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Research Article

Synthesis and Evaluation of novel N-(6-nitrobenzo [d] thiazol-2-yl)-2-acetamide as Anthelmintic Activity

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ABSTRACT

With the aim of obtaining newer biologically active compounds, a series of N-(6-nitrobenzo [d] thiazol-2-yl)-2-acetamide) were synthesized (5a-5i). The structures of all the synthesized compounds were confirmed by spectral (FTIR, IR and MS) data and elemental (C, H, N) analysis. Compounds (5a-5i) were screened for anthelmintic activities. Almost all of these compounds showed moderate to excellent anthelmintic activities against Nematode species (Haemonchus contorts). Among the compounds tested, compounds (5b) showed maximum activity against Haemonchus contorts species, respectively. Further Compound exhibited moderate anthelmintic activity comparable to the standard drugs.

INTRODUCTION

Today, we are observing a tremendous global rise in microbe-caused severe illnesses. Infectious infections are currently the third most common cause of mortality in industrialized nations and the second most common cause of death globally.[1][2] According to medical professionals, immunosuppressant users are more vulnerable to these illnesses. Additionally, a significant issue is the development of microorganism resistance to various antimicrobial treatments.[3] The dangerous infection known as helminthiasis affected a substantial number of people. When helminthes and microbial infections happen together, it can sometimes become more dangerous. The number of people with these infectious illnesses is gradually increasing, despite the availability of effective medications to treat them. This results in higher morbidity and death rates as well as an overall rise in healthcare expenses [4].

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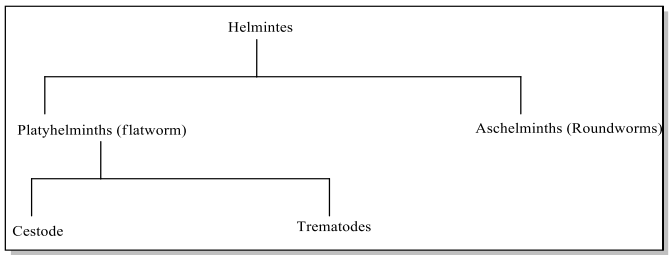
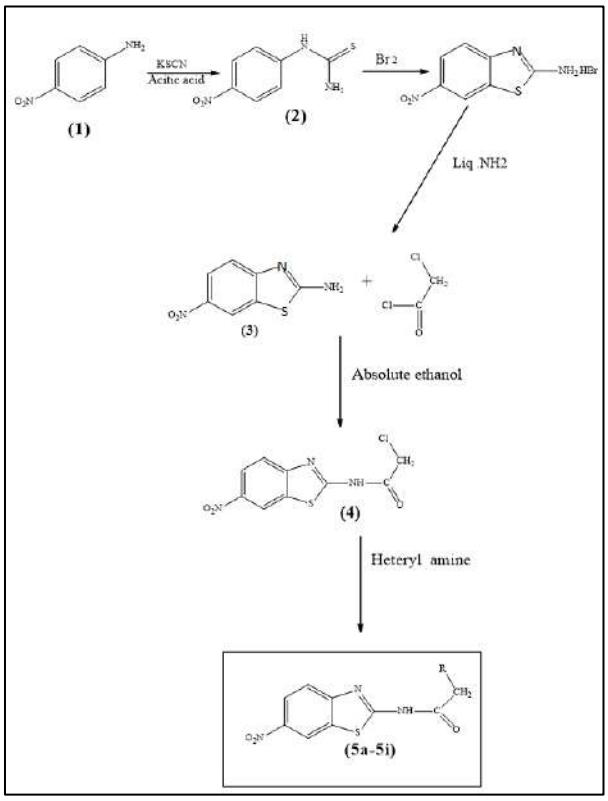


Fig.1 Classification of Helmintic

Due to these issues, medicinal chemists are required and are particularly interested in the discovery and development of novel lead structures and new chemical entities that will function as both antimicrobials and anthelmintics. When screening compounds with natural and marine origins, noteworthy, novel, and structurally distinctive lead structures for the creation of antibacterial and anthelmintic medicines are frequently discovered.[5] The benzothiazole scaffold and its analog are important analogs that are found in many marine compounds or natural plants.[5][6] Due to its chemotherapeutic importance in the discovery and development of novel medicines effective against microorganisms in recent decades, 2-aminobenzothiazoles and its derivatives have drawn a lot of interest, helminthes, cancer convulsion inflammation diuresis etc. [7][8].

