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"SYNTHESIS OF VARIOUS ANTHRAQUINONES DERIVATIVES AND ITS BIOLOGICAL EVALUATION AS NEUROPROTECTIVE AGENTS"

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ABSTRACT

Parkinson's ailment is especially outstanding from other situations based totally on the vital function of tremors. Oxotremorine-triggered oxidative pressure is a commonplace pathway in growing Parkinson's signs like tremors, salivation, and temperature version. Subsequently, the Oxotremorine-precipitated tremor version changed used to assess Antiparkinsonian tablets. Distinct Anthraquinones derivatives compound 1 to16 have been formulated using appropriate schemes 1to 4 to investigate the Antiparkinsonian impact on Oxotremorine-brought on Parkinson's symptoms in mice. Procyclidine, an anticholinergic, Antiparkinsonian drug was administered as a generic drug at a dose of 5 mg/kg p. o., 1hr prior to the administration of Oxotremorine (0.5 mg/kg) S.C. Numerous synthetic Anthraquinones compounds administered 200 mg/kg p. o. route of administration to reduce Parkinson's symptoms. This look at indicates synthetic Anthraquinones compounds 1, 2, 6, eight, 12, and 14 show marked response to Parkinsonism symptoms compared to Procyclidine. From this research it is always worthy to synthesize various novel amino Anthraquinones compounds by considering Carboxamide linkage with various heterocyclic compounds as a neuroprotective agent helpful in PA.

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INTRODUCTION: [4, 5, 6, 8, 15]

Parkinson's ailment (PA), a modern disorder of the good-sized frightened (CNS), is due to the degeneration of dopaminergic neurons within the substantia nigra of the midbrain. PD is characterized by tremors, muscular stress, and bradykinesia, problems with stability and on foot, despair, and dementia. The relaxation tremor is an indication that distinguishes PA from other ailments and its clinical treatment is, to begin with, powerful but may additionally become vain later. Experimental animal models of tremors have predominantly been applied to research tablets with possible recovery fees for PA tremors. Oxotremorine, an energetic metabolite of Tremorine, has been used to provide tremors in mice. Oxotremorine is a selective agonist of the muscarinic acetylcholine receptor and the systemic utility of tremorine stimulates acetylcholine receptors every inside the periphery and moreover within the basal ganglia in the CNS. The numerous insights of preceding portions of the literature approximately Anthraquinones display that Antidepressant moves and neuroprotective movements of compounds from various plant and synthetic Anthraquinone are due to their robust MAO inhibitory (MAO-A and MAO-B) motion and sturdy antioxidants motion. Proceeding investigated the Inhibition of MAO A and B thru a few plant-derived alkaloids, phenols, and anthraquinone. A complete of six Anthraquinones (emodin, rhein, chrysophanol, aloe-emodin, physcion, and 1, eight-dihydroxyanthraquinone) were tested for the inhibitory interest of monoamine oxidase (MAO) A and B from rat mind mitochondrial. Their research showed that the phytochemical piperine, paeonol, and emodin are powerful MAO inhibitors. MAO inhibitory and sturdy antioxidant motion of Anthraquinones helps them to apply in Alzheimer's and Parkinson's disorder (Neuro-degenerative sicknesses). The research evaluation of antioxidant, enzyme inhibition, and cytotoxic activity of three Anthraquinones (alizarin, purpurin, and quinizarin). The studies' insights reveal that AQs may be used as antioxidative compounds in food and medicinal packages. Alternate Anthraquinone with the useful resource of numerous heterocyclic particularly nitrogen-containing fragrant compounds (MAO A and B Inhibitors) can also additionally produce effective Anthraquinone as an antidepressant and neuroprotective seller. Nitrogen heterocyclic has been said to functionality monoamine oxidase inhibitors: synthetic techniques of monoamine oxidase inhibitors (MAO) belonging to a set of nitrogen heterocyclic together with pyrazoline, indole, xanthenes, oxadi-azole, Benzimidazole, pyrrole, quinoxaline, thiazole, and other related compounds confirmed formation of carboxamide linkage of the heterocyclic compound with amino-anthraquinone and numerous research shows the significance of carboxamide linkage and a way to produce carboxamide with heterocyclic compounds and Anthraquinone.

Synthesis and Pharmacological assessment of Novel unsubstituted indole Anthraquinone carboxamide Derivatives as robust anti-hyperlipidemic entrepreneurs had been suggested. With the aid of the use of considering the above prediction, it's miles continually worthy to synthesize anthraquinone derivatives using 2-aminoanthraquinone, 1-amino Anthraquinone, and 1, 4-diamino Anthraquinone the usage of appropriate artificial schemes a good way to shape carboxamide linkage containing compounds. Substitution of Anthraquinones itself can be worthy due to their robust MAO inhibitory (MAO-A and MAO-B) action and strong antioxidant action.

