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Artigo Original

Taurine prodrugs: amino acid anti-inflammatory drug devoid gastric toxicity.

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ABSTRACT

It is estimated that exists more than 50 different non steroidal anti-inflammatory drugs (NSAIDs) in the market, but none of them are wholly without side effects such as gastro toxicity, even newer compounds, selective to COX_2 (cyclooxygenase-2) receptors, as the celecoxib. For this reason none of NSAIDs is recommended for use in chronic inflammatory diseases. Taurine is reported to possess high antioxidant activity, including intestinal anti-inflammatory activity. With this knowledge, we synthetized new anti-inflammatory mutual prodrug from classical NSAIDs (naproxen, diclofenac, salicylic acid, ibuprofen and indomethacin) with taurine. The results showed protection of taurine in NSAIDs treated animals. In a physical mixture of NSAIDs with taurine only taurine promote an decreased on the number of the stomach ulcers compared to NSAID alone in all animals and all prodrugs obtained showed no gastric toxicity. This indicate that taurine can protect gastric toxic effect from NSAID therapy and its use as a carrier of NSAID is a new class of anti-inflammatory drug devoid gastro toxicity

Key words: Anti-inflammatory, prodrug, taurine, gastric toxicity, new drugs

INTRODUCTION

Inflammation is a defense and repair physiological reaction important in response to a physical, chemical or biological aggression of the body, providing the appearance of the four cardinal signs, pain, swelling, heat and redness, including often the loss of function of the tissue or organs. The acute inflammatory process is immediate and nonspecific against the aggressive agent and it is characterized by increased cellular and other tissue elements. Series of substances are involved in the inflammatory process such as prostaglandins, histamine, serotonin and pro-inflammatory cytokines. It is estimated that exists more than 50 different no steroidal anti-inflammatory drugs (NSAIDs) in the market, but none of them are wholly without side effects such as

gastro toxicity with bleeding, renal failure and hepatotoxicity [1,2] even the newer compounds, selective to COX_2 (cyclooxygenase-2) receptors, as the celecoxib [1].

For this reason, none of NSAIDs is recommended for use for more than 5 days in chronic inflammatory diseases. The use of classical NSAIDs that inhibit COX_1 (cyclooxygenase-1) generates an inflammatory process due to excess acid and failure of the gastric defense system. In leukocyte migration to inflamed tissue is the extrusion of hydrolytic enzymes stored in cytoplasmatic granules of neutrophils, such as myeloperoxidase (MPO), present in large amounts in azurophilic granules, which cause damage, together with the NADPH oxidase membrane by formation of reactive oxygen species (ROS) and oxidation of biomolecules [3].

This mechanism is of utmost importance for the defense system against microorganisms during phagocytosis. Two enzymes are essential for this process: NADPH oxidase, which catalyzes the monovalent reduction of molecular oxygen and superoxide anion and MPO, which uses hydrogen peroxide to oxidize chloride ion to hypochlorous acid (HOCl). Lapenna and Cuccurullo [4]., suggested that the chloramines, particularly NH_2Cl are related to injury to the stomach, observed in the presence of *Helicobacter pylori* infection, which produces high amounts of ammonia. Kourounakis and colleagues [5] synthesized prodrugs of *N*-acetylcysteine with NSAIDs and showed that derivatives have reduced the gastric toxicity, however, the mucolytic activity of the N-acetylcysteine undermines the own mucosa, increasing the gastric toxicity and after 4 days treatment showed 80% death rate, higher than standard NSAIDs with score of 50% mortality [5].

Taurine (2-aminoethanesulfonic acid) is a semi-essential amino acid related to be involved in several physiological functions [6] including: trophic factor in the development of central nervous system, maintaining the structural integrity of the membrane, antiplatelet, regulation of transport and binding of calcium, antioxidant and immunomodulation [7-10]. Because its beneficial properties, it is suggested to be useful as therapeutic agent [11-14].

