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Research Article

SYNTHESIS AND ANTHELMINTIC ACTIVITY OF 2-AMINO-6-SUBSTITUTED BENZOTHIAZOLES

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ABSTRACT
A series of 2-amino-substituted benzothiazoles (1-9) were synthesized by treating with KSCN in presence of bromine/glacial acetic acid with different substituted anilines. Structures of the all the synthesized compounds were established basis on melting point, TLC, FT-IR, ^{1}H NMR, and MASS spectral data. All the synthesized compounds were examined for Anthelmintic activity.

KEYWORDS: Amino benzothiazole, Anthelmintic activity

INTRODUCTION

Benzothiazoles are bicyclic ring system with multiple applications which have been the subject of great interest because of their biological activities. 2-substitued benzothiazole has emerged in its usage as a core structure in the diversified therapeutically applications. The studies of structure–activity relationship interestingly reveal that change of the structure of substituent group at C-2 position commonly results the change of its bioactivity. Among those 2-substituted benzothiazole derivatives with fluorine substituted molecules have already received considerable attention due to their potential bioactivities. Literature review revealed the potent inhibition of human immunodeficiency virus type 1 (HIV-1) replication by HIV-1 protease inhibition[1], anti tumor[2], analgesic and anti-inflammatory[3], antimalerial[4], antifungal[5], anticandidous activities[6] and various CNS activities [7,8] of benzothiazoles.

In the present study a series of 2-aminobenzothiazole derivatives were prepared from substituted anilines, in acidic medium and the synthesized compounds were evaluated for anthelmintic activity against *Eudrilus eugeinae* and *Megascoplex konkanensis*. Majority of the compounds showed significant anthelmintic activity as compared to the standard drug mebendazole.

MATERIALS AND METHODS

Analytical grade solvents and commercially available reagents were used without further purification. Melting points were determined in open capillary tube and are uncorrected. The completion of the reaction and purity of the compounds were checked by thin layer chromatography (TLC). IR spectra in KBr disk were recorded from 4000 to 400 cm-1 on Avatar 330 FT-IR spectrometer equipped with DTGS detector. ^{1}H NMR spectra were recorded on GEOL-JMS D–300 (MHz) NMR using $CDCl_3$ as the solvent with trimethylsilane (TMS) as an internal standard. MASS spectra were recorded on Shimandzu GC-MS (at 70 eV) Mass Spectrometer using xenon as the carrier gas.

General procedure for synthesis of 2-amino-6-substituted benzothiazoles (1-8)

A solution of substituted aniline (30 mmol) in 95% acetic acid (20 ml) was added to a solution of KSCN (120 mmol) in 95% acetic acid (20 ml) .The reaction mixture was cooled to 0°C and a solution of Br_2 (1.6 ml) in acetic acid (10 ml) was added over 90 minutes; during the addition the temperature not raise to

5°C. After addition of bromine, the stirring was continued for 3 hr at 10-15°C, and then poured into hot water (300 ml). Separated hydrochloride salt was filtered, washed with acetic acid and dried. It was dissolved in hot water and neutralizes with 26% ammonia hydroxide solution, filtered the solid product, washed with water and recrystallized from ethanol. (Scheme 1)

Anthelmintic activity

All the synthesized compounds were evaluated against two different earth warm species *Eudrilus eugeinae* and *Megascoplex konkanensis* at 200 mg/10 ml concentration following Garg's method[9]. Tween 80 (15%) solution in distilled water was used as a control and mebendazole was used as a control. The paralysis and death times were noted and their mean was calculated for triplicate sets. The Anthelmintic study results are tabulated in Table 2.

Spectral Data

Synthesis of 6-chlorobenzo[d]thiazol-2-amin: IR (KBr pallets): 3454.74(NH Stretch), 3088.36 (aromatic C-H stretch), 1632.51 (C=N stretch), 1444.86 (C-N stretch), 1274.83 (C-S stretch), 815.14, 889.62 (aromatic-H bending), 761.66 (C-Cl stretching) cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ4.221 (2H, s, NH_2), δ7.142-δ7.769 (3H, m, aromatic-H). **FAB Mass: m/z:** 185.20.

