for test were administered at 10 mg/kg po 1 h before capsaicin challenge.

Substance P-Induced Salivation in Rats. Fasted male Sprague-Dawley rats were administered test compound (50 mg/kg ip or po dissolved in 0.05 N hydrochloric acid) or saline 30 min prior to SP challenge. Sodium pentobarbitol (V-pento 65 mg/mL at 1 μL/g ip, 10 min prior to SP challenge) anesthetized animals were challenged with 4.7 nmol/kg (2.0 μL/g) SP by tail vein injection. Saliva was then absorbed into preweighed Q-tips and the saliva weight was calculated by subtraction and recorded until the salivation response subsided (about 4 min). Results are expressed as percent inhibition of the SP response.

Acknowledgment. We acknowledge the enthusiastic support of Dr. M. C. Desai, Dr. F. J. Vinick, Dr. R. W. Spencer, Dr. J. Heym, and Dr. H.-J. Hess.

Supplementary Material Available: Parameters, atomic coordinates, bond lengths, bond angles, anisotropic thermal parameters, and H-atom coordinates from single crystal X-ray data for **7b** as its free base and mesylate salt (11 pages). Ordering information is given on any current masthead page.

Methoxytetrahydropyrans. A New Series of Selective and Orally Potent 5-Lipoxygenase Inhibitors

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Investigation of the SAR of the lead (methoxyalkyl)thiazole 1-[3-(naphth-2-ylmethoxy)phenyl]-1-thiazol-2-ylpropyl methyl ether (1, ICI 211965) led to the methoxytetrahydropyrans, a new series of 5-lipoxygenase (5-LPO) inhibitors exemplified by the parent compound 4-[3-(naphth-2-ylmethoxy)phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (**4f**). In vitro **4f** inhibited leukotriene C_4 (LTC_4) synthesis in zymosan-stimulated plasma-free mouse macrophages and LTB_4 synthesis in A-23187-stimulated human whole blood (IC_{50}s 0.5 nM and 0.07 μM, respectively). In the rat **4f** inhibited LTB_4 synthesis in blood ex vivo and in zymosan-inflamed air pouch exudate with an ED_{50} 3 h after oral dosing of 10 mg/kg in each system. In seeking more potent orally active compounds, strategies were explored in congeners of **4f** for reducing lipophilicity without sacrificing potency. For example, replacement of 2-naphthyl of **4f** by various aza- and oxoheterocycles afforded compounds in which log *P* is reduced by 1.7-2.3 units while potency in human whole blood in vitro was maintained or enhanced relative to **4f**. In addition, the oxoheterocyclic replacements provided compounds with improved oral potency and the preferred compound from this group is 6-[[3-fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]-1-methylquinol-2-one (**4y**). In the in vitro systems, **4y** inhibited LT formation with IC_{50}s in mouse macrophages and human whole blood of 3 nM and 0.02 μM, respectively. **4y** did not inhibit the synthesis of cyclooxygenase (CO) products at concentrations up to 500 μM in human blood, a selectivity for 5-LPO over CO of >20 000-fold. In the rat **4y** inhibited the formation of LTB_4 in blood ex vivo and in inflammatory exudate with ED_{50}s 3 h after oral dosing of 0.9 and 0.3 mg/kg, respectively. **4y** was more potent in vitro in human whole blood and in rat blood ex vivo at 3 h than either the 5-LPO inhibitor A-64077 or the FLAP antagonist MK-886. Based on these data **4y** (ICI D2138) has been entered into development as an orally active, selective 5-LPO inhibitor for clinical evaluation in inflammatory conditions in which LTs are believed to play a role.

Introduction

Arachidonic acid is metabolized to inflammatory mediators by two major oxidative pathways. 5-Lipoxygenase (5-LPO) is the first enzyme in a cascade which produces the leukotrienes (LTs) while cyclooxygenase (CO) initiates the cyclic pathway leading to prostaglandins and thromboxanes. Inhibition of CO is a well-established clinical treatment for inflammation although this mechanism of action is associated, inter alia, with ulceration of the gastrointestinal tract.

The LTs are a family of important biologically active molecules. LTB_4 is a potent chemotactic agent and inflammatory mediator[1] and the peptidoleukotrienes LTC_4 and LTD_4 are powerful spasmogens in vascular and bronchial tissues.[2] Elevated levels of LTs are associated with a number of inflammatory conditions and indeed LTs have been recovered from various pathological tissues. For these reasons it is believed that restricting LT synthesis by inhibition of 5-LPO will have therapeutic utility for the treatment of a variety of inflammatory conditions including asthma, rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Encouraging preliminary clinical results in some of these indications have been reported for one such compound, A-64077.[3-5] However, only when selective, orally active inhibitors of 5-LPO capable of sustained suppression of LT synthesis are evaluated clinically will the value of 5-LPO inhibition in the treatment of inflammatory conditions become clear.

† Chemistry 1.
‡ Bioscience 1.

(1) Foster, S. J.; McMillan, R. M. Leukotriene B_4 and Inflammatory Disease. *Agents Actions* **1988**, *24*, 114-119.
(2) O'Donnell, M.; Welton, A. Comparison of the Pulmonary Pharmacology of Leukotrienes and PAF: Effects of their Antagonists. In *Therapeutic Approaches to Inflammatory Disease*; Lewis, A. J., Doherty, N. S., Ackerman, N. R., Eds.; Elsevier: New York, 1989; pp 169-193.
(3) Knapp, H. R. Reduced Allergen-Induced Nasal Congestion and Leukotriene Synthesis with an Orally-Active 5-Lipoxygenase Inhibitor. *N. Engl. J. Med.* **1990**, *323*, 1745-1748.
(4) Israel, E.; Dermarkarian, R.; Rosenberg, M.; Sperling, R.; Taylor, G.; Rubin, P. The Effects of a 5-Lipoxygenase Inhibitor on Asthma Induced by Cold Dry Air. *N. Engl. J. Med.* **1990**, *323*, 1740-1744.
(5) Laursen, L. S.; Naesdal, J.; Bukhave, K.; Lauritsen, K.; Rask-Madsen, J. Selective 5-Lipoxygenase Inhibition in Ulcerative Colitis. *Lancet* **1990**, *335*, 683-685.

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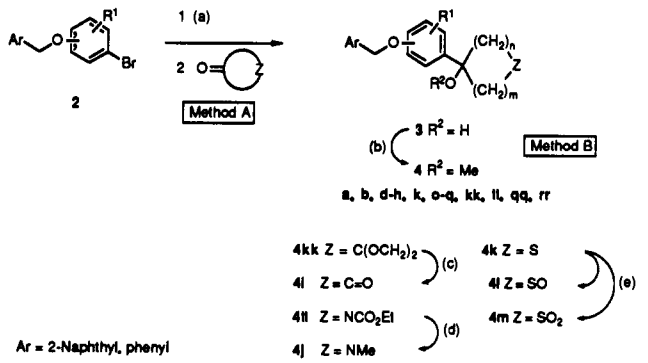
Scheme I.[a] Aryl Compounds



[a] Generic groups are defined in Table V. Reagents: (a) Mg, THF, 35 °C or *n*-BuLi, THF, −70 °C; (b) NaH, THF or DMF, MeI, room temperature; (c) *p*-TsOH, acetone, room temperature; (d) LAH, Et_2O, room temperature; (e) *m*-CPBA, CH_2Cl_2, room temperature.

