Synthesis of 1-substituted indole-3-carboxaldehyde related to acyclic nucleosides and their condensed pyrenyl derivatives

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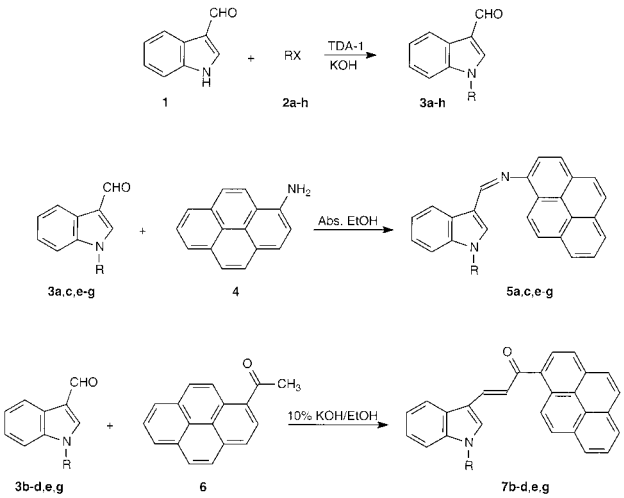
Indole-3-carboxaldehyde was *N*-alkylated to give the corresponding acyclic nucleosides **3a–h** which were condensed with 1-pyrenamine and 1-acetylpyrene to give **5a,c,e–g** and **7b–d,e,g**, respectively. The Schiff's bases **5a** and **5e** with 2-hydroxyethyl and methylthiomethyl *N*-1 substituents were found moderately active against HIV-1.

Keywords: indole-3-carboxaldehyde acyclic nucleosides, phenyl derivatives

Indole and its derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activities.[1–7] Major efforts have been directed by the nucleoside chemists toward the synthesis of analogues of acyclovir and other acyclo nucleosides with various side chains and aglycons.[20] Considering that both indoles as well as acyclic nucleosides with various side chains are potent pharmacophores the combination of these two moieties may result in interesting biological activities and this is the aim of the present investigation.

Indole-3-carboxaldehyde (**1**) was alkylated with the appropriate alkylating agents **2a–h** using powdered KOH and *tris*[2-(2-methoxyethoxy)ethyl] amine (TDA-1).[21] The reaction proceeded at room temperature within few minutes to yield the corresponding acyclic nucleoside derivatives **3a–h** in good yields (76–92%). New indole Schiff's base derivatives having a pyrene nucleous were synthesized through a condensation reaction between an acyclic nucleoside type of indole-3-carboxaldehyde **1a,c,e–g** and 1-aminopyrene in refluxing EtOH for 6 h to give Schiff's bases **5a,c,e–g** in good yields (78–87%).



2,3,5,7	R	X	2,3,5,7	R	X
a	CH_2CH_2OH	Br	**e**	CH_2SCH_3	Cl
b	$CH_2OCH_2CH_3$	Br	**f**	$CH_2CO_2CH_3$	Br
c	$CH_2CH_2CH_2OH$	Br	**g**	$CH_2(CH_2)_2CO_2C_2H_5$	Br
d	$CH_2CH(OC_2H_5)_2$	Br	**h**	$CH(CO_2H)CH(CH_3)_2$	Br

Scheme 1

N-Alkylated indole-3-carboxaldehydes **3b–d,e,g** were condensed with 1-acetylpyrene (**6**) in refluxing ethanol and in the presence of 10% KOH to yield the ethylenic compounds **7b–d,e,g** in good yields (80–84%).

The ^{1}H NMR spectra for compounds **7b–d,e,g** showed the pattern for the CH=CH group as an AB system which appears at δ = 7.85 and 7.52 ppm as two doublets with the coupling constant J = 15.9 Hz. The ^{13}C NMR spectra showed a peak in the range 195–200 ppm characteristic for C=O conjugated to pyrene which also confirmed the structures **7b–d**,**e**,**g** as did microanalysis and FAB MS.

Compounds **3b–g**, **5a**,**c** and **7b–d**,**e**,**g** were examined for possible antiviral activity against HIV-1 using MT-4 cells as target cells. Compounds **5a** and **5e** were found moderately active against HIV-1 with the effective doses ED_{50} = 10 and 18 μM, respectively. The selectivity was low as the cytotoxic doses for the compounds **5a** and **5e** were found to be CD_{50} = 70 and 32 μM, respectively. Compounds **3e** and **7b**,**e**,**g** were toxic to the MT4 cells, but no activity was found against HIV-1 at non-toxic concentrations. The compounds were also screened against herpes simplex virus (HSV-1) replication using Vero cells as target cells, but no activity was found.

Techniques used: ^{1}H, ^{13}C NMR and FAB MS

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