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Review

Synthesis of Antifungal Heterocycle-Containing Mannich Bases: A Comprehensive Review

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Abstract: Mannich bases are a class of organic compounds usually obtained by the condensation reaction between an amine, a compound with active hydrogens, and an aldehyde. They are versatile intermediates in organic synthesis, and those compounds containing this motif find applications in pharmaceutical, agrochemical, and even material fields since they are widely known for their wide range of biological activities, including antimicrobial properties. Thus, as part of our interest in antifungal agents, this narrative review aimed to gather information from the literature on the synthesis of various representative Mannich-base-containing compounds, particularly centered on those exhibiting antifungal properties. In this context, the compilation indicated that Mannich bases could be considered as a relevant toxophore/pharmacophore by incorporating heterocyclic moieties to be implemented for the design of new antifungal agents, given its proven efficacy against phytopathogens, other opportunistic human pathogens, and some dermatophytic fungal species, which can be further exploited as agrochemical agents or in medicinal applications to treat fungal infections. The antifungal effect exhibited by Mannich bases conjugated with oxa and/or aza-heterocycles suggests that compounds that have a heterocyclic system attached to the β-amino core are attractive alternatives oriented to the synthesis of novel and helpful antifungal agents.

Keywords: Mannich bases; antifungal activity; heterocyclic derivatives; agrochemical agents

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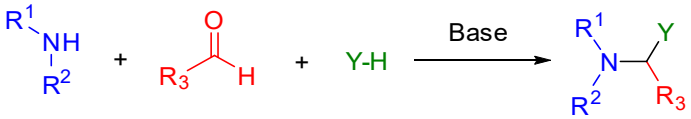
1. Introduction

Mannich bases are structurally defined as 2-amino-ketones, compounds that contain the NCH_2Y fragment with a central electrophilic carbon atom in the presence of two geminal heteroatoms, one of which is nitrogen. Mannich bases have been explored for their potential biological properties in drug design, especially *O*-Mannich bases (>NCH_2OR) or *N*-Mannich bases (>$NCH_2NR^1R^2$) [1,2]. They are usually formed from the condensation of an amine, a non-enolizable aldehyde (e.g., formaldehyde (HCOH)), and a hydrogen-active compound (Scheme 1). This reaction, consisting of the nucleophilic addition of the non-enolizable aldehyde and any primary or secondary amine to form a resonance-stabilized imine intermediate (iminium ion or imine salt), is known as the Mannich reaction. A carbanion of an acid compound with active hydrogens (e.g., any enolizable carbonyl compound, amide, carbamate, hydantoin, or urea) favors an attack on the imine, giving rise to the formation of the Mannich base. The Mannich reaction has been proposed in several alkaloid biosynthetic pathways. Furthermore, it is one of organic synthesis's most versatile carbon–carbon bond formation methodologies [3–5].



Scheme 1. Traditional schematic representation for Mannich reaction.

Numerous adjustments have been implemented to enhance the efficacy of the Mannich reaction to form carbon–carbon bonds. In this sense, exploiting ionic liquids (ILs) amalgamated those merits from conventional molecular solvents and molten salts. These ILs hold promise as innovative reaction mediums, exhibiting broad utility in both catalytic and non-catalytic reactions. Certain Mannich bases were derived from α-imino glyoxylate ethyl substrates by employing an amino acid catalyst (e.g., L-proline) and an IL as a solvent (e.g., [bmim][BF_4]), achieving superior performance, enantioselectivity, and faster reaction times at ambient temperature [6]. Transition metal salts have served as catalysts for diverse Mannich and Mannich-type reactions [7–12]. Moreover, organocatalysis has been harnessed through various activation modes, comprising the activation of (1) nucleophiles through chiral amines to form enamine, (2) nucleophiles via chiral bases to yield chiral enolates, and (3) imines with chiral Brønsted acids [13].

Mannich bases are well recognized as pivotal pharmacophores and bioactive scaffolds, often utilized in the synthesis of potential medicinal agents featuring aminoalkyl chains [14]. These Mannich bases exhibit a wide array of promising properties, encompassing anti-inflammatory, anticancer, antifilarial, antibacterial, antifungal, anticonvulsant, anthelmintic, antituberculous, analgesic, anti-HIV, antimalarial, antipsychotic, and antiviral effects, among others. Beyond their biological roles, Mannich bases are valued for their incorporation into detergents, resins, polymers, and surfactants. Noteworthy instances of clinically relevant Mannich bases containing aminoalkyl chains encompass fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, procyclidine, ranitidine, and biperiden—illustrating their pivotal contributions to pharmaceutical chemistry, both as bioactive compounds and as building blocks in synthesis [15].

Given the relevance involved in controlling fungal infections, particularly opportunistic human and animal pathogens and even plant pathogens that affect crops of economic importance in agriculture, several reports have demonstrated the use of Mannich bases and their potential as antifungal agents, some obtained from natural products [16–20]. In this regard, thymol, a natural monoterpene phenol derived from cymene, used to treat the respiratory, nervous, and cardiovascular systems [21] and protect food from phytopathogens, has been recently used to produce a series of derivatives, including some Schiff and Mannich bases, and assessed against insects [22]. These derivatives were also analyzed under in vitro conditions, identifying their potential as antifungals against three pathogenic fungi of maize, *Fusarium moniliforme, Rhizoctonia solani*, and *Dreschlera maydis*, showing promising results for controlling *D. maydis*. Studies under greenhouse conditions showed that thymol significantly controlled the leaf blight disease of corn, so it can be considered an alternative to synthetic fungicides and pesticides in cereal crops [23]. Recently, Legesse et al. used knipholone (a compound of natural origin isolated from *Kniphofia foliosa hochst*, which possesses a structure based on anthraquinone [24]) as the precursor of a series of Mannich bases, which showed high solubility and potential antimicrobial activity against eight pathogenic bacterial and fungal strains. The potential MIC values of the fungus *Trichophyton mentagrophytes* were around 78.2 μg/mL, evidencing the potential biological activities of these aminoalkyl derivatives of knipholone [25]. Thus, several studies have demonstrated the influence of the chemical structure of Mannich bases and their potential use in the chemical control of opportunistic fungal pathogens.

With these considerations in mind, the current review was constructed based on three significant motivations centered around identified gaps: (1) compiling information particularly centered on those Mannich bases that have antifungal activity against different fungal microorganisms with relevance in the agricultural and medicinal sectors since there is no review dedicated to this topic, (2) providing a valuable perspective by gathering those antifungal Mannich bases that are conjugated with different heterocyclic moieties since there is a lack of such a perspective in the existing literature, and (3) summarizing the main contributions in synthesizing antifungal heterocycle-containing Mannich as a helpful survey on the different synthetic strategies to produce this kind of bioactive agents. Based on these motivations, this review encompasses the period from 2000 to 2023, and it

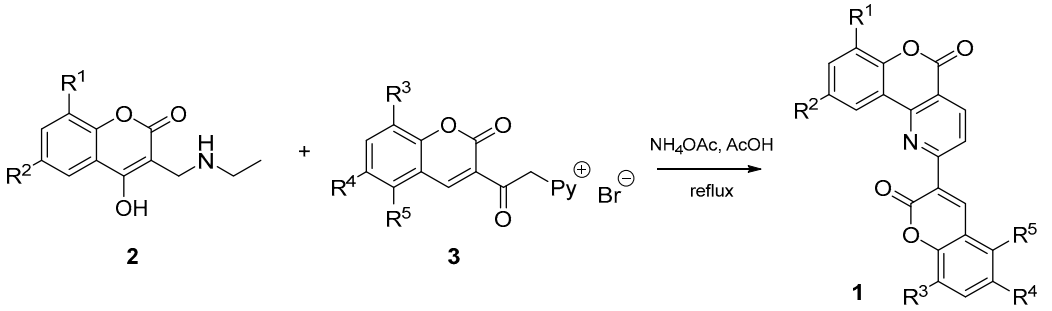
emerges from a comprehensive, non-systematic search across various databases (Scopus, Web of Science, PubMed consulted in Cajicá, Colombia) to aggregate the relevant sources. A meticulous analysis of the compiled information narrows the focus to heterocyclic-based Mannich bases, categorized into three subsections: oxygen-containing heterocycles, nitrogen-containing heterocycles, and heterocyclic systems with mixed heteroatoms.

2. Heterocyclic-Based and/or Oxygenated Mannich Bases

2.1. Oxygen-Containing Heterocyclic Systems and Oxygenated Compounds

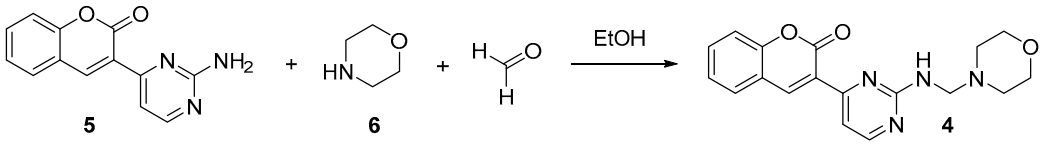
2.1.1. Coumarin Derivatives

Coumarins (2*H*-chromen-2-one) are some of the most abundant natural products and comprise a great diversity. They have been attributed a role as part of the defense system of plants since many of these have been shown to have bactericidal, fungicidal, and/or fungistatic activity and, mainly, an efficient activity as insecticides [26]. A series of coumarins based on 5*H*-chromeno [4,3-*b*]pyridin-5-one, **1**, were synthesized by Patel using two methodologies involving the Mannich base derived from 4-hydroxycoumarin, **2** (Scheme 2), on the one hand, and 4-chloro-3-formylcoumarin as precursors, on the other. The Mannich base is believed to have decomposed, leading to the generation of coumarin methide. This intermediate was condensed with salt **3** under reflux and using ammonium acetate and acetic acid, yielding a coumarin intermediate. This intermediate then undergoes a Krohnke reaction, affording the desired product, **1**. These Mannich base derivatives were found to be active against the fungal pathogens *Aspergillus niger* (MTCC 282) and *Candida albicans* (MTCC 227). Notably, methyl and chlorine substitutions demonstrated enhanced activity compared to other analogs, displaying MIC values of 200 and 250 µg/mL against *C. albicans* (MTCC 227) [27].



Scheme 2. Synthesis of 2-(2-oxo-2*H*-chromen-3-yl)-5*H*-chromeno[4,3-b]pyridin-5-ones.

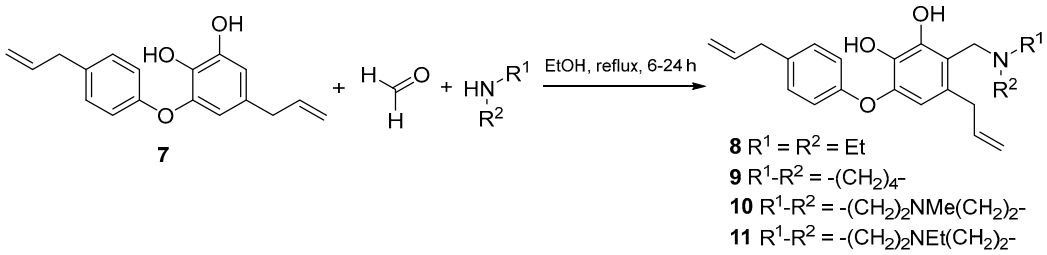
In a separate study, Imran synthesized 3-(2-((morpholinomethyl)amino)pyrimidin-4-yl)-2*H*-chromen-2-one, **4**, by reacting 3-(2-aminopyrimidin-4-yl)-2*H*-chromen-2-one, **5**, with morpholine, **6**, and HCOH (Scheme 3). These morpholine–pyrimidine–coumarin adducts were evaluated for antimicrobial activity against a set of opportunistic pathogens such as *C. albicans* (ATCC 2091), *Aspergillus niger* (MTCC 281), *Aspergillus flavus* (MTCC 277), *Monascus purpureous* (MTCC 369), and *Penicillium citrinum* (NCIM 768). The minimum inhibitory concentrations (MICs) of these compounds were performed through the serial plate dilution method using ofloxacin and ketoconazole as standard drugs. Some test products exhibited weaker antifungal activity than ketoconazole, with higher MIC values. Others failed to match the ketoconazole inhibitory activity even at higher concentrations. Structure–activity relationship considerations identified that the presence of chlorine at position 2 of the aromatic ring, coupled with a chlorobromine-substituted coumarin moiety, was pivotal for activity against certain fungi. Remarkably, these compounds demonstrated more potent antifungal activity than ketoconazole against *P. citrinum* [28].



Scheme 3. Synthesis of 3-(2-((morpholinomethyl)amino)pyrimidin-4-yl)-2*H*-chromen-2-one.

