Int. J. Chem. Sci.: 14(3), 2016, 1777-1788
ISSN 0972-768X
www.sadgurupublications.com

EMPHASIZING MORPHOLINE AND ITS DERIVATIVES (MAID): TYPICAL CANDIDATE OF PHARMACEUTICAL IMPORTANCE

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ABSTRACT

The use of chemicals (drugs) for both medical and recreational purposes is hardly new. In fact, drug use seems to have been a part of human science prehistory. Morpholine (C_4H_9NO, 1-oxa-4-azacyclohexane) is a synthetic simple heterocyclic organic compound having characteristic functional groups of amine and ether and great industrial importance. Chemical manipulations on morpholine based molecules through structure - activity relationship strategy could help developing many interesting candidates of therapeutic significance to tackle broad range of medical ailments. Feasible physico-chemical properties (polarity and solubility), low cost and wide availability make it a suitable candidate for the synthesis of many potent drugs.
Key words: Drugs, Morpholine, Industrial importance, Structure - activity relationship.

INTRODUCTION

The search for chemicals that will provide relief from pain, cure disease and infection, also offer an escape from the real world has been a part of virtually every known human culture. In the earliest period of human civilization, plants, animal products, and minerals were the major sources from which such chemicals were obtained. The natural world contains almost endless supply of yet-to-be-discovered chemicals that will significantly augment the world's supply of drugs. People's dependence on the natural world for drugs began to change, however, at the beginning of the 18th century. During this period, chemists became adept at designing and synthesizing synthetic chemicals with properties similar to or superior to those of natural medications. Compounds originally developed for other purposes, such as dyeing, were also found to have therapeutic value to humans and

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other animals. In addition, it was also found that making relatively minor changes in the chemical structure of a substance resulted in the formation of new compounds that were often safer and/or more efficacious than the original compounds from which they were derived. These compounds include products for the relief of pain, allergies, stomach disorder, protection from environmental hazards, cure of infectious diseases, alleviation of body aches and sores, remedy for poisonous bites and a host of other beneficial results. The lessons learned during these early decades of modern chemistry have continued to drive much of the drug development research that continues in the 21st century. The fruits of that technique in drug development have been a bonanza for the world's pharmaceutical companies and brought relief from pain and suffering for untold numbers of humans around the world. Morpholine and its derivatives (MAID) are one such versatile building block intermediate and find a multitude of pharmaceutical application as catalysts, pesticides, personal care, antioxidants, bactericides, analgesics, anesthetics, antidepressants, appetite suppressants, antitumor agents, antibiotics, antifungal, antileismanial and other physiologically active agents.

Morpholine and its derivatives (MAID): Pharmaceutical importance

Therapeutic agent/s

The term drug refers to a much greater array of chemicals than these health-related substances. It also includes dozens of natural and synthetic products used for recreational or non-therapeutic purposes: mind-altering chemicals that help humans escape from the "real world." Morpholine is a six-membered heterocycle featuring both amine and ether functional groups. Morpholine and its derivatives have several industrial applications, such as corrosion inhibitor, optical bleaching agent, and in textile solvent to dissolve cellulose, and fruit or vegetable preservation/glazing agent. Apart from that, substituted morpholine derivatives are the core of various natural and biologically active compound. This class of compounds has found important application in pharmaceutical field. Morpholine derivatives from synthetic and natural products are known to act as antidepressant, appetite suppressant, analgesic, antitumor agent, antioxidant, antibiotic, antifungal, antileismanial, selective α1-agonist in the treatment of dementia and other central nervous system disorders characterized by symptoms of noradrenergic insufficiency, as well as potent long acting human neurokinin-1 (hNK-1) receptor antagonists (Table 1). Chiral morpholine derivatives have found numerous applications in asymmetric synthesis as chiral auxiliaries as well as chiral ligands too.

