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Original article

Novel thiopyrano[3,2-*b*] and cycloalkeno[1,2-*b*]indole derivatives with high inhibitory properties in LTB_4 production

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Abstract – Series of thiopyrano[3,2-*b*] and cycloalkeno[1,2-*b*]indoles were synthesized and evaluated in order to determine the necessary structural requirements for high leukotrienes biosynthesis inhibition. In vitro experiments showed that compounds **11b** and **12b** belonging to the second series were the most active and selective compounds on LTB_4 production. Further in vivo investigations have shown additional very significant activity in the acute phorbol ester induced mouse ear swelling which is predictive of potential antipsoriatic properties. © Elsevier, Paris

thiopyranoindoles / cycloalkanoindoles / antiinflammatory properties / antipsoriatic properties / LTB_4 production inhibition / 5-lipoxygenase inhibition / 5-lipoxygenase-activating-protein (FLAP)

1. Introduction

Metabolism of arachidonic acid (AA) leads to numerous oxidated metabolites via two major pathways involving two types of enzymes: cyclooxygenases and 5-lipoxygenases [1]. Cyclooxygenases (CO) catalyse an oxydation of AA followed by a ring closure between C-8 and C-12, leading to prostaglandins and thromboxanes, which are for many of them potent pro-inflammatory mediators. Inhibition of CO has been a common target of anti-inflammatory drug investigations, although, due to their mechanism of action, ingestion of high dose of selective CO inhibitors may induce some side effects such as ulceration of the gastrointestinal tract [2]. 5-Lipoxygenase (5LO) catalyses the peroxidation of AA to the 5-hydroperoxy eicosatetranoic acid (5-HPETE) which is then subsequently converted to the 5,6-epoxy leukotriene A_4 (LTA_4), a corner stone in the formation of the leukotrienes. Unlike CO which is widely distributed in mammalian cells, 5LO is restricted mainly to neutrophils, eosinophils, monocytes, macrophages and mast cells [3]. Leukotrienes are clearly implicated in numerous inflammatory and allergic deseases [4, 5], with among others, psoriasis [6, 7], rheumatoid, arthritis [8], inflammatory bowel desease [9, 10], asthma [11] and allergic rhinitis. For these reasons restriction of leukotrienes synthesis by inhibition of 5LO has been a very attractive target for many investigators.

As it has been found that the 5-lipoxygenase-activating-protein (FLAP) is essential for the translocation of the 5LO from the cytosol to the membrane [12, 13] it is possible to inhibit the formation of leukotrienes either by direct inhibition of the 5LO or indirectly by inhibiting the action of FLAP. During the last decades, numerous inhibitors of leukotrienes biosynthesis such as Zileuton [14], MK 591 [15], MK 886 [16], Wy 50295 [17], ZD 2138 [18] *(figure 1)* and others have been identified and have shown promising therapeutic interest.

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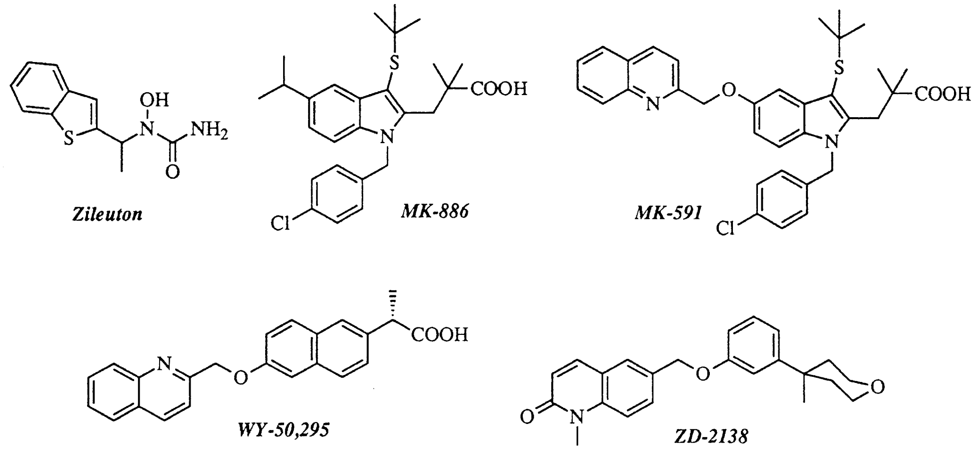


Figure 1.

Inhibitors of 5LO can be classified under three main headings according to their putative mechanisms of enzyme inhibition [19]. The redox inhibitors, such as Phenidone and BW 755C, have a low redox potential which allows the reduction of the enzyme iron from the active form Fe^{3+} to the inactive one Fe^{2+}, and maintain the enzyme in the inactive Fe^{2+} state. Redox inhibitors generally show poor selectivity for 5LO relative to CO. Other iron ligand inhibitors contain functional groups interacting with the iron in the active site of 5LO. Most of these compounds are hydroxyureas and hydroxamic acid derivatives such as Zileuton, BWA4C, and A 78773 [3, 20] *(figure 2)*.

Finally a third category is constituted by non-redox, non-iron ligand inhibitors such as ICI 211965, or ICI D 2138 [21] *(figure 3)*.

Concerning compounds inhibiting 5LO translocation (anti-FLAP) most of them, with exception of MK 886, are quinolyl derivatives [22, 23]. Some representative quinolinyl Anti-FLAP derivatives are WY 47288 [24], WY 50295 [25], MKO591 [26], BAY X1005 [27] and L 674 573 [23] *(figure 4)*.

On the other hand thiopyrano[2,3,4-*c*,*d*]-indole derivatives such as L 699333 or compounds A and B *(figure 5)* have been described by Hutchinson et al. [28] as potent inhibitors of both FLAP and 5LO.

In this paper, we report the synthesis and pharmacological evaluation of new anti-inflammatory thiopyrano[3,2-*b*]- and cycloalkeno[1,2-*b*]-indole derivatives. Chemical modulations were carried out to determine the necessary structural requirements for high leukotrienes biosynthesis inhibition.

