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Preliminary investigations on the synthesis and antitumor activity of 3(2*H*)-furanones

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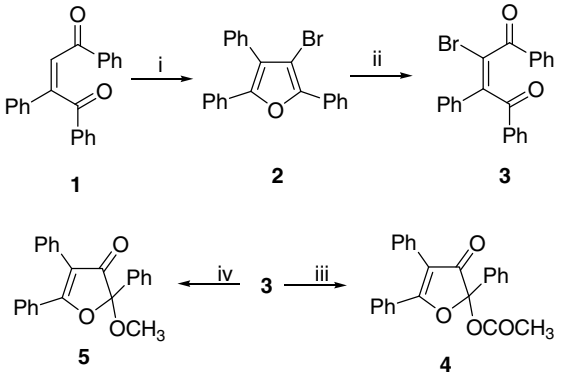
ABSTRACT

Two triaryl-3(2*H*)-furanones were synthesized and their antitumor activity was evaluated. These compounds inhibited the proliferation of DLA cell line in vitro. In vivo studies also showed that these compounds were active against tumor cell proliferation.

3(2*H*)-Furanones widely occur in nature and possess unusual range of biological activities.[1] Their antiallergenic,[2] antibacterial,[3] antifungal,[4] and antidiabetics[5] activities are well established. They are also a promising candidate as insecticides,[6] antioxidants,[7] herbicides[8] and plant growth regulators.[9] Several furanones exhibit cytotoxic and tumor inhibitory properties toward a variety of malignancies.[10] 5-Aryl-2,2-dialkyl-4-phenyl-3(2*H*)-furanones are found to be highly potent and selective COX-II inhibitors.[11] The easily oxidisable nature of the furanones results in their mutagenic and anticarcinogenic activity.[12] The antiproliferative activity of several 3(2*H*)-furanones were evaluated against leukemia-, carcinoma-, neuroblastoma-, and sarcoma-derived human cell lines in comparison to the natural compound geiparvarin.[13]

The 3(2*H*)-furanone ring system may be considered as the determinant pharmacophore for antitumor activity. Interest in the total synthesis of natural product antitumor agents having 3(2*H*)-furanone ring system as a central structural unit has led to the development of efficient methods for the synthesis of a variety of simple 3(2*H*)-furanones. In an attempt to model the biological activity of naturally occurring furanones, we selected two molecules for this preliminary study.

A modified protocol for the generation of 3(2*H*)-furanones is presented in Scheme 1. Conventionally, a 30% solution of HBr in acetic acid is employed to effect the cyclization of 1,2,4-triaryl-but-2-ene-1,4-diones to the corresponding 3-bromofurans in moderate yields and concentrated nitric acid is used to oxidize the bromofuran.[14,15] We found that under these conditions, the product recovery is very poor and many functional groups are not compatible with concentrated nitric acid. So, we attempted to develop a more efficient and milder procedure for the generation of bromodibenzoylalkenes. Passing dry $HBr_{(g)}$ directly into a solution of 1,2,4-triphenylbut-2-ene-1,4-dione **1**[16] in acetic acid resulted in the generation of 3-bromo-2,4,5-triphenylfuran **2** in high yields.[18] Earlier, we had established that ammonium nitrate in aqueous acetic acid (80%, v/v) is a mild and environmentally friendly reagent for the chemoselective oxidative ring cleavage



Scheme 1. Reagents and conditions: (i) $HBr_{(g)}$, AcOH; (ii) NH_4NO_3, AcOH; (iii) Ac_2O, H_2SO_4; (iv) $HCl_{(g)}$, MeOH.

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of furans.[17] When we applied this protocol for the oxidation of 3-bromo-2,4,6-triphenylfuran, (*E*)-2-bromo-1,3,4-triphenylbut-2-ene-1,4-dione **3** was generated in excellent yields.[19] The furanones, 2-acetoxy-2,4,5-triphenyl-2*H*-furan-3-one **4** and 2-methoxy-2,4,5-triphenyl-2*H*-furan-3-one **5**, were prepared according to the reported procedures.[15] It may be noted that different substituents may be introduced on any of the aryl groups or at the 2-position of the furanone ring system. Thus, the improved procedure developed by us has paved way to the generation of several 3(2*H*)-furanones in multigram quantities.

