Design, Synthesis, Characterization, Biological Activity and ADME Study of New 5-arylidene-4-Thiazolidinones Derivatives Having

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Abstract:

New series of Nabumetone containing 5-arylidene-4-thiazolidinones pharmacophore as in compounds 3(a-e) were designed and synthesized by using nabumetone and hydrazinethiocarboamide to synthesize compound (1) (Schiff base), next step compound (1) will react with chloroacetic acid and anhydrous sodium acetate in order to synthesize compound (2) containing 4-thiazolidinone ring this compound will react with 4-benzaldehyde derivatives in the presence of basic media such as piperidine to form compounds 3(a-e). The structures of new intermediate and final synthesized compounds were detected by determination of physical properties (melting points). The structure of synthesized compounds has been confirmed by FT-IR spectroscopy, proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and carbon 13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy the final synthesized compounds were also screened for their antibacterial and antifungal activity.

Key words: Nabumetone, Schiff base, 4-thiazolidinone, 5-arylidene-4-thiazolidinone, antibacterial, antifungal activity.

تحضير وتشخيص مشتقات جديدة من دواء النابيوميتون تحتوي حلقة ٥-ارليدين ٤-ثايوزوليدينون ودراسة النشاط البيولوجي لها

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الخلاصة:

تم تخليق سلسلة جديدة من النابيوميتون تحتوي على حلقة٥-ارليدين ٤-ثايوزوليدينون والتي قد تم تصميمها وتصنيعها بتفاعل النابيوميتون مع الهايدرازين ثايوكاربوامايد لصناعه المركب شيف بيز (١) والذي بدوره يتفاعل مع كلورواسيتك اسيد بوجود الصوديوم اسيتيت لتشكيل المركب (٢) الذي يحتوي على حلقة ٤-ثايزوليدين الذي بدوره يتفاعل مع مشتقات ٤-بينزالديهايد بوجود وسط قاعدي مثل اللبيبريدين لتكوين المركب٣(أ-ج).

تمكنت الدراسة من تخليق المركبات المصممة. تم تأكيد نقاوة وتوصيف المركبات المركبة عن طريق تحديد الخواص الفيزيائية (نقاط الانصهار) وتأكيد التركيب الكيميائي للمركبات الوسطيه والنهائيه من خلال مطياف الأشعة تحت الحمراء ومطياف الرنين المغناطيسي النووي. وقد تم فحص المركبات النهائيه كونها تمتلك فعاليه مضادة للبكتريا و الفطريات .

الكلمات المفتاحية: نابيوميتون, شف بيز, ٤-ثايوزوليدينون, ٥-ارليدين ٤-ثايوزوليدينون, مضاد للبكتريا والفطريات.

Introduction

The most advanced infectious agents and the emergence of antimicrobial resistance, as well as, the very severe use of antibiotics lead to resist antibacterial agents, over time have led to the spread of infection worldwide, causing an increase in mortality, with more than 13 million deaths per year during the 20th century [1]. Discovery of penicillin by Alexander Fleming in 1929 [2], encourage to developed a Large number of antibiotics, which has contributed positively to human health and thus control infection and prevent it from spreading [3].

The Schiff bases were the first reported by Hugo Schiff in 1864 [4], by the condensation of carbonyl compound with primary amine [5] to considered as important class of organic compound because the most common feature of these compound that contain a azomethine group within various natural and synthesized compounds and is shown to be crucial to their a broad range of activities, including antibacterial, antifungal, antimalarial, anti-proliferative, anti-inflammatory and antipyretic properties [6-8].

Thiazolidinone belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five-member ring [9]. The scientific expert has consistently directed over the years mainly as a result of its biological importance [10]. They assumed that these classes of compounds are considered as scaffolding medicinal chemistry to drug development with different biological activities such as antibacterial [11], antifungal [12], anti-inflammatory [13], anticonvulsant [14] and anticancer activities [15].

