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Synthesis, Characterization and Preliminary Anti-Microbial Evaluation of New Flurbiprofen Hydrazide Derivatives

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Abstract

A new series of 2-(2-fluoro-[1,1'-biphenyl]-4-yl) propanoic acid derivatives were synthesized to enhance their Anti-Microbial activities. The new flurbiprofen hydrazon compounds **(4a-e)** prepared by reacting flurbiprofen ethyl ester with hydrazine hydrate to yield flurbiprofen hydrazid**(3)**. Then compound **(3)** reacted with several aromatic aldehydes in absolute ethanol in presence of a small amount of glacial acetic acid to yield final compounds (4a-e). FT-IR and ^{1}H-NMR spectroscopy were utilized for the characterization of the final compounds. Molecular docking showed that there were significant molecular docking results with target protein for compounds 4d and 4a when compared to ciprofloxacin as reference .The ADMET study was conducted in order to predict the pharmacokinetic properties of the final compounds. The final compounds have accepTable estimated drug-like properties as well as desirable pharmacokinetics properties. Each final compound was examined for its Anti-Microbial efficiency against G(+)ve bacteria (*Streptococcus pyogenes, Staphylococcus aureus*), G(-)ve bacteria (*Escherichia coli, Klebsiella pneumoniae*) and strain of fungi (*Candida albicans*). Compound **(4e)** exhibited the highest Anti-Microbial efficiency against both strains G(-)ve and G(+)ve bacteria. Additionally, compound **(4b)** exhibits a good action for both strains. All synthesized compounds exhibit high antifungal activity except compound **(4b)** against *candida albicans* when compared to the standard compound, fluconazole.

Keywords: Flurbiprofen, Hydrazine Hydrate, Anti-Microbial Activity, Aromatic aldehyde, NSAID.

Introduction

One of the causes of death and morbidity nowadays is antimicrobial drug resistance، which has led scientists to focus on the rise in multidrug-resistant microorganisms as a significant issue in recent years [(1)]. Many investigations demonstrate that non-steroidal anti-inflammatory drugs (NSAIDs) have antibacterial action against a variety of Gram-positive and Gram-negative pathogens، which reduces bacterial adhesion and biofilm formation [(2, 3)]. One NSAIDs with anti-inflammatory, antipyretic, and analgesic properties is flurbiprofen, which is widely used to treat rheumatoid arthritis, osteoarthritis, migraines, acute gout, pain, and inflammation [(4-8)]. The review of the literature showed that the aryl carboxylic acid modification of NSAIDs produces anti-inflammatory, anti-bacterial, fungi toxicity, anti-viral, and in vitro cytotoxic effects [(9-11)].

Many studies reveal that hydrazones are known to inhibit a variety of bacterial species [(12)] and also show antitumoral, antimalarial, antiviral, and antitubercular activities [(13-16)].

Hydrazones can be created by the displacement of oxygen from ketone or aldehyde with the$R_1R_2C=NNH_2$ moiety by reacting with hydrazide [(17, 18)].

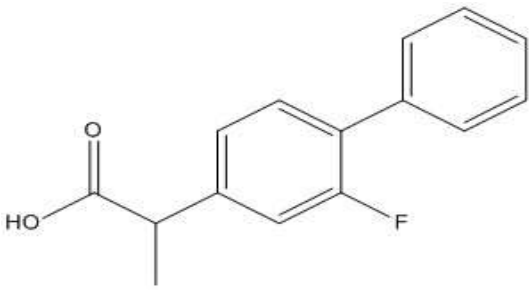

Figure1. Chemical structure of flurbiprofen

Materials and Methods

ADMET studies

In order to assess drug likeness properties , all final compounds are subjected to ADMET prediction using Qikprobe software in Schrodinger maestro

Docking study

Using the Glide application integrated with the maestro software from licensed Schrodinger. The crystal structure of the Staphylococcus aureus gyrase enzyme in combination with DNA and ciprofloxacin was made available by the Protein Data Bank (PDB ID: 2XCT)[(19)]. Eliminate all water molecules and add hydrogen atoms to the amino acid residues to bring them to the correct tautomeric state and ionization[(20)]. The cocrystallized ligand that interacted with the

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protein was used to create the receptor grid. The collection of ligands to be docked was identified and prepared using ligprep.The prepared ligands were docked to the gyrase enzyme (PDB ID: 2XCT) using the default XP docking option, which limited out to 10 poses[21]. The co-crystallized ligand was re-docked into the binding site using the same set of parameters as previously mentioned in order to validate the docking research at the 2XCT-active site [22].

