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Synthesis, Antibacterial, Molecular Docking, and ADEMT Studies of New Mannich Bases of Curcumin

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Abstract

Utilizing natural products in drug development is interesting topic for the human medical science field. In the current work, four of curcumin derivatives (M1-M4) were prepared via Mannich reaction and identified by FT-IR and NMR spectroscopy. The obtained data from in-vitro study of the compounds M1-M4 revealed convincing activities against bacteria strains including *Salmonella, Staphylococcus aureus, Proteus, and Klebsiella* in parallel with Amoxicillin as a standard drug. The compounds M2 and M4 have showed a high antibacterial activity. The potential DNA gyrase inhibitory activity of the compounds (M1-M4) was investigated via Insilco using the molecular docking simulation method. The (PyMOL) software was utilized for the calculation of the binding affinity (kcal/mol) for the prepared compounds with protein (1KZN). The highest binding values (kcal/mol) with protein was (-8.2) for M4 and (-8.1) for M2, whereas the lowest values were found (-7.1) for M1. Furthermore, the findings revealed that amino acids were linked with the synthesized compounds through hydrogen bonding and (aryne -aryne) hydrophobic interactions. Also, the linkage way between proteins and the synthesized compounds was stated via the three dimensions shape. The electronic densities of the prepared compounds were also reported through recognizing the characteristic features of amino acids, which surround these compounds. Drug-like behavior and ADMET prediction study including absorption, distribution, metabolism, excretion, and toxicity of the desired compounds were performed. The yielded results revealed that the majority of the pharmacokinetic parameters were significant and within a normal range.

Keywords: Curcumin, Distribution, Metabolism, Molecular Docking, Toxicity.

Introduction

Pharmaceutical development processes are very important to overcome tumors and microbial strains' resistance towards old drug (MDR). It also provides an appropriate cost and time-efficient strategy for attaining a novel bioactive framework. Mannich method offers an adequate reaction to add aminoalkyl moiety into a compound structure[1-3]. In many cases, the activity of Mannich hybrids better than that of parent molecule. Furthermore, the drug solubility and subsequently its bioavailability rises as a result of existence Mannich substituents in the drug structures. In organic synthesis field, Mannich reaction plays important role in formation of carbon-carbon bonding[4-6]. Sulfonamides compounds considered the main drugs frequently utilized as preventive medications for treating various diseases, especially when they are being chemotherapeutic drugs. Sulfonamide moiety ispresented in a variety of drugs with a significant medicinally and clinically actions as antibacterial, antimalarial and antileprotic medicine. In addition to inhibition of Gram+ and Gram- bacteria, Sulfonamide drugs utilized for the inhibition of some Protozoa as well [7]. They used as inhibitors for enteric bacterial strains including

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Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, antitubercular. They also have active properties and used as anticancer agents. The modification of old drugs sorts usually produced an improved and novel drugs, which ultimately aimed to a better people health. Over the last decades, a significant interesting in natural products properties and their promising applications in healthcare has been apparently increased worldwide. In a comparison with artificial products, the toxicity of natural products is commonly less and rarely cause side effects[8-10]. A curry spice, derived from plant, turmeric has been conceded for the beneficial medicinal applications. In the most worldwide markets, many food supplementary of formulated turmeric are usually present and have various health claims benefits such as making joint more comfortable, developing of mental functioning, movement and flexibility improving, and overcoming cardiovascular problems. On the other hand, turmeric traditionally has been utilizes as a natural coloring material in different fields including fabrics, food manufacturers, make-ups, insect repulsive, and antimicrobial[11-13]. The applications of turmeric are also present in the medical field as it is used for liver disease, respiratory diseases, skin diseases, and injury curing.

A number of polyphenolic materials with bioactivity which are conjointly known as curcuminoids (CCMs) including curcumin (CUR), dimethoxy curcumin (DMC), and bisdemethoxycurcumin (BMC) have been recognized in turmeric[14,15]. Curcuminoids are mostly admitted to be safe compounds(GRAS) as recommended by the American Food and Drug Administration (FDA)[16]. Curcuminoids oral amount consuming (up to 12g per day), which is considered a high single amount, are too tolerated as confirmed and reinforced by advanced clinical investigations[17-19]. Over the last decades, much attention of researchers has been drawn by curcumin, in particular for its therapeutic potential properties such as anti-diabetic, anti-inflammatory, anti-aging, and anti-cancer agent. These therapeutic potentials were reinforced by various clinical studies, in-vitro and in vivo researches [20,21]. Promising treatment applications are also shown by curcumin for injury curing and a number of diseases such as arthritis, and Alzheimer's. Recently, about ten thousand research papers concerning curcuminoid materials have been issued. Nevertheless, because of some properties of curcumin including poor solubility in water, low absorption, and pharmacokinetic profiles, its therapeutic potential is still restricted [22].

The current work aimed to design and prepare compounds based on phytochemicals in order to find a potential therapeutic molecule as an antibacterial. The Mannich reaction was used as a pharmacophore for synthesizing four novel hybrid molecules of curcumin (M1-M4). Analytical techniques including FTIR and NMR are utilized for the characterization of the produced compounds. The designed compounds are subjected to ADMET experiments and molecular docking to understand toxicity, adsorption, distribution, the interactions between (ligands - protein), and the binding affinity of the compounds. The molecular docking studies were performed using PyMOL and BIOVIA\Discovery Studio 2021 for the compounds (M1-M4).

Materials and Methods

The drug, sulfamethoxazole, was acquired from the State Company for the Drugs Industry and Medical Appliances (SDI Company) in Iraq. All reagents and solvents were obtained from Sigma - Aldrich. All the solvents in this study were not purified before use. To observe the reaction proceeding, a thin-layer chromatography (TLC) was employed. TLC was performed on Merck silica gel, visualization with UV light, and using an eluent of ethyl acetate: hexane (1:1). The compounds (M1-M4) spectroscopic measurements were carried out using FT-IR instrument, (KBr disc) Perkin Elmer, tenser 27 (Bruker). ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Bruker– DRX system AL 400 MHz spectrometer with TMS as an internal standard at the University of Basra.