Substituted 5-arylidene moiety demonstrates a fundamental role in improving the antimicrobial effects of thiazolidine-4-one because Antibacterial action is strongly reliant on the nature of the substitutes at C-5 of the thiazolidinone ring.so these compounds have been screened for their antimicrobial activity the objective of this work is to synthesize and initial biological assessment of new analogs of nabumetone which was used as a template (starting compound) react with different molecules to form new heterocyclic compounds with different biological activities (Anti-bacterial and antifungal). [16]

Materials and Methods

Chemicals and Instrumentation

All chemicals and solvents were of annular type and received from the commercial suppliers (Iraq, BDH-England, Himedia-India, Merck-Germany, Fluka AG Switzerland, and Sigma-Aldrich, Germany). Nabumetone was supplied by the MCE (MedChem Express Company in china. Melting points were determined by capillary method on Bamstead /Electro-thermal 9100 an electrical melting point apparatus (England). The identification of compounds was done at College of Pharmacy, AL-Mustansiriyah University using a FT-IR spectrum were recorded on a FTIR-spectrophotometer FT-IR-6100 Type A as KBr disks, ^{1}H-NMR determined by ^{1}H-NMR device 300 MHz Bruker (Japan) and ^{13}C-NMR determined by ^{13}C-NMR device 300 MHz Burker (Japan) both were performed at Tehran University, Collage of Science, Department of Chemistry of Iran.

Synthesis of 2-(4-(6- methoxy-naphthalen-2-yl)butan-2-ylidene)hydrazine-1-carbothioamide compound (1): A mixture of nabumetone (0.228 gm, 0.001mol) and thiosemicarbazide (0.091gm,0.001mol) in methanol(5ml) and ether(2ml) and 4 drops of glacial acetic acid, in a round bottomed flask with continuous stirring for 72 hrs., at the last hour of stirring will add absolute ethanol (5ml) and ether (5ml) with continuous stirring. The solid product formed was filtered off, washed with ethanol and ether. Leaving the mixture to dry. Then recrystallized the product from ethyl acetate collect the white crystals. [17,18]. White crystals (85% yield);

MP 196–197°C; IR): 3421.72 (NH_2), 1504.48 (aromatic), 3221.12(NHC=S), 1593.20(C=N), 1303.88(C=S); ^{1}H-NMR (DMSO-*d*6, 300 MHz): *δ* 10.02 (S, 1H, NH), *δ* 8.12 (S, 2H, NH_2), ^{13}C-NMR (DMSO-*d*6, 300 MHz): *δ*. 154.05 (C=N of thiosemicarbazone).

Synthesis of 2-((4-(6-methoxynaphthalen-2-yl) butan-2- ylidene)hydrazineylidene)thiazolidin-4-one compound(2):

A mixture of compound (1) (0.301gm, 0.001mol), (0.095gm,0.001mol) of chloroacetic acid and (0.082gm, 0.001mol) of anhydrous sodium acetate were refluxed in (10ml) of glacial acetic acid for 8hrs with continuous stirring. The temperature was adjusted to 125°C the mixture was left to cool and poured in to ice-cold water. The product was filtered off, washed with water to get rid of anhydrous sodium acetate then left to dry. Finally, recrystallized from acetic acid. [19]. *(White powder) (82% yield); mp 138–139.5°C;* IR (KBr) *ν* (cm^{-1}): 1724.36 (C=O), 1504.48 (aromatic), 1593.2 (C=N); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 2.65-2.79 (d, 1H, CH_2 of thiazolidinone ring), δ 2.98-3.01(d, 1H, CH2 of thiazolidinone ring), δ 7.75 (s, 1H, NH);^{13}C-NMR (DMSO-d6, 300 MHz): δ 174.49 (C=O of thiazolidinone ring), δ 32.06 (CH2 of thiazolidinone ring).

Synthesisof5-(4-substituted-benzylidene)-2-((4-(6-methoxy-naphthalen-2-yl)butan-2-ylidene)hydrazono)-thiazolidin-4-one 3(a-e):

A mixture of (0.001mol) of compound (2) and (0.001mol) of different aromatic aldehydes (a-e) were dissolved in a minimum volume of absolute ethanol 99% (10ml) containing few drops of piperidine, were refluxed on a water bath for 3hrs with continuous stirring, the temperature was adjusted to 80^{0}C, cooling the mixture, the compound was precipitated, filtered and washed with ethanol, then left to dry. Finally recrystallized from ethanol [20, 21].

