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Research Article

Anthelmintic activity evaluation of 2-arylidene-4-(biphenyl-4-yl) but-3-en-4-olides

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Abstract: In vitro anthelmintic activity of a series of synthetic butenolides (**1-7**), 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides, against two species of earth worms i.e. *Pheretima posthuma* and *Perionyx excavatus* was determined. The bioactivity was determined by noting the mean paralyzing and death times of the worms at concentration 2mg/mL. All the tested compounds showed moderate to good anthelmintic activity; two compounds, **1** and **5**, were found to be potent against *Perionyx excavatus* and *Pheretima posthuma,* respectively. These butenolides exhibited significant anthelmintic activities against both types of worms and the results were comparable to that of the reference drug, Albendazole.

INTRODUCTION

Worm infestation (helminthiasis) is considered as a major health problem in developing countries especially African countries [1]. The worms enter the human body in the form of egg or larvae through different routes- like by direct contact, infected food, mosquitoes (filarial worms), soil, and water [2]. Helminthiasis results in several related diseases and is very harmful to humans and animals [3]. Few anthelmintic drugs are available in the market to kill and remove all parasitic worms from the infected host body. The regular use of these drugs leads to drug resistance in many parasitic worms. Moreover, commonly used anthelmintic drugs (e.g. Albendazole) cause several side effects like abdominal pain, vomiting, headache, dizziness, hair loss, etc. in hosts [4]. The situation is further complexed due to unavailability of an ideal anthelmintic vaccine [5]. Thus the situation requires the discovery of new anthelmintic compounds that could be used effectively to combat the problem.

Majority of clinically used drugs are of synthetic origin possessing heterocyclic ring in their structure [6]. Physiological activity of the natural lactones (butenolides) is known ever since santonin was used as an important anthelmintic and ascaricidal agent [7]. The furanone also known as butyrolactone or butenolide is a heterocyclic ring system that exhibits wide range of interesting biological activities such as anti-inflammatory, analgesic, antipyretic [8-10],antifungal [11], antitumor [12], anticonvulsant [13] and antioxidant [14]. In view of these points and in continuation of our work on synthetic butenolides [8, 9-11, 15], it was thought worthwhile to study the anthelmintic activity of a series of synthetic butenolides; 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides (**1-7**) against two species of earth worms.

MATERIALS AND METHODS

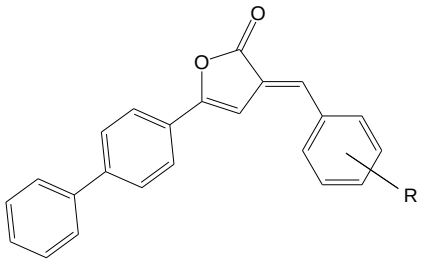
Synthesis of 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides (1-7).

These compounds **(1-7)** were synthesized by us and their chemistry, anti-inflammatory and antimicrobial activities have already been published [15] (**Figure 1**).

Evaluation of Anthelmintic activity

The title compounds (**1-7**) were evaluated for their anthelmintic activities against two species of worms; *Pheretima posthuma* and *Perionyx excavatus*, at a concentration of 2 mg/mL [16,17]. 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).



Compound	R
1	4-Methoxy
2	3,4-Dimethoxy
3	2-Acetoxy
4	3-Acetoxy
5	2,4-Dichloro
6	4-Acetoxy-3-methoxy
7	Anthryl

Figure 1: Structure of 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides (1-7).

RESULTS AND DISCUSSION

The helminthes or worms are the common cause of parasitic diseases. Anthelmintic agents kill and expel the worms from the infected host body but the extensive use of these drugs has led to the development of resistance [18] and therefore, there is a need to design, synthesize and develop potent and safe anthelmintic agents. Indian earthworms, *Pheretima posthuma* and *Perionyx excavatus,* were used for the evaluation of anthelmintic activity of the synthesized compounds as they bear anatomical and physiological resemblance to the intestinal roundworm parasites in humans.

The butenolide derivatives showed moderate to good anthelmintic activity at 2 mg/mL concentration. The results revealed that all the tested compounds are effective against *Perionyx excavatus* and *Pheretima posthuma*, 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 15.12-24.48 and 14.29-26.71 min in comparison to 10.13 and 11.53 min shown by standard drug, Albendazole (**Table 1**). The Results were comparable to that of the standard drug, Albendazole. All the worms were alive and active in the control group. The mean death time observed for Albendazole against *Pheretima posthuma* and *Perionyx excavatus* was 17.92 and 15.72 min. respectively. Compounds **5** and **6** were found to be potent in causing death of worms, Compound **5** took an average time of 25.60 and 23.16 min against *Perionyx excavatus* and *Pheretima posthuma,* respectively, and compound **6** took 20.22 and 20.74 min against *Perionyx excavatus* and *Pheretima posthuma,* respectively. The most potent compound **5** and **6** have 2,4-dichloro and 4-acetoxy-3-methoxy groups in arylidine ring, respectively. Disubstituted ring containing compounds showed good activity.

Table 1: Anthelmintic activity of butenolide derivatives (1-7).

Compound	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]
1	24.48±0.61*	32.43±0.62*	25.60±0.76*	29.80±0.22*
2	20.50±0.71*	28.65±0.54*	20.43±0.21*	27.29±0.22*
3	23.18±0.24*	35.61±0.21*	26.71±0.43*	39.86±0.87*
4	21.50±0.71*	35.14±0.39*	21.11±0.22*	30.09±0.51*
5	18.31±0.48*	25.60±0.76*	18.92±0.12*	23.16±0.32
6	15.12±0.32	20.22±0.12*	14.29±0.61	20.74±0.31
7	20.22±0.12*	27.17±0.76*	23.16±0.32*	28.10±0.22*
Albendazole	10.13±0.69	15.72±0.52	11.53±0.85	17.92±0.59
Control	---	---	---	---

[a]Data are given as mean±S.D (n=5), *p<0.05 when compared with Albendazole by Student`s t test.

CONCLUSIONS

The present study revealed the anthelmintic potential of synthetic butenolides. 2-arylidene-4-(biphenyl-4-yl)but-3-en-4-olides (**1-7**) were good in their action against the two types of worms. Two compounds, **5** and **6**, were promising in their anthelmintic action. The results indicated that furanone derivatives have the potential to paralyze and kill the parasitic worms. Further derivation of the active compounds may result in safer and potential anthelmintic agents.

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COMPETING INTERESTS: The author has declared that no competing interests exist.

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Dr. Asif Husain is currently involved in teaching and research at Jamia Hamdard (Hamdard University), Department of Pharmaceutical Chemistry, Faculty of Pharmacy in a capacity of Sr. Asst. Professor. **Dr. Husain** is working on the design and syntheses of novel prodrugs, mutual prodrugs and heterocyclic compounds. His main interest is in New Heterocyclic Chemical Entities as possible drug molecules. He was conferred `Scientist of the year award-2008` by National Environmental Science Academy, New Delhi. He has published more than 175 manuscripts in reputed National and International journals. **Dr. Husain** has attended several national and international conferences in India and abroad including USA. He is a recipient of several awards and honors including a visiting fellowship from Youngstown State University, Ohio, USA and UGC, AICTE, DST and AYUSH have funded his research. He has collaboration with different research organizations like National Institute of Health (NIH), National Cancer Institute (NCI), The National Institute of Allergy and Infectious Diseases (NIAID), USA, etc. He has guided a number of M. Pharm/Ph.D. students and authored several books in the field of pharmacy.