



EXPLORATION OF HETEROCYCLIC SCAFFOLDS USED TO TREAT PARKINSONISM: A REVIEW

MAYURA KALE* AND ASMITA AMBHORE

*Department of Pharmaceutical Chemistry, Government College of Pharmacy, Osmanpura,
Aurangabad-431 005, Maharashtra, India.*

ABSTRACT

Since past few decades, certain heterocyclic scaffolds have drawn special attention of medicinal chemists due to their biological potential and hence extensive efforts are being undertaken to search potential lead molecules through their design and synthesis. Heterocycles have also been actively involved to treat many neurodegenerative disorders, including Alzheimer's disease, Parkinsonism and a few more. Although, there is currently no cure for Parkinson's disease, but treatments are available to help relieve the symptoms and maintain quality of life of patients. In addition, there is no single drug available to relieve the patient completely from the copious symptoms of this disease. Hence, recent research has been focused on developing new molecules that will resolve all these related issues. The present review includes a rigorous literature survey on the various heterocycles exhibiting direct as well as indirect role in treating Parkinsonism.

KEYWORDS: Heterocycles, Parkinson's disease, dopaminergic, Monoamine oxidase.

*Corresponding author



MAYURA KALE

Department of Pharmaceutical Chemistry, Government College of Pharmacy,
Osmanpura, Aurangabad-431 005, Maharashtra, India.

INTRODUCTION

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense biological and industrial importance. The majority of pharmaceuticals and biologically active compounds are heterocyclic in nature. These are an important class of compounds, making up more than half of all known organic compounds^{1,2}. Many natural drugs such as alkaloids, dyes, luminophores, pesticides and herbicides are also heterocyclic in nature. These are also important components of biomolecules such as proteins, DNA, RNA and vitamins³. All biological processes are also based on chemical reactions involving the participation of many heterocyclic compounds such as vitamins, enzymes, coenzymes, nucleic acids, ATP, serotonin and a few more. Compounds with heterocyclic rings are inextricably woven into the most basic biochemical processes of life. Heterocycles have been used in chemotherapy since a very long time to treat infectious, parasitic or malignant diseases by chemical agents because they have a specific chemical reactivity, resemble essential metabolites and can provide synthons in biosynthetic processes^{4,5}. Among the heterocyclic compounds, five membered heterocyclic moieties fused with aromatic ring systems containing various heteroatoms such as N, S and O have been found to exhibit wide spectrum of pharmacological activities⁶⁻⁹. Of these, some important examples can be cited such as anastrozole which is an aromatase-inhibiting drug, has been approved for the treatment of breast cancer after surgery, as well as for metastasis in both pre and postmenopausal women. Posaconazole is a triazole antifungal drug active against microorganisms such as *Candida*, *Asperigillus*, *Zygomycetes* and a few more. Sumatriptan is a 1,2,4-triazole heterocycle and is the first antimigrain drug. Hence, the heterocycles can be used as molecules having value as human therapeutic agents, which is the foremost objective of organic and medicinal chemistry¹⁰⁻¹². Chemical modifications of heterocycles as bioactive components of naturally occurring metabolites,

has been one of the most common approaches in drug discovery of new drugs with improved therapeutic profile. Phenothiazine heterocycles have been employed as antipsychotic agents such as chlorpromazine and thioridazine. Also, the long-acting antihistaminics like promethazine and ethopropazine have been used in treatment of Parkinsonism many more examples of such heterocyclic traded drugs can be cited. It is thus surmised that these compounds play a significant role in chemotherapy of various diseases¹³⁻¹⁵. The present review focuses on the role of various heterocycles that have been designed and synthesized to treat Parkinson's disease (PD). This disorder has gained attention recently as it has affected approximately 1 million people in the United States and a still larger number in third world countries. It is an age-related neurodegenerative disorder that is characterised by the loss of dopaminergic neurons in the striatum. This results in pathological features such as loss of movement, dyskinesias, tremors and other non-motor symptoms¹⁶.