Although many compounds are known which inhibit 5-LPO, most of these have poor selectivity for 5-LPO or lack oral efficacy. Further, most reported inhibitors possess redox properties and potentially can interfere with physiologically important redox processes. Indeed, methemoglobin formation has been demonstrated with a number of 5-LPO inhibitors with redox properties.[6,7]

Recently, we described a series of novel 5-LPO inhibitors, (methoxyalkyl)thiazoles, exemplified by **1** (ICI211965), which was highly selective for the LT pathway.[8] Inhibition arising from redox or iron-chelating properties is unlikely in this series and, furthermore, data were presented which indicated that inhibition derived from specific and enantioselective interactions between enzyme and inhibitors. Although **1** was active orally, its modest oral potency precluded it from consideration as a clinical candidate. We now report on the discovery of a related series of inhibitors, methoxytetrahydropyrans, which show improved oral potency and from which 6-[[3-fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)-phenoxy]methyl]-1-methylquinol-2-one (**4y**) has been selected for clinical evaluation as an orally administered, selective 5-LPO inhibitor.

Biological Testing

Structure–activity relationships (SAR) were developed based on inhibition of LTB_4 synthesis in A-23187-stimulated human whole blood with selected compounds evaluated further for inhibition of LTC_4 synthesis in a plasma-free mouse macrophage assay. Oral activity was assessed in the rat either in whole blood ex vivo or in zymosan-inflamed air pouch exudate (see Experimental Section).

Statistical Analysis

IC_{50} and ED_{50} values were calculated on an IBM-PC by fitting a four-parameter logistic curve using iterative least squares. Statistical analysis showed 95% confidence limits to be ±5.4-fold and ±2.6-fold for mouse macrophage and human whole blood assays, respectively. Differences between means were assessed by Student's paired *t*-test with $p < 0.05$ regarded as significant.

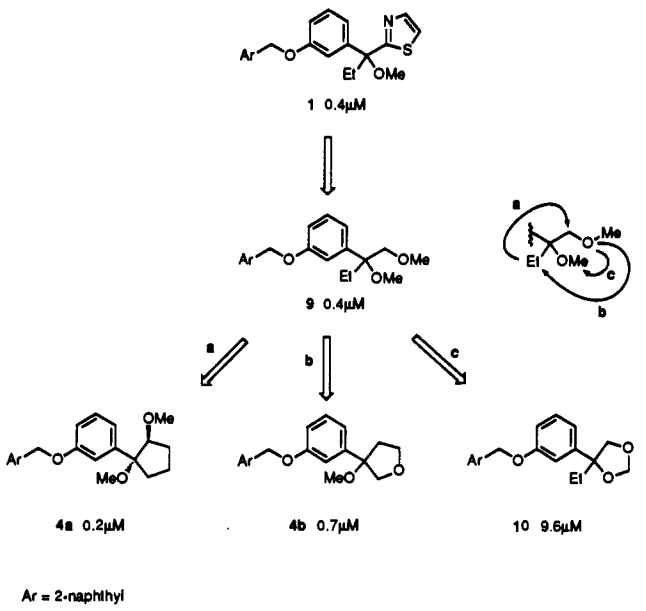


Figure 1.

Chemistry

Methoxy compounds **4** in which Ar is 2-naphthyl or phenyl were prepared from the organomagnesium or -lithium reagents generated from **2** and the appropriate cyclic ketones (Scheme I), followed by methylation of the resulting hydroxy compounds **3**. The group Z was further modified as indicated.

Compounds **4** in which Ar is heteroaryl were synthesized by alkylation of phenols **5** with the required (chloro- or bromomethyl)heteroaryl intermediates (Scheme II). In most cases the latter were prepared either by literature methods or were formed by bromination of the corresponding methylheteroaryl using *N*-bromosuccinimide. In the case of **4x**, the NH of the quinolone was protected by pivaloyloxymethylation before bromination and alkylation. Deprotection of **4mm** gave **4x**. Bromination of *N*,6-dimethylisoquinolone, *N*,6-dimethyl-4-quinolone, and *N*,*N*′,5-trimethylbenzimidazolinone each produced additional ring bromination. The resulting dibromo intermediates were coupled to **5b** giving **4nn**, **4oo**, and **4pp**, respectively, and these bromo compounds were debrominated to the final products **4cc**, **4ee**, and **4gg**. The 2-pyridylpropargyl bromide **6** was isolated as its hydrobromide from bromination of the corresponding propargyl alcohol which in turn was prepared by palladium-catalyzed coupling of 2-bromopyridine and propargyl alcohol.

The glycol ether **9** and dioxolane **10** were prepared from the diol **8** as indicated in Scheme III. The synthesis of **4c** is described in the Experimental Section.

Evolution of Ether Series

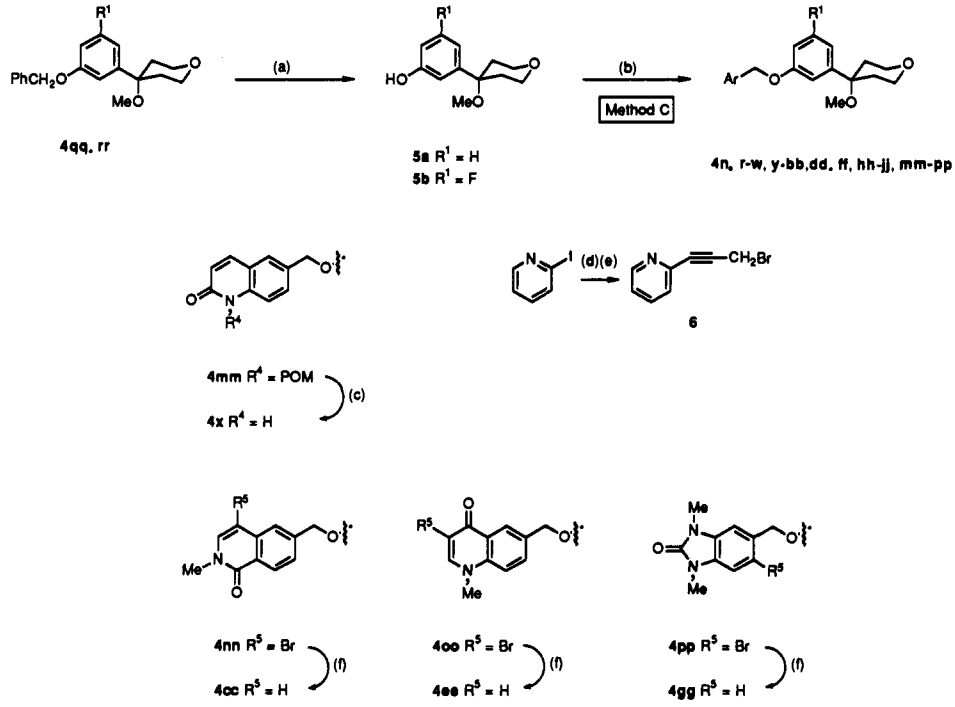
From a wider investigation of the SAR of **1**, inhibitory activity in human whole blood comparable to **1** was found in the dimethyl glycol ether **9** in which a second ether group has replaced 2-thiazolyl. In order to restrict the conformational mobility of **9** various ring systems were constructed incorporating the glycol ether fragment. Thus ring closure by modes a–c (Figure 1) led to the 1,2-dimethoxycyclopentane **4a**, the methoxytetrahydrofuran **4b**, and the dioxolane **10**, respectively. Compounds **4a** and **4b**

(6) Albert, D. H.; Machinist, J.; Young, P. R.; Dyer, R.; Bouska, J.; Brooks, D. W.; Carter, G. W. Metabolism in the Rat of A-53612, a Selective Orally Active 5-Lipoxygenase Inhibitor. *FASEB J.* **1989**, *3*, A735, Abstr. 2954.

(7) Bruneau, P.; Delvare, C.; Edwards, M. P.; McMillan, R. M. Indazolinones: A New Series of Redox-Active 5-Lipoxygenase Inhibitors with Built-In Selectivity and Oral Activity. *J. Med. Chem.* **1991**, *34*, 1028–1036.

