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Mannich Bases: Synthesis, Pharmacological Activity, and Applications: A Review

Sura S. Raoof [1*], Amaal S. Sadiq[2]
[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq*
[2]*Department of chemistry, College of Science for woman, University of Baghdad, Al-Jadiriya, Baghdad, Iraq*

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Abstract

The Mannich reaction is one of the most important types of organic chemistry fundamental reactions. It is a crucial stage in the production of various medicines, natural goods, and industrial chemicals. Chemists' imaginations have always been piqued because of this. In general, the Mannich reactions can be used as part of a tandem reaction sequence to produce complex target molecules in an elegant and often easy manner. The following article examines and summarizes methods for synthesizing Mannich derivatives, in addition to offering a survey of recent advancements in several fields' applications of the Mannich reaction, such as biological applications, antimicrobial activity, anticancer activity, anti-inflammation and antioxidant activity, antimalarial activity, anti-viral activity, and so on. We also go over how mannich base is used in industry and agriculture.

Keywords: Applications, Synthesis, Mannich bases, Biological Activity

قواعد مانخ التحضير والنشاط الدوائي والتطبيقات: مراجعة

سرى صادق رؤوف[1*], امال سمير صادق[2]
[1]قسم الكيمياء , كلية العلوم للبنات , جامعة بغداد , الجادرية , بغداد , العراق
[2] فرع الكيمياء الصيدلانية , كلية الصيدلة , الجامعة المستنصرية , بغداد , العراق

الخلاصة

تفاعل مانخ هو أحد أهم أنواع التفاعلات الأساسية للكيمياء العضوية. إنها مرحلة مهمة في إنتاج نطاق واسع من الأدوية والسلع الطبيعية والمواد الكيميائية الصناعية. لطالما انشغل خيال الكيميائيين نتيجة لهذا. بشكل عام، يمكن استخدام تفاعلات مانخ كجزء من تسلسل تفاعل ترادفي لإنتاج جزيئات مستهدفة معقدة بطريقة سهلة في كثير من الأحيان. تدرس المقالة التالية وتلخص طرق تصنيع مشتقات مانخ ، بالإضافة إلى تقديم مسح للتطورات الحديثة في العديد من مجالات تطبيقات تفاعل مانخ ، مثل التطبيقات البيولوجية ، والنشاط المضاد للميكروبات ، والنشاط المضاد للسرطان ، والنشاط المضاد للالتهابات ومضادات الأكسدة ، والنشاط المضاد للملاريا والنشاط المضاد للفيروسات وما إلى ذلك. نراجع أيضًا كيفية استخدام قاعدة مانخ في الصناعة والزراعة.

* Email: amaalsameer74@gmail.com

1. Introduction

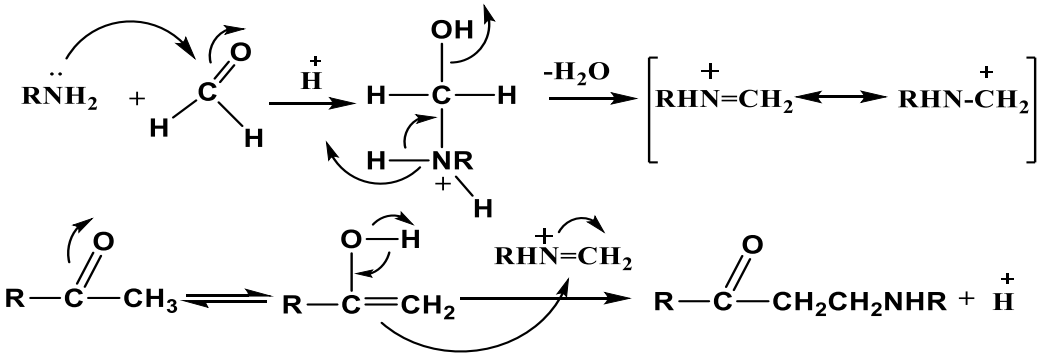
Mannich reactions are more flexible than other reactions. As a result, they have long piqued the interest of chemists [1]. The Mannich reaction's final products are Mannich bases, which are beta-amino ketones carrying compounds [2-4]. Aminomethylations, also known as Mannich reactions, are condensations with three components where the substrate is RH (a molecule with a hydrogen atom that is active) that combines with formaldehyde and an amine to generate Mannich base[5]. The R-H substrates used in Mannich reactions could come from various structurally diverse types of molecules. Because the substrate's active hydrogen atom is on a carbon atom or a heteroatom that can be bonded to sulfur, nitrogen, oxygen, or phosphorus, aminomethylation can produce the C-, S-, N-, O-, and P-Mannich reactions, respectively[6]. For the production of compounds containing nitrogen, the Mannich method is frequently utilized[7]. The chemistry of the Mannich base has attracted a lot of attention recently. Mannich bases have had antifungal[8], antibacterial[9,10], anti-HIV[11], antiviral[12,13], antimicrobial[14], and anticancer[15] properties. On the surfaces of the polymer industry, they are also used as paints and active substances. Due to their anticonvulsant characteristics, Mannich reactions are reported as potential biological agents. They can also be used in other situations such as antituberculars[16], vasorelaxing[17]. Antimalarial[18], anticonvulsant[19], analgesic[20], drugs, biological[21] and pharmacological activity[22,23]. Other uses include agrochemicals such as plant growth regulators[24], contact with enzymes involved in antioxidant processes, suppression of mitochondrial respiration[25,26], suppression of the enzyme topoisomerase [27,28], and tubulin polymerization.

Mannich reaction mechanism

In the 1960s, research focused on the chemistry of Mannich bases, which were considered active intermediates that could be easily converted into a range of mixtures with uses in a variety of industries. The discussion over the mechanism of the Mannich reaction lasted quite a while, and from that point on, it was proposed that the reaction has two mechanisms, as indicated by the reaction conditions[29].

A. In acidic medium

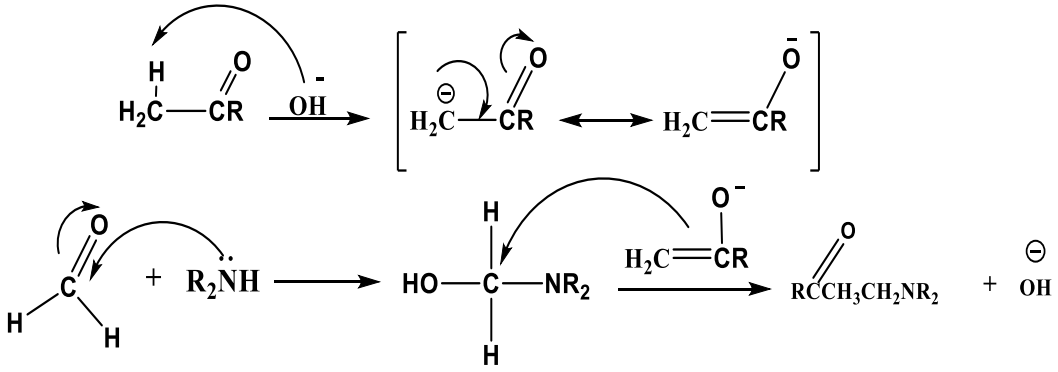
In the reaction of amine with formaldehyde in the acidic medium, the active hydrogen atom in certain chemical compounds is replaced by the methyl amine group (Scheme 1) [30]



Scheme 1 - The mechanism of the Mannich reaction in acidic medium

B. In alkaline medium

Mannich bases could be formed in the alkaline medium by the nucleophilic addition of amines to the carbonyl group of aldehydes before adding an enolizable carbonyl compound (Scheme 2) [31]



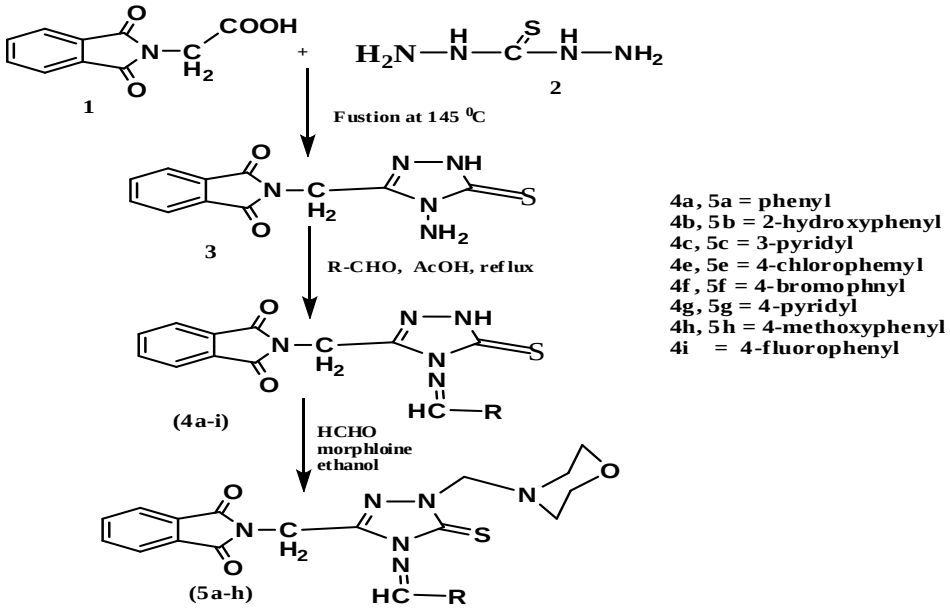
Scheme 2 - The mechanism of the Mannich reaction in alkaline medium

