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Synthesis, and biological evaluation of novel 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid as potential in vivo anti-inflammatory agent

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Abstract: **Novel target compound, 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid 2, was synthesized and evaluated for its anti-inflammatory activity using carrageenan-induced rat paw edema method in comparison with the selective COX-2 inhibitor, celecoxib. The results suggested that compound 2 proved good potency with edema inhibition rates of 22.28 and 25.23% at the third and fifth hours, respectively. More SAR study and optimization are warranted for compound 2, which has the potential to be employed as oral anti-inflammatory drugs.**

Keywords: **Cyanopyridine; Anti-inflammatory; COX; Cyclooxygenase enzymes; Selective COX-2.**

1. INTRODUCTION

Inflammation is a complex physiological response of the immune system against any foreign stimuli or irritants. Immune cells, such as neutrophils, macrophages, and lymphocytes, are activated and recruited and then they release different pro-inflammatory mediators.[1, 2] For example, activated macrophages can stimulate the production of tumor necrosis factor-α (TNF-α), nitric oxide (NO), and pro-inflammatory cytokines, including interleukin-6 (IL-6) and interleukin-1β (IL-1β), among others.[3, 4] This series of events is beneficial in regulating tissue homeostasis, regeneration, repair, and remodeling.[5] When inflammation persists, it can cause cell injury, tissue destruction, and organ dysfunction. This can cause chronic inflammatory conditions, including osteoporosis, Alzheimer's disease, colitis, rheumatic fever, septic shock, atherosclerosis, asthma, rheumatoid arthritis, inflammatory bowel syndrome, and some types of cancer.[2, 5, 6]

Aspirin, ibuprofen, naproxen, and indomethacin (**Figure 1**) are examples of non-steroidal anti-inflammatory drugs that are useful in treating inflammatory symptoms, such as fever, pain, and both acute and chronic inflammations. [7-9] NSAIDs have analgesic, anti-inflammatory, and antipyretic properties due to their ability to inhibit the cyclooxygenase (COX) enzymes (COX-1) and COX-2, which are involved in the manufacture of prostaglandins. [10] There are two main types of non-steroidal anti-inflammatory drugs (NSAIDs): the more modern, selective COX-2 inhibitors that mainly inhibit COX-2 and the older, conventional, non-selective NSAIDs that inhibit both COX-1 and COX-2. [7, 11] Prolonged clinical use of non-selective NSAIDs can lead to a number of adverse effects, including renal damage, ulceration, bleeding, and gastrointestinal irritation because they inhibit COX-1's ability to produce gastro-protective prostanoids in the gastrointestinal tract.[12, 13] Selective COX-2 inhibitors like celecoxib can help lessen side effects related to the gastrointestinal tract. [14, 15]

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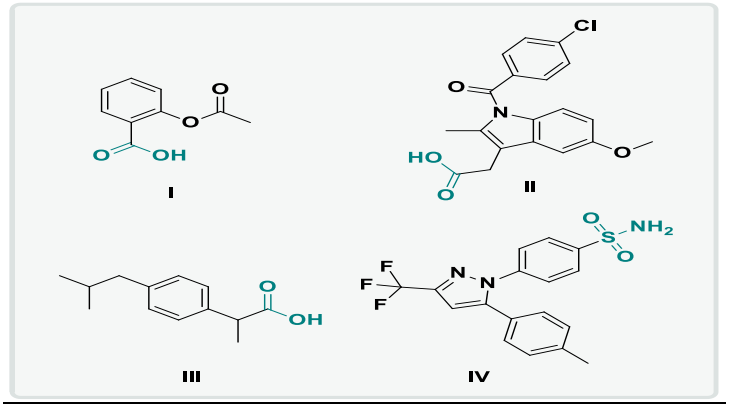

Fig. 1. Examples of NSAIDs: (I) aspirin (II) Indomethacin (III) ibuprofen (IV) celecoxib

In drug design and biochemistry, carboxylic acids and their bioisosteres have highly versatile functionality. Carboxylic moiety is present in numerous endogenous compounds, including prostanoids, triglycerides, fatty acids, DNA, RNA, and amino acids.[16] Since they can form electrostatic interactions with different proteins, carboxylic acids are frequently referred to as privileged structures for building therapeutic agents. In 2010, about 450 commercialized drugs containing carboxylic residue in their structure were marketed globally, including NSAIDs, antibiotics, anticoagulants, and statins, among others.[17-20] Carboxylic acids dissociate to carboxylate ions at pH 7.4, which increases their water solubility and ability to form hydrogen bonds and dipole interactions. [21] Due to their acidity, pKa value of 5, and planar geometry, they comply with optimal physicochemical and bioavailability standards. [22, 23]

