Research Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2015, Volume 3, Issue 4
ISSN: 2321–3647(online)

Synthesis, Characterization and Biological Evaluation of Novel Substituted 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles as Anthelmintic Agents

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ABSTRACT

The aim of our study was to review on design, synthesis and various pharmacological activities associated with the substituted oxadiazoles and thaidiazoles. Series of 5-(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl) N-substituted 1,3,4-thaidiazole-2-amines(**Va-e**) were prepared from thiosemicarbazides (**IIIa-e**) by cyclization using phosphoric acid and 5-(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl) N-substituted 1,3,4-oxadiazole-2-amines (**IVa-e**) were preparedfrom substituted thiosemicarbazides (**IIIa-e)**by treating with Iodine &NaOH. Compounds (**IIIa-e**) were prepared by treating 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbohydrazide (**II**) with isothiocyanates.Compound **II** was synthesized by treating ethyl 2-amino-4,5,6,7-tetra hydrobenzeno [b]thiophene-3-carboxylate (**I**) with hydrazinehydrate. Compound **I** was prepared by one pot synthesis fromcyclohexanone,sulphur,ethylcyanoacetate in presence of diethyl amine. All the synthesized compounds were charecterized by IR, NMR and mass spectrometry and screened for and *in vitro*-antihelmintic activity. They showed moderate to good anthelmintic activity against Indian earthworm *Pheretimaposthuma*.

Keywords: 1,3,4-Oxadiazole, 1,3,4-Thaidiazole; Antihelmintic activity.

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Received 25 March 2015, Accepted 07 April 2015

Please cite this article as: Upadhyay PK *et al*., Synthesis, Characterization and Biological Evaluation of Novel Substituted 1,3,4-Oxadiazoles and 1,3,4-Thiadiazoles as Anthelmintic Agents. American Journal of Pharmacy & Health Research 2015.

INTRODUCTION

The synthesis of nitrogen containing heterocycles derived from 1,3,4-oxadiazole and 1,3,4-thiadiazole attracting increasing interest over the past decade and played an importantrole in the medicinal chemistry[1]. These derivatives have been found to exhibit wide range of biological activities such as antimicrobial[1, 2, 3, 9], anti-inflammatory**[4,13]**anticonvulsant[5] anthelmintic**[6]**, diuretic[7], anti-tubercular[8] and anticancer activities[10]. Looking into the above diverse biological activities exhibited by the compounds containing 1,3,4-oxadiazoles and 1,3,4-thiadiazoles.We decided to synthesize these derivatives in our previous research paper[14]and now, a further attempt to investigate *in vitro* antihelmintic activity of those synthesized compounds.

MATERIALS AND METHODS

Melting points were recorded in open capillary tube and are uncorrected. The progress of reaction and the purity of the compounds (using chloroform: methanol, 7:3 solvent system) were checked by TLC on silica gel G sheets and U.V lamp used as visualizing agent. IR spectra were recorded using KBr pellets on a Thermo Niolet Nexus 670 spectrophotometer with resolution 4 cm^{-1}. ^1H-NMR spectra were recorded on Amx-400 NMR spectrometer at 400 MH_Z spectrophotometer using DMSO assolvent and TMS as internal standard. Mass spectra was done by LCMS-2010 A technique. The reaction scheme of all synthesized compounds **(IIIa-e, IVa-e and Va-e)** is given as[14].

Synthesis of ethyl-2-amino-4,5,6,7-tetrahydrobenzo(b)thiophene-3-carboxylate(I): An equimolar mixture of cyclohexanone (0.1 mol), sulphur (0.1 mol),ethyl cyanoacetate (0.1 mol) and diethyl amine (0.1 mol) in dry ethanol (20 ml) is taken in a 500 ml round bottomed flask and stirred for 1.5 h. The mixture is then poured into ice water with constant stirring and set aside for 3 h at room temperature.The separated solid was collected by filtration, dried and recrystallized from ethanol.Yield: 82.75 % m.p. 102 °c.

Synthesis of ethyl, 2-amino-4,5,6,7-tetrahydro benzo(b)thiophene-3-carbohydrazide (II): Compound **I** (0.1 mol) dissolved in 20 ml ethanol and stirredmagnetically for 0.5 h. Then hydrazine hydrate (99 %) was added and the reactionmixture was heated under reflux on a water bath for 4 h. The mixture then pouredonto ice and colourless crystalline solid separated out. The product was recrystallized from ethanol. Yield: 75.83 %, m.p. 105 °c.