6-fluorobenzo[d]thiazol-2-amine: IR (KBr pallets): 3383.55(NH Stretch), 3079.68 (aromatic C-H stretch), 1638.24 (C=N stretch), 1463.47 (C-N stretch), 1256.61 (C-S stretch), 1111.32 (C-F Stretching) 808.30, 847.29 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ4.134 (2H, s, NH_2), δ7.232-δ7.856 (3H, m, aromatic-H). **FAB Mass: m/z:** 169.32.

6-bromobenzo[d]thiazol-2-amine: IR (KBr pallets): 3449.09 (NH Stretch), 3085.72 (aromatic C-H stretch), 1631.67 (C=N stretch), 1440.54 (C-N stretch), 1276.63 (C-S stretch), 811.51, 861.23 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ3.924 (2H, s, NH_2), δ7.281-δ7.894 (3H, m, aromatic-H). **FAB Mass: m/z:** 230.16.

6-nitrobenzo[d]thiazol-2-amine: IR (KBr pallets): 3424.14(NH Stretch), 2925.46 (aromatic C-H stretch), 1633.67 (C=N stretch), 1471.51 (C-N stretch), 1236.96 (C-S stretch), 820.87, 868.45 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ4.216 (2H, s, NH_2), δ7.041-δ7.759 (3H, m, aromatic-H). **FAB Mass: m/z:** 196.0.

6-methylbenzo[d]thiazol-2-amine: IR (KBr pallets): 3395.61 (NH Stretch), 3121.19 (aromatic C-H stretch), 1627.50 (C=N stretch), 1459.26 (C-N stretch), 1281.74 (C-S stretch), 807.31, 901.46 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ2.289 (3H, s, CH_3), δ3.972 (2H, s, NH_2), δ7.213-δ7.851 (3H, m, aromatic-H). **FAB Mass: m/z:** 165.19.

6-ethylbenzo[d]thiazol-2-amine: IR (KBr pallets): 3430.53 (NH Stretch), 3083.28 (aromatic C-H stretch), 1628.24 (C=N stretch), 1459.48 (C-N stretch), 1286.15 (C-S stretch), 821.94, 900.02 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$): δ1.286 (2H, m, CH2),** δ2.381 (3H, m, CH_3), δ3.916 (2H, s, NH_2), δ7.281-δ7.927 (3H, m, aromatic-H). **FAB Mass: m/z:** 179.37.

6-methoxybenzo[d]thiazol-2-amine: IR (KBr pallets): 3388.26 (NH Stretch), 3091.92 (aromatic C-H stretch), 1641.83 (C=N stretch), 1463.02 (C-N stretch), 1272.95 (C-S stretch), 806.15, 889.904.29 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ3.841 (3H, s, OCH3), δ3.894 (2H, s, NH_2), δ7.128-δ7.936 (3H, m, aromatic-H). **FAB Mass: m/z:** 181.21.

5, 6-dimethylbenzo[d]thiazol-2-amine: IR (KBr pallets): 3451.32 (NH Stretch), 2931.12 (aromatic C-H stretch), 1641.55 (C=N stretch), 1463.63 (C-N stretch), 1279.51 (C-S stretch), 834.07, 900.91 (aromatic-H bending), cm^{-1}. **^{1}H NMR (300 MHz, $CDCl_3$):** δ2.216 (3H, s, CH_3), δ2.351 (3H, s, CH_3), δ4.121 (2H, s, NH_2), δ7.183-δ7.952 (3H, m, aromatic-H). **FAB Mass: m/z:** 179.36

RESULTS AND DISCUSSION

All the synthesized compounds (1-8) were characterized by, FT-IR, ^{1}H NMR, FAB-MASS spectral studies. All the compounds showed moderate and good Anthelmintic activity respective species. In these compounds compound 4 (NO_2 substituted benzothiazole) shown better activity to comparing the all the compounds.

