Faculty of Medical and Health Sciences, University of Poonch Rawalakot
Journal of Pharma and Biomedics
ISSN: 3007-1984(online), 3007-1976 (Print)
https://www.jpbsci.com/index.php/jpbs

Dual MAO-A and MAO-B Inhibition by Newly Synthesized Heterocyclic Acetamide Derivatives of Morpholine: In Vitro and In Silico Insights

Ahmad Sadiq Sheikh[1]*, Sajid Raza[2], Muhammad Noman[1], Muhammad Adnan[1], Tariq Javed[3], Zujaja Khakwani[3], Muhammad Hashim[4]

[1] Department of Pharmacy, MY University Islamabad, Pakistan.
[2] Department of Pharmacy, IBADAT International University Islamabad, Pakistan.
[3] Margalla College of Pharmacy, Margalla Institute of Health Sciences, Rawalpindi, Pakistan.
[4] Carer Pharmaceuticals Islamabad, Pakistan.

Received: August 28, 2025; Revised: October 18, 2025; Accepted: October 20, 2025

A B S T R A C T

Monoamine oxidase (MAO) enzymes are important targets for the treatment of neurological disorders such as Parkinson's disease and depression. This study investigates a series of newly synthesized heterocyclic acetamide derivatives of morpholine (1a–1n) for their potential as neuroprotective agents through MAO-A and MAO-B inhibition. The compounds were evaluated in vitro for their inhibitory activity against both MAO isoforms. Results indicated that several compounds particularly 1e, 1i, and 1m exhibited significant inhibition, with 1f showing selectivity for MAO-A and 1l for MAO-B. Molecular docking studies were performed on human MAO-A and MAO-B to explore binding interactions. Compounds 1i and 1m demonstrated strong binding affinities, comparable or superior to reference inhibitors clorgyline and deprenyl. The findings suggest that these morpholine-based acetamide derivatives represent promising scaffolds for the development of novel MAO inhibitors with potential applications in the treatment of neurodegenerative and affective disorders.

Keywords: *Morpholine, acetamide derivatives, Monoamine oxidase, Neuroprotective agents, Molecular docking, Parkinson's disease*.

Corresponding Authors: *Ahmad Sadiq Sheikh*
Email: dean.pharmacy@myu.edu.pk

INTRODUCTION

Monoamine oxidase (MAO) is a broadly expressed mitochondrial enzyme with significant levels of expression in the gastrointestinal tract, the liver, and neural tissues. This enzyme plays a crucial role in the metabolism of neurotransmitters and the detoxification of a wide range of endogenous and exogenous amines. It catalyzes the oxidative deamination of various monoamines. Medications that suppress MAO are currently used in clinical settings to treat Parkinson's disease (PD) and affective disorders. Aldehyde dehydrogenase and aldehyde reductase further metabolize the aldehydes produced by MAO, resulting in the formation of glycols and carboxylic acids (Westfall and Westfall, 2011). The potential neurotoxicity of MAO's end products is suggested because the reaction initially generates both an aldehyde and H_2O_2, which can produce reactive oxygen species (ROS) (Jenner, 2003). It is important to note that scavenger enzymes, such as catalase and superoxide dismutase, typically metabolize ROS and other reactive species, and dysfunction in these enzyme systems may contribute to neurodegenerative illness (Aluf et al., 2011). In the early stages of Parkinson's disease (PD), the destruction of a percentage of neurons increases oxidative stress levels, leading to heightened activity in the remaining neurons. A recent microdialysis study simulated this condition by perfusing a non-diffusible indicator molecule through a

probe inserted into the striatum. Oxidative stress increased significantly after an intraventricular injection of 6-hydroxydopamine at a dosage sufficient to reduce dopaminergic cells by 50% (Aluf et al., 2011), but was reduced following the systemic injection of an MAO-A or MAO-B inhibitor (Aluf et al., 2013). Biochemically, the two MAO isoforms can be differentiated by their substrate and inhibitor specificities. MAO-A has a greater affinity for hydroxylated amines like noradrenaline (NA) and serotonin (5-HT), while MAO-B prefers non-hydroxylated amines such as benzylamine and beta-phenylethylamine (PEA). Dopamine (DA) and tyramine exhibit similar affinity for both isoforms. Clorgyline is a selective MAO-A inhibitor, while l-deprenyl is a relatively selective MAO-B inhibitor. Some compounds inhibit both forms and are termed non-selective inhibitors, though this label can be misleading as they are still selective for MAO over other enzymes. Research continues to develop new compounds with MAO inhibitory activity. Currently, there is a wide range of therapeutic options using MAO-A and MAO-B inhibitors for treating PD and depression. Prospective development avenues include novel drug administration methods and prodrugs activated by brain enzymes to achieve selective central action and prevent the "cheese effect." New drugs that combine multiple activities in a single molecule could be useful for treating both neuropsychiatric and neurological disorders, and mechanism-based drug combinations may improve efficacy in PD and other diseases.