Table 1: Overview of pharmacological activities of some morpholine derivatives

S. No.	Category description	Pharmaceutical activities	Reference
1	N-substituted morpholines	Leishmanicidal effect	1
2	4-(4-aminophenyl)-morpholine	Antimicrobial agent	2
3	Methoxy(III) and hydroxy-methyl (IV) morpholine phencyclidine	Analgesic effect	3
4	3-methyl-2-phenylmorpholine (Phenmetrazine)	Appetite suppressant	4
5	Morpholine salicylate	Analgesic, antipyretic and anti-inflammatory agent (NSAID)	5
6	2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethanol	Antibiotic and antiprotozoal medication	6
7	Morpholine-4-carboxylic acid {(S)-1-[4-cyano-1-(3-morpholin-4-yl-propyl)-piperidin-4-ylcarbamoyl]-4, 4- dimethyl-hexyl}-amide	Cathepsin S inhibitor	7
8	2-Phenyl-3,6-dimethylmorpholine	Stimulant and anorectic effects,	8
9	(S)-3-[(Benzyloxy)methyl]morpholine hydrochloride	Non-stimulant Appetite suppressant	9
10	Phophorylated morpholine acetal	Neurokinin antagonist	10
11	**(***R*)-(+)-2-[[[3-(Morpholinomethyl)-2*H*-chromen-8-yl]oxy]methyl]morpholine Methanesulfonate	5 HT-1B receptor antagonist	11
12	2-(*R*)-(1-(*R*)-3,5-Bis (trifluoromethyl) phenylethoxy)-3-(*S*)-(4-fluoro) phenyl-4-(3-oxo-1,2,4-triazol-5-yl) methylmorpholine	NK 1 receptor antagonist	12
13	(2R,6S)-2,6-dimethyl-4-{2-methyl-3-[4-(2-methylbutan-2-yl)phenyl]propyl} morpholine (Amorolfine)	Antifungal	13

Key structural component in some natural products and clinical drugs

Morpholine forms the core as well as auxiliary structural component of many synthetic organic molecules including active pharmaceutical ingredients (API), organic/ drug intermediates, colorants, catalysts, coating agents, varnishes etc. Apart from these morpholine is an important building block of some typical secondary metabolites like alkaloids polygonafolin (1), Chelonin A (2), Chelonin C (3), Acotartarin A (4), Acotartarin C (5). In addition, many well-known drugs like Gefitinib (6), linezolid (7), Emorfazone (8) Timolol (9) and Reboxetin (10), possess morpholine as their key structural component[14] (Fig. 1)