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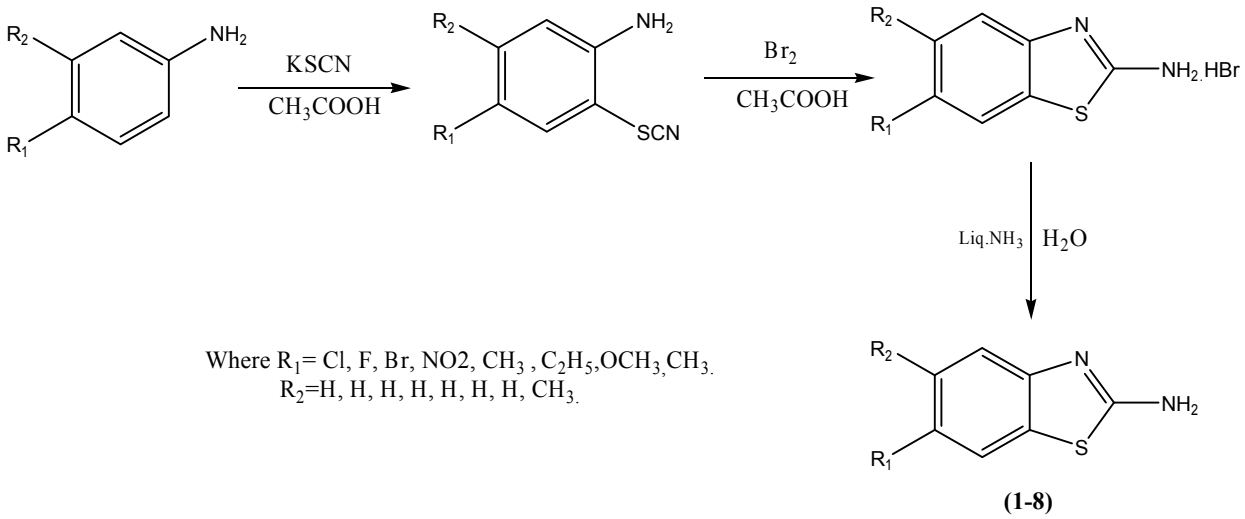
Table 1: Physical data of synthesized 2-amino-5, 6-substituted benzothiazoles

S. No	2-amino-5,6-substituted benzothiazoles	Mol .For	Mol .wt	Physical state	Mp ^{o}C	% yield
1	6-lorobenzo[d]thiazol-2-amine	$C_7H_5ClN_2S$	184.64	White colour crystals	195	78.8
2	6-fluorobenzo[d]thiazol-2-amine	$C_7H_5FN_2S$	168.19	Light yellow colour solid	183	83.4
3	6-bromobenzo[d]thiazol-2-amine	$C_7H_5BrN_2S$	229.09	Light yellow colour solid	201	76.3
4	6-nitrobenzo[d]thiazol-2-amine	$C_7H_5N_3OS$	195.19	Orange colour solid	199	82.1
5	6-methyl benzo[d]thiazol-2-amine	$C_8H_8N_2S$	164.22	White colour solid	135	68.4
6	6-ethylbenzo[d]thiazol-2-amine	$C_9H_{10}N_2S$	178.25	White colour solid	176	79.2
7	6-methoxybenzo[d]thiazol-2-amine	$C_8H_8N_2S$	180.22	White colur solid	187	84.3
8	5, 6-dimethylbenzo[d]thiazol-2-amine	$C_9H_{10}N_2S$	178.25	White colour solid	122	78.5

Table 2: Anthelmintic activity of 2-amino-5, 6-substituted benzothiazoles

S. No	*Eudrilus eugeinae*		*Megascoplex konkanensis*	
	Paralyzing time	Death time	Paralyzing time	Death time
1	9.24	10.16	14.17	14.52
2	11.34	12.43	13.47	14.17
3	13.12	14.16	11.17	12.11
4	8.12	9.48	15.24	15.57
5	9.34	10.52	13.12	14.51
6	11.17	12.34	17.18	18.12
7	10.14	11.33	13.12	15.41
8	12.11	13.12	12.56	13.12
Mebendazole	7.32	8.27	10.51	11.23
control	No effect	No effect	No effect	No effect



Where R_1= Cl, F, Br, NO2, CH_3 , C_2H_5,OCH_3,CH_3.
R_2=H, H, H, H, H, H, H, CH_3.

(1-8)

SCHEME 1

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