Synthesis of Anthraquinones derivatives: [4, 16, 17, 18, 19, 20]

MATERIALS AND METHODS:

Oxotremorine,1H-indole-2-carboxylic acid, 1H-benzimidazole -2-carboxylic acid (sigma Aldrich USA), Procyclidine (GlaxoSmithKline), Trichloroacetic acid (TCA), Ethylene diamine tetra acetic acid (EDTA), (Qualigens fine chemicals Ltd., Mumbai) Thiobarbituric acid (TBA) (Sigma Chemicals, USA.), 5, 5 dithio-bis-2 nitro benzoic acid (DTNB) (Sigma Chemicals, USA.) DCM, SOCl2 (Loba chemicals) and all other agents were of analytical grade.

Synthesis of 1H-indole-2-carbonyl chloride (A):

A mixture of 1H-indole-2-carboxylic acid (1.25 g, 7mmol) and thionyl chloride ($SOCl_2$) (2.5 mL, 34mmol) in 40 mL of dry dichloromethane (DCM) was stirred under reflux for 6 h. After cooling to room temperature, DCM and the excess $SOCl_2$ were evaporated under reduced pressure. The solid residue was suspended in hexane and the suspension was evaporated to dryness to afford 1.55 g (95%) of the solid residue which was used without further purification.

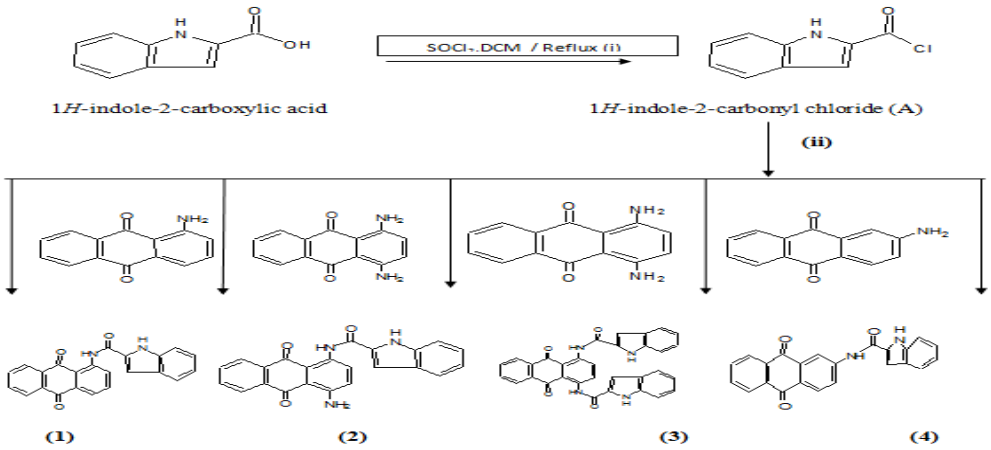

Fig 1: Preparation of Indole-Anthraquinone-2-Carboxamide derivatives (1-4) starting from Indole-2-Carboxylic acid (I) $SOCl_2$, 70-80 ^{0}C, DCM, $CHCl_3$, (II) Reflux at 120 ^{0}C.

General synthetic procedure:

Four novel derivatives of 1*H*-indole-anthraquinone-2-carboxamide were prepared. (1-4)
N-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-indole-2-carboxamide (1)
N-(4-amino-9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-indole-2-carboxamide (2)
N-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1, 4 *Di*--indole-2-carboxamide (3)
N-(9, 10-dioxo-9, 10-dihydroanthracen-2-yl)-1*H*-indole-2-carboxamide (4)

They were synthesized by fusion at high temperature, by which indole-2-carbonyl chloride was thoroughly mixed with aminoanthraquinone derivatives and refluxed at 120 ˚C for 18 h in an air condenser. Then1, 4-dioxane was added and the mixture stirred for additional 24 h at room temp.

The resulting products were filtered and recrystallized to give the compounds 1 – 4 (Fig-1).

Synthesis of 5-chloro-1H-indole-2-carbonyl chloride (B):

A mixture of 5-chloro-1H-indole-2-carboxylic acid (1.25 g, 7mmol) and thionyl chloride ($SOCl_2$) (2.5 mL, 34mmol) in 40 mL of dry dichloromethane (DCM) was stirred under reflux for 6 hrs. After cooling to room temperature, DCM and the excess SOCl2 were evaporated under reduced pressure. The solid residue was suspended in hexane and the suspension was evaporated to dryness to afford 1.55 g (95%) of the solid residue which was used without further purification.