MATERIALS

Chemicals were obtained from Research Lab and Sigma Aldrich. The reaction was carried out by conventional method. Melting point was determined in open capillaries using melting point apparatus and was uncorrected. The purity of synthesized compounds was ascertained by TLC using silica gel-G plate as a stationary phase and iodine vapors as a visualizing agent [10]. The structures of the synthesized compounds were confirmed by IR, and MASS spectral analysis. The IR spectra were recorded on JASCO FTIR-4100. Mass spectra were recorded on Macro mass spectrometer.



Synthesis

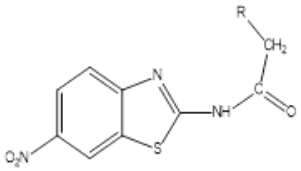


Fig 2: (5a-5i)

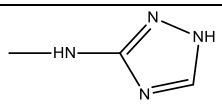
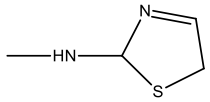
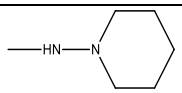
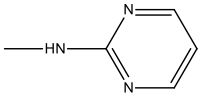
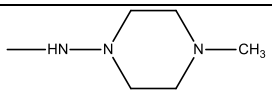
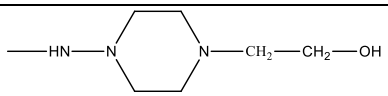
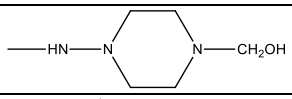
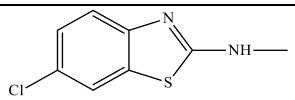
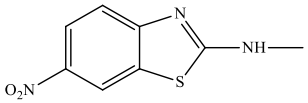
Sr. No	Compounds no	R
1	5a	
2	5b	
3	5c	
4	5d	
5	5e	
6	5f	
7	5g	
8	5h	
9	5i	

Table1. Characterization synthesized benzothiazoles

Sr. No	Compounds	Mol for Mol. Wt	M.P (°C)	State Appearance	Solubility
1)	p-nitro aniline	C_6H_6 H_2 O_2 138	146	Yellow Crystal Powder	Freely Very soluble organic solvent
2)	Pot-Thiocynate	KSCN 97	173	Pellets	Water
3)	Acetic Acid	CH_3 COOH 123	16	colourless Liquid	Water
4)	Bromine	Br_2 159	72	Brown Fuming Liquid	Ethanol, Ether, Toluene, Benzene, Chloroform, Water.
5)	Choroacetyl Chloride	$C_2H_5Cl_2O$ 112.94	22	Colourless to Yellow Liquid	Water, Benzene, aromatic amide
6)	3-Amino - 1,2,4,Triazole	$C_2H_4N_4$ 84	157	Colour less White Crystals	Water

7)	N-(2-Hydroxy ethyl) Piperzine	$C_6H_{14}N_2O$ 130	246	White Crystals	Benzene, DMSO, Water.
8)	Piperidine	$C_5H_{11}NO$ 101	108	Off White Solid	Water Soluble
9)	N-Methyl Piperazine	$C_5H_{12}N_2$ 100	134	Colourless to pale yellow clear	water soluble
10)	2-Amino Pyrimidine	$C_4H_4N_3$ 95	210	Colourless to solid	Water, Ethanol, Chloroform.
11)	2-Amino Thizole	$C_3H_4N_2S$ 100.	86	Light yellow Crystals	Water, Alcohol, Diethyl ether, Chloroform.
12)	7-Nitro-amino-Benzothizole	$C_7H_5N_3O_2S$ 195	228	Yellow Solid Crystals	Water, Alcohol, Chloroform.
13)	7-Chloro-2-amino -Benzothizole	$C_7H_5ClN_2S$ 196	203	Crystals	Water, Alcohol, Di –Ethyl ether ,Chloroform

