

# Synthesis and SAR of morpholine and its derivatives: A review update

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**Abstract.** Morpholine is a stretchy moiety, a special pharmacophore and an amazing heterocyclic compound with wide scopes of pharmacological exercises because of various pharmacological of activity. The capacity of morpholine to upgrade the power of the particle through sub-atomic collaborations with the objective protein (kinases) or to modify the pharmacokinetic properties impelled restorative scientific experts and specialists to orchestrate morpholine ring by the proficient ways and to fuse this moiety to create different lead compound with assorted therapeutic activity. Morpholine is an organic substance compound having a six-membered ring containing two heteroatom nitrogen(N) and oxygen(O), considered as the significant core in restorative and medicinal chemistry. The current study essentially centered around talking about the most encouraging synthesis leads containing compound morpholine ring alongside structure-activity relationship (SAR) to uncover the dynamic pharmacophores responsible for anticancer, mitigating, antiviral, anticonvulsant, antihyperlipidemic, cell reinforcement, antimicrobial and antileishmanial action. This audit will give the essential information base to the medicinal chemistry in rolling out vital basic improvements in structuring morpholine subsidiaries.

**Keywords:** Heterocyclic Compounds, Morpholine, SAR, Synthesis

## 1 Introduction

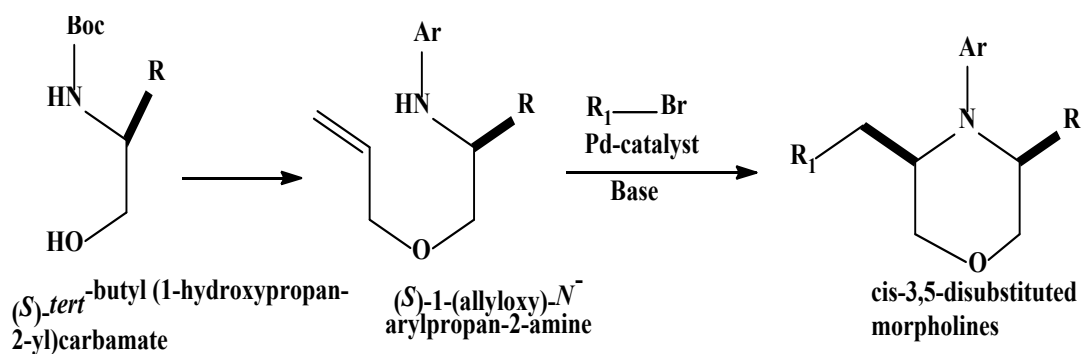
Morpholine is a single of the number of nitrogen (N) and oxygen (O)atoms holding heterocycle that's broadly utilized in a numerous medical too modern industrial preparation[1]. Heterocycles containing nitrogen have increased a lot of significance because of their changed remedial worth. A six-member nitrogen

holding heterocyclic compounds are chemotherapeutic and pharmacotherapy activity[2]. It is utilized in the arrangement of enantiomer unadulterated  $\alpha$ -amino acid,  $\beta$ -amino alcohol and peptide as a beginning substantial. Morpholine is an amine heterocyclic compound that is utilized in a production of solvent and diluent (for example in wax and cleans), elastic added substances, bactericides, colors, erosion inhibitors, crop insurance operators, emulsifiers, enemies of oxidants, impetuses, photosensitive brightener, medical items and is too utilized in industry[3]. The morpholine is a theme pulled in critical consideration because of it's across the board accessibility in regular items and biologically important compounds. This audit portrays ongoing developments in union of morpholine and their carbonyl containing compound equivalents from 1,2-amino alcohol, aziridine, epoxide, and associated compound. Uncommon consideration is rewarded to the combinations acted in a stereoselectivity way and utilizing change metallic catalysis[4].

