Piperazine and morpholine:
Synthetic preview and pharmaceutical applications

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ABSTRACT
This review summarizes the in vitro and in vivo medicinal chemistry investigations for piperazine and morpholine analogues. Piperazine and morpholine nucleus show a broad spectrum of pharmaceutical applications, thus, in recent years, scientists has developed various new methods for the synthesis of their derivatives. This review shows current tendency in the piperazine and morpholine analogues synthesis and reveals their potent pharmacophoric activities.

Keywords Piperazine, morpholine, synthesis, pharmaceutical applications

INTRODUCTION TO NITROGEN HETEROCYCLES
Nitrogen containing heterocycles have drawn considerable attention of the researchers in the past few decades owing to their high therapeutic values. Whether they are natural or synthetic one, owing to their interesting biological properties they are very often involved as key components in biological processes. Many nitrogen containing heterocycles especially, in plant kingdom have made indelible mark as phytochemical drugs such as quinine, ellipticine, theophylline, emetine, papaverine, procaine, codeine, and morphine. Besides the vast distribution of nitrogen containing heterocycles in natural products, they also play a major part in the biochemical processes in living cells and as most of the enzymes have aromatic heterocycles as major constituents while most of coenzymes incorporate non-amino acids moieties are aromatic nitrogen heterocycles and some important vitamins are constructed on aromatic heterocyclic scaffold. In addition, nitrogen heterocycles have been frequently found as a key structural unit in synthetic drugs such as diazepam, isoniazid, chlorpromazine, metronidazole, barbituric acid, captopril, chloroquine, azidothymidine and antipyrine.

Recently considerable attention has been paid to new methods for the synthesis of nitrogen containing heterocycles, which are as a rule pharmacophoric fragments or natural biologically active organic compounds. Generally the development of new trends in this region of chemistry can result both from the creation of new schemes for the formation of heterocycles and from the synthesis of unique and readily available starting compounds capable of certain paths of transformation into the desired nitrogen containing heterocycles. In recent years the research have focused upon many classes of compounds which possess biological properties. Vast numbers of six membered heterocycles containing nitrogen atoms have turned out to be potential chemotherapeutic and pharmacotherapeutic agents. Various useful synthetic analogues with improved therapeutic properties can be obtained from single lead compound by structural modification. Moreover nitrogen containing heterocycles such as piperazine (1) and morpholine (2) derivatives have been extensively investigated by organic chemist due to their close association with various types of biological activities and clinical applications in the therapy of functional diseases.
2. Introduction to piperazine and its derivatives

In the early 1900's piperazine was used about the turn of the century for the treatment of gout. Its first successful use in helminthiasis led to extensive use as a human and animal anthelminthic. For more than 50 years, the drug is used in the treatment of infections caused by *Ascaris lumricoides* and *Enterobius vermicularis* and certain of its compounds have been investigated for the treatment of cancer radiation sickness and angina pectoris.

Piperazine ring is widespread structural motifs in drug discovery, with a high number of positive hits encountered in biological applications. Piperazine template deserves the molecular backbone as it possesses versatile binding properties. Further, it behaves as potent and selective ligands for a range of different biological targets in medicinal chemistry and thus piperazine moiety is considered as privileged structure. In medicinal chemistry the main function of this privileged structure is to provide a way to build a library based on one core motif and screen it against an assortment of different receptors. The piperazine scaffold has been classified as a privileged structural element and is frequently found in biologically active compounds across a number of different therapeutic areas. A database from the journal and patent literature provides additional evidence for the idea of privileged structures of piperazines in many commercially available screening compounds and bioactive molecules containing a piperazine ring. Until now, piperazine isolated from natural products is unsubstituted at any of its carbon atoms. These piperazines are widely exploited in drug discovery because they allow the medicinal chemist to design molecules by retaining its basicity.

2.1. Synthesis methods of piperazine and its derivatives

The biological significance of piperazine derivatives has evoked substantial attention, intensive research has been conducted into general approaches for the synthesis of the piperazine core with increasing potential for applications in biological systems. A range of examples exists for the synthesis of substituted piperazine that includes formation of the ring system and its derivatives by various methods where most of them rely on cyclisation procedures. For instance, Piperazine ring has synthesized by heating of diethylene triamine with raney nickel under high temperature of about 150°C, with the liberation of ammonia (scheme 1).

[Scheme 1]

Aspinall developed the synthesis of 2-phenyl piperazine by reacting bromo-phenyl-acetic acid ethyl ester with ethylenediamine in order to obtain 3-phenyl-piperazin-2-one. The reduction of this compound with lithium aluminum hydride gave 2-phenylpiperazine (scheme 2).