General synthetic procedure:

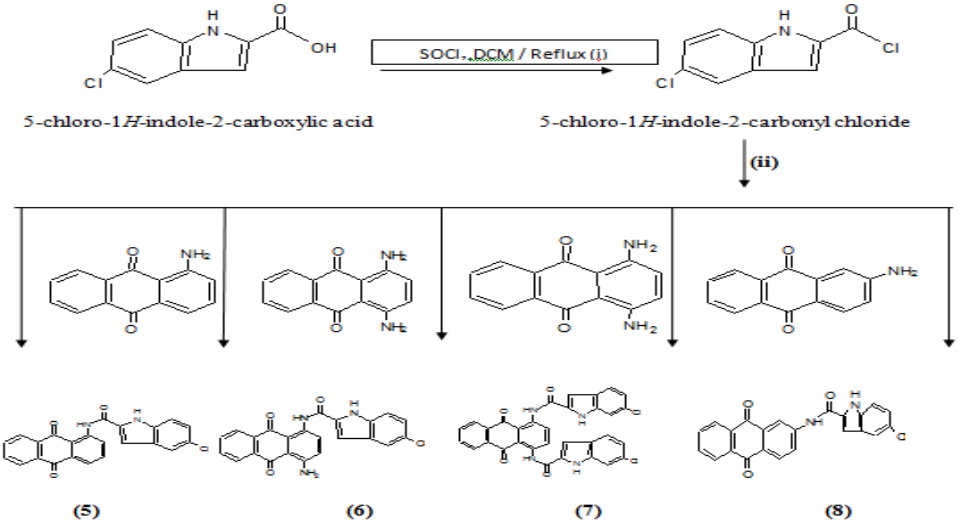

Fig 2: Preparation of 5-chloro-1-H-Indole-Anthraquinone-2-Carboxamide derivatives (5-8) starting from 5-chloro-indole-2-Carboxylic acid (I) $SOCl_2$, 70-80 ^{0}C, DCM, $CHCl_3$, (II) NaH, DMF Reflux at 24hrs.

Four novel compounds of 5-chloro-1H-indole-anthraquinone-2-carboxamide derivatives were prepared. (5-8)
5-chloro-N-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1H-indole-2-carboxamide (5)
N-(4-amino-9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-5-chloro-1H-indole-2-carboxamide (6)
N-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-5, 5-di chloro, 1, 4 Di--indole-2-carboxamide (7)
5-chloro-N-(9, 10-dioxo-9, 10-dihydroanthracen-2-yl)-1H-indole-2-carboxamide (8)

They had been synthesized by means of adding distinctive Anthraquinones to a suspended solution of (zero.098g, three.9mmol) of sodium hydride (NaH) in dry N, N-dimethylformamide (DMF) and stirred for about 30 min at room temperature earlier than the addition of five-choro-1H-indole-2-carbonyl chloride. The reaction combination became refluxed for 24 h, and then cooled to room temperature. DMF changed into evaporated beneath reduced strain and the residue changed into stirred for 10 min in chloroform (CHCl3). The solvent was removed under decreased stress and the product turned into dried in a vacuum. The resulting merchandise was filtered and recrystallized to give the compounds five – eight (Fig 2)

Synthesis of 1H-benzimidazole-2-carbonyl chloride (C):

A mixture of 1H- Benzimidazole -2-carboxylic acid (1.35 g, 7mmol) and thionyl chloride (SOCl2) (2.5mL, 34mmol) in 40 mL of dry dichloromethane (DCM) were stirred under reflux for 6 h. After cooling to room temperature, DCM and the excess SOCl2 were evaporated under reduced pressure. The solid residue was suspended in hexane and the suspension was evaporated to dryness to afford 1.55 g (97%) of the solid residue which was used without further purification.

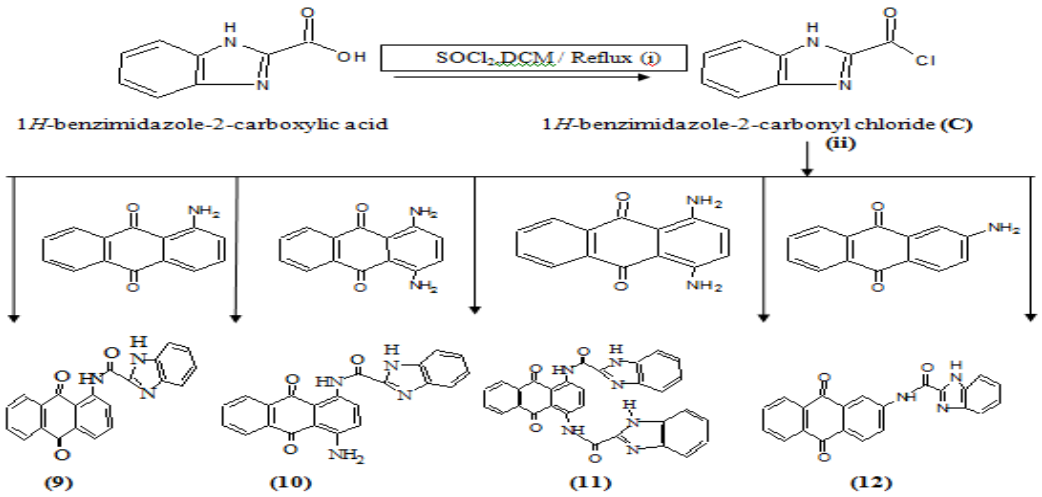

Fig 3:Preparation of 1 H-Benzimidazole-Anthraquinone-2-Carboxamide derivatives (9-12) starting from Benzimidazole-2-Carboxylic acid (I) $SOCl_2$, 70-80 ^{0}C, DCM/ Reflux (II) Reflux at 120 ^{0}C

