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Original Article

Synthesis of Imidazolidine Derivatives by Three Components Reaction as a Novel Non-Steroidal Anti-Inflammatory Drugs

Usama Hamid Ramadhan[1] and Niran Jassim Al-Salihi[2]

ABSTRACT

There are many types of non-steroidal anti-inflammatory drugs (NSAID) act on one or more of cyclooxygenase enzymes (COX), there are at least three types of COX, which is COX-1, COX-2, and COX-3. They are responsible of inflammation and pain. The new compounds has been achieved by Three component reaction by mixed of amino acid (L-tyrosine), triethoxymethane and glycine in acetic anhydride with refluxed to give (compound 1) 3-(4-hydroxy phenyl)-2-(1H-imidazolidine-4-one-3-yl) propanoic acid. In the same way, compounds 2, 3, 4, and 5 were prepared by using the following amino acids: L-asparagine, L-histidine, L-tryptophan and glycine respectively to give 3-carbamido-2-(1H-imidazolidine-4-one-3-yl) propanoic acid (compound 2), 3-(1H-imidazole-5-yl)-2-(1H-imidazolidine-4-one-3-yl) propanoic acid (compound 3), 3-(1H-indole-3-yl) -2- (1H- imidazolidine- 4- one -3 - yl) propanoic acid (compound 4) and 2-(1H-imidazolidine-4-one-3-yl) ethanoic acid (compound 5). Compounds were identifying by CHNS analysis, FT-IR and H^1 NMR. The results certified the chemical structures of the compounds. The compounds were studied by two different tests the hot plate test and writhing test for analgesic activity, and two tests for anti-inflammatory activity they are formalin induced inflammation test and carrageenan induced inflammation test. The compounds were found out, has potent anti-inflammatory and anti-nociceptive activity. The compounds were tested to acute toxicity and fond that they are safety to the dose 5 g/kg orally in mice without any mortality, and suitable for use as new non-steroidal anti-inflammatory drugs.

Key words: Imidazolidine derivatives, Anti-inflammatory agents, Analgesic agents, Anti-nociceptive agents.

INTRODUCTION

The non-steroidal anti-inflammatory drugs (NSAIDs) have been part of our clinical practice. They started out as drugs with anti-inflammatory and analgesic action and gradually used has been expanded to new therapeutic targets. Although NSAIDs share many common properties, their use poses risks, and physicians should be cognizant of their subtle differences and potential complications.[1] The pain is defined as an unpleasant sensation that can be either acute or chronic and that is a consequence of complex neural chemical processes in the peripheral & central nervous system.[2] It acts as a warning signal against disturbances either in the body or in the external environment of an individual. The main objective of treating pain is removal or abolishing its cause. Opioids are the potent & commonly used drugs for pain but are associated with a greater degree of adverse effects. Antidepressant drugs are widely used in management of chronic pain.[3] Ever since the discovery of aspirin, small molecule therapeutics has been widely prescribed to treat inflammation and pain. Aspirin and several small molecule NSAIDs are known to inhibit the enzymes cyclooxygenase-1 (COX-1) and -2 (COX-2). Despite the success of NSAIDs to treat inflammatory disorders, the development of a clinically useful small molecule NSAIDs with decreased side effect profiles is an ongoing effort. The recent discovery and development of selective COX-2 inhibitors was a step toward this direction.[4] Recently the histidine derivatives found potent activity as anti-inflammatory and anti-nociceptive because they are an imidazole compounds.[5] Three-component reactions have emerged as useful methods for the synthesis of compounds because the combination of three components to generate new products in a single step is extremely economical, among the multi-component reactions. The usefulness and importance of these processes is underscored by the large number of articles were published.[6]

METHODS

Imidazolidine derivatives preparation

The synthesis cared by three components reaction of amino acid, triethoxymethane and glycine in a good yield. A mixture of L-tyrosine (1.8 gm, 0.01 mol), triethoxymethane (2.5 ml, 0.01 mol) and (0.75 gm, 0.01 mol) of glycine in acetic anhydride (25 ml) were refluxed for (2 hr). The resulting solid, which formed on cooling, were collected by filtration, the precipitate product were filtered and crystallized from methanol to give compound 1.[7,8]

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Usama Hamid Ramadhan[1] and Niran Jassim Al-Salihi[2]

[1]Department of Laboratories Clinical Sciences College of pharmacy, university of Basrah, Basrah, IRAQ.
[2]Department of Chemistry, College of science, university of Basrah, Basrah, IRAQ.