5-benzylidene-2-((4-(6-methoxynaphthalen-2-yl)butan-2-ylidene)hydrazono)thiazolidin-4-one (3a) (*Yellowish White Crystal*) (81% yield); mp 110-111°C; IR (KBr) *ν* (cm^{-1}): 1708.93 (C=O), 1643.35 (Exo C=CH), 1604.77 (aromatic);^{1}H-NMR (DMSO-*d*6, 300 MHz): *δ* 7.76 (s, 1H, Exo C=CH), *δ* 8.40 (s, 1H, NH), *δ* 7.10-7.75 (m, 11H, aromatic H), *δ* 3.84 (s, 3H, O–CH3), *δ2.88-2.90* (t, 2H, CH_2-CH_2), δ *2.81-2.87* (t, 2H, CH_2-CH_2); ^{13}C-NMR (DMSO-d6, 300 MHz): δ 145.79(Exo C=CH).

5-(4-chlorobenzylidene)-2-((4-(6-methoxynaphthalen-2-yl)butan-2-ylidene)hydrazono)thiazolidin-4-one(3b) *(Yellowish White Crystal)* (78% yield); mp 133-134°C; IR (KBr) *ν* (cm^{-1}): 1712.79(C=O), 1643.35 (Exo C=CH), 1527.62(aromatic);^{1}H-NMR (DMSO-*d*6, 300 MHz): *δ* 7.72 (s, 1H, Exo C=CH), *δ* 8.41 (s, 1H, NH), *δ* 6.91-7.67 (m, 10H, aromatic H), *δ* 3.86 (s, 3H, O–CH3), *δ3.10-3.15* (t, 2H, CH_2-CH_2), δ *3.03-3.05* (t, 2H, CH_2-CH_2); ^{13}C-NMR (DMSO-d6, 300 MHz): δ 141.20(Exo C=CH).

5-(4-nitrobenzylidene)-2-((4-(6-methoxynaphthalen-2-yl)butan-2-ylidene)hydrazono)-thiazolidin-4-one(3c) *(Yellowish White Crystal)* (78% yield); mp 133-134°C; IR (KBr) *ν* (cm^{-1}): 1712.00(C=O), 1639.49 (Exo C=CH), 1512.19(aromatic);^{1}H-NMR (DMSO-*d*6, 300 MHz): *δ* 7.72 (s, 1H, Exo C=CH), *δ* 8.54 (s, 1H, NH), *δ* 7.10-7.71 (m, 10H, aromatic H), *δ* 3.84 (s, 3H, O–CH_3), *δ2.88-2.90* (t, 2H, CH_2-CH_2), δ *2.81-2.87* (t, 2H, CH_2-CH_2); ^{13}C-NMR (DMSO-d6, 300 MHz): δ 148.76(Exo C=CH).

5-(4-methoxybenzylidene)-2-((4-(6-methoxynaphthalen-2-yl)butan-2-ylidene)hydrazono)thiazolidin-4-one(3d)) *(Yellow Crystal)* (83% yield); mp 130-132°C; IR (KBr) *ν* (cm^{-1}):

