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SYNTHESIS AND STUDY OF POTENTIAL COGNITION ENHANCERS DERIVED FROM *M* –NITROPHENOL

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ABSTRACT

Objective: Synthesis and evaluation of some potential memory enhancer derivatives from m-nitrophenol. **Materials and methods:** m-nitrophenol on refluxing with 1-bromo-3-chloropropane in ethyl methyl ketone in presence of anhydrous potassium carbonate synthesize the intermediate (**38**) which on treatment with acylic/ heterocyclic ring systems (N, N-diethyl amine and various cycloamino moieties such as pyrrolidine, morpholine, N-methyl piperazine and imidazole) synthesize target compounds (**D1-D5**) which were screened for nootropic activity. Transfer latency on elevated plus maze was used an index of learning and memory process.

Results: Pharmacological results are expressed as % retention (Mean ± SEM) using ANOVA followed by Dunnet's test using Sigma stat. **Conclusion:** All compounds possess considerable memory enhancing activities when compared with control and standard drug, piracetam (1 mg/kg) of body weight.

KEYWORDS: m-nitrophenol, nootropic activity, 1-bromo-3-chloropropane, heterocyclic ring.

1. INTRODUCTION

Amnesia is a condition in which memory is lost. It is the starting stage of memory impairment[1]. Memory loss may result from two-sided (bilateral) damage to parts of the brain vital for memory storage, processing or recall (the limbic system, including the hippocampus

in the medial temporal lobe)[2]. The causes of amnesia have traditionally been divided into the "organic" or the "functional". Organic causes include damage to the brain through physical injury, neurological disease or the use of certain (generally sedative) drugs. Functional causes are psychological factors, such as mental disorder, post-traumatic stress or, in psychoanalytic terms, defense mechanism[3].

Advances in our understanding of central nervous system functioning in health and disease have brought with them the potential for altering that functioning with psychoactive substances. The search for interventions that might stop cognitive decline was initiated within dementia research and other neurodegenerative and neuro developmental conditions. Much has been discovered about the cellular and molecular basis of learning and memory in several species although we still do not know comprehensively how new information is perceived, stored, consolidated and retrieved or forgotten over timescales that vary from seconds to decades. The next 20 years are likely to bring much greater understanding of learning and memory and our ability to manipulate these pathways will undoubtedly increase. The central mechanism thought to underpin memory is synaptic plasticity [4] changes in the strength and size of synapses that increase or decrease efficiency of transmission. Roles in learning, memory and forgetting are also attributed to new synapse formation (synaptogenesis) and loss, the proliferation and survival of new neurons (neurogenesis), and neuronal cell death (neurotoxicity and apoptosis). Each process provides possible targets for cognition enhancement and selective forgetting in healthy people while processes important in disease-associated cognitive decline are important targets for early therapeutic intervention[5].

Cognition enhancement' is the use of various strategies to boost cognitive functions i.e. mental states that underpin information-processing tasks such as attention, memory, and selective forgetting. The term was originally used for the treatment of disease-associated cognitive impairment, such as in dementia and schizophrenia. Subsequently, the term expanded to encompass the use of interventions for mild cognitive impairment (MCI), currently defined as cognitive deficits that do not overtly impair function. Now 'cognition enhancement' is applied to the use of interventions for normal ageing and in well people for non-medical purposes[6].

Many compounds have been claimed to be endowed with cognition enhancing activity but few of them have reached the market in some countries for memory disturbances. In contrast to previous serendipitous discovery, current research aims to design and synthesize new

compounds, on the basis of present information about neuropathobiology of cognitive processes. Some reported compounds acting with different mechanisms that have been shown to possess cognition enhancing properties and some of them are in development for this use. They are classified under second generation cognition enhancers[7]. It is hoped that the new recently disclosed compounds, that seem to be endowed with unprecedented high potency will contribute to elucidate the mechanism of action of the class and this research has for such more to continue search for such more effective newer cognition enhancers to develop drugs with novel pharmacological profiles and maximal therapeutic benefits[8].