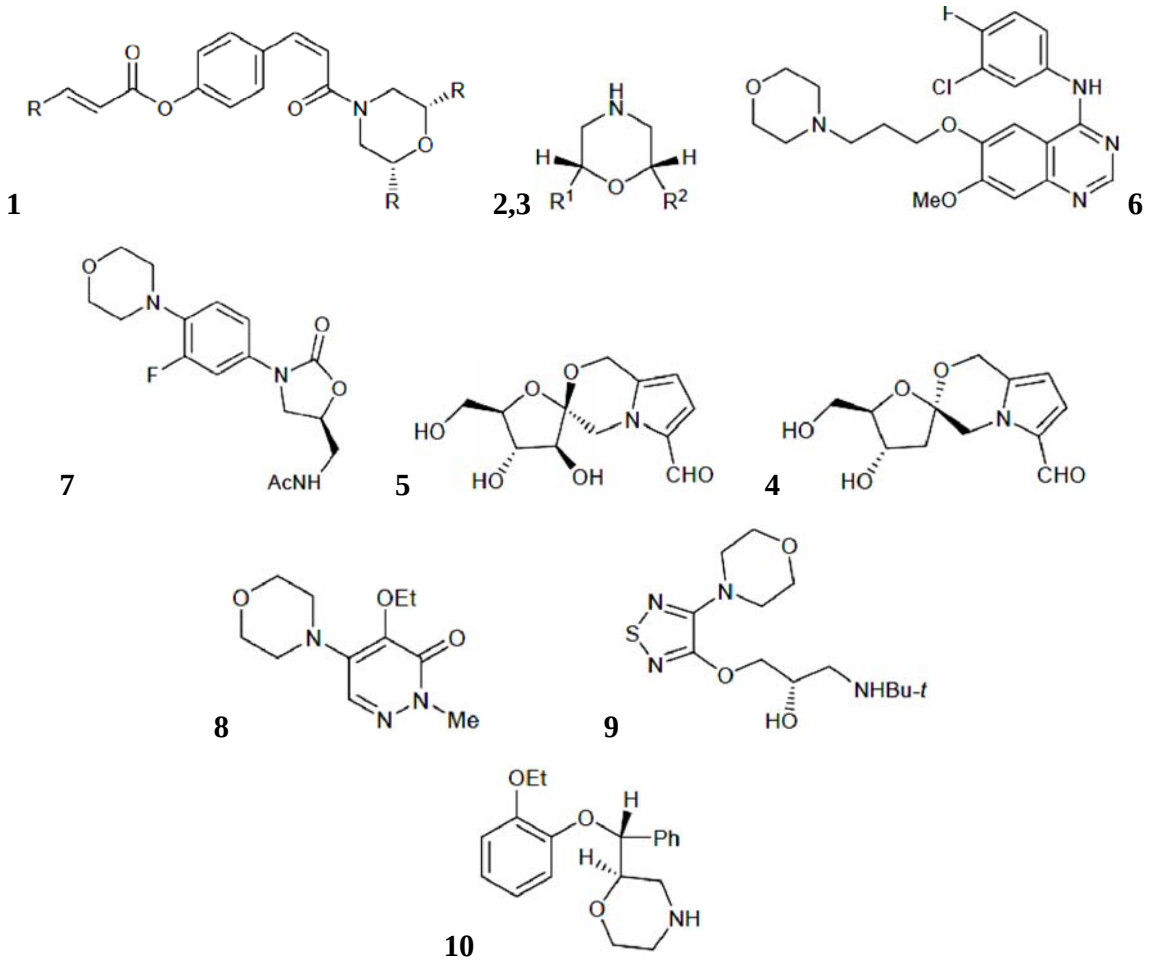
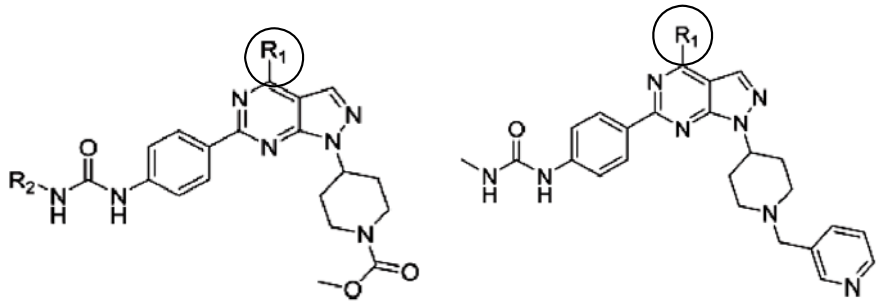


Fig. 1: Chemical structures of various morpholine containing natural and synthetic compounds

Morpholine analogues as selective mTOR inhibitor

Mammalian target of Rapamycin (mTOR) is a serine/threonine kinase, which belongs to the family of Phosphoinositide-3-kinase (PI3K) related kinases. It is a valid target for various metabolic disorders like cancer and Type II diabetes mellitus. The conserved ATP binding pockets of PI3K family poses a big hurdle for the development of selective inhibitors. Morpholine containing pyrazolopyrimidines were found to be selective and potent in inhibiting mTOR in cancer xenograft models of nude mice. Based on this, some pyrazolopyrimidine analogues with morpholine, methyl morpholine and bridged morpholine substitutions at R1 position (Fig. 2 & 3) were synthesized and investigated for mTOR inhibition capacity. In particular substituting R1 with bridged morpholine was found to show dramatic improvement in mTOR selectivity [15].