The antitumor activity of these furanones was evaluated via both in vivo and in vitro methods. Oral administration of compounds **4** and **5** to tumor bearing mice showed a significant decrease in the tumor growth (Fig. 1). This suggests that the furanones efficiently inhibit tumor cell proliferation in vivo.[20]

The anti-proliferate effect of these compounds was studied using DLA cells. These in vitro experiments showed that the presence of compounds **4** and **5** significantly reduced the proliferation of DLA cells (Figs. 2 and 3).[21]

In conclusion, we synthesized two triaryl 3(2*H*)-furanones and evaluated their antitumor activity. Both the in vivo and in vitro studies showed that these compounds were active against tumor cell proliferation.

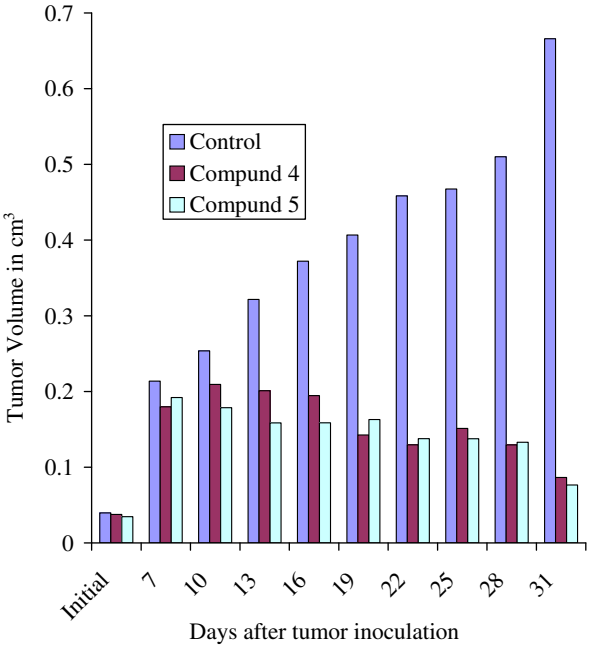

Figure 1. Antitumor activity of compounds **4** and **5** (1 mg/kg of body weight) (in vivo).

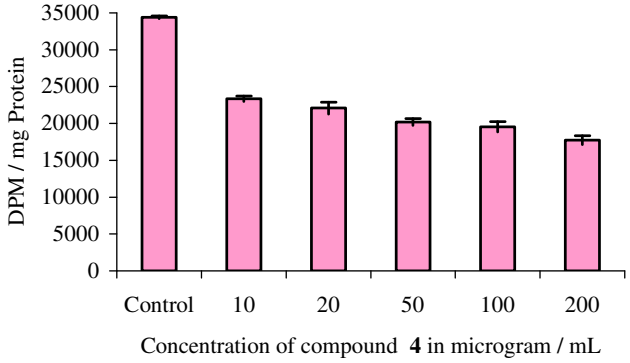

Figure 2. Effect of compound **4** on DNA synthesis of DLA cell line (in vitro).

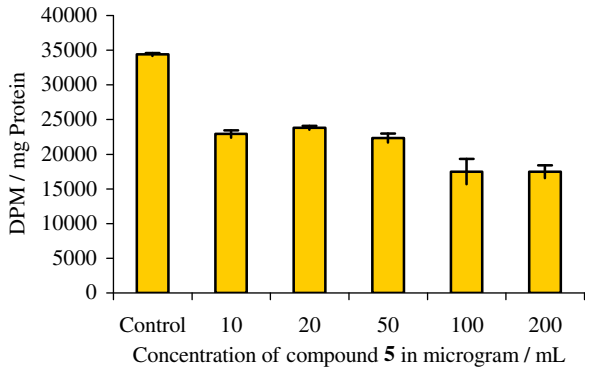

Figure 3. Effect of compound **5** on DNA synthesis of DLA cell line (in vitro).

