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SYNTHESIS OF SUBSTITUTED SULPHONAMIDE DERIVATIVES AND EVALUATION OF THEIR EFFECT ON SPATIAL MEMORY IN ALZHEIMER'S MODELS

Neeraj Masand[1]*, Satya Prakash Gupta[2] and Ratan Lal Khosa[3]

[1]Department of Pharmacy, Lala Lajpat Rai Memorial Medical College, Meerut, Uttar Pradesh, India.

[2]Department of Applied Sciences, National Institute of Technical Teachers Training and Research, Bhopal, Madhya Pradesh, India.

[3]School of Pharmacy, BIT, Meerut (Dr. A. P. J. Abdul Kalam Technical University, Lucknow) Uttar Pradesh, India.

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***Corresponding Author**
Neeraj Masand
Department of Pharmacy, Lala Lajpat Rai Memorial Medical College, Meerut, Uttar Pradesh, India.

ABSTRACT

Alzheimer's dementia is a major cause of disability and mortality and the typical neuropathological hallmarks of Alzheimer's dementia are deposition of protein aggregates/ plaques, formation of neurofibrillary tangles and neuronal cell death. Lack of effective anti-AD drugs and drawbacks of present therapeutic option has helped to design a series of *N*-substituted aryl sulphonamides derivatives (**4a-o**). All the successfully synthesized compounds were evaluated for the treatment of dementia models *i.e.* MWM test. The study confirms ability of *N*-(2-bromo-4-chloro benzyl) sulphonamide analog with *tri*-chloro substitution (**4f**) as effective anti-AD drug based on its ability to overcome the deficit during MWM as well as reduced Aβ deposition.

KEYWORDS: Alzheimer's disease, Morris Water Maze, Aryl sulphonamides, Aβ deposition.

INTRODUCTION

Alzheimer's dementia is a major cause of disability and mortality.[1-2] The typical neuropathological hallmarks of Alzheimer's dementia are deposition of protein aggregates or plaques, formation of neurofibrillary tangles and neuronal cell death.[2] Alzheimer's disease (AD) is a complex neurological condition where several genes act independently/in

coordination with each other and/or with environmental agents. Mutations on the genes coding for the amyloid precursor protein (APP) and presenilin 1 (PS1) alters production of the principle component of senile plaque *i.e*. amyloid-β (Aβ).[3-5] APP mutation has shown increased formation of $A\beta_{1-40}$ and $A\beta_{1-42}$ in brain by its effect on β–secretase cleavage site of the Aβ domain.[6-8] The cytotoxic properties of mature APP are confirmed by amyloid hypothesis which disturbs cellular Ca^{2+} ion homeostasis leading to apoptosis and the resulting excessive influx of Ca^{2+} leads to induction of neurotoxic cascade.[9,10]

The brain hippocampus region is involved in formation, organization and storage of memories and coordination with thalamus and hypothalamus it constitutes the network of limbic system for long-term storage of memories. The memories forms and get stored as cognitive maps.[11-13] In case of Central nervous system (CNS) disorders such as AD, Epilepsy, Schizophrenia, CNS depressions, as well as oxidative stress/reactive oxygen species, the hippocampi neurons get affected causing neuronal loss leading to cognitive impairment. Ii is observed that neuroinflammation is accompanied during the duration of AD.[14]

Memory can be categorized based on temporal and biochemical properties as short term memory (STM; lasts for few hours) or long term memory (LTM; lasts for several hours to days or even longer).[15-19] Some studies have demonstrated role of gene expression and de novo protein synthesis to transform newly learned information into a permanent and stable state.[16,20,21] Role of transcription factor cAMP response element-binding (CERB) protein in LTM has been explained[22-35] and increased phosphorylation of CERB within hippocampus is associated with formation of spatial memory.[36-41] This may be considered as a molecular marker for spatial memory[34,36,40] and hippocampal CERB activation has key role in delineating learning-dependent circuits in memory processes.

