**PHARMACOLOGICAL ACTIVITY OF MORPHOLINE DERIVATIVES AS AN IMPORTANT SCAFFOLD IN MEDICINAL CHEMISTRY: A REVIEW**

**\*KOLICHALA NIRANJAN**

Department of Chemistry, Telangana University,Bhiknoor South Campus, Nizamabad, Telangana-503322. India

\*Corresponding Author: E-mail: kolichala1975@gmail.com

**ABSTRACT**

Morphine derivatives are biologically active chemical molecules with unique structures that have been found in a variety of medications. Morpholine derivatives are widely used as antibacterial, antiemetic, analgesic, anti-inflammatory, anti-pyretic, antiglaucoma, mTOR, anti-platelet, antitumor, proliferative, ACR-induced neurotoxicity, anticancer, antifungal, FGFR3 Kinase, antituberculosis, antimalarial, antirypanosomal, antioxidant, hypolipidemic, hypocholesterolemic, and anti-HIV activity due to their extraordinary action and terminal pharmacophore of action.

**Keywords:** Morpholines, Pharmacological activity, Linezolid, FGFR3, mTOR, Anti-HIV

**INTRODUCTION**

The morpholine is a versatile moiety, a unique pharmacophore, and a remarkable heterocyclic motif with a broad range of pharmacological activity due to its various mechanisms of action. Because morpholine can alter pharmacokinetic characteristics and boost a molecule's potency by molecularly interacting with target proteins (kinases), researchers and medicinal chemists have been motivated to efficiently synthesize morpholine rings and incorporate this moiety into a range of lead compounds with a range of therapeutic activities.

Morpholine derivatives are widely used as Antibacterial Activity1,2,13,18, Antiemetic Activity3, Analgesic4, Anti-inflammatory4,16, Anti-pyretic Activity4, Antiglaucoma Activity5, mTOR Activity6, Anti-platelet Activity7,12, Antitumor Activity8, Proliferative Activity9, ACR-Induced neurotoxicity Activity10, Anticancer Activity11, Antifungal Activity13, FGFR3 Kinase Activity14, Anti-tuberculosis Activity15, Anti-malarial Activity17, Antirypanosomal Activity19, Antioxidant Activity20, Hypolipidemic & Hypocholesterolemic activity20, Anti-HIV Activity21.

**PHARMACOLOGICAL PROFILE**

The aromatic organic heterocycle scaffold morpholin has a six-membered ring with one nitrogen and one oxygen atom. Chemical design produced this adaptable lead ingredient for extremely potent active compounds. This review covers the medicinal chemistry questions for morpholine analogues in vitro and in vivo. Recently, researchers have focused on the morpholine nucleus because of its diverse pharmacological properties. This review illustrates the substantial pharmacophoric effects of the morpholine analogues and highlights their current tendencies. Because of the advances in pharmacokinetic qualities these chemical families may offer, the pharmaceutical industry has made extensive use of them in the manufacture of medications.

N-substituted morpholines are pharmacological agents possessing an extensive spectrum of effects. Pharmacologically, lead compounds containing the morpholine substance are especially beneficial.

A wide range of applications include antibacterial, antiemetic, analgesic, anti-inflammatory, anti-pyretic, antiglaucoma, mTOR, anti-platelet, antitumor, proliferative, ACR-induced neurotoxicity, anticancer, antifungal, anti-tuberculosis, anti-malarial, antirypanosomal, antioxidant, hypolipidemic & hypocholesterolemic, and anti-HIV activities. These applications of morpholinoside derivatives are widely employed.**Figure A.**

**Figure A**

**Figure 1:** The drugs that contain morpholine moiety exhibit remarkable biological properties, such as the antibiotic Linezolid **1**, which contains a morpholine moiety and is a readily available antimicrobial drug22. Morpholine nuclei have generated a lot of interest in recent years due to their variety of biological activities23. The Food and Drug Administration (FDA) has approved the first medication, aprepitant **2**, a neurokinin 1 (NK1) receptor antagonist, to treat chemotherapy-related nausea and vomiting24.