Synthesis of Curcumin Derivatives

A mixture of formaldehyde (0.1mol) and (0.1mol) of (sulfamethoxazole, 4-amino benzene sulfonamide aniline, or 3-hydroxy aniline), respectively in 20 ml ethanol was prepared. Then, the mixture was refluxed for 8 hours at 70 ^{O}C. The mixture was stirred for 8 hours before adding solution of curcumin (0.1 mol) in 20ml ethanol drop by drop. TLC (hexane: ethyl acetate 1:1 as the eluent) was used to monitor the reaction's development. Following the reaction's accomplishment, the precipitated solid product were

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filtered, washed with water, and recrystallized from ethanol.[23]

4-(((E)-5-(4-hydroxy-3-methoxyphenyl)-2-((E)-3-(4-hydroxy-3-methoxy phenyl)acryloyl)-3-oxopent-4-en-1-yl)amino)-N-(5-methylisoxazol-3-yl) benzene sulfonamide. M1

% yield: 41.5, Rf = 0.8; Mp =184-185°C; FT-IR (KBr, ν_{max} cm^{-1}): 1335(C-N), 1634(C=O), 3046 (C-H aromatic), 3357(NH); ^{1}HNMR (DMSO, 400 MHz): δ3.12 (t, 2H, CH_2-NH), 4.23 (t, 1H, CH-C=O), 3.64(s, 3H, OCH_3), (6.77-7.56)(m, 10H, aromatic and 4H in alkene 2(CH=CH), 9.21 (s., 1H, O-H Phenol), 11.0(s, 1H, $NHSO_2$). ^{13}C-NMR (DMSO,400 MHz): C_{18}(41.13), C_{15}(163), $C_{20,24}$ (170.8), 111-129[aromatic carbons and alkene)], C_{14}(95), C_{13}(157), C_{19}, 60.65.

4-(((E)-5-(4-hydroxy-3-methoxyphenyl)-2-((E)-3-(4-hydroxy-3-methoxyphenyl) acryloyl)-3-oxopent-4-en-1-yl) amino)benzene sulfonamide M2

% yield: 63, Rf = 0.35; Mp. 196-198°C; FT-IR (KBr, ν_{max} cm-^{1}): 1341 (C-N), 1624(C=O), 3010(Ar-CH), 3348(NH);^{1}H-NMR (DMSO-d_6, 400 MHz): 1.18(s, 3H, -CH_3), 2.28(t, 2H, CH_2-NH), 3.1(t, 1H, CH-C=O), 3.37(s, 3H, OCH_3), 6.0 (CH, oxazole), (6.7-7.5) (m, 10H, aromatic and 4H in alkene 2(CH=CH), 9.05 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6, 400 MHz): 38-63 (aliphatic carbons), 114-153 (aromatic carbons and alkene carbons), 167(C=O)

(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-4-((phenylamino)methyl)hepta-1,6-diene-3,5-dione M_3

% yield: 62, R_f = 0.53; Mp=191-192°C; FT-IR (KBr, ν_{max} cm^{-1}); 1343(C-N), 1664(C=O), 3083 (C-H aromatic), 3314 (N-H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.31 (d, 2H, CH_2-NH), 3.83 (s, 3H, OCH_3), 4.62(t, H, CHC=O) (6.5-7.6)(m, 11H, aromatic and 4H in ethylene group (CH=CH), 9.8 (s, 2H, phenol); ^{13}C-NMR (DMSO-d_6, 400 MHz): C_8(45.03), C_9 (59.36), C_{34} (53.2), $C_{30,14}$ (176.01), 112-149(aromatic carbons and ethylene group (CH=CH).

(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(((3hydroxyphenyl)amino)methyl)hepta-1,6-diene-3,5-dione M4

% yield: 43, R_f = 0.68; M.p=201-202°C; FT-IR (ν_{max} cm^{-1}, KBr): 1349 (C-N), 1671(C=O), 3089 (C-H aromatic), 3308(NH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.28 (d, 2H, CH_2-NH). 3.91(s, 3H, OCH_3), 4.57(t, H, CHC=O), (6.46-7.82)(m, 10H, aromatic and 4H in ethylene group (CH=CH), 9.76 and 9.81 (d, 3H, phenol); ^{13}C-NMR (400 MHz, DMSO-d_6) δ C10(39.03),C_4(57) ,C_{35} (43), $C_{3,5}$(196), 112-160(aromatic carbons and ethylene groups (C=C).

Molecular Docking

Molecular docking investigation using the PyMOLsoftware were carried out for testing the interaction of synthesized compounds (M1–M4) with enzyme (DNA-gyrase). The PyMOL was exploited for interpreting the results of docking. The (PDB ID: 1KZN) was chosen as a standard sample and downloaded via a protein data bank. Gausin.09 was utilized to sketch of (M1–M4) structure.

The Study of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET)

In this study, all optimized compounds were investigated by ADMET in order to check the toxicity and drug side effects prior to their preparation, and running the clinical experiments. ADMET experiments were carried out on the potential compounds utilizing the online software, ProTox-II, and Swiss adme.

Antibacterial Activity

Table.3 shows all sorts of bacteria utilized in this study. Four bacteria strains (*Staphylococcus aureus Salmonella, Klebsiella, and Proteus*) were supplied by the Department of Biology, College of Science, University of Wasit. A solid-phase nutrient bath was utilized for growing the bacteria at a temperature of 37 ^{0}C for 24 hours. Different quantities from the synthesized compounds (M1-M4) were dissolved in DMSO to prepare solvent with concentrations of 0.1 g/mL for each. The biological activities of these solvents were compared with those of Amoxicillin antibiotic.[24] The measurements of the inhibition zone (in millimeters) were conducted upon incubation of the inculcated plates at the same conditions of the bacteria growth.

