RESEARCH ARTICLE

Synthesis, Characterization of New Isatin-Ibuprofen Derivatives with Expected Biological Activity

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ABSTRACT

Ibuprofen is one of the most important members of NSAIDs, named aryl propionic acid derivative. Isatin (1H-indole-2,3-dione) is an important molecule of heterocyclic compounds that have many biological activities. This work illustrates the synthesis of new ibuprofen-isatin derivatives by connecting ibuprofen hydrazide with different isatin derivatives by a condensation reaction, followed by characterization by fourier-transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. The anti-inflammatory activity was evaluated by using the egg-white induce edema method for all the synthesized compounds (5-8), the compounds 5 and 6 showed better anti-inflammatory activity than ibuprofen as a standard compound. Their antimicrobial activity was evaluated and compared with ciprofloxacin, ampicillin, and fluconazole; the compounds 5 and 7 have moderate antibacterial activity against gram-positive and gram-negative bacteria, with lower antifungal activity.

Keywords: Biological activity, Ibuprofen, Isatin, 5- Methoxy isatin.

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used medications as anti-inflammation, analgesic, and antipyretic agents.[1] The main mechanisms of NSAIDs are competitive inhibitors for cyclooxygenases (COX) enzyme both 1 and 2.[2,3] The COX-1 is responsible for forming main biological mediators such as prostanoids, including prostaglandins, prostacyclin, and thromboxane, and stomach protection.[4] while COX-2 participated in the pain by inflammation and in prostaglandin biosynthesis in inflammatory cells and the central nervous system.[5] The largest and most important group in NSAIDs is aryl propionic acid derivatives,[6] like ibuprofen, naproxen, ketoprofen, and flurbiprofen; among the most widely used pain killers drugs.[7] The first member of the aryl propionic acid family is ibuprofen, chemically named; 2[4-(2-methyl propyl) phenyl] propionic acid. Ibuprofen is the most frequently used and prescribed NSAID, as an anti-inflammatory, an analgesic, and an antipyretic agent.[8,9] It is considered a non–selective inhibitor of COX-1 and COX-2.[10] Recently, aryl propionic acid derivatives have a broad biological activity, including anticancer, antibacterial, and anticonvulsant activities, besides their analgesic and anti-inflammatory activities.[11]

Gupta R. *et al.,*[12] synthesized six derivatives of 2-(4-sec-butyl-phenyl)-propionic acid pyrrolidin-2-yl carbamoyl methyl ester depending on the bioisosteric concept for ibuprofen enhancing anti-inflammatory activity, these derivatives when evaluated for their anti-inflammatory activity most of these compounds showed significant activity.

Other ibuprofen derivatives were synthesized by cyclization of the carboxyl group into five-membered and six-membered heterocyclic rings such as hydrazine, pyrazole, 1,3-oxazin-2-yl, 1,3,4-thiadiazole, quinazolin-2-yl, and oxadiazole under different reaction conditions. Most of the prepared compounds also showed interesting antibacterial activity towards *Staphylococcus aureus* and *Escherichia coli* compared to the ibuprofen drug.[13]

Isatin, 1H-indole 2,3dione, is an indole derivative and a versatile chemical building block able to form many heterocyclic derivatives. Isatin derivatives exhibit different biological activities like antibacterial, antifungal, antiviral, anti-human immunodeficiency virus (HIV), anti-mycobacterial, anticancer, anti-inflammatory, and anticonvulsant activities.[14] The character of substituents at the 2- or 3-position of the indole nucleus of isatin has been shown to significantly regulate their anti-inflammatory and anti-bacterial activities.[15-19]

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Ramana H. *et al.*[20] synthesized a series of the compounds 3-(substituted hydrazone)-1H benzoindol-2(3H)-one derivative. All synthesized compounds were evaluated for antibacterial activity by using the agar diffusion method. All tested compounds showed mild to moderate activity when compared to standard drugs ciprofloxacin and diclofenac, and the most potent ones are those with bromophenyl and hydroxyphenyl groups.