Acknowledgments

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References and notes

1. (a) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423; (b) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707; (c) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1869; (d) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377.
2. Perold, G. W.; Muller, J. C.; Ourisson, G. *Tetrahedron* **1972**, *28*, 5797.
3. Nineham, A. W.; Raphel, R. A. *J. Chem. Soc.* **1949**, 118.
4. Dal Pozzo, A.; Danci, A.; Meneghini, E. *Bull. Chim. Farm.* **1974**, 113.
5. Felman, S. W.; Jirkovsky, I. L.; Memoli, K. A. US Patent No. US 5314913, 1992.
6. Lee, J.; Choe, I.; Kim, H.; Choe, K. Korean Patent No. KR 119908, 1994.
7. Koga, T.; Moro, K.; Matsudo, T. *J. Agric. Food. Chem.* **1998**, *46*, 946.
8. Rebstock, T. L.; Sell, H. M. *J. Chem. Soc.* **1952**, *74*, 274.
9. Iino, Y.; Tanaka, A.; Yamashita, K. *Agric. Biol. Chem.* **1972**, *36*, 2505.
10. Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147.
11. (a) Shin, S. S.; Noh, M. S.; Byun, Y. J.; Choi, J. K.; Kim, J. Y.; Lim, K. M.; Ha, J. Y.; Kim, J. K.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 165; (b) Shin, S. S.; Byun, Y.; Lim, K. M.; Choi, J. K.; Lee, K. W.; Moh, J. H.; Kim, J. K.; Jeong, Y. S.; Choi, Y. H.; Koh, H. J.; Park, Y. H.; Oh, Y. I.; Noh, M. S.; Chung, S. *J. Med. Chem.* **2004**, *47*, 792.
12. Smeds, A.; Vartiainen, T.; Maki-Paakkanen, J.; Kroberg, L. *Environ. Sci. Technol.* **1997**, *31*, 1033.
13. Chimichi, S. O.; Boccalini, M. O.; Cosimelli, B.; Dall'Acqua, F.; Viola, G. *Tetrahedron* **2003**, *59*, 5215.
14. Lutz, R. E.; Tyson, W. R.; Sanders, A. G.; Fink, C. K. *J. Am. Chem. Soc.* **1934**, *56*, 2679.
15. Kuhn, L. P.; Lutz, R. E.; Bauer, C. R. *J. Am. Chem. Soc.* **1950**, *72*, 5058.
16. Lutz, R. E.; McGinn, C. E. *J. Am. Chem. Soc.* **1942**, *64*, 2585.
17. Rappai, J. P.; Prathapan, S.; Vishnu Unni, M. V.; Unnikrishnan, P. A. *Synth. Commun.* **2007**, *37*, 569.
18. Procedure for the synthesis of compound **2**. Dry $HBr_{(g)}$ was passed through a solution of 1,2,4-triphenylbut-2-ene-1,4-dione **1** (9.4 g, 30 mmol) in acetic acid for about 30 min. The solid that separated out was filtered and purified by recrystallization from a 1:1 mixture of methanol and chloroform to yield 3-bromo-2,4,5-triphenylfuran **2** (7.8 g, 70%). Its spectral and analytical data were found to be identical to the one reported in the literature.[14]
19. Procedure for the synthesis of compound **3**. A mixture of 3-bromo-2,4,5-triphenylfuran **2** (3.75 g, 10 mmol), aqueous acetic acid (10 mL, 80%, v/v) and ammonium nitrate (1.3 g, 12.5 mmol) was heated at reflux for 90 min. The reaction mixture was cooled, diluted with cold water and filtered. The solid that separated out was filtered and purified by recrystallization from methanol to yield (*E*)-2-bromo-1,3,4-triphenylbut-2-ene-1,4-dione **3** (2.9 g, 74%). Its spectral and analytical data were identical to those reported in the literature.[14,15]
20. Inbred male Swiss albino mice (6 mices/group) were used to study the in vivo antitumor activity of compounds **4** and **5**. Solid tumor was induced by subcutaneous injection of 1×10^6 Daltons Lymphoma Ascites (DLA) cells. After seven days of tumor induction, experimental groups received the compounds (1 mg/kg body weight) orally while controls received sterile phosphate buffer saline. Tumor development was measured after each three days using vernier calipers and tumor volume calculated.
21. The DLA (1×10^6) cells were cultured in vitro in presence of test compounds **4** and **5** with concentrations varying from 10 to 200 μg. Thymidine (0.01 μCi) was added to all the plates. One set was kept as control. After 24 h of incubation, cells were separated by centrifugation. Cells were digested overnight using sodium hydroxide. Radioactivity was measured by using a liquid scintillation counter.