RESEARCH PAPER

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Synthesis and Pharmacological Activity of some Mannich Bases 1-(4-N-Substituted phenyl)-2-phenyl-4-arylimidazolin-5-ones

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Twelve new 1-(4-N-Substituted phenyl)-2-phenyl-4-aryl- imidazolidin-5-ones (6-17) have been synthesised and their antiviral activity studied against Ranikhet Disease and Vaccinia viruses. Some of the compounds have shown significant activity against vaccinia virus.

MANNICH bases[1,2] and thiones like 4-thiazolidione-2-thione derivatives[3-5] and 6-aryl-7-arylazo-4-(N-Substituted)-aminomethyl-2H-thiazolo-3,2-a)-1,3,5-triazine-2-thiones were reported as antiviral[6] compounds. Based on these observations the synthesis of a series of 1-)4-N-substituted phenyl) 2-phenyl-4-arylimidazolidin-5-ones was carried out.

The known intermediates (2-3) were prepared by treating phenyl glycine (1) and substituted benzaldehydes in presence of $POCl_3$ and DMF. Which when further treated with 4-amino- benzoic acid yielded (4-5) and thereafter treatment with thionylchloride followed by different secondary aromatic amines gives the title compounds 1-(4-N-substituted phenyl)-2-phenyl-4- arylimidazolidin-5-ones (6-17) **(Table-1)**.

EXERIMENTAL

All the compounds were checked by IR recorded on Perkin Elmer 157 infrared spectrophotometer. The structure of the representative compounds wer also checked by PMR recorded on Perkin Elmer R32 spectrometer using TMS as internal reference. Melting points were taken in sulphuric acid bath and are uncorrected. The purity of compounds was checked on silica gel-G plates.

Phenylglycine (1) and 2-phenyl-4-aryl-oxazolidin-5-ones (2&3) were prepared by the known method.[7]

1-Substituted phenyl-2-phenyl-4-arylimidazolidin-5-ones (4 & 5)

Equimolar quntities (0.002 mole) of 2-phenyl-4-aryl-oxazolidin-5- one (2-3) and 4-aminobenzoic acid were heated on a sand bath for 6 hrs. The contents were then poured on crushed ice and the solid thus separated was filtered washed several times with cold water and then dried. The final compound was recrystallised from petroleum ether (40-60%).

4. R_1 = H, R_2=H, m.p. 95°C, yield 65%

5. R_1 = H, R_2 = OCH_3, m.p. 115°C, yield 70%

Ir (KBr): Compounds showed IR spectral bands at 1700 (C=O ring), 1690-1680 (C=O amide), 3500 (-OH), 1648 (CH=C), 3020-3100 (Ar- CH), 1610 (C=N).

PMR ($CDCl_3$): Compoiunds No. 4. 7.20-7.85 (m, 14H, Ar-H), 6.80 (S, 1H, CH=C) 4.50 (m, 1H, -OH)

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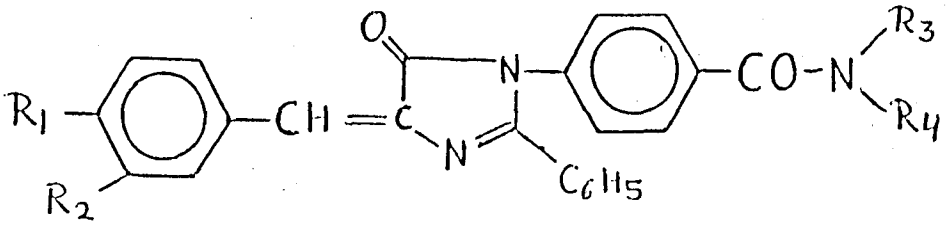
Table 1: 1-(4-N-Substituted phenyl)-2-phenyl-4-arylimidazolidin-5-ones

