ISSN NO. 2320–7418 DOI: 10.22270/jmpas.V10I4.1768

International open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com

Research article

Synthesis and molecular docking analysis of Oxazetidine derivatives for neurological disorders

Lonikar NB.[1], Sangshetti J.N.[2], Bhusnure O.G.[1]*

1. Channabasweshwar Pharmacy College, Channabasweshwar research Centre, Latur, Maharashtra, India
2. Y. B. Chavan College of. Pharmacy, Aurangabad, Maharashtra, India

ABSTRACT

A series of Oxazetidine (NL1-NL12) from reacting tryptophan and aromatic aldehydes were synthesized in good yields by involving 2-{[(4-chlorophenyl) methylidene] amino}-3-(1H-indol-3-yl) propionic acid and chloro acetyl chloride as reactive intermediates. All the synthesized derivatives were screened via spectral techniques. Synthesized molecules were virtually screened against Human A2A Adenosine receptor interactions analysis using molecular docking to elucidate CNS potential. Synthesized derivatives showed excellent binding towards the Human A2A Adenosine receptor.

Keywords: Oxazetidine, Human A2A Adenosine receptor, Docking, CNS

Received - 04-07-2021, Reviewed - 24/07/2021, Revised/ Accepted- 28/08/2021

Correspondence: Bhusnure O.G* ✉ omprakashbhusnure@gmail.com

Channabasweshwar Pharmacy College, Channabasweshwar research centre, Kawa road, Basweshwar Chowk, Latur, Maharashtra, India

INTRODUCTION

Azetidines, one of the important heterocyclic chemical classes which are extensively researched in the scientific world. Chemically the azetidine is a four-member ring structure that contains nitrogen as heteroatom [1-2]. Importance of the azetidine can be understood by the fact it is a constituent of a number of the key chemical structures, raw materials, and important catalysts. Biologically the azetidine class of molecules is active showing a variety of therapeutic potentials like antimicrobial, anticancer, anti-inflammatory, antidepressant, antitubercular, antimalarial, anticancer, antiviral, antioxidant, and cardiovascular activities [3-11]. In recent literature the physical properties of the azetidine are reported this heterocycle is known as a conformationally puckered rigid structure, having bond angles of 10-20 degrees which depends on the type of substitution which is present on it [1-2]. Due to its attractive nature and diverse physicochemical property space associated with it, the azetidine nucleus has been extensively researched and various chemical methodologies were reported for synthesis. The chemical nature and ring stain associated with it the azetidine have become one of the most difficult chemical scaffolds to prepare, due to this reason very few methods have been successfully applied for the development of a diverse set of azetidine derivatives. Methods like Ring Closure by C–N Bond Formation, Ring Closure by C–C Bond Formation, Reduction of β-Lactams, and Cyclo addition Reactions have been the most utilized chemical reactions for the synthesis of the azetidine[12]. Azetidine nucleus is not only biologically useful but its chemical applications can be widely observed in the chemical literature. In reactions like ring-opening to acyclic amines, ring expansion to pyrrolidines and another 5-Membered heterocycle, ring expansion to six-member Heterocycles, ring expansion to medium-sized heterocycle azeditines are commonly utilized. Adenosine is one of the important biochemical components which is present in the human body it can be called autacoids which is one of the important building blocks of the genetic material in the human being. The activity of the adenosine is under the control of the producing/degrading enzymes and receptors like A1, A2A, A2B, and A3 which are specialized receptors that can be classified under G protein-coupled receptors [13-14]. These adenosine receptors are targeted for several aliments, recently the role of the A2A receptor has been proven in neurodegenerative diseases. This research paper reports development of novel Oxazetidine derivatives and their in-silico analysis for potential Adenosine A2A receptor inhibition. 12 different Oxazetidine derivatives have been synthesized and screened in silico

for potential Adenosine A2A receptor inhibition via molecular docking. All the synthesized derivatives showed excellent binding potentials towards adenosine A2A receptor which indicated these scaffolds can be utilized for the development of potent molecules targeting neurodegenerative diseases.

