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Synthesis and Study of Anti Parkinsonism Activity of 8-Azabicyclo [3.2.1] Octane Analogs

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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative condition associated with the degeneration of dopaminergic neurons in the zona compacta of the substantia nigra. 3D QSAR study of 8-azabicyclo [3.2.1] *octane analogs which serves as the pathfinder for the design of novel molecule for anti Parkinsonism. Five compounds of 8-azabicyclo* [3.2.1] *octane analogs are synthesized and the anti Parkinsonism activity and brain dopamine level were studied on albino mice. The anti Parkinsonian activity was determined by the effect of test compound A-E on drug induced catatonia using the method of Morpurgo. Atropine as well as compounds B and E significantly reduced the catatonic responses and tremors induced by chlorpromazine. The level of dopamine was measured after the administration of atropine and the test compounds in brain of mice. The study reveals that the compounds B and E have exhibited significant activity over atropine.*

***Keywords*:** 8-*Azabicyclo* [3.2.1] *Octane*, *Parkinsonism*, *Dopamine*, *Catatonia*

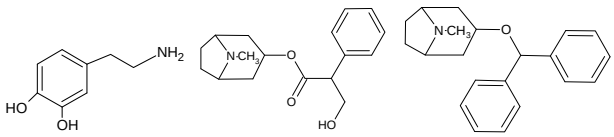
1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease [1]. It was first described by Parkinson and is characterized by four features, namely slowness of movement (bradykinesia), muscular rigidity, resting tremor and impairment of postural balance leading to disturbances of gait and falling. The disease occurs in all ethnic groups and in both sexes. It generally commences in the middle and late age and leads to progressive disability with increasing age. It has been estimated that about 1% of the population of the age group of 45 years or below suffer from Parkinson's disease. In a population of those who are 60 years and above, about 10% suffer, and half of the populations belonging to age group of 85 years and above have this abnormality [2,3].

In Parkinson's disease there are decreased levels of striatal dopamine (1) and this has been found to be due to the loss of neurons in substantia nigra pars compacta that provides dopaminergic innervations to the striatum [4].

At present five distinct dopamine receptors are known. These five dopamine receptors have been divided into two groups on the basis of their pharmacological and structural properties. The D_1 and D_5 receptors have a long carboxyl terminal and belong to pharmacologically defined D_1 class of receptors. The D_2, D_3 and D_4 receptors have a large third intracellular loop and belong to D_2 class [4].

Drugs that are generally used in treatment of Parkinson's disease can be classified into five categories and that include: Drugs that replace dopamine, the monoamine oxidase inhibitor, Dopamine Receptor Agonists, Drugs that inhibit dopamine reuptake, Antimuscarinic agents. The fifth classes of compounds include antimuscarinic agents, atropine (2) and benztropine (3). Muscarinic acetylcholine receptors exert an excitatory effect and also presynaptic inhibitory effect on dopaminergic nerve terminals. Suppression of these effects, thus, makes up for lack of dopamine (1). The antimuscarinic agents diminish the tremor more than the rigidity or hypokinesia. They also have side effects like dry mouth, constipation, and urinary retention [5,6].



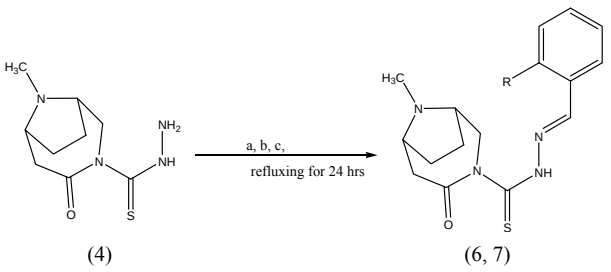
(1) (2) (3)

3D-QSAR models of Comparative Molecular Field Analysis (CoMFA) and Comparative Molecular Similari-

ties Indices Analysis (CoMSIA) of 8-azabicyclo [3.2.1] octane (potent muscarinic receptor blocker) was performed [7]. Results indicate that the CoMFA and CoMSIA models could be reliable model which may be used in the design of novel muscarinic antagonists as leads. The 3D-QSAR models of 8-azabicyclo [3.2.1] octane open the way to design the novel molecules for antimuscarinic and anti Parkinsonism.

