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Il Farmaco 57 (2002) 677–683

IL FARMACO

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Synthesis and biological evaluation of N-substituted indole esters as inhibitors of cyclo-oxygenase-2 (COX-2)

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Received 15 December 2001; accepted 9 March 2002

Abstract

A series of novel N-substituted indole carboxylic, acetic and propionic acid esters have been prepared as possible cyclo-oxygenase-2 (COX-2) enzyme inhibitors. Compounds **20**, **23** were found slightly active against COX-2. The synthesis of indole carboxylic, acetic and propionic acid esters were furnished by using dicyclohexyl carbodiimide (DCC), dimethylamino pyridine (DMAP) as carboxylate activators. N-substitution of indole esters was verified with several benzyl and benzoyl group in presence of NaH in DMF, respectively.

Keywords: Indole esters; COX-2 inhibitors; N-substitution; ^{1}H NMR and mass spectra; Indole carboxylic, acetic and propionic acids

1. Introduction

The first generation of non-steroidal anti-inflammatory drugs (NSAIDs) is non-selective cyclo-oxygenase-1 (COX-1)/COX-2 inhibitor [1]. Recently, several COX-2 selective inhibitors have been reported to have a safer in vivo profile in animal models related with the gastrointestinal side effects [2,3]. Celecoxib [4] and rofecoxib [5] were the first two highly selective COX-2 inhibitors (Fig. 1) to be approved in selected markets for the treatment of certain inflammatory conditions. Many different structural classes of compounds such as thiophenes [6], oxazoles [7], pyrazoles [4], thiazoles [8], furans [5], imidazoles [9], cyclopentens [10], cyclopentadiens [7], cyclopentanons [11], isoindols [12] have been synthesized and evaluated for selective COX-2 enzyme inhibition. The modifications of the non-selective NSAID indomethacin have been intensively studied to obtain COX-2 selectivity. It was found that the alkyl, aryl aralkyl and heterocyclic esters **1** or amides **2**, which were modified from indomethacin, exhibit high potency and selectivity [13] (Fig. 1). Other similar work showed that the carboxylic acid ester and amid derivatives are potent and highly selective COX-2 inhibitors [14]. In addition to these works, we had designed and synthesized *N*-benzyl and *N*-*p*-fluorobenzyl indole 2- and 3-carboxamide derivatives. Compounds **EG-18**–**17** ($IC_{50} = 2.0$, COX-2/COX-1 selectivity index = 0.09), **EG-19**–**18** ($IC_{50} = 1.1$, COX-2/COX-1 selectivity index = 0.07) and **EG-27**–**32** ($IC_{50} = 1.6$, COX-2/COX-1 selectivity index = 0.02) (Fig. 1) were found highly potent and selective COX-2 enzyme inhibitors comparing with celecoxib ($IC_{50} = 0.9$, COX-2/COX-1 selectivity index = 0.08) and rofecoxib ($IC_{50} = 1.06$, COX-2/COX-1 selectivity index = 0.07) [15].

These recent findings of indomethacin and indole derivatives with high degree of selectivity for COX-2 have led us to design new N-substituted indole-2-carboxylic acid (**3**), acetic acid (**4**) and propionic acid (**5**) esters (Fig. 1) as possible selective COX-2 inhibitors.

2. Experimental

Indole-3-acetic acid, indole-3-propionic acid, dimethylamino pyridine (DMAP) from *Fluka*, benzyl bromide, 2,4-dichlorobenzyl chloride, anhydrous Na_2SO_4, AcOH, NaOH, hexanes, ether, MeOH, C_3H_6O, EtOAc, EtOH from *Merck* and indole-2-car-

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0014-827X/02/$ - see front matter
PII: S0014-827X(02)01233-8

boxylic acid, dicyclohexyl carbodiimide (DCC), *p*-bromobenzoyl chloride, *p*-toluoyl chloride, *p*-fluorobenzyl bromide, 1-ethyl-hydroxymethyl pyrrolidine, *o*-cresol, 3-phenyl propanol, 3-hydroxy-*N*-methyl piperidine, 1-hydroxymethyl cyclopropane, 2′-hydroxy-5′-methylacetophenone, 1-cyclopropyl ethanol, KBr, NaH from *Aldrich* were purchased.

