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Original Article

Synthesis and anticonvulsant evaluation of benzothiazole derivatives

Laxmi Tripathi[a], Rashmi Juneja[b,*]

[a]*Moradabad Educational Trust, Group of Institutions–Faculty of Pharmacy, MIT Campus, Ramganga Vihar, Phase-II, Moradabad, Uttar Pradesh, India.*

[b]*Department of Pharmaceutical Chemistry, S.D. College of Pharmacy & Vocational Studies, Muzaffarnagar, Uttar Pradesh, India.*

Corresponding Author. Tel.: +91 8534954084, *E-mail address:* rashmi.mpharma.21@gmail.com

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ABSTRACT

A series of substituted N-benzothiazole derivatives and substituted N-benzthiazole-2-yl-hydrazides were synthesized and their anticonvulsant activity was evaluated after oral administration in the MES model. The synthesized derivatives showed moderate to minor protection in anticonvulsant screening. Among the synthesized derivatives only BZT-4, BZT-5, BZT-11 and BZT-12 showed moderate activity in MES test. None of the compounds showed neurotoxicity at the maximum administered dose.

1. INTRODUCTION

Benzothiazole is an aromatic heterocyclic compound with the chemical formula C_7H_5NS. Benzothiazole consist of a five-membered 1,3 thiazole ring fused with benzene ring. Although the parent compound, benzothiazole is not widely used, many of its derivatives are found in commercial products or in nature. A derivative of benzothiazole is the light-emitting component of luciferin, found in fireflies. Benzothiazole moiety having varied biological activities such as anti-microbial[1-2], anti-cancer[3-5], anti-tumour[6-8], anti-convulsant[9-16], anti-inflammatory[17], anti-oxidant[18-19], anti-bacterial[20-21], anti-depressant[22], anti-fungal[23], anti-psychotic[24] and great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry with application in drug discovery. They have also found application in industry as anti-oxidants, vulcanizations accelerators. Various benzothiazoles such as 2-substituted benzothiazole received much attention due to unique structure and its uses as radioactive amyloidal imagining agents and anticancer agents.

2. EXPERIMENTAL

Material and Methods

All the chemicals and solvents, purchased from Merck (India), Spectrochem (India), Sigma-Aldrich (India), Himedia (India) and S.D. Fine were used without further purification. All melting points were determined by using open capillary melting point apparatus and are uncorrected.

Synthesis of substituted N-benzothiazole derivatives

The substituted benzothiazole derivatives were synthesized according to the scheme given in Fig. 1.

Preparation of Substituted Acyl Chloride

Substituted acid (0.1 mol) and thionyl chloride (28.8 ml, 0.4 mol) are placed in a 250-ml flask equipped with a magnetic stirrer bar and a condenser with a drying tube (hydrogen gas evolved). The reaction mixture is stirred and heated in a 70^0 C oil bath. After 0.5 hour, the flask is removed from the oil bath and cooled to room temperature [25].

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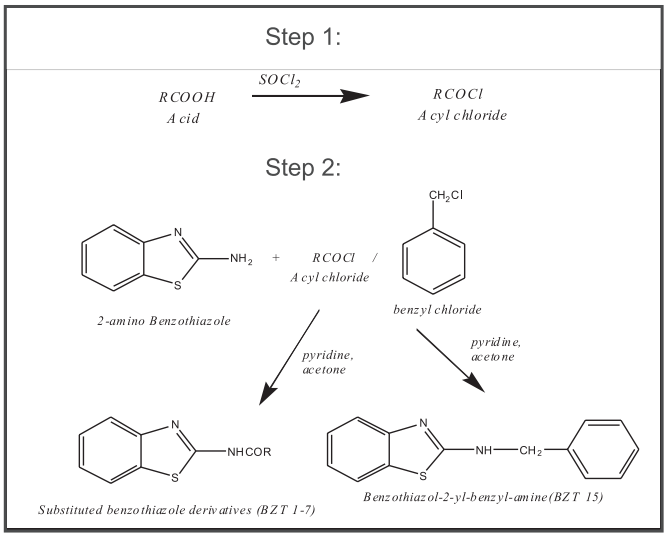

