

2-Naphthyloxy Derivatives of *N,N*-Substituted Acetamides: Synthesis and Pharmacological Evaluation

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The present research was designed to synthesize some 2-naphthyloxy derivatives of *N,N*-substituted acetamides employing the secondary amino moiety and insertion of $-OCH_2-$ group between the aromatic ring and the side chain. 2-Naphthol was condensed with methylchloroacetate followed by fusion with different amines to give target compounds 3a-3f. The compounds synthesized after pharmacological investigations have been found to possess significant anti-amnesic activity when compared with piracetam. Compounds 3b, 3d, 3f showed dose dependent anti-amnesic effect with 3b being most potent. Further, neuropsychopharmacological studies (hypnotic, anti-convulsant, anti-anxiety, locomotor, muscle relaxant, antidepressant and anti-amnesic activities) on 3b confirmed its memory enhancing potential which was comparable to piracetam, a known nootropic agent.

The most comprehensive and integrated approach towards the discovery of memory and cognition facilitating drugs has been based on the functions of central cholinergic system¹. The brains of persons with severe cognition disorders show consistently depleted acetylcholine levels²⁻⁴. Several classes of drugs are useful in improving memory-cognitive ability including acetylcholinesterase inhibitors⁵, muscarinic receptor agonists and antagonists⁶, nicotinic receptor agonists⁷, neurotrophic factor stimulants⁸, neuropeptides⁹ and psychostimulants¹⁰. Nootropics¹¹ like piracetam, nefiracetam, pramiracetam¹², oxiracetam are pyrrolidineacetamides, which show consistently, elevated acetylcholine levels in the cortical and hippocampal areas of the brain, which are mainly affected in memory disorders. The racetams are closely related in structure to the amino acid pyroglutamic acid (2-oxo-pyrrolidine carboxylic acid) and differ only in the side chain¹³. These nootropic agents are among the pharmacological safe drugs¹⁴. Piracetam has been in use for many years as a memory enhancer¹⁵. Besides, it increases blood flow at the capillary level, which is thought to contribute to its memory enhancing action. It also

increases the ATP/ADP turnover ratio, suggesting a direct metabolic effect in the brain¹⁶. Antihypoxic drugs like *N*-(2-dimethylaminoethyl) carboxamides and dimethylaminoethylethers which are most stable analogues of choline-*O*-acetate are quite active in amnesia reversal, as memory and learning disabilities have been reported in the hypoxic state¹⁷. Based on the structural data some common features can be deduced in all the pharmacological divergent classes: a basic nitrogen which may be part of the heteroaromatic ring or cyclic/acyclic system intended to interact electrostatically with the appropriate target, a hydrogen bond acceptor function; an appropriate linker group giving optimal spacing to the hydrogen bond acceptor function from the basic nitrogen.

The nootropics bifemelane, indeloxazine and piracetam¹⁷ also demonstrate certain structural resemblance to various cholinergic compounds in containing one hydrogen bond acceptor moiety and a basic nitrogen. An introspection of the active compounds of different types reveals the correlation of the compounds with the structure of endogenous neurotransmitter acetylcholine and is considered in postulating the design strategy for the compounds included in the current research project.

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MATERIALS AND METHODS

Melting points were determined on a Veego melting point apparatus and were uncorrected. Infrared and ultra-violet spectra were recorded on Perkin-Elmer 882 and Lambda 15 spectrophotometer models respectively. ^1H NMR spectra were recorded on a Bruker AC 300F NMR spectrophotometer (300 MHz) using TMS as internal standard. Chemical shifts are expressed in δ ppm. Elemental analyses were carried out on Perkin Elmer 2400 model. Plates for TLC were prepared with silica gel G according to Stahl (E. Merck) using ethyl acetate as the solvent. Iodine vapours were used to develop the TLC plates. Anhydrous sodium sulphate was used as a drying agent. Laca mice of either sex were taken from Central Animal house of Panjab University and fed with standard diet and water *ad libitum*. All the animal experiments were carried out at University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh and permission for conducting these experiments was obtained from Institutional Animal Ethical Committee. Piracetam (Brown and Burk Pharmaceuticals, Bangalore) was used as the reference drug against which all the test compounds were compared. The results obtained are expressed in mean \pm S.E.M. values and were analyzed by one way analysis of variance (ANOVA) followed by Dunnet's test or Turkey's test.

