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Synthesis, characterization and biological evaluations of some 5-(substituted amino alkyl)-2-{(1, 3- benzothiazole-2-yl)}-thiazolidine-4 one Mannich bases as potent antibacterial agents

Munendra Mohan Varshney[1], Asif Husain[2], Versha Percha[3], Neeraj Fuloria[4]
[1]Dept of Pharmaceutical Sciences, Raj Kumar Goel Institute of Technology, Delhi Meerut Road, Ghaziabad, India.
[2]Dept of Pharmaceutical Chemistry, Jamia Humdard University, New Delhi.
[3]Dept of Pharmaceutical Sciences, Sardar Bhagwan Singh Postgraduate Institute of Biomedical Sciences, Dehradun, India.
[4]Anuradha College of Pharmacy, Chiklhi, Buldana (Maharashtra), India.

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ABSTRACT

Novel Mannich bases of 5-(substituted amino alkyl)-2-{(1, 3 benzothiazole-2-yl)}-thiazolidine-4 one, are synthesized by amination at 5th position of thiazolidine ring of 2-{(1, 3 benzothiazole-2-yl)}-thiazolidine-4 one using formaldehyde and various secondary amines. The synthesized compounds have been characterized by physico-chemical and spectral analysis and screened for their in- vitro antibacterial activity against various strains of bacteria.

INTRODUCTION

Compounds bearing benzothiazole nucleus are of great interest for a long time due to their unique chemical and biological properties related to antimicrobial properties. A number of mannich bases have been reported as potent antimycobecterial, antitumor, antimicrobial, antimalarial, antifungal agents (Srivastava *etal*, 2008). In some cases mannich bases of benzothiazole are even found to have enhanced activity of starting compounds (Gurupadayya *etal*, 2009). Thiazolidine-4-one derivatives have been reported to exhibit a number of pharmacological activities such as antibacterial (Udupi *etal*, 1997), anticonvulsant (Ragab and Eid, 1997), anticancer (Veinberg *etal*, 2004), analgesic (Fahmy and Eleraky, 2001), antiinfalmmatory (Previtera *etal*, 1994), anthelminitics (Suresh *etal*, 2011) and CNS depressants (Rana *etal*, 2007). A molecule with thiazolidinone ring incorporated with a benzothiazole ring and converting them to Mannich bases and screened the newly synthesized novel compounds for their antibacterial activity.

EXPERIMENTAL

1,3-benzothiazole-2-carboxyhydrazide and thiazolidinone used as key intermediate for synthesis. 1,3-benzothiazole-2-carboxyhydrazide was treated with chloroacetyl chloride in presense of K_2CO_3 in acetone. Chloroacetyl hydazolyl-1, 3-bezothiazole was treated with ammonium thiocyanate in absolute ethanol to give 2-{(1, 3 benzothiazole-2-yl)}-thiazolidine-4 one. The product was allowed to undergo Mannich reaction in presence of formaldehyde with different secondary amines.

All Melting points of all synthesized compounds were determined by Theils tubes apparatus. The purity of all synthesized compounds was determined by TLC on silica gel plates by using hexane: ethylacetate: methanol solvent system. IR spectra were recorded (Bruker, alpha E ATR, FTIR spectrometer), H1NMR spectra (Bruker 400 NMR spectrometer) were recorded with TMS as internal standard and Mass spectral data were recorded with a quadrupol mass spectrometer (Shimadzu GC MS QP 5000).

* *Corresponding Author*
Email: munendra_1978@rediffmail.com; Phone: +91 9711899497

Attempted synthesis of ethyl-2-bezothiazole carboxylate (A)

Treating a mixture of o-aminothiophenol (0.1 M) and diethyl oxalate (0.2 M) gave the product ethyl-2-bezothiazole carboxylate (Rajeeva *etal,* 2009) .The product was recrystellized with ethanol.

Attempted synthesis of 1,3 bezothiazole carboxyhydrazide (B)

1,3 bezothiazole carboxyhydrazide was prepared by the treatment of ethyl-2-bezothiazole carboxylate (0.1 M) in ethanol and dropwise addition of hydrazine hydrate (0.5 M) with constant stirring and reflux for 6 hrs. After completion of reaction, reaction mixture was cooled, filtered, washed with water and collect the product (Nassem *etal,* 2008). m.p 170-175^{0}C.