Results and discussion

New Mannich bases were produced by reaction of primary amine compounds including sulfamethoxazole, sulfamide, aniline, and m-amino

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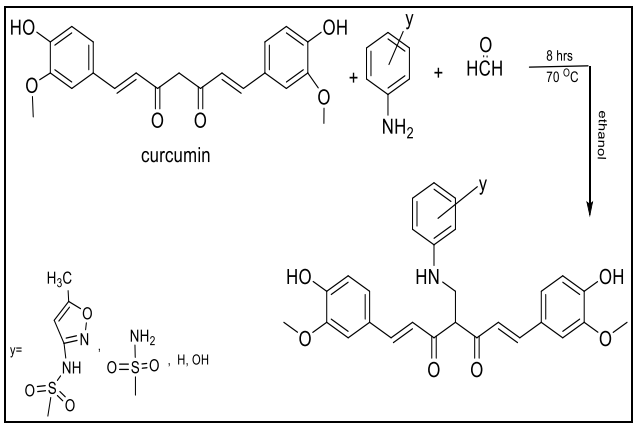
phenol with formaldehyde and an active hydrogen molecule (obtained from curcumin) with the ratio of 1:1:1 in Scheme 1. The Mannich reaction mechanism begins with the formation of an iminium ion from amine and formaldehyde. In the second step, the molecule that contains the carbonyl functional group (curcumin) tautomerizes to the enol form before attacking the iminium ion. FT-IR spectrum confirmed the existence of (C-N) group due to the appearance of sharp peaks at 1357 cm^{-1} attributed to compound M1, and appeared with one peak instead of two peaks in the area of 3426 cm^{-1}, which indicates on reaction NH_2 amine with formaldehyde. The v(C-H) aliphatic peaks are located between 2980 and 2700 cm^{-1}, which refers to the formation of the CH_2-CH_2-NH. Moreover, ^{1}H-NMR spectrum of synthesized compound M1 showed a signal at δ 3.12 ppm due to the proton of the group (CH_2 NH) and a signal at δ 11.0 ppm belongs to proton of $NHSO_2$. All chemical shift values of compounds M1-M4 were shown in the experimental part[25,26]. ^{13}C-NMR spectrum of compound M1 showed signals at δ 111-129 ppm belongs to aromatic carbons and diene groups (C=C), respectively. The signals appeared at δ 41 and 60.7 ppm are assigned to (CH_2) groups.



Scheme 1. Synthetic route for the preparation of Mannich bases (M1-M4).

Descriptors of Global Reactivity

The most important qualities that may be determined from the conceptual density functional theory (DFT) are global reactivity descriptors. They have significant qualities that help us comprehend compound chemical reactivity and kinetic stability[27]. The described energy of the highest occupied molecular orbital (EHOMO), energy of the lowest unoccupied molecular orbital (ELUMO), energy gap (E), global electrophilicity (ω), chemical potential (μ), chemical hardness (η), chemical softness (S) and nucleophilicity (N) are examples of global reactivity descriptors. The following formulas were used to determine the descriptors: (ΔE = ELUMO-EHOMO), (= (ELUMO+EHOMO)/2), (= (ELUMO-EHOMO)/2), (S = 1/(2)), (N = EHOMO (Nucleophile) - EHOMO (TCE)). Fig. 1 shows the energy levels (HOMO-LUMO) orbitals of the studied compounds (M1-M4).

According to the results in Table 1, molecules M3 and M2 exhibited less potential ionization energy (7.648205 and 7.66262 eV, respectively). Compounds M1 and M4, on the other hand, showed the highest affinity (7.711881 and 7.818008 eV, respectively). Compounds M1 and M4 are apparently the best electron acceptors, while M3 and M2 are the optimum electron donors. The energy gap (E) can be utilized to gauge a molecule's reactivity and stability. A little energy gap indicates a high reactivity and low stability. The compound M4 has the slightest energy gap (6.66485 eV), followed by M2 (6.85443 eV) and M3 (6.88490 eV). Nevertheless, compound M1 had the greatest ΔE (6.91484), indicating that compounds M2-M4 are highly polarizable and reactive. Compound M1 had the highest chemical hardness (η) (3.45742), and compound M4 had the lowest (3.33242). Furthermore, compound M4 had the lowest chemical softness (s) (0.1500409) while compound M3 had the greatest (0.291782).

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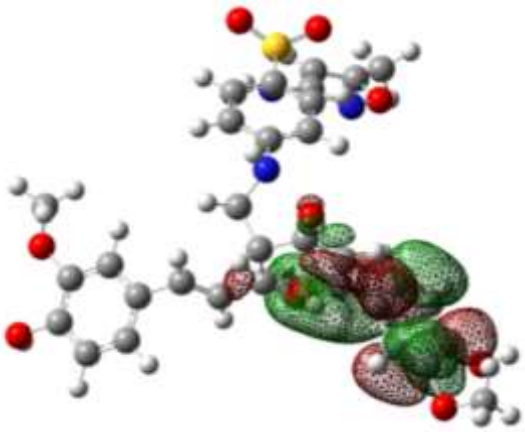
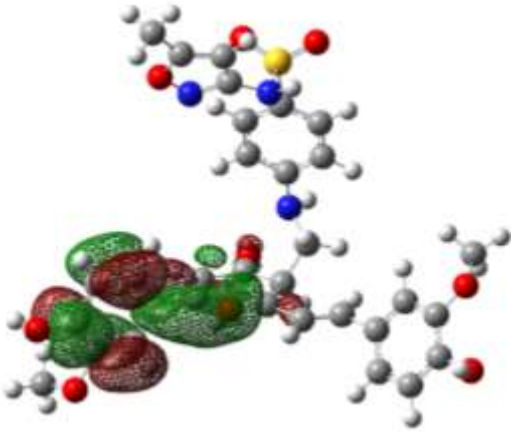
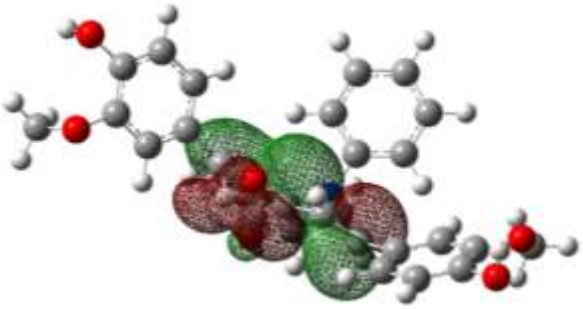