Biological activity and applications of Mannich bases

The enormous curiosity in the chemistry of the Mannich reaction has largely fueled the realities that follow:

1- Anti-microbial activity

The antibacterial activity of a novel Mannich reaction chain containing 4-amino-3-(*N*-phthalimidomethyl)-1,2,4-triazole-5-thione **5a**–**h** (Scheme 3) was tested against several gram-positive and gram-negative bacteria and parasite species. According to the findings, levofloxacin, a traditional treatment, and Mannich base **5h** showed nearly equivalent actions against K. pneumonia and *E. coli*. Among the examined compounds, the greatest activity was found in the Mannich reaction with electron-donating substituents (hydroxyl and methoxy) on the phenyl ring (**5b** and **5h**) or halogens on the phenyl ring (**5e** and **5f**). The Mannich base with the 2-hydroxy group had the greatest level of antifungal efficacy against *Candida albicans*. The findings also show how the inclusion of a morpholine ring in heterocyclic particles increases antibacterial activity [32].



Scheme 3 - Synthesis of compounds **5a**–**h** by Mannich reaction

The corresponding compounds **6a**-**6e** were produced at high yields by reacting substituted benzaldehyde and morpholine or methyl amine with acetanilide. Using matching streptomycin as standards, the researchers discovered the novel heterocyclic Mannich bases. They were examined for antibacterial activity against E. coli using the cup and plate technique. All the

titled compounds showed good antimicrobial activities. Specifically, compounds **6a** and **6b** possessed very good antimicrobial efficacy against *Bacillus* and *Escherichia coli* [33].

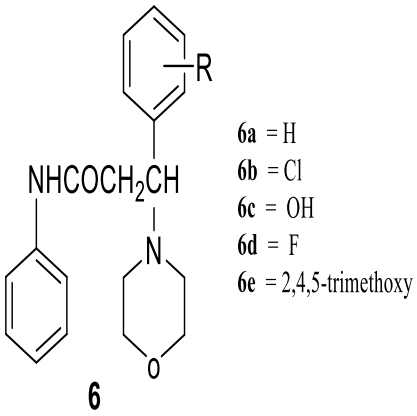
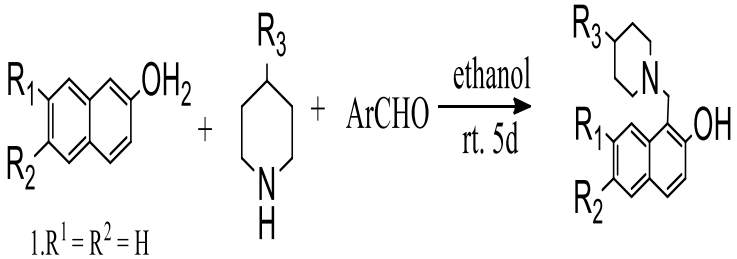


Figure 1: Structures of compounds **6a**-**6e**

The antibacterial efficacy of aminoalkylated-2-naphthols **7**-**29** (Scheme 4) was put to the test against a group of gram-positive (MRSA, *S. aureus*, and *Enterococcus fecalis*) and gram-negative (two strains of P. *aeruginosa*, *Escherichia coli*, *Citrobacter freundii*, K. *pneumonia*, *Enterobacter cloacae*, and *Proteus vulgaris*) and gram-negative, with amoxicillin as a reference. Mannich bases **7**-**30** had little effect on gram-negative bacteria, but several aminoalkylated-2-naphthols demonstrated promise against gram-positive bacteria. The kind of aryl moiety added to the Mannich base framework by the aldehyde component used in amino alkylation is shown to regulate antibacterial efficacy in this series of molecules [34].

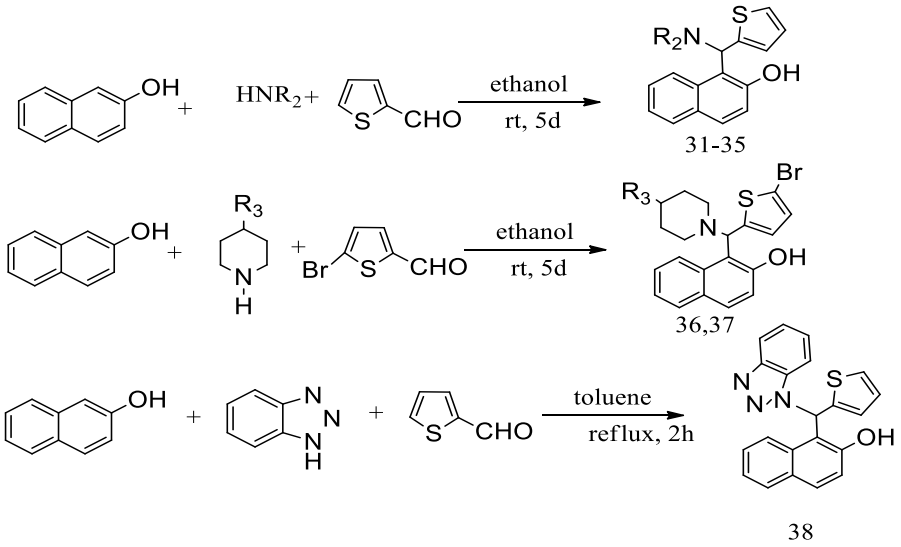


1.$R^1 = R^2 = H$
2.$R^1 = H, R^2 = Br$
3.$R^1 = OCH_3, R^2 = H$
4.$R^3 = H$
5.$R^3 = CH_3$

Scheme 4 - Aminoalkylated-2-naphthols **7**-**30**

2-Naphthol 1 was amino alkylated in the Mannich reaction using 2-carboxaldehyde thiophene as the aldehyde reagent and 1H-benzotriazole as the amine reagent (Scheme 5). The antibacterial action of this new group of Mannich reactions [31-38] versus the original list of bacteria showed that they were all passive against gram-negative bacteria but active against gram-positive bacteria at varying stages. Candidates 34 and 38, which have hydrophobic moieties in this part of the molecule, are inert against *E. fecalis*, suggesting that the nature of the various amino moieties in the structure of these Mannich bases induces some selectivity. The most active compounds in this system against *S. aureus* were Mannich bases **36** and **37**, which were created from 5-bromothiophene-2-carboxaldehyde as the aldehyde component and piperidines as amine reagents. All the candidates showed anti-MRSA activity. When the thiophene ring is replaced with bromine, the antibacterial efficacy of Mannich bases **36** and

37 does not appear to differ, much from that of their unsubstituted equivalents, **15** and **16**, respectively [34].



Scheme 5 - Novel heterocyclic Mannich bases

Secondary amines, benzimidazoles, and formaldehyde are used to make new *N*-Mannich bases (Figure 2). The examined compounds 39 and 40 exhibited different anti-biofilm features and were microbicidal, being active against a wide spectrum of Gram-negative and Gram-positive bacterial strains both in adherent and planktonic states, endorsing their potential in the development of novel anti-microbial and anti-biofilm agents. The presence of nucleophilic groups inside the molecule, like CH_3 or OH, is linked to the compounds' microbicidal activity. As a result, the compounds of OH in both types, benzimidazole and Mannich bases, had the greatest microbicidal and anti-biofilm effects. The molecule's planarity and symmetry both provide substantial support for its antibacterial activity[35].

