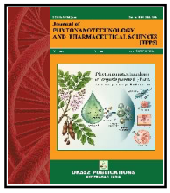
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Mannich bases in medicinal chemistry: Biological activities and structure-activity relationships

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Abstract

Mannich bases represent a structurally diverse class of compounds in which an aminomethyl group is introduced into different molecular scaffolds through the Mannich reaction. Their structural versatility has led to extensive investigation of their biological and pharmacological potential, with particular emphasis on structure-activity relationships (SAR). Over the past decade, considerable attention has been directed toward their anticancer and cytotoxic properties, as well as their antibacterial and antifungal activities. Important advances have also been reported in their application as antimycobacterial, antimalarial, and antiviral agents. In addition, Mannich bases have demonstrated a broad range of pharmacological effects, including anticonvulsant, anti-inflammatory, analgesic, and antioxidant activities. Other reported applications include antihypertensive and antiplatelet effects, antiparasitic and anti-ulcer activity, and potential utility in the management of neurological and psychiatric disorders. Furthermore, several Mannich bases have been investigated as enzyme inhibitors and receptor ligands, highlighting their versatility as scaffolds for drug discovery and pharmaceutical development. Overall, the diverse biological profiles of Mannich bases and their tunable structural features make them valuable candidates for medicinal chemistry and lead optimization.

1. Introduction

The Mannich reaction is a versatile three-component condensation involving an active-hydrogen substrate, an aldehyde (commonly formaldehyde), and an amine, producing compounds known as Mannich bases. This reaction, also termed aminoalkylation or aminomethylation, introduces an aminoalkyl group into the substrate and provides a convenient approach for structural diversification of bioactive molecules. Secondary aliphatic amines are the most frequently used amine components, although primary amines and ammonia can also participate. The substrate's reactivity generally depends on activating functional groups such as carbonyl, phenolic, heterocyclic, or electron-withdrawing groups. Depending on the number of reactive sites and reaction conditions, mono-, bis-, or tris-Mannich bases can be obtained. This structural flexibility makes Mannich chemistry particularly valuable in medicinal chemistry and pharmaceutical research, where aminoalkylation is widely exploited to modify molecular properties and generate compounds with diverse biological activities. (Tramontini *et al*., 1973; Tramontini *et al*., 1990).

Mannich bases possess broad industrial and pharmaceutical relevance and have been employed in the functional modification of natural materials such as leather, paper, and textiles, as well as in polymer synthesis, petroleum additives, water-treatment agents, analytical reagents, cosmetics, and dyes. Their versatile chemical reactivity and structural adaptability also make them valuable scaffolds for medicinal chemistry and pharmaceutical research, particularly for the development and optimization of biologically active compounds (Tramontini *et al.,* 1994). The Mannich reaction has significant importance in medicinal chemistry, as reflected by the growing body of research exploring Mannich-derived compounds. Mannich bases offer a versatile scaffold for generating pharmacologically active molecules, with diverse biological properties that continue to be identified through systematic screening. Importantly, aminomethylation provides a valuable strategy for drug optimization, as incorporation of an aminoalkyl group can enhance polarity and hydrophilicity, potentially improving aqueous solubility, bioavailability, and drug delivery. A well-known example is rolicycline, demonstrating the potential of Mannich modification in improving the pharmaceutical properties of existing drug molecules (Siedel *et al*., 1958). The pharmaceutical properties of drugs can be strategically optimized through Mannich modification. Quaternization of the nitrogen atom in an aminomethylated drug can generate an ammonium salt, thereby enhancing aqueous solubility and potentially improve formulation and drug-delivery characteristics. Conversely, the lipophilicity of a drug can be fine-tuned by selecting suitable amine components during the Mannich reaction, providing a useful approach for modulating physicochemical properties such as membrane permeability and distribution (Saab *et al*., 1990). Aminomethylated derivatives can also serve as prodrug forms of active pharmaceutical agents, undergoing hydrolytic cleavage and subsequent deamino-methylation to regenerate the parent drug. This approach can provide controlled drug release and improved delivery, highlighting the potential of Mannich modification in pharmaceutical drug design (Huttunen *et al*., 2011; Simplicio *et al*., 2007). Despite the significant potential of Mannich bases in medicinal chemistry, recent comprehensive reviews focusing specifically on their structure-

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activity relationships (SAR) and their application as prodrug systems remain limited. This highlights the need for an updated assessment of the field. The present review therefore summarizes key recent advances in the medicinal chemistry of aminomethylated Mannich bases, with emphasis on their reported biological activities and therapeutic potential. Considering the extensive literature available, the discussion primarily focuses on developments reported during the past decade, providing a concise overview of current research trends and emerging pharmaceutical applications.

2. Anticancer activity and cytotoxicity

Ketonic Mannich bases, particularly those derived from acetophenone scaffolds, have attracted considerable interest in medicinal chemistry because of their potential anticancer and cytotoxic activities. Structural modification through Mannich aminomethylation can generate derivatives with diverse pharmacological profiles, making these compounds valuable candidates for further anticancer drug discovery and biological evaluation (Dimmock and Kumar, 1997). Structurally related α, β-unsaturated ketones were comprehensively reviewed approximately 15 years ago, highlighting their established significance in medicinal chemistry and biological research (Dimmock *et al*., 1999). Both groups of compounds have demonstrated cytotoxic activity through alkylation of cellular thiol-containing molecules, particularly glutathione and cysteine. This mechanism may enhance the sensitivity of tumor cells to anticancer agents and has also shown potential for overcoming or reversing drug resistance, highlighting their relevance in cancer drug development (Pati *et al*., 2007). Compounds combining a ketonic Mannich base moiety with an activated α,β-unsaturated carbon-carbon double bond, such as chalcone-derived Mannich bases, have therefore attracted attention as promising candidates for investigating the sequential cytotoxicity mechanism. Their structural features may facilitate interactions with cellular nucleophiles and contribute to enhanced antitumor and cytotoxic potential, supporting further investigation in anticancer drug discovery (Dimmock *et al*., 2000).

The sequential cytotoxicity theory proposes that the stepwise release of two or more cytotoxic agents may produce enhanced antitumor effects, with greater toxicity toward malignant cells while potentially minimizing damage to normal tissues (Dimmock *et al*., 1993). Furthermore, enone-derived Mannich bases, which can be readily synthesized from alkyl aryl ketones through a single-step reaction, have demonstrated significant cytotoxic activity against a range of cancer cell lines, highlighting their potential as promising scaffolds for anticancer drug discovery (Dimmock *et al*., 1998).

Furthermore, *ortho*-phenolic Mannich bases can readily undergo deamination to generate highly reactive *ortho*-quinone methides. Consequently, chalcone-derived Mannich bases prepared from phenolic aldehydes or ketones, represented by structure, have attracted attention as potential cytotoxic and anticancer agents. Their ability to form reactive intermediates may contribute to their observed antiproliferative activity, supporting further investigation in cancer drug discovery (Dimmock *et al*., 1998).

Over the past decade, research has continued to focus on the discovery and optimization of more potent anticancer candidates among the four major classes of cytotoxic Mannich bases. These efforts have aimed to improve their cytotoxic efficacy and therapeutic potential for cancer drug development. Ketonic Mannich bases have been extensively investigated for their cytotoxic and anticancer potential, particularly with respect to aromatic substitution and structural modification. Gul *et al*. (2006) reported that conversion of mono-Mannich bases derived from acetophenone into bis-Mannich bases generally enhanced cytotoxicity against Renca renal carcinoma and Jurkat T-lymphocyte cells, with some derivatives showing greater activity than the reference anticancer agents 5-fluorouracil and melphalan. However, this activity was not consistently observed in the brine shrimp assay, possibly because rapid deamination of the bis-Mannich bases occurred before they reached their biological targets. Further studies of ketonic Mannich bases containing dimethylamino, piperidinyl, and morpholinyl groups, as well as phenyl- and thiophene-based substituents, demonstrated significant cytotoxicity against Jurkat and PC-3 cancer cells. Several derivatives exhibited 2.5-5.2-fold greater cytotoxic activity than 5-fluorouracil. Mannich bases derived from 4-aryloxyacetophenones also showed moderate activity against murine L1210 and human T-lymphocyte cell lines, while selected derivatives demonstrated notable antiproliferative activity against multiple human colon cancer cell lines. Collectively, these findings highlight ketonic Mannich bases as promising scaffolds for anticancer drug discovery and structural optimization (Gul *et al*., 2006; Vashishtha *et al*., 2004). The use of primary aliphatic amines in Mannich reactions can generate structurally diverse products with distinct cytotoxic profiles. Aminomethylation of acetophenones with methylamine produced bis-Mannich bases and piperidinols, with the bis-Mannich derivatives generally showing greater cytotoxicity against Jurkat cells than the corresponding mono-Mannich bases and piperidinols. Their activity may involve cellular glutathione alkylation and inhibition of DNA topoisomerase I, with their linear structure potentially facilitating interactions with DNA nucleotides. In contrast, the use of *isopropylamine* and *n*-butylamine yielded secondary mono-Mannich bases, which demonstrated notable cytotoxicity against Huh-7 hepatoma, Jurkat, and L6 myoblast cells, in several cases exceeding the activity of 5-fluorouracil. Phenethylamine-based aminomethylation afforded either mono-Mannich bases or piperidinols depending on reaction conditions. These derivatives displayed micromolar cytotoxic activity against PC-3 prostate cancer cells, together with measurable DNA topoisomerase I inhibitory activity, supporting their potential as leads for anticancer drug development (Gul *et al*., 2009; Mete *et al*., 2010).

