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Design a Pyrrolizine-Ibuprofen Conjugate Anti-inflammatory Agent Using Modern Technology and biological evaluation (2024)

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Abstract:

As one of the most widely marketed drugs; NSAIDs have drawn the attention of researchers in the last decades. The gastric and renal side effects of nonselective COX inhibitor such as ibuprofen in addition to the cardiovascular side effects of the newly discovered selective COX-2 inhibitors such as celecoxib present a continuous need for the design of new NSAIDs. Herein this work, we have designed and synthesized a new pyrrolizine-ibuprofen hybrid **14** by coupling the pyrrolizine derivative **13** with ibuprofen. The hybrid obtained **14** lack the direct effect of the NDAIDs on gastric mucosa. Also this hybrid represents a synergism combination that could help in decreasing the total dose and the individual side effects on pharmacological use. Synthesis of the designed compound was achieved and structural determination was done using IR. The analgesic activity of the new compound **14** was evaluated using hot-plate method and the results revealed that compound **14** has higher analgesic potency at 50/100mg/kg compared to ibuprofen at 50 mg/kg. Compound **14** should subjected to further investigations to evaluate its GIT safety.

Keywords: -Synthesis, Pyrrolizine-ibuprofen hybrid, Anti-inflammatory Evaluation, Molecular Design

Introduction

The problem of the research:

NSAIDs are dispensed either as prescription or nonprescription drugs; they are the most frequently used drugs in the world.[1] But, administration of NSAIDs is usually associated with GIT complications, such as gastric ulcers (**Fig. 1**) and bleeding in chronic users.[2,3] Sometimes these side effects become life-threatening diseases and lead to death.[4]

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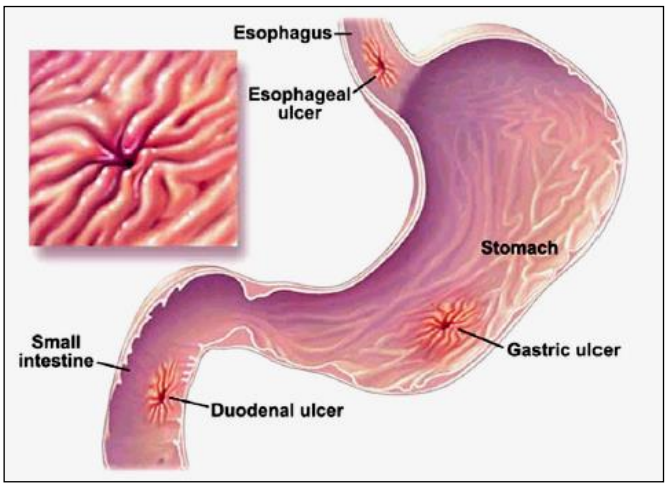

Fig.1. peptic and duodenal ulcers. [5]

There are two sets of factors that maintain acid balance and play an important role in the protection of gastric mucosa.[6] Prostaglandins (PGs) play an important cytoprotective effect on gastric mucosa especially PGE_2 which stimulate the secretion of the protective mucus and bicarbonate ions, in addition to stimulation of gastric circulation. [6,7] GIT side effects of NSAIDs are due to inhibition of prostaglandin synthesis (indirect effect) in addition to their direct necrotic effects on the gastric mucosa; both factors are predisposing factors in gastric ulcer.

Several isoforms of cyclooxygenase (COX). Both the constitutional COX-1 and the inducible COX-2 were found to play an important role in inflammation and GIT side effects. [8-10] Simply increasing the molecular volume of a nonselective COX inhibitor could increase selectivity toward COX-2 rather than COX-1, **Fig. 2**.

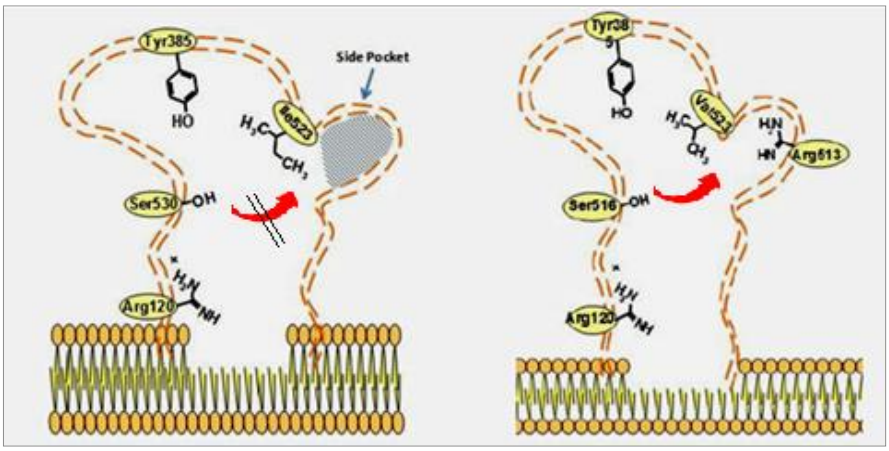

Fig. 2. Difference between active site of COX-1 (left) and COX-2 (right), showing that the active site in COX-2 can accommodate bulker molecules because the isoleucine 523 in COX-1 is exchanged with valine 523 in COX-2. [11]

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Approaches to overcome GIT side effects of the NSAIDs

Several synthetic approaches were done to overcome the GIT side effects associated with the use of the NSAIDs. The following are the five major approaches applied in this field

a) Blocking the acidic carboxylic group in NSAIDs

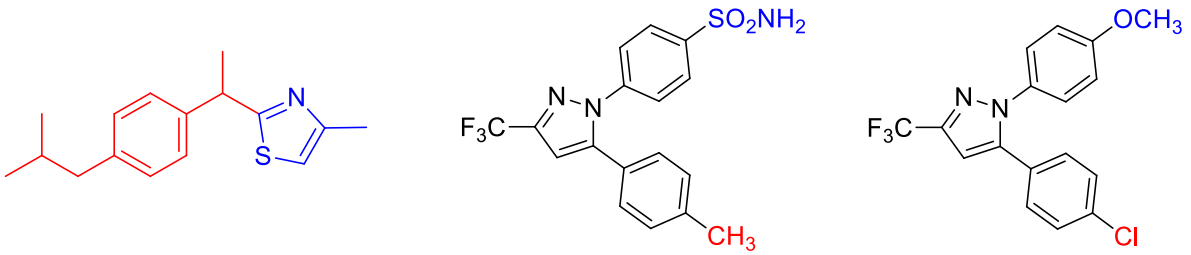
It was previously thought that the GIT side effects of NSAIDs are due primary to the direct necrotic effect of these acidic agents. Masking the carboxylic group as in compound **1** prevent gastric ulceration. [12]

b) Development of the selective COX-2 inhibitors:

The inducible nature of COX-2 in case of inflammatory diseases leads to the development of selective COX-2 inhibitor such as celecoxib **2** that was reported to cause no GIT side effects, but it may cause cardiovascular thrombotic disease, **Fig. 3**. [13]

c) Development of the selective COX-1 inhibitors:

The first selective COX-1 inhibitor **3** (**SC- 560**) induced no gastric injury even at high doses [14], **Fig. 3**.