2. Chemistry

Synthesis of 9-Methyl-4-oxo-3, 9 diazabicyclo [4.2.1] nonane-3-carbothiohydrazide derivatives shown in Scheme-I. [8-11] 9-Methyl-4-oxo-3, 9 diazabicyclo [4.2.1] nonane-3-carbothiohydrazide (4) (2.28 g) was taken in absolute alcohol (25 ml) and treated with glacial acetic acid (1 ml) and benzaldehyde (1.06 ml) or 2-chlorobenzaldehyde (1.405 g). After refluxing the reaction mixture for 24 hrs it was kept in refrigerator when the thiosemicarbazone (6) and (7) precipitated out.



(4) (6, 7)

Scheme 1. a = absolute alcohol, b = glacial acetic acid, c = benzaldehyde (for 6) or 2-chlorobenzaldehyde (for 7) and R = H (6), Cl (7)

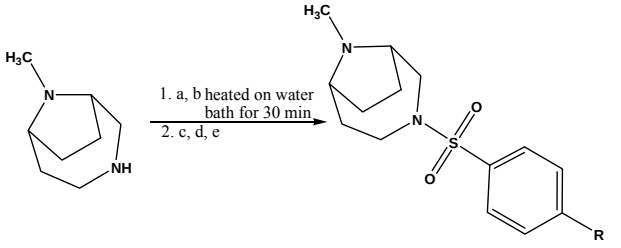
Synthesis of 3-benzenesulphonyl-9-methyl-3, 9-diazabicyclo [4.2.1] nonane hydrochloride derivatives shown in Scheme 2. [8-11] To a solution of 9-methyl-3, 9-diazabicyclo [4.2.1] nonane (5) (0.42g) in dry pyridine was added benzenesulphonyl chloride (0.6 ml) or *p*-toluene sulphonyl chloride (0.8 g) or *p*-chlorobenzene sulphonyl chloride and the reaction mixture heated on a water bath for 30 min. The contents of the flask were poured into ice cold water (10 ml), basified with potassium carbonate, and extracted with chloroform (3 × 10 ml). After working up the chloroform extract in the usual manner, an oily residue (0.65 g) was obtained. This was converted to the hydrochloride and crystallized from acetone.

3. Results and Discussion

The Pharmacological studies of the compounds 6 (A), 7 (B), 8 (C), 9 (D), 10 (E) were carried out for the antiparkinsonian activity.

3.1. Antiparkinsonian Activity

The antiparkinsonian activity was determined by the



(5) (8, 9, 10)

Scheme 2. a = benzenesulfonyl chloride (for 8), p-toluenesulphonylchloride (for 9), *p*-chlorobenzenesulphonyl chloride (for 10), b = dry pyridine, c = potassium carbonate, d = chloroform, e = HCl, R = H (8), CH_3 (9), Cl (10).

effect of Test Compound A-E on drug induced catatonia using the method of Morpurgo [12-14].

Albino mice, weighing 25-30 g maintained on a 12 hrs light and dark cycle and *ad libitum* food and water were throughout used. The catatonia was induced by chlorpromazine at a dose level of 5 mg/kg body weight intra peritoneal (IP). Atropine was administered at a dose level of 2 mg/kg body weight IP. The Test Compounds were administered at a dose level of 200 μg/100 g body weight. All drugs were dissolved in distilled water or saline in concentrations with which the IP administration of 1 ml/100g of mice could be kept constant. Each Test Compound was administered to four animals. The catatonia was induced with chlorpromazine and the Atropine was used as standard anticatatonic. The score for severity of catatonic response was recorded as follows:

Stage 1: Normal movement when placed on the table, score = 0;

Stage 2: Movement only when touched or pushed, score = 0.5;

Stage 3: Animal placed on the table with front paws set alternately on a 3 cm high block fails to correct the posture in 10 seconds, score = 0.5 for each paw with a total of 1 for this stage.