Heterocyclic compounds as shown in (Figure 1) which contain at least one heteroatom in their structure, are among the most important and ubiquitous organic moieties (Heravi and Zadsirjan, 2020). These ring systems are crucial in drug discovery and have significant medicinal and industrial importance, attracting growing attention from researchers worldwide (Enakshi et al., 2021). Furthermore, the ease with which heterocycles can be modified through various chemical reactions allows access to a wide range of biological and chemical properties (Ahmad et al., 2012).

Morpholine (tetrahydro-1,4-oxazine) is a particularly useful heterocycle known for its favorable physicochemical, biological, and metabolic properties, as well as its synthetic versatility. It is considered a privileged scaffold in medicinal chemistry, and its acetamide derivatives exhibit a broad spectrum of biological effects including analgesic, anti-inflammatory, antioxidant, anti-obesity, anti-hyperlipidemic, antimicrobial, anticancer, and neuroprotective activities (Ghorbani et al., 2015; Shrivastava et al., 2015). Given this importance, several morpholine acetamide derivatives were screened for neuroprotective activity by evaluating their MAO inhibitory potential.

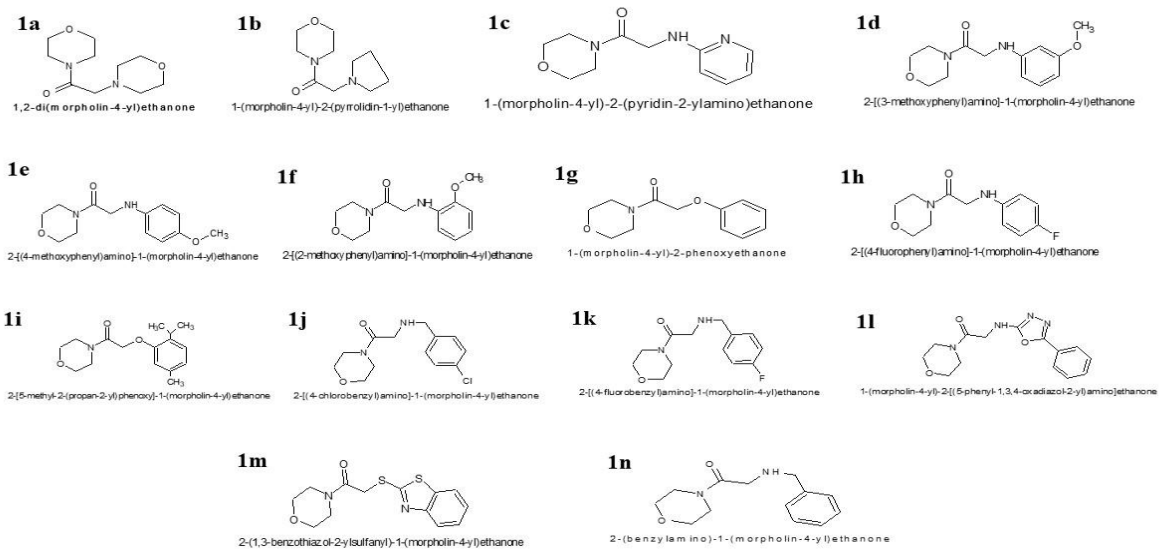


Figure 1: Shown heterocycles for pharmacological evaluations.

MATERIALS AND METHODS

Docking study

The synthesized compounds (1a–1n) were designed and optimized as ligands using Discovery Studio Visualizer, while the target proteins monoamine oxidase A (MAO-A; PDB ID: 2BXR) and monoamine oxidase B (MAO-B; PDB

ID: 2BYB) were retrieved from the Protein Data Bank and prepared using Discovery Studio Visualizer 2017(Luigi et al., 2005). During protein optimization, all co-crystallized ligands and water molecules were removed. Both ligand and protein structures were then converted to PDBQT format using AutoDock Tools 1.5.6. Molecular docking was performed with AutoDock Vina, focusing on the active sites defined by the co-crystallized ligands of the standard inhibitors clorgyline (for MAO-A) and deprenyl (for MAO-B) to validate the docking protocol. The search space was confined around the binding pockets to ensure accurate ligand conformations comparable to those of the reference ligands. Docking results, including binding poses and binding energies (kcal/mol), were analyzed and visualized using Discovery Studio Visualizer, UCSF Chimera, and PyMOL (Md Idris et al 2022).