Fig. 1. Synthesis of substituted N-benzothiazole derivatives

Preparation of Substituted Benzothiazole Derivatives (BZT 1-7)

Substituted acyl chloride (0.1 mol) was dissolved in 20 ml of dry acetone was added dropwise to a stirred solution of 2-amino benzothiazole (0.1) and pyridine in 50 ml acetone. After addition the reaction mixture was stirred for 12 hours at room temperature and then the solvent was evaporated under reduced pressure. The obtained products were purified by crystallization using ethanol/ petroleum ether mixture (1:3) to give crystals [26].

N-benzothiazol-2-yl-2-phenyl-acetamide (BZT 1): IR (KBr, cm^{-1})□: 3051 (NH_{str}), 1649 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.16- 7.58 (a set of signals, 7H Ar-H and benzthiazole-H), 7.85 (s, 1H, NH). MS (m/z, %): 269.2 (M^++1, 100%).

Thiophene-2-carboxylic acid benzothiazol-2-ylamide (BZT 2): IR (KBr, cm^{-1})□ : 3056 (NH_{str}), 1650 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.14- 7.55 (a set of signals, 7H Ar-H and benzthiazole-H), 7.88 (s, 1H, NH). MS (m/z, %): 261.3 (M^++1, 100%).

Furan-2-carboxylic acid benzothiazol-2-ylamide (BZT 3): IR (KBr, cm^{-1}) □ : 3058 (NH_{str}), 1656 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.11- 7.53 (a set of signals, 7H Ar-H and benzthiazole-H), 7.84 (s, 1H, NH). MS (m/z, %): 245.2 (M^++1, 100%).

N-benzothiazol- 2-isonicotinamide (BZT 4): IR (KBr, cm^{-1}) □: 3054 (NH_{str}), 1651 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.19- 7.60 (a set of signals, 7H Ar-H and benzthiazole-H), 7.91 (s, 1H, NH). MS (m/z, %): 256.2 (M^++1, 100%).

N-benzothiazol- 2-yl-2-chloro-nicotinamide (BZT 5): IR (KBr, cm^{-1}) : 3057 (NH_{str}), 1658 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.17- 7.56 (a set of signals, 7H Ar-H and benzthiazole-H), 7.85 (s, 1H, NH). MS (m/z, %): 290.6 (M^++1 for ^{35}Cl, 100%), 292.2 (M^++1 for ^{37}Cl, 34%).

N-benzothiazol- 2-yl-3-phenyl-acrylamide (BZT 6): IR (KBr, cm^{-1}) □ : 3052 (NH_{str}), 1650 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.15- 7.54 (a set of signals, 11H Ar-H and benzthiazole-H), 7.83 (s, 1H, NH). MS (m/z, %): 281.3 (M^++1, 100%).

N-benzothiazol- 2-yl-benzamide (BZT 7): IR (KBr, cm^{-1}) □: 3053 (NH_{str}), 1653 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.12- 7.53 (a set of signals, 7H Ar-H and benzthiazole-H), 7.86 (s, 1H, NH). MS (m/z, %): 255.33 (M^++1, 100%).

Preparation of Benzothiazol-2-yl-benzyl-amine (BZT 15)

Benzyl chloride (0.1 mol) was dissolved in 20ml of dry acetone was added dropwise to a stirred solution of 2-amino benzothiazole (0.1) and pyridine in 50 ml acetone. After addition the reaction mixture was stirred for 12 hours at room temperature and then the solvent was evaporated under reduced pressure. The obtained products were purified by crystallization using ethanol/ petroleum ether mixture (1:3) to give crystals [26].

Benzothiazol-2-yl-benzyl-amine (BZT 15): IR (KBr, cm^{-1}) □: 3058 (NH_{str}). ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.10- 7.50 (a set of signals, 11H, Ar-H and benzthiazole-H), 7.83 (s, 1H, NH). MS (m/z, %): 241.3 (M^++1, 100%).