Synthesis of 2-chloroacetyl hydrazolyl-1, 3-benzothiazole (C)

1,3 bezothiazole carboxyhydrazide (0.01 M) was dissolved in 25 ml of acetone in round bottom flask. K2CO3 (2.0 gm) was added to the solution and then chloroacetyl chloride (0.01 M) was added drop wise with constant stirring for 2 hrs. After completion of reaction the reaction mixture was filtered and the crude product was separated by evaporating the acetone (Sharma *etal,* 2009). Product was recrystellized with ethanol. m.p 154-160^{0}C.

Synthesis of 2-{(1, 3 benzothiazole-2-yl)}-thiazolidine-4 one (D)

2-chloroacetyl hydrazolyl-1, 3-benzothiazole (0.05 M) was taken with ammonium thiocyanate (0.1 M) in 50 ml of ethanol and was reflux on water bath for 1.5 hrs. The reaction mixture was kept overnight and the crude product was filtered and finally recrystellized from absolute ethanol. m.p 145-153^{0}C.

Synthesis of 5-(substituted amino alkyl)-2-{(1, 3 benzothiazole-2-yl)}-thiazolidine-4 one (Ea-i) as Mannich bases

A solution of 0.5 ml of 37% formaldehyde and secondary amine (0.05 M) were added drop wise with vigorous stirring to a suspension of 2- {(1, 3 benzothiazole-2-yl)}- thiazolidine-4 one (0.05 M) in 10 ml of absolute ethanol. The reaction mixture was reflux for 5 hrs of water bath and cooled to room temperature. The precipitated, filtered, dried and recrystellized from ethanol.All the synthesized intermediate compounds (A-D) were subjected to physicochemical and spectral characterization (IR and NMR spectroscopy).

IR (KBr, cm-1): peaks of Ar-CH and CH_2 stretching and C=O stretching (thiazolidinone) were observed in the region 3005-3200cm^{-1} and 1700 cm^{-1} respectively, while -NH stretching for all compounds were found to 3250 cm^{-1} region.1H NMR (DMSO, δ ppm): peaks of aromatic rings of compounds A-D were found to 7.5-8-3 (4H, m, Ar-H), 1.4-1.8 (3H, t, CH_3 of $–COOC_2H_5$) for compound A, 4.6-4.9 (2H, s, NH_2 of $–CONH_2$) were found to compound B and C.

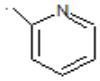
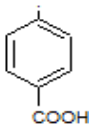
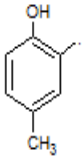
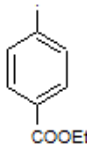
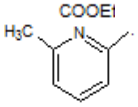
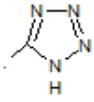
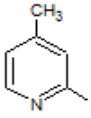
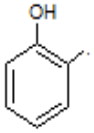
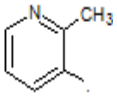
Antibacterial Activity

All 5-substitted -2-{(1, 3 benzothiazole- 2- yl) }-thiazolidine-4 one (Ea-Ei) synthesized compounds were tested for their in vitro antibacterial activity against gram positive bacteria *S.aureus* (ATCC 9144) and *B.subtilis* (ATCC 6399) gram negative bacteria, *E.coli* (ATCC25922) and *P.aeruginosa* (ATCC 17933) by using Mueller-Hinton agar medium (HI-Media laboratories, India) was employed to study the preliminary antibacterial activity (Cruikshank *etal,* 1975).

Paper disc diffusion method

The sterilized (autoclaved at 1200 for 30 minutes) medium (40-500) was inoculated (1 ml/ml of the media) with the suspension of microorganism and poured in to petri dish to give a depth of 3-4 mm the paper impregnated with the test compounds (200 µg/ml in dimethylformamide) was placed on solidify media. All plates were incubated for 1 h at room temperature at 37 ^{0}C for 24 h for antibacterial activities respectively (Gillespie SH, 1994).Ciprofloxacin and Norfloxacin were used as standards for antibacterial activity. The observed Zone of inhibition is represented in the table.

Table. 1: Physical data of compounds (Ea-i).