Jarapula R. *et al.,*[21] synthesized a series of compounds from the reaction of isatin derivatives with benzohydrazide derivatives, all synthesized compounds were evaluated for anti-inflammatory activity by carrageenan-induced paw edema at the dose of 100 mg/kg. Also all tested compounds significantly decrease carrageenan induces edema when compared with an anti-inflammatory drug; indomethacin, the most active compounds are those with electron-withdrawing substituents (5-chloro, 5-bromo, 7-COOH, or 7-chloro) which exhibit essential activity with a reduction in edema.

Considering the biological importance of the two biologically active moieties, isatins, and aryl propionic acid derivatives, it was considered beneficial to study the condensation of isatin derivatives with ibuprofen hydrazide. Then anti-inflammatory efficacy of the produced compounds was tested *in vivo*. Moreover, these derivatives are expected to have lower gastrointestinal side effects compared to ibuprofen itself due to masking the irritant COOH group. Furthermore, the microbial inhibitory effect of the new derivatives has been evaluated *in-vitro* towards gram-positive and gram-negative bacteria, and one fungal strain.

MATERIAL AND METHODS

Chemicals and solvents used during synthesis were as follows:

Ibuprofen was donated by the State Company for Drug Industries (SDI, Samara, Iraq), Isatin purchased from Hi-Media Laboratories, India, and 5-methoxy isatin from Hangzhou Hyper chemicals Limited, China. Hydrazine hydrate 99% was purchased from CDH, India. The melting points were measured by the open capillary method using Stuart SMP30 and were used uncorrected. Thin-layer chromatography (TLC) was used for monitoring the reaction and checking the purity of the products done by using aluminum plates (Merck, Germany) and chromatograms were eluted by using one or more of the following two mobile phases: A: ethanol: ethyl acetate: n.hexane.1:3:6 and B: chloroform: ethyl acetate. 7:3. Infrared spectra were using the fourier-transform infrared spectroscopy (FTIR) spectrometer, Shimadzu, Japan. proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on the nuclear magnetic resonance (NMR) 500 spectrometer model.

Chemical Synthesis

Synthesis of Ethyl 2-(4-isobutylphenyl)propanoate (1)[22]

To prepare Ibuprofen ethyl ester (1), first: dissolving (8.23g, 0.035 mol) of ibuprofen, in 70 mL absolute ethanol, adding 3 mL of H_2SO_4 drop by drop with vigorous stirring. Second: Starting reflux at a temperature of 70ºC for 7 hours. TLC monitored the reaction after completing the reaction the mixture of the solution was poured in a beaker containing crushed ice then the solution was neutralized by (10%w/v) $NaHCO_3$. The final product was obtained by filtration then recrystallization from ethanol.

Ethyl 2-(4-isobutylphenyl)propanoate (1) ($C_{15}H_{22}O_2$): Color and appearance: pale yellowish oil, yield: 81%, IR (υ cm^{-1}): 2954 and 2870 (C-H stretching vibration of CH_3 and CH_2), 1735 (C=O stretching vibration of ester), 1161 (C-O stretching vibration of C-O-C).

Synthesis of 2-(4-isobutylphenyl)propanehydrazide (2)[23]

Mix (4.6 g, 0.02 mol) of ibuprofen ethyl ester (1), with (10 mL, 0.2 mol) of 99% hydrazine hydrate then add 60 mL ethanol in a round boiling flask then reflux the mixture for 24 hours. TLC monitored the reaction after completing the reaction, the mixture was allowed to cool at room temperature; alcohol was evaporated and poured into crushed ice. The solid product was obtained by filtration and recrystallization from ethanol, as shown in scheme 1 (step 1).

2-(4-isobutylphenyl)propanehydrazide (2)($C_{13}H_{20}N_2O$): Color and appearance: off-white powder, Yield: 90%, IR (υ cm^{-1}): 3275, 3209 and 3174 (N-H stretching vibrations of NH_2 and NH), 2959 and 2920 (C-H stretching vibration of CH_3 and CH_2),1685 (C=O stretching vibration).