**Figure 1**

**Figure 2:** In both animal and human models, emorfazone **3** is an effective analgesic, anti-inflammatory, and antipyretic medication25. Gefitinib **4** is a selective inhibitor of epidermal growth factor that is therapeutically used to treat non-small cell lung cancer patients who have developed chemoresistance4. Timolol **5**, on the other hand, is a non-selective beta-adrenergic receptor antagonist that is used to treat glaucoma26. In the pages that follow, some of the significant morpholine-containing heterocyclic compounds with biological activity are briefly discussed.



**Figure 2**

**Figure 3:** According to Zask *et al*.27, bridged morpholines **6** were used in place of morpholine in pyrazolopyrimidine inhibitors to obtain significant increases in mTOR-targeting selectivity. Preparations were made for analogues with subnanomolar mTOR IC(50) values and up to 26000-fold selectivity versus PI3Kalpha. Chiral morpholines produced inhibitors with distinct selectivity and potency profiles for each of their enantiomers. According to molecular modelling, the significant selectivity seen by forming a deeper pocket in mTOR that can accommodate bridging morpholines accounts for the single amino acid difference between PI3K and mTOR (Phe961Leu).



**Figure 3**

**Figure 4:** Significant information about coumarin derivatives' synthesis, *in vitro* antiplatelet activity, and relevant structure-activity relationships are provided by Roma *et al*.28. Milrinone and cilostazol were not as effective at inhibiting pure human platelet PDE3 as the recently reported 8-methyl-4-(1-piperazinyl)-7-(3-pyridylmethoxy) coumarin **7** and its potent 7-(2-morpholinoethoxy)-substituted new analogue **8**. These results were linked, through a molecular modelling study, to the molecular interactions of the four compounds with the human PDE3A catalytic site.



**Figure 4**

**Figure 5:** 4-(1,3-Thiazol-2-yl)morpholine derivatives have been found to be strong and specific inhibitors of phosphoinositide 3-kinase, according to Alexander *et al*.29. For the purpose of illustrating the usefulness of this family of drugs in xenograft models of tumour growth, the SAR data of a few instances are shown, along with the *in vivo* profiling of compound **9**.

The MTT colorimetric test was used to assess the antiproliferative properties of the newly synthesised 1,3-disubstituted urea derivatives **10** against a panel of two human tumour cell lines (KB and K562) and one human liver cell line (L02). The 1,3-disubstituted urea derivative series exhibits potent antiproliferative activity against human cancer cell lines (KB and K562) but not against liver cell lines (L02). These compounds have strong *in vitro* antiproliferative activity, and they are selective for L02, which is a key characteristic for an anticancer treatment candidate with fewer adverse effects 30.



**Figure 5**

**Figure 6:** Both laboratory animals and humans have been proven to be neurotoxic by acrylamide (ACR). New functionalized melatonin compounds with promising heterocyclic moiety were synthesised, according to Hanaa *et al*.31, and they are anticipated to exhibit protective effects against ACR-induced neurotoxicity in adult female rats. The brain's malondialdehyde level (MDA) and lactate dehydrogenase (LDH) activity significantly increased after the administration of ACR (50 mg/kg/b.wt.) alone, whereas the levels of monoamines and the activity of antioxidant enzymes significantly decreased. Prior to ACR, treatment with melatonin derivatives **11** (i.p., 50 mg kg-1 b. wt.) generated a significant decrease in brain MDA level and LDH activity with a concurrent significantly increased level of brain monoamines and antioxidant enzyme activity.