M.p.s were taken on a Buchi SMP 20 m.p. apparatus. ^{1}H NMR data were consistent with molecular structures and recorded on a Bruker AC 400 spectrometer. Elemental analyses were performed on LECO-932 CHNS-O Elemental Analyzer. The IR values were determined with Pye Unicam 1025 spectrophotometer. High-resolution mass spectra were run on FISIONS-instruments, VG Platform II.LC MS spectrometer.

2.1. Synthesis of compounds *6–9*, *13*, *15–19*

A reaction mixture containing indole acids in dry CH_2Cl_2 was treated with equivalent amount of DCC and DMAP, followed by corresponding alcohols. The reaction was stirred at room temperature (r.t.) overnight. The mixture was filtered and the filtrate concentrated in vacuo. The residue was diluted with water and extracted with EtOAc (2 × 50 ml). The combined organic solution was washed with 5% AcOH (2 × 50 ml), 1 N NaOH (2 × 50 ml), and water (2 × 50 ml), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (EtOAc–hexanes, 20:80). All physicochemical properties and spectral data are given in Table 1.

2.2. Synthesis of compounds *10–12*, *14*, *20–24*

To a solution of intermediate esters **6–9**, **13**, **15–19** in 5 ml of anhydrous DMF, NaH (60% mineral oil) was added at 0 °C under Ar. The reaction mixture was stirred at 0 °C for 30 min and then treated with corresponding benzyl, benzoyl or substituted benzyl and