Methyl 2-(2-naphthyloxy)acetate 2:

Methylchloroacetate (2.0 ml, 2.74 mmol) and potassium iodide (20 mg) were added to a refluxing solution of 2-naphthol (1) (1.0 g, 6.94 mmol) and anhydrous potassium carbonate (2.0 g) in ethyl methyl ketone (50 ml) and the contents were refluxed further with continuous stirring for 7 h. The slurry obtained was cooled, filtered and the solvent was removed under reduced pressure. The residue obtained was crystallized to afford¹⁸ methyl 2-(2-naphthyloxy)acetate 2. Crystallization solvent- methanol, Yield-44.33%, MP-68-70°, UV_{max} (MeOH) E_1 band 229.4 ($\log \epsilon$ 1.3), IR (KBr; cm^{-1}): 3020 (aromatic C-H), 1745 ($>\text{C}=\text{O}$), 1580 (C-C ring stretch), 1200 (C-C(=O)-O), 1075 (ν_{as} C-O-C), 820 (aromatic C-H bend), ^1H NMR (δ ppm) 3.81 (3H, s, $-\text{COOCH}_3$), 4.74 (2H, s, $-\text{OCH}_2-$), 7.06 (1H, d, ortho to alkoxy), 7.22 (Ar-H ortho to alkoxy), 7.40 (2H, m, Ar-H), 7.73 (3H, m, Ar-H). Calculated for $\text{C}_{13}\text{H}_{12}\text{O}_3$: C, 72.20; H, 5.60, found: C, 72.40, H, 5.19.

General Procedure:

Methyl 2-(2-naphthyloxy)acetate (2) (2 ml, 2.74 mmol) was fused with 2 ml of different amines like *N*-methylpiperazine, pyrrolidine, piperidine, morpholine, 3-pipecoline and *N,N*-dimethylamine respectively at fusion

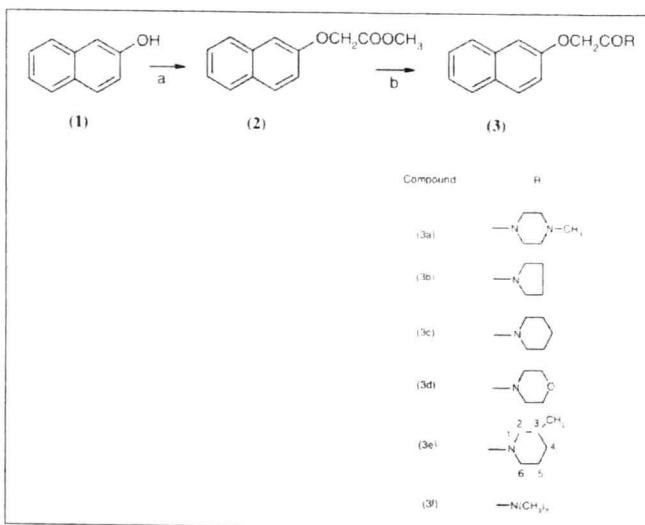
temperatures and reaction was monitored with the help of TLC. The oily product obtained was treated with ice-cold water to obtain the precipitate which was filtered, dried and crystallized to afford the target compounds 3a-3f (Scheme 1).