Progress in treating Parkinsonism

The main strategic developments that have led to progress in the medical management of PD have focused on improvements in dopaminergic therapies. Despite all the recent research, there are only a few classes of drugs which are approved for the treatment of motor related symptoms of PD which primarily act on the dopaminergic neurons system: L-dopa, dopamine agonists, monoamine oxidase-B (MAO-B) and catechol-o-methyl transferase (COMT) inhibitors. Anticholinergic drugs and glutamate antagonists are also available, but are not commonly used in routine practice. As no effective therapeutic strategy has yet been attended, other solutions are under investigation. Privileged aromatics and heterocycles such as indoles, arylpiperazines, biphenyls and benzopyrans are currently ascribed as helpful approaches. Different families of nitrogen and oxygen heterocycles,

such as pyrazoles, hydrazinylthiazoles, xanthenes, coumarins or chromones have also been extensively used as scaffolds in medicinal chemistry programs for searching novel MAO-B inhibitors¹⁷. Nitrogen derivatives have also been shown to play a key role in this matter with several studies suggesting hydrazines, thiazoles and indoles as important scaffolds for the development of novel MAO-B inhibitors¹⁸. Also, selective MAO-B inhibitors such as deprenyl and rasagiline are in current use, alone or in combination with levodopa, in the symptomatic treatment of PD. Their irreversible mechanism of inhibition and the potential application of MAO-B inhibitors as anti-Alzheimer agents are at the moment the driving forces for the discovery of novel potent and selective MAO-B inhibitors¹⁹.

Recent approaches to treat Parkinsonism

Afshin Zarghi *et al* have reviewed the structure activity relationships (SARs) of some selective cyclooxygenase-2 (COX-2) inhibitors. It is known that non-steroidal anti-inflammatory drugs (NSAIDs) are the competitive inhibitors of COX and their use is associated with the side effects such as gastrointestinal and renal toxicity. The anti-inflammatory action of these

drugs is produced by the inhibition of COX-2, while the undesired side effects arise from inhibition of COX-1 enzyme. The authors have realized that selective COX-2 inhibitors would reduce these side effects and would open new avenues for these in cancer chemotherapy and neurological diseases such as PD and Alzheimer's diseases. It has attracted further investigations on the development of COX-2 inhibitors. This review has highlighted various structural classes of selective COX-2 inhibitors (Fig 1) with special emphasis on their SARs. The NSAIDs reduce the dopaminergic neuron degeneration in animal models of PD while COX-2 is up-regulated in brain dopaminergic neurons of both PD postmortem specimens and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD. It has been shown that COX-2 inhibition prevented formation of the oxidant species dopamine-quinone that is involved in the pathogenesis of PD²⁰. It has been revealed that the characteristic methanesulfonyl, sulfonamido, azido, methanesulfonamide or tetrazole pharmacophore group on one of the aryl rings of these tricyclic compounds (Fig 1) play a key role on COX-2 selectivity²¹.

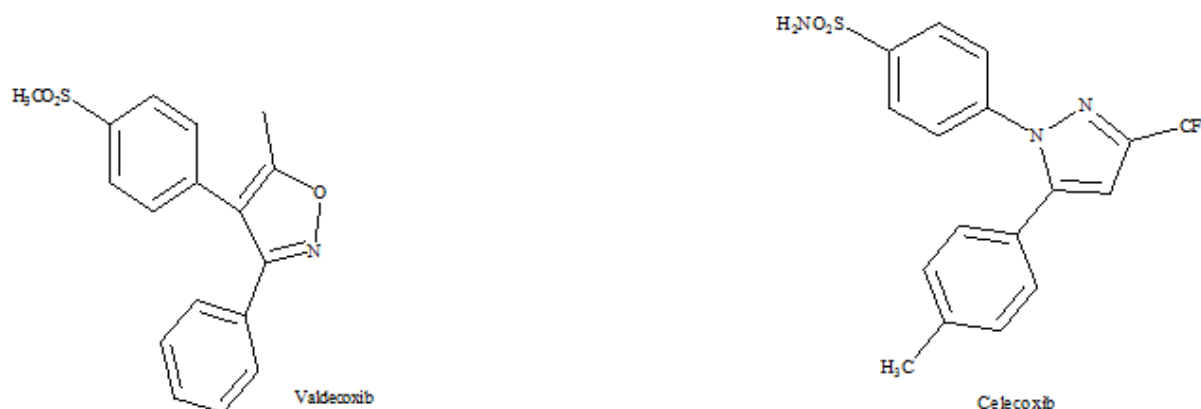


Figure 1

Hiroshi Ichinose *et al* have investigated the effects of various heterocyclic amines in food on nigro-striatal dopaminergic neurons. Among the compounds tested, 3-amino-1,4-dimethyl-5-pyrido[4,3-b] indole and 3-amino-1-methyl-5H-pyrido[4,3-b] indole (Fig 2) were shown to

cause substantial decrease in 3,4-dihydroxyphenylalanine (DOPA) formation in striatal tissue slice system. Both the compounds were found to produce a transient increase of dopamine (DA) and continuous decrease in the metabolites, homovanillic acid

(HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC). This has suggested that the two compounds inhibit MAO *in vivo*. Hence, these

MAO inhibitors could be clinically used for neural diseases such as depression and PD²²⁻²⁴.

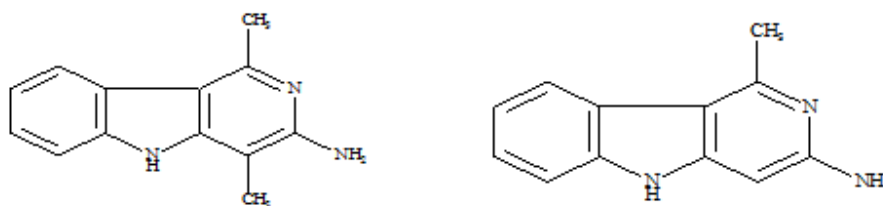


Figure 2

Hui-Po Wang *et al* have investigated the pharmacological activities of a novel tripeptide mimetic dopamine prodrug. In this study, d-p-hydroxyphenylglycine-l-proline was attached to l-dopa as delivery tool for improving the oral absorption. This tripeptide prodrug (Fig 4) of dopamine was well absorbed in a perfusion

study in rat intestine, devoid of dopamine-like side effects on isolated smooth muscles and significantly inhibited the (+)-methamphetamine-induced rotation in nigrostriatal-lesioned rats, suggesting anti-Parkinsonism effect²⁵.

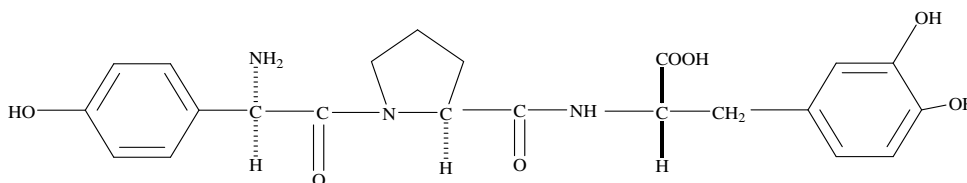


Figure 4

Omid Tavassoly *et al* have mentioned the use of nanopore analysis for discovering drugs which bind to α -synuclein enzyme for treatment of PD²⁶. This study is based on the fact that in PD, there is formation of Lewy bodies in dopaminergic neurons which consist of misfolded α -synuclein. The binding of natural products to α -synuclein has been evaluated by nanopore analysis and caffeine, curcumin and nicotine all caused large conformational changes which may be related to their known neuroprotective effect in PD. It has been proposed that (-)-nicotine causes the folding of α -synuclein into a loop with interaction between the N- and C-termini. In case of (+)-nicotine, the binding was found to be weaker and mainly involved residues in the N-terminus. Caffeine

and nicotine bind to α -synuclein simultaneously and may provide lead structures for the development of other compounds for the treatment of PD. Maria Galuppo *et al* have studied anti-inflammatory and anti-apoptotic effects of (RS)-glucoraphanin bioactivated with myrosinase enzyme (bioactive RS-GRA) in murine sub-acute and acute MPTP-induced PD. RS-GRA is one of the most important glucosinolates (Fig 5) a thiosaccharidic compound found in Brassicaceae, notably in Tuscan black kale seeds. The studies have shown that RS-GRA was able to reduce dopamine transporter degradation which suggests its neuroprotective action in PD via an anti-apoptotic and anti-inflammatory action²⁷.