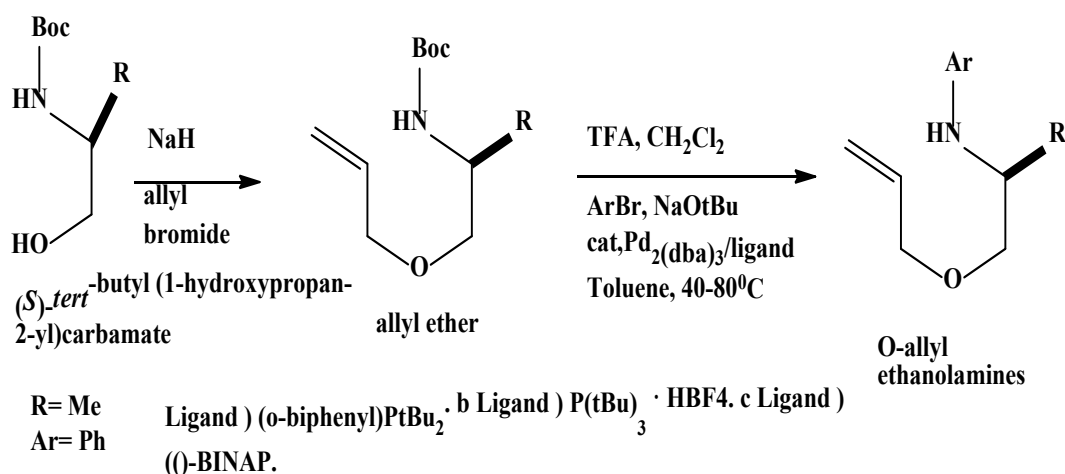
## 2 Synthesis of Morpholines

The (S)-tert-butyl (1-hydroxypropan-2-yl) carbamate might be transformed over to (S)-1-(allyloxy)-N-arylpropan-2-amine utilizing ordinary techniques. The combinations be changed to the ideal heterocycle concluded Pd-catalysis coupling through an aryl or alkenyl halide. This procedure ought to give entree to a wide cluster of enantiopure cis-3,5-disubstituted morpholines that are hard to produce utilizing prevailing technique Scheme 1[5]. A four-steps preparation of cis-3,5-disubstituted morpholine from enantiomer unadulterated amino alcohol portrayed[6]. The important advance in amalgamation is a Pd-catalysis carboamination reaction between a subbed ethanolamine subsidiary an aryl and alkenyl bromide. Morpholine items remain produced as on its own stereoisomer in modest to great produce[7]. The methodology additionally gives admittance to melded bi-cyclic morpholine just as 2,3-and 2,5-disubstituted product Scheme 1. The substrate for the Pd-catalysis carboamination reaction were produced in 3 states from economically accessible beginning ingredients.

Action of a N-secured amino alcohol with Sodium hydride ion and allyl bromide managed allyl ether. The cleavage of Boc-bunch tracked by Pd-catalysis N-arylation of subsequent NH<sub>3</sub> trifluoroacetate salt gave in modest to great produce[8]. Toward a start of investigations be chose to look at the join off with 2-bromotoluene underneath reaction surroundings that's needed demonstrated ideal in associated piperazine-framing carboamination reaction. The appeared in utilization an impetus made of Palladium (II) acetate and Tri(2-furyl) phosphine gave in 66% produce. A primary sideways item saw right now, albeit modest quantities of an uncommon extra anonymous sideways items were likewise identified. A review of different ligand (e.g., triphenylphosphine, Bis[(2-diphenylphosphino)phenyl] ether) didn't give enhanced outcomes, and underlying decision of dissolvable toluene and base (Sodium-tert-butoxide) additionally demonstrated ideal[5].