General Synthetic Procedure:

Following derivatives of 1H-benzimidazole-anthraquinone-2-carboxamide were prepared (9-12)

N-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-benzimidazole-2-carboxamide (9)

N-(4-amino-9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-benzimidazole-2-carboxamide (10)

N-(4-(2, 3-dihydro-1H-1, 3-benzodiazole-2-amino) 9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-1, 3-Benzodiazole-2-carboxamide (11)

N-(9, 10-dioxo-9, 10-dihydroanthracen-2-yl)-1*H*-benzimidazole-2-carboxamide (12)

They were synthesized by fusion at high temperature, by which 1*H*-benzimidazole-2-carbonyl chloride was thoroughly mixed with aminoanthraquinone derivatives and refluxed at 120 ◦C for 18 hrs in an air condenser.Then1, 4-dioxane was added and the mixture stirred for additional 24 h at room temperature. The resulting products were filtered and recrystallized to give the desired compounds 9 – 12 (Fig 3)

Synthesis of 5-chloro-1*H*-benzimidazole-2-carbonyl chloride (D):

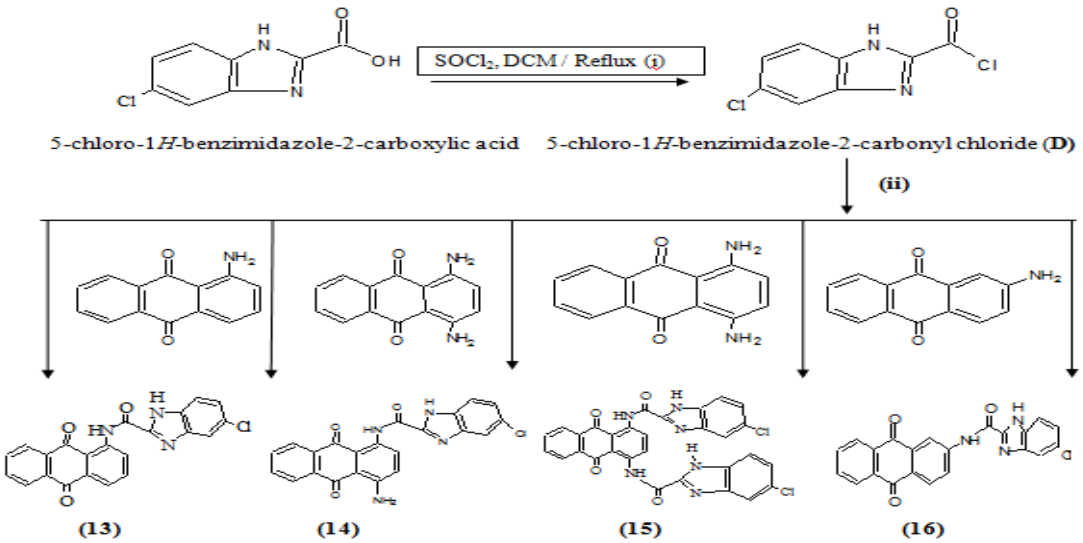

Fig 4: Preparation of 5-chloro-1-H-Benzimidazole-Anthraquinone-2-Carboxamide derivatives (12-16) starting from -5-chloro-1H-Benzimidazole-2- Carbonyl Chloride. (I) $SOCl_2$, DCM/ Reflux (II) NaH, DMF, Reflux 24hrs.

Synthesis of 5-chloro-1*H*-benzimidazole-2-carbonyl chloride (D):

A mixture of 5-chloro-1*H*-benzimidazole-2-carboxylic acid (1.20 g, 7mmol) and thionyl chloride ($SOCl_2$) (2.5 mL, 34mmol) in 40 mL of dry dichloromethane (DCM) was stirred under reflux for 6 hrs. After cooling to room temperature, DCM and the excess $SOCl_2$ were evaporated under reduced pressure. The solid residue was suspended in hexane and the suspension was evaporated to dryness to afford 1.50 g (90%) of the solid residue which was used without further purification.