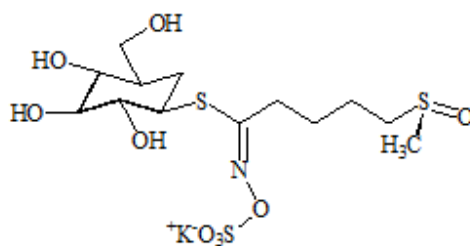


Figure 5

Werner J Geldenhuysa has studied the synthesis and biological evaluation of pentacyclo [5.4.0.02,6.03,10.05,9] undecane derivatives as potential therapeutic agents in PD. In this study, he has examined these compounds for their effects on DA release, uptake and inhibition in murine striatal synaptosomes and also inhibition in baboon liver. The compound shown (Fig 6) blocked the uptake of DA. The activity value obtained was

comparable to that of amantadine used in Parkinsonian therapy. SARs of this series of compounds support the importance of geometric and steric, rather than electronic effects in determining biological activity. The present study suggests that blockage of the dopamine transporter may be due to their neuroprotective effects against MPTP-induced PD²⁸.

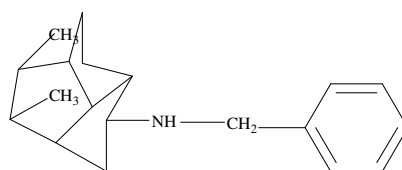


Figure 6

Michikazu Kitabatake has studied facile synthesis and *in vitro* properties of 1-alkyl- and 1-alkyl-N-propargyl-1,2,3,4-tetrahydroisoquinoline derivatives (TIQs) on PC12 cells. Their synthesis has been achieved by modified Pictet–Spengler cyclization of the formyliminium ion. The direct cytotoxicity and preventative effects towards MPP⁺ mediated death of PC12 cells were estimated. The introduction of N-propargyl substituent was found to reduce cytotoxicity. 1-methyl-, 1-

methyl-N-propargyl- and 1-cyclopropyl-tetrahydroisoquinoline derivatives (Fig 7) partially inhibited MPP⁺-induced cell death, whereas relatively large alkyl substituents did not enhance the viability of PC12 cells. The findings thus suggest a crucial role for the N-propargyl functional group for the effective reduction of cytotoxicity and also reveal the importance of size and lipophilicity of substituents at the 1-position of 1-alkyl-TIQs²⁹.

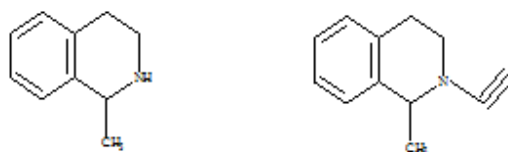


Figure 7

Richard T. Carroll *et al* have studied SAR and docking studies of thiazolidinedione-type (TZD) compounds (Fig 8) with MAO-B inhibitory activity. These compounds were able to inhibit MAO-B over several log units of magnitude

from 82 nM to 600 μ M concentrations. Initial SAR studies suggested that substitutions on the aromatic group and the TZD nitrogen were the pharmacophoric regions responsible for enhancing the activity³⁰.

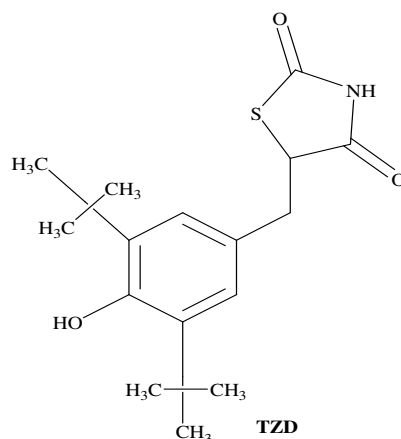


Figure 8

Eduardo Coelho Cerqueira *et al* have studied the nonselective and reversible inhibitory effect of 1,4-naphthoquinone derivatives (1,4-NQ) shown in (Fig. 9) on human MAO. The kinetic and molecular details of this inhibition have been evaluated by molecular modeling tools and biochemical assays. It was observed that MAO-B was inhibited competitively by 1,4-NQ whereas MAO-A was inhibited by non-

competitive mechanism. Also, fluorescence and molecular modeling data have confirmed the interaction of these inhibitors with the flavin moiety at the active site of the enzyme. Docking studies too suggest the phenyl side groups of Tyr407 and Tyr444 (for MAO-A) or Tyr398 and Tyr435 (for MAO-B) to play a crucial role in the interaction of the enzyme with 1,4-NQ scaffold through dispersive forces³¹.