Pyridine moiety is a highly significant class in both organic and medicinal chemistry, it serves as the essential structural basis for almost 7000 known drugs and also has tremendous applications in medicinal chemistry[24-29]. Fused cyanopyridines, especially 3-cyano-2-pyridones, possess a variety of pharmacological and biological activities, including antioxidant[30, 31] , sedatives [32] ,analgesic[33] , antiviral [34] , anticonvulsant [35], antibiotic[36-38], antidepressant [39], anti-inflammatory[33, 40, 41], antimicrobial [42-47] , cardiotonic [48, 49] , and anticancer activity [44, 50-54] .

The nucleus of 2-oxo-3-cyanopyridine (**V**) bears similarities to that of ricinine (**VI**), the first alkaloid with a cyano group that is known to exist. Milrinone (**VII**) (**Figure 2**), an inhibitor of dipyridinephosphodiesterase, is a non-glycosidic cardiotonic drug. Its synthesis and investigation underscored the significance of 2-oxo-3-cyanopyridine as a pharmacologically and physiologically active prospective chemical [55]. Olprinine (**VIII**) , is also an inhibitor of phosphodiesterase III, which has both vasodilator and positive inotropic effects [56]. In 2023, a novel series of 2-oxo-3-cyanopyridine derivatives was synthesized as dual EGFR/BRAF^{V600E} inhibitors. **Compound IX**, showed the highest antipoliferative activity against Panc-1 cancer (IC_{50} = 0.80 µM) surpassing doxorubicin (IC_{50} = 1.00 µM). Similar to erlotinib (IC_{50} = 60 nM and 80 nM), **compound IX** exhibits comparable suppression of EGFR and BRAF^{V600E} (IC50 = 89 nM and 65 nM) [57] .

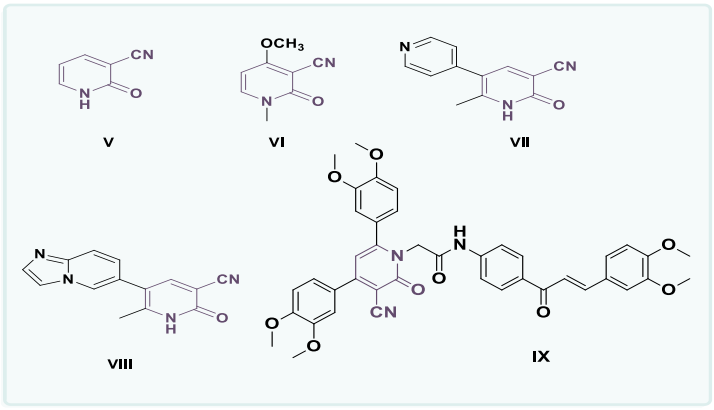

Fig. 2. General structure of 2-oxo-3-cyanopyridine(V), and examples of biologically important cyanopyridine derivatives: ricinine (VI), Milrinone (VII), Olprinone (VIII), 2-oxo-3-cyanopyridine derivative as EGFR/BRAF inhibitor (IX).

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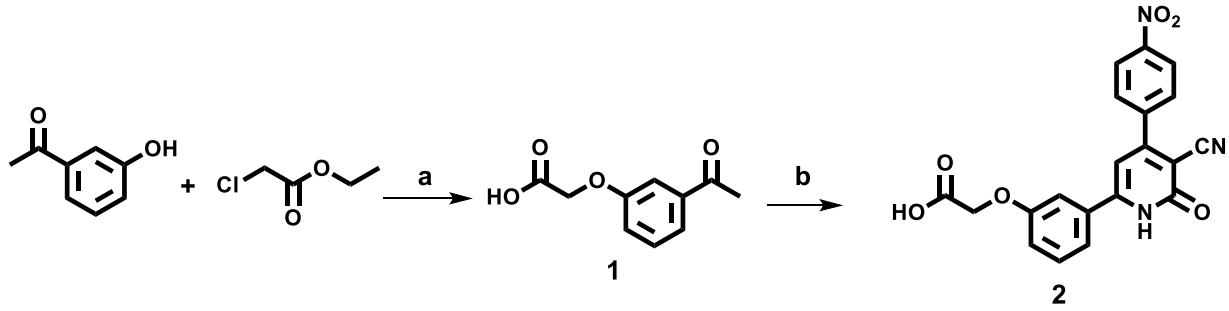
There is a pressing need for developing therapeutic agents that fulfill the pharmacophoric standards of anti-inflammatory drugs without causing any of their side effects. In this research, hybrids of 2-oxo-3-cyanopyridines and carboxyl moiety were synthesized to create promising anti-inflammatory agents. Target compound, 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid **2** was synthesized and tested for their *in vivo* anti-inflammatory activity *via* carrageenan-induced rat paw edema in comparison with the selective COX-2 inhibitor, celecoxib.