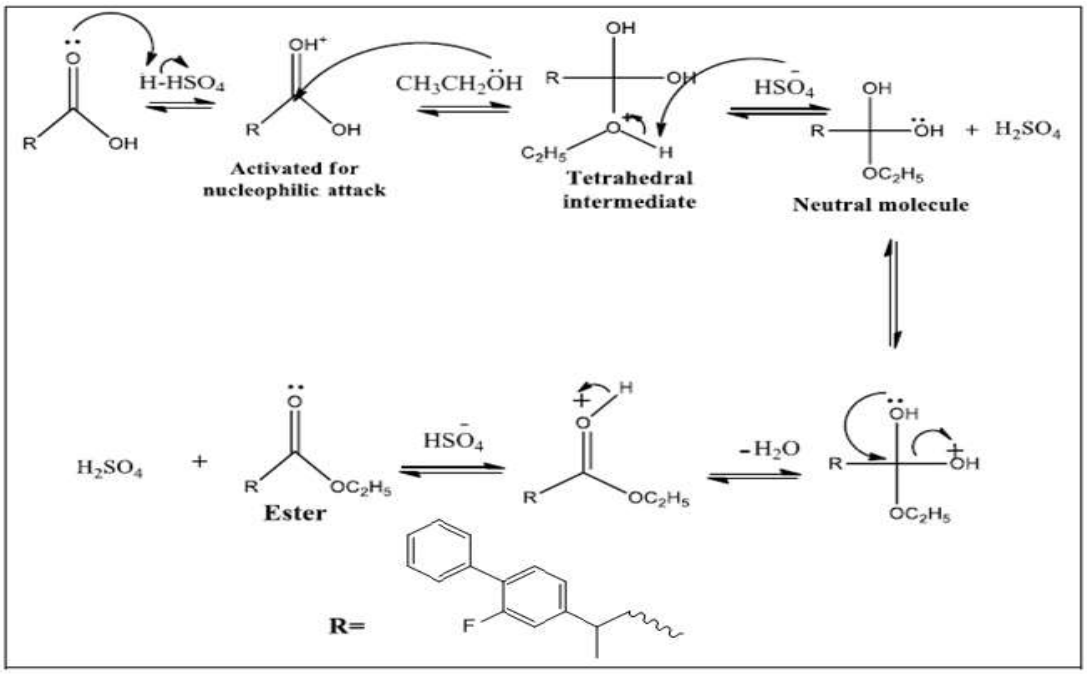
Chemicals

Flurbiprofen and 4-hydroxy-2-nitrobenzaldehyde are obtained from Picasso-e Company, ethanol from Honeywell Company, ,hydrazine hydrate from Thomas Baker Company, and all other compounds from Sigma-Aldrich Company, including 3-thiophencarboxyaldyhed, Syringaldehyde, pyrrole-3-carboxaldehyde. The melting points were uncorrected and measured using the Stuart SMP30 apparatus. Reaction completion and the products' purity were examined by Thin-Layer Chromatography (TLC) method with an Aluminum-Precoated silica sheet material (Germany, Merck). Each target compound dot was observed by a UV 254 nm lamp. The infrared spectra were obtained at Bagdad University, Pharmacy College using ATR–FTIR (Shimadzu, Japan) device with the unit of measurement symbol (ύ,cm^{-1}). ^{1}H-NMR was done using a Brucker model 400 MHz at Basra, Iraq, and DMSO was used as a solvent. The synthesized target compounds were tested for antibacterial properties, minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) at the office located in Baghdad, Iraq named chemistry analysis center (CAC) .

Chemical synthesis

Synthesis of flurbiprofen ester[ethyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate] Compound 2[23,24]:

After dissolving flurbiprofen (5g,0.02mol) in absolute ethanol,15 drops of H_2SO_4 were added, mixed, and refluxed at 78 ◦C for 6 hours(hrs). Reaction completion is checked by utilizing TLC. The solution then was neutralized by 10% $NaHCO_3$. Diethyl ether was used to separate the oily crude product. To get compound 1 , the organic layer was evaporated. Yellowish oil was obtained. Yield: 88%, **R_f** = 0.8 (ethanol: n-hexane 4:6), Infra R_{ed} (v cm^{-1}): 1732.08:(carbonyl) strch. Ester func. group, 1180:(C-O bond) strch. ether.



Scheme 1. Synthetic mechanism of flurbiprofen ethyl ester compond 2[25]

Synthesis of flurbiprofen hydrazide [2-(2-fluoro-[1 ,1 '- biphenyl] – 4 – yl)propanehydrazide] Compound 3 [26,27]

Hydrazine hydrate 99% (5mL, 0.11 mole) mixed with solution of compound 2 (2g, 0.007 mole) in 30 mL of absolute ethanol, then the combination refluxed at 78 ◦C for twenty hours. The solution was then cooled at(25◦C) temperature ,then decanted over ice with continuous mixing. The solid after that filtered and recrystallized by ethanol. Yield: 85%, MP (114-116ºC), R_f = 0.3 (ethanol :n-hexane 4:6), Infra-Red{IR} (v cm^{-1}): 1631 (Carbonyl) strch. of amide functionality, 3309.85, 3286.7 ((N-H)) strch. of NH_2 , 3032.10: (C-H bond) strch. of Ar. C-H.

