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OXIRANES WITH QUINOLINE SUBSTITUTION : STEREOSELECTIVE SYNTHESIS AND ANTIVIRAL ACTIVITY

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Abstract : A series of new quinoline substituted oxiranes were synthesised by the reaction of 2-N-(chloroacetyl)-1-(4'-methyl -2'- quinolinyl) hydrazide and aromatic aldehydes . These compounds were tested against encephalomyocarditis virus (EMCV) and only two compounds exhibited protection against the virus.

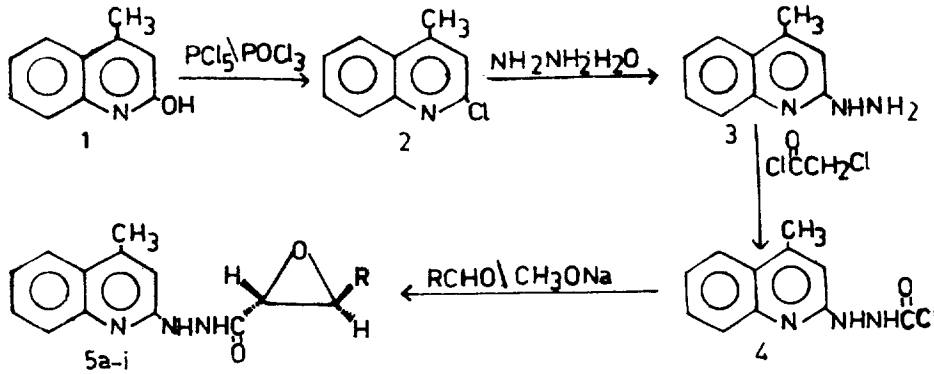
Quinoline and their derivatives have been extensively investigated by the organic chemsits due to their close association with the biological activities like amoebicidal[1], antibacterial[2], antifungal[3] and antifilarial[4] activities. In addition, naturally occurring oxiranes are associated with various biological activities[5-7]. In recent years, search for new and less toxic antiviral agents are in great demand due to the typical viral infections. EMC virus, recognised as strains of a single virus, are immunologically indistinguishable. Human infection with EMC virus have been associated with a variety of clinical signs varying from a mild febrile illness to a severe encephalomyelitis. Keeping in view, it was thought worthwhile to synthesize new quinoline substituted oxiranes and screened for their antiviral activity against EMC virus[8,9].

4-Methyl carbostyril **1** was obtained[10] by cyclization of acetoacetanilide which on treatment with $PCl_5/POCl_3$ afforded 2-chloro-4-methyl quinoline **2**. This on condensation with hydrazine hydrate yielded corresponding hydrazide product **3**, which on treatment with chloroacetyl chloride in benzene gave 2-N- (chloroacetyl)-1-(4'-methyl-2'-quinolinyl)hydrazide **4**.

Finally, N-[(4'-methyl-2'-quinolinyl)amino]-3-(substituted)-2,3-epoxypropanamide **5a-i** were prepared[11,12] by treating **4** with different aromatic aldehydes in the presence of sodium methoxide. After finishing of the reaction, the solvent was evaporated to dryness under reduced pressure. Column chromatography of the residue on silica gel with petroleum ether/ethyl acetate as eluent gave the desired product. Recrystallisation of these solids afforded **5a-i** as crystals.

^{1}H-NMR spectral studies reveal that oxiranes **5a-i** were identified as trans-isomers by their small coupling constant. Two distinct doublet appeared in the region at δ 3.40-4.35 with J ~2 Hz. (vicinal coupling constant), each of the signal corresponds to one proton. The small value of this coupling constant is consistent with a trans-isomer as reported in literature data[13,14]. The structure of all products was

established by ^{1}H-NMR, IR and elemental analysis.



5a	$R=C_6H_5$	**d**	$R=C_6H_4CH_3(p)$	**g**	$R=C_6H_4NO_2(p)$
b	$R=C_6H_4Cl(p)$	**e**	$R=C_6H_3OCH_2O(m,p)$	**h**	$R=C_6H_4NO_2(m)$
c	$R=C_6H_4OCH_3(p)$	**f**	$R=C_5H_4N(p)$	**i**	$R=C_6H_4F$ (p)

The antiviral activity of compounds **5 b,c,e,f,h** was tested against Encephalomyocarditis Virus (EMCV) in Swiss unbred mice. Vero cells used were tripsinised by standard method[15]. Cytotoxic assays of the compounds were done according to Sidwell and Hofmann[16]. The antiviral activity in vitro was conducted according to Pandey procedure[17]. Percent protection was calculated according to Reed and Muench[18].

Compounds **5c** and **5e** were evaluated in vivo against EMCV. In prophylactic administration compound **5c** showed 25% protection of the infected mice at 0.25 mg/mouse, while **5e** in the above dose showed only 10% protection. Compounds **5c** and **5e** inhibited cytopathic effect caused by EMC virus to an extent of 75% at 15.6 μg/ml and 7.8 μg/ml respectively whereas other compounds were found to be antivirally insignificant.

Table 1 Antiviral screening results of compound **5b,c,e,f,h** against EMC virus in mice.