2. RESULTS AND DISCUSSION

2.1 Chemistry

Cyanopyridine derivatives are considered a rich moiety that possesses various applications in medicinal chemistry[58-61]. There are several known synthetic processes for producing 3-cyano-2-oxa-4-substituted pyridines, such as condensation of chalcones with ethyl cyanoacetate and excess ammonium acetate in ethanol under refluxing conditions[62-66]. *via* a one-pot, four-component reaction with substituted acetophenone, ethyl cyanoacetate or malononitrile, suitable aldehyde, and an excess of ammonium acetate, either without using a solvent or *via* using a variety of solvents, such as ethanol, toluene, and butanol[49, 67-71]. Utilizing a catalytic quantity of piperidine with an activated nitrile, suitable aldehyde in ethanol [72-75], or by stirring for 15 minutes while refluxing equimolar amounts of the relevant -dicarbonyl chemical with malononitrile and triethylamine in ethanol [76, 77].

Target compound **2**, was synthesized, as shown in Scheme 1, *via* a single-pot reaction of (3-acetylphenoxy) acetic acid **1**, *p*-nitro benzaldehyde, excess ammonium acetate, and ethyl cyanoacetate in refluxing conditions in ethanol for 22 hours to yield 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid **2** in 92.5% yield ranging. The proposed structure has been validated by spectroscopic and elemental analysis.



Scheme 1. Synthesis of 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid 2.

Reagents and conditions: (i) K_2CO_3, DMF, reflux, 9 h, then HCl; (ii) *p*-nitro benzaldehyde, ethyl cyanoacetate, ammonium acetate, EtOH, reflux, 22 h; (ii) acetophenone, ethyl cyanoacetate, ammonium acetate, EtOH, reflux, 22 h.

3. PHARMACOLOGICAL SCREENING

3.1 *In vivo* investigation of the anti-inflammatory activity (Carrageenan-induced Acute Inflammatory Model).

The results in **Table 1** showed that compound **2** at the third and fifth hours exhibited a good anti-inflammatory efficacy compared to celecoxib-treated group, Consequently, the anti-inflammatory properties of compound **2** seems to be promising.

Table 1: *In vivo* anti-inflammatory effect of tested compound 2 and celecoxib as reference drug.

	Diameter inflammation (mm)				% Edema inhibition			
Treatment	**0h**	**1h**	**3h**	**5h**	**0h**	**1h**	**3h**	**5h**
Control	3.83±0.2	3.83±0.2	3.83±0.2	3.83±0.2		---------	----------	---------
Carrageenan	6.1±0.1	7.06± 0.05	7.63±0.20	8.52±0.37		--------	----------	---------
Celecoxib	6.13±0.15	5.16± 0.15	4.9± 0.1	5.1 ±0.1	0.00	26.90	**35.77**	**40.14**
2	5.1±0.1	6.4±0.65	5.93±0.97	6.13±0.77	16.39	9.34	22.28	25.23

Values are displayed as mean ±S.D. (n=6). The % of inflammation inhibition was calculated according to the following equation % inhibition = (WC-WT/WC) × 100, where WC is the increase in paw thickness of the control group while WT is the increase in paw thickness of treated rats with test compounds.

4. CONCLUSION

To sum up, a novel cyanopyridine compound **2** was synthesized and screened for its *in vivo* anti-inflammatory activity using carrageenan-induced rat paw edema, using the selective COX-2 inhibitor, celecoxib as reference drug. The results proved that compound **2** displayed a good antiinflammatory activity and can be useful in treatment of inflammations. More SAR study and optimization are warranted for compound **2**, which has the potential to be employed as oral anti-inflammatory drugs.