Table 2: Raw material characterization

General synthetic procedure for the synthesis of the 6-Nitrobenzo[d] thiazole-2-amine. A mixture of p-nitro aniline (0.01 mol) and potassium thiocyanide (0.01 mol) in 10 ml of glacial acetic acid was cooled and stirred. After cooling to this solution mixture bromine (0.01 mol) in 5ml of glacial acetic acid was added drop wise at such rate to keep temperature below 10°C throughout addition. Stirring was continued for additional 4 hr. After this addition the solution mixture was dissolved in hot water and filtered. The filtrate was cooled and then neutralized with aq. ammonia solution (25%). The soil was filtered and washed with water, dried and recrystalize from benzene. 2-Chloro-N-(6-nitrobenzo[d]thiazol-2-yl) acetamide. 6-Nitrobenzo[d]thiazole-2-amine (0.01 mol) was transferred to 10 ml of absolute ethanol in conical flask and it was stirred for 10 min. To this solution 0.01 mol of 2-chloroacetyl chloride was added and stirring was continued for additional 3 hours. The product obtained was filtered, washed with water and recrystallized to obtained pure product (5a-5i).

N-(6-Nitrobenzo[d]thiazol-2-yl)-2-(3H-1,2,4-triazol-5-yl)acetamide (5a)- 0.01 mole was taken in conical flack in 10 ml of absolute ethanol and it was stirred for 10 min. To this solution, 3-amino-1,2,4-triazole was added and stirring was continued for additional 5 hours .The produced obtained was filtered , washed with water and recrystalized from to obtained pure products was obtain .M.F- $C_7H_5N_3O_2S$, FTIR (KBr, nmax, cm-1): 3318 (NH str), 3250 (aromatic stir), 2911 (aliphatic CH str), 2950 (C=N stir of benzothiazole), 1650 (C=O(s) of amide), (R_f value):0.44,solvent- Benzene: methanol (4:1)]mass m/z: 270.1 (M+1).

(4, 5-Dihydrothiazol-2-yl)-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide(5b)-2-Chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide in was transferred conical flack and (0.01) 10 ml of absolute ethanol was added and stirred for 10 min. To this solution,(0.01 mol) of 2-amino-2,5-dihydrothaizole was added and stirring was continued for additional 5 hours .The produced obtained was filtered washed with water and recrystalized to obtained pure products. Yield:68%, M.F- $C_{11}H_9N_5O_3S_2$, M.W-323,FTIR (KBr, nmax, cm-1): 3243 (NH str), 3250 (aromatic stir), 2911 (CH str), 2355 (C=N str of benzothiazole), 1650 (CO-NH), (R_f value): :0.55,solvent-[Benzene: methanol (4:1)]mass m/z: 315.1 (M+1).

N-(6-Nitrobenzo[d]thiazol-2-yl)-2-(piperidin-1-yl-amino)acetamide(5c)-2-Chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide (0.01 mol) was taken in 10 ml of absolute ethanol and it was stirred for 10 min. To this solution, 0.01 mol of 4-

N- methyl piperidine was added and stirring was continued for additional 6 hours .The produced obtained was filtered , washed with water and recrystalized to obtained pure products. Yield:44%, M.F- $C_{14}H_{16}N_4O_4S$, M.W-335,FTIR (KBr, nmax, cm-1): 3243 (NH str), 3250 (aromatic stir), 2911 (CH str), 2355 (C=N str of benzothiazole), 1650 (CO-NH), (R_f value): : 0.48,solvent-[Benzene: methanol (4:1)]mass m/z: 332.1 (M+1).