2. MATERIALS AND METHODS

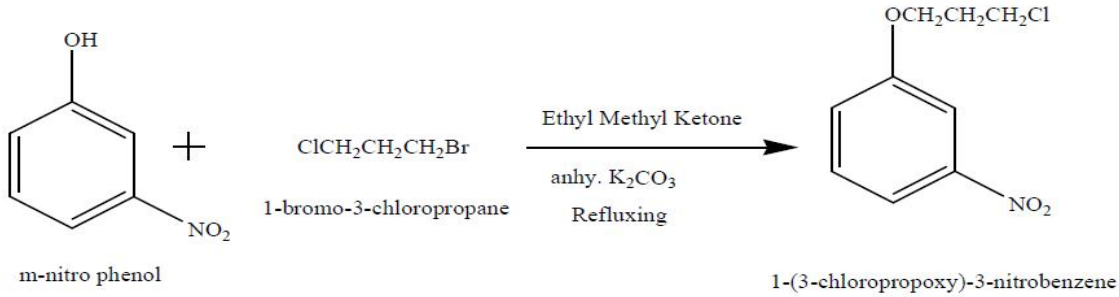
2.1. Chemicals and Equipments

Melting points were determined by thieles's tube method using liquid paraffin and were uncorrected. Infared (IR) spectra were recorded on a Shimadzu (Japan) 8201PC FTIR spectrophotometer model using nujol and potassium bromide and on Perkin Elmer RX1 using potassium bromide cell for liquid sample and potassium bromide pellets for solid samples (υ in cm-1). Nuclear magnetic resonance (NMR) were recorded on a Bruker DRX–300 spectrometers model. The purity of compounds was established by thin layer chromatography (TLC). Iodine was used to develop the TLC plates. All the solvents were distilled prior to use according to standard procedures. Anhydrous potassium carbonate was used as drying agent. Piracetam (Ranbaxy), 1 mg/kg of body weight was used as the reference drug against which all the test compounds were compared. *m*-nitrophenol (SDFCL fine chemicals), morpholine (Merck), diethyl amine (Merck), pyrrolidine (Himedia), imidazole (Rankem), ethyl methyl ketone (Rankem). And anhydrous potassium carbonate (Rankem). Organic solvents - Ethyl alcohol, methanol, hexane, chloroform from Loba Chemicals and all are laboratory grade.

2.2. Experimental

2.2.1. Preparation of 1-(3-chloropropoxy)-3 –nitrobenzene

m-nitrophenol **(37)** (1 g) was dissolved in ethyl methyl ketone (25 ml) and anhydrous potassium carbonate (2.0 g) was added to the solution. The reaction mixture was refluxed for half an hour at 80 ^{o}C. Then, chlorobromo propane (2.5 ml) was added, continued refluxing for 5 hours and reaction was monitored with the help of TLC. The slurry was filtered and the solvent was removed under reduced pressure.



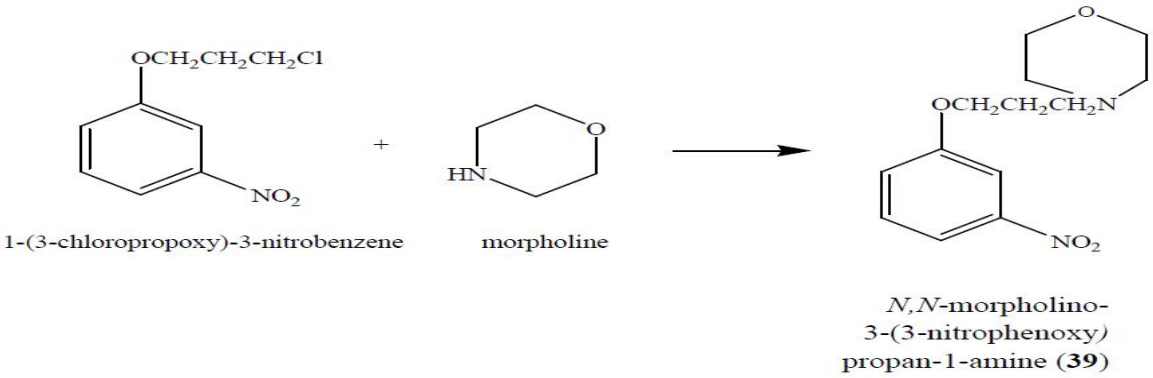
(**38**)

IR spectrum (ν_{max}, cm^{-1}): 2979.7 (C-H stretch), 1248.4 (C-O-C asym. stretch), 1038.3 (C-O-C sym. stretch), 588.8 (C-Cl stretch).

^{1}H NMR ($CDCl_3$) (δ, ppm) : 7.83(d, 1H, Ar*p* proton to alkoxy group), 7.75(t, 1H, Ar*m* proton to alkoxy group) 7.46 (d, 1H, Ar*p* proton to nitro group), 7.33 (s,1H, Ar*o* proton in between nitro & alkoxy group),4.22 (t, 2H, -OCH2CH2CH2-), 3.57 (t, 2H,-OCH2CH2CH2-), 2.31(p, 2H, -OCH2CH2CH2).