Synthesis of 2-[(2-amino-4,5,6,7-tetrahydro-1-benzothiene-3yl)carbonyl]-
N-substituted hydrazine carbothioamide (IIIa-e): A suspension of compound **II**(0.1 mol) in dry benzene was reacted with an appropriate isothiocyanate (0.1 mol).The mixture was heated

under reflux for 3 h on steam bath then poured onto ice. Thethiosemicarbazide separated was collected, dried and recrystallized from ethanol (Table-2.1).

Figure 1: Reaction Scheme

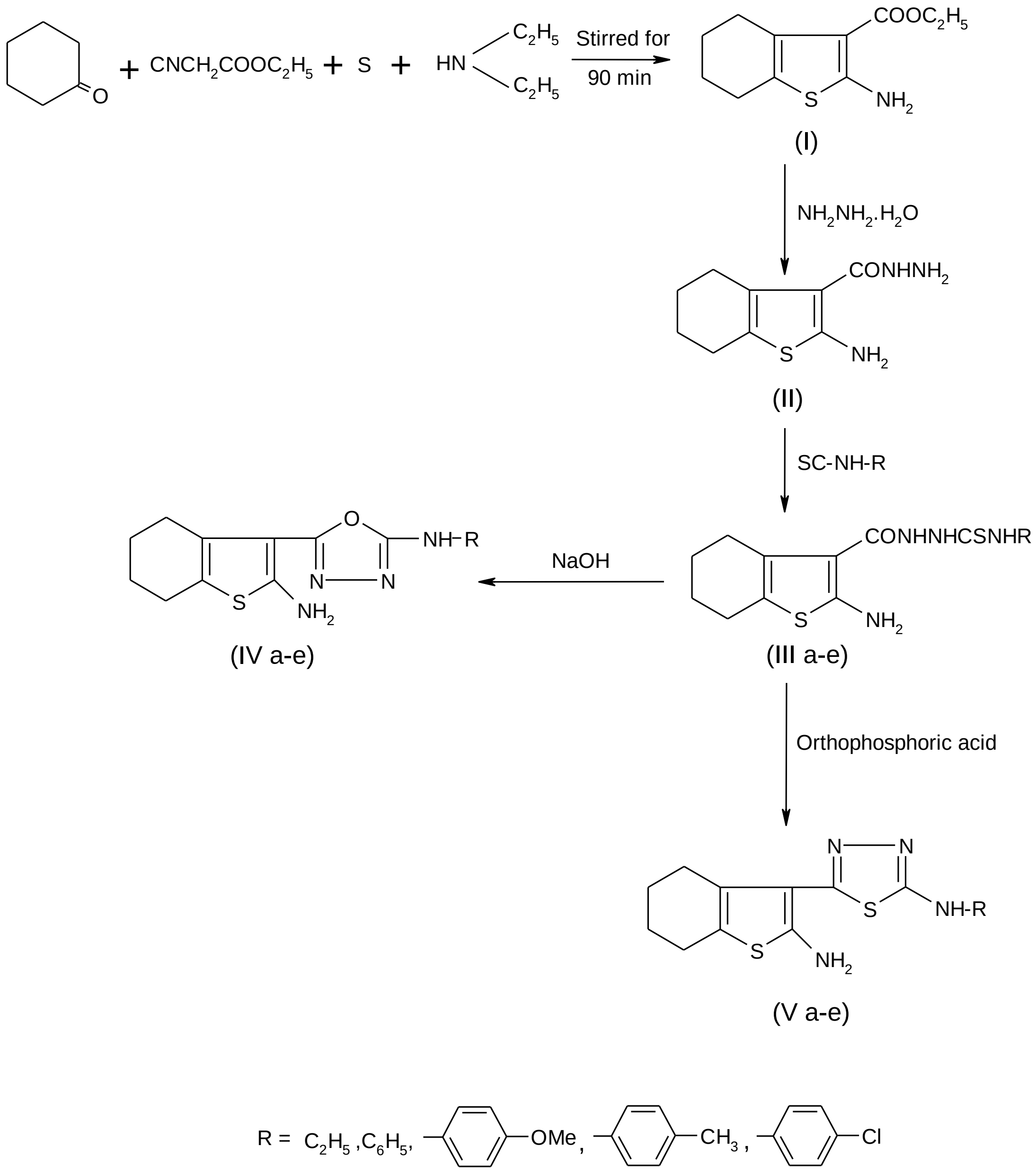


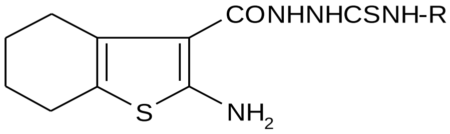
Figure 1: Reaction Scheme

Synthesis of 5-(2-amino-4,5,6,7-tetrahydro-1-thiene-3-yl)-N-substituted-1,3,4-oxadiazole-2-amines (IVa-e): An equimolar mixture of compound **IIIa-e** (0.1 mol)in ethanol was slightly heated to form a solution in which cold sodium hydroxide(4 %) was added. To this a solution of iodine in potassium iodide (aqueous, 5 %)was added in portions with vigorous shaking until the colour of iodine persisted atroom temperature. The reaction mixture was heated under reflux for

1 h and concentratedunder reduced pressure; transferred to crushed ice and recrystallized from petroleum ether (Table-2.2).

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-substituted-1,3,4-

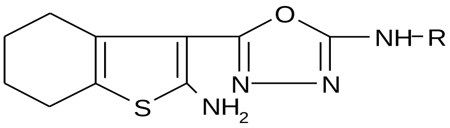
Thiadiazole-2-amine (Va-e): Phosphoric acid[7], (10 ml, 0.1 mol) was added slowly to the compound **IIIa-e** (0.1 mol). Then the mixture was heated at 110-130 °c for 0.5 h and then poured on to crushed ice with continuous stirring. The product was obtained, dried and recrystallized from petroleum ether (Table-2.3). The physicochemical properties of all synthesized compounds **(IIIa-e, IVa-e and Va-e)** are-