EXPERIMENTAL

Synthesis of the targeted Oxazetidine derivatives was achieved in two steps as shown in figure no1 and table no1

Step 1: Synthesis of 2-{[(4-chlorophenyl) methylidene] amino}-3-(1H-indol-3-yl) propionic acid

0.01M tryptophan mixed with 0.02M Benz aldehyde in 45 ml methanol and 30 ml water (60:40 ratio). This solution refluxed for 12 hours. After the reflux solution was cooled and the solvent was evaporated. The residue (reaction product) was collected and is recrystallized from methanol.

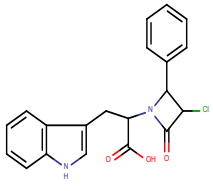
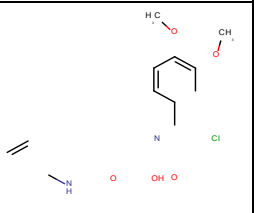
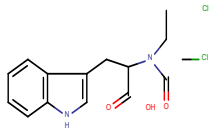
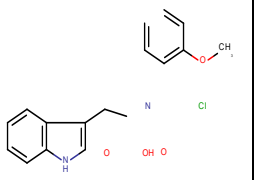
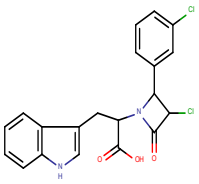
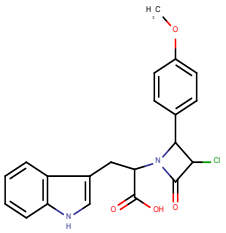
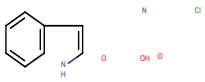
Step 2: Synthesis of Oxazetidine derivatives (NL1-NL12)

0.02M step-I product dissolved in 30 ml dioxane then stirred for 10 minutes in magnetic stirrer. After 10 minutes of stirring added 0.025M chloroacetyl chloride by using a dropping funnel and again stirred for 10 minutes. After 10 minutes of stirring added 0.025M triethylamine by using a dropping funnel and the solution stirred for 04 hours. After completion of stirring, the solution

Figure 1: Scheme of Synthesis of the designed Molecules

Refluxed for 18 hours. After reflux, the final solution was poured in ice-cold water, and the formation of aqueous solution extract 02 times with 25ml ethyl acetate and then take ethyl acetate layer and evaporated and product was recrystallized from methanol.

Table 1: Synthesized Derivatives

Code	Structure	Code	Structure
NL-1		NL-7	
NL-2		NL-8	
NL-3		NL-9	
NL-4			

chloroacetyl chloride were carried out to get Oxazetidine derivatives. The formation of the derivatives was ascertained by the thin layer chromatography, meting point, and various spectral techniques.

NL1:

IR (ATR, cm-1)- 3361.68 (NH stretching) , 2923.70 (COOH Stretching), 1622.82 (C=O Stretching), 1230.98 (C-N stretching),

NL2:

IR (ATR, cm-1)- 3361.68 (NH stretching) , 2917.23 (COOH Streaching), 1668.15 (C=O Stretching), 1230.98 (C-N stretching), 744.02 (Ar-Cl)

NL3:

IR (ATR, cm-1)- 3365.68 (NH stretching) , 2912.23 (COOH Streaching), 1657.30 (C=O Stretching), 1232.22 (C-N stretching), 741.30 (Ar-Cl)

NL4:

IR (ATR, cm-1)- 3354.09(N-H stretching), 2923.70 (COOH Stretching), 1622.82 (C=O Stretching),1231.81 (C-N stretching), 744.93 (Ar-Cl)).

1H NMR :([D,]DMSO): δ 3.27(s,3H–CH3), 3.32 (s, 2H,-CH2), 3.32 (s, 2H,-CH2),3.39 (s, 2H,-CH),3.42 (s, 2H,-CH),3.42 (s, 2H,=CH2),7.04-7.09 (d, 2H, Ar-H), 7.01-7.05(d, 2H, Ar-H),10.89(s, 1H,NH),12.93(s, 1H,OH).

