

Synthesis, Characterization and Preliminary Anti-inflammatory Evaluation of New Etodolac Derivatives

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Abstract

Three new hydrazone derivatives of Etodolac were synthesized and evaluated for their anti-inflammatory activity by using egg white induced paw edema method. All the synthesized target compounds were characterized by CHN- microanalysis, FT-IR spectroscopy, and ¹HNMR analysis. The synthesis of the target (P1-P3) compounds was accomplished following multistep reaction procedures. The synthesized target compounds were found to be active in reducing paw edema thickness and their anti-inflammatory effect was comparable to that of the standard (Etodolac).

Keywords: Etodolac hydrazone derivatives, Anti-inflammatory, Paw edema method.

تحضير وتشخيص وتقييم اولي لمشتقات جديدة للايتودولاك كمضادات للالتهاب

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الخلاصة

تم تحضير ثلاثة مشتقات هيدرازون جديدة للايتودولاك وتم تقييم فعاليتها المضادة للالتهابات باستخدام طريقة وذمة المخلب المستحث ببياض البيض. جميع المركبات المحضرة شخّصت بالتحليل الدقيق لذرات العناصر الكربون والهيدروجين والنتروجين، مطياف الأشعة تحت الحمراء وجهاز الرنين النووي المغناطيسي. وتم تحضير المركبات P1-P3 باتباع طرق تفاعلات متعددة الخطوات. وجدت المركبات المحضرة بان لها فعالية في تقليل سمك ورم المخلب وان تأثيرها المضاد للالتهابات كان مشابهها للايتودولاك. كلمات مفتاحية: مشتقات ايتودولاك هيدرازون، مضادة للالتهابات، طريقة وذمة المخلب.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds that are used for the treatment of various inflammatory conditions, pain and fever ⁽¹⁾. The principal mechanism of action of NSAIDs involves the inhibition of cyclooxygenase (COX) enzyme also known as prostaglandin-endoperoxide synthase (PTGS). COX is the enzyme that catalyzes the synthesis of prostanoids (Thromboxane and Prostaglandins) from arachidonic acid⁽²⁾. COX-inhibitors are believed to act as an analgesic ⁽³⁾, anti-inflammatory and antipyretic by decreasing prostaglandin synthesis⁽⁴⁾. This decrease in prostaglandin synthesis is associated with the occurrence of several unwanted effects accompanied with the use of NSAIDs, especially gastrointestinal (GI) irritation and ulceration. Additionally, several NSAIDs have a free carboxylic acid group ⁽⁵⁾; therefore, oral administration is linked with the side effects on the gastric system ⁽⁶⁾, which are due to direct GI

irritation. NSAIDs can be categorized by the site of action into nonselective (COX) inhibitors which target COX I and COX II and selective (COX) inhibitors that selectively target COX II though decrease gastric side effect that comes with COX I inhibitors ⁽⁷⁾. Etodolac (2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl) acetic acid) (Figure.1) which is a NSAID, is a derivative of pyrano - indoleacetic acid . It is recommended for the treatment of pain and inflammation caused by osteoarthritis and rheumatoid arthritis.

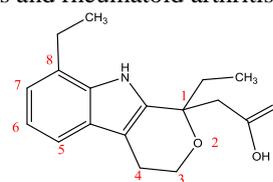


Figure (1) Chemical structure of etodolac

The carboxylic acid group of NSAIDs can be replaced with other groups while these agents still exert a potent anti-inflammatory activity ⁽⁸⁾.

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Hydrazones are an important class for new drug development and an exceptional class of organic compounds in the Schiff base family. They are synthesized by heating an appropriately substituted hydrazide with aldehydes or ketones in solvents like ethanol, methanol, tetrahydrofuran, butanol, with few drops of glacial acetic acid as a catalyst ⁽⁹⁾. Hydrazone have a wide range of biological activities like anti-bacterial, antiviral, antidepressant, cardioprotective activities and anticancer activities ⁽¹⁰⁾, alongside with anti-inflammatory action. This study focused on the synthesis of new Etodolac hydrazone derivatives and the evaluation of their anti-inflammatory activity.