2.2.2. Preparation of *N, N*-morpholino-3-(3-nitrophenoxy*)* propan-1-amine (D2)

1-(3-chloropropoxy)-3-nitrobenzene (**38**) and morpholine (1ml) were stirred magnetically for 14 hours and the solid obtained was crystallized from methanol to obtain the target compound (**39**).



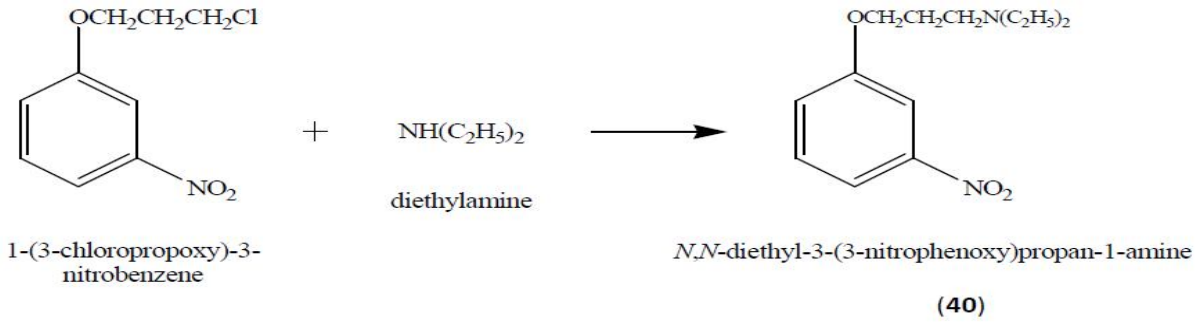
IR spectrum (ν_{max}, cm^{-1}): 3014.6 (C-H stretch), 1247.0 (C-O-C asym. stretch), 1038.1 (C-O-C sym. stretch), 1287.3 (C-N stretch), 1117.0 (C-O-C ring stretch), 1038.1 (3°Amine C-N stretch).

^{1}H NMR ($CDCl_3$) (δ, ppm) : 7.82 (d, 1H, Ar*p* proton to alkoxy group), 7.75 (t, 1H, Ar*m* proton to alkoxy group), 7.47 (s, 1H, Ar*o* proton in between nitro & alkoxy group), 7.25 (d, 1H, Ar*p* proton to nitro group), 3.85 (t, 2H,-OCH2CH2CH2), 2.68 (t, 4H, -CH2-

NCH2CH2O- of morpholino ring), 2.52 (t, 4H,C-H2NCH2CH2O), 2.29 (p, 2H, -OCH2CH2CH2-), 2.06 (t, 2H, -OCH2CH2CH2).

2.2.3. Preparation of *N, N*-diethyl-3-(3-nitrophenoxy) propan-1-amine (D5)

1-(3-chloropropoxy)-3-nitrobenzene (**38**) and diethyl amine (1ml) were magnetically stirred at 80 ^{o}C temperature for 32 hours and the solid obtained was crystallized from methanol to obtain the target compound (**40**).



1-(3-chloropropoxy)-3-nitrobenzene

N,N-diethyl-3-(3-nitrophenoxy)propan-1-amine

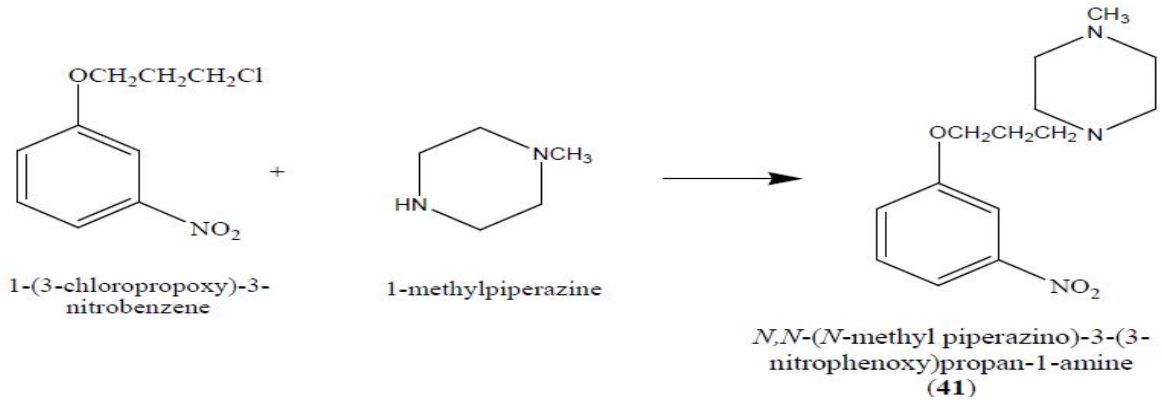
(40)