Takeuchi and colleagues[15] suggested that taurine has gastro protective activity by reducing acid secretion by increasing the release luminal anion bicarbonate and not due to inhibition of acid secretion in the stomach. Furthermore, pretreatment of rats with inhibitors of nitric oxide (NO) synthesis such as NG-nitro-L-arginine methyl ester (L-NAME) and indomethacin did not affect the protective effect of taurine. In 2000, the same group published the role of the interaction of endogenous prostaglandin (PG) and NO in the regulation of acid secretion, which induces damage in the stomach of rats, suggesting the critical role of NO in the mechanisms of injury[16]. Based on this knowledge and the lack

of non-gastro toxic anti-inflammatory drug in the current market, the purpose of this work was to design new anti-inflammatory drugs devoid this toxicity. For this, we synthesized NSAIDs prodrugs of taurine according fig. 1. It was expected that *in vivo*, when NSAIDs and taurine were released, taurine can protect gastric toxicity from NSAIDs.

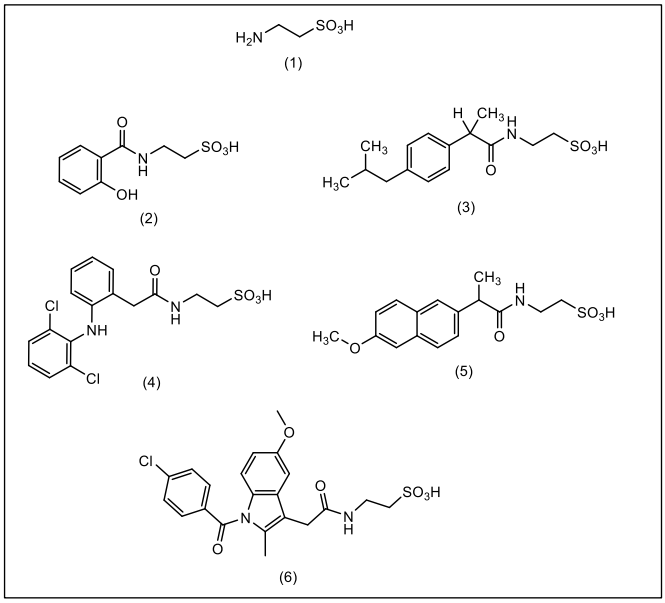

Fig. 1 Structures of taurine (**1**) and anti-inflammatory (NSAID) prodrug derivatives of taurine (**2**) as-tau (2-[(2-hydroxybenzoyl) amido] ethane sulfonic acid); (**3**) ibu-tau 2-(2-(4-isobutylphenyl)propanamide)ethane-1-sulfonic acid; (**4**) dic-tau 2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetamido)ethane-1-sulfonic acid; (**5**) nap- 2-(2-(6-methoxynaphthalen-2-yl)propanamide) ethane-1-sulfonic acid; (**6**) indo-tau (2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetamido)ethane-1-sulfonic acid.

MATERIALS AND METHODS

Chemistry

All the compounds were obtained following the same general synthesis process. A mixture of NSAID (1 mol) and dried dimethylformamide (DMF) was added in an ice bath, then were added diethyl cyano phosphonate (DEPC) (0,9 mL), taurine (1,2 mol) and trimethylamine (7,8 mL), the mixture was stirred for 2 hours under room temperature. At the end of the reaction, the base excess is removed through drag by nitrogen, and the remainder is treated with chloroform, filtered and the solvent removed by evaporation at reduced pressure. The obtained residue is added, in small portions over ice and saturated aqueous $NaHCO_3$. The formed precipitate is collected by filtration, washed with small portion of cold water and dried over phosphorus pentoxide. The obtained dry mass is milled in THF and the solid residue filtered and dried, The compounds were characterized by Nuclear

Magnetic Resonance (NMR) ^{1}H ^{13}C, using Bruker DRX- 400 (400 MHz) NMR spectrometer with DMSO-d6 as a solvent.

Animals

Male Wistar rats (250-280 g) from UNESP (Universidade Estadual Paulista), the animals were maintained at 25 °C, food and water were supplied *ad libitum*. The experiments were carried out according to the Brazilian College of Animal Experimentation – COBEA and approved by Research Ethics Committee of the School of Pharmaceutical Sciences - UNESP, Araraquara. SP, Brazil

Anti-inflammatory activity

The experiments were carried out following acute inflammation of the paw edema model based on Winter et al [17] which induced the formation of inflammatory exudates per share of carrageenan. The groups were formed randomly (n=6), all groups received the irritant agent carrageenan (200 µg/paw, in 0,1ml) in the right hind paw and saline (NaCl 0,9%, in 0,1 mL) in the left hind paw by subplantar. The negative control group received the vehicle (Arabic gun) and the positive control groups the standard NSAIDs (salicylic acid, naproxen, ibuprofen, diclofenac and indomethacin) at 100 and 300 µ*M* orally; the other groups received the NSAID prodrugs (2-6) at 100 and 300 µ*M* orally. The compounds were administered 60 minutes before carrageenan. The thicknesses (mm) of hind paws were measured before and after treatment, hourly for 6 hours after administration of carrageenan. The results were expressed as the difference between the readings of the legs before and after treatments, 7 hours after the start of the experiment, the animals were euthanized with CO_2.