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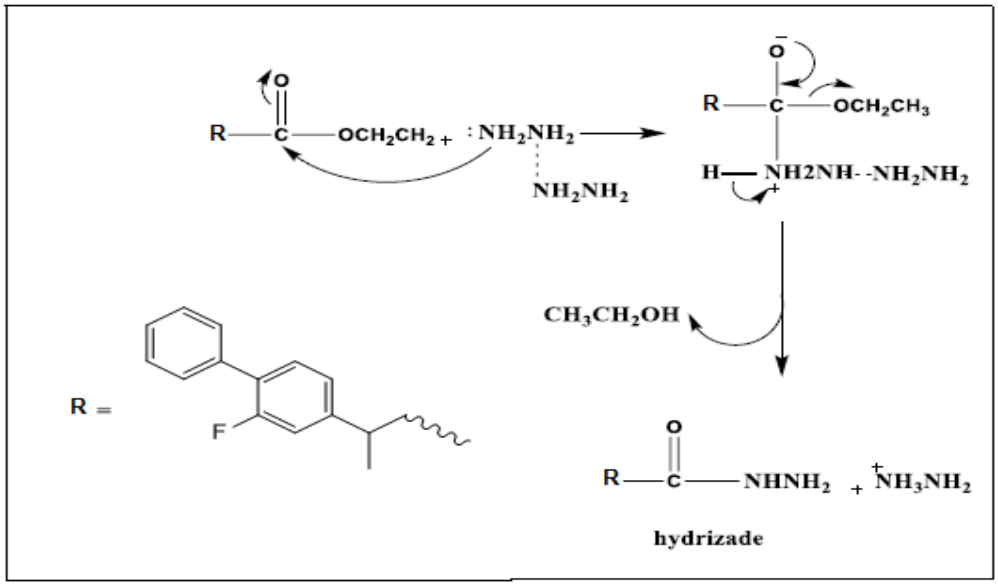
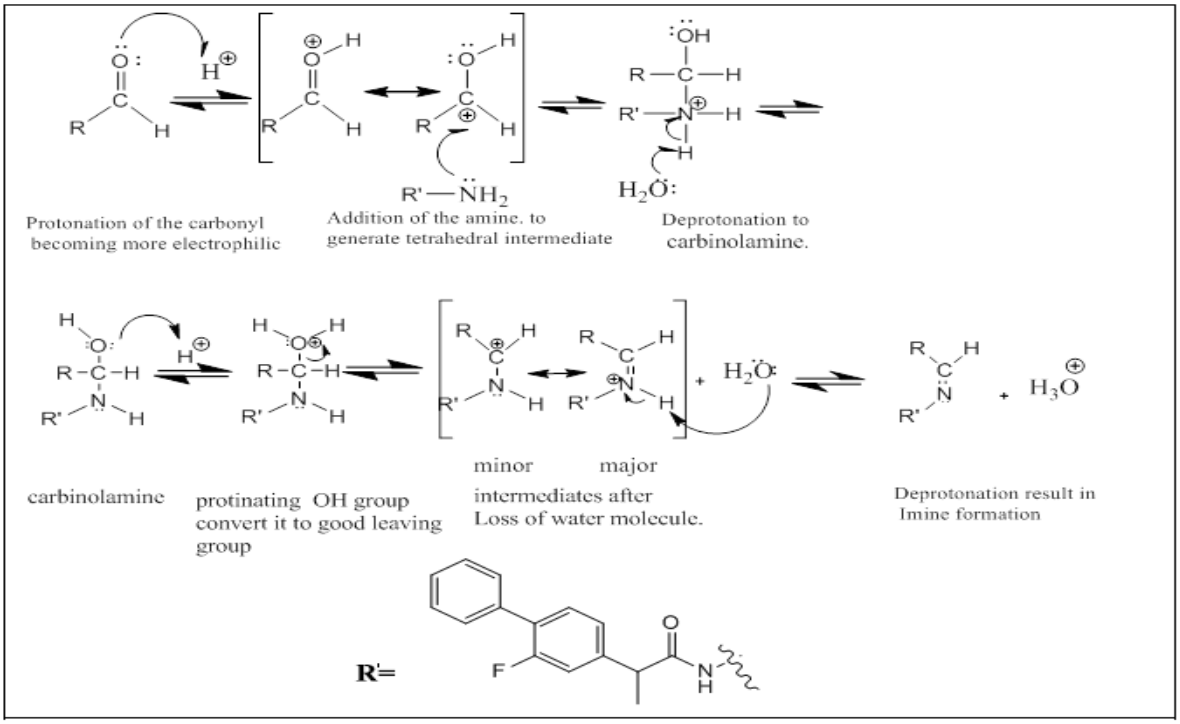


Scheme 2. Synthetic mechanism of flurbiprofen hydrazide compound 3[28]

Synthesis of Hydrazone [2-(2-fluoro-[1, 1'-biphenyl]-4-yl)propanehydrazide] derivatives. Compounds 4(a-e) [29,30]

Several aromatic aldehydes (a-e) (0.005 moles) were mixed with Compound 3 (0.005 moles, 0.8 gm) in 30 mL of absolute ethanol and 4 drops of glacial acetic acid. At 76ºC, the solution then was refluxed for 20 hours then left till to cool at (25^{0}C) temperature, filtered and ethanol was used to re-crystallize the solid compound.



Scheme 3. Synthetic mechanism of hydrazone compounds (Iva-e)[31] ***2-(2-fluoro-[1,1'-biphenyl]-4-yl)-N'-(thiophen-3-ylmethylene)propanehydrazide(4a)*** gray powder, Yield =96%, MP=159-161 ºC, **R$_f$** =0.94 (ethanol, n-hexane 4:6), IR (v cm-1):3194.12(N-H) str. of secondary amide,3097,3020: (C-H) str. of Ar- ring ,2985: (C-H) asymm. str. of CH_3 CH, 2850:(C-H) Symm.str. of CH_3, CH, 1651:(C=O) str. Of amide,1604: (C=N) str. of imin,1512:(N-H) bending vibration, 694:(C-S) str. ^{1}HNMR: 1.44(3H,d- CH_3 , 3.76-4.75 (1H, qq - CH),7.28-8.01(11 H, m -Ar-H),8.02- 8.29 (1H, ss- N=CH),11.34-11.54(1H , ss-NH).

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2-(2-fluoro-[1,1'-biphenyl]-4-yl)-N'-(4-hydroxy-2-nitrobenzylidene)propanehydrazide(4b) yellow powder, Yield = 94% MP= (176-178ºC), R_f = 0.76 (ethanol, n-hexane 4:6), IR (v cm^{-1}):3267.41:(O-H) str. of OH, 3194.12 :(N-H) str. of secondary amide,3036.96: (C-H) str. of Ar-H, 2984:(C-H) Asymmtr. strch. of CH3,CH, 2904:((C-H)) Symmtr. str. Of aliph. CH3,CH ,1654.92(C=O) strch. of amide fun. Gp., 1624.06:((C=N)) strch. of imin, 1535,1319.31(nitro) of NO_2. ^{1}HNMR,1.43(3H , d – CH_3), 3.75-4.73 (1H , qq – CH),7.18- 7.91(11H , m– Ar_H), 8.17 (1H , s- N=CH), 11.08(1H , s – OH),11.44-11.68(1H ,ss-NH).