[Scheme 2]
Synthesis of 2-phenylpiperazine was reported by Pollard et al.\textsuperscript{18} by starting with synthesis of 2-(2-aminoethylamino)-1-phenyl-ethanol from the reaction of 2-phenyl-oxirane and ethylenediamine in methanol under reflux temperature, followed by reduction of 2-(2-withraney nickel (Scheme 3).

\[
\begin{align*}
\text{C}_6\text{H}_5\text{O} & \quad + \quad \text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2 \\
\text{reflux} & \quad \rightarrow & \quad \text{H}_2\text{N} & \quad \text{HO} & \quad \text{HN} \\
\text{MeOH} & \quad \text{Raney Ni} & \quad \text{dioxane} & \rightarrow & \quad \text{HN} & \quad \text{NH} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5
\end{align*}
\]

Scheme 3

Nenajdenko et al.\textsuperscript{19} have described a novel effective approach to chiral substituted pyrroloketopiperazines via a three-component Ugi reaction with chiral 2-(2-formyl-1\textit{H}-pyrrol-1-yl)acetic acids, isocyanides and primary amines (Scheme 4).

\[
\begin{align*}
\text{H}_3\text{C} & \text{C} & \text{O} \\
\text{O} & \quad \text{BnNH}_2, \text{RNC} & \quad \text{MeOH, 40}{}^\circ\text{C} \\
\text{MeOH, 40}{}^\circ\text{C} & \rightarrow & \text{R} & \quad \text{Bn} & \quad \text{O} & \quad \text{N} \\
\text{R=} & \quad \text{Bn, t-Bu} & \quad \text{CH}_3 & \quad \text{R} & \quad \text{N} & \quad \text{O}
\end{align*}
\]

Scheme 4

A palladium catalyzed carboamination reaction has been applied to achieve piperazines in high yield.\textsuperscript{20} The diastereoselective carboamination reaction of \textit{N}{\textsuperscript{1}}-allyl-\textit{N}{\textsuperscript{2}}-aryl-\textit{N}{\textsuperscript{3}}-vinyl-propane-1,3-diamine in the presence of palladium catalysts and aryl bromide yielded \textit{cis}-piperazine (Scheme 5).

\[
\begin{align*}
\text{Ph} & \quad \text{HN} & \quad \text{Me} \\
\text{Ar} & \quad \text{cat. Pd}_{(2\text{dba})_3} & \quad \text{cat. P(2-fur)_3} \\
\text{NaOt-Bu, Toluene} & \rightarrow & \text{Ar} & \quad \text{Ph} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

Scheme 5

Patino-Molina et al.\textsuperscript{21} developed an intramolecular reductive amination of 4-(2-benzoxycarbonylamino-propionylamino)-3-oxo-butyric acid methyl ester to prepare (6-methyl-5-oxo-piperazin-2-ylidene)-acetic acid methyl ester. The desired piperazinones were obtained in good yields using Palladium catalyst (Scheme 6).

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{O} & \quad \text{OMe} & \quad \text{H}_2\text{Pd} & \quad \text{MeOH} \\
\text{OBn} & \quad \text{Me} & \quad \text{N} & \quad \text{O} & \quad \text{Me} \\
\text{O} & \quad \text{N} & \quad \text{CO}_2\text{Me} & \quad \text{HN} & \quad \text{Me}
\end{align*}
\]

Scheme 6

Preparation of diketopiperazine derivatives was reported by the condensation of 2-chloroacetyl chloride and the appropriate amine, followed by cyclization between two molecules of chloroacetoamide in the presence of strong base. (Scheme 7).\textsuperscript{22}
Napolitano et al., have readily synthesized substituted piperazine as shown in scheme 8. The double alkylation of the $N,N'$-dibenzylethlyendiamine with 3,4-dibromobutyronitrile in base media afforded (1,4-dibenzyl-piperazin-2-yl)-acetonitrile.

Nordstrom et al., developed a green and economical method for synthesis of piperazine by cyclocondensation of 1-phenyl-ethane-1,2-diol and ethylenediamine in aqueous media in the presence of a catalytic amount of $[\text{CpIrCl}_2]^2$ (scheme 9).

Another efficient strategy for synthesis of piperazine analogues by diastereoselective hydrogenation of a chiral pyrazine derivative with Palladium catalyst has been reported (scheme 10).

Moreover, Huang et al., have reported synthesis of tosylpiperazine derivatives under mild conditions in good yields from the reaction of substituted alkyl-toluensulfonate with a primary amine in basic condition (scheme 11).

Recently, Ma et al., have synthesized a novel piperazine containing 2-chloropyrimidine moiety via an efficient nucleophilic substitution reaction between the 2,4-dichloropyrimidine and $N$-methYlpiperazine under nitrogen flow (scheme 12).
Rotta et al. have synthesized 1-(9H-fluoren-9-yl)-piperazine bearing benzoyl moiety, by condensing 1-(9H-fluoren-9-yl)-piperazine with benzoic acid in the presence of O-benzotriazole-N,N,N,N-tetramethyluronium-hexafluoro-phosphate (HBTU) catalyst and triethylamine through SN$_2$ nucleophilic substitution reaction (scheme 13).