Gastro toxicity bioassay

The ulcerogenic of stomach injury was seen in the same animal groups used for the model of paw edema, including the group treated with physical mixing taurine (300 µ*M*) and NSAID 300 µ*M* (salicylic acid, naproxen, ibuprofen, diclofenac and indomethacin). After euthanasia with CO_2, the animals had their stomachs removed, opened towards the greater curvature and washed with saline. Exposed the mucosa, it was observed through a microscope-stereoscope *Leica MZAPO*, as the color and integrity. In the case of the existence of injuries, these were counted and measured by the *LIDA-user* program, obtaining the number of ulcers with different degrees of injury, following the rate of gastric ulcerogenesis (RGU), according the numerical criteria for the classification of gastric mucosal lesions [18,19]: grade 1: < 1,5 mm lesions; grade 2: 1,5 to 2,5 mm lesions; grade 3: 2,5 to 3,5 mm lesions; grade 4: 3,5 to 4,5 mm lesions; grade 5: > 4,5 mm lesions.

Statistical Method

The results were tested for homogeneity of variance (Levene test). The results with p not significant (above 0.05) were subsequently subjected to variance analysis (ANOVA), followed by multiple comparison test (*post hoc* analysis) and the Newman Keuls test. $P < 0.05$ were considered significant

RESULTS

The results obtained for the anti-inflammatory activities of NSAID-tau showed similar activity when compared to standard NSAIDs, but sometimes lower at the first´s hours. This effect was expected while the compounds are prodrugs that need to be hydrolyzed before action.

The treatment with 100 μ*M* of NSAID (table 1) showed lower or similar anti-inflammatory activity when comparable with the NSAID standard and present anti-inflammatory activity when comparable to positive control (carrageenan) at the first hours, while the treatment with the dose of 300 μ*M* were observed same behavior of standard except at 120 (dic-tau) or 180 minutes (nap-tau, ibu-tau). The response of derivative indo-tau was similar for the two doses used. After first hour, the anti-inflammatory behavior is similar to indomethacin. Salicylic acid derivative as-tau, showed similar activity after 120 minutes with 100 μ*M* and after 60 minutes with the treatment of 300 μ*M*. (Table 2)

Table 3 shows the results of ulcerogenic effect observed with administration of NSAIDs and physical mixture of NSAIDs with taurine. All NSAIDs tested have caused ulceration average number of 48 to 69, the extent of injury consistent with the highest RGU in grade 5.

For salicylic acid, was observed beyond the lesions with hemorrhagic spots, marked a striking change in the mucosa. The addiction of taurine decrease the injury grade 5 of diclofenac and naproxen to grade 1. To ibuprofen, indomethacin and salicylic acid, the reduction was to grade. In addition to the injury observed to indomethacin, there is a change in color from normal gastric tissue. With the presence of taurine we observed a slight discoloration of the mucosa, but without the presence of lesions. The results showed that the presence of taurine (physical mixture), reduced the lesion index NSAIDs (grade 5 to grade 3 or 1). In all associations the reduction in lesion area was accompanied by no changes of gastric mucosa and bleeding points. Figure 2 show the photographs of the gastric mucosa

TABLE 1. Acute inflammatory activity test of NSAIDs and their prodrugs given orally at a dose of 100 m*M*.

