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Oxazole-Based Compounds: Synthesis and Anti-Inflammatory Studies †

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Abstract

A series of linear and angular naphthoxazoles bearing chlorophenyl or aminochlorophenyl substituents at position 2 of the tricyclic system were synthesized and their anti-inflammatory potential was evaluated. Synthesized molecules proved to inhibit multiple pro-inflammatory pathways, providing valuable insights for future drug design.

Keywords: oxazole; naphthoxazole; natural products; inflammation; anti-inflammatory activity

1. Introduction

Inflammation is a protective response of the immune system to various stimuli, including infections and external aggressions like injuries that result in tissue damage, leading to symptoms such as redness, pain, swelling, and warmth [1,2]. The Nuclear Factor kappa B (NF-kB) mediates one major inflammatory signaling pathway. Once activated, it mediates the transcription of genes that encode pro-inflammatory cytokines, adhesion molecules, anti-apoptotic proteins, chemokines, and enzymes such as cyclooxygenase-2 (COX-2), in an attempt to restore homeostasis [3]. COX-2 and lipoxygenase (LOX) are key inflammatory mediators involved in the arachidonic acid cascade, that mediates phospholipid conversion into prostaglandins through the action of COX-2, and the LOX-mediated production of leukotrienes. These lipid mediators, in turn, regulate inflammation and immunity and play roles in multiple diseases, including inflammatory bowel disease, rheumatoid arthritis, asthma, and cancer progression [4].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat inflammation. However, they have been associated with various adverse effects, including cardiovascular diseases, gastrointestinal and kidney complications [4]. Natural products are an important source of anti-inflammatory agents, providing promising alternatives or complements to synthetic drugs. Their importance stems from their structural diversity and ability to target multiple inflammatory pathways. Being associated with a lower risk of side effects, natural products can be attractive therapeutic options against chronic diseases [4–6]. Oxazoles and benzene-ring-fused oxazoles are heterocyclic compounds of natural origin that are currently employed in pharmaceuticals and functional materials

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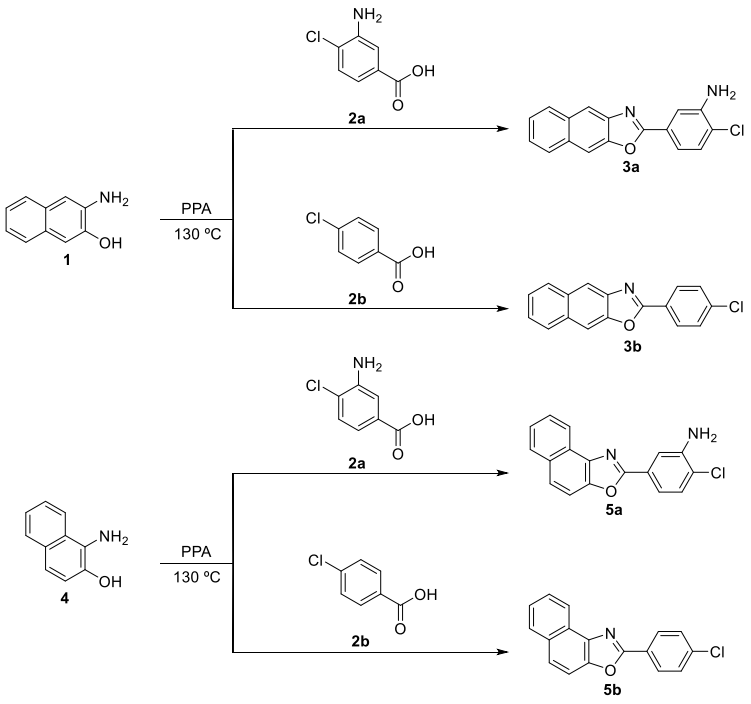
[7]. They occur mostly in marine organisms, such as sea sponges, and their diverse biological activities have sparked interest in research into their biosynthesis, chemical synthesis, and potential applications [8–11]. The five-membered ring structure of these heterocycles, containing nitrogen and oxygen, allows their interaction with various enzymes and receptors, making them attractive for drug development [12]. In fact, natural oxazoles and their derivatives exhibit a wide range of biological activities, showing potential applications against cardiovascular and respiratory diseases, thrombosis, as well as anticancer [13], antimicrobial [14], antifungal [15], anti-inflammatory [16] and analgesic [17] properties.