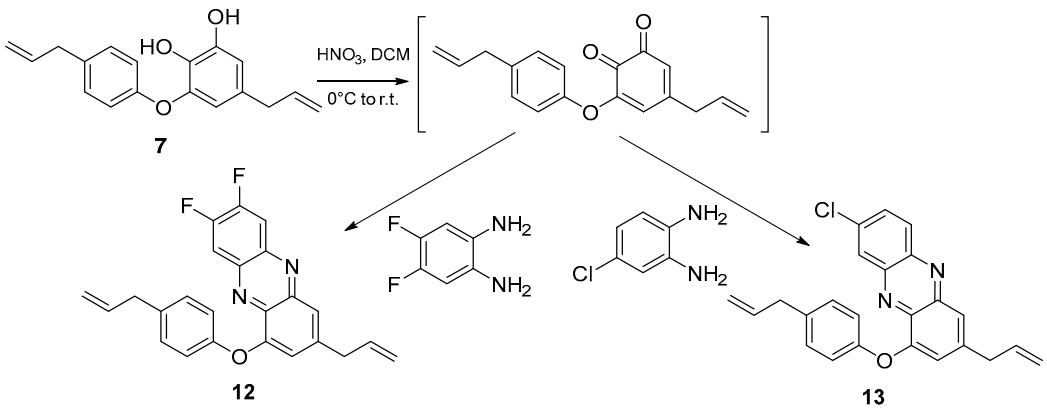
2.1.2. Allylphenol Derivatives

Obovatol, **7**, a natural dimeric allylphenol isolated from various sources, possesses antioxidant, antiplatelet, antifungal, and anti-inflammatory properties. Recent investigations have examined Mannich base derivatives of **7** as plausible fungicides (Scheme 4). These derivatives, obtained through C-4-amino methylation of **7**, were evaluated for inhibitory effects on spore germination and mycelial growth against phytopathogenic fungi. Notably, compounds **8** and **9** significantly inhibited *Botrytis cinerea* spore germination, while compounds **10**, **11**, and **9** exhibited a potent inhibition of *B. cinerea* mycelial growth. The structure–activity relationship analysis indicated that certain substituents at the C-4 position of **7** led to more potent antifungal derivatives. Chlorine substitution and chlorobromine-substituted coumarin residues were particularly effective [29–31].



Scheme 4. Synthesis of 4-allyl-6-(4-allylphenoxy)-3-(dialkylaminomethyl)benzene-1,2-diol type compounds.

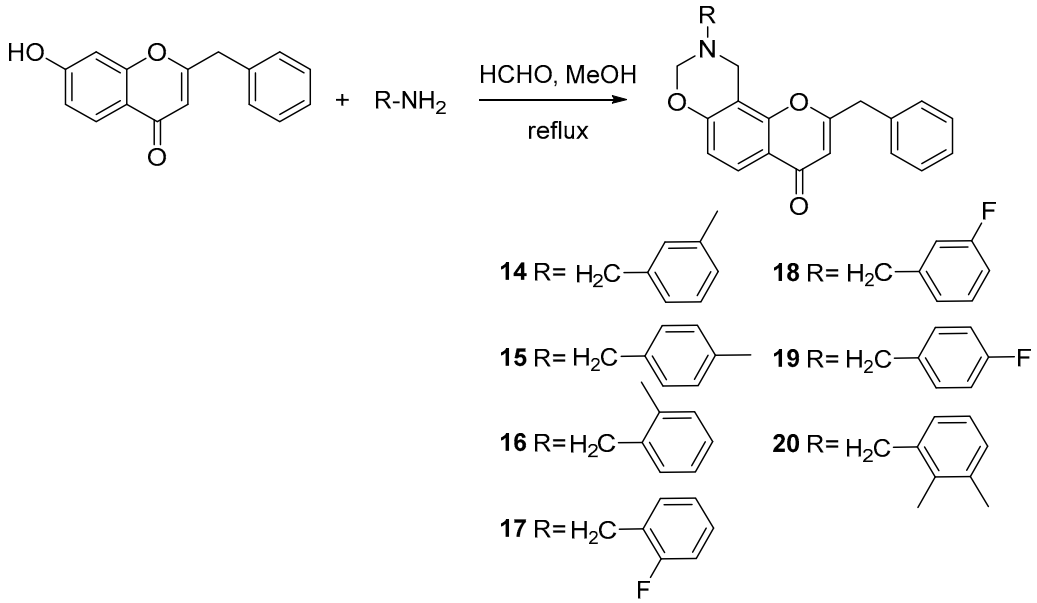
Continuing their studies, Yang et al. obtained sixteen novel derivatives via a cyclization methodology. They treated **7** with nitric acid and then reacted it with aromatic 1,2-diamine (Scheme 5). These derivatives were also evaluated for antifungal activity against phytopathogenic fungi. Interestingly, most compounds exhibited reduced antifungal activity compared to the precursor **7**, contrary to prior findings for Mannich bases. While none displayed antifungal activity against *Alternaria solani*, certain compounds showed better inhibitory activity against *Fusarium solani*. Specifically, compounds **12** and **13** demonstrated the highest inhibitory activity against *F. solani*. These findings suggested that introducing a monosubstituted benzene ring with electron-withdrawing groups (EWG) might lead to potential antifungal compounds [32].



Scheme 5. Synthesis of halogenated 3-allyl-1-(4-allylphenoxy)-phenazine.

2.1.3. Flavonoid Derivatives

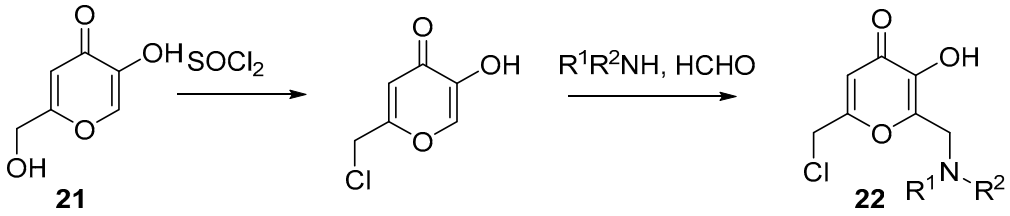
Flavonoids, a class of polyhydroxyphenolic natural products, are characterized by the flavan nucleus (2-aryl-2*H*-chromene). They are abundant in fruits, vegetables, and plant-based beverages and are known for their various antioxidant, antibacterial, and anti-inflammatory properties. Flavonoids have shown promise in synergistic combination therapy with conventional drugs against fungal pathogens, addressing the rising drug resistance in fungal infections. A series of oxazine flavonoids were synthesized by Ma et al. through a double Mannich reaction cyclization (Scheme 6). These oxazine flavonoids exhibited broad-spectrum fungicidal activities against several plant pathogenic fungi. Some compounds displayed excellent bioactivities against specific fungal phytopathogens, so introducing the oxazine motif in these adducts provided better activity. In addition, the position of the substituents on the benzene ring influenced fungicidal activity. In this regard, the EWG substituents on the benzene ring generally enhanced inhibitory activity [33–35].



Scheme 6. Synthesis of 2-benzyl-9-alkyl-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-ones.

2.1.4. 4*H*-Pyran-4-one Derivatives

Kojic acid, **21**, is a heterocyclic compound of natural origin having a 4*H*-pyran-4-one moiety, which can be obtained from several fungal fermentations. It is usually used as a depigmentation product, mainly attributed to tyrosinase inhibition. Antioxidant, antibacterial, and anti-inflammatory activities have also been reported [36]. Aytemir et al. synthesized a series of compounds related to **22** from **21** (Scheme 7). The antifungal activity of these derivatives against dermatophyte fungi such as *Microsporum gypseum*, *Trichophyton mentagrophytes varerinacei*, and *Epidermophyton floccosum* was evaluated, showing that some derivatives showed high activity against *E. floccosum* (MIC: 4 μg/mL). The current activity of the starting material chlorokojic acid (MIC: 8 μg/mL) was increased by these Mannich bases. According to the cytotoxicity assessment, Mannich bases were also found to be active as chlorokojic acid but safer (MNTC: ≥512 μg/mL and ≥256 μg/mL). The activity against *E. floccosum* was found to range between 4 and 8 μg/mL, showing high action compared with the chlorinated precursor (MIC: 8–16 μg/mL). Regarding the antidermatophytic activity against *M. gypseum*, the MIC values were around 4 μg/mL. These results confirmed the enhancing effect of Mannich bases on biologically active heterocyclic natural compounds [37].

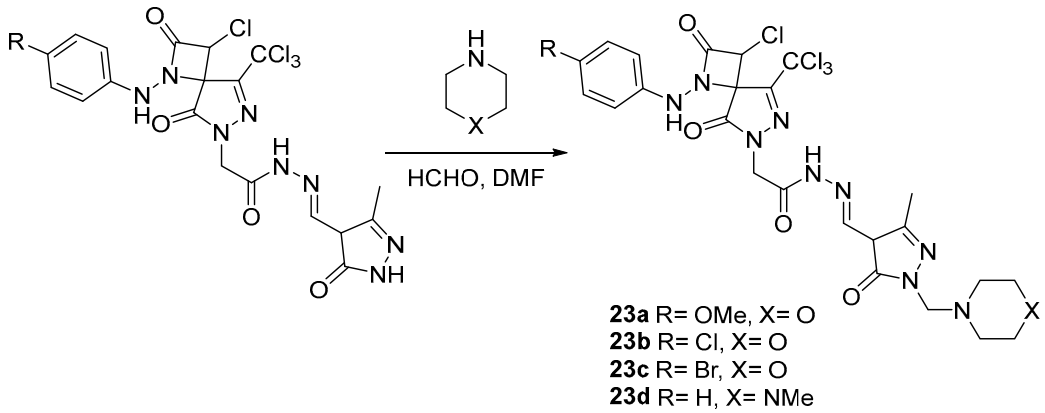


Scheme 7. Synthesis of 2-(dialkylaminomethyl)-6-(chloromethyl)-3-hydroxy-4H-pyran-4-ones.

2.2. Nitrogen-Heterocycle Derivatives

2.2.1. 2-Azetidinone Derivatives

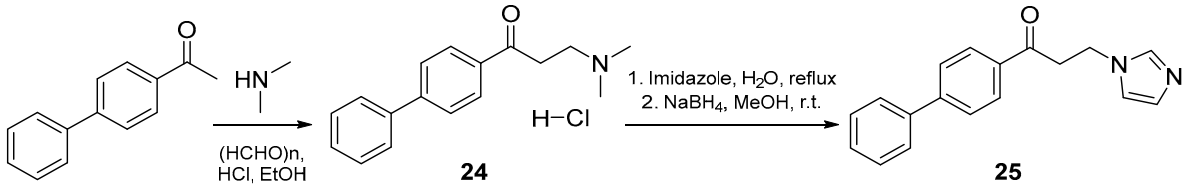
Within small heterocyclic systems, the 2-azetidinone structural core is exceptionally versatile and helpful and has appeared in many widely used biologically active chemical compounds [38]. Some 2-azetidinone derivatives have shown potent ability as cephalosporinase and ezetimibe inhibitors, cholesterol absorption inhibitors, mechanism-based inhibitors of various enzymes such as human tryptase, chymase, thrombin, leukocyte elastase, protease of the human cytomegalovirus, and the enzyme serine protease. In addition, its antituberculous, anti-inflammatory, antitumor, anti-HIV, antiparkinsonian, antidiabetic, antimicrobial, and antifungal activities have been described [39]. Mannich bases derived containing the 2-azetidinone motif (**23**) have recently been synthesized (Scheme 8), and their antimicrobial activity was also evaluated, whose outcome involved significant bioactivity. In particular, the activity of **23a**, **23b**, **23c**, and **23d** was comparable to that of the standard antibiotics commonly employed. Compound **23d** with the *N*-methylpiperazine substituent showed a satisfactory result, allowing them to infer that the presence of the halogen and methoxy groups in position 4 and also that the presence of the *N*-CH_3 group in the piperazine ring improved the tested biological activities [40].



Scheme 8. Synthesis of 1,6,7-triazaspiro[3.4]oct-7-en-6-yl)-*N*′-((1,3-dimethyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)methylene)acetohydrazide type compounds.

