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QUINOLINE-SUBSTITUTED DIHYDROINDOLES AS cysLT$_1$ (LTD$_4$ RECEPTOR) ANTAGONISTS[1]

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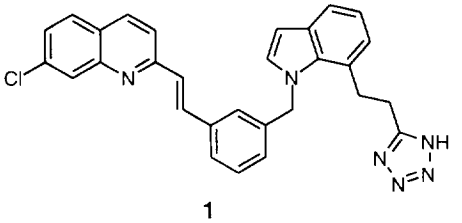
Abstract: A series of quinoline-substituted dihydroindoles has been synthesized and evaluated as antagonists of the cysLT$_1$ receptor. This series, exemplified by **2** (LY302905, pKi = 8.3 for inhibition of binding of ^{3}H-LTD$_4$ to guinea pig lung membranes), represents reduced analogues of the corresponding indoles that were previously shown to be potent, orally active cysLT$_1$ receptor antagonists. These dihydroindole compounds generally displayed increased *in vitro* and *in vivo* (oral) activity.

Recently the synthesis and pharmacologic activity of a series of quinoline/indole cysLT$_1$ (LTD$_4$) receptor antagonists, represented by clinical candidate **1** (LY290324), was described.[2] The series was characterized by good *in vitro* and excellent *in vivo* activity. In the guinea pig, compound **1** was highly effective via the intravenous, oral, and inhaled routes in the inhibition and reversal of LTD$_4$-induced bronchospasm, and in reducing antigen-induced bronchospasm after oral administration. Due to the proven efficacy potential of cysteinyl leukotriene receptor antagonists in the treatment of asthma,[3] we decided to prepare and evaluate a short series of dihydroindole analogues of **1**, represented by compound **2**, to further elucidate the SAR of this unique class.



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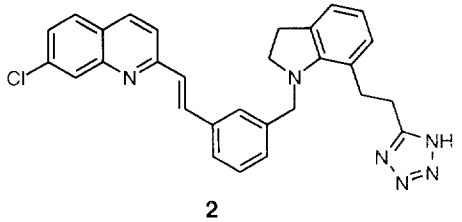
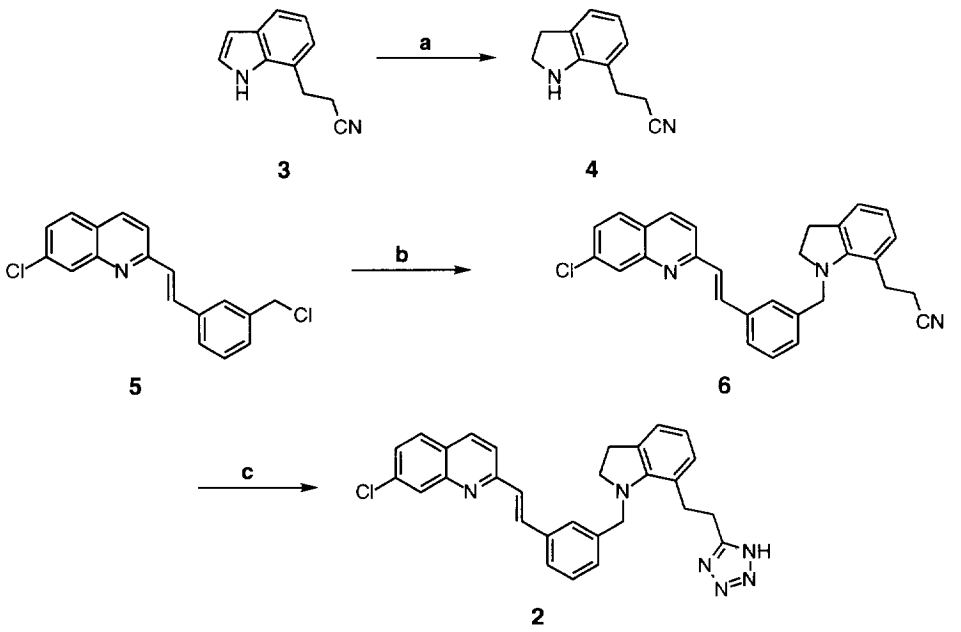


2

The synthetic sequence for the preparation of dihydro analogue **2** was identical to that of **1**[4] with the exception of an additional reduction step (conversion of **3** to **4**, Scheme I).[5] Reduction of the C-7 carbon-substituted indole **3** with an acidic suspension of sodium cyanoborohydride proceeded in high yield. In the case of the C-7 oxygen-substituted quinoline/dihydroindole (compound **10**, Table 1), reduction of the analogous indole resulted in a 90% yield of the expected dihydro product, which proved to be less stable at room temperature than the corresponding carbon analogue. Alkylation and tetrazole formation proceed uneventfully as previously described. All final products were prepared using the representative route depicted in Scheme I.

Scheme I



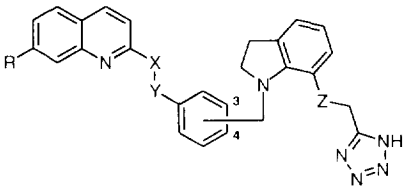
3 4 5 6 2

(a) $NaCNBH_3$, HOAc, 99%; (b) **4**, K_2CO_3, DMF, 85 °C, 47%; (c) Bu_3SnN_3, 95 °C, 36%

Comparison of the ability of the dihydro analogues to inhibit the binding of [^{3}H]LTD_4 to guinea pig lung membrane, ileum, and trachea is presented in Table 1. Generally, the qualitative SAR paralleled that observed with the indole series. Of particular note are compounds **7**, **9**, and **13**, where pK_B values for trachea were comparable to those for ileum, suggesting the presence of receptors with similar characteristics on each tissue.[6] The results on ileum represent an improvement of approximately 1 log unit over the corresponding indoles. Small changes in activity were observed by moving the dihydroindole substituent to the 4-position of the central phenyl ring (compounds **11-13**), but overall the series reflects the previous optimization of prototypical indole **1**.