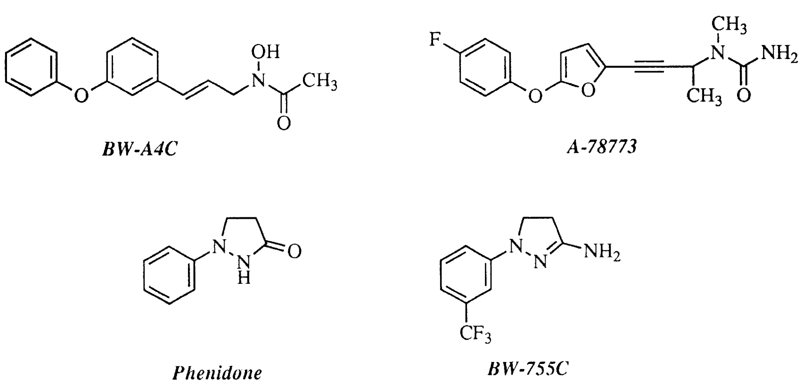
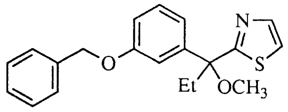


Figure 2.



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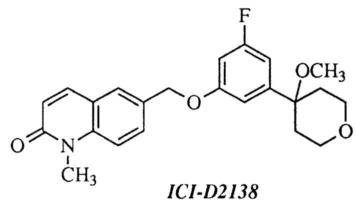
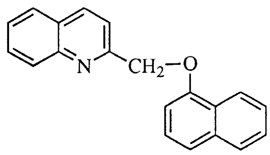


ICI-D2138

Figure 3.



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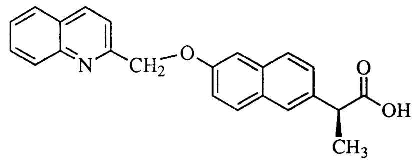

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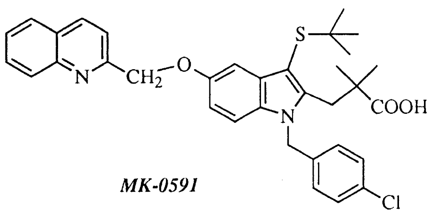
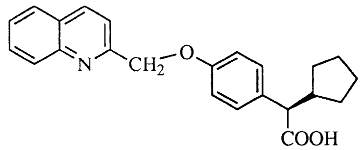
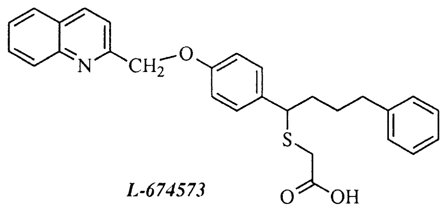


MK-0591

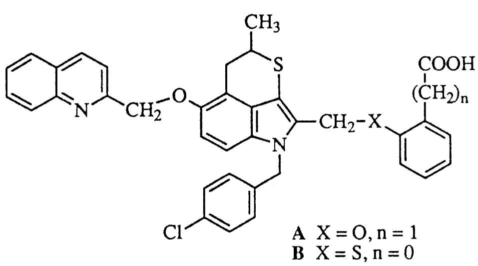


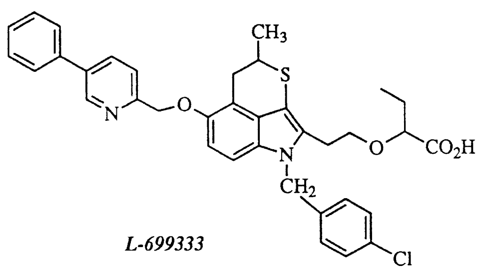
BAY-X1005



L-674573

Figure 4.





L-699333

Figure 5.

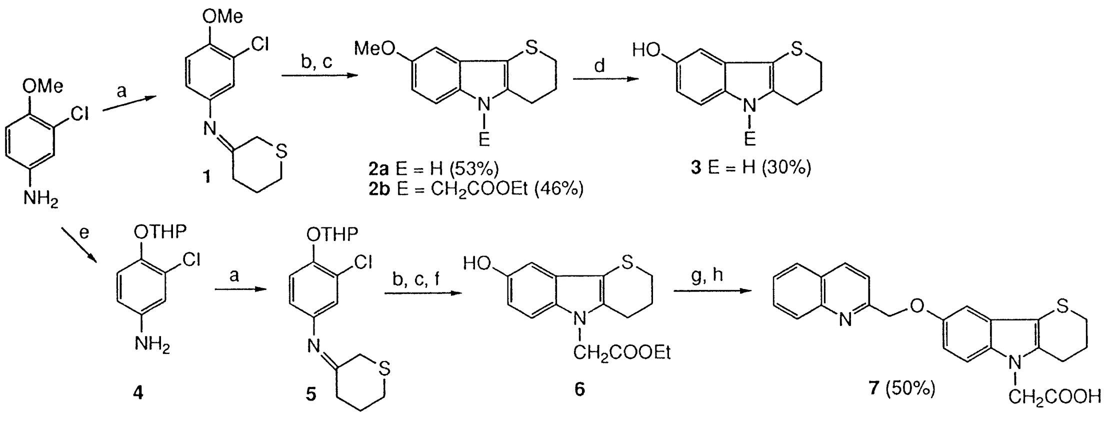


Figure 6. (a) 3-Thiopyranone, C_6H_6, Δ; (b) $NaNH_2$-*t*-BuONa, THF, RT; (c) H_2O, 0 °C for **2a**, $BrCH_2COOEt$, DMF, RT for **2b** and **6**; (d) Pyr-HCl, Δ; (e) (i): CH_3COCl, Pyr, DMAP, RT, (ii): $AlCl_3$–$PhCH_2SH$, 0 °C to RT, (iii): DHP, PPTS, RT, (iv): KOH/MeOH, Δ; (f) PTSA, MeOH, RT; (g) 2-chloromethylquinoline, K_2CO_3, $Bu_4N^+HSO_4^-$, DMF, Δ; (h) KOH/EtOH, Δ.

2. Chemistry

Four thiopyrano[3,2-*b*]- and seven cycloalkeno[1,2-*b*]indole derivatives were synthesized and evaluated. The thiopyranyl indoles were obtained by two ways *(figure 6)* which key step was an intramolecular arynic cyclisation [29] of the corresponding imines in the presence of a complex base [30].

