Research in Pharmacy and Health Sciences.2022,8(3):186-190. • https://doi.org/10.32463/RPHS.2022.v08i03.01 e-ISSN: 2455-5258

RESEARCH ARTICLE OPEN ACCESS

Synthesis and biological evaluation of novel thiozolidine-2,4-dione derivatives

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Received: 12 July, 2022
Accepted: 30 September, 2022

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Published by: OZZIE Publishers
Web: www.ozziepublishers.com

Abstract

Objective: Despite the optimal use of available anti-helminthetic drugs (AHDs), many patients with worm infections fail to experience worm control and others do so only at the expense of significant toxic side effects. The limitations with the conventional AHDs highlighted the need for developing newer agents to treat worm infestations.

Method: A series of 3-(2-substituted) benzyl) thiazolidine-2, 4-diones (TND 1-9) were obtained by the condensation of thiazolidine-2, 4-diones with substituted aldehydes in presence of toluene and piperidine. The synthesized compounds were characterized by chromatographic, spectrometric methods, and elemental analysis. All the synthesized compounds, (TND 1-9) were screened for anthelmintic activity at two concentrations (20 and 40mg/ml), using adult earth worm Pheretima posthuma. The test compounds were found to possess significant anthelmintic activity.

Result: Among the test compounds, compound 3-(4-(dimethylamino) cinnamoyl-ylidene) thiazolidine-2, 4-dione (TND 2) was found to exhibit potent anthelmintic activity with significantly shorter paralyzing time and the death of worms when compared to the reference standard piperazine. The compound 3-(2-hydroxyphenyl) ethyl) thiazolidine-2,4-dione (TND 4) showed equipotent activity to that of the standard drug.

Conclusion: Since, the compound 3-(4-(dimethylamino) cinnamoyl-ylidene) thiazolidine-2, 4-dione exhibited moderately more potent activity than the reference standard piperazine, it can be selected as a lead molecule for further worm exploitation.

KEY WORDS: anthelmintic, worm infections, new drugs, thiazolidine 2,4-dione, piperazine, 3-(2-substituted) benzyl) thiazolidine-2, 4-diones.

1. INTRODUCTION

Anthelminthics are drugs that are used to expel parasitic worms (helminths) from the body, by evacuation (vermifuges) or killing(vermicides)[1]. Helminthes infections are now recognized as cause of many acute as well as chronic ill health's in more than half of the population of the planet. Worms that are resistant to treatment will accumulate and finally treatment failure occurs. Generally, intestinal worm infections are more easily treated than those in other locations in the body[2]. The introduction of Piperazine into human and veterinary medicine, relaxes the large intestinal roundworms (ascarids) and pinworms (oxyurids) of man and domesticated animals which are then eliminated with the feces. Pyrvinium pamoate has replaced piperazine for the treatment of human pinworm infection[3,4]. Traditional system of medicine reports the efficacy of several natural plants in eliminating worms[5]. The present work was conceived to evaluate the anthelmintic activity of various 3-substituted thiazolidinedione derivatives using adult earthworm Pheritima posthuma.

Majority of anthelmintics are limited in their action, as they are used in the treatment of most humans infected with trematodes or cestodes by disrupting calcium homeostasis[6] but not effective against nematodes. Despite the prevalence of parasitic worms, anthelmintic drug discovery is relatively poor due to the fact that the country which suffer greatly from these tropical diseases have little money to invest in drug development. This is the reason that the drugs available for human treatment were first developed as veterinary medicines. This situation has been exacerbated by the remarkable success of ivermectin over the last thirty years[7], which has contracted the need for anthelmintic drug discovery programs[8].

Despite the optimal use of available anti-helminthetic drugs (AHDs), many patients with worm infections fail to experience worm control and others do so only at the expense of significant toxic side effects. The limitations with the conventional AHDs highlighted the need for developing newer agents to treat worm infestations and therefore new, less toxic and more effective drugs are required. Thiazolidin-4-ones had reported to exhibit anthelmintic properties[9]. Thiazolidin-2,4-diones are five-member heterocyclic ring system containing sulphur and nitrogen atom and received much attention of medicinal chemists due to their potential biological activities. Various substituents at N-3 and C-5 of thiazolidinedione results in potent anti-helminthetic activity. Prompted by these reports, we aimed to prepare the following

series of 3-substituted-thiazolidinedione derivatives as potent antihelminthetics.

