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Synthesis, Characterization, and biological activity of some Heterocyclic compounds that derived from Ibuprofen

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Abstract

A simple, easy method for preparation of new thiazoldine derivatives was done and new compound were elucidated on bases of spectroscopic analyses. Ibuprofen reacted with hydrazine hydrate to afford hydrazide derivative which reacted with aldehydes to afford Schiff bases that cyclized with Thioglycolic acid to afford thiazolidine derivatives. Antimicrobial activity of new compounds was carried out using diffusion plate method.

Keywords: Thizaolidine derivatives; Antimicrobial Activity; spectroscopic analyses.

1. Introduction

Ibuprofen is a propionic acid derivative (2-arylpropionic acids) that was first introduced as a superior alternative to aspirin in 1969[1]. Ibuprofen is chemically related to fenoprofen and naproxen. It is widely used to alleviate non-rheumatic inflammation, pain, acute arthritis, fever, and primary dysmenorrhea because to its good pharmacological properties and greater tolerability [2]. Ibuprofen is effective in reducing high body temperature, and an anti-inflammatory which inhibits normal platelet function. Ibuprofen is reported to be better for joint and muscle pain than other pain killer and has been used by people for arthritis for years. However, it can cause gastrointestinal upset and bleeding.[3, 4]

Besides, propane-amide derivatives of NSAIDs showed good antibacterial activity against Gram-positive bacteria as *Staphylococcus aureus* and *Bacillus subtilis* and Gram-negative bacteria as *Escherichia coli* and *Pseudomonas aeruginosa* comparable to standard drugs ampicillin for Gram-positive and ciprofloxacin for Gram-negative bacteria[5].

In the same manner, azomethine group is synthesized from reaction of amines, hydrazides or aromatic amino acids with aldehyde or ketones due to presence of non-associate electronic pair in nitrogen of amino group to resonance cycle.[6, 7] Heterocycles as Schiff bases and azomethine derivatives were synthesized via reaction of carbonyl compounds with amine compounds. These heterocycles have a wide variety of biological activities such as antimicrobial, antitumor, and anti-inflammatory with pharmacological activity.[8-12]

Also, Thiazolidin-4-one ring system [13- 15] has been widely used for management of Type-II diabetes mellitus [16], it refers to a family of drugs used in the treatment of diabetes mellitus type 2 that were introduced in the late 1990s and it has antimicrobial [17], antibacterial [18], antitumor [19]anti-inflammatory[14] and various biological activities.[20-23]

According to this survey, our aim to synthesized Thiazolidin-4-one ring system via reaction of ibuprofen hydrazides with aldehyde derivatives as Schiff bases with cyclization and test the activity of new compounds as antimicrobial agents.

2. Experimental and methods

2.1. Synthesis of 2-(4-isobutylphenyl)propanoate (2)

0.01mol of ibuprofen is dissolved in 50 mL absolute ethanol with 2ml conc. sulfuric acid. This mixture was refluxed for 4h and the reaction was followed by (TLC), the reaction residue was evaporated, washed with sodium bicarbonate, extracted with diethyl ether (3*20mL). The solvent fraction was evaporated at reduced pressure and then poured over ice to provide a precipitate filter, washed with 10% sodium bicarbonate and recrystallized with ethanol to get compound 2 in good yield.

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2.2. Synthesis of 2-(4-isobutylphenyl)propanehydrazide (3)

A mixture of 0.01 mol ibuprofen ester 2 and 5mL hydrazine hydrate (80%) in 25mL absolute ethanol was refluxed for 5h and the reaction was followed by (TLC) then this mixture left to cool to afford a precipitate which filter, washed with cold water, dried and recrystallized from absolute ethanol to afford compound 3 in pure form with M.P. 197-199ºC.

2.3. Synthesis of N'-substitutedbenzylidene-2-(4-isobutylphenyl)propanehydrazide 4a-c

A mixture of compound 3 (0.02g, 0.01 mol) and 0.01 mol of aldehydes; benzaldehyde, 2,4-dihydroxybenzaldehyde, or 4-methoxybenzaldehyde was refluxed in absolute ethanol (20mL) for 4h and the reaction was followed by (TLC) and the precipitate is collected and recrystallized with ethanol to afford compounds 4a-c it's physical properties in Table 1 and IR peaks in Table 2.

