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One-pot derivatization of medicinally important 9-aminoacridines by reductive amination and S_NAr reaction

Gary Gellerman *, Vladimir Gaisin, Tamara Brider

Department of Biological Chemistry, Ariel University Center of Samaria, PO Box 3, Ariel 40700, Israel

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ABSTRACT

A new highly efficient one-pot derivatization of medicinally important 9-aminoacridines (9-AA) at the amine position is described. Simple reductive amination and S_NAr reaction using easily accessible starting materials give a fast entry to novel 9-AA derivatives for biological screening.

The 9-aminoacridine (9-AA) core is a structure of interest to medicinal chemists and appears in many biologically active compounds, mostly with anticancer and antimalarial applications. 9-AA derivatives such as quinacrine[1] are able to intercalate with DNA, and consequently, can inhibit DNA transcription in parasites.[2] 9-Anilinoacridines have good antimalarial activities and are potent parasite DNA topoisomerase II inhibitors.[3] N-alkylated 9-AA analogs have been shown to be potent inhibitors of prion disease in cultured neuroblastoma cells, which also show inhibition by lysosomotropic agents and cysteine protease inhibitors.[4]

In the field of antitumor DNA-intercalating agents, 9-AA derivatives play an important role due to their antiproliferative properties.[5] Several cancer chemotherapeutics such as Amascrine and Ledakrin based on the 9-aminoacridine scaffold have been developed.[6a] In addition, a series of potential topoisomerase II-mediated anticancer 9-anilinoacridines, which are designed to avoid bioxidation and which possess long durations of drug action, have been reported.[7] Among these substances, 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA) (Fig. 1) and its alkylcarbamate derivatives have been developed for potential clinical application.[8]

9-Aminoacridines have also been investigated as potential photoaffinity labels[9] and as fluorescent probes used to detect cancer cells.[10]

Recently, 9-aminoacridine analogs, including the antimalarial drug quinacrine, were found to present strong induction of p53 function in renal cell carcinomas (RCCs) and other types of cancer cells.[11] Interestingly, induction of p53 function by these compounds does not involve genotoxic stress and is mediated by the suppression of NF-κB activity. Active NF-κB signaling provides selective advantages to tumor cells by inhibiting apoptosis and promoting proliferation by stimulating expression of antiapoptotic factors.

These findings, together with those mentioned above, indicate that 9-AA derivatives have potential for anticancer applications and this has inspired us to look for a short and efficient method for the derivatization of 9-AA suitable for the rapid generation of new compounds for evaluation.

Herein we report a new, highly-efficient, one-pot derivatization of 9-AA at the amine position by simple reductive amination or S_NAr reaction, using commercially available synthons. Reductive amination of aldehydes and ketones is an important and direct method for the transformation of these functionalities into amines.[12] In this carbon–nitrogen bond-forming process, the intermediate imine is not pre-formed.[13] Thus, the chosen reducing agent should be stable enough for the in situ formation of the imine and avoid undesirable carbonyl reduction to alcohol by-products. Mild $NaCNBH_3$ in a weak acidic media is a widely reported reducing reagent for reductive amination and was therefore employed as the reagent of choice. To demonstrate the synthetic potential of $NaCNBH_3$ in the reductive amination of 9-AA under standard conditions (1% AcOH in MeOH, rt, 3 h) we employed two classes of aldehydes: aromatic and aliphatic (Scheme 1), yielding *N*(9)-benzylacridines **1a–h** and 2-(acridin-9-ylamino)acetic acid **1i**, respectively, in moderate to good yields (Table 1).[14] The *N*(9)-aminobenzyl analogs synthesized bear representative electron-donating (ED) and electron-withdrawing (EW) groups as well as aryl and indolyl systems at various positions around the benzyl

* Corresponding author. Tel.: +972 3 937 1442; fax: +972 3 906 6634.
E-mail address: garyg@ariel.ac.il (G. Gellerman).