Correspondence

Usama Hamid Ramadhan

Department of Laboratories Clinical Sciences, College of pharmacy, university of Basrah, Basrah, IRAQ.

Phone no: +9647709026140

E-mail: usama_ramadhan@yahoo.com

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3-(4-hydroxy phenyl)-2-(1H-imidazolidine-4-one-3-yl) propanoic acid **(1)** white powder, yield 97.6%; mp, 237 °C; IR (KBr) υ_{max} cm^{-1}: 1407, 1600 (C=O), 1512, 2600, 3206 (N-H), 2897, 2940, 2960 (aliphatic C-H), 3100 (aromatic C-H), 3440 (O-H); ^{1}H-NMR (acetone) δ, ppm: 13 (1H, s, COOH), 8.19 (1H, s, NH), 7.19-6.76 (4H, m, Ar-H), 4.81 (2H, s, NCH_2N), 4.17 (2H, s, $COCH_2N$), 3.43 (1H, m, CH), 3.24 q,3.13 q (2H, CH2, ABX system), 5.23 (1H, q, phenolic-OH). Anal. calcd for $C_{12}H_{14}N_2O_4$: C, 57.6; H, 5.6; N, 11.2. Found: C, 56.48; H, 5.3; N, 11.8.

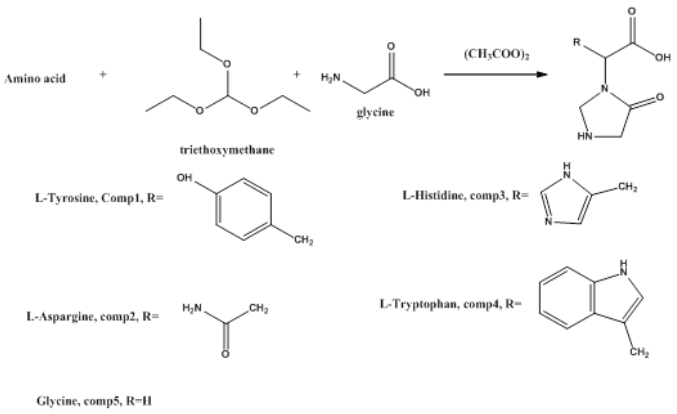
In the same way, compounds 2, 3, 4, and 5 were prepared by using L-asparagine, L-histidine, L-tryptophan and glycine respectively to give:

4-amino-4-oxo-2-(1H-imidazolidine-4-one-3-yl) butanoic acid **(2)** white powder, yield 99%; mp, 202 °C; IR (KBr) υ_{max} cm^{-1}: 1411, 1600 (C=O), 1520, 2610, 3100, 3160, 3382 (N-H), 2925, 2970 (aliphatic C-H), 3448 (O-H); ^{1}H-NMR (DMSO) δ, ppm: 2.94 (1H, s, NH), 7.7 (2H, s, NCH_2N), 6.99 (2H, s, $COCH_2N$), 2.72 (1H, q, CH), 2.3 (2H, q, CH2). Anal. calcd for $C_7H_{11}N_3O_4$: C, 41.74; H, 5.46; N, 20.87. Found: C, 40.43; H, 5.62; N, 20.21.

3-(1H-imidazole-5-yl)-2-(1H-imidazolidine-4-one-3-yl) propanoic acid **(3)** white powder, yield 93.7%; mp, 235-236 °C; IR (KBr) υ_{max} cm^{-1}: 1411, 1596, 1618 (C=O), 1519, 2614, 3425 (N-H), 2898, 2970 (aliphatic C-H), 3425 (O-H); ^{1}H-NMR (acetone) δ, ppm: 8.2, 5.5q (NH), 7.71 (1H, s, CH=C), 4.83 (2H, s, NCH_2N), 4.17 (2H, s, $COCH_2N$), 3.75 (1H, m, CH), 2.63-2.75 (2H, d, CH2), 9.02 (1H, d, CH=N). Anal. calcd for $C_9H_{12}N_4O_3$: C, 45.13; H, 5.01; N, 23.40. Found: C, 45.74; H, 5.19; N, 23.17.