Kun *et al*.32 developed and synthesised a number of liquiritigenin thiosemicarbazone derivatives **12** in an effort to create powerful and targeted anticancer drugs. These compounds *in vitro* cytotoxicities were tested on the K562, DU-145, SGC-7901, HCT-116, and Hela cell lines. According to the pharmacological findings, the majority of the synthesised compounds exhibited high selective cytotoxicity against K562 and DU-145 cells, and found that from the structure-activity connections that adding a thiosemicarbazone functional group to the 4-position of liquiritigenin's skeleton is linked to an increase in cytotoxicity.



**Figure 6**

**Figure 7:** According to Kaylene *et al*.33, several 2-morpholino substituted benzoxazines have been created and are being tested for their ability to prevent platelet aggregation caused by ADP and collagen. The chemical was tested for antiplatelet activity. **13** demonstrated strong anti-ADP and collagen-induced platelet aggregation activities. Further, Mithun *et al*.34 synthesised new series of Mannich bases **14** and were also screened for their antibacterial and antifungal activities against a variety of microorganisms and the results of such studies have been discussed.



**Figure 7**

**Figure 8:** According to Lotfi *et al*.35 an effective and adaptable synthetic route has been used to create two novel series of C-nucleosidic ATP imitators. These compounds were synthesised using purine as the main scaffold to function as FGFR3 inhibitors. In order to investigate any potential binding modes, the two substituents, a polyhydroxylated ribose mimic **15** and a lipophilic moiety **16**, were connected either in position 2 or 6 of the purine ring. At a concentration of 50 M, all the substances were able to block the activity of FGFR3 kinase. Unexpectedly, one of the 13 synthesised intermediates with an iodine atom in position 2 turned out to be the best inhibitor. Its position in the ATP binding site has been validated by docking experiments, which also indicated halogen bonding as one of the important interactions.



**Figure 8**

**Figure 9:** Acording to Fereidoon *et al*.36 a group of compounds known as **17** were developed and produced in light of the structural resemblance between N-substituted glycolamides and the N-glycolyl muramic acid residues found in the cell wall of Mycobacterium TB. Using the Microplate Alamar Blue Assay, the minimum inhibitory concentration (MIC) against *M. tuberculosis* H37Rv in BACTEC 12B medium was found (MABA). All of the synthetic compounds with disubstituted amide structures and one or two heteroatoms that lend a pair of electrons to the amide nitrogen showed some anti-tuberculosis action, while all of the monosubstituted amides had no anti-tuberculosis activity.

Novel *N*-Mannich bases of benzimidazole derivatives were synthesised and tested for their ability to reduce pain and inflammation. Diclofenac was found to be less efficacious than compound **18** at 40 mg/kg. Quantum chemical computations and corneal permeability measurements were used to connect the hydrogen bonding capacity with permeability and activity. Pharmacological action was associated with the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). The semi-empirical PM3 calculations (quantum chemical calculations) revealed that ELUMO and energy gap ΔE were capable of accounting for the high in vitro bovine corneal permeability and activity of the compounds37.



**Figure 9**

**Figure 10:** Ashok *et al*.38 described the synthesis of a novel class of hybrid 4-anilinoquinoline triazines and their *in vitro* testing for their cytotoxicity toward the VERO cell line as well as their antimalarial activity against the CQ-sensitive 3D7 strain of *P. falciparum*. These compounds demonstrated higher antimalarial potency to CQ. Compound **19** was discovered to have oral activity at a dose of 100 mg/kg for 4 days against a strain of *P. yoelii* that was resistant to CQ.



**Figure 10**

**Figure 11:** By employing the strains of *Acinetobacter baumanii, Citrobacter freundii, Pseudomonas aeruginosa, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, and Bacillus subtilis*, Gabriela *et al*.39 reported the synthesis of various 4-substituted 5-[4-(4-X-phenylsulfonyl)phenyl] Mannich bases **20** and found that some of the synthesized compounds have demonstrated positive anti-A. baumanii and anti-B. subtilis behaviours in their prospective antibacterial effects.