Compounds **2** resulted from the trapping with the appropriate electrophile of the anion resulting from the arynic cyclisation. Demethylation of **2a** with the previously used reagent $AlCl_3$–$PhCH_2SH$ [31] was presently unsuccessful, the thiopyran ring being simultaneously opened [29]. On the contrary with pyridinium hydrochloride [32] the demethylation took place although in moderate yields. Exploratory experiments showed that the above synthesis could not be easily used in the preparation of **7**. So we developed another pathway also starting from the unexpensive 3-chloro anisidine which was first easily transformed into **4** on a large scale. Indole **6** was obtained from **4** in a good overall yield by arynic cyclisation of the corresponding imine followed by the

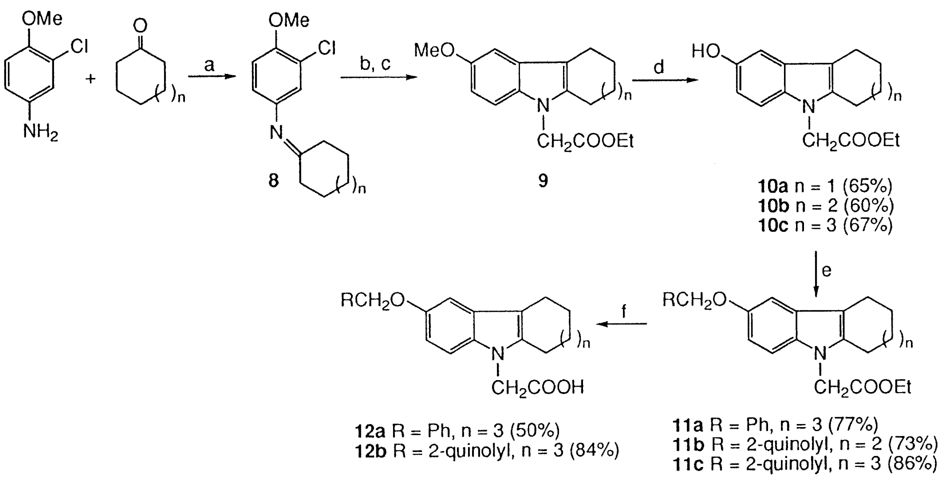


Figure 7. (a) C_6H_6, Δ; (b) $NaNH_2$-*t*-BuONa, THF, RT; (c) $BrCH_2COOEt$, DME, RT; (d) $AlCl_3$–$PhCH_2SH$, 0 °C to RT; (e) RCH_2Cl, K_2CO_3, $PhCH_2N^+Et_3Cl^-$, DMF, Δ; (f) KOH, EtOH, Δ.

removal of the phenol protecting group. Finally condensation of 2-chloromethyl quinoline under phase transfer catalysis (PTC) condition followed by saponification led to **7**. Similarly the cycloalkeno-indole derivatives were obtained according to *figure 7*.

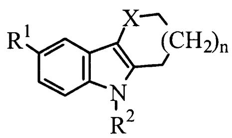
In the present case the demethylation of indoles **9** nicely took place with the $AlCl_3$–$PhCH_2SH$ reagent [33, 34]. Finally compounds **11** were efficiently obtained by condensation under PTC conditions of benzyl chloride and 2-chloromethyl quinoline respectively and **12a** and **12b** by saponification of the corresponding **11** compound.

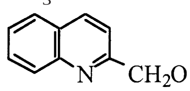
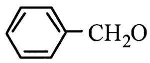
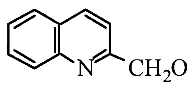
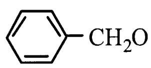
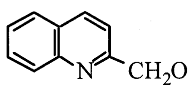
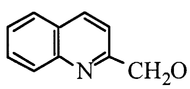
3. In vitro results and discussion

All compounds were prescreened in vitro for their ability to inhibit PGE_2 and LTB_4 production by A 23187 stimulated Rabbit granulocytes. Results were expressed as IC_{50} (concentration inhibiting 50% of the PGE_2 or LTB_4 production) or, in case of low activity, by the percentage of inhibition of PGE_2 or LTB_4 production at a concentration of 10 μM *(table I)*.

Compound **10c** is a moderate inhibitor of both LTB_4 and PGE_2 production with IC_{50} of respectively 5.5 and

Table I. In vitro inhibition of the production of LTB_4 and PGE_2 in A23187 stimulated rabbit granulocytes.



Compound	*n*	X	R^1	R^2	PGE_2 (IC_{50}) [a]	LTB_4 (IC_{50}) [b]
10a	1	CH_2	OH	CH_2COOEt	40% at 10 μM [c]	6 μM
3	1	S	OH	H	0% at 10 μM [c]	26% at 10 μM [d]
2a	1	S	OCH_3	H	5.5 μM	12 μM
2b	1	S	OCH_3	CH_2COOEt	0% at 10 μM [c]	14% at 10 μM [d]
7	1	S		CH_2COOH	NT	4.5 μM
10c	3	CH_2	OH	CH_2COOEt	4.2 μM	5.5 μM
11a	3	CH_2		CH_2COOEt	900 nM	22% at 10 μM [d]
11b	2	CH_2		CH_2COOEt	0% at 10 μM [c]	100 nM
12a	3	CH_2		CH_2COOH	3.9 μM	1.7 μM
11c	3	CH_2		CH_2COOEt	0% at 10 μM [c]	200 nM
12b	3	CH_2		CH_2COOH	0% at 10 μM [c]	100 nM
Indomethacine					2.7 nM	NT
NDGA [e]					NT	470 nM

[a] Concentration inhibiting 50% of the PGE_2 product; [b] concentration inhibiting 50% of the LTB_4 product; [c] % of inhibition of PGE_2 synthesis at 10 μM; [d] % of inhibition of LTB_4 synthesis at 10 μM; [e] NDGA = Nordehydroguaiacetic acid.

4.2 μM. On the contrary, its 2-benzyloxy analog **11a** is a selective inhibitor of CO with an IC_{50} of 900 nM and has virtually no effect on LTB_4 production (22% inhibition at 10 μM).

As expected, compound **11c** is a potent inhibitor of leukotriene biosynthesis (IC_{50} = 200 nM on LTB_4) with not effect on PGE_2 production. There are no difference in activity between **11c** which is an ethyl ester and its corresponding acid **12b** (IC_{50} of respectively 200 and 100 nM on LTB_4 production and no effect at 10 μM on PGE_2). Surprisingly this is not the case for compounds **11a** and **12a** (R^1 = $PhCH_2O$). Whilst the ethyl ester **11a** is a selective inhibitor of CO, the corresponding acid **12a** is almost equipotent in both LTB_4 and PGE_2 production with IC_{50} of respectively 1.7 and 3.9 μM. The size of the cycloalkeno ring seems to have only little influence on LTB_4 production inhibition. Compounds **11c** and **11b** have exactly the same activity (IC_{50} = 100 nM on LTB_4, no effect on PGE_2 at 10 μM).