3-(1H-indole-3-yl)-2-(1H-imidazolidine-4-one-3-yl) propanoic acid **(4)** white powder, yield 85.2%; mp, 244-246 °C decomposition; IR (KBr) υ_{max} cm^{-1}: 1409, 1593, 1602 (C=O), 1521, 2611, 3160, 3402 (N-H), 2925, 2975 (aliphatic C-H), 3010, 3050 (aromatic C-H); ^{1}H-NMR (DMSO) δ, ppm: 10.88 (1H, s, COOH), 7.19 (1H, s, indole NH), 7.02 (4H, m, Ar-H), 7.55 (2H, s, NCH_2N), 7.33 (2H, d, $COCH_2N$), 2.9 (1H, s, CH), 2.95 (2H, s, CH2). Anal. calcd for $C_{14}H_{15}N_3O_3$: C, 61.52; H, 5.49; N, 15.3. Found: C, 60.92; H, 5.71; N, 15.52.

2-(1H-imidazolidine-4-one-3-yl) ethanoic acid **(5)** white powder, yield 97.2%; mp, 244 °C; IR (KBr) υ_{max} cm^{-1}: 1406, 1598, 1610 (C=O), 1525, 2616, 3169 (N-H), 2900, 2956 (aliphatic C-H), 3400 (O-H); ^{1}H-NMR (acetone) δ, ppm: 12.35 (1H, s, COOH), 8.28 (1H, s, NH), 4.84 (2H, s, NCH_2N), 4.18 (2H, s, $COCH_2N$), 2.7 (2H, s, CH2). Anal. calcd for $C_5H_8N_2O_3$: C, 41.6; H, 5.55; N, 19.4. Found: C, 41.13; H, 5.78; N, 18.96.



Scheme 1: The reaction and the chemical structures of compounds.

Pharmacology part

Animals

Male and female albino mice (20-30 gm) were obtain from animal house of university of Basrah, college of sciences. Animals were house in colony room (12/12 h) light/ dark cycle at (23 ± 2°C) and had free access to food and water. Mice were divided into groups of six in each experiment (n= 6, 3 male and 3 female).

Drugs preparation

The drugs were used in the experiments were diluted in away to obtained injection volume of (0.2 ml). Each drug was dissolved in appropriate solvent as following: aspirin and diclofenac in water; carrageenan 1% in normal saline; acetic acid 0.7% in water; formalin 1% in water.

Anti-nociceptive activity

Hot plate test

A mouse was place on a hot plate maintained at (55 ± 1°C) and the latency of its reaction to this nociceptive stimulus (number of seconds before it licked its paw or jumping) was quantify, with interruption time of (20 sec). The latency was measure just before (zero time) and 1, 2, 3, and 4 hours after injections. The hot plate test was carry out to assess the effects of agent on the thermal nociceptive threshold. The compounds was give orally (50 mg/kg) and control group received (0.2 ml, p.o.) distilled water. Aspirin (50 mg/kg, p.o.) and diclofenac (25 mg/kg, p.o.) were use as test standards.[9]

Writhing test

The anti-nociceptive effect was also evaluated by the writhing test, induced by acetic acid (0.7%) v/v (0.2 ml, i.p.) mice were placed in large glass beaker, and intensity of nociceptive was quantified by counting the total numbers of writhing occurring between zero and 30 min after stimulus injection. The writhing response consists of a contraction of the abdominal muscles together with a stretching of the hind limbs. The compounds (50 mg/kg, p.o.) were administered (1 h) before the nociceptive agent in treated group. Five minutes after the acetic acid injection, we observed the numbers of writhes for a period of 25 minutes. Control group was received (0.2 ml, p.o.) distilled water. Aspirin (50 mg/kg, p.o.) and diclofenac (25 mg/kg, p.o.) were use as test standards.[10]

Anti-Inflammatory activity

Formalin induced inflammation test

The inflammation was produce by subaponeurotic injection of (20 µl) of (1%) formaldehyde in the left hind paw of the mice on the first hour after the oral administration of the compounds (50 mg/kg, p.o.). The control group was received distilled water (0.2 ml, p.o.). Aspirin (50 mg/kg, p.o.) and diclofenac (25 mg/kg, p.o.) were use as references drugs. The changes in paw size was measured at zero and then at 1-hour intervals up to the 5-hour with a micrometer device.[11]