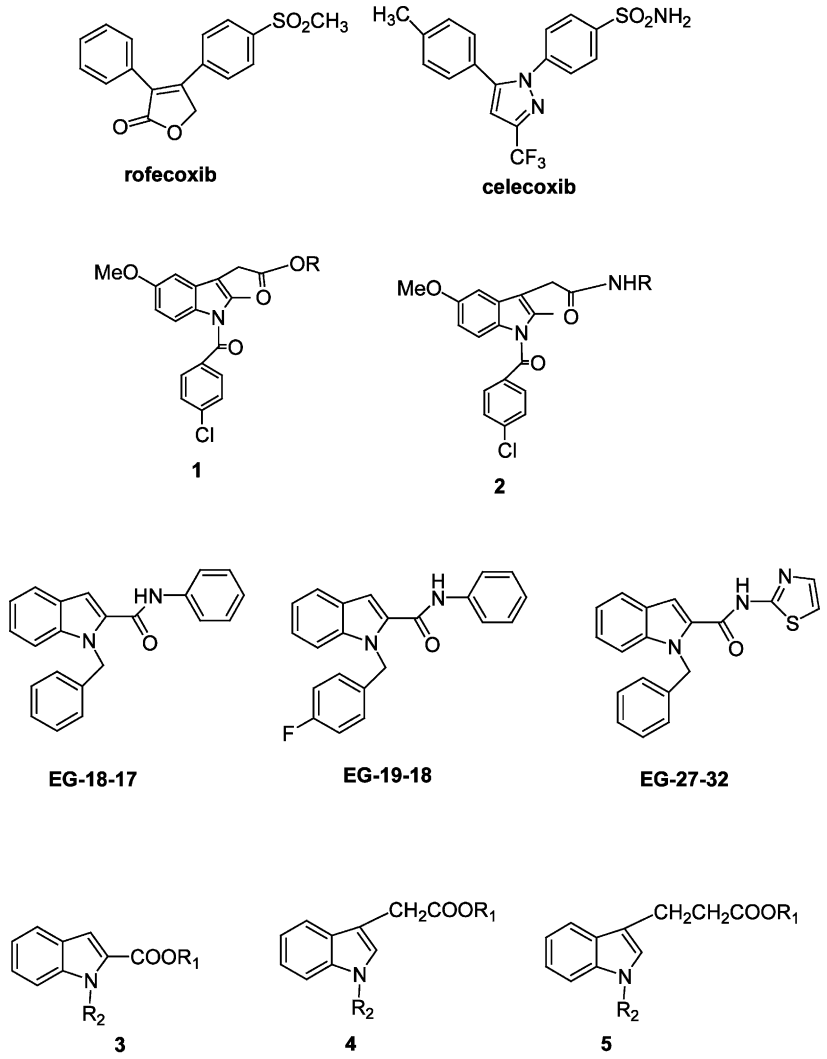
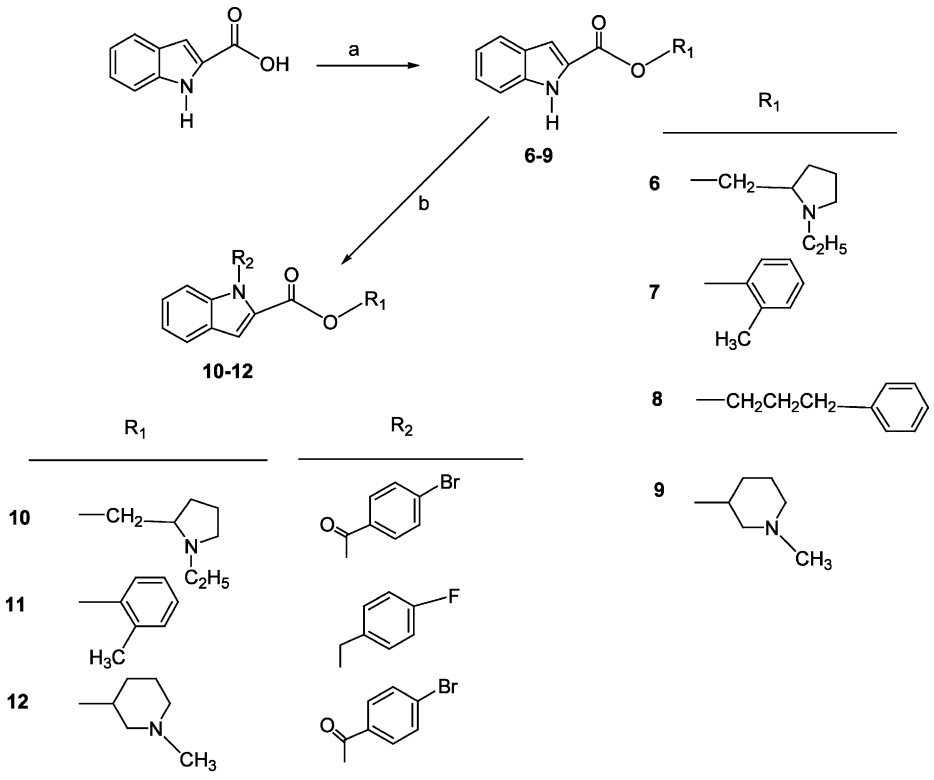


Fig. 1. Structure of rofecoxib, celecoxib and several designed compounds as COX-2 selective inhibitors.

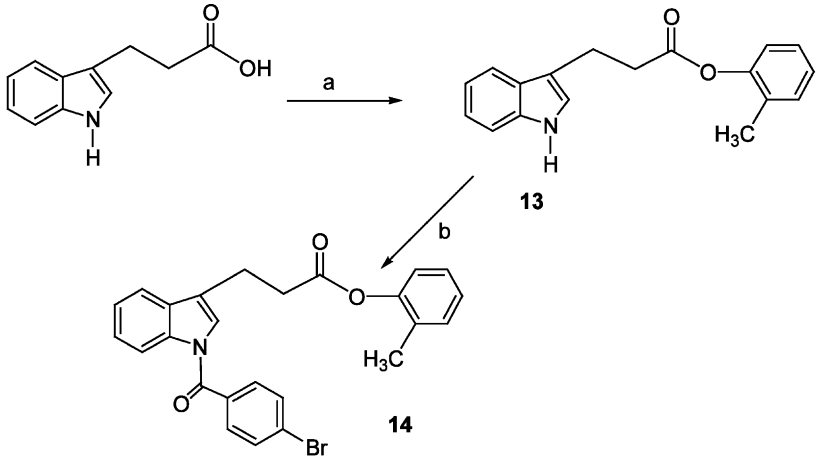
Table 1
Physical and spectral data of compounds **6–24**