Recent literature contains relatively few reports on the cytotoxic potential of Mannich bases derived from α,β-unsaturated ketones. Mannich bases, derived from 1-arylidene-2-tetralones, demonstrated markedly enhanced cytotoxicity compared with their parent enones against human T-lymphocyte and murine leukemia cell lines, with IC_{50} values ranging from 0.2-10 μM. Several derivatives bearing chloro, carboxyl, methoxy, or cinnamoyloxy substituents showed significant antitumor and antileukemic activity, with some displaying selective cytotoxicity. Similarly, Mannich bases derived from 2-benzylidenecyclohexanones generally exhibited greater cytotoxicity than the corresponding enones, with selected derivatives showing low-micromolar growth-inhibitory activity that exceeded that of melphalan. Although, N-myristoyl transferase was initially considered a potential target, the relatively weak inhibition observed suggests that this enzyme is unlikely to be the primary mediator of their cytotoxic effects. Further investigations indicated that these compounds may act through multiple mechanisms, including thiol

alkylation, disruption of mitochondrial electron transport, and membrane damage leading to ATP leakage. Mannich bases also displayed substantial cytotoxicity against MCF-7, MCF-7/Adr breast cancer, and HL-60 leukemia cells, accompanied by glutathione binding and inhibition of glutathione-S-transferase π (GST-π). Hydrogenation of the conjugated double bond slightly reduced activity, emphasizing the importance of the α,β-unsaturated carbonyl pharmacophore. Overall, these findings highlight the role of the conjugated enone system and appropriate aromatic substitution in modulating the anticancer potency and cellular mechanism of Mannich-based scaffolds (Das *et al*., 2012; Dimmock *et al*., 2004; Wang *et al*., 2006).

3. Antibacterial activity

Over the past decade, Mannich bases have attracted considerable attention as potential antibacterial agents, with numerous studies reporting activity across a broad range of structural classes. These compounds have been evaluated against diverse Gram-positive and Gram-negative bacterial pathogens, demonstrating promising antimicrobial potential. However, differences in experimental protocols and the use of non-standardized screening methods can make direct comparison of antibacterial activity between studies challenging. Given the major clinical importance of tuberculosis, studies investigating the activity of Mannich bases against *Mycobacterium* species are particularly relevant and are therefore considered separately. Ketonic Mannich bases have been extensively investigated for their antibacterial potential, with activity strongly influenced by the carbonyl scaffold, ring size, and amine substituent. Aminomethylation of α, β-unsaturated cyclic ketones produced Mannich bases, which showed preferential activity against Gram-positive bacteria, generally with MIC values below 12.5 μg/ml, although their potency remained lower than that of standard antibiotics. Activity against *Pseudomonas aeruginosa* was not observed, while only limited activity was detected against *Escherichia coli*. Interestingly, variations in the amine group and aromatic methoxy substitution produced little change in antibacterial activity. Mannich bases, derived from benzo-fused cyclic ketones such as indanone, tetralone, and benzosuberone, displayed comparatively stronger antibacterial activity. Indanone derivatives showed activity against both Gram-positive and Gram-negative bacteria, with MIC values of 1.56–25 μg/ml, whereas tetralone and benzosuberone derivatives were predominantly active against Gram-positive organisms. Both the amine component and alkoxy substitution contributed to the observed structure activity relationship. Further structural modification of oxazolidinone-inspired Mannich bases demonstrated that replacing an acetamido group with a thioacetamido or thiourea functionality substantially enhanced antibacterial activity. One derivative even exhibited activity exceeding that of linezolid, highlighting the potential of sulfur-containing modifications in antibacterial lead optimization. Double Mannich bases derived from 4,6-dimethoxybenzofuranone also showed moderate-to-strong antibacterial activity, particularly against *E. coli*. Selected derivatives containing pyrrolidine, diethylamine, or di-*n*-butylamine groups produced inhibition zones comparable to gentamicin. In contrast, several acetophenone- and 2-acetylthiophene-derived Mannich bases showed little or no antibacterial activity. The methiodide derivative displayed only weak activity against *Staphylococcus aureus*, with an MIC of 500 μg/ml, substantially lower than the reference antibacterial agent. Overall, these findings indicate that the core carbonyl framework, ring architecture, amine substituent, and sulfur-containing functional groups can substantially influence the antibacterial profile of Mannich bases, providing useful directions for structure activity relationship studies and antimicrobial drug discovery (Lóránd *et al*., 2001; Srivastava *et al*., 2004; Gul *et al*., 2005). Phenolic Mannich bases have also demonstrated promising antibacterial potential, although their activity varies considerably with structural modification. Mannich bases, derived from 4-*tert*-butylcatechol and secondary aliphatic amines, showed low-to-moderate antibacterial activity, whereas selected Cu(II) complexes exhibited improved potency, with MIC values comparable to chloramphenicol. Similarly, phenolic Mannich bases displayed only moderate inhibition against common bacterial pathogens and were less active than ofloxacin. Aminomethylated derivatives of the natural antibiotic novobiocin were developed with the aim of improving penetration into Gram-negative bacteria. However, these derivatives showed substantially reduced antibacterial activity compared with the parent drug. In contrast, lawsone-derived phenolic Mannich bases demonstrated more encouraging activity, with some compounds exhibiting antibacterial potency comparable to or exceeding chloramphenicol against *Bacillus subtilis*, *E. coli*, and *S. aureus*. Interestingly, most Mannich bases were more active than their corresponding Cu(II) complexes, possibly because of their greater solubility and bioavailability. These findings highlight phenolic Mannich scaffolds as useful candidates for antimicrobial lead development and structural optimization (Gres *et al*., 2012; Husain *et al*., 2010; Neves *et al*., 2009).

4. Antimycobacterial activity

Tuberculosis (TB) remains a major infectious disease, further complicated by the increasing prevalence of drug-resistant and latent infections. This has stimulated the search for new antimycobacterial chemotypes with improved potency and activity against resistant *Mycobacterium* strains. Mannich bases have emerged as promising candidates because their structural diversity allows substantial optimization of both biological activity and pharmacological properties. Several ketonic Mannich bases have demonstrated activity against *Mycobacterium tuberculosis* H37Rv. Dimethylamine derivatives of 2-benzylidenecyclohexanones showed MIC values ranging from 0.39 to >12.5 μg/ml. Among them, the methoxy-substituted analogue exhibited promising activity (MIC = 0.78 μg/ml) together with moderate mammalian-cell toxicity, and retained activity against selected drug-resistant strains. Mannich bases targeting isocitrate lyase, an essential enzyme of the mycobacterial glyoxylate cycle, also showed inhibitory potential, highlighting this metabolic pathway as a viable target for antimycobacterial drug discovery. Phenolic Mannich bases derived from isoniazid acetophenone hydrazones displayed MIC values of 0.56-4.61 μM against *M. tuberculosis* H37Rv, with several derivatives outperforming isoniazid in vitro. Some compounds also demonstrated promising *in vivo* reduction of pulmonary bacterial burden. Mannich bases derived from allomaltol, chlorokojic acid, piperazines, and piperidines further confirmed the importance of amine substitution and substituent position in controlling antimycobacterial potency. Pyrrole-based Mannich bases represent one of the most successful series. The lead compound BM212 and its analogues exhibited potent activity against *M. tuberculosis*, including drug-resistant strains. SAR studies established the importance of lipophilic substituents, particularly fluorinated phenyl groups and thiomorpholine