SCHEME 1. Synthetic Strategy of Morpholine



SCHEME 2. Synthesis of Substrates

### 3 SAR of morpholine

The compound was seen as generally strong as contrasted and standard medication SAR study recommended that C-4 subbed phenyl and 4-hydroxy substitution were positive for the activity1 Fig2. The presentation of alkyl substitution at the third position of morpholine prompts increment in anticancer activity. Subbed morpholine was found to show great restricting partiality with mTOR. Among all the synthesis compounds were seen as most active[9]. The 2-ureidophenyltriazines bearing spanned morpholines were planned and incorporated that were best obliged in mTOR dynamic site and furthermore in vivo investigations demonstrated the promising outcomes[10]. Alongside this, sub-atomic displaying recommended that spanned morpholine moiety can enter profoundly in the pocket of mTOR making it particular and powerful mTOR inhibitor2 and 3 Fig2. Among all the mixes, compounds containing 3,5-ethylene crossed over morpholine indicated the intense potent activity. The synthesis and assessment of different chromone, quinoline and pyrazolopyrimidine subbed morpholine derivative[11]. SAR study finished up the significance of pyrazolopyrimidine substituent for powerful inhibitory action4 Fig2. Among all, compound indicated great activity[12]. In another examination,

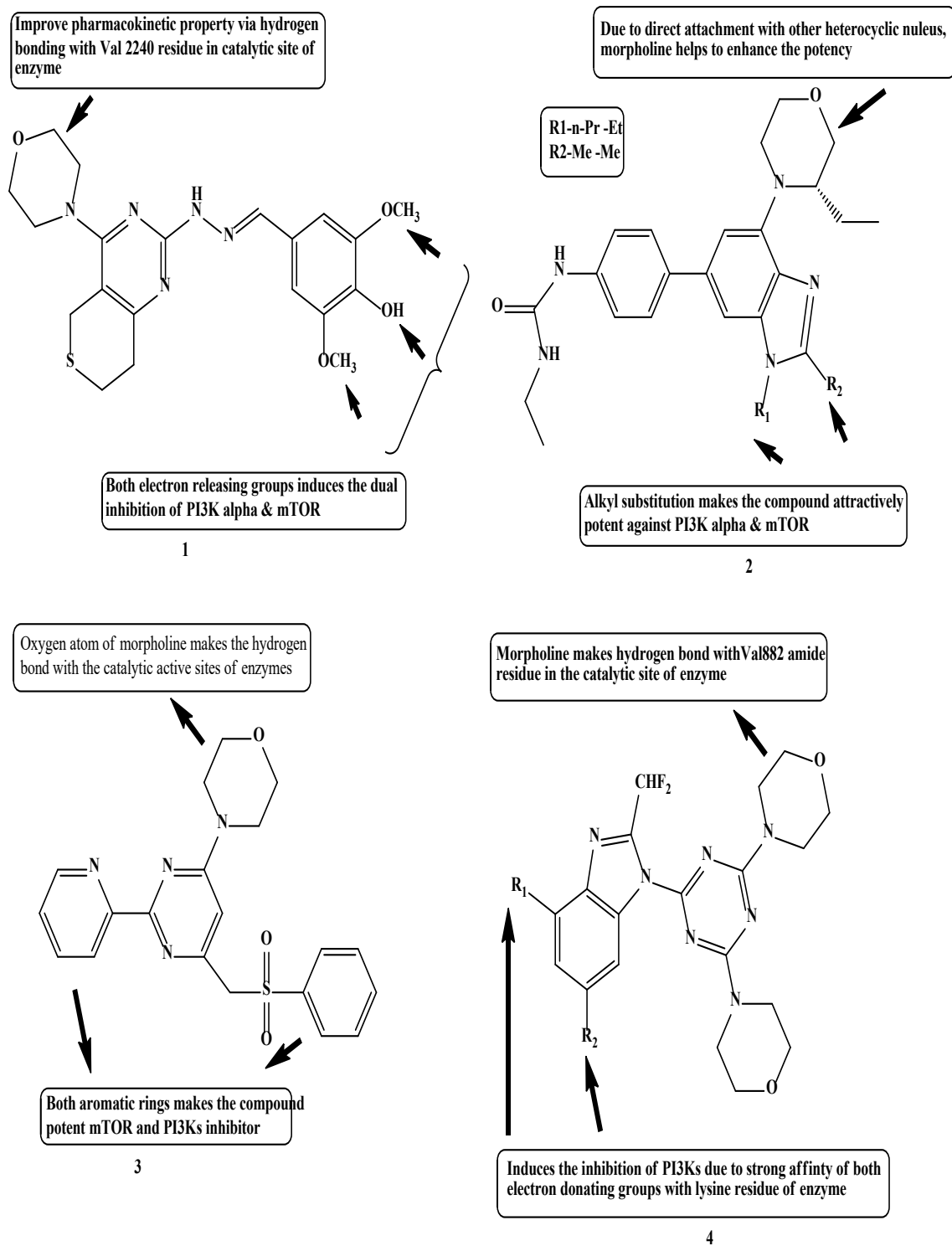
different morpholine-benzimidazole subordinates as anticancer operators. All the incorporated subordinates were additionally assessed against PI3K inhibitors and furthermore in vivo examinations were directed on U87MG (human glioblastoma tumor) malignant growth cell line. Among all the synthesis derivatives. The union of chalcone subbed morpholine substituted and further assessed against C6 and cell lines5 Fig3. SAR examines finished up the job of unsubstituted morpholine for potent activity. Among the synthesis compound for C6 and cell lines individually) indicated the most noticeable anticancer action practically proportionate to standard medication 5-flouro uracil for C6 and cell lines separately). Compound was most potent against HepG-2 cell line and furthermore moderate against as contrasted and strong medication cisplatin 6 Fig3.