2.4. Synthesis of thizaolidine derivatives 5a-c

(0.02mol, 0.7mL) Thioglycolic acid and derivatives of (4-isobutylphenyl)propanehydrazide 4a-c (0.02mol) were added to 10mL1,4-dioxane and catalysed with 0.002g anhydrous zinc chloride. This mixture was refluxed for 12-15h and the reaction was followed by (TLC) then left to cool and poured on crushed ice to give a precipitate that filtered dried and recrystallized with ethanol to afford compounds 5a-c it's physical properties in Table 3 and IR peaks in Table 4.

2.5. Antimicrobial Activity

The microbial activities [24, 25]were carried out in microbiology Lab, Department of Biology, College of Pure Education Science at Tikrit University using the diffusion plate method [26]. A filter paper sterilized disk saturated with the measured quantity (25 μL) of the sample (1 mg/mL) was placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar) that was seeded with the spore suspension of the test organism. After incubation at 37ºC for 24 h for bacteria (in case of fungi, at 25ºC for 72 h), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter × 100). All measurements were done in methanol as a solvent that has zero inhibition activity. The antimicrobial activity of the new compounds was examined against Gram positive bacteria *Staphylococcus aureus*, as well as Gram negative bacteria *Pseudomonas aeruginosa*, Table 5 contains data of the antibacterial testing.

3. Results and discussion

Ibuprofen as pain relief is used in pure form and has been reacted with ethanol at reflux temperature to afford ethyl 2-(4-isobutylphenyl)propanoate (2). This ibuprofen ester was reacted with hydrazine hydrate at reflux temperature to afford hydrazide derivative of 2-(4-isobutylphenyl)propanehydrazide (3) in an excellent yield (Scheme 1).

Table 1: Physical properties of compound **4a-c**

	Mol.F	M.P ºC	Yield %	Color
4a	$C_{20}H_{24}N_2O$	166-164	%67	Brown
4b	$C_{20}H_{24}N_2O_3$	171-169	%61	Brown
4c	$C_{21}H_{26}N_2O_2$	209-207	%54	Brown

Table 2: IR peaks of **4a-c**

	IR ν (cm^{-1})					
	NH	ArH	CH	C=O	C=N	C=C
4a	3307	3074	2864	1701	1654	1602
4b	3313	3046	2908	1735	1647	1602
4c	3482	3073	2923	1720	1663	1607

Table 3: Physical properties of compound **5a-c**

	Mol.F	M.PºC	Yield %	Color
5a	$C_{22}H_{26}N_2O_2S$	178-176	%37	White
5b	$C_{22}H_{26}N_2O_4S$	191-189	%41	Brown
5c	$C_{23}H_{28}N_2O_3S$	184-182	%34	White

Table 4:IR peaks of 5a-c

	IR ν (cm^{-1})					
	OH	**NH**	**ArH**	**CH**	**C=O**	**C=C**
5a	3476	3371	3018	2927	1715	1618
5b	3443	3346	3005	2919	1717	1605
5c	3625	3344	3070	2916	1709	1611

Table 5:Data of the antibacterial testing

Compound No	Concentration (ml/mg)	*Staphylococcus*	*Pseudomonas*
5a	1×10^{-4}	++	+
	1×10^{-3}	+	++
	1×10^{-2}	+	+
5b	1×10^{-4}	++	+
	1×10^{-3}	+	+
	1×10^{-2}	+	+
5c	1×10^{-4}	++	++
	1×10^{-3}	+	+
	1×10^{-2}	+	+

+: inhibition with diameter 5-10, ++: inhibition with diameter 15-20.

The structures of compound **2** and **3** were elucidated on IR, NMR. The most important features of compound **3** are the presence of stretching bands at 1716 (C=O), 3339, 3473 cm^{-1} (NH and NH_2) in its IR spectrum (KBr disk, Figure 1).

