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Synthesis and biological screening of some novel 6-substituted 2-alkylpyridazin-3(2*H*)-ones as anti-inflammatory and analgesic agents

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Abstract

Some novel derivatives of 2-alkyl 6-substituted pyridazin-3(2*H*)-ones were synthesized by condensation of 3,6-dichloropyridazine with the sodium salt of benzyl cyanide, followed by hydrolysis and coupling with alkyl halides. The synthesized compounds were screened as cyclooxygenase (COX)-1/COX-2 inhibitors and as analgesic and anti-inflammatory agents. Among the synthesized compounds, 6-benzyl-2-methylpyridazin-3(2*H*)-one (**4a**), 6-benzoyl-2-propylpyridazin-3(2*H*)-one (**8b**), and 6-(hydroxy(phenyl)methyl)-2-methylpyridazin-3(2*H*)-one (**9a**) displayed the highest COX-2 selectivity indices of 96, 99, and 98, respectively, and analgesic efficacies of 47%, 46%, and 45% protection, respectively. Also, compounds **4a**, **8b**, and **9a** showed anti-inflammatory activities of 65%, 60%, and 62% inhibition of edema, respectively, at a dose of 10 mg/kg, which is higher than that of diclofenac (58% inhibition of edema).

KEYWORDS
analgesic activity, anti-inflammatory activity, COX-1, COX-2, pyridazinone

1 | INTRODUCTION

The prostaglandins (PGs) are produced by enzymes called cyclooxygenases (COX). There are two types of COX enzymes, COX-1 and COX-2. Both enzymes produce PGs but with different roles inside the body. COX-2 pathway is the main pathway that promotes inflammation, pain, and fever. On the contrary, COX-1 produces PGs that activate platelets and protect the stomach and intestinal lining.

PGs are classified into many categories and are involved in many processes in the human body.[1] PGE_2 and PGI_2 are important inflammatory mediators and pain-producing mediators. The pain and inflammation induced by PGs affect the lifestyle of patients, and, hence, nonsteroidal anti-inflammatory drugs (NSAIDs) are used to control their synthesis and relieve pain.[2,3]

The classical types of NSAIDs block COX-1 and COX-2 enzymes in different ratios. The newer COX-2 inhibitors block only the COX-2 enzyme. Since COX-2 inhibitors do not block COX-1 they do not cause ulcers or increase the risk of bleeding as much as the older NSAIDs. One of the older NSAIDs is diclofenac (Figure 1). It works by decreasing the production of prostaglandin by blocking both COX-1 and COX-2.[4,5] The new isoform of COX was discovered in the early 1990s, providing a novel target to develop anti-inflammatory agents with superior safety profiles compared to the older NSAIDs.[1,6] Celecoxib is one of the drugs that are selective COX-2 inhibitors.[1,6] The recent drug discovery efforts have been oriented toward developing novel small molecule ring templates as NSAIDs and selective COX-2 inhibitors.[7]

The pyridazin-3-one moiety has a diverse set of biological activities. A wide range of biological activities was recorded for pyridazine derivatives such as antiangiogenic,[8] anticancer,[9] antimicrobial,[10] analgesic,[10,11] antidepressant,[12] antihypertensive,[13] antifungal, antifeedant,[14] phosphodiesterase-4 (PDE4), inhibitors are effective anti-inflammatory, selective COX-2 inhibitors,[15,16] and antiplatelet[17] activities. Various drugs include pyridazinone ring as a core nucleus like sulmazole, levosimendan, amipizone, indolidan, imazodan, pimobendan, emorfazone, zardaverine, and milrinone.[18–25]

In the previous work of our research group[16] focusing on the synthesis of 2,6-disubstituted pyridazin-3(2*H*)-one derivatives as analgesics, anti-inflammatories, we derived the conclusion that the presence the propyl group at position 2 of the pyridazinone ring

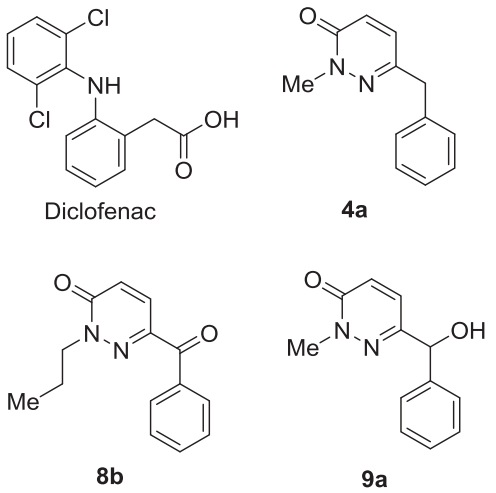
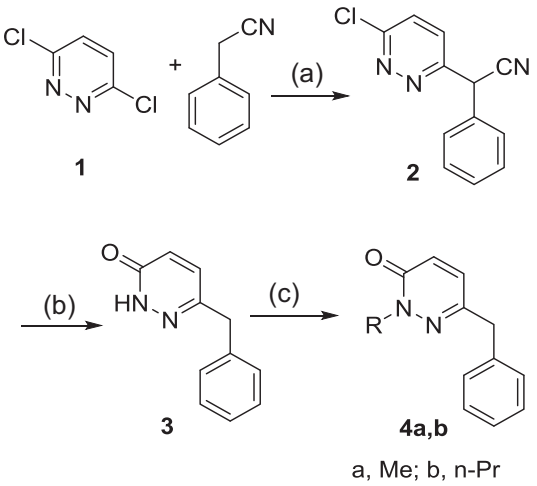


FIGURE 1 Structure of diclofenac and the most active synthesized compounds **4a**, **8b**, and **9a**



SCHEME 1 Synthesis of compounds **4a,b**. Reagents and conditions: (a) NaH, DMF, RT; (b) 4 M HCl, AcOH, reflux; (c) R-X, K_2CO_3, DMF, RT

provided better substituents than arylmethyl groups required for good in-vitro COX-2 inhibition and anti-inflammatory activity. In the present work and in continuation of the previous work, 6-substituted 2-alkylpyridazin-3(2*H*)-ones were synthesized and screened as COX-1/COX-2 inhibitors, analgesic, and anti-inflammatory agents. Alkyl groups (methyl and propyl) were selected at position 2 with different substituents at position 6 for optimization and enhancing their COX-2 selectivity index (SI) and anti-inflammatory activity.