**Figure 11**

**Figure 12:** *Leishmania donovani*, three different strains of *Trypanosoma*, and *Plasmodium falciparum* K1 were tested for their *in vitro* antitrypanosomal activity by Sabine *et al*.40 after the synthesis of a series of novel 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives. Interestingly, the IC50 values of the β-diketone precursors **21** ranged from 1.0 to 3.4 *µ*M and showed good antitrypanosomal activity toward the insect stage.

A variety of 2-biphenylyl morpholine derivatives that are structurally related to several substituted morpholines with antioxidant activity and to hypocholesterole- mic 3-biaryl-quinuclidines were synthesised and their antioxidant and hypochole- sterolemic activity was assessed by Michael et al.41 The ferrous/ascorbate-induced lipid peroxidation of microsomal membrane lipids is shown to be inhibited by the new compounds, with the most powerful derivative, **22**, having an IC50 value of 250 µM. Compound **22** also exhibits hypolipidemic and hypocholesterolemic effects. At 28 mol/kg, the most active molecule, **22**, reduces plasma levels of triglycerides, low density lipoprotein, and total cholesterol in Triton WR-1339-induced hyperlipidemic rats by 54%, 51%, and 49%, respectively (ip).



**Figure 12**

**Figure 13:** The human immunodeficiency virus type-1 (HIV-1) encodes three enzymes necessary for viral replication: a reverse transcriptase, a protease, and an integrase, according to Cristina *et al*.42. The latter is in charge of integrating the viral genome into the human genome and is a prime candidate for chemotherapeutic intervention in the fight against AIDS. A novel family of drugs that are metabolically stable and demonstrate potent suppression of the HIV integrase strand transfer step have been identified as benzoyl-dihydroxypyrimidine-carboxamides. The 2-*N*-methyl-morpholino derivative **23**, which has a CIC95 of 65 nM in the cell in the presence of serum, is one of the more intriguing compounds in this family.



**Figure 13**

**CONCLUSION**

This review provided a resource for basic and application study on the topic by outlining morpholine and its derivatives.

**ACKNOWLEDGEMENTS**

The author expresses gratitude to the chair of the Chemistry Department of Telangana University in Nizamabad, Telangana, India, for the facilities and support given.

**AUTHORS CONTRIBUTION**

The author writes technical articles and collects data.

**CONFLICTS OF INTERESTS**

There is no conflict of interest with the publication of this essay, according to the author.

**AUTHORS FUNDING**

Department of chemistry, telangna university.