Nevertheless, 2-{3-[4-(3-Chloro-phenyl)-piperazin-1-yl]-propyl}-1,5-dihydro-2H-[1,2,4]triazolo [4,3-a]pyridin-3-one (Trazodone) was synthesized by alkylation of 3-chlorophenyl-N-piperazine with 1,3-dibromopropane using sodium hydride to afford 1-(3-bromo-propyl)-4-(3-chloro-phenyl)-piperazine which was reacted with 2H-[1,2,4]triazolo[4,3-a]pyridin-3-one to gave trazodone in good yield (scheme 14).

2.2. Pharmaceutical application of piperazine derivatives

The piperazine template contains some building features and pharmacological points that provides potent and selective ligands for a range of different biological targets in medicinal chemistry. Piperazine analogues have been a great interest of biological activities that can be found across number of different therapeutic areas. These include anticancer, antifungal, antibacterial, antimalarial and antipsychotic agents, as well as HIV protease inhibitors and antidepressants. A numerous useful compounds contain the piperazine derivatives in drug molecules, specifically those with substitution on the nitrogen atoms. Some examples include the antihistamine drug like, cyclizine (3) which is used as an antiemetic and also exhibits strong anticholinergic effect. Amoxapine (4) is an antidepressant drug used to treat depression, as well as anxiety or agitation associated with depression. Trimetazidine (5) is an antischismic agent free of hemodynamic effects, it reduces intracellular acidosis and electrolyte abnormalities, Bifeprunox (6) is an antipsychotic drug and preclinical studies have been shown to be a D$_2$/D$_3$ receptor and 5-HT$_{1A}$ agonist and Ropizine (7) is an anticonvulsant drug utilizing a modified maximal electroshock seizure test in rats. The piperazine moiety is also presented in antihypertensive agents, Prazosin (8) it is a selective $\alpha$-adrenergic receptor antagonist used to treat hypertension and benign prostatic hyperplasia, Flunarizine (9) is a calcium channel blockers which effective in the prophylaxis of migraine, occlusive peripheral vascular disease, Oxatomide (10) is an H1 antihistaminic drug that also inhibits mediator release from mast cells, Ranolazine (11) is a new antianginal agent approved for the treatment of chronic stable angina pectoris for use as combination therapy when angina is not
adequately controlled with other antianginal agents, Indinavir (12) is a potent and selective human immunodeficiency virus type 1 (HIV-1) protease inhibitor widely used in antiretroviral therapy for suppression of HIV and antibiotic ciprofloxacin (13) is useful for the treatment of a number of bacterial infections (figure 1).

Here, only a few of the many examples have been mentioned in which the piperazine core has been used as a scaffold to generate biologically active molecules. Thus, it appears that the piperazine core acts as a privileged structural element for the construction of bioactive molecules. The literature survey revealed that the remarkable array of piperazines as biochemical and pharmacological actions, suggest that certain members of this group of compounds may significantly affect the function of various mammalian cellular systems. The piperazines are extremely variable in structure, due to the various types of substitutions in their basic structure, which can influence their biological activity. The pharmacological properties as well as therapeutic applications of piperazine depend upon the pattern of substitution on the piperazine ring and this was recently reported by many researchers and some of the investigated piperazine has been discussed here.
For instance, Kumar et al.\textsuperscript{15} have designed a series of novel 1-benzhydryl-sulfonyl-piperazine derivatives by a nucleophilic substitution reaction of 1-benzhydryl-piperazine with various benzoyl chlorides. These compounds were evaluated for their efficacy in inhibiting breast cancer cell proliferation. Among them, compound 1-benzhydryl-4-(4-tert-butyl-benzenesulfonyl)-piperazine (14) showed significant inhibitory activity.

Beside, new purine ribonucleoside analogues containing a 4-substituted piperazine have been synthesized and evaluated for their cytotoxicity on mahlavu liver (Huh7, HepG2, FOCUS), breast (MCF7), and colon carcinoma (HCT116) cell lines.\textsuperscript{31} The purine nucleoside analogues were analyzed initially by an anticancer drug-screening method based on a sulforhodamine B assay. Among the synthesized compounds, two nucleoside derivatives (15 and 16) showed promising cytotoxic activities, further they analyzed these on the hepatoma cells. Interestingly, compound 15 displayed the best antitumor activity, as well as interfere with cellular ATP reserves, possibly through influencing cellular kinase activities. Furthermore, compound (15) has shown to induce senescence-associated cell death, as demonstrated by the SAB\textbeta-gal assay. The senescence-dependent cytotoxic effect of (15) was also confirmed through phosphorylation.