Carrageenan induced inflammation test

For the determination of effects on acute inflammation, carrageenan induced inflammation model was used. Inflammation was induce by sub-planter injection of a homogenous suspension of (1%) carrageenan in physiological saline (25 µl). Mice were orally give compounds in a single dose (50 mg/kg, p.o.) one hour before induction of paw inflammation. The control group was give aspirin (50 mg/kg, p.o.) and diclofenac (25 mg/kg, p.o.) one hour before induction, while the blank group was received distilled water (0.2 ml, p.o.) only. Paw oedema was measure in every mouse hourly during four hours after induction with a micrometer device.[12]

Statistical analysis

All values in the tables and figures are express as mean ± standard error. Comparison between groups made by analysis of variance student's t-test (2-tailed, 3-typed) two-tailed distribution, two-sample unequal variance,

with Microsoft Excel software. Differences with P<0.05 or less between experimental groups were consider statistically significant.[13,14]

Acute toxicity

In order to verify the LD_{50}, mice (n=10; 5 male and 5 female) in each group administered the material (1, 3 and 5 gm/kg; p.o.) dissolved in (0.5 ml) distilled water, control group received (0.5ml) distilled water only. The mortality was observe during 48 hours.[15]

RESULTS AND DISCUSSION

The H^1 NMR characteristics of compounds (1-5), the COOH appears between (13-10.88 ppm), the NH bands between (8.28-5.5 ppm). Two bands for the imidazolidine appear between (7.7-4.17 ppm). The phenol group because hydrogen bonding appear at (5.23 ppm), the other aliphatic groups appears between (3.49-2.3 ppm). Compound 3 show two bands for the imidazole in histidine at (9.02 and 5.5 ppm). The appendix shows the spectra of NMR of the compounds. Figure 5-9 shown the H-NMR spectra of the compounds.

Table 1 and Figure 1 show the results of hot plate test of imidazolidine derivatives. All the derivatives show significant effect at different hours except compound 3.

Table 2 and Figure 2 show the results of writhing test of imidazole derivatives, compounds (3, 4, 5) show significant effect. Only compound 5 show high significant activity as analgesic.

Table 3 and Figure 3 show the results of formalin induced inflammation test of imidazole derivatives. All derivatives show significant effect

Table 1: Hot plate tests of imidazolidine derivatives

comp.	latency time in sec on hot plate				
	0 h	1 h	2 h	3 h	4 h
control	3.4±1.37	3.7±1.5	4.4±1.75	5.6±2.5	4±0.5
aspirin	2±1.0	4.8±1.25	9±1.5*	7.2±2.75	9.11±1.0*
diclofenac	3±0.5	7.8±3.25	14±2.5*	14.1±3.5*	9.6±3.5
1	6±1.33	5.6±1.5	11.6±3.1*	17.3±0.18^{3*}	10.6±2.4*
2	5.6±0.8	12.3±0.4^{3*}	10±1.3*	6.6±0.9	16.6±2.2^{2*}
3	6±0.6	6±1.3	6.3±1.7	8.3±2.4	5±0.66
4	4±1.1	12±1.3^{2*}	10.6±0.88^{2*}	7.6±1.7	15.6±1.5^{2*}
5	5.3±1.1	10±1.3^{2*}	9.3±1.1*	9.3±0.9	9±3.3

* =P<0.05; 2* =P<0.01; 3* =P<0.005

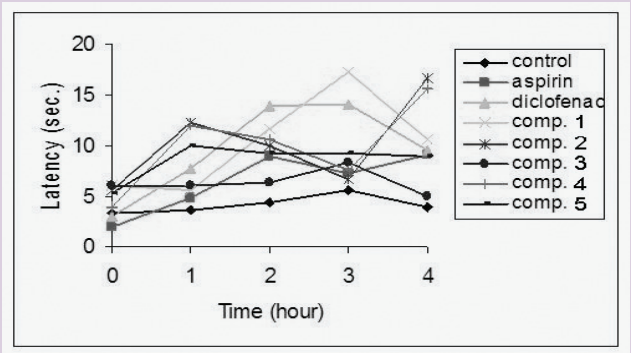


Figure 1: Hot plate tests of imidazolidine derivatives.