**REFERENCES**

1. Russell M.G, Jamison T.F. Seven-step continuous flow synthesis of linezolid without intermediate purification. *Angew. Chem. Int. Ed. Engl*.2019; 58,7678-7681.
2. Bosnjak S.M, Gralla R.J, Schwartzberg L. Prevention of chemotherapy-induced nausea: the role of neurokinin-1 (NK1) receptor antagonists. *Support Care Cancer*.2017; *25*, 1661-1671.
3. Takaya M, Sato M, Terashima K, Tanizawa H, Maki Y. A new nonsteroidal analgesic-antiinflammatory agent. Synthesis and activity of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone and related compounds. *J. Med. Chem.1979;* *22*, 53-58.
4. Nakamura Y, Sano K, Soda H, Takatani H, Fukuda M, Nagashima S, Hayashi T, Oka M, Tsukamoto K, Kohno S. Pharmacokinetics of gefitinib predicts antitumor activity for advanced non-small cell lung cancer. *J. Thoracic Oncol.* 2010;*5*, 1404-1409.
5. Sacca S.C, La Maestra, Micale R.T, Larghero P,Travaini G, Baluce B, Izzotti A. Ability of dorzolamide hydrochloride and timolol maleate to target mitochondria in glaucoma therapy. *Arch. Ophthalmol*.2011;129, 48-55.
6. Zask A, Kaplan J, Verheijen J.C, Richard D.J, Curran K, Brooijmans N, Bennett E.M, Toral B.L, Hollander I, Ayral K.S,Yu K. Morpholine derivatives greatly enhance the selectivity of mammalian target of rapamycin (mTOR) inhibitors. *J. Med. Chem*.2009; *52*, 7942-7945.
7. Roma G., Di Braccio M, Grossi G, Piras D, Leoncini G, Bruzzese D, Signorello M.G, Fossa P ,Mosti L. Synthesis and *in vitro* antiplatelet activity of new 4-(1-piperazinyl)coumarin derivatives. Human platelet phosphodiesterase 3 inhibitory properties of the two most effective compounds described and molecular modeling study on their interactions with phosphodiesterase 3A catalytic site. *J. Med. Chem.2007;* *50*, 2886-2895.
8. Alexander R, Balasundaram A, Batchelor M, Brookings D, Crepy K, Crabbe K, Deltent M.F, Driessens F, Gill A, Harris S, Hutchinson G, Kulisa C, Merriman M, Prakash M, Parton T, James T ,Whitcombe I ,Wright S. 4-(1,3-Thiazol-2-yl)morpholine derivatives as inhibitors of phosphoinositide 3-kinase. *Bioorg. Med. Chem. Lett.2008;18*, 4316-4320.
9. Huan Q.L, Tao T.Z, Tao Y, Yin L , Hai L.Z. Design, synthesis and structure–activity relationships of antiproliferative 1,3-disubstituted urea derivatives. *Eur. J. Med. Chem*.2009; *44*, 453-459.
10. Hanaa H.A, Gamal A.E, El-Sayed M., El-Sayed M.M, Abd-Elhalim W.G.S, Reham W.S. Potent neuroprotective role of novel melatonin derivatives for management of central neuropathy induced by acrylamide in rats. *Eur. J. Med. Chem.2010;* *45*, 5452-5459.
11. Kun H, Ze-hua Y, Sha S.P, Hua-jin X, R. Jie R. Synthesis and antitumor activity of liquiritigenin thiosemicarbazone derivatives. *Eur. J. Med. Chem.2010;* *45*, 3453-3458.
12. Kaylene M.P, Jasim A.R, Christopher B. Synthesis, identification and antiplatelet evaluation of 2-morpholino substituted benzoxazines. *Eur. J. Med. Chem.2007* *42*, 1200-1210.
13. Mithun A, Bantwal S.H, Boja P. Convenient one pot synthesis and antimicrobial evaluation of some new Mannich bases carrying 4-methylthiobenzyl moiety. *Eur. J. Med. Chem.* *42*, 1095-1101.
14. Lotfi T.T, Florent B, François M, Patricia B , Yves L. M. Synthesis of purin-2-yl and purin-6-yl-aminoglucitols as C-nucleosidic ATP mimics and biological evaluation as FGFR3 inhibitors. *Eur. J. Med. Chem.2011;* *46*, 1254-1262.