1 2 3 SC-560

Fig. 3. Chemical structure of compounds **1-3**

d) Use of NSAIDs that release cytoprotective agents (NO)

Nitric oxide release from drug such as **4** and **5** increase cGMP that play an important role in protection of gastric mucosa as it possess many actions of PGs in GIT.[15] NO–NSAIDs combine two mechanisms in the same drug, where they have anti-inflammatory and antipyretic activities comparable to the parent NSAID [16] with the cytoprotective effect of NO, which may be due to the increase of mucosal blood flow and mucous fluid secretion by the gastric epithelial cells, **Fig. 4**.[17]

e) Balanced COX /LOX inhibition:

Dual inhibitor of COX/5-LOX such as **6 (**S-2474) that showed excellent anti-inflammatory activity in rats without ulcerogenic effects.[18] In addition it can be used to overcome adverse effects of NSAIDs in asthmatic patients, **Fig. 4**. [19]

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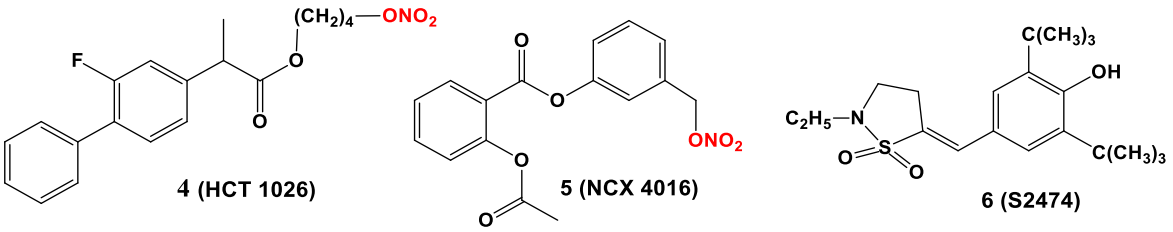
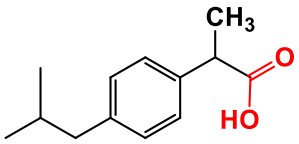


Fig. 4. Chemical structure of compounds **4-6**

Ibuprofen as a NSAID:

As a nonselective COX inhibitors; (±)-Ibuprofen **7** showed GIT side effect that may be attributed to its low selectivity to COX-2 [20], **Fig. 5**. It was found that the S(+) enantiomer of ibuprofen is the most active isomer. [21] (±)-Ibuprofen is a nonselective COX inhibitor that causes GIT side effects due to both direct toxic effects (local irritation to the GIT mucosa) and indirect toxic effects (inhibiting COX enzymes).



7 (+)-Ibuprofen

IC_{50} = 2.4 μM (COX-1),
= 5.7 μM (COX-2),
IS = 0.24

Fig. 5. Chemical structure of ibuprofen

In attempt to reduce the GIT side effects of ibuprofen, several derivatives have been synthesized through marking the carboxylic acid group. The ester prodrug **8** displayed good anti-inflammatory activity with reduced gastric ulceration. [22] Also, the amide prodrug **9** of ibuprofen showed good anti-inflammatory activities with low GIT side effects. Results revealed that these compounds are stable in HCl buffer (**pH 1.2**) indicating that the prodrugs did not break in stomach and there was no release of ibuprofen at gastric pH, **Fig. 6**. [23]

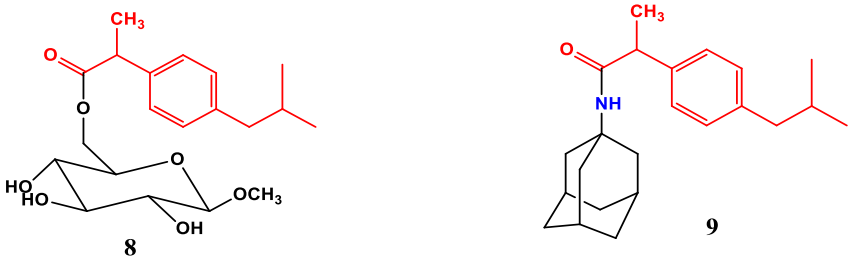


Fig. 6. Chemical structure of compounds **8** and **9**

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Pyrrolizine derivatives as NSAID:

Many pyrrolizine derivatives were observed to have anti-inflammatory, analgesic and antipyretic activities. [24,25] Ketorolac **10** is a pyrrolizine derivative that afford nonselective inhibition of COX enzymes. It is used in treatment of severe neuropathic pain.[26] Several prodrugs have been prepared from ketorolac as the amide prodrug **11** that showed significant stability and was converted to ketorolac only in rat liver, **Fig. 7**. [27]

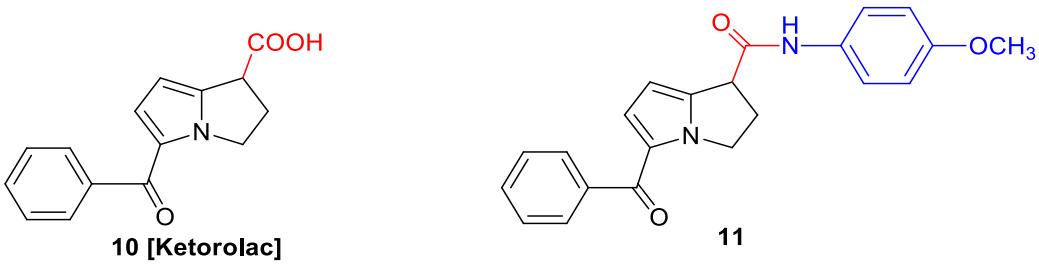

Fig. 7. Chemical structure of compounds **10** (ketorolac) and **11**

3. Aim and design

Rational design of our target compound:

In a previous work we have synthesized compound **12**, showing nearly 50% of the anti-inflammatory activity of ketorolac but high GIT side effects were observed. [28] We have tried in this work to develop a new hybrid of two analgesic agents (compound **12** and ibuprofen **7**). We have started the design by masking the free carboxylic group in compound **12**. Then we have planned to couple the designed ester derivative **13** with ibuprofen **7**.