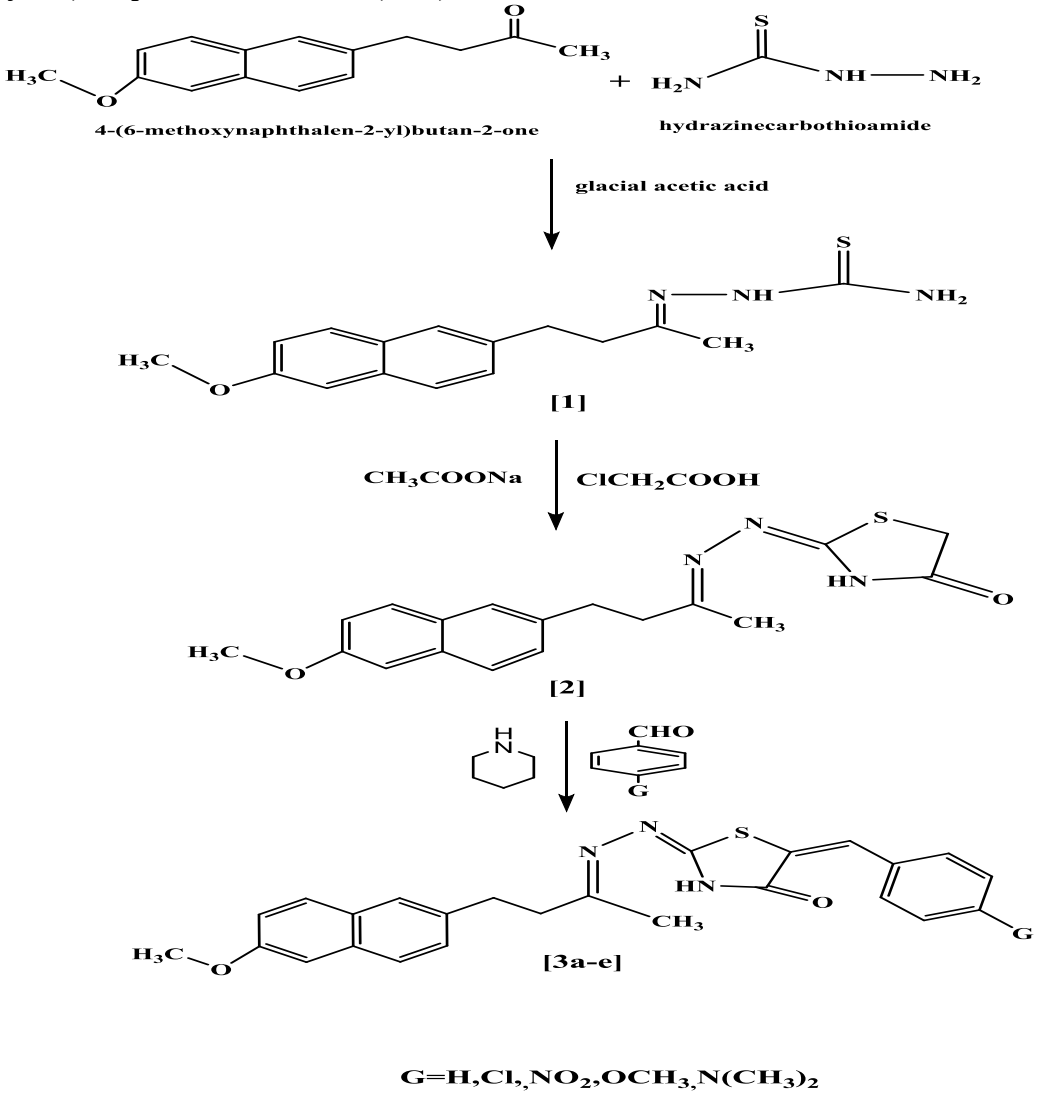
1712.85(C=O), 1637.62(Exo C=CH), 1502.62(aromatic);1H-NMR (DMSO-*d*6, 300 MHz): *δ* 7.76 (s, ^{1}H, Exo C=CH), *δ* 8.36 (s, 1H, NH), *δ* 7.05-7.71 (m, 10H, aromatic H), *δ* 3.82 (s, 3H, O–CH_3), *δ2.89-2.95* (t, 2H, CH_2-CH_2), δ *2.83-2.87* (t, 2H, CH_2-CH_2); ^{13}C-NMR (DMSO-d6, 300 MHz): δ 156.24(Exo C=CH).

5-(4-(dimethylamino)benzylidene)-2-((4-(6-methoxynaphthalen-2-yl)butan-2-ylidene)hydrazineylidene)thiazolidin-4-one(3e)

(Dark Orange Crystal) (80% yield); mp 160-162°C; IR (KBr) *ν* (cm^{-1}): 1693.50(C=O), 1635.64(Exo C=CH), 1523.76 (aromatic);^{1}H-NMR (DMSO-*d*6, 300 MHz): *δ* 7.75 (s, 1H, Exo C=CH), *δ*8.33(s, 1H, NH), *δ* 6.73-7.72 (m, 10H, aromatic H), *δ* 3.86 (s, 3H, O–CH_3), *δ2.89-2.95* (t, 2H, CH_2-CH_2), δ *2.81-2.83* (t, 2H, CH_2-CH_2), δ *2.89* (s, 6H, N(CH_3)$_2$); ^{13}C-NMR (DMSO-d6, 300 MHz): δ 152.30(Exo C=CH).

Chemical Synthesis

The chemical synthesis of new Intermediates and target compounds 3(a-e) was achieved following the procedure shown in scheme (1).



Scheme (1): Synthesis of new intermediates and final compounds.

Computational Method

The pharmacokinetic profile, i.e., absorption, distribution, metabolism, excretion (ADME) of the synthesized compounds was predicted with the help of Swiss ADME

ADME procedures

All ligands 1–3(a-e) were drawn by Chem Sketch (v. 12), converted to SMILE name by Swiss ADME tool which predicts the physicochemical descriptors and pharmacokinetic properties. BOILED-EGG was used to compute the lipophilicity and polarity of the small molecule [22].

