ORIGINAL RESEARCH

SYNTHESIS OF THIADIAZOLE CLUBBED THIAZOLIDINONE DERIVATIVES AND THEIR ANTHELMINTIC ACTIVITY

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ABSTRACT:

The present study was designed to synthesize and investigate the anthelmintic activity of thiadiazole clubbed thiazoledinone derivatives. Among all the synthesized compounds {*2-(4-Chlorophenyl)-3-(5-heptadecyl-1,3,4-thidiazole-2-yl)thiazolidin-4-one* (6a), *2-(2-Fluorophenyl)-3-(5-heptadecyl-1,3,4-thidiazole-2-yl)thiazolidin-4-one*(6b), *3-(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(2-nitro phenyl)thiazolidin-4-one*(6c), *3-(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(3-hydroxyphenyl)thia zolidin-4-one (6d) and 3-(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one (6e)] compound (d)* showed potent anthelmintic activity with time for paralysis and death 16.52±0.01 min and 18.23±0.05 min respectively. While other compounds showed time of death in the range 22.88±0.12 min to 31.44±0.01. The standard drug piperazine citrate at 2 mg/ml concentration showed paralysis and death at 24.85±0.055 to 25.41±0.06 min respectively.

KEY WORDS: Thiadiazole, thiazoledinone, anthelmintic.

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1. INTRODUCTION

Medicinal chemistry is an interdisciplinary science. It has been stated that "medicinal chemistry concerns the discovery, the development, the identification and interpretation of the mode of action of biologically active compounds at the molecular level". Evidently it touches all branches of chemistry and biology. The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. The process of establishing a new drug is exceedingly complex and involves talents of people from variety of disciplines. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and pharmacological activity (1).Thiazolidinone is a saturated form of thiazole with carbonyl group on fourth carbon and has been considered as a magic moiety which posses almost all types of biological activities. It belongs to an important group of heterocyclic compounds containing sulphur and nitrogen in a five membered ring. The derivatives of 4-thiazolidinone nucleus have occupied a unique place in the field of medicinal chemistry due to wide range of biological activities(2-4)

Helminth parasitism remains an underappreciated of humans in most of the developing world. As many as two billion individuals harbour these parasites, infected with filariae, hookworms, whipworm, large roundworms and schistosomes, major causes of morbidity in animals and humans (5) Several classes of anthelmintics are currently available. Anthelmintics are the therapeutic agents used to destroy the parasitic worms or to remove them from infected host. Anthelmintics are highly effective against the immature and mature stages of gastrointestinal nematodes and extraintestinal helminth species. There are many methods for evaluating the anthelmintic activity. In the present work anthelmintic activity of newly synthesized (thiazolidinones) compounds was evaluated against *Eisemia foetide* earthworm.

