ISSN: 2279 - 0594

Journal of Biomedical and Pharmaceutical Research

Available Online at www.jbpr.in

CODEN: - JBPRAU (Source: - American Chemical Society)

Volume 4, Issue 5: September-October: 2015, 32-35

Research Article

BIOLOGICAL EVALUATION OF 2-ARYLIDENE-4-(METHOXYPHENYL)BUT-3-EN-4-OLIDES

Mohammad Maaz[1], Aftab Ahmad[2], Shah Alam Khan[3], Asif Husain[4]*

[1]Faculty of Medicine (Unani), Jamia Hamdard (Hamdard University), New Delhi-110062, India

[2]Health Information Technology Department, Jeddah Community College, King Abdulaziz University, Jeddah-21589, KSA

[3]Dept of Pharmacy, Oman Medical College, PO Box 620, PC 130, Muscat, Sultanate of Oman

[1]Dept of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi-110062, India

Received 10 October 2015; Accepted 28 October 2015

ABSTRACT

A series of 2-Arylidene-4-(methoxyphenyl)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, compound **II**, 2-(3,4,5-trimethoxy-benzylidene)-4-(methoxyphenyl)but-3-en-4-olide, was found to be the most potent against *Pheretima posthuma*. The anthelmintic activity of compound **II** was observed to be comparable with positive control albendazole in terms of paralytic and lethal time.

Keywords: Furnaone, Butyrolactone, *Pheretima posthuma*, Anthelmintic.

INTRODUCTION

Butenolide or butyrolactone is a versatile scaffold for the synthesis of chemotherapeutic agents[1]. It is an important structural feature of several biologically active compounds. This heterocyclic lactone exhibits important pharmacological actions and because of its chemistry and broad spectrum of activity, it has received considerable attention in the past few decades[2]. Numerous biological activities exhibited by butenolide include anti-inflammatory & analgesic[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 macrocyclic lactone derivatives which also display potent anthelmintic and insecticidal properties[12]. All these findings suggest that lactone rings 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-(methoxy phenyl)but-3-en-4-olides[13]. The results of their biological activity were quite encouraging which encouraged 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-(methoxyphenyl)but-3-en-4-olides.

MATERIALS AND METHODS:

Synthesis:

2-Arylidene-4-(methoxyphenyl)but-3-en-4-olides (I-VII)

These compounds were synthesized in our laboratories and their chemistry and anti-inflammatory activity has already been published[13] (**Figure 1**).

Anthelmintic activity:

The title compounds (**I-VII**) 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

*Corresponding author: Asif Husain | E-mail: drasifhusain@yahoo.com

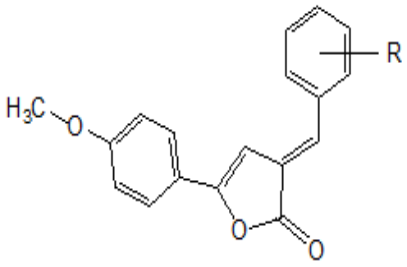
matter. Suspensions of samples were prepared by triturating synthesized compounds (100 mg) with 0.5% Tween 80 and normal saline solution and the resulting mixtures were stirred for 30 min. The suspensions were diluted to obtain conc. of 0.2% w/v of the test samples. Suspension of reference drug; Albendazole (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 anthelminitic activity of the synthesized compounds as they bear anatomical and physiological resemblance to the intestinal roundworm parasites in humans.

The five membered heterocyclic furanone 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 14.12-24.83 min in comparison to 10.13 min shown by standard drug, Albendazole (**Table 1**).

Compound no **II** and **V** 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 **II**, 2-(3,4,5-trimethoxy-benzylidene)-4-(methoxyphenyl)but-3-en-4-olide, took an average time of 18.25 min to kill worms. It was observed that presence of an electron donating group such as methoxy group on arylidine ring increases the anthelmintic activity while substitution with an electron withdrawing groups reduces the activity.



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

Compound No	R
I	3,4-dimethoxy
II	3,4,5-trimethoxy
III	2-acetoxy
IV	4-chloro
V	2,6-dichloro
VI	2-thenyl
VII	4-dimethylamine

Figure 1: Structure of 2-Arylidene-4-(methoxyphenyl)but-3-en-4-olides (I-VII).

