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Amberlite IR-120H catalyzed MCR: Design, synthesis and crystal structure analysis of 1,8-dioxodecahydroacridines as potential inhibitors of sirtuins

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ABSTRACT

A rapid, inexpensive and high yielding method has been developed for the synthesis of 1,8-dioxodecahydroacridines using Amberlite IR-120H as a reusable catalyst under open air. These compounds were designed as potential inhibitors of sirtuins and prepared via the MCR of 5,5-dimethyl-1,3-cyclohexanedione, (hetero)aryl aldehydes and (hetero)aromatic amines under mild conditions. Further structure elaboration of a representative compound was performed via Pd catalyzed C–C bond forming reactions. The crystal structure analysis and H-bonding patterns along with in vitro inhibitory activity against yeast Sir2 of the same compound is presented. Docking studies indicated that the compound interacts well with the yeast Sir2.

The identification of suitable drug targets is one of the major challenges in cancer drug discovery. In the recent years, majority of the efforts have been devoted by focusing on signaling molecules mostly kinases as drug targets. However, with the emergence of kinase inhibitor resistant cancers, there is a growing need to identify newer targets and develop new drugs. Recently, inhibition of sirtuins has been described as a new approach for the discovery of novel anticancer drugs. The sirtuins (class III NAD-dependent deacetylases that catalyze NAD+ dependent removal of acetyl group to generate deacetylated proteins, nicotinamide, and *O*-acetyl-ADP-ribose) function in diverse biological processes such as transcriptional silencing, regulation of apoptosis by deacetylation of p53, fatty acid metabolism, cell cycle regulation, and aging.[1] The mammalian sirtuin family consists of seven members for example SIRT1–7 and among the seven human sirtuins, SIRT1 has been studied well which has several substrates such as p53, Ku70, NF-B, forkhead proteins etc.[2] Since sirtuins are up-regulated in many cancers hence they are considered as important targets for cancer therapeutics. Indeed, inhibition of sirtuins allows re-expression of silenced tumor suppressor genes, leading to reduced growth of cancer cells. Several small molecule inhibitors of sirtuins, such as nicotinamide, sirtinol, splitomicin, cambinol, tenovins, and the indole derivative EX527[3] have been shown to induce cell death in cancer cells. However, no sirtuin inhibitors except EX527 (which is presently undergoing Phase 1a clinical trial for the treatment of Huntington's disease) have progressed into clinical trials as anticancer agents. Recently we have reported the synthesis of 1,8-dioxo-octahydroxanthenes (**A**, Fig. 1) as potential anticancer agents.[4] In continuation of that work and our interest in the identification of inhibitors of sirtuins[5] we now report the

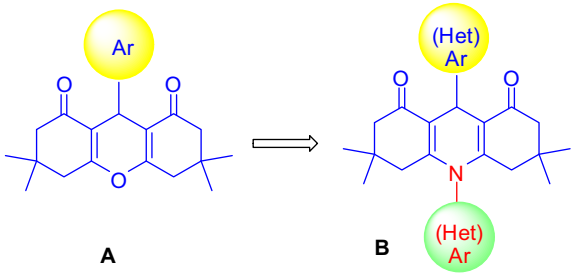

Figure 1. Novel 1,8-dioxodecahydroacridine derivatives (**B**) derived from **A**.

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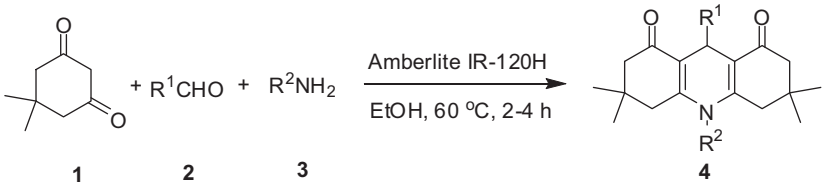
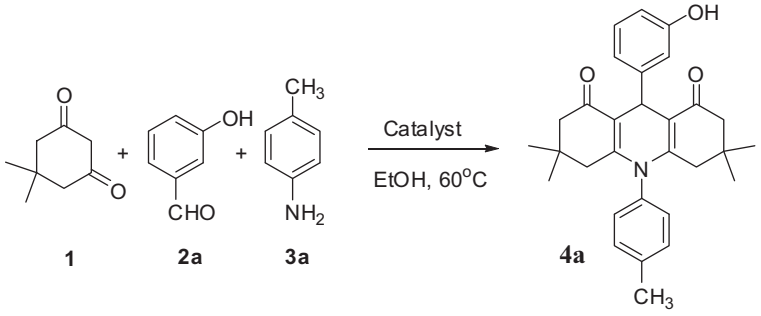


Scheme 1. Amberlite IR-120H catalyzed synthesis of 1,8-dioxodecahydroacridines.