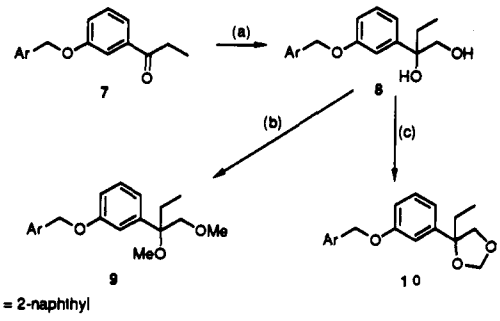
(8) Bird, T. G. C.; Bruneau, P.; Crawley, G. C.; Edwards, M. P.; Foster, S. J.; Girodeau, J.-M.; Kingston, J. F.; McMillan, R. M. (Methoxyalkyl)thiazoles: A New Series of Potent, Selective and Orally Active 5-Lipoxygenase Inhibitors Displaying High Enantioselectivity. *J. Med. Chem.* **1991**, *34*, 2176–2186.

Scheme II.[a] Heteroaryl Compounds



[a] Generic groups are defined in Table V. POM = pivaloyloxymethyl. Reagents: (a) 10% Pd/C, H_2, EtOH; (b) K_2CO_3, $ArCH_2Cl$ or $ArCH_2Br$, DMF, room temperature; (c) 2 M NaOH, EtOH, room temperature; (d) $HC{\equiv}CCH_2OH$, $(PPh_3)_2PdCl_2$, CuI, Et_3N, MeCN, 55 °C; (e) Br_2, PPh_3, CH_2Cl_2, −5 °C; (f) HCO_2Na, $Pd(Ph_3)_4$, DMF, 110 °C.

Scheme III[a]



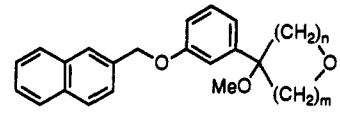
[a] Reagents: (a) *i*-$PrOMe_2SiCH_2Cl$, Mg, THF, 0 °C; (b) NaH, MeI, DMF, room temperature; (c) $(CH_2O)_x$, *p*-TsOH, PhH, reflux.

showed similar potency to **1** and **9** in human blood while **10** was less active. Further developments of ether series represented by **4a**, **9**, and **10** will be the subjects of future publications. In this paper we will concentrate on the series which has evolved from **4b**.

The preferred ring size and the position of the oxygen atom for optimal in vitro potency were determined with compounds **4b–g** (Table I). Inhibition in whole blood was improved with a ring size of 6 or more provided the benzylic carbon and ring oxygen were separated by at least two methylenes. Specifically, the tetrahydropyran **4f** was an order of magnitude more potent than **4b**. The importance of the ring oxygen atom in **4f** was emphasized (Table II) by the marked drop in potency when it was replaced by methylene (**4h**), carbonyl (**4i**), *N*-methylamino (**4j**), sulfide (**4k**), sulfoxide (**4l**), or sulfone (**4m**).

Although the ethyl and thiazolyl groups of **1** have been replaced by tetrahydropyran in **4f**, many similarities exist in the SAR of the two series implying that each binds at the same locus on 5-LPO with several binding points in common. For example, in vitro potency was maintained at the same level in each series when 2-naphthyl was replaced by phenylethynyl (Table III; **1** vs **12** and **4f** vs **4n**).

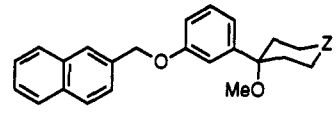
Table I. Variation of in Vitro LT Synthesis Inhibitory Potency with Ring Size and Ring Oxygen Position



	n	*m*	IC_{50} (μM) human blood[a]
4c	1	1	2.5
4b	1	2	0.7 ± 0.3 (3)
4d	1	3	1.7; 2.8
4e	1	4	2.5
4f	2	2	0.07 ± 0.02 (3)
4g	2	3	0.2

[a] IC_{50}s are single determinations except where indicated otherwise. Where more than two values have been determined, IC_{50}s are shown ±SE (number of determinations).

Table II. Variation of in Vitro LT Synthesis Inhibitory Potency with Ring Functionality

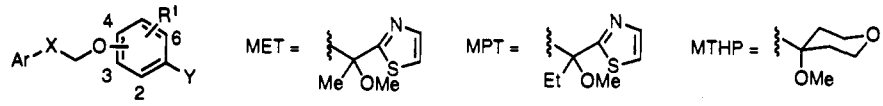


	Z	IC_{50} (μM) human blood[a]
4h	CH_2	2.6 ± 1.5 (3)
4i	C=O	3.4
4j	NMe	>40
4f	O	0.07 ± 0.02 (3)
4k	S	0.4; 0.4
4l	SO	4.2
4m	SO_2	10.6

[a] IC_{50}s are single determinations except where indicated otherwise. Where more than two values have been determined, IC_{50}s are shown ±SE (number of determinations).

Similarly, attachment of the naphthylmethyloxy fragment at the para rather than meta position of the central phenyl

Table III. In Vitro SAR Comparison of LT Synthesis Inhibitory Potency of Representative (Methoxyalkyl)thiazoles and Methoxytetrahydropyrans



	Ar	X	$ArXCH_2O$[a]	R^1	Y	IC_{50} (μM) human blood[b]
11	2-naphthyl	bond	3	H	MET	0.5
1	2-naphthyl	bond	3	H	MPT	0.4 ± 0.2 (3)
4f	2-naphthyl	bond	3	H	MTHP	0.07 ± 0.02 (3)
12	Ph	C≡C	3	H	MPT	0.9; 1.0
4n	Ph	C≡C	3	H	MTHP	0.07
13	2-naphthyl	bond	4	H	MPT	~40
4o	2-naphthyl	bond	4	H	MTHP	19
14	2-naphthyl	bond	3	6-Me	MET	~40
4p	2-naphthyl	bond	3	6-Me	MTHP	~40
15	2-naphthyl	bond	3	2-Me	MET	0.5; 1.0
4q	2-naphthyl	bond	3	2-Me	MTHP	0.6

[a] Position of $ArXCH_2O$ in phenyl ring. [b] IC_{50}s are single determinations except where indicated otherwise. Where more than two values have been determined, IC_{50}s are shown ±SE (number of determinations).

ring in either series resulted in 100-fold losses of potency in the whole blood assay (1 vs 13 and 4f vs 4o). In the (methoxyalkyl)thiazole series, in vitro potency was maintained when the central phenyl ring was substituted by methyl at the 2 position (11 vs 15) but was significantly reduced when methyl was at position 6 (11 vs 14). The same situation obtained in the methoxytetrahydropyran series in which **4q** was somewhat reduced in potency relative to **4f** but **4p** was at least 100-fold less active.

Enhancement of in Vitro Potency

Compound **4f** is a potent inhibitor of LT synthesis in vitro in mouse macrophages (IC_{50} 0.5 nM) and human whole blood (IC_{50} 0.07 μM) and is active orally (ED_{50} 5 mg/kg) in rat blood ex vivo taken 1 h after dosing. In seeking methoxytetrahydropyrans with greater ex vivo potency, we anticipated that **4f** would have low aqueous solubility rendering formulation for oral dosing difficult. Further, low aqueous solubility might restrict oral potency by virtue of solubility-limited absorption from the gastrointestinal tract. High lipophilicity is responsible for the predicted[9] low aqueous solubility of **4f** and in order to find more soluble inhibitors we sought, in congeners of **4f**, to reduce lipophilicity without sacrificing potency. It was not clear at the outset that this could be achieved as there have been several reports indicating a dependency between 5-LPO inhibitory potency and lipophilicity.[10,11] The naphthyl fragment of **4f** makes the major contribution to its calculated *n*-octanol–water partition coefficient (*P*),[12] and one approach we applied to this problem was to replace the naphthyl fragment by heterocycles. In addition to their log *P* lowering properties, heterocycles were chosen for their potential to form extra interactions with the enzyme which could compensate for any loss in potency arising from reduced lipophilicity.

