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Synthesis and antiviral activity of 1-(n-substituted amino acetyl)-2-(5-substituted phthalimidomethyl) benzimidazoles

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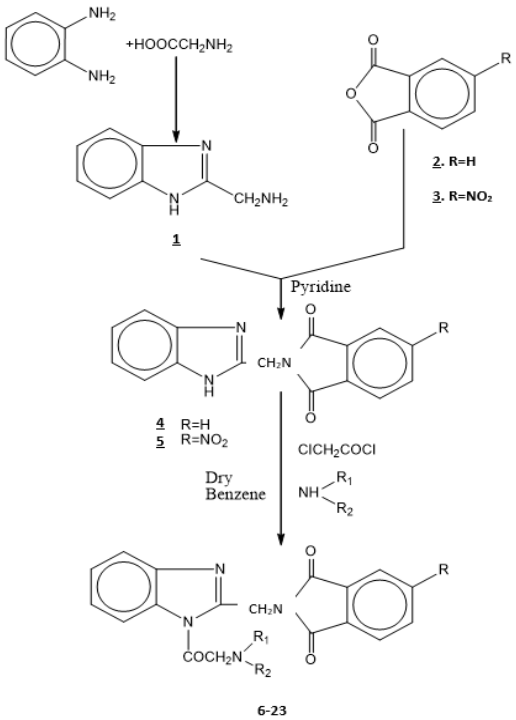
Abstract
Phthalic anhydride and 3-Nitro Phthalic anhydride were reacted with 2-aminomethyl benzimidazole in pyridine to give 2- (5-substituted phthalimidomethyl) bezimidazoles. These benzimidazoles were refluxed with chloroacetyl chloride in dry benzene followed by reaction with different secondary amines to give 1-(N-substituted amino acetyl)-2-(5-substituted phthalimidomethyl) benzimidazoles. Antiviral activity of these compounds was studied against Ranikhet Disease Virus (RDV) and Vaccinia Virus (VV). Some of these compounds have been found to be active against RDV.

Keywords: benzimidazoles, phthalic anhydride, ranikhet disease virus, vaccinia virus

Introduction
A number of compounds containing benzimidazole nucleus have been found to possess various antiviral activities [1, 2]. Various benzimidazole derivatives have been found to be active against Vaccinia Virus [3]. Some other benzimidazole derivatives have been found to be associated with antiviral activity against Ranikhet Disease Virus [4]. These results encouraged the author to synthesise1-(N-substituted amino acetyl)-2-(5-substituted phthalimidomethyl) benzimidazoles and to study their pharmacological action.

Scheme



Methodology

3-nitrophthalic anhydride (3) was prepared according to the method reported earlier [5].

To phthalic anhydride (2) (25 gm) and concentrated sulphuric acid (32.5 ml) fuming nitric acid (10.5 ml) was added at such a rate so as to maintain the temp. At 100-100^{0}C. Then conc. nitric acid (45 ml) was added to the whole mass. The mixture was heated on water bath with stirring for 2 hrs. It was kept overnight and then poured into cold water. The resultant mixture of 3-and 4-nitrophthalic acid was filtered and the wet cake was dissolved in hot water so as to dissolve a large amount of 4-nitro acid. It was then filtered and the hot filtrate was stirred mechanically until crystallization commenced. Then it was left overnight and filtered so as to obtain 3-nitrophthalic acid. m. p. 210-212^{0}C [216-218^0]^4, yield 70%.

To 3-nitrophthalic acid (0.01 mile), acetic anhydride (65 ml) was added. It was heated gently to boiling till a clear solution was obtained and then heated for about 10 min. more. The hot mixture was poured into a large porcelain dish and was allowed to cool. The crystalline mass was grinded thoroughly in a mortar and filtered at pump. 3-nitrophthalic anhydride thus obtained was again grinded with 50 ml of dried ether and finally recrystallized from benzene.

3- m. p. 161^{0}C [163-164^{0}C] ^{4} yield 70%.