2-(2-fluoro-[1,1'-biphenyl]-4-yl)-N'-(4-hydroxy-3,5-dimethoxybenzylidene)propanehydrazide(4c) White powder, Yield =70% MP= (201-203ºC), R_f=0.64 (ethanol, n-hexane4:6), (IR) (vcm^{-1}):3545:(hydroxyl) strch. of OH group, 3186.4 :(N-H) strch. of 2° amide func. group, 3056: (C-H) strch. of Aromatic C-H, 2978:(C-H) asymm.strch. of CH, CH3,2846.93: (C-H) symm.strch. of CH, CH3, 1662.64 (C=O) strech. of amide func. group, 1643.35:(C=N) strch. of imin func. group,1581.63:(N-H) bending vibration band, ^{1}HNMR, 1.44(3H, d, CH_3), 3.83(6H, s, CH_3), 4.71(1H, q-CH) , 6.93-7.79(10H , m- Ar_H) ,8.09-8.87(1H , ss.- N=CH),8.93(1H , s-OH),11.31-11.48(1H , ss-NH).

N'-((1H-pyrrol-3-yl)methylene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide(4d)brown powder, Yield =80% MP= (181-182ºC),R_f=0.44 (ethanol, n-hexane 3:7), IR spectroscopy (v cm^{-1}): 3267.41: (N-H) strch. of pyrrole,3194:(N-H) strch. of 2° amide gp.,3051:(C-H) strch. of Ar. C-H,2981:(C-H) asymm.strch. of aliphatic CH, CH_3,2854.65:(C-H) symm.strch. of CH,CH_3, 1651:(C=O) strch. of amide functionality,1608 (C=N bond) strch. of imin group, ^{1}HNMR, 1.43(3H , d-CH3) ,3.73-4.90(1H , qq-CH) , 6.11-7.8(11H , m.-Aroma._H) ,7.8-8.05 (1H ,ss- N=CH) ,11.09-11.29 (1H , ss-ArNH), 11.41-11.47(1H , ss-NHC=O).

N'-(4-chlorobenzylidene)-2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanehydrazide(4e)white powder Yield = 94% MP = (176-177ºC), R_f= 0.9 (ethanol, n-hexane 2:8) , IR spectro.(v cm-1):3178 :(N-H)) strch. of 2° amide grp., 3059.10 (C-H) strch. of Ar. C-H bond, 2974:((C-H))asymmtr. Strech. Of alphtc. CH_3,CH, 2877:(C-H) symm. Srech. Of CH_3,CH, 1662(C=O) strch. of amide, 1612(C=N) strch. of imin, 763,694:(C-Cl)str. ^{1}HNMR,1.44 (3H, d, CH_3), 3.81-4.75(1H, qq, CH),6.88-7.97(12H , m-Ar_H),8.26(1H , s- N=CH), 11.46-11.81(1H , ss-NH).

Antimicrobial Activity [32]

Each ultimate compound (4a–e) was evaluated for its Anti-Microbial property against number of bacteria{ two G(-)ve bacteria (*E. coli* ,*Klebsiella pneumonia*), two G(+)ve bacteria (*Streptococcus aureus and Staphylococcus aureus*)}, and one fungus (*Candida albicans*) utilizing the disc diffusion technique. All the final compounds had a 1000µg/ML concentration, using DMSO as a solvent. The activity was then confirmed through measurement the inhibition zone in unit millimeters(ml) and comparing it to the antibacterial agents (amoxicillin, ciprofloxacin) and antifungal one (fluconazole) as reference.

Results and Discussion

Docking study

Compounds (4a-e) were subjected to molecular docking to explore their possible interactions within the active site of gyrase enzyme (PDB: 2XCT). Protein residues, the Mn^{+2} ion, and DNA bases make up the binding pocket for the reference medication, ciprofloxacin. The binding process between the ligand and protein requires Mn^{+2} ion interaction with the ligand. In this work compounds 4d and 4a have higher docking score than that of ciprofloxacin that is -8.430 for compound 4d ,-8.197 for compound 4a and -8.164 for ciprofloxacin. As illustrated in Figure (2) Compound 4d has hydrogen bond interaction between NH of pyrrole ring and amino acid residue GLU1088 also there was metal coordination interactions between pyrrole ring and Mn2000 . Another hydrogen bond interaction occurred between NH of amide group and DNA nucleotide DG8. pi-pi stacking interactions between aromatic ring of compound 4d and DNA nucleotides DG8 and DG9 . Compound 4a has metal coordination interactions between thiophene ring and Mn2000 , hydrogen bond interaction between NH of amide group and DNA nucleotide DG8, hydrogen bond interaction between C=O group amino acid residue SER1084, pi-pi stacking interactions between aromatic ring of compound 4a and DNA nucleotides DG8 ,DG9 and DC13 . In contrast ciprofloxacin has pi-pi stacking interactions between its aromatic rings and DNA nucleotides DG8 and DG9 as well as metal coordination interactions between Mn^{2+} and two C=O groups.