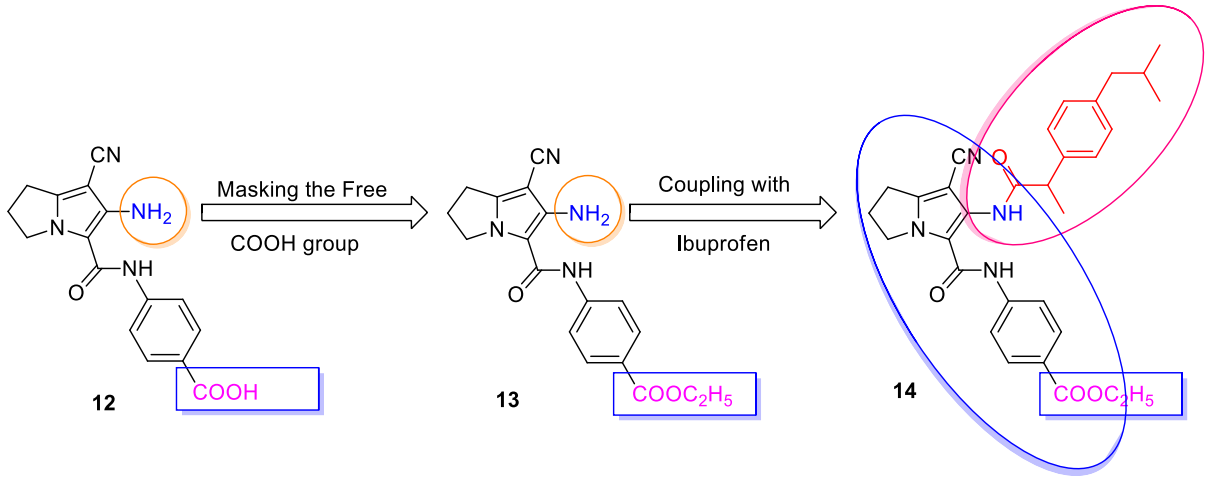

Fig. 8. Design strategies of compound **14**

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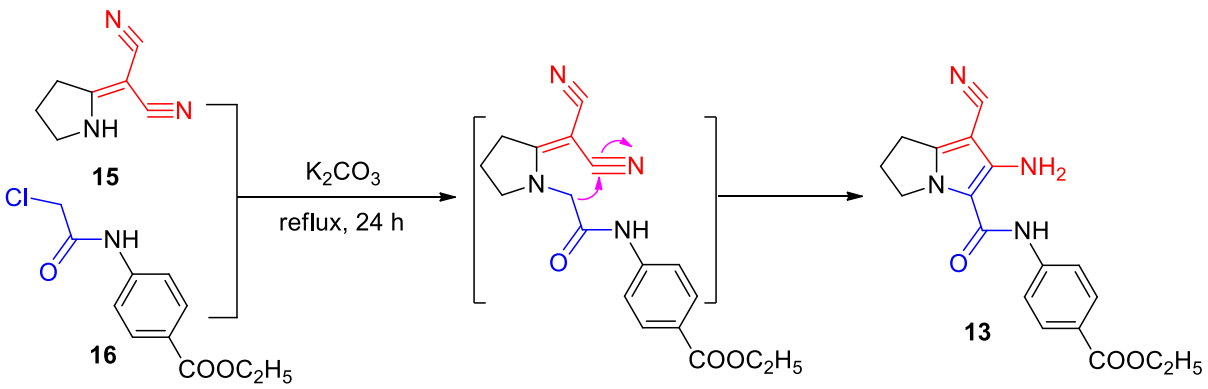
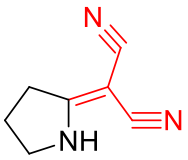
Masking the free carboxylic group of compound **12** could improve the GIT safety of this compound. In addition, coupling of this ester with ibuprofen mask also the free carboxylic group of ibuprofen. Since many reports have attributed the GIT toxicity of traditional NSAIDs partly to the free carboxylic group, we expected that the designed hybrid **14** could show synergistic effect of the two analgesic with better GIT safety.

4. Discussion of the Experimental

Scheme 1:



a) 2-Pyrrolidin-2-ylidene-malononitrile (15):



15

Compound 15 was obtained as amorphous powder. It was recrystallized from ethanol, m.p., 159-61ºC (reported 158-9ºC). [29] The IR spectrum was done for further structural study, Fig. 9.

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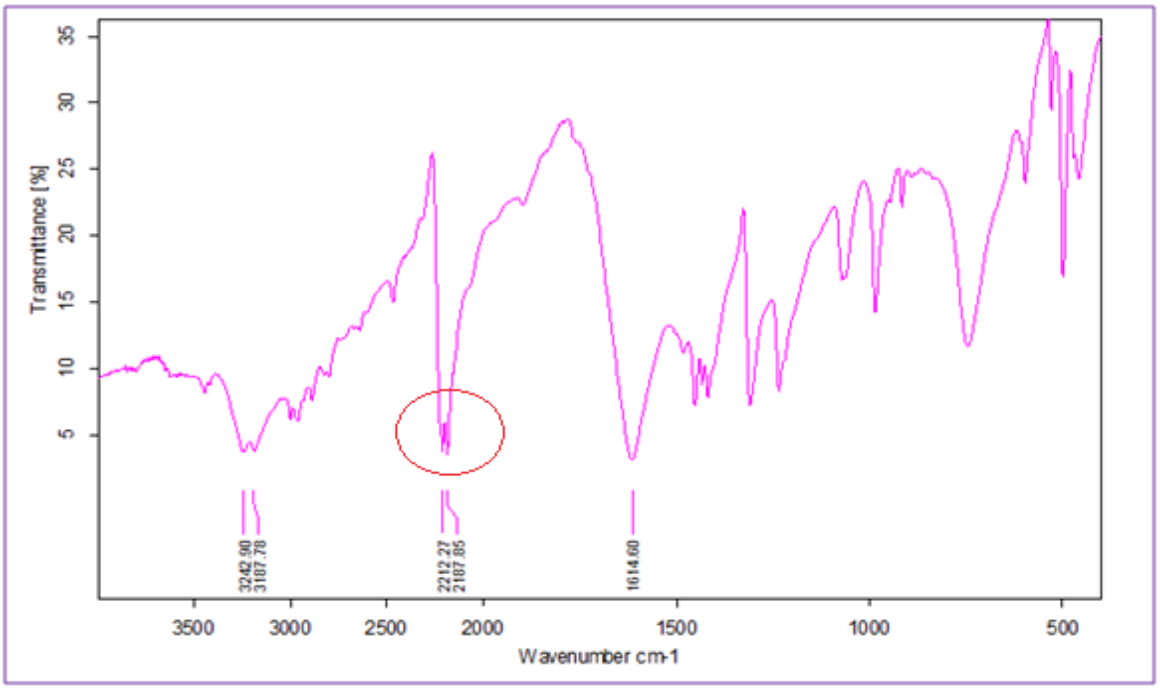
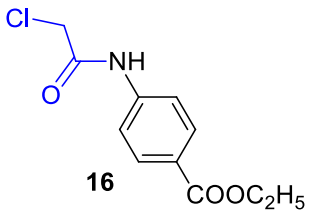


Fig. 9. IR spectrum of compound **15**.