Compounds (µM)	n	thickness (mm) mean ± S.E.M					
		60 min.	120 min.	180 min.	240 min.	300 min.	360 min.
Negative control	6	1,53 ± 0,10	1,70 ± 0,01	1,51 ± 0,02	1,30 + 0,01	0,87 ± 0,02	0,51 ± 0,01
Salicylic Acid	6	0,36 ± 0,02[a b]	0,66 ± 0,02[a]	0,44 ± 0,02[a]	0,36 ± 0,03[a]	0,29 ± 0,01[a]	0,20 ± 0,02[a]
as-tau	6	0,52 ± 0,01[a]	0,70 ± 0,01[a]	0,41 ± 0,01[a]	0,35 ± 0,01[a]	0,31 ± 0,01[a]	0,23 ± 0,01[a]
Ibuprofen	6	0,29 ± 0,06[a]	0,39 ± 0,06[a]	0,25 ± 0,05[a b]	0,23 ± 0,05[a]	0,18 ± 0,06[a]	0,14 ± 0,06[a]
ibu-tau	6	0,42 ± 0,12[a]	0,49 ± 0,11[a]	0,49 ± 0,12[a]	0,36 ± 0,10[a]	0,32 ± 0,09[a]	0,20 ± 0,09[a]
Diclofenac	6	0,36 ± 0,06[a b]	0,49 ± 0,05[a b]	0,47 ± 0,05[a b]	0,37 ± 0,05[a]	0,36 ± 0,05[a]	0,22 ± 0,05[a]
dic-tau	6	0,80 ± 0,07[a]	1,20 ± 0,07[a]	0,73 ± 0,07[a]	0,42 ± 0,09[a]	0,31 ± 0,06[a]	0,20 ± 0,09[a]
Naproxen	6	0,35 ± 0,03[a]	0,69 ± 0,02[a]	0,47 ± 0,02[a b]	0,30 ± 0,01[a]	0,23 ± 0,02[a]	0,16 ±0,01[a]
nap-tau	6	0,38 ± 0,05[a]	0,65 ± 0,04[a]	0,59 ± 0,06[a]	0,41 ± 0,04[a]	0,29 ± 0,05[a]	0,06 ± 0,06[a]
Indomethacin	6	0,20 ± 0,09[a b]	0,46 ± 0,10[a]	0,33 ± 0,09[a]	0,30 ± 0,08[a]	0,26 ± 0,10[a]	0,21 ± 0,09[a]
indo-tau	6	0,46 ± 0,01[a]	0,54 ± 0,02[a]	0,41 ± 0,01[a]	0,32 ±0,01[a]	0,31 ± 0,01[a]	0,27± 0,01[a]

(a) denotes the levels of significance between negative control and compounds; (b) denotes the levels of significance between the standards NSAIDs and NSAID-tau (2-6). $p \leq 0,05$.

TABLE 2 . Acute inflammatory activity test of NSAIDs and their prodrugs given orally at a dose of 300 m*M*

Compounds (µM)	n	thickness (mm) mean ± S.E.M					
		60 min.	120 min.	180 min.	240 min.	300 min.	360 min.
Negative control	6	1,53 ± 0,10	1,70 ± 0,01	1,51 ± 0,02	1,30 + 0,01	0,87 ± 0,02	0,51 ± 0,01
Salicylic Acid	6	0,36 ± 0,02[a b]	0,66 ± 0,02[a]	0,44 ± 0,02[a]	0,36 ± 0,03[a]	0,29 ± 0,01[a]	0,20 ± 0,02[a]
as-tau	6	0,52 ± 0,01[a]	0,70 ± 0,01[a]	0,41 ± 0,01[a]	0,35 ± 0,01[a]	0,31 ± 0,01[a]	0,23 ± 0,01[a]
Ibuprofen	6	0,29 ± 0,06[a]	0,39 ± 0,06[a]	0,25 ± 0,05[a b]	0,23 ± 0,05[a]	0,18 ± 0,06[a]	0,14 ± 0,06[a]
ibu-tau	6	0,42 ± 0,12[a]	0,49 ± 0,11[a]	0,49 ± 0,12[a]	0,36 ± 0,10[a]	0,32 ± 0,09[a]	0,20 ± 0,09[a]
Diclofenac	6	0,36 ± 0,06[a b]	0,49 ± 0,05[a b]	0,47 ± 0,05[a b]	0,37 ± 0,05[a]	0,36 ± 0,05[a]	0,22 ± 0,05[a]
dic-tau	6	0,80 ± 0,07[a]	1,20 ± 0,07[a]	0,73 ± 0,07[a]	0,42 ± 0,09[a]	0,31 ± 0,06[a]	0,20 ± 0,09[a]
Naproxen	6	0,35 ± 0,03[a]	0,69 ± 0,02[a]	0,47 ± 0,02[a b]	0,30 ± 0,01[a]	0,23 ± 0,02[a]	0,16 ±0,01[a]
nap-tau	6	0,38 ± 0,05[a]	0,65 ± 0,04[a]	0,59 ± 0,06[a]	0,41 ± 0,04[a]	0,29 ± 0,05[a]	0,06 ± 0,06[a]
Indomethacin	6	0,20 ± 0,09[a b]	0,46 ± 0,10[a]	0,33 ± 0,09[a]	0,30 ± 0,08[a]	0,26 ± 0,10[a]	0,21 ± 0,09[a]
indo-tau	6	0,46 ± 0,01[a]	0,54 ± 0,02[a]	0,41 ± 0,01[a]	0,32 ±0,01[a]	0,31 ± 0,01[a]	0,27± 0,01[a]