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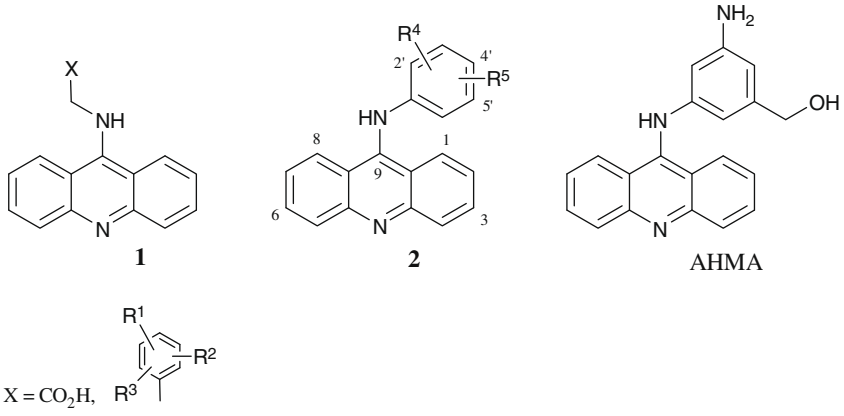
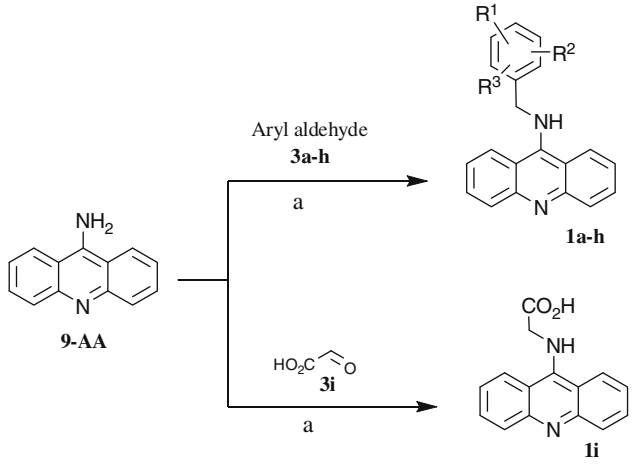


Figure 1. General structures of 9-aminoacridines.



Scheme 1. Synthesis of 9-aminoacridine derivatives **1** by reductive amination. Reagents and conditions: (a) $NaCNBH_3$, 1% AcOH in MeOH, 3 h, rt.

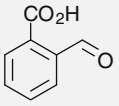
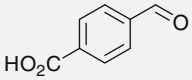
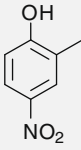
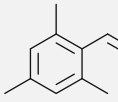
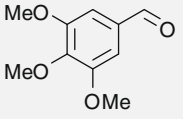
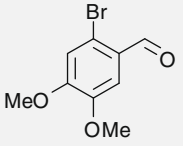
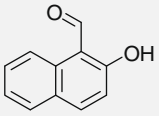
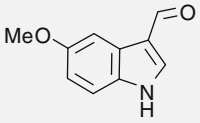
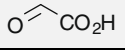
ring. Such syntheses are more difficult to accomplish using the classical 'reverse' synthetic approach in which 9-chloroacridine reacts with benzylamines,[15] due to the poor commercial availability of substituted benzylamines. The aliphatic analog **1i** was prepared in the same manner using the corresponding glyoxylic acid hydrate (**3i**).

In the context of exploring the rapid derivatization of the 9-AA scaffold we found that the amine (NH_2) at position nine is nucleophilic enough to take part in nucleophilic aromatic substitution (S_NAr) to give medicinally important 9-anilinoacridines.[16]

We successfully reacted representative electrophilic haloaryls **4a–e** (Scheme 2), bearing one or two strongly electron-withdrawing groups, with 9-AA in the presence of one equivalent (half molar ratio) of Cs_2CO_3 in DMF at 90 °C to afford the substituted 9-anilinoacridines **2a–e** in good yields (Table 2).[17] The uniqueness of this method is in its ability to form the anilino tether in 9-AAs with two EW groups which is very difficult to accomplish using the standard 'reverse' approach, namely nucleophilic substitution of the deactivated anilines on 9-chloroacridines.

The anilinic amine in such a 'reverse' reaction is strongly deactivated by EW groups leading mostly to unreacted materials or black tars. The additional advantage of the S_NAr reaction with 9-AAs is the extensive commercial availability of appropriately substituted haloaryls. Interestingly, 4-chloro-3-nitrobenzoic acid

Table 1
Reaction data for reductive amination of 9-AA

Entry		Aldehyde	Product	Yield (%)
1	**3a**		**1a**	92
2	**3b**		**1b**	89
3	**3c**		**1c**	87
4	**3d**		**1d**	66[a]
5	**3e**		**1e**	68[a]
6	**3f**		**1f**	72[a]
7	**3g**		**1g**	83
8	**3h**		**1h**	58[a]
9	**3i**		**1i**	91

[a] After chromatography.

(**4c**) which bears an acidic CO_2H group smoothly undergoes the S_NAr reaction to give product **2c** even in the presence of basic Cs_2CO_3. Moreover, the CO_2H group in **2c** (as well as in the