The IR spectrum revealed the appearance of two characteristic absorption bands of the geminal cyano groups, at 2212 and 2188 cm^{-1} and absorption band at 1614 cm^{-1} due to C=C stretching.

b) N-(4-Bromo-phenyl)-2-chloro-acetamide (16):



The ethyl 4-(2-chloroacetamido)benzoate 16 was obtained as amorphous powder. Purification of the obtained powder through crystallization and TLC was done to obtain a white crystalline product with melting point192-4°C (reported 193-5 °C). [30] The IR spectrum was done for further structural study, Fig. 10.

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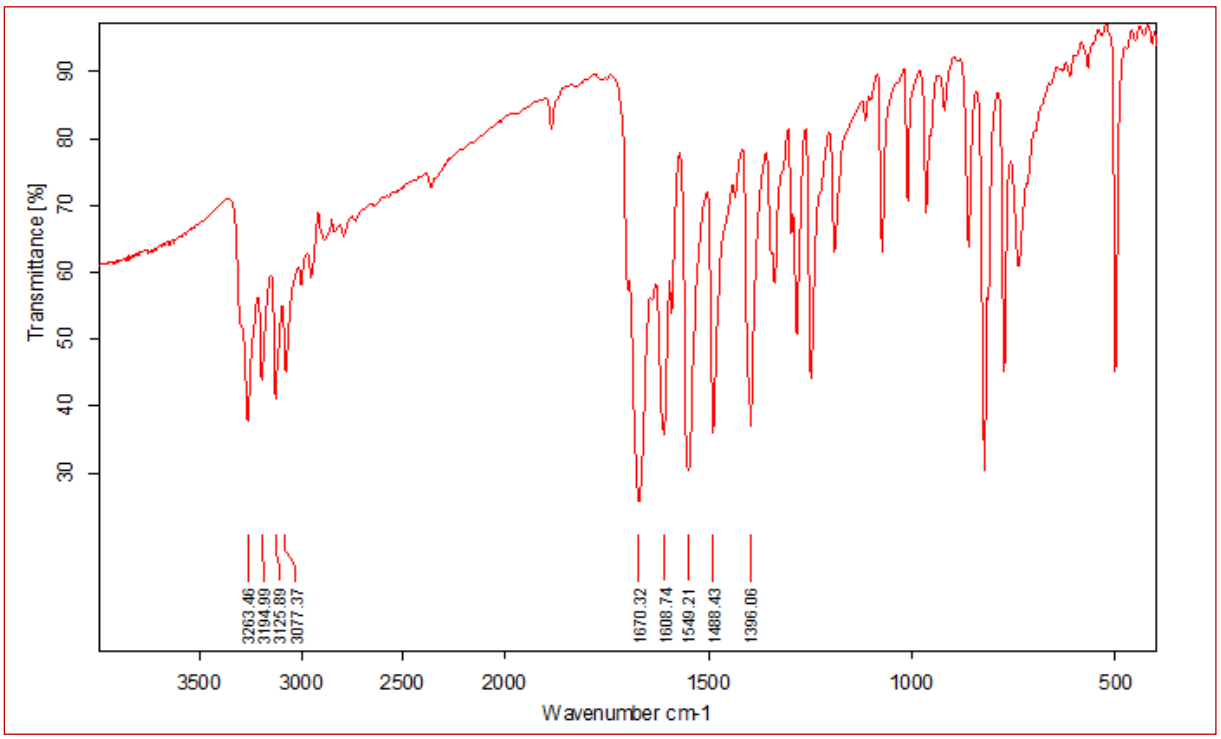
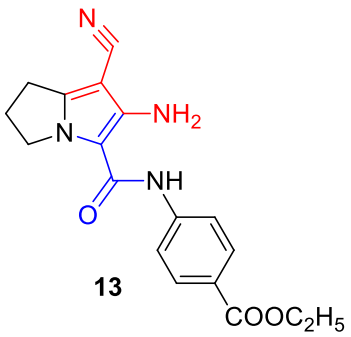


Fig.10. IR spectrum of compound **16**.

The IR spectrum of compounds **16** revealed the presence of absorption band at 3263 cm^{-1} indicating the amidic NH group, broad band due to aromatic C-H at 3077 cm^{-1} and carbonyl group stretching band appearing at 1670 cm^{-1}.

c) Ethyl 4-(6-amino-7-cyano-2,3-dihydro-1H-pyrrolizine-5-carboxamido)-benzoate (13):



13

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Compound **13** was synthesized by refluxing compound **15** and **16** in acetone using the procedures reported by Ebeid et al. [31] The reaction proceeded via an intermediate, which cyclizes spontaneously by addition of the α-methylene group to one of the two nitrile groups to give compounds **13**.

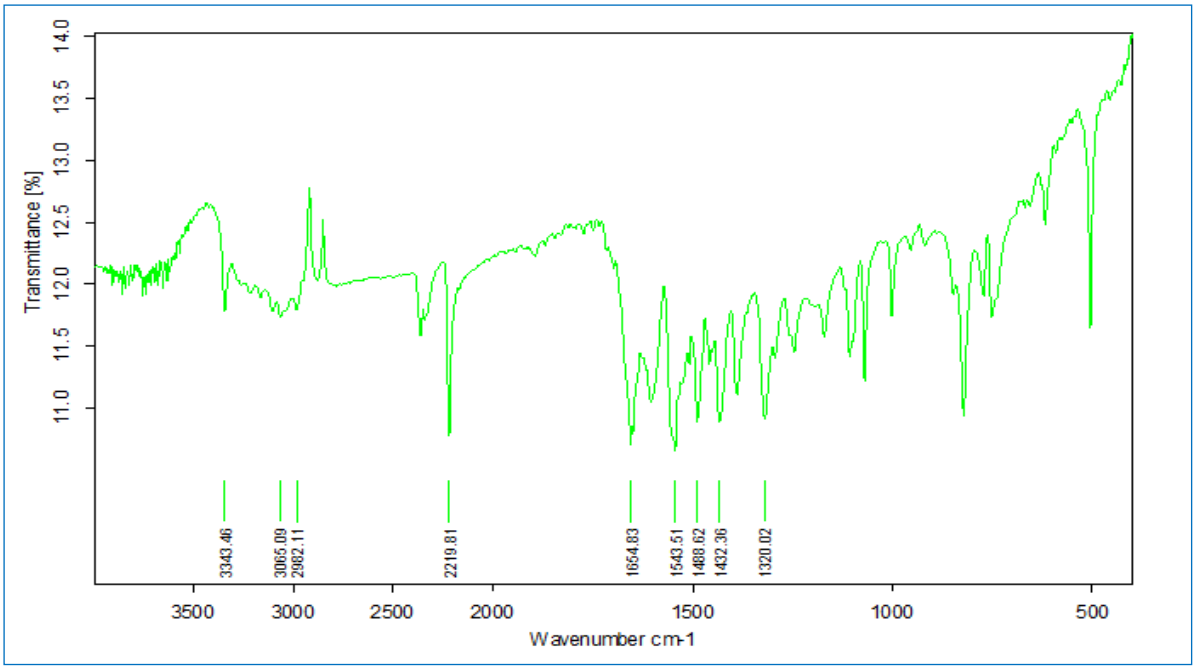

Fig.11. IR spectrum of compound **13**:

The IR spectrum of compound **13** showed absorption band at 3343 cm^{-1} attributed to the NH_2 group, a strong and sharp band at 2219 cm^{-1}, and absorption band at 1654 cm^{-1} attributed to the carbonyl group, **Fig. 11**.

d) (RS)-Ethyl 4-(7-cyano-6-(2-(4-isobutylphenyl)propanamido)-2,3-dihydro-1H-pyrrolizine-5-carboxamido)benzoate (14):

Scheme 2

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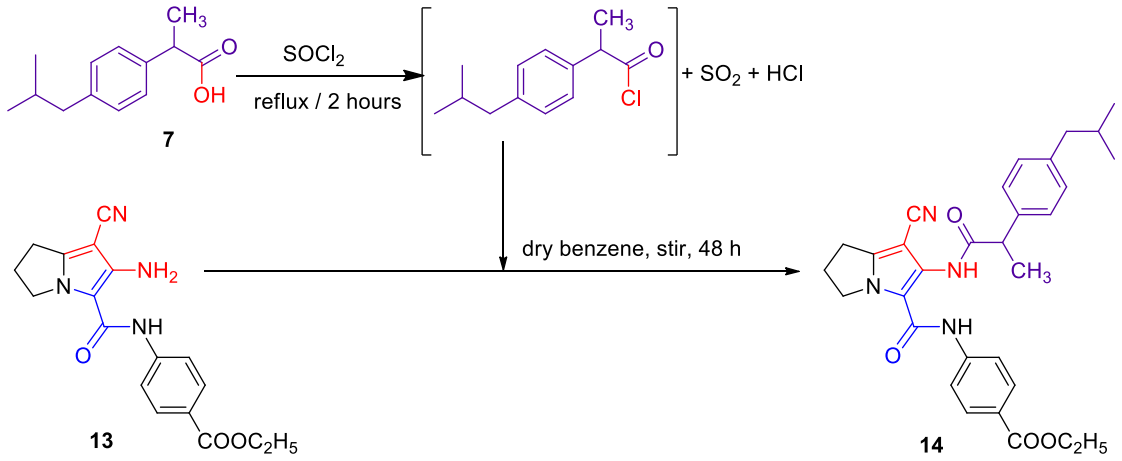

The acid chloride of ibuprofen was obtained by heating ibuprofen with thionyl chloride for 2 hours, followed by removal of the excess thionyl chloride under vacuum**.** The hybrid compound **14** was obtained by treatment of the pyrrolizine derivative **13** with ibuprofen acid chloride **V** with in dry benzene and structural identification was done using IR analysis. **Fig. 12**.

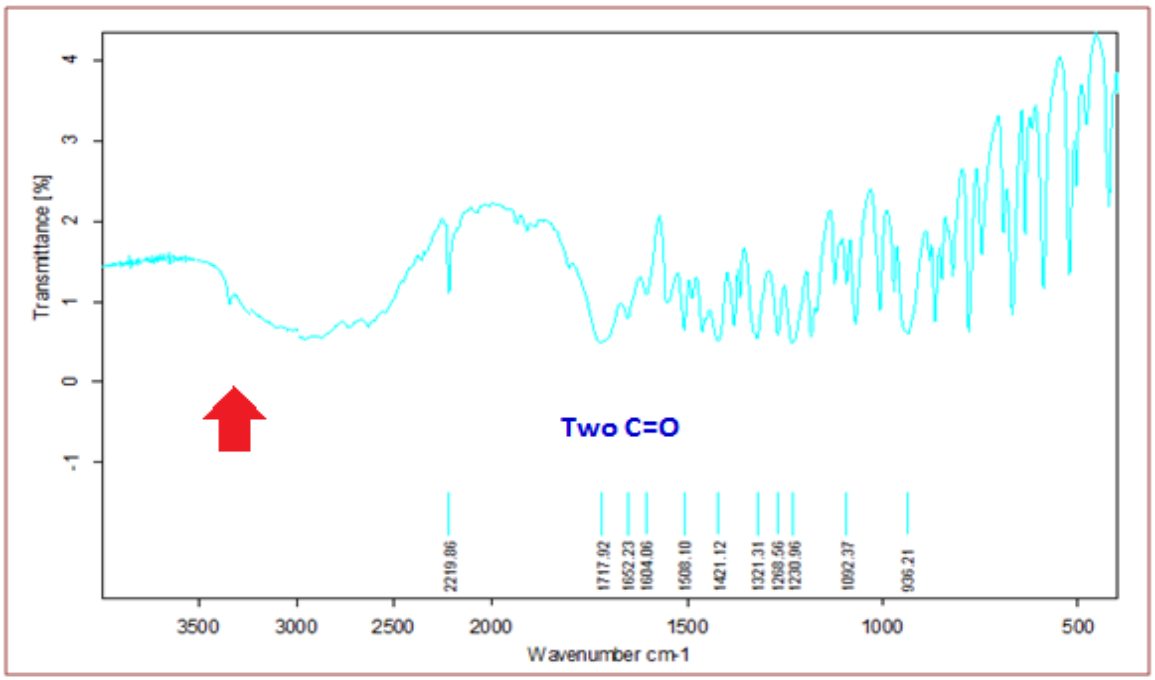

Fig. 12. IR spectrum of compound **14**

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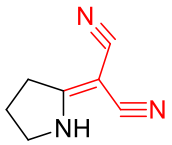
The IR spectrum of compound **14** revealed the disappearance of the characteristic absorption band attributed to the ibuprofen **14** COOH group, and pyrrolizine **13** NH_2 group. Appearance of two bands at 1718 and 1652 cm^{-1} due to the two C=O groups.

5. Experimental (chemistry)

Apparatus and software used:

1. Melting points were determined by open capillary tube method using IA 9100MK-Digital Melting Point Apparatus, at Faculty of pharmacy, Umm Al-Qura University..
2. Infrared spectra were made on BRUKER Vector 22 (Japan), infrared spectrophotometers and were expressed in wavenumber (cm^{-1}) using potassium bromide disc, at Faculty of pharmacy, Umm Al-Qura University.
3. IUPAC chemical nomenclature were assigned using ACD / Labs program, ACD / Name software, version 1.0 (1995) and
10. Thin layer chromatography, using Macherey–Nagel Alugram Sil G/UV254 silica gel plates and benzene-ethanol (9:1) as the eluting system.