To test this strategy, the naphthyl group was replaced by azaheterocycles and quinolones as probes for hydrogen bond donor–acceptor interactions with the enzyme. Thus, the human blood potencies of the 2-pyridylethynyl (**4r**), 2-quinazolinyl (**4s**), 6-quinazolinyl (**4t**), and 6-quinoxalinyl (**4u**) replacements were reduced 6-fold or less relative to naphthyl (**4f**) whereas log *P* is reduced by 1.8 to 2.1 units (Table IV). The 2-quinolones **4v** and **4x** which have both hydrogen bond donating and accepting potential were also less potent than **4f** in vitro. However, whereas N-methylation of the 2-quinolone when attached at the 3-position (**4w**) had little effect on in vitro potency, N-methylation when the point of attachment is at position 6 (**4y**) produced a 30-fold enhancement. Compound **4y** is less lipophilic than **4f** by 1.7 log *P* units but showed a small but significant ($p < 0.05$) increase in blood potency in vitro. The IC_{50}s in plasma-free macrophages of **4y** (3 nm) and **4f** (0.5 nM), when compared with their IC_{50}s in whole blood, suggest that the enhanced potency of **4y** in human whole blood arises from lower plasma protein binding relative to **4f**.

The position of the amidic fragment in the quinolone ring system is important. Thus, the compounds in which *N*-methyl-2-quinolone is attached through positions 3 (**4w**), 5 (**4aa**), and 7 (**4bb**) were all less effective inhibitors than **4y** in which the point of attachment is position 6. (The absence of a fluorine substituent in the central phenyl ring of **4aa** and **4bb** is expected to have little effect on in vitro potency, cf. **4y** vs **4z**.) Similarly, the isoquinolone **4cc**, the 1,2-benzopyranone **4dd**, and the 4-quinolone **4ee** all showed reduced potency in vitro, most noticeably in the case of **4ee**.

These results demonstrate a specific requirement in the quinolone series for both the *N*-methyl and carbonyl groups to be oriented as in **4y** for potent in vitro inhibition. Heterocycles other than quinolones have also been investigated. The 3,4-ethylene fragment of 2-quinolone was replaced by CMe_2 (**4ff**), NMe (**4gg**), S (**4ii**), and CH=N (**4jj**) without affecting potency in human blood significantly but replacement by O produces **4hh** which was 1 order of magnitude less potent than **4y**. The quinoxalinone **4jj** shows most clearly how such heterocycles have achieved

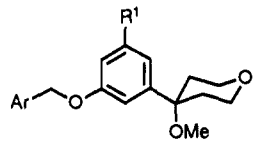
(9) Yalkowsky, S. H.; Valvani, S. C. Solubility and Partitioning I: Solubility of Non-Electrolytes in Water. *J. Pharm. Sci.* **1980**, *69*, 912–922.

(10) Hammond, M. L.; Kopka, I. E.; Zambias, R. A.; Caldwell, G. C.; Boger, J.; Baker, F.; Bach, T.; Luell, S.; MacIntyre, D. E. 2,3-Dihydro-5-benzofuranols as Antioxidant-Based Inhibitors of Leukotriene Biosynthesis. *J. Med. Chem.* **1989**, *32*, 1006–1020.

(11) Hlasta, D. J.; Casey, F. B.; Ferguson, E. W.; Gangell, S. J.; Heimann, M. R.; Jaeger, E. P.; Kullnig, R. K.; Gordon, R. J. 5-Lipoxygenase Inhibitors: The Synthesis and Structure-Activity Relationships of a Series of 1-Phenyl-3-pyrazolidinones. *J. Med. Chem.* **1991**, *34*, 1560–1570.

(12) Discussion of log *P* is limited to consideration of Δlog *P*'s relative to **4f** which were estimated from fragment values contained within: CLOGP version 3.53, Daylight CIS, Irvine, CA. A correction factor was applied to the Δlog *P* of **4s** based on data presented in: Taylor, P. J.; Bradshaw, J. Rationalisation Among Heterocyclic Partition Coefficients. Part 3: π-Excessive Heterocycles. Some Comments on the CLOGP Algorithm. *Quant. Struct.-Act. Relat.* **1989**, *8*, 279–287.

Table IV. Inhibition of LT Synthesis and Physicochemical Data for Heteroaryl Analogs of **4f**



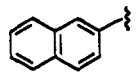
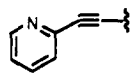
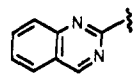
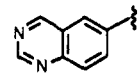
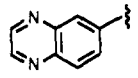
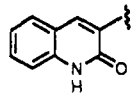
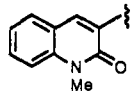
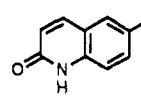
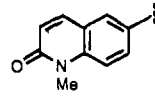
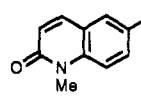
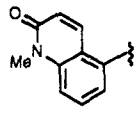
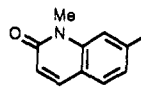
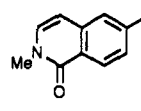
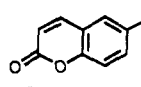
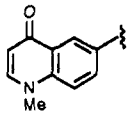
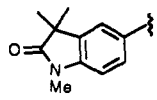
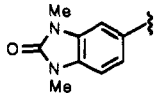
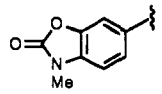
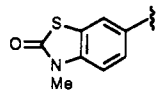
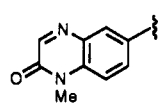
	Ar	R^1	IC_{50} (μM) human blood[a]	rat ED_{50} (mg/kg po)[b] ex vivo blood	rat ED_{50} (mg/kg po)[b] inflamed exudate 3 h	$\Delta\log P$[c]	$\Delta\log S$[d]
4f		H	0.07 ±0.02 (3)	5 at 1 h (4) 10 at 3 h (1)	10 (7)		
4r		H	0.4	100 at 1 h (1)			
4s		F	0.2	>10 at 1 h (1)		-1.9	1.9
4t		F	0.2	>100 at 1 h (1)		-2.1	1.5
4u		F	0.3	30 at 1 h (2)	30 (2)	-1.8	1.8
4v		F	0.2	>100 at 1 h (1)			
4w		F	0.4		>1.5 (1)		
4x		F	0.6	>3 at 3 h (1)			
4y		F	0.02 ±0.005 (4)	1 at 1 h (2) 0.9 at 3 h[e]	0.3[e]	-1.7	0.9
4z		H	0.03	1.5 at 3 h (1)	3 (1)	-2.0	1.8
4aa		H	1.3	>3 at 3 h (1)			
4bb		H	0.2	>3 at 3 h (1)			
4cc		F	0.2		>1.5 (1)		
4dd		F	0.3	>3 at 3 h (1)			
4ee		F	~30				
4ff		F	0.08		>1.5 (1)		
4gg		F	0.08		1.5 (1)	-1.7	1.0

Table IV (Continued)

	Ar	R^1	IC_{50} (μM) human blood[a]	rat ED_{50} (mg/kg po)[b] ex vivo blood	rat ED_{50} (mg/kg po)[b] inflamed exudate 3 h	$\Delta\log P$[c]	$\Delta\log S$[d]
4hh		F	0.2		>1.5 (1)		
4ii		F	0.04		1.5 (1)	-1.2	0.8
4jj		F	0.05		1.5 (2)	-2.3	1.8

[a] IC_{50}s are single determinations except where indicated otherwise. Where more than two values have been determined, IC_{50}s are shown ±SE (number of determinations). [b] Number of determinations in parentheses. [c] Relative to 4f. [d] Aqueous solubility S relative to 4f calculated using $\Delta\log S = -1.05\Delta\log P - 0.012\Delta T_m$. [e] Figure 3.

the objective of reducing lipophilicity (Δ log P -2.3) without compromising in vitro potency.