substitution. Optimization subsequently produced highly potent derivatives with MIC values as low as 0.125 μg/ml and excellent selectivity toward mycobacteria. One optimized analogue demonstrated low cytotoxicity (selectivity index >1000), while another showed favourable pharmacokinetic properties and significant reduction of pulmonary bacterial load in a murine TB model. Genetic studies implicated mutations in the mmpl3 gene, suggesting Mmpl3 as a potential molecular target for this class. Isatin-based Mannich bases have also shown considerable promise. Semicarbazide-containing derivatives displayed activity comparable to isoniazid, while selected compounds were active against multidrug-resistant *Mycobacterium*. Mannich conjugates incorporating fluoroquinolones such as ciprofloxacin, gatifloxacin, 8-methoxyciprofloxacin, and moxifloxacin produced potent antimycobacterial effects, with some derivatives exhibiting nanomolar MIC values. These findings suggest that hybridization of Mannich scaffolds with established antimycobacterial pharmacophores can enhance activity and broaden the chemical space for TB drug discovery. Other heterocyclic Mannich bases, including oxadiazole, triazole, imidazothiadiazole, indole, pyrazolone, and tetracycline-derived analogues, have demonstrated moderate to excellent antimycobacterial activity. Notably, oxadiazole-2-one derivatives were generally more active than their thione counterparts, indicating the influence of heteroatom composition on potency. Mannich modification of tetracyclines and pyrazinamide also generated derivatives with improved activity against *M. tuberculosis* and, in some cases, multidrug-resistant strains. Overall, these studies demonstrate that Mannich bases constitute a versatile platform for antimycobacterial drug discovery. Their activity is strongly influenced by the nature and position of aromatic substituents, lipophilicity, heterocyclic amine incorporation, and hybridization with established pharmacophores. The identification of highly potent derivatives active against drug-resistant strains, together with evidence for favourable selectivity and *in vivo* efficacy, supports further optimization of Mannich-based scaffolds as potential leads for next-generation antitubercular agents (WHO 2010/2011; Das *et al*., 2010; Berk *et al*., 2011; Karakaya *et al*., 2013).

5. Antifungal activity

Fungal infections are an increasing global health concern, particularly among immunocompromised patients, and are associated with substantial morbidity and mortality. The emergence of resistance to existing antifungal therapies further limits treatment options and highlights the need for novel antifungal scaffolds with distinct mechanisms of action. In this context, Mannich bases have attracted growing attention as structurally diverse candidates for antifungal drug discovery (Pfaller and Diekema, 2010). In this context, Mannich bases have attracted considerable attention because their readily tunable structures permit optimization of potency, selectivity, and pharmacological properties. Early studies demonstrated that ketonic Mannich bases derived from acetophenones generally possessed weak antifungal activity; however, quaternization of the amino group markedly enhanced potency. The resulting methiodide derivatives showed activity superior to amphotericin B against several yeasts and dermatophytes, indicating that permanent cationic character can be an important determinant of antifungal activity. Structural modification of the aromatic ring alone produced comparatively limited improvement. Bis-Mannich bases and related piperidinols showed broader activity, particularly against dermatophytes such as *Trichophyton rubrum* and *Microsporum canis*. Small changes in N-substitution also produced significant changes in activity, demonstrating the sensitivity of this scaffold to electronic and steric modifications. Mannich bases derived from enones and substituted aromatic ketones have shown broader antifungal profiles. Several derivatives exhibited greater activity than amphotericin B against selected phytopathogenic fungi, while coumarin- and benzofuran-based Mannich bases displayed activity comparable to fluconazole against *Candida* and *Aspergillus* species. Mannich bases derived from cyclic ketones also demonstrated appreciable anti-*Candida* and anti-*Saccharomyces* activity. Their potency generally decreased as the ring size increased, whereas the α, β-unsaturated carbonyl system appeared essential for activity. Reduction of this carbonyl group to amino alcohols resulted in a marked loss of antifungal potency, supporting the importance of the enone pharmacophore. Further optimization of fused cyclic ketone Mannich bases produced derivatives with improved MIC values compared with their non-fused analogues. Transcriptomic studies suggested that these compounds induce oxidative stress in *Candida albicans*, providing evidence for a mechanism distinct from conventional ergosterol biosynthesis inhibition. Thiocroman-4-one Mannich bases also demonstrated broad antifungal activity, with selected derivatives exceeding the potency of ketoconazole against tested fungi. Phenolic Mannich bases constitute another important class of antifungal agents. Although several salicylaldehyde-derived derivatives were less potent than clotrimazole against *Candida*, some displayed strong activity against *Aspergillus niger*. Aminomethylated catechols and their copper(II) complexes showed substantial inhibition of phytopathogenic fungi, in some cases matching or exceeding the activity of nystatin and terbinafine. Mannich modification of the echinocandin-related antifungal lipopeptide mulundocandin also produced derivatives with improved solubility and, in selected cases, anti-*Candida* activity comparable to fluconazole, demonstrating the potential of Mannich functionalization for pharmacological optimization of existing antifungal scaffolds. Isatin-based Mannich bases have demonstrated moderate to good activity against *Candida* and *Aspergillus* species. Incorporation of heteroarylamines, morpholine, piperidine, and other nitrogen-containing groups influenced antifungal potency, although many derivatives remained less active than established azole antifungals. Selected derivatives, however, achieved activity comparable to fluconazole or griseofulvin, indicating that isatin provides a useful pharmacophore for further optimization. Among heterocyclic Mannich bases, 1,2,4-triazole-, 1,3,4-oxadiazole-, thiazolidinone-, pyrimidine-, and related scaffolds have produced variable but occasionally significant antifungal activity. Several oxadiazole Mannich bases exhibited MIC values comparable to ciclopiroxolamine against dermatophytes and *Aspergillus* species, while imidazole-containing derivatives frequently showed enhanced activity against *C. albicans* and *Trichophyton* species. Selected derivatives were equipotent or superior to fluconazole, ketoconazole, amphotericin B, or ciclopiroxolamine, emphasizing the importance of heterocyclic nitrogen and appropriate lipophilic substitution in antifungal activity. Mannich bases derived from miscellaneous pharmacophores have also yielded promising leads. Imidazopyridine derivatives demonstrated greater activity than griseofulvin against selected *Aspergillus* and *Candida* species, while aminomethylated pyrazolines produced MIC values comparable to or better than clotrimazole. Acetylenic Mannich bases showed ketoconazole-like activity against *C. albicans*, and selected quinoxaline and

quinazolinone derivatives exhibited activity comparable to or greater than conventional azole antifungals. Overall, the antifungal activity of Mannich bases is strongly dependent on the nature of the parent pharmacophore, amine substituent, lipophilicity, ring size, and electronic characteristics of the molecule. Important SAR trends include the beneficial effect of quaternary ammonium formation in selected ketonic systems, the requirement for an intact α, β-unsaturated carbonyl group in certain cyclic ketone derivatives, and the contribution of nitrogen-containing heterocycles to antifungal potency. Evidence for oxidative-stress-mediated activity in *C. albicans* further suggests that some Mannich bases may act through mechanisms distinct from conventional ergosterol-targeting drugs. Collectively, these findings establish Mannich bases as a versatile and chemically adaptable platform for the discovery of novel antifungal agents, particularly against resistant fungal pathogens (Gul *et al*., 2002; Kenchappa *et al*., 2013).