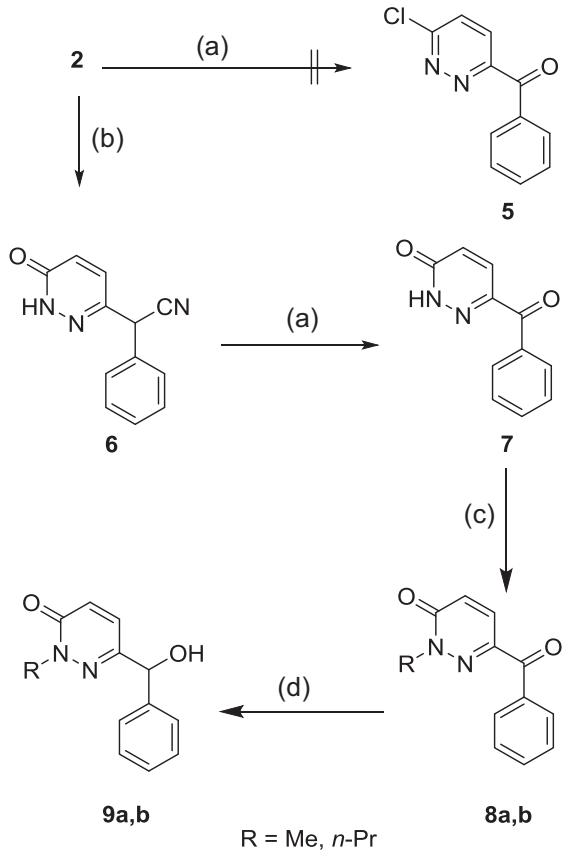
2 | RESULTS AND DISCUSSION

2.1 | Chemistry

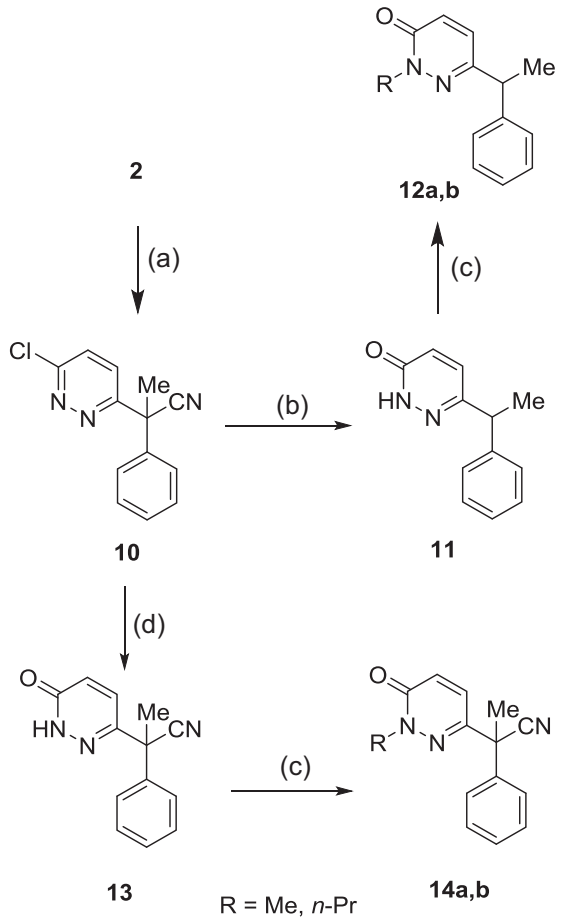
Treatment of 2,6-dichloropyridazine (**1**) with the sodium salt of benzyl cyanide in anhydrous *N*,*N*-dimethylformamide (DMF) as a solvent gave 2-(6-chloropyridazin-3-yl)-2-phenylacetonitrile (**2**) in 78% yield, which was hydrolyzed in a mixture of 4 M hydrochloric acid and acetic acid to afford 6-benzylpyridazin-3(2*H*)-one (**3**). Compound **2** was previously prepared by Bemis et al.[26] in 54% yield through a reaction of compound **1** with benzyl cyanide using sodium amide as a base and tetrahydrofuran as a solvent at room temperature. The melting point of compound **2** and its spectroscopic analysis were not published by Bemis et al.[26] The significant *CH*–CN in compound **2** appeared as a singlet in ^{1}H-NMR (nuclear magnetic resonance) at δ 5.70 ppm, which was converted to the singlet CH_2 in compound **3** at δ 3.88 ppm. 2-Alkyl-6-benzylpyridazin-3(2*H*)-ones **4a,b** were obtained by alkylation of compound **3** with methyl iodide or *n*-propyl bromide in basic medium using dimethylformamide as a solvent (Scheme 1).

In an attempt to get the 6-benzoylpyridazin-3-one (**7**), a trial to oxidize the sodium salt of compound **2** in *N*,*N*-dimethylformamide with a stream of oxygen bubbled through the reaction mixture did not furnish the desired (6-chloropyridazin-3-yl)(phenyl)methanone (**5**), according to the procedure described by Loksha et al.[27] Hydrolysis of compound **2** by acetic acid furnished 2-(6-oxo-1,6-dihydropyridazin-3-yl)-2-phenylacetonitrile (**6**), which was treated with sodium hydride in dimethylformamide followed by oxidation using oxygen air to afford the desired compound **7**. Compound **7** was previously synthesized by Heinisch et al.[28] as an intermediate to be reduced to the hydroxyl derivative through the treatment of compound **2** with an aqueous solution of sodium hydroxide followed by a stream of oxygen. It was separated from the reaction and was used for the further reduction step without identification of its melting point, yield, and spectroscopic analyses.[28] ^{13}C-NMR of compound **7** showed the disappearance of CH and CN, which were detected in compound **6** at δ 40.51 and 118.44 ppm, respectively. CO–NH and *C*O–Ph were detected in the spectrum of compound **7** at δ 160.53 and 189.49 ppm, respectively. Alkylation of compound **7** with methyl iodide and/or *n*-propyl bromide in basic medium using *N*,*N*-dimethylformamide as a solvent afforded 2-alkyl-6-benzoylpyridazin-3(2*H*)-ones **8a,b**. The carbonyl group of CO–Ph in compounds **8a,b** was reduced by sodium borohydride in methanol to the corresponding hydroxyl derivatives **9a,b** (Scheme 2).

