RESEARCH PAPER

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Synthesis and Antiviral Activity of Some New Farmazans

MURALI MANOHAR TIWARI, MANISH AGARWAL, V.K. SAXENA*, MS. S.K. BAJPAI**, AND M.M. JOSHI**
Dept. of Chemistry, Lucknow University, Lucknow 226 007.

Fifteen new 1-aryl-3-(5-substituted indolyl)-5(1-naphthylacetyl) farmazans have been synthesised and investigated for their antiviral effect against Ranikhet Disease Virus (RDV) and Vaccinia Virus (V.V.). Some of the compounds have shown promising activity against either one of these or both the viruses *in vitro*.

FARMAZANS have been associated with antiviral activity[1], 1- Aryl-3-(3'-nitromethoxyphenyl)-5-(4'-nitrophenyl) farmazans have shown significant antiviral activity against Gomphrena moseic and Sun Hemp Rossette Virus[2]. 1-Aryl-3-(3'-nitro-4'-methoxyphenyl)- 5-phenyl farmazans have also shown to be active against Sun Hemp Rossette Virus.[3] 1-Aryl-3-(4-hydroxy-3-methoxyphenyl)-5-nitro aroyl farmazans were synthesised as potent antivirial agents.[4]

Known formylindoles (2-4) were condensed with 1-naphthylacetyl hydrazide (1) to get 2-substituted indole-3-aldehyde-1- naphthyl-acetic acid hydrazones (5-7). Treatment of the latter with diazotised different aromatic primary amines gave 1-aryl-3- (5-substituted indolyl)-5-(1-naphthylacetyl) farmazans (8-22) **(Table-1)**.

EXPERIMENTAL

All the compounds were checked by I.R. recorded on Perkin Elmer- 157 infrared spectrophotometer. The structure of the representative compounds were also checked by PMR recorded on Perkin Elmer R-32 spectrophotometer using TMS as internal reference. Melting points were taken in sulphuric acid bath and are uncorrected. The purity of compounds were checked on silica gel G plates.

1-Naphthylacetic acid hydrazide (1) was prepared by the general method of preparation of acid hydrazides[5], 5-substituted indolyl-3-aldehydes (2-4) were prepared by the known method of Smith.[6]

5-Substituted indole-3-aldehyde-1-naphthyl acetic acid hydrazones (5-7)

Equimolar (0.2 mole) quantities of an appropriate indole-3- aldehyde and 1-naphthylacetic acid hydrazide in 25 ml of ethanol containing 2-3 drops of glacial acetic acid were heated under reflux on water bath for 4 hrs. The solid obtained by cooling the content was filtered washed and recrystallised from ethanol.

5, R=H; m.p. 85-87°C; yield 70%

6, R=C1; m.P. 109-111°C; yield 65%

7, R=CH_3; m.p. 134-136°C; yield 70%

I.R. (KBr) Compounds showed IR bands at 1710 (C=O); 3280 (N-H); 3340 (N-H indole); 1530 & 1320 (NO_2). Cm^{-1}.

1-Aryl-3-(5-substituted indolyl)-5-(1-naphthyl acetyl) farmazans (8-22)

An appropriate amine (0.015 mole) was dissolved in 5 ml of glacial acetic acid and 4 ml of conc. hydrochloric acid, the solution was then cooled

Table 1: 1-Aryl-3-(5-substituted indolyl-5-(1-naphthylacetyl) farmazans

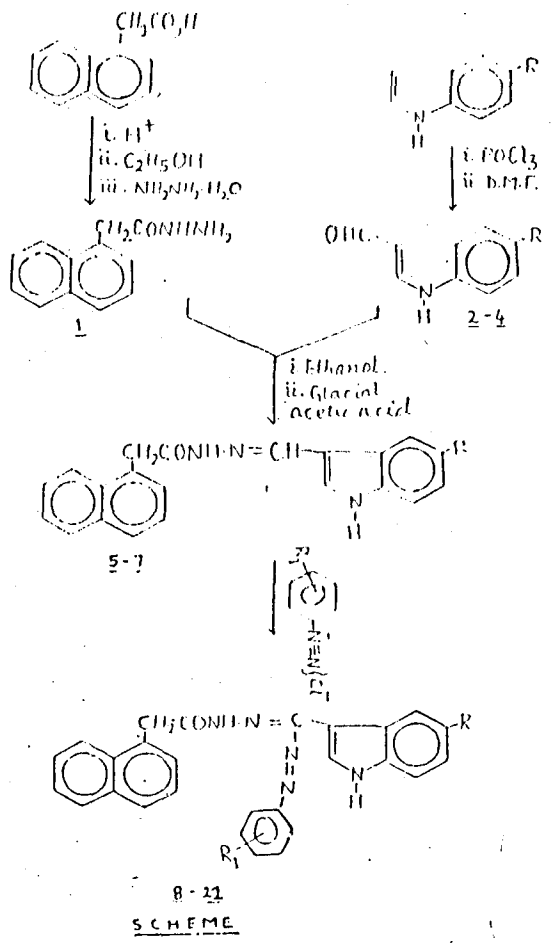
Compound No.	R_2	Molecular Formular	m.p.	% Inhibition Antiviral acitivity against	
				RDV	Vaccinia Virus
1	2	3	4	5	6
		R_1 = H			
8	H	$C_{27}H_{21}N_5O$	102	63	40
9	C_1	$C_{27}H_{20}N_5OCl$	105	53	50
10	CH_3	$C_{28}H_{23}N_5O$	98	30	10
11	OCH_3	$C_{28}H_{23}N_5O_2$	102	46	20
12	COOH	$C_{28}H_{21}N_5O_3$	134	N.N.	N.S.
		$R_1 = C_1$			
13	H	$C_{27}H_{20}N_5OCl$	116	46	40
14	Cl	$C_{27}H_{19}N_5OCl_2$	109	46	30
15	CH_3	$C_{28}H_{22}N_5OCl$	125	10	30
16	OCH_3	$C_{28}H_{22}N_5O_2Cl$	98	31	20
17	COOH	$C_{28}H_{20}N_5O_3Cl$	105	N.S.	N.S.
		$R_1 = CH_3$			
18	H	$C_{28}H_{22}N_5OCl$	118	70	40
19	Cl	$C_{28}H_{22}N_5OCl$	138	0	40
20	CH_3	$C_{29}H_{25}N_5O$	125	30	0
21	OCH_3	$C_{29}H_{25}N_5O$	152	46	20
22	COOH	$C_{29}H_{23}N_5O_3$	105	N.S.	N.S.