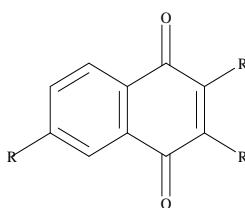


Figure 9

Janusz Skolimowska *et al* have evaluated antiparkinsonian activity of some novel aminoadamantane derivatives (Fig. 10). Their antioxidant activity towards reactive oxygen species (ROS) has also been evaluated in which the compound with nitroxide substituent displays higher anti-oxidative capacity than those containing hydroxylamine. The *in vivo* study of ROS-involving compounds was

conducted by using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin—rat model induced parkinsonism. The results clearly exhibited that nitroxide free radical moiety of the compounds is necessary for their neuroprotective action on dopaminergic neurons and these analogues can be used to either to block or to reduce the ROS-mediated

neuronal damage and death in Parkinsonian syndromes³².

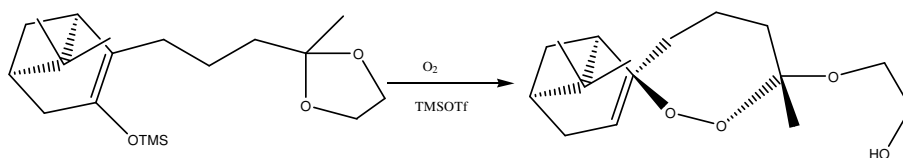


Figure 10

Alexandra Gaspar et al have developed some chromone 3-phenylcarboxamides (Fig. 11) as potent and selective MAO-B inhibitors. The synthetic compounds have been screened

towards human MAO isoforms (*h*MAO) for evaluating their potency and selectivity. These have shown selectivity to *h*MAO-B, exhibiting IC50 values at nanomolar range³³.

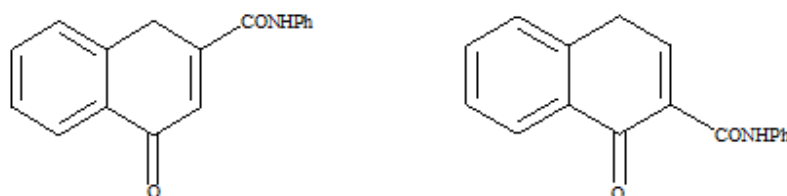


Figure 11

Naif O. Al-Harbi et al have studied anti-parkinsonism, hypoglycemic and anti-microbial activities of new poly fused pyrazolothienopyrimidine derivatives (Fig. 12).

The newly synthesized compounds were found to exhibit anti-parkinsonism activity comparable to the standard drug benzotropene³⁴.

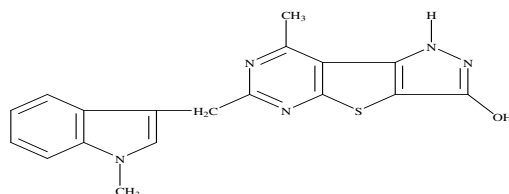


Figure 12

CONCLUSION

We are well aware of the contribution of heterocycles in treatment of several diseases. This literature search reveals that newer heterocycles analogs effective in treating and also those that are being researched, focus on

higher selectivity towards a receptor or an isoform of an enzyme to make the treatment a targeted one. The present review highlights such analogs with anti-parkinsonian activity comparable to the traded drugs.

ABBREVIATIONS

PD = Parkinson's disease
MAO-B = monoamine oxidase-B
COMT = catechol-O-methyl transferase
NSAIDs = Non-steroidal anti-inflammatory drugs
COX = cyclooxygenase
MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
TZD = thiazolidinedione
NQ = 1,4-naphthoquinone
TMN = 2,3,6-trimethyl-1,4-naphthoquinone