Synthesis of substituted N-benzothiazole-2-yl-hydrazides

The Substituted N- benzothiazole-2-yl-hydrazides were synthesized according to the scheme given in Fig. 2.

Preparation of Benzothiazole hydrazide

To a suspension of 2-amino benzothiazole (0.1 mole) in ethylene glycol (8 ml), hydrazine hydrate (0.3 mole) and conc. HCl (2 ml) was added at 5-6°C This mixture was refluxed for 5-6 hours to obtained to 2-hydrazynyl benzothiazole.

Preparation of Substituted N'benzothiazole-2-yl-hydrazide (BZT-H 8-13)

Substituted acyl chloride (0.1 mol) was dissolved in 20 ml of dry acetone was added dropwise to a stirred solution of benzothiazole hydrazide (0.1) and pyridine in 50 ml acetone. After addition the reaction mixture was stirred for 12 hours at room temperature and then the solvent was evaporated under reduced pressure. The obtained products were purified by crystallization using ethanol/ petroleum ether mixture (1:3) to give crystals [26].

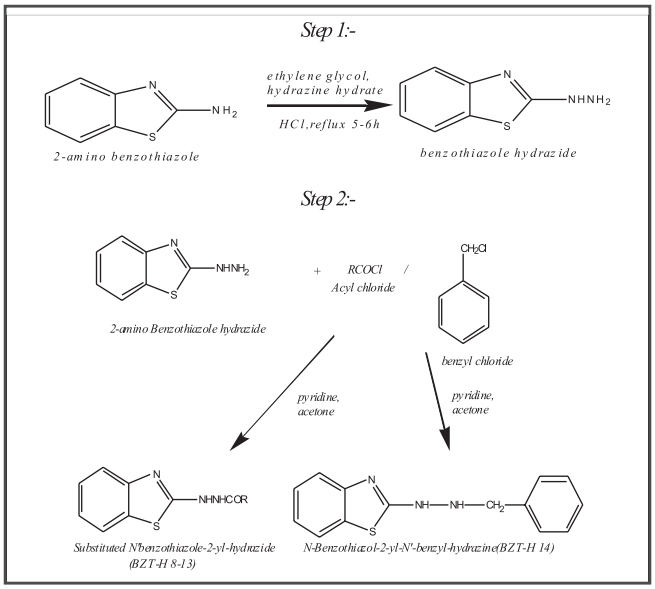

Fig. 2. Synthesis of substituted N- benzothiazole-2-yl-hydrazides

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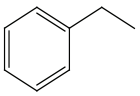
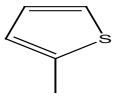
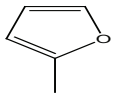
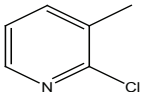
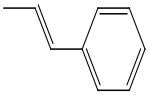
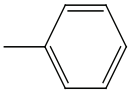
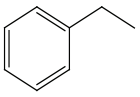
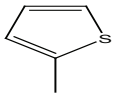
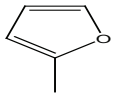
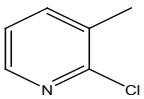
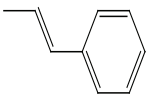
Table 1. Physical and elemental data of synthesized derivatives

