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Pyrazoles and Pyrazolines as Anti-Inflammatory Agents

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Abstract: The five-membered heterocyclic group of pyrazoles/pyrazolines plays important role in drug discovery. Pyrazoles and pyrazolines present a wide range of biological activities. The synthesis of the pyrazolines and pyrazole derivatives was accomplished via the condensation of the appropriate substituted aldehydes and acetophenones, suitable chalcones and hydrazine hydrate in absolute ethanol in the presence of drops of glacial acetic acid. The compounds are obtained in good yields 68–99% and their structure was confirmed using IR, 1H-NMR, 13C-NMR and elemental analysis. The novel derivatives were studied in vitro for their antioxidant, anti-lipid peroxidation (AAPH) activities and inhibitory activity of lipoxygenase. Both classes strongly inhibit lipid peroxidation. Compound 2g was the most potent lipoxygenase inhibitor (IC50 = 80 µM.) The inhibition of the carrageenin-induced paw edema (CPE) and nociception was also determined, with compounds 2d and 2e being the most potent. Compound 2e inhibited nociception higher than 2d. Pyrazoline 2d was found to be active in a preliminary test, for the investigation of anti-adjuvant-induced disease (AID) activity. Pyrazoline derivatives were found to be more potent than pyrazoles. Docking studies of the most potent LOX inhibitor 2g highlight hydrophobic interactions with VAL126, PHE143, VAL520 and LYS526 and a halogen bond between the chlorine atom and ARG182.

Keywords: pyrazolines; pyrazoles; antioxidant activities; anti-inflammatory activities; lipoxygenase inhibition; analgesic activity; anti-arthritis; docking study

Introduction :

Pyrazoles constitute a principal heterocyclic family containing two nitrogen atoms in their five-membered heterocyclic ring [1] exhibiting a wide range of chemical, biological, agrochemical and pharmacological properties [2]. Pyrazole is a versatile lead molecule; its derivatives are reported to possess innumerable biological activities such as anti-microbial, anti-fungal, anti-tubercular, anti-inflammatory, anti-convulsant, anticancer, anti-viral, angiotensin converting enzyme (ACE) inhibitory, neuroprotective, cholecystokinin-1 receptor antagonist, and estrogen receptor (ER) ligand activity [3]. Since 1883, when Knorr, L. [4] gave the generic name “pyrazole” to the above class of compounds synthesizing the first pyrazolin-5-one (3-methyl-1-phenyl-2-pyrazolin-5-one), many papers have reported the antipyretic, anti-inflammatory and analgesic activity of several pyrazoles, pyrazolin-3-ones and pyrazolidine-3,5-diones [5–9]. Many of these derivatives have been clinically applied as non- steroidal anti-inflammatory agents, such as anti-pyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) or phenazone (analgesic and antipyretic), metamizole or dipyrone (analgesic and antipyretic), phenylbutazone (anti-inflammatory and antipyretic), aminopyrine or aminophenazone (anti-inflammatory, antipyretic and analgesic), sulfinpyrazone (chronic gout) and oxyphenbutazone (antipyretic, analgesic, anti-inflammatory, mild uricosuric) [10]. It is well known that non-steroidal anti-inflammatory drugs (NSAIDs) are important therapeutic agents for the treatment of various inflammatory disorders. The pharmacological activity is based on: (a) the suppression of prostaglandin biosynthesis from arachidonic acid via the inhibition of cyclooxygenases (COXs) and thromboxane synthase with a different degree of selectivity, and (b) the biotransformation of arachidonic acid via 5-lipoxygenase (5-LOX) to potent mediators of inflammation leukotrienes (LTs) and prostaglandins (PGs) [11–13]. COX enzymes exist in two isoforms: COX-1 (constitutive) expressed in most tissues and COX-2 (inducible) induced at sites of inflammation. Currently used NSAIDs exert their activity via the inhibition of both isoforms including major side effects at the gastrointestinal and renal level [14] due to their inhibition of COX-1-mediated physiological prostaglandins. Commercially available pyrazole moiety examples as potent COX-2 inhibitors are Celecoxib [15], Ramifenazone [16], Lonazolac (NSAID) [17] and Rimonabant [18] (Figure 1). The search for safer NSAIDs continues with the failure of anticipated “ideal” anti-inflammatory drugs, the coxibs, on long term usage [19]. Design and synthesis of NSAIDs with a potential for clinical use with less adverse side effects captured the heed of chemists and pharmacists.