Product code	R	Molecular formula	M.P (0^oC)	M.W	% yield
Ea		$C_{17}H_{15}N_7O_2S_2$	180-190	398	54
Eb		$C_{19}H_{16}N_6O_4S_2$	210-215	456	45
Ec		$C_{19}H_{18}N_6O_3S_2$	214-221	442	58
Ed		$C_{20}H_{20}N_6O_4S_2$	189-198	472	61
Ee		$C_{17}H_{17}N_7O_2S_2$	201-205	401	70
Ef		$C_{12}H_{12}N_{10}O_2S_2$	196-207	392	52
Eg		$C_{17}H_{17}N_7O_2S_2$	207-217	415	67
Eh		$C_{16}H_{16}N_6O_3S_2$	187-184	404	68
Ei		$C_{17}H_{17}N_7O_2S_2$	178-188	415	72

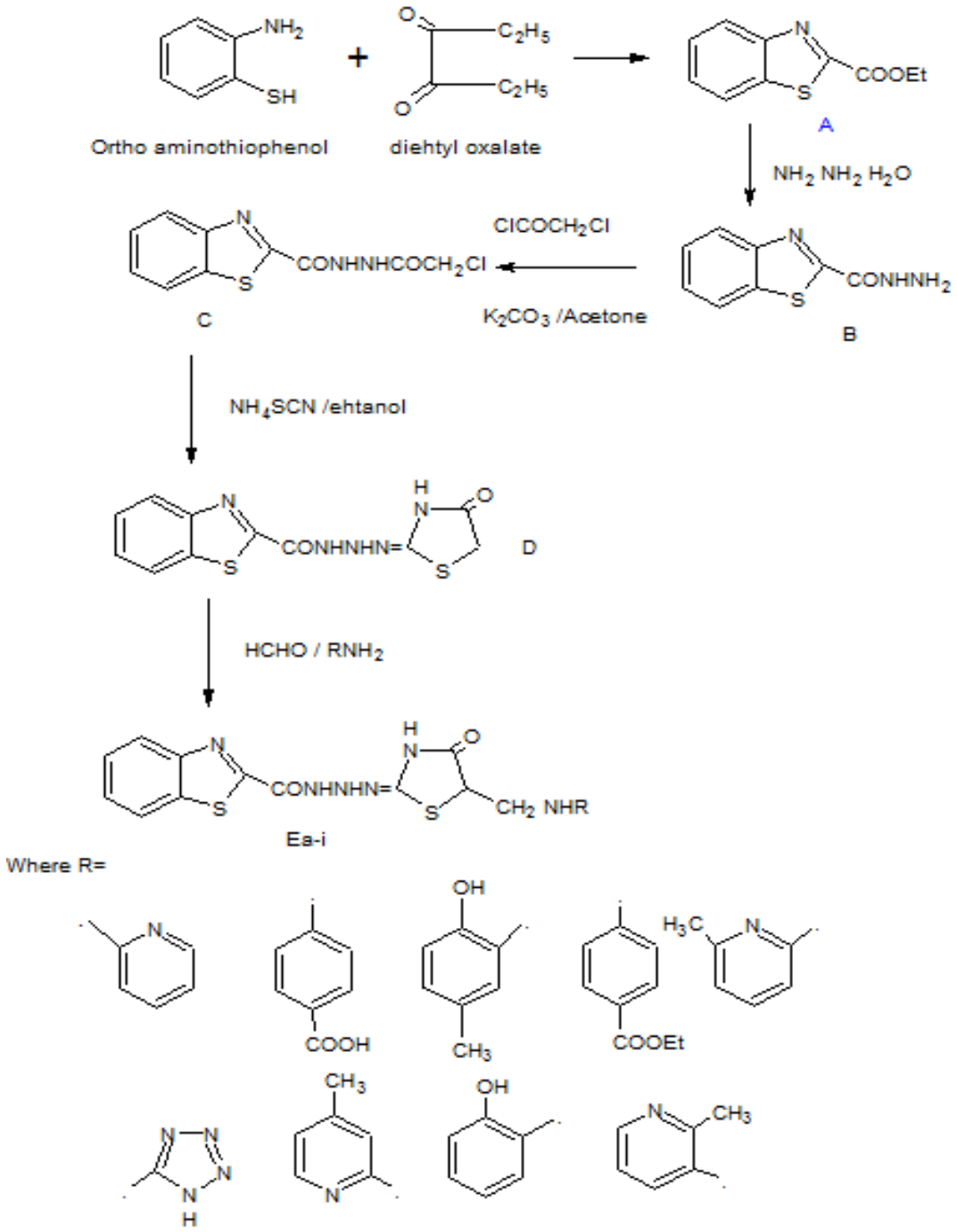


Table. 2: Spectral Characterization Of Synthesized Compounds (Ea-Ei).

