Biological evaluation of 2-Arylidene-4-(substituted aryl)but-3-en-4-olides

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ABSTRACT

*The aim of this study was to evaluate the in vitro anthelmintic activity of 2-Arylidene-4-(substituted aryl)but-3-en-4-olides (**I-IX**) against Indian earthworm i.e. Pheretima posthuma. The anthelmintic activity of nine butenolide derivatives was determined by recording the mean paralyzing and death times of the worms at concentration of 2 mg/mL. The results indicated that few of the tested butenolide derivatives possess significant anthelmintic activity comparable to positive control, albendazole.*

Keywords: *Furanone, Pheretima posthuma, Anthelmintic, Albendazole.*

INTRODUCTION

Worm infestation is considered as a major health problem in most of the developing countries [1]. Though a good number of anthelmintic drugs are available in the market to combat the infections but some of the widely used drugs such as albendazole causes several side effects in hosts including gastrointestinal symptoms (epigastric pain, diarrhea, nausea, vomiting), headache, dizziness and allergic phenomena reactions [2].

The butenolide, also known as furanone, is a heterocyclic ring system that is associated with wide range of interesting pharmacological activities such as antitumor [3], anticonvulsant [4], antifungal [5], anti-inflammatory, analgesic, antipyretic[6-8], and antioxidant [9] etc. As part of our research interest in heterocyclic compounds, we have previously reported the synthesis, anti-inflammatory and antimicrobial activity of 2-arylidene-4-(substituted aryl)but-3-en-4-olides [10]. The results of their biological activity were quite encouraging which prompted us to further screen the synthesized compounds for *in vitro* anthelmintic activity. Therefore, the present work is aimed at the evaluation of the anthelmintic activity of 2-arylidene-4-(substituted aryl)but-3-en-4-olides.

MATERIALS AND METHODS

2-Arylidene-4-(substituted aryl)but-3-en-4-olides (I-IX): These compounds were synthesized by us and their chemistry, anti-inflammatory and antimicrobial activities have already been published [10] (Fig 1).

Anthelmintic activity: The title compounds (**I-IX**) were evaluated for their anthelmintic activities against *Pheretima posthuma* worms, at a concentration of 2 mg/mL [11,12]. 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

The anthelmintic activity of the butenolides derivatives was evaluated at 2 mg/ml concentration by recording the time taken by the compounds to paralyze and kill the *Pheretima posthuma* worms. The mean paralyzing time (min) of tested compounds against *Pheretima posthuma*, was observed to be 15.13-36.65 min in comparison to 11.53 min shown by standard drug, Albendazole (**Fig 2**).

The most and the least potent anthelmintic compound in terms of mean paralyzing time against *Pheretima posthuma*, was noted to be **I** and **VIII**. The mean death time observed for albendazole against *Pheretima posthuma* was 17.92 min. Compound **I** took an average lethal time of 21.53 min. It was observed that presence of methyl or ethyl groups on aryl rings is associated with the better activity in comparison to

chloro substituted benzene. Presence of electron donating substituents on arylidine ring also increased the anthelmintic activity of butenolides.

Compd. No.	R	R'
I	methyl	3,4,5-trimethoxy
II	methyl	4-chloro
III	methyl	9-anthryl
IV	ethyl	2-methoxy
V	ethyl	3,4,5-trimethoxy
VI	ethyl	2-thenyl
VII	chloro	3,4,5-trimethoxy
VIII	chloro	2,6-dichloro
IX	chloro	2-thenyl

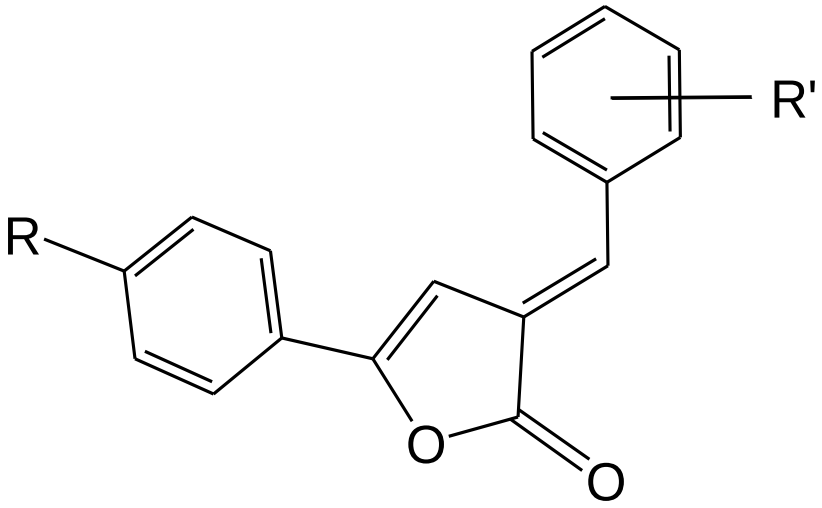

Figure 1: Structure of the substituted butenolide derivatives (**I-IX**).