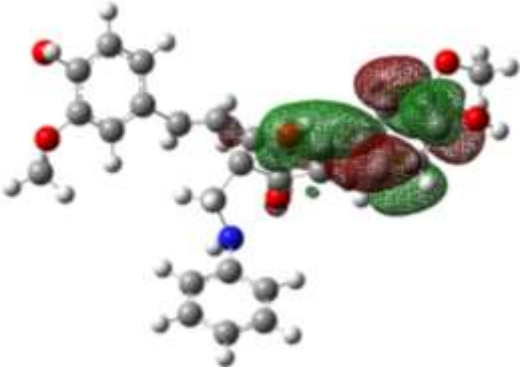
D3 LOMO Compound M1



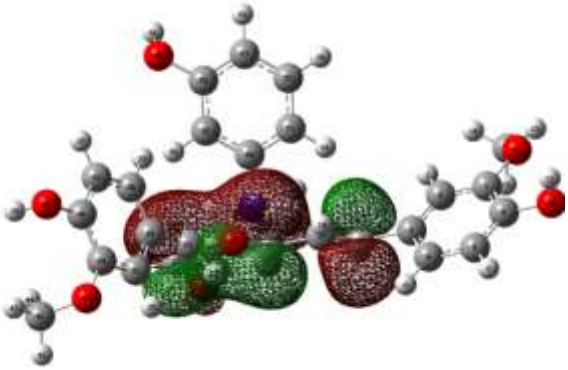
D3 HOMO Compound M1



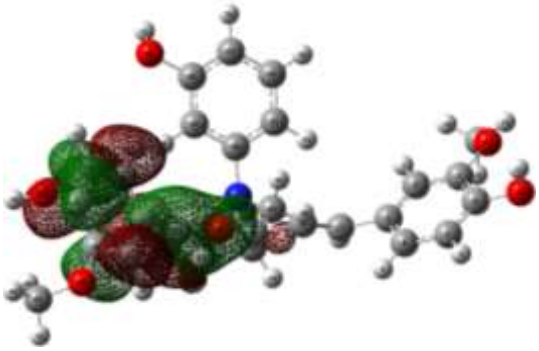
D3 HOMO Compound M_2



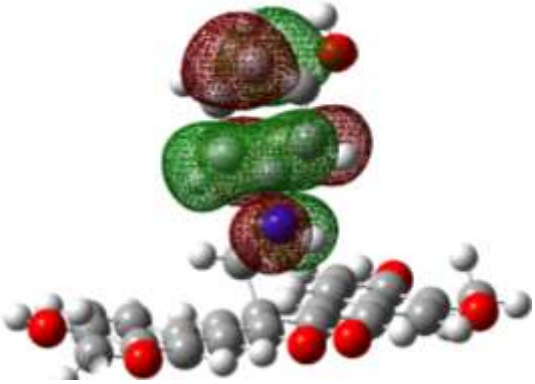
D3 LOMO CompoundM2



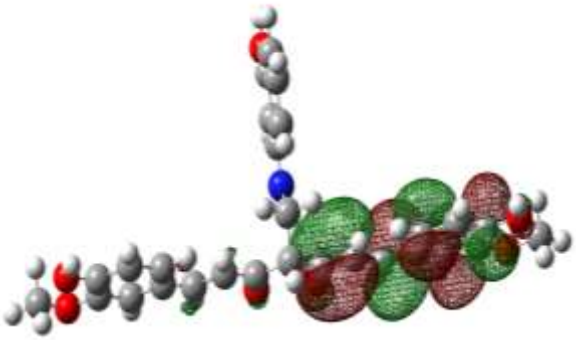
D3 HOMO Compound M3



D3 LOMO Compound M3



D3 HOMO Compound M4



D3 LOMO Compound M4

Figure 1. The energy levels (HOMO-LUMO) orbitals of the studied compounds (M1-M4).

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Amongst other deravitaves, compound M3 without a doubt has the highest softness and reactivity. The electrophilicity (ω) and nucleophilicity (N) indexes could be used to predict the reactivity of chemicals. Organic molecules, for example, can be categorized into strong (N>3 eV), fair (2.0 eV ≤ N ≤ 3.0 eV), or marginal (N< 2.0 eV) nucleophiles based on their nucleophilicity (N). Furthermore, a value (ω) greater than 2.0 eV indicates reactivity in a polar reaction[28]. Compound M3 is the most powerful nucleophile (N= 0.389234 eV), and compound M4 is the most powerful electrophile (= 3.01889).

Table1. Global reactivity descriptors of compound M1-M2.