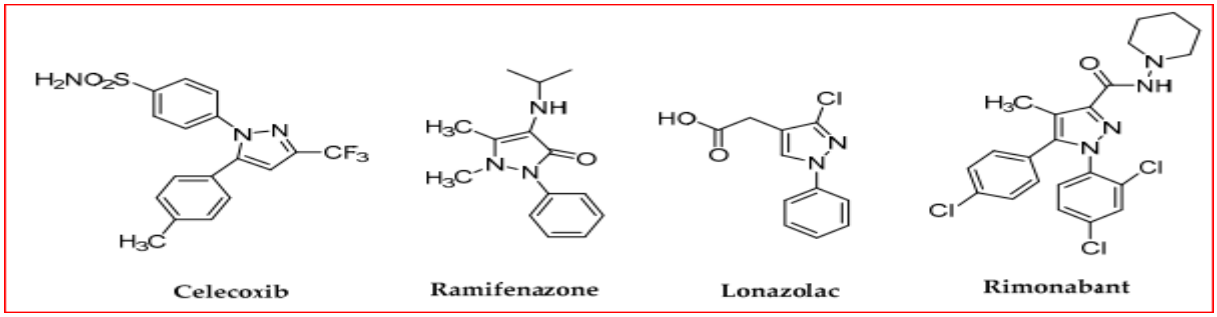


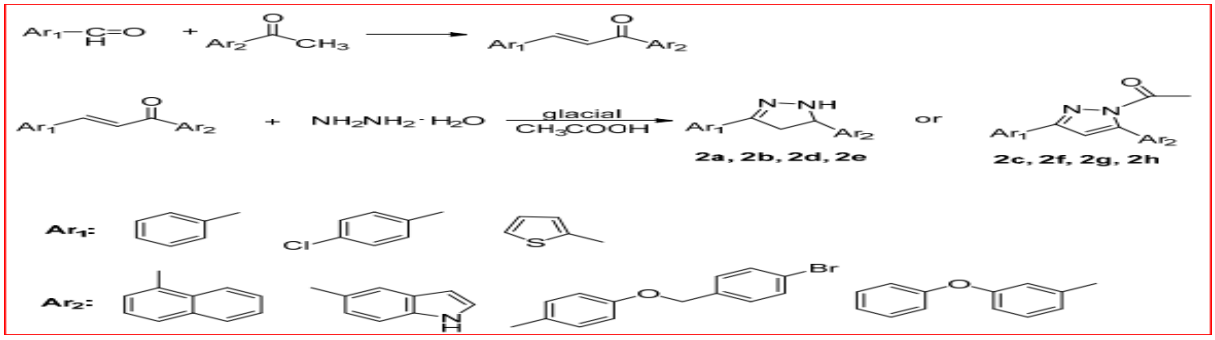
Figure 1. Structures of drugs bearing the pyrazole moiety.

Moreover, chalcones have played a crucial part in the development of heterocyclic compounds, and they have been used extensively in organic synthesis for the synthesis of several bioactive compounds. A classical synthesis of these compounds involves the base-catalyzed Claisen–Schmidt reaction of substituted ketones and aldehydes to give α, β-unsaturated ketones. Chalcones represent an important scaffold responsible for various biological activities such as anti-inflammatory, antimicrobial, antifungal, antioxidant and anticancer [20,21]. Thus, they can be used as intermediates undergoing a subsequent reaction with hydrazine hydrate affording pyrazoles/pyrazolines. It has been reported that pyrazolines possess analgesic, anti-inflammatory [22–24] and antimicrobial activities [25– 27]. It is well known that, during inflammation, free radicals are produced, leading to peroxides and other reactive oxygen species [28]. Several researchers [29–33] have reported the implication of reactive oxygen species (ROS), e.g., hydroxyl radical, superoxide anion and hydrogen peroxide, in disorders associated with oxidative stress (e.g., coronary artery disease, inflammatory injury, cancer and cardiovascular diseases). Based on these observations and in continuation with our work related to the synthesis of anti-inflammatory agents, we now describe the synthesis and the in vitro evaluation of a number of novel pyrazole and pyrazoline derivatives as antioxidants, lipoxygenase inhibitors and in vivo as anti-inflammatory and analgesic agents influencing adjuvant-induced arthritis.