Compounds	R	Mol. Formula	(Mol.wt)	M. Pt. [K]	Yield (%)	Elemental Analysis Found (Calc.)		
						C	H	N
BZT 1		$C_{15}H_{12}N_2OS$	268.33	680.33	77.22	67.14 (67.12)	4.51 (4.48)	10.44 (10.41)
BZT 2		$C_{12}H_8N_2OS_2$	260.33	732.73	75.44	55.36 (55.34)	3.10 (3.07)	10.76 (10.73)
BZT 3		$C_{12}H_8N_2O_2S$	244.27	675.85	76.33	59.00 (58.97)	3.30 (3.27)	11.47 (11.44)
BZT 4		$C_{13}H_9N_3OS$	255.30	729.33	74.21	61.16 (61.13)	3.55 (3.52)	16.46 (16.45)
BZT 5		$C_{13}H_8ClN_3OS$	289.74	771.77	78.74	53.89 (53.86)	2.78 (2.75)	14.50 (14.47)
BZT 6		$C_{16}H_{12}N_2OS$	280.34	686.52	80.22	68.55 (68.52)	4.31 (4.28)	9.99 (9.96)
BZT 7		$C_{14}H_{10}N_2OS$	254.31	669.06	81.25	66.12 (66.10)	3.96 (3.94)	11.02 (11.00)
BZT-H 8		$C_{15}H_{13}N_3OS$	283.35	732.99	74.23	63.58 (63.55)	4.62 (4.59)	14.83 (14.80)
BZT-H 9		$C_{12}H_9N_3OS_2$	275.35	785.39	78.56	52.34 (52.30)	3.29 (3.25)	15.26 (15.22)
BZT-H 10		$C_{12}H_9N_3O_2S$	259.28	728.51	83.55	55.59 (55.56)	3.50 (3.47)	16.21 (16.19)
BZT-H 11		$C_{13}H_{10}N_4OS$	270.31	781.99	72.27	57.76 (57.74)	3.73 (3.71)	20.73 (20.71)
BZT-H 12		$C_{13}H_9ClN_4OS$	304.75	824.43	71.75	51.23 (51.20)	2.98 (2.95)	18.38 (18.35)
BZT-H 13		$C_{16}H_{13}N_3OS$	295.36	739.18	74.28	65.06 (65.02)	4.44 (4.41)	14.23 (14.20)
BZT-H 14	-	$C_{14}H_{13}N_3S$	255.34	608.17	78.49	65.85 (65.79)	5.13 (5.09)	16.46 (16.43)
BZT 15	-	$C_{14}H_{12}N_2S$	240.32	555.51	73.27	69.97 (69.72)	5.03 (4.98)	11.66 (11.51)

Phenyl-acetic acid N'- benzothiazol-2-yl-hydrazide (BZT-H 8): IR (KBr, cm^{-1}) □: 3202, 3053 (NH_{str} associated), 1678 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.29 - 7.61 (a set of signals, 11H, Ar-H and benzthiazole-H), 8.21- 8.22 (d, 1H, -NH-NH-). MS (m/z, %): 284.2 (M^++1, 100%).

Thiophene-2-carboxylic acid N'- benzothiazol-2-yl-hydrazide (BZT-H 9): IR (KBr, cm^{-1}) □: 3204, 3055 (NH_{str} associated), 1675 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.27 - 7.64 (a set of signals, 7H, Ar-H and benzthiazole-H), 8.24- 8.27 (d, 1H, -NH-NH-). MS (m/z, %): 276.3 (M^++1, 100%).

Furan-2-carboxylic acid N'- benzothiazol-2-yl-hydrazide (BZT-H 10): IR (KBr, cm^{-1}) □: 3203, 3058 (NH_{str} associated), 1679 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.23 - 7.67 (a set of signals, 7H, Ar-H and benzthiazole-H), 8.22- 8.26 (d, 1H, -NH-NH-). MS (m/z, %): 260.3 (M^++1, 100%).

Isonicotinic acid N'- benzothiazol-2-yl-hydrazide (BZT-H 11): IR (KBr, cm^{-1}) □: 3208, 3051 (NH_{str} associated), 1674 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.26 - 7.64 (a set of signals, 7H, Ar-H and benzthiazole-H), 8.20 - 8.26 (d, 1H, -NH-NH-). MS (m/z, %): 271.3 (M^++1, 100%).

2-chloro nicotinic acid N'- benzothiazol-2-yl-hydrazide (BZT-H 12): IR (KBr, cm^{-1}) □: 3206, 3050 (NH_{str} associated), 1678 (C=O), 1063 (Ar-Cl), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.26 - 7.64 (a set of signals, 8H, Ar-H and benzthiazole-H), 8.23- 8.25 (d, 1H, -NH-NH-). MS (m/z, %): 305.2 (M^++1 for ^{35}Cl, 100%), 307.12 (M^++1 for ^{37}Cl, 34%).