2-(5-substituted phthalimidomethyl) benzimidazoles (4&5)

2-aminomethyl benzimidazole (1) (0.01 mole) and an appropriate phthalic anhydride (2&3) (0.01 mole) were refluxed in 10 ml of pyridine for 5-6 hrs. Excess pyridine was distilled off and the contents were poured in ice cold water containing few drops of conc. hydrochloric acid. The solid, so obtained was washed with water, dried and recrystallized from methanol.

4. m. p. 240^{0}C [242-244^{0}C]^5 yield 70%. (R = H)

5. m. p. 270^{0}C [275^{0}C]^5 yield 70%. (R = NO_2)

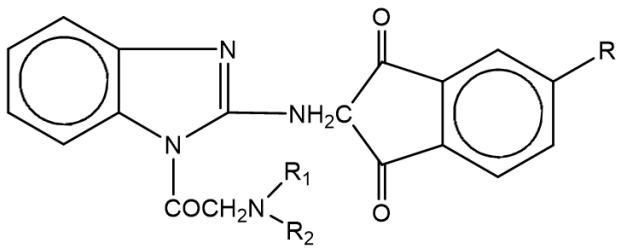


Table 1: Characterisation data of 1-(N-substituted amino acetyl)-2-(5 substituted phthalimidomethyl) benzimidazoles (6-23)

Compd. No.	R_1------ N----- R_2	Molecular formula	M.P. ^{0}C	Analysis: Calculated			Analysis: Found		
				C	H	N	C	H	N
R = H									
6	Diethanolamino	$C_{22}H_{22}N_4O_5$	192	62.56	5.21	13.27	62.14	5.14	13.20
7	Morpholino	$C_{22}H_{20}N_4O_4$	216	65.35	4.95	13.86	65.29	4.85	13.72
8	N-ethylanlino	$C_{26}H_{22}N_4O_3$	190	71.23	5.02	12.78	71.03	5.09	12.52
9	N-methylanilino	$C_{25}H_{20}N_4O_3$	170	70.75	4.72	13.21	70.72	4.52	13.01
10	N-phenylpiperazino	$C_{28}H_{25}N_5O_3$	215	70.15	5.22	14.61	70.10	5.20	14.60
11	N-methylpiperazino	$C_{23}H_{23}N_5O_3$	215	66.18	5.52	16.79	66.07	5.07	16.70
12	Diethylamino	$C_{22}H_{22}N_4O_3$	235	67.69	5.64	14.36	67.09	5.03	14.30
13	Piperidino	$C_{23}H_{22}N_4O_3$	226	68.66	5.47	13.93	68.60	5.42	13.85
14	Diphenylamino	$C_{30}H_{22}N_4O_3$	240	74.07	4.53	11.52	74.02	4.50	11.38
$R = NO_2$									
15	Diethanolamino	$C_{22}H_{21}N_5O_7$	206	56.53	4.49	14.99	56.08	4.52	14.98
16	Morpholino	$C_{22}H_{19}N_5O_6$	213	58.79	4.23	15.59	58.54	4.21	15.32
17	N-ethylanilino	$C_{26}H_{21}N_5O_5$	222	64.59	4.35	14.49	64.58	4.02	14.04
18	N-methylanilino	$C_{25}H_{19}N_5O_5$	209	63.97	4.05	14.92	63.02	4.02	14.62
19	Diethylamino	$C_{22}H_{21}N_5O_5$	202	60.69	4.83	16.09	60.09	4.87	16.25
20	Piperidino	$C_{23}H_{21}N_5O_5$	185	61.74	4.69	15.66	61.20	4.62	15.62
21	N-phenylpiperazino	$C_{28}H_{24}N_6O_5$	210	64.12	4.58	16.03	64.05	4.35	16.00
22	N-methylpiperazino	$C_{23}H_{22}N_6O_5$	226	59.74	4.76	18.18	59.52	4.71	18.08
23	Diphenylamino	$C_{30}H_{21}N_5O_5$	240	67.79	3.95	13.18	67.10	3.85	13.05

Yields ranged from 65-70%.

