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OXIMES: A NEW CLASS OF METHOXYTETRAHYDROPYRANYL INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS WITH HIGH *IN VITRO* AND *IN VIVO* POTENCY.

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Abstract
Work aimed at further improving the *in vivo* activity of methoxytetrahydropyranyl inhibitors of leukotriene biosynthesis has led to the discovery of a series of oximes, members of which are more potent *in vivo* than ZD2138.

1. Introduction
Leukotrienes are a family of important inflammatory mediators produced by an enzymatic cascade, which is initiated by the action of 5-lipoxygenase (5-LO) on arachidonic acid leading to leukotriene (LT) A_4, precursor to the family of LTs B_4, C_4, D_4 and E_4.[1,2] Limiting the synthesis of LTs through inhibition of 5-LO should provide clinical benefits in a number of inflammatory conditions such as asthma[3], allergic rhinitis, rheumatoid arthritis, psoriasis and ulcerative colitis. In 1991, we reported the discovery of a novel series of lipoxygenase inhibitors, the (methoxyalkyl)thiazoles,[4] which had neither iron-liganding nor redox properties, and exhibited enantioselective inhibition of 5-LO. Further development of this series produced the methoxytetrahydropyranyl ZD2138 which is presently undergoing clinical evaluation.[5,6] Here we present recent work in this area concerning the discovery of a series of oximes, some of which are more potent *in vivo* than ZD2138.

2. Biological testing
Structure Activity Relationships (SAR) were developed based on *in vitro* inhibition of LTB_4 synthesis in A-23187 stimulated human whole blood (HB1, expressed as an IC_{50} in μM).[7] Statistical analysis showed 95% confidence limits to be ±2.6 fold. Oral activity was assessed in the rat using zymosan-inflamed air pouch exudate (RAP, expressed as an ED_{50} in mg/kg at 3 hrs post dose).[5]

3. Development of the oxime series from ZD2138
The search for a follow-up for the development compound ZD2138 (RAP: 0.3 mg/kg) led to the discovery of a new series of LTs inhibitors.[8] Previous SAR studies[5] revealed that important binding elements in the 1-methylquinol-2-one moiety present in ZD2138 were the oxygen atom of the carbonyl function and the N-methyl group. Modification of these elements could further improve the potency of the LTs inhibitors and offered the possibility of varying their physicochemical and biological properties. It was envisioned that a phenylketoxime group could provide these oxygen and methyl elements necessary for good binding to 5-LO. Simple modelling showed that a ketoxime group superimposed well on the lactam portion of the 1-methylquinol-2-one.

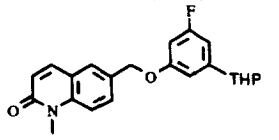
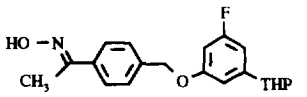
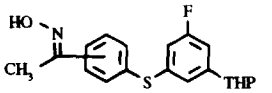
			HB1 IC_{50} (μM)
ZD2138			0.025
1a			0.04
1b		para	0.08
1c		meta	2.91
1d		ortho	>10

Table 1. *Optimization of the Position of the Oxime Group.*

Encouragingly, the first compound made (**1a**, Table 1) gave excellent *in vitro* activity. *In vivo* potency was achieved when the methyleneoxy link was replaced by sulfur, to give **1b** (ED_{50} 0.5 mg/kg). The optimum position of the oxime relative to the sulfur atom was determined to be *para* by synthesizing the *meta* (**1c**) and *ortho* (**1d**) analogs. The HB1 results appeared to confirm our initial hypothesis, since only the *para* ketoxime can be superimposed onto the 1-methylquinol-2-one.

4. Optimization of the potency of the oxime function

4a. α-substituted oximes

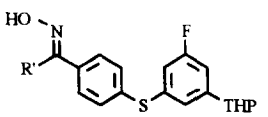
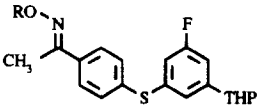
		Isomer[9]	pKa	HB1 IC_{50} (μM)
2a	H	E	10.7	0.12
2b	iPr	E/Z	10.8	0.30
2c	$(CH_3)_2N$	E or Z	14.1	0.28
2d	H_2NCH_2	E or Z	11.5	2.53
2e	CH_3S	E or Z	-	0.19
2f	COOEt	E or Z	9.3	0.17
2g	CH_3CO	E or Z	8.4	0.85
2h	CF_3	E/Z	7.68	0.28
2i	NC	E/Z	6.2	0.25

Table 2. *Influence of the pKa of the Oxime Group on In Vitro Potency.*

Electron withdrawing and electron donating groups were introduced in the vicinity of the oxime in order to probe the influence of pKa on binding with the enzyme (Table 2). Somewhat surprisingly, the large variations of pKa[10] did not cause dramatic changes in *in vitro* activity, even though some of the compounds were substantially ionized at physiological pH.