When R^1 = OH, compounds **10a** and **10c** have similar effects on LTB_4 production (IC_{50} of respectively 6 and 5.5 μM) but are not equipotent on PGE_2 production (IC_{50} of 4.2 μM for **10c**, 40% inhibition at 10 μM for **10a**).

Concerning the thiopyrano[3,2-*b*]indoles, the only derivative showing some significant, though moderate, activity on LTB_4 production is, as expected, the 8-(quinol-2-yl) methyloxy substituted compound **7** (IC_{50} = 4.5 μM). As the thiopyrano derivatives appeared to be less active than their cycloalkeno analogs, no further synthesis were undertaken.

In conclusion to this preliminary evaluation, three compounds (**11b**, **11c** and **12b**) were found to be more potent selective inhibitors of the leukotriene pathway than NDGA, all of them being substituted by a quinol-2-yl methyloxy.

4. In vivo pharmacology

Due to their activity and selectivity on LTB_4 production, compounds **11b** and **12b** were selected for further investigation in vivo in the acute phorbol ester (PMA)-induced mouse ear swelling test *(table II)*. This model of topical inflammation affords some degrees of success in the search of potential antipsoriatic compounds with anti-inflammatory properties, as LTB_4 antagonists or leukotriene production inhibitors [33, 34].

After topical application of 3 mg/ear, compounds **11b** and **12b** exerted a significant reduction in ear thickness of respectively 61 and 71% (compared to 66% for indomethacin).

Table II. Effects of **11b** and **12b** in the acute PMA-induced mouse ear swelling test.

Compound	Inhibition, % after topical application of tested compound		
	10 mg/ear	3 mg/ear	1 mg/ear
11b	75% [a]	61% [a]	11% [a]
12b	83% [a]	71% [a]	0%
Indomethacine		66% [a]	

[a] $p < 0.001$; $n = 5$.

5. Conclusion

The chemical modulations performed on both thiopyrano[3,2-*b*]indole and cycloalkeno[1,2-*b*]indole series led us to display new compounds inhibiting potently and selectively LTB_4 production. Among the three compounds more active than NDGA, two were selected for in vivo evaluation (**11b**, **12b**) and showed very significant activity in the acute phorbol ester-induced mouse ear swelling test which is predictive of potential antipsoriatic properties. Both deserve further investigations currently under exploration.

6. Experimental protocols

6.1. Chemistry

Spectral datas will be given below only for pharmacologically tested products.

6.1.1. General methods

Melting points were determined on a Totoli melting point apparatus and are uncorrected. ^{13}C NMR spectra were recorded with a Bruker AM 400 or a Bruker 300 MHz spectrometer (Attached Proton Test method, APT). ^1H-NMR spectra were recorded on a Jeol PMX 60 at 60 MHz, or a Brucker AM 400 instrument at 400 MHz. Me_4Si was the internal standard. Infrared (IR) spectra of thin liquid films between NaCl plates or KBr pellets were recorded with a Perkin-Elmer 841 instrument. Elemental analyses were performed by CNRS Laboratory (Vernaison) and by E.N.S.C.M. Microanalysis Department of Montpellier. Mass spectra were recorded on a Hewlett Packard 5971A instrument. Thin-layer chromatography (TLC) was performed with plates coated with kieselgel G (Merck). The plates were eluted with petroleum ether(PE)/EtOAc or acetone/hexane as eluents. The silica gels used for column chromatography and flash chromatography were kieselgels of 0.063–0.2 mm and 0.04–0.063 mm particle size, respectively. A capillary

HP1(6m) was used for gpc. Imines **1**, **5** and **8** were classically obtained in yields varying from 40% to 75% by azeotropic dehydration of an equimolar amount of amine and ketone. They were either purified by fast distillation under vacuum or used as crude product after classical work-up without other purification.

*6.1.2. Synthesis of amine **4***

6.1.2.1. N-Acetyl-3-chloro-paraanisidine

To a stirred suspension of 0.05 eq. of 4-N, N-dimethylaminopyridine and 1 eq. of acetyl chloride in Et_2O (1 mL/1 mmol) were added at RT, a solution of 1 eq. of pyridine in Et_2O (1 mL/4 mmol), a solution of 1 eq. of 3-chloro-paraanisidine in Et_2O (2 mL/4 mmol) and dioxane (1 mL/4 mmol). The mixture was stirred 5 h at RT and the reaction monitored by TLC. At the end of the reaction, the mixture was acidified with HCl 1 N and the organic layer washed with water and dried over $MgSO_4$. The solvents were removed under vacuum and crude N-acetyl-3-chloro-paraanisidine was washed with petroleum ether to give 89% of pure product.

6.1.2.2. N-Acetyl-3-chloro-4-hydroxy-aniline

To a stirred suspension of 1.5 eq. of $AlCl_3$ and 10 eq. of $PhCH_2SH$ at 0 °C was added 1 eq. of N-acetyl-3-chloro-paraanisidine in CH_2Cl_2 (5 mL/1 mmol). After stirring at 0 °C 30 min, 0.75 eq. of $AlCl_3$ were further added. The reaction was monitored by TLC. After 3 h at RT, an acid hydrolysis with HCl 1 N at 0 °C was done. The mixture was extracted with CH_2Cl_2 and the organic layer washed with H_2O and a saturated solution of NaCl, and dried over Na_2SO_4. The solvents were removed under vacuum to give 76% of crude N-acetyl-3-chloro-4-hydroxyaniline which was directly used for next step.

6.1.2.3. N-Acetyl-3-chloro-4-tetrahydropyrannyloxy-aniline

To a solution of 1 eq. of N-acetyl-3-chloro-4-hydroxyaniline in ethyl acetate (3 mL/1 mmol) and CH_2Cl_2 (3 mL/1 mmol) were added 6 eq. of dihydropyrane and 0.5 eq. of pyridinium paratoluene sulfonate. The reaction was monitored by TLC. After stirring 2 days at RT, the mixture was diluted with H_2O. The organic layer was dried over $MgSO_4$ and the solvents removed under vacuum to give 84% of pure product.