Preliminary antibacterial and antifungal of the synthesized compound 3(a-e) have been done.

Bacterial isolates: The antimicrobial activity of the Intermediates and Target Compounds was done in college of pharmacy, Mustansiriyah University. A preliminary antibacterial & antifungal activity has been carried out according to Well Diffusion Method: The synthesized compounds have been studied for their antimicrobial activity in vitro against four tested bacteria. Four species of bacteria were used to assay the bacteriological activity of compounds in this study, two of them are gram positive (*Staphylococcus aureus & Streptococcus pneumonia*) and the others are gram negative (*Pseudomonas aeruginosa& Acinetobacter species*) and against fungus (*Candida albicans*).The bacterial diagnosis based on morphological examination, biochemical tests and diagnostic kits. Ciprofloxacin and Fluconazole were used as a standard drug for antibacterial and antifungal activity respectively.

Sensitivity Assay:

The antibacterial and antifungal activity of each derivatives were determined by agar well diffusion assay and carried out by using pure culture for all species of bacteria and fungus, inoculum of bacteria was first sub cultured in brain heart infusion broth and incubated at 37°C for 18-24 hour while in fungus incubated at 37°C for 72hour. After incubation, a loopful of each species transferred to tube containing 3mL normal saline and vortex well. The concentration of (1.5×108 CFU/mL) was obtained by using McFarland turbidity standard (number 0.5) of each bacteria and fungus inoculated by use glass spreader on the surface of Mueller Hinton Agar (MHA) plates previously prepared. The plate was allowed to dry and punched wells (five) in diameter of 6 mm. into agar. Subsequently, in each agar plate of tested bacteria and fungus five wells were made and (100µl) of dilutions of the derivatives (500,250,125 and 62.5) introduced into wells on MHA plate. DMSO used as the negative controller. The plates were kept warm at 37 °C for 24 hours and the antimicrobial action was estimated by determining the diameter of the inhibition zone. And also the plates were keep warm at 37 °C for 72hour and the antifungal action was estimated by determining the diameter of the inhibition zone The evaluation of antibacterial and antifungal action was based on extent of the diameter of inhibition zone formed all over the place of the well as shown in Table (1&2).

Table (1): Antibacterial activity of ciprofloxacin and compound 3(a-e) against tested bacteria.

Comp. no.	Conc. µg/ml	Inhibition zone (mm)			
		Gram positive		Gram negative	
		Staphylococcus aureus	Streptococcus pneumonia	Pseudomonas aeruginosa	Acinetobacter species
CPR	500	50	30	0	60
	250	32	26	0	50
	125	30	24	0	40
	62.5	26	12	0	30
DMSO	Pure				
3a	500	22	20	20	20
	250	22	20	20	16
	125	18	20	0	20
	62.5	14	14	0	20
3b	500	0	0	0	10
	250	0	0	16	16
	125	0	0	0	8
	62.5	0	0	0	24
3c	500	0	16	26	16
	250	0	10	20	6
	125	0	4	20	8
	62.5	0	30	16	0
3d	500	0	12	6	6
	250	0	0	10	8
	125	0	12	10	0
	62.5	0	20	10	8
3e	500	0	10	12	0
	250	0	8	10	10
	125	0	8	10	12
	62.5	0	6	10	8

CPR=ciprofloxacin.