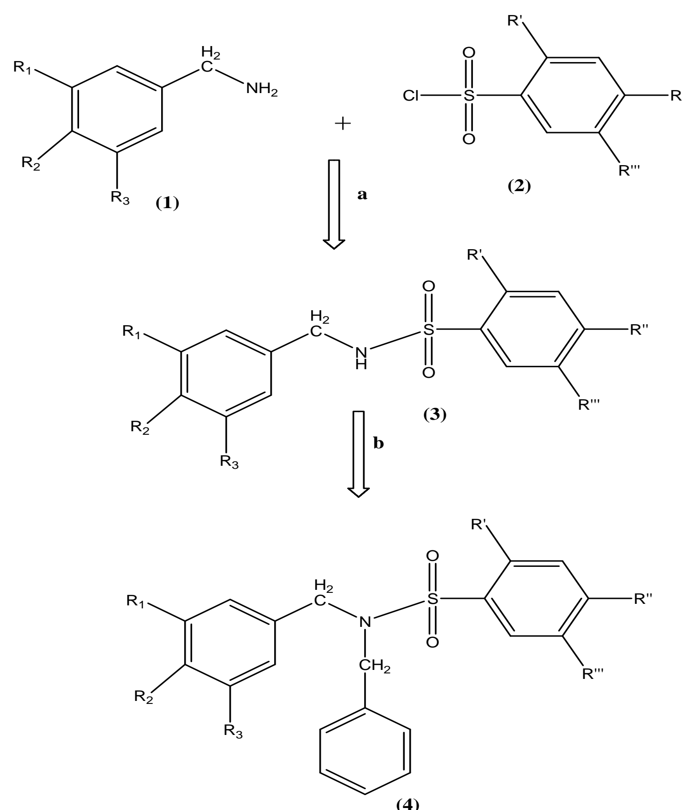
The role of sulphonamide functional moiety in design of anti-AD agents is well supported by various research groups.[42-58] A recent example is Verubecestat prepared by Cu-catalyzed C-N coupling as well as diastereoselective Mannich type reaction.[59]

The present work aims to provide a possible solution for AD. In view of this, some substituted aryl sulphonamide derivatives will be synthesized followed by structural characterization. The synthesized compounds will be evaluated using Morris Water Maze test to evaluate their effect on spatial and temporal memory through CERB phosphorylation.

MATERIALS AND METHODS

Synthetic details

The synthetic scheme employed for preparing substituted sulphonamide compounds is as depicted in Fig. 1. It includes two steps *i.e*. synthesis of sulphonamides and followed by their arylation.[60-62] All the starting materials and reagents were obtained from commercial sources (CDH, E Merck AG) and were used without further purification. The purity of synthesized compounds was checked using Thin Layer Chromatography (TLC) with different solvent systems (methanol, n-hexane and ethyl acetate) giving single spot. The IR spectra were recorded in KBr pellet method (Perkin Elmer 79225). Nuclear magnetic resonance spectra were recorded in $CDCl_3$/DMSO on Bruker spectrometer operating at 300 MHz.



(**a**: Anhydrous pyridine, O°C; **b**: C_6H_5-CH_2-Cl, NaH, THF, 1N HCl, 6 Hrs)

Figure 1: Synthetic scheme for proposed compounds (4a-o).

Animals and Chemicals

Swiss Albino mice (male and female) weighing 20-25 g were used and throughout the experimental protocol they were kept and maintained under laboratory conditions of temperature and humidity. They were allowed free access to food (standard pellet diet) and drinking tap water *ad libitum* and a 12 hr light/dark cycle was maintained. All the animals

were fasted for 24 hrs before experiment but allowed free access to water. The animals were divided into groups (n = 6) *i.e*. Control group I (saline, 1 ml/kg, *p.o*.), Negative control group II (Scopolamine, 1 mg/kg, *i.p*.), Standard group III (Piracetam, 200 mg/kg, *i.p*.), and Test drug treated groups (Synthesized aryl sulphonamides (*i.p*.). Scopolamine (1 mg/kg, *i.p*.) was administered to all group animals 30 minutes after receiving the control/standard/test drug.

EXPERIMENTAL METHOD

General Procedure for synthesis

Substituted primary aromatic amine (**1**) and substituted sulfonyl chloride (**2**) mixture was prepared in equimolar amount by dissolving in anhydrous pyridine (10 ml). The temperature of reaction mixture was maintained at 0°C using ice salt bath and was stirred for 5-10 hrs to get the secondary amine derivative (**3**). The sulfonamides **(3)** individual solution in tetrahydrofuran (10 ml) and sodium hydride (0.1 g) was stirred at room temperature for 15 minutes and to this a mixture of benzyl chloride in tetrahydrofuran (5 ml) and 1N hydrochloric acid (2 ml) was added. Both the solutions were stirred for approximately 6 hrs and the progress of reactions was monitored using thin layer chromatography (TLC). The resulting products were filtered, washed with distilled water and dried to yield the corresponding *N*-benzyl sulfonamide derivatives (**4**) (Fig. 1). The MP (°C) and percentage yield were calculated for all the synthesized compounds.