6.1.2.4. 3-Chloro-4-tetrahydropyranyloxyaniline

A mixture of Claisen base [KOH, H_2O (1 mL/30 mmol) and MeOH (5 mL/30 mmol)] and N-acetyl-3-chloro-4-tetrahydro pyranyloxyaniline (3 mL/1 mmol) was warmed at 40 °C for 18 h. The MeOH was then removed under vacuum and the residue diluted with CH_2Cl_2. The organic layer was washed with H_2O and dried over $MgSO_4$. The solvents were removed under vacuum and the pure aniline derivative obtained in 100% yield.

*6.1.3. Arynic synthesis: General procedure for the preparation of indoles **2** and **9***

To a stirred suspension of 7 eq. of $NaNH_2$ in THF (1 mL/7 mmol) was slowly added at 0 °C 2 eq. of *t*-BuOH in the minimum amount of THF. The stirred reaction mixture was then warmed to 42 °C for 2 h. The complex base thus obtained was cooled to 0 °C, and a solution of imine **1** or **8** in THF (3 mL/1 mmol) was added dropwise. The stirred reaction mixture was then allowed to warm to RT for 12 h (indoles **2**) and 24 h (indoles **9**), and the resulting salt was trapped with various electrophiles.

(1) Trapping with $E^+ = H_2O$. The reaction mixture was pourred into ice and extracted with Et_2O, the organic phase was dried over $MgSO_4$, and the solvent removed under vacuum. Indoles were isolated by flash chromatography with EtOAc/PE as eluent.

*6.1.3.1. 8-Methoxy-thiopyrano[3,2-b]indole **2a***

M.p.: 122–124 °C. IR (NaCl): 3390 cm^{-1} (NH), 2999–2938–2834 cm^{-1} (C–H). ^{1}H-NMR ($CDCl_3$): δ 7.50 (1 H, s, NH), 7.40–6.70 (3 H, m, arom. H), 3.8 (3 H, s, OCH_3), 3.20–2.60 (4 H, m, $2CH_2$), 2.50–2.00 (2 H, m, CH_2). ^{13}C-NMR ($CDCl_3$): δ 153.70 (arom. *C*OCH_3), 129.98 (arom. C), 129.69 (arom. C), 126.47 (arom. C), 100.52 (arom. C), 111.63 (arom. CH), 111.15 (arom. CH), 99.61 (arom. CH), 55.68 (OCH_3), 26.73 (CH_2), 24.02 (CH_2), 22.64 (CH_2). Anal. calc. for $C_{12}H_{13}ONS$: C, 65.72; H, 5.97; N, 6.38; S, 14.62. Found: C, 65.95; H, 6.03; N, 6.53; S, 14.93.

(2) Trapping with $E^+ = BrCH_2COOEt$. The reaction mixture was decanted and the supernatant liquid was transferred into a flask containing a stirred solution of 3 eq. of bromoester in DMF (final ratio of THF/DMF = 1/2) at RT. The reaction was monitored by TLC. When the unsubstituted indole had disappeared, the reaction mixture was then poured into ice and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and solvents removed under vacuum. The N-substituted indoles were recovered by flash chromatography using acetone/hexane as eluents.

*6.1.3.2. 2-(8-Methoxy-thiopyrano[3,2-b]indol-5-yl) ethyl acetate **2b***

M.p.: 97–99 °C. IR (NaCl): 2923 cm^{-1} (CH), 1750 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.20–6.50 (3 H, m, arom. H), 4.50 (2 H, s, NCH_2), 4.30–3.90 (2 H, q, CH_2), 3.80 (3 H, s, OCH_3), 3.10–2.00 (6 H, m, $3CH_2$), 1.40–1.00 (3 H, t, CH_3). ^{13}C-NMR ($CDCl_3$): δ 168.49 (C=O), 154.11 (arom. *C*OCH_3), 131.35 (arom. C), 130.68 (arom. C), 126.49 (arom. C), 111.73 (arom. CH), 109.08 (arom. CH), 101.22 (arom. C), 100.20 (arom. CH), 61.48 (COO*C*H_2), 55.80 (OCH_3), 44.58 (NCH_2), 26.62 (CH_2), 24.37 (CH_2), 21.53 (CH_2), 14.04 ($COOCH_2$*C*H_3). Anal. calc. for $C_{16}H_{19}O_3NS$: C, 62.92; H, 6.27; N, 4.58; S, 10.49. Found: C, 62.58; H, 6.32; N, 4.69; S, 10.36.

*6.1.3.3. Demethylation of methoxy indole **2a***

A mixture of **2a** and pyridinium chlorhydrate (5 eq. in weight) was refluxed 3 h at 150 °C under nitrogen. The reaction was monitored by gpc. When all the methoxy indole had disappeared, an acid hydrolysis with HCl 1 N was done and the mixture extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and solvents removed under vacuum. The hydroxy indole **3** was isolated by flash chromatography with acetone/hexane 20% as eluent.

*6.1.3.4. 8-Hydroxy-thiopyrano[3,2-b]indole **3***

M.p.: 182–185 °C. IR (NaCl): 3400 cm^{-1} (OH), 3307 cm^{-1} (NH). ^{1}H-NMR ($CDCl_3$/DMSO): δ 9.61 (1 H, s, OH), 8.27 (1 H, s, NH), 7.07–7.04 (1 H, d, arom. H), 6.70 (1 H, s, arom. H), 6.65–6.62 (1 H, d, arom. H), 3.00–2.70 (4 H, m, $2CH_2$), 2.25–2.10 (2 H, m, CH_2). ^{13}C-NMR ($CDCl_3$/DMSO): δ 150.16 (arom. *C*OH), 130.17 (arom. C), 129.84 (arom. C), 126.62 (arom. C), 111.06 (arom. CH), 111.05 (arom. CH), 101.96 (arom. CH), 98.60 (arom. C), 26.68 (CH_2), 24.14 (CH_2), 22.74 (CH_2). Anal. calc. for $C_{11}H_{11}ONS$: C, 64.36; H, 5.40; N, 6.82; S, 15.62. Found: C, 64.54; H, 5.60; N, 6.55; S, 15.69.