Synthesis of N-benzyl isatin (4a) and N-benzyl 5-methoxy isatin (4b)[24, 25]

(0.88 g, 0.006 mole) of isatin, (1.06 gr) of 5-methoxy isatin was added to a flask containing 45 mL acetonitrile then add (0.966 g, 0.0072 mole) K_2CO_3 and (0.198 g, 0.0012 mole) KI stirring for 10 minutes then (1.137 g, 0.009 mole) benzyl chloride was added drop by drop. After 5 hours of reflux, the mixture was filtered, then the filtrate was dried under a vacuum, dissolved in ethyl acetate, extracted in a separatory funnel with hot water several times, then dried the product and recrystallized from ethanol.

1-benzylindoline 2, 3-dione (4a) ($C_{15}H_{11}NO_2$): Color and appearance: orange crystals, yield: 78% IR (υ $cm^{-1)}$: 3032(C-H stretching vibration of aromatic), 1728 and 1608 (C=O stretching vibration of two carbonyl groups).

1-benzyl-5-methoxyindoline-2, 3-dione (4b) ($C_{16}H_{13}NO_2$): Color and appearance: brown crystals, yield: 65%, IR (υ cm^{-1}): 3070 (C-H stretching vibration of aromatic), 2962 (C-H stretching vibration of aliphatic CH_2), 1720 and 1620 (C=O stretching vibration of two carbonyl groups).

Synthesis of the Targeted Compounds (5-8)[26]

In a round bottom flask, add equimolar about 0.002 mol of each compound 3a, 3b, 4a, or 4b, separately, with 0.002 mol of compound 2 in presence of 40 mL ethanol then add 1-mL of glacial acetic acid as a catalytic reagent, starting the reflux for 12 hours the reaction monitoring by TLC, after the reaction complete the solvent removed under vacuum then the product recrystallization from ethyl acetate, as shown in scheme 1 (step 2).

2-(4-isobutylphenyl)-N'-(2-oxoindolin-3-ylidene) propanehydrazide (5) ($C_{21}H_{23}N_3O_2$):color and appearance: yellow powder, m.p.:174–177ºC, yield: 82%.

IR (υ cm^{-1}): 3167 (N-H (stretching vibration of NH), 2954 and 2870 (C-H stretching vibration of CH_2 and CH_3), 1716 (C=O stretching vibration of aliphatic amid), 1693 (C=O stretching vibration of cyclic amid), 1616 (C=N stretching vibration of imine).

^{1}H-NMR: (DMSO-*d6*) δ ppm: 0.81(3H, d, methyl of isobutyl group of ibuprofen). 1.45(3H, d, CH_3 of ibuprofen). 1.46-1.82 (1H, m, CH of isobutyl group of ibuprofen), 2.37-2.42 (2H, d, CH_2 of ibuprofen), 3.88 (1H, q, aliphatic CH group of Ibuprofen), 6.91-7.27(4H, m, aromatic ring of ibuprofen), 7.29-7.37(2H, d, aromatic ring of isatin), 7.5-7.6(2H, d, protons of gr ortho to heterocyclic ring), 11.19 (1H, s, cyclic amide of pyrrolidin ring), 12.43 (1H, s, amide group).

2-(4-isobutylphenyl)-N'-(5-methoxy-2-oxoindolin-3 ylidene)propanehydrazide (6)($C_{22}H_{25}N_3O_3$): color and appearance: brown powder, m.p: 159-161ºC, yield: 70%.

IR (υ cm^{-1}): 3167 (N-H stretching vibration of NH), 2954 and 2870 (C-H stretching vibration of CH_2 and CH_3), 1716 (C=O stretching vibration of aliphatic amid), 1693 (C=O stretching vibration of cyclic amid), 1616 (C=N stretching vibration of imine).

