Synthesis and Pharmacological Activities of 2-Methyl-8-quinolyloxypropylamines

Y. S. R. REDDY*[1], MD. AFZAL AZAM, J. T. LEONARD, B. SURESH AND I. E. CHAKRAVARTHY[2]

J. S. S. College of Pharmacy, Rockland's, Ootacamund-643 001, [1]G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad–500 028, [2]Department of Chemistry, S. K. U. P. G. Center, Kurnool-518 002, India.

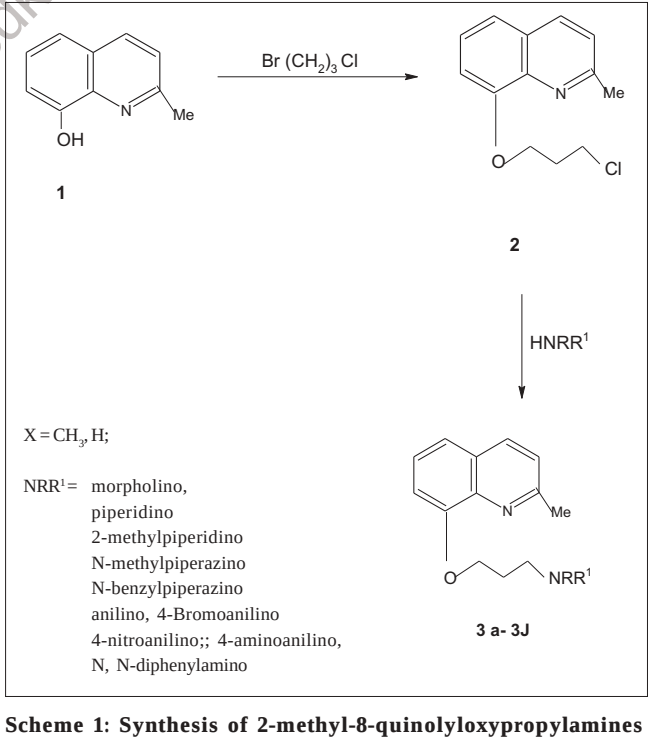
Starting chloropropane derivative (2) was prepared by the reaction of 2-methyl-8-hydroxyquinoline (1) with 1-bromo-3-chloropropane in presence of a base. Various new 1-(2-methyl-8-quinolyloxy)-3-propylamines (3a–3j) have been synthesized by the condensation of 1-(2-methyl-8-quinolyloxy)-3-chloropropane (2) with different amines. Compounds were screened for the possible central nervous system depressant activities. Some of them showed moderate central nervous system depressant activity.

Quinoline ring associated with various pharmacological activities[1]. An 8-substituted quinoline is a versatile lead molecule for designing potential bioactive agents. Due to the potent central nervous system depressant and hypotensive activities[2-4] exhibited by various aminopropanes, it was felt appropriate to synthesize 1-(2-methyl-8-quinolyloxy)-3-substitutedaminopropanes to evaluate their possible central nervous system depressant activities.

The required 1-(2-methyl-8-quinolyloxy)-3-chloropropane (2) was synthesized by condensation of 2-methyl-8-hydroxyquinoline (1) with 1-bromo-3-chloropropane in presence of anhydrous potassium carbonate and dry acetone. Condensation of compounds (2) with various amines yielded the title compounds 1-(2-methyl-8-quinolyloxy)-3-substituted-aminopropanes (3a-3j) as shown in Scheme 1.

Melting points were determined in open capillaries and were uncorrected. The structures of these compounds were assigned on the basis of elemental analysis and spectral data. An IR spectrum was recorded on a Perkin-Elmer Infracord spectrophotometer and PMR on Varian EM-390 spectrophotometer in DMSO-d_6 using TMS as internal reference. The mass spectra were recorded on Jeol 300 at 70 ev. All the compounds gave quite comparable C, H, N elemental analysis with their structures. Purity of the synthesized compounds checked on TLC using silica gel G as an adsorbent with suitable solvent system. The institutional animal ethics committee (IAEC) approved the animal experimentation protocols.