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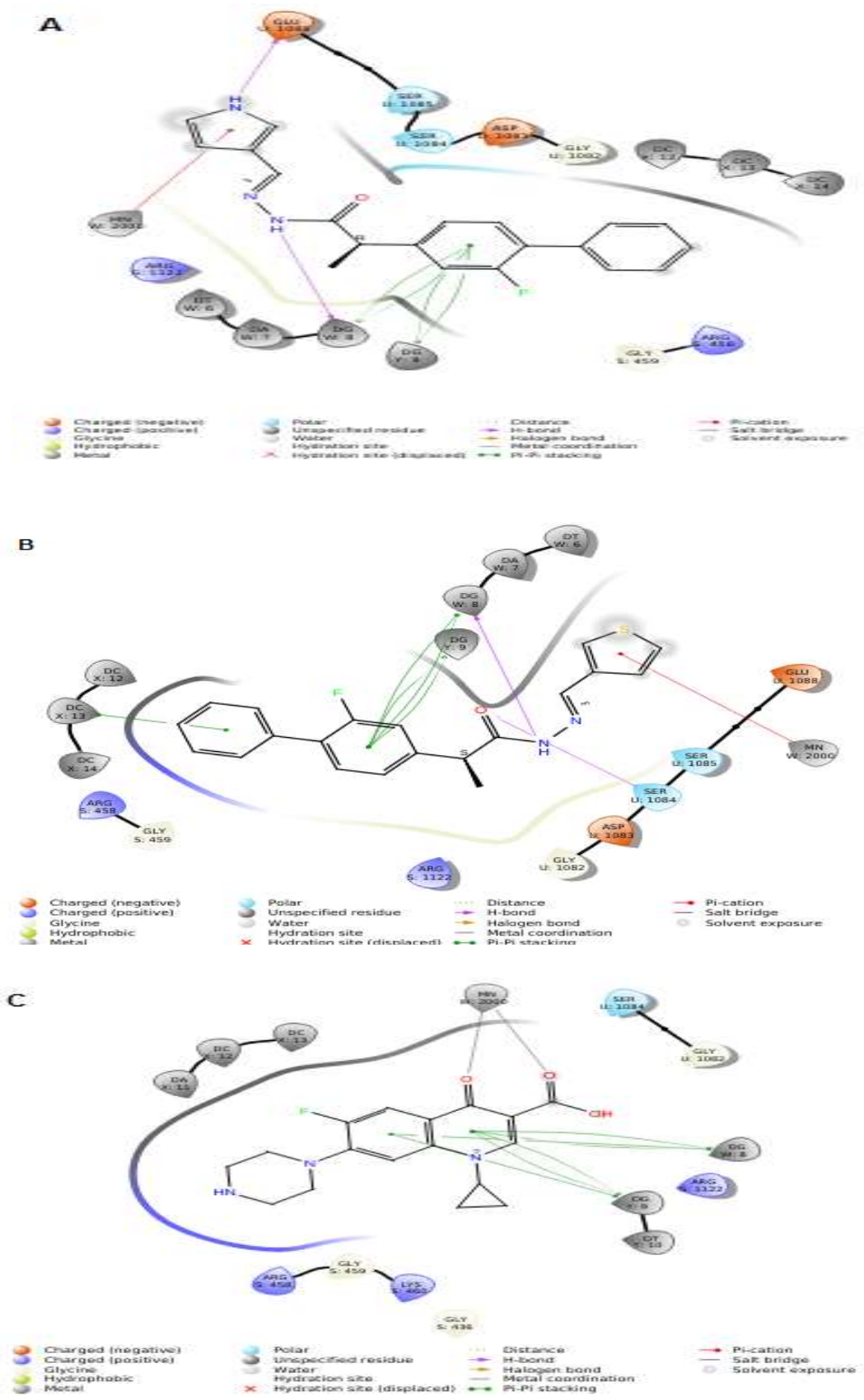

Fiure2. Two-Dimensional docking pose of A:4d, B:4a and C: ciprofloxacin into the gyrase active site (PDB:2XCT)

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ADMET Studies

As illustrated in Table(1), all final compounds had appropriate expected pharmacokinetic parameters such as Percent oral absorption, rule of five, rule of three, and metabolism **.**Since compound 4b and 4c don't activate CNS, they have no CNS side effects. All synthesized compounds (4a-e) have between one and four metabolic reactions. Every synthesized compound has a high proportion of oral absorption. All synthesized compounds (4a-e) have only one rule of three violation, while compounds 4b and 4d do not violate the rule of five.

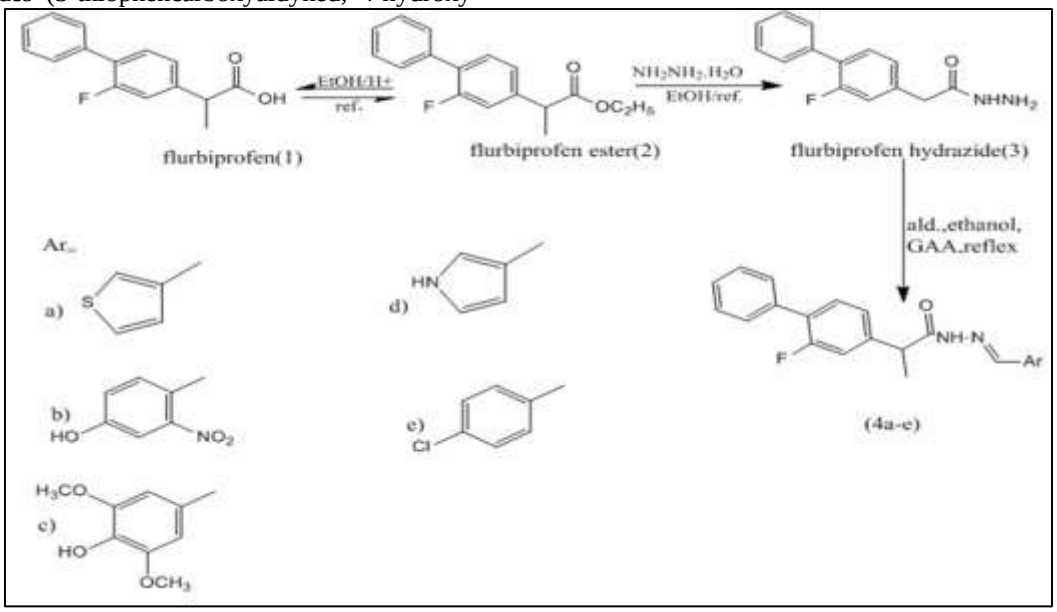
Table1.The predicted ADMET data for the final compounds(4a-e)

Compound	CNS	#metab	Percent Human Oral Absorption	Rule Of Five	Rule Of Three
4a	0	2	100	1	1
4b	-2	3	93	0	1
4c	-2	4	100	1	1
4d	0	1	100	0	1
4e	0	1	100	1	1

CNS; suggested a scale for central nervous system activity ranging from –2 (inactive) to +2 (active). **#metab;** Probable number of metabolic reactions: 1–8. **Percent Human Oral Absorption;** >80% is high, <25% is poor. **Rule Of Five;** There are a maximum of four instances of breaking Lipinski's rule of five. **Rule Of Three**; There are a maximum of three violations of Jorgensen's rule of three[33].