(i) **(ii)**

Fig. 2: Pyrazolopyrimidine analogues with morpholine, methyl morpholine and bridged morpholine substitutions at R1 position (Encircled regions)
i = 2-Methylmorpholine and bridged morpholine containing analogues and
ii = cis-2,6-Dimethylmorpholine and bridged morpholine containing analogues

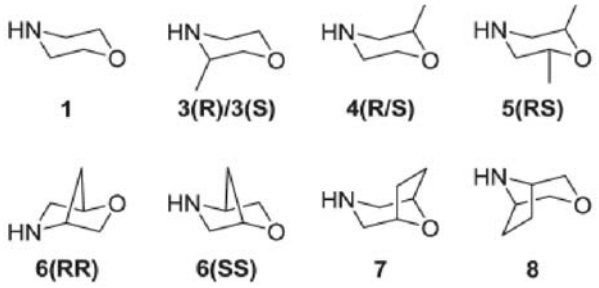


Fig. 3: Morpholine (1) and some of its analogues substituent (3-8) at R1 position of pyrazolopyrimidine. [(3, 4: chiral morpholine) (5: achiral methyl substituted morpholine) (6: chiral bridge morpholine) and 7, 8: achiral bridged morpholine]

Morpholine derivatives as anti-parasitic agent

Malaria, leishmaniasis and trypanosomiasis comprise the three major forms of diseases caused by parasites. The causative organisms include *Plasmodium falciparum, Leishmania donvani* and *Tyrpanosomabruceig ambiense* respectively. Among these, malaria is known to be the most dreadful disease with 214 million attacks and more than four hundred thirty eight thousand deaths in 2015.[16] Drug resistance and unacceptable adverse effects are known to be the primary limitations associated with currently available drug classes. Despite of the attempts to improve existing drugs and validation of novel targets only few drugs have been entered into pre-clinical/clinical trials with a great demand for anti-parasitic leads. Some novel 4-[5-(4-phenoxyphenyl)-2H-pyrazole-3-yl]morpholine derivatives were developed and tested against *T. rhodesiense*, *T. cruzi*, and *P. falciparum K1* in vitro. Among those compounds A and D (Fig. 4) were found to the most potent anti-trypanosomal candidates in the series with least cytotoxicity[17].