Solomon et al.\textsuperscript{32} have designed novel piperazine derivatives based on the isatin scaffold and examined for their cytotoxic effects on two human breast tumor cell lines, MDA-MB468 and MCF7 and two non-cancer breast epithelial cell lines, 184B5 and on MCF10A. Compounds (17 and 18) caused apoptosis to MCF7 cancer cells, but not for MCF10A non-cancer cells.
Laszkielewicz et al. have designed a new series of xanthone derivatives with piperazine moiety and evaluated them for their biological activity. Among the derivatives, Compound (19) exhibited significantly higher affinity for serotoninergic 5-HT1A receptors than other substances. In terms of anticonvulsant activity, compound (20) has proved showing the best properties. As per the result combining xanthone with piperazine moiety increased the bioavailability on oral administration.

\[ \text{(19), } R = \text{Ph} \]
\[ \text{(20), } R = \text{CH}_3 \]

Novel piperazine derivatives were designed, synthesized, and evaluated for their cellular target-effector fusion activities and in vitro antiviral activities against HIV-1. Among the analogues, compound (21) was found to be a CCR5 antagonist with an IC$_{50}$ value of 6.29 mM and an anti-HIV-1 inhibitor with an IC$_{50}$ value of 0.44 mM.

\[ \text{(21)} \]

Karolina et al. have synthesized piperazine-xanthen-9-one dihydrochloride derivatives and investigated their antidepressant property by forced swim test in mice. Among the investigated series, compound (22) reduced immobility time in mice in forced swim test (FST) at the doses 5 and 10 mg/kg, whereas fluoxetine at 15 mg/kg, reboxetine at 10 mg/kg and bupropion at 5 mg/kg. also compound (22) demonstrated a potent antidepressant activity in FST than that of fluoxetine and reboxetine, and seems to mediate its effect through serotonergic system.

\[ \text{(22)} \]

A series of piperazine derivatives have synthesized by Baliet al. and evaluated for a typical antipsychotic activity in apomorphine induced mesh climbing and stereotypy assays in mice. The compounds (23 and 24) showed potential a typical antipsychotic profile. The physicochemical similarity of these analogues with respect to the standard drugs clozapine, ketanserin, ziprasidone and risperidone was assessed by calculating from a set of 10 physicochemical properties using software programs. The test compounds demonstrated good similarity values with respect to the standard drugs. The potential of these compounds to penetrate into the blood brain barrier was computed through an online software program and the values obtained for the compounds suggested good brain permeation.

\[ \text{(23), } R = 4-\text{Cl} \]
\[ \text{(24), } R = 2-\text{Cl} \]
Further, Bucle et al.\textsuperscript{37} have designed and synthesized novel \(N\)-benzylpiperazino derivatives and evaluated for their antihistamine activity on guinea pig ileum. Among the synthesized compounds, compound (25), showed the most potent activity against histamine on guinea pig ileum, comparable to the mepyramine standard.

\[
\text{Cl} \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 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cytokines (TNF-a and IL-6) and antibacterial and antifungal activities. Among all the screened compounds, compound (32) found to be highly promising anti-inflammatory agent at concentration of 10 µM while compound (33) found to be potent antimicrobial agent showing even 2 to 2.5-fold more potency than that of standard.

Nevertheless, a series of azole-containing piperazine derivatives have been synthesized and investigated in vitro for their antibacterial, antifungal and cytotoxic activities. The preliminary results showed that most compounds exhibited moderate to significant antibacterial and antifungal activities in vitro. Compounds (34 and 35) gave remarkable and broad-spectrum antimicrobial efficacy against all tested strains with MIC values ranging from 3.1 to 25 µg/mL, and exhibited comparable activities to the standard drugs chloramphenicol and fluconazole in clinic. Moreover, compound (36) was found to be the most effective in vitro against the PC-3 cell line.

Yu et al. have synthesized 1-ethyl-6-fluoro-7-[4-(furan-2-carbonyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (Norfloxacin) (37) derivatives and evaluated for their antimicrobial activity against five plant pathogenic bacteria and three fungi in vitro. The activities of compounds against Xanthomonas oryzae were better than norfloxacin and some tested compounds were better in antibacterial activities as compared to the agricultural streptomycin sulfate against X. oryzae, Xanthomonas axonopodis and Erwiniaaroideae. Among the series, compound (37) displayed good antifungal activities against Rhizoctonia solani having 83% inhibition of fungal growth.

3. Introduction to morpholine and its derivatives
Morpholine is a heterocyclic organic compound (2) which is an important class of building block in organic synthesis and several derivatives of morpholine have received attention due to their remarkable and wide variety of applications. Morpholine is preferred as synthetic intermediate which often has been selected as a starting material for the preparation of enantiomerically pure α-amino acids, β-amino alcohols, and peptides.

High popularity of the morpholine moiety is caused by several factors. First, the oxygen atom in the morpholine core can participate in the donor-acceptor type interactions with the corresponding receptor, increasing binding affinity. Second, the electronegative effect of the oxygen atom reduces the basicity of the nitrogen atom.

Morpholine derivatives are an important core structures innumerable natural products. Various morpholine derivatives were extracted from natural sources and structures of these morpholine derivatives were elucidated by spectral analysis. For example, alkaloid polygonapholine (38) was isolated from the methanol extract of the rhizome of Polygonatum altelobatum being used as a tonic drug by Taiwanese, the alkaloids chelonin (39) and Chelonin (40)
were the first natural products incorporated 2,6-disubstituted morpholine fragment isolated from the marine sponge *Chelonaplysilla* sp. from a lake in Palau, chelonin exhibited antimicrobial activity against *Bacillus subtilis* and also anti-inflammatory effect, the two new spiro alkaloids showing antioxidant properties, acortatarins (41 and 42) were isolated from the rhizome of *Acorus tatarinowii*, it was presumed that alkaloids (41 and 42) are valuable starting compounds for the design of new antidiabetic and anticancer drugs.