Results and Discussion

Chemistry

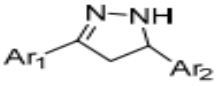
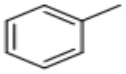
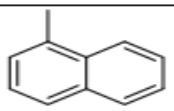
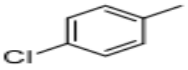
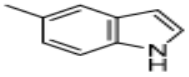
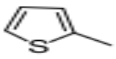
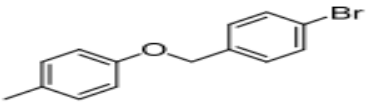
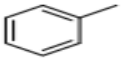
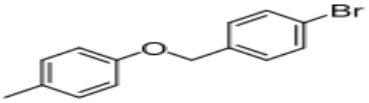
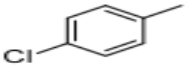
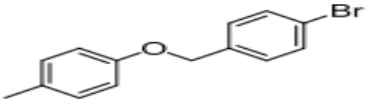
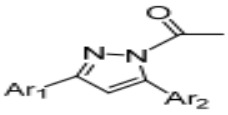
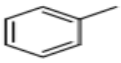
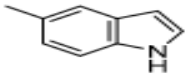
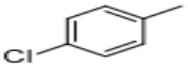
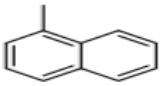
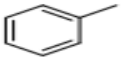
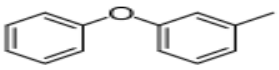
The synthesis of the pyrazolines and pyrazole derivatives was accomplished via the condensation of the appropriate substituted aldehydes, suitable chalcones and hydrazine hydrate in absolute ethanol in the presence of drops of glacial acetic acid, as presented in Scheme 1 [34]. Chalcones as starting materials were successfully synthesized via Claisen– Italics Schmidt condensation using 15% KOH from the corresponding aldehydes with acetophenone in methanol (Scheme 1) [35].



Scheme 1. Synthesis of the novel derivatives.

Products 2a–2h (Table 1) were obtained in satisfactory yields (68–99%). The pure final products were recrystallized from ethanol, acetone or preparative TLC while the chalcones were recrystallized from methanol. Structurally, compounds 2a, 2b, 2d and 2e are pyrazolines, whereas 2c, 2f, 2g, 2h are acetyl-substituted pyrazoles. Compound 2a has been previously reported [36]. IR spectra for pyrazolines and pyrazole derivatives revealed the presence of a N-N bond at 1500–1510 cm−1, N-H at 3220–3400 cm−1 and C=N at 1660–1680 cm−1. 1H-NMR, 13C-NMR and elemental analysis were used for the confirmation of the synthesized compounds' structures. The physical data of the synthesized compounds are given in detail in the Experimental Section.

Table 1. Substituted pyrazoles and pyrazoline derivatives.

Compd	Template	Ar_1	Ar_2
2a			
2b			
2c			
2d			
2e			
2f			
2g			
2h			

2.2. Physicochemical Studies

2.2.1. Determination of Lipophilicity Lipophilicity is the key physicochemical parameter of a bioactive molecule, linking solubility, ligand-target binding interactions and membrane permeability with absorption, distribution, bioavailability, metabolism and elimination (ADME) and toxicological effects, crucial for its biological activity. The reverse phase thin layer chromatography (RPTLC) method was used for the experimental determination of the lipophilic character of the synthesized compounds as RM values (Table 2) [37]. Lipophilicity was also theoretically calculated as clog P values, using the CLOGP Program of Biobyte Corp. [38] and as LPSP-lipophilicity values through Spartan v.5.1.3. (Wavefunction Inc., Irvine, CA, USA). According to the calculated clog P values, as well as LPSP, the most lipophilic compounds were the compounds 2c, 2d, 2e and 2g. This observation was supported by the RM values (with the exception of 2g).