Compound **2** was alkylated with methyl iodide in strong basic medium (sodium hydride in anhydrous *N*,*N*-dimethylformamide) to furnish 2-(6-chloropyridazin-3-yl)-2-phenylpropanenitrile (**10**), which was hydrolyzed in strong acidic medium of a mixture of acetic acid and 4 M hydrochloric acid to 6-(1-phenylethyl)pyridazin-3(2*H*)-one (**11**). Hydrolysis of compound **10** by only acetic acid gave 2-(6-oxo-1,6-dihydropyridazin-3-yl)-2-phenylpropanenitrile (**13**). The significant CH–*C*H_3 for compound **11** appeared in ^{1}H-NMR as a doublet at δ 1.49 ppm and a quartet at δ 4.09 ppm for *C*H–CH_3. The signal of *C*H_3–C–CN in compound **13** appeared as a singlet at δ 2.04 ppm. Both of the compounds **11** and **13** were alkylated in basic medium with methyl iodide or *n*-propyl bromide to afford 2-alkyl-6-(1-phenylethyl)pyridazin-3(2*H*)-ones **12a,b** and 2-(1-alkyl-6-oxo-1,6-dihydropyridazin-3-yl)-2-phenylpropanenitriles **14a,b** (Scheme 3).



SCHEME 2 Synthesis of compounds **9a,b**. Reagents and conditions: (a) NaH, DMF, O_2, RT; (b) AcOH, reflux; (c) R-X, K_2CO_3, DMF, RT; (d) $NaBH_4$, MeOH, RT



SCHEME 3 Synthesis of compounds **12a,b** and **14a,b**. Reagents and conditions: (a) NaH, MeI, DMF, RT; (b) 4 M HCl, AcOH, reflux; (c) R-X, K_2CO_3, DMF, RT; (d) AcOH, reflux

2.2 | Biology

2.2.1 | In-vitro inhibition assay for COX enzymes

The IC_{50} results for COX inhibition as well as the SI are shown in Table 1. The assay results demonstrated that all compounds exhibited potent inhibitory activity on COX-2 enzyme with IC_{50} values that were lower than those on COX-1 in the range of 0.04–0.41 μM for COX-2. On the contrary, the inhibitory concentrations against COX-1 were found to be in the range from 4.23 to 11.64 μM for COX-1. Among these compounds, **8b** possess the highest activity with an IC_{50} value of 5.33 μM for COX-1 and 0.054 μM for COX-2, and also showed the highest SI of 99. Furthermore, compounds **2**, **3**, **4a,b**, **6**, **8a**, **9a,b**, **12b**, and **14a,b** exhibited high COX-2 SIs.

2.2.2 | Analgesic activity

The analgesic activity of the compounds was screened to confirm their in vivo activity using a 10-mg/kg dose by applying writhing test as reported by Gawade[29] and evaluated compared to the same dose level of the drug diclofenac as a reference drug (Table 2). The writhing response was counted, and %protection was calculated.[30]

Compounds **4a**, **8b**, and **9a** (Figure 1) exhibited the highest analgesic activity among the synthesized compounds of 47%, 46%, and 45%, respectively in a dose of 10 mg/kg, which was around the same activity of diclofenac (47%). In addition, the analgesic activity of the mentioned compounds agreed with its anti-inflammatory activity. Compounds **3**, **6**, **12b**, and **14a** showed the lowest activity that can be explained depending on different pharmacokinetic parameters of these compounds that affect absorption and metabolism of the compounds in an in vivo study.

2.2.3 | Anti-inflammatory activity

From the previous results, the selected compounds were **4a,b**, **8a,b**, **9a,b**, **12a**, **13**, and **14b**. Carrageenan-induced paw edema in rats was used to evaluate the anti-inflammatory activity of these compounds as reported by Puttaswamy et al.[31] All compounds exhibited significant ($p < .05$, $p = .01–.0001$) anti-inflammatory activity by reducing paw height and, hence, rat paw edema was reduced after 3 hr in comparison with the control group, as shown in Table 3. The compounds **4a**, **8b**, and **9a** exhibited the highest anti-inflammatory activity among all the synthesized

TABLE 1 IC_{50} and selectivity index (SI) values of the compounds

Compound	COX-1 IC_{50} (μM)[a]	COX-2 IC_{50} (μM)[a]	COX-2 (SI)[b]
Celecoxib	16.10	0.059	273
Diclofenac	4.80	0.940	5
2	6.94	0.093	75
3	11.64	0.150	78
4a	7.62	0.079	96
4b	10.21	0.110	93
6	8.63	0.140	62
7	10.34	0.340	30
8a	7.52	0.098	78
8b	5.33	0.054	99
9a	4.23	0.043	98
9b	6.21	0.100	62
12a	11.23	0.410	27
12b	5.61	0.088	64
13	9.87	0.220	45
14a	7.32	0.088	83
14b	9.34	0.260	36

[a]The concentration of the compound producing 50% inhibition of ovine cyclooxygenase (COX)-1 and COX-2 enzymes, the result is the mean of two determinations obtained by assay of enzyme kits obtained from Cayman Chemicals Inc., Ann Arbor, MI.
[b]The in-vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50})

compounds. These activities appeared from the first hour of inflammation with an edema inhibition percentage of 65, 60, and 62 in a dose of 10 mg/kg for compounds **4a**, **8b**, and **9a**, respectively, and were superior to diclofenac with rapid onset of action after 1 hr. The duration sustained until the third hour after the administration of each compound.

2.2.4 | Serum level of interleukin-1β (IL-1β)

At the end of the paw edema test, serum was prepared for enzyme-linked immunosorbent assay (ELISA) determination of IL-1β concentration in the most significant groups; the selected compounds were **4a**, **8b**, and **9a**. As shown in Table 4, compound **4a** exhibited the most significant reduction in the IL-1β concentration, which confirmed the in-vitro inhibition of COX activity and also inhibition of the inflammatory mediators from this pathway. The relation between COX activity and ILs was studied and illustrated in many studies.[32–34] ILs were produced from macrophages during inflammation process to induce the production of PGs.[34] COX pathway was reported in many studies to be upregulated and over expressed by many proinflammatory mediators such as IL-1β in inflammatory and cancer diseases.[35]

Form the data of in-vitro COX-1, COX-2 inhibition (Table 1), analgesic activity (Table 2), and anti-inflammatory activity (Table 3), the activity was increased with the derivatives that included methyl group at position 2 of the pyridazine ring with flexible methylene derivatives (benzyl, 1-phenylethyl, hydroxyl(phenyl)methyl) at position 6 (compound **4a**, **9a**, and **12a**). The activity