2. MATERIALS AND METHODS

Melting points (MP) were recorded using Thomas Hoover melting point apparatus and were uncorrected. The IR spectra were recorded on a Perkin-Elmer 398 spectrometers. DPX-500 MHz Bruker FT-NMR spectrometer was used to record ^1H spectra. Using tetramethylsilane (TMS) as an internal standard, the chemical shifts were reported as parts per million (δ ppm). JEOL-SX-102 instrument using fast atom bombardment (FAB positive) was employed to obtain mass spectra. Silica gel plates (Merck) using chloroform-methanol (9:1) as a solvent system was used to monitor the progress of the reaction. Iodine was used as a developing agent. The structures of the synthesized compounds were confirmed by spectral data (IR, NMR and mass spectra). Microanalysis was conducted to ascertain the purity of synthesized compounds. Elemental (C, H, N) analysis performed on a Perkin-Elmer 2400 C, H, N analyzer, indicated that the calculated and observed values were within the acceptable limits (± 0.4%).

The entire chemicals and reagents used were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification.

2.1. GENERAL PROCEDURE FOR SYNTHESIS OF THIAZOLIDIN-2,4-DIONE[10,11]

In a 250 ml three necked flask, to a solution of chloroacetic acid (0.02 mol) in 30 ml of water was added a solution of thiourea (0.02 mol) dissolved in 60 ml of water (Figure:1). Stirring of mixture was continued for 15 min to obtain a white precipitate, after considerable cooling. To the content of the flask was then added slowly 20 ml concentrated HCl drop wise, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed 8 hr at 100-110ºC. Cluster of white needles were formed on cooling the contents of the flask. The product was filtered and washed with cold water to remove traces of HCl and dried. Finally, it was purified by recrystallization using ethyl alcohol.