Table 1: Structural details for synthesized compounds.

R_1-N(-SO_2-R_2)-CH_2-C_6H_5

Compd No.	R_1	R_2	Compd No.	R_1	R_2
4a	Cl, Cl		4i	H_3C, H_3C	Cl, Cl, Cl
4b	Cl, Cl	Cl, Cl, Cl	4j	H, H_2C, C, Cl	
4c	N, Cl		4k	H, H_2C, C, Cl	Cl, Cl, Cl
4d	N, Cl	Cl, Cl, Cl	4l	HO, Cl	
4e	Br, Cl		4m	HO, Cl	Cl, Cl, Cl
4f	Br, Cl	Cl, Cl, Cl	4n	Cl, H_3C—$(CH_2)_2O$, Cl	
4g	H_3C, CH_3		4o	Cl, H_3C—$(CH_2)_2O$, Cl	Cl, Cl, Cl
4h	H_3C, CH_3	Cl, Cl, Cl			

Compound 4a: $C_{20}H_{17}Cl_2NO_2S$, MW 405, Y 76%, MP (78°C) 92-94; IR (KBr, cm^{-1}) 3060 (C-H, Ar), 1523 (C=C, Ar), 1321 (-SO_2), 1184 (SO_2-N), 947 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 4.41-4.43 (*s*, 2H, N-C<u>H_2</u>-Ar(Cl)), 4.46-4.48 (*s*, 2H, N-C<u>H_2</u>-Ar), 7.10-7.15 (*m,* 8H, Ar-<u>H</u>), 7.27 (*s,* 2H, Ar-<u>H</u>), 7.56-7.60 (*m,* 3H, Ar-<u>H</u>).

Compound 4b: $C_{20}H_{14}Cl_5NO_2S$, MW 507, Y 76%, MP (74°C) 92-94; IR (KBr, cm^{-1}) 3051 (C-H, Ar), 1543 (C=C, Ar), 1320 (-SO_2), 1192 (SO_2-N), 960 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 4.31-4.36 (*m*, 4H, N-C$\underline{H_2}$-Ar), 7.09-7.12 (*m,* 5H, Ar-$\underline{H}$), 7.21-7.25 (*m,* 3H, Ar-$\underline{H}$), 7.46 (*s,* 1H, Ar-$\underline{H}$), 7.51 (*s,* 1H, Ar-$\underline{H}$).

Compound 4c: $C_{25}H_{21}ClN_2O_2S$, MW 448, Y 76%, MP (102°C) 92-94; IR (KBr, cm^{-1}) 3063 (C-H, Ar), 1555 (C=C, Ar), 1328 (-SO_2), 1194 (SO_2-N), 959 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 4.46 (*s*, 2H, N-C$\underline{H_2}$-Ar), 4.48 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.10-7.14 (*m,* 5H, Ar-$\underline{H}$), 7.20 (*s*, 1H, Ar-$\underline{H}$) 7.22-7.25 (*m,*2H, Ar-$\underline{H}$), 7.71-7.86 (*m,* 9H, Ar-$\underline{H}$).

Compound 4d: $C_{25}H_{18}Cl_4N_2O_2S$, MW 549, Y 76%, MP (65°C) 92-94; IR (KBr, cm^{-1}) 3058 (C-H, Ar), 1551 (C=C, Ar), 1322 (-SO_2), 1190 (SO_2-N), 961 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 4.39-4.43 (*m*, 4H, N-C$\underline{H_2}$-Ar), 7.12-7.16 (*m,* 5H, Ar-$\underline{H}$), 7.24-7.31 (*m,* 2H, Ar-$\underline{H}$), 7.56-7.64 (*m,* 4H, Ar-$\underline{H}$), 7.79-7.82 (*m,* 3H, Ar-$\underline{H}$).

Compound 4e: $C_{20}H_{17}BrClNO_2S$, MW 450, Y 76%, MP (62°C) 92-94; IR (KBr, cm^{-1}) 3063 (C-H, Ar), 1555 (C=C, Ar), 1328 (-SO_2), 1194 (SO_2-N), 959 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 4.36-4.38 (*s*, 2H, N-C$\underline{H_2}$-Ar), 4.46 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.16-7.21 (*m,* 7H, Ar-$\underline{H}$), 7.37-7.43 (*m,* 2H, Ar-$\underline{H}$), 7.76-7,82 (*m,* 5H, Ar-$\underline{H}$).