*6.1.4. Procedure for the synthesis of indole **7***

Indole **6** was obtained from 3-thiopyranone [35] using the general procedure of arynic cyclisation and quenching with $BrCH_2COOEt$. The crude mixture reaction was diluted in MeOH (1 mL/1 mmol) with 0.2 eq. of PTSA. At the end of the reaction, monitored by TLC, the methanol was removed under vacuum and the residue diluted with Et_2O, washed with a solution of $NaHCO_3$ 5%. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. The hydroxy indole **6** was isolated by flash chromatography with a acetone/hexane 20% as eluent, with 25% yield from **4**. [IR (NaCl): 3449 cm^{-1} (OH), 1741 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.00–6.70 (3 H, m, arom. H), 4.80 (1 H, s, OH), 4.70 (2 H, s, C*H_2*COOEt), 4.15 (2 H, q, COOC*H_2*CH_3), 3.00–2.20 (6 H, m, $3CH_2$), 1.20 (3 H, t, $COOCH_2$C*H_3*)]. To a solution of 1 eq. of **6** in DMF (10 mL/1 mmol) was twice added at RT 2 eq. of K_2CO_3, then 1.5 eq. of 2-chloromethylquinoline chlorhydrate and 0.2 eq. (× 2) of $Bu_4N^+HSO_4^-$. After stirring at 40 °C during 27 h, the mixture was hydrolyzed on ice and extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$ and the solvents removed under vacuum. Indole **7** was purified by flash chromatography with a MeOH/CH_2Cl_2 0.2% as eluent.

*6.1.4.1. 2-{8-[(Quinol-2-yl)methyloxy]thiopyrano[3,2-b]indol-5-yl}acetic acid **7***

M.p.: 213–216 °C. IR (NaCl): 3463 cm^{-1} (OH), 1724 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$/DMSO): δ 8.40–7.50 (7 H, m, arom. H + OH), 7.40–7.20 (1 H, m, arom. H), 7.00–6.80 (2 H, m, arom. H), 5.35 (2 H, s, OCH_2), 4.80 (2 H, s, NCH_2), 3.00–2.00 (6 H, m, $3CH_2$). ^{13}C NMR ($CDCl_3$/DMSO): δ 168.41 (C=O), 156.28 (arom. C), 150.32 (arom. C–O), 145.10 (arom. C), 134.84 (arom. CH), 129.78 (arom. C), 129.63 (arom. C), 127.70 (arom. CH), 126.63 (arom. CH), 125.92 (arom. CH), 125.27 (arom. C), 124.43 (arom. C), 123.87 (arom. CH), 117.54 (arom. CH), 109.38 (arom. CH), 108.07 (arom. CH), 99.36 (arom. CH), 97.75 (arom. C), 69.63 (OCH_2), 42.19 (NCH_2), 24.16 (CH_2), 22.03 (CH_2), 19.11 (CH_2). Anal. calc. for $C_{23}H_{20}O_3N_2S$: C, 68.30; H, 4.98; N, 6.92; S, 7.93. Found: C, 68.42; H, 5.07; N, 6.85; S, 7.67.

*6.1.5. Demethylation of methoxy indoles **9***

To a suspension of 20 eq. of $PhCH_2SH$ and 1.5 eq. of $AlCl_3$ at 0 °C was slowly added a solution of 1 eq. of indole **9** in CH_2Cl_2 (2 mL/mmol). The reaction mixture was stirred for 0.5 h at 0 °C and 20 eq. of $PhCH_2SH$ and 1.5 eq. of $AlCl_3$ were added. After stirring for 1.5 h at 0 °C, acid hydrolysis with HCl 10% was done at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic phase washed with H_2O and brine and dried over Na_2SO_4. The solvent was removed under vacuum and indoles **10** were isolated by flash chromatography using EtOAc/PE as eluent.

*6.1.5.1. 2-(6-Hydroxy-1,2,3,4-tetrahydrocarbazol-9-yl)ethyl acetate **10a***

M.p.: 104–106 °C. IR (NaCl): 3396 cm^{-1} (OH), 2926–2851 cm^{-1} (CH), 1739 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.20–6.50 (3 H, m, arom. H), 4.60 (2 H, s, CH_2), 4.70–4.50 (1 H, s, OH), 4.40–3.90 (2 H, q, COOC*H_2*CH_3), 2.90–2.40 (4 H, m, $2CH_2$), 2.30–1.60 (4 H, m, $2CH_2$), 1.50–1.10 (3 H, t, $COOCH_2$C*H_3*). ^{13}C-NMR ($CDCl_3$): δ 169.40 (C=O), 149.37 (arom. COH), 136.15 (arom. C), 131.72 (arom. C), 128.18 (arom. C), 110.14 (arom. CH), 109.61 (arom. C), 108.49 (arom. CH), 103.01 (arom. CH), 61.49 (COO*C*H_2), 44.42 (NCH_2), 22.90 ($2CH_2$), 21.72 (CH_2), 20.79 (CH_2), 13.94 ($COOCH_2$*C*H_3). Anal. calc. for $C_{16}H_{19}O_3N$: C, 70.30; H, 7.00; N, 5.12. Found: C, 70.03; H, 7.03; N, 5.28.

*6.1.5.2. 2-(2-Hydroxy-5,6,7,8,9,10-hexahydrocyclohept[b]indol-5-yl)ethyl acetate **10b***

Liquid. IR (NaCl): 3403 cm^{-1} (OH), 2921–2850 cm^{-1} (CH), 1738 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.00–6.50 (3 H, m, arom. H), 6.07 (1 H, s, OH), 4.68 (2 H, s, NCH_2), 4.20–4.00 (2 H, q, $COOCH_2$), 2.75–2.60 (4 H, m, $2CH_2$), 1.90–1.65 (6 H, m, $3CH_2$), 1.30–1.10 (3 H, t, $COOCH_2CH_3$). ^{13}C-NMR ($CDCl_3$): δ 169.47 (C=O), 149.42 (arom. COH), 139.51 (arom. C), 130.89 (arom. C), 128.68 (arom. C), 113.75 (arom. C), 110.10 (arom. CH), 108.67 (arom. CH), 102.73 (arom. CH), 61.50 ($COOCH_2$), 44.64 (NCH_2), 31.38 (CH_2), 28.08 (CH_2), 26.74 (CH_2), 26.28 (CH_2), 24.20 (CH_2), 13.94 ($COOCH_2CH_3$). Anal. calc. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.36; N, 4.87. Found: C, 71.00; H, 7.65; N, 4.78.