Considering these aspects, naphtho[2,3-*d*]oxazole and naphtho[1,2-*d*]oxazole derivatives were synthesized using polyphosphoric acid (PPA), fully characterized by standard analytical techniques and evaluated for their potential anti-inflammatory activity. The results indicate that naphthoxazole derivatives can modulate multiple inflammatory pathways.

2. Results and Discussion

2.1. Synthesis of Naphthoxazole Derivatives

The naphthoxazoles derivatives **3a**,**b** and **5a**,**b** were prepared by reacting 3-amino-2-naphthol **1** or 1-amino-2-naphthol **4** with the 3-amino-4-chlorobenzoic acid **2a** or 4-chlorobenzoic acid **2b** in PPA, a moderately strong mineral protic acid with powerful dehydrating properties [18], at 130 °C with stirring, followed by dry flash, column or preparative layer chromatography on silica gel using mixtures with increasing polarity of light petroleum and chloroform or dichloromethane (1:1 or 6:4 for **5a**) as eluents. The expected 2-chloro-5-(naphtho[2,3-*d*]oxazol-2-yl)aniline **3a**, 2-(4-chlorophenyl)naphtho[2,3-*d*]oxazole **3b**, 2-chloro-5-(naphtho[1,2-*d*]oxazol-2-yl)aniline **5a** and 2-(4-chlorophenyl)naphtho[1,2-*d*]oxazole **5b** (Scheme 1) were isolated as yellow solids and their structures confirmed by the usual analytical techniques.



Scheme 1. Synthesis of naphthoxazole derivatives **3a**,**b** and **5a**,**b**.

The ^{1}H NMR spectra of compounds **3a**,**b** showed the peaks correspondent to protons of the naphthalene ring system: H-4 appeared as singlets (δ_H 8.21–8.31 ppm), while H-9 appeared as singlet or multiplet in the case of **3a** (δ_H 7.96–8.23 ppm). For compounds **5a**,**b** the peaks corresponding to H-4 (δ_H 7.73–7.76 ppm) and H-5 (δ_H 7.81–7.82 ppm) were observed as doublets. The protons associated with the carboxylic acid moiety showed characteristic signals: for **3a**, H-4 appeared as a multiplet (δ_H 7.40–7.46 ppm) and H-6 as a meta doublet (δ_H 7.75 ppm). In **3b**, H-2 and H-6 appeared as a doublet of doublets (δ_H 8.28 ppm). For **5a**, H-4 and H-6 of the carboxylic acid ring appeared as a triplet (δ_H 7.56 ppm) and a meta doublet (δ_H 7.41 ppm), respectively; compound **5b** exhibited H-2 and H-6 as a double triplet (δ_H 8.27 ppm).

Regarding the ^{13}C NMR spectra, the quaternary carbon corresponding to the C-2 of the oxazole ring of **3a**,**b** (δ_C 164.04–164.14 ppm) and **5a**,**b** (δ_C 161.32–161.75 ppm) is exhibit. Signals of the naphthalene ring were also observed: C-4 (δ_C 116.92–117.46 ppm) and C-9 (δ_C 106.42–106.44 ppm) for **3a**,**b** and C-4 (δ_C 110.74 ppm) and C-5 (δ_C 114.07–126.30 ppm) for **5a**,**b** were shown.

2.2. LOX Inhibition

The naphthoxazole derivatives **3a**,**b** and **5a**,**b** were submitted to a LOX inhibition screening in order to evaluate their activity as potential LOX inhibitors (Figure 1). Compound **3b** was tested at varying concentrations up to a maximum of 100 μM, while the remaining compounds were tested at 25 μM or 12.5 μM due to limited solubility. Compound **3a** significantly inhibited LOX activity at 25 μM, whereas the other compounds were inactive.

In this study, quercetin was used as a positive control due to its well-known ability to inhibit the LOX enzyme [19]. Quercetin is a flavonoid, meaning that it contains a rich structure in hydroxyl groups and a conformation that allows the blockage of the enzyme's catalytic activity through iron chelation.

The activity of **3a** might be associated with the linear structure of the naphthalene in the molecule, complemented by the amino group. Accordingly, the inactivity of the remaining compounds might be due to the absence of the amino group, in the case of **3b**, or the angular structure of the naphthalene, in **5a**,**b**. A limitation of this assay is that the enzyme is derived from soybean, and, accordingly, the results warrant subsequent validation in a human model of 5-LOX.