^{1}H-NMR (DMSO-*d6*) δ ppm: 0.8(6H, d, CH_3 of isobutyl group of ibuprofen), 1.44 (3H, d, CH_3 of ibuprofen), 1.46–1.83 (1H, m, CH of isobutyl group of ibuprofen), 2.34–2.42(2H, d, CH_2 of ibuprofen), 3.96 (1H, q, aliphatic CH group of ibuprofen), 4.78 (3H,s, protons of methoxy group), 6.82–6.9 (2H, m, protons ortho to methoxy group), 7.04–7.13 (4H, m, proton of aromatic ring), 7.14–7.31(1H, d, proton ortho to heterocyclic ring), 11.01 (1H, s, Proton of cyclic amide), 12.45 (1H, s, proton of amide group).

N'-(1-benzyl-2-oxoindolin-3-ylidene)-2-(4- isobutylphenyl) propanehydrazide (7) ($C_{28}H_{29}N_3O_2$): color and appearance: yellow powder, m.p:134–136, yield: 82%.

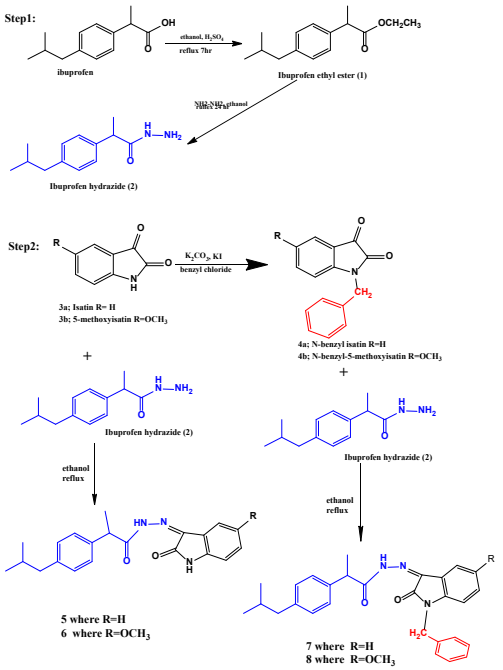
IR (υ cm^{-1}): 3217 (N-H stretching vibration of NH), 2966 and 2961 (C-H stretching vibration of CH_2 and CH_3), 1678 (C=O stretching vibration of cyclic amid), 1612 (C=O stretching vibration of aliphatic amid), 1512 (C=N stretching vibration of imine).

^{1}H-NMR (DMSO-*d6*) δ ppm: 0.81 (6H, d, CH_3 of isobutyl group of ibuprofen), 1.45 (3H, d, CH_3 of ibuprofen), 1.78 (1H, m, CH group of isobutyl of ibuprofen), 2.38 (2H, d, CH_2 of ibuprofen), 3.96 (1H, q, CH of aliphatic ibuprofen), 4.8 (2H, s, CH_2 aliphatic), 6.99–7.2 (9H, m, protons of aromatic rings), 7.25–7.4 (2H, d, protons of aromatic ring), 7.5–7.6 (2H, d, proton ortho to heterocyclic ring), 12.36 (1H, s, amide group).

N'-(1-benzyl- 5-methoxy-2-oxoindolin- 3-ylidene) -2- (4-isobutylphenyl) propane hydrazide (8) ($C_{29}H_{31}N_3O_3$): Color and appearance: orange powder, m.p:105-107, yield: 85%.

IR (υ cm^{-1}): 3390 (N-H stretching vibration), 2962 and 2931(C-H stretching vibration of CH_2 and CH_3), 1674 (C=O stretching vibration of cyclic amid), 1631 C=O (stretching vibration of aliphatic amid), 1604 (C=N stretching vibration of imine), 1288 (C-O stretching vibration of ether).

^{1}H-NMR (DMSO-*d6*) δ ppm: 0.83 (6H, d, CH_3 of isobutyl group of ibuprofen), 1.46 (3H, d, aliphatic CH_3 of ibuprofen),



Scheme 1: Synthesis of target compounds (5-8).