(a) denotes the levels of significance between negative control and compounds; (b) denotes the levels of significance between the standards NSAIDs and NSAID-tau (2-6). $p \leq 0,05$.

TABLE 3. Ulcerogenic effect of NSAIDs and physical mixture (NSAID + taurine)

Compounds	Number of ulcers	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Naproxen	48 ± 11	37,6 ± 5,3 (78,3 %)	1,4 ± 3,4 (2,9 %)	3,1 ± 6,1 (6,4 %)	3,6 ± 4,2 (7,6 %)	2,3 ± 2,1 (4,8 %)
Naproxen + Taurine	5 ± 3[a]	5,0 ± 3,0 (100 %)	-	-	-	-
Diclofenac	69 ± 6	43,0 ± 7,8 (62,0 %)	2,9 ± 2,5 (4,3 %)	6,62 ± 3,2 (9,6 %)	5,1 ± 2,1 (7,4 %)	4,6 ± 1,9 (6,7 %)
Diclofenac + Taurine	8 ± 3[a]	8,0 ± 3,0 (100 %)	-	-	-	-
Ibuprofen	66 ± 7	29,0 ± 1,3 (44,0 %)	14,8 ± 7,5 (22,4 %)	5,5 ± 5,2 (8,4 %)	10,6 ± 9,2 (16,0 %)	6,1 ± 3,3 (9,2 %)
Ibuprofen + Taurine	26 ± 9[a]	23,3 ± 2,2 (89,5 %)	1,3 ± 1,3 (5,2%)	1,4 ± 3,4 (5,3%)	-	-
Salicylic acid	52 ± 10	13,7 ± 7,2 (26,2 %)	8,8 ± 8,2 (17,0 %)	6,4 ± 4,1 (12,3 %)	9,6 ± 5,0 (18,5 %)	13,5 ± 3,2 (26,0%)
Salicylic acid + Taurine	41 ± 4[a]	25,8 ± 2,8 (63,0 %)	12,6 ± 3,3 (30,7 %)	2,6 ± 2,2 (6,3%)	-	-
Indomethacin	57 ± 11	4,5 ± 9,1 (7,9 %)	8,4 ± 10,2 (14,8 %)	9,6 ± 5,4 (16,6 %)	12,9 ± 6,3 (22,7 %)	21,6 ± 4,8 (38,0 %)
Indomethacin + Taurine	29 ± 8[a]	6,0 ± 1,0 (20,8 %)	11,7 ± 5,1 (40,2 %)	11,3 ± 6,7 (39,0 %)	-	-

(a) denotes the levels of significance between negative control and physical mixture (NSAID + taurine).