Oral Potency

Having maintained or enhanced in vitro potency in significantly less lipophilic congeners of **4f**, we have analyzed oral potency in terms of the resulting predicted improvement in aqueous solubility (Table IV). The azaheterocycles **4s–u** are less lipophilic than **4f** by 1.8–2.1 log P units and aqueous solubilities are estimated to be 30–90-fold higher. In spite of this each compound was less active orally in rat blood ex vivo than **4f** even though in vitro potencies were only slightly reduced. In contrast, the oxoheterocyclic compounds **4y**, **4z**, **4gg**, **4ii**, and **4jj**, which had in vitro potencies comparable to **4f** or better, were all more active orally in rat blood ex vivo and/or inflammatory exudate. In the case of this group, Δ log P is in the range -1.2 to -2.3 and solubilities are estimated to be increased by 6- to 60-fold. Increases in solubility alone are unlikely to account for the improved oral potencies of this group since **4y** was the most potent even though its solubility increase is one of the least. Intriguingly, **4z**, which was comparable in vitro to **4y** and is estimated to be almost 1 order of magnitude more soluble, was uniformly less active in rat blood ex vivo and inflammatory exudate.

One explanation of these results is that the polar nature of the amidic fragment of the oxoheterocycles imparts enhanced resistance to metabolism in these molecules relative to naphthyl as in **4f** and azaheterocycles as in **4s–u**. Furthermore, the azaheterocycles could be less active orally than **4f** because, with lowered lipophilicities, their volumes of distribution could be expected to be reduced which would lead to greater exposure to metabolizing enzymes.

Detailed Evaluation of 4y

The most potent compound **4y** shown in Table IV has been examined in more detail. Figure 2 shows a representative experiment in human blood which illustrates that **4y** (ICI D2138) inhibits LT synthesis selectively. In four separate experiments the IC_{50} for LTB_4 synthesis was 24 ± 5 nM (range 12–30 nM). In three experiments no significant inhibition of TxB_2 synthesis was detected at concentrations up to 500 μM. Thus the selectivity ratio (IC_{50} CO/IC_{50} 5-LPO) in human whole blood was >20 000. Following oral administration in the rat, **4y** exhibited comparable inhibitory potency against LTB_4 synthesis in zymosan-inflamed air pouch and in A23187-stimulated whole blood ex vivo (Figure 3) with ED_{50}s 3 h after dosing of 0.3 and 0.9 mg/kg, respectively.

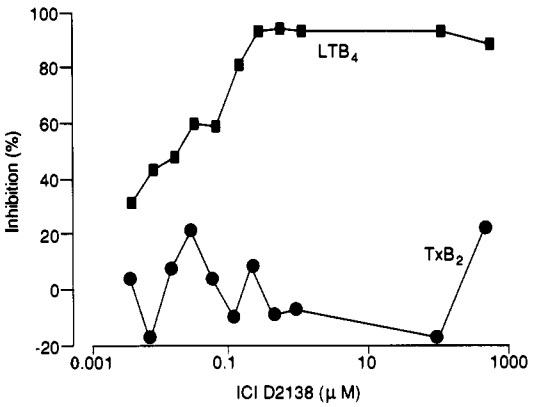


Figure 2. In vitro potency and selectivity of **4y** (ICI D2138). Human whole blood was incubated with **4y** and then stimulated with A23187. Points are means of duplicate incubates.

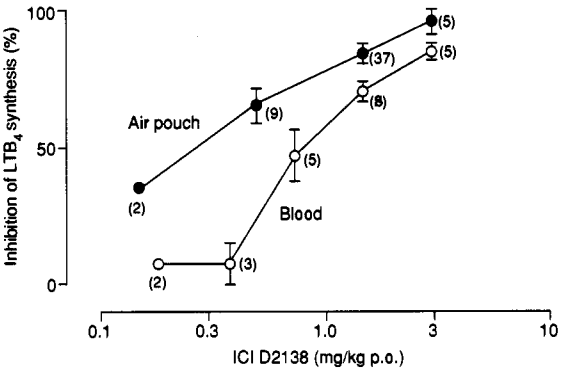
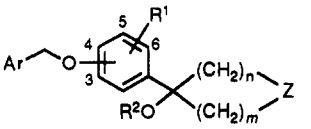


Figure 3. Oral activity of **4y** (ICI D2138) in rat. Rats were dosed orally with **4y** and 3 h later LTB_4 synthesis was measured in zymosan-inflamed air pouch or A23187-stimulated blood ex vivo. Results are composite dose–responses. Points represent mean ± SE. The number of experiments is shown in parentheses.

Conclusions

A series of methoxytetrahydropyrans has been developed which shows enhanced in vitro and ex vivo inhibition of the 5-LPO enzyme over the related series of (methoxyalkyl)thiazoles. Less lipophilic congeners of the lead methoxytetrahydropyran **4f** have been found in which lipophilicity is reduced by more than 2 log P units and in vitro potency in human whole blood has been maintained at broadly the same level or improved. This was achieved by replacing the naphthyl group in **4f** by various heterocycles. Among these are *N*-methyl-2-quinolones, appended