13C NMR ([D,] DMSO): δ = 54.72 (-CH2), 27.14(-CH3)118.27-136.33 (Ar-C), 109.63(=CH) 160.20(N=C) 169.90 (C=O).

EIMS (M/z) : Molecular weight Correspond to 311.1molecular ion peak

NL5:

IR (ATR, cm-1)- 3368. 83 (N-H stretching), 2984. 89 (COOH Stretching), 1648.91 (C=O Stretching), 1231.10 (C-N stretching), 746. 82 (Ar-Cl)).

NL6:

IR (ATR, cm-1)- 3344.08 (N-H stretching), 2917.29 (COOH Stretching), 1626.45 (C=O Stretching), 1230.98 (C-N stretching), 744.02 (Ar-OH)).

NL7:

IR (ATR, cm-1)- 3351.06 (N-H stretching), 2984.75 (COOH Stretching), 2688.60 (Ar-OCH3), 1626.45 (C=O Stretching),1267.49 (C-N stretching),
781.17 (Ar-Cl)).

NL8:

IR (ATR, cm-1)- 3344.08 (N-H stretching), 2984.65 (COOH Stretching), 2688.60 (Ar-OCH3), 1626.45 (C=O Stretching), 1242.69 (C-N stretching), 743.95 (Ar-Cl)

NL9:

IR (ATR, cm-1)- 3384.40 (N-H stretching), 2922.78 (COOH Stretching), 2682.40 (Ar-OCH3), 1652.00 (C=O Stretching), 1341.13 (C-N stretching), 742.53 (Ar-Cl).

1H NMR :([D,]DMSO): δ 3.56(s,H–CH3), 3.08(s,H–CH2), 3.10 (s, H,-CH2), 4.08 (s, H,-CH), 4.48 (s, H,-CH), 4.50 (s, H,-CH), 6.90-7.00 (m, Ar-H), 7.13-8.48(m, Ar-H),10.88(s, 1H,NH),12.83(s, 1H,OH),

EIMS (M/z) : Molecular weight Correspond to 380.2 molecular ion peak

NL10:

IR (ATR, cm-1)- 3260.08 (N-H stretching), 2928.58 (COOH Stretching), 1627.45 (C=O Stretching), 1347.13 (C-N stretching), 731. 85 (Ar-Cl).

1H NMR :([D,]DMSO): δ 3.18(s,H–CH2), 3.20 (s, H,-CH2), 4.08 (s, H,-CH), 4.48 (s, H,-CH), 4.50 (s, H,-CH), 6.95-7.00 (m, Ar-H), 7.13-8.48(m, Ar-H),10.88(s, 1H,NH),12.83(s, 1H,OH),

EIMS (M/z) : Molecular weight Correspond to 397.3 molecular ion peak

NL11:

IR (ATR, cm-1) - 3368.83 (N-H stretching), 2917.73 (COOH Stretching), 1656.11 (C=O Stretching), 1231. 81 (C-N stretching), 740. 89 (Ar-Cl).

NL12:

IR (ATR, cm-1)- 3344.08 (N-H stretching), 2984.65 (COOH Stretching), 1626.45 (C=O Stretching), 1233.55 (C-N stretching), 747.40 (Ar-Cl), 555.71 (Ar-Br).

Molecular Docking

Molecular docking analysis was utilized to predict the possible binding mode of the developed molecules against the human adenosine A2A receptor. Docking analysis revealed that all the developed molecules have a good binding ability with the human adenosine A2A receptor. Derivative NL-1 Showed hydrogen bond interaction with ILE66and aromatic interactions with ILE66, hydrophobic interactions with LEU167 as shown in figure no2. Derivative NL-2 Showed hydrogen bond interaction with SER67and aromatic interactions with HIS264, TYR271, hydrophobic interaction with LEU167 as shown in figure no 3