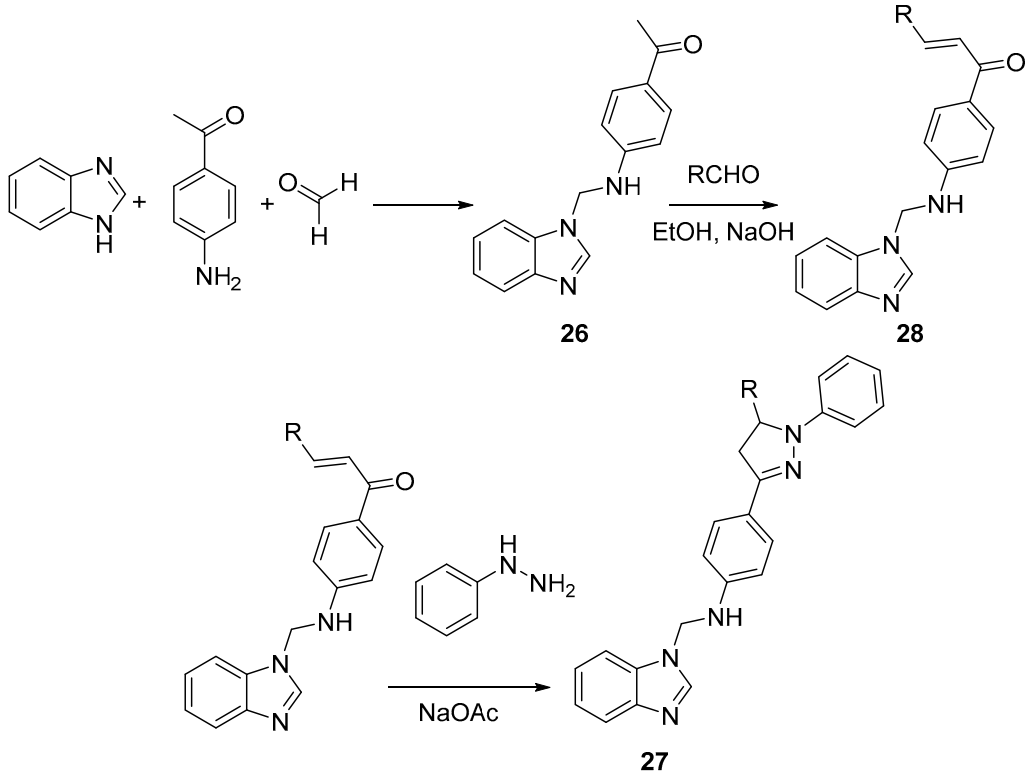
2.2.2. Azole Derivatives

Heterocyclic compounds such as imidazoles and benzimidazoles have distinctive roles in the scope of chemistry and pharmacology due to their versatile properties. They exhibit a wide array of bioactivities, encompassing antibacterial, anticancer, antituberculosis, analgesic, anti-HIV, and antifungal effects [41,42]. This class of derivatives has demonstrated potential in inhibiting various agriculturally relevant fungi, including *Fusarium oxysporum*, *Rhizoctonia solani*, *Botrytis cinerea* Pers, *Gibberella zeae*, *Dothiorella gregaria*, and *Colletotrichum gossypii* [43]. In a notable study by Roman et al., a series of β-aminoketone Mannich bases were synthesized through the *N*-alkylation of imidazole with 3-dimethylamino-1-aryl-1-propanone hydrochloride, **24** (Scheme 9). The antifungal potency of these compounds was assessed against sixteen *Candida* strains. Particularly, 3-(1*H*-imidazol-1-yl)-1-(4-biphenylyl)-1-propanone, **25**, was recognized as a broad-spectrum antifungal compound, even surpassing fluconazole against certain *Candida* strains [44].



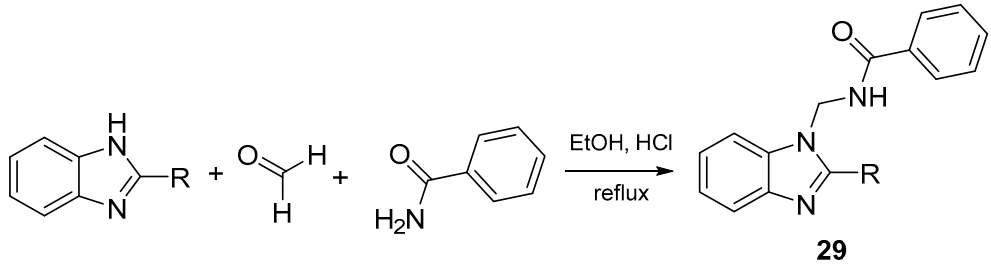
Scheme 9. Synthesis of 1-([1,1′-biphenyl]-4-yl)-3-(1*H*-imidazol-1-yl)propan-1-one.

Krishnanjaneyulu et al. explored the potential of Mannich bases featuring the benzimidazole heterocyclic moiety, **26**, in developing new antifungal agents (Scheme 10). They synthesized *N*-((1*H*-benzoimidazol-1-yl)methyl)-4-(1-phenyl-5-substituted-4,5-dihydro-1*H*-pyrazol-3-yl)benzenamine compounds, **27**. These derivatives demonstrated promising antimicrobial properties against human pathogenic fungi and bacteria [45].



Scheme 10. Synthesis of *N*-((1*H*-benzo[d]imidazol-1-yl)methyl)-4-(5-alkyl-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl)anilines.

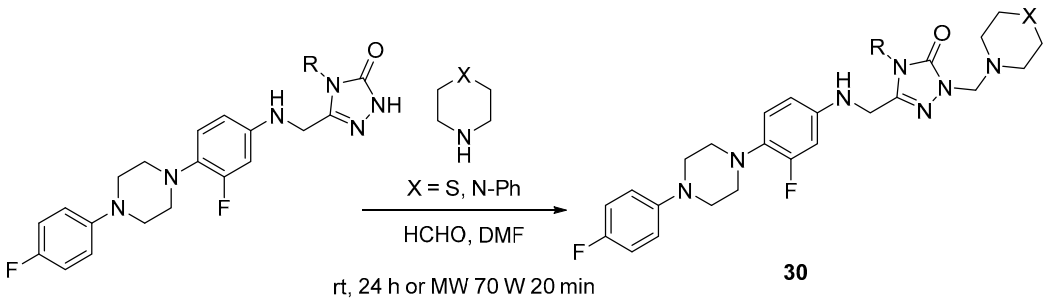
Sethi et al. obtained *N*-benzimidazol-1-yl-methylbenzamide derivatives, **29** (Scheme 11), through Mannich reactions, exhibiting substantial antimicrobial activity against various strains, particularly those containing electron-accepting substituents on the benzene ring [46].



Scheme 11. Synthesis of N-((2-alkyl-1H-benzo[d]imidazol-1-yl)methyl)benzamides.

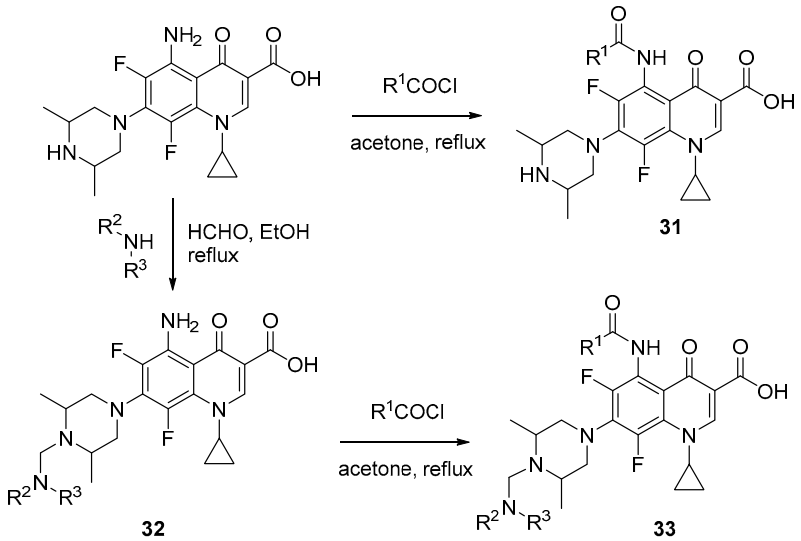
2.2.3. Piperazine Derivatives

The piperazine heterocyclic system, known for its versatile biological activities, has attracted attention in drug development [47]. Piperazine's distinct structural features allow for diverse modifications. Recent endeavors involve piperazine-based antimicrobial polymers despite challenges in their handling and stability [48]. Ozdemir et al. synthesized Mannich bases, **30** (Scheme 12), featuring piperazine and 2,4-dihydro-3*H*-1,2,4-triazol-3-one heterocyclic rings, revealing good-to-moderate antimicrobial action [49].



Scheme 12. Mannich reaction using piperazines as precursors.

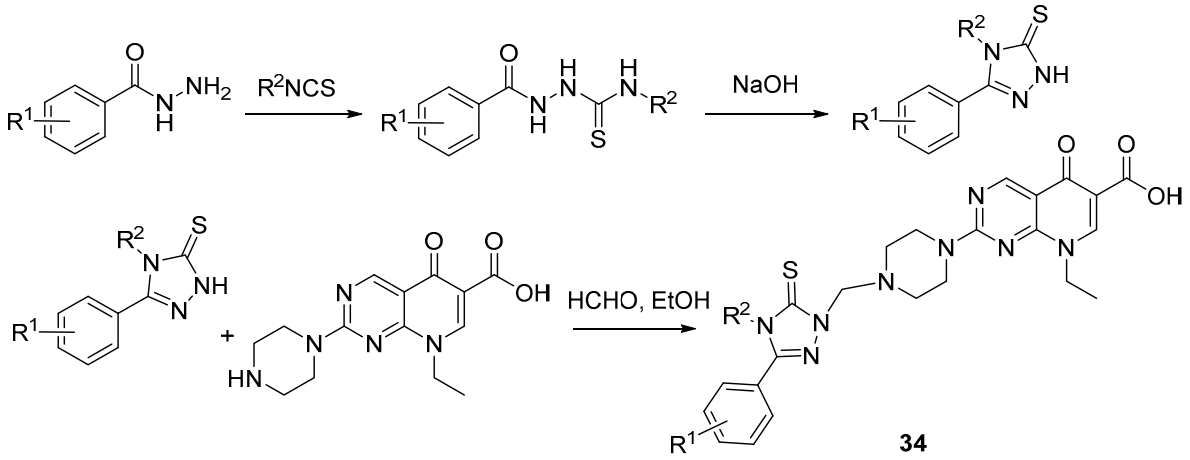
Furthermore, Kumar et al. introduced a novel class of compounds containing the piperazine ring, particularly derivatives of sparfloxacin, a fluoroquinolone antibiotic with potent antifungal properties (Scheme 13). These compounds exhibited promising antimicrobial activities against selected bacterial strains and significant antifungal effects against *C. albicans* and *A. niger* [50–53].



Scheme 13. Synthesis of 3,5-dimethylpiperazin-1-yl)-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids.

Popiolek et al. described the synthesis of some derivatives of pipemidic acid, a compound widely known in the literature for its bactericidal activity, and its use for gastrointestinal, biliary, and urinary infections [54,55]. Using a three-step synthesis strategy, the new compound series **34** was obtained using 4,5-disubstituted-1,2,4-triazol-3-thiones, which reacted with pipemidic acid. First, thiosemicarbazide derivatives were synthesized from the respective carboxylic acid hydrazides and isothiocyanates. Subsequently, the thiosemicarbazide compounds were subjected to a cyclization reaction using sodium hydroxide as the basic catalyst, producing the 1,2,4-triazol-3-thione derivatives. Finally, 1,2,4-triazol-3-thiones reacted with pipemidic acid, affording compounds **34** (Scheme 14). Some pipemidic acid derivatives, **34**, exhibited moderate or mild activity against reference

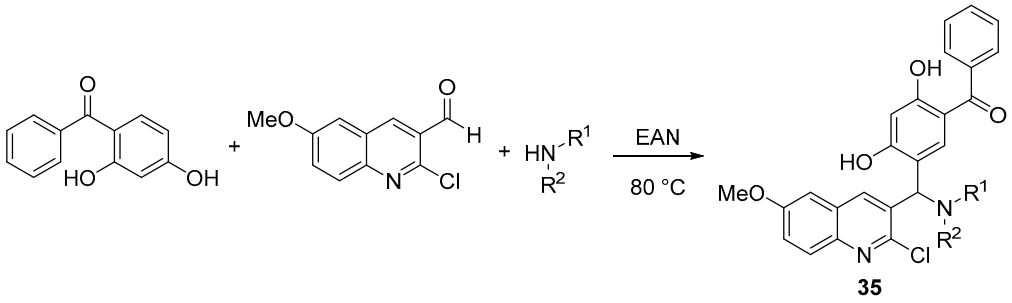
yeast fungi. Among them, compounds with R^1 = 3-OMe and R^2 = 4-OMePh inhibited the growth of all *Candida* spp. (MIC = 500–1000 µg/mL and MFC > 1000 µg/mL). However, slight activity or inactivity against *Candida* spp. was observed for the other derivatives [56].



Scheme 14. Synthesis of pipemidic acid derivatives.