TABLE 2 Analgesic activity of the compounds using writhing test

Compound	No. of writhing in 20 min (mean ± SEM)	Analgesic activity (% protection)
Control	50 ± 0.8	0
Diclofenac	26 ± 1.5[a]	47 ± 1.36[a]
2	40 ± 1.6[a,b]	20 ± 1.28
3	51 ± 2.2[b]	3 ± 1.96
4a	27 ± 1.6[a]	47 ± 1.2[a]
4b	44 ± 0.4[a,b]	12 ± 0.4
6	50 ± 0.5[b]	0
7	44 ± 1.8[a,b]	12 ± 1.6
8a	44 ± 1.9[a,b]	11 ± 1.74
8b	27 ± 1.6[a]	46 ± 1.47[a]
9a	28 ± 1.8[a]	45 ± 1.62[a]
9b	35 ± 0.4[a,b]	30 ± 0.4
12a	34 ± 2.5[a,b]	32 ± 2.23
12b	50 ± 0.5[b]	1 ± 0.49
13	34 ± 1.1[a,b]	32 ± 0.98
14a	50 ± 0.4[b]	0
14b	45 ± 2.2[a,b]	11 ± 1.96

Note: The value is expressed as mean ± standard error of the means (SEM; n = 5). Data were analyzed using one-way analysis of variance followed by Bonferroni's test as post hoc test. A p value is considered as significant if it is <.05 compared to control (p = .0001).
[a]Significantly different from control group.
[b]Significantly different from the diclofenac group.

was decreased for the 2-methyl derivatives with benzoyl and/or (1-cyano)(1-phenyl)ethyl groups at position 6 of the pyridazine ring (compounds **4b**, **9b**, and **12b**). Meanwhile, the activity was increased with benzoyl and group at position 6 when the substituent at position 2 was *n*-propyl group (compound **8b**) and decreased when the substituent at position 2 was the methyl group (compound **8a**).

3 | CONCLUSION

It could be concluded that when the group at position 6 of the pyridazine ring is flexible, the alkyl substituent at position 2 is preferred to be short as a methyl group (**4a**, **9a**, and **12a**) but it showed high activity when the alkyl group was long as a *n*-propyl group with the rigid substituent at position 6 as the benzoyl group (**8b**).

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

NMR spectra were recorded on Bruker NMR spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C, with tetramethylsilane

TABLE 3 Percentage changes in rat paw height after carrageenan-induced paw edema in rats

Compound	% Change in paw height (mean ± SEM)			Anti-inflammatory activity (% inhibition of edema)
	1 hr	2 hr	3 hr	3 hr
Control	0.38 ± 0.02	0.46 ± 0.02	0.52 ± 0.02	–
Diclofenac	0.17 ± 0.04[a]	0.15 ± 0.03[a]	0.22 ± 0.02[a]	58
4a	0.21 ± 0.01[a]	0.16 ± 0.02[a]	0.18 ± 0.02[a]	65
4b	0.34 ± 0.02[b]	0.32 ± 0.02[a,b]	0.34 ± 0.02[a,b]	35
8a	0.38 ± 0.02[b]	0.34 ± 0.02[b]	0.38 ± 0.02[a,b]	27
8b	0.24 ± 0.02[a]	0.22 ± 0.02[a]	0.21 ± 0.02[a]	60
9a	0.24 ± 0.02[a]	0.18 ± 0.02[a]	0.20 ± 0.03[a]	62
9b	0.36 ± 0.02[b]	0.32 ± 0.020[a,b]	0.38 ± 0.02[a,b]	27
12a	0.36 ± 0.02[b]	0.30 ± 0.03[a,b]	0.28 ± 0.02[a]	46
13	0.38 ± 0.02[b]	0.34 ± 0.02[b]	0.34 ± 0.02[a,b]	35
14a	0.42 ± 0.02[b]	0.38 ± 0.02[b]	0.38 ± 0.02[a,b]	27

Note: The value is expressed as mean ± standard error of the means (SEM; n = 5). Data were analyzed using one-way analysis of variance followed by Bonferroni's test as a post hoc test. A p value considered significant if it is <.05 compared to control (p = .01–.0001).
[a]Significantly different from the control group.
[b]Significantly different from the diclofenac group.

(TMS) as an internal standard for all compounds except ^{1}H-NMR of compound **11** was recorded on Mercury-300BB NMR spectrometer at 300 MHz with TMS as an internal standard. Mass spectra were recorded on Shimadzu Qp-2010 plus spectrometer for compounds **7**, **8a,b**, **9a,b**, **11**, **13**, and **14a**, Thermo Scientific Trace GC Ultra/ISQ spectrometer for compounds **4a**, **6**, and **10**, and Advion compact mass spectrometer (CMS) NY using atmospheric pressure chemical ionization (APCI) as ion source technique for compounds **4b**, **12a,b**, and **14b**. Melting points (m.p.) were determined on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were performed at Micro Analytical Center, Cairo University, Cairo, Egypt. Reactions were monitored by thin-layer chromatography (TLC) and performed on silica gel TLC plate 60 F254 that was purchased from Merck. The starting material 3,6-dichloropyridazine (**1**) is commercially available and was purchased from Sigma-Aldrich.

TABLE 4 Serum level of IL-1β after paw edema in rats

Groups	IL-1β concentration (pg/ml)
Normal animals	22 ± 1.53
Paw edema-bearing animals	41 ± 0.58[a]
Diclofenac	30 ± 0.67[b]
4a	31 ± 0.67[b]
8b	34 ± 1.33[b]
9a	35 ± 0.58[b]

Note: The value is expressed as mean ± standard error of the means (SEM; n = 5). Data were analyzed using one-way analysis of variance followed by Bonferroni's test as post hoc test. A p value is considered significant if it is <.05 compared to control (p = .0001). Normal animals mean control animals that did not take any medications during the experiment and exhibit no edema.
[a]Significant from normal animals.
[b]Significant from paw edema-bearing animals.

The InChI codes of the investigated compounds together with some biological activity data are provided as supporting information.