ACKNOWLEDGEMENT

The authors are thankful to the Principal, Government College of Pharmacy, Aurangabad, Maharashtra, India for providing literature survey facilities for the review article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Dua R., Shrivastava S., Pharmacological significance of synthetic heterocycles scaffold: A Review. *Advances in Biological Research*, 5 (3): 120-144, (2011).
2. Valverde M., Torroba T., Sulfur-Nitrogen the heterocycles. *Molecules*, 10 (1): 318-320, (2005).
3. Cordell G.A., Quinn-Beattie M.L., Farnsworth N.R., The potential of alkaloids in drug discovery. *Phytother Res.*, 15 (3): 183-205, (2001).
4. Horton R., Lotronex and the FDA: A fatal erosion of integrity. *Lancet*, 375: 1544-1545, (2001).
5. Nitin S., Gonjare L., Suhas S., Synthesis and anti-inflammatory activity of some novel 1,2-pyrazoline derivatives. *Der Pharma Chemica*, 5(3): 86-91, (2013).
6. George V.D., Kim U.T., Liang J., Cordova B., Klabe R.M., Garber S., Bacheler L.T., Lam G. N., Wright M.R., Logue K.A., Viitanen S.E., Ko S.S., Trainor G.L., Nonsymmetric P2/P2' cyclic urea HIV protease inhibitors. Structure-activity relationship, bioavailability, and resistance profile of monoindazole-substituted P2 analogues. *J. Med. Chem.* 41, 2411-2423, (1998).
7. Kale M., Mene D., Synthesis and anti-bacterial screening of some novel fused iminopyrimido benzothiazole and its Schiff's bases. *Int. J. Pharm. Bio Sci.*, 4 (3): 503-511, (2013).
8. Mokhtar H., Faidallah H., Potential antineoplastics-1-substituted thiocarbamoyl-3,5-disubstituted pyrazoles. *Pharmazie*, 42 (7): 481-483, (1987).
9. Palazzo G, Corsi G, Baiocchi L, Silvestrini B., Synthesis and pharmacological properties of 1-substituted 3-dimethylaminoalkoxy-1H-indazoles. *J Med Chem.*, 9 (1): 38-41, (1966).
10. López-Vallejo F., Caulfield T., Martínez-Mayorga K., Giulianotti M., Nefzi A., Houghten R., Medina-Franco J., Integrating virtual screening and combinatorial chemistry for accelerated drug discovery. *Combinatorial Chemistry and High Throughput Screening*, 14, 1-13, (2011).
11. Nefzi A., Ostresh J.M., Yu Y., Houghten R.A., Combinatorial chemistry: libraries from libraries, the art of the diversity-