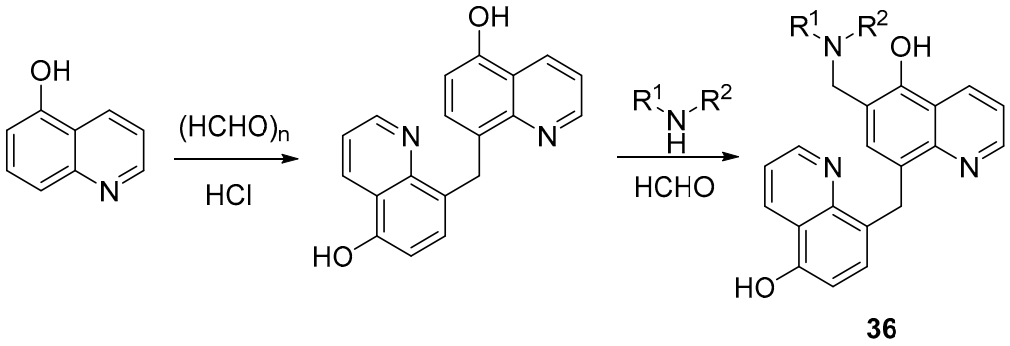
2.2.4. Quinoline Derivatives

Quinoline is a bicyclic heteroaromatic compound consisting of a six-membered benzene ring fused with pyridine, reported as an essential component in chemistry and medicine. Their quaternary ammonium salt can be used to synthesize multiple derivatives [57]. They have been demonstrated to have high biological potential due to their anticancer, antimycobacterial, antimicrobial, anticonvulsant, anti-inflammatory, cardiovascular, antibacterial, antifungal, and antiviral activities, among others reported [58,59]. Patel reported the multicomponent synthesis of several Mannich bases, **35**, with a quinoline moiety in good yield using a methodology under solvent-free conditions (Scheme 15). Thus, 2,4-dihydroxybenzophenone, a chlorinated derivative from quinoline-3-carboxaldehyde, various amines, and ethylammonium nitrate (EAN) were mixed at 80 °C. The products were in vitro explored against Gram-positive and Gram-negative bacteria and fungi, demonstrating that all compounds showed excellent antifungal activity against *C. albicans* and *A. niger*, even though some were more potent than nystatin and griseofulvin [60].



Scheme 15. Synthesis of (5-((2-chloro-6-methoxyquinolin-3-yl)(dialkylamino)methyl)-2,4-dihydroxyphenyl)(phenyl)methanones.

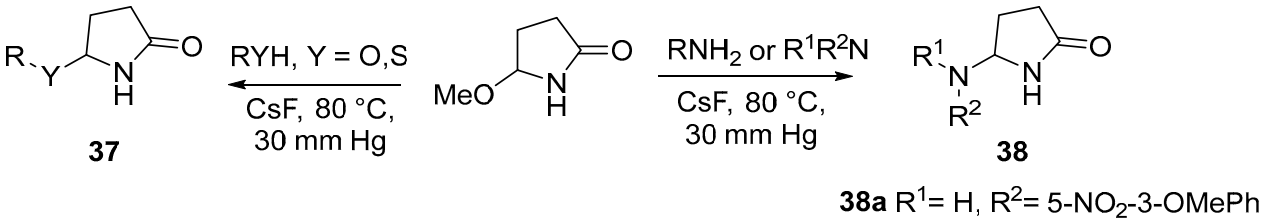
For their part, Shehab et al. synthesized several Mannich bases derived from quinolinol, **36** (Scheme 16), which were evaluated using in vitro experiments against relevant microorganisms. The antimicrobial bioassay outcome suggested that most synthesized compounds showed moderate antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. However, most compounds showed suitable activities against the evaluated fungi. In such a case, the most active compounds against *Aspergillus niger* and *Penicillium* sp. exhibited MIC values ranging from 0.25 to 2.5 mg/mL [61].



Scheme 16. Synthesis of Mannich bases derivated from 8-hydroxyquinoline.

2.2.5. Pyrrole Derivatives

Pterolactam, also recognized as 5-methoxypyrrolidin-2-one, represents a heterocyclic compound naturally occurring within the leaves of ferns, specifically *Phyteuma japonicum* [62]. Dascalu et al. devised, synthesized, and evaluated the antifungal activities of a pterolactam-derived Mannich base series, namely **37** and **38**, against nine fungal strains and three non-albicans *Candida* yeast species. These compounds were synthesized employing a solvent-free protocol at 80 °C by maintaining a mixture of pterolactam, CsF, and the nucleophile. Under these conditions, *N*,*O*-, *N*,*S*-acetals, and *N*,*N*′-aminals were produced with varying yields, ranging from moderate to excellent (Scheme 17). The inhibitory potential of these derivatives was assessed against a comprehensive spectrum of fungal and yeast strains. Based on structure–activity correlations, pterolactam *N*,*N*′-aminals demonstrated heightened antimicrobial potency compared to *N*,*O*- or *N*,*S*-acetals. Moreover, aromatic compounds featuring a nitro group showed significant promise, particularly against *F. solani*. This selection highlighted compound **38a**, characterized by R^1 = H and R^2 = 5-NO_2-3-OMePh, combining pyrrolidin-2-one and 3-methoxy-5-nitroaniline moieties, as a versatile antifungal agent boasting fungicide-like attributes and negligible cytotoxicity [63].

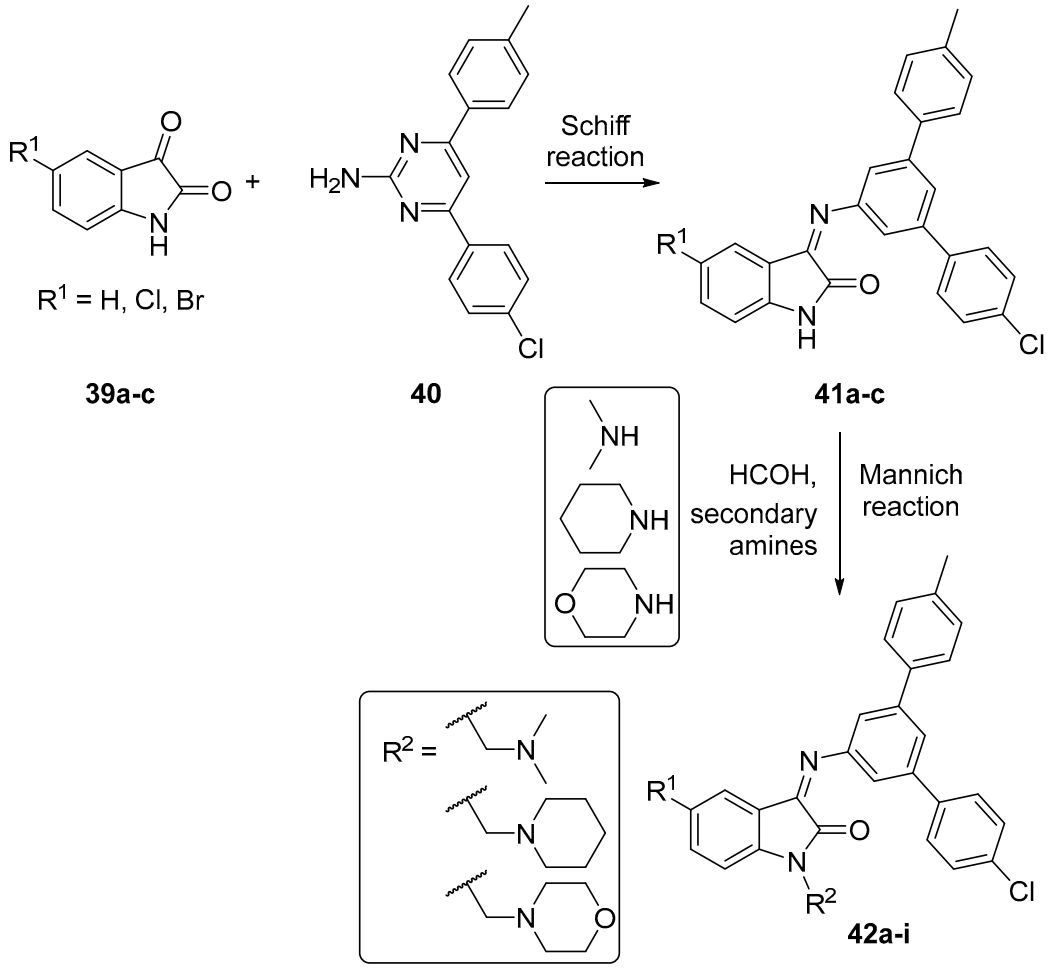


Scheme 17. Synthesis of pyrrolidin-2-one type compounds.

2.2.6. 2-Oxoindole Derivatives

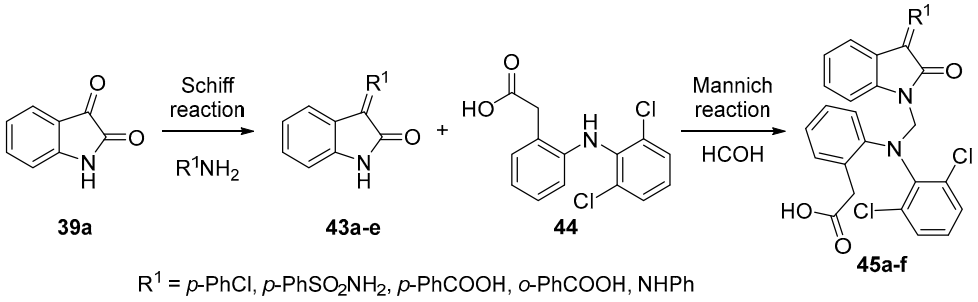
Isatin (**39a**) is a naturally occurring indole derivative (1*H*-indole-2,3-dione) renowned for its distinct structure and array of biological activities, manifesting both in natural settings and through laboratory synthesis, catering to diverse applications [64]. With its adaptable structure, isatin is a valuable foundational material for generating an extensive spectrum of compounds with diverse functions. This quality has garnered significant attention in medicinal chemistry and organic synthesis as it is a pivotal building block for intricate molecular architectures [65]. Serving as a precursor, it facilitates the creation of myriad biologically active compounds, pharmaceuticals, and dyes. Some of its derivatives stand out for their remarkable medicinal attributes, encompassing antiviral, antitumor, anti-inflammatory, and especially antimicrobial properties [66]. In this sense, a set of nine *N*-Mannich bases was prepared from the corresponding Schiff bases of 4-(4′-chlorophenyl)-6-(4″-methylphenyl)-2-aminopyrimidine (40). The Schiff bases (**41a–c**) were formed by condensing 40 with isatin derivatives (**39a–c**), and, subsequently, the corresponding *N*-Mannich bases (**42a–i**) through the reaction of the isatin acidic imino moiety with symmetrical secondary amines (substituted with methyl, morpholine, or

piperidine) and HCOH (Scheme 18). Conjugates were produced in moderate-to-good yields (47–91%) and subsequently evaluated against a panel of pathogenic bacteria and fungi (twenty-eight and eight, respectively) [67]. The target compounds displayed robust effectiveness against dermatophytes, including *Microsporum gypseum*, *M. audouinii*, and *Trichophyton mentagrophytes*, with a minimum inhibitory concentration (MIC) below 10 μg/mL. In fact, six compounds displayed an equivalent potency (4.88 μg/mL) to that of clotrimazole (the reference antifungal agent), while one compound (**42e**) demonstrated heightened activity against *M. audouinii* (MIC = 2.44 μg/mL).



Scheme 18. Synthesis of 3-iminoindolin-2-one type Mannich bases.

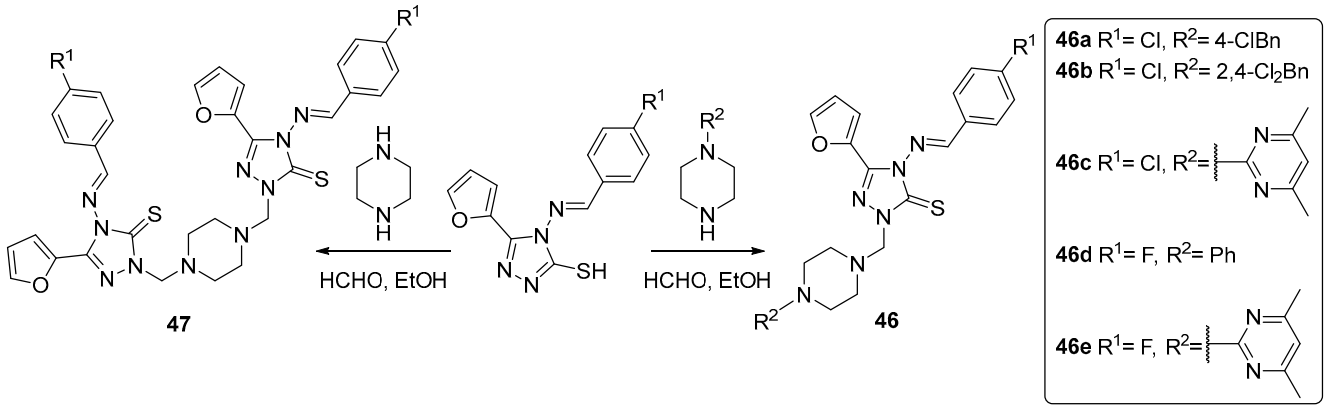
A similar strategy was employed to produce a set of six 2,3-dihydro-2-oxo-1,3-disubstituted indoles (**45a**–**f**) through condensation between isatin Schiff bases **43a**–**e** and unmodified isatin, 2-[(2,6-dichlorophenyl)amino]phenylacetic acid (**44**) and HCOH (Scheme 19). The Schiff bases were synthesized by reacting isatin with substituted anilines. The compounds yielded in the range of 43 to 78% and were also assessed against six bacteria and three fungi [68]. Within the array of synthesized Mannich bases, **45b** exhibited a moderate antibacterial effect on *B. subtilis*, while **45a**–**d** displayed a moderate response against *P. aeruginosa*. Regarding antifungal properties, **45e** (hydrazone-containing Schiff base) and **45f** (Mannich base from unmodified isatin) exhibited moderate-to-good antifungal effects on *P. notatum* (MIC = 6.25 and 12.5 μg/mL, respectively), while **45a** and **45e** moderately inhibited *A. niger* (MIC = 12.5 μg/mL). *C. albicans* was not inhibited by the test compounds (MIC > 50 μg/mL).