Table 2: The Writhing tests of the imidazolidine derivatives

control	aspirin	diclofenac	com.1	com.2	com.3	com.4	com.5
43±2	6.3±2.4^{5*}	10.6±2.4^{5*}	41±2.3	45±2.5	33±3.1*	31.5±4.2*	15±1.8^{5*}

* =P<0.05; 5* =P<0.0005

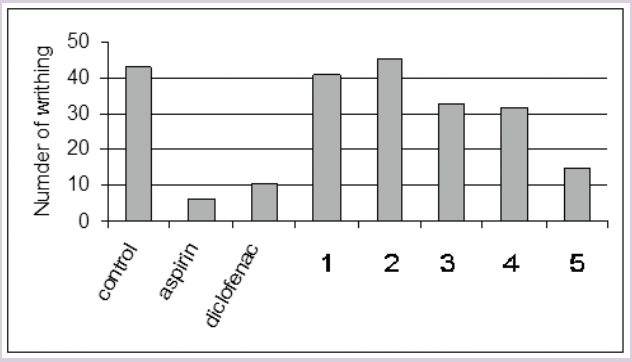


Figure 2: The Writhing tests of the imidazolidine derivatives.

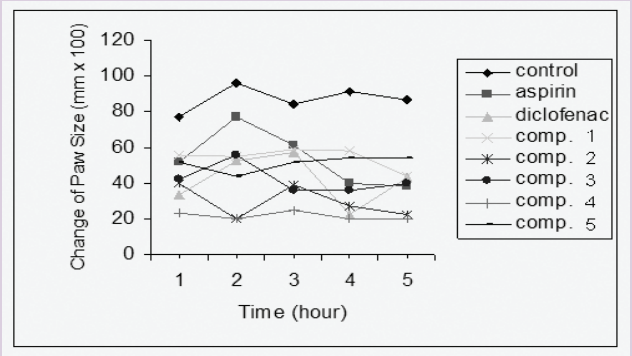


Figure 3: Formalin induced inflammation tests of imidazole derivatives.

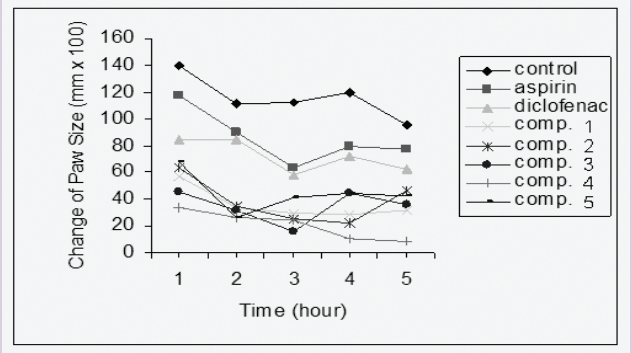


Figure 4: Carrageenan induced inflammation tests of imidazole derivatives.

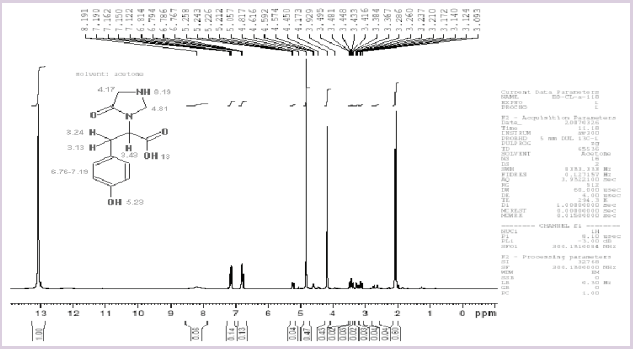


Figure 5: The H[1] NMR spectrum of compound 1.