N-(6-Nitrobenzo[d]thiazol-2-yl)-2-(pyrimidin-1-yl-amino) acetamide (5d)-2-Chloro-N-(6-nitrobenzo[d]thiazol-2-yl) acetamide (0.01 mol) was taken in(0.01)was taken 10 ml of absolute ethanol and it was stirred for 10 min. To this solution, 0.01 mol was dissolved amino pyrimidine pyrazine was added and stirring was continued for additional 3 hours .The product obtained was filtered, washed with water and recrystalized to obtained pure products. Yield: 66%, M.F- $C_{13}H_{10}N_6O_3S$, M.W-330,FTIR (KBr, nmax, cm-1): 3213 (N-H str), 3250 (aromatic stir), 2911 (C-H str), 2355 amino pyridine), 1670 (CO), (R_f value): : 0.66,solvent-[Benzene: methanol (4:1)]mass m/z: 329.1 (M+1).

(4-Methylpiperazin-1-yl)amino)N-(6-nitrobenzo[d]thiazol-2-yl)acetamide(5e)-2-Chloro-N-(6-Nitrobenzo[d]thiazol-2-yl)acetamide in 10 ml of absolute ethanol and it was stirred for 10 min. (0.01) mole To this solution, (0.01 mol)was dissolved a 4-N- methyl piperazine was added and stirring was continued for additional 3 hours .The produced obtained was filtered washed with water and recrystalized to obtained pure products. Yield: 66%, M.F- $C_{14}H_{18}N_6O_3S$, M.W-350,FTIR (KBr, nmax, cm-1): 3543 (N-H str), 3250 (aromatic stir), 2911 (C-H str), 2355 (C=N stir of benzothiazole), 1670 (CO), (R_f value): : 0.43,solvent-[Benzene: methanol (4:1)]mass m/z: 329.1 (M+1).

(N-4-Methylpiperazin-1yl) –N-(6-nitrobenzo[d] thiazol-2-yl acetamide (5f)-2-Chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide(0.01) was taken in 10 ml of absolute ethanol and it was stirred for 10 min. To this solution, 0.01 mol of 2-(4-Methylpiperazine-1-yl)ethanol was added and stirring was continued for additional 2 hours .The produced obtained was filtered washed with water and recrystalized to obtained pure product. Yield: 66%, M.F- $C_{15}H_{20}N_6O_4S$, M.W-380,FTIR (KBr, nmax, cm-1): 3225 (N-H str), 3067 (aromatic stir), 2911 (C-H str), 2355 (NO_2-3067), 1685 (CO), (R_f value): : 60,solvent-[Benzene: methanol (4:1)]mass m/z: 364.1 (M+1).

(4- Hydroxymethyl) piperazin-1yl) amino –N-(6-nitrobenzo[d] thiazol-2-yl acetamide (5g)2-Chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide(0.01) was taken in 10 ml of absolute ethanol and it was stirred for 10 min. To this solution, 0.01 mol of (N-N hydroxyl methylpiperazine-1-yl) added and stirring was continued for additional 6 hours .The produced obtained was filtered , washed with ethanol and recrystalized to obtained pure product Yield: 62%, M.F- $C_{14}H_{18}N_6O_4S$, M.W-366,FTIR (KBr, nmax, cm-1): 3285 (N-H str), 3067 (C-H str), 2355 (NO_2-3067), 1685 (CO), (R_f value): : 0.57,solvent-[Benzene: methanol (4:1)]mass m/z: 354.1 (M+1).

(6-Chloro benzo[d] thiazole-2-yl amine)-N-(6-Nitrobenzo[d] thiazole-2-yl- acetamide (5h):2Chloro-N-(6-Nitrobenzo[d]thiazol-2-yl)acetamide in 10 ml of absolute ethanol and it was stirred for 10 min. (0.01) mole To this solution, (0.01 mol) was dissolved a was 6-Chloro-N-benzo[d] thiazol-2-amine added and stirring was continued for additional 3 hours .The produced obtained was filtered , washed with water and recrystallized to obtained pure product Yield: 61%, M.F- $C_9H_6ClN_3O_3S$, M.W-270,FTIR (KBr, nmax, cm-1): 3150 (N-H str), 2950 (C-H str), 2355 (NO_2-3067), 1650 (CO), (R_f value): : 0.57,solvent-[Benzene: methanol (4:1)]mass m/z: 356.1 (M+1).

