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DIENYL DIKETONES AS ANTICANCER AGENTS: SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME AROMATIC DERIVATIVES

Po Chuen Shieh[a]* and Chi Wi Ong[b]

[a] Department of Pharmacy, Tajen Junior College of Pharmacy, 20, Wei-hsin Road, Yen-pu 907, Ping-Tung, Taiwan.
[b] Department of Chemistry, National Sun Yat Sen University, Kaoshiung, Taiwan 804

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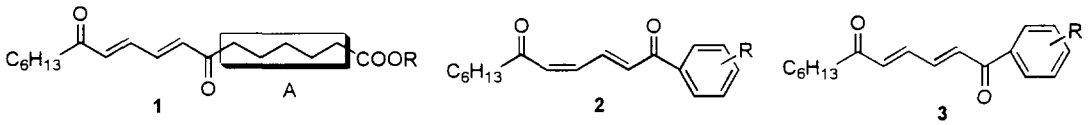
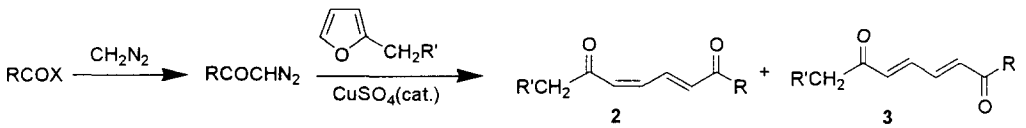
Abstract: Aiming to develop anticancer agents, synthesis and *in vitro* evaluation of aromatic dienyl diketone derivatives were carried out. All the aromatic (*Z,E*)-dienyl diketones synthesized exhibit strong *in vitro* inhibition of tumor cell growth against Colon cell line.

Ostopanic acid **1** with a unique (*E, E*)-dienyl diketone chromophore shows interesting cytotoxicity against P-388 lymphocytic leukemia *in vitro*.[1] Previous researches have been directed towards the synthesis of ostopanic acid,[2,3] but biological activity of the dienyl diketone system has not been systematically explored. In an effort to develop novel anticancer agents based on the dienyl diketone chromophore, we have synthesized the (*Z-E*)- and (*E, E*)-isomer **2** and **3**, and explored the effect of incorporation of an aromatic ring. It was envisioned that the aromatic ring can provide some rigidity to the molecule and at the same time increases hydrophobicity of the molecules.



We have previously synthesized aromatic dienyl diketone[4] using the method of Wenkert[5] from aromatic diazo ketone and 2-alkylfuran. This method was found to give a mixture of (*Z, E*)-dienyl diketone and (*E, E*)-dienyl diketone with preponderance of the (*E, E*)-isomer during prolong reaction time or the addition of iodine. The diazo carbonyl compounds were prepared from the corresponding acid chlorides with diazomethane. Thus reaction of methyl 4-diazoacetobenzoate with 2-hexylfuran gave rise to a mixture of (*Z, E*)-dienyl ketone and (*E, E*)-dienyl ketone **2a** and**3a**.

Scheme 1. Preparations of 1,6-Dioxo-2,4-Dienes from Diazo Ketones and Furan Derivatives



a:R=4-$MeO_2CC_6H_4$, R'=C_5H_{11} b:R=C_6H_5, R'=CH_3 c:R=C_6H_5, R'=H d:R=C_2H_5, R'=H e:R=C_2H_5, R'=*i*-C_3H_7

Evaluation of *in vitro* cytotoxicity[6] (Table 1) against KB, HEP-2, Hela and Colon-205 revealed that **2a** having the (*Z, E*)-configuration shows selective inhibition against Colon-205 tumor cell growth, whereas the (*E, E*)-isomer **3a** is inactive towards the cell lines tested. Of interest, the (*Z, E*)-dienyl diketone aromatic analogue **2a** was found to be the active isomer. It has been reported that (*Z, E*)-geometry is required for a favorable acid catalyzed intramolecular cyclization to form furanonium intermediate[4] which can undergo

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reversible nucleophilic addition. [4] Antitumor effect exhibited by **2a** might have resulted from the acid catalyzed covalent binding of furanonium intermediate with nucleophilic DNA residue. This suggests that it is promoted in tumor cells with low pH. This assumption is in close correlation to the antitumor activity of pyrrolo(1,4)benzodiazepines which resulted from the covalent binding of iminium intermediate with the 2-amino group of guanine residue of DNA, whereby inhibiting DNA directed RNA synthesis.[7] Furthermore, the selective inhibition against colon tumor cell growth by **2a** is noteworthy.

Table 1:In Vitro Cytotoxicity of Compounds

Compounds	LD_{50}(μg/ml)				Compounds	LD_{50}(μg/ml)			
	Hela	Hep-2	Colo-205	KB		Hela	Hep-2	Colo-205	KB
2a	>10[a)]	>10	0.8	>10	**2d**	>10	>10	>10	>10
2b	>10	>10	1.0	>10	**2e**	>10	>10	>10	>10
2c	>10	>10	1.0	0.8	**3a**	>10	>10	>10	>10

a)Drug concentration 0f 10 μg/ mL did not inhibit the growth of cells by 50% and considered inactive.

The above results prompted us to further examine the structural requirement for biological activity and selectivity, which includes: (1) the requirement of carboxylate group in the benzene ring and (2) the chain length of alkyl group. Furthermore, we concentrated our attention on the (*Z, E*)-isomer. Reactions of α-diazoacetophenone with 2-ethylfuran and 2-methylfuran for short reaction times gave **2b** and **2c** as the major products, respectively. The compounds **2b** and **2c** exhibited similar selectivity for *in vitro* cytotoxicity against colon cancer cell line (Table 1). Only the simplest aromatic (*Z, E*)-dienyl diketone **2c** also showed potent inhibition against KB cell line.

Next, the structural requirement for an aromatic ring in the (*Z, E*)-dienyl diketone for the expression of biological activity was also studied. Reactions of diazoacetate and 1-diazo-2-oxo-3-methylbutane with 2-ethyl furan gave the (*Z, E*)-dienyl diketones **2d** and **2e** respectively, after short reaction times. These compounds were found to be inactive towards all the cell lines tested.

In our opinion, the presence of aromatic ring in (*Z, E*)-dienyl diketone is important for cytotoxic activity. Work is in progress to design, synthesize, and evaluate (*Z, E*)-dienyl diketones linked to groove binding aromatic moities.

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