N.S. = Not screened. Yield ranged between 55% to 70%. Concentration of compound was 0.05 mg/ml/culture against RDV and 0.5 mg/ml/culture against vaccinia virus.

All the compounds analysed for C, H and N were found satisfactory.

PMR ($CDCl_3$) Compound No. 8 : 3.20 (S, 2H, CH_2); 5.80 (S, 1H, =CH); 7.16-7.85 (m, 16H, Ar-H); 9.60 & 11.10 (2br, S, =N-N-H & N=C-N)

at 0-5°C in a freezing mixture, to which solution of sodium nitrate (1.5 gm) in 5 ml ice cold water was then added under vigorous stirring, keeping the temperature at)-5°C. After the complete addition of sodium nitrite solution salt solution was then added, dropwise with continuous stirring, to a solution of compound (5-7) (0.01 mole) in pyridine (20 ml) keeping the temperature below 10°C. The reaction mixture was allowed to stand for four hours and then poured into 250 ml of ice cold water with continuois stirring. The solid obtained was filtered, washed with cold water followed by hot water and finally recrystallised from petroleum ether. The compounds (8-22) thus synthesised are listed in Table-1. The structures of these compounds were supported by IR and PMR spectra.



SCHEME

BIOASSAY

Antiviral activity against Ranikhet Disease Virus (RDV)

In vitro tests against RDV were performed in the chorio-allantoic membrane (CAM) of 10-11 days old chick embroys as described earlier.[7,8,9] For this study the non toxic dose (0.05 mg/ml/culture) of each test compound was given simultaneously with virus (0.064 Haemagglutination (HA) units/ml culture), using six replicated for each compound. The percent inhibition of virus replication was calculated as reported earlier.[10]

Antiviral activity against Vaccinia Virus

All compounds which were synthesised were tested against vaccinia virus **in vitro**. The system used was chick embryo fibroblast monolayer system derived from 9-11 days old chick embryo.[10-12] The compounds were tested in their non-tixic doses 0.5 mg/ml along with 50 pfu/ml of vaccinia virus using 6 test bottles/compounds. The treated challenged monolayers were incubated for 72 hrs at 37°C. The plagues formed by vaccinia virus in control and treated ones were counted and percentage calculated.

RESULTS AND DISCUSSION

All the compounds were tested against Ranikhet Disease (RNA) and vaccinia (DNA) viruses **in vitro** system. The results of antiviral activity against the two test virus viruses revealed that compound 8, 9 and 18 have shown significant antiviral activity against RDV while 1, 13, 14 and 21 have also shown activity more than 40%. The compound No. 9 has reduced the plaques formed by vaccinia virus upto 50% while 8, 13, 18 and 19 have shown 40% plaque reduction.

The compounds which are active against the test viruses may be divided in 3 groups;

(1) active against RDV- 8,9,11,13,14 18 and 21

(2) active against V.V.-8,9,13,18 and 19

All the compounds analysed for C, H and N were found satisfactory.

PMR (CDCl1v3) No. 8 : 3.20(S,2H,CH_2); 5.80(S,1H, =CH); 7.16-.85(m, 16H, Ar-H); 9.60 & 11.10(2br,S, -N-N-H & N=C-N)

(3) active against both the test viruses-8,9,13 and 18

The results indicate that compounds containing chloro and methyl substitution are more active against the two test viruses (DNA & RNA Viruses). One could therefore, infer that 4-chloro and methyl substitution against R_1 & R_2 in the above farmazan

increases the antiviral activity of the compounds and can be used as potential antiviral agents.

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