Table V. Physical and Synthetic Data for Compounds 3 and 4



no.	Ar	sub.	R^1	R^2	n	m	Z	formula	anal.[a,b]	mp, °c	method[c] (yield %)
4a	naphth-2-yl	3	H	Me	0	3	CHOMe	$C_{24}H_{26}O_3$	C,H	77–9[d]	A (56);[e] B (53)
4b	naphth-2-yl	3	H	Me	1	2	O	$C_{22}H_{22}O_3 \cdot 0.1H_2O$	C,H	93–4	A (65); B (37)
4c	naphth-2-yl	3	H	Me	1	1	O	$C_{21}H_{20}O_3 \cdot 0.4H_2O$	C,H	71–2	*f*
4d	naphth-2-yl	3	H	Me	1	3	O	$C_{23}H_{24}O_3$	C,H	80–1	A (46); B (47)
4e	naphth-2-yl	3	H	Me	1	4	O	$C_{24}H_{26}O_3$	C,H	oil	A (30); B (58)
4f	naphth-2-yl	3	H	Me	2	2	O	$C_{23}H_{24}O_3$	C,H	73	A (42); B (94)
4g	naphth-2-yl	3	H	Me	2	3	O	$C_{24}H_{26}O_3$	C,H	69.5–70	A (24); B (36)
4h	naphth-2-yl	3	H	Me	2	2	CH_2	$C_{24}H_{26}O_2$	C,H	75	A (58); B (54)
4i	naphth-2-yl	3	H	Me	2	2	C=O	$C_{24}H_{24}O_3 \cdot 0.3H_2O$	C,H	99–101	*f*
4j	naphth-2-yl	3	H	Me	2	2	NMe	$C_{24}H_{27}NO_2 \cdot HCl \cdot 0.3H_2O$	C,H,N	207–8	*f*
4k	naphth-2-yl	3	H	Me	2	2	S	$C_{23}H_{24}O_2S \cdot 0.1H_2O$	C,H	106–7	A (60); B (58)
4l	naphth-2-yl	3	H	Me	2	2	SO	$C_{23}H_{24}O_3S \cdot 0.4H_2O$	C,H	111	*f*
4m	naphth-2-yl	3	H	Me	2	2	SO_2	$C_{23}H_{24}O_4S$	C,H	142	*f*
4n	phenylethynyl	3	H	Me	2	2	O	$C_{21}H_{22}O_3 \cdot 0.5CH_2Cl_2$	C,H	oil	C (27)
4o	naphth-2-yl	4	H	Me	2	2	O	$C_{23}H_{24}O_3$	C,H	135–6	A (30); B (45)
4p	naphth-2-yl	3	6-Me	Me	2	2	O	$C_{24}H_{26}O_3$	C,H	98–9	A (37), B (92)
4q	naphth-2-yl	3	2-Me	Me	2	2	O	$C_{24}H_{26}O_3$	C,H	104.5–105	A (45); B (71)
4r	pyrid-2-ylethynyl	3	H	Me	2	2	O	$C_{20}H_{21}NO_3 \cdot 0.1H_2O$	C,H,N	oil	C (56)
4s	quinazolin-2-yl	3	5-F	Me	2	2	O	$C_{21}H_{21}FN_2O_3 \cdot 0.25EtOAc$	C,H,N	76–7	C (77)
4t	quinazolin-6-yl	3	5-F	Me	2	2	O	$C_{21}H_{21}FN_2O_3$	C,H,N	126–8	C (79)
4u	quinoxalin-6-yl	3	5-F	Me	2	2	O	$C_{21}H_{21}FN_2O_3$	C,H,N	80–1	C (56)
4v	quinol-2-on-3-yl	3	5-F	Me	2	2	O	$C_{22}H_{22}FNO_4 \cdot 0.05EtOAc$	C,H,N	208–10	C (44)
4w	1-Me-quinol-2-on-3-yl	3	5-F	Me	2	2	O	$C_{23}H_{24}FNO_4$	C,H,N	138	C (51)
4x	quinol-2-on-6-yl	3	5-F	Me	2	2	O	$C_{22}H_{22}FNO_4$	C,H,N	220	*f*
4y	1-Me-quinol-2-on-6-yl	3	5-F	Me	2	2	O	$C_{23}H_{24}FNO_4$	C,H,F,N	147	C (88)
4z	1-Me-quinol-2-on-6-yl	3	H	Me	2	2	O	$C_{23}H_{25}NO_4 \cdot 0.8H_2O$	C,H,N	96–9	C (74)
4aa	1-Me-quinol-2-on-5-yl	3	H	Me	2	2	O	$C_{23}H_{25}NO_4$	C,H,N	112–3	C (56)
4bb	1-Me-quinol-2-on-7-yl	3	H	Me	2	2	O	$C_{23}H_{25}NO_4$	C,H,N	74–6	C (66)
4cc	2-Me-isoquinol-1-on-6-yl	3	5-F	Me	2	2	O	$C_{23}H_{24}FNO_4 \cdot 0.2H_2O$	C,H,N	162–5	*f*
4dd	2-oxo-2*H*-1-benzopyran-6-yl	3	5-F	Me	2	2	O	$C_{22}H_{21}FO_5 \cdot 0.15$toluene	C,H	145–6	C (51)
4ee	1-Me-quinol-4-on-6-yl	3	5-F	Me	2	2	O	$C_{23}H_{24}FNO_4 \cdot 0.2H_2O$	C,H,N	173–4	*f*
4ff	1,3,3-Me_3-2-oxo-indolin-5-yl	3	5-F	Me	2	2	O	$C_{24}H_{28}FNO_4$	C,H,N	124–6	C (17)
4gg	1,3-Me_2-2-oxo-benzimidazolin-5-yl	3	5-F	Me	2	2	O	$C_{22}H_{25}FN_2O_4$	C,H,N	136–7	*f*
4hh	3-Me-2-oxo-benzoxazolidin-6-yl	3	5-F	Me	2	2	O	$C_{21}H_{22}FNO_5 \cdot 0.25H_2O$	C,H,N	139–141	C (80)
4ii	3-Me-2-oxo-benzthiazolidin-6-yl	3	5-F	Me	2	2	O	$C_{21}H_{22}FNO_4S$	C,H,N	104–6	C (77)
4jj	1,2-H_2-1-Me-2-oxo-quinoxalin-6-yl	3	5-F	Me	2	2	O	$C_{22}H_{23}FN_2O_4$	C,H,N	122–4	C (65)
4kk	naphth-2-yl	3	H	Me	2	2	$C(OCH_2)_2$	$C_{26}H_{28}O_4 \cdot 0.25H_2O$	C,H	111–2	A (80); B (30)
4ll	naphth-2-yl	3	H	Me	2	2	NCO_2Et	$C_{26}H_{29}NO_4$	C,H,N	70.5–72	A (30); B (61)
4mm	1-POM-quinol-2-on-6-yl	3	5-F	Me	2	2	O	$C_{26}H_{32}FNO_6$	C,H,N	133–5	C (65)
4nn	4-Br-2-Me-isoquinol-1-on-6-yl	3	5-F	Me	2	2	O	$C_{23}H_{23}FBrNO_4$	C,H,N	136–9	C (64)
4oo	3-Br-1-Me-quinol-4-on-6-yl	3	5-F	Me	2	2	O	$C_{23}H_{23}FBrNO_4$	C,H,Br,N	177–8	C (72)
4pp	5-Br-1,3-Me_2-benzimidazolin-2-on-6-yl	3	5-F	Me	2	2	O	$C_{22}H_{24}FBrN_2O_4$	C,H,N	161–2	C (50)
4qq	phenyl	3	H	Me	2	2	O	$C_{19}H_{22}O_3$	C,H	56	A (73); B (88)
4rr	phenyl	3	5-F	Me	2	2	O	$C_{19}H_{21}FO_3$	C,H	48–9	A (62); B (72)
3e	naphth-2-yl	3	H	H	1	4	O	$C_{23}H_{24}O_3$		115–6	A (30)
3f	naphth-2-yl	3	H	H	2	2	O	$C_{22}H_{22}O_3$		130–1	A (42)
3h	naphth-2-yl	3	H	H	2	2	CH_2	$C_{23}H_{24}O_2$	C[g],H	oil	A (58)
3k	naphth-2-yl	3	H	H	2	2	S	$C_{22}H_{22}O_2S$		140.5	A (60)
3o	naphth-2-yl	4	H	H	2	2	O	$C_{22}H_{22}O_3$	C,H	166–8	A (30)
3q	naphth-2-yl	3	2-Me	H	2	2	O	$C_{23}H_{24}O_3$	C,H	152.5–153	A (45)
3kk	naphth-2-yl	3	H	H	2	2	$C(OCH_2)_2$	$C_{26}H_{26}O_4$	C,H	120–3	A (80)
3ll	naphth-2-yl	3	H	H	2	2	NCO_2Et	$C_{25}H_{27}NO_4$		128–9	A (30)
3qq	phenyl	3	H	H	2	2	O	$C_{19}H_{20}O_3$	C,H	81–2	A (73)

[a] Elemental analyses were within ±0.4% of the calculated value except where stated otherwise. [b] In most cases compounds 3 were converted directly to compounds 4; where physical data is available for compounds 3 they are presented in this table. [c] Methods A and B indicated in Scheme I and method C in Scheme II. [d] trans isomer. [e] 30:70 mixture of cis–trans isomers produced. [f] Synthesis described in Experimental Section. [g] C: calcd, 83.1; found, 82.6.

at position 6, and related oxoheterocycles which are of particular interest demonstrating potent inhibition in vitro in human whole blood and orally in the rat in blood ex vivo and in inflammatory exudate. The compound of choice from this series is 4y which was more potent in vitro in human whole blood and ex vivo in rat blood at 3 h than the 5-LPO inhibitor A-64077[13] and the 5-lipoxygenase activating protein (FLAP) antagonist MK-886[14] (Table VI)

Table VI. Comparison of LT Synthesis Inhibition of A-64077, MK-886, and 4y (ICI D2138)

	human blood in vitro IC_{50}, μM		rat ED_{50}, mg/kg po at 3 h	
	LTB_4	TxB_2	ex vivo blood	inflammatory exudate
A-64077	2.6	40	5	3
MK-886 Na salt	1.1	NT[a]	3	2
ICI D2138	0.02	>500	0.9	0.3

[a] NT = not tested.

which have been the subjects of clinical investigations.[3-6,15,16]

(13) Carter, G. W.; Young, P. R.; Albert, D. H.; Bouska, J.; Dyer, R.; Bell, R. L.; Summers, J. B.; Brooks, D. W. 5-Lipoxygenase Inhibitory Activity of Zileuton. *J. Pharmacol. Exp. Ther.* 1991, *256*, 929–937.