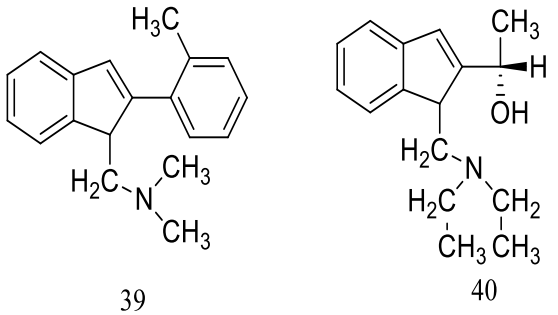
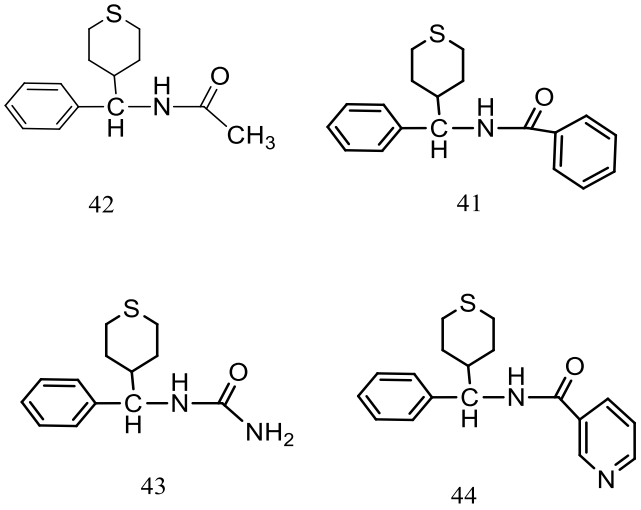


Figure 2: *N*-Mannich bases for benzimidazole

Microwave helped from benzaldehyde, thiomorpholine, and benzamide, acetamide, carbamide(urea)/nicotinamide yielded good production of Mannich bases such as *N*-((thiomorpholino)phenyl methyl)benzamide (41), *N*-((thiomorpholino)phenyl methyl) acetamide (42), 1-*N*-(phenyl(thiomorpholino)methyl)carbamide (43) and *N*-(phenyl (thiomorpholino)methyl)nicotinamide (44) (Figure 3). All the bacterial and fungal strains tested were active against total chemicals. The compounds (41-44) Mannich bases are moderately active or very efficient against fungal and bacterial strains when used as typical antibacterial medications. *N*-(Phenyl(thiomorpholino)methyl)acetamide (42) has superior antibacterial and antifungal activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*,

and *Escherichia coli* compared to other Mannich bases. The compound *N*-((thiomorpholino)phenylmethyl)carbamide (43) has excellent activity against *Candida albicans*, *Penicillium* species, and *Aspergillus niger* in parallel with other Mannich bases. The procedure has several advantages, including being a green chemical approach, having a simple handling method, having a short reaction time, having an easy experimental setup, and using a cheap and environmentally benign kind of catalyst[36].

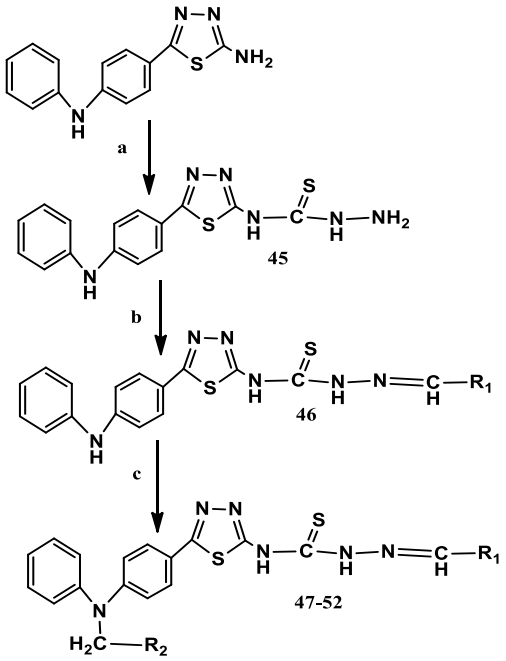


42 41

43 44

Figure 3: Structure of [41-44]

Various *N*-Mannich reactions of heterocyclic 1,3,4-thiadiazoles 47-52 (a-c) were designed and synthesized (Scheme 6), and their antimicrobial and anti-inflammatory effects were tested *in vitro*. Compounds **47b** and **48a** had the strongest antibacterial efficiency against *S. aureus*, whereas compounds **47a** and **47b** had the highest antibacterial activity efficiency against *B. subtilis*. It was discovered that compound **3b** had prime antibacterial efficacy against both microorganisms. When compared to the common antibiotic ciprofloxacin, the compounds **47c**, **51c**, and **52c** exhibited extremely similar actions against the pathogen *E.coli*. The pipiridine ring is thought to be required in Mannich for antibacterial action against gram-negative *E. coli*. The most potent compound against *K. pneumoniae* was found to be compound **3a**. The cup-plate method was used to assess the synthesized compounds' antifungal efficacy *in vitro*. The compounds **47a**, **48a**, **49a**, and **52a** were found to be the most effective against the fungus *A. niger* in the study. In Mannich base compounds, the structural dimethylamine group is required for antifungal action against *A. niger*. The compounds **48a**, **48b**, **49c**, **50b**, **52a**, and **52c** exhibited outstanding action against the fungus *C. albicans* compared to the conventional medicine Fluconazole. The anti-inflammatory efficacy of the randomly selected compounds was assessed in albino rats using the carrageen-induced rat paw oedema model and the standard medication, diclofenac sodium. The experiment lasted 2 hours, with intervals of 0.5, 1.0, and 2.0 hours. When compared to normal medicine, the compounds **47a**, **48b**, **51b**, and **52c** of fluconazole have a stronger anti-inflammatory effect. To summarize the chemical **51b** entire performance, it showed good anti-inflammatory pharmacological efficacy. The chemical **51b** has more unsaturated hydrocarbons in its structure than the Schiff base, which has high lipophilic characteristics due to the electron-rich morpholine ring in the Mannich base[37].



Compound	R1	R2 a	R2 b	R2 c
47	C_6H_5	$N(CH_3)_2$	N O	N
48	O-C_6H_4-OH	$N(CH_3)_2$	N O	N
49	P -C_6H_4-Cl	$N(CH_3)_2$	N O	N
50	p -C_6H_4-$N(CH_3)_2$	$N(CH_3)_2$	N O	N
51	CH=CH -C_6H_5	$N(CH_3)_2$	N O	N
52	$C_4H_3O_3$*	$N(CH_3)_2$	N O	N

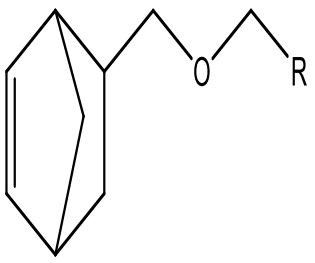
*Furan

a) NaOH, DMF, CS_2, $NH_2NH_2H_2O$, 60C^0. b) Aromatic aldehydes, few drops CH_3COOH, C_2H_5OH, c) THF, CH2O, conc.HCl, Dimethylamine, Morpholine and Piperidine(a-c), rt for 1h

4-(5-(4-(N-phenyl-N-(R2-substituted)methylamino)phenyl)-1,3,4-thiadiazol-2-yl)-1-R1-substituted-thiosemicarbazide, 47(a-c), 48(a-c), 49 (a-c), 50 (a-c), 51 (a-c), 52(a-c),

Scheme 6 - A graphic representation of the produced title compounds

In the formation of formaldehyde, norbornene methanol interacts with secondary amines(Figure 5), yielding new norbornene-containing Mannich bases(53). The chemicals created have high antibacterial and antifungal action against organisms such as Klebsiella pneumoniae, Staphylococcus aureus, Candida albicans, albicans yeast-like fungus, and Escherichia coli, which outperform reference agents in clinical practice (ethanol, furacilinum, rivanol, chloramine, and phenol). The compounds' lowest inhibitory and bactericidal concentrations were specified. At very low concentrations, the chemicals are effective against bacteria and fungi (S. aureus, E. coli, and C. albicans) [38].



R= -$N(C_2H_5)_2$
-$N(C_3H_7)_2$
-$N(C_4H_7)_2$
-$N(C_5H_9)_2$
-$N(C_6H_{11})_2$
-$N(CH_2)_5$
-$N(CH_2CH_2)O$
-$N(CH_2)_6$

53

Figure 5: Norbornene-containing Mannich bases

2- Anti-inflammation and antioxidant activity

A chain of five new Mannich bases of dehydrozingerone (DHZ) derivatives (54a-e) was synthesized successfully and evaluated for their anti-inflammatory activity. To assess antioxidant and anti-inflammatory activity, inhibition of denaturation of heat-induced albumin and the free radical DPPH method are used, respectively. All of the produced compounds (54a-e) demonstrated antioxidant and anti-inflammatory activity. Compound 54c contained

the *N*-methylpiperazine moiety, which has the best anti-inflammatory efficacy. The efficacy was identical to that of diclofenac sodium 54e contains a dimethylamine moiety, which has the best antioxidant activity. When compared to quercetin as a reference, the molecule demonstrated moderate activity. The antioxidant efficacy of Mannich base derivatives of DHZ compounds was often much better than that of DHZ[39].