Stage 4: Animal fails to remove the paw when front paws are placed alternately on a 9 cm block, score = 1 for each paw and a total score of 2 for this stage.

Thus for a single animal the maximum possible score could be 3.5 revealing total catatonia. The results are tabulated in **Table 1**. The results clearly indicate that atropine as well as Compounds B and E significantly reduced the catatonic responses and tremors induced by chlorpromazine. In order to confirm this further, the levels of dopamine were measured after the administration of atropine, Test Compounds B and E in the brain of mice.

3.2. Determination of Brain Dopamine Level in Mice

The method of estimation of dopamine was based on

Table 1. Degree of catatonic responses on mice of Atropine and Test Compounds A to E.

Group		Degree of Catatonic Response		
		15 min	30 min	45 min
1	Control	1.0	2.0	3.5
		1.0	2.0	3.5
		0.5	2.0	3.5
		1.0	1.0	2.0
Mean (S.D)		0.875(0.25)	1.75(0.5)	3.125(0.75)
2	***Atropine****	0.0	0.0	0.0
		0.5	0.0	0.0
		0.0	0.0	0.0
		0.5	0.0	0.0
Mean (S.D)		0.25(0.288)	0.0(0.0)	0.0(0.0)
3	***A*****	0.5	1.0	3.0
		0.5	1.0	2.0
		0.5	1.5	1.5
		1.0	1.5	2.0
Mean (S.D)		0.625(0.25)	1.25(0.288)	2.125(0.629)
4	***B****	0.0	0.0	0.0
		0.5	0.5	0.5
		0.0	0.5	0.0
		0.5	0.0	0.0
Mean (S.D)		0.25(0.288)	0.25(0.288)	0.125(0.25)
5	***C*****	1.0	1.5	2.0
		1.0	1.5	3.0
		0.5	1.0	1.5
		0.5	1.0	2.0
Mean (S.D)		0.75(0.288)	1.375(0.25)	2.125(0.629)
6	***D*****	1.0	1.5	2.0
		1.0	1.5	2.0
		1.0	1.0	1.5
		1.0	1.5	2.0
Mean (S.D)		1.0 (0.0)	1.375(0.25)	2.125(0.629)
7	***E****	0.0	0.0	0.0
		0.0	0.0	0.0
		0.0	0.5	0.0
		0.5	0.0	0.0
Mean (S.D)		0.125(0.25)	0.125(0.25)	0.0(0.0)

Value in parenthesis indicates standard deviation; *p < 0.01, **p > 0.05 when compared to control (Dunnett's Multiple Comparison test); *p < 0.05, **p > 0.05 when compared to control (Paired t-Test)

development of fluorescence by chemical reaction. The catecholamine was oxidized to the fluorescent hydroxyl indole derivative. The iodine was used to oxidize the amine. The fluorescence was measured when the reaction mixture irradiated with ultraviolet light [15-17].

Adult inbreed albino mice of either sex weighing between 30 - 35 g were used for the experiments. They were divided into four groups each containing four mice. Two groups, group 3 and 4 were treated with the two test drugs (B and E) and group 2 was treated with atropine. One group, group 1 which was treated with vehicle was used as control.

The mice were sacrificed by cervical decapitation after half an hour of intraperitoneal injection of the drug/Atropine/vehicle. The brain of mice was removed quickly and chilled immediately to less than 0˚C in a beaker containing a weighed mixture of ice and calcium chloride and were weighed again.

3.2.1. Extraction of Dopamine

This is essentially the method described by Kent Shellenberger and J. H. Gordon and developed for estimation of dopamine [15,16].

Perchloric acid (0.4 *N*) for use in tissue extraction was prepared by adding sodium metabisulfite (1.0 gm) and ethylene diamine tetra acetate-disodium salt (EDTA, 0.5 gm), to each liter of diluted acid.

The brain samples were homogenized in 2.5 ml of the 0.4 *N* perchloric acid reagent using Teflon tissue homogenizer. The homogenates are left to stand in ice for 10 min and then centrifuged at 14 000 rpm for 15 min at 0˚C in refrigerated centrifuge. The supernatant was transferred to another test tube and brain samples were re-homogenized in 2.0 ml perchloric acid reagent. Following the second centrifugation, the supernatants were pooled and adjusted to 5 ml.