Compound 4f: $C_{20}H_{14}BrCl_4NO_2S$, MW 550, Y 76%, MP (53°C) 92-94; IR (KBr, cm^{-1}) 3058 (C-H, Ar), 1547 (C=C, Ar), 1321 (-SO_2), 1190 (SO_2-N), 962 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 2.31-2.33 (*d*, 2H, N-C-C$\underline{H_2}$-Ar), 3.46-3.48 (*d*, 2H, N-C$\underline{H_2}$-C-Ar), 4.46 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.11-7.16 (*m,* 9H, Ar-$\underline{H}$), 7.47 (*s,* 1H, Ar-$\underline{H}$), 7.76 (*s,* 1H, Ar-$\underline{H}$).

Compound 4g: $C_{22}H_{23}NO_2S$, MW 365, Y 76%, MP (70°C) 92-94; IR (KBr, cm^{-1}) 3057 (C-H, Ar), 1548 (C=C, Ar), 1323 (-SO_2), 1190 (SO_2-N), 963 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 2.31-2.33 (*d*, 2H, N-C-C$\underline{H_2}$-Ar), 3.46-3.48 (*d*, 2H, N-C$\underline{H_2}$-C-Ar), 4.46 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.11-7.16 (*m,* 9H, Ar-$\underline{H}$), 7.47 (*s,* 1H, Ar-$\underline{H}$), 7.76 (*s,* 1H, Ar-$\underline{H}$).

Compound 4h: $C_{22}H_{20}Cl_3NO_2S$, MW 467, Y 76%, MP (83°C) 92-94; IR (KBr, cm^{-1}) 3065 (C-H, Ar), 1558 (C=C, Ar), 1330 (-SO_2), 1188 (SO_2-N), 963 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 2.31-2.33 (*s*, 6H, C$\underline{H_3}$-Ar), 4.41-4.44 (*s*, 2H, N-C$\underline{H_2}$-Ar), 4.46-4.47 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.14-7.23 (*m,* 8H, Ar-$\underline{H}$), 7.49 (*s,* 1H, Ar-$\underline{H}$), 7.86 (*s,* 1H, Ar-$\underline{H}$).

Compound 4i: $C_{22}H_{20}Cl_3NO_2S$, MW 467, Y 76%, MP (92°C) 92-94; IR (KBr, cm^{-1}) 3067 (C-H, Ar), 1556 (C=C, Ar), 1332 ($-SO_2$), 1191 (SO_2-N), 960 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 2.31-2.32 (*s*, 6H, C$\underline{H_3}$-Ar), 4.40-4.42 (*s*, 2H, N-C$\underline{H_2}$-Ar), 4.44-4.46 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.15-7.18 (*m,* 3H, Ar-$\underline{H}$), 7.24-7.27 (*m,* 5H, Ar-$\underline{H}$), 7.76-7.81 (*m,* 2H, Ar-$\underline{H}$).

Compound 4j: $C_{22}H_{20}ClNO_2S$, MW 397, Y 76%, MP (95°C) 92-94; IR (KBr, cm^{-1}) 3066 (C-H, Ar), 1557 (C=C, Ar), 1331 ($-SO_2$), 1186 (SO_2-N), 950 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 2.31-2.33 (*d*, 2H, N-C-C$\underline{H_2}$-Ar), 3.46-3.48 (*d*, 2H, N-C$\underline{H_2}$-C-Ar), 4.46 (*s*, 2H, N-C$\underline{H_2}$-Ar), 7.11-7.16 (*m,* 9H, Ar-$\underline{H}$), 7.47 (*s,* 1H, Ar-$\underline{H}$), 7.76 (*s,* 1H, Ar-$\underline{H}$).

Compound 4k: $C_{22}H_{17}Cl_4NO_2S$, MW 498, Y 76%, MP (98°C) 92-94; IR (KBr, cm^{-1}) 3068 (C-H, Ar), 1550 (C=C, Ar), 1322 ($-SO_2$), 1186 (SO_2-N), 961 (S-N); ^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 4.31-4.33 (*s*, 4H, N-C$\underline{H_2}$-Ar), 5.16-5.23 (*d*, 2H, C$\underline{H_2}$=C-Ar), 6.46-6.49 (*t*, 1H, CH_2=C$\underline{H}$-Ar), 7.13-7.19 (*m,* 8H, Ar-$\underline{H}$), 7.47 (*s,* 1H, Ar-$\underline{H}$), 7.76 (*s,* 1H, Ar-$\underline{H}$).