III(a-e)

Table 2.1: Physical data of synthesized substituted thiosemicarbazides

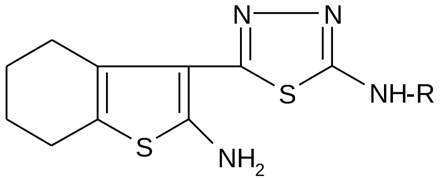
S. No	Product Code	R	Molecular Formula	Melting Point (°C)	R_f Value	Yield (%)
1	IIIa	Ethyl	$C_{12}H_{18}N_4S_2O$	112	0.78	74
2	IIIb	Phenyl	$C_{16}H_{18}N_4S_2O$	116	0.68	72
3	IIIc	4-Methoxy Phenyl	$C_{17}H_{20}N_4S_2O_2$	111	0.67	78
4	IIId	4-Methyl Phenyl	$C_{17}H_{20}N_4S_2O$	112	0.64	76
5	IIIe	4-Chloro Phenyl	$C_{16}H_{17}N_4S_2OCl$	118	0.72	79



IV(a-e)

Table 2.2: Physical data of synthesized substituted 1, 3, 4-oxadiazoles

S. No.	Product Code	R	Molecular Formula	Melting Point ss(°C)	R_f Value	Yield (%)
1	IVa	Ethyl	$C_{12}H_{16}N_4SO$	108	0.82	39
2	IVb	Phenyl	$C_{16}H_{16}N_4SO$	105	0.80	37
3	IVc	4-Methoxy Phenyl	$C_{17}H_{18}N_4SO_2$	107	0.75	36
4	IVd	4-Methyl Phenyl	$C_{17}H_{18}N_4SO$	106	0.78	34
5	IVe	4-Chloro Phenyl	$C_{16}H_{15}N_4SOCl$	109	0.71	35



V(a-e)

Table 2.3: Physical data of synthesized substituted 1, 3, 4-thiadiazoles

S.No.	Product Code	R	Molecular Formula	Melting Point (°C)	R_f Value	Yield (%)
1	Va	Ethyl	$C_{12}H_{16}N_4S_2$	98	0.90	34
2	Vb	Phenyl	$C_{16}H_{16}N_4S_2$	106	0.88	29
3	Vc	4-Methoxy Phenyl	$C_{17}H_{18}N_4S_2O$	105	0.74	26
4	Vd	4-Methyl Phenyl	$C_{17}H_{18}N_4S_2$	102	0.76	24
5	Ve	4-Chloro Phenyl	$C_{16}H_{15}N_4S_2Cl$	101	0.86	32