IR spectrum (ν_{max}, cm^{-1}): 3022.0 (C-H stretch), 1247.5(C-O-C asym. stretch), 1039.9(C-O-C sym. stretch), 1287.2(C-N stretch), 1093.5 (3^{0}Amine C-Nstretch).

^{1}H NMR ($CDCl_3$) (δ, ppm) : 7.84 (d, 1H, Ar*p* proton to alkoxy group), 7.74 (t, 1H, Ar*m* proton to alkoxy group), 7.71 (d, 1H, Ar*p* proton to nitro group), 7.69 (s, 1H, Ar*o* proton in between nitro & alkoxy group), 3.77 (t, 2H, -OCH2CH2CH2-), 2.96 (t, 2H, -OCH2CH2CH2-), 2.93 (p, 2H, -OCH2CH2CH2-), 2.31 (q, 4H, -N $(CH2CH3)_2$, δ1.52 (t, 3H, $N(CH2CH3)_2$, 1.25 (t, 3H, $-N(CH2CH3)_2$.

2.2.3. Preparation of *N, N*-(N-methyl piperazino)-3-(3-nitrophenoxy) propan-1-amine (D4)

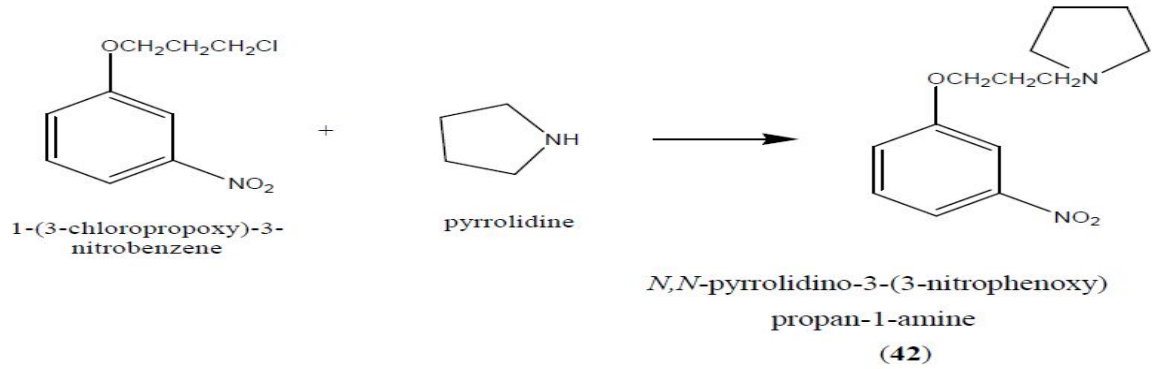
1-(3-chloropropoxy)-3-nitrobenzene (**38**) and N-methyl piperazine (1ml) were magnetically stirred for 6 hours and then solid obtained was crystallized from methanol to obtain target compound (**41**).



IR spectrum (ν_{max}, cm^{-1}): 3022.1 (C-H stretch), 1246.9 (C-O-C asym. stretch), 1039.5 (C-O-C Sym stretch), 1286.9 (C-N stretch), 1096.2 (3º Amine C-N stretch).