Comp.	M.p. (°C)	Yield (%)	IR (KBr, per cm)	Mass (m/z)	^{1}H NMR (δ ppm, $CDCl_3$)
6	209	89	1690 (*CO*O), 3298 (NH)	271 [M^+-1], 242, 224, 186, 159, 143, 115, 89, 67, 55, 41	9.03 (br s, 1H, NH), 7.57–6.93 (m, 5H, aromatic protons), 4.27 (d, 2H, $J=7.4$, COOCH_2), 3.25 (q, 2H, N-CH_2CH_3), 3.05–1.27 (m, 10H, pyrrolidine protons and N-CH_2CH_3)
7	117	58	1729 (*CO*O), 3371 (NH)	251 [M^+], 224, 210, 182, 148, 129, 97, 82, 69, 55, 43	8.27 (br s, 1H, NH), 7.62–6.92 (m, 9H, aromatic protons), 2.34 (m, 3H, Ph–CH_3)
8	172	58	1740 (*CO*O), 3338 (NH)	279 [M^+], 242, 196, 160 143, 114, 91, 77, 55, 41	9.09 (br s, 1H, NH), 7.68–6.93 (m, 10H, aromatic protons), 4.37 (t, 2H, COOCH_2), 3.66 (m, 2H, CH_2CH_2–Ph), 3.44 (t, 2H, CH_2CH_2–Ph)
9	178	52	1697 (*CO*O), 3296 (NH)	258 [M^+], 242, 179, 142, 115, 89, 77, 55, 41	9.02 (br s, 1H, NH), 7.58–6.93 (m, 5H, aromatic protons), 4.36–2.13 (m, 9H, pyrrolidine protons), 2.09 (s, 3H, N-CH_3)
10	173	36	1692 (*CO*O), 1681 (*CO*Ph)	454 [M^+], 425, 397, 370, 342, 297, 269, 184, 170, 143, 112, 84	7.89–6.62 (m, 9H, aromatic protons), 4.18 (d, 2H, $J=7.1$, COOCH_2), 3.29 (q, 2H, N-CH_2CH_3), 3.10–1.34 (m, 10H, pyrrolidine protons and N-CH_2CH_3)
11	61	47	1727 (*CO*O)	359 [M^+], 334, 267, 252, 224, 142, 109, 89, 41	7.56–6.62 (m, 13H, aromatic protons), 5.69 (s, 2H, CH_2–Ph), 2.14 (s, 3H, Ph–CH_3)
12	129	32	1691 (*CO*O)	441 [$M^+ +1$], 397, 297, 253, 182, 171, 143, 115, 41	7.65–6.79 (m, 9H, aromatic protons), 2.34–2.19 (m, 9H, piperidine protons), 2.13 (s, 3H, N-CH_3)
13	107	90	1748 (*CO*O), 3415 (NH)	280 [$M^+ +1$], 269, 235, 224, 171, 143, 129, 78, 55	7.92 (br s, 1H, NH), 7.58–6.85 (m, 9H, aromatic protons), 3.91 (t, 2H, CH_2CH_2COO), 2.95 (t, 2H, CH_2CH_2COO), 2.11 (s, 3H, Ph–CH_3)
14	47	43	1737 (*CO*O), 1698 (*CO*Ph)	461 [M^+], 369, 325, 290, 182, 154, 107, 77, 50	8.02–7.04 (m, 13H, aromatic protons), 4.24 (t, 2H, CH_2CH_2COO), 2.98 (t, 2H, CH_2CH_2COO), 2.15 (t, 3H, Ph–CH_3)
15	167	75	1739 (*CO*O), 3301 (NH)	229 [M^+], 224, 157, 143, 130, 125, 102, 82, 55, 41	8.73 (br s, 1H, NH), 7.55–6.93 (m, 5H, aromatic protons), 5.23 (d, 2H, $J=7.1$, COOCH_2), 4.02 (s, 2H, CH_2COO), 3.28–2.06 (m, 5H, cyclopropyl protons)