Table 2. Theoretical calculation of the properties associated with energy and charge distribution with the program Spartan v.5.1.3. Lipophilicity values: experimental RM% (RM values are the average of at least five measurements; SD: standard deviation < 10%). Theoretically calculated clog P values calculated using the C-QSAR Program, Biobyte.

Compd.	$E_{(HOMO)}$ (eV)	$E_{(LUMO)}$ (eV)	$\Delta E_{(HOMO-LUMO)}$ (eV)	SM_2 (kcal/mol)	SURFACE (Å²)	(Å³) (MV)	Dipole (D)	LPSP	R_M [a] (±SD) [a]	clog *P* (C-QSAR)
2a	−7.65	2.15	9.80	−6.29	321.20	318.74	2.66	4.19	0.22 ± 0.2	4.77
2b	−7.67	2.64	10.31	−11.04	329.46	320.31	5.84	3.36	0.23 ± 0.03	4.30
2c	−8.44	2.39	10.83	−25.72	450.99	439.09	2.44	4.84	0.68 ± 0.05	7.40
2d	−7.84	2.86	10.70	−8.24	419.96	410.67	1.57	5.63	0.72 ± 0.06	6.15
2e	−8.08	2.78	10.86	−10.96	434.69	422.90	4.27	5.96	0.87 ± 0.07	6.69
2f	−7.73	2.48	10.21	−12.79	349.38	340.28	2.32	2.22	−0.07 ± 0.01	4.97
2g	−7.78	2.07	9.85	−7.37	382.80	376.11	1.44	4.17	−0.59 ± 0.05	6.89
2h	−8.46	2.23	10.69	−7.27	412.08	403.67	2.38	3.64	0.41 ± 0.02	6.78

a SD standard deviation < 10%

Attempts to correlate clog P and RM values as well as RM values with LPSP values resulted to the following Equations (1) and (2).

$$clog\ P\ (C\text{-}QSAR) = 2.714\ (\pm 2.658)\ RM + 4.515\ (\pm 1.474) \ldots\ldots\ldots\ldots\ldots\ldots\ (1)$$

$$n = 6,\ r = 0.817,\ r2 = 0.668,\ q2 = 0.222,\ s = 0.786,\ F1,4 = 8.03,\ \alpha = 0.05$$

$$RM = 0.241 (\pm 0.093) LPSP - 0.588 (\pm 0.413) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots. (2)$$

$$n = 7, r = 0.948, r2 = 0.898, q2 = 0.851, s = 0.117, F1,5 = 43.84, \alpha = 0.01$$

From our results (Table 2), it can be concluded that RM values could be used as a successful relative measure of the overall lipophilic/hydrophilic properties of these molecules. 2.2.2. Theoretical Calculation of Physicochemical Properties The physicochemical properties were determined with the program Spartan v.5.1.3. (Wavefunction Inc., Irvine, CA, USA) in the conformation of minimum energy (Table 2). 2.3. Biological Evaluation Reactive oxygen species and free radicals can be formed either from normal essential metabolic processes or external sources e.g., smoking, chemicals etc. [39]. They can be derived either from enzymatic (phagocytosis, prostaglandin synthesis, P-450) or non-enzymatic reactions (ionizing reactions, reaction of oxygen with organic compounds) [40]. Free radicals can be highly toxic, attacking macromolecules [41] leading to homeostatic disruption and cell damage, thus detoxification is of absolute necessity. Antioxidants (glutathione, ubiquinol, vitamin E, vitamin C etc) can delay or inhibit cellular damage due to their free radical scavenging activities and can terminate chain reactions before damaging vital molecules. In this study, the novel derivatives were evaluated: (i) in vitro for their antioxidant activities and inhibition of soybean lipoxygenase, and (ii) in vivo for their anti-inflammatory activities using the carrageenin-induced edema, and for their analgesic activity, anti-nociception applying the writhing test and for the induction of adjuvant-induced disease (AID). The antioxidant profile of the studied derivatives was determined through two different methods: (i) by measuring the scavenging ability by donating a hydrogen or an electron on a free radical, and (ii) by generating a free radical from an antioxidant system. The in vitro antioxidant activity was measured in terms of: (a) the interaction with the stable free radical DPPH; (b) the ABTS+· radical cation reduction-decolorization ability; and (c) anti-lipid peroxidation (AAPH). Factors such as solubility or steric hindrance seemed to be important, and influenced the experimental conditions.