1-(2-Naphthyloxymethylcarbonyl)-4-methylpiperazine 3a:

Crystallization solvent- ethanol, yield-78.17%, MP- 110-112°, UV_{max} (MeOH) E_1 band 229 ($\log \epsilon$ 2.50), E_2 band 270.2 ($\log \epsilon$ 1.67), B band 325 nm ($\log \epsilon$ 1.22), IR (KBr; cm^{-1}): 3010 (aromatic C-H), 1650 ($>\text{C}=\text{O}$), 1450 (C-N stretch), 1200 (ν_{as} C-O-C), 1020 (ν_{s} C-O-C), ^1H NMR (δ ppm) 2.27 (3H, s, $>\text{NCH}_3$), 2.36 (4H, quin, $>\text{N}$ -methylenes of *N*-methyl piperazine), 3.63 (4H, quin, methylenes adjacent to *N*-function of *N*-methylpiperazine), 4.70 (2H, s, $-\text{OCH}_2-$), 7.20 (2H, m, Ar-H ortho to alkoxy), 7.40 (2H, m, Ar-H), 7.75 (3H, m, Ar-H). Calculated. for $\text{C}_{17}\text{H}_{20}\text{O}_2\text{N}_2$: C, 71.80; H, 7.09; N, 9.85, found: C, 72.20, H, 7.40; N, 10.21.

1-(2-Naphthyloxymethylcarbonyl)pyrrolidine 3b:

Crystallization solvent- acetone, yield-86.39%, MP- 124-126°, UV_{max} (MeOH) E_1 band 230.2 ($\log \epsilon$ 2.46), E_2 band 270.2 ($\log \epsilon$ 1.76), B band 325 nm ($\log \epsilon$ 1.32), IR (KBr; cm^{-1}): 3010 (aromatic C-H), 1660 ($>\text{C}=\text{O}$ stretch), 1440 (C-N stretch), 1260 (ν_{as} C-O-C), 1075 (ν_{s} C-O-C), ^1H NMR (δ ppm) 1.85 (4H, m, pyrrolidine protons), 3.50 (4H, m, $>\text{N}$ -methylenes of pyrrolidine function), 4.70 (2H, s, $-\text{OCH}_2-$), 7.20



Scheme 1: Synthetic procedure of naphthyloxy acetamides 3a-3f.

Reagents and conditions: (a) $\text{ClCH}_2\text{COOCH}_3$, reflux. (b) amines, fusion.

2H, m, Ar-*H* ortho to alkoxy), 7.40 (2H, m, Ar-*H*), 7.75 (3H, m, Ar-*H*). Calculated for C₁₆H₁₇O₂N: C, 75.27; H, 6.71; N, 5.48, found: C, 75.27, H, 6.30; N, 5.87.

1-(2-Naphthyloxymethylcarbonyl)piperidine 3c:

Crystallization solvent-petroleum ether, yield-84.14%, MP- 80-84°, UV_{max} (MeOH), E₁ band 230.4 (log ε 2.51), E₂ band 270.4 (log ε 1.85), B band 325.2 nm (log ε 1.42), IR (KBr; cm⁻¹): 3010 (aromatic C-H), 1680 (>C=O stretch), 1420 (C-N stretch), 1260 (ν_{as} C-O-C), 1070 (ν_s C-O-C), ¹H NMR (δ ppm) 1.55 (6H, m, piperidine protons), 3.46 (2H, t, *N*-methylene of piperidino function), 3.55 (2H, t, *N*-methylene of piperidino function), 4.75 (2H, s, -OCH₂-), 7.20 (2H, m, Ar-*H* ortho to alkoxy), 7.39 (2H, m, Ar-*H*), 7.74 (3H, m, Ar-*H*). Calculated for C₁₇H₁₉O₂N: C, 75.81; H, 7.11; N, 5.20, found: C, 76.01, H, 7.24; N, 5.11.