- oriented transformation of resin-bound peptides and chiral polyamides to low molecular weight acyclic and heterocyclic compounds. *J. Org. Chem.*, 69 (11): 3603-3609, (2004).
12. Merrifield R., Beginnings of solid phase synthesis: Peptides. *J. Am. Chem. Soc.*, 85 (14): 2149-2154, (1963).
 13. Kale M., Narute A., Kalyankar T., Synthesis and pharmacological studies of novel 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents. *Clinical Anti-Inflammatory & Anti-Allergy Drugs*, 1 (1): 39-44, (2014).
 14. Sinha S., Pandey S., Verma N., Yadav A., Synthesis and biological activity of phenothiazine derivatives. *Int. J. of Res. Ayur. Pharm.*, 2 (4): 1130-1137, (2011).
 15. Borbely A., Hinkkanen M., Synthesis and antifungal activity of some substituted phenothiazine and related compounds. *Mod. Pharmacol. Toxicol.*, 16: 403-426, (1979).
 16. Reld W., Wright J., Kollofe G., Hunter J., Synthesis and antimicrobial activity of 10N{[(aryl)-amino]-methyl}3-methoxy-10,10adihydro-4aH-phenothiazine-9-carboxylic acid. *J. Am. Chem. Soc.*, 70 (9): 3121-3125 (1948).
 17. Carpi S., Carotenuto A., Colucci L., Ziello R., Manzo V., Amenta F., Fasanaro A., Non-motor symptoms in Parkinson's disease. *Current Neurobiology*, 4 (1&2): 53-65, (2013).
 18. Shimon L., Haroutiunian S., Hoffman A., Lazarovici P., Rasagiline: A novel MAO B inhibitor in Parkinson's disease therapy, *Ther. Clin. Risk Manag.*, 3(3): 467-474, (2007).
 19. Jimenez H., 4-(1-Phenyl-1H-pyrazol-4-yl)quinolines as novel, selective and brain penetrant metabotropic glutamate receptor 4 positive allosteric modulators. *Bioorg. & Med. Chem. Lett.*, 22: 3235-3239, (2012).
 20. Zarghi A., Javid F., Ghodsi R., Dadrass O., Daraei B., Hedayati M., Design, synthesis and biological evaluation of new 5,5-diarylhydantoin derivatives as selective cyclooxygenase-2 inhibitors. *Sci. Pharm.*, 79: 449-460, (2011).
 21. Asanuma M., Miyazaki I., Nonsteroidal anti-inflammatory drugs in experimental Parkinsonian models and Parkinson's disease. *Curr. Pharm. Des.*, 14: 1428-1434, (2008).
 22. Hiroshi I., Norio O., Daiichirou N., Mokoto N., Keiji W., Takashi S., Effects of heterocyclic amines in food on dopamine metabolism in nigro-striatal dopaminergic neurons. *Biochemical Pharmacology.*, 10 (88): 90641-90647, (1988).
 23. Dowson J., MAO inhibitors in mental disease: their current status. *J. Neural Transm.*, 23: 121-138, (1987).
 24. Sandler M., Monoamine oxidase inhibitors and their pharmacological significance. *Actu. Neural Stand.*, 95: 37-41, (1983).
 25. Hui-Po W., Leea J., Tsaib M., Luc H., Hsu W., Synthesis and pharmacological activities of a novel tripeptide mimetic dopamine prodrug. *Bioorg. & Med. Chem. Lett.*, 5 (19): 2195-2198, (1995).
 26. Omid T., Kakish J., Nokhrin S., Dmitriev O., Lee J., The use of nanopore analysis for discovering drugs which bind to α -synuclein for treatment of Parkinson's disease. *Eur. J. of Med. Chem.*, 88: 42-54, (2014).
 27. Maria G., Iorib R., Nicolab G., Bramantia P., Mazzon E., Anti-inflammatory and anti-apoptotic effects of (RS)-glucoraphanin bioactivated with myrosinase in murine sub-acute and acute MPTP-induced Parkinson's disease. *Bioorg. & Med. Chem.*, 21 (17): 5532-5547, (2013).
 28. Werner G, Malanb S., Murugesanc T., Van der Schyfb C., Bloomquist J., Synthesis and biological evaluation of pentacyclo[5.4.0.02,6.03,10.05,9]undecane derivatives as potential therapeutic agents in Parkinson's disease. *Bioorg. & Med. Chem.*, 12 (7): 1799-1806, (2004).
 29. Toshiaki S., Kenji A., Masami I., Masanao N., Seiichiro S., Noriyuki S., Fumio Y., Kyoji T., Yoshie H., Synthesis and in vitro cytotoxicity of 1,2,3,4-tetrahydroisoquinoline derivatives. *Eur. J. Med. Chem.*, 41 (2): 241-252, (2001).

30. Carroll R., Dluzen D., Stinnett H., Awale P., Funk S., Geldenhuys W., Structure-activity relationship and docking studies of thiazolidinedione-type compounds with monoamineoxidase B. *Bioorg. & Med. Chem. Lett.*, 21: 4798-4803, (2011).
31. Eduardo C., Netzb P., Diniza C., Cantob V., Follmer C., Molecular insights into human monoamine oxidase (MAO) inhibition by 1,4-naphthoquinone: Evidences for menadione (vitamin K3) acting as a competitive and reversible inhibitor of MAO. *Bioorganic & Medicinal Chemistry*, 19 (24): 7416–7424, (2011).
32. Janusz S., Kochmanb A., Gębickac L., Metodiewa D., Synthesis and antioxidant activity evaluation of novel antiparkinsonian agents, aminoadamantane derivatives of nitroxyl free radical. *Bioorg. & Med. Chem.*, 11 (6): 3529-3539, (2003).
33. Alexandra G, Joana Reisa, André Fonseca, Nuno Milhazes, b, Dolores Viñac, d, Eugenio Uriartec,d, Fernanda Borges, Chromone 3-phenylcarboxamides as potent and selective MAO-B inhibitors, *Bioorg. & Med. Chem. Lett.*, 21 (2): 707–709, (2011).
34. Naif O., Al-Harbia., Saleh A., Bahashwanb, Ahmed A., Fayed B., Anti-parkinsonism, hypoglycemic and antimicrobial activities of new poly fused ring heterocyclic candidates. *Int. J. of Biol. Macromol.*, 57: 165– 173, (2013).