1-(4-N-Substituted phenyl)-2-phenyl-4-arylimidazolidin-5-ones

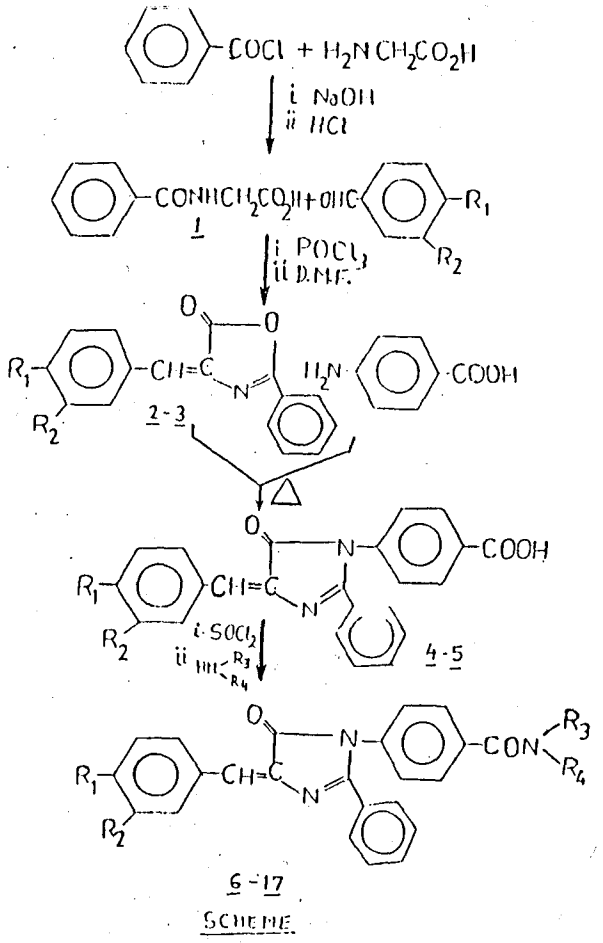


Compound Number	N	R_3 / R_4	Molecular Formula	m.p. (°C)	Antiviral Activity % inhibition RDV	Vaccinia Virus % inhibition
			$R_1=R_2=H$			
6.	N-methylphenylamino		$C_{30}H_{23}O_2N_3$	132	35	60
7.	N-ethylphenylamino		$C_{31}H_{25}O_2N_3$	142	0	60
8.	N,N-diphenylamino		$C_{35}H_{25}O_2N_3$	116	0	70
9.	N-methylpiperazino		$C_{28}H_{26}O_2N_4$	105	35	30
10.	Morpholino		$C_{27}H_{23}O_3N_3$	97	0	40
11.	Piperidino		$C_{28}H_{25}O_2N_3$	109	0	40
			R_1=OH, R_2=-OCH_3			
12.	N-methylphenylamino		$C_{31}H_{25}O_4N_3$	132	0	40
13.	N-ethylphenylamino		$C_{32}H_{27}O_4N_3$	148	0	30
14.	N,N-diphenylamino		$C_{36}H_{27}O_4N_3$	102	0	30
15.	N-methylpiperazino		$C_{29}H_{28}O_4N_4$	98	30	20
16.	Morpholino		$C_{28}H_{25}O_5N_3$	109	0	60
17.	Piperidino		$C_{29}H_{27}O_4N_3$	115	0	20

Concentration of synthesised compound was 0.05 mg/ml in 0.064 RA unit/ml RDV and 50 pfu/ml vaccinia virus.

All the compound analysed for C, H and N were found satisfactory. Yield ranged between 55-70%.

PMR ($CDCl_3$) Compound No. 11: 1.34-1.60 (m,6H, CH_2); 2.44-2.64(m,4H,N-CH_2); 6.90 (S, 1H, CH=C); 7.40-7.80 (m, 14H, Ar-H).



6-17

SCHEME

1-(4-N-Substituted) phenyl-2-phenyl-4-arylimidazolidin-5-ones (6-17)

1-substituted phenyl-2-phenyl-4-arylimidazolidin-5-one (4-5) (0.01 mole) was treated with suitable amount of $SOCl_2$ and then an appropriate amount (0.01 mole) of secondary amine was added to it. The mixture was then refluxed on a water bath for 6-8 hrs. Thereafter, the mixrures was poured on crushed ice, the solid thus separated was filtered, washed with water and recrystallised from, ethanol. The compounds (6-17) are listed in table-1.

IR (KBr) : compounds showed IR bands at 1705 (C-O ring), 1690- 1680 (C=O amide, 1645 (CH=C), 3050-3100 (Ar-CH) 1600 (C=N).

BIOASSAY

All the compounds were screened **in vitro** against RNV and vaccinia viruses and the results are recorded in Table-1.

a. Antiviral Activity against Ranikhet Disease Virus (RDV)

The strain of RDV and methods of virus maintenance have already been detailed earlier.[8] **In vitro** studies were performed in chorioallantoic membrane (CAM) culture of 11-12 days old chick embryos. For this study each compound at a non toxic dose of 0.05 mg/ml/culture was given along with virus/0.064 HA/ml/culture), using six replicates/compound. The percent inhibition of virus replication was calculated by the method as reported earlier.[8]

b. Antiviral Activity against Vaccinia Virus

All the synthesised compounds were tested against vaccinia virus on chick embryo fibroblast, monolayer.[9] The monolayers were treated with 0.15 mg/ml of synthesised compound with 50 PF/ml of vaccinia virus and incubated for 72 hrs at 37°C. The plaque formation of vaccinia virus were counted in different treated flasks and the percentage activity was calculated by $\frac{C - T}{T} \times 100$

RESULTS AND DISCUSSION

The results (Table-1) indicate that the compound No. 6,7,8 and 16 have shown significant antiviral activity reducing the plaque formation of vaccinia virus upto 60-70% while the remaining compounds have shown 20-40% activity. Anti RDV activity indicates only 15-35% inhibition in four of the compounds No. 6,9,15 and 14 while remaining are totally inactive. The above activity result shows that prepared thione derivatives were active against DNA (Vaccinia virus) virus and check the multiplication of virus without cytotoxicity.

From the above results it is clear that compounds were active at R_1=R_2=H and R_1=H, R_2=OCH_3 and $N\begin{smallmatrix}R_3\\R_4\end{smallmatrix}$=N-methylphenyl-amino, N-ethlphenylamino, N,N-diphenylamino & morpholino. One could therefore infered that potential antiviral activity of the compounds are due to presence of the above substitutions in the title compounds.

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