6. Antimalarial activity

Malaria remains a major global health challenge, particularly because of the emergence of *Plasmodium falciparum* strains resistant to conventional drugs such as chloroquine. Mannich chemistry has contributed substantially to antimalarial drug discovery, most notably through amodiaquine, a phenolic Mannich base based on the 4-amino-7-chloroquinoline scaffold. Early SAR studies established that the 7-chloro substituent and phenolic aminomethyl moiety are important pharmacophores for activity. However, amodiaquine undergoes CYP-mediated bioactivation to a reactive quinone-imine metabolite, prompting the development of safer analogues. Isoquine, an isomeric Mannich analogue, retained potent activity against both chloroquine-sensitive and resistant *P. falciparum* strains, with sub-10 nM activity and greater potency than chloroquine. Further optimization produced N-tert-butyl isoquine (GSK369796), which maintained low-nanomolar antimalarial activity and oral efficacy while showing improved metabolic stability, exposure, and preclinical safety. These studies highlight the importance of metabolic stability and resistance-independent activity during Mannich-base optimization. Structural diversification of isoquine and related aminoquinoline Mannich bases further demonstrated that the nature and number of aminomethyl groups strongly influence activity. Several analogues retained nanomolar potency against chloroquine-resistant parasites, while mono-Mannich derivatives were generally more active than their bis-Mannich counterparts. Double-Mannich benzoxazine derivatives also displayed good activity against sensitive and resistant strains, although chemical instability under acidic conditions limited their development. Among amodiaquine analogues, incorporation of a morpholine-containing aminomethyl group produced a compound with a MIC of 63 ng/ml, superior to chloroquine (250 ng/ml). These findings indicate that appropriate modification of the Mannich side chain can improve both potency and resistance profiles. The Mannich pharmacophore is also present in pyronaridine, in which the quinoline nucleus is replaced by a naphthyridine system. This scaffold inspired extensive exploration of fused heteroaromatic Mannich bases. Although many derivatives showed good activity against both chloroquine-sensitive and resistant *P. falciparum*, only a few approached the potency of established antimalarials. A pyrrolidinyl-substituted analogue exhibited IC_{50} values of 50 nM and 38 nM against sensitive and resistant strains, respectively, and completely suppressed detectable parasites in a murine malaria model. These studies demonstrate that heteroaromatic scaffold modification combined with Mannich functionalization can generate promising antimalarial leads, although potency alone does not guarantee superiority over established drugs. An important strategy has been pharmacophore hybridization, in which the phenolic Mannich moiety is combined with established antimalarial pharmacophores. Tetraoxane-Mannich hybrids ("mannoxanes") showed low-nanomolar activity and superior curative efficacy to several reference agents in murine models. Similarly, artemisinin-Mannich hybrids displayed enhanced antimalarial activity, improved aqueous solubility and oral suitability, while potentially avoiding formation of undesirable artemisinin metabolites. Other phenolic Mannich hybrids exhibited strong activity against both chloroquine-sensitive and resistant *P. falciparum*; for example, one analogue showed IC_{50} values of 42 nm against NF54 and 9.5 nm against K1, together with nanomolar activity against *P. berghei*. These results support Mannich-based hybridization as an effective approach for achieving dual pharmacology and improved antimalarial efficacy. Pyrrole-containing Mannich bases have likewise produced encouraging results. Several artemisinin-derived pyrrole Mannich bases surpassed artemisinin and chloroquine against sensitive and resistant *P. falciparum*. Selected derivatives completely eliminated parasites in murine suppressive assays, with effective doses of approximately 4.3-5.3 mg/kg. Notably, one methyl-substituted morpholine/piperazine derivative achieved complete clearance of parasitemia and prolonged animal survival, demonstrating that appropriate heterocyclic amine substitution can translate in vitro potency into meaningful in vivo efficacy. Other phenolic Mannich bases derived from chalcones, hydroxybenzaldehydes, quinoline-containing systems, pyridones and lawsone have also demonstrated antimalarial potential. Some quinoline-containing derivatives exhibited potent activity against chloroquine-resistant *P. falciparum*, with the most active bis-quinoline Mannich analogue showing an IC_{50} of 77 nm. The activity of chalcone-derived Mannich bases has been associated with possible inhibition of parasite thioredoxin reductase, whereas quinoline-based compounds may retain pharmacological features associated with interference in parasite heme detoxification. Although several lawsone-ferrocenyl Mannich derivatives were active, their potency remained below that of atovaquone. Overall, Mannich bases provide a versatile platform for antimalarial drug discovery, with activity strongly influenced by the heteroaromatic core, number and nature of aminomethyl substituents, lipophilicity, metabolic stability and pharmacophore hybridization. The most successful examples demonstrate that Mannich functionalization can overcome aspects of chloroquine resistance, enhance potency and improve pharmacokinetic properties. Future optimization should therefore integrate parasite selectivity, metabolic stability, resistance profiles and in vivo efficacy rather than relying solely on high in vitro potency (Baramee *et al*., 2006; Chipeleme *et al*., 2007; Pacorel *et al*., 2010; Chadwick *et al*., 2011).

7. Antiviral activity

Mannich bases have demonstrated promising antiviral potential, particularly against hepatitis B virus (HBV), herpes viruses, HIV, and other clinically relevant viruses. Arbidol, a phenolic Mannich base, provided an important lead for developing anti-HBV analogues. Several arbidol-derived derivatives showed stronger HBV inhibitory activity than lamivudine. SAR studies indicated that halogen substitution, particularly fluorine or chlorine, could enhance antiviral potency, while the nature of the aminoalkyl group also influenced

activity. Quinoline-based Mannich bases demonstrated strong inhibition of HBV DNA replication, with selected derivatives exhibiting 10-66-fold greater activity than lamivudine. Other phenolic Mannich bases also displayed significant anti-HBV effects, although their activity depended on the heterocyclic scaffold, sulfur oxidation state, and amino substituent. These findings highlight the importance of structural optimization in improving antiviral efficacy and reducing cytotoxicity. Chlorokojic acid-derived Mannich bases exhibited activity against herpes simplex virus type 1 (HSV-1) and parainfluenza-3 virus, with selected derivatives showing potency comparable to acyclovir. Other phenolic Mannich bases demonstrated selective antiviral effects, including a coumarin derivative with notable activity against respiratory syncytial virus and low cytotoxicity. Mannich bases derived from 5-chloro-8-hydroxyquinoline were also identified as potential HIV latency-reversing agents, suggesting possible applications in strategies targeting latent HIV reservoirs. Isatin-derived Mannich bases generally showed limited antiviral activity, although selected compounds demonstrated activity against yellow fever virus or inhibition of HIV reverse transcriptase. Mannich bases incorporating fluoroquinolone pharmacophores exhibited activity against HIV and hepatitis C virus (HCV), while selected derivatives also inhibited Japanese encephalitis and West Nile viruses, including activity against Japanese encephalitis virus in an animal model. Other Mannich bases derived from tetracyclines, efavirenz, and indole scaffolds have also demonstrated antiviral potential, although cytotoxicity varied among compounds. Overall, Mannich bases represent versatile scaffolds for antiviral drug discovery. Their activity is influenced by the core structure, heteroatom functionality, halogen substitution, aminoalkyl group, and lipophilicity. Further optimization of selectivity, mechanism of action, pharmacokinetic properties, and *in vivo* efficacy is required to advance these compounds as potential antiviral agents. (Sriram *et al*., 2009; Selvam *et al*., 2012). Mannich bases have emerged as promising anticonvulsant scaffolds, with activity evaluated primarily using maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) seizure models. Ketonic Mannich bases and related piperidinols demonstrated protection mainly in the MES model, with several compounds showing activity below neurotoxic doses. Structural modification of the acetophenone scaffold influenced potency, while azine analogues generally displayed weaker activity. Bis-Mannich bases and piperidinols containing a 4-chlorophenyl group showed particularly favorable anticonvulsant profiles, indicating the importance of this substituent. Phenolic Mannich bases derived from allomaltol and kojic acid also exhibited significant anticonvulsant activity. Several derivatives provided protection in both MES and scPTZ models, with activity strongly dependent on the amine substituent and aromatic substitution pattern. Kojic acid-derived piperazine Mannich bases generally showed greater anticonvulsant potency than the corresponding allomaltol derivatives, possibly due to additional hydrogen-bonding interactions. Hydantoin- and succinimide-based Mannich bases represent another important class because these heterocyclic cores are established pharmacophores in antiepileptic drug design. Several hydantoin Mannich bases demonstrated activity in MES and/or scPTZ models, with selected derivatives showing greater potency than phenytoin. Succinimide-derived Mannich bases also produced substantial anticonvulsant protection, although a consistent SAR was difficult to establish. In general, 3,3-diphenylsuccinimide derivatives were more potent than alkyl-phenyl and dialkyl analogues. Mechanistic studies further indicated that anticonvulsant activity correlated with NaV1.2 sodium-channel blockade, rather than directly with serotonin-receptor affinity. Mannich modification of barbituric acid, thiobarbituric acid, and quinazolinone scaffolds also generated compounds with substantial anticonvulsant activity. Selected derivatives produced 40-90% seizure protection in MES and scPTZ models without significant neurotoxicity, sedation, or hypnotic effects. Fused heterocyclic Mannich bases, including benzoxazepine, benzothiazepine, and benzodiazepine derivatives, further demonstrated promising anticonvulsant activity. Some benzoxazepine derivatives showed potency comparable to phenytoin, lamotrigine, and valproate, while sulfur-containing benzothiazepine analogues generally provided greater MES protection than their oxygen counterparts. Overall, these findings establish Mannich aminoalkylation as a useful strategy for enhancing anticonvulsant activity across diverse pharmacophoric scaffolds, although further optimization of potency, duration of action, and neurotoxicity is required for therapeutic development (Garg *et al*., 2010; Obniska *et al*., 2012; Pandeya and Rajput, 2012).