![Some natural morpholine analogues](image.png)

**Figure 2.** Some natural morpholine analogues

### 3.1. Synthetic methods of morpholine and its derivatives

Morpholines are extensively used in organic synthesis, and their application is most frequently as a simple bases, *N*-alkylating agents, catalysts and chiral auxiliaries in various organic transformations. Several efforts have been devoted towards the synthesis of morpholines from amino acids, amino alcohols, epoxides, olefins, carbohydrates, vinyl sulfonium salts, and various metal catalyzed cyclizations, aziridines or aziridinium ion intermediate. Several reported methods for the synthetic efforts towards morpholine are explained as fellow.

In 1956 the first synthesis of an enantiomerically pure morpholine from amino alcohols has been reported. In 1956 the first synthesis of an enantiomerically pure morpholine from amino alcohols has been reported. 45 2-methylamino-1-phenyl-propan-1-ol (L-Ephedrin) was reacted with chloroethanol to give 3,4-dimethyl-2-phenyl-morpholine (scheme 15).

![Scheme 15](image.png)

**Scheme 15**

Leathen et al, 46 have synthesized *cis*-2,3-disubstituted morpholine via palladium-catalyzed cyclization of [2-(1-methyl-allyloxy)-ethyl]-phenyl-amine and 3-bromo-benzonitrile. Interestingly, the morpholine product is generated as single stereoisomers in good yield (scheme 16).

![Scheme 16](image.png)

**Scheme 16**
Also, epoxide was used as a starting material to form the morpholine ring. In this example, (R)-2-benzyl-morpholine was achieved by reacting epoxide with ethanolamine sulfonate. Ethanolamine sulfonate was used for the ring opening of epoxide under basic condition, followed by ring closure of sulfate ester upon treatment with base resulted (R)-2-benzylmorpholine in good yield (scheme 17).

\[
\begin{align*}
\text{Ph} & \quad \text{HN} & \quad \text{Ph} \\
\text{O} & \quad \text{Br} & \quad \text{NC}
\end{align*}
\]
\[
\begin{align*}
P(2\text{-furyl})_3 & \quad \text{Pd(OAC)}_2 \\
\text{NaOtBu}, \text{toluene}, & \quad 105^\circ C
\end{align*}
\]

Scheme 16

The synthesis of the substituted morpholin-3-ones was achieved by the reaction of L-phenylalanine methyl ester hydrochloride with chloroacetyl chloride to give (2-chloro-acetylamino)-benzyl-acetic acid methyl ester. Which on reduction with \( \text{NaBH}_4 \) afforded 2-chloro-N-(2-hydroxy-1-phenyl-ethyl)-acetamide, finally reduced product on treatment with potassium tert-butoxide in isopropyl alcohol provided the 5-arylmorpholin-3-one in excellent yield(scheme 18).

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{NH}_2 \\
\text{Ph} & \quad \text{H}_2 & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} & \quad \text{K}_2\text{CO}_3, 0^\circ C \\
\text{CH}_2\text{Cl}_2, \text{H}_2\text{O} & \quad \text{MeOH, CH}_2\text{Cl}_2 & \quad \text{NaBH}_4, 0^\circ C
\end{align*}
\]

Scheme 17

An efficient procedure for synthesis of substituted morpholine was reported by Matsuoka et al, starting with 2-(5-hydroxymethyl-imidazol-1-yl)-2-phenyl-ethanol and oxalyl chloride then, the resulting compounds transformed into chloro derivative and the subsequent cyclization by the action of sodium hydride afforded 5-phenyl-5,6-dihydro-8H-imidazo[5,1-c][1,4]oxazine (scheme 19).

\[
\begin{align*}
\text{Cl} & \quad \text{H} & \quad \text{Cl} \\
\text{OH} & \quad \text{Cl} & \quad \text{Ar} \\
\text{N} & \quad \text{N} & \quad \text{H}
\end{align*}
\]

Scheme 18

Berree et al, have successfully synthesized morpholine derivatives by applying three-component Petasis coupling reaction, methyl-protected amino alcohol reacted with ethanedial and then with phenyl boronic acid to produce 2-hydroxymorpholines(scheme 20).

\[
\begin{align*}
\text{Ph} & \quad \text{HO} & \quad \text{N} \\
\text{O} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]
\[
\begin{align*}
\text{DMF} & \quad \text{MeCN}, 0\text{-}20^\circ C \\
\text{MeCN}, 0\text{-}20^\circ C & \quad \text{NaH/ DMF}
\end{align*}
\]

Scheme 19
Synthesis of morpholin-2,6-dione was reported by Hadley et al.\textsuperscript{51} by heating the carboxymethoxy-acetic acid in the presence of but-3-enylamine (scheme 21).