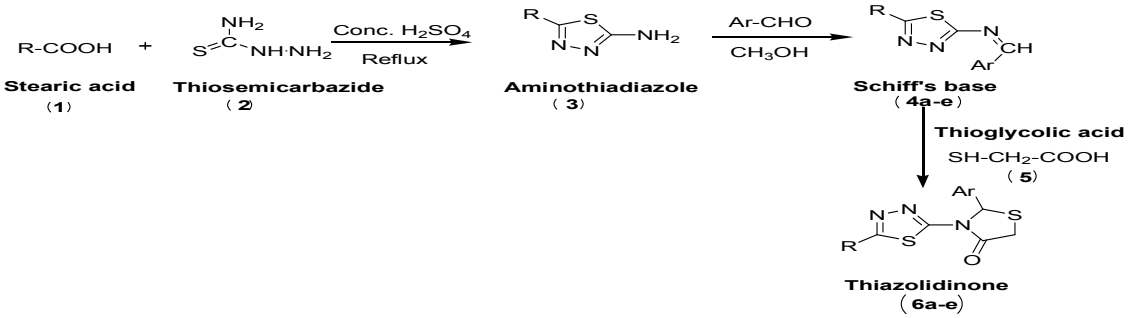
2. MATERIAL AND METHODS

2.1. General

All chemicals and all solvents used in this study were purchased from M/s Sisco Research Laboratories Pvt. Ltd. (Mumbai), India.NMR spectra were performed on a Bruker DPX 300 spectrometer (300 MHz for ^1H). Samples were dissolved in $CDCl_3$ or DMSO-d_6 with TMS as internal reference; the chemical shifts are given in ppm. Thin-layer chromatography (TLC) was performed on TLC plates (silica gel 60 F_{254}, Merck). Melting points were determined on a Labindia MR-VIS visual melting range apparatus and are uncorrected.

2.2. General procedure for synthesis

2.2.1 General scheme of synthesis



R = $CH_3(CH_2)_{16}$ -

Ar =(a)= 4-Cl-C_6H_5-, (b) 2-F-C_6H_5-, (c) 2-NO_2-C_6H_5-, (d) 3-OH-C_6H_5- , (e) 4-OH-C_6H_5-

Figure 1. Synthetic route for the preparation of thiadiazole clubbed thiazolidinones (6a-6e)

Step-1

2.2.2 General procedure for synthesis of thiadiazole:

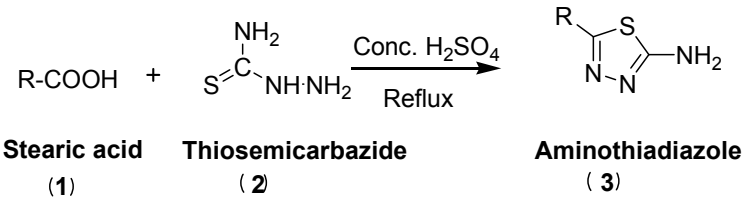


Figure 2. Synthetic scheme for preparation of amino thiadiazoles

Firstly H_2SO_4 (10mL) was added drop wise to the mixture of stearic acid **1** (0.01 mol) and thiosemicarbazide **2** (0.01mol). The mixture was refluxed for 3-4h. On cooling, the reaction mixture was poured on to crushed ice and the precipitated solid **3** was filtered and collected when dried (Pattan et al, 2009).

Step-2

2.2.3 General Procedure for synthesis of Schiff's base:

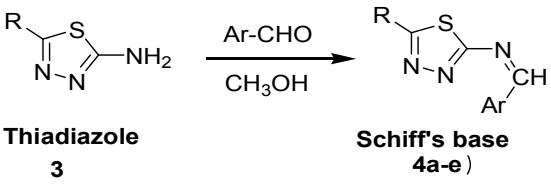


Figure 3. Synthetic scheme for preparation of amino Schiff's bases

A mixture of the synthesized thiadiazole **3** and respective aromatic aldehydes (0.025 M) was refluxed in methanol (50 ml) in the presence of small amount of glacial acetic acid for about 2 h. The mixture was cooled and poured in ice cold water. The solid thus obtained was separated by filtration and recrystallized from methanol to give the corresponding Schiff's bases (**4a-e**) (Kumar et al, 2011).