3.2.2. Estimation of Dopamine

The reagents were prepared and estimation of dopamine in mice brain was carried out. Phosphate buffer -EDTA solution was prepared by adding 9.0 gm of disodium EDTA to 1.0 liter of 0.1 M phosphate buffer and adjusting the pH to 7.0 with 5.0 N NaOH. The phosphate buffer is made with 4.27 gm Na_2HPO_4 (anhydrous) and 9.32 gm KH_2PO_4 per liter. Iodine reagent was prepared by dissolving 2.0 gm of potassium iodide and 0.5 gm iodine in 40.0 ml of distilled water.

Alkaline sodium sulfite solution 2.5% w/v was prepared by diluting 1.0 ml of a solution containing 250 mg sodium sulfite, to 10 ml of 5.0 *N* NaOH. 1 ml of the aliquot of the perchloric acid elute was brought to pH 6.5 ± 0.2 with 1.0 ml of 0.1 M phosphate buffer-EDTA solution. 0.2 ml iodine reagent was added, and mixed and kept for exactly 2 min. After this 0.4 ml of alkaline sodium sulfite solution was added and kept for another 2 min. It was acidified to pH 4.4 - 4.8 with 0.4 ml of glacial acetic acid and heated in an oven maintained at 100˚C for 40 min to develop the fluorescence. Next, the tubes were taken out from the oven and placed in an ice bath for cooling. The fluorescence was measured at the activation wavelength of 300 nm and emission wave-

length of 335 nm using spectrofluorophotometer (RF 1603-PC, Shimadzu, Japan). The standard plot was prepared by taking appropriate concentrations of dopamine and the same depicted in **Figure 1**. Dopamine levels in the brain of mice treated with atropine and test compounds B and E were calculated using the standard plot. Out of these, Compound E showed significantly higher brain dopamine level, this was followed by Compound B and Atropine (2) (**Table 2**).

4. Experimental

4.1. General

The melting points reported are uncorrected. The spectral data was obtained from Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow, Orchid Chemicals and Pharmaceuticals, Chennai, Ranbaxy Research Laboratory, Gurgaon and Central Instrumentation Facility at B.I.T. Mesra. The purity of compounds was ascertained by running the samples on TLC.

4.2. Synthesis

4.2.1. 9-methyl-4-oxo-n-(phenylmethylene)–3, 9-diazabicyclo [4.2.1] nonane-3-carbothiohydrazide (6)

9-Methyl-4-oxo-3,9 diazabicyclo [4.2.1] nonane-3-carbothiohydrazide (4) (2.28 g) was taken in absolute alcohol (25 ml) and treated with glacial acetic acid (1 ml) and benzaldehyde (1.06 ml). After refluxing the reaction mixture for 24 hrs it was kept in refrigerator when the thiosemicarbazone (6) precipitated out. Mp: 203ºC; yield 1.4 g (44.3%); I.R. :1692 cm^{-1} (C═O stretch); 1106 cm^{-1} (C═S stretch); 1404 cm^{-1} (C═N stretch); 1258 cm^{-1} (C—N stretch); 746 cm^{-1} (aromatic C—H bending); ^{1}HNMR (δ, ppm): δ = 1.643 ppm, (3H, singlet, N—CH_3); δ = 7.990 ppm, (1H, singlet, aldehydic proton ═C—H); δ = 2.076 ppm, (1H, multiplet, bridgehead proton —CH—); δ = 7.019 ppm, (1H, singlet, amine proton —NH); δ = 4.155 ppm, (2H, quartet, axial methylene proton —CH_2—) ; δ = 7.161 ppm, (3H, triplet, aromatic proton- meta, para); δ = 2.837 ppm, (2H, triplet, equatorial methylene proton —CH_2—); δ = 7.629 ppm, (1H, doublet, aromatic proton -ortho position). FAB-MS (m/z): M^{+1} peak at 317.0.

Table 2. Levels of dopamine in mice brain after administration of atropine, test compounds b and e.

