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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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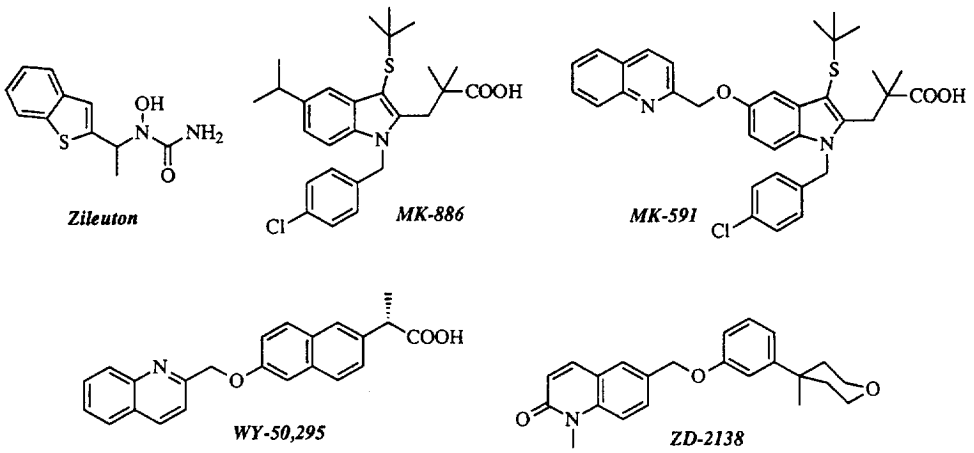



**Figure 1.**

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.