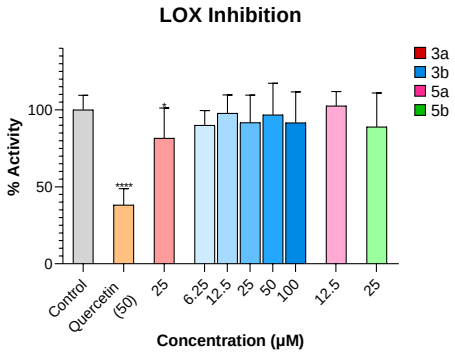


Figure 1. LOX inhibition in compounds **3a**,**b** and **5a**,**b** at 25 μM, 6.25–100 μM, 12.5 μM and 25 μM, respectively. Quercetin (50) refers to quercetin used as a positive control at a concentration of 50 μM. Experiments carried out in triplicate. **** $p < 0.0001$.

2.3. MTT Reduction Assays

Viability assays in the presence of naphthoxazole derivatives **3a**,**b** and **5a**,**b** were carried out in THP1-Dual™ cells through MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reduction assays (Figure 2).

The results have shown that compound **3a** exerts a statistically significant viability loss from 25 μM. In contrast, compound **3b** does not exhibit any statistically significant cytotoxicity. Compound **5a** caused a statistically significant decrease in viability from 12.5 μM, whereas compound **5b** was significantly cytotoxic only at 100 μM. These results suggest that the angular structure of the naphthalene and the presence of the amino group in the molecule increases the cytotoxicity in THP1-Dual™ cells.

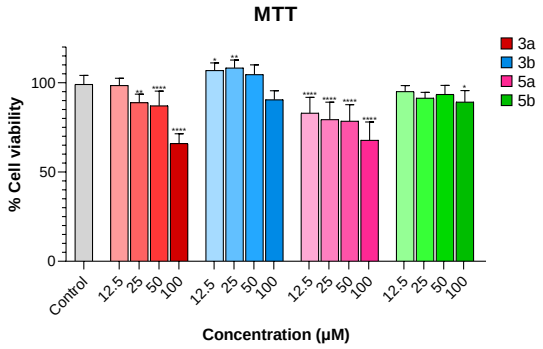


Figure 2. Effects of **3a**,**b** and **5a**,**b** in the cell viability of THP1-Dual macrophages after 24 h of incubation, determined by MTT reduction assays. Experiments carried out in triplicate. **** $p < 0.0001$.

2.4. TLR Stimulation Assay

Most of the tested molecules failed to inhibit lipopolysaccharide (LPS)-induced NF-κB activation. The exception was compound **3b**, which significantly inhibited TLR (Toll-Like Receptor) signalling at 100 μM (Figure 3). This observation suggests that either the angular structure of the naphthoxazole moiety or the presence of the amino group in the linear naphthalene structure may be responsible for the activity of these compounds as NF-kB inhibitors (Figure 3).

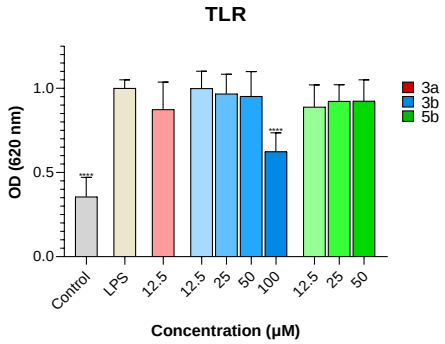


Figure 3. Effect of the nontoxic concentrations of each studied molecule upon NF-κB activation by LPS in in THP1-Dual™ cells. Results express relative NF-kB expression compared to the positive control, LPS. Experiments carried out in triplicate. **** $p < 0.0001$.

2.5. IFN Induction Assay

Results revealed that all three evaluated compounds inhibited Interferon Regulatory Factor (IRF) activation. Compound **3a** displayed the strongest activity at a 12.5 μM concentration, followed by compound **5b**. The latter showed a clear dose-dependent

inhibitory activity, while compound **3b** exhibited a weaker inhibitory effect (Figure 4). Given that compound **5b** combines a stronger inhibitory potency with low cytotoxicity, it may be considered a promising IRF inhibitor candidate. This activity might be due to the presence of its angular naphthalene moiety and the absence of an amino substituent.