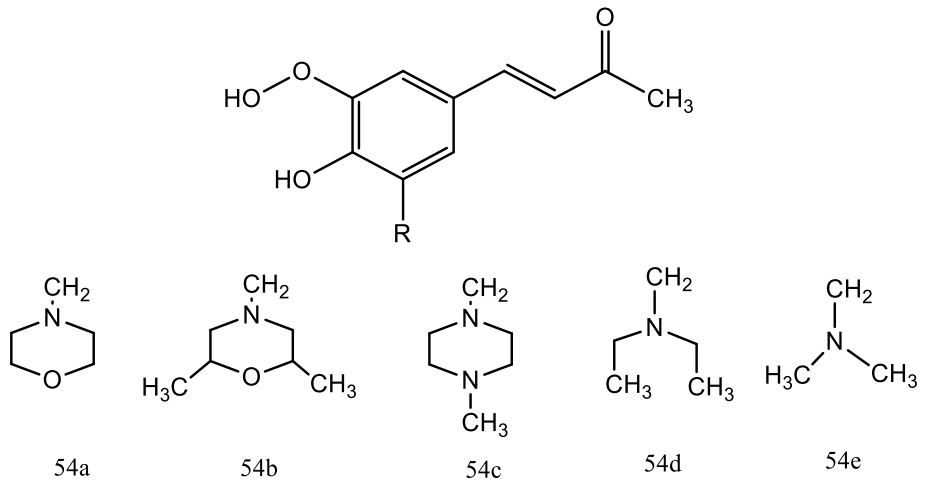


Figure 6: Synthesis of dehydrozingerone (DHZ) derivatives using Mannich reaction

The corresponding compounds 55a-55c were synthesized by reacting substituted benzimidazole, aldehydes, and an active hydrogen molecule (Figure 7); they were tested for anti-inflammatory and analgesic properties. Analgesic and anti-inflammatory efficiency. All compounds possess very good analgesic and anti-inflammatory efficiency[40].

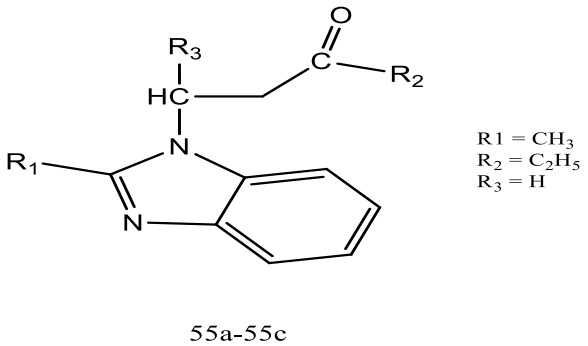
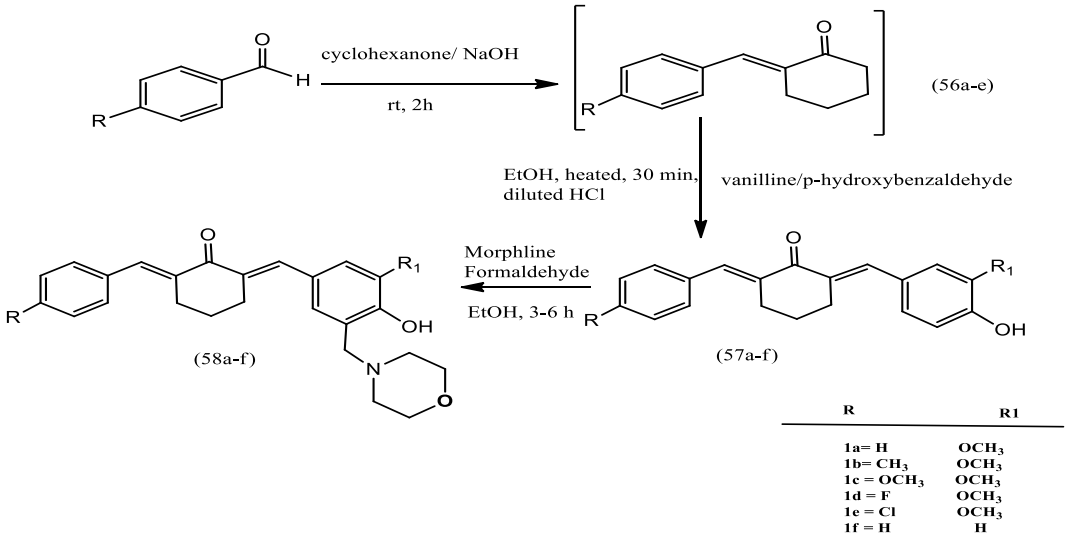


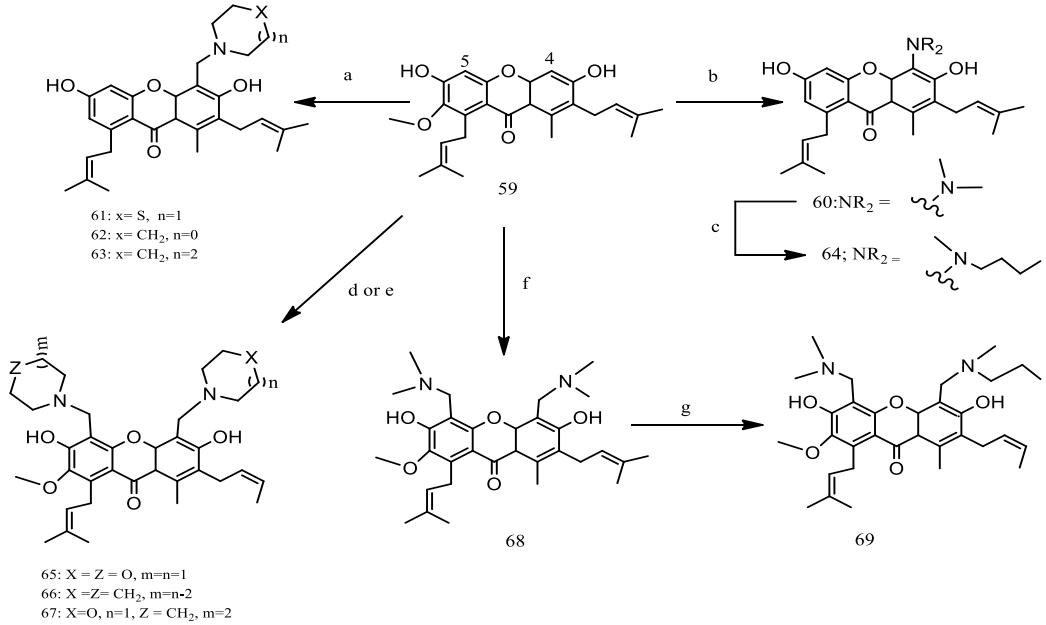
Figure 7 : Mannich bases with a 2-substituted benzimidazole moiety

A chain of mono-carbonyl analogs of curcumin (AMACs), including the morpholine Mannich[(2*E*,6*E*)-2-(4-hydroxy-3-[morpholin-4-yl-)methyl]phenylmethylidene)-6(phenyl methylidene)cyclohexane-1-one)] was synthesized (Scheme 7). The antioxidant and anti-inflammatory properties of the title and the original compounds were determined using the 2,2-diphenyl-2-picrylhydrazyl (DPPH) technique free radicals and the technique of denaturation of proteins, respectively. Of the tested compounds, only compound 57d had similar antioxidant efficacy as to cyclovalone. All the AMACs exhibited lower anti-inflammatory activity compared to cyclovalone. Despite this, compounds 58c and 58d had potent anti-inflammatory action that was nearly identical to cyclovalone and conventional diclofenac sodium [41].

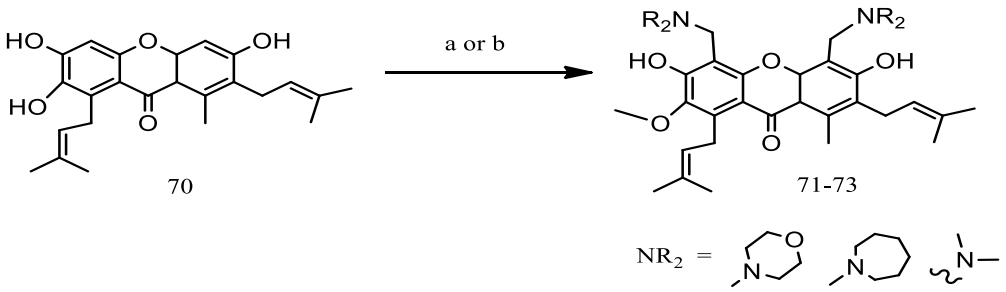


Scheme 7- The title compounds' structures and synthesis routes

Based on α-mangostin and γ-mangostin (C-4 and C-4/C-5) aminomethyl derivatives synthesized, several new mangostin derivatives have been developed, demonstrating the feasibility of C-4 and C-4/C-5 placement of -mangostins and -mangostins 1,2 using the Mannich process. Furthermore, new aminomethyl derivatives [61-69].The chelating capacity of the study compounds was shown to have a strong positive association with RSA. The addition of substituents in positions C-4 and C-4/C-5 scores significantly; all synthesized compounds show a lessening in hemolytic activity, while the C-4-CH_2NMe_2-group includes compounds with the highest cytotoxicity against RBCs compared to other mangostin derivatives. In AOA, mangostin 70 and its fundamental components 71-73 appeared to be significantly more dominant than mangostin 1 and its derivatives 62-69 for all factors studied. At low concentrations, Mannich bases 62, 63, and 66-17 protect RBCs from mammalian acute oxidative stress better than mangostins and -mangostins 1, 2. The findings propose that additional research into the pharmacological characteristics of produced C-4 and C-4/C-5-aminomethyl derivatives could yield beneficial results (Schemes 8 and 9)[42].