MAO-A and MAO-B inhibitory assay of synthesized derivatives (1a-1n)

The inhibitory activity of all synthesized compounds against MAO-A and MAO-B was analyzed according to a previously reported protocol (Narayan et al., 2014). The enzyme solution was freshly prepared 15-20 minutes before the assay and kept at a cool room temperature. To irreversibly block MAO-A and MAO-B activity, Clorgyline (60 nM) or Deprenyl (300 nM) were used, respectively. A 96-well plate was used for the assay. The total assay volume was 100 µL, consisting of 60 µL of buffer (pH 7.4), 10 µL of the test compound (0.1 mM in 10% DMSO), and 10 µL of the enzyme solution (26 µg of protein for MAO-A and 5.0 µg for MAO-B). The mixture was incubated for 15-20 minutes. Subsequently, 10 µL of substrate and 10 µL of freshly prepared Amplex Red reagent were added to the mixture. A final concentration of 0.1 mM clorgyline or deprenyl was used to determine non-MAO-A and non-MAO-B activity, respectively. Fluorescence changes were measured using a fluorescence plate reader (BMG Labtech GmbH, Ortenberg, Germany). Compounds that exhibited over 50% inhibition of either MAO-A or MAO-B activity were selected for further evaluation to determine their IC_{50} values. All experiments were performed in triplicate and repeated twice. The IC_{50} values were calculated using the non-linear curve-fitting program PRISM 5.0 (GraphPad, San Diego, California, USA) (Mazzio E et al 2013).

RESULTS

Docking analysis

Compounds with good *in vitro* MAO-A and MAO-B inhibitory potential were subjected to docking analysis using Human MAO-A (2BXR) and MAO-B (2BYB) to assess potential interactions. The binding pockets of the standard drugs clorgyline and deprenyl were used as a reference. All compounds showed good binding affinities with the target proteins.

Notably, compounds 1i and 1m exhibited exceptionally strong affinities of -9.9 kcal/mol and -9.2 kcal/mol against MAO-A, and -10.0 kcal/mol and -10.2 kcal/mol against MAO-B, respectively. These values indicate superior binding compared to the standard molecules clorgyline (-7.2 kcal/mol for MAO-A) and deprenyl (-7.1 kcal/mol for MAO-B) as shown in (Table 1). The 2D binding interactions are shown in (Figure 2 and 3).

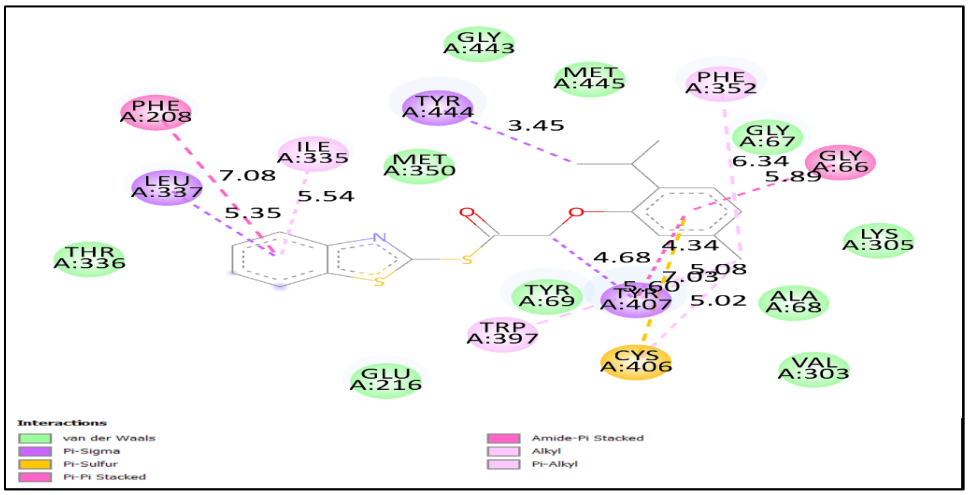


Figure 2: The compound 2i binding interactions with MAO-A and MAO-B.

Table 1: Binding energy values of compounds against MOA-A and MOA-B.