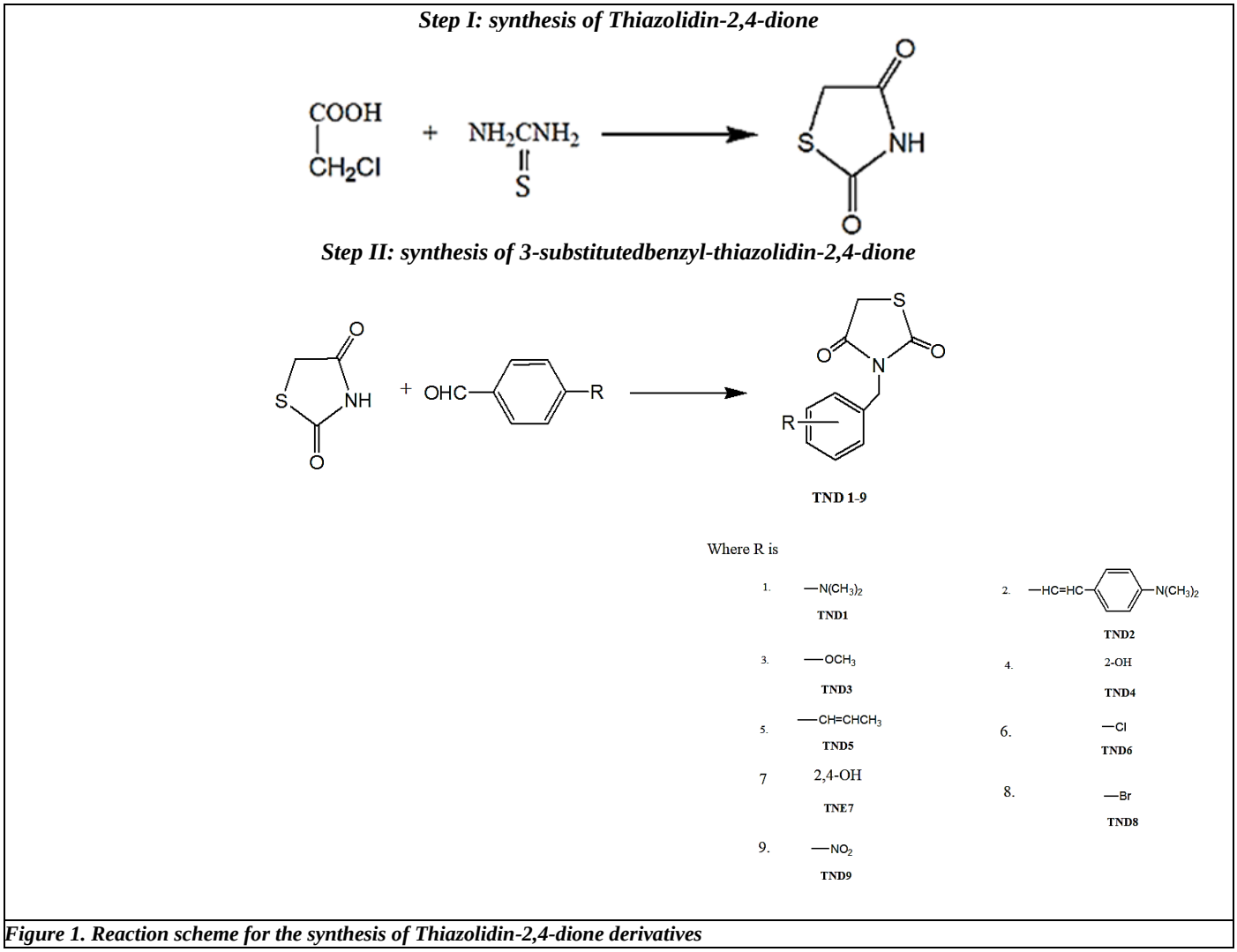

Figure 1. Reaction scheme for the synthesis of Thiazolidin-2,4-dione derivatives

2.12 GENERAL PROCEDURE FOR SYNTHESIS OF 3-(2 OR 4-SUBSTITUTED BENZYL) THIAZOLIDINE-2, 4-DIONES (TND 1-9)

In a 250 ml three necked flask, a substituted benzaldehydes (para dimethyl amino benzaldehyde (0.02 mol), para dimethyl amino cinnamaldehyde (0.02 mol), 4-methoxy benzaldehyde (0.02 mol), 2-hydroxy benzaldehyde (0.02 mol), crotanaldehyde (0.02 mol), 2-chlorobenzaldehyde (0.02 mol), 2, 4-dihydroxy benzaldehyde (0.02 mol), 2-bromobenzaldehyde (0.02 mol) and 2-nitrobenzaldehyde were separately suspended in toluene. To this a catalytic amount of piperidine (1 ml) was added. The mixture was stirred and refluxed. After the complete removal of water and

when the temperature reached above 110ºC the reaction mixture was stirred for further 5 hr. On colling the product precipitated out toluene. The formed products were filtered and cleansed with water. Finally, it was purified by recrystallization using ethyl alcohol.

2.3 ANTI-HELMINTHETIC ACTIVITY[12-16]

Adult earthworm phertima prosthuma were collected (due to its anatomical and physiological resemblance with the intestinal roundworm parasites of human being) from moist soil, obtained from Tamilnadu Agriculture University, Coimbatore, India. Eleven groups of approximately equal size earthworms (8+1 cm) consisting of six earthworms in each group were used for the present study[17-18]. Piperazine citrate was taken as standard drug and the concentration of the standard drug was prepared in 1% normal saline to obtained to obtained 20 and 40 mg% concentration[19]. The test compounds were prepared in minimum quantity of tween 80 and diluted to 20 ml with normal saline to obtained 20 and 40 mg/ % concentration.

Observations were made for the time taken to paralysis and death of individual worms. Paralysis was said to occur when the worms do not regain life even in normal saline. Death was concluded when the worms lost their motility followed with fading away of their body color[12].