8. Anti-inflammatory activity

Inflammation is a protective immune response to tissue injury, infection, or chemical stimuli and is characterized by the release of inflammatory mediators that promote leukocyte recruitment and tissue responses. Although NSAIDs remain widely used for managing inflammation, their prolonged use is associated with adverse effects such as gastrointestinal injury, renal toxicity, and cardiovascular complications. Consequently, Mannich bases have attracted attention as potential anti-inflammatory scaffolds. Ketonic Mannich bases derived from arylidenecyclohexanones demonstrated significant activity in xylene-induced ear edema and carrageenan-induced paw edema models, with selected derivatives showing greater efficacy than ibuprofen. Other ketonic derivatives enhanced neutrophil phagocytic activity, complement activation, and catalase levels in chronic inflammation models. Double Mannich bases derived from benzofuranones also markedly suppressed TNF-α and IL-6 production, although their cytotoxicity was higher than that of dexamethasone. Methionine-containing Mannich bases produced substantial inhibition of acute and chronic inflammation, approaching the activity of diclofenac and indomethacin. Phenolic Mannich bases have shown promising activity through multiple anti-inflammatory pathways. Several derivatives inhibited carrageenan-induced paw edema, TNF-α and IL-6 production, and inducible nitric oxide synthase (iNOS)-mediated NO production. Chalcone-derived Mannich bases demonstrated selective COX-2 inhibition, with some derivatives showing greater activity than aspirin, while halogen substitution influenced their potency. Benzoxazine and chalcone-derived Mannich bases also produced significant inhibition of paw edema, with selected compounds exhibiting activity comparable to or greater than indomethacin. Coumarin-based Mannich bases were particularly notable, with selected derivatives showing approximately 1.6-fold greater anti-inflammatory activity than indomethacin without significant COX-1 inhibition. Mannich modification of irisolidone further enhanced inhibition of nitric oxide production compared with the parent compound. Heterocyclic Mannich bases, particularly derivatives of 2,3-dihydro-1,2,4-triazole-3-thiones, have also demonstrated substantial anti-inflammatory potential. Several compounds showed activity comparable to ibuprofen, celecoxib, or diclofenac in carrageenan-induced paw edema models, while selected derivatives exhibited low-nanomolar COX-2 inhibition. Morpholine

and methylpiperazine substituents were frequently associated with enhanced activity. Related oxadiazole-thione and benzoxazolinone Mannich bases also produced moderate-to-potent inhibition of inflammatory edema, with selected derivatives approaching the efficacy of diclofenac or indomethacin. Isatin-derived Mannich bases generally showed moderate-to-significant anti-inflammatory activity, with potency influenced by the nature of the aminoalkyl substituent. In some series, increasing lipophilicity of the amino group reduced activity, indicating the importance of physicochemical properties in optimizing efficacy. Benzimidazole Mannich bases also significantly reduced paw edema, although their activity varied with substitution and dose. Mannich bases derived from diverse heterocyclic and natural-product scaffolds have further expanded the anti-inflammatory profile of this chemical class. Pyrimidinoazepine derivatives produced moderate activity, whereas aminomethylated pyridazinones bearing thiophene showed substantial inhibition of paw edema, with one derivative achieving approximately 95% of the activity of indomethacin. Betulonic-acid-derived Mannich bases also demonstrated scaffold-dependent activity, with the piperidine derivative approaching the efficacy of indomethacin. Overall, these findings demonstrate that Mannich bases represent versatile anti-inflammatory scaffolds capable of modulating multiple inflammatory pathways, including COX-2, iNOS, TNF-α, IL-6, and oxidative-stress-related mechanisms. Their activity is strongly influenced by the core pharmacophore, amino substituent, aromatic substitution, and lipophilicity, providing useful directions for structure–activity relationship studies and the development of safer anti-inflammatory agents (Refaat *et al*., 2007; Vasilevsky *et al*., 2009).

9. Analgesic activity

Pain commonly accompanies inflammation; therefore, the analgesic potential of Mannich bases is frequently evaluated alongside their anti-inflammatory activity. Several ketonic Mannich bases derived from 2-arylidenecyclohexanones demonstrated analgesic effects comparable to ibuprofen in acetic acid-induced writhing and hot plate models. A *p*-toluidine-derived derivative showed particularly strong activity, while selected methylsulfonyl-substituted analogues also exhibited effective analgesic action. Phenolic Mannich bases derived from naphthol scaffolds have also been investigated, although evidence remains limited because only a small number of compounds were evaluated without comparison with standard analgesics. One derivative produced 92% inhibition of writhing, whereas its oxygen analogue showed only 30% inhibition, indicating a strong influence of structural modification on analgesic efficacy. Heterocyclic Mannich bases, particularly 2,3-dihydro-1,2,4-triazole-3-thiones, demonstrated promising analgesic activity. Selected derivatives showed efficacy comparable to ibuprofen, while other analogues produced tail-flick responses approaching pentazocine. Ibuprofen-derived oxadiazole-thione Mannich bases were particularly notable, with selected compounds exhibiting greater analgesic activity than diclofenac. Benzoxazolinone Mannich bases also showed moderate-to-potent analgesic effects, with several derivatives achieving activity comparable to or exceeding aspirin. In some series, analgesic activity was consistently greater than anti-inflammatory activity, suggesting a possible central analgesic component. Isatin-derived Mannich bases generally produced moderate analgesic protection, although quinazoline-containing derivatives bearing dimethylamine or diethylamine exhibited analgesic activity comparable to or greater than diclofenac at early time points. Benzimidazole Mannich bases similarly demonstrated moderate-to-good analgesic activity, with selected 2-styrylbenzimidazole derivatives showing activity approaching that of paracetamol. However, some derivatives required substantially higher doses than the reference analgesics, indicating limitations in potency and therapeutic selectivity. Mannich bases derived from substituted isothiazolopyridines also demonstrated analgesic potential in both writhing and hot plate models. Derivatives containing aryl- or benzyl-substituted piperidine and substituted phenylpiperazine groups were among the most active. Subsequent structural optimization produced compounds with analgesic potency 2-10-fold greater than aspirin, although they remained 1.5-10-fold less potent than morphine. Overall, Mannich bases represent versatile scaffolds for analgesic drug discovery, with activity influenced by the pharmacophoric core, aminoalkyl substituent, aromatic substitution, and lipophilicity. The repeated observation of activity comparable to established analgesics supports further optimization of these compounds, particularly toward improved potency, duration of action, and safety (Srivastava *et al*., 2013; Malinka *et al*., 2005).