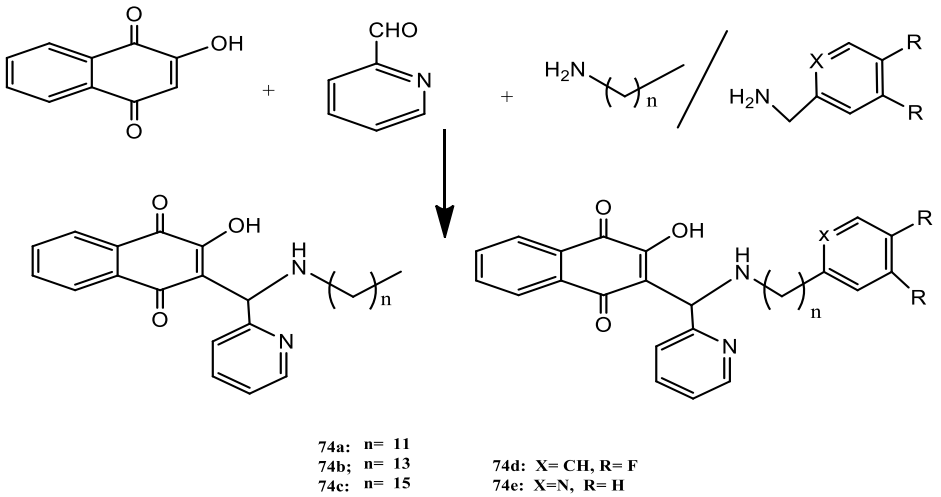
Synthesis of C-4- and C-4/C-5-aminomethylated derivatives of a-mangostin. Reagents and conditions: (a) 1.1 eq. HCHO/thiomorpholine, pyrrolidine or azepane, PhH, reflux, 60–75 min; (b) 1.1 eq. CH2(NMe2)2, PhH, rt, 45 min; (c) BuNH2 (excess), reflux, 45 min; (d) 2.5 eq. HCHO/morpholine or azepane, PhH, reflux, 4 h; (e) 1.1 eq. HCHO/morpholine, PhH, reflux, 1.5 h, then 1.5 eq. HCHO/azepane, PhH, reflux, 45 min; (f) 2.2 eq. CH2(NMe2)2, PhH, rt, 2 h, then reflux, 45 min; (g) see conditions (c).



Schemes 9 - Synthesis of C-4/C-5-aminomethylated derivatives of ?-mangostin. Reagents and conditions: (a) 2.2 eq. HCHO/morpholine or azepane, PhH, reflux, 45-75 minutes; (b) 2.7 eq. $CH_2(NMe_2)_2$, PhH, room temerature, 60 min minutes

3- Anti-cancer activity

Lawsone has been used to successfully synthesize novel Mannich reactions that are effective against a wide range of parasites and cancer cell lines. The anti-proliferative action is determined by the *N*-alkyl chain's length. Whereas *N*-tetradecyl and *N*-dodecyl derivatives 74a and 74b outperformed *N*-heptyl compound 1, *N*-hexadecyl derivative 74c had the highest efficiency. The dodecyl derivative 74a was obtained with maximum efficiency from the *N*-hexadecyl 74c and the *N*-heptyl derivative 1 in the panc-1 cancer cells in the pancreas and the vinblastine-resistant cervical carcinoma KBV1 (Vbl). Compounds 74a-c significantly increased the production of reactive oxygen species (ROS) in cancer cells. In general, the 2-pyridylmethylamine and benzyl compounds were less active. The reason for compound [74a-c]'s unusually strong activity in PC-3 prostate cancer cells that are negative for androgen receptors remains unknown. Compound 74c, as well, has an anti-parasitic effect, which was linked to a significant distortion of T.B. Brucei parasites' microtubule cytoskeleton. Furthermore, 74c's significantly stronger activity in cells of E. histolytica compared to the anti-parasitic medication metronidazole encourages additional research into 74c and its linked analogs in this area of tropical disorders. The novel lawsone Mannich reactions (74a-c) demonstrate to be appealing multi-targeted curative filters for the treatment of tumors and parasite turmoil (Scheme 10), owing to their ease of manufacture [43].



Scheme 10 - New lawsone derivatives

The docking consequences of Mannich bases and tamoxifen with estrogen receptor protein (PDB ID 2YAT) and their interactions with the dynamic site of an objective protein are given in Figures 8-14. In this study, tamoxifen was utilized as a standard ligand for the comparison of docked compound results. Tamoxifen triphenylethylene is an estrogen receptor agonist. It

has "estrogenic and antiestrogenic activities" depending on the target tissue. It is strongly antiestrogenic on the mammary epithelium, so it is used in both the prevention and treatment of cell-pernicious growth. "It is proestrogenic on the uterine epithelium," thus the current debate about its safety in cancer prevention, especially since an increased rate of endometrial cancer has been discovered and is being treated systematically in women with tamoxifen. Tamoxifen's CDOCKER value of 7.62965 kcal/mol. This implies that tamoxifen has shown lower binding affinity with the 2YAT protein compared with our compounds. There is no hydrogen bond required between tamoxifen and the receptor. There was only one Pi-Pi interaction between the phenyl ring of tamoxifen and His524. Moreover, several electrostatic and Van der Waals interactions are included to increase the binding affinity of tamoxifen. The docking outcomes of compounds with active-site amino acids at the 2YAT receptor showed better binding interactions. The affinity of *N*-(diphenylamino)methyl acetamide was discovered to be four times greater than standard. One strong hydrogen bond (distance 1.98 Å) connects the ketone group of the *N*-(diphenylamino)methyl acetamide atom to the Arg 394 residue [44].

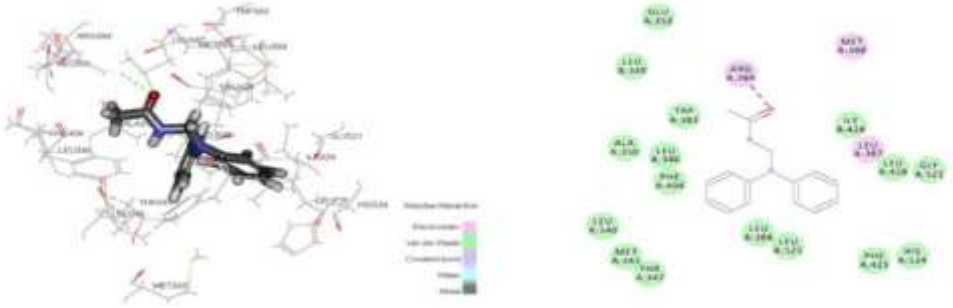


Figure 8: Interaction details of *N*-(diphenylamino)methyl acetamide with active-site amino acids of 2YAT receptor

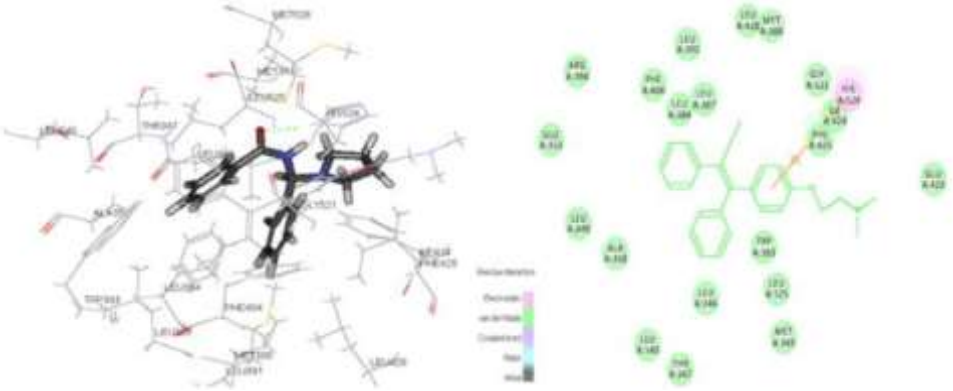


Figure 9: Linteraction details of *N*-(diphenylamino)methyl acrylamide with active-site amino acids of 2YAT receptor