On the basis of these data, 4y has been entered into development as a selective 5-LPO inhibitor for clinical evaluation by oral administration in inflammatory conditions in which LTs are believed to play a role.

Experimental Section

Biological Tests. Eicosanoid Generation in Murine Peritoneal Macrophages. Inhibition of LTC_4 and PGE_2 synthesis in plasma-free cultures of peritoneal macrophages was performed as described by Foster et al.[17]

Eicosanoid Generation in Whole Blood. The potency and selectivity of 5-LPO inhibitors were evaluated by studying eicosanoid generation in heparinized rat or human blood as described by Foster et al.[17] with the following modifications. For ex vivo studies in the rat, compounds were dissolved in dimethyl sulfoxide and a dosing suspension was then prepared by mixing 300 μL of this solution with 15 mL of 0.5% (hydroxypropyl)methylcellulose containing 0.1% polysorbate 80. Experimental animals were dosed with 1 mL/kg of drug suspensions, and control animals received the same volume of vehicle.

Eicosanoid Generation in Inflammatory Exudate. Groups of male Alderley Park rats (130–150 g), 18 controls and six per treated group, were anaesthetized with halothane, and an air pouch was formed by injecting sterile air (20 mL) into the subcutaneous tissue of the back of each animal using a 0.22 μm millipore filter attached to a syringe. Three days later the air pouches were reinflated with a second injection of sterile air (10 mL). After a further 3 days, the animals were dosed orally with compound, formulated as described for ex vivo blood, or vehicle. Immediately following dosing, a 1% suspension of zymosan in physiological saline (PS) (1 mL) was injected directly into each air pouch. Before injection, the zymosan suspension was boiled for 30 min in PS, washed three times by centrifugation in PS at 3000 rpm for 5 min, resuspended in PS to 1%, and then autoclaved. The rats were killed 3 h after zymosan injection using a rising concentration of carbon dioxide, and the air pouches were lavaged with PS (1 mL) containing 20 U of heparin. Lavage fluids were immediately placed on ice, centrifuged in an Eppendorf bench centrifuge, and the supernatants analyzed for LTB_4 by radioimmunoassay.

Synthetic Chemistry. All reactions (excluding catalytic hydrogenations) were performed in argon atmospheres. THF was dried and distilled from sodium and benzophenone under argon. Aqueous NH_4Cl refers to a saturated aqueous solution. Unless stated otherwise, organic solutions were dried over $MgSO_4$. All evaporations were carried out in vacuo using Buchi rotary evaporators. Chromatography refers to column chromatography on silica (E Merck, 70–230 or 230–400 mesh). Flash chromatography was performed as described.[18] Melting points were determined in Buchi or Mettler FP62 apparatuses in glass capilliary tubes or in a Reichert Jung microscope and are uncorrected. NMR spectra were recorded on Bruker WM200, WM250, WM400, or Jeol FX90Q instruments and are reported as δ values (parts per million) relative to Me_4Si as internal standard. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical value. Physical and synthetic data for all final compounds and isolated precursors are shown in Table V where this data is not given in the Experimental Section.

5-(Benzyloxy)-3-fluorophenyl Bromide (2b). NaH (60% dispersion in oil, 82.9 g, 2.07 mol) was added portionwise to a stirred solution of benzyl alcohol (222 g, 2.05 mol) in DMA (4 L). After 1 h, 1-bromo-3,5-difluorobenzene (400 g, 2.07 mol) was added at such a rate to maintain the temperature at <40 °C (ca. 1 h). The reaction was stirred at room temperature overnight, added to water (40 L), and extracted with EtOAc (2 × 7.5 L). The combined EtOAc solution was dried and evaporated. Flash chromatography with hexanes as eluant gave **2b** as a colorless oil (279 g, 48%): ^1H NMR ($CDCl_3$) δ 7.48 (5 H, s), 6.94 (1 H, s), 6.85 (1 H, m), 6.6 (1 H, m), 5.08 (2 H, s).

Method A. (a) 4-[3-Fluoro-5-(benzyloxy)phenyl]-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (3rr). *n*-BuLi (620 mL, 1.6 M solution in hexanes, 1 mol) was added dropwise over 1 h to a stirred solution of **2b** (279 g, 1 mol) dissolved in THF (4 L) maintaining the reaction temperature at ≤−70 °C during the addition. After a further 1 h at −70 °C, a solution of 3,4,5,6-tetrahydro-2*H*-pyran-4-one (91.5 mL, 1 mol) in THF (600 mL) was added dropwise over 0.75 h. The reaction mixture was maintained at −70 °C for 1 h and allowed to warm to 0 °C over 2 h. Aqueous NH_4Cl (2 L) was added and the organic phase separated, dried, and evaporated. Flash chromatography with EtOAc–toluene (1:9) as eluant gave **3rr** as a clear oil (185 g, 62%): ^1H NMR ($CDCl_3$) δ 7.4 (5 H, m), 6.9 (1 H, m), 6.8 (1 H, dt, J_1 = 10 Hz, J_2 = 2 Hz), 6.6 (1 H, dt, J_1 = 10 Hz, J_2 = 2 Hz), 5.1 (2 H, s), 3.9 (4 H, m), 2.1 (2 H, m), 1.65 (2 H, dd, J_1 = 14 Hz, J_2 = 2 Hz), 1.57 (1 H, s).

(b) 4-[3-(Benzyloxy)phenyl]-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (3qq). 3,4,5,6-Tetrahydro-2*H*-pyran-4-one (10 g, 100 mmol) was added at room temperature to a stirred Grignard solution prepared from 3-(benzyloxy)phenyl bromide (26.3 g, 100 mmol), Mg (2.38 g, 100 mmol), and THF (110 mL). After stirring overnight, the reaction mixture was added to ice–water (200 mL) and extracted with EtOAc (2 × 100 mL), and the combined organic layers were dried and evaporated. Chromatography with Et_2O–CH_2Cl_2 (1:9) as eluant gave **3qq** as white crystals (20 g).

Method B. 4-[3-Fluoro-5-(benzyloxy)phenyl]-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (4rr). To a stirred solution of **3rr** (185 g, 0.61 mol) in DMF (2.25 L) cooled to 5 °C was added NaH (60% dispersion in oil, 27 g, 0.68 mol) portionwise. After 1 h methyl iodide (46 mL, 0.74 mol) was added over 0.5 h. The reaction mixture was allowed to warm to room temperature overnight, poured into water (25 L), and extracted with EtOAc (3 × 3 L). The combined EtOAc solutions were washed with water (2 × 5 L) and then brine (5 L) and dried and evaporated. Flash chromatography with EtOAc–hexane (1:9) as eluant gave **4rr** as white crystals (141 g): ^1H NMR ($CDCl_3$) δ 7.4 (5 H, m), 6.8 (1 H, m), 6.7 (1 H, dd, J_1 = 10 Hz, J_2 = 2 Hz), 6.6 (1 H, dd, J_1 = 10 Hz, J_2 = 2 Hz), 5.0 (2 H, s), 3.8 (4 H, m), 3.0 (3 H, s), 1.9 (4 H, m).