General Synthetic Procedure:

Following derivatives of 5-cholro-1-H-benzimidazole-anthraquinone-2-carboxamide were prepare (13-16)

5-chloro-*N*-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-benzimidazole-2-carboxamide (13)

N-(4-amino-9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-5-chloro-1*H*-benzimidazole-2-carboxamide (14)

5-chloro-*N*-(4-(5-chloro-1H-1, 3-benzodiazole-2-amido)-9, 10-dioxo-9, 10-dihydroanthracene-yl) 1H- 1, 3-benzodiazole-2-carboxamide (15)

5-chloro-*N*-(9, 10-dioxo-9, 10-dihydroanthracen-1-yl)-1*H*-benzimidazole-2-carboxamide (16)

They were synthesized by adding different Anthraquinones to a suspended solution of (0.098 g, 3.9mmol) of sodium hydride (NaH) in dry N, N-dimethylformamide (DMF) and stirred for about 30 min at room temperature before the addition of 5-choro-1H-benzimidazole-2-carbonyl chloride the reaction mixture was refluxed for 24 h, and then cooled to room temperature. DMF was evaporated under reduced pressure and the residue was stirred for 10 min in chloroform (CHCl3). The solvent was removed under reduced pressure and the product was dried in a vacuum. The resulting products were filtered and recrystallized to give compounds (13– 16) (Fig 4)

MATERIALS AND METHODS

Oxotremorine,1H-indole-2-carboxylic acid, 1H- Benzimidazole -2-carboxylic acid (sigma Aldrich USA), Procyclidine (GlaxoSmithKline), Trichloroacetic acid (TCA), Ethylene diamine tetra acetic acid (EDTA), (Qualigens fine chemicals Ltd., Mumbai) Thiobarbituric acid (TBA) (Sigma Chemicals, USA.), 5, 5 dithio-bis-2 nitro benzoic acid (DTNB) (Sigma Chemicals, USA.) DCM, SOCl2 (Loba chemicals), and all other agents were of analytical grade.

Animal selection:

Male mice weighing about 18-20g were used for Antiparkinsonian activity. Mice were kept in polypropylene cages and led on a standard laboratory diet i.e. oil extracted groundnut feed was given. The animals were kept under 12 hr light and dark cycles. Mice were divided into five groups. Each group contained four animals.

Antiparkinsonian activity determination: [7, 14]

Antiparkinsonian activity was determined according to the method described in Vogel H.G, in drug discovery and evaluation of pharmacological assay, with some modification.

Method- Groups of four mice weighing 18-22 g were used for the activity. The dose of test Synthetic compounds 1to16 (200mg/kg) was given orally and the standard compound (Procyclidine 5mg/kg) 1h prior to the administration of Oxotremorine (0.5mg/kg) S.C. Rectal temperatures were measured before administration of the compound (basal value) and 1h after Oxotremorine administration.

Evaluation of Antiparkinsonian activity:

Rectal temperature was measured before administration of compound (basal value) and 1 h after Oxotremorine administration. Tremor was scored after Oxotremorine dosage in observations periods every 15 min for 1 h. Salivation and lacrimation was also scored 15 and 30 min after Oxotremorine injection.

Table 1: Antiparkinsonian activity –

Tremor	Score	Salivation	Score
Absent	0	Absent	0
Slight	1	Slight	1
Medium	2	Medium	2
Severe	3	Severe	3

Evaluation:

Hypothermia:

The difference in body temp after 1 h versus basal temp. Was summarized for each animal in the control and test group, and average values were compared statistically. Tremor: The scores for all animals in each group at 4 observation periods were summarized. All treated groups were compared with that the standard group.

RESULT & DISCUSSION:

Result:

Tremor Score after Administration of Oxotremorine:

Table 2: Effect of Synthetic Anthraquinones compounds, and standard drug Procyclidine on tremor induced by Oxotremorine.

Tremors Score	15 min	30 min	45 min	60 min
Oxotremorine	1.75	2.5	2.75	3
Drug (Procyclidine)	1	2	1.5	1.25
Comp 1*	1.25	2.25	1.75	1.25
Comp 2*	1.5	1.75	2.25	1.25
Comp 3	1.75	2	2.5	2.75
Comp 4	1.85	2.15	2.25	2.5
Comp 5	1.75	2.5	2.75	3
Comp 6*	1.25	2.25	1.75	1.25
Comp 7	1.5	1.75	2.25	2
Comp 8*	1.5	1.75	2.25	1.25
Comp 9	1.85	2.1	2.6	2.8
Comp 10	1.75	2.5	2.75	3
Comp 11	1.75	2.5	2.75	3
Comp 12*	1.25	2.25	1.75	1.25
Comp 13	1.85	2.1	2.6	2.8
Comp 14*	1.5	1.75	1.50	1.50
Comp 15	1.75	2.5	2.75	3
Comp 16	1.85	2.1	2.6	2.8