Novel derivative, where the pyrazoline moiety and morpholine are connected have been combined synthesis[13]. All the synthesis derivatives were additionally assessed against HepG2, MCSF-7 and HeLa malignant growth cell lines. Among all the incorporated mixes, was seen as generally potent against HepG2 and normal activity against MCSF-7 and HeLa when contrasted with standard medication doxorubicin ( $GI_{50} < 0.05 \mu\text{m}$ ). SAR considers uncovered that morpholine substituted with aromatic ring containing halogen bunch prompts an expansion in inhibitory action against HepG2 cell line7 Fig3. Structured, orchestrated and assessed different N-substituted indolines and morpholines against osteosarcoma and human early-stage kidney cells[14].

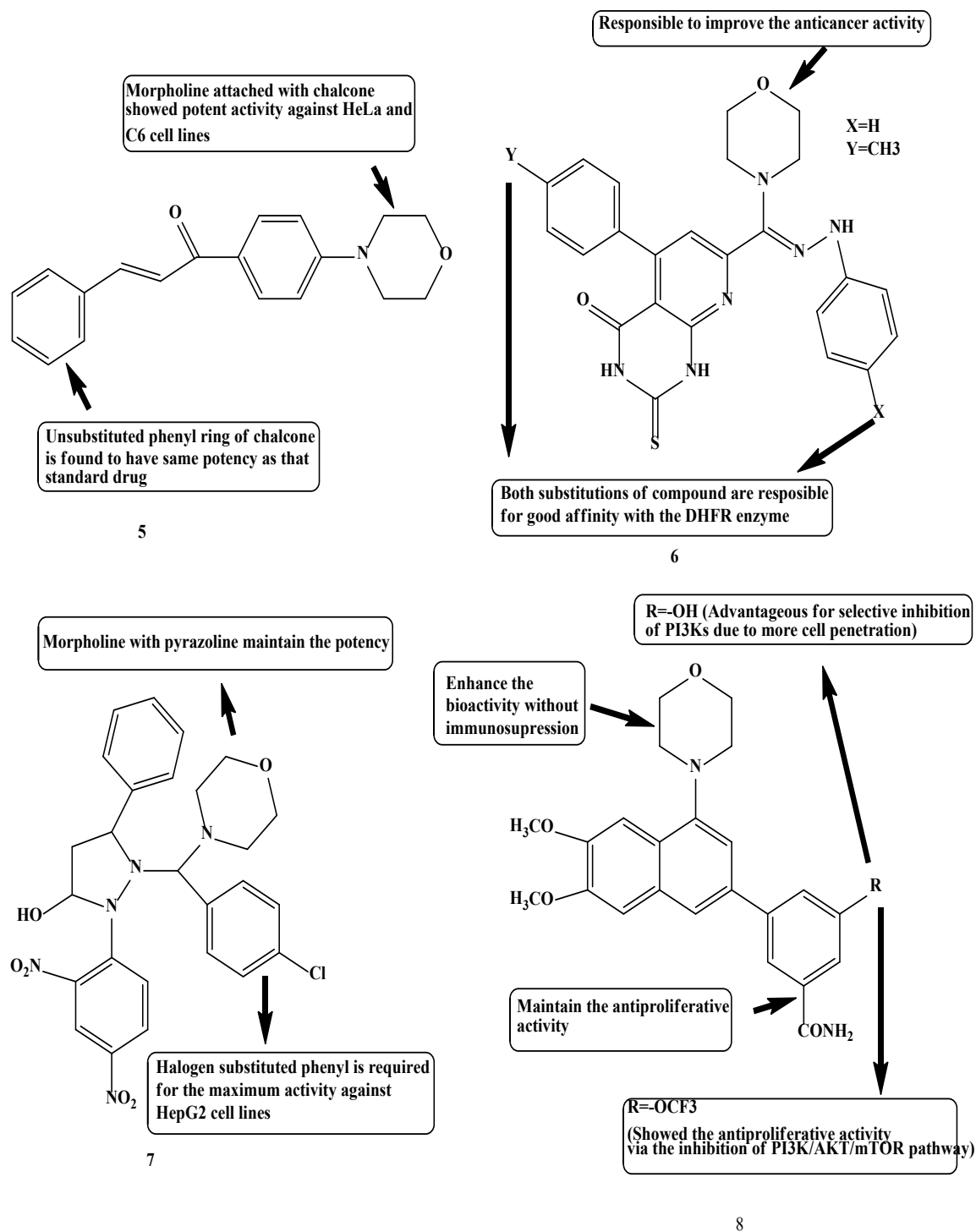
Notwithstanding, the indoline substituted demonstrated better cytotoxic impact thought about than the morpholine substituted. Compound was seen as the most potent among all the morpholine substituted. Among all the synthesis compounds, showed strong action against HCT-116, MCF-7, U-87, while was seen as successful against the whole cell lines contemplated practically identical to standard medication. SAR contemplates uncovered that benzamide moiety was significant for the activity. Trifluoromethoxy at the m-position of the amide gathering and methoxy at the 6 and 7 places of quinazoline ring appended with morpholine ring were likewise seen as urgent for the activity. Compound were seen as generally potent against all the isoforms (P).

These derivatives demonstrated the most extreme H-holding with amino acids in the active site of the enzymatic active site8 Fig3. Where, morpholine indicated hydrogen holding with the Val851 buildup and different substituent bound with Tyr836, Asp810, Lys802 deposits of the p11 $\alpha$  compound dynamic site. SAR contemplates uncovered that both 3-morpholinoalkyl-pyrimidopyrrolopyrimidinonesandthe3-aryl-1-morpholinopyridopyrrolopyrimidine-2-carbonitriles are both demonstrated strong activity[15].