4b. O-Substitution of the oxime function



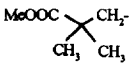
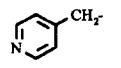
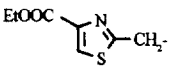
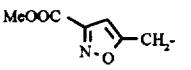
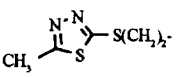
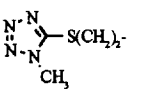
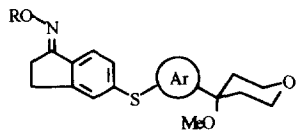
	R	HB1 IC_{50} (μM)		R	HB1 IC_{50} (μM)
1b	H	0.08	**3i**	CH_3CO-	0.05
3b	CH_3-	0.11	**3j**	tBuCO-	0.04
3c	NC-CH_2-	0.02	**3k**	$(CH_3)_2NCO$-	2.61
3d	FCH_2-CH_2-	0.04	**3l**	EtOOC-CH_2-	0.61
3e	iPr-	0.92	**3m**	HOOC-CH_2-	0.74
3f		0.42	**3n**		0.3
3g		0.15	**3o**		0.10
3h		0.23	**3p**		0.12

Table 3. *Substituted Oximes in the Aryl Series: Activity in HB1 Test.*

The *in vitro* data presented in Table 3 clearly show that the enzyme can accommodate a wide variety of large and/or polarized groups attached to the oxime with the exception of very bulky groups. Taken together, data presented in Tables 2 and 3 tend to indicate that groups appended to oxime oxygen or carbon atoms play little part in binding to enzyme.

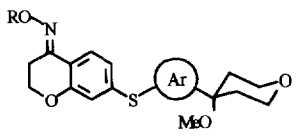
4c. Constrained oximes

The effect of the suppression of free rotation of the oxime was investigated by synthesizing indanone and chromanone oximes in the fluorophenyl and thiophene series[11] (Tables 4 and 5). The molecules prepared showed activities comparable to the open chain oximes with the exception of the chromanone thiophene (**5d**) which gave a significant improvement in activity *in vivo* (ED_{50} 0.15 mg/kg) over **1b**.



	Ar	R	HB1 IC_{50} (μM)
4a		H	0.29
4b		$NCCH_2$-	0.03
4c		H	0.13
4d		$NCCH_2$-	0.04

Table 4. *Indanone Oxime Series*



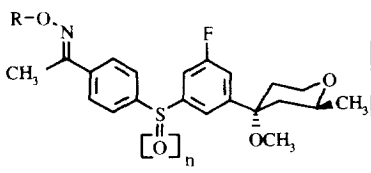
	Ar	R	HB1 IC_{50} (μM)
5a		H	0.05
5b		$NCCH_2$-	0.04
5c		H	0.04
5d		$NCCH_2$-	0.06

Table 5. *Chromanone Oxime Series*

5. Search for solubility improvements

Unfortunately, the most highly potent oximes were poorly soluble in water (generally in the μM range). Chemical efforts were thus aimed at improving this important parameter, in order to improve their bioavailability. Several modifications were made to increase the hydrophilicity of these molecules : oxidation of the sulfide link into a sulfone, replacement of the central phenyl ring with thiazoles and, alkylation of the oxime with hydrophilic groups.

5a. Sulfones



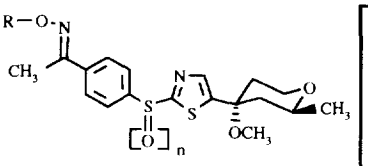
	R	n	IC_{50} HB1 (μM)	ED_{50} RAP 3h (mg/kg)	Solub. (μM)
6a	H	0	0.04	0.05	0.6
6b	NC CH_2-	0	0.04	0.15	
6c	CH_3-	0	0.14	0.15	
6d	H	2	0.02	0.10	4.6
6e	NC CH_2-	2	0.06	0.10	

Table 6. *Sulfides and Sulfones Activities in the Chiral Fluorophenyl Series*

In this series the THP group was replaced by a 2(S)-2-methyl-THP[12] group since we had previously found that this chiral group increased substantially the *in vivo* activity of our LTs inhibitors (unpublished results). Indeed,

the sulfide (**6a**) proved to be the most potent compound found in the oxime series. The aqueous solubility[13] of the corresponding sulfone (**6d**) was significantly improved (4.6 μM vs 0.6 μM for **6a**) and was comparable to ZD2138 (3.8 μM). However, this eight fold improvement was still perceived as insufficient.