Selected compounds were evaluated *in vivo* for their ability to inhibit LTD_4-induced airway obstruction in the guinea pig. The bronchospastic effect of aerosol administered LTD_4 was quantitated by measuring pulmonary gas trapping using the excised lung gas volume (ELGV) method.[7] Putative antagonists were administered orally at a dose of 1.0 mg/kg and airway obstruction was evaluated at 2 or 6 hours post dose. Direct comparison of dihydroindole **2** with corresponding indole **1** revealed that double bond reduction produces a significant increase in $cysLT_1$ receptor antagonist activity at both the 2 and 6 hour time points, with better activity for both compounds observed at 2 hours (Table 2). The complete dose-response for compound **2** at 2 hours is presented in Figure 1. The 4-substituted methyleneoxy dihydroindole **12** was also found

Table 1. Inhibition of specific binding of [^{3}H]LTD$_4$ to guinea pig lung membranes, ileum, and trachea.



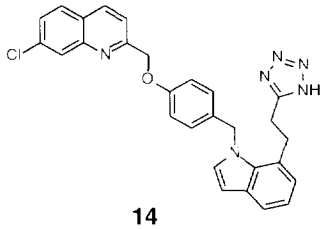
Cmpd	R	X-Y	Z	Pos.	GP Lung Membrane Binding, pK_i	GP Ileum Binding, pK_B	GP Trachea Binding, pK_B
2	Cl	CH=CH	CH_2	3	8.3	8.6 ± 0.16 (5)	7.0 ± 0.23 (4)
7	Cl	CH_2O	CH_2	3	8.0	8.4	7.8
8	H	CH=CH	CH_2	3	7.8	8.6 ± 0.14 (2)	ND
9	H	CH_2O	CH_2	3	7.3	8.0	7.8
10	Cl	CH=CH	O	3	8.3	8.6 ± 0.22 (2)	ND
11	Cl	CH=CH	CH_2	4	7.5	8.6 ± 0.01 (2)	ND
12	Cl	CH_2O	CH_2	4	7.6	8.5	7.6
13	H	CH_2O	CH_2	4	7.8	8.3	7.9

ND = Not Determined

Table 2. Inhibition of aerosol administered LTD$_4$-induced airway obstruction by orally administered antagonists (1.0 mg/kg) in the guinea pig.

Compound	%Inhibition @ 2 hours	%Inhibition @ 6 hours
1 (indole)	69 (n = 4)	21 (n = 6)
2 (dihydroindole analogue)	91 (n = 4)	74 (n = 11)
14 (indole)	16 (n = 4)	ND
12 (dihydroindole analogue)	51 (n = 4)	81 (n = 4)

ND = Not Determined

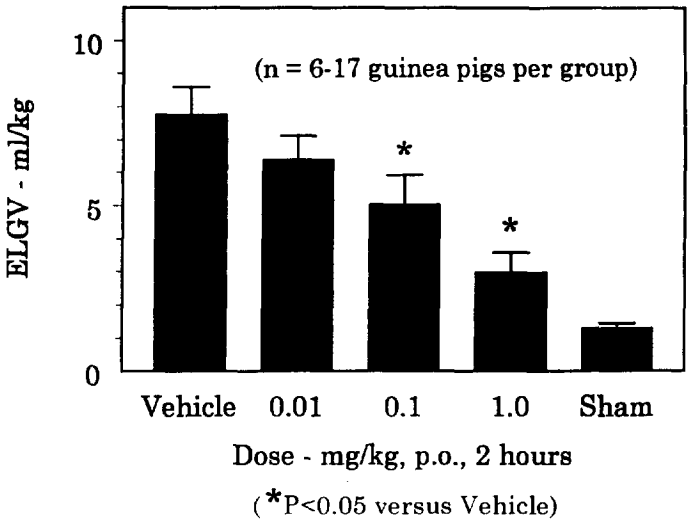


14

to be more potent orally than the corresponding indole **14**, but this compound showed peak activity at the 6 hour time point.

The differences in oral activity observed between compounds **1** and **2** may relate to GI absorption, as these compounds are of similar potency *in vitro*. As expected, the dihydroindoles

Figure 1. Inhibition of aerosol administered LTD_4-induced airway obstruction by orally administered **2** in the guinea pig at 2 hours post dose.



tended to display better solubility characteristics than the corresponding indoles, although we have not conducted a rigorous evaluation of this observation. *In vitro*, both series appear to dissociate slowly from the tissue preparations examined and to have a somewhat exaggerated affinity for glass. This latter phenomenon may account for the significant differences between *in vitro* and *in vivo* activity observed for both series.

In summary, we have synthesized and evaluated eight dihydroindole analogues of compound **1**, a previously described potent $cysLT_1$ receptor antagonist. These compounds displayed slightly better *in vitro* activity as compared to the original indole series. When tested *in vivo*, representative dihydroindoles demonstrated superior oral activity relative to the corresponding indoles in a model of LTD_4-induced airway obstruction in the guinea pig.

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(1) Portions of this work have been presented previously: Sawyer, J. S.; Thrasher, K. J.; Bach, N. J.; Stengel, P. W.; Cockerham, S. L.; Silbaugh, S. A.; Roman, C. R.; Froelich, L. L.; Fleisch, J. H. Quinoline-substituted dihydroindoles as leukotriene D_4 receptor antagonists. Second World Congress on Inflammation, Brighton, UK, September 17-22, 1995, Abstract W11/22.

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