4.1.2 | Procedure for the synthesis of 2-(6-chloropyridazin-3-yl)-2-phenylacetonitrile 2

To a stirred solution of 3,6-dichloropyridazine (5, 1.49 g, 0.01 mol) and benzyl cyanide (1.2 ml, 0.01 mol) in anhydrous DMF (25 ml), sodium hydride (0.92 g, 0.021 mol, 55% suspension in paraffin oil) was added portionwise at 0°C. The reaction mixture was left to reach room temperature gradually with stirring, then poured on ice-cold water (100 ml) with stirring, and the precipitated material was collected by filtration and dried to give 1.8 g of compound **2** as a pure white solid; yield: 78%; m.p.: 120–122°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.70 (s, 1H, CH), 7.37–7.50 (m, 5H, H_{arom}), 7.57 (s, 2H, H4 & H5). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 43.08 (CH), 117.54 (CN), 127.42 (C4), 127.69, 129.10, 129.59 (C_{arom}), 129.63 (C5), 132.73 (C_{arom}), 156.92 (C3), and 157.83 (C6); electron ionization mass spectrometry (EI-MS): m/z = 228 (100%), 229 (M^+, 37%). Anal. calcd. for $C_{12}H_8ClN_3$ (229.67): C, 62.76; H, 3.51; N, 18.30. Found: C, 63.05; H, 3.61; N, 18.11.

4.1.3 | General procedure for the synthesis of 6-benzylpyridazin-3(2*H*)-one (3) and 6-(1-phenylethyl) pyridazin-3(2*H*)-one (11)

Compound **2** and/or **10** (5 mmol) was refluxed in a mixture of concentrated hydrochloric acid (20 ml), acetic acid (10 ml), and water (10 ml) for 30 hr. The solvents were evaporated under reduced

pressure, then water (20 ml) was added to the residual material and neutralized with saturated solution of sodium bicarbonate. The solid product formed was collected by filtration and dried to give compounds **3** and **11** as pure white solids.

*6-Benzylpyridazin-3(2H)-one **3***

Yield: 79%; m.p. 76–78°C; ^{1}H-NMR (400 MHz, dimethyl sulfoxide [DMSO]-d_6) δ (ppm): 3.88 (s, 2H, CH_2), 6.82 (d, 1H, J = 9.8Hz, H5), 7.21–7.34 (m, 6H, H4 and H_{arom}), and 12.88 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 38.78 (CH_2), 126.68, 128.72 (C_{arom}), 128.89 (C5), 130.12 (C_{arom}), 134.21 (C4) 138.19 (C_{arom}), 146.91 (C6), and 160.29 (C3); EI-MS: m/z = 186 (M^+, 100%). Anal. calcd. for $C_{11}H_{10}N_2O$ (186.21): C, 70.95; H, 5.41; N, 15.04. Found: C, 70.70; H, 5.58; N, 14.98.

*6-(1-Phenylethyl)pyridazin-3(2H)-one **11***

Yield: 86%; m.p.: 118–120°C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 1.49 (d, 3H, J = 7.0 Hz, CH_3–CH), 4.09 (q, 1H, J = 7.0 Hz, CH_3–CH), 6.77 (d, 1H, J = 9.6 Hz, H5), 7.20–7.33 (m, 5H, H4 & H_{arom}), and 12.86 (bs, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 19.39 (CH_3), 43.26 (CH_3–CH), 126.67, 127.42, 128.66 (C_{arom}), 129.92 (C5), 133.58 (C4), 143.60 (C_{arom}), 149.93 (C6), and 160.26 (C3); EI-MS: m/z = 200 (M^+, 100%). Anal. calcd. for $C_{12}H_{12}N_2O$ (200.24): C, 71.98; H, 6.04; N, 13.99. Found: C, 72.06; H, 6.27; N, 13.82.

4.1.4 | General procedure for the synthesis of the 2-alkylpyridazin-3(2*H*)-one derivatives 4a,b, 8a,b, 12a,b and 14a,b

A mixture of **3**, **6**, **8**, and/or **12** (1 mmol), methyl iodide and/or *n*-propyl bromide (1.1 mmol), and anhydrous potassium carbonate (0.41 g, 3 mmol) in anhydrous DMF (10 ml) was stirred at room temperature for 6 hr. The reaction mixture was poured on ice-cold water (25 ml) with continuous stirring. To obtain compounds **4a,b**, **12a,b** and **14a,b**, the mixture was extracted with ether (3 × 15 ml). The combined ethereal extracts were dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residual material was chromatographed on a column of silica gel using petroleum ether/ethyl acetate (2:1, v/v). To obtain compounds **8a,b**, the solid product formed was filtered off, washed with water followed by petroleum ether, and dried to give a pure white solid.

*6-Benzyl-2-methylpyridazin-3(2H)-one **4a***

White crystals; yield: 45%; m.p.: 63–65°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.78 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 6.82 (d, 1H, J = 9.5 Hz, H5); 7.02 (d, 1H, J = 9.5 Hz, H4), and 7.20–7.33 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 39.91 (CH_2), 40.71 (CH_3), 126.89, 128.70, 128.72 (C_{arom}), 129.58 (C5) 132.48 (C_{arom}), 137.23 (C4), 159.93 (C6), and 164.64 (C3); EI-MS: m/z = 200 (M^+, 100%). Anal. calcd. for $C_{12}H_{12}N_2O$ (200.24): C, 71.98; H, 6.04; N, 13.99. Found: C, 72.20; H, 6.18; N, 13.68.

*6-Benzyl-2-propylpyridazin-3(2H)-one **4b***

Yield: 43%, as an oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (t, 3H, J = 7.5 Hz, CH_2CH_3), 1.78 (sxt, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$), 3.84 (s, 2H, CH_2–Ph), 4.05 (t, 2H, J = 7.5 Hz, $CH_2CH_2CH_3$), 6.75 (d, 1H, J = 9.7 Hz, H5), and 7.12–7.27 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 11.11 ($CH_3CH_2CH_2$), 21.73 ($CH_3CH_2CH_2$), 40.96 (CH_2–Ph), 53.23 (CH_2–N), 126.98, 128.80, 128.84 (C5), 130.04 (C_{arom}), 132.18 (C4), 137.48 (C_{arom}), 146.60 (C6), and 159.78 (C3); APCI-MS ($C_{14}H_{16}N_2O$): m/z = 229.5 (M^+ + 1, 100%).