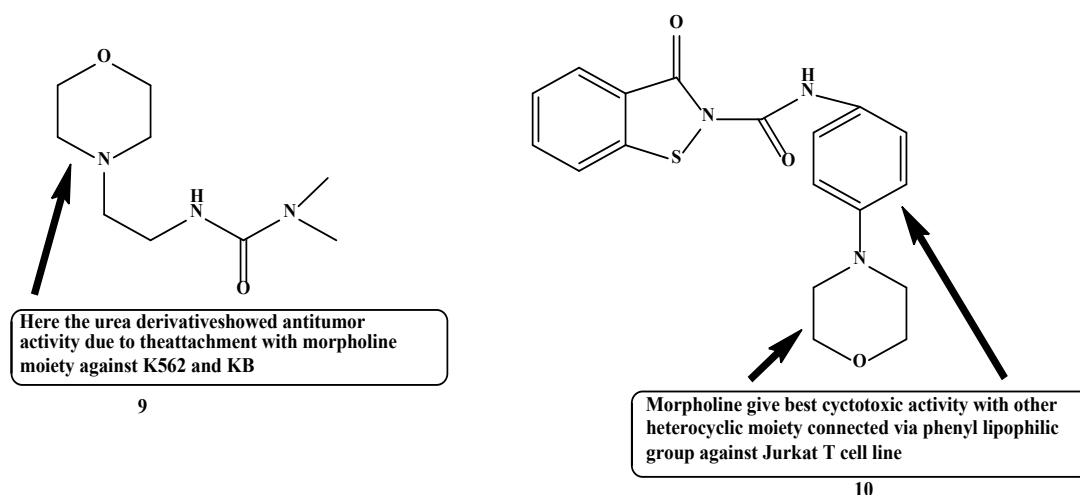
Furthermore 4-OCH<sub>3</sub> phenyl substitution is good9 Fig 4. Compound was seen as the most potent. The different quinoline substituted morpholine derivative as 12 caspase 3 inhibitors were synthesis. SAR considers features the significance of 4-methyl and 4-phenyl substituents are the most potent compound. Among the synthesis compound 10 was seen as a potent one Fig4.



**Fig.2** Chemical structures and SAR studies of anticancer morpholine containing compounds 1-4



**Fig. 3** Chemical structures and SAR studies of anticancer morpholine containing compounds



**Fig. 4** Chemical structures and SAR studies of anticancer morpholine containing compounds 9-10

## 4 Future Prospects

Morpholine and its derivatives are poised for significant growth and development in various industrial and scientific fields. One of the key future prospects for morpholine is its role in pharmaceuticals, where it serves as a building block for the synthesis of a wide range of therapeutic agents, including antibiotics, antifungals, and anticancer drugs [16]. The continuous demand for novel drugs drives the research and development of new morpholine derivatives with enhanced biological activities and improved safety profiles.

In the agrochemical industry, morpholine derivatives are expected to see increased use as fungicides and herbicides. The ongoing need for sustainable agriculture practices and the rising demand for high-yield crops will likely boost the development of new agrochemicals based on morpholine structures. Additionally, morpholine's role as a corrosion inhibitor in water treatment processes will continue to be essential, given the growing emphasis on infrastructure maintenance and the protection of industrial equipment.

The polymer and materials science sectors also present promising opportunities for morpholine derivatives. Their application as curing agents, stabilizers, and cross-linking agents in the production of polymers and resins will be critical in developing advanced materials with superior mechanical and thermal properties. Furthermore, morpholine's versatility as a solvent and catalyst in various chemical reactions will enhance its utility in organic synthesis and industrial processes.

Overall, the future prospects of morpholine and its derivatives are bright, driven by their diverse applications in pharmaceuticals, agrochemicals, water treatment, and materials science. Continuous research and innovation in these areas will likely expand their usage and contribute to advancements in multiple industries.

## 5 Conclusion

Morpholine is a versatile nucleus as it is involved in a wide range of pharmacological activities. The present review covers synthetic medicinal chemistry, SAR and pharmacological significance of morpholine derivatives. Various morpholine containing drugs under clinical trial having different mechanism of actions are also mentioned.

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