16	120	64	1754 (*CO*O), 3431 (NH)	265 [M^+], 236, 225, 204, 193, 172, 157, 130, 107, 77, 63, 51	8.22 (br s, 1H, NH), 7.32–6.90 (m, 9H, aromatic protons), 4.97 (s, 2H, CH_2COO), 2.97 (s, 3H, Ph–CH_3)
17	189	23	1753 (*CO*O), 1687(*CO*CH_3), 3406 (NH)	323 [M^+], 285, 242, 224, 165, 143, 107, 89, 77, 55, 41	9.28 (br s, 1H, NH), 7.54–6.83 (m, 8H, aromatic protons), 4.72 (s, 2H, CH_2COO), 3.81 (s, 3H, OCH_3), 2.62 (s, 3H, COCH_3)
18	181	36	1728 (*CO*O), 3311 (NH)	272 [M^+], 256, 242, 224, 201, 173, 157, 143, 129, 102, 97, 82, 55, 41	8.30 (br s, 1H, NH), 7.53–7.06 (m, 5H, aromatic protons), 3.93 (s, 2H, CH_2COO), 3.90–1.97 (m, 9H, piperidine protons), 1.92 (s, 3H, N-CH_3)
19	170	59	1672 (*CO*O), 3312 (NH)	243 [M^+], 224, 185, 143, 129, 102, 97, 82, 55, 41	8.09 (br s, 1H, NH), 7.54–7.04 (m, 5H, aromatic protons), 5.22 (s, 2H, CH_2COO), 3.85 (q, 1H, $CH$$CH_3$), 3.55 (d, 3H, $J=0.8$, CHCH_3), 2.96–1.99 (m, 5H, cyclopropyl protons)
20	oily	52	ND	347 [M^+], 332, 276, 248, 185, 233, 156, 143, 128, 120, 91, 71	7.88–7.18 (m, 9H, aromatic protons), 5.27 (d, 2H, $J=6.9$, COOCH_2), 4.07 (s, 2H, CH_2COO), 3.91 (s, 3H, Ph–CH_3), 3.12–1.88 (m, 5H, cyclopropyl protons)
21	67	49	1744 (*CO*O), 1662 (*CO*Ph)	383 [M^+], 353, 279, 235, 226, 191, 182, 165, 128, 119, 91, 43	7.69–6.89 (m, 13H, aromatic protons), 4.52 (s, 2H, CH_2COO), 3.85 (s, 3H, Ph–CH_3), 3.78 (s, 3H, CO–Ph–CH_3)
22	93	33	1748 (*CO*O), 1685 (*CO*CH_3)	481 [M^+], 439, 324, 281, 161, 158, 137, 122, 108, 89, 43	7.40–6.86 (m, 11H, aromatic protons), 5.74 (s, 2H, CH_2COO), 5.09 (s, 2H, CH_2–Ph), 3.73 (s, 3H, OCH_3), 2.53 (s, 3H, COCH_3)
23	oily	50	ND	362 [M^+], 347, 333, 305, 278, 271, 262, 248, 228, 199, 171, 91, 77, 43	7.65–6.79 (m, 10H, aromatic protons), 5.21 (s, 2H, CH_2Ph), 4.27 (s, 2H, CH_2COO), 3.98–2.13 (m, 9H, piperidine protons), 1.96 (s, 3H, N-CH_3)
24	110	40	1681 (*CO*O)	425 [M^+], 411, 369, 356, 312, 240, 225, 171, 127, 112, 69, 41	8.28–7.16 (m, 9H, aromatic protons), 5.16 (s, 2H, CH_2COO), 3.88 (q, 1H, $CH$$CH_3$), 3.51 (d, 3H, $J=0.9$, CHCH_3), 2.96–1.92 (m, 5H, cyclopropyl protons)