5b. Thiazoles



	R	n	IC_{50} HB1 (μM)	ED_{50} RAP 3h (mg/kg)	Solub. (μM)
7a	H	0	0.04	0.3	
7b		2	0.32	1.0	31
7c	NC CH_2-	0	0.04	0.3	
7d		2	0.14	0.5	1

Table 7. *Sulfides and Sulfones Activities in the Chiral Thiazole Series*

Replacement of the fluorophenyl or thiophenyl group by a thiazolyl would be expected to reduce the Log P of the series by up to 1.5 units and hence possibly improve solubility. Some of the molecules made in the sulfide and sulfone series are shown in Table 7. It was very satisfactory to find that one compound in this series (**7b**) gave a 50 fold improvement in solubility over **6a** (31 μM vs 0.6 μM). However, the potency of **7b**, while still acceptable, did not match that of **6a**.

5c. Substituted oximes

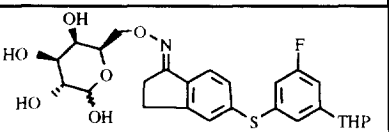
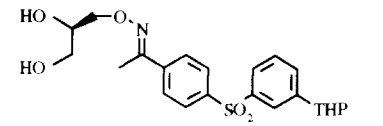
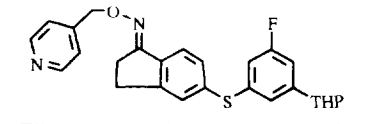
		HB1 IC_{50} (μM)	Solub. (μM)
8a		>2.5	81
8b		0.16	
8c		0.09	100

Table 8. *O-alkylated Oximes with Hydrophilic Groups on the Oxime Function*

Two families of compounds were studied in particular: neutral, hydrophilic groups such as polyols and sugars and ionized groups in the form of pyridine hydrochlorides. The sugar derivatives proved to substantially increase the solubility (**8a**, 81 μM), but failed to show activity in the HB1 test, possibly owing to lack of cell penetration. In the pyridine series the most interesting compound was **8c** which was not active *in vivo* at 1.5 mg/kg but conversion to its hydrochloride salt gave a soluble compound (100 μM in pure water) which showed activity at 0.5 mg/kg.

6. Conclusion

We have found that the 1-methylquinol-2-one fragment of ZD2138 can be successfully replaced by a phenyl ketoxime moiety. This has led to the synthesis of a large family of oximes possessing a wide range of physicochemical properties including pKas and solubilities. The most potent compounds *in vivo* proved to be the most lipophilic ones (i.e. **6a**) but it is possible to incorporate hydrophilic/ionizable fragments that achieve good water solubility while still retaining excellent *in vivo* potency (**8c**). Thus, the activities and solubilities of these new LTs inhibitors can be modulated.

References and Notes

Abbreviations used: LT: leukotriene, THP: 4-(4-methoxytetrahydropyran-4-yl).
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7. Foster, S. J.; Bruneau, P.; Walker, E. R. H.; McMillan, R. M. *Br. J. Pharmacol.* **1990**, *99*, 113-118.
8. For the syntheses of the molecules presented here see the european patent EP 0555068 (11AUG93).
9. E/Z refers to a roughly equimolar mixture of E and Z oximes. E or Z refers to one single isomer of unknown configuration. Unless otherwise specified, the oximes presented in this paper have the E configuration. Z isomers of unsubstituted oximes equilibrate very quickly in solution in the presence of light or mild acid to give the E oxime. Alkylation of the Z isomer with bromoacetonitrile give stable compound whose biological results are very similar to the E isomers. Hence, the relative stereochemistry of the oximes does not seem to be of importance for 5-LO inhibition.
10. The pKas were measured according to: Kurtz, P. A.; D'Silva, T. D. J. *J. Pharm. Sci.* **1987**, *76*, 599-610.
11. Replacement of the fluorophenyl central ring by a thiophenyl had been shown to be sometimes beneficial for *in vivo* activity in the oxime series (unpublished results).
12. Crawley, G. C.; Briggs, M. T.; Dowell, R. I.; Edwards, P. N.; Hamilton, P. M.; Kingston, J. F.; Oldham, K.; Waterson, D.; Whalley, D. P. *J. Med. Chem.* **1993**, *36*, 295-6.
13. Solubilities were measured for key compounds only (25°C in a 10^{-2} M phosphate buffer, pH 7.4, containing 0.15 M NaCl).

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