Lippur et al.\textsuperscript{52} have investigated the nucleophilic substitution reaction of 6-fluoro-7-chloroquinolone carboxylic acid with morpholine using a large excess of amine in MW to yield 6-fluoro-7-fluoroquinolones-morpholines (scheme 22).

A novel series of Schiff bases of 4-(4-aminophenyl)-morpholine was synthesized by multistep reaction sequence, begun, reaction of morpholine with chloro-nitrobenzene, the reduction of 4-(2-nitro-phenyl)-morpholine produced 4-(2-aminophenyl)-morpholine which was refluxed with the benzaldehyde in absolute alcohol containing 2–3 drops of glacial acetic acid to give the benzylidene-(4-morpholin-2-yl-phenyl)-amine (scheme 23)\textsuperscript{53}

Khanum et al.\textsuperscript{54} synthesized of benzophenone-N-ethyl morpholine ether by condensation of substituted hydroxyl benzophenones with 4-(2-chloroethyl) morpholine hydrochloride in presence of anhydrous potassium carbonate and dimethyl sulphoxide (scheme 24).
1-(4-Hydroxy-3-morpholin-4-yl-methyl-phenyl)-3-aryl-propenone was synthesized by condensing of manich base (1-(4-hydroxy-3-morpholin-4-yl-phenyl)-ethanone with aromatic aldehyde.\textsuperscript{55} The manich base prepared from refluxing of hydroxy acetophenone with morpholine and formaldehyde (scheme 25).

\begin{align*}
\text{HO-} & \text{CH}_3 + \text{H} + \text{CH}_2\text{O} \quad 120^\circ\text{C} \\
& \text{reflux} \quad \text{base} \\
\text{Ar-CHO} & \quad \text{HO-} \text{O} \text{N} \text{H} \text{CH}_2 \text{O} + + \quad \text{O} \text{N} \text{O} \\
\text{Ar} & \quad \text{O} \text{N} \text{O} \text{ArSO} \text{2Cl} 110-120^\circ\text{C} \text{DCM} \text{metallic sodium}
\end{align*}

\text{Scheme 25}

Synthesis of 2-aryl-sulfonyl-5-benzyl-4-(2-morpholin-4-yl-ethyl)-2,4-dihydro-pyrazol-3-ones were achieved by cyclocondensation of 3-ethoxy-4-phenyl-but-2-enoic acid ethyl ester with N-morpholinoethanamine. Further, condensation of 5-benzyl-4-(2-morpholin-4-yl-ethyl)-2,4-dihydro-pyrazol-3-one with several aryl sulfonyl chloride in ethanol in the presence of metallic sodium generated the 5-benzyl-4-(2-morpholin-4-yl-ethyl)-2-(aryl-sulfonyl)-2,4-dihydro-pyrazol-3-one (scheme 26).\textsuperscript{56}

\begin{align*}
\text{Bn-} & \text{OEt} + \text{N} \text{NH} \text{NH}_2 \quad 110-120^\circ\text{C} \\
& \text{OEt} + \text{ArSOCl} \text{DCM} \text{metallic sodium} \\
\text{N} \text{N} & \text{O} \text{O} \text{Bn} \text{S} \text{Ar}
\end{align*}

\text{Scheme 26}

Zheng et al, were synthesized morpholine-4-carboxylic acid phenyl amide from the key intermediates 4-morpholinecarbonyl chloride which on treatment with appropriate arylamine in the presence of triethylamine as a basic catalyst in anhydrous DCM under reflux (scheme 27).\textsuperscript{57}

\begin{align*}
\text{O} \text{N} \text{O} & \quad \text{POCl}_3 \quad \text{MeCN} \\
& \quad \text{Arylamine, TEA} \quad \text{DCM} \\
\text{O} \text{N} \text{O} & \quad \text{HN-}
\end{align*}

\text{Scheme 27}

\textbf{3.2. Pharmaceutical application of morpholine derivatives}

Morpholines are significant class of heterocyclic compounds found great interest in recent years due to their variety of biological activities including anti-inflammatory, analgesic, local anesthetic, HIV-protease inhibitors, anticancer, appetite suppressant, antidepressant, antiplatelet, selective inhibitor of protein kinase C, neuroprotective, antitumor, antituberculosis, antimalarial, antiparasitic, hypocholesterolemic and hypolipidemic activities.