15. Fereidoon D, Farzad K, Ali K , Parisa F. Synthesis and evaluation of in vitro anti-tuberculosis activity of N-substituted glycolamides. *Eur. J. Med. Chem.2009;* *44*, 289-295.
16. Jesudason E.P, Sridhar S.K, Padma Malar E.J, Shanmugapandiyan P, Inayathullah M, Arul V, Selvaraj D, Jayakumar R. Synthesis, pharmacological screening, quantum chemical and in vitro permeability studies of N-Mannich bases of benzimidazoles through bovine cornea. *Eur. J. Med. Chem.2009;* *44*, 2307-2312.
17. Ashok K, Srivastava K, Raja Kumar S, Siddiqi M.I, Sunil K.P, Jitendra K.S.P, Chauhan M.S. 4-Anilinoquinoline triazines: a novel class of hybrid antimalarial agents. *Eur. J. Med. Chem.* 2011;*46*, 676-690.
18. Gabriela L.A, Stefania F.B, Eva R.A, Constantin D, Gabriel S. Synthesis characterization and antibacterial activity of some triazole Mannich bases carrying diphenylsulfone moieties. *Eur. J. Med. Chem.2009;* *44*, 3083-3089.
19. Sabine K, Alfonso Z, Marcel K, Reto B, Leonardo S , Remo P. Synthesis and evaluation of antiparasitic activities of new 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives, *J. Med. Chem*. 2007; *50*, 5833-5839.
20. Michael C.C, Eleni A.R, Panos N.K. Hypocholesterolemic and hypolipidemic activity of some novel morpholine derivatives with antioxidant activity. *J. Med. Chem*. 2007;*43*,609-612.
21. Cristina G, Emanuela N, Ester M, Benedetta C, Marco F, Federica O, Paola P, Giovanna P, Marco P, Maria R.R.F, Rita S, Carl F.H, Norihiro I, Anna A, Maria V, Fabio B, Odalys G.P, Marina T, Edith M, Silvia P, Ralph L, Peter F, Kara A.S, Daria H, Michael R, Vincenzo S. Discovery and synthesis of HIV integrase inhibitors:  development of potent and orally bioavailable N-nethyl pyrimidones, *J. Med. Chem.2007;50*, 4953-4975.
22. Russell M.G, Jamison T.F. Seven-step continuous flow synthesis of linezolid without intermediate purification. *Angew. Chem. Int. Ed. Engl*.2019; 58,7678-7681.
23. Bosnjak S.M, Gralla R.J, Schwartzberg L. Prevention of chemotherapy-induced nausea: the role of neurokinin-1 (NK1) receptor antagonists. *Support Care Cancer*.2017; *25*, 1661-1671.
24. Takaya M, Sato M, Terashima K, Tanizawa H, Maki Y. A new nonsteroidal analgesic-antiinflammatory agent. Synthesis and activity of 4-ethoxy-2-methyl-5-morpholino-3(2H)-pyridazinone and related compounds. *J. Med. Chem.1979;* *22*, 53-58.
25. Nakamura Y, Sano K, Soda H, Takatani H, Fukuda M, Nagashima S, Hayashi T, Oka M, Tsukamoto K, Kohno S. Pharmacokinetics of gefitinib predicts antitumor activity for advanced non-small cell lung cancer. *J. Thoracic Oncol.* 2010;*5*, 1404-1409.
26. Sacca S.C, La Maestra, Micale R.T, Larghero P,Travaini G, Baluce B, Izzotti A. Ability of dorzolamide hydrochloride and timolol maleate to target mitochondria in glaucoma therapy. *Arch. Ophthalmol*.2011;129, 48-55.
27. Zask A, Kaplan J, Verheijen J.C, Richard D.J, Curran K, Brooijmans N, Bennett E.M, Toral B.L, Hollander I, Ayral K.S,Yu K. Morpholine derivatives greatly enhance the selectivity of mammalian target of rapamycin (mTOR) inhibitors. *J. Med. Chem*.2009; *52*, 7942-7945.
28. Roma G., Di Braccio M, Grossi G, Piras D, Leoncini G, Bruzzese D, Signorello M.G, Fossa P ,Mosti L. Synthesis and *in vitro* antiplatelet activity of new 4-(1-piperazinyl)coumarin derivatives. Human platelet phosphodiesterase 3 inhibitory properties of the two most effective compounds described and molecular modeling study on their interactions with phosphodiesterase 3A catalytic site. *J. Med. Chem.2007;* *50*, 2886-2895.
