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BIOLOGICAL ACTIVITY OF 3-ARYLIDENE-5(SUBSTITUTED PHENYL)-1- BENZYL-2(*3H*)-PYRROLONE DERIVATIVES

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ABSTRACT

The present study aimed to investigate the *in vitro* anthelmintic activity of 1-Benzyl-2(3H)-Pyrrolone derivatives against two species of earthworms i.e. *Pheretima posthuma* and *Perionyx excavatus*. The anthelmintic activity of eleven benzyl pyrrolone derivatives was determined by recording the mean paralyzing and death times of the worms at concentration of 2mg/mL. The screened compounds showed promising anthelmintic activities against both types of worms and the results were comparable to positive control albendazole.

KEYWORDS: Benzyl pyrrolone, *Pheretima posthuma*, *Perionyx excavatus*, Anthelmintic.

INTRODUCTION

The chemistry of nitrogen containing heterocyclic compounds such as pyrrolones has attracted more attention during recent years due to their reactivity and interesting pharmacological activities. Pyrrolones are either either Δ^1 or Δ^2 five-membered heterocyclic lactams which are present in several biologically active natural products.[1] These are reported to to possess important pharmacological activities, especially antibacterial, antifungal, anti-tubercular,[2,4] anticonvulsant activity,[5] immunosuppressive activity,[6] anticancer activity,[7] analgesic and anti-inflammatory activity,[8] etc.

As part of our research interest in nitrogen containing heterocyclic compounds and their biological activities, we have previously reported the synthesis, anti-inflammatory and antimicrobial activity of 3-arylidene-5(substituted phenyl)-1- benzyl-2(*3H*)-Pyrrolone derivatives.[3,9,10] The results of their biological activity were quite encouraging which prompted us to further screen 3-arylidene-5(substituted phenyl)-1- benzyl-2(*3H*)-Pyrrolone derivatives for *in vitro* anthelmintic activity.

MATERIALS AND METHODS

Synthesis of 3-arylidene-5(substituted phenyl)-1- benzyl-2(*3H*)-Pyrrolones (I-XI).

These compounds were first time synthesized by our group and their chemistry, anti-inflammatory and antimicrobial activity has already been published (Fig 1).[3, 9,10]

Anthelmintic activity

The title compounds (**1-XI**) were evaluated for their anthelmintic activities against two species of worms; *Pheretima posthuma* and *Perionyx excavatus*, at a concentration of 2 mg/mL.[11] Collected earthworms were washed with normal saline water to remove soil and fecal matter. Suspensions of samples were prepared by triturating synthesized compounds (100 mg) with 0.5% Tween 80 and normal saline solution and the resulting mixtures were stirred for 30 min. The suspensions were diluted to obtain conc. of 0.2% w/v of the test samples. Suspension of reference drug; Albendazole (0.2% w/v), was prepared in the same manner. Three sets of five earthworms of almost similar sizes (approx. 2 inch in length) were placed in Petri plates of 4 inch diameter containing 50 mL of suspension of test samples and reference drug. Another set of five earthworms was kept as control in 50 mL suspension of distilled water and 0.5% Tween 80. The time taken for paralysis and death of both types of worm were recorded and their mean was calculated for triplicate sets. The anthelmintic activity of the test compounds is compared with the standard drug, Albendazole and is reported as mean±SD (n=5).

RESULTS AND DISCUSSION

A helminthiasis or worm infestation is a major health problem in developing countries which have warm, moist environments with poor sanitary conditions.[12] Currently available anthelmintic agents are associated with several side effects in host and many worms have developed resistance to these drugs. Thus, there is a need to design, synthesize and develop potent and safe anthelmintic agents.

The five membered heterocyclice pyrrolone derivatives showed good to excellent anthelmintic activity at 2 mg/mL concentration. The results revealed that all the tested compounds are effective against *Pheretima posthuma* and *Perionyx excavatus*, possessing significant activity in respect of mean paralyzing and mean lethal time. The mean paralyzing time (min) of tested compounds against *Perionyx excavatus* and *Pheretima posthuma*, was observed to be 11.12-23.65 and 14.44- 25.25 min in comparison to 10.13 and 11.53 min shown by standard drug, Albendazole (Table 1). Similarly, the mean death time of pyrrolone derivatives against *Perionyx excavatus* and *Pheretima posthuma*, was noted to be 17.76-34.84 and 19.26-32.92 min, respectively. The mean death time taken by Albendazole to kill *Pheretima posthuma* and *Perionyx excavatus* was 17.92 and 15.72 min.