1-(N-substituted amino acetyl)-2-(5-substituted phthalimidomethyl) benzimidazoles (6-23)

2-(5-substituted phthalimidomethyl) benzimidazole (4-5) (0.01 mole) was refluxed with chloroacetyl chloride (0.1 mole) in dry benzene for 8-10 hrs. Thereafter, an appropriated secondary amine (0.01 mole) was added to the reaction mixture and it was again refluxed on water bath for 6 hrs. Excess of benzene was distilled off and solid obtained was filtered and recrystallised from DMSO. Compounds 6-23, thus synthesized are listed in Table-1.

IR (KBr): Compounds showed IR spectral bands at 2780-2770 (N-CH_2), 1725 (acyclic C=O. 1700-1690 (Cyclic C=O), 1610-1600 (C=N), 1540-1535 and 1315-1310 (NO_2),

PMR ($CDC1_3$): Compound 13: 1.42-1.54 (m, 6H, C-CH_2), 2.60-2.74 (m, 6H, N-CH_2), 3.80-3.82 (s, 2H, N-CH_2 –C=O) and 7.18-.85 (m 8H, Ar-H).

Antiviral activity against RDV

Compounds were tested against RDV in a stationary culture of minced chorioallantoic membrane of chick embryo. The strain of the Ranikhet Disease Virus was the same as employed by Babber and Dhar [7]. Chorioallantoic membrane (CAM) of 10 days old chick embryos were taken and the culture prepared according to the method of Babbar [8, 9]. The soluble compounds were dissolved in a nutrient fluid and the insoluble compounds were suspended in it in the presence of Tween 80 and the pH adjusted to 7.2 before sterilization. The solutions were then sterilized by autoclaving at 15 lbs pressure for 15 min. Two fold serial dilutions were then made and 1 ml of each dilution added to each of the test tubes containing the CAM culture. The dilution of a compound causing toxic symptoms in 50% of the CAM culture was taken as the end point.

The highest nontoxic dose was given to each culture along with the virus (0.64 HA units/ml). Virus multiplication was measured by the haemagglutination (HA) titre (mean of log_2) of the culture collected after 48 hrs of incubation at 37°C. Inhibition in virus multiplication was obtained by subtracting this titre from that of the control. The mean difference (d) of 2 log_2 HA units is significant at 50% or more than 50% level.

Antiviral activity against vaccinia virus

All the eighteen compounds were also tested [10] against Vaccinia Virus on chick embryo fibroblast monolayers. 0.05 mg/ml compound was given along with Vaccinia virus (50 p/ml) and incubated at 37°C for 72 hrs. After 72 hrs the monolayers were strained and the numbers of plaques/monolayers were counted. The activity was calculated by the formula C-T/C×100.

Table 2: Antiviral Activity of Compounds 6-23 against RDV

Compound. No.	Percent inhibition against RDV	Compound. No.	Percent inhibition against RDV
6	0	15	30
7	60	16	10
8	40	17	0
9	30	18	60
10	40	19	46
11	20	20	30
12	40	21	36
13	60	22	0
14	40	23	0

Compounds were tested at the dose of 0.1 mg/ml against 0.064 units/ml of RDV

Results and discussion

Eighteen benzimidazoles (6-23, Table-1) were tested against RDV and Vaccinia virus. Results of testing against RDV are recorded in Table-2.These results indicate that compounds 7, 13 and 18 were active against the virus. Compounds 6, 17, 22 and 23 possessed no activity while other compounds showed 10-46% inhibition against the virus.

From these results, presented in Table-2, it appears that compounds have been found to be more active when R=H, rather than when R=-NO_2. Also, substitution of dialkyl amino group by morpholino, piperidino and N-methyl anilino groups increases the antiviral activity of compounds, whereas substitution by diethanolamino, N-ethylanilino and N-phenyl piperazino groups considerably reduces the activity of compounds.

Compounds 6-23 were also screened against Vaccinia virus. However no compound was found to be active against this virus. Author recommends broad range research in this field, as the some viruses may cause cancer [11]. Now it is possible to reactivate the tumor suppressor genes by using natural products [12], which is a good sign for human health.

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