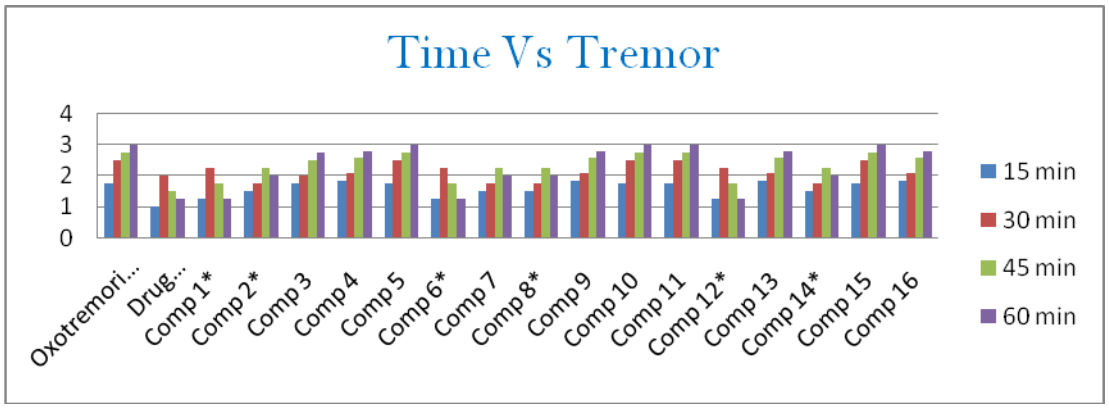

Fig 5: Effect of Synthetic Anthracene Nine, 10 -Dione compounds and standard drug Procyclidine on Oxotremorine induced Parkinson's symptoms like a tremor. Synthetic Anthracene 9,10 -Dione compounds no. 1, 2, 6, 8, 12, and 14 show a marked decrease in tremors from 30 min to 60 min in comparison with Procyclidine as a standard drug.

Table: 3. Effect of Synthetic Anthraquinones compounds and standard drug Procyclidine on Salivation induced by Oxotremorine.

Salivation	15 min	30 min	Salivation	15 min	30 min
Oxotremorine	1.75	2.85	**Comp 8***	**Comp 8***	**Comp 8***
Drug (Procyclidine)	1.15	2	Comp 9	Comp 9	Comp 9
Comp 1*	1.25	2.15	Comp 10	Comp 10	Comp 10
Comp 2*	1.5	1.75	Comp 11	Comp 11	Comp 11
Comp 3	1.75	2.5	**Comp 12***	**Comp 12***	**Comp 12***
Comp 4	1.85	2.5	Comp 13	Comp 13	Comp 13
Comp 5	1.75	2.5	**Comp 14***	**Comp 14***	**Comp 14***
Comp 6*	1.25	1.75	Comp 15	Comp 15	Comp 15
Comp 7	1.75	2.75	Comp 16	Comp 16	Comp 16

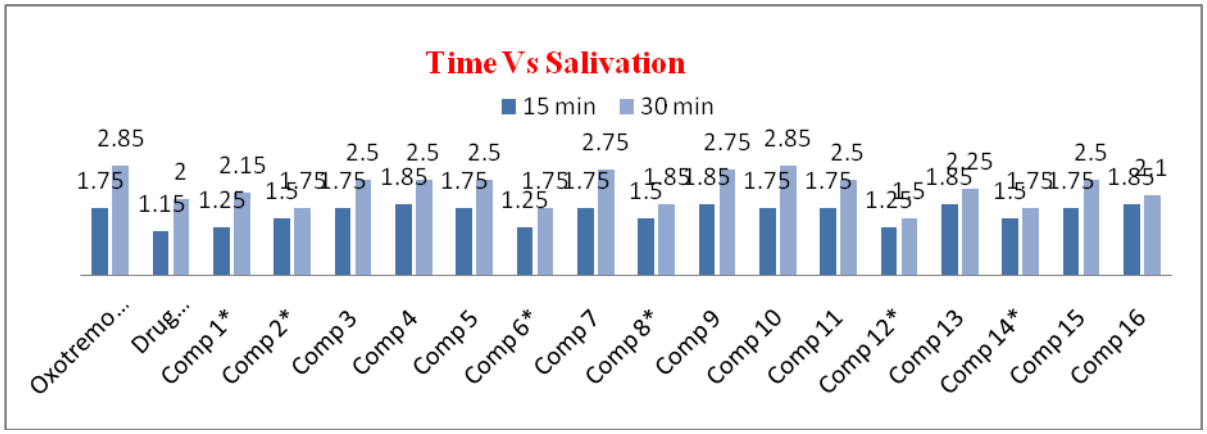

Fig 6: Effect of Synthetic Anthraquinones compounds and standard drug Procyclidine on Oxotremorine induced Salivation. Compounds no. 1, 2, 6, 8, 12, and 14 shows a marked decrease in salivation in comparison with Procyclidine as a standard drug.

Table 4: Effect of Synthetic Anthraquinones compounds and standard drug Procyclidine on temperature deviation induced by Oxotremorine.