3. RESULTS

3.1 SYNTHESIS OF 4-(4-SUBSTITUTED) BENZYLIDENE) THIAZOLIDINE-2, 4-DIONES

The 3-(2-substituted) benzyl) thiazolidine-2, 4-diones **(TND 1-9)** were obtained by the condensation of thiazolidine-2, 4-diones with substituted aldehydes in presence of toluene and piperidine. The formations of the thiazolidine-2, 4-diones were confirmed by the presence of characteristic peaks in the IR spectra. The NMR spectrum of the compounds TND 1-9 showed the characteristic peak at around δ 2.80 ppm for CH_3 group, δ 3.00 ppm for CH_2 and δ 10.00 ppm for NH and also shows multiplet in the range of δ 6.70-7.54 ppm owing to aromatic protons. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

	TZD	TND 1	TND 2	TND 3	TND 4	TND 5	TND 6	TND 7	TND 8	TND 9
Yield	2.91g; 92.0%	2.86g; 91.0%	2.47g; 82.3 %	2.32g; 75.8%	2.65g; 88.2 %	1.85g; 82.6%	2.85g; 89.6%	2.12g; 78.3%	1.96g; 87.1%	2.20g; 85.4%
Melting Point	121-124 °C	156-159 °C	194-197 °C	142-145 °C	181-184 °C	24-128 °C	156-159 °C	204-206 °C	187-189 °C	176-179 °C
Rf Value	0.72	0.85	0.78	0.71	0.81	0.72	0.79	0.81	0.75	0.89
MF	$C_3H_3NO_2S$	$C_{12}H_{12}N_2O_2S$	$C_{13}H_{14}N_2O_2S$	$C_{11}H_{11}NO_3S$	$C_{10}H_9NO_3S$	$C_7H_9NO_2S$	$C_{10}H_8ClNO_2S$	$C_{10}H_9NO_4S$	$C_{10}H_8BrNO_2S$	$C_{10}H_8N2O_4S$
MW	117.13 (M+)	250.32 (M+)	262.33 (M+)	237.27 (M+)	223.25 (M+)	171.22 (M+)	241.69 (M+2)	239.25 (M+)	286.15 (M+2)	253.25 (M+)
IR (KBr) cm^{-1}	3329(NH),3066 (Ar-CH),1716 (C=O, Str), 688 (C-S-C	3085 (Ar-CH), 2948 (CH_2),1696 (C=O,Str), 688 (C-S-C).	3085 (Ar-CH), 2948 (CH_2), 1712 (C=O, Str), 1597 (CH=CH)688 (C-S-C)	3085 (Ar-CH), 2910 (CH_2),1674 (C=O,Str), 688 (C-S-C).	3532 (OH), 3085 (Ar-CH), 2967 $N(CH_3)$2,1710 (C=O, Str), 688 (C-S-C).	3058 (Ar-CH), 2910 $(N(CH_3)_2$, 1698(C=O, Str),688 (C-S-C).	3076 (Ar-CH), 2918 (CH_2),1712 (C=O,str), 746 (C-Cl), 688 (C-S-C)	3510 (OH), 3048 (Ar-CH),2910 (CH_2),1696 (C=O,Str), 688 (C-S-C).	3033 (Ar-CH), 2948 (CH_2),1713 (C=O, Str), 688 (C-S-C), 752 (C-Br).	3071(Ar-CH), 2968 (CH_2), 1707 (C=O, Str), 1376 & 1537 (NO_2), 688 (C-S-C).
^{1}H NMR ($CDCl_3$) δ (ppm	3.76 (s,2H,CH_2), 10.0 (s,1H,NH).	^{1}H NMR ($CDCl_3$) δ (ppm):2.85 (s, 3H, CH_3),3.74 (s,2H,CH_2) 4.74 (s, 2H, CH_2), 7.07 (d, *J = 8.0 Hz*, 2H, Ar-H), 7.38 (d, *J = 8.0 Hz*, 2H, Ar-H).	^{1}H NMR ($CDCl_3$) δ (ppm): 2.85 (s, 3H, CH_3), 6.44 (d, *J=8.0 Hz*,2H, Ar-H), 6.88 (d,*J=8.0 Hz*, 2H, Ar-H), 6.65(1s,1H,CH),6.85 (s,1H, CH) 7.01 (s,1H, CH).	^{1}H NMR ($CDCl_3$) δ (ppm):3.73 (s,3H,OCH_3) 4.74 (s, 2H, CH_2), 6.65 (d,*J = 8.0 Hz*, 2H, Ar-H), 6.95 (d, *J=8.0 Hz*, 2H, Ar-H), 7.15 (s,1H, CH).	^{1}H NMR ($CDCl_3$) δ (ppm): 5.22 (s, 1H, OH), 6.77-7.13 (m, *J = 8.0 Hz*, 4H, Ar-H), 7.42(s, 1H, CH)).	^{1}H NMR ($CDCl_3$) δ (ppm):1.71 (s,3H,CH_3) 5.72 (s, 1H, CH), 6.27 (s, 1H, CH), 7.01(s, 1H, CH).	^{1}H NMR ($CDCl_3$) δ (ppm): 3.76 (s, 2H, CH_2), 4.72(s,2H, CH_2), 6.27 (s, 1H, CH), 7.01-7.15 (m, *J = 8.0 Hz*, 4H, Ar-H).	^{1}H NMR ($CDCl_3$) δ (ppm):3.76 (s, 2H CH_2), 4.72 (s,2H,CH_2) 5.02(s,1H,OH) 6.08-6.72 (m, *J = 8.0 Hz*, 4H, Ar-H), 7.01(s,1H,CH) CH).	^{1}H NMR ($CDCl_3$) δ (ppm):3.72 (s, 2H, CH_2), 4.74 (s, 2H,CH_2) 6.32(s,1H,CH),7.01-7.15 (m, *J = 8.0 Hz*, 4H, Ar-H).	^{1}H NMR ($CDCl_3$) δ (ppm): 3.74 (s, 2H, CH_2), 4.76 (s, 2H,CH_2) 6.24 (s, 1H, CH), 7.32-8.08 (m, *J = 8.0 Hz*, 4H, Ar-H).
Calculated	C, 30.72; H, 2.57; N,11.94	C, 57.58; H, 5.64; N, 11.19	C, 59.52; H, 5.38; N,10.68	C, 55.68; H, 4.67; N, 5.90	C, 53.80; H, 4.06; N, 6.27	C, 49.10; H, 5.30; N, 8.18.	C, 49.69; H, 3.34; N,5.80.	C, 50.20; H, 3.79; N, 5.85	C, 41.97; H,2.82; N,4.89	C, 47.61; H, 3.20; N, 11.11.
Found	C, 30.76; H, 2.58, N, 11.96.	C, 57.49; H, 5.63, N, 11.18	C, 59.48; H, 5.37; N, 10.66.	C, 55.65; H, 4.65, N, 5.91	C, 53.78; H, 4.05, N, 6.26	C, 49.08; H, 5.29, N, 8.20.	C, 49.65; H, 3.33, N, 5.78.	C, 50.18; H, 3.77, N, 5.86.	C, 41.95; H, 2.81, N, 4.90.	C, 47.59; H, 3.19, N, 11.10