The required 1-(2-Methyl-8-quinolyloxy)-3-chloropropane (2) prepared from a mixture of 2-methyl-8-hydroxyquinoline (20.67 g, 0.13 mol), 1-bromo-3-chloropropane (26.32 g, 0.167 mol) and anhydrous potassium carbonate (26 g, 0.195 mol) was refluxed in dry acetone (420 ml) for 40h, filtered and the solvent was removed under reduced pressure. The residue was recrystallized from ether. Yield: 23.57 g, 77%; mp: 84°; IR(KBr)cm^{-1}: 2960 (C-C), 1610 (C=N), 1565-1590 (C=C) , 1220 (C-O) and 694 (C-Cl); ^{1}H NMR ($CDCl_3$) δ ppm: 1.84 (q, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.62 (m, 2H, CH_2-Cl), 3.79 (m, 2H, OCH_2), 7.14-7.41 (br m, 5H, Ar-H); EI-MS (m/z): 236.103(M^+) . The compound, 1-(2-methyl-8-quinolyloxy)-3-(1-morpholino) propane (3a) prepared from a mixture of 2a



Scheme 1: Synthesis of 2-methyl-8-quinolyloxypropylamines X=CH3, H; NRR'= morpholino, piperidino, 2-methyl piperidino, N-methyl piperazino, N-benzylpiperazino, anilino, 4-bromoanilino, 4-nitroanilino, 4-aminoanilino, N,N-diphenylamino

TABLE 1: PHYSICAL DATA OF THE COMPOUNDS

Compound	X	Y	NRR[1]	Molecular formula	Yield (%)	mp°
2	CH_3	H	-	$C_{13}H_{14}NOCl$	77	84[a]
3a	CH_3	H	morpholino	$C_{17}H_{22}N_2O_2$	68	85[b]
3b	CH_3	H	N-methylpiperazino	$C_{18}H_{25}N_3O$	45	54[b]
3c	CH_3	H	N-benzylpiperazino	$C_{24}H_{29}N_3O$	55	53[b]
3d	CH_3	H	piperidino	$C_{18}H_{24}N_2O$	63	oil
3e	CH_3	H	2-methylpiperidino	$C_{19}H_{26}N_2O$	59	60[c]
3f	CH_3	H	anilino	$C_{19}H_{20}N_2O$	54	oil
3g	CH_3	H	p-nitroanilino	$C_{19}H_{19}N_3O_3$	74	123[d]
3h	CH_3	H	p-aminoanilino	$C_{19}H_{21}N_3O$	59	235[b]
3i	CH_3	H	p-bromoanilino	$C_{19}H_{19}N_2OBr$	73	135[b]
3j	CH_3	H	N, N-diphenylamino	$C_{25}H_{24}N_2O$	50	oil

*Solvents for crystallization: [a]ether, [b]methanol, [c]petroleum ether (40-60°), [d]acetone-ethyl acetate. All the compounds gave satisfactory spectral and elemental analysis data

(2.35 g, 0.010 mol), morpholine (1.044 g, 0.012 mol), anhydrous sodium carbonate (7.42 g, 0.07 mol) and sodium iodide (0.44 g, 0.00 34 mol) was refluxed in dry acetone (40 ml) for 70 h. The reaction mixture was filtered and the filtrate on concentration gave oil, which was purified by column chromatography over silica gel using chloroform as an eluent. Yield: 68%; bp: 85°; IR (KBr) cm^{-1}: 3412 (C-H), 1640 (C=N), 1542-1605 (C=C), 1261 (C-O); ^1H NMR ($CDCl_3$) δ ppm: 1.7 (q, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.65 (t, 4H, CH_2NCH_2) , 3.52 (t, 2H, OCH_2) 3.73 (t, 4H, CH_2OCH_2), 7.23 (m, 5H, Ar-H); EI-MS (m/z): 286.24 (M^+). Similarly other compounds 3b-3j were prepared (Table 1).

The antagonism of pentylenetetrazole-induced convulsions was carried out according to the method suggested by Barnes *et al*[5]. Adult albino mice of either sex weighing between 25-30 g were divided into seven groups of six mice each. Compounds 3a, 3b, 3c, 3e and 3g were given orally as a fine suspension of 0.5% w/v carboxymethylcellulose, 30 min before the administration of pentylenetetrazole at a dose of 0.2 LD_{50} for 2 to 6 groups and pentylenetetrazole (60 mg/kg) to the group 1. The time of onset of action and the time of death/ recovery was noted. Diazepam (5 mg/kg) was used as a standard anticonvulsant drug and the results are recorded in Table 2.

