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LTD4 Receptor Binding Activity of Novel Pyridine Chromanols: Qualitative Correlation with pKa.

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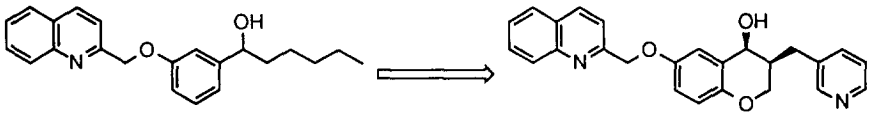
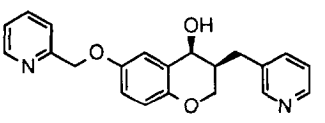
Abstract: A series of pyridine chromanols were synthesized and evaluated as LTD_4-antagonists (LTD_4-A). The quinoline sidechain of this class of such agents, as exemplified by REV-5901, has until now been deemed as essential for potent activity. However, by manipulating substituents on a pyridine ring, quinoline-like potency can be achieved. The results indicate that this is a function of pKa.

The pharmacological modulation of the peptidoleukotrienes has been the subject of intensive efforts over the past decade and some of our efforts in this regard have been described in the previous paper.[1] In that article, we describe our early leukotriene D_4 antagonist (LTD_4-A) research program based on the weak antagonist REV-5901 **1.** The primary objective of the research program was to develop a more potent LTD_4-A and this was achieved with the discovery of CP-80,798 **2** as a clinical candidate for the treatment of asthma. The racemate of **2** had a K_i of 1.64 μM (± 0.28, n = 5) as an inhibitor of [^{3}H]-LTD_4 binding in guinea pig lung membranes[2], compared to REV-5901 which has a K_i of 8.0 μM (± 2.4, n = 4).



1 **2**

One of the striking features of this quinoline class of compounds was the apparent necessity for the 2-substituted quinoline functionality for potent LTD_4 antagonist activity,[3] which was observed in these Pfizer compounds as well. For example, a compound such as **3**, where the quinoline has been replaced by a 2-substituted pyridine, did not inhibit [^{3}H]-LTD_4 binding in the guinea pig lung membrane assay (K_i > 100 μM, n = 3).

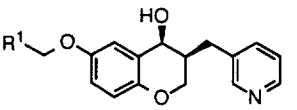


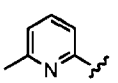
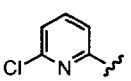
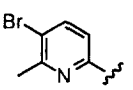
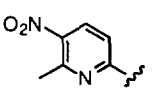
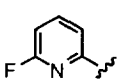
3

However, the idea of a monocyclic heterocyclic bioisostere for the quinoline ring[4] was appealing to us because we were interested in downsizing the molecule to improve its pharmacokinetic and physicochemical properties, as well as reducing its aromaticity. In addition, the introduction of structural diversity at this center was attractive as a goal. Therefore, a small synthetic program was undertaken with the aim of developing monocyclic heterocyclic quinoline replacements which maintain LTD_4 antagonist activity. We found that by placing various substituents on the pyridine ring, we were able to reintroduce the LTD_4 antagonist activity of the lead structure, and in fact improve it approximately 10 fold. This paper describes our findings on the relationship of pKa and logP of the pyridine ring with respect to LTD_4 receptor binding.

The syntheses were performed in a similar manner to that outlined in the previous paper, to yield the desired compounds as shown in Table I (these are described as compounds **11** in the previous paper).

Table I. Physicochemical Data and Yields of Pyridine Analogs

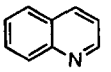


Cpd	Het (R^1)	mp	yield (%)[a]	formula	anal.
3		108.0 - 110.0	15	$C_{21}H_{20}N_2O_3$	CHN
4		glass	29	$C_{22}H_{22}N_2O_3$	*b*
5		144.0 - 145.0	44	$C_{21}H_{19}ClN_2O_3$	CHN
6		134.0 - 137.0	16	$C_{22}H_{21}BrN_2O_3$	*c*
7		155.0 - 156.5	14	$C_{22}H_{21}N_3O_5$	CHN
8		148.0 - 149.0	44	$C_{21}H_{19}FN_2O_3 \cdot 0.25H_2O$	CHN

[a]Unoptimized yield of the last step. For other yields, see previous paper. [b]HRMS m/z M^+ = 362.1630 (calc), 362.1631 (found). [c]HRMS m/z M^+ = 440.0736 (calc), 440.0714 (found).