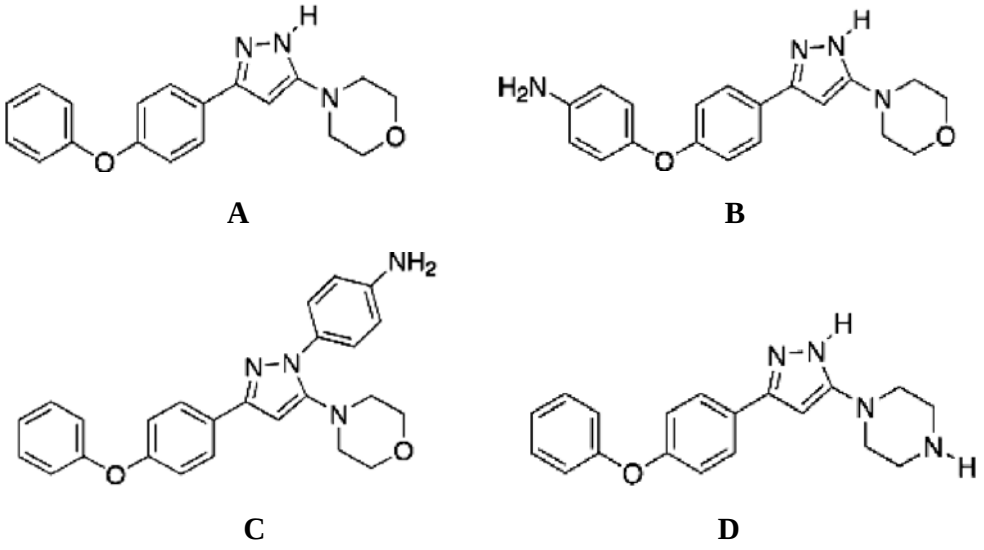


Fig. 4: Some active anti-parasitic agents of morpholine derivatives

Caspase 3 inhibition potential of morpholine analogues

Caspases are one of the important enzymatic mediators of cellular apoptosis belonging to the family of cysteine-dependent aspartate proteases. Caspase 3 acts as a mediator between intrinsic and extrinsic apoptotic pathways which makes it an ideal drug target. Caspase inhibitors were widely used as neuroprotective agents, anti-arthritic agents, immunomodulatory agents, etc. A series of 4 substituted 2-(2-acetyloxyethyl)-8-(morpholine-4-sulfonyl)-pyrrolo-[3,4-c]-quinoline-1,3-diones with a general chemical

structure as shown in Fig. 5 have been reported, which were considered as non-peptide caspase inhibitors[18].

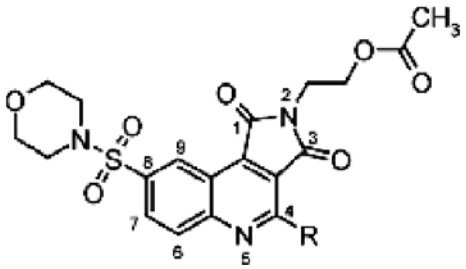
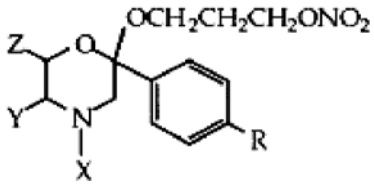


Fig. 5: A caspase 3 inhibitor

Nitric oxide releasing anti-hyperlipidemic morpholine derivatives

Nitric oxide esters of morpholine derivatives (Fig. 6) were reported to inhibit lipid peroxidation in-vitro and potently influence plasma levels of low density lipoproteins (LDL), triglycerides and cholesterol[19]. Nitric oxide is a crucial endogenous mediator of vascular homeostasis, which maintains the endothelial tone. Pathological conditions affecting vascular integrity like atherosclerosis and coronary artery disease adversely alters the nitric oxide pathway. Hence agents which could actively donate nitric oxide exogenously would most suitable therapeutic candidates.



Where; X = CH_3, Y, Z = H, R = C_6H_5

X = CH_3, Y, Z, R = C_6H_5

X, Y = $(CH_2)_4$, Z = H, R = C_6H_5

X = CH_3, Y, Z, R = H

Fig. 6: Nitric oxide donating morpholine derivatives

Role of morpholine ring in development of serine/threonine kinase inhibitors

Phosphatidylinositol 3-kinases (PI3Ks) and phosphatidylinositol 3-kinase-related protein kinases (PIKKs) comprises important family of serine/threonine kinases, which are actively involved in various cellular processes like cell proliferation, migration, apoptosis,

survival, metabolism, and stress response including DNA damage. Members of the family includes DNA dependent Protein Kinase (DNA PK), Ataxia Telangiectasia-RAD3-related (ATR), Ataxia Telangiectasia Mutated (ATM) etc. which are known to take part in crucial cellular repair processes in response to DNA damage[20].

An alteration in PI3K pathway is associated with diverse pathological conditions like neuro-degeneration, cancer, metabolic syndrome, aging either directly or indirectly. Targeting the kinase family members could offer a big hope for treating cancer, several inflammatory and autoimmune disorders in future. Furthermore, development of molecules, which can actively target the DNA damage response pathway could be really an encouraging attempt. Several potent morpholine based derivatives (Fig. 7) have been synthesized which were known to interact through active hydrogen bonding at the catalytic site of the enzyme as shown in Fig. 8.