Scheme 19. Synthesis of Mannich bases **45** derived from isatin.

2.2.7. Heterocyclic Hybrid Derivatives

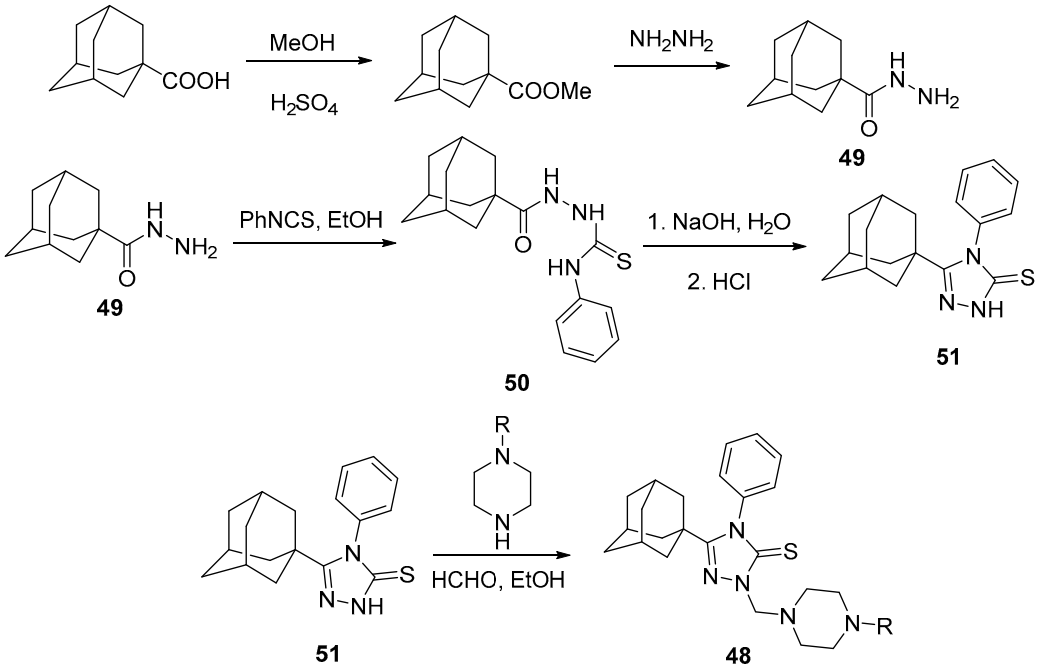
Numerous instances of combining diverse biologically active moieties within Mannich bases have been documented. Zhang et al. synthesized a novel set of piperazine- and triazole-based compounds, denoted **46** and **47**, through Mannich reactions involving a variety of triazole Schiff bases, substituted piperazine, and HCOH. This process, carried out under moderate conditions, resulted in commendable yields, thereby underscoring its industrial potential (Scheme 20). The in vitro antifungal efficacy of Mannich bases **46** and **47** was gauged by their mycelial growth inhibitory impact on several test fungi, including *F. oxysporum*, *Cercospora arachidicola*, *Phytophthora piricola*, and *R. cerealis*. Notably, compounds **46a–c** exhibited superior inhibition against *F. oxysporum* when compared to tridimefon, with compound **46a** standing out by maintaining inhibitory rates surpassing those of the commercial controls, i.e., tridimefon and chlorothalonil. The presence of a 4-chlorophenyl group (R^1 = Cl) consistently correlated with enhanced antifungal activity against *F. oxysporum*, while compounds **46d** and **46e**, with R^1 = F, R^2 = phenyl, and dimethylpyrimidyl, demonstrated heightened efficacy against *Cercospora arachidicola*. Encouragingly, all the tested compounds displayed remarkable antifungal activity against *Phytophthora piricola*, with those containing trifluoromethyl (R^1 = CF_3) displaying a distinct advantage. For *R. cerealis*, most compounds maintained robust inhibition rates ranging from 80.2% to 97.5%. Additionally, all the compounds exhibited commendable antifungal properties against *A. solani* and *G. sanbinetti*. Applying a comparative molecular field analysis (CoMFA) based on antifungal activity data established a 3D-QSAR model, highlighting steric and electrostatic fields as pivotal contributors to compound bioactivity. This insight can potentially guide the optimization of novel structures to develop more potent agrochemicals [69].



Scheme 20. Synthesis of heterocyclic hybrid Mannich bases 46.

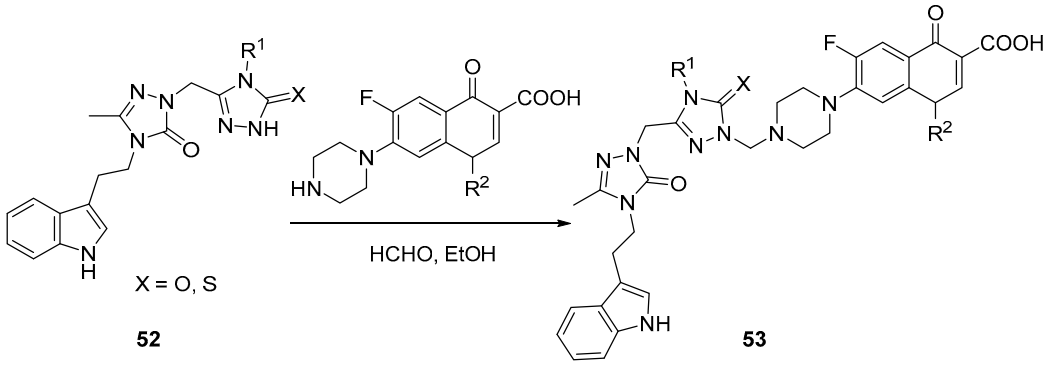
The condensation between 5-(1-adamantyl)-4-phenyl-1,2,4-triazoline-3-thione and HCOH and 1-substituted piperazines produced the respective *N*-Mannich bases, **48**. Adamantane-1-carbohydrazide, **49**, was obtained via the extended heating of methyl adamantane-1-carboxylate with hydrazine. The reaction of compound **49** with phenyl isothiocyanate produced intermediate 1-(1-adamantylcarbonyl)-4-phenylthiosemicarbazide, **50**,

which was cyclized to 5-(1-adamantyl)-4-phenyl-1,2,4-triazoline-3-thione, **51**, by heating in 10% aqueous sodium hydroxide. Compound **51** was condensed with the corresponding 1-substituted piperazine and ethanol/HCOH solution to produce the corresponding *N*-Mannich bases, **48**, in good yields (Scheme 21). The outcome of this reaction was found to be influenced by the substituent nature, reaction solvent, temperature, and the presence of a catalyst. Notably, polar protic solvents such as ethanol in the presence of strong alkaline agents favored the formation of *S*-alkyl derivatives as the main products, with *N*-alkyl derivatives having lower yields. The synthesized compounds underwent a comprehensive antimicrobial evaluation against a range of Gram-positive bacteria, Gram-negative bacteria, and *C. albicans*. The antimicrobial activity was found to be influenced by the nature of the 4-piperazine substituent and the lipophilicity. The substitution of aliphatic groups with aromatic, benzyl, or 2-pyridyl substituents increased activity against Gram-positive bacteria and imparted substantial-to-moderate activity against Gram-negative bacteria. Interestingly, the 2-pyridyl substituent demonstrated optimal bioactivity, exhibiting broad-spectrum antibacterial activity and a notable effect against *C. albicans*, notwithstanding its lipophilic nature [70].



Scheme 21. Synthesis of 5-((3r,5r,7r)-adamantan-1-yl)-2-((4-alkylpiperazin-1-yl)methyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones.

Cebeci et al. embarked on the synthesis of novel Mannich bases and conazole derivatives, incorporating a 1,2,4-triazol-3-one nucleus derived from tryptamine via a microwave-assisted methodology. The synthesis entailed the transformation of tryptamine-derived carbox(thio)amides into 1,2,4-triazole derivatives, which were subsequently subjected to HCOH-mediated Mannich reactions with various heterocyclic secondary amines (Scheme 22). The MIC values indicated that the synthesized compounds exhibited antimicrobial activity against *E. coli*, *Yersinia pseudotuberculosis*, *P. aeruginosa*, *S. aureus*, *Enterococcus faecalis*, *Bacillus cereus*, *Mycobacterium smegmatis*, *C. albicans*, and *Saccharomyces cerevisiae*. The authors concluded that the amino alkylation of triazole derivatives **52** and **53** with fluoroquinolones such as ciprofloxacin and norfloxacin improved the bioactivity of Mannich bases, with MIC values between 0.24 and 3.9 μg/mL [71,72]. The authors established that, in addition to the 1,2,4-triazole moiety, known for its biological properties, the presence of the *N*-methylpiperazine, morpholine, norfloxacin, and ciprofloxacin motifs is critical in aiding the net bioactivity of this kind of hybrid.

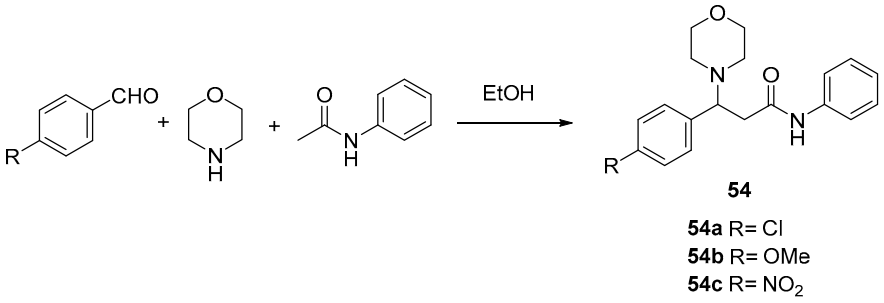


Scheme 22. Synthesis of Mannich bases derived from tryptamine.

2.3. Some Heterocyclic Derivatives with Different Mixed Heteroatoms

2.3.1. Morpholine Derivatives

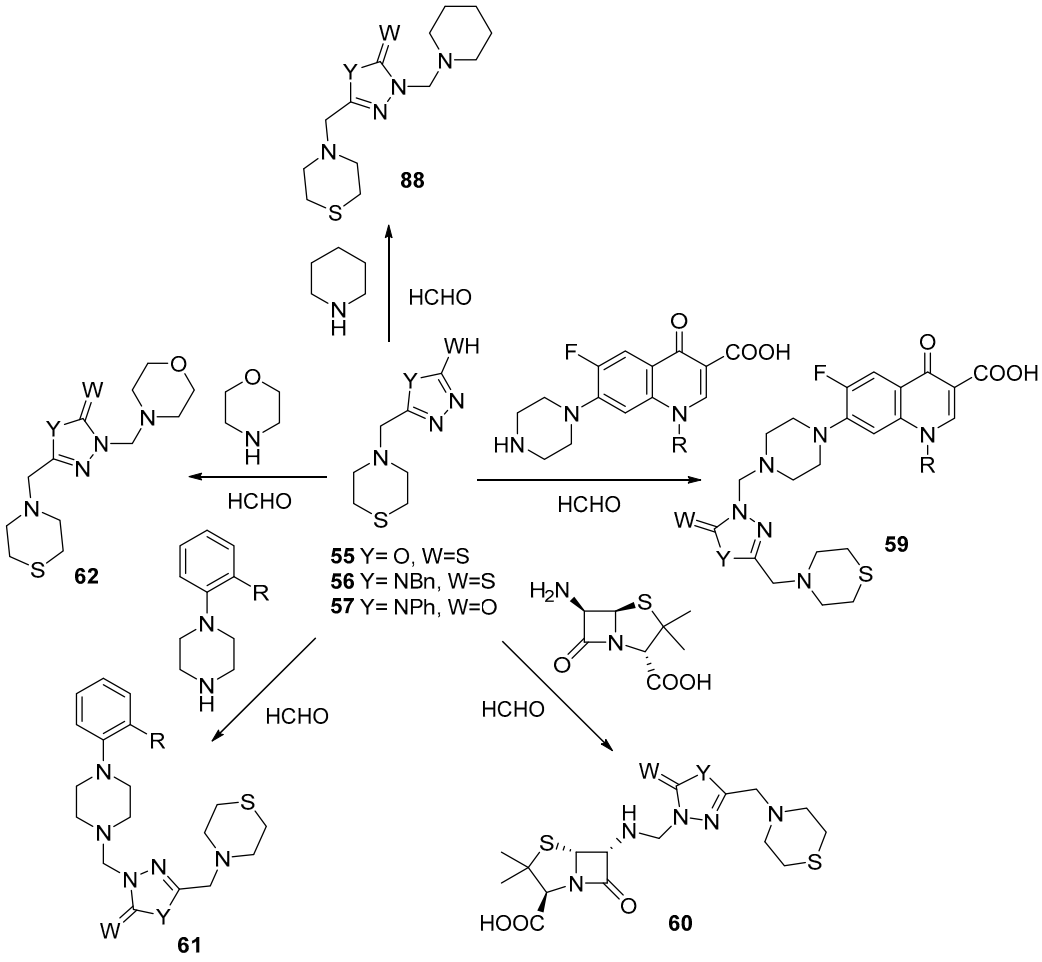
The 1,4-oxazines (morpholines) are heterocycles that can be present in numerous drugs and multiple molecules with potential biological activity, often used in medicinal chemistry. Morpholine synthesis typically involves the transformation of vicinal amino alcohols, oxiranes, and aziridines. Moreover, the morpholine ring serves as a valuable foundational component, facilitating its incorporation through standard amine reactions. Due to its favorable pharmacokinetic attributes, the morpholine nucleus has been recognized as a pharmacophore against specific enzyme inhibitors [73,74]. Idhayadhulla et al. documented the synthesis of a series of Mannich bases, characterized as 2-(phenyl)-2-(morpholine-4-yl)-*N*-phenylacetamide, **54**, employing morpholine, acetanilide, and aromatic aldehydes (Scheme 23). The antibacterial and antifungal activities of these derivatives were rigorously assessed against multiple strains, and several compounds exhibited noteworthy potential. Specifically, 3-(4-chlorophenyl)-3-(morpholine-4-yl)-*N*-phenylpropanamide, **54a**, displayed significant antibacterial activity against *Streptococcus epidermidis*, while compounds **54b** and **54c** exhibited equipotent activity against fungal strains *M. audouinii* and *C. albicans*, respectively, comparable to the established standard clotrimazole. These findings underscored the potency of these Mannich bases, further accentuating the advantageous effect of the morpholine moiety [75].