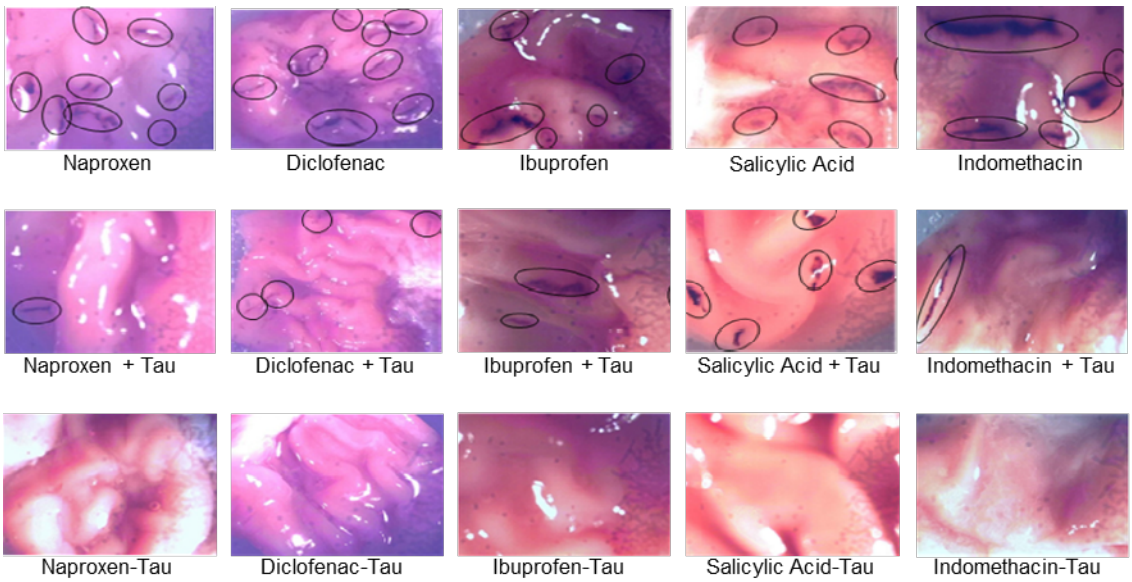

Fig. 2. Photograph of the stomachs of rats treated with single dose (300 µM), NSAIDs and physical mixture of NSAIDs and taurine (300 µM 1:1), NSAIDs-tau in Leica MZAPO stereoscopic microscope (8-16 x), Circled hemorrhagic le

DISCUSSION

The design of mutual prodrugs, it was expected the increase on anti-inflammatory activity by taurine because the effect of it in the ability to inhibit iNOS present in the macrophages during the inflammatory process. However, the inhibition of NO test showed the inhibition of iNOS by taurine but not by NSAIDs and taurine derivatives, suppressed the NO production, similarly to that of taurine (not publised), suggesting that the binding of NSAIDs to taurine did not alter this activity. One of the mechanisms of action of taurine gastroprotection proposed based on Grimble (1994), involves the interaction of taurine with hydrogen peroxide and chloride in the reaction of myeloperoxidase, generating taurine chloramine (Tau-Cl), a product that is also pro-oxidant, but low reactivity, thereby neutralize the formation of free radicals during the inflammatory process. In addition, Tau-Cl could inhibit the formation of inflammatory mediators such as NO, TNF-alpha and PGE_2. This effect seems to be observed with Tau-Cl, but not for taurine alone, dose dependent (Marcinkiewicz et al. 1998). In 2006, Kontny et al. also observed inhibition by Tau-Cl FLS proliferation of synovial cells (fibroblast like synoviocytes), cells that participate in the process of synovitis and synovial hyperplasia, regarded as important factors in the characterization of rheumatoid arthritis. Klam and Shacter (2005) demonstrated that Tau-Cl minimize the effects of uncontrolled inflammatory responses responsible for cell death (necrosis) caused by HOCl. Maraghi and co-workers [(24)] reported that taurine is able to protect the liver from the deleterious action of gamma-irradiation, trough anti-inflammatory and anti-apoptotic pathway. These data strongly suggest that the gastroprotective action of the prodrug is bullish not only for its immunomodulatory actions that involve multiple mechanisms, such as participation in apoptosis [(25)] and regulation of the inflammatory cascade by inhibiting pro-inflammatory factors such as TNF-α, the NFκB and iNOS, but also in inhibiting the formation of ROS to form Tau-Cl.

These results demonstrate that taurine can be useful to obtain new compounds such prodrugs NSAIDs with success. These new compounds are potential candidates for clinical anti-inflammatory trial as alternative for replacing the classics NSAIDs.

CONCLUSION

Currently, there aren't in the world market, NSAIDs devoid of adverse reactions. Among these, the gastro toxicity is the most frequent. The discovery of new NSAIDs is extremely important in view of the involvement of the inflammatory process as triggers of various diseases and the worldwide use of NSAIDs. Our results are promising to the therapeutic of inflammatory processes, especially for those patients who currently need the drug, but are unable to use them, such as hypertension, diabetic patients with renal / hepatic dysfunction, among others because the side effects.