Step-3

2.2.4 General Procedure for Synthesis of thiadiazole clubbed thiazolidinones:

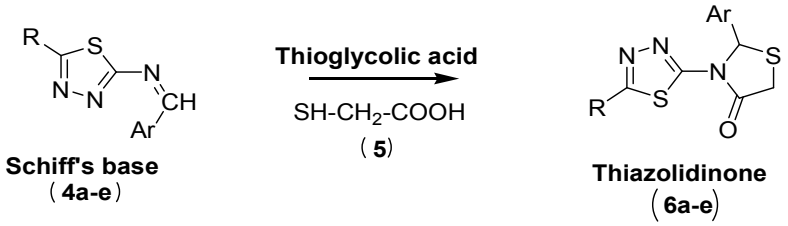


Figure 4. Synthetic scheme for preparation of thiazolidinones

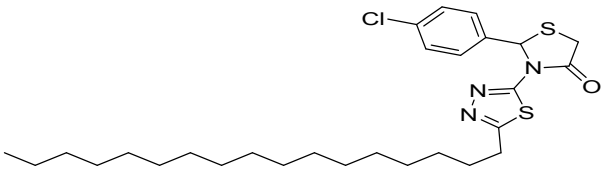
Synthesized Schiff's base (0.02M) **(4a-e)** and appropriate quantity of thioglycollic acid **5** (0.02 M) in dimethyl formamide (DMF) (50 mL), containing a pinch of anhydrous $ZnCl_2$ were refluxed for about 6 h. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water and the product **(6a-e)** was recrystallized from ethanol. By adopting this method, total five compounds have been synthesized. Physicochemical data of synthesized thiazolidinone derivatives are presented in Table 1.

Table 1 Physicochemical data of synthesized thiazolidinone derivatives

Compound	R	AR	Molecular Formula	Molecular Weight	Melting Point (°C)	Yield (%)
6a	$CH_3(CH_2)_{16}$	4-Chlorophenyl	$C_{28}H_{42}ClN_3OS_2$	536.24	175-178	56
6b	$CH_3(CH_2)_{16}$	2-Fluorophenyl	$C_{28}H_{42}FN_3OS_2$	519.78	178-180	51
6c	$CH_3(CH_2)_{16}$	2-Nitrophenyl	$C_{28}H_{42}N_4O_3S_2$	546.79	198-200	44
6d	$CH_3(CH_2)_{16}$	3-Hyroxyphenyl	$C_{28}H_{43}N_3O_2S_2$	517.79	181-183	58
6e	$CH_3(CH_2)_{16}$	4-Hydroxyphenyl	$C_{28}H_{42}N_4O_3S_2$	517.79	188-190	59

2.2.5. Spectral characteristics of thiadiazole clubbed thiazolidinone derivatives (6a-6e)

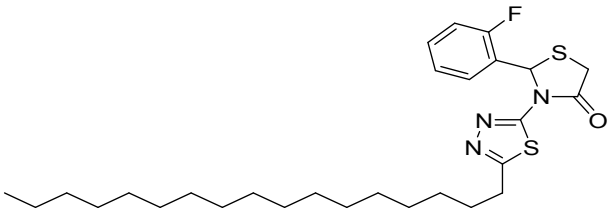
2-(4-Chlorophenyl)-3-(5-heptadecyl-1,3,4-thidiazole-2-yl)thiazolidin-4-one **(6a)**



(6a)

Yield 56% Melting point = 175-178°C, IR: 2944 (CH in alkyl chain), 1735 (C=O thiazolidinone ring), 722 (C-S-C). ^{1}H NMR (DMSO): δ 0.99- 1.15 (t, 3H terminal CH_3), 1.19-1.73(m, 32H CH_2 in alkyl chain), 7.3-8.8 (m 4H Ar- H), 3.45 (s, 2H, CH2), 3.79 (1H,s, N-CH).

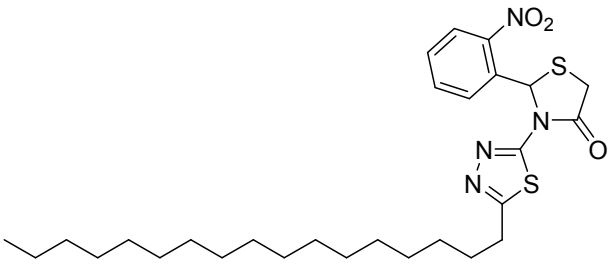
2-(2-Fluorophenyl)-3-(5-heptadecyl-1,3,4-thidiazole-2-yl)thiazolidin-4-one **(6b)**



(6b)

Yield 51% Melting point = 178-180°C, IR: 2940 (CH in alkyl chain), 1735 (C=O thiazolidinone ring), 723 (C-S-C). ^{1}H NMR (DMSO): δ 0.98- 1.05 (t, 3H terminal CH_3), 1.19-1.73(m, 32H CH_2 in alkyl chain), 7.2-8.5 (m 4H Ar- H), 3.46 (s, 2H, CH_2), (s, 2H, CH_2), 3.78 (1H,s, N-CH).