Also, ^{1}H NMR of compound **3** revealed signals at δ 1.6-1.8ppm (s, 9H, Me), 2.23-2.27ppm (d, 2H, CH_2),3.4-3.5ppm(1H,CH), 5.3ppm (s, 1H, NH_2), aromatic protons appeared at δ 7.3-7.87 as multiplate together with signal at 8.28 ppm that related to NH group (Figure 2).

Also, compound **3** reacted with various aldehydes namely, benzaldehyde, 2,4-dihydroxybenzaldehyde, 4-methoxybenzaldehyde at refluxed temperature in absolute ethanol to afford Schiff base derivatives **4a-c** (Scheme 1).

The structures of new compounds **4a-c** were confirmed on the bases of spectroscopic analyses. Compound **4c** revealed characteristic band in its IR at 3346 cm^{-1} (NH), 1717 cm^{-1} (amide C=O), 1605 cm^{-1} (C=C) (Figure 3).

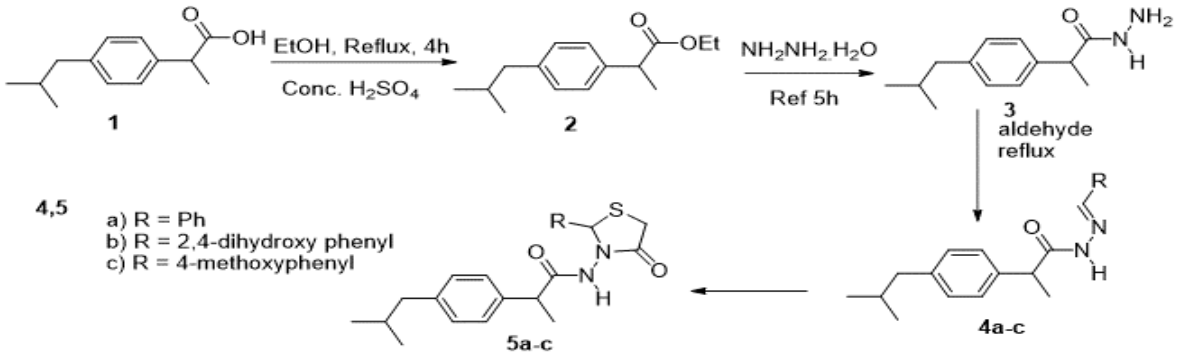
Also, 1HNMR of compounds **4a-c** revealed signals at δ 1.3-1.9ppm (d, 9H, Me), 2.37- 2.92ppm (d, 2H, CH_2), 3.8 ppm(s, 3H, OMe), 4.30-4.37ppm(q,1H,CH), 6.9-7.9 (m, H $_{arom.}$), 8.67-8.78ppm(s,1H,N=CH) and 8.89- 9.78 , 11.94 and 11.97 ppm for NH and OH signals, respectively (Figure 4,5).

In the same manner, Thioglycolic acid and Schiff base derivatives **4a-c** were added to dioxane as solvent and the mixture was catalysed with anhydrous zinc chloride. Then, was refluxed for 12-15h (TLC) to afford thiazolidine derivatives **5a-c** (Scheme 1). The structures of new compounds **4a-c** were confirmed on the bases of spectroscopic analyses. Compound 5c revealed characteristic band in its IR at (Table 4) and show in (Figure 6).

The most characteristic features of compounds **5a-c** in its 1HNMR were appearance of signals at δ 1.2-1.28ppm (s, 3H, Me), 2.27-2.87ppm (s, 2H, CH_2), 3.36ppm(s,3H,OMe), 3.30-4.13ppm(s,CH) 4.30-4.32ppm(s,2H,CH_2, ring thiazolidine) 4.42-5.10ppm(s,1H,CH,ring thiazolidine), 7.3-7.9 (m, H $_{arom.}$) and 8.44-9.26 and 9.49-9.65 ppm for NH and OH signals, respectively (Figure 7-8).

3.1. Antibacterial activity

The new compounds were screened to determine their antimicrobial activity *in vitro* against Gram positive bacteria *Staphylococcus aureus*, and Gram-negative bacteria *Pseudomonas aeruginosa* using the diffusion plate method, the results depicted in Table 5 and Figures 9-11.