3-phenyl- acrylic acid N'- benzothiazol-2-yl-hydrazide (BZT-H 13): IR (KBr, cm^{-1}) □: 3204, 3059 (NH_{str} associated), 1676 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.23 - 7.69 (a set of signals, 7H, Ar-H and benzthiazole-H), 8.23 - 8.28 (d, 1H, -NH-NH-). MS (m/z, %): 296.3 (M^++1, 100%).

Preparation of N-Benzothiazole-2-yl-N'-benzyl-hydrazine (BZT-H 14)

Benzyl chloride (0.1 mol) was dissolved in 20ml of dry acetone was added drop wise to a stirred solution of benzothiazole hydrazide (0.1) and pyridine in 50 ml acetone. After addition the reaction mixture was stirred for 12 hours at room temperature and then the solvent was evaporated under reduced pressure. The obtained products were purified by crystallization using ethanol/ petroleum ether mixture (1:3) to give crystals [26].

N'- benzothiazol-2-yl-N-benzyl hydrazine (BZT-H 14): IR (KBr, cm^{-1}) □: 3208, 3053 (NH_{str} associated), 1676 (C=O), ^1H NMR ($CDCl_3$, 300 MHz) δ in ppm: 7.27 - 7.64 (a set of signals, 7H, Ar-H and benzthiazole-H), 8.21 - 8.22 (d, 1H, -NH-NH-). MS (m/z, %): 296.3 (M^++1, 100%).

The physical and elemental analysis data of the synthesized derivatives are given in Table 1.

Anticonvulsant activity

Some of the synthesized derivatives were screened for anticonvulsant activity using the Maximal Electroshock Seizure (MES) and a toxicity screen (rotorod in rats) [27]. The synthesized derivatives were suspended in 0.5% hydroxyl propyl methyl cellulose and the test compound was usually manipulated with a motor pestle to help preparation of suspension. In the preliminary screening by MES tests, each compound was administered as an oral at one dose levels (30mg/kg) and anticonvulsant and neurotoxic effects were assessed at 30 min and 4h intervals after administration.

3. RESULTS AND DISCUSSION

MES Test

Compounds **BZT 4, BZT 5, BZT 11** and **BZT 12** were found to be active in MES test (Table 9). The compound **BZT 4** showed 50% protection (3/6, 4.0h) at a dose of 30 mg/kg, compound **BZT 5** showed 60% protection (4/6, 4.0h), **BZT 11** showed 60% protection (4/6, 4.0h) and **BZT 12** showed 50% protection (3/6, 0.5h) and 66% protection (4/6, 4.0h) at a dose of 30 mg/kg. This shows the ability **BZT 4, BZT 5, BZT 11** and **BZT 12** to prevent seizure spread.

Neurotoxicity Screen

None of the other compounds showed neurotoxicity in the highest administered dose.

Table 2. Anticonvulsant activity and neurotoxicity of synthesized derivatives

Compound	Oral Administration to Rats*			
	MES(h)		Neurotoxicity (h)	
	0.5	4.0	0.5	4.0
BZT 4	2/6	3/6	0/6	0/6
BZT 5	2/6	4/6	0/6	0/6
BZT-H 11	2/6	4/6	0/6	0/6
BZT-H 12	3/6	4/6	0/6	0/6
Phenytoin	6/6	6/6	6/6	6/6

*Doses of 30 mg/kg were administered. The figures in the table indicate the minimum dose whereby bioactivity was demonstrated in half or more of the rat.

4. CONCLUSION

It may conclude that moderate anti-convulsant protection and neurotoxicity was observed in substituted benzothiazole derivatives and substituted N-benzothiazole-2-yl hydrazide. Further studies are required to be carried out to evaluate the anti-convulsant activity of synthesized compounds in other seizures models such as scMET, INH induced seizure model, Pilocarpine induced seizure model etc. Also studies should be carried out to ascertain the precise mechanism of action of active derivatives.

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