Compound[19]	In vitro Screening		In vivo Screening	
	Concentration	% protection	Dose	% Protection
4	1000-1 μg/ml	0	-	-
5 b	1000-1 μg/ml	0	-	-
5 c	15.6 μg/ml	75	0.25mg/mouse	25
5 e	7.8 μg/ml	75	0.25mg/mouse	10
5 f	1000-1 μg/ml	0	-	-
5 h	1000-1 μg/ml	0	-	-

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19. 5a: mp. 110-113°C; Yield: 55%; ^{1}H-NMR ($CDCl_3$): δ 10.30 (2H, br, 2xNH), 7.0-7.80 (10H, m, Ar-H), 3.70 (1H, d, J=1.9Hz, 2-CH), 3.45 (1H, d, J=1.9Hz, 1-CH), 2.70, (3H, s, 4-CH_3); IR (Nujol): 3240, 3040, 1665, 1625, 1590, 1525, 760 cm^{-1}. Anal Calcd. for $C_{19}H_{17}N_3O_2$: C 71.47; H 5.33; N 13.17. Found: C 71.52; H 5.41; N 13.12.

    5b: mp. 120-121.5°C; Yield: 81%; ^{1}H-NMR ($CDCl_3$): δ 10.50 (2H, br, 2xNH), 7.3-7.9 (9H, m, Ar-H), 3.88(1H, d, J=1.9Hz, 2-CH), 3.65 (1H, d, J=1.9Hz, 1-CH), 2.80 (3H, s, 4-CH_3); IR (Nujol): 3250, 3050, 1660, 1615, 1590, 1525, 780 cm^{-1}. Anal. Calcd. for $C_{19}H_{16}N_3O_2Cl$: C 64.50; H 4.53; N 11.88. Found : C 64.59; H 4.49; N 11.85.

5c: mp. 102-103°C; Yield: 65%; ^{1}H-NMR ($CDCl_3$): δ 10.00 (2H, br, 2xNH), 7.30-8.15 (9H, m, Ar-H), 3.90 (3H, s, OCH_3), 3.75 (1H, d, J=1.9Hz, 2-CH), 3.55 (1H, d, J=1.9Hz, 1-CH), 2.65 (3 H, s, 4-CH_3); IR (Nujol): 3250, 3050, 1665, 1615, 1585, 1530, 780, cm^{-1}. Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C 68.77; H 5.44; N 12.03. Found: C 68.65; H 5.55; N 12.12.

5d: mp. 105-108°C; Yield: 50%; ^{1}H-NMR ($CDCl_3$): δ 10.70 (2H, br, 2xNH), 7.10-7.75 (9H, m, Ar-H), 3.78 (1H, d, J=2Hz, 2-CH), 3.45 (1H, d, J=2Hz, 1-CH), 2.75 (6H, s, 2x CH_3); IR (Nujol): 3230, 3040, 1665, 1610, 1590, 1525, 780 cm^{-1}. Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C 72.07; H 5.70; N 12.61. Found: C 72.15; H 5.62; N 12.55.

5e: mp. 96°C; Yield: 78%; ^{1}H -NMR ($CDCl_3$): δ 10.50 (2H, br, 2xNH), 7.25-7.95 (8H, m, Ar-H), 5.80 (2H, s, OCH_2O), 3.95 (1H, d, J=2Hz, 2-CH), 3.70 (1H, d, J=2Hz, 1-CH), 2.70 (3H, s, 4-CH_3); IR (Nujol) :3310, 3060, 1670, 1620, 1580, 1520, 780 cm^{-1} . Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C 66.11; H 4.68; N 11.57. Found: C 65.89; H 4.65; N 11.56.

5f: mp. 92-94°C; Yield: 48%; ^{1}H-NMR (DMSO-d_6): δ 10.75 (2H, br, 2xNH), 7.30-9.23 (9H, m, Ar-H), 9.35 (1H, d, J=2Hz , 2-CH), 4.10 (1H, d, J=2Hz , 1-CH), 2.70 (3H, s, 4-CH_3); IR (Nujol): 3250, 3075, 1670, 1625, 1580, 1540, 790 cm^{-1}. Anal. Calcd. for $C_{18}H_1N_4O_2$: C 67.50; H 5.00; N 17.50. Found: C 67.57; H 5.08; N 17.42.

5g: mp. 115-118°C; Yield: 62%; ^{1}H-NMR ($CDCl_3$): δ 10.50 (2H, br, 2xNH), 7.25-7.90 (9H, m, Ar-H), 3.80 (1H, d, J=2Hz, 2-CH), 3.65 (1H, d, J=2Hz, 1-CH), 2.75 (3H, s, 4-CH_3); IR (Nujol) : 3310, 3060, 1670, 1615, 1580, 1535, 1440, 1360, 790 cm^{-1}. Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C 62.64; H 4.40; N 15.38. Found: C 62.72; H 4.45; N 15.29.

5h: mp. 106°C; Yield: 38%; ^{1}H-NMR (DMSO-d_6): δ 10.50 (2H, br, 2xNH), 7.20-7.88 (9H, m, Ar-H), 3.75 (1H, d, J=2Hz, 2-CH), 3.55 (1H, d, J=2Hz, 1-CH), 2.70 (3H, s, 4-CH_3); IR (Nujol): 3280, 3060, 1665, 1615, 1575, 1520, 1485, 1355, 785 cm^{-1}. Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C 62.64; H 4.40; N 15.38. Found: C 62.71; H 4.42; N 15.40.

5i : mp. 93-96°C ; Yield: 62% ^{1}H-NMR($CDCl_3$): δ 10.55 (2H, br, 2xNH), 7.30-7.85 (9H, m, Ar-H), 3.80 (1H, d, J=2Hz, 2-CH), 3.55 (1H, d, J=2Hz, 1-CH), 2.70 (3H, s, 4-CH_3) ; IR (Nujol) : 3280, 3050, 1670, 1615, 1570, 1505, 775 cm^{-1}. Anal. Calcd. for $C_{19}H_{16}N_3O_2F$: C 67.65; H 4.75; N 12.46. Found: C 67.70; H 4.82; N 12.38.

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