*6-Benzoyl-2-methylpyridazin-3(2H)-one **8a***

Yellow solid; yield: 84%; m.p.: 130–132°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.84 (s, 3H, CH_3), 7.01 (d, H, J = 9.7 Hz, H5), 7.47–7.50 (m, 2H, H_{arom}), 7.59–7.62 (m, 1H, H_{arom}), 7.97 (d, 1H, J = 9.7 Hz, H4), and 8.03 (d, 2H, J = 7.6 Hz, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 40.89 (CH_3), 128.06 (C_{arom}), 128.83 (C5), 130.41, 131.41, 133.00 (C_{arom}), 134.33 (C4), 142.06 (C6), 160.04 (C3), and 188.57 (Ph–*C*=O); EI-MS: m/z = 105 (100%) and 214 (M^+, 39%). Anal. calcd. for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.00; H, 5.03; N, 13.09.

*6-Benzoyl-2-propylpyridazin-3(2H)-one **8b***

Yellow crystals; yield: 46%; m.p.: 192–194°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, J = 7.4 Hz, $CH_3CH_2CH_2$), 1.78 (sxt, 2H, J = 7.4 Hz, $CH_3CH_2CH_2$), 4.09 (t, 2H, J = 7.4 Hz, $CH_3CH_2CH_2$), 6.91 (d, 1H, J = 9.7 Hz, H5), 7.38–7.41 (m, 2H, H_{arom}), 7.50–7.53 (m, 1H, H_{arom}), 7.86 (d, 1H, J = 9.7 Hz, H4), and 7.94 (d, 2H, J = 7.6 Hz, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 10.96 ($CH_3CH_2CH_2$–N), 21.48 ($CH_3CH_2CH_2$–N), 53.80 ($CH_3CH_2CH_2$–N), 127.99 (C_{arom}), 129.09 (C5), 130.57, 130.97, 132.92 (C_{arom}), 135.41 (C4), 141.96 (C6), 159.77 (C3), and 188.71 (Ph–*C*=O); EI-MS: m/z = 105 (100%) and 242 (M^+, 37%). Anal. calcd. for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.47; H, 5.58; N, 11.90.

*2-Methyl-6-(1-phenylethyl)pyridazin-3(2H)-one **12a***

White solid; yield: 55%; m.p.: 60–62°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.52 (d, 3H, J = 7.4 Hz, CH_3–CH), 3.72 (s, 3H, CH_3–N), 3.98 (q, 1H, J = 7.4 Hz, CH_3–CH); 6.72 (d, 1H, J = 9.5, H5), 6.90 (d, 1H, J = 9.5 Hz, H4), and 7.15–7.34 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 19.44 (CH_3–CH), 40.15 (CH_3–N), 44.24 (CH_3–CH), 126.95, 127.43, 128.77 (C_{arom}), 129.46 (C5) 132.13 (C_{arom}), 142.97 (C4), 150.21 (C6), and 160.16 (C3); APCI-MS: m/z = 215.5 (M^+ + 1, 100%). Anal. calcd. for $C_{13}H_{14}N_2O$ (214.27): C, 72.87; H, 6.59; N, 13.07. Found: C, 73:00; H, 6.66; N, 12.88.

*6-(1-Phenylethyl)-2-propylpyridazin-3(2H)-one **12b***

Yield: 41%; as an oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.92 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.52 (d, 3H, J = 7.0 Hz, CH_3CH), 1.80 (sxt, 2H, J = 7.5 Hz, $CH_3CH_2CH_2$), 3.98 (q, 1H, J = 7.0 Hz, CHCH$_3$), 4.07 (t, 2H, J = 7.5 Hz, $CH_3CH_2CH_2$–N), 6.71 (d, 1H, J = 9.6 Hz, H5), and 6.87 (d, 1H, J = 9.6 Hz, H4); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 11.15 ($CH_3CH_2CH_2$–N), 19.51 (CH_3CH), 21.69 ($CH_3CH_2CH_2$–N), 44.35 (CH_3CH), 53.19 ($CH_3CH_2CH_2$–N), 126.92, 127.43 (C_{arom}), 128.78

(C5), 129.77, 131.75 (C_{arom}), 143.15 (C4), 149.94 (C6), and 159.89 (C3); APCI-MS ($C_{15}H_{18}N_2O$): *m/z* = 243.2 (M^+ + 1, 100%).

2-(1-Methyl-6-oxo-1,6-dihydropyridazin-3-yl)-2-phenylpropanenitrile ***14a***

White solid; yield: 72%, m.p.: 98–100°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.03 (s, 3H, CH_3–C), 3.82 (s, 3H, CH_3–N), 6.84 (d, 1H, *J* = 9.7 Hz, H5), 7.08 (d, 1H, *J* = 9.7 Hz, H4), and 7.32–7.42 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 25.83 (CH_3–C), 40.31 (CH_3–N), 46.39 (CH_3–*C*), 120.83 (CN), 125.81, 128.52 (C_{arom}), 129.23 (C5), 130.22, 130.96 (C_{arom}), 138.31 (C4), 144.38 (C6), and 159.40 (C3). EI-MS: *m/z* = 239 (M^+, 100%). Anal. calcd. for $C_{14}H_{13}N_3O$ (239.28): C, 70.28; H, 5.48; N, 17.56. Found: C, 70.55; H, 5.70; N, 17.29.

2-(6-Oxo-1-propyl-1,6-dihydropyridazin-3-yl)-2-phenylpropanenitrile ***14b***

Yield: 44%; as an oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, 3H, *J* = 7.5 Hz, CH_3CH_2), 1.82 (sxt, 2H, *J* = 7.5 Hz, $CH_3CH_2CH_2$), 4.10 (t, 2H, *J* = 7.5 Hz, $CH_3CH_2CH_2$), 6.79 (d, 1H, *J* = 9.6 Hz, H5), 7.00 (d, 1H, *J* = 9.6 Hz, H4), and 7.19–7.36 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 11.13 ($CH_3CH_2CH_2$–N), 21.61 ($CH_3CH_2CH_2$–N), 26.06 (CH_3CH), 46.65 (CH_3CH), 53.45 ($CH_3CH_2CH_2$–N), 121.05 (CN), 125.89, 128.65 (C_{arom}), 129.39 (C5), 130.66, 130.69 (C_{arom}), 138.56 (C4), 144.32 (C6), and 159.32 (C3); APCI-MS ($C_{16}H_{17}N_3O$): *m/z* = 268.2 (M^+ + 1, 100%).