2.2.4. Preparation of *N, N*-pyrrolidino-3-(3-nitrophenoxy) propan-1-amine (D3)

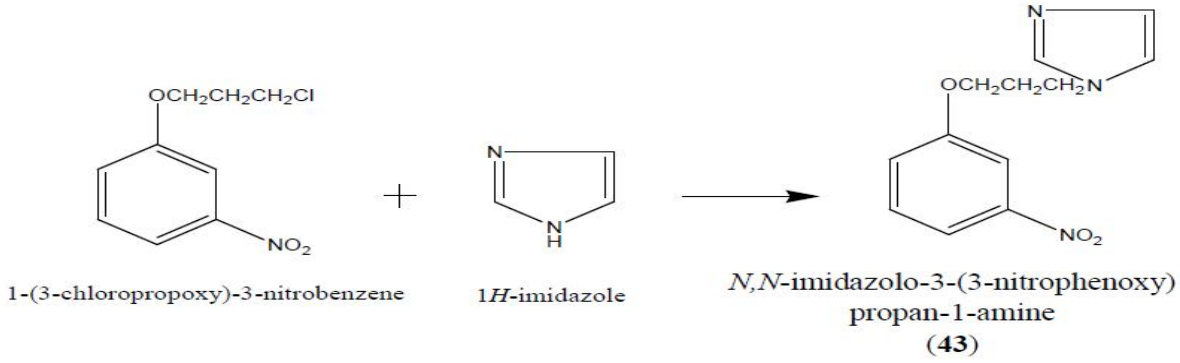
1-(3-chloropropoxy)-3-nitrobenzene (**38**) and pyrrolidine (1ml) were magnetically stirred at 80 ^{o}C temperature for 18 hours and the semisolid obtained was crystallized from a mixture of acetone and methanol to obtain target compound (**42**).



IR spectrum (ν_{max}, cm^{-1}): 2965.0 (C-H stretch), 1246.4 (C-O-C asym. stretch), 1029.6 (C-O-C sym. stretch), 1288.4 (C-N stretch), 1029.6 (3ºAmie C-N stretch).

2.2.5. Preparation of *N, N*-imidazolo-3-(3-nitrophenoxy) propan-1-amine (D1)

1-(3-chloropropoxy)-3-nitrobenzene (**38**) and imidazole were magnetically stirred at 80 ^{o}C temperature for 35 hours. Crushed ice was added to the contents and the semisolid obtained which was separated with chloroform by separating funnel and compound obtained in chloroform layer by the help of TLC and concentrated, the chloroform layer to obtain target compound (**43**).



1-(3-chloropropoxy)-3-nitrobenzene 1*H*-imidazole *N,N*-imidazolo-3-(3-nitrophenoxy) propan-1-amine (**43**)

IR spectrum (ν_{max}, cm^{-1}): 3097.4 (C-H stretch), 1246.7 (C-O-C asym. stretch), 1035.8 (C-O-C sym. stretch), 1286.6 (C-N stretch), 1529.7 (C=N stretch), 1096.5 (3°Amine C-N stretch).

^{1}H NMR ($CDCl_3$) (δ, ppm) : 7.81 (d, 1H, Ar*p* proton to alkoxy group), 7.81 (d, 1H, Ar*p* proton to nitro group), 7.31 (t, 1H,Arm proton to alkoxy group), 7.28 (s, 1H, Ar*o* proton in between nitro & alkoxy group), 7.23 (d, 1H, -N-CH-CH-N of imidazole ring), 7.25 (d, 1H, -N-CH-CH-N of imidazole ring), 7.24 (s,1H,-N-CH=N- of imidazole ring).

2.3. Animals

Adult Wister albino rats of either sex weighing up to 200 gm were housed in polypropylene cages and fed with standard diet (Ashirwad Feeds Ltd., Chandigarh, India) and *ad libitum*. The animals were exposed to alternate cycle of 12 h of light and dark. The study protocol was reviewed and approved by the Institution Animal Ethical Committee (Registration no. IAEC/273/CPCSEA/09/I/2256/15) and conforms to the CPCSEA Guidelines for the use and care of experimental animals in research. The animal house was maintained at the temperature 26-28 °C and relative humidity was about 65-68 %.

2.4. Acute Toxicity Study

All the compounds before screening for their pharmacological activity were tested for their toxicity studies. The acute toxicity studies were performed in which a drug is tested to determine LD_{50} i.e. lethal dose for 50 % of mortality in a group of animals. Therefore, from the toxicological data obtained the safest dose for the pharmacological activity was selected as 1mg/kg[9].

2.5. Memory Enhancer Activity

All the compounds from **39-43** were screened for memory enhancer activity using Elevated Plus Maze Model. Mazes are the traditional tool in assessing learning and memory

performance in laboratory animal. Elevated plus maze measures the transfer latency (TL) i.e., the time in which the mouse moves from open arm to the enclosed arm was markedly shortened if animal had previously experienced entering the open arms, and this shortened transfer latency has been shown to be related to memory processes. Transfer latency (TL) on elevated plus maze was used as an index of learning and memory processes. The time taken by each mouse to move from the end of open arm to any enclosed arm of elevated plus maze was measured on 1st day and 2nd of drug treatment[10].