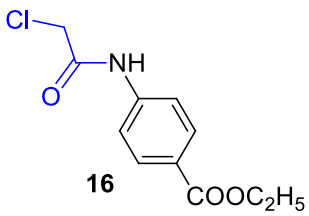
2-Pyrrolidin-2-ylidene-malononitrile (15):



15

Obtained as amorphous powder, recrystallized from ethanol, m.p., 159-61ºC (reported 158-9ºC). [29]

2-Chloro-1N-[4-bromophenyl)-acetamide (16)



16

Obtained as amorphous powder, recrystallized from water, m.p., 192-4 °C (reported 193-5°C). [30]

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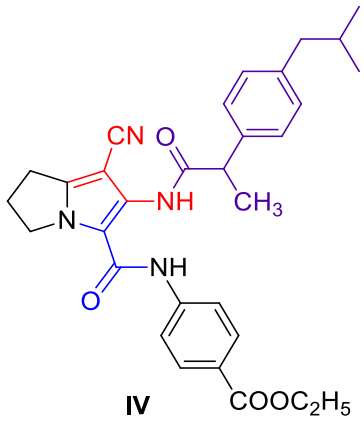
Ibuprofen acid chloride:

Dry ibuprofen powder (1.545 gm, 7.5 Mm) in dry round bottom flask, thionyl chloride 5 mL was added and reaction mixture is heated in water path for 2 hours, then the excess thionyl chloride is removed under reduced pressure, **Scheme 2**.

2: (RS)-7-Cyano-N-[4-bromophenyl]-6-[2-(4-isobutylphenyl)-propionylamino]-2,3-dihydro-1H-pyrrolizine-5-carboxamide (14):



IV

A mixture of the acid chloride of ibuprofen (7.5 mmol) and compound **13** (3.75 mmol) in 20 ml dry benzene was stirred for one hour then left to stand for 48 hours at room temperature. The precipitate formed was filtered, dried, and recrystallized from ethanol-acetone (table 4 and 5).

6. Pharmacology

Introduction:

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience which is primarily associated with tissue damage or described in terms of such damage, or both.” [32, 33]. An unpleasant sensory and emotional experience associated with actual or potential tissue damage" is called pain [34]. Pain motivates to withdraw from damaging situations, to protect a damaged body part while it heals, and to avoid similar experiences in the future [35]. Pain resolves promptly once the painful stimulus is removed and the body has healed, but sometimes pain persists despite removal of the stimulus and apparent healing of the body; and sometimes pain arises in the absence of any detectable stimulus, damage or disease [36]. Nociception involves the relay of peripherally originated from the nociceptors in the tissues to the central structures within the brain:

Nociceptors → primary afferent fibres → dorsal horn of spinal cord → secondary afferent fibres → tertiary afferent fibres

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However, the perception of pain is not simply a biological response, but rather a complex interaction that involves sensory, emotional and behavioral factors. Its definition and ultimate treatment must include all of these aspects.

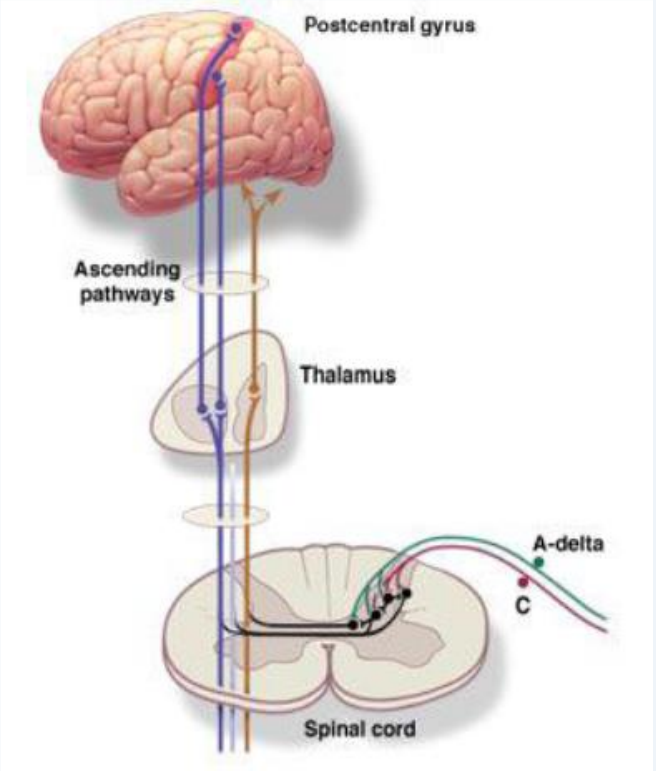

Fig. 13. Pain Modulatory Pathways [32]

Endorphins and their receptors are present in various tissues (e.g., immune cells and the gastrointestinal tract), on nerve endings, and in multiple areas of the CNS. The endorphinergic pain modulatory pathways are characterized by multiple endogenous ligands and different types of opioid receptors: mu, delta, and kappa as shown in, **Fig. 13**.

There are following classes of pain:

1. Nociceptive pain
2. Inflammatory pain is associated with tissue damage and the infiltration of immune cells.
3. Neuropathic pain which is a disease state caused by damage to the nervous system or by its abnormal function (dysfunctional pain, like in fibromyalgia, irritable bowel syndrome, tension type headache, etc.) [37].

Aim of the Study

The present study was planned to evaluate the analgesic effect of newly synthesized compound and compare the analgesic effects with Ibuprofen.

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Material & Methods

Animals:

Male and female Albino mice weighing between 25 to 35g were used for the study. The animals were obtained from animal house of King Abdulaziz University Medical Research Centre, Jeddah, Kingdom of Saudi Arabia. Mice were stock randomly and distributed to treatment groups in polypropylene cages with husk as bedding. Mice maintained at a temperature of 24 ± 2oC. A 12:12 light: dark cycle followed. Mice were given free access to water and fed with standard commercial pelleted diet. Experimental methods and protocols used in this study were reviewed by the Institutional review Board Committee and were in agreement with the guidelines.

Drugs

Ibuprofen (Sigma-Aldrich) and DMSO (Sigma-Aldrich) compound **14**.

Study Design

The mice were randomly divided into four groups of six mice each for the analgesic activities.

- Group I received DMSO p.o.
- Group II received Ibuprofen 50 mg/kg, p.o.
- Group III, received compound **14** in 50mg/kg, p.o.
- Group IV received compound **14** in 100 mg/kg, p.o.

Analgesic activity

Hot-plate test

- The anti-nociceptive activity of extract compound **14** was evaluated by using the hot plate test following a modified method of Raafat and coworkers [38] as an animal model in order to evaluate the pain relieving property.

  Animals were placed individually onto a hot plate with temperature fixed at 55± 0.5°C (Harvard Apparatus Ltd., Kent, UK). Exposure to heat was continued till the animal shows withdrawal response in the form of hind paw licking, shaking or lifting or jumped off. To minimize tissue damage, a cut-off time (removing from the plate) of 30 seconds was adopted. The withdrawal latency was defined as the time period between the moment .It showed with drawalresponse. Baseline latency (pretreatment value) was determined just before Ibuprofen or saline injection for each mouse. The withdrawal latency was again determined at 15, 30, 45, 60, 75, 90, min after. The prolongation in the withdrawal latency was taken as an index for the anti-nociceptive effect of Ibuprofen.