Compound 4l: $C_{24}H_{24}ClNO_3S$, MW 441, Y 76%, MP (87°C) 92-94; IR (KBr, cm^{-1}) 3065 (C-H, Ar), 1557 (C=C, Ar), 1332 ($-SO_2$), 1196 (SO_2-N), 962 (S-N).

Compound 4m: $C_{24}H_{21}Cl_4NO_3S$, MW 543, Y 76%, MP (120°C) 92-94; IR (KBr, cm^{-1}) 3059 (C-H, Ar), 1549 (C=C, Ar), 1334 ($-SO_2$), 1187 (SO_2-N), 963 (S-N).

Compound 4n: $C_{23}H_{23}Cl_2NO_3S$, MW 463, Y 76%, MP (101°C) 92-94; IR (KBr, cm^{-1}) 3064 (C-H, Ar), 1549 (C=C, Ar), 1332 ($-SO_2$), 1192 (SO_2-N), 965 (S-N).

Compound 4o: $C_{23}H_{20}Cl_5NO_3S$, MW 564, Y 76%, MP (57°C) 92-94; IR (KBr, cm^{-1}) 3060 (C-H, Ar), 1551 (C=C, Ar), 1322 ($-SO_2$), 1190 (SO_2-N), 962 (S-N).

Pharmacological studies

All the synthesized substituted aryl sulphonamide compounds were evaluated for acute toxicity, behavioural assessment and histopathological study as per the CPCSEA guidelines. Permission was been granted by Institutional Animal Ethics Committee (819/04/ac/CPCSEA).

Anti-Alzheimer's Activity

All the animals were trained as per the Morris Water Maze (MWM) test protocol to evaluate the effect of synthesized compounds on behavior and spatial memory of experimental animals.[63] MWM test consisted of a black circular pool (90 cm diameter, 45 cm height) filled up to a depth of 30 cm with water (opaque) and temperature was maintained at 25ºC. The pool was divided theoretically into four equal quadrants for the purpose of analysis using two threads fixed at right angles to each other on the rim of the pool. A submerged/escape platform (6 cm diameter and 29 cm height) was placed inside the tank at the centre of the pool 1 cm below the water level. The position for platform was unaltered throughout the training session. For all the selected animals, two consecutive trials at 30 minute time interval per day with different starting point were performed. Trial was performed for four consecutive days. During the four day trial session animals were allowed to escape on the hidden platform and to remain there for 10 sec. During the training session the mice were gently placed in the water from different locations facing the wall of the pool and were allowed 60 sec to locate the submerged platform. If the mice fail to locate the platform within 60 sec, it was guided gently on to the platform and allowed to remain there for 10 sec. On fifth day *i.e.* retrieval day of training session, the platform was removed and the mice were placed in the pool from any of the point and allowed to explore the target quadrant for 60 sec. The mean time spent in target quadrant of the pool in search of the missing platform which is an index of retrieval of memory, was recorded.

After 30 minutes of administration of Scopolamine, MWM test was performed. The data thus obtained was analyzed by ANOVA and Student *t* test. The details are reported in Table 2.

Histopathology studies

To perform histopathological studies, the brain samples of experimental animals were collected as per the reported procedure.[64-66] Mice were anesthetized (Pentobarbital, 100 mg/kg, *i.p.*), perfused transcardially using isotonic saline (25 ml) and the brains were removed rapidly. One hemisphere of brain was immersed for 24 h in phosphate-buffered 4% paraformaldehyde following to cryoprotection in a series of sucrose solutions. Using a sliding microtome, 25-µm frozen sections were collected in a horizontal plane and stored at 4°C in Dulbecco's PBS. Analysis was performed for total Aβ and $A\beta_{1-40}$ using the Congo red histolopathological staining performed on slide-mounted sections rehydrated for approximately 30 sec before staining. Initially hydrated sections were incubated for 20

minute in alkaline alcoholic saturated NaCl solution (freshly prepared, 2.5 mM NaOH in 80% reagent alcohol). It was incubated for 30 min in 0.2% Congo red in alkaline alcoholic saturated NaCl solution. After rinsing in three changes of 100% ethanol, sections were cleared through three changes of xylene, then coverslipped with Permount for image analysis (Fig. 2).