Scheme 1

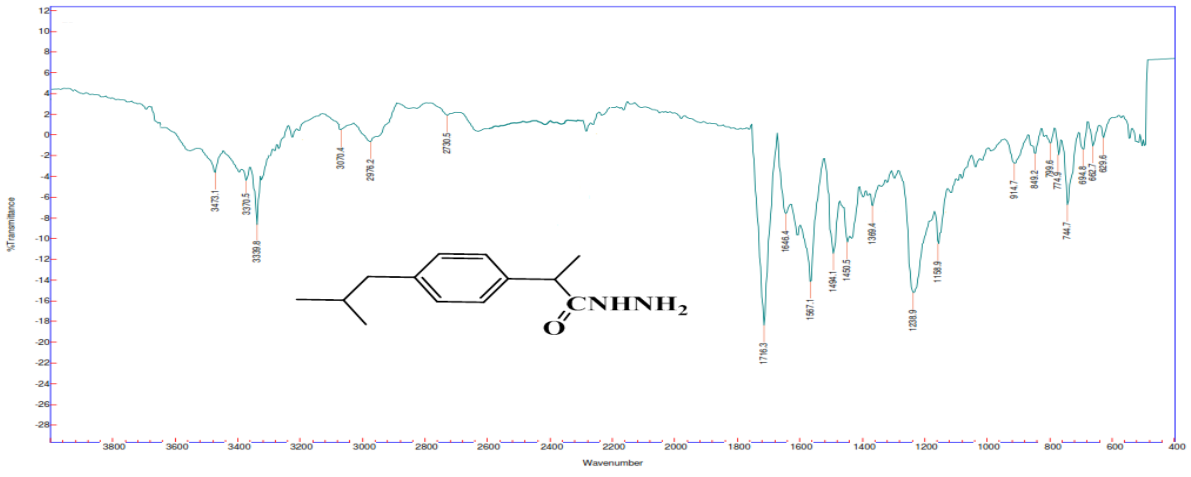


Figure 1: IR spectrum of compound 3

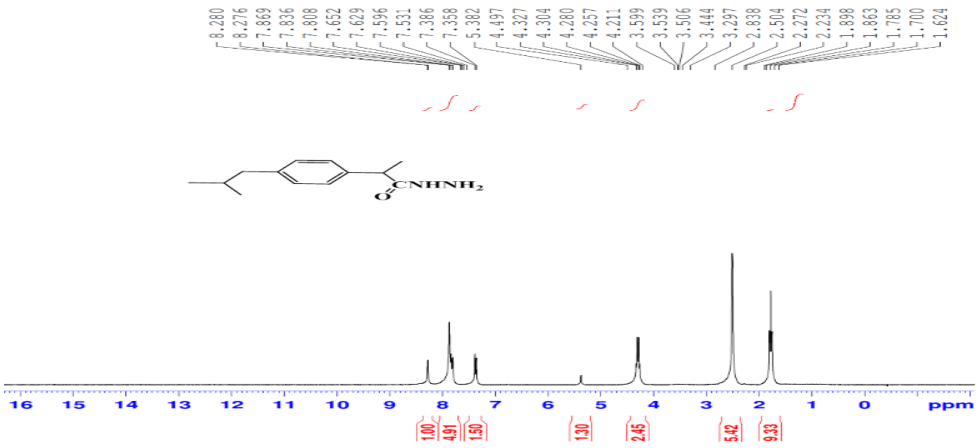


Figure 2: ^{1}H NMR spectrum of compound 3

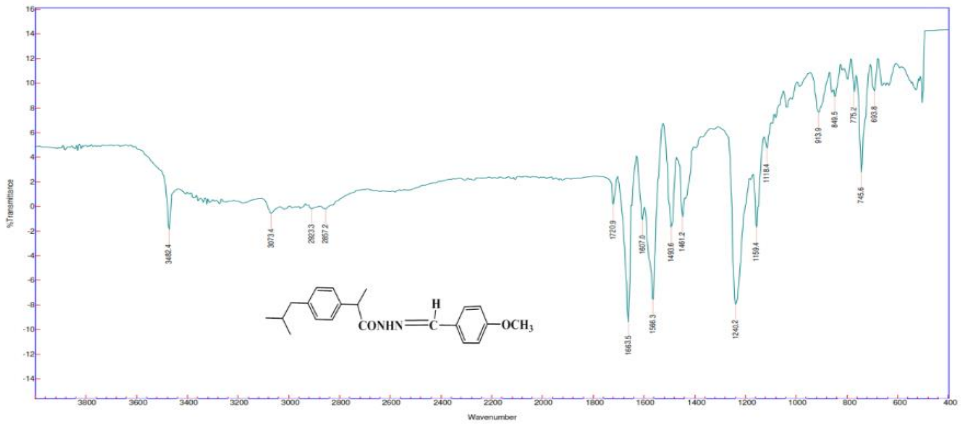


Figure 3: IR spectrum of compound 4c

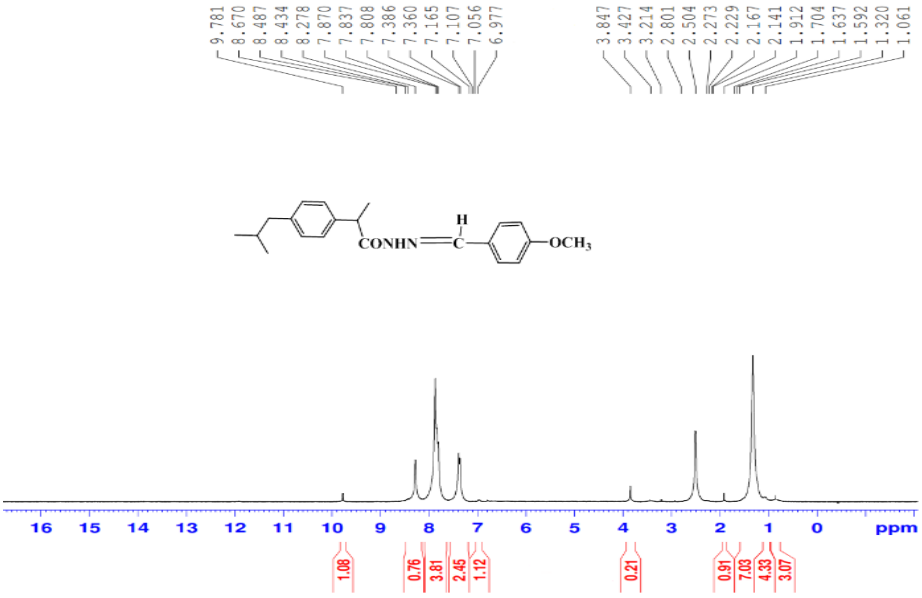