Table 1. Spectral characterisation of the synthesized compounds

3.2 STATISTICAL ANALYSIS

All the synthesized compounds were evaluated for anti-helminthetic activity. The results were analyzed for statistical significance using one-way ANOVA followed by Dunnett's 't' test.

All values are expressed as mean ± SEM. Data were analyzed by non-parametric ANOVA followed by Dunnett's multiple comparison tests, and other data was evaluated using GraphPad PRISM software. A p-value < 0.05 was considered significantly different.

3.3 PHARMACOLOGICAL INVESTIGATION

The test compounds were prepared in minimum quantity of tween 80 and diluted to 20 ml with normal saline to obtained 20 and 40 mg/ % concentration. The anthelmintic data of all the test compounds are presented in Table **2.**

Compound name	Concentration (mg/ml)	Time of paralysis (minutes)	Time of death (minutes)
TND 1	20	11.67 ± 0.40	32.17 ± 0.79
	40	5.5 ± 0.61	31.50 ± 0.61
TND 2	20	5.5 ± 0.22	8.0 ± 0.22***
	40	4.67 ± 0.33	7.50 ± 0.50 **
TND 3	20	13.83 ± 0.61	23.33 ± 0.61
	40	10.50 ± 0.34	16.67 ± 0.33
TND 4	20	13.83 ± 0.61	23.33 ± 0.61
	40	4.83 ± 0.30	8.67 ± 0.33**
TND 5	20	8.83 ± 0.40	27.50 ± 1.02
TND 6	40	6.33 ± 0.42	11.17 ± 0.40*
	20	12.85 ± 0.56	28.41 ± 0.74
TND 7	20	8.56 ± 0.45	19.25 ± 0.21
	40	7.49 ± 0.26	13.28 ± 0.52
TND 8	20	9.78 ± 0.64	17.96 ± 0.39
TND 9	40	8.32 ±0.35	14.18 ± 0.77
	20	11.87 ± 0.41	30.74 ± 0.51
Piperazine	40	10.25 ± 0.87	19.47 ± 0.63
	20	5.54 ± 0.32	9.16 ± 0.66
	40	4.85 ± 0.16	8.50 ± 0.33