No.	ELUMO (eV)	EHOMO (eV)	ω	η	EA	ΔE	ΔN
S	-2.0618	-0.0251	-0.5346	-1.018	2.06185	-2.0367	-2.9245
C	-0.177694	-9.793327	2.58488	4.80782	0.59676	9.61563	0.2095
M1	-0.79703	-7.711881	2.61762	3.45742	0.79703	6.91484	0.39705
M2	-0.808196	-7.662627	2.61709	3.427215	0.80819	6.85443	0.40332
M3	-0.763297	-7.648205	2.56914	3.442454	0.763297	6.88490	0.40585
M4	-1.15316	-7.818007	3.01889	3.33242	1.15316	6.66485	0.37727
No.	**CP**	**N_{max}**		**So**	**N**	**IE**	**S**
S	-1.04348	-1.02465		-0.49098	-0.18706	0.0251	-0.98195
C	-4.98551	1.036959		4.807816	0.3868642	9.79332668	
M1	-4.25446	1.23053		0.144616	0.382026	7.711881	0.289233
M2	-4.23541	1.235817		0.145891	0.382103	7.66262	0.291782
M3	-4.20575	1.22173		0.145245	0.389234	7.648205	0.29049
M4	-4.4856	1.34604		0.15004	0.33125	7.818008	0.1500409

C= curcumin S= sulfamethoxazole

Antibacterial Activity

Table 2 gives the outcome of the antimicrobial activity against three strains of Gram-positive bacteria (*Salmonella, Staphylococcus aureus, and Proteus*) and one strain of Gram-negative bacteria (*Klebsiella*). Amoxillin was used in the control[29-31]. The outcomes of compounds M_1-M_4 showed an excellent bioactivity against all bacteria in a concentration 100 µL. Also, compound M_2 had the highest activity. Fig. 2 shows the inhibition zone of compounds M_1-M_4.

Table 2. Activity of curcumin derivatives M1-M4 against bacteria.

NO.	*Klebsiella pneumoniae*	*Salmonella*	*S-aureus*	*Proteus*
M1	++	++	++	++
M2	+++	+++	+++	+++
M3	+	+	+	+
M4	+++	+++	++	++
Amoxicillin	-	-	-	-

Inhibition zone (mm)= 1-10> +, 10-15> ++, 15-35 > +++

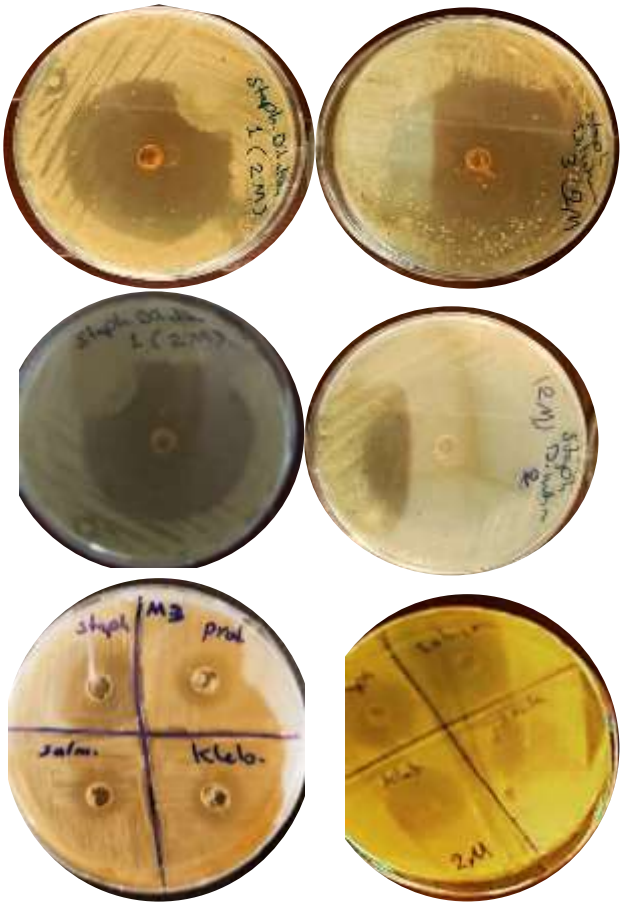

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Figure 2. Inhibition zone of compounds M1-M4 on four series of bacteria (*Klebsiella, Salmonella, Staphylococcus aureus, and Proteus).*

The Docking Molecular

The study Insilco was worked on compounds M1-M4, so as to foretell their closeness to a bacterial enzyme (DNA-gyrase)[32-34].

Analysis of the compounds M1-M4 displayed that they inhabit the different domains of DNA-gyrase binding pockets with perfect docking interaction scores Table 3. As explained in the empirical outcomes, these compounds M1-M4 were exhibited an activity toward enzyme (DNA-gyrase). The docking studies of curcumin derivatives uncovered their ability as antibacterial. The compounds M1-M4 have aromatic rings, it is showing remarkable hydrophobic interactions along with the amino acid in enzyme. Also docking outcomes principally for M1-M4 showed H-bonds interactions with enzyme (DNA-gyrase in the residues [(lone pair in nitrogen or oxygen in compounds with hydrogen in amino acid in enzyme as shown in Table 4.

The docking study of antibacterial activity results showed that the docking scores of compounds M1-M4 with DNA-gyrase were ranging from -7.1 to -8.2 kcal/mol. The compound M4 shows the lowest binding energy with -8.2 kcal/mol and two H-bonds. In general, the docking study indicates that the compound's M1-M4 bonding with DNA-gyrase is higher than the reference. Fig. 3-6 show the binding site with DNA-gyrase.

Table 3. Binding affinity with bacteria protein and hydrophobic contacts in ligands M1-M4.