*6.1.5.3. 2-(2-Hydroxy-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indol-5-yl) ethyl acetate **10c***

M.p.: 99–101 °C. IR (NaCl): 3406 cm^{-1} (OH), 2980–2927–2850 cm^{-1} (CH), 1753 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.00–6.60 (3 H, m, arom. H), 6.31 (1 H, s, OH), 4.67 (2 H, s, NCH_2), 4.20–4.00 (2 H, q, $COOCH_2$), 2.80–2.60 (4 H, m, $2CH_2$), 1.70–1.23 (8 H, m, $4CH_2$), 1.21–1.00 (3 H, t, $COOCH_2CH_3$). ^{13}C-NMR ($CDCl_3$): δ 169.53 (C=O), 149.31 (arom. COH), 137.14 (arom. C), 131.55 (arom. C), 128.17 (arom. C), 111.75 (arom. C), 110.05 (arom. CH), 108.55 (arom. CH), 102.65 (arom. CH), 61.43 ($COOCH_2$), 44.52 (NCH_2), 29.95 ($2CH_2$), 28.43 (CH_2), 25.58 (CH_2), 22.77 (CH_2), 22.61 (CH_2), 13.76 ($COOCH_2CH_3$). Anal. calc. for $C_{18}H_{23}O_3N$: C, 71.73; H, 7.69; N, 4.64. Found: C, 71.49; H, 7.67; N, 4.77.

*6.1.6. Procedure for the synthesis of compounds **11***

To a stirred solution of 1 eq. of indole **10** in DMF (10 mL/1 mmol) was added 1.8 eq. (R = Ph) or 4 eq. (R = 2-quinolyl) of K_2CO_3, 1.2 eq. of benzyl chloride or 1.5 eq. of 2-methylquinoline hydrochloride, and 0.2 eq. (R = Ph) or 0.4 eq. (R = 2-quinolyl) of $PhCH_2N^+Et_3Cl^-$ at RT. The mixture was warmed to 35–40 °C for 5 h (R = Ph) or 20 h (R = 2-quinolyl). Compounds **11** were isolated by flash chromatography using EtOAc/PE 15% as eluent.

*6.1.6.1. 2-(2-Benzyloxy-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indol-5-yl)ethyl acetate **11a***

Liquid. IR (NaCl): 3032–2927–2850 cm^{-1} (CH), 1753 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 7.60–6.60 (8 H, m, arom. H), 4.95 (2 H, s, NCH_2), 4.55 (2 H, s, OCH_2), 4.40–3.85 (2 H, q, $COOCH_2$), 3.10–2.60 (4 H, m, $2CH_2$), 2.10–1.00 (11 H, m + t, $4CH_2$ + $COOCH_2CH_3$). ^{13}C-NMR ($CDCl_3$): δ 169.04 (C=O), 153.27 (arom. C–O), 137.82 (arom. C), 137.31 (arom. C), 131.99 (arom. C), 128.39 (2arom. CH), 128.09 (arom. C), 127.62 (2arom. CH), 127.55 (arom. CH), 112.37 (arom. C), 110.91 (arom. CH), 108.87 (arom. CH), 102.00 (arom. CH), 70.97 (OCH_2), 61.40 ($COOCH_2$), 44.76 (NCH_2), 30.17 (CH_2), 28.66 (CH_2), 25.83 (CH_2), 25.78 (CH_2), 23.05 (CH_2), 22.87 (CH_2), 14.06 ($COOCH_2CH_3$). Anal. calc. for $C_{25}H_{29}O_3N$: C, 76.69; H, 7.46; N, 3.57. Found: C, 76.76; H, 7.51; N, 3.61.

*6.1.6.2. 2-{2-[Quinol-2-yl)methyloxy]-5,6,7,8,9,10-hexahydrocyclohept[b]indol-5-yl)}ethyl acetate **11b***

M.p.: 64–67 °C. IR (NaCl): 2921–2849 cm^{-1} (CH), 1753 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 8.10–7.10 (6 H, m, arom. H), 7.00–6.60 (3 H, m, arom. H), 5.25 (2 H, s, NCH_2), 4.50 (2 H, s, OCH_2), 4.20–3.80 (2 H, q, $COOCH_2$), 2.90–2.40 (4 H, m, $2CH_2$), 2.00–1.50 (6 H, m, $3CH_2$), 1.40–1.00 (3 H, t, $COOCH_2CH_3$). ^{13}C-NMR ($CDCl_3$): δ 168.59 (C=O), 158.50 (arom. C), 152.59 (arom. C–O), 147.14 (arom. C), 139.36 (arom. C), 136.40 (arom. CH), 131.06 (arom. C), 129.19 (arom. CH), 128.44 (arom. CH), 128.31 (arom. C), 127.33 (arom. CH), 127.15 (arom. C), 125.86 (arom. CH), 118.88 (arom. CH), 113.85 (arom. C), 110.38 (arom. CH), 108.73 (arom. CH), 101.79 (arom. CH), 71.69 (OCH_2), 61.01 ($COOCH_2$), 44.35 (NCH_2), 31.10 (CH_2), 27.85 (CH_2), 26.51 (CH_2), 26.06 (CH_2), 24.00 (CH_2), 13.76 ($COOCH_2CH_3$). Anal. calc. for $C_{27}H_{28}O_3N_2$: C, 75.67; H, 6.58; N, 6.53. Found: C, 75.49; H, 6.37; N, 6.42.

*6.1.6.3. 2-{2-[Quinol-2-yl)methyloxy]-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indol-5-yl)}ethyl acetate **11c***

M.p.: 59–61 °C. IR (NaCl): 2925–2852 cm^{-1} (CH), 1753 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 8.20–8.00 (2 H, m, arom. H), 7.80–7.60 (3 H, m, arom. H), 7.55–7.40 (1 H, m, arom. H), 7.20–6.85 (3 H, m, arom. H), 5.42 (2 H, s, NCH_2), 4.68 (2 H, s, OCH_2), 4.20–4.00 (2 H, q, $COOCH_2$), 2.90–2.70 (4 H, m, $2CH_2$), 1.75–1.60 (4 H, m, $2CH_2$), 1.45–1.30 (4 H, m, $2CH_2$), 1.30–1.10 (3 H, t, $COOCH_2CH_3$). ^{13}C-NMR ($CDCl_3$): δ 168.82 (C=O), 158.65 (arom. C), 152.67 (arom. C–O), 147.31 (arom. C), 137.29 (arom. C), 136.58 (arom. CH), 131.89 (arom. C), 129.37 (arom. CH), 128.63 (arom. CH), 127.49 (arom. CH), 126.03 (arom. CH), 127.99 (arom. C), 127.32 (arom. C), 119.05 (arom. CH), 112.21 (arom. C), 110.42 (arom. CH), 108.83 (arom. CH), 101.85 (arom. CH), 71.79 (OCH_2), 61.22 ($COOCH_2$), 44.55 (NCH_2), 29.97 ($2CH_2$), 28.48 (CH_2), 25.63 (CH_2), 22.88 (CH_2), 22.69 (CH_2), 13.91 ($COOCH_2CH_3$). Anal. calc. for $C_{28}H_{30}O_3N_2$: C, 75.98; H, 6.83; N, 6.33. Found: C, 75.70; H, 6.79; N, 6.05.