The novel derivatives were studied for their interaction with the stable 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH) at concentrations 50 µM, 100 µM, 200 µM and after 20 and 60 min (Table 3) [42]. This assay is based on the reduction of the DPPH by transferring an electron from the antioxidant. Nordihydroguaretic acid (NDGA) was used as a reference compound [43]. In general, the compounds present low or medium activity. However, it seems that the interaction is dependent on the concentration and on the reaction time. From this point of view, it can be concluded that the acetyl pyrazolyl derivatives 2c and 2f seem to present the highest scavenging activities. An increase in concentration favors the activity. On the contrary, time does not seem to affect the activity apart from compounds 2a and 2d at 100 µM. As for compounds 2a, 2b, 2c and 2f, activity seems to be time dependent at 200 µM. The acetyl pyrazole is more potent than the corresponding 2d pyrazoline derivative. The presence of a chlorine group in 2e pyrazoline leads to an activity increase (compared to 2d) in concentration 200 µM. The acetyl derivative 2f presents better activity than 2b at 200 µM.

Table 3. Interaction with the stable radical 1,1-diphenyl-picrylhydrazyl (DPPH), In vitro lipoxygenase (LOX) inhibitory activity at 100 µM (LOX%).

Compd.	RA% 50 µM 20 min	RA% 50 µM 60 min	RA% 100 µM 20 min	RA% 100 µM 60 min	RA% 200 µM 20 min	RA% 200 µM 60 min	LOX % Inhibition at 100 µM
2a	15.0	20.0	22.9	32.0	37.2	49.3	35
2b	19.3	25.0	26.1	33.6	34.9	44.4	17
2c	17.1	22.4	41.9	44.0	49.4	59.2	42
2d	6.3	9.5	19.4	37.4	9.4	14.9	13
2e	9.5	13.0	14.8	17.8	25.6	30.1	16
2f	21.0	24.7	34.7	38.8	50.1	59.5	3
2g	9.0	12.7	11.2	13.6	22.5	27.7	60 (IC_{50} = 80 µM)
2h	6.7	9.5	7.8	9.6	17.2	20.9	26
NDGA	81	83	87	93	94	96	93 (0.45 µM)

For the lipid peroxidation study, 2,2′-azobis(2-amidinopropane) hydrochloride (AAPH) was used for the generation of peroxyl radicals. The generation of the conjugated diene hydroperoxide derived from the oxidation of sodium linoleate in an aqueous solution was recorded at 234 nm [43,44]. The compounds presented high anti-lipid peroxidation activity (78–100%) (Table 4). Pyrazolines 2a and 2b present lower anti-lipid peroxidation activity (89% and 78% respectively). All the others are almost equally potent. Lipophilicity does not seem to influence this activity. Pyrazolines 2d and 2e which are the most lipophilic compounds, showing antioxidant activity using the ABTS radical cation (ABTS•+) generated through potassium persulfate by oxidation with no participation of an intermediary radical. This reduction is completed by adding electron-donating antioxidants [43]. It seems that lipophilicity influences the activity, since both present high lipophilicity values. The compounds presented low to moderate antioxidant activity with most potent compound, 2e, attributed to the presence of an electron acceptor substituent p-Cl at the molecule (Table 4). Lipoxygenase (LOX) is the key enzyme implicated in membrane lipid peroxidation by forming hydroperoxides, thus it is considered a target for inflammatory diseases. LOX inhibitors may act either as radical scavengers or inhibitors of free radical production, since lipoxygenation occurs via a carbon centered radical [45]. LOX inhibitors bearing an antioxidant profile could be expected to offer protection in inflammatory conditions, and lead to potentially effective drugs. For the in vitro study,

soybean lipoxygenase was used, based on the homology to mammalian lipoxygenase [46,47]. It has been found that, under the experimental conditions, all the synthesized derivatives inhibited soybean lipoxygenase (13–60%) apart from compound 2f. Compound 2g is the most potent among the synthesized derivatives. For the most promising compound, 2g, IC50 value was calculated.

