

Catalysis by molecular iodine: A rapid synthesis of 1,8-dioxo-octahydroxanthenes and their evaluation as potential anticancer agents

Naveen Mulakayala^a, P.V.N.S. Murthy^b, D. Rambabu^{a,b}, Madhu Aeluri^a, Raju Adepu^a, G.R. Krishna^c, C. Malla Reddy^c, K.R.S. Prasad^b, M. Chaitanya^d, Chitta S. Kumar^d, M.V. Basaveswara Rao^{e,*}, Manojit Pal^{a,*}

^a Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, Andhra Pradesh, India

^b Department of Chemistry, K L University, Vaddeswaram Guntur 522 502, Andhra Pradesh, India

^c Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, West Bengal 741 252, India

^d Department of Biochemistry, Sri Krishnadevaraya University, Anantapur 515 003, Andhra Pradesh, India

^e Department of Chemistry, Krishna University, Machilipatnam 521 001, Andhra Pradesh, India

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ABSTRACT

Molecular iodine facilitated the reaction of 5,5-dimethyl-1,3-cyclohexanedione with aromatic aldehydes in *iso*-propanol affording a variety of 1,8-dioxo-octahydroxanthenes in high yields. Most of the compounds synthesized showed good anti-proliferative properties *in vitro* against three cancer cell lines and 9-(2-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione possessing a 2-hydroxy phenyl group at C-9 position was found to be promising. Further structure elaboration of the same compound and the crystal structure analysis and hydrogen bonding patterns of another compound that is, 9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione prepared by using this methodology is presented.

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Xanthene derivatives have attracted considerable interest because of their various pharmacological properties such as anti-bacterial, antiviral and anti-inflammatory activities.^{1,2} Apart from their use as valuable synthetic precursors for many organic compounds³ and dyes⁴ they also found uses in laser technologies,^{5a} and fluorescent materials for visualization of biomolecules.^{5b} While the cancer cell cytotoxicity of xanthene derivatives **A** (Fig. 1) has been documented^{6a} recently the anticancer properties of their saturated analogs for example, 1,8-dioxo-octahydroxanthenes **C** designed via **B** (Fig. 1) has not been investigated earlier. Moreover, in view of the fact that cancer is the second leading cause of death^{6b} worldwide there is a need for the identification of new and more effective anticancer agents. This prompted us to synthesize and assess the anticancer potential of 1,8-dioxo-octahydroxanthenes *in vitro*.

One of the commonly used methods reported for the synthesis of xanthene derivatives involved the condensation of aldehyde with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione. This reaction can be carried out in the presence of protonic acids⁷ or a range of Lewis acids such as $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$,⁸ $\text{FeCl}_3 \cdot 8\text{H}_2\text{O}$,⁹ NaHSO_4 ,¹⁰ or heterogeneous catalysts, such as Dowex-50W,¹¹

$\text{NaHSO}_4 \cdot \text{SiO}_2$,¹² silica sulfuric acid,¹³ polyaniline *p*-toluenesulfonate,¹⁴ $\text{PPA} \cdot \text{SiO}_2$,¹⁵ TiO_2/SO_4 ,^{2–16} Amberlyst-15,¹⁷ $\text{SbCl}_3/\text{SiO}_2$,¹⁸ or Fe^{3+} -montmorillonite.¹⁹ Among the other catalysts used include trimethylsilylchloride,²⁰ *p*-dodecylbenzenesulfonic acid,^{21,22} triethylbenzylammonium chloride²³ or $\text{NH}_2\text{SO}_3/\text{SDS}$.²⁴ Additionally, the above condensation reaction can also be carried out in ionic liquid²⁵ or ethylene glycol.²⁶ However, some of these methodologies suffer from disadvantages, such as low yields,^{14,15} prolonged reaction time,^{8,12,21–23} harsh reaction conditions,⁷ and the requirement of excess catalysts²⁰ or special apparatus.²² Recently, iodine being an inexpensive and commercially available reagent have attracted considerable interest due to its non-hazardous nature and efficiency in various organic transformations.²⁷ Due to our continuing interest in the use of iodine as a reagent or catalyst²⁸ we have observed that 5,5-dimethyl-1,3-cyclohexanedione (**1**) undergoes smooth condensation with aromatic aldehydes (**2**) in the presence of elemental iodine to give 1,8-dioxo-octahydroxanthene derivatives (**3**) (Scheme 1) within short period of time. Herein we report our preliminary results on the development of an iodine-mediated simple and highly efficient method for synthesis of our target xanthene derivatives **C** (or **3**) and their evaluation as potential anticancer agents. To the best of our knowledge synthesis of xanthenes using such a methodology and their anticancer properties has not been disclosed earlier.