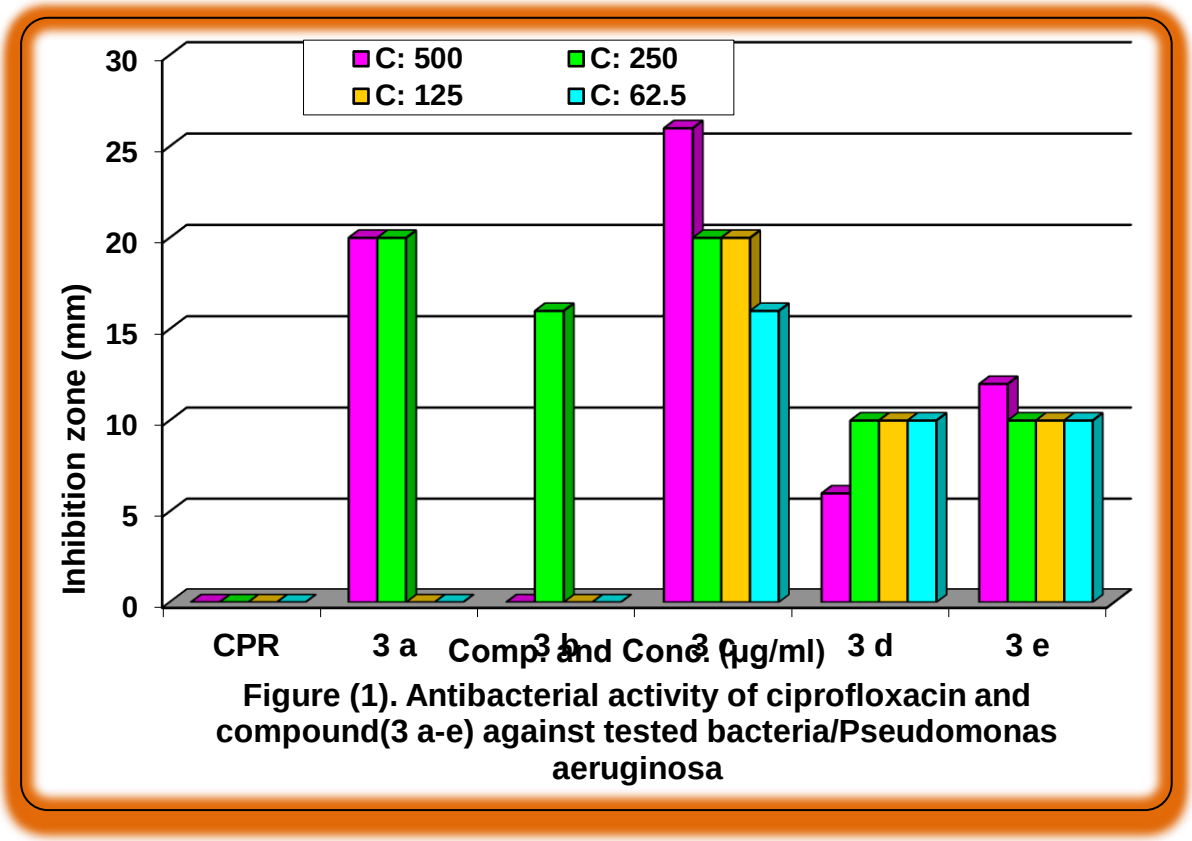
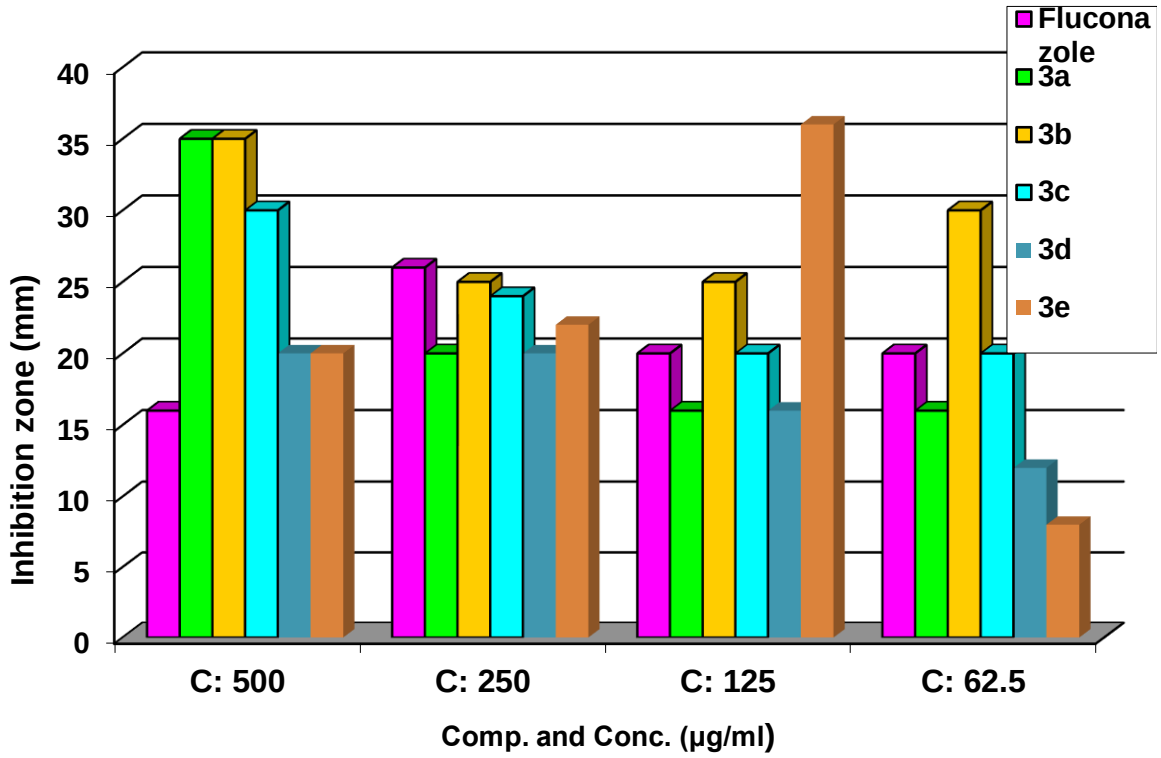