In an attempt to determine the type of LOX inhibition (competitive or non-competitive) for the most potent compound, 2g, the study was conducted varying the concentration of the substrate, sodium linoleate (LLA) and keeping stable the enzyme's and compound's 2g concentration. From the results, it can be concluded that 2g LOX inhibition remained steadily strong, compared to the reference compound nordihydroguaeretic acid NDGA (Table 5). This underlines a competitive inhibition. In competitive inhibition, the inhibitor "competes" with the substrate at the binding site of the enzyme, and high substrate concentrations can break down the enzyme-inhibitor complex.

Table 4. % Anti-lipid peroxidation (AAPH), decolorization activity ABTS+·% assays. In vivo anti-inflammatory activity (CPE%).

Compd.	AAPH% 100 μM	ABTS+·% 100 μM	CPE [a] %
2a	89	no	no
2b	78	no	27.0 *
2c	100	no	38.0 *
2d	96	15	63.0 **
2e	98	30	56.0 **
2f	95	no	30.0 *
2g	100	no	33.0 *
2h	97	no	16.0 *
Trolox	93	91	-
Indomethacin	-	-	47 **

** p < 0.01, ** p < 0.05. a % of reduction in the rat paw edema (CPE%) induced by carrageenin at the dose of 0.0057 mmol/Kg/body weight. No: no action under the experimental conditions.*

Table 5. In vitro assay for the determination of the type of inhibition of lipoxygenase (LOX).

LLA *-C	2g-LOX (% Inhibition 100 μM)	NDGA-LOX (% Inhibition 100 μM)
50 μM	89.6	39.3
100 μM	-	36.2
200 μM	-	6.6

** Linoleic acid sodium salt concentration.*

The carrageenin-induced rat paw edema assay was used, as a model of acute inflammation [48]. Inflammation induced by carrageenan is acute, non-immune, well-researched, and highly reproducible, and is described as a biphasic event. Cardinal signs of inflammation—edema, hyperalgesia, and erythema, are developed immediately following subcutaneous injection, resulting from the action of pro-inflammatory agents: bradykinin, histamine, tachykinins, complement reactive oxygen and nitrogen species. It is known that NSAIDs act during the second phase of prostaglandin release, presenting weak activity in the first phase of histamine and serotonin release. Pyrazolines 2d and 2e presented the highest anti-inflammatory activity among the synthesized derivatives, exhibiting even higher activity compared to indomethacin used as a reference compound. Compounds were administered intraperitoneally in order to ensure systemic response via fast bioavailability, while carrageenin's intradermal administration, as inflammatory agent, aimed at a local response. Compound 2a was proven to be inactive and 2h exhibited low activity. Compounds 2b, 2c, 2f and 2g presented medium activity. Lipophilicity seems to be important, since 2d and 2e are the most lipophilic derivatives within the set. The presence of a p-Cl at the benzyl ring slightly reduces the activity (2e < 2d). It seems that the acetyl-substituted pyrazoles are less active.

Correlation of the in vivo anti-inflammatory activity (CPE%) with LPSP (lipophilicity values calculated from Spartan v.5.1.3), showed that lipophilicity governs the in vivo anti-inflammatory activity (Equation (3)).

$$log\ (CPE\ \%) = 0.183\ (\pm 0.130)\ LPSP + 0.706\ (\pm 0.611) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (3)$$

$$n = 6,\ r = 0.890,\ r2 = 0.793,\ q2 = 0.475,\ s = 0.111,\ F1,4 = 15.35,\ \alpha = 0.05$$

Compounds 2d and 2e, presenting the highest anti-inflammatory activity, were examined for their analgesic activity as peripheral nociception using the writhing test. The acetic acid-induced writhing test is a quick, simple and reproducible method, despite the fact that it lacks specialization. Pyrazoline 2e proved to be more effective than pyrazoline 2d (Table 6).

Table 6. In vivo analgesic activities of 2d and 2e, % inhibition of writhing responses (Writhing inhibition%).

