

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

Asif Husain

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi, India

Email: ahusain@jamiahamdard.ac.in.

**Abstract—** A series of nine 2-arylidene-4-(4-methoxy/phenoxy-phenyl)but-3-en-4-olides (I-IX) were screened against *Pheretima posthuma* earthworm species to assess the anthelmintic activity of the synthetic derivatives. The in vitro effects of compounds were evaluated at a concentration of 2mg/mL and time taken by the derivatives to paralyze and subsequently kill the worms was recorded. Synthetic butenolide derivatives exhibited moderate to good anthelmintic activity but among all tested compounds, compound VII was found to be the most potent against *Pheretima posthuma*. The anthelmintic activity of compound VII could be comparable to that of the standard drug.

**Index Terms—** Furnaone, *Pheretima posthuma*, worms, anthelmintic.

## I. INTRODUCTION

Butenolide or butyrolactone or furanone is an important heterocyclic moiety. It is utilized for the synthesis of various biologically active compounds including chemotherapeutic agents [1]. This heterocyclic lactone owing to its useful pharmacological actions has received considerable attention during recent decades [2]. Several biological actions are shown by butenolides; anti-inflammatory, analgesic, antipyretic, antimicrobial, antitumor, anticonvulsant, antioxidant and anthelmintic, etc [3-9].

The presence of butenolide ring system in naturally occurring stemofoline inspired scientists to discover 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 macrocyclic lactones which show potential anthelmintic and insecticidal actions [12]. All these findings indicate that lactone rings possess anthelmintic activity. Our research group has extensively worked on this versatile moiety to develop agents of potential pharmaceutical interest [13,14].

In view of these points, it was considered worthwhile to evaluate the anthelmintic activity of synthetic butenolides; 2-arylidene-4-(4-methoxy/phenoxy-phenyl)but-3-en-4-olides.

Therefore, the present work is aimed at the evaluation of the anthelmintic activity of 2-arylidene-4-(4-methoxy/phenoxy-phenyl)but-3-en-4-olides against a species of Indian earth worm, *Pheretima posthuma*.

## II. MATERIALS AND METHODS

### A. Synthesis of 2-arylidene-4-(4-methoxy/phenoxy-phenyl)but-3-en-4-olides (I-X).

The synthesis of these compounds along with their chemistry, antimicrobial and anti-inflammatory activities has already been published by my group (Fig. 1) [13,14].

### B. Anthelmintic activity

The title compounds (I-IX) were evaluated for their anthelmintic activities against *Pheretima posthuma* worms at a concentration of 2 mg/mL [15,16]. 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 in Table 1.

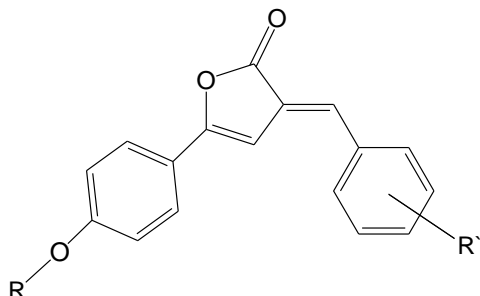
## III. RESULTS AND DISCUSSION

Indian earthworms, *Pheretima posthuma* were used for the evaluation of anthelmintic activity of the title compounds as they bear anatomical and physiological resemblance to the intestinal roundworm parasites in humans.

The parasitic worms are the 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 [17]. Thus, there is a need to search and develop new, potent and safer anthelmintic compounds.

The five membered heterocyclic furanone derivatives (I-IX) 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 was observed to be 14.33-32.65 min in comparison to 10.13 min shown by the standard drug, Albendazole (Table 1).



Compound	R	R'
I	-CH <sub>3</sub>	H
II	-CH <sub>3</sub>	4-OCH <sub>3</sub>
III	-CH <sub>3</sub>	3-NO <sub>2</sub>
IV	-CH <sub>3</sub>	4-NO <sub>2</sub>
V	-CH <sub>3</sub>	3-Cl
VI	-CH <sub>3</sub>	4-F
VII	-CH <sub>3</sub>	3-OCH <sub>3</sub> ; 4-OCOCH <sub>3</sub>
VIII	-C <sub>6</sub> H <sub>5</sub>	3,4-(OCH <sub>3</sub> ) <sub>2</sub>
IX	-C <sub>6</sub> H <sub>5</sub>	3-OCOCH <sub>3</sub>

**Figure 1:** Structure of the synthetic butenolide derivatives (I-IX).

Compounds VII and I 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 VII took an average time of 19.32 min against the worm.

It was observed that presence of electron donating group(s) such as methoxy or acetoxy group on arylidene ring increases the anthelmintic activity. Further, as the number of methoxy group increases, the anthelmintic activity also increases.

Compound	Earthworm species ( <i>Pheretima posthuma</i> )	
	Mean paralyzing time (min) <sup>a</sup>	Mean death time (min) <sup>a</sup>
I	25.53±2.52	31.23±1.32
II	22.42±1.39	30.44±2.99
III	23.85±1.84	29.32±1.32
IV	24.23±1.39	30.23±1.32
V	20.44±1.22	28.54±2.9
VI	20.75±3.3	27.98±1.66
VII	15.12±1.2	19.32±1.1
VIII	19.55±1.84	24.22±1.23
IX	19.32±0.88	26.90±1.45
Albendazole	10.13±0.69	15.72±0.52
Control	--	--

**Table 1:** Anthelmintic activity of the title compounds (I-IX).

#### IV. CONCLUSIONS

The present study evaluated the anthelmintic activity of nine synthetic butenolides; 2-arylidene-4-(4-methoxy/phenoxy-phenyl)but-3-en-4-olides (I-IX) against Indian earthworms. The results indicated that the butenolide derivatives have the potential to paralyze and kill the parasitic worms. One compound, VII, emerged as lead compound. It is conceivable that further derivatization of the lead compound could result in safer and potent anthelmintic agents.