Compd.	RMSD lower bound	Binding affinity (kcal/mol)	Type of bond (Bond length(A^o))
M1/1KZN	2.701	-7.1	Conventional hydrogen bond , VAL; 120(2.17), Conventional hydrogen bond, ALA;96(2.37), Pi-Anion , ASP;46(3.43). Alkyl, ILE; 78(4.26), Pi-Alkyl, ALA,47 (5.03). Pi-Sigma;ILE;90(3.76).
M2/1KZN	2.721	-8.1	Conventional hydrogen bond, VAL;167(2.68), Conventional hydrogen bond, THR;165(2.43). Conventional hydrogen bondVAL;71(2.11). Alkyl, ILE;78(4.36), VAL;120(5.33).Unfavorable Donor-Donor VAL;167(2.28)
M3/1KZN	2.322	-7.5	Conventional hydrogen bond, SER,121(2.62). Conventional hydrogen bond, GLY;117(2.63). Pi-Alkyl, Pi-Sigma, ILE;90(3.75) ALA;47 (5.07). Unfavorable Doner-Doner Asp;45(2.13)
M4/1KZN	0.894	-8.2	Conventional hydrogen bond GLY,77 (3.07), Conventional hydrogen bond ASP,73 (3.07). Unfavorable Doner-Doner, VAL,118(1.33). Unfavorable Acceptor-Acceptor HIS;95(2.94). Alkyl;ILE;90(4.41), ALA;96(3.98), Pi-Alkyl: ALA;47(4.53), Pi cation ARG;66(4.0). Pi-Anion GLU;50(4.21).
Amoxicillin	2.373	-6.3	Conventional hydrogen bond,ASN;46(2.13), HIS;95(2.98), VAL;93 (2.55)SER;121(2.31) Pi-Alkyl:ALA;96(5.45) ILE;90 (5.33).

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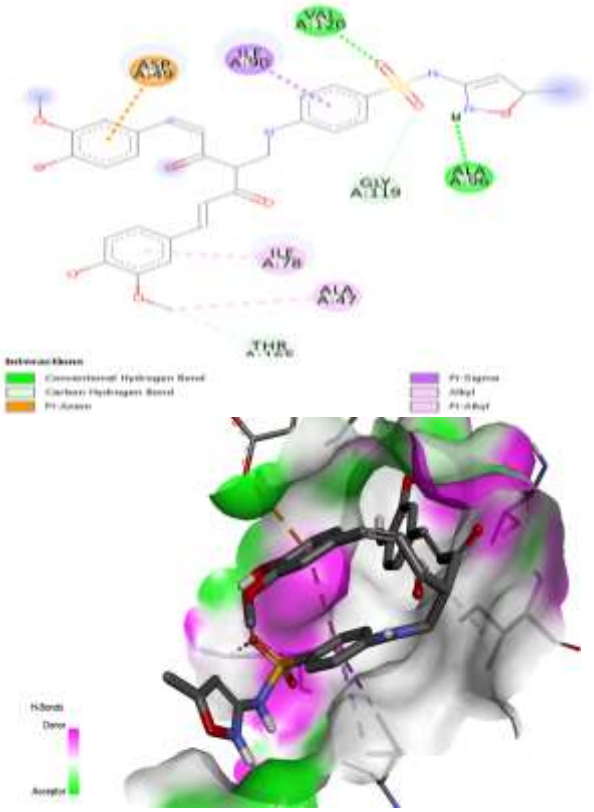


Figure 3. 3D and 2D binding site interaction of compound M1 with 1KZN .

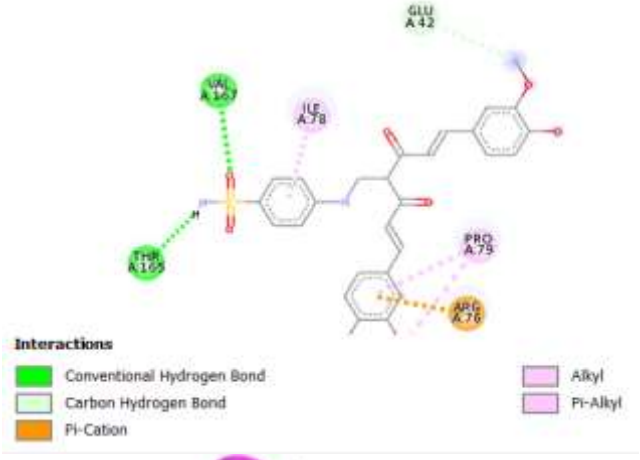
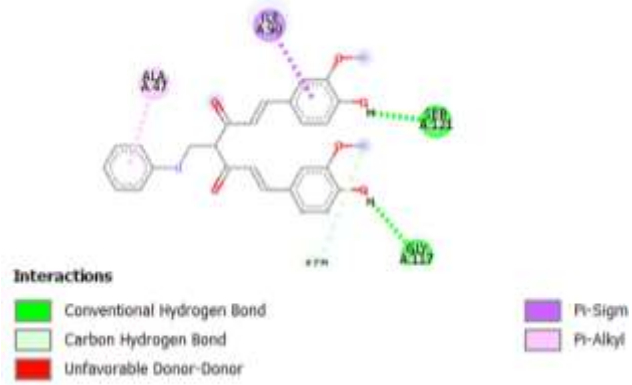


Figure 4. 3D and 2D binding site Interaction of compound M2 with 1KZN.



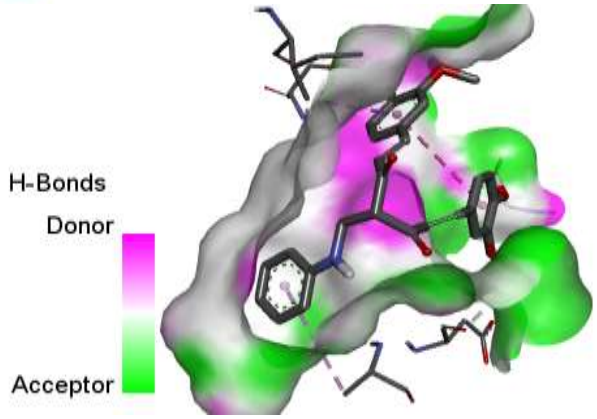
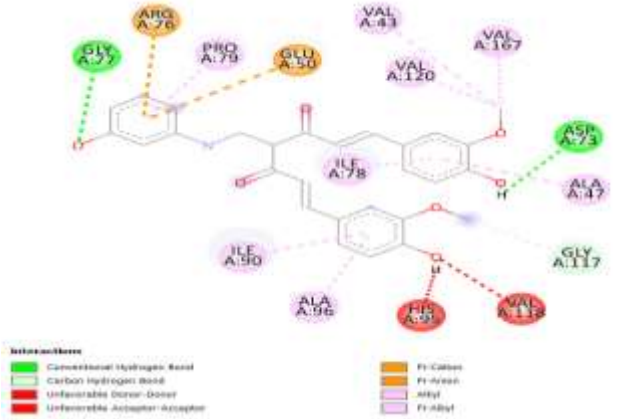


Figure 5. 3D and 2D Binding site interaction of compound M3 with 1KZN.