*6.1.7. Procedure for the synthesis of indoles **12***

A stirred solution of 1 eq. of indole **11** in KOH/EtOH (10%) was refluxed until all the ester had disappeared (monitored by TLC). Then the mixture was poured on ice and extracted with Et_2O. The aqueous phase was acidified and extracted with Et_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, and the solvent removed under vacuum. Indoles **12** were purified by flash chromatography using EtOAc/PE 70% as eluent.

*6.1.7.1. 2-(2-Benzyloxy-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indol-5-yl)acetic acid **12a***

M.p.: 104–106 °C. IR (NaCl): 3700–200 cm^{-1} (OH), 2923–2849 cm^{-1} (CH), 1720 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ 9.50 (1 H, s, OH), 7.50–7.10 (5 H, m, arom. H), 7.10–6.60 (3 H, m, arom. H), 5.05 (2 H, s, NCH_2), 4.70 (2 H, s, OCH_2), 3.00–2.60 (4 H, m, $2CH_2$), 2.00–1.10 (8 H, m, $4CH_2$). ^{13}C-NMR ($CDCl_3$): δ 175.04 (C=O), 153.34 (arom. CO), 137.70 (arom. C), 137.16 (arom. C), 131.82 (arom. C), 128.39 (2arom. CH), 128.12 (arom. C), 127.65 (2arom. CH), 127.57 (arom. CH), 112.61 (arom. C), 110.10 (arom. CH), 108.76 (arom. CH), 102.19 (arom. CH), 71.01 (OCH_2), 44.21 (NCH_2), 30.07 ($2CH_2$), 28.63 (CH_2), 25.73 (CH_2), 23.02 (CH_2), 22.82 (CH_2). Anal. calc. for $C_{23}H_{25}O_3N$: C, 76.00; H, 6.93; N, 3.85. Found: C, 75.99; H, 7.23; N, 3.94.

*6.1.7.2. 62-{2-[Quinol-2-yl)methyloxy]-6,7,8,9,10,11-hexahydro-5H-cyclooct[b]indol-5-yl)}acetic acid **12b***

Chlorhydrate. m.p.: 133–166 °C. IR (NaCl, Nujol): 3600–3200 cm^{-1} (OH), 1750 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$/DMSO): δ 8.30–6.80 (10 H, m, arom. H + OH), 5.41 (2 H, s, NCH_2), 4.71 (2 H, s, OCH_2), 3.00–2.60 (4 H, m, $2CH_2$), 1.80–1.20 (8 H, m, $4CH_2$). ^{13}C-NMR ($CDCl_3$/DMSO): δ 170.69 (C=O), 158.36 (arom. C), 152.26 (arom. CO), 146.97 (arom. C), 137.31 (arom. C), 136.48 (arom. CH), 131.75 (arom. C), 129.35 (arom. CH), 128.29 (arom. CH), 127.63 (arom. C), 127.34 (arom. CH), 127.09 (arom. C), 125.94 (arom. CH), 118.96 (arom. CH), 111.56 (arom. C), 110.04 (arom. CH), 108.74 (arom. CH), 101.66 (arom. CH), 71.61 (OCH_2), 44.19 (NCH_2), 29.73 ($2CH_2$), 28.16 (CH_2), 25.41 (CH_2), 22.67 (CH_2), 22.45 (CH_2). Anal. calc. for $C_{26}H_{26}O_3N_2$: C, 75.34; H, 6.32; N, 6.75. Found: C, 75.54; H, 6.30; N, 6.80.

6.2. Biology

Acute phorbol ester-induced mouse ear swelling test.

Male or female Charles River derived ICR mice (20–24 g) were purchased from Animal Ressources Center (College of Medecine, National Taiwan University) and housed (10 mice per cage) in a light-controlled (12 h light/day) and temperature-controlled (23 ± 1 °C) environment. The animals were housed in plastic boxes on sawdust and had ad libitum access to tap water and laboratory chow (Taiwan Co. Sugar Products).

12-*O*-tetradecanoylphorbol-13-acetate (TPA) (Sigma) (5 mL in 20 mL ethanol:water in ratio 8:2) was applied topically, in a single dose, to the inner and outer surfaces of the right ear of mice [33]. The mice were randomly divided into five groups: vehicle; 1, 3 and 10 mg pper ear of **11b**, **12b** and reference compounds, indomethacin at 3 mg/ear. The appropriate doses of **11b** and **12b** were dissolved in 95% ethanol (vol./vol.) and applied topically on the right ears 2 × 20 mL at 5 min intervals in absolute alcohol), 30 min before TPA application. The intact group of the left ears of the **11b** and **12b** treated groups received the vehicle only.

Ear thickness (mn) as an index of inflammation was then measured by a Dyer model micrometer gauge (Dyer Co. Inc., Lancaster, USA), after 6 h, in five mice per group.

The Newman–Keuls test (ANOVA) was used to compare data in the studies with ethanol or compounds topical application.

6.3. Inhibition of PGE_2 and LTB_4 production

Isolated rabbit granulocytes were preincubated during 15 min at 37 °C with seven different concentrations of compounds (between 10 μM and 10 nM in DMSO). Each concentration was performed in triplicate. Calcic ionophore A 23187 (5 μM in DMSO) was added during 15 min. For each compound at each concentration cyclooxygenase and 5-lipoxygenase inhibition were evaluated by dosing respectively PGE_2 and LTB_4 formation using the enzymo-immunoassay (EIA) method [36]. Then the IC_{50} value was calculated using linear regression analysis. The reference compounds used were indomethacine (IC_{50} = 2.7 nM) and NDGA (IC_{50} = 400 nM) respectively for inhibition of PGE_2 and LTB_4 formation.

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