Antagonism of nikethamide-induced hyperactivity in an actophotometer was carried out according to the method of Piala *et a/*[6]. Adult albino mice weighing 25-30 g were taken for this study and were divided into seven groups of six mice each. The compounds 3a, 3b, 3c, 3e and 3g were given orally at a dose of 0.2×LD_{50} mg/kg. After half an hour, nikethamide was given 10 mg/kg ip. Motor activity was measured for 15 min after 5 min of injection of the stimulant. Diazepam (5 mg/kg) was used as a standard drug and the results are recorded in Table 3.

TABLE 2: ANTAGONISM OF PENTYLENETETRAZOLE-INDUCED CONVULSIONS

Compound	Onset of convulsions (min)	Death (min)	Recovery
Pentylenetetrazole	1.30	9.15	-
3a	10.42±0.55*	-	All alive
3b	4.71±0.34	15.5	-
3c	5.64±0.28	45.3	-
3e	14.44±0.29*	-	All alive
3g	17.44±0.25*	-	All alive
Diazepam	No convulsions	-	All alive

Dose of all compounds was fixed at 0.2×LD_{50} value (160, 80, 80, 160, 160 mg/kg, respectively), *p<0.001

TABLE 3: ANTAGONISM OF NIKETHAMIDE-INDUCED HYPERACTIVITY

Compounds	No. of movements observed (15 min)	% reduction in hyperactivity
Nikethamide	48.23	-
3a	22.81±1.13	50.00
3b	20.84±0.88*	56.25
3c	22.46±1.05	52.08
3e	21.27±0.88*	56.42
3g	31.65±0.89	35.42
Diazepam	14.88±0.99*	68.72

All compounds were administered at a dose corresponding to 0. 2×LD_{50}. *p value <0.001 as compared to control group

A newly synthesized five compounds were screened for biological activities. LD_{50} values and gross behavioral study of compounds 3a, 3b, 3c, 3e and 3g were studied by the method of Turner[7]. In general, the entire test compounds shown significant depressant action at a dose of 0.2 LD_{50} level. Compounds 3a, 3e and 3g have maximally increased the onset of pentylenetetrazole-induced convulsions and also have protected the animals from death. Compounds 3b and 3c have moderate anticonvulsant activity (Table 2). Compounds 3a, 3b, 3c and 3e have significantly reduced nikethamide-induce hyperactivity to 50%, while compound 3g shown moderate reduction (Table 3). For anticonvulsant activity, piperazinyl group (3b and 3c) at

3-position of propane is not essential because p-nitroaniline derivative (3g) showed maximum activity. Compounds bearing substituted piperazinyl and piperidinyl groups at 3-position on propane exhibited maximum CNS depressant activity. In general all these compounds were found to be less active than diazepam.

ACKNOWLEDGEMENTS

Authors wish to place their regards to His Holiness Jagadguru Sri Sri Sri Shivarathri Deshikendra Mahaswamigalavaru of Sri Suttur Mutt, Mysore for providing facilities.

REFERENCES

1. Anand, N. and William, A.R., In ; Donald, J.A., Ed ., Burger's Medicinal Chemistry and Drug Discovery, 6th Edn, Vol. V, John Wiley and Sons, New Jersey, 2003, 537.
2. Agarwal, S.K., Kumar, Y., Saxena, A.K., Jain, P.C. and Anand, N., **Indian J. Chem.**, 1982, 21, 435.
3. Sur, R.N., Shankar, G., Rathore, R.K.S., Chak, I.M., Agarwal, S.K. and Jain, P.C., **Indian J. Exp. Biol.**, 1980, 18, 1190.
4. Agarwal, S.K., Saxena, A.K., Jain, P.C., Anand, N., Srimal, R.C. and Dhawan, B.N., **Indian J. Chem.**, 1990, 30, 413.
5. Barnes, J.H., Margnerite, V.A., Chapman, O., Mccrea, P.A., Marshall, P.G. and Walsh, P.A., **J. Pharm. Pharmacol.**, 1961,13, 39.
6. Piala, J.J., Hogh, J.P., Hassert, G.L., Burke, J.C. and Craver, B.N., **J. Pharmacol. Exp. Therap.,** 1959,127, 55.
7. Turner, R.A., In; Screening Methods in Pharmacology, 2nd Edn, Academic press, New York, 1965, 302.

Accepted 7 February 2007
Revised 7 April 2006
Received 14 July 2005
Indian J. Pharm. Sci., 2007, 69 (1): 112-114