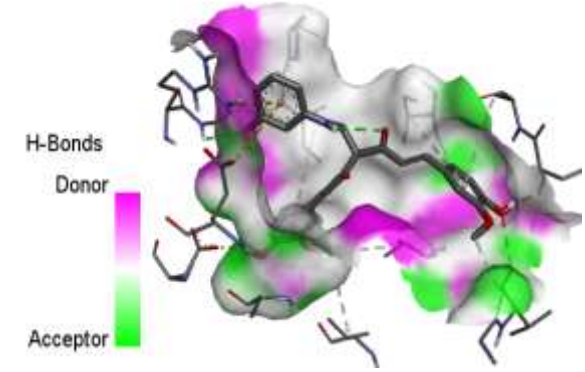


Figure 6. 3D and 2D Binding site Interaction of compound M4 with 1KZN.

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Analysis of ADMET Properties

Physicochemical Characteristics

Table 4 shows the physicochemical parameters of M1-M4 including molecular weight (M.Wt), lipophilicity, topological polar surface area (TPSA), acceptors (HBA), donors of hydrogen bonds (HBD), the number of heavy atoms (No heavy atoms), and drug-likeness. These parameters meet Lipinski's Rules of Three and Five. Table 4 displays the ADME properties of the designed compounds. These new compounds are unable to cross the BBB (Blood-Brain Barrier)[35-37]. The four chemical analogs (M1-M4) exhibited lipophilic properties with low bioavailability, reflecting a poor oral adsorption and distribution profiles, which indicating their appropriateness as a therapeutic compounds. Fig. 7 shows Spider shape and Boiled egg plot of synthesized compounds M1-M4 from the Swiss ADME. Fig. 7 shows that the compounds M3 and M4 have four of parameters within the desired therapeutic levels, whereas the compound M1 has not any of these sixth parameters within the desired therapeutic levels.

Table 4. Drug-likeness and Insilco of synthesized compounds (M1-M4).

Parameters	Standard value	M1	M2	M3	M4
M. wt. (g/mol)	<500	633.67	552.60	473.52	489.52
Consensus Log $_{Po/w}$	≤4.15	3.88	3.09	4.21	3.68
HBA	≤10	10	9	6	7
HBD	≤5	4	4	3	4
Lipinski's Rule	Yes;0 or 1violation	No;2violations:MW >500, Nor O>10	Yes; 1 violation: MW>500	Yes;0 violation	Yes;0 violation
TPSA (Å²)	≤131.6	185.67	173.63	105.09	125.32
Egan's Rule	Yes; 0 violation	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>131.6	Yes	Yes
Bioavailability Score		0.17	0.55	0.55	0.55
P-gp substrate (P-glycoprotein)	Yes – substrate; No -non-substrate	No	No	No	No
	Distribution				
BBB (Blood Brain Barrier)	Log BB> 0.3(high);Log BB <−1(poor)	No	No	No	No
Permeability (log BB)					
Metabolism					
CYP1A2 inhibitor		No	No	No	No
CYP2C19 inhibitor		No	Yes	Yes	Yes
CYP2C9 inhibitor		Yes	Yes	Yes	Yes
CYP2D6 inhibitor		No	Yes	No	Yes
CYP3A4 inhibitor		No	Yes	Yes	Yes
Log Kp (skin permeation)cm/s		-6.49 cm/s	-6.81	-5.30	-5.66
GI absorption		Low	Low	High	High

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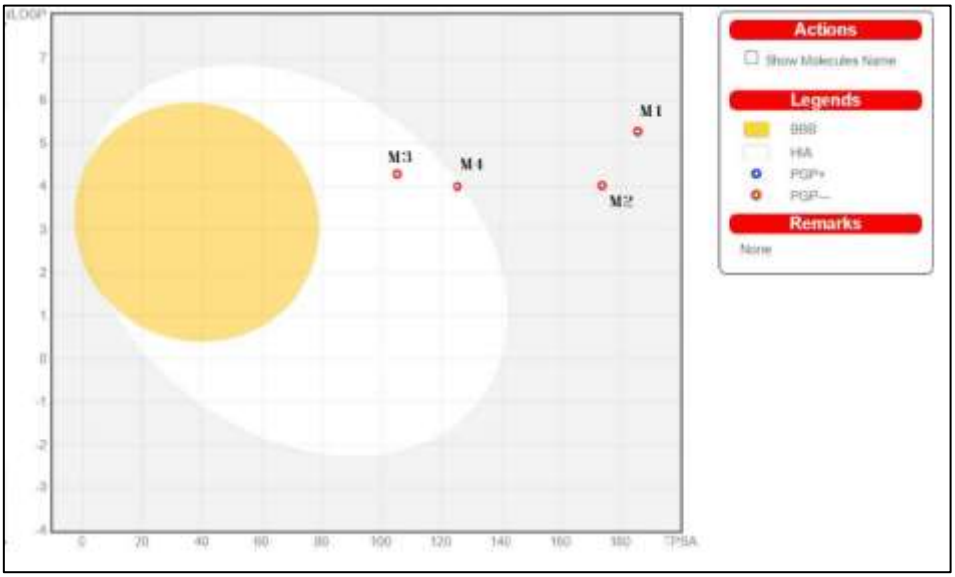

Figure 7. Spider shape and Boiled egg plot of synthesized compounds M1-M4 from the SwissADME.