Target	Compound	PDB ID	Kcal/mol
MOA-A	1i and 1m	2BXR	-9.9, -9.2
MOA-B	1i and 1m	2BYB	-10.0, -10.2

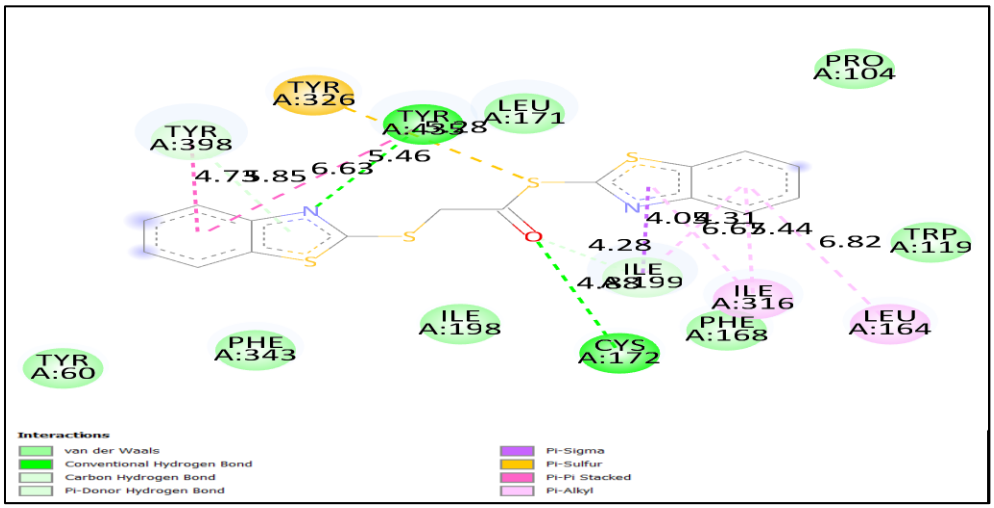


Figure 3: The compound 2m binding interactions with MAO-A and MAO-B.

MAO-A and MAO-B inhibition assay of synthesized compounds (1a-1n)

The MAO-A and MAO B inhibitory activity of all newly synthesized compounds was measured. Clorgyline (60 nM) and Deprenyl (300 nM) were used as standard irreversible inhibitors of MAO-A and MAO-B, respectively. Compounds exhibiting over 50% inhibition of either MAO-A or MAO-B activity were selected for further evaluation to determine their IC_{50} values. All experiments were performed in triplicate and repeated twice. IC_{50} values were calculated using the non-linear curve-fitting program PRISM 5.0 (GraphPad, San Diego, California, USA). Among the series of synthesized compounds (1a-1n), compounds 1e, 1i and 1m showed promising inhibition of both enzymes. In contrast, compound 1f was active only against MAO-A, and compound 1l was active only against MAO-B, as shown in (Table 2).

Table 2: MAO A and MAO B with IC50 and % inhibition for series of compounds (1a-1n).

S. No	Code	MAO A	MAO B
		IC_{50} &	% age inhibition
1.	1a	20 %	30 %
2.	1b	29 %	24 %
3.	1c	11%	00 %
4.	1d	27 %	39 %
5.	1e	2.917 ± 0.036	2.76 ± 0.567
6.	1f	1.094 ± 0.384	26 %
7.	1g	29 %	27 %
8.	1h	25 %	28 %
9.	1i	16.2 ± 2.36	1.111 ± 0.054
10.	1j	29 %	10 %
11.	1k	00 %	00 %
12.	1l	36 %	1.473 ±1.55305
13.	1m	1.430 ± 0.260	2.812 ± 0.16
14.	1n	25 %	27 %

Standard	Clorgyline[b]	0.0045 ± 0.0003	61.35 ± 1.13
	Deprenyl[b]	67.25 ± 1.02	0.0196 ± 0.001