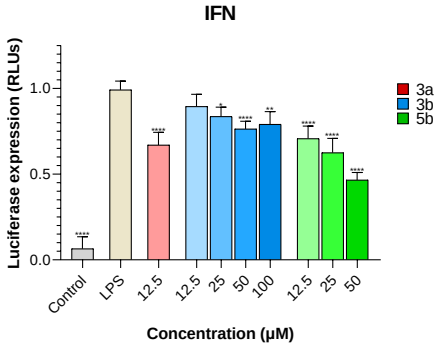


Figure 4. Effect of each studied molecule upon LPS-induced IRF activation in THP1-Dual™ cells. Results express relative IRF compared to the positive control. Experiments carried out in triplicate. **** $p < 0.0001$.

3. Materials and Methods

3.1. Synthesis of Naphthoxazole Derivatives

General Procedure for the Preparation of Naphthoxazole Derivatives **3a**,**b** and **5a**,**b** (Illustrated for **5b**)

A mixture of 1-aminonaphthalen-2-ol hydrochloride **4** (0.196 g, 1 mmol) and 4-chlorobenzoic acid **2b** (0.157 g, 1 mmol) in PPA (1 g) was gradually heated to 130 °C under stirring for 7 h. The reaction was followed by TLC (light petroleum/dichloromethane, 1:1) and once finished, the mixture was poured into ice-cold water and stirred for 1 h to afford a fine precipitate. The solid was collected by vacuum filtration, washed with cold water to remove the remaining PPA, air-dried, and purified by preparative layer chromatography using light petroleum and dichloromethane (1:1) as the eluent, yielding compound **5b** as a yellow solid (0.035 g, 13% yield). Rf = 0.55 (light petroleum/dichloromethane, 1:1). m.p. = 189.0–191.8 °C. IR: υ_{max} (solid) 3057, 2918, 1638, 1602, 1528, 1476, 1237, 1089, 784, 728 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.53 (2H, dt, J = 8.8 and 2.4 Hz, H-3 (4-Cl-Ph) and H-5 (4-Cl-Ph)), 7.57(1H, td, J = 6.8 and 1.2 Hz, H-7), 7.70 (1H, td, J = 6.8 and 1.2 Hz, H-8), 7.73 (1H, d, J = 8.8 Hz, H-4), 7.82 (1H, d, J = 8.8 Hz, H-5), 7.98 (1H, d, H-6), 8.27 (2H, dt, J = 8.8 and 2.4 Hz, H-2 (4-Cl-Ph) and H-6 (4-Cl-Ph)), 8.58 (1H, dt, J = 8.4 and 1.0 Hz, H-9) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 110.74 (C-4), 122.20 (C-9), 125.49 (C-7), 126.00 (C-1 (4-Cl-Ph)), 126.30 (C-5), 126.51 (C-9a), 127.08 (C-8), 128.56 (C-2 (4-Cl-Ph) and C-6 (4-Cl-Ph)), 128.60 (C-6), 129.24 (C-3(4-Cl-Ph) and C-5 (4-Cl-Ph)), 131.25 (C-5a), 137.23 (C-4 (4-Cl-Ph)), 137.54 (C-9b), 148.07 (C-3a), 161.32 (C-2) ppm.

3.2. Biological Assays

3.2.1. Statistical Analysis

GraphPad Prism 8 software was utilized for the statistical analysis, namely, to perform One-way ANOVA Multiple comparisons Dunnett test to compare single treatments with control groups, with values of $p < 0.05$ considered statistically significant. Furthermore, outliers were detected with the Grubbs' test.

3.2.2. LOX Inhibition Procedure

The LOX activity assay from Glycine max (soybean) was based on the linoleic acid oxidation. The formation of conjugated hydroperoxides was spectrophotometrically monitored at 234 nm, and the procedure was carried out at 25 °C in a sodium phosphate buffer solution (pH 9.0, 0.1 M).

Samples were added in phosphate buffer in a 96-well UV transparent microplate. Quercetin at 50 μM was used as a positive control for enzyme inhibition. Enzyme at 1.25 μL/mL, previously dissolved in phosphate buffer, was added, and the microplate was incubated at 25 °C for 5 min. At this point, linoleic acid at 1.3 μL/mL was added, and the reaction was monitored for 3 min at 234 nm.