RESULTS AND DISCUSSION

A series of *N*-substituted aryl sulphonamides was synthesized in good to moderate yields as per the reported synthetic methodology (Fig. 1). All the obtained compounds were purified and recrystallized and their MP (°C) was recorded. The chemical structures of synthesized compounds were found to be in agreement with the observed IR and ^{1}H-NMR spectra. Thus the structures for the synthesized compounds can be confirmed.

A large number of models have been reported by various research groups[67-74] and MWM has been found to the method of choice to evaluate the cognitive disability in rodent models. Lack of ability to find hidden platform during MWM *i.e.* MWM performance could be related to the intellectual decline in Alzheimer's patients. In MWM, Scopolamine intracerebral injection impairs learning ability.[75,76] During and after intracerebroventricular infusion of Aβ protein has shown impaired acquisition of hidden-platform in MWM rats.[77,78] A relationship between MWM deficit and Aβ deposition has been reported.[69-83] Age-related histopathological changes such as hippocampal cell loss, decreased hippocampal LTP and Aβ plaque deposition has been found in MWM animals.[84,85]

During MWM test, for all the animals in the test drug treated groups (**4a-o),** a gradual reduction in escape latency time (ELT) was observed during the training trial session from day 1 to day 4. On day 4 of training trial session, the ELT for Compounds **4d, 4e, 4g, 4h, 4i, 4k, 4l, 4n,** and **4o,** was found to be less in comparison to that of the positive control group. While the ELT for compound **4f** was found to be quiet similar to that of the positive control treated group.

On day 5th *i.e*. the retrieval day the time spent in target quadrant (TSTQ) by control animals was found to be 30.17 ± 0.82 sec. For negative control group where the animals on the probe trial day (*i.e*. day 5) received scopolamine 30 min before the trial, a significant reduction in TSTQ was observed as compared to the control group ($p < 0.001$) (Table 2). Animals from positive control group which were administered the standard drug Piracetam followed by

scopolamine on the 5th day showed a significant ($p < 0.01$) increase in TSTQ as compared to the scopolamine treated negative control group. Similarly the animals of the test groups which on the 5th day received test compounds (**4a-o**) (47.5 mg/kg, *p.o.*) followed by scopolamine showed a significant ($p < 0.05$) increase in the time spent in the target quadrant (TSTQ) as compared to the negative control group animals (Table 2). For compound **4m,** the TSTQ was found to be nearly equal to that of the positive control group while Compounds **4c, 4f, 4g, 4i, 4j,** and **4k** the TSTQ was found to be nearly equal to that of the positive control group. The obtained results indicate significant improvement in the short-term memory on treatment with the synthesized compounds.

During histopathological studies, the brain samples of experimental animals have shown reduced plaque formation as compared to control group (Fig. 2).

Table 2: Effect of test drugs on acquisition in scopolamine induced amnesia.

Groups	ESCAPE LATENCY TIME (ELT) (in sec)				TSTQ (in sec)
	Day 1	Day 2	Day 3	Day 4	Day 5
I	54.5 ± 0.66	35.75 ± 0.64	24.17 ± 0.32	20.08 ± 0.57	30.17 ± 0.82
II	58.25 ± 0.420	51.42 ± 0.57	49.41 ± 0.431	41.33 ± 0.78	16.25 ± 0.694
III	57.08 ± 0.78	49.33 ± 0.526	33.58 ± 0.477	18.16 ± 0.429	26.08 ± 0.334***
4a	54.24 ± 0.787	41.51 ± 0.314	29.34 ± 0.467	21.25 ± 0.403	21.22 ± 0.616
4b	52.55± 0.423	43.13 ± 0.246	28.16 ± 0. 432	20. 52 ± 0.165	23.34 ± 0.385
4c	58.45 ± 0.25	51.78 ± 0.425	34.91 ± 0.312	19.54 ± 0.376	30.00 ± 0.453*
4d	55.27 ± 0.361	41.19 ± 0.693	31.32 ± 0.652	15.86 ± 0.617	25.33 ± 0.431
4e	57.34 ± 0. 954	47.35 ± 0.706	30.64 ± 0.912	17.73 ± 0.454	25.03 ± 0.512
4f	56.64 ± 0.454	43.75 ± 0.501	33.12 ± 0.720	18.04 ± 0.121	31.61 ± 0.355*
4g	57.74 ± 0.665	44.73 ± 0.312	26.38 ± 0.654	14.52 ± 0.335	30.45 ± 0.326*
4h	54.15 ± 0.524	47.51 ± 0.224	31.25 ± 0.621	16.57 ± 0.412	25.13 ± 0.515
4i	56.24 ± 0.363	48.47 ± 0.354	33.45 ± 0.531	16.54 ± 0.524	29.26 ± 0.525*
4j	54.37 ± 0.545	42.51 ± 0.248	28.19± 0.245	21.23 ± 0.403	27.61 ± 0.325***
4k	56.01 ± 0.308	49.75 ± 0.451	32.36 ± 0.613	16.86 ± 0.622	28.46 ± 0.421**
4l	57.31 ± 0.651	41.16 ± 0.720	27.38 ± 0.450	15.53 ± 0.452	20.24 ± 1.458
4m	55.65 ± 0.352	45.36 ± 0.536	28.41 ± 0.854	22.64 ± 0.253	26.43 ± 0.273
4n	56.61 ± 0.265	41.34 ± 0.846	30.39 ± 0.731	17.28 ± 0.321	21.75 ± 0.623
4o	57.41± 0.616	42.28 ± 0.954	25.32 ± 0.232	15.75 ± 0.513	25.21 ± 0.231