Figure (1). Antibacterial activity of ciprofloxacin and compound(3 a-e) against tested bacteria/Pseudomonas aeruginosa

Table (2): Antifungal activity of fluconazole and compound 3(a-e) against Candida albicans.

Comp. no.	Conc. µg/ml	Inhibition zone (mm)
		Candida albicans
fluconazole	500	16
	250	26
	125	20
	62.5	20
DMSO	Pure	
3a	500	35
	250	20
	125	16
	62.5	16
3b	500	35
	250	25
	125	25
	62.5	30
3c	500	30
	250	24
	125	20
	62.5	20
3d	500	20
	250	20
	125	16
	62.5	12
3e	500	20
	250	22
	125	36
	62.5	8



Figure(2):Antifungal activity of fluconazole and compounds 3(a-e) against Candida albicans

ADME Studies

The ADME properties profile of our synthesized compounds were studied by Swiss ADME server to detect the safer and potential drug candidate(s) to filter out the compounds which are most likely to fail in the subsequent stages of drug development due to unfavorable ADME properties. We assessed all synthesized compounds ADME method. Also, we calculated the topological polar surface area (TPSA), since it is another critical property that has been linked to the drug bioavailability. Thus, passively absorbed molecules with a TPSA > 140 Å are thought to have low oral bioavailability. [23] Our results showed that all synthesized compounds have TPSA below 140, which is in the range of 24–64 and the bioavailability for all ligands was 0.55 which mean that all ligands reach the systemic circulation.

Compound 1, 2, 3a, 3b, 3c, 3d and 3e fulfilled fulfilled Lipinski rule. Also, it also fulfilled the topological descriptors and fingerprints of molecular drug-likeness structure keys as Log*P* and Log*S*.

The GI absorption score is a measure of the extent of absorption of a molecule from the intestine following oral administration. The absorption could be excellent if the result were high. In this study, the GI absorption of all compounds was high except

3c predicting them to be well absorbed from the intestine.

The ADME properties profile for the synthesized compounds is illustrated in Table 3.

Table 3. ADME properties profile of the synthesized compounds

Comp.	Formula	M.Wt. (g/mol)	H-bond acceptors	H-bond donors	MR	TPSA	GI Abs.	BBB permeant	Lipinski violations
N	$C_{15}H_{16}O_2$	228.29	2	0	70.03	26.30 Å2	High	Yes	0
1	$C_{16}H_{19}N_3O_5$	301.41	2	2	91.62	91.73 Å2	High	No	0
2	$C_{18}H_{19}N_3O_5$	341.43	4	1	104.01	88.35 Å2	High	No	0
3a	$C_{25}H_{23}N_3O_2S$	429.53	4	1	133.62	88.35 Å2	High	No	0
3b	$C_{25}H_{22}CLN_3O_2S$	463.98	4	1	138.63	88.53 Å2	High	No	1
3c	$C_{25}H_{22}N_4O_4S$	474.53	6	1	142.45	134.17 Å2	High	No	0
3d	$C_{26}H_{25}N_3O_3S$	459.56	5	1	140.12	97.58 Å2	High	No	0
3e	$C_{27}H_{28}N_4O_2S$	472.60	4	1	147.83	91.59 Å2	High	No	0

Results and Discussion:

The synthesis of the target compounds 3(a-e) through their new intermediates achieved successfully. In the current work, we predict the synthesis of new derivatives of 5-arylidene-4-thiazolidinones, the target compounds were derived from thiosemicarbazone (1) which obtained from the reaction of different aldehydes and ketones such as nabumetone with hydrazine carbothioamide in a good yields as schemes (3-1),the structure of compound (1) (Schiff base) was identified by their FT-IR spectroscopy. the FT-IR spectrum of compound (1) shows disappearance of strong band of both primary amine υNH2 stretching at region 3367cm^{-1} of hydrazine thiocarboamide and υC=O stretching of nabumetone at 1705 $cm^{-1}$and other bands appear at 3421 cm^{-1} is for υ NH2 stretching, 3221cm^{-1} for υNHC=S, υ C=S stretching at region 1303 cm^{-1} stretching, The formation of Schiff's bases was indicated by the presence of the azomethine group υC=N stretching band at region 1593cm^{-1}.