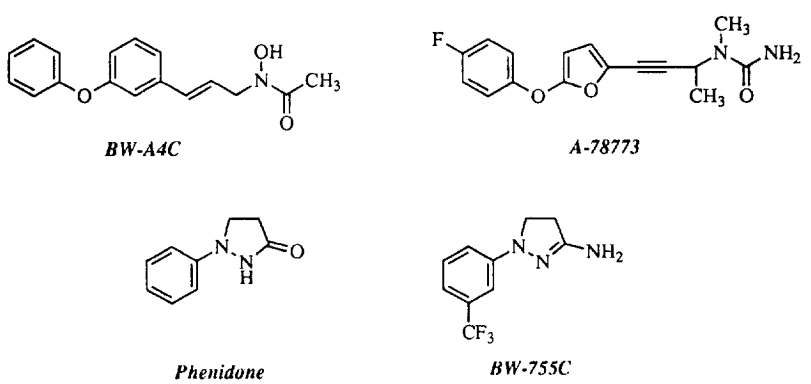



**Figure 2.**

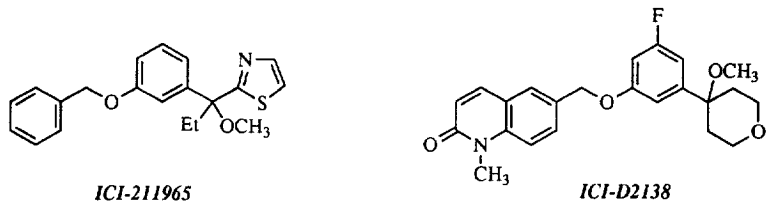



**Figure 3.**

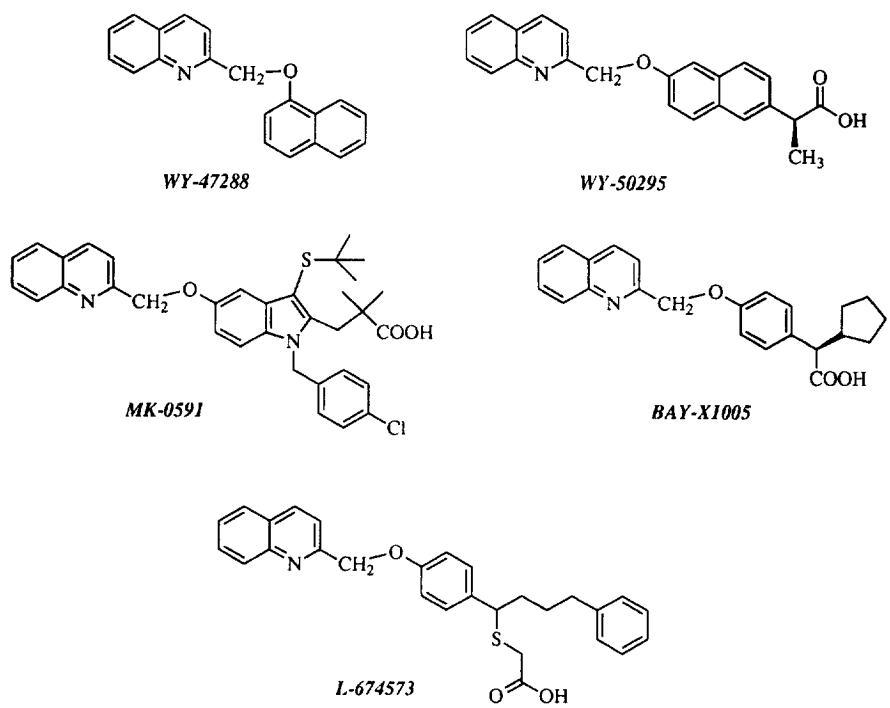



**Figure 4.**

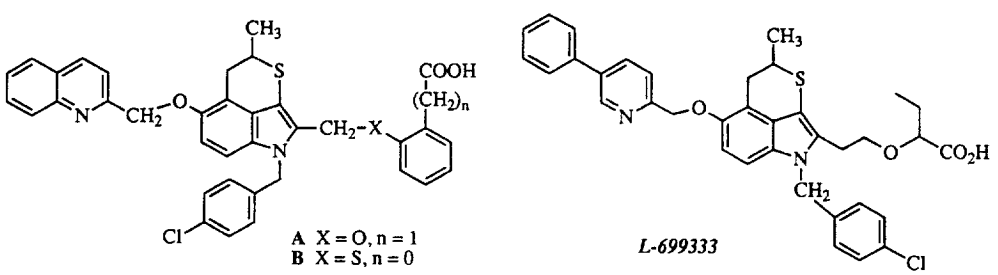



**Figure 5.**

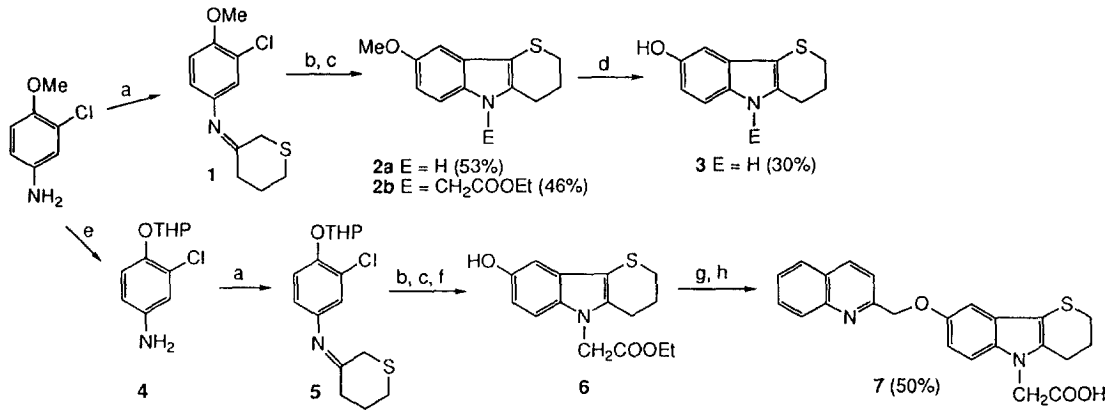



**Figure 6**. (a) 3-Thiopyranone, $C_6H_6$, Δ; (b) $NaNH_2$-*t*-BuONa, THF, RT; (c) $H_2O$, 0 °C for **2a**, $BrCH_2COOEt$, DMF, RT for **2b** and **6**; (d) Pyr-HCl, Δ; (e) (i): $CH_3COCl$, Pyr, DMAP, RT, (ii): $AlCl_3$–$PhCH_2SH$, 0 °C to RT, (iii): DHP, PPTS, RT, (iv): KOH/MeOH, Δ; (f) PTSA, MeOH,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