10. Antioxidant activity

Reactive oxygen species (ROS) can cause oxidative stress by promoting lipid peroxidation, DNA damage, and protein oxidation. Although endogenous antioxidant systems protect cells, synthetic antioxidants may be useful when ROS levels exceed physiological control. Mannich reaction has therefore been widely explored to develop antioxidant molecules with improved radical-scavenging properties. Several ketonic Mannich bases derived from 3-acetylcoumarin and 2-acetylbenzofuran showed moderate DPPH radical-scavenging activity, with the most active derivatives achieving about 65% inhibition compared with 90% for butylated hydroxy-toluene (BHT). Electron-withdrawing substituents generally reduced antioxidant activity. Phenolic Mannich bases, particularly derivatives of thymol and 4,6-diacetylresorcinol, demonstrated enhanced inhibition of lipid peroxidation and xanthine oxidase compared with their parent compounds. Some piperidine-containing derivatives also showed moderate-to-high DPPH scavenging activity. Mannich modification of established antioxidants and flavonoids has produced several promising compounds. Apigenin, scutellarein, and quercetin Mannich derivatives exhibited concentration-dependent radical-scavenging activity, with selected derivatives showing greater antioxidant potential than the parent flavonoids. Quercetin Mannich bases were also effective in inhibiting A2E photooxidation, indicating potential relevance to oxidative retinal damage. In contrast, some chalcone-derived Mannich bases showed only weak DPPH activity, highlighting the importance of structural features in determining antioxidant efficacy. Notably, Mannich bases derived from 2,3-dihydro-1,2,4-triazole-3-thiones showed DPPH scavenging activity comparable to ascorbic acid. A particularly promising series containing a 2,3-dihydrobenzo[b][1,4]dioxine moiety demonstrated strong and broad-spectrum antioxidant activity in DPPH, ABTS, and ferric-reducing assays. Selected derivatives also inhibited lipid peroxidation more effectively than Trolox, suggesting that appropriate incorporation of antioxidant pharmacophores through Mannich functionalization can substantially enhance activity. N-Mannich bases of succinimide, phthalimide, saccharin, and pyrazoline have likewise displayed antioxidant effects through DPPH, ABTS, nitric oxide, and lipid-peroxidation assays. In several cases, their activity was comparable to established standards such as ascorbic acid,

vitamin E, or rutin. Overall, these findings demonstrate that Mannich functionalization is a valuable strategy for optimizing antioxidant activity, particularly when phenolic, heterocyclic, or electron-donating pharmacophores are incorporated into the molecular framework (Chernyshenko *et al*., 2010; Hamama *et al*., 2011).

11. Antihypertensive activity

Although relatively few studies have explored Mannich bases as antihypertensive agents, several derivatives have demonstrated promising blood-pressure-lowering effects. Phenolic Mannich bases, particularly those containing thiomorpholine, produced dose-dependent reductions in systolic, diastolic, and mean arterial pressure, along with a significant decrease in heart rate. Among these, a double Mannich base (283) showed particularly strong antihypertensive activity in spontaneously hypertensive rats. Replacement of thiomorpholine with morpholine and incorporation of a 1,4-dihydropyridine moiety resulted in reduced activity, suggesting that amine substitution and steric features around the phenolic group influence antihypertensive potency. Mannich derivatives of 2-naphthol and naphthyloxybutanoic acids also exhibited significant blood-pressure-lowering effects. Some derivatives produced responses comparable to or greater than propranolol in experimental animal models, indicating potential cardiovascular activity of aminomethylated naphthol scaffolds. Other Mannich bases containing imidazo[1,2-a]benzimidazole frameworks significantly reduced arterial blood pressure in rats, with some derivatives showing greater potency than the reference drug dibazole. Substituent variation also influenced activity, with selected aminomethylated analogues demonstrating improved antihypertensive effects. In contrast, several octahydroquinazoline Mannich derivatives showed little effect on blood pressure or heart rate. However, specific structural modifications produced significant reductions in systolic and diastolic pressure with rapid onset and minimal cardiac effects. Interestingly, one chloro-substituted derivative produced a sustained increase in blood pressure without tachycardia, suggesting that appropriate Mannich modification may generate compounds with potential hypotensive as well as antihypertensive activity. Overall, these findings indicate that Mannich functionalization can generate structurally diverse cardiovascular agents, with antihypertensive activity strongly influenced by the phenolic pharmacophore, amine substituent, steric environment, and heterocyclic scaffold (Siddiqui *et al*., 2010; El-Sabbagh *et al*., 2010).

12. Antiparasitic activity

Mannich bases have been investigated against several parasitic pathogens beyond *Plasmodium*, particularly *Trypanosoma*, *Leishmania*, *Entamoeba histolytica*, and *Schistosoma*. Their activity is of interest because these parasites are responsible for important neglected tropical diseases. The trypanothione-trypanothione reductase system is a promising antiparasitic target because it is essential for parasite survival and differs significantly from mammalian antioxidant systems. Unsaturated ketonic Mannich bases were shown to inhibit trypanothione reductase after enzymatic reduction, with their reactive deamination products acting as the actual inhibitors. Although, their activity against intracellular parasites was modest, selected derivatives showed significant activity against extracellular *Trypanosoma brucei*. Subsequent melarsoprol-inspired Mannich bases also inhibited trypanothione reductase and displayed activity against *T. brucei*, although cytotoxicity limited their therapeutic potential. Pyrazolopyridine-based Mannich derivatives demonstrated promising antileishmanial activity against *Leishmania amazonensis*, with selected compounds showing nanomolar IC_{50} values and greater activity than the reference aminoquinoline drug amodiaquine. These findings also support the potential of the pyrazolopyridine scaffold as a quinoline bioisostere. Mannich bases have also shown significant antiamoebic activity against *E. histolytica*. Piperazine-containing derivatives of 2,3-dihydro-1,3,4-oxadiazole-2-thione were active against the parasite, and selected compounds exhibited greater potency than metronidazole with relatively low cytotoxicity. In addition, praziquantel-derived Mannich bases displayed in vitro activity against *Schistosoma*. Two derivatives produced complete parasite killing at micromolar concentrations, although their potency remained lower than that of praziquantel. Overall, these findings indicate that Mannich functionalization can generate diverse antiparasitic scaffolds, with trypanothione reductase inhibition, reactive electrophilic groups, and appropriate heterocyclic/amine substituents contributing to activity. However, cytotoxicity and limited intracellular activity remain important challenges for further optimization (Wenzel *et al*., 2009; Kamel *et al*., 2013).

13. Antiplatelet activity

Platelet aggregation is essential for normal hemostasis, but excessive activation can lead to pathological thrombus formation and contribute to cardiovascular disorders such as myocardial infarction, stroke, and peripheral vascular disease. Consequently, inhibition of platelet aggregation is an important therapeutic strategy, and several Mannich bases have demonstrated promising antiplatelet and antithrombotic activity. A series of phenolic Mannich bases showed significant inhibition of ADP- and collagen-induced platelet aggregation, with several derivatives exhibiting greater potency than clopidogrel. Some compounds produced 90-100% inhibition in both models. Structure–activity studies indicated that a pyridyl group and a meta-hydroxyl substituent relative to the carbonyl group enhanced platelet aggregation inhibition, highlighting the importance of appropriate electronic and hydrogen-bonding features. Mannich derivatives of scutellarein also showed enhanced thrombin inhibition compared with the parent compound. The morpholine-containing derivative was particularly potent, with docking studies suggesting that the morpholinylmethyl group occupies the S3 pocket of thrombin while the scutellarein moiety forms multiple hydrogen bonds within the active site. These interactions may contribute to its improved anticoagulant potential. Mannich bases incorporating an imidazo [1, 2 - a] benzimidazole scaffold were also effective against ADP-induced platelet aggregation, with several derivatives showing lower EC_{50} values than acetylsalicylic acid. In addition, indole-based Mannich derivatives designed as PAR-1 antagonists effectively inhibited thrombin-mediated platelet aggregation. Selected 6-aminoindole derivatives demonstrated approximately five-fold greater potency than the reference PAR-1 antagonist, whereas corresponding 5-aminoindole analogues were weak or inactive. Overall, these studies demonstrate that Mannich functionalization can enhance antiplatelet activity through multiple mechanisms, including inhibition of platelet aggregation, thrombin inhibition, and PAR-1 antagonism. Phenolic hydroxyl groups, pyridyl substituents, morpholine-containing aminomethyl groups, and appropriately positioned indole pharmacophores appear particularly important for activity (Severino *et al*., 2008; Vijaya Bhaskar Reddy *et al*., 2011).