The ^{1}H-NMR spectrum of compound (1), showed the broad singlet at 10.02 (δ, ppm) integrated for NHC=S and signal at 8.12(δ, ppm) integrated for NH2 proton and disappearance signal of NH2 proton of hydrazine thiocarboamide.

^{13}C-NMR spectra of compound (1), showed disappear of carbonyl group of nabumetone that appear at 208 (δ, ppm) and replaced by C=N group at 154.05(δ, ppm).

The compound (1) was cyclized successfully to 4-thiazolidinones compound (2) in good yields, the procedure includes the reaction of compound (1) with chloroacetic acid and anhydrous sodium acetate in ethanol under reflux for 8 hrs.

FT-IR spectrum of compound (2) showed disappearance of strong band related to υ C=S stretching which was present in the previous compound (1) and the appearance of the FT-IR characteristic absorption bands of υC=O stretching of thiazolidinone at 1724cm^{-1} and υC-S stretching band at 813cm^{-1}.

1H-NMR spectra of compound (2) showed doublet-doublet for CH2 proton of thiazolidinone ring at 2.65-2.79 and 2.98-3.01 (δ, ppm), and singlet for NH protons of thiazolidinone ring at 7.75(δ, ppm).

^{13}C-NMR spectra of compound (2) showed disappearance of C=S group at 179.00 (δ, ppm) that present in the previous compound and replaced by C=O group of thiazolidinone ring at 174.49(δ, ppm), C=N of the thiazolidinone ring at 162.38 (δ, ppm) and CH2 of the thiazolidinone ring at 32.06 (δ, ppm).

The second step of our plan is to make double bond at position 5 of the thiazolidinone ring to give alkene compounds 3(a-e) this step was carried out by fusion reaction of compound (2) with Benzaldehyde derivatives in presence of piperidine. The piperidine as a base was to remove the most acidic proton at position 5 of the ring. The resulted carbanion would easy attack the carbon of the carbonyl group of the benzaldehyde to produce compounds 3(a-e).

FT-IR spectrum of compound 3(a-e) showed the appearance of υC=O stretching bands at 1693-1712cm-1and υC=C stretching at 1635-1643cm^{-1}.

1H-NMR spectra of compounds 3(a-e) showed disappearance signal of CH2 proton of thiazolidinone ring that present in the previous compound (2) and appearance singlet for Exo υC=CH proton in the range 7.72-7.76 (δ,ppm).

^{13}C-NMR spectra of compounds 3(a-e) showed appearance of Exo C=CH in the range 141.20-156.42(δ, ppm).

Ciprofloxacin used as a reference, DMSO used as a control and the synthesized compounds 3(a-e) were screened for their antibacterial activity against gram negative bacteria (Pseudomonas aeruginosa& Acinetobacter species) and gram positive bacteria (Staphylococcus aureus& Streptococcus pneumonia) at concentrations of (62.5,125, 250 & 500 µg/mL) except the control which used in pure state Table (1): illustrates the inhibition zone in (mm) for each concentration of the tested compounds.

The anti-bacterial and anti-fungal assessment of target compounds 3(a-e) indicates that the incorporation of 5-arylidene-4-thiazolidinones pharmacophore into nabumetone which a resulted in a biological activity (anti-bacterial and anti-fungal activity) which did not find in the starting product (nabumetone). Tested compounds showed good inhibition on the growth of gram-negative bacteria especially (Pseudomonas aeruginosa) in comparison with ciprofloxacin with highest activity for 3c and lowest for 3b as in Figure (1)

All tested compounds showed good inhibition on the growth of fungus (Candida albicans) verses control (fluconazole) with highest activity for 3b and lowest for 3d as in Figure (2) & Table (2): illustrates the inhibition zone in (mm) for each concentration of the tested compounds against (Candida albicans).

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