Table 2. Anthelmintic activity of synthesized compounds (TND 1-9)

Values are expressed as mean ± SEM (n = 6). Significantly different from standard at *p < 0.05; **p < 0.01; ***p < 0.001.

4. DISCUSSION

All the tested compounds displayed promising anthelmintic activity against adult earthworm phertima prosthuma. From the results (Table 1) it was found that the compound 3-(4-(dimethylamino) benzyl) thiazolidine-2,4-dione, 3-(4-methoxyphenyl) ethyl) thiazolidine-2,4-dione and 3-(but-2-enylidene) thiazolidine-2, 4-dione were found to exhibit less anthelmintic activity than other title compound reference piperazine. Within the title compounds synthesized, 3-(4-(dimethylamino) cinnamoyl-yl) thiazolidine-2, -dione and 3-(2-hydroxyphenyl) ethyl) thiazolidine-2,4-dione (**TND 2** and **TND 4)** showed better activity than corresponding dimethylamino, methoxy, chloro, bromo, dihydroxy, nitro and crotonaldehyde analogs (**TND 1, TND 3, TND5, TND 6**, **TND 7, TND 8** and **TND 9**). Among various substituents tested at N-3 position of thiazolidinediones, compound possessing hydroxyl and dimethylamino cinnamoyl substituted analogs (**TND 2** and **TND 4**) exhibited significant anthelmintic activity, which was found to be more than rest of substituents tested. Replacement of cinnamoyl and hydroxyl groups by aromatic ring systems like $CH_3CH=CH$ group and methoxy phenyl or dimethylamino group results in decreased anthelmintic activity. In the present study, it was found that introduction of p-substituted aryl halogens at N-3 position of thiazolidinedione ring favours the anthelmintic activity. Among the test compounds, compound 3-(4-(dimethylamino) cinnamoyl-yl) thiazolidine-2, -dione **(TND2)** was found to be the most active agent. This compound exhibited moderately more potent activity than the reference standard piperazine.

3.3 CONCLUSION

In summary, a new series of 3-substituted benzyl thiazolidin-2, 4-dion derivatives were synthesized. These title compounds containing nine different substituents at N-3 position were screened for their anthelmintic activity. Most of the test compounds were found to exhibit significant anthelmintic activity. Among the substituents at N-3, 4-dimethylaminocinnamoyl phenyl substituent showed maximum potency, while 4-hydroxy phenyl substituent showed equipotent activity but the 4-(dimethylamino) phenyl, 4-methoxyphenyl and but-2-enylidene substituents exhibited least activity when compare to other substituents. The order of activity at N-3 is 4-dimethylaminocinnamoyl phenyl ≥ 2-hydroxy phenyl ≥ 4-dimethylamino) phenyl ≥ 2-chlorophenyl ≥ 2-bromo phenyl ≥ 2,4-dihydroxyphenyl ≥ 2-nitrophenyl ≥ 4-methoxyphenyl ≥ but-2-enylidene group.

Among the test compounds, compound 3-(4-(dimethylamino) cinnamoyl-ylidene) thiazolidine-2, 4-dione (TND2) was found to be the most active agent. This compound exhibited moderately more potent activity than the reference standard piperazine. Hence this molecule can be selected as a lead molecule of the present study for further worm exploitation.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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Cite article as: Gigi Sam. Synthesis and biological evaluation of novel thiozolidine-2,4-dione derivatives. Res Pharm Healt Sci. 2022,8(3):186-90. Doi: 10.32463/RPHS.2022.v08i03.01