Future studies

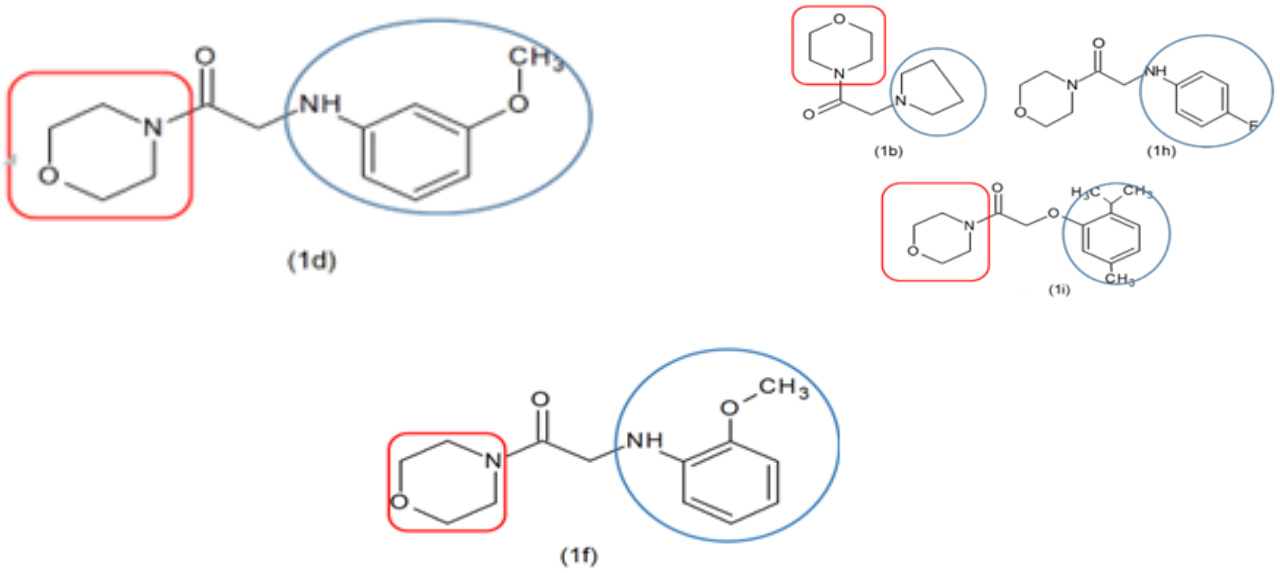
In the present work, several new heterocyclic acetamide derivatives of morpholine were found to be active in monoamine oxidase (MAO)-A and MAO-B inhibition assays. Further studies are required to evaluate the potential of these synthetic derivatives as future pharmaceutical candidates. The necessary investigations include.

***In-Vivo* evaluation and selectivity profiling**

Given that most compounds exhibit good *in vitro* MAO-A and MAO-B inhibitory potential at low doses, *in vivo* enzyme inhibitory assays are warranted. For instance, compounds 1e**,** 1i**,** and 1m showed promising dual inhibition, while 1f was a selective MAO-A inhibitor and 1l effectively inhibited MAO-B compared to the standard drugs deprenyl and clorgyline. Consequently, comprehensive selectivity studies must be conducted.

Toxicity assessment

Detailed acute and chronic toxicity studies are essential to determine the safety profile of these derivatives.



Pharmacophores of acetamide derivatives

DISCUSSION

The present study focused on the pharmacological exploration of newly synthesized heterocyclic acetamide derivatives of morpholine as potential monoamine oxidase (MAO) inhibitors with neuroprotective potential. Since heterocyclic moieties are known to serve as versatile frameworks in medicinal chemistry owing to their diverse biological and physicochemical properties (Heravi and Zadsirjan, 2020; Enakshi et al., 2021), the incorporation of morpholine and acetamide functionalities into the designed molecules was intended to enhance both lipophilicity and receptor binding potential. Morpholine, in particular, is recognized as a privileged scaffold with broad pharmacological activities including antioxidant, anti-inflammatory, and neuroprotective effects (Ghorbani et al., 2015; Shrivastava et al., 2015). These properties justified its selection for structural modification aimed at generating derivatives capable of modulating MAO-A and MAO-B enzyme activities.

In the current work, molecular docking studies were initially performed to predict the binding interactions and affinities of the synthesized compounds toward the active sites of human MAO-A (PDB ID: 2BXR) and MAO-B (PDB ID: 2BYB). Docking serves as a rational in silico approach to

evaluate the complementarity between ligands and target proteins and to guide the identification of potential inhibitors before experimental validation (Luigi et al., 2005; Md Idris et al., 2022). The docking protocol was validated using the co-crystallized inhibitors clorgyline for MAO-A and deprenyl for MAO-B. The results demonstrated that the designed morpholine-based acetamide derivatives exhibited favorable binding orientations and interactions within the catalytic pockets of both enzymes. The molecular interactions observed for the active compounds involved key residues responsible for catalytic activity and substrate stabilization, supporting their potential as dual or selective inhibitors. Particularly, the compounds containing heteroaromatic and benzothiazole moieties were found to exhibit strong binding complementarity, as suggested by multiple hydrogen bonding and π–π stacking interactions with residues lining the FAD-binding cavity. These interactions are crucial for stable ligand accommodation and competitive inhibition of substrate binding, consistent with the binding pattern reported for known MAO inhibitors (Chaurasiya et al., 2014). The presence of electron-donating or electron-withdrawing substituents on the aromatic ring also appeared to influence the docking scores, implying that subtle modifications in the acetamide linkage or ring substituents may modulate affinity and selectivity toward MAO isoforms (Langdon et al., 2010; Welsch et al., 2010). The predicted affinities of some derivatives were comparable to or greater than those of the reference inhibitors, suggesting efficient engagement with the catalytic site and potential for enhanced inhibitory potency.