Thus, it can be seen that pyrrolone derivatives are more active against *P. excavatus* in comparison to *P. posthuma* in paralyzing or killing the worms. Substitution of aryl ring at 5th position and presence of electron donating groups in benzylidine ring at position 3 of pyrrolone ring seems to play an important role in exhibiting anthelminitic activity. The most potent anthelmintic activity was exhibited by compound **VIII**, which possess phenoxy phenyl group at 5th position of pyrrolone and 3,4 methylene dioxy group attached to benzylidine ring at 3rd position. However, a decrease in activity was observed when electron withdrawing groups such as chloro or nitro are added to benzylidine ring. Anthelmintic activity of pyrrolones having biphenyl or tolyl ring at 5th position showed better activity than chlrophenyl substituted derivatives.

Compd no	**R**	**R'**
I	phenyl	3,4-dimethoxy
II	phenyl	3,4,5-trimethoxy
III	phenyl	4-chloro
IV	phenyl	4-hydroxy-3-ethoxy
V	phenyl	2-thenyl
VI	phenoxy	4-chloro
VII	phenoxy	3-nitro
VIII	phenoxy	3,4-methylene-dioxy
IX	methyl	2-thenyl
X	chloro	2,6-dichloro
XI	chloro	2-thenyl

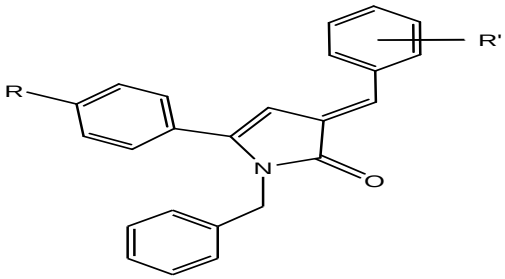

Figure 1: Structure of 1-Benzyl-2-(*3H*) pyrrolones (I-XI)

Table 1. Anthelmintic activity of Benzyl-2-(*3H*) pyrrolone derivatives (I-XI).

Compound number	Earthworm species			
	Perionyx excavatus		*Pheretima posthuma*	
	Mean paralyzing time (min)[a]	Mean death time (min)[a]	Mean paralyzing time (min)[a]	Mean death time (min)[a]
I	17.25±2.3	24.25±1.33	17.5±1.5	25.1±2.1
II	16.68±2.66	25.81±2.45	17.23±1.21	25.9±1.4
III	19.92±1.62	27.55±3.1	20.54±0.95	26.2±2.5
IV	16.98±1.98	24.76±2.2	17.8±0.76	22.12±1.1
V	17.55±2.34	24.65±1.88	19.2±1.58	24.65±1.8
VI	17.15±0.95	25.54±1.22	18.8±2.3	26.29±2.8
VII	15.87±1.1	24.98±1.1	16.2±1.6	24.98±1.1
VIII	12.12±1.42	17.76±1.4	14.44±0.92	19.26±2.2
IX	18.95±2.32	24.23±2.22	19.2±1.4	27.73±2.5
X	23.65±2.1	34.84±2.43	25.25±1.7	32.92±1.8
XI	23.43±1.55	33.56±1.43	23.65±2.32	31.6±1.33
Albendazole	10.13±0.69	15.72±0.52	11.23±0.85	17.92±0.59
Control	---------	---------	--------	--------

[a]Data are given as mean±S.D (n=5)

CONCLUSION

The present study evaluated the *in vitro* anthelmintic activity of eleven compounds containing pyrrolone ring system. The synthesized 3-arylidene-5(substituted phenyl)-1- benzyl-2(*3H*)-Pyrrolones showed good to excellent activity against two types of worms. Further studies to ascertain their mechanism of actions is currently underway in our lab.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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