Chemistry

Scheme 4 showed the overall synthetic process leading to the final compounds (4a–e). It begins with flurbiprofen ethyl ester (2), which is produced by reacting ethanol with flurbiprofen that has been dissolved in ethanol in the presence of H_2SO_4. Compound 2's ATR─FTIR spectra revealed an absorption bond at (1732.08 cm^{-1}) owing to the ester carbonyl's C=O and (1180 cm^{-1}) due to the ether's C-O stretching vibration. Compound 2 was refluxed with 99% hydrazine hydrate in absolute ethanol to produce flurbiprofen hydrazide. Compound 3's ATR─FTIR spectroscopy analysis revealed an absorption band at (1631.78 cm^{-1}) for the amide's carbonyl stretching vibration, and (3309.85, 3286.7 cm^{-1}) for the primary amine's stretching vibration. Compound 3 was refluxed with various aromatic aldehydes (3-thiophencarboxyaldyhed, 4-hydroxy-2-nitrobenzaldehyde, Syringaldehyde, pyrrole-3-carboxaldehyde, 4-Chlorobenzaldehyde) in absolute ethanol with the presence of glacial acetic acid to create compound (4a-e). ATR─FTIR of compounds (4a–e) spectra reveal an absorption band of the amide's C=O str. at (1662–1651 cm^{-1}) and the imin's C=N str. vibration at (1643–1604 cm^{-1}) and disappearance of amine's band. ^{1}HNMR spectroscopy revealed a signal at (11.68–11.31) representing the NH proton and a singlet signal at (8.06–8.29) representing the proton of the imin group. The presence of C=N group explains the existence of E and Z geometrical isomers and appearance of two signals for N=CH and CO-NH. Hydrazone generally occurs as cis/trans amide conformers and as an E or Z isomer around the C=N double bond [34,35].



Scheme4. Chemical synthesis of final compounds (4a-e)

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Anti-microbial activity

Using amoxicillin, ciprofloxacin and fluconazole as positive controls, the Anti-Microbial activity of the synthesized derivatives (4a–e) was assessed using the disc well diffusion method on G(+)ve ,G(-)ve bacteria and fungi. As indicated in the following Table (2), DMSO was employed as both a solvent and a negative control. Compound (4e) revealed maximal Antibacterial property for both strains of bacteria{ G(+)ve and G(-)ve Figure(3). The (4b) compound also exhibited good Antibacterial property for both bacterial strains. All synthesized compounds except compound (4b) exhibited high antifungal activity compared with fluconazole.

Table2. The zone of inhibition of final compounds (4a-e)

Compound	Inhibition zone (mm)					
	Conc. µg/ml	S. aureus	S. pyogenes	K. Pneumonia	E.Coli	C.albicans
4a	10^3	18	17	18	22	22
4b	10^3	20	22	18	25	8
4c	10^3	18	16	20	25	20
4d	10^3	14	15	15	24	22
4e	10^3	22	25	18	25	20
Amoxicillin	10^3	24	25	22	20	-
Ciprofloxacin	10^3	25	25	25	30	-
Fluconazole	10^3					20
DMSO	Control and solvent					

No activity= (-), slightly active=(zone of inhibition between 5–10 mm, moderately active=(zone of inhibition between 10-15mm), highly active =(zone of inhibition more than 15 mm)

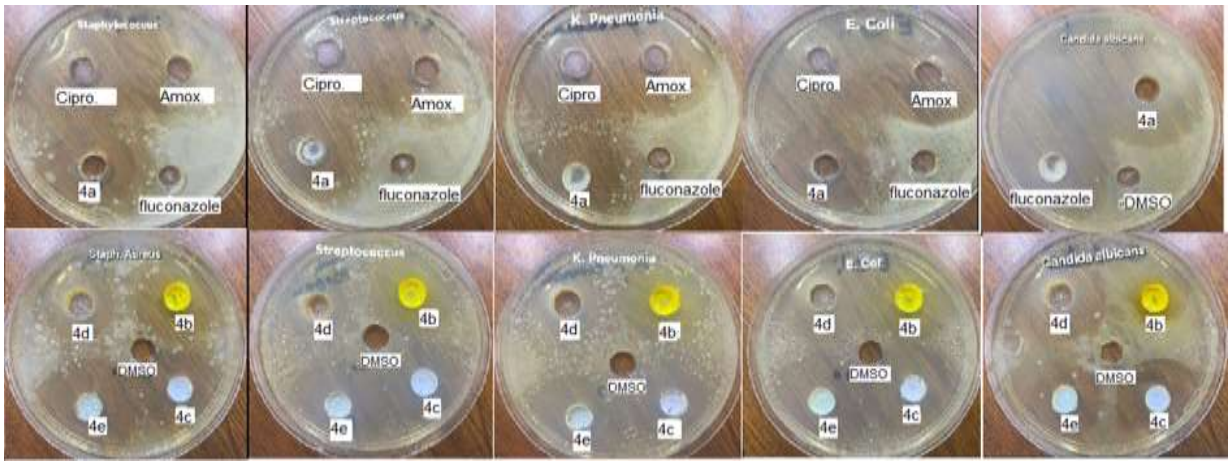

Figure 3 .Zone of inhibition(mm) of compounds (4a-e)

Statistical analysis

Two-factor without replication ANOVA TEST was used for antibacterial activity(Table3, Figure4) and one-way ANOVA TEST was used for antifungal activity (Table4, Figure5) . The α value is equal to 0.05, and the values are shown as the mean ± SEM of triplicate measurements of the zone of inhibition.