Scheme 23. Synthesis of 3-morpholino-*N*,3-diphenylpropanamides.

Thiomorpholines, saturated heterocycles comprising N and S atoms in 1,4 positions, parallel the nucleophilicity and *N*-alkylation(acylation) feasibility observed in secondary amines such as morpholine. These attributes render thiomorpholines valuable synthetic precursors [76]. Demirci et al. prepared a group of thiomorpholine-containing compounds through condensation with 1,3,4-oxadiazole, arylidenehydrazide, and 1,2,4-triazole. In addition, Mannich bases were prepared from compounds **55**–**57** using piperidine, β-lactam, fluoroquinolone, piperazine, or morpholine core, affording compounds **58**–**62**, respectively (Scheme 24). For this, three methods were used, including conventional and microwave (MW)-assisted synthesis and a catalyst. The MW irradiation offered a more efficient and greener path for Mannich-type condensation with good to high yields compared to the

long reflow time. The Mannich reaction in the presence of Lewis and Brønsted–Lowry acids demonstrated the latter's superiority, attributed to its facilitation of electrophilic iminium ion formation. The synthesized compounds were comprehensively evaluated for their antimicrobial, antiglucosidase, antilipase, antiurease, and antioxidant activities. Several compounds displayed favorable antibacterial and antifungal potential, with derivatives containing norfloxacin or ciprofloxacin backbone attached to a thiomorpholine core through an azole bond proving particularly potent. Importantly, most of these compounds exhibited MIC values surpassing those of established standard drugs such as ampicillin and fluconazole. These findings accentuate the therapeutic promise of these compounds and the synergistic role of the morpholine moiety in these Mannich bases [77].

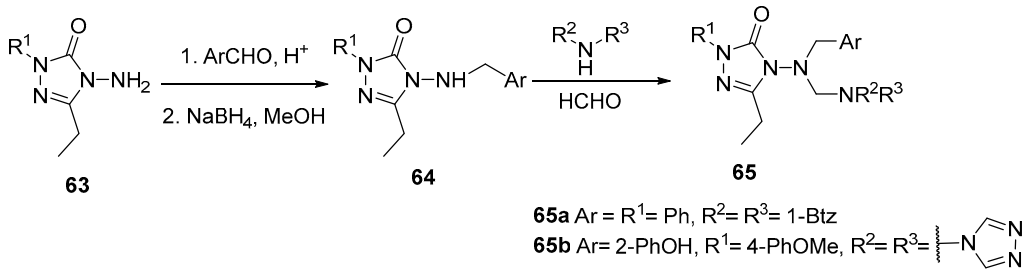


Scheme 24. Schematic representation for the synthesis of some Mannich bases derived from piperidine, β-lactam, fluoroquinolone, piperazine, and morpholine.

2.3.2. Oxadiazole Derivatives

Sydnone compounds, characterized by a 1,2,3-oxadiazole nucleus bearing a keto group at position 5, have exhibited compelling pharmacological and biological activities, rendering them relevant in plant growth regulation, fungicidal, herbicidal, and anti-algae applications [78]. Arylsydnone serves as a precursor for Mannich bases through a sequence involving the transformation of 1,3,4-oxadiazole into 1,2,4-triazolones. The condensation of compound **63** with aromatic aldehydes followed by reduction yielded a secondary amine derivative (**64**), subsequently serving as the precursor for Mannich bases **65** upon reaction with HCOH and secondary amines catalyzed by acid (Scheme 25). The synthesized compounds were rigorously evaluated for their antifungal activity against *C. albicans*, with certain compounds displaying notable promise. Remarkably, compound **65a** exhibited superior activity compared to the standard fluconazole, and compound **65b** displayed com-

parable activity. While some derivatives exhibited sensitivity to higher drug concentrations, others demonstrated potential for further development [79].



Scheme 25. Synthesis of 2,4-dihydro-3*H*-1,2,4-triazol-3-one type compounds.

3. Considerations and Future Outlook

Fungal infections significantly threaten human health and agriculture [80,81]. As traditional antifungal agents face challenges of resistance and limited efficacy [82], the exploration of innovative solutions has led researchers to a promising avenue based on heterocycle-containing Mannich bases. As described, Mannich bases are structurally defined as 2-amino-ketones with central electrophilic carbon atoms and heteroatoms such as nitrogen or oxygen. They are formed through the Mannich reaction, an essential method of carbon–carbon bond formation in organic synthesis. Notably, the Mannich reaction with various oxa- and/or aza-heterocycles has garnered attention for its remarkable potential against opportunistic fungi [83]. Indeed, the antifungal activity of Mannich bases stems from their unique molecular structure, which often combines a β-amino functionality with a carbonyl-containing moiety. This arrangement plausibly provides a platform for multifaceted interactions with fungal cells, disrupting vital cellular processes and ultimately inhibiting their growth and proliferation [84]. In addition, one of the pivotal factors contributing to the potency of Mannich bases is the possibility of expanding their structural diversity. By tailoring the substituents and heterocyclic components, their physicochemical properties can be fine-tuned, influencing their interactions with fungal membranes and intracellular targets. This diversity allows for compounds that exhibit broad-spectrum and targeted antifungal effects to be developed [84]. However, the mechanisms of action for diverse heterocycle-containing Mannich bases have not been extensively investigated. This gap in knowledge presents a valuable avenue for future research, particularly concerning compounds that display promising activity. As the field advances, incorporating computational techniques, structural biology, and high-throughput screening accelerates the discovery of potent Mannich-based antifungal candidates. Nevertheless, challenges remain in optimizing compound selectivity, pharmacokinetic properties, and formulation for clinical or practical applications [83]. Furthermore, the emergence of resistance to existing antifungal agents underscores the urgency of finding new solutions [85]. In this regard, heterocycle-containing Mannich bases, with their novel structures, offer a fresh approach to combating resistant fungal strains, and it would be even better if a multitarget action could be explored.

In this context, synthesizing antifungal heterocycle-containing Mannich bases represents a dynamic and promising field with substantial potential for scientific advancement and practical applications for managing diseases, particularly fungal infections [15]. The fusion of heterocyclic moieties with Mannich bases has proven to be an effective strategy, endowing these compounds with enhanced biological properties and expanding their scope in various fields, including pharmaceuticals and agriculture. As reflected in the current landscape, it becomes evident that the synthesis of these compounds has matured significantly. Much research has been devoted to investigating diverse heterocyclic scaffolds, refining synthetic methodologies, and uncovering structure–activity relationships. The efforts of researchers have yielded a multitude of insights into the intricate interplay between heterocyclic architecture and antifungal efficacy at in vitro levels. Looking ahead,

several exciting directions emerge that will likely shape the future of this field. First, the continual exploration of novel heterocyclic motifs remains fundamental. The quest for hitherto unexplored heterocycles, especially those with unprecedented antifungal potential, promises to unveil compounds with superior efficacy and reduced resistance. The convergence of computational techniques and experimental synthesis can accelerate this process, enabling the targeted design of innovative structures [83]. Second, the integration of sustainable and eco-friendly synthesis methodologies is gaining prominence. Green chemistry principles can guide the development of synthetic routes that minimize environmental impact and resource consumption [86]. These endeavors align with the global pursuit of greener and more sustainable practices in chemical synthesis. Furthermore, the incorporation of Mannich bases into materials science can lead to the development of functional materials with antimicrobial properties, enriching fields such as coatings, textiles, and medical devices. Finally, collaboration between interdisciplinary fields is poised to play a pivotal role in advancing the synthesis and applications of these compounds. The synergy between synthetic chemists, biologists, pharmacologists, and materials scientists will accelerate the translation of novel compounds from the laboratory to real-world solutions.

Although the synthesis of heterocycle-containing Mannich bases can be achieved in a few steps and the yields were found to be moderate-to-good (>40%), employing heterocycle-containing Mannich bases as antifungal agents can present several limitations and challenges that must be considered. The studies covered demonstrated high variability in the target microorganisms, although some relevant pathogens can be shared, which limits a broad trend about several factors. Additionally, specificity and selectivity for fungal pathogens while avoiding harm to host cells are missing, and, therefore, designing compounds that effectively target fungal cells while sparing human cells should be preferred since some heterocycle-containing Mannich bases may exhibit cytotoxicity towards human cells and other non-target organisms, which restricts their therapeutic potential or agrochemical application. Balancing antifungal activity with acceptable levels of toxicity is a significant hurdle. Finally, there is a lack of comprehensible structure–activity relationships for heterocycle-containing Mannich bases, and this is very important due to the diverse range of heterocycles and substituents involved, which can hinder rational design strategies. Addressing these limitations require interdisciplinary collaboration, innovative drug-design strategies, thorough preclinical evaluations, and a deep understanding of fungal biology.

Despite these challenges, heterocycle-containing Mannich bases hold promise as potential antifungal agents, and research efforts continue to explore ways to overcome these limitations and harness their potential applications. In this context, Mannich bases as precursors or raw materials for the preparation and development of new antifungal agents and their broader relevance in the pharmaceutical and agricultural sectors demonstrate that the Mannich reaction corresponds to one of the most valuable and versatile tools of organic chemists to carry out the correct and rational design of new bioactive molecules that can contribute to the challenging endeavor of reducing the impact of various fungal pathogens that affect sustainable development. Hence, novel Mannich bases should be aimed at the search for multitarget bioactive agents, which may be more effective by reducing resistance outbreaks and generating less environmental impact since, for instance, many of the commercial antifungal agents against phytopathogens reported in the literature are associated with residuality, soil contamination, and cytotoxicity. In this context, considering Mannich bases are labile molecules under certain pH conditions and/or moisture, their use must be subject to their stability and subsequent degradation, and, thus, the least possible environmental impact will be generated.

4. Concluding Remarks

The present survey led to the recognition of the importance of Mannich bases in designing drugs, particularly those containing heterocyclic systems, for possible biological activities and their applications as antifungal agents. Various modifications and

improvements to the Mannich reaction to improve its efficiency have been described, including using ionic liquids and transition metal catalysts. Although these Mannich bases have shown various biological activities (e.g., antibacterial, antifungal, antiviral, and anticancer), the widespread examination of this compound class has focused on their potential as antifungal agents for agricultural and medicinal purposes. Regarding the bioactivity of heterocycle-containing Mannich bases against different fungal phytopathogens, their antifungal effect has been demonstrated against *Fusarium oxysporum*, *F. graminearum*, *F. solani*, *Botrytis cinerea*, *Colletotrichum capsici*, *Cercospora arachidicola*, *Physalospora piricola*, and *Rhizoctonia cerealis*. On the other hand, various heterocycle-containing Mannich bases have been found to be active against several human pathogens such as *Aspergillus niger*, *A. fumigatus*, *Candida albicans*, *C. krusei*. and *C. parapsilosis*, as well as some dermatophytic fungi species such as *Microsporum gypseum*, *Trichophyton mentagrophytes* var. *erinacei*, and *Epidermophyton floccosum*, which are of great interest due to their opportunistic and pathogenic nature. These findings highlight the use of different oxygenated and/or nitrogenated heterocyclic systems, demonstrating that various structural modifications considerably influence their effectiveness as agrochemical or medicinal agents. In this regard, the antifungal effects demonstrated by Mannich bases that are coupled with heterocycles, e.g., chromenes, 2-arylchromen-4-ones (such as flavonoids), chromen-2-ones (such as coumarins), piperazines, imidazoles, benzimidazoles, triazoles, quinolines, pyrrolidines, 2-oxoindoles, 1,4-oxazines, 1,4-thioxazines, and 1,2,3-oxadiazoles, imply a promising avenue for future research. These findings suggest the potential of these compounds as synthetic candidates for developing useful antifungal agents in both medical and agricultural applications.