Figure 2: Docking Interactions of derivative NL1

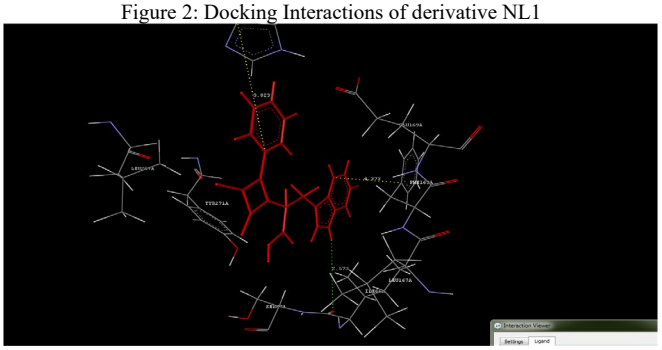
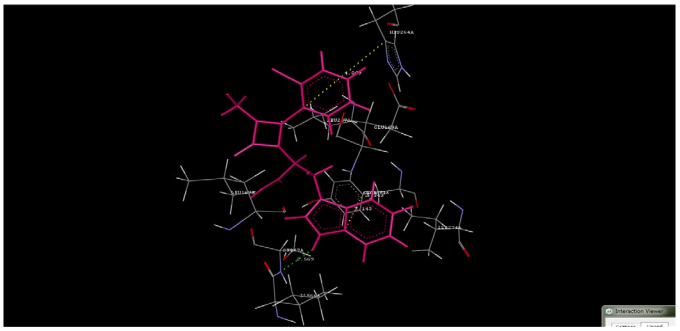
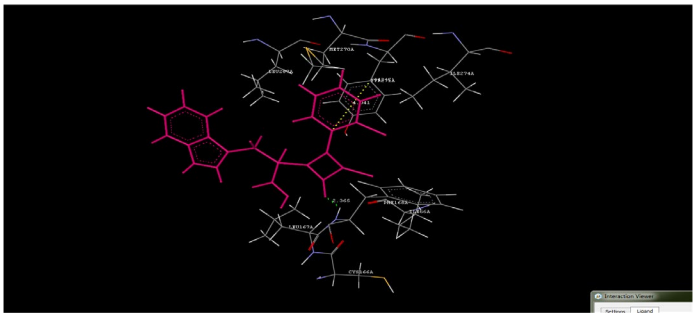


Figure 3: Docking Interactions of derivative NL2



Derivative NL-3 Showed hydrogen bond interaction with PHE168and aromatic interactions with TYR271, hydrophobic interaction with LEU167, LEU267 as shown in figure no 4.

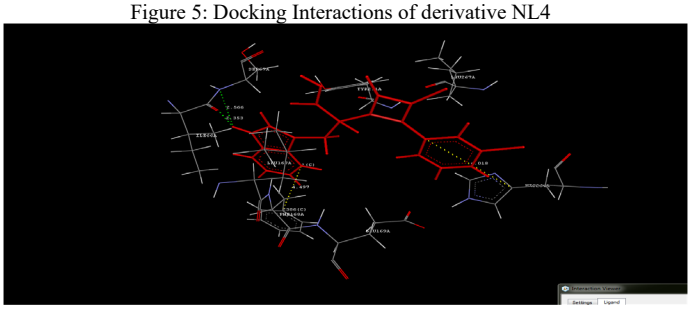
Figure 4: Docking Interactions of derivative NL3



Derivative NL-4 Showed hydrogen bond interaction with

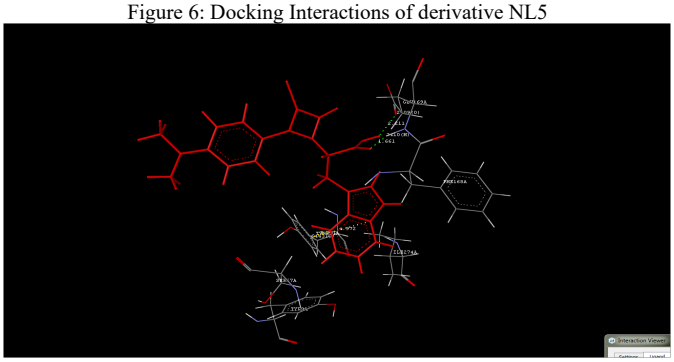
SER67, ILE66and aromatic interactions with PHE168, HIS264 as shown in figure no 5.

