the region 1613-1606 cm^{-1} in all the spectra shows the presence of C=N, as has been characterized [17] in 1,5-benzodiazepines. The compounds 3a-c showed absorptions for the halogens in their respective regions. The spectra did not show the absorptions for asymmetric and symmetric stretching vibrational absorptions in the region around 3350 cm^{-1}, characterizing primary amino group. Thiol group is reported to absorb in the range of 2600-2500 cm^{-1}. The absence of absorption bands in this region indicated that thiol group had participated in the reaction to give the product. Thus, the absence of these bands indicated that the respective thiols had reacted with substituted benzoyl acrylic acid to give the products without the isolation of the intermediate.

^{1}HNMR SPECTRA

The ^{1}HNMR spectra of all the compounds showed a singlet at δ 7.78-7.98 may be assigned to carboxylic acid protons. The spectra showed a set of three double doublets in the ABX pattern. Each of the three double doublets in the regions δ 3.16-3.20, δ 3.23-3.49 and δ 4.24-4.29 were found to integrate for one proton each. The spectra also showed a signal corresponding to six protons of the two methyl groups between δ 2.32-2.40 in all the compounds. The absorption signal in the region of δ 6.81-7.93(m, 6H) occurred as multiplets corresponding to the aromatic protons.

The characteristic methyl, methoxy and ethoxy proton signals were also observed, as given in table-2.

Mass Spectral Analyses

The mass spectra of 3b showed cluster of the molecular ion peak, m/z, $[M]^+$, $[M+2]^+$ and $[M+4]^+$ at 345,347 and 349 respectively, corresponding to the molecular mass of the product. The intensity of the $[M+2]^+$ peak was found nearly one third of the M^+ peak, which ascertained the presence of chlorine in the compound. The mass spectra of 3c showed molecular ion peaks, m/z, $[M]^+$ and $[M+2]^+$ at 390 and 392; the intensity of $[M+2]^+$ peak was found to be nearly equal to the M^+ peak which confirmed the presence of bromine. The results of elemental analyses were found to be satisfactory being within the permissible limits of error.

Antibacterial activity

Most of the synthesized compounds were found to show activity against the bacteria *Staphylococcus aureus*. Most of the compounds exhibited lower activity (activity index≥1), than the reference compound. Compounds 3c and 3d showed highest activity (activity index= 0.62), while others showed moderate activity, lying in the range of activity index = 0.41-0.58. Compounds 3a and 3f did not show any activity. Against the bacteria *Escherichia coli*, most of the compounds showed activity index between 0.61-0.71.

Antifungal activity

Against the fungus, *Candida albicans*, most of the compounds exhibited lower activity (activity index≥1), than the reference compound, in a duration of 48 hrs incubation; compound 3e was found to have higher activity (activity index= 0.56). Compounds 3b-d showed moderate activity in the range of activity index 0.48-0.52.

CONCLUSION

The target compounds were obtained by single pot reactions in acidic medium. Some of the compounds showed antibacterial and antifungal activity against all the microorganisms for which they were tested, mainly the 8-chloro and 8-methoxy compounds. Compound 3d having three methyl groups showed good activity against the gram-negative bacteria *E. coli.*

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Table. 1 Physical and antimicrobial data of 8-substituted- 2, 3-dihydro-4-(3,4-dimethylbenzoyl)-1,5-benzothiazepine-2-carboxylic acids (3a-f)