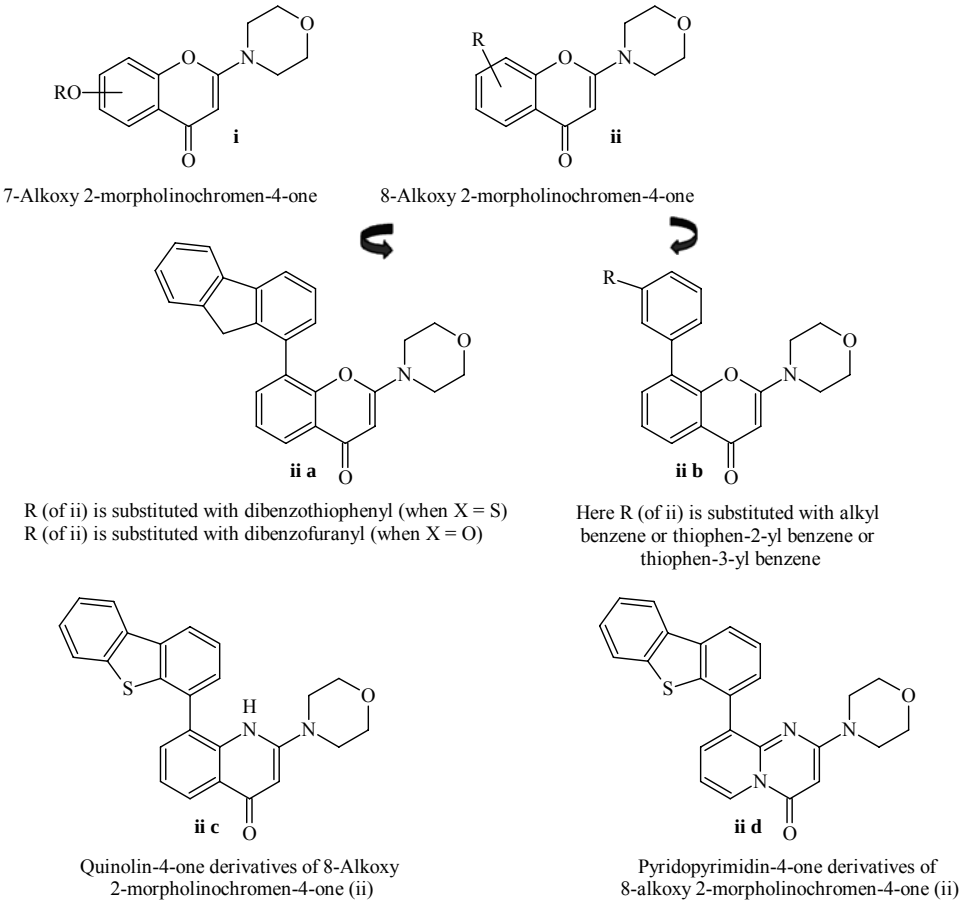
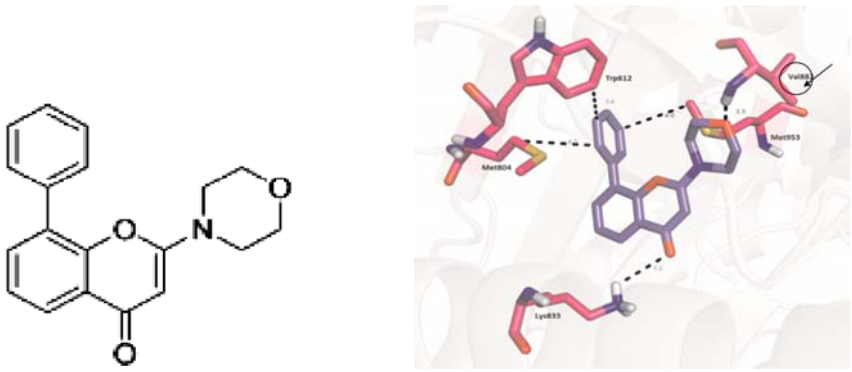


Fig. 7: Structures of chromone (i, ii, iia, iib), quinolone (iic) and pyridopyrimidone (iid)



A **B**

Fig. 8: (A) Structure of a first generation PI3K inhibitor (B) Binding of A at the active site (morpholino ring has attained H-bond with Val 882, the encircled region pointed out with an arrow)