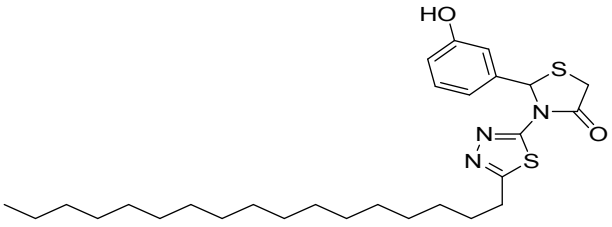
***3-(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(2-nitrophenyl)thiazolidin-4-one* (6c)**



(6c)

Yield 44% Melting point 198-200°C IR (KBr): IR: 2963 (CH in alkyl chain), 1726 (C=O thiazolidinone ring), 732 (C-S-C), 1537 (N=O stretching). ^{1}H NMR (DMSO): δ 0.99-1.10 (t, 3H terminal CH_3), 1.09-1.73 (m, 32H CH_2 alkyl chain), 7.1-7.8 (m 4H Ar- H), 3.5 (2H, s,CH_2), 2.89 (1H,s, N-CH).

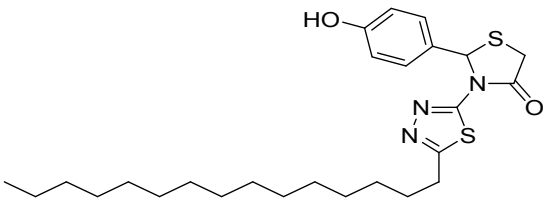
3-(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(3-hydroxyphenyl)thiazolidin-4-one (6d)



(6d)

Yield 58% Melting point =181-183°C, IR: 2924 (CH in alkyl chain), 3172 (OH), 1726 (C=O thiazolidinone ring), 740 (C-S-C).^{1}H NMR (DMSO): δ 0.97-1.11 (t, 3H terminal CH_3), 1.29-1.33(m, 32H CH_2 in alkyl chain), 2.89 (1H,s, N-CH), 3.5 (2H,s,CH_2), 6.3-8.1 (m 4H Ar- H), 8.9 (s, 1H OH).

3-(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one (6e)



(6e)

Yield 59% Melting point = 188-190°C, IR: 2928 (CH in alkyl chain), 3176 (OH), 1726 (C=O thiazolidinone ring), 742 (C-S-C).^{1}H NMR (DMSO): δ 0.99-1.10 (t, 3H terminal CH_3), 1.27-1.34(m, 32H CH_2 in alkyl chain), 2.89 (1H,s, N-CH), 3.3 (2H,s,CH_2), 6.3-8.1 (m 4H Ar- H), 8.7 (s, 1H OH).

2.3 Evaluation of Anthelmintic Activity

2.3.1 *Pheretima posthuma*

Earthworm (*Pheretima posthuma*) was procured from the Department of Agriculture, Gurukul, Kurukshetra. The earthworms, 4-5 cm in length and 0.1 - 0.2 cm in width were used for all experimental protocol

2.3.2 Procedure

Suspensions of the samples were prepared by triturating the samples with 0.5% tween 80 and distilled water. The resulting mixture was than stirred for 30 min. The resulting suspensions were diluted to contain 2 mg/ml of the test samples. These suspensions were used for anthelmintic activity. The standard drug piperazine citrate was also used in suspension form in the same concentration and in the similar way. Suspension of distilled water and tween 80 (0.5%) were used as control.

Anthelmintic activity was carried out by procedure (6). Five earth warms of a variety and similar size were placed in a petridish of 3.5-4 inches diameter containing 50 ml of suspension of the standard drug (piperazine citrate) at room temperature. Another set of five earthworms was kept as control in a 50 ml of distilled water and 0.5% Tween 80. Then, 50 ml suspensions of each test sample were added in to separate petri plates containing five earthworms in each. The time required for paralysis and death of the worms were noted. The death time was ascertained by placing the paralyzed worms in the warm water at 50°C which stimulated the movement if the worm was alive. The mean paralyzing time and death time were calculated and summarized in table 2.