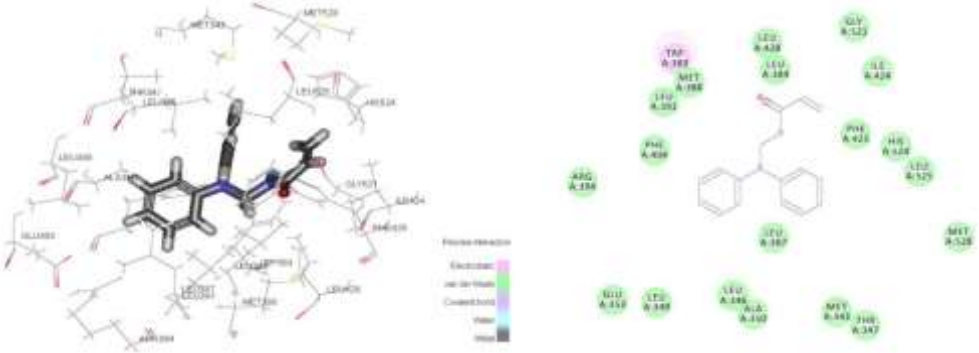


Figure 10: Interaction details of *N*-morpholino(phenyl)methyl acetamide with active-site amino acids of 2YAT receptor

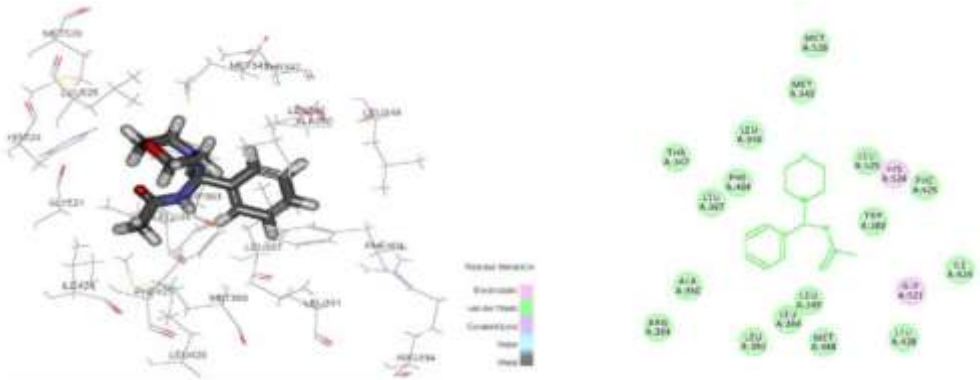


Figure 11: Interaction details of morpholino(phenyl)methyl] benzamide (MBB) with active-site amino acids of 2YAT receptor

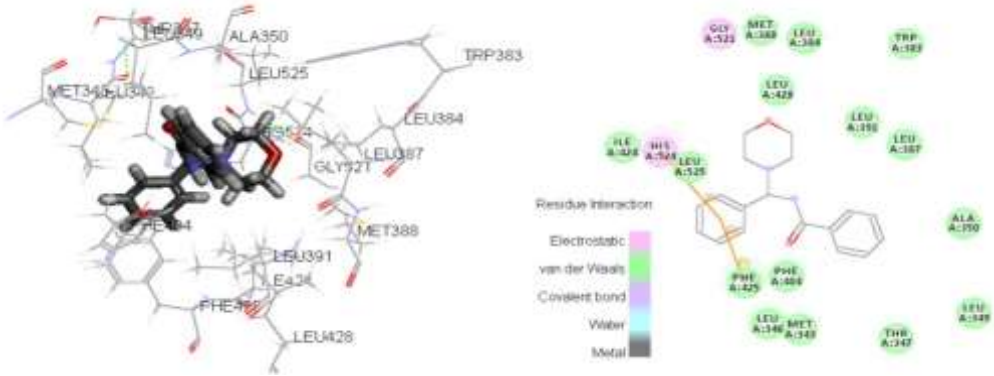


Figure 12: Interaction details of *N*-phenyl(pyrrolidin-1-yl)methyl acetamide with active-site amino acids of 2 YAT receptor

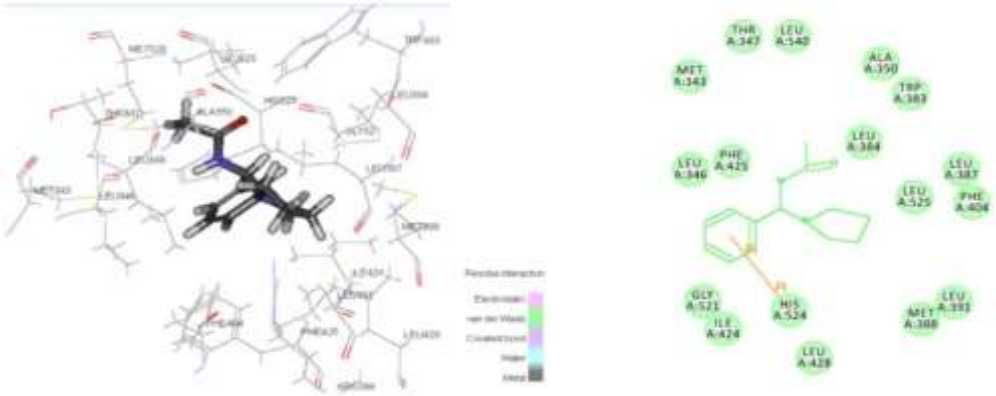


Figure 13: Interaction details of *N*-phenyl(pyrrolidin-1-yl)methyl benzamide (PBB) with active-site amino acids of 2YAT receptor

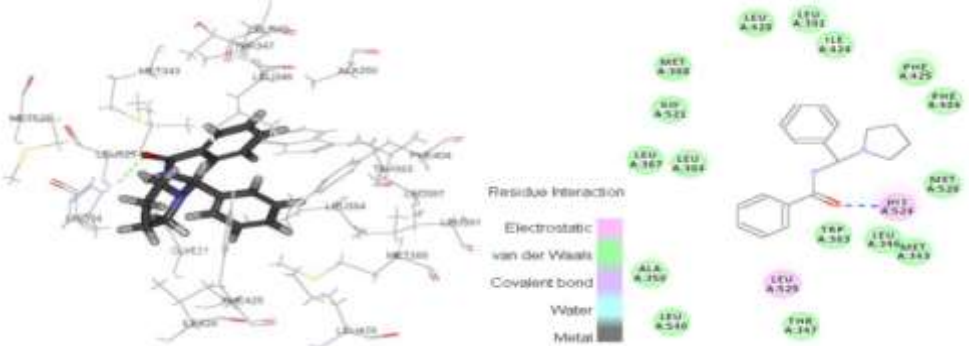
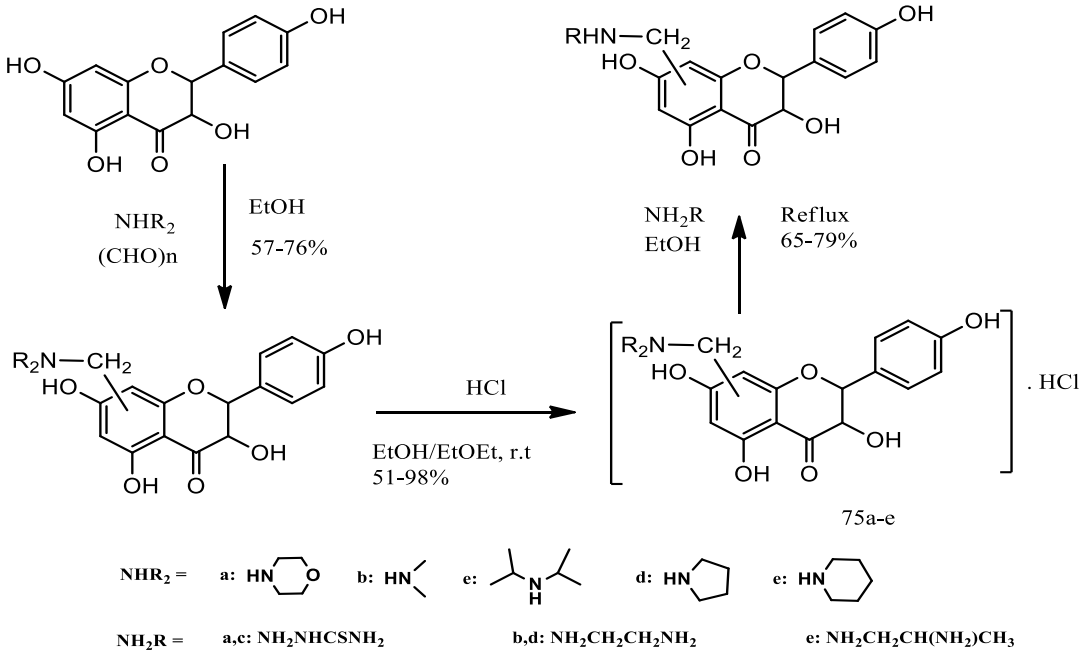