Chemistry

nap-tau (2-{[2-(6-methoxy-2-naphtyl) propanoyl] amide} ethane sulphonic acid): RMN ^{1}H (400 MHz, DMSOd6): 1,37 (3H, d, J = 6,90); 2,67 (2H, t, J = 7,15); 2,94 (3H, s); 2,96 (2H, t, J = 7,15); 3,66 (1H, q, J = 6,90); 6,59 (2H); 7,10 (1H, dd, J = 5,10; J = 1,66); 7,25 (1H, d, J = 8,08); 7,43 (1H, dd, J = 9,26 J = 4,29); 7,68 (1H, dd, J = 8,08 J = 5,10); 7,73 (1H, d, J = 4,29); 8,09 (1H, d, J = 9,26); RMN ^{13}C (400 MHz, DMSO d6):

19,4; 36,5; 55,2; 46,8; 40,2; 105,7; 106,8; 118,4; 125,3; 129,0; 132,9; 138,9; 149,3; 154,0; 156,8; 176,7.

ibu-tau (2-{[2-(4-isobutylphenyl) propanoyl] amide} ethane sulphonic acid]}): RMN ^{1}H (400 MHz, DMSOd6): 0,85 (6H, d, J = 6,85); 1,27 (3H, d, J = 7,36); 1,78 (1H, hept., J = 6,85); 2,38 (2H, d, J = 7,38); 2,63 (2H, t, J = 7,15); 2,92 (2H, t, J = 7,15); 3,44 (1H, q, J = 7,36); 3,70 (2H); 6,58 (1H, dd, J = 5,12 J = 1,65); 7,02 (1H, dd, J = 5,12 J = 1,65); 7,17 (1H, dd, J = 5,12 J = 1,65); 8,10 (1H, dd, J = 5,12 J = 1,65); RMN ^{13}C (400 MHz, DMSO d6): 19,3; 22,1; 29,6; 36,6; 44,2; 46,3; 50,2; 106,6; 127,0; 128,4; 138,4; 140,8; 149,2; 176,5.

indo-tau (2-{[4-chlorobenzamide-5-methoxy-2-methyl-indol) 3-acetil] amide} ethane sulphonic acid): RMN ^{1}H (400 MHz, DMSOd6): 2,17 (3H, s); 2,50 (2H, s); 2,66 (2H, t, J = 7,15); 2,95 (2H, t, J = 7,15); 3,42 (3H, s); 3,73 (2H); 6,58 (1H, d, J = 1,66); 6,68 (1H, dd, J = 5,11 J =1,66); 6,94 (1H, dd, J = 6,93 J = 1,35); 7,05 (1H, dd, J = 6,93 J = 1,35); 7,63 (2H, dd, J = 3,38 J = 1,35); 8,10 (1H, d, J = 5,11); RMN ^{13}C (400 MHz, DMSO d6): 13,4; 32,5; 36,4; 38,6; 55,3; 102,1; 107,3; 114,4; 110,9; 116,6; 129,0; 131,6; 133,8; 133,9; 134,5; 149,2; 155,4; 167,8; 173,2.

as-tau (2-[(2-hydroxybenzoyl) amide] ethane suphonic acid): RMN ^{1}H (400 MHz, DMSOd6): 2,73 (2H, t, J = 7,15); 3,02 (2H); 3,04 (2H, t, J = 7,15); 6,60 (1H, ddd, J = 7,42 J = 7,42 J = 1,95); 6,62 (1H, dd, J = 7,42 J = 1,95); 6,71 (1H, dd, J = 7,42 J = 7,42 J = 1,95); 7,65 (1H, dd, J = 7,42 J = 1,95); RMN ^{13}C (400 MHz, DMSO d6): 35,9; 47,4; 106,7; 115,8; 129,8; 131,3; 145,8.

dic-tau (2-{[2-(2,6-diclophenyl)amine] phenyl} acetyl) amide]} etane sulphonic acid): RMN ^{1}H (400 MHz, DMSO d6): 2,64 (t, 2H, J = 7,15); 2,93 (t, 2H, J = 7,15); 2,96 (s,2H); 3,39 (3H); 6,24 (d, 1H, J = 8,23); 6,58 (dd, 1H, J = 5,10 J = 1,66); 6,72 (dd, 1H, J = 7,53 J = 7,53); 6,92 (ddd, 1H, J = 8,47 J = 8,47 J = 1,66); 7,07 (ddd,1H, J = 8,47 J = 8,47 J = 1,66); 7,45 (d, 1H, J = 8,23); 8,09 (dd, 1H, J = 8,47 J = 1,66); RMN ^{13}C (400 MHz, DMSO d6): 36,9; 50,8; 44,4; 106,6; 115,4; 119,7; 123,7; 125,6; 128,2; 128,9; 129,9; 138,0; 143,2; 149,2; 175,2.

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