5. EXPERIMENTAL

5.1 Chemistry

The melting points were ascertained using the Stuart electro-thermal melting point instrument, with uncorrected findings. Infrared spectra are obtained on KBr disks using a Shimaduz 408 instrument spectrophotometer at Sohag University's Faculty of Science. Using TMS as the internal reference, JEOL JNM-ECA400 (^{1}H: 400 *MHz*, ^{13}C: 100 *MHz*) NMR spectra were examined. Coupling constants (*J*) in Hertz and chemical shifts (δ) in *ppm* were reported relative to the remaining deuterated solvent DMSO-d6 (2.5 for proton and 39.50 for carbon). Elemental analysis was within ± 0.4% of the theoretical values, according to the Regional Center for Mycology and Biotechnology at Al-Azhar University in Cairo, Egypt. The development of the reactions was observed using pre-coated TLC plates (Kiesslgel 60 F254, Merck).

5.1.1 General procedure for the synthesis of 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid **2.**

To a vigorously stirred suspension of 2-(3-acetylphenoxy)acetic acid **1** (1.94 g, 10 mmol), 4-nitrobenzaldehyde (10 mmol), ethyl cyanoacetate (1.131 g, 10 mmol), and excess ammonium acetate (6.2 g, 80 mmol) using ethanol as a solvent (50 mL). the reaction mixture was heated under reflux for 22 hours. At the end of the reaction (TLC monitoring), The precipitate was filtered, washed with cold water, dried, and recrystallized from ethanol to yield 2-(3-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyridin-2-yl)phenoxy)acetic acid **2** as yellow powder; yield (1.6 g, 92.5%); mp 333-335 ^{o}C; IR (KBr, cm^{-1}): ῡ 3668 (NH), 3118 (O=C-OH), 3084 (CH-Pyridine), 2912 (CH_2), 2219 (CN), 1712 (O=C-OH), 1623 (C=O-pyridine), 1230 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.89 (s, 2H, OH, NH), 7.73 (dd, 2H, *J* = 8, 4 Hz, HC-C-CH), 7.60 – 7.54 (m, 3H), 7.51 (d, 1H, *J* = 8 Hz, CH-CH=CH), 7.46 (t, 1H, *J* = 8 Hz, CH-CH=CH), 7.42 (d, 1H, *J* = 8 Hz, CH-CH=CH), 7.12 (dd, 1H, *J* = 8, 4 Hz, OC-CH-CH=CH), 6.87 (s, 1H, pyridine-CH), 4.81 (s, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 170.32, 162.22, 160.13, 158.23, 151.12, 136.18, 133.59, 130.66, 130.40, 129.01, 128.42, 120.77, 118.27, 116.69, 113.19, 106.51, 98.82, 64.91; Anal. Calcd. For $C_{20}H_{14}N_2O_4$ (346.34): C, 69.36; H, 4.07; N, 8.09, Found: C, 69.54; H, 4.23; N, 8.27.

5.2 Biological Evaluation

5.2.1 In vivo anti-inflammatory activity

For *in vivo* anti-inflammatory activity investigation, We utilized 200 g weighing male Wister rats.

The test was carried out in compliance with the laboratory animal care criteria established by the Institutional Animals Ethics Committee (IAEC). For the in vivo assessment of the anti-inflammatory activity using the carrageenan induced paw oedema model of the novel compound **2**, celecoxib was used as the reference medication. We used nine groups of rats: Rats from groups 1 and 2 administered the vehicle. Rats in group three were given a 50 mg/kg dosage of celecoxib. Rat group 4 was receiving our synthetic compound **2**, respectivley. Thirty minutes prior to the injection of carrageenan, the tested compound was injected with dose of 50 mg/kg. Before tested compound was administered to the rats orally, it was dissolved in recently made carboxymethyle cellulose CMC (0.5%). A subplanter injection of 100 µL of freshly made 1% carrageenan soln in distilled water was used to form changes in the thickness of each rat's left hind paw (percentage of edema inhibition) [78]. The thickness of the paws was measured using a Vernier caliper following injections of carrageenan at 1, 3, and 5 hours. GraphPad Prism (version 9) was used to process the acquired data, which were then presented as mean ± SD. Using a one-way ANOVA and the Tukey-Kramer test to assess the significance of the mean difference, values with $p < 0.05$ were deemed significant [79].

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