Materials and Methods

Etodolac and different aldehydes were bought from HyperChem / China, while other chemicals and solvents (Ethanol, methanol, acetone, glacial acetic acid, concentrated H₂SO₄, hydrazine hydrate, n-hexane, petroleum ether, and ethyl acetate) were bought from commercial sources and used without further purification. Thin layer chromatography (TLC plates (254F) /Merck-Germany) was used to check reaction completion and purity of the product under UV light (254 nm). Melting points were measured (uncorrected) by using the capillary tube on Stuart SMP30 Electronic Melting Point Apparatus. CHN elemental microanalysis was carried out on Euro EA Elemental analyzer (Italy). IR spectra were recorded on FTIR-600 Spectrophotometer (Biotech engineering management, UK) using KBr disc. ¹H NMR spectra were recorded on BRUKER model Ultra shield 300 MHz spectrophotometer using DMSO-d₆ as a solvent.

Synthesis of etodolac ester [methyl 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano [3,4-b] indol-1-yl) acetate] (compound A)

A mixture of Etodolac (0.021 moles, 6g) and methanol (40 mL) in a 250 ml round bottom flask was stirred till a clear solution is achieved. The obtained solution was cooled to 0°C by using an ice bath and 3 mL of concentrated sulfuric acid (H₂SO₄) was added dropwise with continuous stirring, then, the mixture was set to reflux with stirring at 75°C for 5 h. After completion of the reaction (monitored by TLC (acetone: petroleum ether 5:5)), the solution was cooled down to room temperature, then it was thrown over 75 mL of cold distilled water, followed by the addition of saturated sodium bicarbonate solution (5% w/v) in order to neutralize the excess acid. A yellowish precipitate of Etodolac methyl ester was produced. The precipitate was collected by filtration, washed with chilled distilled water and dried, then recrystallized from ethanol. Yellowish powder, **yield** = 67%, **m.p.** (128-130°C). **R_f** = 0.78 (Acetone 5: Petroleum Ether 5). **IR** (KBr disc), (ν cm⁻¹): 3379: (NH) str. of Indole, 3062: Aromatic (C-H) str., 2968: (C-H) asymm. str. of CH₃ and CH₂, 2875: (C-H) symm. str. of CH₃ and CH₂, 1709:

(C=O) str. of ester, 1236: (C-O-C) str. of ether. **¹H NMR**: (300 MHz, DMSO-d₆, δ =ppm): 0.62 (3H, t, -CH₂-CH₃ at C1), 1.26 (3H, t, -CH₂-CH₃ at C8), 1.9-2.11 (2H, m, -CH₂-CH₃ at C1), 2.5-3.04 (6H, m, -CH₂-CH₃ at C8, -CH₂-COOCH₃ at C1 and -CH₂ at C4), 3.56 (3H, s, -COOCH₃), 3.80 (2H, dd, -CH₂ at C3), 6.79- 7.00 (2H, m, Ar-H5, H6), 7.23 (1H, d, Ar-H7), 10.48 (1H, s, Indole, N-H).

Synthesis of etodolac hydrazide (2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b] indol-1-yl) acetohydrazide) (compound B)

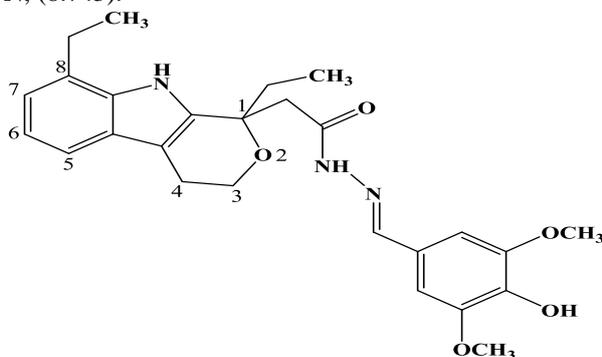
To a solution of compound A (0.02 moles, 6 g) in absolute ethanol (70 mL), an excess amount of hydrazine hydrate 80% (0.2 moles, 10mL) was added, and the mixture was refluxed at 80 °C for 6 h. At the end of the reflux time, the mixture was left to be cooled down to room temperature (r.t.), then cold distilled water was added to the mixture, a white precipitate was formed which was left overnight. The obtained precipitate was filtered, washed several times with cold distilled water, dried and recrystallized from ethanol. White powder, **yield** = 88%, **m.p.** (187-189 °C). **R_f** = 0.41 (Acetone 5: Petroleum Ether 5). **IR** (KBr disc), (ν cm⁻¹): 3354, 3313: (NH) str. of Indole and hydrazide, 3062: Aromatic (C-H) str., 2970: (C-H) asymm. str. of CH₃ and CH₂, 2875: (C-H) symm. str. of CH₃ and CH₂, 1655: (C=O) str. of amide, 1620: (NH) bend., 1242: (C-O-C) str. of ether. **¹H NMR**: 0.61 (3H, t, -CH₂-CH₃ at C1), 1.25 (3H, t, -CH₂-CH₃ at C8), 2.04 (2H, q, -CH₂-CH₃ at C1), 2.61-2.9 (6H, m, CH₂-CONHNH₂, -CH₂-CH₃ at C8, -CH₂ at C4), 3.95 (2H, dd, -CH₂ at C3), 4.25 (2H, b.s. NH-NH₂), 6.80-6.98 (2H, m, Ar-H5, H6), 7.22 (1H, d, Ar-H7), 8.92 (1H, s, NH-NH₂), 10.54 (1H, s, Indole N-H).