ND, non-determined.



Scheme 1. (a) Corresponding alcohols, DCC, DMAP, DMF, r.t.; (b) *p*-bromo benzoyl chloride, *p*-fluorobenzyl chloride, NaH, DMF, 0 °C to r.t.

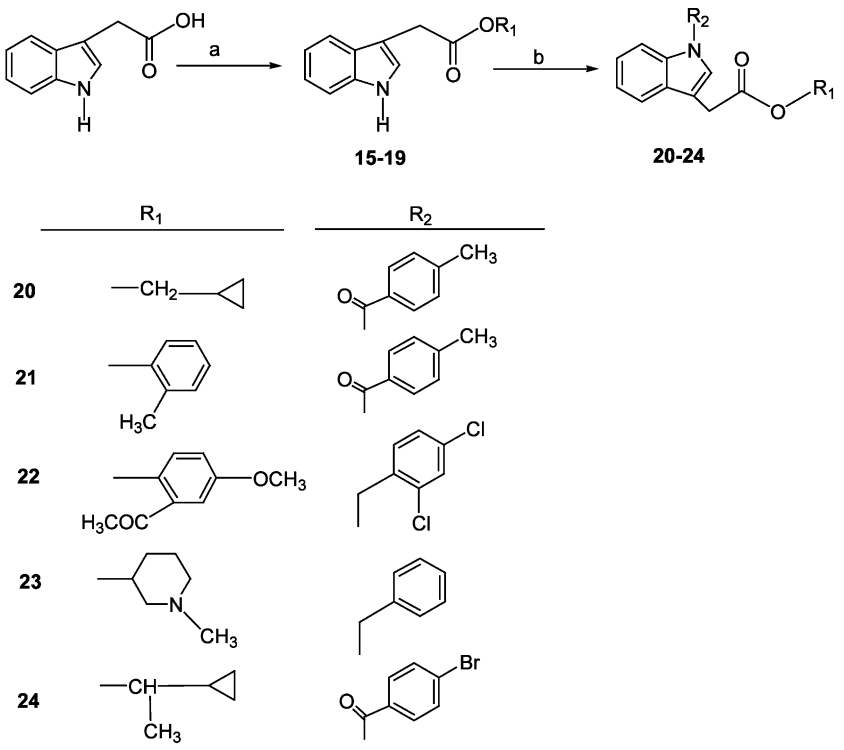


Scheme 2. (a) *o*-Cresol, DCC, DMAP, DMF, r.t.; (b) *p*-bromo benzoyl chloride, NaH, DMF, 0 °C to r.t.

benzoyl chlorides. The temperature was allowed to attain r.t. and the reaction mixture was stirred for 24–48 h. The reaction mixture was poured into the ice-water and extracted with ether (2×20 ml). The combined organic layer was washed with water (2×20 ml), dried over Na_2SO_4 and filtered. The solvent was removed in vacuo and the residue was chromatographed on silica gel (EtOAc–hexanes, 30:70) to afford the title compounds. All physicochemical properties and spectral data are given in Table 1.

2.3. Enzyme assays

Arachidonic acid was purchased from Nu Chek Prep and Sigma Chemical Co. [1-^{14}C] Arachidonic acid ($\sim$40–60 mCi/mmol) was purchased from NEN Dupont and Sigma Chemical Co. Hematin was purchased from Sigma Chemical Co. COX-1 was purified from ram seminal vesicles (Sigma Chemical Co.). The specific activity of the protein was 20 (μMO_2/min)/mg, and the percentage of haloprotein was 13.5%. ApoCOX-1 was prepared as described before [16].



Scheme 3. (a) Corresponding alcohols, DCC, DMAP, DMF, r.t.; (b) *p*-toluoyl chloride, *p*-bromo benzoyl chloride, 2,4-dichlorobenzyl chloride, benzyl bromide, NaH, DMF, 0 °C to r.t.

Apoenzyme was reconstituted by the addition of hematin to the assay mixtures. Human COX-2 was expressed in SF-9 insect cells by means of the pVL 1393 expression vector and purified by ion-exchange and gel filtration chromatography.

