Synthesis, Cytotoxicity and Antitumor Activity of 2,3-Diarylcyclopent-2-ene-1-ones

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INTRODUCTION

In our preceding paper we have reported compound 1a as a potent cytotoxic agent in both murine and human tumor cell lines (Nam et al., 2002a). Further manipulation carried out on this small molecule revealed that substitution of the electron-withdrawing groups like bromine into α-carbon led to compound 1a with decreased cytotoxicity. Replacement of the a-bromide by a methyl group also decreased activity. However, when the phenyl ring was attached at this position, compound 1d was found to have twice activity of 1a. Thus, the phenyl group seemed to be favorable for the bioactivity of this compound. It was postulated that the phenyl moiety probably enhanced interaction of the compound with a complementary aryl moiety at a binding site on receptors through a van der Waals bonding. If that, introduction of different substituents on this phenyl ring may significantly affect the bioactivity of the compound. In this study, we have prepared a series of compound 2 and found that the 3,4,5-trimethoxy substituent deemed optimal for this formula's activity. We fixed this substituted pattern on this ring and continued to investigate various substitutes for the 2,5-dihydroxy moiety. In this paper we would like to detail the results obtained from these investigations.

RESULTS AND DISCUSSION

Chemistry

The synthesis of a series of 3-(2,5-dihydroxyphenyl)-2-arylcyclopent-2-ene-1-one (2a-2f) was completed using the same method described in our previous report (Nam et al., 2002a). Briefly, alkylation of dimethyl malonate with 4, which was prepared as detailed in literature (Nam et al., 2002a), gave 5. The alkylation was found most effective by slow addition of a solution of 4 in acetone to a mixture of dimethyl malonate and K₂CO₃ in anhydrous acetone at 45°C. Acetylation of 5 to give 6 was mediated by
MgBr₂·Et₂O using pyridine as base. The optimal procedure for this acetylation involved preparation of the Mg enolate, using MgBr₂·Et₂O-pyridine in a mixture of MeCN and THF at 0°C, followed by reaction with acetyl chloride at 30°C. THF was used as a co-solvent to prevent acetonitrile from freezing. This procedure gave 6 in good yield (49-77%). Cyclization of 6 was readily achieved using TEA as base. Decarboxylation of 7 was effected by refluxing in 3M H₂SO₄-AcOH at 90°C for 10 h. Conveniently, under this condition both benzyl groups used to protect the phenol hydroxyls were removed to afford 2 in one step.

A series of 3-aryl-2-(3,4,5-trimethoxyphenyl)cyclopent-2-ene-1-one (3a-3i) was obtained by yet the same method for 2, starting from bromoacetophenones (10). Most of the bromoacetophenones 10 were commercially available. Those not purchasable were easily synthesized by bromination of the corresponding acetophenones, protected as benzylacetophenone wherever the phenolic hydroxy group(s) was present (Nam et al., 2001a).

Alkylation of dimethyl manolate with 10 gave the intermediates 11 which were then acylated with 3,4,5-trimethoxyphenylacetyl chloride to give 12. Subsequent cyclization of 12 led to the pentenones 13. Decarboxylation of 13 and concomitant removal of the benzyl protecting group(s) furnished the final products 3a-3i. Compound 3j was obtained in moderate yield (68%) by reduction of the nitro group in 3i using Zn/AcOH.

Cytotoxicity and antitumor activity

We reasoned that if the cytotoxicity of compound 1d was potentiated by enhancement of the binding affinity of the compound toward the complementary hydrophobic moiety at a binding site on receptors through a van der Waals bonding, the introduction of the electron rich groups should be beneficial. Therefore we focused on these kinds of substituents. Accordingly a series of 2's analogues, compounds 2a-f, having various electron releasing groups (ERGs) were prepared. For the purpose