(6-Nitrobenzo[d] thiazole-2-yl – amine)-N-(6-Nitrobenzo [d] thiazole-2-yl-acetamide (5i)

2Chloro-N-(6-nitrobenzo[d]thiazol-2-yl)acetamide (0.01) was taken in 10 ml of absolute ethanol and it was stirred for 10 min. To this solution, 0.01 mol 6-nitrobenzo[d] thiazole-2-amine added and stirring was continued for additional 3 hours .The produced obtained was filtered , washed with ethanol and recrystallized to obtained pure product Yield: 58%, M.F-$C_9H_8N_4O_3S$, M.W-252,FTIR (KBr, nmax, cm-1): 3750 (N-H str), 2950 (C-H str), 2355 (NO_2-3067), 1650 (CO), (R_f value): : 0.4,solvent-[Benzene: methanol (4:1)]mass m/z: 221.1 (M+1).

Physical and Spectral Characterization

The N-(6-nitrobenzo[d]thiazol-2-yl)-2-acetamide derivative **(5a-5i)** were solid compound melting in the range of 112-114^{0}C. These compound were soluble in the ethanol, methanol and in benzene insoluble in water. The compounds crystalline to were amorphous with yellow to off white color.

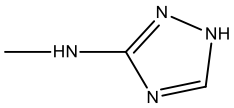
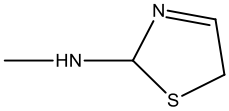
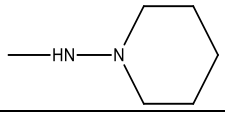
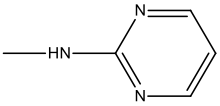
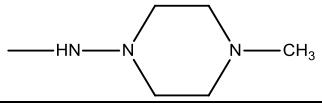
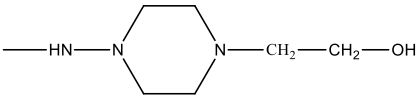
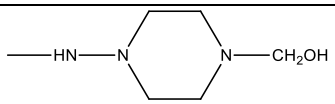
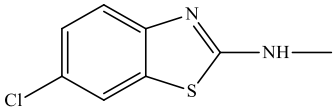
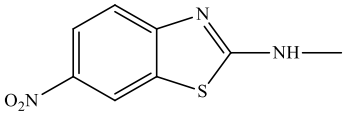
Comp. No	R	Mol. Form/ Mol. Wt.	M.P (^{0}C)	% yield	R_f value
5a		$C_7H_5N_3O_2S$ 195	114	68	0.44
5b		$C_{11}H_9N_5O_3S_2$ 323	126	65	0.55
5c		$C_{14}H_{16}N_4O_3S$ 335	140	44	0.48
5d		$C_{13}H_{10}N_6O_3S$ 330	126	66	0.66
5e		$C_{14}H_{18}N_6O_3S$ 350	108	65	0.43
5f		$C_{15}H_{20}N_6O_4S$ 380	118	60	0.64
5g		$C_{14}H_{18}N_6O_4S$ 366	118	62	0.57
5h		$C_9H_6ClN_3O_3S$ 270	184	61	0.57
5i		$C_9H_8N_4O_3S$ 252	182	58	0.4

Table 3: Physical characterization of compounds (5a-5i)

Pharmacological Screening:

Anthelmintic activity The Anthelmintic activity was performed on Haemonchus contorts_isolated from abomasums of sheep at various concentration 50, 100, 200, 400µg/ ml for standard Albendazole and test compounds **(5a-5i).** The time in minutes

for paralysis and death of worm was recorded for control, test and standard groups. The observation were made up to 2.5 hrs based on the time required by std. Albendazole for paralysis and death of the worm. The results of the activity indicate that the compound **(5b)** was found to be most active at all concentrations, All other compound exhibit moderate activity at all concentration.