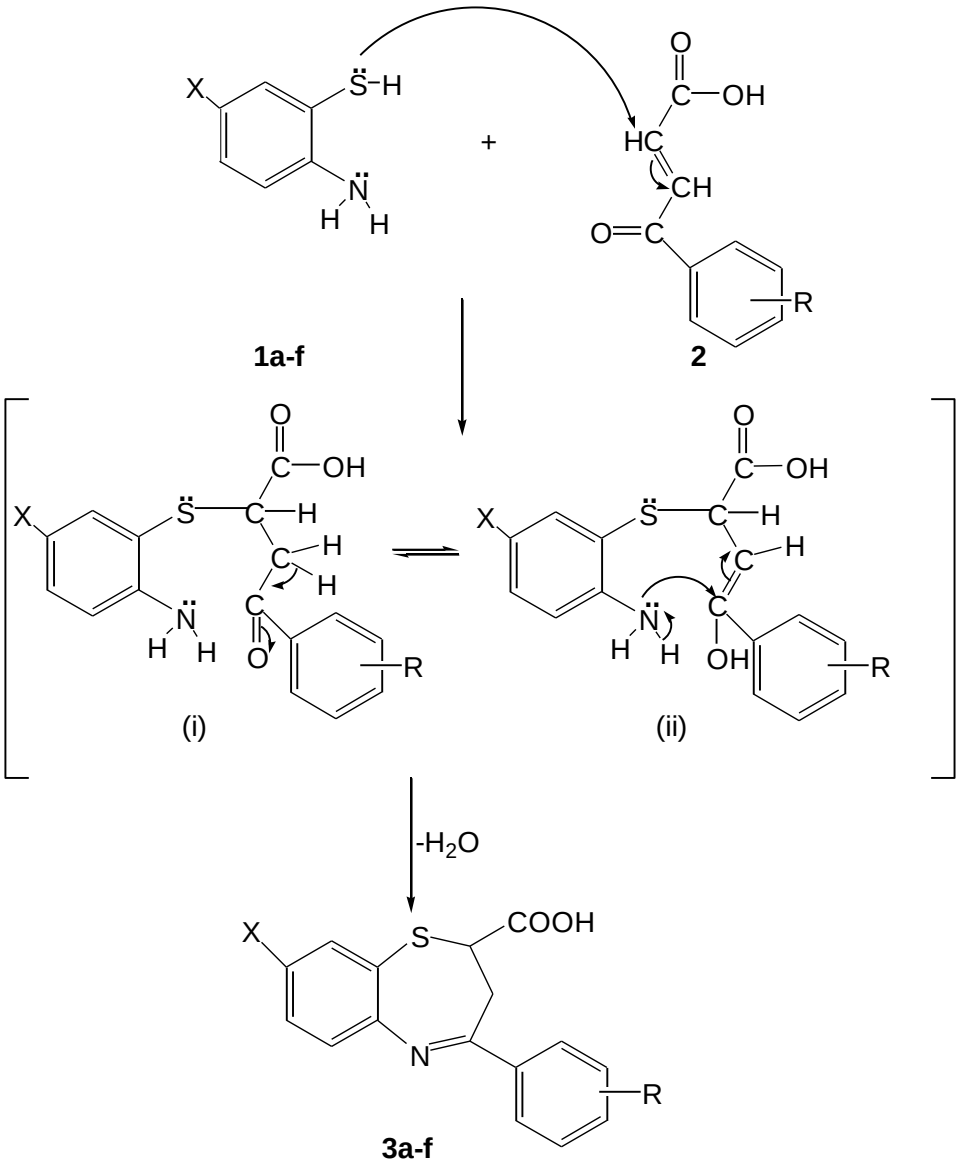
C. No.	M.P °C	Yield (%)	Elemental Analyses (%) Found (Calculated)				Antimicrobial Activity		
			C	H	N	S	*S. a.*	*E. c.*	*C. a.*
3a	158-160	62	64.71 (65.63)	3.90 (4.90)	–	8.53 (9.73)	-	14 (0.66)	-
3b	85-87	81	–	–	3.73 (4.05)	8.37 (9.27)	14 (0.58)	14 (0.66)	12 (0.48)
3c	198-200	59	54.52 (55.39)	–	2.53 (3.59)	7.21 (8.22)	15 (0.62)	-	13 (0.52)
3d	135	74	–	4.87 (5.83)	3.60 (4.30)	–	15 (0.62)	15 (0.71)	13 (0.52)
3e	80	83	–	–	3.20 (4.10)	8.48 (9.39)	10 (0.41)	13 (0.61)	14 (0.56)
3f	162	85	66.40 (67.58)	–	3.60 (3.94)	–	-	-	-

Zones of inhibition are given in mm; Values in parentheses represent activity index
Zone of inhibition of Vancomycin for Staphylococcus aureus is 24 mm
Zone of inhibition of Colistin-Polymyxin-B for Escherichia coli is21mm
Zone of inhibition of Fluconazole for Candida albicans is 25mm
Concentration of test and reference compounds were 100µg/disc.

Table. 2 ^{1}HNMR data of 8-Substituted-4-((3,4-dimethylphenyl)-2,3-dihydro-1,5-benzothiazepine-2-carboxylic acids (3a-f)

C. No.	C_3-H_A (dd; J_{AB}16, J_{AX} 7 ;1H)	C_3-H_B (dd; J_{AB} 16, J_{BX} 7 ;1H)	C_2-H_X (dd; J_{AX} 7, J_{BX} 7 ;1H)	C_8-X	CH_3 (s, 6H)	COOH (s, 1H)	Aromatic protons (6H, m)
3a	3.16	3.24	4.28	-	2.33	7.94	6.81-7.74
3b	3.17	3.33	4.26	-	2.35	7.98	6.87-7.79
3c	3.18	3.23	4.27	-	2.38	7.88	6.83-7.83
3d	3.17	3.34	4.24	2.23(s,3H)	2.40	7.92	6.83-7.93
3e	3.20	3.49	4.29	3.75(s,3H)	2.32	7.78	6.84-7.86

3f	3.20	3.47	4.27	1.27(t,3H), 4.11(q ,2H)	2.36	7.91	6.84-7.71



R=3,4-dimethyl

Compd. 3	a	b	c	d	e	f
X	F	Cl	Br	CH_3	OCH_3	OC_2H_5

Scheme-I