Group I: Vehicle treated control group; Group II: Scopolamine treated negative control group; Group III: Standard drug (Piracetam) treated group; Group **4a-o**: Test drug treated group; Values are expressed as Mean ± SEM; *$p<0.05$, **$p<0.01$, ***$p<0.001$; Negative control group was compared with the vehicle control group, Standard and test groups were compared with the negative control group.

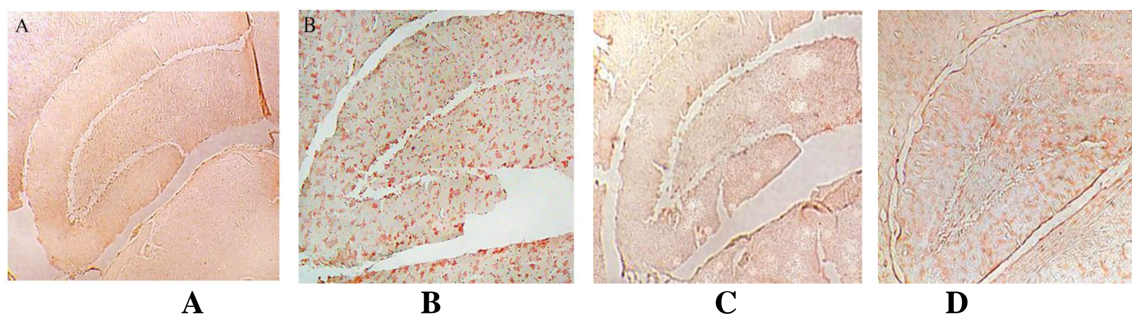


Figure 2: Control group, indicating no beta amyloid plaques in the brain; **B**: Brain in the animals 20 days after intracerebroventricular injection of beta amyloid indicating an obvious different between the beta amyloid and vehicle treated mice brain (Negative control group). **C:** Brain in the mice treated with Piracetam after i.c.v. injection of beta amyloid indicating clearance of beta amyloid plaques (Positive control group). **D:** Brain of Alzheimeric mice after 20 days treatment with Compound **4f** (47.5 mg/kg). The beta amyloid plaques are fairly observable so that the difference between this micrographs and that of the Alzheimer brain.

CONCLUSION

The *N*-substituted aryl sulphonamides derivatives (**4a-o**) were successfully synthesized and their potency in the treatment of dementia models *i.e*. MWM test has been successfully evaluated. The study confirms ability of *N-(*2-bromo-4-chloro benzyl) sulphonamide analog with *tri*-chloro substitution (**4f**) has helped to overcome the lack of ability to find hidden platform during MWM. Thus its possible role could be correlated to prevention of AD as well as reduced Aβ deposition. Thus it can be concluded that, this series of *N*-substituted aryl sulphonamides (**4a-o**) acts as anti-AD agent by preventing chemically-induced and/or age-related histopathological changes such as hippocampal cell loss, decreased hippocampal LTP and Aβ plaque deposition. Further structural optimization and molecular modeling studies are required to establish more potent anti-AD agents.

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