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A Novel Route to the Synthesis of Acridine Derivatives and Assay of their Antiviral Activity

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ABSTRACT

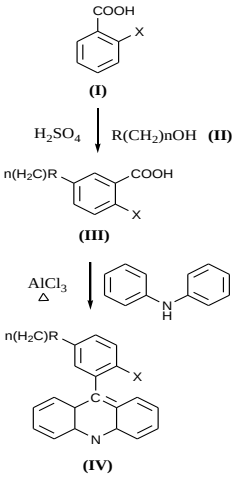
A simple and convenient procedure was adopted for the synthesis of N-(3-acridin-9-yl-4-chloro/hydroxy-phenyl-alkyl)-arylamides/imides starting from 5-(arylamido/imido-alkyl)-2-chloro/2-hydroxy benzoic acids. The compounds were obtained in the yields ranging from 40 to 45% and exhibited less pronounced antiviral activity.

Keywords Arylamido/imidoalcohols, 2 substituted anthranilic acids, Antiviral activity

INTRODUCTION

Acridine derivatives as antiviral agents have been less investigated however their antibacterial activity has been fully established [1-3]. The acridine compounds exert both bactericidal and bacteriostatic actions against both gram positive and gram Negative organisms and are not inhibited by the serum [4].

It has been observed that bacteria can acquire resistance to acridines on prolonged use [5,6]. In addition, later studies proved the usefulness of acridines against malarial infections. Some such acridines are chemically effective and are available in the market [7-9]. Our ongoing programme in the design and development of the potential bioactive compounds led us to undertake the synthesis of some acridine derivatives for studying their antiviral activity (Scheme).



SCHEME

EXPERIMENTAL

Arylamido/imidoalcohols (ll)

Literature methods [10-12] were followed for the synthesis of arylamido/imidoalcohols.

5-(Arylamido/imidomethyl) -2 chloro/ 2 hydroxy benzoic acid (lll)

A mixture of an arylamido/imidoalcohols (ll) (0.01 Mole) and orthosubstituted benzoic acid (0.01 mole) was resolved in conc H_2SO_4 (50 ml) by stirring. During the course of dissolution the contents were cooled. The solution thus obtained was stirred mechanically for one hour and left under refrigeration overnight. It was poured into Ice cold water 250 ml slowly and carefully after each addition the stiring was done. When the addition was completed, the separated solid mass was allowed to settle down. It required about half an hour. The solid was filtered off and was successively with cold water and dried *in vacuo*. The crude amido/imidoalkylated acid thus obtained was recrystallized from acetone 5 (Benzoylamino-methyl) 2-chlorobenzoic acids, m.p. 134°C (133 to 134°C) [13] yield 75%

5-(1,3Dioxo- 1,3 dihydro-Isoindol-2-yl-methyl) 2- hydroxy-benzoic acid m.p. 167-168oC [169∝C] [14] ,yield 70%.

5-(Benzoylamino-methyl)-2-hydroxy benzoic acid, m.p. 109-110°C [110°C] [15] yield 77%.

N-(3-Acridin-9-yl-4-chloro/4-hydroxy-phenyl-alkyl)-arylamides/imides (IV)

A mixture consisting of properly powdered diphenyl amine(0.9mole) and 5-(arylamido/imido-alkyl) -2- chloro/ 2-hydroxy benzoic acid (III) (0.0l mole) and anhydrous aluminium chloride (1.0 g) was heated in such a manner that the temperature did not increase 160o C for a longer period of times (11 hrs). Subsequently, dark green mixture was cooled till it attained the room temperature. The resulting solid was thoroughly washed initially with sodium bicarbonate (10%) solution to dissolve any unreacted carboxylic acid. It was further washed repeatedly with water and dried *in vacuo*. The crude acridine derivatives thus synthesized, were recrystallized from benzene and are recorded in Table 1(Because of the labrymatric nature of the acridine derivatives, these compounds were handled with much care.)

Table 1: Characterization data of N-(3-acridin-9-yl-4-chloro/4-hydroxy-phenyl-methyl)-arylamides/imides (IV).