Author Contributions: Conceptualization, D.Q.; methodology, D.Q. and E.C.-B.; formal analysis, D.Q. and E.C.-B.; investigation, resources, data curation, writing—original draft preparation, D.Q.; writing—review and editing, D.Q. and E.C.-B.; project administration, funding acquisition, D.Q. and E.C.-B. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Marco-Contelles, J.; Pérez-Mayoral, E.; Ballesteros, P. Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 2:1. In *Comprehensive Heterocyclic Chemistry III*; Elsevier: Amsterdam, The Netherlands, 2008; pp. 199–305. [CrossRef]
2. Testa, B. Prodrug Objectives and Design. In *Comprehensive Medicinal Chemistry II*; Elsevier: Amsterdam, The Netherlands, 2007; pp. 1009–1041. [CrossRef]
3. Das, S.; Kashyap, N.; Kalita, S.; Bora, D.B.; Borah, R. A Brief Insight into the Physicochemical Properties of Room-Temperature Acidic Ionic Liquids and Their Catalytic Applications in C–C Bond Formation Reactions. *Adv. Phys. Org. Chem.* **2020**, *54*, 1–98. [CrossRef]
4. Dent, A.H. Conjugation Methods. In *The Immunoassay Handbook*; Elsevier: Amsterdam, The Netherlands, 2013; pp. 301–313. [CrossRef]
5. Heravi, M.M.; Zadsirjan, V. Recent Advances in Applications of Mannich Reaction in Total Synthesis of Alkaloids. In *Recent Applications of Selected Name Reactions in the Total Synthesis of Alkaloids*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 153–190. [CrossRef]
6. Mishra, R.; Mishra, S.; Chaubey, S.A.; Barot, Y.B. Ionic Liquids as Alternative Greener Solvents and Catalysts in Organic Transformations. In *Handbook of Greener Synthesis of Nanomaterials and Compounds*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 359–404. [CrossRef]
7. Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. Catalytic, Enantioselective Alkylation of α-Imino Esters Using Late Transition Metal Phosphine Complexes as Catalysts. *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549. [CrossRef]
8. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. A Ternary Complex Reagent for an Asymmetric Reaction of Lithium Ester Enolates with Imines. *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061. [CrossRef]

9. Fujii, A.; Hagiwara, E.; Sodeoka, M. Mechanism of Palladium Complex-Catalyzed Enantioselective Mannich-Type Reaction: Characterization of A Novel Binuclear Palladium Enolate Complex. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458. [CrossRef]
10. Hagiwara, E.; Fujii, A.; Sodeoka, M. Enantioselective Addition of Enol Silyl Ethers to Imines Catalyzed by Palladium Complexes: A Novel Way to Optically Active Acylalanine Derivatives. *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475. [CrossRef]
11. Ishitani, H.; Ueno, M.; Kobayashi, S. Catalytic Enantioselective Mannich-Type Reactions Using a Novel Chiral Zirconium Catalyst. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154. [CrossRef]
12. Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. Anti-Selective Direct Catalytic Asymmetric Mannich-Type Reaction of Hydroxyketone Providing β-Amino Alcohols. *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713. [CrossRef]
13. Akiyama, T. 6.3 C–C Bond Formation: Mannich Reaction. In *Comprehensive Chirality*; Elsevier: Amsterdam, The Netherlands, 2012; pp. 69–96. [CrossRef]
14. Kousar, F.; Nosheen, S.; Zahra, S.N.; Kousar, S.; Jahan, N. Synthesis and Biological Activity of Important Phenolic Mannich Bases. *Asian J. Chem.* **2013**, *25*, 59–62. [CrossRef]
15. Bala, S.; Sharma, N.; Kajal, A.; Kamboj, S.; Saini, V. Mannich Bases: An Important Pharmacophore in Present Scenario. *Int. J. Med. Chem.* **2014**, *2014*, 191072. [CrossRef]
16. Gul, H.; Ojanen, T.; Vepsalainen, J.; Gul, M.; Erciyas, E.; Hanninen, O. Antifungal Activity of Some Mono, Bis and Quaternary Mannich Bases Derived from Acetophenone. *Arzneimittelforschung* **2011**, *51*, 72–75. [CrossRef]
17. Medić-Šarić, M.; Maysinger, D.; Movrin, M.; Dvoržak, I. Antibacterial and Antifungal Activities of Nitroxoline Mannich Bases. *Chemotherapy* **1980**, *26*, 263–267. [CrossRef]
18. Pishawikar, S.A.; More, H.N. Synthesis, Docking and in-Vitro Screening of Mannich Bases of Thiosemicarbazide for Anti-Fungal Activity. *Arab. J. Chem.* **2017**, *10*, S2714–S2722. [CrossRef]
19. Rossignol, T.; Kocsis, B.; Bouquet, O.; Kustos, I.; Kilár, F.; Nyul, A.; Jakus, P.B.; Rajbhandari, K.; Prókai, L.; d'Enfert, C.; et al. Antifungal Activity of Fused Mannich Ketones Triggers an Oxidative Stress Response and Is Cap1-Dependent in Candida Albicans. *PLoS ONE* **2013**, *8*, e62142. [CrossRef] [PubMed]
20. Tret'yakova, E.V.; Zakirova, G.F.; Salimova, E.V.; Kukovinets, O.S.; Odinokov, V.N.; Parfenova, L.V. Convenient One-Pot Synthesis of Resin Acid Mannich Bases as Novel Anticancer and Antifungal Agents. *Med. Chem. Res.* **2018**, *27*, 2199–2213. [CrossRef]
21. Salehi, B.; Mishra, A.P.; Shukla, I.; Sharifi-Rad, M.; Contreras, M.D.M.; Segura-Carretero, A.; Fathi, H.; Nasrabadi, N.N.; Kobarfard, F.; Sharifi-Rad, J. Thymol, Thyme, and Other Plant Sources: Health and Potential Uses: Thymol, Health and Potential Uses. *Phytother. Res.* **2018**, *32*, 1688–1706. [CrossRef] [PubMed]
22. Escobar, A.; Pérez, M.; Romanelli, G.; Blustein, G. Thymol Bioactivity: A Review Focusing on Practical Applications. *Arab. J. Chem.* **2020**, *13*, 9243–9269. [CrossRef]
23. Gaba, J.; Sharma, S.; Kaur, H.; Kaur, P. Thymol and Its Derivatives for Management of Phytopathogenic Fungi OfMaize. *Curr. Bioact. Compd.* **2022**, *18*, e301221199683. [CrossRef]
24. Wube, A.A.; Bucar, F.; Asres, K.; Gibbons, S.; Adams, M.; Streit, B.; Bodensieck, A.; Bauer, R. Knipholone, a Selective Inhibitor of Leukotriene Metabolism. *Phytomedicine* **2006**, *13*, 452–456. [CrossRef] [PubMed]
25. Legesse, M.; Abebe, A.; Degu, S.; Alebachew, Y.; Tadesse, S. Synthesis and Antimicrobial Activity of Knipholone Analogs. *Nat. Prod. Res.* **2022**, 1–7. [CrossRef]
26. Sharifi-Rad, J.; Cruz-Martins, N.; López-Jornet, P.; Lopez, E.P.-F.; Harun, N.; Yeskaliyeva, B.; Beyatli, A.; Sytar, O.; Shaheen, S.; Sharopov, F.; et al. Natural Coumarins: Exploring the Pharmacological Complexity and Underlying Molecular Mechanisms. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 6492346. [CrossRef]
27. Patel, A.A.; Lad, H.B.; Pandya, K.R.; Patel, C.V.; Brahmbhatt, D.I. Synthesis of a New Series of 2-(2-Oxo-2H-Chromen-3-Yl)-5H-Chromeno [4,3-b]Pyridin-5-Ones by Two Facile Methods and Evaluation of Their Antimicrobial Activity. *Med. Chem. Res.* **2013**, *22*, 4745–4754. [CrossRef]
28. Abida, M.I.; Alsalman, A.J. Synthesis and Evaluation of Antimicrobial Activity of Some 2-Morpholinomethylamino-4-(7-Unsubstituted/Substituted Coumarin-3-Yl)-6-Chlorosubstitutedphenyl Pyrimidines. *Trop. J. Pharm. Res.* **2016**, *15*, 393. [CrossRef]
29. Choi, D.-Y.; Lee, J.W.; Peng, J.; Lee, Y.J.; Han, J.-Y.; Lee, Y.H.; Choi, I.S.; Han, S.B.; Jung, J.K.; Lee, W.S.; et al. Obovatol Improves Cognitive Functions in Animal Models for Alzheimer's Disease: Obovatol Improves Memory Function. *J. Neurochem.* **2012**, *120*, 1048–1059. [CrossRef] [PubMed]
30. Lim, Y.; Kwon, J.-S.; Kim, D.-W.; Lee, S.-H.; Park, R.-K.; Lee, J.-J.; Hong, J.-T.; Yoo, H.-S.; Kwon, B.-M.; Yun, Y.-P. Obovatol from Magnolia Obovata Inhibits Vascular Smooth Muscle Cell Proliferation and Intimal Hyperplasia by Inducing P21Cip1. *Atherosclerosis* **2010**, *210*, 372–380. [CrossRef]
31. Yang, C.; Li, T.; Jiang, L.; Zhi, X.; Cao, H. Semisynthesis and Biological Evaluation of Some Novel Mannich Base Derivatives Derived from a Natural Lignan Obovatol as Potential Antifungal Agents. *Bioorganic Chem.* **2020**, *94*, 103469. [CrossRef]
32. Yang, C.; Song, L.; Miao, Z.; Jiang, L.; Li, T.; Zhi, X.; Hao, X.; Cao, H. Discovery of Novel Obovatol-Based Phenazine Analogs as Potential Antifungal Agents: Synthesis and Biological Evaluation in Vitro. *Z. Für Naturforschung B* **2021**, *76*, 173–179. [CrossRef]
33. Babu, P.V.A.; Liu, D. Flavonoids and Cardiovascular Health. In *Complementary and Alternative Therapies and the Aging Population*; Elsevier: Amsterdam, The Netherlands, 2009; pp. 371–392. [CrossRef]
34. Al Aboody, M.S.; Mickymaray, S. Anti-Fungal Efficacy and Mechanisms of Flavonoids. *Antibiotics* **2020**, *9*, 45. [CrossRef] [PubMed]