Following the docking analysis, the inhibitory potential of all synthesized compounds was experimentally validated through an in vitro MAO-A and MAO-B inhibition assay following the protocol of Narayan et al. (2014). This bioassay provided direct evidence of the ability of the derivatives to suppress enzymatic activity under physiological conditions. Among the tested series, several derivatives demonstrated appreciable inhibition of both isoforms, indicating a balanced interaction with hydroxylated (MAO-A) and non-hydroxylated (MAO-B) amine substrates (Westfall and Westfall, 2011). Some compounds exhibited selectivity toward a specific isoform, which could be attributed to the structural variations within the heterocyclic acetamide framework influencing molecular orientation in the enzyme's active site. Compounds containing electron-rich aromatic substituents or oxygen/nitrogen donor atoms showed enhanced MAO-A inhibition, whereas derivatives bearing bulky heterocycles such as benzothiazole displayed preferential affinity toward MAO-B. This trend aligns with earlier findings that structural rigidity and steric factors within the heterocyclic core influence the size and shape compatibility with the substrate cavities of MAO isoforms (Jenner, 2003; Aluf et al., 2011). The experimental results supported the computational predictions, as compounds demonstrating strong docking affinities also exhibited potent inhibition in vitro. This parallel validation underscores the reliability of molecular docking as a predictive screening method and highlights the potential of these morpholine-acetamide derivatives as scaffolds for future drug optimization. In particular, the dual inhibitory behavior of certain derivatives is of pharmacological significance because simultaneous inhibition of both MAO-A and MAO-B can enhance neurotransmitter levels, reduce oxidative deamination, and mitigate oxidative stress—factors critically involved in the pathogenesis of neurodegenerative disorders like Parkinson's disease (Aluf et al., 2013; Jenner, 2003). Furthermore, the selective inhibitors observed among the series may offer therapeutic value in managing specific neuropsychiatric conditions where modulation of a single MAO isoform is beneficial. Structurally, the observed variations in activity could be attributed to differences in electronic distribution and steric configuration around the acetamide linkage and morpholine ring. These structural motifs are known to contribute to improved binding through hydrogen bonding and hydrophobic interactions (Kumari et al., 2020; Pattabiraman and Bode, 2011). Moreover, the combination of morpholine with other heteroatoms in the ring system can enhance metabolic stability and central nervous system penetration—two essential pharmacokinetic properties for neuroprotective agents (Rupak et al., 2016; Naim et al., 2015). Overall, the integrated docking and enzymatic inhibition findings collectively suggest that the synthesized morpholine-based heterocyclic acetamide derivatives possess the structural features necessary for potent and selective MAO inhibition. These compounds can therefore be considered promising leads for the development of new neuroprotective agents. Further in vivo validation, pharmacokinetic profiling, and toxicity evaluations are warranted to substantiate their therapeutic potential and optimize their structure–activity relationships for clinical application.

CONCLUSION

The synthesized heterocyclic acetamide derivatives of morpholine demonstrated strong potential as monoamine

oxidase inhibitors. Several compounds exhibited dual inhibition of MAO-A and MAO-B, while others showed selective activity. Molecular docking confirmed favorable binding interactions with both enzyme isoforms. These findings highlight the morpholine-acetamide scaffold as a promising framework for neuroprotective drug design. The compounds may serve as lead candidates for treating neurodegenerative and affective disorders. Further in vivo and toxicity studies are recommended to validate their therapeutic potential.

REFERENCES

Adedeji, W.A. (2016) 'The treasure called antibiotics', *Annals of Ibadan Postgraduate Medicine*, 14(2), p. 56.

Ahmad, T. & Ullah, N. (2021) 'The oxa-Michael reaction in the synthesis of 5- and 6-membered oxygen-containing heterocycles', *Organic Chemistry Frontiers*, 8(6), pp. 1329–1344.

Al-Ghorbani, M., Bushra, B.A., Mamatha, S.V. & Khanum, S.A. (2015) 'Piperazine and morpholine: Synthetic preview and pharmaceutical applications', *Research Journal of Pharmacy and Technology*, 8(5), pp. 611–628.

Al-Rashida, M. & Iqbal, J. (2014) 'Therapeutic potentials of ecto-nucleoside triphosphate diphosphohydrolase, ecto-nucleotide pyrophosphatase/phosphodiesterase, ecto-5′-nucleotidase, and alkaline phosphatase inhibitors', *Medicinal Research Reviews*, 34(4), pp. 703–743.

Alterio, V., Di Fiore, A., D'Ambrosio, K., Supuran, C.T. & De Simone, G. (2012) 'Multiple binding modes of inhibitors to carbonic anhydrases: how to design specific drugs targeting 15 different isoforms', *Chemical Reviews*, 112(8), pp. 4421–4468.