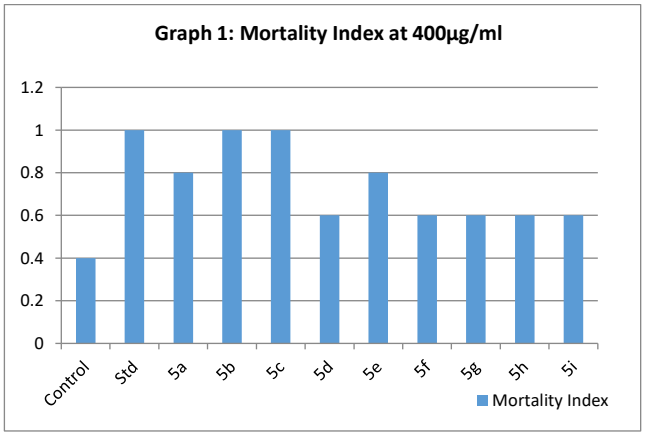
Sr. No.	Compounds	Dilutions (µg/ml)	Time in minutes for paralysis	Time in minutes for death
1	Control	-	330	345
2	Albendazole (Ref.drug)	50	135	144
		100	118	130
		200	98	120
		400	70	91
3	5a	50	154	165
		100	139	152
		200	122	139
		400	102	127
4	5b	50	138	147
		100	122	129
		200	98	122
		400	71	95
5	5c	50	135	148
		100	123	127
		200	99	122
		400	74	91
6	5d	50	160	170
		100	145	154
		200	128	138
		400	109	130
7	5e	50	155	175
		100	147	150
		200	130	141
		400	108	132
8	5f	50	170	181
		100	167	178
		200	143	153
		400	112	123
9	5g	50	158	170
		100	147	168
		200	132	141
		400	122	130
10	5h	50	172	185
		100	168	179
		200	148	154
		400	118	132
11	5i	50	178	186
		100	165	182
		200	145	156
		400	122	136

Table 4: Anthelmintic activity of test comp(5a-5i) on Haemonchus contorts worms n = 5, where n is the total no. of worm in each Petridish.

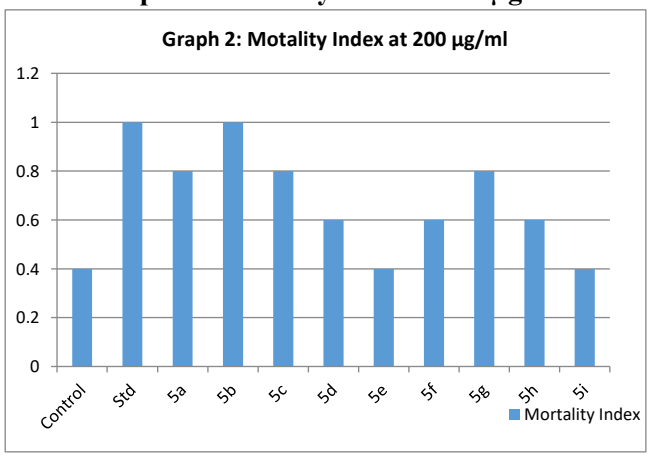
Compound	400µg/ml	200µg/ml	100µg/ml	50µg/ml
Control	0.40**	0.4**	0.40**	0.20**
Albendazole (Ref.drug)	1**	1**	1**	1**
5a	0.80**	0.80**	0.80**	0.60**
5b	1**	1**	0.80**	0.80**
5c	0.70*	0.80**	0.80**	0.60**
5d	0.60**	0.60**	0.40**	0.40**
5e	0.80**	0.40**	0.60**	0.80**
5f	0.60**	0.60**	0.40**	0.60**
5g	0.60**	0.80**	0.60**	0.60*
5h	0.60**	0.60**	0.40**	0.40**
5i	0.60**	0.40**	0.40**	0.20**

Table 5: Mortality index (M.I) of test compounds (5a-5i) for (in –vitro Anthelmintic) activity **p<0.01, ANOVA followed by Dennett test.