Two possible explanations for the difference in LTD_4 receptor binding between compounds **2** (K_i = 1.64 μM) and **3** (Ki >100 μM) include lipophilicity (as measured by logP) and basicity (as measured by pKa). As indicated in Table II, there is a significant difference in logP and pKa between quinoline and pyridine. Assuming that the chromanol portion contributes equally to both molecules,[5] then **2** is more lipophilic and less basic than **3**. Thus, the potentiated LTD_4 receptor binding could be due to the increased lipophilicity, lower pKa of the quinoline nitrogen, or both. We decided to investigate both parameters.

Table II. Physicochemical Data of Quinoline and Pyridine

	logP	pKa
	2.04[6]	4.81[7]
	0.66[6]	5.25[8]

The first target side chain was 2-methylpyridine, since with a pKa = 5.96[9] and logP = 1.11[10], it had the desired characteristic of increased lipophilicity, while maintaining a reasonably similar basicity. As can be seen from the biological activity illustrated in Table III, **4**, like **3**, had no LTD_4 receptor binding activity, suggesting that an incremental change in lipophilicity was not enough to increase affinity for the receptor.

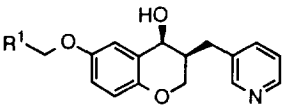
Next, to determine whether lowering the pKa would afford demonstrable binding activity, 2-chloropyridine was chosen as the next quinoline replacement. With a logP of 1.27,[10] 2-chloropyridine is similar to 2-methylpyridine, but it is much less basic (pKa = 0.72[11]). We were excited to see the K_i of 23.4 μM for the resulting compound **5**, since this was the first demonstration of LTD_4 receptor binding in a monocyclic heterocycle of the REV-5901 series, and the first hint that this monocyclic approach might be fruitful.

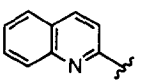
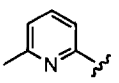
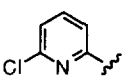
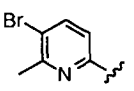
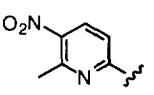
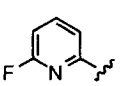
Disubstitution of the pyridine ring was then examined, as this offered better control of the desired parameters. Compound **6** was an appealing target, since the 3-bromo-2-methylpyridine side chain with a clogP = 2.09[12] and an estimated pKa = 3.55[13], appeared to be very similar to the quinoline side chain from a lipophilicity perspective, while at the same time decreasing the basicity with respect to quinoline.[14] It was gratifying to see that compound **6** had identical LTD_4-A activity to the quinoline **2** (Table III) although we were as yet unsure whether logP or pKa was the more important factor.

From examples **4** and **5**, lipophilicity seemed less important for strong binding, so we focussed further effort on pKa. Our hypothesis was that by further lowering the pKa, additional LTD_4 potency should be gained and indeed, this was found to be the case when **7** was synthesized. The clogP[12] of

2-methyl-3-nitropyridine is 0.99 and the estimated pKa is 1.52.[15] The resulting compound, **7**, was actually more potent than the starting lead quinoline **2**.

Table III. Inhibition of [^{3}H]-LTD$_4$ Receptor Binding in Guinea Pig Lung Membranes[16]



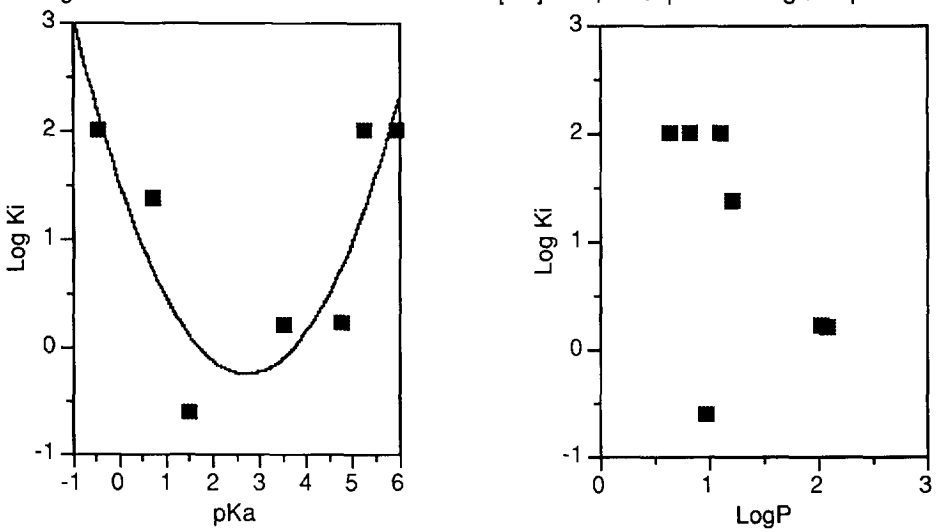
Cpd	Het (R^1)	LogP of R^1	pKa of R^1	K_i (μM)[a]
2		2.04	4.81	1.64 ± 0.28
3		0.66	5.25	>100
4		1.11	5.96	>100[b]
5		1.27	0.72	23.4 ± 9.4
6		2.09[c]	3.55[d]	1.56[b]
7		0.99[c]	1.52[d]	0.24 ± 0.05
8		0.84	-0.44	>100