1-(2-Naphthyloxymethylcarbonyl)morpholine 3d:

Crystallization solvent- acetone, yield-84.80%, MP- 143-145°, UV_{max} (MeOH) E₁ band 230.8 (log ε 2.51), E₂ band 270.4 (log ε 1.86), B band 325 nm (log ε 1.41), IR (KBr; cm⁻¹): 1660 (>C=O stretch), 1420 (C-N stretch), 1205 (ν_{as} C-O-C), 1010 (ν_s C-O-C), ¹H NMR (δ ppm) : 3.64 (8H, s, morpholine protons), 4.76 (2H, s, -OCH₂-), 7.15 (2H, m, Ar-*H* ortho to alkoxy), 7.40 (2H, m, Ar-*H*), 7.75 (3H, m, Ar-*H*). Calculated for C₁₆H₁₇O₃N: C, 70.83; H, 6.32; N, 5.16, found: C, 71.01, H, 6.72; N, 5.26.

3-Methyl-*N*-(2-naphthyloxymethylcarbonyl)piperidine 3e:

Crystallization solvent- acetone, yield-76.01%, MP- 90-92°, UV_{max} (MeOH) E₁ band 231.6 (log ε 2.53), E₂ band 270.4 (log ε 1.90), B band 325.2 nm (log ε 1.45), IR (KBr; cm⁻¹): 1650 (>C=O stretch), 1430 (C-N stretch), 1245 (ν_{as} C-O-C), 1075 (ν_s C-O-C), ¹H NMR (δ ppm) 0.89 (3H, m, -CH₃), 1.12 (1H, m, 3-*CH*), 1.45 (2H, m, 4-*CH*₂), 1.65 (1H, m, 5-*CH*), 1.80 (1H, m, 5-*CH*), [2.30 (t, *J*=12Hz) and 3.0 (t, *J*=12Hz)] both integrated for one proton 2-*CH*, 2.68 (1H, q, 6-*CH*), 3.85 (1H, t, 2-*CH*), 4.40 (1H, m, 6-*CH*), 4.78 (2H, s, -OCH₂-), 7.20 (2H, m, Ar-*H* ortho to alkoxy), 7.40 (2H, m, Ar-*H*), 7.75 (3H, m, Ar-*H*). Calculated for C₁₈H₂₁O₂N: C, 76.29; H, 7.47; N, 4.94, found: C, 76.83, H, 7.93; N, 4.87.

N,N-Dimethyl-2-(2-naphthyloxy)acetamides:

Crystallization solvent- acetone, yield-46.21%, MP- 72-76°, UV_{max} (MeOH) E₁ band 230 (log ε 2.43), E₂ band 270.4 (log ε 1.90), B band 325 nm (log ε 1.46), IR (KBr; cm⁻¹): 1650 (>C=O stretch), 1430 (C-N stretch), 1070 (ν_s C-O-C), ¹H NMR (δ ppm) : 2.97 (3H, s, >*N*-CH₃), 3.09 (3H, s, >*N*-CH₃), 4.78 (2H, s, -OCH₂-), 7.15 (2H, m, Ar-*H* ortho to alkoxy),

7.40 (2H, m, Ar-*H*), 7.75 (3H, m, Ar-*H*). Calculated for C₁₄H₁₅O₂N: C, 73.34; H, 6.60; N, 6.11, found: C, 74.00, H, 6.26; N, 6.27.

Antiamnesic activity:

All the compounds 3a-3f were screened for antiamnesic activity using elevated plus maze model. Transfer latency (TL) on elevated plus maze was used as an index of learning and memory processes¹⁹⁻²². Mice weighing 20-25 g were divided into five groups of five animals each. All the drugs 3a-3f were suspended in 0.5% CMC and administered per orally. The time taken by each mouse to move from the end of open arm to any of closed arm of elevated plus-maze was measured on 1st d and after 24 h of drug treatment. The results are expressed as percent retention in fig. 1. The antiamnesic activity of these active compounds was more pronounced as compared to standard drug piracetam with 3b showing maximal antiamnesic effect and was therefore investigated in detail. The test compound 3b was suspended in 0.25% carboxymethylcellulose (CMC) and administered intraperitoneally at various doses up to 40 mg/kg. Piracetam was used as a positive standard and diazepam as a negative standard. The results are expressed as percent retention (Table 1 and 2).