Synthesis of aryl hydrazones 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b] indol-1-yl) acetohydrazide derivatives (P1 - P3)

Three drops of glacial acetic acid were added to an ethanolic solution of each of the following aldehydes (scheme 1): (1) [3,5-dimethoxy-4-hydroxybenzaldehyde (0.005 moles, 0.91g)], (2) [4-hydroxy-3-nitrobenzaldehyde (0.005 moles, 0.84g)], (3) [2-pyridine carboxaldehyde (0.005 moles, 0.6g)], placed in round bottom flask equipped with magnetic stirrer. Compound B (0.005 moles, 1.55g) dissolved in absolute ethanol (20mL) was added to a stirred solution of each of the above mentioned aldehydes mixtures separately. Then each reaction mixture was refluxed at 80 °C for 8 h. At the end of the reaction (monitored by TLC), 50 mL of cold ice water was added to the mixture. The precipitate formed was collected, dried and recrystallized from solvents (80% ethanol for P2, 70%, 75% ethanol for P1 and P3 respectively) to get the intended products.

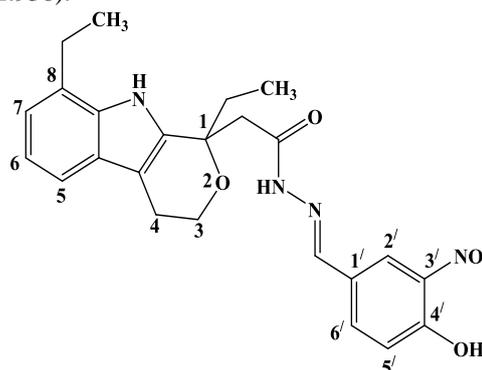
(P1) 2-(1,8-diethyl-1,3,4,9-tetrahydropyranof[3,4-b]indol-1-yl) - N' - (4-hydroxyl-3,5-dimethoxy-benzylidene) acetohydrazide.

White powder, **Yield** = 81%, **m.p.** (173-175 °C). **R_f** = 0.46 (Ethyl acetate 6: n-Hexane 4). **IR** (KBr disc), (ν cm⁻¹):3555-3210: (OH) str. broad band, 3377, 3271: (NH) str. of Indole and hydrazone,3060: Aromatic (C-H) str.,2964: (C-H) asymm. str. of CH₃ and CH₂. 2875: (C-H) symm. str. of CH₃ and CH₂, 1641: (C=O) str. of amide.1589: (C=N) str., 1512: Ar. (C=C) str., 1213: (C-O-C) str. of ether. **¹H NMR**: 0.59,0.68(3H, tt, -CH₂-CH₃ at C1), 1.25 (3H, t, -CH₂-CH₃ at C8), 2.07 (2H, q, -CH₂-CH₃ at C1), 2.66 (2H, q, -CH₂-CH₃ at C8),2.77-3.04 (4H, m, -CH₂CONH, -CH₂ at C4), 3.74, 3.79 (6H, 2s, 2-OCH₃), 3.99 (2H, dd, -CH₂ at C3), 6.85-7.0, 7.19-7.29 (5H, 2m, Ar-H), 7.88, 8.08 (1H, ss, N=CH), 8.85 (1H, bs, OH), 10.50 (1H, s, Indole N-H), 11.0, 11.22 (1H, ss, -CO-NH). **CHN**: C₂₆H₃₁N₃O₅, M.wt:465.55, **Calculated** C;(67.08), **H**; (6.71),**N**; (9.03). **Observed** C;(68.88), **H**;(6.483), **N**; (8.743).