Table 1
Effect of catalysts on the MCR of **1**, **2a** and **3a**[a]



Entry	Catalyst (amount)	Time (h)	Yield[b] (%)
1	Con. HCl (1–2 drops)	5	88
2	*p*-TSA (30 mg)	5	62
3	Amberlyst-15 (50 mg)	4	80
4	Amberlite IR-120H (50 mg)	2	95[c] (91, 87)
5	Amberlite IR-120H (50 mg)	1	72
6	No catalyst	5	0
7	Amberlite IR-120H (50 mg)	4	58[d]
8	Amberlite IR-120H (50 mg)	4	67[e]
9	Amberlite IR-120H (50 mg)	2	62[f]

[a] All the reactions were carried out by using **1** (2 mmol), **2a** (1 mmol), **3a** (1 mmol) and a catalyst in EtOH (4 mL) at 60 °C under open air.
[b] Isolated yields.
[c] Catalyst was reused for additional two runs and figures within parentheses indicate the corresponding yield for each run.
[d] DMF was used in place of EtOH.
[e] MeCN was used in place of EtOH. The product isolated was found to be 9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**4aa**) instead of **4a** in this case.
[f] Dichloromethane was used in place of EtOH.

synthesis and sirtuin inhibiting properties of analogous 1, 8-dioxodecahydroacridine derivatives (**B**, Fig. 1) the design and selection of which was further supported by the docking studies (see later for a discussion).

The synthesis of 1,8-dioxodecahydroacridines is generally carried out by using a multi-component reaction (MCR) of dimedone, aldehydes, and different anilines or ammonium acetate in the presence of a range of catalysts for example *p*-dodecylbenezenesulfonic acid (DBSA),[6] $[B(C_6F_5)_3]$,[7] proline,[8] carbon-based solid acid (CBSA),[9] NH_4Cl,[10] Brønsted acidic imidazolium salts[11] and ceric ammonium nitrate (CAN).[12] Synthesis of these compounds by the classical Hantzsch's procedure[13] or reaction of aldoximes with dimedone, under microwave irradiation have also been reported.[14] The use of a resin based catalyst for example Amberlyst-15 was also found to be effective.[15] While, many of these methods are quite effective and can be performed under environmental friendly conditions we were in search for a resin based inexpensive, faster, operationally simple and high yielding method for the synthesis of our target compound **B**. We have found that the rapid synthesis of **B** (or **4**, Scheme 1) can be carried out in high yields by using Amberlite IR-120H as an inexpensive and recyclable catalyst[16] in the MCR of 5,5-dimethylcyclohexane-1,3-dione (**1**), aldehyde (**2**), and aniline (**3**) (Scheme 1). To the best of our knowledge this is the first example of synthesis of compound **B** (or **4**) catalyzed by Amberlite IR-120H. The preliminary results of this study are presented.

Initially, we carried out the reaction of diketone **1**, 3-hydroxybenzaldehyde (**2a**), and *p*-toluidine (**3a**) in EtOH at 60 °C in the presence of con. HCl and *p*-TSA when the desired product **4a** was isolated in 88% and 62% yield, respectively (entry 1 and 2, Table 1). However, to identify an environmental friendly condition the same reaction was performed in the presence of known catalyst Amberlyst-15 when the reaction was completed within 4 h affording **4a** in 80% yield (entry 3, Table 1). The use of another resin based catalyst for example Amberlite IR-120H was found to be more effective as the reaction was completed within 2 h affording **4a** in 95% yield (entry 4, Table 1). A further decrease in reaction time decreased the product yield (entry 5, Table 1) whereas the reaction did not proceed in the absence of catalyst indicating the key role played by the catalyst in the present MCR. To assess the recyclability of Amberlite IR-120H the catalyst was recovered by filtration (followed by washing with EtOAc and drying) and reused when **4a** was isolated without significant loss of its yield (entry 4, Table 1). While all these reactions were performed in EtOH the use of other solvents for example DMF (entry 7, Table 1), MeCN (entry 8, Table 1), dichloromethane (entry 9, Table 1) etc. was also explored and found to be less effective. In case of MeCN a different product that is 9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**4aa**) was isolated instead of **4a** whereas a mixture of both was formed when water was used as a solvent.