* Corresponding authors. Tel.: +91 40 6657 1500; fax: +91 40 6657 1581.

E-mail address: manojitpal@rediffmail.com (M. Pal).

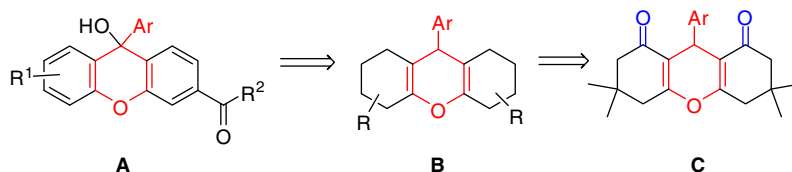


Fig. 1. Design of 1,8-dioxo-octahydroxanthenes (C) from the known cytotoxic xanthenes (A) as potential anticancer agents.

The reaction was carried out using a mixture of compound **1** (2.0 equiv) and aldehyde **2** (1.0 equiv) in the presence of iodine (0.2 equiv) in *i*-propanol (3.0 mL) at 70–80 °C. The reaction proceeded smoothly and was completed within 20 min to give the 9-aryl substituted xanthenes derivatives **3** in good to excellent yields (Table 1). A range of functionalized aromatic aldehydes including mono and disubstituted derivatives were employed in the present iodine-mediated condensation reaction. Both electron-donating groups for example, fluoro (entry 2), chloro (entry 3), bromo (entries 4, 10 and 11), methyl (entry 9), hydroxy (entries 5, 6, 10, 13 and 14) or methoxy (entries 8, 14 and 15) and electron-withdrawing group for example, nitro (entries 7 and 12) present in the aldehyde were well tolerated. All the 1,8-dioxo-octahydroxanthenes **3** prepared were well characterized by spectral (¹H NMR, IR and MS) data. The appearance of (i) a singlet in the region 4.6–4.8 δ for C-9 proton and two singlets in the region 0.99–1.15 δ each for two methyl hydrogens in the ¹H NMR spectra and (ii) IR signals in the region 1680–1660 cm^{−1} for carbonyl group characterized the compound **3**. Additionally, the molecular structure of a representative compound for example, **3i** was established unambiguously by single crystal X-ray diffraction (Fig. 2).²⁹ Further, crystal structure analysis was carried out to understand the packing and/or hydrogen bonding patterns in crystal of these molecule and results are summarized in the following section.

Compound **3i** crystallizes in orthorhombic Pca2 (1) space group with two molecules in the asymmetric unit (Z: 11 Z': 0) (Fig. 3). The two *p*-methoxyphenyl rings of the molecules in the asymmetric unit are found to be not in coplanar with 3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione. The torsion angles of the *p*-methoxyphenyl ring with 3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione are (C5–C6–C7–C18 76.9 (5), C18–C7–C8–C9 –78.0(4) and C42–C31–C32–C33 77.5(4) and C29–C30–C31–C42 –77.9(5). The two molecules in the asymmetric unit form same hydrogen bonding patterns in the crystal structure. They also participated in weak Vander-Waal interactions through the keto functional group, and are stabilized by methylene interactions. These interactions propagated in 3D network packing as shown in Figure 4.

