Synthesis and antiviral activity of some new naphthazacinnolines

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Abstract : The titled compound naphthazacinnoline derivatives have been synthesized by refluxing 2-hydrazino-quinolinyl-3-acetyl chloride in presence of 10% NaOH solution. The products have been screened for the evaluation of antiviral activity against papaya ring spot virus developed on chenopodium ampranticulor.

Index Terms **- Naphthazacinnoline, Antiviral activity, Papaya ring spot virus, chenopodium ampranticulor**

I. INTRODUCTION

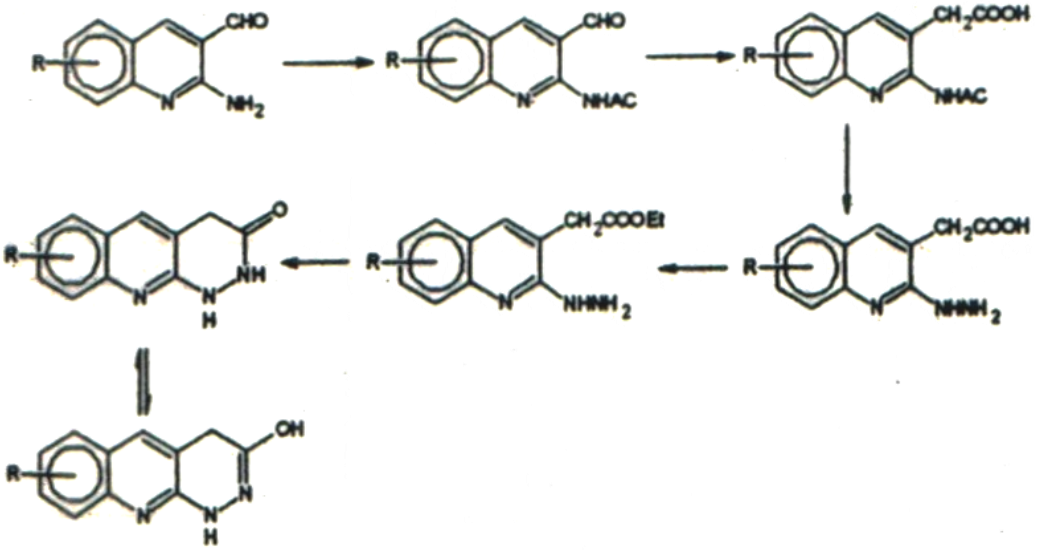
Azacinnoline derivatives have been extensively studied for antiviral activity. Encouraged by antiviral properties of many azacinnoline derivatives, a larg number of derivatives of this series of compounds were prepared and tested, 4-methoxy methyl and 1-hydroxymethyl derivatives of naphthazacinnoline were found to inhbibit Polio virus in culture of rabbit kidney cell. A number of 2-(hydroxyl substituted) naphthazacinnolines, 4-thiazolylnaphthazacinnoline and 5-methyl, benzyl, chloronaphthazacinnoline also have been patented as potent antiviral agents.

A part from this benzyl group is also present in penicillin; an antibiotics and hydrocarbon are reported to be effective antiviral as well as antifungal agents.

In view of these observations, we have synthesised the titled compound 1, 4-dihydro-3-hydroxynaphthazacinnolines by incorporating 2-hydrizino-quinoline-3-crboxyl chloride and substituted 2-hydrazinoquinoline-3-formyl quinoline and some substituted 2-amino-3-formylquinoline with a series of reaction using standard method of preparation. The resulted compounds were characterized by elemental analysis, IR, ^{1}H NMR spectra.

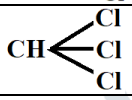
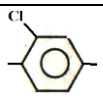
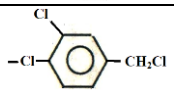
II. EXPERIMENTAL

Melting points were taken in open glass capillary tube and are uncorrected. IR spectra were recorded in $CDCL_3$ on varian 3100cm^{-1} FTIR and ^{1}H NMR spectra on Global 300 FTNMR. Elemental analysis performed using a vario EL III as elemental analyser. The following reaction sequences were performed. The starting material employed in this synthesis was taken 2-amino-3-formyl quinoline as well as some substituted 2-amino-3-formyl quinoline.