[a]Triple determinations, unless otherwise indicated. [b]Single determination. [c]cLogP of sidechain R^1. [d]Estimated pKa of sidechain R^1.

Finally, with compounds such as **8**, we discovered that there is an optimal pKa and that the trend of increasing LTD$_4$-A activity with decreasing pKa could not be indefinitely continued. The 2-

fluoropyridine side chain is considerably less basic (pKa = -0.44[11]) and of similar lipophilicity to the side chain of **7** (logP = 0.84[10]), but results in a compound that no longer displays LTD_4 receptor binding affinity. This bell-shaped dependence on pKa is portrayed graphically in Figure I with the line fit indicating that the optimal pKa is approximately 2.5 - 3.0. There was no similar correlation with logP.

Figure I. Correlation Between Inhibition of [^{3}H]LTD_4 Receptor Binding and pKa.



In summary, this paper describes the discovery of monocyclic heterocyclic bioisosteres for the quinoline in the REV-5901 class of LTD_4-A. This discovery was made using a qualitative correlation of basicity and lipophilicity with receptor binding activity. The results suggest that the pKa of the ring nitrogen is very important for the interaction of this side chain with a binding site on the enzyme.

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References and Notes

1. See previous paper in this journal and references cited therein.
2. Internal data.
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4. This concept is perhaps exemplified by compounds such as Ro 24-5913, which is of a structurally different class of leukotriene antagonists. In these compounds, the thiazole ring could be thought of as a replacement for the quinoline ring. O'Donnell, M.; Crowley, H.J.; Yaremko, B.; O'Neill, N.; Welton, A.F. Pharmacologic Actions of Ro 24-5913, a Novel Antagonist of Leukotriene D_4. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 751-758.

5. The pKa's were not directly measurable due to solubility difficulties, as well as to problems in distinguishing the pKa contribution from the pyridine sidechain acting as the "quinoline replacement" versus the pyridine sidechain attached at the 3 position of the chromanol ring. All pKa's reported in this paper are either from the literature or are estimated.
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12. Calculated using the Medchem program, version 3.55 from Biobyte, P.O. 517, Claremont, CA 91711
13. Estimated by using the pKa value of 3-bromopyridine (Nakanishi, K.; Harada, R.; Yamazaki, F.; Ohashi, M.; Katsuta, C.; Kurono, M.; Kojima, T.; Kurono, S. Acid Dissociation Constants of Amines. In *Series of Comprehensive Organic Chemistry*; Goto, R.; Imoto, M.; Kubota, T.; Sakan, T.; Shimamura, O.; Yukawa, Y., Eds.; Asakura Publishing Co.: Tokyo, 1963; p 597) and adding 0.71 which is the difference between the pKa's for pyridine and 2-methylpyridine (Dominy, B.; Molecular Modelling Dept., Pfizer, Inc. Private communication).
14. The use of clogP and estimated pKa has been found to be comparatively reliable in many instances. For example, see Moriguchi, I.; Hirono, S.; Nakagome, I.; Hirano, H. Comparison of Reliability of logP Values for Drugs Calculated by Several Methods. *Chem. Pharm. Bull.* **1994**, *42*, 976-978 and Barlin, G.B.; Perrin, D.D. Prediction of the Strengths of Organic Acids. *Quart. Rev.*, **1966**, *20*, 75-101, respectively.
15. Estimated by using the pKa value of 3-nitropyridine (Bryson, A. The Ionization Constants of 3-Substituted Pyridines, 3-Substituted Quinolines and 4-Substituted Isoquinolines. *J. Am. Chem. Soc.* **1960**, *82*, 4871-4876) and adding 0.71 which is the difference between the pKa's for pyridine and 2-methylpyridine (Dominy, B.; Computational Chemistry Dept., Pfizer, Inc. Private communication).
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