Table3. Antibacterial statistical analysis of final compounds (4a-e)

Mean ± SEM				
Compounds	***S. aureus***	***S. pyogene***	***K. pneumonia***	***E. coli***
4a	17.667±0.459$^{*\#}$	16.667±0.459$^{*\#}$	17.667±0.459$^{*\#}$	21.333±0.459$^{\#}$
4b	21.000±0.459$^{*\#}$	22.333±0.459$^{*\#}$	17.000±0.459$^{*\#}$	24.667±0.459$^{*\#}$
4c	17.667±0.459$^{*\#}$	16.333±0.459$^{*\#}$	20.333±0.459$^{*\#}$	24.333±0.459$^{*\#}$
4d	14.333±0.459$^{*\#}$	14.667±0.459$^{*\#}$	14.667±0.459$^{*\#}$	22.333±0.459$^{*\#}$
4e	22.333±0.459$^{\#}$	24.667±0.459	17.667±0.459$^{*\#}$	24.667±0.459$^{*\#}$

.*Significant difference with respect to Amoxicillin P<0.05). #Significant difference with respect to Ciprofloxacin P<0.05)

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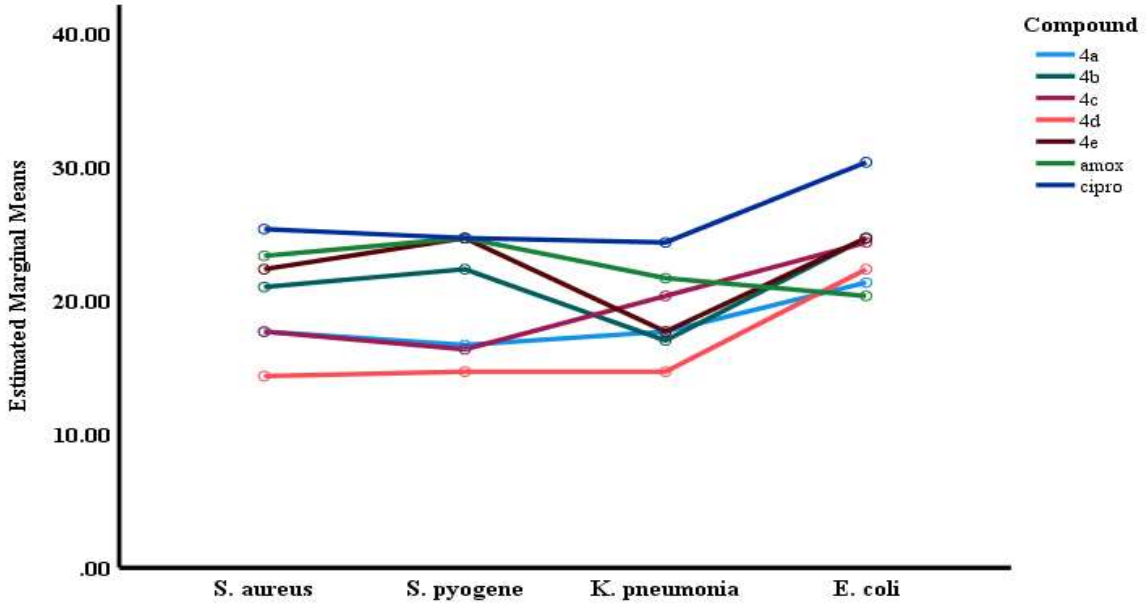

Figure4. Histogram of the antibacterial inhibition zone of tested compounds (4a-e)

Table4. Antifungal statistical analysis of final compounds (4a-e)

Mean ± SEM	
Compounds	***C. albicans***
4a	21±0.544
4b	7.333±0.544*
4c	19.666±0.544
4d	21.666±0.544*
4e	20.333±0.544

*Significant difference with respect to Fluconazole P<0.05).

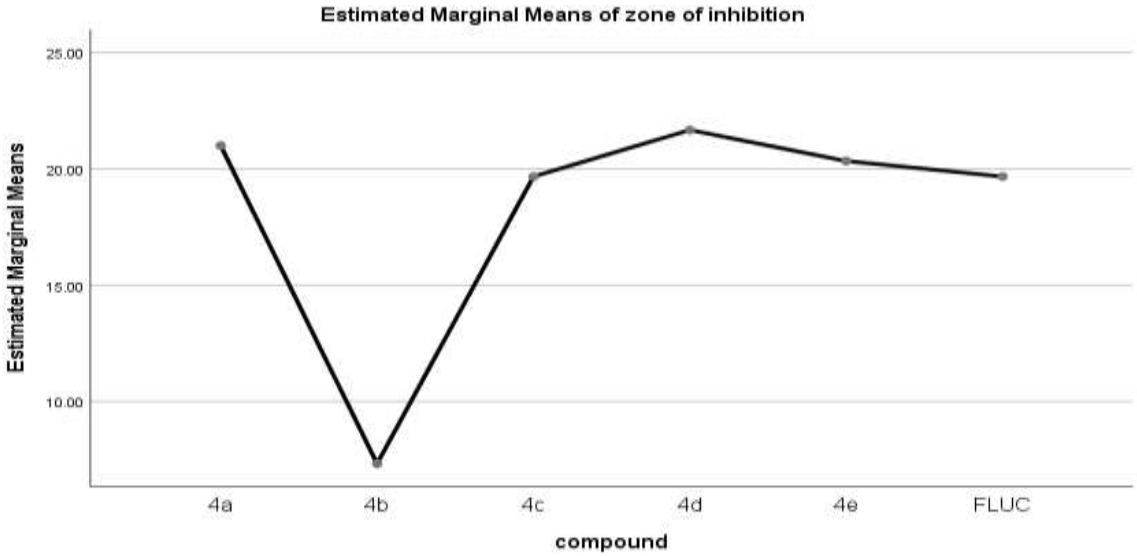

Figure5. Histogram of the antifungal inhibition zone of tested compounds(4a-e)

Minimum bactericidal concentration (MBC)

Compound (4a) was more effective than amoxicillin against both G(+)ve and G(-)ve bacteria, although it had less bactericidal activity than ciprofloxacin and same MBC in comparison to fluconazole. Although compound(4d) also had good MBC, it was less effective than compound(4a) **(**Table5**)**.