Temp	Basal Temp	60 min (oxo Temp)	Temp	Basal Temp	60 min (oxo Temp)
Oxotremorine	36.5	33.2	Comp 8*	36.5	37
(Procyclidine)	37.1	37.3	Comp 9	37.1	34
Comp 1*	37.5	37	Comp 10	37.1	32.9
Comp 2*	36.5	37.1	Comp 11	36.5	34.6
Comp 3	37.1	34	Comp 12*	36.9	37.1
Comp 4	37.2	34.2	Comp 13	37.1	32.9
Comp 5	37.5	33.5	Comp 14*	37.1	36.9
Comp 6*	37.1	36.9	Comp 15	36.5	34
Comp 7	37.5	33.1	Comp 16	37.1	33.3

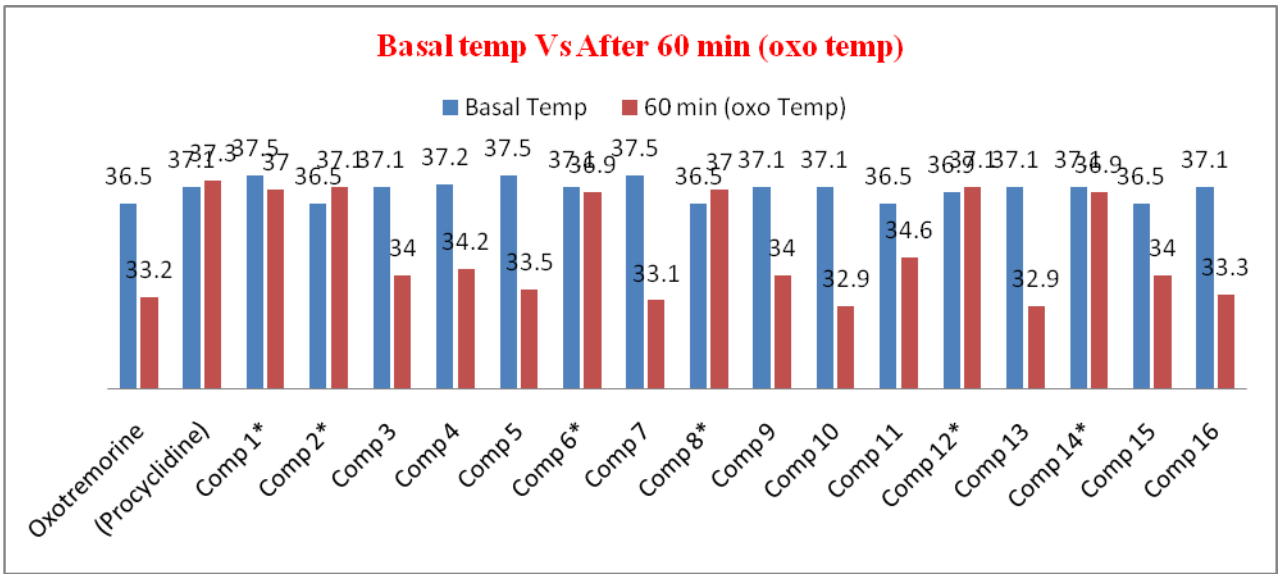

Fig 7: Effect of Synthetic Anthraquinones compounds and standard drug Procyclidine on Oxotremorine induced temperature deviation. Synthetic compounds no. 1, 2, 6, 8, 12, and 14 maintain oxo temperature (after 60 min administration of Oxotremorine) in comparison with Procyclidine as a standard drug.

DISCUSSION

Parkinson's ailment (PA) results from the degeneration of dopamine neurons in the substantia nigra and this depression of dopaminergic function promote an increase in cholinergic action. The brain areas that initiate cholinergic tremors are uncertain although, the striatum with its very high density of muscarinic cholinergic receptors is a favored area. Oxotremorine, a cholinergic muscarinic agonist induces its effects by stimulating neurons of basal ganglia and producing tremors that resemble the rest tremor that is characteristic of patients with PA. Administration of Oxotremorine, within 5 or 10 min, produced tremors, profuse salivation, urination, and a decrease in temperature. It is assumed that these effects produced by Oxotremorine originate in brain areas that have muscarinic receptors and a motor function. Hence the site of tremor production by Cholinomimetics in the mice might be the neostriatum. Therefore, drugs with anti-muscarinic and anti-nicotinic activity are used for the treatment of PA. Procyclidine one of the centrally acting anticholinergic, Antiparkinsonian drugs by exhibiting a blocking effect on the central cholinergic excitatory pathway and retarding the reuptake of dopamine into presynaptic nerve endings revert the Oxotremorine induced-tremors. The tremors score shows that 5 mg/kg orally of Procyclidine reduced the effects of Oxotremorine (0.5 mg/kg s.c) in mice thus the effect of Procyclidine was compared with the results obtained with synthetic compounds 1 to 16.