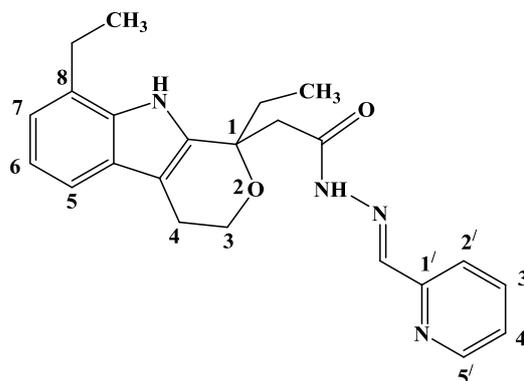
**(P2) 2-(1,8-diethyl-1,3,4,9-tetrahydropyranof[3,4-b] indol-1-yl)-N'-(4-hydroxy-3-nitro-benzylidene) acetohydrazide.**

Pale yellow powder, **Yield**=77%, **m.p.** (122-125 °C). **R_f** = 0.83 (Ethyl acetate 4: n-Hexane 6). **IR** (KBr disc), (ν cm⁻¹):3417, 3249: NH str. of Indole and hydrazone overlapping with (OH) str. of Phenol,3089: Aromatic (C-H) str., 2964: (C-H) asymm. str. of CH₃ and CH₂, 2875: (C-H) symm. str. of CH₃ and CH₂, 1666: (C=O) str. of amide, 1622: (C=N) str., 1522: Ar. (C=C) str. and asymm. (NO₂) str., 1323: symm. (NO₂) str., 1257: (C-O-C) str. of ether. **¹H NMR**: 0.59, 0.66 (3H, tt, -CH₂-CH₃ at C1), 1.25(3H, t, -CH₂-CH₃ at C8), 2.10 (2H, q, CH₂-CH₃ at C1), 2.66 (2H, q, CH₂-CH₃ at C8), 2.83-2.99 (4H, m, -CH₂CONH at C1, -CH₂ at C4), 3.98 (2H, dd, -CH₂ at C3), 6.84-6.97 (2H, m, Ar-H5, H7), 7.12-7.28 (2H, m, Ar-H6, H5'), 7.83 (1H, dd, Ar-H6'), 7.93, 8.08(1H, ss, N=CH), 8.18 (1H, s, Ar-H2'), 8.93 (1H, bs, OH), 10.48 (1H, s, Indole N-H), 11.17, 11.34 (1H, ss, -CO-NH). **CHN**: C₂₄H₂₆N₄O₅, M.wt:450.50. **Calculated** C; (63.99), **H**; (5.82), **N**;

(12.44). **Observed** C; (62.634), **H**; (6.027), **N**; (12.938).

**(P3) 2-(1,8-diethyl-1,3,4,9-tetrahydropyranof[3,4-b]indol-1-yl)-N'-(pyridin-2-ylmethylene) acetohydrazide.**

Off-white powder, **Yield** = 54%, **m.p.** (148-153 °C). **R_f** = 0.61 (Ethyl acetate 6: n-Hexane 4). **IR** (KBr disc), (ν cm⁻¹):3298, 3247: (NH) str. of Indole and hydrazone, 3053: Aromatic (C-H) str., 2964: (C-H) asymm. str. of CH₃ and CH₂, 2873: (C-H) symm. str. of CH₃ and CH₂, 1672: (C=O) str. of amide, 1606: (C=N) str., 1556: Ar. (C=C) str., 1230: (C-O-C) str. of ether. **¹H NMR**: 0.59, 0.68 (3H, tt, -CH₂-CH₃ at C1), 1.26 (3H, t, -CH₂-CH₃ at C8), 2.11 (2H, q, CH₂-CH₃ at C1), 2.61-2.73, 2.82-3.01 (6H, 2m, CH₂-CH₃ at C8, -CH₂CONH at C1, -CH₂ at C4), 4.06 (2H, dd, -CH₂ at C3), 6.82-7.00 (2H, m, Ar-H5, H6), 7.23 (1H, d, Ar-H7), 7.33-7.45 (1H, m, Ar-H4'), 7.50-7.59 (1H, m, Ar-H3'), 7.78-7.92 (1H, m, Ar-H2'), 8.03, 8.22 (1H, ss, N=CH), 8.53-8.63 (1H, m, Ar-H5'), 10.50 (1H, s, Indole N-H), 11.40, 11.51 (1H, ss, -CO-NH). **CHN**:C₂₃H₂₆N₄O₂, M.wt:390.49, **Calculated** C; (70.75), **H**; (6.71), **N**; (14.35), **Observed** C; (69.722), **H**; (7.006), **N**; (14.868).