2.3.1. Time- and concentration-dependent inhibition of ovine COX-1 and human COX-2 using thin layer chromatography (TLC) assay

COX activity of ovine COX-1 (44 nM) or human COX-2 (66 nM) was assayed by TLC. Reaction mixtures of 200 μl consisted of hematin-reconstituted protein in 100 nM Tris–HCl, pH 8.0, 500 μM phenol, and [1-^{14}C] arachidonic acid (50 μM, ~40–60 mCi/mmol). For the time-dependent inhibition assay, hematin reconstituted COX-1 (44 nM) or COX-2 (66 nM) was preincubated at r.t. for 20 min with varying inhibitor concentrations in DMSO followed by the addition of [1-^{14}C] arachidonic acid (50 μM) for 30 s at 37 °C. Reactions were terminated by solvent extraction in Et_2O–CH_3OH–1 M citrate, pH 4.0 (30:4:1). The phases were separated by centrifugation at 2000 × *g* for 2 min and the organic phase was spotted on a TLC plate (J.T. Baker). The plate was developed in EtOAc–CH_2Cl_2–glacial AcOH (75:25:1) at 4 °C. Radiolabelled prostanoid products were quantitated with a radioactivity scanner (Bioscan, Inc.). The percentage of total products observed at different inhibitor concentrations was divided by the percentage of products observed for protein samples preincubated for the same time with DMSO.

3. Results and discussion

Well-established methodology was utilized in the synthesis of ester derivatives as indicated in Schemes 1–3. Among the several methods of synthetic pathway to obtain ester derivatives [17,18], we have derived the method of Hassner and Alexanian [19]. The intermediate ester derivatives were prepared by treatment with appropriate alcohol in the presence of DCC and DMAP. N-substitution of intermediate esters with several benzyl and benzoyl group in presence of NaH afforded the resulted compound [20]. In most cases, good yields of esters were obtained for intermediate compounds. N-substitution of intermediate esters with several benzyl and benzoyl group in presence of NaH afforded the resulted compounds with reasonable yield. The intermediate esters were obtained as solid whereas the resulted compounds were obtained as solid with very low m.p. Besides, compounds **20**, **23** were obtained as oily. The structure of the compounds was characterized by ^{1}H NMR, IR, and mass spectral data (Table 1). Elemental analysis indicated at 96% a minimum purity of target compounds.

Table 2
In vitro COX-2 potencies of indole esters **6**–**24**

Comp.	IC_{50} (μM) [a]		Selectivity [b]
	COX-2	COX-1	
LM4108	0.1	>66.0	>660
Indomethacin	0.75	0.05	0.067
6–**19**, **21**, **22**, **24**	>50.0	ND	ND
20	2.0	>38.0	>19.0
23	2.5	>29.0	>11.6

[a] IC_{50} values were determined by incubating concentration at 2 and 10 in μM in DMSO with human COX-2 (66 nM) or ovine COX-1 (44 nM) for 20 min at r.t. followed by initiation of the COX reaction with the addition of ^{14}C-AA (50 μM) at 37 °C for 30 s. Assays were run in duplicate.

[b] Ratio of IC_{50} (COX-1)–(COX-2).

Biological activity tests were applied by comparing the inhibition effects of COX-2 for these compounds with indomethacin and LM4108 that is reported by Kalgutkar et al. [14]. Our synthesized compounds **20** and **23** were slightly active at 2 and 10 μM. The results were summarized in Table 2. These compounds contain cyclopropyl methyl and cyclopropyl ethyl group on the ester side chain. However, there is no significant selectivity for compounds **20** and **23**, when they were compared with indomethacin and LM4108. None of other compounds were found active against COX-2 concentration at 2 and 10 μM. Many ester and amide derivatives were found highly active and selective to inhibition of COX-2 enzyme in the literature [13–15]. On the contrary, it was surprising that our compounds were not. This suggests that not all carboxylate-, acetate- and propionate-containing indole derivatives can be converted into COX-2 inhibitors by esterification. Consequently, the results of activity tests showed that the synthesized ester derivatives were not promising compounds for selective COX-2 inhibition while the amide derivatives were.

Acknowledgements

This work was partially supported by a grant from the Turkish Scientific and Technical Research Institute (SBAG-AYD-341). The authors thank Dr Larry Marnett (Vanderbilt School of Medicine, Department of Biochemistry, Tennessee, USA) for performing some of COX-2 enzyme inhibition tests.

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