Scholars Academic Journal of Biosciences (SAJB) **ISSN 2321-6883 (Online)**
Sch. Acad. J. Biosci., 2015; 3(10):842-844 **ISSN 2347-9515 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Biological evaluation of 2-arylidene-4-(4-phenoxy-phenyl) but-3-en-4-olides

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Abstract: A series of 2-Arylidene-4-(4-Phenoxy-Phenyl) But-3-en-4-olides were screened against *Pheretima posthuma* earthworm for anthelmintic activity. The *in vitro* effects of compounds were evaluated at a concentration of 2mg/mL and time taken by the compounds to paralyze and subsequently kill the worms was recorded. Butyrolactone derivatives exhibited moderate to good anthelmintic activity but among all tested compounds IV was found to be the most potent against *Pheretima posthuma*. The anthelmintic activity of compound IV was observed to be comparable with positive control albendazole.
Keywords: Furnaone, *Pheretima posthuma*, Anthelmintic.

INTRODUCTION

Butenolide or butyrolactone is a privileged scaffold for the synthesis of chemotherapeutic agents [1]. It is an important structural feature of several biologically active compounds. This heterocyclic lactone owing to its useful pharmacological actions has received considerable attention in the past few decades [2]. Numerous biological activities exhibited by butenolide include anti-inflammatory, analgesic, antipyretic [3-5], antifungal [6], antitumor [7], anticonvulsant [8] and antioxidant [9] etc. Nauen *et al.;* inspired by the presence of butenolide ring system in naturally occurring stemofoline, discovered a potent and safe insecticide flupyradifurone [10]. Another natural lactone santonin is a well known example of anthelmintic and ascaricidal agent [11]. The avermectins are macro cyclic lactone derivatives which also display potent anthelmintic and insecticidal properties [12]. All these findings suggest that lactone ring might possess anthelmintic activity.

Our research group has extensively worked on this versatile moiety in order to develop potent pharmaceutical agents. We have previously reported the synthesis, anti-inflammatory and antimicrobial activity of 2-arylidene-4-(4-phenoxy-phenyl) but-3-en-4-olides [13]. The results of their biological activity were quite encouraging which promoted us to further screen the synthesized compounds for the anticipated in vitro anthelmintic activity. Therefore, the present work is aimed at the evaluation of the anthelmintic activity of 2-arylidene-4-(4-phenoxy-phenyl) but-3-en-4-olides.

MATERIALS AND METHODS

Synthesis of 2-arylidene-4-(4- phenoxy-phenyl)- but-3-en-4-olides (I-XIV).

These compounds were first time synthesized by our group and their chemistry and anti-inflammatory activity has already been published (Fig 1) [13].

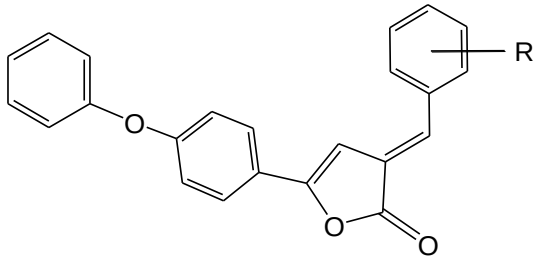
Anthelmintic activity

The title compounds (**I-XIV**) were evaluated for their anthelmintic activities against *Pheretima posthuma* worms at a concentration of 2 mg/mL [14, 15]. 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 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

The helminthes or worms are the common cause of parasitic diseases in developing nations having warm, moist environments with poor sanitary conditions [16]. 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 and therefore, there is a need to design, synthesize and develop potent and safe anthelmintic agents. Indian earthworms, *Pheretima posthuma* 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 five membered heterocyclic furanonone derivatives showed moderate to good anthelmintic activity at 2 mg/mL concentration. The results revealed that the tested compounds are quite effective against *Pheretima posthuma* possessing significant activity in respect of mean paralyzing and mean lethal time. The mean paralyzing time (min) of tested compounds against *Pheretima posthuma*, was observed to be 14.33-32.65 min in comparison to 10.13 min shown by standard drug, Albendazole (Table 1). Compound no **IV** and **VI** were found to be the most and the least potent anthelmintic compound in terms of mean paralyzing time against *Pheretima posthuma*. The Results were comparable to that of the standard drug. The mean death time observed for Albendazole against *Pheretima posthuma* was 15.72 min while Compounds **IV** took an average time of 20.35 min against *Pheretima posthuma*. It was observed that presence of an electron donating group such as methoxy group on arylidine ring increases the anthelmintic activity. Further, as the number of methoxy group increases, the anthelmintic activity also increases.



2(3*H*)Furanones (I-XIV)

Fig-1: Structure of 2(3H) furanone derivatives (1-XIV)

Compound No	R	Compound No	R
I	H	VIII	3-nitro
II	2-methoxy	IX	4-acetoxy-3-methoxy
III	3-methoxy	X	4-acetoxy-3-ethoxy
IV	3,4,5-trimethoxy	XI	2-thenyl
V	2-acetoxy	XII	3,4-methylene-dioxy
VI	4-chloro	XIII	9-anthryl
VII	2,6-dichloro	XIV	cinnamaldehyde

Table 1: Anthelmintic activity of furanone derivatives (I-XIV).

Compound number	Earthworm species (*Pheretima posthuma*)	
	Mean paralyzing time (min)[a]	Mean death time (min)[a]
I	29.15±0.76	37.54±1.98
II	16.32±1.6	24.54±1.48
III	15.4±0.82	24.11±1.5
IV	14.33±0.98	20.35±1.86
V	28.35±0.16	33.23±2.61
VI	32.65±2.12	40.23±3.65
VII	30.86±2.65	34.53±3.43
VIII	29.97±1.58	34.41±2.66
IX	28.7±1.2	38.1±3.33
X	28.4±0.51	36.92±3.12
XI	24.84±3.2	33.43±4.48
XII	26.45±1.31	38.32±2.39
XIII	23.76±2.46	30.32±1.8
XIV	25.87±2.34	33.54±2.96
Albendazole	10.13±0.69	15.72±0.52
Control	---------	---------

[a]Data are given as Mean±SD (n=5)

CONCLUSION

The present study evaluated the anthelmintic activity of fourteen 2-Arylidene-4-(4-Phenoxy-Phenyl) But-3-en-4-olides against Indian earthworms. The results indicated that furanone derivatives have the potential to paralyze and kill the parasitic worms. Synthesis of new analogs and derivatives having electron donating furanones should be attempted to obtain safe and potent anthelmintic agents based on this heterocyclic moiety.

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