35. Ma, Y.; Wang, L.; Lu, A.; Xue, W. Synthesis and Biological Activity of Novel Oxazinyl Flavonoids as Antiviral and Anti-Phytopathogenic Fungus Agents. *Molecules* **2022**, *27*, 6875. [CrossRef]
36. Zilles, J.C.; Dos Santos, F.L.; Kulkamp-Guerreiro, I.C.; Contri, R.V. Biological Activities and Safety Data of Kojic Acid and Its Derivatives: A Review. *Exp. Dermatol.* **2022**, *31*, 1500–1521. [CrossRef]
37. Aytemir, M.D.; Özçelik, B.; Karakaya, G. Evaluation of Bioactivities of Chlorokojic Acid Derivatives against Dermatophytes Couplet with Cytotoxicity. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3646–3649. [CrossRef]
38. Holley, R.W.; Holley, A.D. 2-Azetidinone (β-Propiolactam). *J. Am. Chem. Soc.* **1949**, *71*, 2129–2131. [CrossRef]
39. Mehta, P.D.; Sengar, N.P.S.; Pathak, A.K. 2-Azetidinone—A New Profile of Various Pharmacological Activities. *Eur. J. Med. Chem.* **2010**, *45*, 5541–5560. [CrossRef]
40. Raju, K.R.; Prasad, A.R.G.; Kumar, B.S.; Ravindranath, L.R.K.R. Synthesis and Medicinal Evaluation of Mannich Bases Carrying Azetidinone Moiety. *J. Clin. Anal. Med.* **2015**, *6*, 720–725. [CrossRef]
41. Gujjarappa, R.; Kabi, A.K.; Sravani, S.; Garg, A.; Vodnala, N.; Tyagi, U.; Kaldhi, D.; Velayutham, R.; Singh, V.; Gupta, S.; et al. Overview on Biological Activities of Imidazole Derivatives. In *Nanostructured Biomaterials*; Materials Horizons: From Nature to Nanomaterials; Swain, B.P., Ed.; Springer: Singapore, 2022; pp. 135–227. [CrossRef]
42. Pathare, B.; Bansode, T. Review—Biological Active Benzimidazole Derivatives. *Results Chem.* **2021**, *3*, 100200. [CrossRef]
43. Verma, A.; Joshi, S.; Singh, D. Imidazole: Having Versatile Biological Activities. *J. Chem.* **2013**, *2013*, 329412. [CrossRef]
44. Roman, G.; Mareş, M.; Năstasă, V. A Novel Antifungal Agent with Broad Spectrum: 1-(4-Biphenylyl)-3-(1 *H* -Imidazol-1-Yl)-1-Propanone. *Arch. Pharm.* **2013**, *346*, 110–118. [CrossRef]
45. Krishnanjaneyulu, I.; Saravanan, G.; Sunil Kumar, M.; Supriya, P.; Vamsi, J.; Bhavana, J. Synthesis, Characterization and Antimicrobial Activity of Some Novel Benzimidazole Derivatives. *J. Adv. Pharm. Technol. Res.* **2014**, *5*, 21. [CrossRef]
46. Sethi, R.; Arora, S.; Saini, D.; Jain, S. Synthesis, Characterization, Molecular Docking Studies and Antimicrobial Evaluation of N-Benzimidazol-1-Yl-Methyl-Benzamide Derivatives. *Indian J. Pharm. Educ. Res.* **2016**, *50*, 424–434. [CrossRef]
47. Zhang, R.-H.; Guo, H.-Y.; Deng, H.; Li, J.; Quan, Z.-S. Piperazine Skeleton in the Structural Modification of Natural Products: A Review. *J. Enzyme Inhib. Med. Chem.* **2021**, *36*, 1165–1197. [CrossRef]
48. Jalageri, M.D.; Nagaraja, A.; Puttaiahgowda, Y.M. Piperazine Based Antimicrobial Polymers: A Review. *RSC Adv.* **2021**, *11*, 15213–15230. [CrossRef]
49. Ozdemir, S.B.; Demirbas, N.; Cebeci, Y.U.; Bayrak, H.; Mermer, A.; Ceylan, S.; Demirbas, A. Synthesis and Antimicrobial Activities of Hybrid Heterocyclic Molecules Based on 1-(4-Fluorophenyl)Piperazine Skeleton. *Lett. Drug Des. Discov.* **2017**, *14*, 1014–1034. [CrossRef]
50. Gibbs, N.K. Drug-Induced Skin Phototoxicity: Lessons from the Fluoroquinolones. In *Comprehensive Series in Photosciences*; Elsevier: Amsterdam, The Netherlands, 2001; Volume 3, pp. 337–356. [CrossRef]
51. Goa, K.L.; Bryson, H.M.; Markham, A. Sparfloxacin: A Review of Its Antibacterial Activity, Pharmacokinetic Properties, Clinical Efficacy and Tolerability in Lower Respiratory Tract Infections. *Drugs* **1997**, *53*, 700–725. [CrossRef]
52. Scholar, E. Sparfloxacin. In *xPharm: The Comprehensive Pharmacology Reference*; Elsevier: Amsterdam, The Netherlands, 2007; pp. 1–8. [CrossRef]
53. Kumar, A.; Grewal, A.S.; Singh, V.; Narang, R.; Pandita, D.; Lather, V. Synthesis, Antimicrobial Activity and QSAR Studies of Some New Sparfloxacin Derivatives. *Pharm. Chem. J.* **2018**, *52*, 444–454. [CrossRef]
54. Appelbaum, P.C.; Bryskier, A. Quinolones. In *Antibiotic and Chemotherapy*; Elsevier: Amsterdam, The Netherlands, 2010; pp. 306–325. [CrossRef]
55. Shimizu, M.; Takase, Y.; Nakamura, S.; Katae, H.; Minami, A.; Nakata, K.; Inoue, S.; Ishiyama, M.; Kubo, Y. Pipemidic Acid, a New Antibacterial Agent Active Against *Pseudomonas Aeruginosa*: In Vitro Properties. *Antimicrob. Agents Chemother.* **1975**, *8*, 132–138. [CrossRef] [PubMed]
56. Popiołek, Ł.; Biernasiuk, A.; Paruch, K.; Malm, A.; Wujec, M. Synthesis and in Vitro Antimicrobial Activity Screening of New Pipemidic Acid Derivatives. *Arch. Pharm. Res.* **2018**, *41*, 633–645. [CrossRef] [PubMed]
57. Yadav, P.; Shah, K. Quinolines, a Perpetual, Multipurpose Scaffold in Medicinal Chemistry. *Bioorganic Chem.* **2021**, *109*, 104639. [CrossRef]
58. Kumar, S.; Bawa, S.; Gupta, H. Biological Activities of Quinoline Derivatives. *Mini-Rev. Med. Chem.* **2009**, *9*, 1648–1654. [CrossRef]
59. Matada, B.S.; Pattanashettar, R.; Yernale, N.G. A Comprehensive Review on the Biological Interest of Quinoline and Its Derivatives. *Bioorg. Med. Chem.* **2021**, *32*, 115973. [CrossRef]
60. Patel, H.M. Synthesis, Characterizations and Microbial Studies of Novel Mannich Products Using Multicomponent Reactions. *Curr. Bioact. Compd.* **2018**, *14*, 278–288. [CrossRef]
61. Shehab, M.A.S.; El-Naggar, M.; Ismail, R.A.; El Kafrawy, H.M.; Abood, A.; Ismail, S.A.; Sabry, N.M.; El Sayed, M.T. Synthesis of Some Novel Quinolinols with In-Vitro Antimicrobial, and Antioxidant Activity. *Curr. Bioact. Compd.* **2020**, *16*, 514–520. [CrossRef]
62. Arciniegas, A.; Pérez-Castorena, A.L.; González, K.; Reyes-Lezama, M.; Villaseñor, J.L.; Vivar, A.R.D. Pyrrolizidine Alkaloids and Diterpenes from *Villasenoria Orcuttii*. *J. Braz. Chem. Soc.* **2013**, *24*, 1167–1171. [CrossRef]
63. Dascalu, A.-E.; Ghinet, A.; Lipka, E.; Furman, C.; Rigo, B.; Fayeulle, A.; Billamboz, M. Design, Synthesis and Antifungal Activity of Pterolactam-Inspired Amide Mannich Bases. *Fitoterapia* **2020**, *143*, 104581. [CrossRef]
64. Chauhan, G.; Pathak, D.P.; Ali, F.; Bhutani, R.; Kapoor, G.; Khasimbi, S. Advances in Synthesis, Derivatization and Bioactivity of Isatin: A Review. *Curr. Org. Synth.* **2021**, *18*, 37–74. [CrossRef]

65. Varun, V.; Sonam, S.; Kakkar, R. Isatin and Its Derivatives: A Survey of Recent Syntheses, Reactions, and Applications. *MedChemComm* **2019**, *10*, 351–368. [CrossRef]
66. Nath, P.; Mukherjee, A.; Mukherjee, S.; Banerjee, S.; Das, S.; Banerjee, S. Isatin: A Scaffold with Immense Biodiversity. *Mini-Rev. Med. Chem.* **2021**, *21*, 1096–1112. [CrossRef] [PubMed]
67. Pandeya, S.N.; Sriram, D.; Nath, G.; De Clercq, E. Synthesis and Antimicrobial Activity of Schiff and Mannich Bases of Isatin and Its Derivatives with Pyrimidine. *Il Farm.* **1999**, *54*, 624–628. [CrossRef] [PubMed]
68. Ravichandran, V.; Mohan, S.; Kumar, K.S. Synthesis and Antimicrobial Activity of Mannich Bases of Isatin and Its Derivatives with 2-[(2,6-Dichlorophenyl)Amino]Phenylacetic Acid. *Arkivoc* **2007**, *2007*, 51–57. [CrossRef]
69. Zhang, Y.; Zhan, Y.-Z.; Ma, Y.; Hua, X.-W.; Wei, W.; Zhang, X.; Song, H.-B.; Li, Z.-M.; Wang, B.-L. Synthesis, Crystal Structure and 3D-QSAR Studies of Antifungal (Bis-)1,2,4-Triazole Mannich Bases Containing Furyl and Substituted Piperazine Moieties. *Chin. Chem. Lett.* **2018**, *29*, 441–446. [CrossRef]
70. El-Emam, A.; Al-Abdullah, E.; Asiri, H.; Lahsasni, S.; Habib, E.; Ibrahim, T. Synthesis, Antimicrobial, and Anti-Inflammatory Activity, of Novel S-Substituted and N-Substituted 5-(1-Adamantyl)-1,2,4-Triazole-3-Thiols. *Drug Des. Devel. Ther.* **2014**, *505*, 505–518. [CrossRef]
71. Cebeci, Y.U.; Ceylan, S.; Demirbas, N.; Karaoğlu, Ş.A. Microwave-Assisted Synthesis of Novel Mannich Base and Conazole Derivatives Containing Biologically Active Pharmacological Groups. *Lett. Drug Des. Discov.* **2021**, *18*, 269–283. [CrossRef]
72. Cebeci, Y.U.; Karaoğlu, Ş.A. Design and Microwave-Assisted Synthesis of a Novel Mannich Base and Conazole Derivatives and Their Biological Assessment. *Heterocycl. Commun.* **2021**, *27*, 100–111. [CrossRef]
73. Pal'chikov, V.A. Morpholines. Synthesis and Biological Activity. *Russ. J. Org. Chem.* **2013**, *49*, 787–814. [CrossRef]
74. Kourounakis, A.P.; Xanthopoulos, D.; Tzara, A. Morpholine as a Privileged Structure: A Review on the Medicinal Chemistry and Pharmacological Activity of Morpholine Containing Bioactive Molecules. *Med. Res. Rev.* **2020**, *40*, 709–752. [CrossRef] [PubMed]
75. Idhayadhulla, A.; Surendra Kumar, R.; Abdul Nasser, A.J.; Selvin, J.; Manilal, A. Synthesis of Some Mannich Base Derivatives and Their Antimicrobial Activity Study. *Arab. J. Chem.* **2014**, *7*, 994–999. [CrossRef]
76. Aitken, R.A.; Aitken, K.M. 1,4-Thiazines and Their Benzo Derivatives. In *Comprehensive Heterocyclic Chemistry III*; Elsevier: Amsterdam, The Netherlands, 2008; pp. 607–675. [CrossRef]
77. Demirci, S.; Mermer, A.; Ak, G.; Aksakal, F.; Colak, N.; Demirbas, A.; Ayaz, F.A.; Demirbas, N. Conventional and Microwave-assisted Total Synthesis, Antioxidant Capacity, Biological Activity, and Molecular Docking Studies of New Hybrid Compounds. *J. Heterocycl. Chem.* **2017**, *54*, 1785–1805. [CrossRef]
78. Shih, M.-H. Studies on the Syntheses of Heterocycles from 3-Arylsydnone-4-Carbohydroximic Acid Chlorides with N-Arylmaleimides**,** [1,4]Naphthoquinone and Aromatic Amines. *Tetrahedron* **2002**, *58*, 10437–10445. [CrossRef]
79. Dorababu, A.; Kamble, R.R.; Kamble, A.A.; Kumbar, M.N.; Shaikh, S.J.; Netalkar, S.P. Mannich Bases of 1,2,4-Triazolones as Potent Anti-Tubercular and Antifungal Agents. *ChemistrySelect* **2019**, *4*, 2881–2885. [CrossRef]
80. Wiederhold, N.P. Emerging Fungal Infections: New Species, New Names, and Antifungal Resistance. *Clin. Chem.* **2021**, *68*, 83–90. [CrossRef]
81. Dean, R.; Van Kan, J.A.L.; Pretorius, Z.A.; Hammond-Kosack, K.E.; Di Pietro, A.; Spanu, P.D.; Rudd, J.J.; Dickman, M.; Kahmann, R.; Ellis, J.; et al. The Top 10 Fungal Pathogens in Molecular Plant Pathology: Top 10 Fungal Pathogens. *Mol. Plant Pathol.* **2012**, *13*, 414–430. [CrossRef]
82. Roy, M.; Karhana, S.; Shamsuzzaman, M.; Khan, M.A. Recent Drug Development and Treatments for Fungal Infections. *Braz. J. Microbiol.* **2023**, *54*, 1695–1716. [CrossRef]
83. Roman, G. Mannich Bases in Medicinal Chemistry and Drug Design. *Eur. J. Med. Chem.* **2015**, *89*, 743–816. [CrossRef]
84. Biersack, B.; Ahmed, K.; Padhye, S.; Schobert, R. Recent Developments Concerning the Application of the Mannich Reaction for Drug Design. *Expert Opin. Drug Discov.* **2018**, *13*, 39–49. [CrossRef] [PubMed]
85. Revie, N.M.; Iyer, K.R.; Robbins, N.; Cowen, L.E. Antifungal Drug Resistance: Evolution, Mechanisms and Impact. *Curr. Opin. Microbiol.* **2018**, *45*, 70–76. [CrossRef] [PubMed]
86. Iwanejko, J.; Wojaczyńska, E.; Olszewski, T.K. Green Chemistry and Catalysis in Mannich Reaction. *Curr. Opin. Green Sustain. Chem.* **2018**, *10*, 27–34. [CrossRef]