**Evaluation of the anti-inflammatory activity (II)**

Albino rats of both sexes weighing (190 ± 10 g) were delivered by the animal house of the College of Pharmacy, University of Baghdad, and are kept in the same place under consistent conditions. Animals

were fed commercial chaw and had access to water freely. Animals were divided into five groups (each group consists of 6 rats) including standard (Etodolac), control (DMSO) and P1, P2 and P3 groups. Dose determination of the final synthesized compounds (Table 1) was done according to the equation below, Egg white induced edema model⁽¹²⁾ was used to study the anti-inflammatory activity of the target compounds. This was achieved by the administration of an intraperitoneal (i.p) injection of each of the final products, Etodolac or control, individually to the five animal groups. Thirty minutes after that subcutaneous injection (S.C.) of 0.05 mL of undiluted egg-white was injected into the plantar side of the left hind paw of the rats of each group. Vernea was used to measure paw thickness at six-time intervals (0, 30, 60, 120, 180, and 240 min.), where zero time was the time at which the products, standard, and control were administered intra-peritoneally.

$$\frac{\text{Dose of Reference Compound}}{\text{Molecular weight of reference compound}} = \frac{\text{Dose of tested compound}}{\text{Molecular weight of tested compound}}$$

Table (1) Doses determined for the synthesized final products

Product no.	M.wt.	Dose mg/kg
Etodolac (Std.)	287.359	10^(a)
P1	465.550	16.20 ^(b)
P2	450.495	15.68 ^(b)
P3	390.487	13.59 ^(b)

(a)The standard dose for Etodolac in mg/kg.

(b)The determined dose which is equivalent to Etodolac dose.

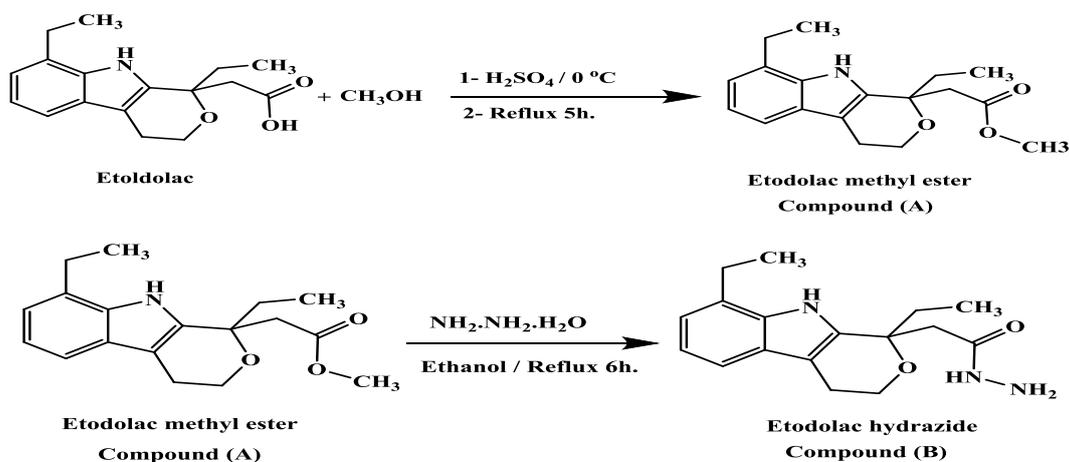
Multiple comparisons between the synthesized target compounds against control and reference drug were done using one-way ANOVA test, then to see the significance between each pair of compounds, post hoc Tukey test was used, which offers an advantage over the use of independent t-test for more powerful accuracy for calculating the p-value. Graph Pad Prism 8.0.0 program was used to carry out the statistical analysis.