These classes of compounds have been utilized widely by the pharmaceutical industry in drug design, because of the improvement in pharmacokinetic properties that it can confer. The biological utility of molecules containing the morpholine moiety is wide-ranging, particularly, nitrogen-substituted morpholines are drug candidates with a wide spectrum of biological activities. The antibiotic Linezolid (43) contains a morpholine cycle is commercially available antimicrobial agent. Aprepitant (44) is a substance which is neurokinin 1 (NK1) receptor antagonist and it is the first drug approved by Food and Drug Administration for the treatment of chemotherapy-induced nausea and vomiting. Other molecule such as (45) has displayed an anti-schizophrenic activity via interaction with the N-methyl-D-aspartate receptor in the brain. Gefitinib (46) is a selective inhibitor of epidermal growth factor and
clinically used for the treatment of chemoresistant non-small cell lung cancer patients. On the other hand, timolol (47) is non-selective beta-adrenergic receptor antagonist indicated for treating of glaucoma. Finafloxacin (48) is a new drug used to treat acute otitis externa, commonly known as swimmer’s ear, and moclobemide (49) is a drug used in depression and phobic states. Furthermore, Emorfazone (50) is an effective analgesic, anti-inflammatory and anti pyretic drug in animal models, as well as in humans and reboxetine mesylate (51) is an active antidepressant drug, and is marketed under the trade names Edronax, Norebox, Prolift, Vestra, and Integrex in Europe and Latin America, phendimetrazine (52) is an effective and widely prescribed appetite suppressant. Preclinical findings show that it displays stimulant properties similar to amphetamine. Further, fenpropimorph (53) is a fungicide whose major use is to control diseases in cereals.

Figure 3. Drugs containing morpholine moiety
Based on the importance of morpholine as synthetic intermediates and its good potential as medicinally active molecules, researchers have attracted much interest in the development of morpholine derivatives over the years. For example, isoflav-3-enes (54) are an important class of chromene intermediates that are useful in the synthesis of many natural products and medicinal agents such as potassium channel activating drugs. Morpholine basic structural framework is a common feature of many tannins and polyphenols found in fruits, vegetables, teas, and red wines, which have gained popularity because of their health-promoting effects.

Chrysselis et al. have reported the evaluation of antioxidant and hypocholesterolemic activities for a number of 2-biphenyl morpholine derivatives. The novel derivatives are found to inhibit the ferrous/ascorbate induced lipid peroxidation of microsomal membrane lipids. The most potent 2-(4-biphenyl)-4-methyl-octahydro-1,4-benzoxazin-2-ol (55) decreases total cholesterol, low density lipoprotein, triglycerides in plasma of triton WR-1339 induced hyperlipidemic rats by 54%, 51%, and 49%, respectively, at 28 \( \mu \text{mol} / \text{kg} \) which demonstrate hypocholesterolemic and hypolipidemic action. The results indicate that the new molecule may be proven useful as it leads for the design of novel compounds as potentially antiatherogenic factors.

Compound 2-morpholin-4-yl-8-phenyl-chroman-4-one (56) well-known as the first synthetic ATP competitive phosphatidylinositol 3-kinase (PI3K) inhibitor, synthesized by Lilly in the early 1990’s. The morpholine ring of quercetin in (56), extending from the C-2 position of the core was found to be critical for activity but when substituted with non-hydrogen bond acceptors ablated activity. Introduction of an aromatic ring into the C-8 position was found to improve potency 5-fold over the hydrogen substituent.

A novel 6-isopropyl-3-methyl-morpholine-2,5-dione analogues have been studied for its potential effect on rat thymocytes and have been evaluated for proliferative activity, viability, reactive oxygen species and mitochondrial membrane potential. Compound (57) at 10 \( \mu \text{g/well} \) concentration inhibited thymocytes proliferative activity mainly through induction of oxidative stress and resulting cytotoxicity, without any mitochondrial membrane potential alterations in thymocytes. The presence of methyl group in position 4 or/and the length of alkyl chain in position 3 of 6-isopropyl-3-methyl-morpholine-2,5-dione core playing a role for the obtained differences in the biological activity.
Dhahagani et al. thought it was worthwhile to pursue synthesis of metal complex of Schiff base-morpholine in order to develop more potent derivatives. The ligands and their metal complexes screened for their biopotency anticancer activity in human heptocarcinoma cells. The preliminary bioassay indicates that compound (58) exhibit inhibitory activity against the human gastric cancer cell lines.

The efficient synthesis of novel pyrimidine derivatives possessing morpholine ring were reported by Liu et al., these compounds were evaluated for their anticancer activity. Most compounds displayed good to excellent potency against four tested cancer cell lines as compared with pictilisiband sorafenib. A promising compound (59) showed the most potent antitumor activities with IC_{50} values of 0.057 mM, 0.039 mM, 0.25 mM, and 0.23 mM against human lung cancer (H460), colon cancer (HT-29), gastric cancer (MKN-45) and breast cancer (MDA-MB-231) cell lines, respectively.

Recently, Zhuet al. synthesized thiopyrano[4,3-d] pyrimidine- morpholine derivatives and evaluated for the inhibitory activity against mammalian target of rapamycin kinase (mTOR) at 10 µM level and some of them against phosphoinositide 3-kinase alpha at 10 µM level and two cancer cell lines. Among the compounds, compound (60) showed strong antitumor activities against mTOR kinase, human large cell lung cancer and prostate cancer cell lines which were 1.28 to 1.71-fold more active than BMCL-200908069-1.