The toxicity of synthesized compounds MI-M4 were calculated using the online software ProTox-II. Toxicological endpoint results suggested that the compound M1 was predicted to be hepatotoxicity and immunotoxicity, and compounds M1 – M4 were predicted to be non-cytotoxicity, non-Mutagenicity, and non-carcinogenic. The toxicity class of compounds M1 and M2 was 5, while for compounds M3 and M4 was 6. [Category 1: fatal if swallowed ($LD50 \leq 5$) category 2: fatal swallowed ($5 < LD50 \leq 50$) category 3: toxic if swallowed ($50 < LD50 \leq 300$) category 4: deleterious if swallowed ($300 < LD50 \leq 2000$) category 5: maybe deleterious if swallowed ($2000 < LD50 \leq 5000$), category 6: non-toxic ($LD50 > 5000$). The expected LD50. As shown in Table 5, the results indicated that the synthesized compounds M1 and M2 were deleterious if swallowed and belong to category 5, but the synthesized compounds M3 and M4 were non-toxic if swallowed and belong to category 6.

Table 5. The compounds M1-M4 were subjected to an insilico toxicity evaluation.

Comp	Organ Toxicity	Toxicity - endpoints				Predicted LD50 (mg/kg)	Predicted Toxicity Class
	Hepatotoxicity	Carcino-genicity	Immunotoxi-city	Mutagenicity	Cytotoxicity		
M1	Active	Inactive	Active	Inactive	Inactive	3471	5
M2	Inactive	Inactive	Active	Inactive	Inactive	5000	5
M3	Inactive	Inactive	Active	Inactive	Inactive	10000	6
M4	Inactive	Inactive	Active	Inactive	Inactive	10000	6

Conclusion

In the proposed study, four novel hybrid molecules of curcumin were synthesized via Mannich reaction and evaluated in-vitro as a potential antibacterial. Although the prepared bases had a less antibacterial effect than the standard compound, two compounds (M2 and M4) exhibited a promising inhibitory impact against (*Klebsiella pneumoniae, Salmonella, S-aureus, and Proteus*). Thus, they could serve as auspicious candidates for the development of a new class of antibacterial. The results of four novel curcumin correspondents that were subjected to ADMET experiments showed that they are lipophilic and have a low bioavailability. This is reflecting weak oral adsorption and toxicity profiles, and indicating their suitability as medicinal molecules. In an attempt to understand the ligands - enzyme interactions in terms of the binding affinity, molecular docking studies were performed using PyMOL and BIOVIA\Discovery Studio 2021 for the compounds (M1-M4). The binding affinities

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calculated were in agreement with the activity values. Hence, the current work opens a new entrance for developing novel and finest anti-bacterial drugs through performing various constructional arrangements in the base of curcumin structure.

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Author's Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee at University of Waist.
- No animal studies are present in the manuscript.
- No human studies are present in the manuscript.
- No potentially identified images or data are present in the manuscript.

Author's Contribution Statement

S.A. G. contributed to the design and implementation of the study, simulations, and the analysis of the results. A. J. K. contributed to the writing of the manuscript. A. A.F. contributed to analyzing the data. The MS All authors have read and agreed to the final draft of the manuscript.

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دراسات التحضير والمضادة للبكتيريا والالتحام الجزيئي وADEMT لقواعد مانخ الجديدة للكركمين

عذراء كطامي صكر ، جواد كاظم عبيس ، عمار فرمان عبود

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الخلاصة

يعد استخدام المنتجات الطبيعية في تطوير الأدوية موضوعًا مثيرًا للاهتمام في مجال العلوم الطبية البشرية. في العمل الحالي، تم تحضير أربعة من مشتقات الكركمين (M4-M1) عن طريق تفاعل مانخ وشخصت بواسطة مطيافية الاشعة تحت الحمراء FT-IR و الرنين النووي المغناطيسي NMR. أظهرت البيانات التي تم الحصول عليها من الدراسة المختبرية للمركبات (M4-M1) نشاطا مقنعا ضد سلالات البكتيريا (السالمونيلا، المكورات العنقودية الذهبية، المتقلبة، والكلبسيلا) بالتوازي مع الأموكسيسيلين كدواء قياسي. اضهرت المركبات M2 و M4 نشاطا مضادا للبكتريا عاليا. تم دراسة النشاط المثبط لانزيم(DNA gyrase) المحتمل لهذه المركبات (M1- M4) بواسطة الكمبيوتر باستخدام طريقة محاكاة الالتحام الجزيئي. تم استخدام برنامج (PyMOL) لحساب ألفة الارتباط (kcal/mol) للمركبات المحضرة مع البروتين (1KZN). وكانت أعلى قيم الارتباط (كيلو كالوري/مول) مع البروتين وجد أنها (8.2-) مع المركب M4 و (8.1-) مع المركب M2، في حين أن أقل القيم وجدت (7.1-) مع المركب M1. علاوة على ذلك، أظهرت النتائج ارتباط الأحماض الأمينية مع المركبات المحضرة من خلال الروابط الهيدروجينية والتفاعلات الكارهة للماء(أرين-آرين). كما تم تسجيل الكثافات الإلكترونية للمركبات المحضرة من خلال التعرف على الخصائص المميزة للاحماض الامينية التي تحيط بهذه المركبات . تم إجراء دراسة السلوك الشبيه بالادوية ودراسة تنبؤات ADMET بما في ذلك الامتصاص والتوزيع والتمثيل الغذائي والإفراز وسمية المركبات المرغوبة. كشفت النتائج التي تم الحصول عليها أن غالبية المعلمات الدوائية كانت جيدة وضمن المعدل الطبيعي.

الكلمات المفتاحية: كركمين، توزيع، الاستِقْلاب، الالتحام الجزيئي، السمية.