3.2.3. Cell Culture Conditions

THP1-Dual™ monocytes, containing the NF-kB and IRF reporter systems, were maintained at 37 °C with 5% CO_2 in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS), 2 mM L-glutamine, 25 mM HEPES, 100 μg/mL Normocin™ and Pen-Strep (100 U/Ml–100 μg/mL). Additionally, as recommended by the supplier, 10 μg/mL of Blasticidin and 100 μg/mL of Zeocin® were added to the growth medium every other passage to ensure selective pressure.

3.2.4. MTT Reduction Assays

Cellular viability was assessed by MTT reduction assays conducted in 96-well plates. THP1-Dual™ monocytes were seeded at a density of 6×10^4 cells/well. To promote the monocyte differentiation into macrophages, PMA at 50 nM was added when seeding. After 24 h, the medium containing PMA was discarded and replaced with fresh medium. Macrophages were then incubated with the test compounds for 24 h. Then, medium was replaced with MTT at 0.5 mg/mL. After incubation for 2 h, the MTT solution was removed, and the resulting formazan crystals were dissolved in a 3:1 DMSO:isopropanol solution. Absorbance was then measured at 560 nm in a Thermo Scientific™ Multiskan™ GO microplate reader.

3.2.5. TLR Stimulation Assay

The NF-κB pathway in THP1-Dual™ cells was monitored by the colorimetric quantification of the expression of a secreted embryonic alkaline phosphatase (SEAP) acting as a reporter gene. Activation of this pathway was induced by LPS, a TLR agonist. Cytotoxic concentrations were excluded from this assay to preserve the veracity of the results. Seeding of THP1-Dual™ monocytes was performed as described for the MTT reduction assays. After 2 h of incubation with the molecules of interest, LPS (from *Escherichia coli*) at 1 μg/mL was added to all wells except for the control group, promoting polarization of the macrophages into their pro-inflammatory phenotype. After 24 h of incubation with compounds, or after 22 h of the addition of LPS, 20 μL of medium from each well was transferred to a flat-bottom 96-well plate, where 50 μL of QUANTI-Blue™ Solution, a SEAP detection reagent, was added to each well, as according to the instructions from the supplier. To determine SEAP levels, absorbance was read at 620 nm using a CytationTM 3 (BioTek) microplate reader 620 nm.

3.2.6. IFN Induction Assay

The IRF pathway was monitored by resorting to a luciferase reporter gene in the THP1-Dual™ cells. Increased luciferase activity indicates IRF activation and consequent interferon (IFN) production. As in the TLR activation assay, LPS at 1 μg/mL was employed as a positive control for IFN activation, and concentrations that compromised cell viability

were excluded. THP1-Dual™ monocyte seeding was performed as described for the TLR assay. After 24 h of incubation with compounds, or after 22 h of the addition of LPS, 10 µL of THP1-Dual™ cell culture medium from each well per well was transferred to a 96-well white (opaque) plate, where 50 µL of QUANTI-Luc™ 4 Lucia/Gaussia substrate solution, a Lucia and Gaussia luciferase detection reagent, was added to each well, as according to the instructions from the supplier. Luminescence was immediately read in a CytationTM 3 (BioTek) microplate reader.

4. Conclusions

The present work involved the synthesis and characterization of naphthoxazole derivatives and the evaluation of their potential anti-inflammatory activity in the LOX, NF-kB and IRF pathways. Regarding their activity as LOX inhibitors, compound **3a** exhibited activity, which might be associated with the linear structure of the naphthalene in the molecule, complemented by the amino group. At nontoxic concentrations, compound **3b** exerted statistically significant activity as NF-kB inhibitor and compound **3a** exhibited the most significant inhibition as IRF inhibitor. These results enable the acquisition of structure-activity relationship knowledge for the design of new derivatives with improved activity.

Future prospects may include new trials to better characterize these compounds as anti-inflammatory agents, particularly through performing additional COX-2 inhibitor screening assays.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

COX-2	Cyclooxygenase-2
IFN	Interferon
IRF	Interferon Regulatory Factor
LOX	Lipoxygenase
LPS	Lipopolysaccharide

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NF-kB	Nuclear Factor kappa B
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
PPA	Polyphosphoric Acid
SEAP	Secreted Embryonic Alkaline Phosphatase
TLR	Toll-Like Receptor

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