Anthelmintic Activity

Antihelmintic activity studies were evaluated on Indian earthworm *Pheretimaposthuma* due to its anatomical resemblance with the intestinal roundworm parasites of human beings and nearly equal size (6 cm) were collected and carried out by Garg and Atal method[15]. The worms were acclimatized to laboratory conditions before experimentation. The earth worms were divided into three groups namely group I [control], group II [standard] and group III [test compounds] containing six worms in each group (n=6). Albendazole (20mg/ml) suspended with 0.5 % CMC and served as standard and is poured into petri-dishes. The synthesized compounds were suspended in minimal quantity of CMC and diluted to prepare 20 mg/ml concentrations of each compound. CMC, 0.5% suspension served as a control. The time taken for complete paralysis and death was recorded. The mean paralysis time and mean lethal time were calculated for each compound. The time taken for worms to become motionless was noted as paralysis time. To ascertain death, each worm was frequently subjected to external stimuli that stimulate and induce movement in earth worms, if alive.

Table 2.4: Data for Anthelmintic activity of Synthesized Compounds-

Compounds	Time for paralysis (min)	Time for death (min)
Control	-------	-------
Standard (Albendazole)	18.52±0.12	22.69±0.24
IV (a)	13.06±0.04	25.63±0.28
IV (b)	17.28±0.46	32.72±0.97
IV (c)	20.33±1.12	30.38±0.43
IV (d)	19.79±1.48	31.25±1.28
IV (e)	18.32±1.68	32.16±1.15
V (a)	14.80±0.93	31.47±0.70

V (b)	18.36±1.62	27.04±1.20
V (c)	20.08±1.12	30.48±0.75
V (d)	21.05±0.89	29.93±1.23
V (e)	16.82±1.06	29.34±1.85

RESULTS AND DISCUSSIONS

2-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-N-(4-ethyl)-Hydrazine carbothioamide (IIIa): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 3.8 (s, 3H of 3.NH), 7.7 (s, 2H of NH_2), 5.9-6.2 (m, 4H of Ar-H), 4.2 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 aliphatic). MS m/z (%): M+1 = 376.

2-[(2-Amino-4, 5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-N-(4- phenyl)-Hydrazine carbothioamide (IIIb): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 3.8 (s, 3H of 3.NH), 7.7 (s, 2H of NH_2), 5.9-6.2 (m, 4H of Ar-H), 4.2 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 aliphatic). MS m/z (%): M+1 = 376.

2-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-N-(4-methoxy Phenyl)hydrazinecarbothioamide (IIIc): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 3.8 (s, 3H of 3.NH), 7.7 (s, 2H of NH_2), 5.9-6.2 (m, 4H of Ar-H), 4.2 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 Aliphatic). MS m/z (%): M+1 = 376.

2-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-N-(4-methyl Phenyl)hydrazinecarbothioamide (IIId): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 3.8 (s, 3H of 3.NH), 7.7 (s, 2H of NH_2), 5.9-6.2 (m, 4H of Ar-H), 4.6 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 Aliphatic). MS m/z (%): M+1 = 376.

2-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)carbonyl]-N-(4-chloro Phenyl)hydrazinecarbothioamide (IIIe): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*) 3405 (NH) 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 3.8 (s, 3H of 3.NH), 7.7 (s, 2H of NH_2), 5.9-6.2 (m, 5H of Ar-H), 1.4-2.7 (m, 8H of CH_2 aliphatic). MS m/z (%): M+1 = 376.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-ethyl-1,3,4-oxadiazole-2-amine (IVa): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C). ^{1}H NMR (DMSO-d_6) δ: 4.2 (s, 3H of 3.NH), 7.7 (s, 2H of NH_2), 4.2 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 aliphatic), 4.2-4.3 (t, 3H of CH_3), 1.2-1.3 (q, 2H of CH_2). MS m/z (%): M+1 = 265.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-phenyl-1,3,4-oxadiazole-2-amine (IVb): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C). ^{1}H NMR (DMSO-d_6) :δ 7.7 (s, 1H of NH_2), 3.8 (s, 3H of 3.NH), 5.9-6.2 (m, 5H of Ar-H), 1.4-2.7 (m, 8H of CH_2 aliphatic). MS m/z (%): M+1 = 312.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(4-methoxy phenyl)-1,3,4-oxadiazole-2-amine (IVc): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 7.7 (s, 1H of NH_2), 3.8 (s, 3H of 3.NH), 5.9-6.2 (m, 4H of Ar-H), 4.2 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 Aliphatic). MS m/z (%): M+1 = 343.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(4-methyl phenyl)-1,3,4-oxadiazole-2-amine (IVd): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) :δ 7.7 (s, 1H of NH2), 3.8 (s, 3H of 3.NH), 5.9-6.2 (m, 4H of Ar-H), 4.4 (s, 3H of CH_3), 1.4-2.7 (m, 8H of CH_2 Aliphatic). MS m/z (%): M+1 = 327.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(4-chloro phenyl)-1,3,4-oxadiazole-2-amine (IVe): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH_2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H aliphatic), 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 7.7 (s, 1H of NH_2), 3.8 (s, 3H of 3.NH), 6.2-7.1 (m, 4H of Ar-H), 1.4-2.7 (m, 8H of CH_2 Aliphatic). MS m/z (%): M+1 = 347.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-ethyl-1,3,4- thiadiazole-2-amine (Va): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H) aliphatic, 1366 (C=N), 1274 (N-N), 781 (C-S-C). 1H NMR (DMSO-*d6*) δ: 7.7 (s, 2H of NH2), 4.2 (s, 3H of 3.NH), 4.2 (s, 3H of CH3), 1.4-2.7 (m, 8H of CH2 aliphatic), 4.2-4.3 (t, 3H of CH3), 1.2-1.3 (q, 2H of CH2). MS m/z (%):