Compound	Writhing Inhibition (%) [a]
2d	54.2 *
2e	66.1 *
Aspirin	77 **

** p < 0.01, ** p < 0.05; a Dose of the administered 0.0057 mmol/kg body weight.*

Free radicals are particularly important in the inflammatory process [49–51]. ROS produced by phagocytes have been connected with the induction of inflammation and tissue damage. However, recently, ROS are also implicated in the regulation of inflammation and protection from autoimmunity. Evidence for the latter comes from association of ROS-deficiency with severe chronic inflammation in animal models and human patients in an ever-growing number of pathologic conditions, such as arthritis, lupus and neurodegenerative diseases. Since it has been reported that anti-inflammatory drugs may also be effective in the prevention of free radical mediated damage [52], it is therefore to be considered that the action of some anti-inflammatory agents may be due to their antioxidant and free radical scavenging properties. Taking into consideration the above, our biological findings as a whole show an agreement between anti-inflammatory and antioxidant activity for compounds 2c, 2d, 2e, 2g. They could indicate that organic peroxy-radicals, such as lipoperoxy-radicals, can be scavenged by these compounds, and this may be implicated in the mechanism of their anti-inflammatory ability. In the literature are referred, antioxidants possessing anti-inflammatory activity [52]. Compound 2d exerts an effect greater than that of indomethacin, which has potent anti-inflammatory activity. The inhibition observed by compound 2d was greater than that of indomethacin. Furthermore, the antioxidant-anti lipid peroxidation activities of compounds 2d and 2e are in correlation to their anti-inflammatory and analgesic activity. Furthermore, it has been claimed that compounds acting as antioxidants could act as cyclooxygenase and/ or lipoxygenase inhibitors [53]. Thus, the above tested compound 2d appeared to be an effective agent not only on acute, but also on chronic inflammation of arthritis, and it is possibly effective in autoimmune diseases in correlation to its antioxidant activity. Rats treated with compound 2d either did not develop or developed very mild arthritis, and simultaneously indicated anti-inflammatory activity.

Conclusions:

The synthesized compounds present antioxidant and anti-inflammatory activities, scavenging of free radicals, and inhibition of lipid peroxidation. In the DPPH assay, the novel derivatives showed medium antioxidant activity with small differences dependent on time and concentration. Only compounds 2d and 2e moderately reduced the ABTS radical cation (ABTS•+) at 100μM, while all compounds highly inhibited lipid peroxidation. Lipophilicity plays a significant role. Compound 2g presents the best lipoxygenase inhibition within the data test, in a competitive mode. Docking studies reveal that 2g possibly interacts in an allosteric mode, presenting hydrophobic interactions with VAL126, PHE143, VAL520 and LYS526 and a halogen bond between the chlorine atom and ARG182. Pyrazolines 2d and 2e seem to be the best anti-inflammatory agents. Simultaneously, they present satisfactory analgesic activity, whereas 2d diminishes the severity and the onset of adjuvant-induced arthritis. Thus, it can be considered to be a lead compound with a multifunctional profile. Supplementary Materials: The following are available online, Table S1: Docking scores. Hydrophobic interactions, hydrogen bonds, π-cation interactions and halogen bonds of the synthesized derivatives with different residues, Figure S1: Preferred docking poses of pyrazoles (2a [pink], 2b [blue], 2d [purple] and 2e [cyan]) bound to soybean lipoxygenase (LOX-1), Figure S2: Preferred docking poses of pyrazolines (2c [light sea green], 2f [light purple], 2g [light green] and 2h [peach pink]) bound to soybean lipoxygenase (LOX-1).

Abbreviations:

AA: Arachidonic acid; AAPH: 2,2'-azinobis(2-amidinopropane) hydrochloride; ACE: angiotensin converting enzyme; ADME: Absorption, Distribution, Bioavailability, Metabolism and Elimination; AID: Adjuvant-induced disease; clog P: theoretical calculated lipophilicity; COX: cycloxygenase; CPE: carrageenin-induced rat paw edema; DPPH: 2,2-diphenyl-1-picrylhydrazyl free radical; ER: estrogen receptor; LOX: Lipoxygenase; LPSP: lipophilicity values through Spartan v.5.1.3.; LTs: leucotrienes; NDGA: nordihydroguaeretic acid; NSAIDs: non-steroidal anti-inflammatory drugs; PGs: prostaglandins; QSAR: Quantitative Structure Activity Relationships; ROS: Reactive Oxygen Species; RPTLC: Reverse Phase Thin Layer Chromatography.

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