CONCLUSION

Synthetic Anthraquinones compounds no. 1, 2, 6, 8, 12, and 14 showed a significant protection against Parkinson's symptoms (tremor, salivation and temperature variation) as compared to that of standard drug Procyclidine (5mg/kg) orally. While Synthetic Anthraquinones compounds 3, 4, 5, 7, 9, 10, 11, 13, 15, and 16 failed to reduce Parkinson's symptoms. Thus the Antiparkinsonian effect of Synthetic Anthraquinones compounds no. 1, 2, 6, 8, 12, and 14 might be is due to its antioxidant property. From this research it is always worthy to synthesize various novel amino Anthraquinones compounds by considering carboxamide linkage with various heterocyclic compounds as a neuroprotective agent helpful in PA.

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Disclosure of conflict of interest:

The authors hereby declare that there is no conflict of interest.

REFERENCES

1. Friesner Richard A., et.al, Glide: A New Approach for Rapid, Accurate Docking and Scoring Method and Assessment of Docking Accuracy. J. Med. Chem. 2004, 47, 1739-1749
2. Dhananjay D. J. et.al. Introduction to methods for molecular docking and HT virtual Screening International Centre for Genetic Engineering and Biotechnology 2016, 1- 20
3. Renyuan Hong and Xun Li., et.al. Discovery of monoamine oxidase inhibitors by medicinal Chemistry approaches. Med. Chem. Commun. Nov (2018)
4. Gouda M.A., Berghot M.A, et al.Chemistry of 2-aminoanthraquinones.Turk J Chem.34 (2010), 651 – 709
5. Sies H. Neurological disease: Antioxidants in Disease Mechanism and Therapy, edited by Academic press Academic Press, 1997; 38: 557
6. Morais LS, Quintans-junior LJ, Antiparkinsonian-like effects of Plumbago Scandens on Tremorine-induced tremors methodology. Pharmacol. Biochem. Behaviour. 2006; 79:745-49
7. Yang SF, Wu Q, Sun AS, Huang XN and Shi JS, Protective Effect and Mechanism of Ginkgo Biloba Leaf Extracts for Parkinson Disease induce by 1-methyl-4-phenyl- 1, 2, 3, 6 tetrahydropyridine.Acta Pharmacol.2001; 12: 1089-93.
8. Choi J S, Lee HJ and Park KY, In vitro Antimutagenic effect of Anthraquinone aglycone and napthopyrone glycosides from Cassia tora. Planta Medica.1997; 63: 11-14
9. Kim YM, Lee CH, and Kim H G, Anthraquinones isolated from cassia tora seeds show an Antifungal property against phytopathogenic fungi. J. Agri. Food Chem. 2004; 52: 6096-6100
10. Patil UK, Saraf S and Dixit VK, Hypolipidemic activity of seeds of cassia tora Linn. J. Ethnopharmacol. 2004; 90: 249-252
11. Wu C H and Yen, GC, Antigenotoxic properties of cassia tora L: mechanism of action and The influence of roasting process. Life Science. 2004; 76: 85 -101
12. Yang YC, Lim MC, and Lee HS, Emodin isolated from cassia tora shows larvicidal activity Against three mosquito species. Agri. Food chem. 2003; 26: 7629- 31
13. Hidume FC, Kwanashie HO and Wambebe C, Antinociceptive and muscle contracting Activities of the methanolic extracts of cassia tora leaf. J. Ethnopharmacol.2002; 81: 205-209
14. Vogel HG, Antiparkinsonism activity. In Drug Discovery and Evaluation, edited by Springer Verglag Berlin Heidelberg, New York. 2002; 2nd ed: pp 577-78.
15. Yen GC, Duh PD and Chaung DY, Antioxidant activity of anthraquinones and anthrones Food Chemistry. 2000; 70: 437- 441
16. Patil P.O., et.al. Synthesis and Antidepressant Activity of Some New 5-(1*H*-Indol-3-yl) -3-(Substituted aryl)-4, 5 -dihydroisoxazoline Derivatives. Journal of Chemistry (2013) 1-7
17. Regina L.A., Silvestri R., et.al. Synthesis, structure–activity relationships and molecular Modeling studies of new indole

inhibitors of monoamine oxidase A and B. Bioorganic & Medicinal Chemistry 16 (2008) 9729–9740
18. Najdawia M.A., Hiaria Y.A., Shattatb G., et al. Synthesis and Pharmacological Evaluation of Novel Unsubstituted Indole-Anthraquinone Carboxamide Derivatives as Potent Antihyperlipidemic Agents. Z. Naturforsch. 69c, (2014), 21 – 28
19. Silvestri R. Regina G.L., et.al. Simple, Potent, and Selective Pyrrole Inhibitors of Monoamine Oxidase Types A and B. *J. Med. Chem. (*2003) *46*, 917-920
20. GHASSAN F. SHATTAT, et.al. Hypotriglyceridemic and hypocholesterolemic effects of novel *n*-(9, 10- dihydro-9,10-dioxoanthracen-1-yl)-1*h*-pyrrole-2-carboxamides in triton wr-1339-induced hyperlipidemic rats. IJBPAS, December, 2015, 4(12): 6712-6723.

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