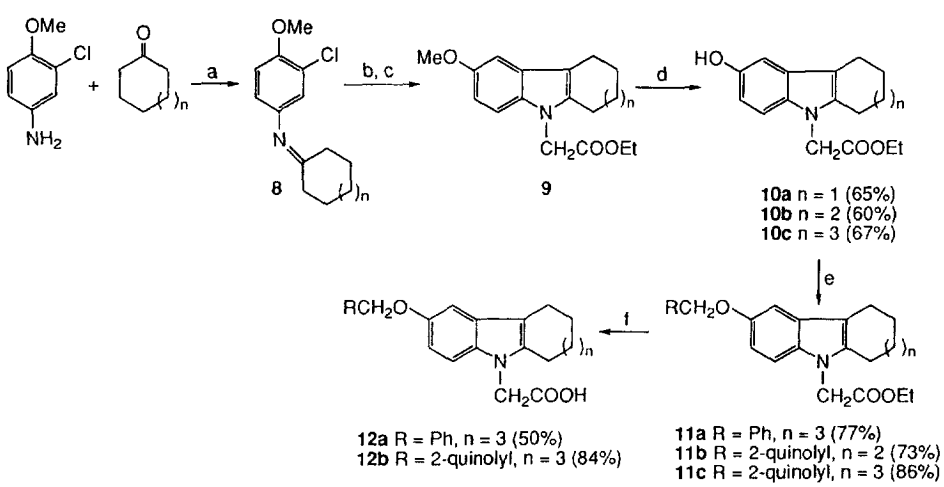



**Figure 7**. (a) $C_6H_6$, Δ; (b) $NaNH_2$-*t*-BuONa, THF, RT; (c) $BrCH_2COOEt$, DME, RT; (d) $AlCl_3$–$PhCH_2SH$, 0 °C to RT; (e) $RCH_2Cl$, $K_2CO_3$, $PhCH_2N^+Et_3Cl^-$, DMF, Δ; (f) KOH, EtOH, Δ.

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*.

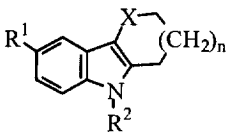
In the present case the demethylation of indoles **9** nicely took place with the $AlCl_3$–$PhCH_2SH$ reagent [33, 34]. Finally compounds **11** were efficiently obtained by condensation under PTC conditions of benzyl chloride and 2-chloromethyl quinoline respectively and **12a** and **12b** by saponification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

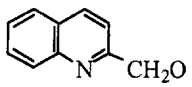
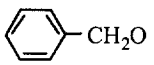
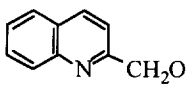
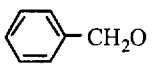
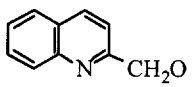
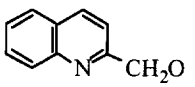
## 3. In vitro results and discussion

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-dimethyl-aminopyridine 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 ($COOCH_2$), 55.80 ($OCH_3$), 44.58 ($NCH_2$), 26.62 ($CH_2$), 24.37 ($CH_2$), 21.53 ($CH_2$), 14.04 ($COOCH_2CH_3$). 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, $CH_2COOEt$), 4.15 (2 H, q, $COOCH_2CH_3$), 3.00–2.20 (6 H, m, $3CH_2$), 1.20 (3 H, t, $COOCH_2CH_3$)]. 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, $COOCH_2CH_3$), 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, $COOCH_2CH_3$). $^{13}$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 ($COOCH_2$), 44.42 ($NCH_2$), 22.90 ($2CH_2$), 21.72 ($CH_2$), 20.79 ($CH_2$), 13.94 ($COOCH_2CH_3$). 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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