CONCLUSION

Target selectivity is the primary pre-requisite for a drug development program. From decades medicinal chemists have been seeking strategies to achieve promising target selectivity in drug designing. However, only few strategies were found to be successful in reaching clinical phase, while rest of them lag behind at the bench level itself. Morpholine is a simple and easily available heterocycle, which was found to occur widely in many chemical compounds of natural and synthetic origin with diverse scientific applications. In particular role of morpholine linked to pharmaceutical applications like drug design and development seems to be encouraging. Being an important substituent, it could profoundly influence parameters of structural activity relationship (SAR) in lead optimization process. In addition, it is very feasible to incorporate morpholine/modified morpholine units in bioactive molecular scaffolds through conventional synthetic approaches. Since several enzymatic targets possess conserved active pocket which could allow ligands to bind through a specific interaction (vanderwaals/ionic/hydrogen bonding) and both the atoms of morpholine could serve as efficient hydrogen bond acceptors and donors, making the moiety ideal for improving selectivity during lead optimization process. Apart from this MAID may pose minimal pharmacokinetic burden due to their polar and water soluble nature. Hence, strategies for synthesis of morpholine based derivatives could set a stage for the development of several interesting therapeutic molecules which may stand promising especially in terms of target selectivity and safety.

REFERENCES

1. K. M. Khana, M. Z. Khana, M. Tahaa, G. M. Maharvia, Z. S. Saifya, S. Parveenb and M. Iqbal Choudharya, Leishmanicidal Potential of N-substituted Morpholine Derivatives: Synthesis and Structure–Activity Relationships, Natural Prod. Res., **23(5)**, 479-484 (2009).
2. Perumal Panneerselvam, R. R. Nair, Gudaparthi Vijayalakshmi, Ekambaram Harihara Subramanian and Seshaiah Krishnan Sridhar, Synthesis of Schiff Bases of 4-(4-aminophenyl)-morpholine as Potential Antimicrobial Agents, European J. Med. Chem., **40(2)**, 225-229 (2005).
3. A. Ahmadi, M. Khalili, R. Hajikhani and M. Naserbakht, New Morpholine Analogues of Phencyclidine: Chemical Synthesis and Pain Perception in Rats, Pharmacol. Biochem. Behav., **98(2)**, 227-233 (2011).
4. https://pubchem.ncbi.nlm.nih.gov/compound/phenmetrazine#section=Top.
5. A. Koda, K. Sakai, H. Nagai, Y. Suzuki and T. Kobayashi, Pharmacological Action of Salicylic Acid Morpholine, Folia Pharmacologica Japonica, **63(5)**, 409-414 (1967).
6. R. Gao, L. Li, C. Xie, X. Diao, D. Zhong and X. Chen, Metabolism and Pharmacokinetics of Morinidazole in Humans: Identification of Diastereoisomeric Morpholine N+ -Glucuronides Catalyzed by UDP Glucuronosyl Transferase 1A9: The Am. Soc. Pharmacol. Experimental Therapeutics, **40(3)**, DMD 40, 556-567 (2012).
7. B. Latli, M. Hrapchak, J. C. Lorenz, C. A. Busacca and C. Senanayake, Synthesis of a Potent Cathepsins Inhibitor Labeled with Deuterium and Carbon-14, Curr. Radiopharm., **5(4)**, 314-317 (2012).
8. H. Siemer and A. Doppstadt, Verfahrenzur Herstellung Von 2-Phenyl-3,6-dimethylmorpholine, DE Patent 1143201 (1967).
9. G. R. Brown, A. J. Foubister, G. Forster and D. Stribling, (S)-3-[(Benzyloxy)methyl]morpholine Hydrochloride: A Nonstimulant Appetite Suppressant without Conventional Neurotransmitter Releasing Properties, J. Med. Chem., **29**, 1288-1290 (1986).
10. J. J. Hale, S. G. Mills, M. MacCoss, C. P. Dorn, P. E. Finke, R. J. Budhu, R. A. Reamer, S.-E. W. Huskey, D. Luffer-Atlas, B. J. Dean, E. M. McGowan, W. P. Feeney, S.-H. L. Chiu, M. A. Cascieri, G. G. Chicchi, M. M. Kurtz, S. Sadowski, ElzbietaBer, F. D. Tattersall, N. M. J. Rupniak, A. R. Williams, W. Rycroft, R. Hargreaves, J. M. Metzger and D. E. MacIntyre, Phosphorylated Morpholine Acetal

Human Neurokinin-1 Receptor Antagonists as Water-Soluble Prodrugs, J. Med. Chem., **43**, 1234-1241 (2000).