  Results;

  The results of the effect of compound VI on the hot plate method are presented in Table 1 and Fig 15.

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I. Effect of Ibuprofen

After administration of Ibuprofen, the withdrawal latency was gradually and significantly (P≤0.05) increased, starting 15 min after administration, reaching a maximum of **14.18*±0.04** seconds after 90 min as compared to corresponding control value **6.53+0.39**.

II. Effect of Compound 14

The dose 50mg/kg of the compound exhibited maximum reaction time being 14.68 sec at 60 min. It was statistically significant (P≤0.05) as compared to corresponding control. The effect of compound was more pronounced than Ibuprofen, it showed the maximum response time 11.85 sec at 60 min at the dose of 50 mg/kg (Table 1) but the difference between compound **14** was not statistically significant (P≤0.05). The results demonstrated that the compound significantly ($p < 0.05$) raised pain threshold as compared to control and the effects was persistent throughout the entire observation period of 90 min.

When increased the dose of 100 mg/kg of the compound, it also shows significantly increase the Latency period up to 17.12+3.96 at 60min when compared to its control as shown in (**Fig.1**). The results showed that the compound significantly ($p < 0.05$) increased pain threshold as compared to control and the effects was persistent throughout the entire observation period of 90 min

Table 1: Effect of Compound 14 on analgesic activity by hot plate method.

Groups	0min	15min	30min	45min	60min	75min	90min
DMSO	5.96±0.43	6.83±0.25	6.53±0.33	7.96±0.84	6.90±0.38	6.06±0.59	6.53±0.39
14 (50mg/kg)	8.24±0.50	15.42*±1.23	15.7*±1.84	16.73*±1.81	14.68*±1.56	13.42±1.55	12.05±1.46
14 (100mg/kg)	6.68±0.45	12.97*±0.30	13.42*±0.21	15.93*±2.94	17.12*±3.96	15.32*±3.02	12.48±2.24
Ibuprofen (50mg/kg)	5.71±0.17	10.31±0.28	10.71±0.31	11.95±0.251	11.85±0.73	13.45*±0.08	14.18*±0.04

*Indicate significant difference as compared to its control value P<0.05

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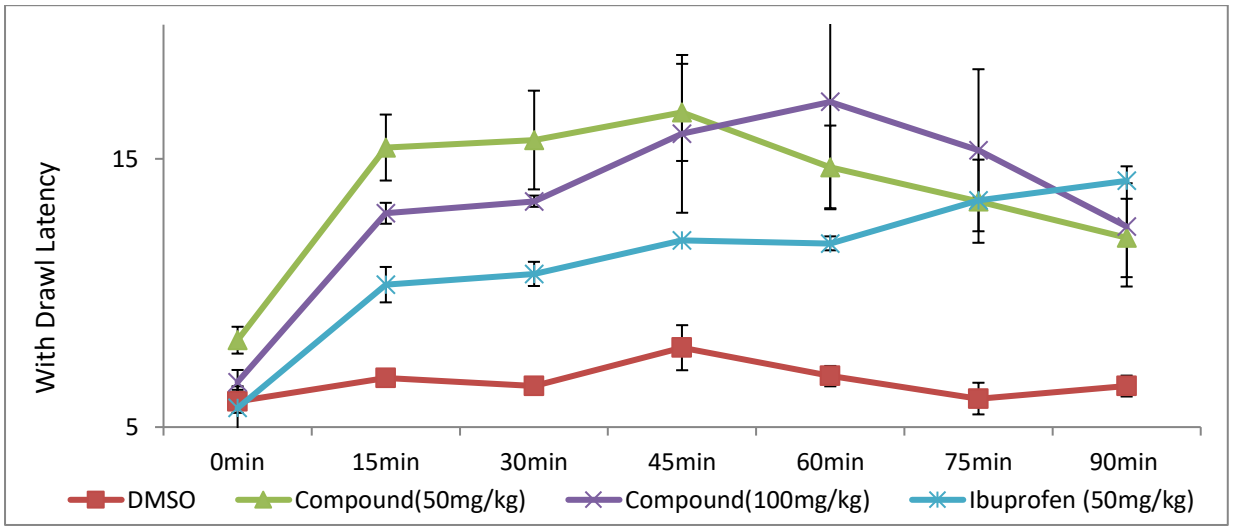

Fig. 15. Effect of Compound **14** on analgesic activity

Discussion:

The present study of the compound at the 50-100mg/kg shows significant analgesic activity, in a dose-dependent manner.

Pain management is considered one of the major issues of healthcare systems worldwide. Analgesics used to treat nociceptive pain traditionally follow the World Health Organization ladder, stepping through paracetamol, NSAIDs, and finally opioids. However, neuropathic pain conditions respond better to antidepressant and anticonvulsant classes of medication [39]. The antinociceptive and anti-inflammatory effects of NSAIDs are mainly due to their common property of inhibiting COX enzymes involved in the formation of prostaglandins. Prostaglandins are potent hyperalgesic mediators which modulate multiple sites along the nociceptive pathway and enhance both transduction (peripheral sensitizing effect) and transmission (central sensitizing effect) of nociceptive information which in turn leads to normalization of the increased pain threshold associated with inflammation [40, 41]. A full inflammatory response, however, is sustained by prostanoids generated by both constitutive and inducible COX. The most prominent signs of acute inflammation due to prostaglandin-induced vasodilatation and increased blood vessel permeability, erythema, and edema have been shown to be inhibited by both traditional nonselective NSAIDs and selective COX-2 inhibitors through inhibition of prostaglandin synthesis [40].

The hot plate model has been used to study centrally acting analgesics [42]. In this model, sensory nerves sensitize the nociceptors and the involvement of endogenous substances such as prostaglandins are minimized [43]. From the results, though they showed analgesic actions

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in the hot plate models, it was pronounced as presented in the **Table1**. It may suggest that the activity of the compound may be entirely mediated through the central mechanism.

7. Conclusion

1. At dose of 100mg/kg, the hybrid **14** showed higher analgesic activity than ibuprofen at the same dose.
2. At dose of 50mg/kg, the hybrid **14** showed higher analgesic activity than ibuprofen at the same dose.
3. The analgesic activity of **14** at 50 mg/kg was higher than that produced at 100 mg/kg dose in the first hour.
4. The designed hybrid **14** succeeded to produce analgesia higher than that produced by ibuprofen.
5. Compound **14** should subjected to further investigation to evaluate its GIT safety.