Table 1: Anthelmintic activity of compounds (I-VII)

Compound No.	Earthworm species (*Pheretima posthuma)*	
	Mean paralyzing time (min)[a]	Mean death time (min)[a]
I	19.32±0.88	26.90±1.45
II	14.12±1.2	18.25±1.1
III	20.4±1.22	28.54±2.9
IV	22.42±1.39	31.23±1.32
V	24.83±2.52	30.44±2.99
VI	20.75±3.3	27.98±1.66
VII	18.53±1.84	23.22±1.23
Albendazole	10.13±0.69	15.72±0.52
Control	---------	---------

[a]Data are given as mean±S.D (n=5)

CONCLUSION:

The present study evaluated the anthelmintic activity of seven 2-arylidene-4-(methoxy phenyl)but-3-en-4-olides against an Indian earthworm (*Pheretima posthuma*). 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 safer and potent anthelmintic agents based on this heterocyclic moiety.

Acknowledgements

One of the authors (AH) is thankful to Hamdard National Foundation (HNF), New Delhi for financial support.

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES:

1. Blanco Jaimes MC, Ahrens A, Pflästerer D, Rudolph M, Hashmi ASK; Synthesis of highly substituted γ-butyrolactones by a gold-catalyzed cascade reaction of benzyl esters. Chemistry-A European Journal, 2015; 21(1): 427-433.
2. Mao B, Geurts K, Fananas-Mastral M, Van Zij AW, Fletcher SP, Minnaard AJ, Feringa BL; Catalytic enantioselective synthesis of naturally occurring butenolides via hetero-allylic alkylation and ring closing metathesis**.** Organic Lett., 2011; 13(5): 948-951.
3. Husain A, Khan MSY, Hasan SM, Alam MM; 2-arylidene-4(4-phenoxy-phenyl) but-3-en-4-olides. Eur. J. Med. Chem., 2005; 40: 1394-1404.
4. Husain A, Alam MM, Siddiqui N; Synthesis, reactions and biological activity of 3-arylidene-5-(4-methylphenyl)-2(3*H*)-furanones. J. Serb. Chem. Soc*.,* 2009; 74: 103-115.
5. Khokra SB, Monga J, Husain A, Vij M, Saini R; Docking studies on butenolide derivatives as Cox-II inhibitors. Med. Chem. Res*.,* 2013; 22: 5536–5544.
6. Husain A, Lal S, Alam MM, Shaharyar M; Antimicrobial activity of some synthetic butenolides & their pyrrolone derivatives. J. Enzy. Inh. Med. Chem*.,* 2010; 25: 54-61.
7. Chimchi S, Boccalini M, Cosimelli B, Viola G, Vedaldi D, Dall' Acqua F; New geiparvarin analogues from 7-(2-oxoethoxy)coumarins as efficient in vitro antitumoral agents. Tetrahedron Lett*.,* 2002; 43: 7473-7476.
8. Faizul Azam Lal S, Prakash O, Ismail A;. Synthesis of some novel *N4*-(naphtha[1,2-d]thiazol-2-yl) semicarbazides as potential anticonvulsants. Eur. J. Med. Chem*.,* 2009; 44, 203-221.
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;. Novel 4,5 diaryl-3-hydroxy-2(5*H*)-furanones as anti-oxidants and anti-inflammatory agents. Bioorg. Med. Chem., 2002; 10: 1647-1658.
10. Nauen R, Jeschke P, Velten R, Beck ME, Ebbinghaus-Kintscher U, Thielert W, Wölfel K, Haas M, Kunz K, Raupach G; Flupyradifurone: a

brief profile of a new butenolide insecticide. Pest Managment Science, 2015; 71(6): 850-862.

11. Shillinger JE; Anthelmintic properties of Santonin. J. Agriculture Res., 1927; 34(9): 839-845.

12. Satoshi O, Kazuro S; Discovery, chemistry, and chemical biology of microbial products. Pure and Applied Chemistry, 2007; 79 (4): 581-591.

13. 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.

14. Dahiya R, Pathak D; Synthetic studies on novel benzimidazolopeptides with antimicrobial, cytotoxic and anthelmintic potential. Eur. J. Med. Chem., 2007; 42, 772–798.

15. Sharma MC, Sahu NK, Kohli DV; Synthesis, characterization and biological evaluation of some 1-(Nicotinylamino)-2-substituted azetidine-4-ones as potential antibacterial agents. Digest J. Nanomaterials and Biostructures, 2009; 4: 361-367.

16. Sarnim G, Sanjay ST, Roshan A, Vedamurthy AB, Joy HH; *Artemisia indica* extracts as anthelminthic agent against *Pheretima posthuma.* Int. J. Pharmacy Pharm. Sci., 2013; 5 (Suppl 3): 259-262.