Table 3: Formalin induced inflammation tests of imidazole derivatives

comp.	change of paw size(mm ×10 $^{-2}$)					
	0 h	1 h	2 h	3 h	4 h	5 h
control	0±2	77±2.5	96±9	84±2	91±14	87±14
aspirin	0±10	52±16	77±21	61±13	40±12*	38±11.5*
diclofenac	0±23	33.5±21^{2*}	52.5±25	57.5±25	22.5±20^{2*}	43±24
1	0±17	56±5.5^{2*}	55±13*	59±17.5	58±5.3	44±17*
2	0±6	40±14*	20±8 ^{2*}	39±9 *	27±12*	22±17 ^{2*}
3	0±10.6	42±11.7	56±18	35.6±10*	36±22	40±23
4	0±16	23±13^{2*}	20±16^{2*}	25±13^{2*}	20±9.5^{2*}	20±16^{2*}
5	0±9.1	51.3±20	44±13*	51.3±2^{3*}	54±10.4	54±6.7^{2*}

* =P<0.05; 2* =P<0.01; 3* =P<0.005

Table 4: Carrageenan induced inflammation tests of imidazole derivatives

comp.	change of paw size(mm ×10 $^{-2}$)					
	0 h	1 h	2 h	3 h	4 h	5 h
control	0±5	140±15	111±21	112.5±12	120±15	95±25
aspirin	0±22	118±1	90±2	64±4	80±2	77±5
diclofenac	0±1	85±15	85±29	58.5±3	72±22	62±7
1	0±12	57±14	34±15*	30±9.5*	29±17*	32±13*
2	0±12	64±13	35±13*	25±8*	22±3.5^{2*}	47±6.3
3	0±10	46±26	32±4*	16±8^{2*}	44.6±10	36±12*
4	0±8.2	34±3.1*	27±8.6*	24±5*	11±4.8^{2*}	8±5.5^{3*}
5	0±7.1	68±23	27±17*	41±12	45±17	42±18

* =P<0.05; 2* =P<0.01; 3* =P<0.005

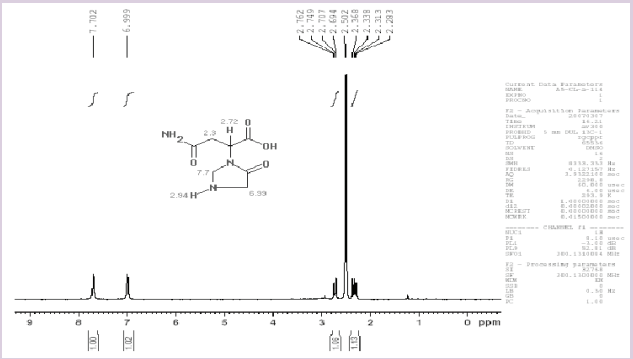


Figure 6: The H[1] NMR spectrum of compound 2.

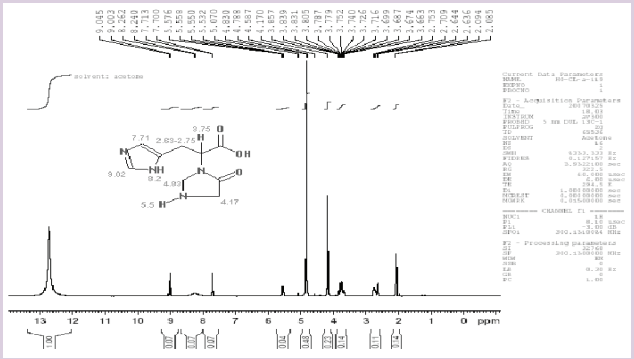


Figure 7: The H[1] NMR spectrum of compound 3.

at different hours, compound 4 show the high significant activity as anti-inflammatory at all hours of the test.

Table 4 and Figure 4 show the results of carrageenan induced inflammation test of imidazole derivatives. All derivatives have a significant effects at different hours, compound 4 (2-(4-carbonyltetrahydroimidazol) tryptophan) was the most active than other derivatives and show significant activity at all hours of the test. The indole compound was active as analgesic and anti-inflammatory, and imidazole compound active as analgesic and anti-inflammatory. Compound 4 was containing imidazole and indole ring so it well be potent analgesic and anti-inflammatory drug.

On the previous result and according to the statistical analysis the compounds can be considered as following compound 1 good anti-inflammatory; good analgesic effects on CNS, compound 2 good anti-inflammatory; good analgesic effects on CNS, compound 3 weak anti-inflammatory; not analgesic, compound 4 potent anti-inflammatory; good analgesic effects on CNS and compound 5 moderate anti-inflammatory; potent analgesic acts peripherally.