Compd. No	R	X	m.p. ^{0}C	Yield	Colour	Molecular Formula	Molecular Weight	Analysis Nitrogen%	
								Calcd.	Found
1.	benzamido	Cl	110-111	45	Dark brown	$C_{27}H_{19}N_2OCl$	422.5	6.63	6.28
2.	benzamido	OH	125	40	Dark brown	$C_{27}H_{20}N_2O_2$	404	6.93	6.56
3.	phthalimido	OH	112	40	Dark brown	$C_{28}H_{18}N_2O_3$	430	6.51	6.44

IR(KBr, cm^{-1}) : 1690 (sec. amide C= O), 1635(C=N), 3505(ArOH), 3420 (amide NH)
^{1}HNMR (DMSO, d_6) (δppm) :6.75-7.82 (m, 16H,Ar<u>H</u>), 3.85(s, 2H,C-C<u>H</u>$_2$-NH), 8.85(brs,1H,CON<u>H</u>), 5.50 (s,1H,ArO<u>H</u>)
^{13}CNMR (DMSO,d_6) (δppm): 43.4,115.2, 118.5, 121.4, 125.2, 127.3, 128.6, 130.5, 131.4, 135.6, 147.7, 165.7, 170.5
MS (FAB) : 404(M+), other Important peaks appeared at m/z 404, 587, 226, 178, 134, 127, 120, 107, 105(base peak), 101**.**

Antiviral activity

All the three target compounds were evaluated for their antiviral activity against Japanese *encephalites virus* (JEV), a RNA virus of greater pathogenicity obtained from National Institute of virology, Pune (India) *in vitro* [16,17]. These compounds were also screened for their antiviral activity against the plant virus viz; *Tobacco mosaic virus* (TMV). From the *Nicotiana Glutinosa* plant both *in vitro* and *in vivo* [18,19]. The antiviral activity data of these compounds are recorded in the Table 2 and Table 3.

Table 2: Anti-Japanese encephalitis virus (JEV) activity data of N-(3-acridin-9-yl-4-chloro/4-hydroxy-phenyl-methyl)-arylamides/imides

Compound number	R	X	Dose (µg/ml)	CT_{50} (µg/ml)	EC_{50} (µg/ml)	TI	%CPE inhibition
1	benzamido	Cl	500-4	500	-	-	-
2	benzamido	OH	500-4	500	-	-	-
3	phthalamido	OH	500-4	500	250	02	20

CT_{50}=50% cytotoxic concentration, EC_{50}=50% effective concentration,
TI= Therapeutic index, CPE= Cytopathic effect

Table 3: Anti-Tobacco mosaic virus (TMV) activity data of N-(3-acridin-9-yl-4-chloro/4-hydroxy-phenyl-methyl)-arylamides/imides

Compound no.	R	X	Percent inhibition of TMV	
			Invitro	***Invivo***
1	Benzamido	Cl	30	10
2	Benzamido	OH	20	-
3	Phthalimido	OH	50	30

RESULTS AND DISCUSSIONS

Anti JEV activity data incorporated in Table-II clearly suggest that these compounds having substituents in the phenyl group joined at 9 position of the acridine nucleus are unable to provoke good activity. Only a very lower order of anti JEV activity *in vitro* was demonstrated by the compound no. 3. However some correlation can be made with regard to anti-viral activity and the molecular structure of the compound. Thus the compound no.2 bearing R= benzamide and X'= OH substituents was found completely devoid of any measurable degree of anti JEV activity while compound no. 3 having R= phthalimido and X=OH showed observable magnitude of anti JEV activity (20% net protection). This observation clearly suggests that a phthalimido substituent is comparatively more appropriate than a benzamido substituent. It is suggested that these compounds are unable to penetrate the glycoprotein of the JEV to exert their desirable biologic effect and are unable to find the better fit at the receptor sites.

All the three acridine compounds displayed moderate to lower order of antiviral activity against TMV *in vitro*. However, *in vivo* antiviral activity against TMV was found to be less pronounced. From the anti -TMV activity data recorded in Table 3, it is clear that only one compound out of three , is showing some satisfactory virus inhibitory properly both *in vitro* and *in vivo*. Thus, the compound number 3 bearing R= phthalimido and X=OH exhibited antiviral activity to the extent of 50% *in vitro* and 30% *in vivo*. The acridine compound no. 2 having R= benzamido and X=OH showed a comparatively low order of activity. This compound provoked only 20% inhibition of TMV *in vitro* and no measurable degree of anti TMV activity in vivo could be detected. However the compound number one containing R=benzamido and X=Cl showed 30% and 10% anti TMV activity both *in vitro* and *in Vivo* respectively. It seems quite reasonable to suggest here that such compounds with other substituents need further probe for generating potential candidate molecules.

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