Hypnotic activity:

Pentobarbitone-induced loss of righting reflex in mice

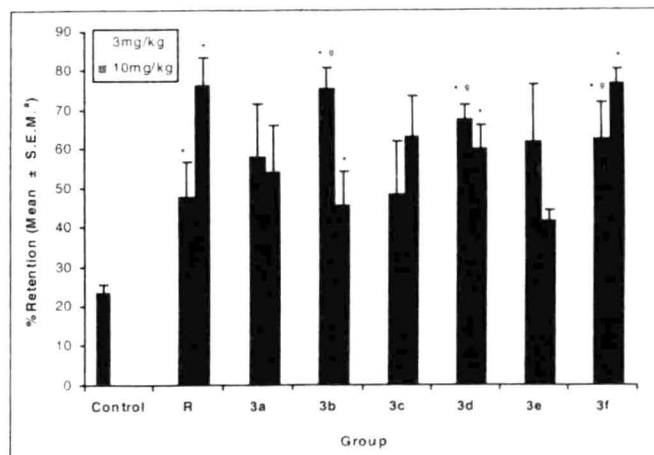


Fig. 1: Percent retention measured on elevated plus maze in mice.

Effect of various compounds (3a-3f) and reference drug piracetam, (R)(3 and 10 mg/kg, p.o.) **p*<0.05 as compared to the control group, °*p*<0.05 as compared to the reference drug. (ANOVA followed by Turkey's test). n=5, S.E.M., Standard Error of Mean.

TABLE 1: EFFECT OF COMPOUND 3b AND PIRACETAM ON TRANSFER LATENCY

Treatment	Dose(mg/kg)	Transfer latency (sec) Mean±S.E.M	
		d 1	d 2
Control	--	37.4±2.2	26.2±1.4
Compound 3b	10	29.0±1.2	8.2±1.06*
Compound 3b	20	28.8±2.5	6.2±0.86*
Compound 3b	40	28.2±2.2	6.4±0.81*
Piracetam	10	30.2±1.9	6.6±1.07*
Diazepam	2	42.0±2.0	37.0±2.0

n=5, *p≤0.05 as compared to control group.

was used to evaluate the hypnotic activity²³. Three groups of five mice each (18-25 g) were selected and pentobarbitone (dose 45 mg/kg, i.p.) was injected. Onset of sleep and duration of sleep were recorded after the injection of pentobarbitone in each mouse. The mean value for each group was calculated and compared with the control. Chlorpromazine was used as standard for comparison and results are recorded in Table 3.

Reversal of scopolamine-induced amnesia:

Reversal of scopolamine-induced amnesia²⁴ by the test compound was studied using elevated plus-maze. Five groups of five mice each were selected and scopolamine at a dose 0.3 mg/kg was administered to four groups. One group received only vehicle and was treated as control group. The time taken by each mouse to move from the end of open arm to any of closed arm on the 1st d and 2nd d was measured and used for comparison. Piracetam was used as a positive standard and each drug was suspended in 0.25% CMC and administered intraperitoneally. The results are expressed in Table 4 as mean±SEM.

Passive avoidance step down task paradigm:

The acquisition and retention of learned task is stud-

ied by using passive-avoidance step down task paradigm²⁵. Four groups of six mice each (18-25 g) were selected and all drugs suspended in 0.25% CMC were administered intraperitoneally. Each mouse was trained individually, then after 1 h, 24 h and 7 d the latency in reaching shock free zone (SFZ) and number of mistakes were noted as parameters for acquisition and retention respectively. The mean

TABLE 2: EFFECT OF COMPOUND 3b ON PERCENT RETENTION

Treatment	Dose (mg/kg)	%Retention (mean±S.E.M.)
Control	--	29.70±0.83
Compound 3b	10	71.60±3.4*
Compound 3b	20	78.41±3.5*
Compound 3b	40	77.20±2.5*
Piracetam	10	78.54±2.4*
Diazepam	2	11.96±0.87*

*p≤0.05 as compared to control group.