Figure 4: ^{1}H NMR spectrum of compound 4c

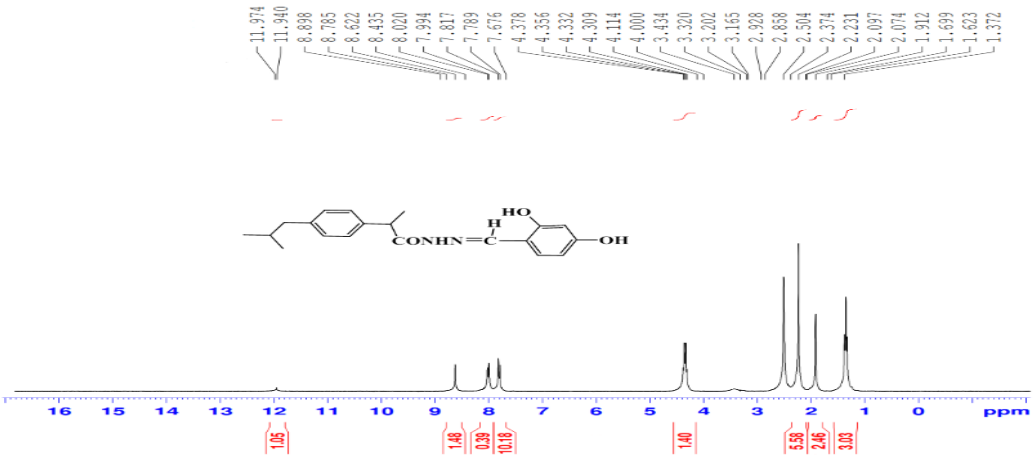


Figure 5: ^{1}H NMR spectrum of compound 4b

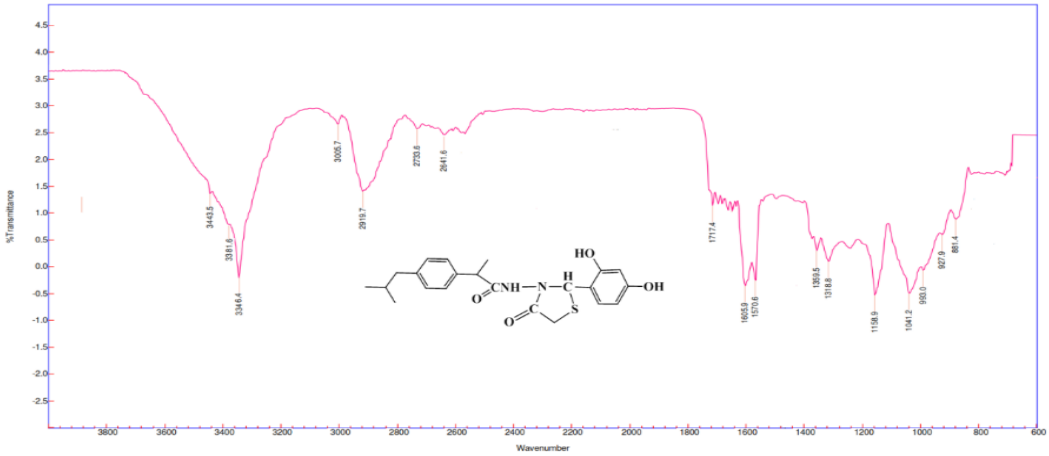


Figure 6: IR spectrum of compound 5c

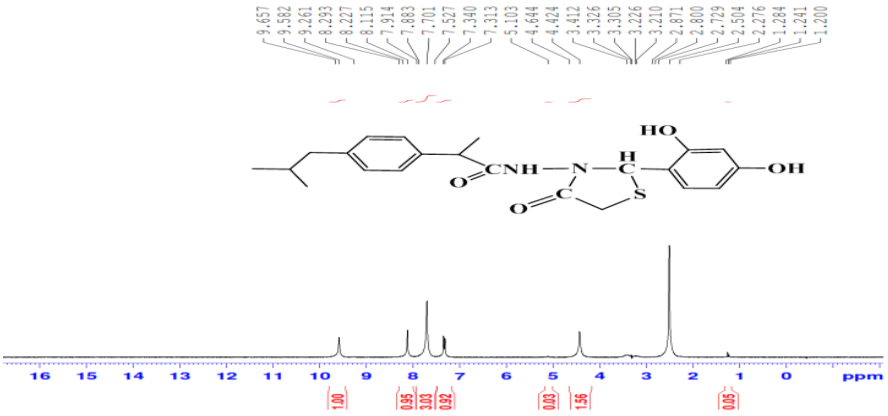


Figure 7: ^{1}H NMR spectrum of compound 5b