Figure 5: Docking Interactions of derivative NL4



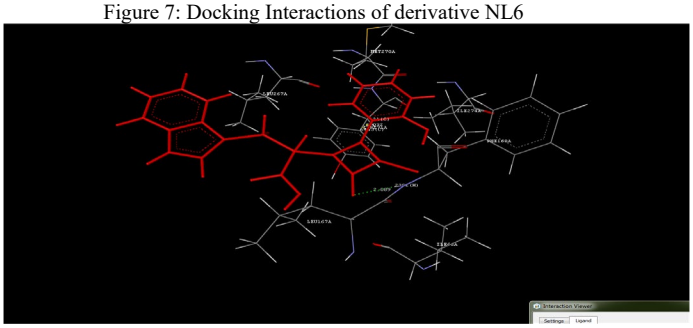
Derivative NL-5 Showed hydrogen bond interaction with GLU169 and aromatic interactions with TYR271 as shown in figure no 6.

Figure 6: Docking Interactions of derivative NL5



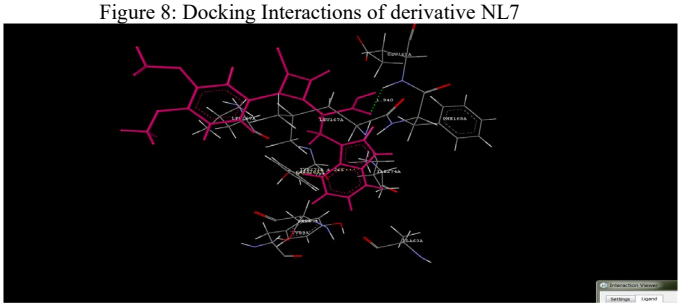
Derivative NL-6 Showed hydrogen bond interaction with PHE168 and aromatic interactions with TYR271 has shown in figure no 7.

Figure 7: Docking Interactions of derivative NL6



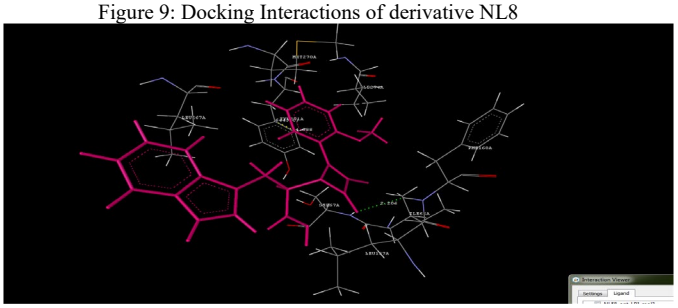
Derivative NL-7 Showed hydrogen bond interaction with GLU169 and aromatic interactions with TYR271 has shown in figure no 8.

Figure 8: Docking Interactions of derivative NL7



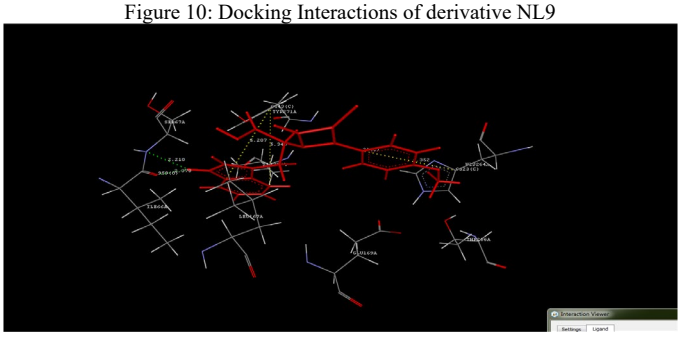
Derivative NL-8 Showed hydrogen bond interaction with PHE168 and aromatic interactions with TYR271 has shown in figure no 9.