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Table5. Minimum bactericidal concentration of final compounds (4a-e)

Compound	Minimum bactericidal concentration µg/ml				
	S. aureus	***S. pyogenes***	***K. Pneumonia***	***E.Coli***	***C.albicans***
4a	250	500	1000	500	250
4b	500	1000	500	500	500
4c	500	1000	1000	1000	500
4d	250	500	500	1000	500
4e	500	1000	1000	1000	1000
Amoxicillin	500	500	500	1000	-
Ciprofloxacin	250	250	250	500	-
Fluconazole					250

The minimum inhibitory concentration (MIC)

All compounds are less effective than ciprofloxacin and have the same potency as amoxicillin against gram negative bacteria, however compounds 4a and 4d are more potent than amoxicillin and have the same potency of ciprofloxacin against gram positive bacteria. Compound 4a is the only one that has the same antifungal potency as fluconazole **(**Table6**,** Figure6**)**.

Table6. The minimum and sub-minimum inhibitory concentration of the final compounds (4a-e)

Isolates	4a		4b		4c		4d		4e		AMOX.		CIP.		FLC.	
	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB	MIC	SUB
S. aureus	125	62.5	250	125	250	125	125	62.5	250	125	250	125	125	62.5	125	62.5
S. pyogen	250	125	500	250	500	250	250	125	500	250	250	125	125	62.5	125	62.5
K. Pneumonia	250	125	250	125	1000	500	500	250	500	250	500	250	250	125	250	125
E. coli	500	250	250	125	500	250	250	125	500	250	250	125	125	62.5	125	62.5
C.albicans	125	62.5	250	125	250	125	250	125	250	125	250	125	125	62.5	125	62.5

AMOX: amoxicillin, CIP: ciprofloxacin, FLC: fluconazole

Figure6. The minimum inhibitory concentration of final compounds (4a-e)

Conclusion

New flurbiprofen derivatives synthesized and examined for Anti-Microbial activity by using the disc diffusion method. Among which compound(4e) exhibited the highest Anti - Microbial activity

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and Compound (4 b) also showed a good antibacterial activity which is may be due to the presence of electon withdrawing groups (CL) for (4e) and (NO_2) for (4b) compound. Also presence of OH group and formation of H bond may influence antibacterial activity of compound (4 b). Whole synthesized compounds except compound (4b) exhibited a high antifungal activity. The virtual ADMET studies revealed that the final compounds(4a-e) had acceptable pharmacokinetic characteristics. Compound 4d and 4a had higher docking score than ciprofloxacine, according to a docking study. Each ultimate compound was distinguished by ATR-FTIR and ^{1}HNMR.

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Conflicts of Interest

There is no conflict of interest regarding the publication of this manuscript.

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Ethics Statements

The authors emphasized that no ethics committee permission was required for the preparation of the target compounds.

Author Contribution

The two authors furnished the design, preparation of target compounds and interpretation of FTIR and ^{1}HNMR and antimicrobial activity of final compounds.

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تصنيع وتشخيص و تقييم أولي للمضادات الميكروبات لمشتقات فلوربيبروفين هيدرازيد الجديدة

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الخلاصة

تم تحضير سلسلة جديدة من مشتقات فلوربيبروفين لزيادة فعاليتها المضادة للميكروبات. تم تحضير مركبات فلوربيبروفين هيدرازون الجديدة **(4a-e)** من تفاعل إستر إيثيل فلوربيبروفين مع هيدرازين هيدرات لتحضير فلوربيبروفين هيدرازيد **(٣)**. ثم تم مفاعلة مركب**(٣)** مع الدهيدات عطرية مختلفة في وجود حمض الخليك الثلجي. تم استخدام الأشعة تحت الحمراء و طيف الرنين المغناطيسي النووي لتحديد هياكل المركبات النهائية. أظهر برنامج التصميم الدوائي أن هناك ارتباط قوي مع البروتين المستهدف للمركبين **(4d)** و**(4a)** عند مقارنتهما بالدواء سيبروفلوكساسين كمرجع .أُجريت دراسة تنبؤيه للحركية الدوائية و السمية لجميع المركبات النهائية. تتميز المركبات النهائية بخصائص تقديرية مقبولة شبيهة للأدوية وخصائص دوائية مرغوبة. تم فحص جميع المركبات النهائية لفعاليتها المضادة للميكروبات ضد البكتيريا الموجبة لصبغة الغرام(*البكتيريا العقدية المقيحة، البكتيريا الكروية العنقودية)*والبكتيريا السالبة لصبغة الغرام (*الكلبسيلا الرئوي والإشريكية القولونية)* وسلالة الفطريات (*المبيضات البيضاء*). أظهر المركب **(4e)** أعلى نشاط مضاد للميكروبات ضد كلا السلالتين السالب و الموجب لصبغة الغرام من البكتيريا. بالإضافة إلى ذلك، يُظهر المركب **(4b)** فعالية جيده لكلا السلالتين. تظهر جميع المركبات المصنعة باستثناء المركب **(4b)** فعالية عالية مضادة للفطريات *المبيضات البيضاء* عند مقارنتها بالمركب القياسي، فلوكونازول.

الكلمات المفتاحيه: فلوربيبروفين، هيدرات الهيدرازين، الفعالية المضادة للميكروبات، مضادات الالتهاب غير الستيرويدية