A novel optically active morpholine analogues possess spiro-piperidine moity were synthesized with regards to tachykinin receptor binding affinity. The substituents at 2-position of the morpholine ring were employed to introduce the required stereochemistry. In addition, all stereoisomers were prepared to fully explore the stereochemical preferences of compounds (61 and 62). Compared to all stereoisomers, (S,R)-61 and (S,R)-62 showed the higher binding affinities to tachykinin receptors. These compounds exhibited excellent high binding affinities for tachykinin receptor.
Synthesis and antiepileptic activity using maximal electroshock (MES) and subcutaneous pentylenetetrazol (scPTZ) seizures tests of novel isatin-morpholine derivatives were investigated by Saravanan et al. Among the derivatives, compound (63) has revealed protection ability in MES at a dose of 30 mg/kg. This molecule also provided protection in the scPTZ at a dose of 100 mg/kg and 300 mg/kg.

Li et al. have synthesized a series of scutellarein derivatives containing (morpholine, piperazine, alkylamine) and tested for their thrombin inhibition activity through the analyzation of prothrombin time, activated partial thromboplastin time, thrombin time and fibrinogen, the antioxidant activity of synthesized compounds were assessed by DPPH assay. The results showed that morpholine derivative (64) demonstrated stronger anticoagulant activity and good antioxidant activity compared with scutellarein (65).

A series of 3-butylquinazolinedione linked with morpholine and others substituent to N1 of quinazoline have been synthesized and tested in vitro for their inhibitory activity against phosphodiesterase 4B, which is the enzyme responsible for the hydrolysis of cyclic adenosine mono phosphate, the second messenger involved in the regulation of important cell functions. Compound (66) showed 100% inhibition better than rolipram 90% inhibition, while the other tested compounds showed moderate activity. Also, docking study has been done to rationalize the obtained biological results.

\[
\text{(61), } X=\text{SO} \\
\text{(62), } X=\text{CHOH}
\]

\[
\text{(63)}
\]

\[
\text{(64)}
\]

\[
\text{(65)}
\]

\[
\text{(66)}
\]
A novel series of pyrimidine conjugated with morpholine, piperidine and pyridine were synthesized by conventional and MW method. All the compounds screened at a dose of 20 mg/kg body weight by \textit{in vivo} analgesic activity. Among all the synthesized compounds, compounds (67 and 68) showed significant analgesic activity and compounds (68 and 69) showed highly significant activity against the standard drug diclofenac sodium using acetic acid-induced writhing model. Compounds (68 and 69) also were found to be most promising analgesic agent devoid of ulcerogenic effects.

\begin{align*}
(67), & \ R_1=\text{Cl}, \ R_2=\text{H} \\
(68), & \ R_2=\text{Cl}, \ R_1=\text{H} \\
(69), & \ R_1, R_2=\text{Cl}
\end{align*}

Khanum et al. have described \textit{in vivo} anti-inflammatory activity\textsuperscript{54} of benzophenone-N-ethyl morpholine ethers and \textit{in vitro} antibacterial and antifungal activities.\textsuperscript{78} The anti-inflammatory activity of the synthesized compounds were determined by carrageenan-induced hind paw oedema test in rats. The antibacterial activity were tested against \textit{S. aureus}, \textit{E. aerogenes}, \textit{M. luteus}, \textit{K. pneumonia}, and \textit{S. typhimurium}, \textit{P. vulgaris} bacterial strains and antifungal activity against \textit{C. albicans}, \textit{B. cinerea}, \textit{M. pachydermatis}, and \textit{C. krusei} fungal strains. The bioassays indicated that most of the synthesized compounds exhibited anti-inflammatory agent, compound (70) was found to be the most potent anti-inflammatory activity while antibacterial and antifungal activities showed that compound (71) exhibited more activity than standard drugs.

\begin{align*}
(70), & \ R_1=\text{Br}; \ R_2, R_3=\text{H} \\
(71), & \ R_1, R_3=\text{H}, \ R_2=\text{Cl}
\end{align*}

A series of \textit{N}-morpholinoacetyl-2,6-diarylpiperidin-4-ones have been synthesized and were evaluated for their \textit{in vitro} antibacterial activity against \textit{Staphylococcus aureus}, \textit{Escherichia coli}, \textit{Pseudomonas aeruginosa} and \textit{Salmonella typhi} and antifungal activity against \textit{Candida albicans}, \textit{Rhizopus sp.}, \textit{Aspergillus niger} and \textit{Aspergillus flavus}. Structural activity relationship resulted for these compounds have shown that compounds (72 and 73) exerted excellent antibacterial activity against most of the strains. Compound (74) recorded excellent antifungal activity against \textit{rhizopus sp}, the obtained results may be used as key step for the building of novel chemical compounds with interesting antimicrobial profiles comparable to that of the standard drugs.

\begin{align*}
(72), & \ R_1, R_2=\text{OCH}_3 \\
(73), & \ R_1, R_2=\text{CH}_3 \\
(74), & \ R_1, R_2=\text{Cl}
\end{align*}
REFERENCES