1.79 (1H, m, CH of isobutyl group of ibuprofen), 2.38–2.41 (2H, d, CH_2 of ibuprofen), 3.4 (1H, q, aliphatic CH of ibuprofen), 3.7 (3H, s, protons of methoxy group), 4.85 (2H, m, CH_2), 6.7–6.8 (2H, m, protons ortho to methoxy group), 6.9–7.1 (9H, m, protons of aromatic rings), 7.2–7.3(1H, d, protons of aromatic rings), 12.38 (1H, s, proton of amide group).

Evaluation of the Anti-inflammatory Activity of the Synthesized Target Compounds

Albino rats of both sexes weighing (190 ± 10 g) were supplied by the animal house of the College of Pharmacy, the University of Baghdad, and the animals were housed in the same location under standardized conditions. Animals were fed commercial chew and had free access to water.

Animals were separated into 6 groups (each group consisting of six rats) as follows:

Group A: Six rats that were considered as control and treated with dimethyl sulfoxide (DMSO) intraperitoneally.

Group B: Consists of six rats treated with Ibuprofen as a reference drug in a dose of 50 mg/kg dissolved in DMSO.

Groups C-F: Six rats for every four groups (C-F) injected with the tested compounds (5-8), dissolved in DMSO. In doses that are illustrated in Table 1.

Table 1: Doses of compounds with their molecular weight

Compound	*Molecular weight*	*Dose mg/kg*
Ibuprofen	206.29	50
5	349.4	84.68
6	379.4	91.98
7	439.6	106.5
8	469.6	113.8

Table 2: Effect of control (DMSO) and standard (Ibuprofen) on paw edema thickness

Paw edema thickness (mm)			
Time (min)	*Control (DMSO) Mean ± STD*	*Standard (Ibuprofen)*	*p-value*
Zero time	5.54 ± 0.10	5.14 ± 0.06	0.29
30	5.89 ± 0.25	5.46 ± 0.19	0.20
60	5.96 ± 0.12	5.18 ± 0.19	0.006
120	6.33 ± 0.15	5.02 ± 0.14	0.0001
180	5.93 ± 0.19	5.09 ± 0.11	0.004
240	5.62 ± 0.17	4.74 ± 0.08	0.001
300	5.05 ± 0.17	4.54 ± 0.14	0.04

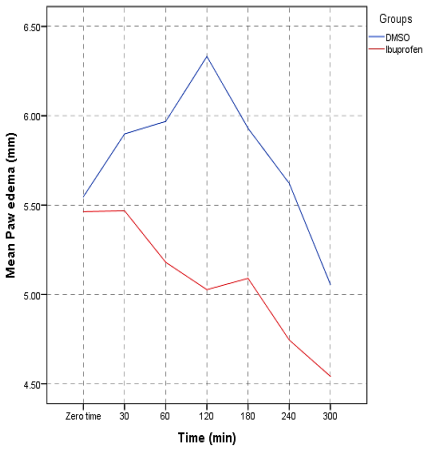


Figure 1: Effect of control (DMSO) and standard (Ibuprofen) on paw edema thickness

Inflammation was produced by subcutaneous injection of undiluted egg white (0.1 mL) into the planter side of the hind paw of the rats 30 minutes after i.p. injection of the drugs or their vehicle. Vernier caliper measured the paw width at seven-time intervals (0, 30, 60, 120, 180, 240, and 300 minutes) after drug injection.[27] The data was manifested as the mean ± SEM and results were analyzed for statistical significance using independent t-test to assess the significant differences between the means of two groups and one-way ANOVA and least significant differences (LSD) post hoc test were performed to assess significant differences among means. $p < 0.05$ is considered statistically significant.

RESULT AND DISCUSSION

Comparison of the Effect of Standard Drug Versus Control (DMSO)

At zero and 30 minutes, there is no significant difference in paw edema thickness reduction when compared to control (DMSO) with standard (Ibuprofen). At times 60, 120, 180, 240, and 300 minutes the standard showed a significant reduction in paw edema thickness compared with control as shown in Figure 1 and Table 2.