Figure 9: Docking Interactions of derivative NL8



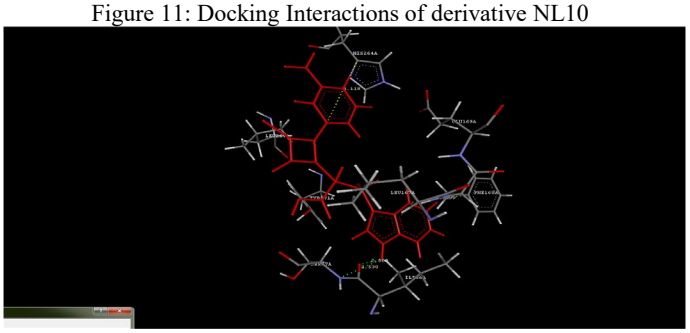
Derivative NL-9 Showed hydrogen bond interaction with SER67, ILE66 and aromatic interactions with HIS264, TYR271 has shown in figure no 10.

Figure 10: Docking Interactions of derivative NL9



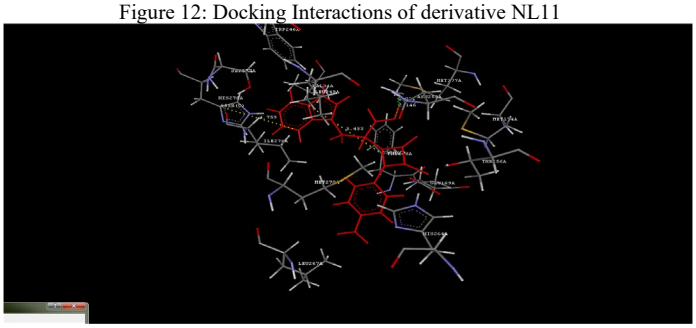
Derivative NL-10 Showed hydrogen bond interaction with SER67, ILE66 and aromatic interactions with PHE168, HIS264has shown in figure no 11

Figure 11: Docking Interactions of derivative NL10



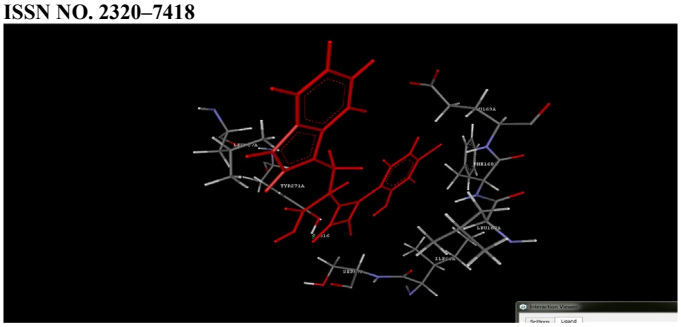
Derivative NL-11 Showed hydrogen bond interaction with ASN253 and aromatic interactions with PHE168, HIS278has shown in figure no 12

Figure 12: Docking Interactions of derivative NL11



Derivative NL-12 Showed hydrogen bond interactions with has shown in figure no 13.

Figure 13: Docking Interactions of derivative NL2



CONCLUSION

New Oxazetidine derivatives incorporating various heterocyclic Benzaldehyde substituents are prepared by using 2-{[(4-chlorophenyl) methylidene] amino}-3-(1H-indol-3-yl) propionic acid and chloro acetyl chloride as reactive intermediates. All these derivatives are characterized by spectral data. All the synthesized products are screened for their in silico Human A2A binding analysis via docking analysis. The majority of the tested compounds exhibited significant Human A2A binding ability. Hence this study has widened the scope of development potent molecules targeting neurological diseases.