14. Antiulcer activity

Peptic ulcer disease results from an imbalance between gastric aggressive factors, including acid, *Helicobacter pylori*, NSAID use, alcohol, and oxidative stress, and protective mechanisms such as mucus, bicarbonate, prostaglandins, mucosal blood flow, and antioxidant defenses. Although, only a limited number of studies have examined Mannich bases as antiulcer agents, several derivatives have shown promising gastroprotective and antisecretory effects. S-aminomethyl derivatives of 4,6-diaryl-2-mercaptopyrimidines demonstrated protection against aspirin-induced gastric ulcers in rats. Several compounds provided more than 50% ulcer protection, although their efficacy remained below that of omeprazole, which showed approximately 99% protection. These findings suggest that appropriate aryl substitution can contribute to the gastroprotective activity of Mannich derivatives. Mannich bases derived from 1,4-dihydropyrimidines and sulfanilamide also exhibited significant antiulcer activity by reducing gastric acid secretion. Selected derivatives containing methoxy-, hydroxy-methoxy-, or furyl substituents produced low ulcer indices, although omeprazole remained more potent at a lower dose. Aminomethylated furo[3,2-g]flavones showed moderate gastroprotective activity in an ethanol-induced ulcer model, with protection indices of approximately 20-44%. Notably, derivatives containing a methoxy group were more active than their corresponding hydroxy analogues, indicating that substitution pattern and lipophilicity may influence gastroprotective efficacy. Overall, available evidence suggests that Mannich modification can impart antiulcer activity through gastroprotective and acid-suppressive mechanisms. Methoxy-substituted aromatic groups, heterocyclic scaffolds, and suitable aminomethyl functionalities appear to contribute to activity, although further pharmacological and mechanistic studies are required to establish their therapeutic potential (Ragab *et al*., 2007; Subudhi *et al*., 2009).

15. Psychiatric and CNS activity

Mannich bases have been investigated as potential antidepressant, anxiolytic, and sedative-hypnotic agents, reflecting the ability of aminomethylation to generate structurally diverse CNS-active molecules. Ketonic Mannich bases derived from substituted acetophenones and 4-benzylpiperidine were developed as analogues of selective serotonin reuptake inhibitors (SSRIs). Although, the final SSRI-like derivatives lacked significant antidepressant activity, the intermediate ketonic Mannich bases demonstrated antidepressant effects comparable to fluoxetine, sertraline, and imipramine in the forced-swimming test in mice. This finding highlights the potential of the Mannich ketone pharmacophore itself for CNS activity. Computer-assisted screening using the PASS prediction approach identified several Mannich bases as potential anxiolytics. Compounds based on ketonic, imidazobenzothiazole, and imidazopyridine scaffolds produced significant anxiolytic effects in the conflict test, with selected derivatives showing activity comparable to or greater than medazepam. One nitro- and phenyl-substituted imidazopyridine Mannich base demonstrated approximately two-fold greater potency than the reference drug. Mannich bases containing a benzoxepin scaffold also exhibited sedative-hypnotic activity in the phenobarbital-induced sleep model. Selected piperidine-, methylpiperazine-, and morpholine-containing derivatives reduced sleep latency and prolonged hypnotic duration, with some compounds showing activity comparable to phenobarbital. Importantly, the nature of the amine moiety markedly influenced activity, indicating a clear structure-activity relationship. Overall, these findings demonstrate that Mannich functionalization is a useful strategy for developing CNS-active compounds, with activity extending across antidepressant, anxiolytic, and sedative-hypnotic profiles. The biological response appears strongly dependent on the heterocyclic scaffold, carbonyl-containing Mannich framework, and nature of the incorporated amine substituent (Köksal *et al*., 2007; Abdel Gawad *et al*., 2012).

16. Enzyme inhibitory activity

Mannich bases have been extensively investigated as enzyme inhibitors, with activity reported against cholinesterases, α-glucosidase, purine nucleoside phosphorylase (PNP), transglutaminase, carbonic anhydrase, cyclin-dependent kinases, methionine aminopeptidase, squalene-hopene cyclase, tyrosinase, and other therapeutic targets. These studies demonstrate that Mannich functionalization can generate potent enzyme-directed pharmacophores, although most evidence remains in vitro, and direct therapeutic efficacy has not been established.

16.1 Cholinesterase inhibitors

Tacrine-based Mannich hybrids incorporating an 8-hydroxyquinoline pharmacophore were designed as multifunctional inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), while also providing antioxidant and metal-chelating properties. Compounds containing an unsubstituted 8-hydroxyquinoline ring and a 7-10-carbon linker showed the highest potency, with selected derivatives exhibiting nanomolar inhibition of human AChE (0.5-5.5 nm) and BuChE (6.5-55 nm). The derivative with a seven-carbon linker was the most potent dual inhibitor. Other Mannich hybrids combining tacrine and indanone pharmacophores showed dual-site cholinesterase inhibition. One derivative displayed good BuChE inhibition (0.6 nM) and moderate AChE inhibition (25 nm), highlighting the influence of linker length on enzyme binding. 2-Benzoxazolone mono- and bis-Mannich bases produced moderate AChE inhibition, with the piperazine-derived bis-Mannich derivative being the most active. Phenolic xanthone Mannich bases also showed moderate-to-good AChE/BuChE inhibition relative to galantamine. Diethylamine-containing derivatives were generally more potent, while increasing the bulk of the substituent favored BuChE selectivity. These findings indicate that amine substitution, linker length, phenolic functionality, and molecular flexibility strongly influence cholinesterase inhibition.

16.2 α-Glucosidase inhibitors

Phenolic Mannich derivatives of the flavanone oroxylin A showed improved inhibition of intestinal α-glucosidase compared with the parent compound, although they remained less potent than acarbose. The nature of the amine component was important, with alicyclic secondary amines generally providing better activity than acyclic analogues. Ketonic Mannich bases derived from nabumetone exhibited modest α-glucosidase and protein-tyrosine phosphatase-1B inhibition, while some derivatives also acted as peroxisome proliferator-activated receptor agonists. Further structural modification using sulfanilamide or 3-amino-5-methylisoxazole generated additional α-glucosidase inhibitors. Sulfonamide-containing derivatives were more active than their aminoisoxazole analogues, with a 4-bromo derivative producing approximately 80% inhibition at 10 μg/ml. Incorporation

of a 4-aminobenzoic acid moiety also improved activity compared with ethyl 4-aminobenzoate analogues, demonstrating the importance of acidic and hydrophilic substituents for enzyme inhibition.

16.3 Purine nucleoside phosphorylase inhibitors

Mannich chemistry has also contributed to the development of transition-state analogues of purine nucleoside phosphorylase (PNP). Aminomethylated 9-deazahypoxanthine derivatives, known as immucilin-type inhibitors, mimic the transition state of purine metabolism. Although several directly synthesized Mannich derivatives showed only modest PNP inhibition, simplified open-chain analogues displayed remarkable potency, with *K*i values of 9.0 and 5.0 pM. These findings demonstrate that appropriate stereochemistry, amino-alcohol functionality, and transition-state mimicry are critical for high-affinity PNP inhibition. Mannich-based transition-state inhibitors have similarly been explored against other purine-metabolizing enzymes.

16.4 Inhibitors of other enzymes

Ketonic Mannich bases have shown particularly strong inhibition of transglutaminase, with activity highly dependent on both the ketone-derived aryl group and the amine substituent. Heteroaryl groups such as thienyl, benzothienyl, furyl, pyridyl, and pyrazinyl generally outperformed phenyl or naphthyl groups. Secondary aliphatic amines containing *tert*-butyl, isopropyl, benzyl, or hydroxyethyl substituents produced potent inhibitors, with one derivative exhibiting an IC_{50} of 81 nM. Incorporation of disulfide-containing amine fragments further enhanced activity, with some Mannich derivatives showing approximately 300-fold greater potency than the corresponding parent disulfides. Other enzyme-directed Mannich bases include phenolic derivatives with limited activity against carbonic anhydrase, while baicalein-derived Mannich bases showed a marked improvement in cyclin-dependent kinase inhibition, being 6-20 times more potent than the parent flavone. The presence of an aminomethyl group at C-8 and an additional heteroatom-containing amine such as morpholine, thiomorpholine, or N-methylpiperazine appeared favorable for activity. Nitroxoline Mannich bases efficiently inhibited methionine aminopeptidase-1 from *Burkholderia pseudomallei*, with IC_{50} values extending from low micromolar concentrations to approximately 30 nM, and some derivatives also inhibited bacterial growth *in vitro*. Acetylenic Mannich bases derived from chromenone inhibited squalene-hopene cyclase, with one derivative displaying approximately half the potency of the reference inhibitor Ro 48-8071. A particularly notable example was provided by oxadiazolethione N-Mannich bases, which inhibited mushroom tyrosinase and were reported to be 6-10 times more potent than kojic acid. Their activity was attributed to the thione group capable of copper chelation, together with hydrophobic interactions of the cyclic amine within the enzyme-binding site. In contrast, several Mannich bases tested against protein kinases and *Schistosoma mansoni* cercarial elastase were inactive, emphasizing the importance of scaffold-specific structural requirements. Overall, these findings demonstrate that Mannich functionalization is a versatile strategy for enzyme-targeted drug discovery. Enzyme inhibition is strongly influenced by the nature of the heteroaromatic/phenolic pharmacophore, amine substituent, linker length, hydrogen-bonding capacity, metal-chelating groups, and overall molecular topology. Nevertheless, most reported activities are based on biochemical or cellular assays, and further selectivity, pharmacokinetic, toxicity, and in vivo studies are required to establish the therapeutic potential of these compounds (Lam *et al*., 2010; Wangtrakuldee *et al*., 2013; Bektaº *et al*., 2013).