Figure 14 : Interaction details of tamoxifen with active-site amino acids of 2YAT receptor

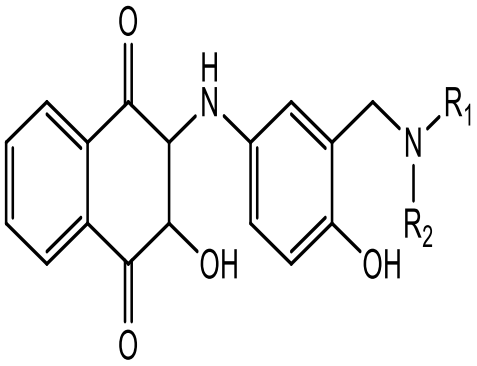
An original chain of kaempferol Mannich compounds was obtained by combining the Mannich reaction with the substituted amine (Scheme 11). The amino methylation of kaempferol occurred primarily in positions [C-6 and C-8] of the A-ring. For the main substitution reaction, the experiential and computational results point to a hydrogen bond-assisted S_N2 mechanism. An anti-proliferative test on HeLa, HCC1954, and SK-OV-3 are three human cancer cell lines that have already been studied. The number of chemicals studied displayed intermediate to powerful cytotoxicity in opposition to the three cells of cancer; compound 75e, which is identical to the control sample cisplatin, had specific anti-proliferative action against HeLa cells. Kaempferol molecules and their lanthanide compounds emit blue-green fluorescence depending on the solution conditions (neutral, acidic, or alkaline). These findings are predictable to aid future research into the synthesis and implementation of various nitrogen-containing flavone derivatives, particularly with primary amines[45].



Scheme 11 - Preparation of kaempferol derivatives

4- Anti-malarial activity

The *in vitro* activity of the new antimalarial Mannich bases (2-hydroxy-1,4-naphthoquinone-4-hydroxyaniline hybrid) was developed, produced, and assessed (Scheme 15). The measured dosage (1 mg/mL), was significantly lower than that of the reference treatment, chloroquine (0.1 mg/mL). All of the synthesized compounds showed *in vitro* efficacy versus antimalarial chloroquine-sensitive descent (P. Falciparum RKL-2) compounds with morpholinyl 76f (IC50 is 0.391 g/mL) and propyl 76a (IC50 is 0.453 g/mL) substitutions. On the other hand, they are far more effective than the rest of the manufactured analogues. Compound 76f (IC50 is 0.993 g/mL) was reported to be more efficient against the resistant strain (RKL-9) of plasmodium falciparum than compound 5a (IC50 is 2.92 g/mL). These chemicals were also less effective against the resistant strain than chloroquine (IC50 is 0.299 g/mL). Compounds with the least saturated heterocyclic moiety (morpholinyl, 76f) or alkyl groups (*n*-propyl, 76a, and isopropyl, 76b) show a more powerful antimalarial efficacy than those substituted for bulky aryl (phenyl, 76e) or alkyl (diisopropyl, 76c, and *n*-butyl, 76d) moieties. Furthermore, because all the compounds showed promising drug-like properties, it appeared that a plausible link between drug-likeness and antimalarial activity existed [46].

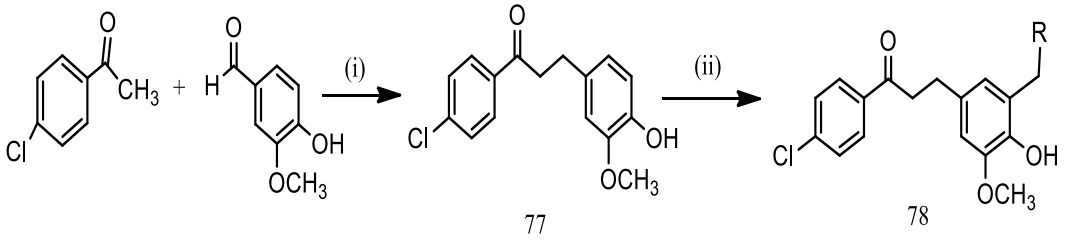


Compounds, 76a-76f

76a: R_1=H , R_2= n-propyl
76b: R_1=H , R_2= i- propyl
76c: R_1=H , R_2= n-butyl
76d: R_1, R_2= i-pr
76e: R_1, R_2= phenyl
76f: R_1, R_2= $-(CH_2)_2O(CH_2)_2$

Figure 15 :Synthesis of compounds **5a-5f**

The Mannich reaction was used to successfully add secondary amines to the chalcone compounds (Scheme 12), and the spectroscopic investigation confirmed this. The antimalarial efficacy of the created compounds was examined *in vitro* versus the Plasmodium falciparum 3D7 strain (sensitive CQ); all of the compounds showed high activity. Molecular docking was used to analyze the interactions with the binding site of the created compounds in place of the wild type (plasmodium falciparum dihydrofolate reductase thymidylate synthase (Pf-DHFR-TS), PDB ID: IJ3I), and quadruple mutant (PDB ID: IJ3K and Pf-DHFR-TS). Together, the wild and mutant Pf-DHFR kinds form various hydrogen bonds and interactions with the side chains of Cys15, Asp54, Ala16, Leu164, Tyr170, and Met55 and exhibit acceptable drug-like behavior that is beneficial to membrane permeability. According to the molecular docking results, compound 78b has the lowest energy and the maximum number of hydrogen bonds, indicating that it has the best antimalarial activity[47].



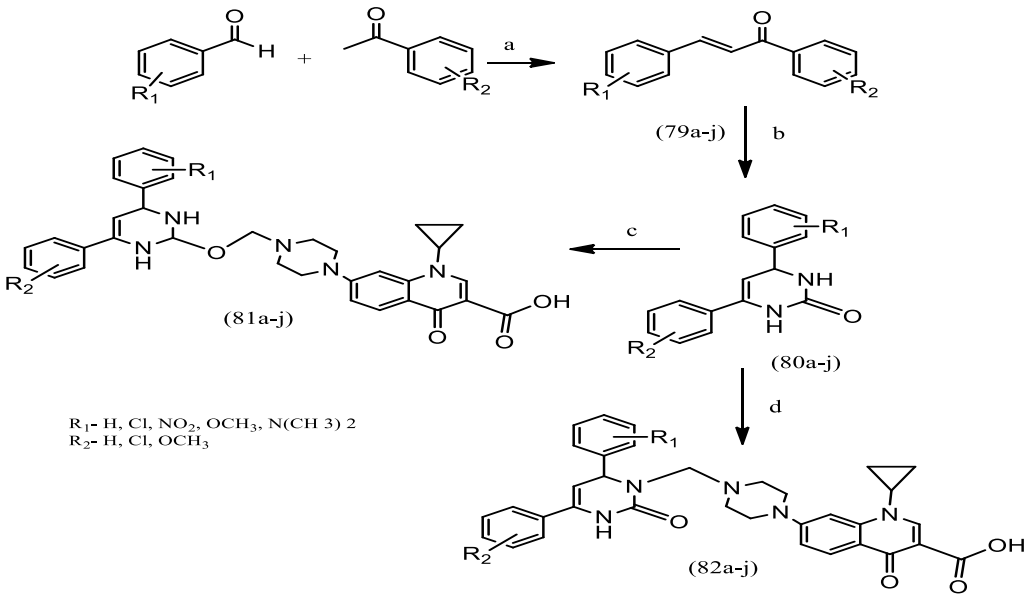
(i) ethanol, [sodium hydroxide40 %], stir at rom temperrature overnight
(ii) [formaldehyde, secondary amine , ethanol, stir overnight]