REFERENCES

1. Bott TM, West FG, 2012. Preparation and Synthetic Applications of Azetidines, Heterocycles, 84(1): 223 – 264.
2. Goethals EJ, Schacht EH, Bogaert YE, Ali SI, Tezuka Y, 1980. The Polymerization of Azetidines and Azetidine Derivatives, Polymer Journal, 12(9): 571-581.
3. Asif M, 2018. Antimicrobial potential of various substituted azetidine derivatives, MOJ Biorg Org Chem 2(2):36-40.
4. Mandal MK, Ghosh S, Bhat HR, Naesens L, Singh UP, 2020. Synthesis and biological evaluation of substituted phenyl azetidine-2-one sulphonyl derivatives as potential antimicrobial and antiviral agents, Bioorg Chem 104:104320.
5. Kim EA, Na JM, Kim J, Choi SY, Ahn JY, Cho SW, 2017. Neuroprotective Effect of 3-(Naphthalen-2-Yl (Propoxy) Methyl) Azetidine Hydrochloride on Brain Ischaemia/Reperfusion Injury, J Neuroimmune Pharmacol 12(3):447-461.
6. Yang SJ, Kim J, Lee SE, Ahn JY, Choi SY, Cho SW, 2017. Anti-inflammatory and anti-oxidative effects of 3-(naphthalen-2-yl (propoxy) methyl) azetidine hydrochloride on β-amyloid-induced microglial activation, BMB Rep 50(12):634-639.
7. Yang JW, Yang SJ, Na JM, Hahn HG, Cho SW, 2018. 3-(Naphthalen-2-yl (propoxy) methyl) azetidine hydrochloride attenuates NLRP3 inflammasome-mediated signaling pathway in lipopolysaccharide-stimulated BV2 microglial cells, Biochem Biophys Res Commun 495(1):151-156.
8. Arefi H, Naderi N, Shemirani ABI, Kiani Falavarjani M, Azami Movahed M, Zarghi A, 2020. Design, synthesis, and biological evaluation of new 1,4-diarylazetidin-2-one derivatives (β-lactams) as selective cyclooxygenase-2 inhibitors, Arch Pharm (Weinheim) 353(3):e1900293.
9. Mehta PD, Sengar NP, Pathak AK, 2010. 2-Azetidinone--a new profile of various pharmacological activities, Eur J Med Chem 45(12):5541-60.
10. Parmar DR, Soni JY, Guduru R, Rayani RH, Kusurkar RV, Vala AG, 2021. Azetidines of pharmacological interest, Arch Pharm (Weinheim) e2100062.
11. Pizzonero M, Dupont S, Babel M, Beaumont S, Bienvenu N, Blanqué R, Cherel L, Christophe T, Crescenzi B, De Lemos E, Delerive P, Deprez P, De Vos S, Djata F, Fletcher S, Kopiejewski S, L'Ebraly C, Lefrançois JM, Lavazais S, Manioc M, Nelles L, Oste L, Polancec D, Quénéhen V, Soulas F, Triballeau N, van der Aar EM, Vandeghinste N, Wakselman E, Brys R, Saniere L, 2014. Discovery and optimization of an azetidine chemical series as a free fatty acid receptor 2 (FFA2) antagonists: from hit to clinic, J Med Chem 57(23):10044-57.
12. Mehra V, Lumb I, Anand A, Kumar V, 2017. Recent advances in synthetic facets of immensely reactive azetidines, RSC Advance, 7, 45763.
13. Franco R, Navarro G, 2018. Adenosine A2A Receptor Antagonists in Neurodegenerative Diseases: Huge Potential and Huge Challenges, Front. Psychiatry, 9:68.
14. Jaakola V, Griffith MT, Hanson MA, Cherezov V, Chien EYT, Lane JR,2 IJzerman AP, Stevens RC, 2008. The 2.6 Angstrom Crystal Structure of a Human A2A Adenosine Receptor Bound to an Antagonist, Science, 322(21), 1211-1217.

How to cite this article

Lonikar NB, Sangshetti J.N., Bhusnure O.G., 2021. "Synthesis and molecular docking analysis of oxazetidine derivatives for neurological disorders". Jour. of Med. P'ceutical & Allied. Sci. V 10 - I 4, 1768, P- 3251-3255. doi: 10.22270/ jmpas.V10I4.1768