Angre, T., Kumar, A., Singh, A.K., Thareja, S. & Kumar, P. (2022) 'Role of collagen regulators in cancer treatment: A comprehensive review', *Anti-Cancer Agents in Medicinal Chemistry*, 22(17), pp. 2956–2984.

Arshad, F., Khan, M.F., Akhtar, W., Alam, M.M., Nainwal, L.M., Kaushik, S.K. *et al.* (2019) 'Revealing quinquennial anticancer journey of morpholine: A SAR based review', *European Journal of Medicinal Chemistry*, 167, pp. 324–356.

Bahuguna, A., Khan, I., Bajpai, V.K. & Kang, S.C. (2017) 'MTT assay to evaluate the cytotoxic potential of a drug', *Bangladesh Journal of Pharmacology*, 12(2), pp. 115–118.

Balouiri, M., Sadiki, M. & Ibnsouda, S.K. (2016) 'Methods for in vitro evaluating antimicrobial activity: A review', *Journal of Pharmaceutical Analysis*, 6(2), pp. 71–79.

Cesaro, S., Tridello, G., Castagnola, E., Calore, E., Carraro, F., Mariotti, I. *et al.* (2017) 'Retrospective study on the incidence and outcome of proven and probable invasive fungal infections in high-risk pediatric onco-hematological patients', *European Journal of Haematology*, 99(3), pp. 240–248.

Chaurasiya, N.D., Ibrahim, M.A., Muhammad, I., Walker, L.A. & Tekwani, B.L. (2014) 'Monoamine oxidase inhibitory constituents of propolis: kinetics and mechanism of inhibition of recombinant human MAO-A and MAO-B', *Molecules*, 19(11), pp. 18936–18952.

De Figueiredo, R.M., Suppo, J.S. & Campagne, J.M. (2016) 'Nonclassical routes for amide bond formation', *Chemical Reviews*, 116(19), pp. 12029–12122.

Dua, R., Shrivastava, S., Sonwane, S.K. & Srivastava, S.K. (2011) 'Pharmacological significance of synthetic heterocycles scaffold: a review', *Advances in Biological Research*, 5(3), pp. 120–144.

Elliott, T.S., Slowey, A., Ye, Y. & Conway, S.J. (2012) 'The use of phosphate bioisosteres in medicinal chemistry and chemical biology', *MedChemComm*, 3(7), pp. 735–751.

Gomtsyan, A. (2013) 'Heterocycles in drugs and drug discovery', *Chemistry of Heterocyclic Compounds*, 1, pp. 12–15.

Heravi, M.M. & Zadsirjan, V. (2020) 'Prescribed drugs containing nitrogen heterocycles: an overview', *RSC Advances*, 10(72), pp. 44247–44311.

Irfan, A., Batool, F., Naqvi, S.A.Z., Islam, A., Osman, S.M., Nocentini, A. *et al.* (2020) 'Benzothiazole derivatives as anticancer agents', *Journal of Enzyme Inhibition and Medicinal Chemistry*, 35(1), pp. 265–279.

Jana, R., Begam, H.M. & Dinda, E. (2021) 'The emergence of the C–H functionalization strategy in medicinal chemistry and drug discovery', *Chemical Communications*, 57(83), pp. 10842–10866.

Jenner, P. (2003) 'Oxidative stress in Parkinson's disease', *Annals of Neurology*, 53(S3), pp. S26–S38.

Kabir, E. & Uzzaman, M. (2022) 'A review on biological and medicinal impact of heterocyclic compounds', *Results in Chemistry*, 100606.

Kalgutkar, A.S., Gardner, I., Obach, R.S., Shaffer, C.L., Callegari, E., Henne, K.R. *et al.* (2005) 'A comprehensive listing of bioactivation pathways of organic functional groups', *Current Drug Metabolism*, 6(3), pp. 161–225.

Klingspor, L. & Jalal, S. (2006) 'Molecular detection and identification of *Candida* and *Aspergillus* spp. from clinical samples using real-time PCR', *Clinical Microbiology and Infection*, 12(8), pp. 745–753.

Kumar, A., Bhagat, K.K., Singh, A.K., Singh, H., Angre, T., Verma, A. *et al.* (2023) 'Medicinal chemistry perspective of pyrido [2,3-d] pyrimidines as anticancer agents', *RSC Advances*, 13(10), pp. 6872–6908.

Kumar, R., Vulichi, S.R. & Kapur, S.K. (2016) 'Emphasizing morpholine and its derivatives (MAID): typical candidate of pharmaceutical importance', *International Journal of Chemical Sciences*, 14(3), pp. 1777–1788.