M+1 = 281.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-phenyl-1,3,4- thiadiazole-2-amine (Vb): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H) aliphatic, 1366 (C=N), 1274 (N-N), 781 (C-S-C). ^{1}H NMR (DMSO-*d6*) δ: 7.7 (s, 1H of NH2), 3.8 (s, 3H of 3.NH), 5.9-6.2 (m, 5H of Ar-H),1.4-2.7 (m, 8H of CH_2 Aliphatic). MS m/z (%): M+1 = 329.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(4-methoxy phenyl)-1,3,4-thiadiazole-2-amine (Vc): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H) aliphatic, 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-*d6*) δ: 7.7 (s, 1H of NH2), 3.8 (s, 3H of 3.NH), 5.9-6.2 (m, 4H of Ar-H), 4.2 (s, 3H of CH3), 1.4-2.7 (m, 8H of CH2 aliphatic). MS m/z (%): M+1 = 359.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(4-methyl phenyl)-1,3,4-thiadiazole-2-amine (Vd): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H) aliphatic, 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-*d6*) δ: 7.7 (s, 1H of NH2), 3.8 (s, 3H of 3.NH), 5.9-6.2 (m, 4H of Ar-H), 4.4 (s, 3H of CH3), 1.4-2.7 (m, 8H of CH2 aliphatic). MS m/z (%): M+1 = 343.

5-[(2-Amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-N-(4-chloro phenyl)-1,3,4- thiadiazole-2-amine (Ve): IR (KBr, ν_{max}, cm^{-1}): 3384 (NH *str.*), 3299 (NH2), 2938 (CH *str.*), 3405 (NH), 2840 (C-H) aliphatic, 1366 (C=N), 1274 (N-N), 781 (C-S-C).^{1}H NMR (DMSO-d_6) δ: 7.7 (s, 1H of NH2), 3.8 (s, 3H of 3.NH), 6.2-7.1 (m, 4H of Ar-H), 1.4-2.7 (m, 8H of CH_2 aliphatic). MS m/z (%): M+1 = 364.

The results showed that compounds **IV(c), IV(d), , V(c),** and **V(d)** showed significant paralytic time (mean, n=6)with that of standarddrug Albendazole, at given concentrations and compounds **IV (e)**and **V (b)** also showed the death time (mean, n=6) of earthworms close to that of standard drug Albendazole (Table 2.4). After all, the synthesized compounds in overall estimation confirms the better activity against *Pheretima posthuma* (Indian earthworms). Perhaps the 4-methyl phenyl-, and 4-methoxyphenyl- groups at nitrogenon 2nd position of Oxadiazole orThiadiazolering and -N=C-N-linkage present in these derivatives is contributing to significant antihelmintic activity.

CONCLUSION

In summary, the prime objective of the present work was to design, synthesize and biologically screening of some novel Oxadiazole or Thiadiazole derivatives and the synthesized compounds were charecterized by IR, NMR and mass spectrometry and also progress of reaction was checked by TLC. In anthelmintic activity, compounds **IV(c), IV(d), V(c),** and **V(d)** showed significant paralytic time with that of standard drug Albendazole, at given concentrations and compounds**IV (e)**and **V (b)** also showed the death time of earthwormsclose to that of standard drug Albendazole.

ACKNOWLEDGEMENT

The authors thank the Management of GLAUniversity, Mathura for providing the necessary facilities for carrying outresearch work.

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