Comparison of the Effect of the Control versus Final Synthesized Compounds

At 0, 30, and 60 minutes there is no significant difference between the control and final synthesized compounds (5-8). Compounds (5, 6) at time 120–300 minutes showed a significant difference in reduction of paw edema thickness when compared to control. At the same time compounds (7, 8) showed a moderate difference in reduction in paw edema thickness when compared to control, as shown in Figure 2 and Table 3.

Comparison of the Effect of the Standard versus Final Synthesized Compounds

As shown in Figure 3 and Table 4 show no significant difference between the final synthesized compounds and standard (Ibuprofen) at times 0, 30, 60, and 120 minutes. At times 180, 240, and 300 minutes, the compounds (5, 6) showed significant activity in reducing paw edema thickness more than standard.

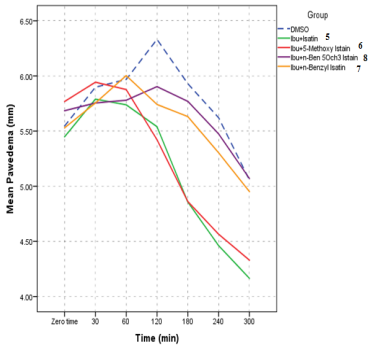


Figure 2: Effect of control and final synthesized compounds (ibuprofen derivatives) on reduction paw edema thickness.

Table 3: Effect of control and final synthesized compounds on reduction paw edema thickness

Paw edema thickness (mm)					
Time (min)	*DMSO*	*Ibuprofen-Isatin der. (5)*	*Ibuprofen-5-methoxy isatin der. (6)*	*Ibuprofen- n-benzylisatin der. (7)*	*Ibuprofen- n-benzyl-5-methoxyisatin der. (8)*
Zero time	5.54 ± 0.10ab	5.44 ± 0.13b	5.76 ± 0.10a	5.53 ± 0.06ab	5.68 ± 0.18ab
30	5.89 ± 0.25ab	5.79 ± 0.19b	5.94 ± 0.06a	5.75 ± 0.12ab	5.75 ± 0.12ab
60	5.96 ± 0.12a	5.73 ± 0.13a	5.87 ± 0.02a	6.00 ± 0.19a	5.78 ± 0.07a
120	6.33 ± 0.15a	5.54 ± 0.04bc	5.42 ± 0.10c	5.74 ± 0.13bc	5.90 ± 0.18b
180	5.93 ± 0.19a	4.85 ± 0.09b	4.86 ± 0.16b	5.63 ± 0.11a	5.77 ± 0.21a
240	5.62 ± 0.17a	4.46 ± 0.05b	4.56 ± 0.11b	5.30 ± 0.09a	5.47 ± 0.07a
300	5.05 ± 0.17a	4.16 ± 0.04b	4.33 ± 0.06b	4.95 ± 0.06a	5.07 ± 0.10a

Table 4: Effect of standard (Ibuprofen) and final synthesized compounds on reduction paw edema thickness.

	Paw edema thickness (mm)				
Time (min)	*Ibuprofen*	*Ibuprofen –Isatin der. (5)*	*Ibuprofen -5-methoxy isatin der. (6)*	*Ibuprofen -n-benzyl isatin der. (7)*	*Ibuprofen -n-benzyl 5-methoxy isatin der. (8)*
Zero time	5.46 ± 0.12b	5.44 ± 0.13a	5.76 ± 0.10a	5.53 ± 0.06a	5.68 ± 0.18a
30	5.46 ± 0.19b	5.79 ± 0.19ab	5.94 ± 0.06a	5.75 ± 0.12ab	5.75 ± 0.12ab
60	5.18 ± 0.19b	5.73 ± 0.13a	5.87 ± 0.02a	6.00 ± 0.19a	5.78 ± 0.07a
120	5.02 ± 0.14c	5.54 ± 0.04ab	5.42 ± 0.10b	5.74 ± 0.13ab	5.90 ± 0.18a
180	5.09 ± 0.11b	4.85 ± 0.09b	4.86 ± 0.16b	5.63 ± 0.11a	5.77 ± 0.21a
240	4.74 ± 0.08b	4.46 ± 0.05c	4.56 ± 0.11bc	5.30 ± 0.09a	5.47 ± 0.07a
300	4.54 ± 0.14b	4.16 ± 0.04c	4.33 ± 0.06bc	4.95 ± 0.06a	5.07 ± 0.10a