Group	Compounds	Dopamine level (ng/gm of brain weight)
1	Vehicle treated (control)	254.97 (3.56)*
2	Atropine (2) treated**	284.84 (3.15)*
3	Compound B(7) treated**	295.44 (2.01)*
4	Compound E (10) treated**	314.32 (1.24)*

*Values in parentheses indicate standard deviation (n = 4); ** $p < 0.01$ when compared to control (Paired t-test).

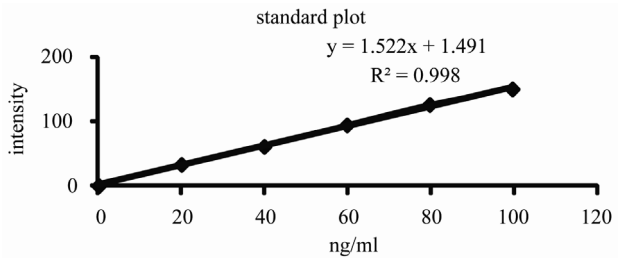


Figure 1. Standard curve of dopamine.

4.2.2. 9-methyl-4-oxo-n-(2-chlorophenyl) methylene 3, 9-diazabicyclo [4.2.1] nonane-3-carbothiohydrazide (7)

9-Methyl-4-oxo-3,9diazabicyclo[4.2.1]nonane-3-carbothi ohydrazide (**4**) (2.28 g) was taken in absolute alcohol (25 ml) and treated with 1 ml of glacial acetic acid and 2-chlorobenzaldehyde (1.405 g). The reaction mixture was next processed in the same fashion as 9-methyl-4-oxo-N-(phenyl-methylene)-3,9 diazabicyclo [4.2.1] nonane-3-carbothiohydrazide (**7**). mp: (260˚C); yield 1.8 g (51.3%); I.R.: 1635 cm^{-1} (C═O stretch in tertiary amide); 1127 cm^{-1} (C═S stretch); 1446 cm^{-1} (C═N stretch); 1250 cm^{-1} (C—N stretch); 757 cm^{-1} (aromatic C—H bending); ^{1}HNMR (δ, ppm): δ = 2.048 ppm, (3H, singlet, N—CH_3); δ = 1.385 ppm, (2H, sextet, equatorial methylene —CH_2); δ = 4.130 ppm, (2H,quartet, methylene proton —CH_2—); δ = 4.448 ppm, (2H, sextet, axial methylene proton —CH_2—); δ = 7.335 ppm, (1H,quartet, aromatic proton- meta, para); δ = 7.283 ppm, (1H, singlet, amino proton —NH—); δ = 8.153 ppm, (1H, singlet, aldehydic proton ═C—H); δ = 8.511 ppm, (1H, doublet, aromatic proton -ortho position). FAB-MS (m/z): M^{+1} peak at 352.9.

4.2.3. 3-benzenesulphonyl-9-Methyl-3, 9-diazabicyclo- [4.2.1] nonane (8) hydrochloride

To a solution of 9-methyl-3, 9-diazabicyclo [4.2.1] nonane (5) (0.42g) in dry pyridine was added benzenesulphonyl chloride (0.6 ml) and the reaction mixture heated on a water bath for 30 min. The contents of the flask were poured into ice cold water (10 ml), basified with potassium carbonate, and extracted with chloroform (3 × 10 ml). After working up the chloroform extract in the usual manner, an oily residue (0.65 g) was obtained. This was converted to the hydrochloride and crystallized from acetone. yield 0.32 g (34.4 %); mp 223-225˚C; I.R.: 1342 cm^{-1}, 1163 cm^{-1} (sulfonamides); 750 cm^{-1} (mono substituted aromatic C—H bending); 1285 cm^{-1} (C—N