4.1.5 | Synthesis of 2-(6-chloropyridazin-3-yl)-2-phenylpropanenitrile 10

Sodium hydride (1.2 g, 55% suspension in paraffin oil, 36 mmol) was added portion-wise to a solution of compound **2** (6.87 g, 30 mmol) in anhydrous DMF (15 ml) with stirring for 15 min at room temperature. Methyl iodide (2.28 ml, 36 mmol) was added in one portion to the reaction mixture and stirred for an additional 3 hr. The reaction was quenched with ethanol (1 ml) followed by the addition of cold water (50 ml). The solid product formed was filtered off, washed with water and dried to afford 6.5 g of compound **10** as pure white crystals; yield: 71%; m.p.: 115–117°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.33 (s, 1H, CH_3) and 7.35–7.57 (m, 7H, H_{arom}, H4 & H5); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 26.70 (CH_3), 47.81 (*C*–CN), 121.46 (CN), 126.12 (C4), 128.34, 128.68, 129.12 (C_{arom}), 129.40 (C5), 138.85 (C_{arom}), 156.87 (C3), and 160.43 (C6); EI-MS: *m/z* = 242 (100%), 243 (M^+, 75%), and 244 (44%). Anal. calcd. for $C_{13}H_{11}N_3O$ (243.69): C, 64.07; H, 4.14; N, 17.24. Found: C, 63.93; H, 3.83; N, 17.04.

4.1.6 | General procedure for the synthesis of compounds 6 and 13

Compound **2** and/or **5** (3 mmol) was refluxed in acetic acid (20 ml) for 6 hr. The solvent was concentrated to 10 ml and cooled. The reaction mixture was neutralized with saturated solution of sodium bicarbonate. The solid product formed was filtered off, washed with water followed by petroleum ether and dried to afford compounds **6** and/or **13 as** pure white solids.

2-(6-Oxo-1,6-dihydropyridazin-3-yl)-2-phenylpropanenitrile ***13***

White solid; yield: 89%; m.p.: 53–55°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.04 (s, 3H, CH_3), 6.90 (d, 1H, *J* = 9.9 Hz, H5), 7.31 (d, 1H, *J* = 9.9 Hz, H4), 7.37–7.48 (m, 5H, H_{arom}), and 13.23 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 24.85 (CH_3), 46.15 (*C*–CN), 121.39 (CN), 126.23 (C_{arom}), 128.60 (C5), 129.37, 131.25, 131.34 (C_{arom}), 138.44 (C4), 145.40 (C6), and 159.89 (C3); EI-MS: *m/z* = 225 (M^+, 100%). Anal. calcd. for $C_{13}H_{11}N_3O$ (225.25): C, 69.32; H, 4.92; N, 18.66. Found: C, 69.23; H, 5.25; N, 18.53.

2-(6-Oxo-1,6-dihydropyridazin-3-yl)-2-phenylacetonitrile ***6***

White solid; yield: 95%; m.p. 183–185°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 5.84 (s, 1H, CH–CN), 6.91 (d, 1H, *J* = 9.8 Hz, H5), 7.33 (d, 1H, *J* = 9.8 Hz, H4), 7.38–7.48 (m, 5H, H_{arom}), and 13.23 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 40.51 (CH–CN), 118.44 (CN), 127.97 (C_{arom}), 128.82 (C5), 129.56, 131.18, 132.49 (C_{arom}), 134.05 (C4); 142.55 (C6), and 160.03 (C3); EI-MS: *m/z* = 210 (100%) and 211 (M^+, 85%). Anal. calcd. for $C_{12}H_9N_3O$ (211.22): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.08; H, 4.53; N, 20.00.

4.1.7 | Synthesis of 6-benzoylpyridazin-3(2H)-one 7

Sodium hydride (1.44 g, 55% suspension in paraffin oil, 60 mmol) was added to a solution of compound **6** (4.22 g, 20 mmol) in anhydrous DMF (20 ml). The reaction mixture was stirred in open air for 5 hr. The reaction mixture was poured on ice-cold water and the solid product formed was filtered off, washed with water followed by petroleum ether and dried to afford 3.1 g of the pure white solid of compound **7**; yield: 78%; m.p.: 194–196°C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 7.04 (d, 1H, *J* = 9.8 Hz, H5), 7.51–7.55 (m, 2H, H_{arom}), 7.64–7.68 (m, 1H, H_{arom}), 7.93–7.96 (m, 3H, H4 & H_{arom}), and 13.54 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ (ppm): 128.17 (C_{arom}), 129.68 (C5), 130.38, 131.97, 132.95 (C_{arom}), 135.63 (C4), 142.53 (C6), 160.53 (C3), and 189.49 (Ph–C═O); EI-MS: *m/z* = 106.05 (100%) and 200 (M^+, 34%). Anal. calcd. for $C_{11}H_8N_2O_2$ (200.20): C, 66.00; H, 4.03; N, 13.99. Found: C, 66.15; H, 4.18; N, 13.95.

4.1.8 | Synthesis of 2-alkyl-6-(hydroxy(phenyl) methyl)-pyridazin-3(2H)-ones 9a,b

Under an ice cooling bath, sodium borohydride (0.21 g, 5.5 mmol) was added portionwise to a stirred solution of **8a,b** (5 mmol) in methanol (10 ml). The reaction mixture was left to reach room temperature gradually with stirring for 0.5 hr. Acetic acid (1 ml)

was added followed by addition of water (20 ml). The mixture was extracted with ethyl acetate (3 × 15 ml). The combined organic layers were dried over sodium sulfate and filtered. Then, petroleum ether (20 ml) was added with scratching by glass rod. The crystalized product formed was filtered off and dried to afford **9a,b** as pure white solids.

6-(Hydroxy(phenyl)methyl)-2-methylpyridazin-3(2H)-one ***9a***

White solid; yield: 88%; m.p.: 102–104°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.97 (bs, 1H, OH), 3.81 (s, 3H, CH_3), 5.69 (s, 1H, CH), 6.97 (d, 1H, J = 9.5 Hz, H5), 7.18 (d, 1H, J = 9.5 Hz, H4), and 7.34–7.40 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 40.17 (CH_3), 74.03 (CH-OH), 126.39, 128.39 (C_{arom}), 128.82 (C5), 130.09, 130.48 (C_{arom}), 140.55 (C4), 148.24 (C6), and 160.30 (C3); EI-MS: m/z = 111 (100%) and 216 (M^+, 31%). Anal. calcd. for $C_{12}H_{12}N_2O_2$ (216.24): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.86; H, 5.44; N, 12.66.