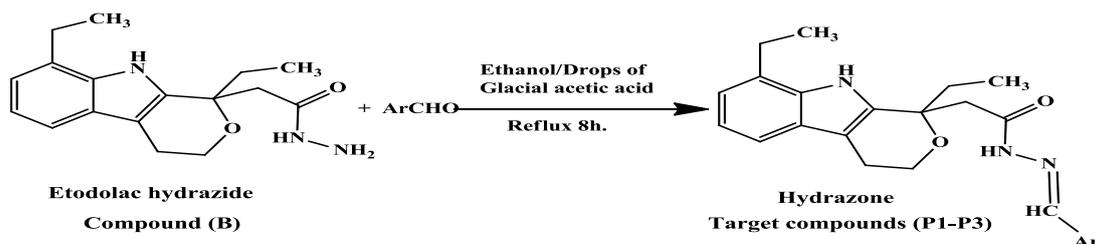
Results and Discussion

Chemistry

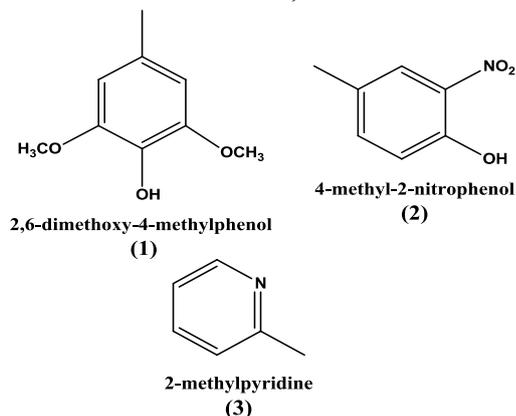
The synthetic pathways used for the preparation of the target Etodolac hydrazone derivatives (P1-P3) are summarized in scheme (1).

Etodolac methyl ester Compound (A) was synthesized by the reaction of Etodolac with methanol along with the use of few drops of concentrated H₂SO₄. Compound (B) was synthesized by the reaction of Etodolac methyl ester with hydrazine hydrate (NH₂NH₂.H₂O). The synthesis of the final Etodolac hydrazone derivatives involves the reaction of Etodolac hydrazone with different types of aldehydes by using glacial acetic acid as a catalyst.





ArCHO: are listed below;



Scheme (1) The synthesis of target compounds (P1-P3).

The structures of all the synthesized compounds were characterized by FT-IR, ¹HNMR and CHN elemental microanalysis. The infrared spectra of the hydrazone derivatives (P1-P3) showed the characteristic absorption band at (1641-1672) cm⁻¹ due to (C=O) stretching of amide as well as the appearance of bands at (1589-1622) cm⁻¹ attributed to the (C=N) stretching of the imine. Additionally, two other absorption bands were displayed at (3298-3417) cm⁻¹ and (3247-3271) cm⁻¹ attributed to (N-H) stretching of indole and hydrazone, respectively.

The ¹HNMR spectra of the target compounds (P1 - P3) confirmed the synthesis of hydrazone derivatives. Characteristic signals of hydrazone were shown in the region (7.83-8.22 ppm) as two singlets attributed to the azomethine proton N=CH, another characteristic signal of hydrazone due to -CO-NH proton was displayed as two singlets resonating at 11.00-11.54 ppm, in addition to the loss of signal at 4.25 ppm for the two hydrazone protons NH-NH₂.

Generally, hydrazones may exist as E and Z geometrical isomers⁽¹²⁾. This explains the appearance of each of azomethine N=CH and CO-NH proton as two singlets.

Evaluation of the anti-inflammatory activity

Comparison of reference drug (Etodolac) versus control (DMSO)

At baseline and after 30 minutes, there was no significant difference between control and etodolac in paw edema reduction, but after 60 minutes the difference becomes significant in which etodolac offer more reduction in the percent paw thickness compared to the control. Further reduction was continued significantly at 120 minutes, up to 240 minutes as shown in Figure (2) below;

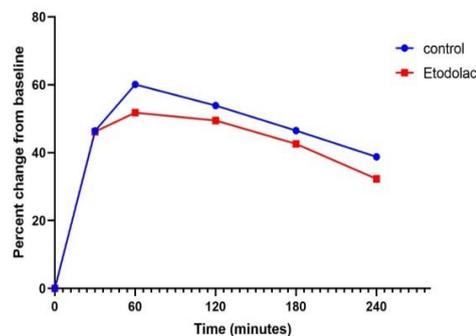


Figure (2) Effect of etodolac (reference), and dimethyl sulfoxide (control) on egg-white induced paw edema in rats measured in percentage.

Note: Time (30) min. is the time of egg-white injection.