R=a: morpholine
b: piperidine
c: diethylamine

Scheme 12 - Reagents and conditions of synthesis

5- Anti-viral activity

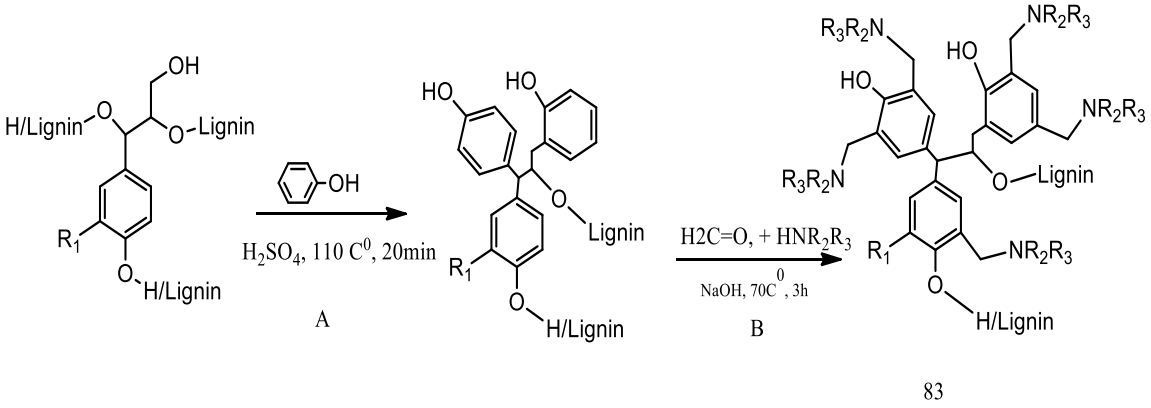
A unique chain of *N* and *O*-Mannich bases of diaryl-dihydropyrimidines was synthesized utilizing conventional and microwave methods, synthesized, and tested against various viral strains (Scheme 13), reagents, and conditions of synthesis. An intermediate chalcone was used to add the aromatic groups at 4 and 6-positions right away, and the title compounds were created by combining the chalcone with ciprofloxacin's piperidinyl ring. Some chemicals exhibit strong antiviral activities against certain virus strains. Hepatitis B (EC50 = 1; SI = 300), cowpox (EC50 = 15.1; SI = 19.9), and vaccinia (EC50 = 20.9; SI = 14.4) were the three virus strains against which compound 81f demonstrated activity. Compound 81a showed significant restrained action versus influenza A (H1N1) California strain EC50-0.52M; SI-94, which was equivalent to ribavirin EC50-5.1M; SI-63 ([48]).



Scheme 13 - Reagents and conditions of synthesis

6- In the field of agriculture

Mannich reaction synergy with phenolation pre-treatment was applied to amination biorefinery technological lignin to improve a modern, lignin-based, highly effective nitrogen fertilizer (Scheme 14): reagents and conditions of synthesis. Following that, a leaching experiment in a soil column was used to study the nitrogen emission from aminated lignin's action in the soil. The number of active sites in lignin increased significantly after phenolation, from 2.91 mmol/g to 8.26 mmol/g, according to the findings. Furthermore, in this study, the amount of nitrogen in aminated lignin was significantly dependent on the type of amination reagent rather than the number of reactants. Lignin that has been amined and contains a higher quantity of nitrogen (10.13 %) and a low C/N rate (6.08) may be produced under ideal conditions. Furthermore, with the APL that was created in this study, the mechanism through which nitrogen is released into the soil is perfect, which is notable. As a result, it has been thought that these aminated lignin derivatives 83 might be utilized to make a variety of lignin-based, high-efficiency nitrogen fertilizers[49]

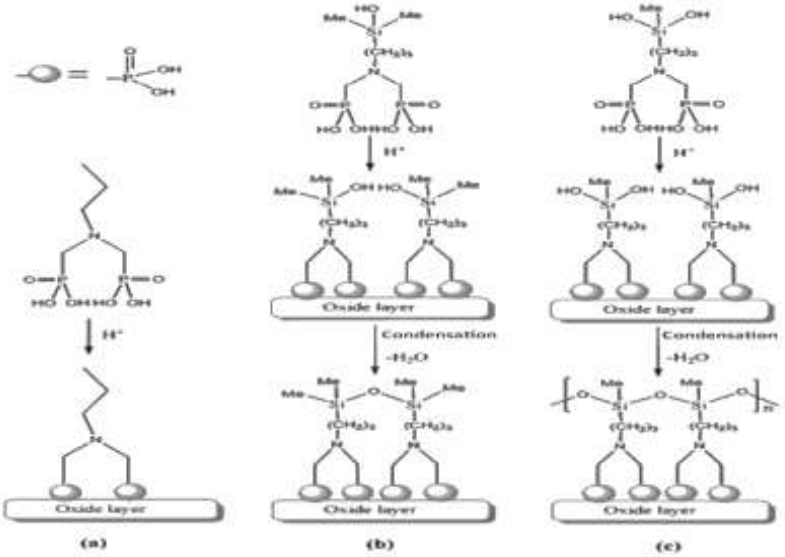


Scheme 14: Chemosynthesis scheme of the aminated lignin with high nitrogen content (A) The phenolation of lignin; (B) The Mannich reaction of phenolated lignin under alkaline condition.

7- In the field of industry

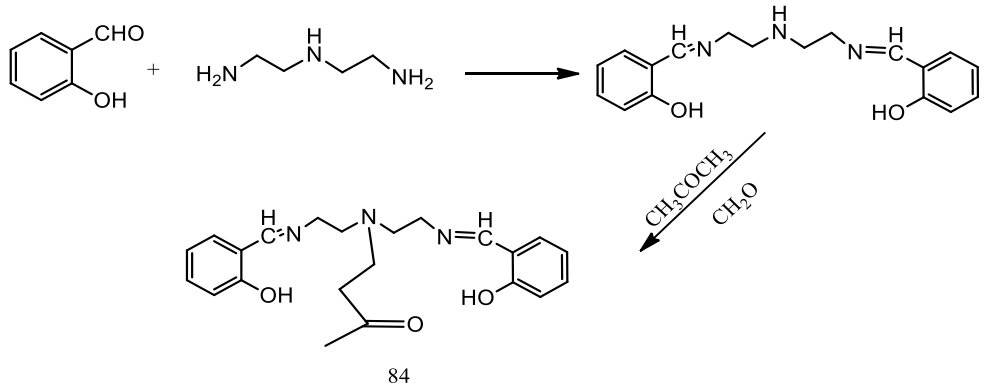
The iron corrosion inhibitors *N,N'*-dimethylenephosphonyl aminopropylmethylsilanol (DPMS) and *N,N'*-dimethylenephosphonyl aminopropyl dimethylsilanol (DPDS) were

produced using a simple Mannich technique (Scheme 15), reagents and conditions of synthesis. *N*,*N*'-dimethylenephosphonyl propyl amine (DPPA) was too well chosen to be examined with the help of these two silanes to investigate the relationships between corrosion inhibition characteristics and molecular configuration. The number of phosphonyl groups in each of these three compounds is the same, but the number of hydrolysis groups is different. Electrochemical methods were used to evaluate the iron's corrosion inhibition characteristics in sulfuric acid solutions. The effect of these three inhibitors on iron corrosion grew at first and then declined when the concentration reached its highest value, according to electrochemical data. The chemical evaluation of the absorption operation was based on the equilibrium constant and standard Gibbs free energy. Furthermore, DPMS outperformed DPDS and DPPA in terms of corrosion inhibition. To explain the differences between these three inhibitors, a concept of their organization on the surface of the iron was proposed [50].



Scheme 15 - On the oxidized ionophore (a) DPPA, (b) DPDS, and (c) DPMS molecules self-assemble and reinforce each other

A corrosion inhibitor was created with nitrogen atoms, and a conjugated link was found in this compound. (Scheme 16). Reagents and conditions of synthesis, and the final product was dubbed multi-Mannich base (MBT 84) because it was synthesized under the optimal circumstances of the orthogonal test results. In a solution of CO_2-saturated steel with a [3 wt% NaCl] concentration, the corrosion inhibitor has an inhibitory effect, which was investigated. The corrosion rate was 0.0446 mm/a with a 90.4% corrosion inhibition rate. MBT is a blended corrosion inhibitor that primarily demonstrates cathode suppression capacity, according to electrochemical and adsorption theory studies. The Langmuir adsorption isotherm governs the MBT adsorption on the surface of steel sheets. It can self-adsorb on the roof of N80 steel sheets, giving it a good corrosion inhibitor. An atomic force microscope was used to characterize the surface of the N80 steel sheets (AFM). The results show that the MBT-added N80 steel sheet differs considerably from the blank control group; the steel sheet's surface is rather smooth, showing "that MBT forms an effective protective film on the N80 steel's surface", preventing the steel sheet from rusting[51].



84

Scheme 16 - The synthesis of MBT (84)

8. Conclusion

Mannich bases and their derivatives are shown to have robust and diversified actions, as explained by the structure of the work described in this paper. This review examined several biological functions of Mannich base derivatives in the current scenario. Mannich bases, it might be inferred, offer tremendous biological potential that has yet to be realized. In addition to endorsing the researchers' efforts to develop new Mannich bases bearing heterocyclic compounds in order to be widely used for industrial and agricultural purposes.

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