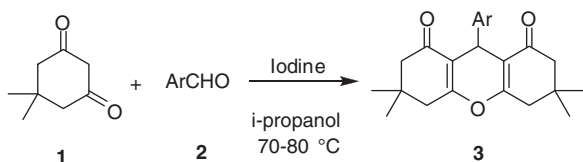
Mechanistically, the present iodine-mediated reaction seemed to proceed via in situ generation of intermediate **E** that subsequently afforded the desired product **3** (Scheme 2). Thus (i) aldol-type condensation between 1,3-cyclohexanedione (**1**) and aldehyde (**2**) followed by (ii) intramolecular Michael addition involving the hydroxyl group and enone moiety of the resulting

intermediate **E** afforded the compound **3**. It is mention worthy that possible interaction of molecular iodine with carbonyl oxygen has been indicated in the literature earlier.³⁰ Moreover, the intermediacy of compound **E** was supported by the fact that this compound was isolated when the iodine-mediated reaction was carried out at room temperature for 10 min. No cyclic product **3** was obtained even after continuing the reaction for 12 h. However, the intermediate **E** was converted to **3** when heated to reflux in isopropanol for 20 min in the presence of iodine.

To demonstrate the further scope of this reaction one of the compound synthesized was used for further structure elaboration. Thus, the compound **3e** was propargylated³¹ using propargyl bromide (Scheme 3) and the resulting alkyne **4** was then reacted with *p*-iodophenol in the presence of (PPh₃)₂PdCl₂ and CuI under a Sonogashira condition.

Most of the xanthene derivatives synthesized for example, **3, 4** and **5** were tested for their anticancer properties in vitro. We evaluated our compounds for their anti-proliferative properties in vitro against a number of cancer cell lines for example, human chronic myeloid leukemia cells (K562), human colon carcinoma cells (Colo-205), and human neuroblastoma cells (IMR32). The test compounds were examined at various concentrations in a MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and the IC₅₀ values obtained for each compounds are summarized in Table 2. Harmine, a member of β-carboline family of compounds showed cytotoxicity against HL60 and K562 cell lines³² was used as a reference compound. While most of these compounds showed inhibition of leukemia cell growth as reflected by their IC₅₀ values the good results however were obtained using compounds **3b, 3c, 3e, 3f, 3g, 3i, 3j, 3l, 3n, 3o, 4** and **5** (IC₅₀ < 50 μM, Table 2). Similarly, except compounds **3i** and **3k** all other compounds (IC₅₀ < 50 μM, Table 2) were found to be active against colon carcinoma cells and except compounds **3c, 3h, 3i, 3k, 3l, 3m** and **3o** rest of the compounds (IC₅₀ < 50 μM, Table 2) showed good activities against breast cancer cells. Overall, compound **3e** possessing a 2-hydroxy phenyl group at C-9 position was found to be promising (IC₅₀ ~ 23–38 μM, Table 2) and further functionalization of the 2-hydroxy phenyl ring (e.g., compounds **3f, 3j, 4** and **5**) did not improve the activity.

In conclusion, we have demonstrated the efficiency of molecular iodine as a catalyst for the preparation of 1,8-dioxo-octahydroxanthenes as potential anticancer agents. Both activated and inactivated aromatic aldehydes participated well in the present condensation reaction affording the expected products in high yields. The advantages of the present method include (i) short reaction time, (ii) operational simplicity and easy handling, (iii) functional group tolerability, (iv) cleaner reaction products and (v) does not involve the use of expensive and hazardous catalysts/co-catalysts or reagents. The crystal structure analysis and hydrogen bonding patterns of one compound prepared by using this methodology are presented. Most of the compounds synthesized showed good anti-proliferative properties in vitro against three cancer cell lines and the compound **3e** possessing a 2-hydroxy phenyl group at C-9 position was found to be promising. Overall, our study suggests that 1,8-dioxo-octahydroxanthenes presented here



Scheme 1. Reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1**) with aldehydes (**2**) in the presence of molecular iodine.

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