Substituted and unsubstituted 2-amino-3-formyl quinoline was acetylated and then converted to corresponding quinolinlyl-3-acetic acid by azlactone synthesis. This result was converted to 2-hydraziniquinoline-3-carboxylic acid and finally to 2-hydrizanoquinoline-3-acetic acid ester. This result on heating using different cyclising reagent and specific solvents, the corresponding unsubstituted -3-hydroxy-1, 4-dihydronaphthazacinnolines.

Table-1

S.N	R	Molecular formula	% yield	m.p(°C)	%of Nitrogen
1.	H	$C_{11}H_9N_3O$	80	144	21.1
2.	CH_3	$C_{12}H_{11}N_3O$	75	167	19.18
3.	- CH_2Cl	$C_{12}H_{10}N_3OCl$	72	152	16.96
4.		$C_{12}H_9N_3OCl_2$	76	186	14.89
5.		$C_{12}H_8N_3OCl_3$	75	192	13.27
6.	°- Cl - Cl	$C_{11}H_8N_3OCl$	75	116	17.98
7.	p- Cl - Cl	$C_{11}H_8N_3OCl$	76	148	17.98
8.	m- Cl	$C_{11}H_8N_3OCl$	74	184	17.98
9.	- OCH_3	$C_{11}H_{11}N_3O_2$	72	177	19.35
10.	- NO_2	$C_{11}H_8N_4O_3$	72	198	22.95
11.		$C_{17}H_{11}NOCl_2$	75	156	12.17
12.		$C_{18}H_{13}N_3OCl_2$	74	182	11.70

The product thus obtained was filtered, washed with water and crystallized from ethanol. The melting point and physical data of different 3-hydroxy, -1, 4 dihydronaphthazacinnolines were reported in following table.

IR Stretching Frequencies

KBr 1595 ~1610 cm^{-1} for C=N stretching frequencies

Nmax 1605~1640 cm^{-1} for substituted benzene and quinoline ring

2920~2935 cm^{-1} for C-H (showing $–CH_2$-group)

3250~3275 cm^{-1} for –NH-stretching frequencies

1420~1425 cm^{-1} for $–\overset{\|}{C}\text{-OH}$ (group)

NMR

The NMR spectrum had adsorption for various sets of protons. The four aromatic protons had resonance at d6.2 and for –NH-grouping a singlet for >C→OH grouping at δ8.1.

Antiviral screening

The antiviral screening of compounds 1-12 was evaluated against PRSV (Papaya ring spot virus) developed on chenopodium ampranticolor by petriplate technique at 3000, 2000, 1000 ppm concentration of compound. The culture of PRSV maintained on chenopodium ampranticular leaves in a inspect proof glass house in the division of plant pathology. Inoculums of each virus was prepared by grinding 5 gms of papaya diseased leaves in a mortar and pestle and the juice was squeezed through muslin cloth and diluted to 1:10 with distilled water after centrifugation at 5000 rpm for 10 minutes.

Chenopodium ampranticular was used as local lesion host for PRSV antiviral assays. Each extract in dilution of 1:1000, 1:2000 was mixed with different virus. Inoculate in equal amount of methanol and kept for 15 minutes before inoculation on ten leaves of plant C. ampranticular (the control consisted of each inoculums mixed with equal volume of methanol instead of extract).

Table - 2

Compound	1000 ppm	2000ppm	3000ppm
1	40	50	60
2	45	55	65
3	55	65	70
4	60	75	85
5	55	60	65
6	65	70	85
7	65	75	90
8	70	80	95
9	60	70	81
10	65	75	85
11	65	80	85
12	75	85	95

Then the antiviral test was performed and percentage virus inhibition was statically determined between control and extract.

Average percentage inhibition

Percentage virus inhibition = C – r/c x 100

Where C = number of lesion or no. of infected plant in control set and T=number of local lesion or number of infected plant on treated set.

III. Results and Discussion

The infra red spectrum of the compound as given in experimental part. Simultaneously the NMR spectrums of the compound are also mentioned in the experimental. These spectral data are in agreement with the structural proof of the 3-Hydroxy-1, 4-dihyronaphthazacinnolines compounds.

The results of antiviral effect of different derivatives of 1N are given in table-2.

All the compounds exhibited strong to moderate antiviral activity. A general trend of enhancement in activity is observed by the presence of chloride group impart much antiviral activity than one chlorine atom.

Therefore compound 4, 5, 6, 11, 12 can be recommended for further studies. However the change of position of chlorine atom Ortho to Para increases antiviral activity. The most active compound of our study of investigation was 12.

The association of chloral group increases viral toxicity in this series of compound.

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