The results are expressed as % retention (Mean ± S.E.M) calculated as:

$$\% \text{ Retention} = \frac{\text{TL on 1st day} - \text{TL on 2nd day} \times 100}{\text{TL on 1st day}}$$

3. RESULTS

Table 1: Physico-Chemical Properties of Compounds

Compounds	M.P. (ºC)	Yield (%)	Molecular Weight	Molecular formula
39	136-140	81.7	266.297	$C_{13}H_{18}N_2O_4$
40	119-123	52.6	252.314	$C_{13}H_{20}N_2O_3$
41	91-95	62.9	279.340	$C_{14}H_{21}N_3O_3$
42	117-120	85.3	250.298	$C_{13}H_{18}N_2O_3$
43	144-146	73.7	247.254	$C_{12}H_{13}N_3O_3$

Table 2: Effect of Compounds on Elevated plus Maze

Compounds	Treatment	% Retention
Piracetam	Piracetam	43.59± 3.537
Control	Normal saline	26.44± 1.781
D1 (43)	D1 (43)	39.02± 0.869*
D2 (39)	D2 (39)	26.28± 2.228
D3 (42)	D3 (42)	36.25± 4.302*
D4 (41)	D4 (41)	37.34± 3.620*
D5 (40)	D5 (40)	27.92± 3.759

Each value represent the mean of 5 mice P*≤0.05 as compared to the control

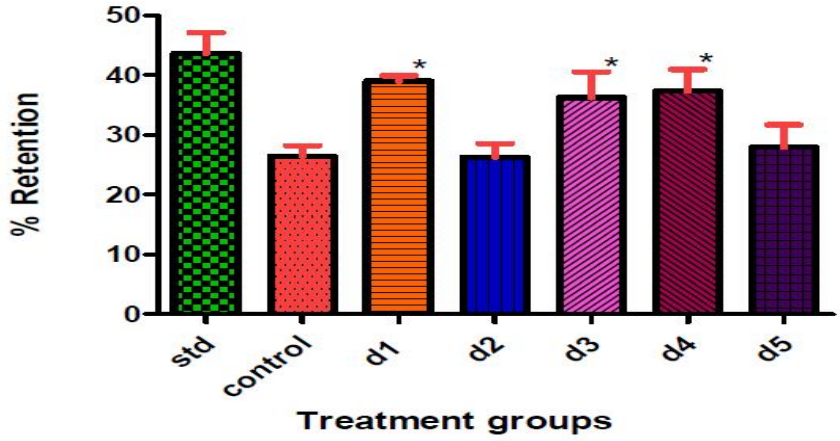


Figure 1: Effect of various compounds (39-43) and reference drug (piracetam) (1 mg/kg i.p.) on % retention measured on elevated plus maze in mice. P*≤0.05 as compared to standard treated mice. (ANOVA followed by Dunnetts's test).

4. DISCUSSION

The preceding discussion would have convinced the reader that the design and development of cognition enhancing drugs is going to be a challenging task for medicinal chemist in the near future. The inherent complexity of the problem, several new chemical and neurological deficits associated with cognitive disorders and lack of common generally accepted mechanism of action are some of the obstacles that still stand in the way of developing effective and safe drug.

Development of memory enhancing agents has been pursued utilizing a number of diverse pharmacological approaches. Although there have been numerous studies of drug effects on learning and memory are going on during the past several decades, research in this area has gained impetus only in the recent past after the biochemical and physiological basis of these processes have been understood. Search for safe and effective antiamnesics agents continues in order to develop drug with novel pharmacological profiles and with maximal therapeutics benefits. Mild form of dementia and age related impairement have just become a major problem and age associated memory impairement have an increased risk of developing dementia, this finding has generated concern and provided the impetus for rigorous investigation.

Nevertheless, many academic researchers are dedicating their efforts to identify compounds that can help in restoring impaired cognitive functions, either directly or through the cure of

the pathologies that produce cognitive dysfunction. All the synthesized compounds (**39-43**) were found to be consistent with their proposed structure. Imidazole derived compound is more significant. In the series of *m*-nitrophenol derived compounds, D1 (**43**), D3 (**42**) & D4 (**41**) have shown significant activity in comparison to reference drug piracetam at 1mg/kg, whereas rest of the other compounds, {D2 (**39**), D5 (**40**)} shows significant activity in comparison to control group. Design of palliative agents (cholinergics, nootropics etc.) is to improve cognition, but there is limitation in therapeutics efficacy, these improve cognitive task in animals but in humans it limits due to appearance of central and peripheral side effect.

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