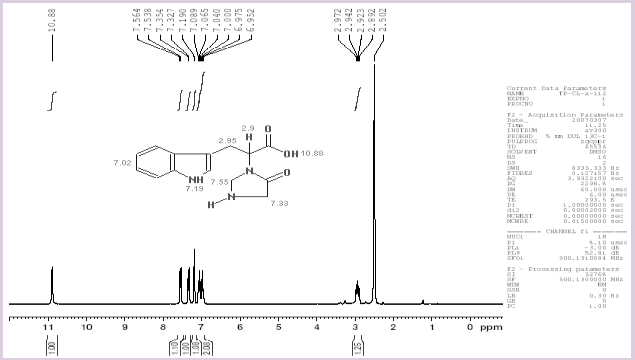


Figure 8: The H[1] NMR spectrum of compound 4.

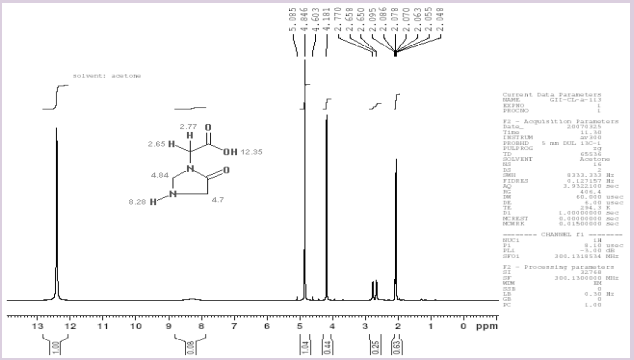


Figure 9: The H[1] NMR spectrum of compound 5.

CONCLUSION

The present study revealed the following conclusions: The present of imidazolidine ring in compound increased the activity as anti-inflammatory and analgesic. The substitution on amino acid in more than one site should be with small groups to give more active compound. The Imidazolidine derivatives with amino acids have very low toxicity, LD_{50} > 5 gm/kg.

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CONFLICT OF INTEREST

None

ABBREVIATION USED

COX: Cyclooxygenase; NSAIDs: Non-Steroidal Anti-inflammatory Drugs; LD_{50}: Median Lethal Dose; NS: Central Nervous System.

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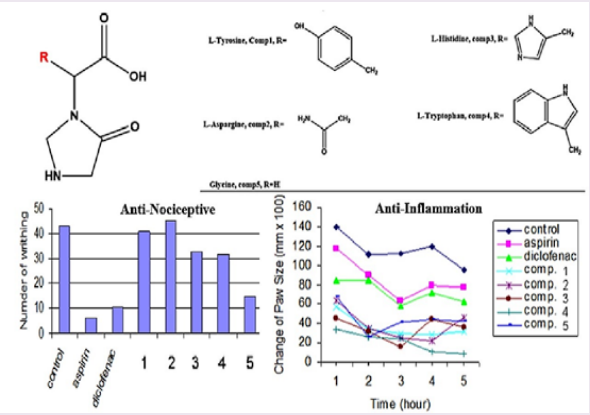
PICTORIAL ABSTRACT



SUMMARY

- The new compounds have been achieve by three components reaction by mixed of one amino acid (L-tyrosine, L-asparagine, L-histidine, L-tryptophan and glycine), triethoxymethane and glycine in acetic anhydride.
- Compounds were identifying by CHNS analysis, FT-IR and H1 NMR. Compounds were study by two different tests the hot plate test and writhing test for analgesic activity, and two tests for anti-inflammatory activity they are formalin-induced inflammation test and carrageenan induced inflammation test. Compounds found have potent anti-inflammatory and anti-nociceptive activity.
- Compounds were tested to acute toxicity and found out that they are safety up to the dose 5 g/kg orally in mice without any mortality, and suitable for use as new non-steroidal anti-inflammatory drugs.

ABOUT AUTHORS

Dr. Usama Hamid Ramadhan is an assistant professor in biochemistry, college of pharmacy, university of Basrah, Basrah, Iraq. The Ph. D. in biochemistry from department of chemistry, college of science, university of Basrah. He has many researches in medicinal chemistry, medicinal plant and phytochemistry.

Dr. Niran Jassim Al-Salihi is a professor in analytical chemistry. College of science, university of Basrah. Basrah, Iraq. She was graduate many Ph.D. and M.Sc. students. She has many researches in chemistry, analytical chemistry and plant chemistry.