#### ACKNOWLEDGMENT

The author is thankful to the Hamdard National Foundation (HNF), New Delhi for financial support.

#### REFERENCES

- [1] M. C. B. Jaimes, A. Ahrens, D. Pflasterer, M. Rudolph and A. S. K. Hashmi, "Synthesis of highly substituted  $\gamma$ -butyrol actones by a gold-catalyzed cascade reaction of benzyl esters," *Chemistry- A Eur. J.*, vol. 21(1), pp. 427-433, 2015.
- [2] B. Mao, K. Geurts, M. Fananas-Mastral, A. W. Van Zij, S. P. Fletcher, A. J. Minnaard and B. L. Feringa, "Catalytic enantio selective synthesis of naturally occurring butenolides via hetero-allylic alkylation and ring closing metathesis," *Organic Letters*, vol. 13(5), pp. 948-951, 2011.
- [3] M, Maaz, A. Ahmad, S. A. Khan and A. Husain, "Biological evaluation of 2-arylidene-4-(methoxyphenyl)but-3-en-4-olides," *J. Biomed. Pharm. Res.*, Vol. 4(5), pp.32-35, 2015.
- [4] M. S. Y. Khan, A. Husain, S. Sharma, "Studies on butenolides- 2-arylidene-4-(substituted aryl)but-3-en-4-olides: synthesis, reactions and biological activity," *Ind. J. Chem.*, vol. 41B, pp. 2160-2171, 2002.

- [5] S. L. Khokra, J. Monga, A. Husain, M. Vij and R. Saini, "Docking studies on butenolide derivatives as Cox-II inhibitors," *Med. Chem. Res.*, vol. 22, pp. 5536-5544, 2013.
- [6] A. Husain, S. Lal, M. M. Alam and M. Shaharyar, "Antimicrobial activity of some synthetic butenolides & their pyrrolone derivatives," *J. Enzy. Inh. Med. Chem.*, vol. 25, pp. 54-61, 2010.
- [7] S. Chimchi, M. Boccalini, B. Cosimelli, G. Viola, D. Vedaldi and F. D. Acqua, "New geiparvarin analogues from 7-(2-oxoethoxy) coumarins as efficient in vitro anti tumoral agents," *Tetrahedron Letters*, vol. 43, pp. 7473-7476, 2002.
- [8] F. Azam, I. A. Alkskas, S. L. Khokra and O. Prakash, "Synthesis of some novel N4-(naphtha [1,2-d]thiazol-2-yl)semicarbazides as potential anticonvulsants." *Eur. J. Med. Chem.*, vol. 44(1), pp. 203-211, 2009.
- [9] V. Weber, P. Coudert, C. Rubat, E. Duroux, et al., "Novel 4,5 diaryl-3-hydroxy-2(5H)-furanones as anti-oxidants and anti-inflammatory agents," *Bioorg. Med. Chem.*, vol. 10, pp. 1647-1658, 2002.
- [10] R. Nauen, P. Jeschke, R. Velten, M. E. Beck, et al., "Flupyradifurone: a brief profile of a new butenolide insecticide," *Pest Management Science*, vol. 71(6), pp. 850-862, 2015.
- [11] J. E. Shillinger, "Anthelmintic properties of Santonin," *J. Agri. Res.*, vol. 34(9), pp. 839-845, 1927.
- [12] Satoshi O, Kazuro S; Discovery, chemistry, and chemical biology of microbial products. *Pure and Applied Chemistry*, 2007; 79 (4): 581-591.
- [13] A. Husain, M. S. Y. Khan, S. M. Hasan and M. M. Alam, "2-arylidene-4(4-phenoxy-phenyl) but-3-en-4-olides; Synthesis, reactions and biological activity," *Eur. J. Med. Chem.*, Vol. 40, pp.1394-1404, 2005.
- [14] A. Husain, S. M. Hasan, A. Kumar, M. M. Alam, "Synthesis and biological evaluation of 2-arylidene-4-(4-methoxy-phenyl)but-3-en-4-olides," *Asian J. Chem.*, vol.17(3), pp. 1579-1584, 2005.
- [15] R. Dahiya and D. P. Pathak, "Synthetic studies on novel benzimidazolo peptides with antimicrobial, cytotoxic and anthelmintic potential" *Eur. J. Med. Chem.*, vol. 42, pp.772-798, 2007.
- [16] M. C. Sharma, N. K. Sahu and D. V. Kohli, "Synthesis, characterization and biological evaluation of some 1-(Nicotinylamino-2-substituted azetidine-4-ones as potential antibacterial agents," *Digest J. Nano materials Bio structures*, vol. 4, pp. 361-367, 2009.
- [17] G. Sarnim, S. T. Sanjay, A. Roshan, A. B. Vedamurthy, H. H. Joy, "Artemisia indica extracts as anthelmintic agent against *Pheretima posthuma*". *Int. J. Pharmacy and Pharm. Sci.*, vol. 5 (3), pp. 259-262, 2013.