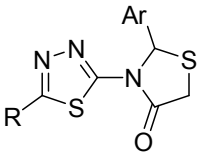
2.3.4. Statistical Analysis

All the results were expressed as mean ± Standard Error Mean (SEM). Statistical analysis was done by using one way ANOVA followed by Dunnett's 't' test and critical range for significance difference between two groups of observations was taken as *p<0.05, **p<0.01, compared with control.

3. RESULTS AND DISCUSSION

In recent decades, there has been constant interest in the chemistry of azoles containing thiadiazole fragments. Thiadiazole scaffold has played a vital role in development of several medicinal agents .They exhibit anti-inflammatory, analgesic, anthelmintic, anti-convulsant and anti-cancer activities Thiazolidinones substituted thiadiazole heterocycles have also received considerable attention during last decades as they endowed wide variety of biological activities and find wide use in medicine and industry.

In our present study we synthesised compounds (6a-6e). The compounds were synthesized starting from stearic acid. In the first step stearic acid was reacted with thiosemicarbazide in presence of sulphuric acid and the reaction mixture was refluxed for 3to 4 hours to yield thiadiazole. In the next step thiadiazole was reacted with different aromatic aldehyde in presence of methanol for approximately two hours to yield corresponding Schiff's bases. All the Schiff's bases thus obtained were reacted with thioglycolic acid to yield the title compounds. The synthesized title compounds were recrystallized and purity of the compounds was ascertained by using appropriate solvent systems (ethyl acetate: benzene: water).



Thiazolidinone
(6a-e)

The structures of all newly synthesized compounds were confirmed by suitable spectroscopic methods such as IR and NMR spectral data.

Table.2. Anthelmintic evaluation of the synthesized compounds synthesized compounds (6a-e)

Compound	Concentration (mg/mL)	Mean paralysis time (min.)± S.E.	Mean death time (min.)±S.E.
6a	2	25.18±0.05	31.44±0.01
6b	2	22.22±0.03	22.88±0.12
6c	2	18.53±0.02	24.69±0.01
6d	**2**	**16.52±0.01**	**18.23±0.05**
6e	2	21.44±0.02	26.72±0.01
Control	-	-	-
Piperazine citrate	2	24.85±0.055	25.41±0.06

*Significantly potent derivatives are shown in bold face

All the synthesized compounds were subjected to anthelmintic activity. Anthelmintic activity was done against *Eisemia foetida*. Five earth warms of a variety and similar size were placed in a petridish of 3.5-4 inches diameter containing 50 ml of suspension of each test sample. The time required for paralysis and death of the worms were noted. From the results it is evident that all the compounds exhibited moderate to good anthelmintic activity at low concentration. Most potent compound (6d) caused paralysis of 16.52±0.01 min and time of death of 18.23±0.05 min while most of the other compounds showed time of death in the range 22.88±0.12 min to 28.44±0.01. The standard drug piperazine citrate at 2 mg/ml concentration showed paralysis and death at 24.85±0.055 to 25.41±0.06 min respectively. The function of the anthelmintic drugs like piperazine is to cause paralysis of worms so that they are expelled in the feaces of man and animals. The synthesized compounds not only demonstrated this property, they also caused death of the worms, especially at 2 mg/mL as compared with the standard drug. Least active compound of the series is **6(a)** which caused paralysis in 25.18±0.05min and 31.44±0.01 death in min with p value < 0.01, compared with standard.

4. CONCLUSION

The present investigation revealed that, the compound 3-*(5-Heptadecyl-1,3,4-thiadiazol-2-yl)-2-(3-hydroxyphenyl)thiazolidin-4-one (6d)* showed potent anthelmintic activity.

5. REFERENCE

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CONFLICT OF INTEREST REPORTED: NIL ; SOURCE OF FUNDING: NONE REPORTED