11. Stefan Berg, Lars-Gunnar Larsson, Lucy Re´nyi, Svante B. Ross, Seth-OlofThorberg and Gun Thorell-Svantesson, (R)-(+)-2-[[[3-(Morpholinomethyl)-2H-chromen-8-yl]oxy]methyl]morpholine Methanesulfonate: A New Selective Rat 5-Hydroxytryptamine 1B Receptor Antagonist, J. Med. Chem., **41**, 1934-1942 (1998).

12. J. J. Hale, S. G. Mills, M. MacCoss, P. E. Finke, M. A. Cascieri, S. Sadowski, E. Ber, G. G. Chicchi, M. Kurtz, J. Metzger, G. Eiermann, N. N. Tsou, F. D. Tattersall, Nadia M. J. Rupniak, A. R. Williams, W. Rycroft, R. Hargreaves and D. E. MacIntyre, Structural Optimization Affording 2-(R)-(1-(R)-3,5-Bis(trifluoromethyl) phenylethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-oxo-1,2,4-triazol-5-yl)methylmorpholine, a Potent, Orally Active, Long-Acting Morpholine Acetal Human NK-1 Receptor Antagonist, J. Med. Chem., **41**, 4607-4614 (1998).

13. https://pubchem.ncbi.nlm.nih.gov/compound/Amorolfine.

14. V. A. Pal'chikov, Morpholines, Synthesis and Biological Activity, Russian J. Org. Chem., **49(6)**, 787-814 (2013).

15. A. Zask, J. Kaplan, J. C. Verheijen, D. J. Richard, K. Curran, N. Brooijmans, E. M. Bennett, L. Toral-Barza, I. Hollander, S. Ayral-Kaloustian and K. Yu, Morpholine Derivatives Greatly Enhance the Selectivity of Mammalian Target of Rapamycin (mTOR) Inhibitors, J. Med. Chem., **52**, 7942-7945 (2009).

16. http://www.who.int/gho/malaria/en

17. S. Kuettel, A. Zambon, M. Kaiser, R. Brun, L. Scapozza and R. Perozzo, Synthesis and Evaluation of Antiparasitic Activities of New 4-[5-(4-Phenoxyphenyl)-2H-pyrazol-3-yl] morpholine Derivatives, J. Med. Chem., **50**, 5833-5839 (2009).

18. D. V. Kravchenko, Y. A. Kuzovkova, V. M. Kysil, S. E. Tkachenko, S. Maliarchouk, I. M. Okun, K. V. Balakin and A. V. Ivachtchenko, Synthesis and Structure-Activity Relationship of 4-Substituted 2-(2-Acetyloxyethyl)-8-(morpholine-4-sulfonyl)pyrrolo [3,4-c]quinoline-1,3-diones as Potent Caspase-3 Inhibitors, J. Med. Chem., **48**, 3680-3683 (2005).

19. M. C. Chrysselis, E. A. Rekka, I. C. Siskou and P. N. Kourounakis, Nitric Oxide Releasing Morpholine Derivatives as Hypolipidemic and Antioxidant Agents, J. Med. Chem., **45**, 5406-5409 (2002).

20. M. Andrs, J. Korabecny, D. Jun, Z. Hodny, J. Bartek and K. Kuca, Phosphatidylinositol 3-Kinase (PI3K) and Phosphatidylinositol 3kKinase-Related Kinase (PIKK) Inhibitors: Importance of the Morpholine Ring, J. Med. Chem., **58**, 41-71 (2015).

Revised : 17.06.2016 *Accepted : 19.06.2016*