Ea	IR (KBr, cm-1): 3215, -NH stretching, 3001-3060, Ar stretching and –CH_2 stretching, 1700 ,C=O, thiazolidinone, ^{1}H NMR (DMSO, δ ppm): 5.5 (2H, s, CH_2), 6.4 (1H, s, -NH), 7.3-8.6 (m, Ar-H), MS m/z 398 (M^+)
Eb	IR (KBr, cm-1): 3218, -NH stretching, 3001-3060, Ar stretching and –CH_2 stretching, 1695 ,C=O, thiazolidinone, 1044, C-N stretching, ^{1}H NMR (DMSO, δ ppm): 5.9 (2H, s, CH_2), 6.7 (1H, s, -NH), 7.4-8.6 (m, Ar-H), MS m/z 456 (M^+)
Ec	IR (KBr, cm-1): 3217, -NH stretching, 3014-3045, Ar stretching and –CH_2 stretching, 1700 ,C=O, thiazolidinone, ^{1}H NMR (DMSO, δ ppm): 5.9 (2H, s, CH_2), 8.5 (1H, s, -NH), 7.3-8.6 (m, Ar-H), MS m/z 442 (M^+)
Ed	IR (KBr, cm-1): 3215, -NH stretching, 3003-3060, Ar stretching and –CH_2 stretching, 1690 ,C=O, thiazolidinone, ^{1}H NMR (DMSO, δ ppm): 5.8 (2H, s, CH_2), 8.4 (1H, s, -NH), 7.3-8.6 (m, Ar-H), MS m/z 472 (M^+)
Ee	IR (KBr, cm-1): 3215, -NH stretching, 3001-3060, Ar stretching and –CH_2 stretching, 1704 ,C=O, thiazolidinone, 1043, C-N stretching, ^{1}H NMR (DMSO, δ ppm): 5.3 (2H, s, CH_2), 6.4 (1H, s, -NH), 7.3-8.6 (m, Ar-H), MS m/z 401 (M^+)
Ef	IR (KBr, cm-1): 3215, -NH stretching, 3001-3044, Ar stretching and –CH_2 stretching, 1700 ,C=O, thiazolidinone, 1043, C-N stretching, ^{1}H NMR (DMSO, δ ppm): 6.4 (2H, s, CH_2), 6.4 (1H, s, -NH), 7.3-8.8 (m, Ar-H), MS m/z 492 (M^+)
Eg to Ei	IR (KBr, cm-1): 3370, -NH stretching, 3001-3060, Ar stretching and –CH_2 stretching, 1690-1700 ,C=O, thiazolidinone, 1060-1100, C-N stretching, ^{1}H NMR (DMSO, δ ppm): 6.1-6.4 (2H, m, CH_2), 7.4-8.9 (m, Ar-H)

Table. 3: Data Of Antimicrobial Activities Of Synthesized Compounds Inhibition Of Zone Diameter (In Mm).

Compounds	*S.aureus* ATCC 9144	*B.subtilis* ATCC 6399	*E.coli* ATCC25922	*P.aeruginosa* ATCC 17933
Ea	11	9	12	9
Eb	13	8	15	10
Ec	10	10	17	8
Ed	7	14	11	10
Ee	12	9	10	14
Ef	14	11	8	11
Eg	11	10	9	12
Eh	8	15	10	7
Ei	6	11	11	10
Ciprofloxacin(200 µg/disc)	24	22	21	24
Norfloxacin(200 µg/disc)	24	23	22	23
Dimethyl formamide(DMF)	-	-	-	-

Highly active = inhibition zone ≥ 12 mm
Moderate active = inhibition zone 9-12 mm
Slightly active = inhibition zone 6-9 mm
Inactive = inhibition zone ≤ 6 mm

RESULTS AND DISCUSSION

All the synthesized compounds were tested for their antibacterial activity using quinolones antibiotics as standards. The data of Table-3 indicate that among all the compounds, compounds Eb, Ed, Ef and Eh were found to highly active for gram positive bacteria *S.aureus* and *B.subtilis*. Compounds Eb, Ec, Ee were found to exhibit highly active against gram negative bacteria *E.coli* and *P.aeruginosa*. While compounds Ea, Ei, Eg were found to be remarkably effective compounds with respect to their inhibitory activity against gram positive and gram negative bacteria.

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