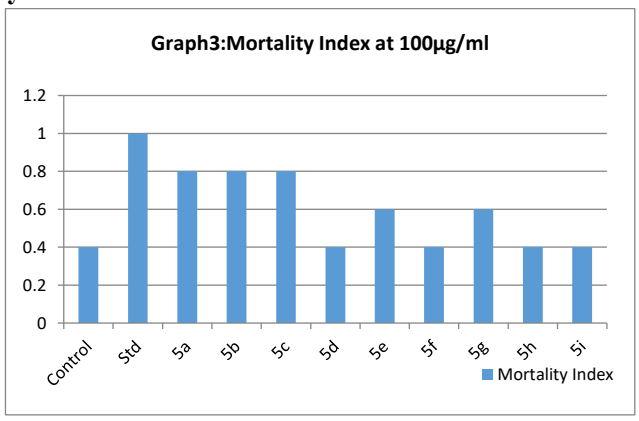
Time for death of worms in standard concentration and its comparison with test compound concentration to determine M.I.



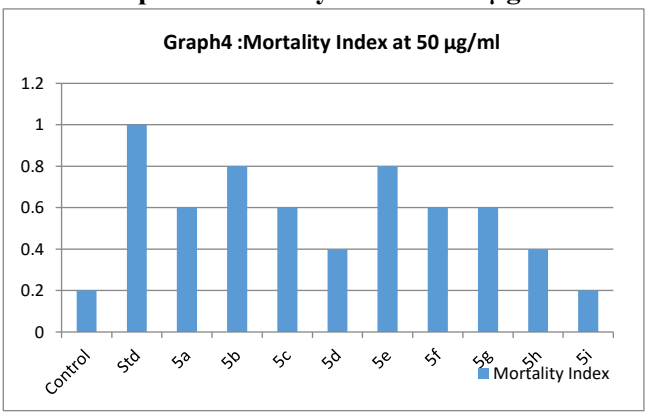
Graph 1: Mortality index at 400µg/ml



Graph 2: Mortality index at 200µg/ml



Graph 3: Mortality index at 100µg/ml



Graph 4: Mortality index at 50µg/ml

Graphs: Mortality index of test compound (5a-5i) at various concentrations against Hamonchus contorts worms.

RESULT

The standard procedure was used to create all 9 of the final derivatives. By recrystallization, the

compounds were made pure, and TLC analysis was used to verify purity. By using spectrum analysis techniques like IR and MASS, all the produced compounds were identified, and their structures were determined. The anthelmintic activity of derivatives (5a–5i) against the worm Haemonchus contorts was examined. Compound (5b) was discovered to be the most active at all dilutions among the complete compound tested for anthelmintic activity. According to the results of this investigation, the compounds (5a–5i) have good anthelmintic activity against the nematode Haemonchus contorts and can be further improved to become more effective anthelmintic compounds.

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CONFLICT OF INTEREST

"No potential conflict of interest relevant to this article was reported."

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ABBREVIATION

FTIR- Fourier transforms infrared
IR- *Infrared radiation*
MS- *Mass Spectrometry*
TLC- *Thin-layer chromatography*
Rf- Retardation factor

List of Figure/Table/Graphs

Figure/Table/Graphs	Topic
Fig.1	Classification Of Helmentic
Fig2	(5a-5i) Derivatives
Table1	Characterisation synthesized benzothiazoles
Table no2.	Raw material characterization
Table no.3	Physical characterization of compounds (5a-5i)
Table no. 4	Anthelmintic activity of test comp.
Graph 1:	Mortality index at 400µg/ml
Graph 2:	Mortality index at 200µg/ml
Graph 3:	Mortality index at 100µg/ml
Graph 4:	Mortality index at 50µg/ml

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