6-(Hydroxy(phenyl)methyl)-2-propylpyridazin-3(2H)-one ***9b***

White solid; yield: 66%; m.p.: 66–68°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, 3H, J = 7.5 Hz, $CH_3CH_2CH_2$), 1.87 (sxt, 2H, J = 7.5 Hz, $CH_3CH_2CH_2$), 4.15 (m, 2H, $CH_3CH_2CH_2$), 5.69 (s, 1H, CH-OH), 6.86 (d, 1H, J = 9.5 Hz, H5), 7.14 (d, 1H, J = 9.5 Hz, H4), and 7.34–7.40 (m, 5H, H_{arom}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 11.10 ($CH_3CH_2CH_2$), 21.65 ($CH_3CH_2CH_2$), 53.34 ($CH_3CH_2CH_2$), 74.04 (CH-OH), 126.38, 128.35 (C_{arom}), 128.82 (C5), 130.06, 139.36 (C_{arom}), 140.67 (C4), 148.06 (C6), and 159.99 (C3); EI-MS: m/z = 57 (100%) and 244 (M^+, 3%). Anal. calcd. for $C_{14}H_{16}N_2O_2$ (244.29): C, 68.83; H, 6.60; N, 11.47. Found: C, 68.59; H, 6.31; N, 11.85.

4.2 | Biological screening

4.2.1 | Chemicals and drugs

Carrageenan, celecoxib, and diclofenac sodium were purchased from Sigma-Aldrich. IL-1β ELISA Kit was purchased from Reddot Biotech., Inc. (Canada).

4.2.2 | Animals

Male albino rats and mice were used for the evaluation of anti-inflammatory and analgesic activities, respectively. The animals were purchased from the animal house at The Holding Company for Biological products; vaccines and drugs (VACSERA, Giza, Egypt) were acclimatized for 2 weeks before the experiments at the animal house of Faculty of Pharmacy, Damanhour University. The animals were divided to different separated groups, five animals in each group. The food and water were supplied ad libitum to the animals. All the protocols used in this study were approved and agreed by the Ethical Committee at the Faculty of Pharmacy, Damanhour University, Damanhour, Egypt (with ethical code number 120PO18).

4.2.3 | In-vitro COX assay

Compounds **2**, **3**, **4a,b**, **6,7**, **8a,b**, **9a,b**, **12a,b**, **13**, and **14a,b** were screened for in-vitro COX-inhibiting activity[16] using an enzyme immunoassay (EIA) kit (Cayman Chemical Company, Ann Arbor, MI). The IC_{50} values for the compounds were determined using diclofenac and celecoxib as the reference drug, which are considered as non-selective and selective COX-inhibiting medicine, respectively. Furthermore, the SI for COX-2 (COX-1 IC_{50}/COX-2 IC_{50}) was calculated for the compounds. The inhibition ability of the compounds to inhibit ovine COX-1 and the human recombinant COX-2 form was determined and evaluated using a COX inhibitor screening assay kit (catalog no. 560131; Cayman Chemical Company) in agreement with the instructions recommended and mentioned by the supplier. An inhibitor-screening assay kit was used in this assay. The kit contained two types of COX-1 and 2 enzymes. The inhibitory activity of compounds was measured using the immune assay technique.

4.2.4 | Screening of analgesic activity

The analgesic activity of the compounds was performed using the writhing test as described by Gawade.[29] Mice weight ranged from 25 to 30 g. The mice were then divided into 17 different groups, each containing five animals. The animals were fasted for 8 hr before the experiment. The administration of the compounds (10 mg/kg, p.o.) was performed orally. Equal dose of diclofenac as the reference drug and saline as negative control were also administrated orally. Writhing was induced after 1 hr from compounds administration by using 0.1 ml of 1% glacial acetic acid in a volume of 0.1 ml/10 g body weight. The number of writhing responses (stretching of the abdomen, extension of hind limbs, twisting of the trunk, and elongation of the body) observed were counted for 20 min. The protection percentile against acetic acid-induced writhing was calculated according to the following formula[16]:

$$\%\ \text{Analgesic activity} = \frac{n - n'}{n} \times 100,$$

where n is the mean of writhes of the control group and n' is the mean of writhes of the tested compound group.

4.2.5 | Evaluation of the anti-inflammatory activity

The method of paw edema, reported by Puttaswamy et al.,[31] was used for the evaluation and screening of the activity of the compounds that exhibited analgesic activity against inflammation-induced. Albino rats (150–180 g) were used. The rats were divided into 11 experimental groups of five rats each. One hour after oral administration of the compounds (10 mg/kg), 0.1 ml of 1% carrageenan solution was injected in the left hind paw of each animal. Rat paw volumes were measured using a digital caliper (Germany) used to measure inflammation height at 0, 1, 2, and 3 hr, after carrageenan injection. The percentage increase in left hind paw, in comparison to the uninjected right hind paw, was determined, calculated, and expressed as the amount of inflammation. All the tested compounds were orally administered at equivalent doses of the reference drug diclofenac (10 mg/kg, p.o.).

The anti-inflammatory activity of the selected analgesic compounds after 3 hr was expressed as percentage inhibition of edema that was calculated according to the following equation[16]:

$$\% \text{ Inhibition of edema} = \frac{V_{cont} - V_{test}}{V_{cont}} \times 100,$$

where V_{cont} is the edema volume in the control group and V_{test} is the edema volume in the group of the screened compound.

4.2.6 | ELISA determination of IL-1

IL-1 is one of the important inflammatory mediators used to confirm the anti-inflammatory activity of new anti-inflammatory compounds. At the end of the paw edema test, blood samples were collected from the orbital axis of the eye under light ether anesthesia of the rats. Sera were separated after centrifugation of blood at 5,000 rpm for 15 min; the sera were stored at −80°C until the ELISA assay was performed according to the manufacturer's instructions.

4.2.7 | Statistical analysis

Data were expressed as mean ± standard error of the means. One-way ANOVA followed by Bonferroni's post hoc test was used to analyze the data using the Statistical Package for Social Sciences, version 19 (SPSS, Inc., Chicago, IL). $p < .05$ was considered to be statistically significant.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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