List of Abbreviations

- **COX-1:** Cyclooxygenase 1
- **COX-2**: Cyclooxygenase 2
- **PGs:** Prostaglandins
- **IR:** infra-red
- **IC_{50}:** inhibitory concentration that cause 50% inhibition
- **DMSO:** Dimethyl sulfoxide

References

1. Smalley, W. E.; Ray, W. A.; Daugherty, J. R.; Griffin, M. R. Am. J. Epidemiol. **1995**, 141, 539–545.
2. Mounier, G.; Guy, C.; Berthoux, F.; Beyens, M. N.; Ratrema, M.; Ollagnier, M. Therapie **2006**, 61, 255–266.
3. Schneider, V.; Levesque, L. E.; Zhang, B.; Hutchinson, T.; Brophy, J. M. Am. J. Epidemiol. **2006**, 164, 881–889.
4. Singh, G. Am. J. Med. **1998**, 105, 31S–38S.
5. K.S. Jain, A.K. Shah, J. Bariwal, S.M. Shelke, A.P. Kale, J.R. Jagtap, et al. Bioorganic Med. Chem. 15 (2007) 1181–1205. doi:10.1016/j.bmc.2006.07.068.
6. Jain, K.S.; Shah, A.K.; Bariwal, J.; Shelke, S.M.; Kale, A.P.; Jagtap, J.R.; Bhosale, A.V. (2007). Bioorg. & Med. Chem. **15**:1181–1205.
7. Miller, T.A. (1983). Am. J. Physiol., **245**:G601–23.
8. Xiaoxia, Z.; Hiroyuki, O.; Yuki, S.; Hiroki, K. (2008). J. Pharmaceut. Sci., **97**, 5446-5452.
9. Kennedy, B.; Chan, C., Culp, S.; et al. (1993). Biochem Biophys Res Commun., **197**:494–500.
10. Chang, H.W.; Jahng, Y.(1998). Korean J. Med. Chem., **8**:48–79.

Power System Technology
ISSN:1000-3673
Received: 16-09-2024 Revised: 05-10-2024 Accepted: 02-11-2024

11. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Pak, J.Y.; Penning, T.D.; Seibert, K.; Stallings, W. C. (1996). Nature, **384**, 644-648.
12. Woods, K. W.; McCroskey, R. W.; Michaelides, M. R.; Wada, C. K.; Hulkower, K.I.; Bell, R.L. ((2001). Bioorg. Med. Chem. Lett., **11**, 1325-1328.
13. Vivaldi, A.; Ciampi, R.; Tacito, A.; Molinaro, E.; Agate, L.; Bottici, V.; Pinchera, A.; Collecchi, P.; Elisei, R. (2012). Molecular and Cellular Endocrinology, **355**:41–48.
14. Wallace, J. L, McKnight, W.; Reuter, B. K. Vergnolle N. (2000). Gastroenterology, **119**:706–14.
15. Kubes, P.; Wallace, J. Med. Inflamm. 1995, **4**, 397.
16. Wallace, J.; Reuter, B.; Cicala, C.; McKnight, W.; Grisham, M.; Cirino, G. Eur. J. Pharmacol. 1994, **257**, 249.
17. Chiroli, V.; Benedini, F.; Ongini, E.; Soldato, P.D. Eur. J. Med. Chem. 2003;**38**:441-446.
18. Inagaki, M.; Tsuri, T.; Jyoyama, H.; Ono, T.; Yamada, K.; Kobayashi, M.; Hori, Y.; Arimura, A.; Yasui, K.; Ohno, S.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kawai, S.; Kato, M.; Matsumoto, S. J. Med. Chem. 2000;**43**:2040–8.
19. Birnbaum, J.E.; Birkhead, N.C.; Oronsky, A.L.; Dessy, F.; Rihoux, J.P.; VanHumbeeck, L. Prostaglandins 1981; **21**, 457–69.
20. Chandrasekharan, N.V.; Dai, H.; Roos, K.L.T., et al. (2002) Proc. Natl. Acad. Sci. U S A, **99**:13926–13931.
21. Adams, S. S.; Bresloff, P.; Mason, C. G. (1976). J. Pharm. Pharmacol. **28**:256–257.
22. Zhao, X.; Tao, X.; Wei, D. Qingxun Song, Q. (2006). Eur. J. of Med. Chem., **41**:1352–1358.
23. Prins, L. H. A.; du Preez, J. L.; Dyk, S. V.; Malan, S. F. (2009). Eur. J. of Med. Chem., **44**:2577–2582.
24. Tries, S.; Laufer, S. (2001). Inflammopharmacology, **9**, 113-124.
25. Laufer, S. (2001). Discovery and development of ML3000, Inflammo-pharmacology, **9**, 101–112.
26. Lashbrook, J. M.; Ossipov, M. H.; Hunter, J. C.; Raffa, R. B.; Tallarida, R. J. and Porreca, F. (1999). Pain, 82, 65-72.
27. Kim, B.Y.; Doh, H.J.; Le, T.N.; Cho, W.J.; Yong , C.S.; Choi, H.G.; Kim, J.S.; Lee, C.H. and Kim, D.D. (2005). Int. J. Pharmaceutics, **293**:193-202.
28. Abbas, S. A.; Awadallah, F. M.; Ibrahim, N. A.; Ahmed M. Gouda, A. M. (2010). Eur. J. Med. Chem., **45**:482–491**.**
29. Etienne, A.; Correia, Y. (1969). Derivatives of 2-pyrrolidone", Bull. Soc. Chem., **10**:3704-12.
30. Harte, A. J.; Gunnlaugsson, T. (2006). Synthesis of α-chloroamides in water", Tetrahedron Lett., **47**:6321–6324.
31. Ebeid, M. Y.; El. Moghazy, S. M.; Hanna, M. M.; Romeih, F. A. and Barsoum, F. F. (1997). Bull. Fac. Pharm. (Cairo Univ.), **35**:171.
32. Merskey H. Pain terms: A list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain 1979; 6: 249-252.

Power System Technology
ISSN:1000-3673
Received: 16-09-2024 Revised: 05-10-2024 Accepted: 02-11-2024

33. Melzack R, Casey KL. Sensory, motivational, and central control determinants of pain: A new conceptual model. In: Kenshalo D, ed. The Skin Senses. Springfield, IL: Charles C. Thomas; 423-429.
34. Astin, JA "Why patients use alternative medicine: Results of a national study". Journal of the American Medical Association (1998). 279 (19): 1548–1553.
35. Lynn B. Cutaneous nociceptor. In: Winlow W, Holden AV. The neurobiology of pain: Symposium of the Northern Neurobiology Group, held at Leeds on 18 April 1983. Manchester: Manchester University Press; (1984). ISBN 0-7190-0996-0. p. 106.
36. Raj PP. Taxonomy and classification of pain. In: Niv D, Kreitler S, Diego B, Lamberto A. The Handbook of Chronic Pain. Nova Biomedical Books; 2007. ISBN 1-60021-044-9.
37. Woolf CJ. What is this thing called pain?. Journal of Clinical Investigation. 2010;120(11):3742–4. doi:10.1172/JCI45178. PMID 21041955. 6 Pharm
38. Raafat et al, Paroxetine Augments while Naloxone Abolishes the Analgesic Effect of Paracetamol in Acute Nociceptive Pain in Mice**.** Pharmacology & Pharmacy 2013, 4 , 398-405.