Kumari, S., Carmona, A.V., Tiwari, A.K. & Trippier, P.C. (2020) 'Amide bond bioisosteres: Strategies, synthesis, and successes', *Journal of Medicinal Chemistry*, 63(21), pp. 12290–12358.

Langdon, S.R., Ertl, P. & Brown, N. (2010) 'Bioisosteric replacement and scaffold hopping in lead generation and optimization', *Molecular Informatics*, 29(5), pp. 366–385.

Mason, B.P., Price, K.E., Steinbacher, J.L., Bogdan, A.R. & McQuade, D.T. (2007) 'Greener approaches to organic synthesis using microreactor technology', *Chemical Reviews*, 107(6), pp. 2300–2318.

Mazzio, E., Deiab, S., Park, K. & Soliman, K.F.A. (2013) 'High throughput screening to identify natural human monoamine oxidase B inhibitors', *Phytotherapy Research*, 27(6), pp. 818–828.

Md Idris, M.H., Mohd Amin, S.N., Nyokat, N., Khong, H.Y., Selvaraj, M. *et al.* (2022) 'Flavonoids as dual inhibitors of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX): molecular docking and in vitro studies', *Beni-Suef University Journal of Basic and Applied Sciences*, 11(1), p. 117.

Miethke, M., Pieroni, M., Weber, T., Brönstrup, M., Hammann, P., Halby, L. *et al.* (2021) 'Towards the sustainable discovery and development of new antibiotics', *Nature Reviews Chemistry*, 5(10), pp. 726–749.

Naim, M.J., Alam, O., Alam, M.J., Alam, P. & Shrivastava, N. (2015) 'A review on pharmacological profile of morpholine derivatives', *International Journal of Pharmacology and Pharmaceutical Sciences*, 3, pp. 40–51.

Ochwang'i, D.O., Kimwele, C.N., Oduma, J.A., Gathumbi, P.K., Mbaria, J.M. & Kiama, S.G. (2014) 'Medicinal plants used in treatment and management of cancer in Kakamega County, Kenya', *Journal of Ethnopharmacology*, 151(3), pp. 1040–1055.

Pattabiraman, V.R. & Bode, J.W. (2011) 'Rethinking amide bond synthesis', *Nature*, 480(7378), pp. 471–479.

Scheidt, K. (2010) 'Amide bonds made in reverse', *Nature*, 465(7301), pp. 1020–1022.

Sortino, M., Delgado, P., Juárez, S., Quiroga, J., Abonía, R., Insuasty, B. *et al.* (2007) 'Synthesis and antifungal activity of (Z)-5-arylidenerhodanines', *Bioorganic & Medicinal Chemistry*, 15(1), pp. 484–494.

Soto, C.J., John, O.P., Gosling, S.D. & Potter, J. (2011) 'Age differences in personality traits from 10 to 65: Big Five domains and facets in a large cross-sectional sample', *Journal of Personality and Social Psychology*, 100(2), pp. 330–348.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. & Bray, F. (2021) 'Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries', *CA: A Cancer Journal for Clinicians*, 71(3), pp. 209–249.

Ugwu, D.I. & Okoro, U.C. (2014) 'Synthesis, characterization and antifungal activities of [4-methyl phenyl sulphonamido]-N-(pyridin-2-yl) acetamide derivatives', *Medicinal Chemistry*, 4(2), pp. 330–333.

Wang, Y., Yin, L., Cui, Y., Wang, L., Wu, J., Wang, J. *et al.* (2021) 'Prognostic significance of membranous carbonic anhydrase IX expression in patients with nonmetastatic clear cell renal cell carcinoma of different tumor stages', *Cancer Biotherapy & Radiopharmaceuticals*, 37(6), pp. 494–502.

Welsch, M.E., Snyder, S.A. & Stockwell, B.R. (2010) 'Privileged scaffolds for library design and drug discovery', *Current Opinion in Chemical Biology*, 14(3), pp. 347–361.

Westfall, P.H., Tobias, R.D. & Wolfinger, R.D. (2011) *Multiple Comparisons and Multiple Tests Using SAS*. Cary, NC: SAS Institute.

Yasuda, K., Miyake, K., Horikawa, Y., Hara, K., Osawa, H., Furuta, H. *et al.* (2008) 'Variants in KCNQ1 are

associated with susceptibility to type 2 diabetes mellitus', *Nature Genetics*, 40(9), pp. 1092–1097.

Zalaru, C., Dumitrascu, F., Draghici, C., Tarcomnicu, I., Marinescu, M., Nitulescu, G.M. *et al.* (2022) 'New pyrazolo-benzimidazole Mannich bases with antimicrobial and antibiofilm activities', *Antibiotics*, 11(8), p. 1094.