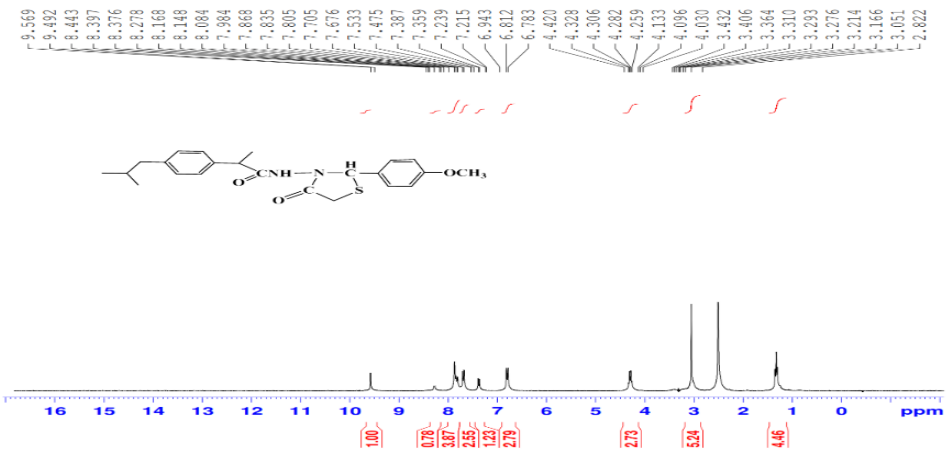


Figure 8: ^{1}H NMR spectrum of compound 5c

Figure 9: Inhibition of compound 5a

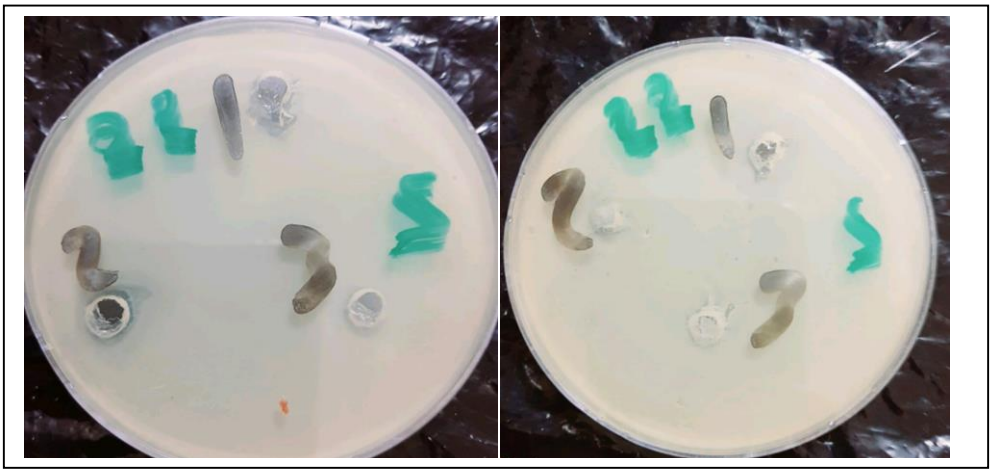


Figure 10: Inhibition of compound 5b

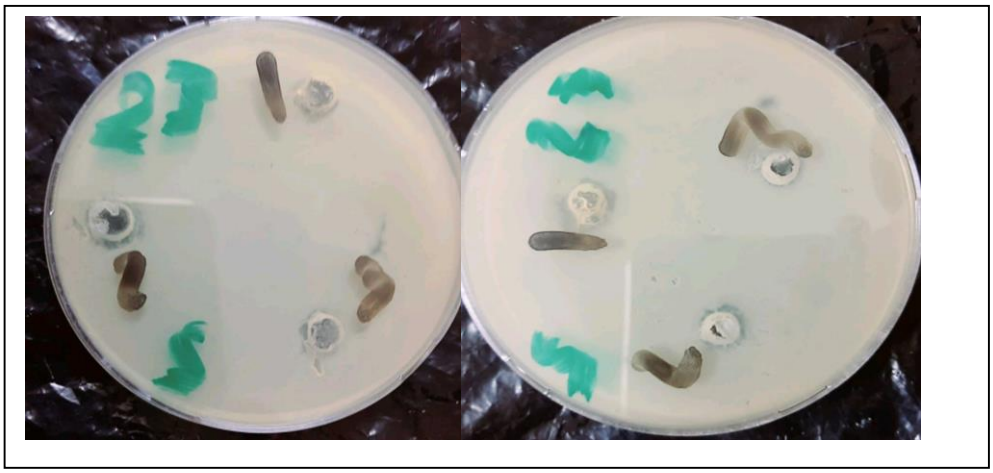


Figure 11: Inhibition of compound 5b

4. Conclusions

Thiazolidetones can be prepared from ibuprofen acid from Schiff bases. Antimicrobial activity of new compounds was carried out using diffusion plate method.

5. Conflicts of interest

"There are no conflicts to declare".

6. Acknowledgments

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