Table 5: The anti-microbial activity of final synthesized compounds at 100mg/mL concentration

Compound	*Inhibition zone in mm*				
	Gram-negative		*Gram-positive*		*Fungi*
	E. coli	*Pseudomonas aeruginosa*	*S. aureus*	*Streptococcus pyogenes*	*Candida albicans*
5	12	10	11	8	5
6	5	4	-	6	-
7	18	13	11	10	7
8	-	-	-	-	-
Ciprofloxacin*	30	28	27	27	-
Ampicillin*	20	24	26	18	-
Fluconazole**	-	-	-	-	22

*Standard for bacterial strains, ** Standard for fungi.
(----) = No activity, slightly active (inhibition zone between 5–10 mm), moderately active= (inhibition zone between 10–20 mm), highly active= (inhibition zone more than 20 mm).[28]

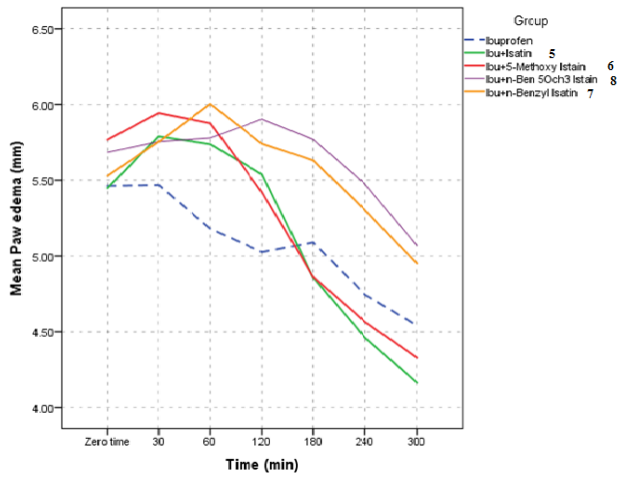


Figure 3: Effect of standard (Ibuprofen) and final synthesized compounds on reduction of paw edema thickness.

Evaluation of the Anti-microbial Activity of Targets Synthesized Compounds

The synthesized target compounds were evaluated for their anti-microbial activity by using well- diffusion method, against gram-negative and gram-positive bacteria as well as fungi. The anti-bacterial drugs were (ciprofloxacin and ampicillin), while the standard compound used as an antifungal agent was (Fluconazole). DMSO was used as a solvent and control.

As shown above, in Table 5, the compounds (5 and 7) have moderate antibacterial activity against gram-positive and gram-negative bacteria; the other compounds have weak activity. No antibacterial activity showed for compound (8) at 100 mg/mL concentration, and the most potent one is compound 7, while all these compounds showed lower effects compared to ciprofloxacin and ampicillin as standard drugs.

The compounds (5 and 7) exhibited lower antifungal activity when compared to fluconazole as a standard drug.

CONCLUSION

New ibuprofen-isatin derivatives have been successfully synthesized. The structure of all synthesized compounds was confirmed using FTIR and ^{1}HNMR spectroscopy, and their biological activity was evaluated for anti-inflammatory and anti-microbial properties. Compounds 5 and 6 significantly reduced paw edema thickness compared to ibuprofen. Furthermore, compounds 5 and 7 have moderate antibacterial activity compared to ciprofloxacin and ampicillin, whereas compounds 5 and 7 have low antifungal activity compared to fluconazole.

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