strecth); ^{1}HNMR (δ, ppm): δ = 1.215 ppm (3H, singlet, N—CH_3 proton); δ = 7.717 ppm (1H, doublet, aromatic –meta proton); δ = 7.513 ppm (1H, doublet, aromatic – ortho proton); δ = 1.941 ppm (2H, triplet, —CH_2— axial proton; at C_1 and C_2); δ = 1.812 ppm (2H,triplet, —CH_2— equatorial proton; at C_1 and C_2); δ = 4.1537 ppm (1H, doublet, —CH_2— axial proton; at C_7); δ = 3.630 ppm (1H, doublet, —CH_2— equatorial proton, at C_7); δ = 2.035 ppm (1H, quartet, —CH— proton at bridge junction); δ = 2.269 ppm (1H, quartet, —CH— proton at bridge junction); δ = 4.137 ppm (1H, doublet, —CH_2— axial proton at C_4); δ = 3.906 ppm (1H, doublet, —CH— proton at C_4.

4.2.4. 3-(P-Toluenesulphonyl)-9-Methyl-3, 9 Diazabicyclo [4.2.1] Nonane (9) Hydrochloride

To a solution of 9-methyl-3, 9-diazabicyclo [4.2.1] nonane (5) (0.42 g) in dry pyridine (10 ml) was added *p*-toluenesulphonylchloride (0.8 g) and heated on a water bath for 30 min. The contents of the flask were next poured into ice cold water (10 ml), basified with potassium carbonate and extracted with chloroform (3 × 10 ml). The chloroform extract was dried, filtered and evaporated to yield an oily residue (0.72 g). This was converted to the hydrochloride and crystallized from absolute ethanol. yield 0.45 g (45.4%), mp 245-247˚C; I.R.:1339 cm^{-1}, 1106 cm^{-1} (sulfonamides); 852 cm^{-1} (aromatic C—H bending), 1290 cm^{-1} (C—N stretch); ^{1}H NMR: δ = 2.9171 ppm (3H, singlet, N—CH_3 proton); δ = 7.306 ppm (1H, doublet, aromatic –meta proton); δ = 7.6124 ppm (1H, doublet, aromatic – ortho proton); δ = 1.2532 ppm (3H, singlet, —CH_3 proton); δ = 2.4379 ppm (1H, quentet, —CH— proton at bridge junction;); δ =3.8151 ppm (1H, doublet, —CH_2— axial proton at C_7); δ = 2.0120 ppm (1H, doublet, —CH_2— equatorial proton at C_7); Mass: M^{+1} peak at 294.6.

4.2.5. 3-(4-chlorobenzesulphonyl)-9-methyl-3, 9-diazabicyclo [4.2.1] nonane (10)hydrochloride

To a solution of 9-methyl-3,9-diazabicyclo[4.2.1]nonane (5) (0.71 g) in 5 ml dry pyridine was added *p*-chlorobenzenesulphonyl chloride (1.05 g). The mixture was heated on a water bath for 30 min. The contents of flask were poured into ice-cold water (10 ml), basified with potassium carbonate and extracted with chloroform (3 x10 ml). After working up the chlorform extract the oily residue was converted to hydrochloride and crystallized from absolute ethanol. mp. 132˚C, yield 0.26 g (14.8%); I.R.: 1329 cm^{-1}, 1159 cm^{-1} (sulfonamides); 825 cm^{-1} (aromatic C—H bending), 1280 cm^{1} (C—N stretch); ^{1}H NMR: δ = 2.637 ppm (3H, singlet, N—CH_3 proton); δ = 7.2632 ppm (1H, doublet, aromatic – meta proton); δ = 7.33 ppm (1H, doublet, aromatic – ortho proton); δ = 1.6222ppm (2H, triplet, —CH_2— axial proton; at C_1 and C_2); δ = 1.388 ppm (2H,triplet, —CH_2— equatorial proton; at C_1 and C_2); δ = 3.10 ppm (1H, doublet, —CH_2— axial proton; at C_7); δ = 3.0 ppm (1H, doublet, —CH_2— equatorial proton, at C_7); δ = 2.10 ppm (1H, quartet, —CH— proton at bridge junction); δ = 4.20 ppm (1H, triplet, —CH_2— axial proton at C_5); δ = 3.80 ppm (1H, multiplet, —CH— proton at bridge junction;); δ = 1.99 ppm (1H, quartet, —CH_2— proton at C_4); Mass :M^{+1} peak at 315.1.

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