17. Receptor and receptor ligands modulators

Mannich bases have been investigated as ligands and modulators of several G-protein-coupled and nuclear receptors, particularly serotonin, dopamine, androgen, histamine, sigma, adrenergic, muscarinic, and chemokine receptors. Their activity is strongly influenced by the heteroaromatic scaffold, amine substituent, linker length, and electronic properties of aromatic substituents.

17.1 5-Hydroxytryptamine (5-HT) receptor ligands

Mannich bases were evaluated for affinity toward 5-HT_1A and 5-HT_2 A receptors in relation to their potential anticonvulsant activity. The compounds showed moderate-to-low affinity, with *K*i values of 81-370 nM for 5-HT A and 126-1370 nM for 5-HT, A. Cyclohexyl-substituted analogues were slightly more active than cyclopentyl derivatives, while substitution on the aryl group of piperazine influenced receptor selectivity. A 2-methoxy substituent favored 5-HT_2A affinity, whereas a 3-CF_3 group enhanced 5-HT_2 A binding. Computer-aided design also identified imidazolidine-2,4-dione Mannich bases with a desirable dual 5-HT_1A receptor/serotonin transporter profile. Phenolic Mannich derivatives of quinoxaline-2-carboxamides were investigated as 5-HT_3 receptor antagonists. Mono-Mannich derivatives generally outperformed the corresponding bis-Mannich analogues. One chlorinated derivative containing a 4-methylpiperazine aminomethyl group showed antagonistic activity comparable to ondansetron. Replacement of chlorine by methoxy or ethoxy groups reduced potency, while piperazine substituents were generally more favorable than other cyclic amines.

17.2 Dopamine receptor ligands

Mannich functionalization has been particularly successful in generating dopamine D_4 receptor-selective ligands. Imidazo [1, 2-*a*] pyridine and pyrrole Mannich bases showed selective D_4 binding, with the imidazopyridine derivatives being more potent. Selected compounds containing 2-ethoxy, dichloro, or trifluoromethyl substituents exhibited low-nanomolar D_4 affinity and greater selectivity than clozapine. Several other heteroaromatic Mannich bases also demonstrated selective D_4 receptor binding. Pyrrolo [3,2-*d*] pyrimidine derivatives displayed *K*i values of approximately 2.4–3.8 nm, whereas the nature of the cyclic amine markedly influenced activity; pyrrolidine-containing derivatives were superior to morpholine analogues. Indole Mannich bases were particularly potent, with one derivative exhibiting an exceptional D_4 affinity of 0.03 nm. Collectively, these findings highlight the importance of indole/azaindole pharmacophores and appropriately substituted piperazine or pyrrolidine groups for D_4 receptor recognition. In contrast, replacement of arylpiperazine groups with other monocyclic or bicyclic amines generally produced weaker dopamine receptor ligands. Some derivatives displayed moderate D_3 or D_4 affinity, but selectivity was usually limited. Thus, amine-ring architecture is a major determinant of dopamine receptor subtype selectivity.

17.3 Thyroid hormone receptor–coregulator interaction inhibitors

Ketonic Mannich bases have emerged as a distinctive class of thyroid hormone receptor (TR) antagonists that interfere with the interaction

between TR and steroid receptor coactivator-2 (SRC2). Initial compounds showed preferential activity toward the TRβ isoform. Mechanistic studies demonstrated that these Mannich bases can undergo deamination to generate reactive α, β-unsaturated ketones, which act as the true inhibitory species. The unsubstituted enone generated from the Mannich precursor showed the highest activity and was found to alkylate a cysteine residue within the TRâ activation-function-2 pocket, thereby blocking coactivator recruitment. Subsequent SAR optimization demonstrated that electron-withdrawing aromatic substituents, together with sulfonyl-containing groups and piperazinone/4-acetylpiperazine moieties, improved potency and reduced cytotoxicity. Optimized derivatives displayed strong TR-SRC2 inhibition, favorable therapeutic indices, and minimal hERG-related ion-channel activity, illustrating the potential of Mannich bases as covalent receptor modulators.

17.4 Ligands of other receptors

Ketonic Mannich bases were also developed as non-steroidal androgen receptor (AR) antagonists. SAR studies showed that a para-chloro substituent and an electron-withdrawing group were favorable for AR binding, while phenyl, 2-furyl, and 2-thienyl groups were tolerated. Selected derivatives showed stronger AR binding than 5α-dihydrotestosterone and inhibited androgen-responsive cell proliferation, while heteroaryl analogues generally displayed lower cytotoxicity. Related Mannich bases were subsequently identified as selective progesterone receptor antagonists, demonstrating how substituent combinations can tune receptor selectivity. Mannich bases have additionally been explored against muscarinic, nicotinic, sigma, histamine H_3, α-adrenergic, and CCR_3 receptors. Quaternary aminomethylated derivatives showed limited muscarinic M, activity but greater affinity for muscle-type nicotinic acetylcholine receptors. An indole Mannich base displayed moderate affinity for both sigma-1 and sigma-2 receptors, whereas cyclic ketonic Mannich derivatives showed receptor selectivity dependent on the amine and fused-ring system. Six-membered fused-ring analogues were generally more favorable, and one derivative showed approximately 10-fold preference for sigma-2 over sigma-1 receptors. Indole Mannich bases bearing carboxamide groups exhibited promising histamine H*f* receptor antagonism, particularly with 3,6-substitution and piperidine or morpholine-containing aminomethyl groups. In contrast, 4-substituted piperazines were poorly tolerated. Mannich bases derived from tetrahydrocarbazolones and 3-acetylindole showed only modest α-adrenergic receptor affinity, although the open-chain indole analogues provided a slight improvement. Pyrazolone Mannich bases were also identified as CCR_3 ligands, a receptor implicated in allergic asthma. Initial compounds showed nanomolar binding but suffered from poor solubility and metabolic stability. Subsequent introduction of ionizable groups improved physicochemical properties, with optimized derivatives reaching IC_{50} values as low as 12 nm. Conversely, some pyrazole-derived Mannich bases showed negligible activity against neurokinin NK-2/NK-3 receptors. Overall, receptor-focused studies demonstrate that Mannich functionalization can efficiently generate selective receptor ligands, particularly for 5-HT, dopamine D_4, nuclear, histamine H_3, sigma, and chemokine receptors. The biological response is highly dependent on heteroaromatic topology, amine identity, linker geometry, electronic substituents, and receptor-specific hydrophobic and hydrogen-bonding interactions. These SAR observations provide useful guidance for designing Mannich-based receptor modulators with improved potency and selectivity (Borioni *et al*., 2007; Romeo *et al*., 2006; Du *et al*., 2010).

18. Conclusion

Over the past decade, extensive research on Mannich bases has demonstrated their versatility as bioactive molecules, prodrugs, and modulators of diverse therapeutic targets. The growing structure activity relationship data obtained from structurally diverse Mannich scaffolds have provided valuable insights for rational optimization and the development of more potent drug candidates. Particular progress has been achieved in anticancer and antimicrobial research, where the Mannich reaction has been widely employed to modify established drugs and biologically active natural products to enhance their pharmacological properties. Beyond introducing biological activity, aminomethylation can also modulate key physicochemical characteristics, including solubility, lipophilicity, stability, and bioavailability, thereby influencing overall drug performance. Collectively, these findings establish the Mannich reaction as a valuable medicinal chemistry strategy for generating structurally diverse chemical entities and optimizing existing pharmacophores toward improved therapeutic efficacy.

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