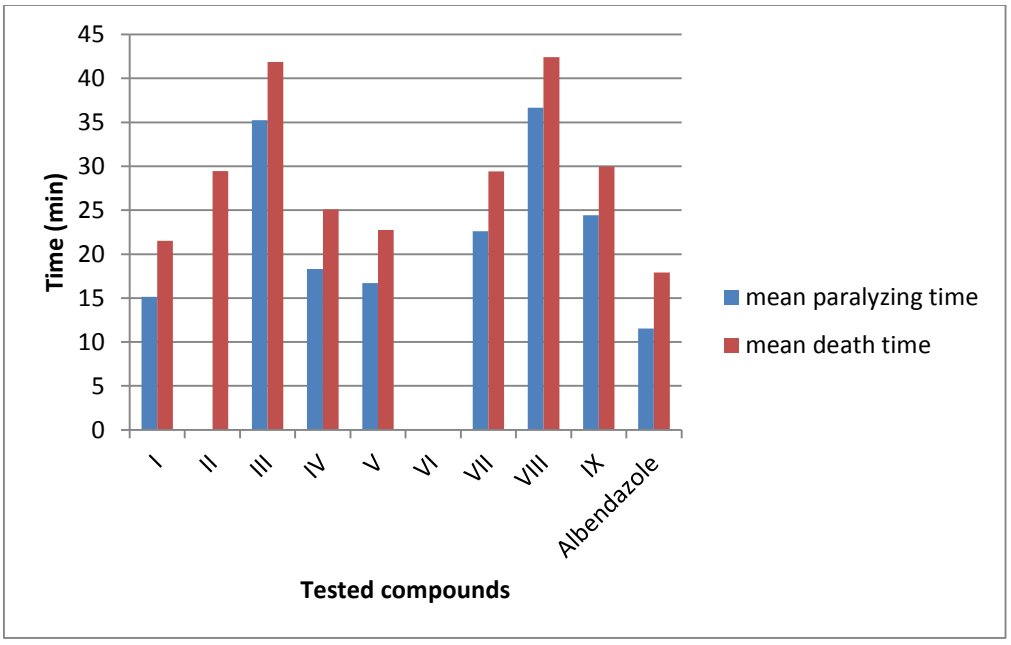

Figure 2: Anthelmintic activity of butenolide derivatives (**I-IX**).

CONCLUSION

The present study evaluated the anthelmintic activity of nine 2-Arylidene-4-(substituted aryl) but-3-en-4-olides against Indian worms. The results indicated that butenolide derivatives have the potential to paralyze and kill the parasitic worms. It was observed that presence of methyl or ethyl groups on aryl rings is associated with the better activity in comparison to chloro substituted benzene. Presence of electron donating substituents on arylidine ring also increased the anthelmintic activity of butenolides. Synthesis of new analogs and derivatives of butenolide should be attempted to obtain safer and potent anthelmintic agents based on this heterocyclic moiety.

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

REFERENCES

1. Dhar DN, Sharma RL, Bansal GC. (1982). Gastrointestinal nematodes in sheep in Kashmir. *Vet Parasitol*, 11, 271-77.
2. Selvam TP, Ramu P, Kumar AS. (2011). Synthesis, characterization and anthelmintic activity of novel 3-benzyl-2-(4'-substituted phenyl)-4(5H)-(4"-nitrophenyl amino)-1, 3-oxazolidines derivatives. *JPRHC*, 3(1), 9-14.
3. Chimchi S, Boccalini M, Cosimelli B, Viola G, Vedaldi D, Dall' Acqua F. (2002). New geiparvarin analogues from 7-(2-oxoethoxy)coumarins as efficient in vitro antitumoral agents. *Tetrahedron Lett*, 43, 7473-76.
4. Azam F, Lal S, Prakash O, Ismail A. (2009). Synthesis of some novel N4-(naphtha[1,2-d]thiazol-2-yl) semicarbazides as potential anticonvulsants. *Eur J Med Chem*, 44, 203-21.
5. Husain A, Lal S, Alam MM, Shaharyar M. (2010). Antimicrobial activity of some synthetic butenolides & their pyrrolone derivatives. *J Enz Inhib Med Chem*, 25, 54-61.
6. Husain A, Khan MSY, Hasan SM, Alam MM. (2005). 2-arylidene-4(4-phenoxy-phenyl) but-3-en-4-olides. *Eur J Med Chem*, 40,1394-1404.
7. Khan MSY, Husain A, Sharma S. (2002). Studies on butenolides: 2-arylidene-4-(substituted aryl) but-3-en-4-olides. *Indian J Chem*, 41B, 2160-71.
8. Khokra SB, Monga J, Husain A, Vij M, Saini R. (2013). Docking studies on butenolide derivatives as Cox-II inhibitors. *Med Chem Res*, 22, 5536–44.
9. Weber V, Coudert P, Rubat C, Duroux E, Goyet DV, Gardette D, Bria M, Albuisson E, Leal F, Gramain JC, Couquelet J, Madesclaire M. (2002). Novel 4,5 diaryl-3-hydroxy-2(5H)-furanones as anti-oxidants and anti-inflammatory agents. *Bioorg Med Chem*, 10, 1647-58.
10. Khan MSY, Husain A, Sharma S. Studies on butenolides 2-Arylidene-4-(substituted aryl) but-3-en-4-olides: synthesis, reactions and biological activity Ind. J. Chem. 2002, 41B, 2160-2171.
11. Dahiya R, Pathak D. (2007). Synthetic studies on novel benzimidazolopeptides with antimicrobial, cytotoxic and anthelmintic potential. *Eur J Med Chem*, 42,772–98.
12. Sharma MC, Sahu NK, Kohli DV. (2009). Synthesis, characterization and biological evaluation of some1-(Nicotinylamino-2-substituted azetidine-4-ones as potential antibacterial agents. *Digest J Nanomaterials and Biostructures*, 4, 361-67.