Comparison of the effect of synthesized compounds P1, P2 and P3 versus control

No significant difference was found between the target compounds compared to the control at baseline and after 30 minutes. However, compound (P3) produced a significant difference in the reduction of paw thickness at 60, 180 and 240 minutes compared to the control. Whereas, a significant difference compared to the control in percent reduction of paw thickness was shown for compound (P2) at 120 and 240 minutes. These results are shown in table (2) and figure (3).

Table (2) Effect of dimethyl sulfoxide (control) and target compounds (P1-P3) on egg-white induced paw edema

	Time (min)	Control n=6	P1 n=6	P2 n=6	P3 n=6
Paw thickness (mm)	0	3.77±0.10	3.78±0.13	3.65±0.09	3.70±0.07
	30	5.51±0.09	5.24±0.16	4.98±0.10	5.04±0.18
	60	6.03±0.18	5.68±0.14	5.53±0.08	5.36±0.14*
	120	5.80±0.22	5.56±0.12	5.08±0.08*	5.22±0.13
	180	5.52±0.18	5.31±0.11	4.92±0.14	4.85±0.08*
	240	5.23±0.12	4.97±0.14	4.57±0.09*	4.58±0.09*

Data are expressed in mm paw thickness as mean ± SEM.

n= number of animals.

Time (0) is the time of i.p. injection of tested compounds, and DMSO (2ml/kg)

Time (30) is the time of injection of egg-white (induction of paw edema).

Significantly different compared to control: p-value * < 0.033 (GP system)

Comparison of the effect of synthesized compounds P1, P2 and P3 versus etodolac

There was no significant difference in the reduction of paw thickness between the synthesized target compounds compared to Etodolac at baseline

and after 30, 60, 120, 180 and 240 minutes. All the synthesized compounds produce reduction in paw thickness which was comparable to the standard (Etodolac) as presented in table (3) and figure (3).

Table (3) Effect of etodolac (reference) and target compounds (P1-P3) on egg-white induced paw edema

	Time (min)	Etodolac n=6	P1 n=6	P2 n=6	P3 n=6
Paw Thickness (mm)	0	3.51±0.11	3.78±0.13	3.65±0.09	3.70±0.07
	30	4.70±0.09	5.24±0.16	4.98±0.10	5.04±0.18
	60	5.33±0.12	5.68±0.14	5.53±0.08	5.36±0.14
	120	5.24±0.08	5.56±0.12	5.08±0.08	5.22±0.13
	180	5.00±0.17	5.31±0.11	4.92±0.14	4.85±0.08
	240	4.64±0.13	4.97±0.14	4.57±0.09	4.58±0.09

Data are expressed in mm paw thickness as mean ± SEM.

n= number of animals.

Time (0) is the time of i.p. injection of tested compounds, and Etodolac.

Time (30) is the time of injection of egg-white (induction of paw edema).

Note: In this case all compounds with no significant difference compared to Etodolac

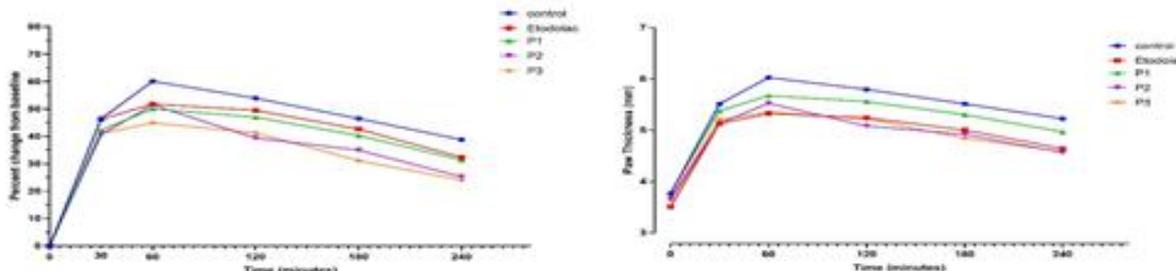


Figure (3) Effect of etodolac, dimethyl sulfoxide (DMSO), compounds P1, P2, and P3 on egg-white induced paw edema in rats. Results are expressed as mean ± SEM & Percent. (n=6 for each group).

Note: Time (30) is the time of egg-white injection.

Conclusion

Three new etodolac hydrazone derivatives (P1-P3) were synthesized, and their structures were characterized by FT-IR, ¹HNMR and CHN microanalysis. The compounds synthesized in this study exhibited anti-inflammatory action when tested on rats by using egg white induced paw edema and showed comparable effect as the used standard drug (Etodolac) with no significant difference.

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