TABLE 3: EFFECT OF COMPOUND 3b AND CHLORPROMAZINE ON PENTOBARBITONE-INDUCED SLEEP TIME

Treatment	Dose(mg/kg)	Mean±S.E.M.	
		Onset of action	Duration of action
Pentobarbitone (PB)	45	2.5±0.13	111±2.5
Compound 3b+PB	20+45	2.8±0.1*	89.4±2.5*
Chlorpromazine+PB	3+45	2.2±0.1	167±3.7*

n=5, *p≤0.05 as compared to pentobarbitone alone.

TABLE 4: EFFECT OF COMPOUND 3b AND ITS COMBINATION WITH PIRACETAM ON TRANSFER LATENCY

Treatment	Dose(mg/kg)	Transfer latency (sec) Mean±S.E.M	
		d 1	d 2
Control	-	44.4±2.4	33.2 ±2.4
Scopolamine	0.3	36.0±1.8	54.2±1.2*a
Comp.3b+Scopolamine	20+0.3	44.0±1.7	16.4±1.2*a
Piracetam+Scopolamine	10+0.3	37.8±21.6	13.8±1.4*a
Comp.3b+Piracetam+Scopolamine	10+10+0.3	34.4±1.6	6.6±0.9*a

n=5, *p<0.05 as compared to control group, ^ap<0.05 as compared to scopolamine.

TABLE 5: EFFECT OF COMPOUND 3b AND CHLORPROMAZINE ON PENTOBARBITONE-INDUCED SLEEP TIME

Treatment	Dose (mg/kg)	Mean±S.E.M.					
		1 h		24 h		7 days	
		Latency (sec)	Mistakes (No)	Latency (sec)	Mistakes (No)	Latency (sec)	Mistakes (No)
Control	-	8.5±0.7	10.5±1.1	8.3±1.0	8.0±0.57	8.8±0.6	6.8±0.6
3b	20	8.5±0.7	4.0±0.6*	5.0±0.6*	2.3±0.57*	2.5±0.4*	2±0.4*
Piracetam	10	6.0±0.6*	3.1±0.47*	3.0±0.6*	2.4±0.6*	2.1±0.5*	1.8±0.5*
Diazepam	2	69.8±2*	2.8±0.6*	5.8±0.9*	96±0.8	13.8±1*	7.1±0.6

Latency to reach shock free zone and no. of mistakes are reported after 1 h, 24 h and 7 days, *p<0.05 as compared to control group.

value for each group was calculated and compared with control. The results are expressed in Table 5. Diazepam was used as a negative standard.

RESULTS AND DISCUSSION

All the compounds synthesized are consistent with their proposed structures²⁶⁻²⁸. The compounds showed characteristic IR peaks at 1020-1075, 1200-1260 (C-O-C stretching), 1420-1450 (C-N stretching), 1650-1680 (C=O stretch of amides) and 3010-3080 cm⁻¹ (aromatic stretching). The compounds 3a-3f showed the characteristic peaks in ¹H NMR at δ 4.7-4.8, which confirms presence of -OCH₂ group and δ 7-8 ppm confirms the presence of aromatic protons. Of all the test compounds, synthesized compounds 3b, 3d, 3f showed significant dose-dependent anti-amnesic effect (fig. 1) with peak effect at 5 mg/kg and with 3b showing maximal anti-amnesic effect. Neuropsychopharmacological profile studies on 3b demonstrated that it had memory enhancing potential when tested on elevated plus-maze (Table 1) and

modified passive avoidance paradigms (Table 2). It may have acted via cholinergic mechanisms because it reversed the scopolamine-induced amnesia and its effect was comparable to piracetam, a known nootropic agent. It showed decrease in onset and increase in the duration of action of pentobarbitone-induced sleep time (Table 3) while it had no anti-anxiety, anticonvulsant and antidepressant activities and showed no effect on locomotor activity and muscle relaxant property.

ACKNOWLEDGEMENTS

The authors are grateful to University Grants Commission, New Delhi, India for providing financial assistance to carry out this work.

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