29. Alexander R, Balasundaram A, Batchelor M, Brookings D, Crepy K, Crabbe K, Deltent M.F, Driessens F, Gill A, Harris S, Hutchinson G, Kulisa C, Merriman M, Prakash M, Parton T, James T ,Whitcombe I ,Wright S. 4-(1,3-Thiazol-2-yl)morpholine derivatives as inhibitors of phosphoinositide 3-kinase. *Bioorg. Med. Chem. Lett.2008;18*, 4316-4320.
30. Huan Q.L, Tao T.Z, Tao Y, Yin L , Hai L.Z. Design, synthesis and structure–activity relationships of antiproliferative 1,3-disubstituted urea derivatives. *Eur. J. Med. Chem*.2009; *44*, 453-459.
31. Hanaa H.A, Gamal A.E, El-Sayed M., El-Sayed M.M, Abd-Elhalim W.G.S, Reham W.S. Potent neuroprotective role of novel melatonin derivatives for management of central neuropathy induced by acrylamide in rats. *Eur. J. Med. Chem.2010;* *45*, 5452-5459.
32. Kun H, Ze-hua Y, Sha S.P, Hua-jin X, R. Jie R. Synthesis and antitumor activity of liquiritigenin thiosemicarbazone derivatives. *Eur. J. Med. Chem.2010;* *45*, 3453-3458.
33. Kaylene M.P, Jasim A.R, Christopher B. Synthesis, identification and antiplatelet evaluation of 2-morpholino substituted benzoxazines. *Eur. J. Med. Chem.2007* *42*, 1200-1210.
34. Mithun A, Bantwal S.H, Boja P. Convenient one pot synthesis and antimicrobial evaluation of some new Mannich bases carrying 4-methylthiobenzyl moiety. *Eur. J. Med. Chem.* *42*, 1095-1101.
35. Lotfi T.T, Florent B, François M, Patricia B , Yves L. M. Synthesis of purin-2-yl and purin-6-yl-aminoglucitols as C-nucleosidic ATP mimics and biological evaluation as FGFR3 inhibitors. *Eur. J. Med. Chem.2011;* *46*, 1254-1262.
36. Fereidoon D, Farzad K, Ali K , Parisa F. Synthesis and evaluation of in vitro anti-tuberculosis activity of N-substituted glycolamides. *Eur. J. Med. Chem.2009;* *44*, 289-295.
37. Jesudason E.P, Sridhar S.K, Padma Malar E.J, Shanmugapandiyan P, Inayathullah M, Arul V, Selvaraj D, Jayakumar R. Synthesis, pharmacological screening, quantum chemical and in vitro permeability studies of N-Mannich bases of benzimidazoles through bovine cornea. *Eur. J. Med. Chem.2009;* *44*, 2307-2312.
38. Ashok K, Srivastava K, Raja Kumar S, Siddiqi M.I, Sunil K.P, Jitendra K.S.P, Chauhan M.S. 4-Anilinoquinoline triazines: a novel class of hybrid antimalarial agents. *Eur. J. Med. Chem.* 2011;*46*, 676-690.
39. Gabriela L.A, Stefania F.B, Eva R.A, Constantin D, Gabriel S. Synthesis characterization and antibacterial activity of some triazole Mannich bases carrying diphenylsulfone moieties. *Eur. J. Med. Chem.2009;* *44*, 3083-3089.
40. Sabine K, Alfonso Z, Marcel K, Reto B, Leonardo S , Remo P. Synthesis and evaluation of antiparasitic activities of new 4-[5-(4-phenoxyphenyl)-2*H*-pyrazol-3-yl]morpholine derivatives, *J. Med. Chem*. 2007; *50*, 5833-5839.
41. Michael C.C, Eleni A.R, Panos N.K. Hypocholesterolemic and hypolipidemic activity of some novel morpholine derivatives with antioxidant activity. *J. Med. Chem*. 2007;*43*,609-612.
42. Cristina G, Emanuela N, Ester M, Benedetta C, Marco F, Federica O, Paola P, Giovanna P, Marco P, Maria R.R.F, Rita S, Carl F.H, Norihiro I, Anna A, Maria V, Fabio B, Odalys G.P, Marina T, Edith M, Silvia P, Ralph L, Peter F, Kara A.S, Daria H, Michael R, Vincenzo S. Discovery and synthesis of HIV integrase inhibitors:  development of potent and orally bioavailable N-nethyl pyrimidones, *J. Med. Chem.2007;50*, 4953-4975.