4-Methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]cyclohexanone (4i). 4-Methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]-cyclohexanone ethylene ketal (**4kk**) (1.1 g, 2.7 mmol) dissolved in acetone (20 mL) was treated with *p*-TsOH (0.05 g, 0.3 mmol) at room temperature. After 3 h the reaction mixture was basified with $NaHCO_3$, evaporated, and extracted into $CHCl_3$, which was dried and evaporated. Flash chromatography with EtOAc–hexane (1:9) as eluant gave **4i** as white crystals after trituration with Et_2O (0.25 g, 26%).

1-Methyl-4-methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]-piperidine (4j). 1-Carbethoxy-4-methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]piperidine (**4ll**) (1 g, 2.4 mmol) dissolved in Et_2O (5 mL) was added dropwise to a suspension of LAH (0.23 g, 6 mmol) in Et_2O (5 mL), and the mixture was stirred at room temperature during 7 h. EtOAc (10 mL) and water (0.5 mL) were added. The organic phase was decanted from solid which was

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washed with EtOAc (3 × 5 mL). The combined organic solutions were dried and evaporated. Treatment with ethereal HCl gave **4j**·HCl as white crystals (0.3 g, 33%).

4-Methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]-3,4,5,6-tetrahydro-2*H*-thiopyran 1-Oxide (4l) and 4-Methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]-3,4,5,6-tetrahydro-2*H*-thiopyran 1,1-Dioxide (4m). 4-Methoxy-4-[3-(naphth-2-ylmethoxy)phenyl]-3,4,5,6-tetrahydro-2*H*-thiopyran (**4k**, 0.36 g, 1 mmol) dissolved in CH_2Cl_2 (4 mL) was treated with *m*-chloroperoxybenzoic acid (50%, 0.34 g, 1 mmol). After 4 h the solution was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$, and the organic phase was separated, washed with brine, dried, and evaporated. Chromatography with CH_2Cl_2 as eluant gave **4m** (0.1 g, 25%), and further elution with Me_2CO–CH_2Cl_2 (1:4) gave **4l** (0.1 g, 25%) both as white solids.

4-(3-Fluoro-5-hydroxyphenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (5b). **4rr** (100 g, 0.32 mol) was hydrogenated over 10% Pd/C (5 g) in methylated spirits (1 L) until uptake of hydrogen ceased (ca. 2 h). The catalyst was removed by filtration, and evaporation of the filtrate gave **5b** as an off-white crystalline solid (68 g, 95%): mp 129–31 °C; ^{1}H NMR ($CDCl_3$) δ 6.7 (2 H, m), 6.5 (1 H, dt, J_1 = 10 Hz, J_2 = 2 Hz), 6.3 (1 H, s) 3.9 (4 H, m), 3.05 (3 H, s), 2.0 (4 H, m). Anal. ($C_{12}H_{15}FO_3$) C, H.

4-(3-Hydroxyphenyl)-4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (5a). The procedure used to prepare **5b** applied to **4qq** gave **5a** (89%): mp 116 °C. Anal. ($C_{12}H_{16}O_3$) C, H.

Method C. 6-[[3-Fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]quinoxaline (4u). 6-(Bromomethyl)quinoxaline (2.94 g, 13.2 mmol), **5b** (2.75 g, 12 mmol), anhydrous K_2CO_3 (2.52 g, 18.3 mmol), and DMF (30 mL) were stirred at room temperature overnight. The reaction mixture was filtered, evaporated and redissolved in EtOAc (200 mL). The EtOAc solution was washed with water (4 × 20 mL) and then brine (20 mL) and dried and evaporated. Flash chromatography with EtOAc–toluene (1:1) as eluant gave **4u** as a white solid (2.48 g): ^{1}H NMR ($CDCl_3$) δ 8.9 (2 H, s), 8.15 (2 H, m), 7.85 (1 H, dd, J_1 = 8 Hz, J_2 = 1.7 Hz), 6.8 (1 H, m), 6.75 (1 H, dt, J_1 = 10 Hz, J_2 = 2 Hz), 6.65 (1 H, dt, J_1 = 10 Hz, J_2 = 2 Hz), 5.3 (2 H, s), 3.8 (4 H, m), 3.0 (3 H, s), 1.95 (4 H, m).

6-Methyl-1-[(pivaloyloxy)methyl]quinol-2-one (16). To a stirred solution of 6-methylquinol-2(1H)-one (4.8 g, 30 mmol) in DMF (225 mL) cooled to 5 °C was added NaH (55% dispersion in oil, 1.3 g, 30 mmol). When hydrogen evolution had ceased, chloromethyl pivalate (4.75 mL, 33 mmol) was added and the reaction mixture stirred to room temperature overnight. The solvent was evaporated and the residue partitioned between EtOAc (200 mL) and water (100 mL). The aqueous layer was separated and reextracted with EtOAc (2 × 50 mL), and the combined EtOAc solutions were washed with water (2 × 20 mL), dried, and evaporated. Flash chromatography with EtOAc–toluene (1:4) as eluant gave **16** as a solid (3.7 g, 45%): mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 7.7 (3 H, m), 7.3 (1 H, m), 6.7 (1 H, d, J = 10 Hz), 6.3 (2 H, s), 4.55 (2 H, s), 1.2 (9 H, s). Anal. ($C_{16}H_{19}NO_3$) C, H, N.

6-(Bromomethyl)-1-[(pivaloyloxy)methyl]quinol-2-one (17). A stirred suspension of **16** (1.86 g, 6.8 mmol), *N*-bromosuccinimide (1.2 g, 6.8 mmol), α,α'-azoisobutyrylnitrile (100 mg), and CCl_4 (50 mL) was refluxed and illuminated with a 275-W bulb for 2 h. The reaction mixture was filtered hot and evaporated. Flash chromatography with EtOAc–toluene (1:4) as eluant gave **17** as an oil (1.6 g, 67%) which was used directly.

6-[[3-Fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]quinol-2-one (4x). 6-[[3-Fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]-1-[(pivaloyloxy)methyl]quinol-2-one (**4mm**) (1.34 g, 2.7 mmol) dissolved in EtOH (60 mL) was treated with 2 N aqueous NaOH (3 mL, 1.1 equiv) and stirred at room temperature for 2 h. The reaction mixture was evaporated, dissolved in CH_2Cl_2, washed with water, and dried. Evaporation gave **4x** as a white solid (0.8 g, 78%).

3-(2-Pyridyl)prop-2-yn-1-ol (18). To a stirred solution of 2-bromopyridine (23.7 g, 0.15 mol), $(PPh_3)_2PdCl_2$ (1.5 g), and CuI (1.5 g) was added propargyl alcohol (35 mL, 0.6 mol) followed by Et_3N (21 mL, 0.15 mol). The reaction mixture was heated at 55–60 °C for 2 h and added to water, and the pH was adjusted to 6–7 with 2 N HCl and extracted with CH_2Cl_2. The organic phase was dried and evaporated. Flash chromatography with CH_2Cl_2–EtOAc (1:1) as eluant gave **18** as white crystals (13.9 g, 70%): mp 78–80 °C (from EtOAc). Anal. (C_8H_7NO·0.1H_2O) C, H, N.

3-(2-Pyridyl)prop-2-yn-1-yl Bromide (6). A solution of bromine (2 mL, 38.5 mmol) in CH_2Cl_2 (2 mL) was added with stirring to a solution of triphenylphosphine (10.1 g, 38.5 mmol) in CH_2Cl_2 (72 mL) cooled to −5 °C. If a faint yellow color persisted it was discharged with a few crystals of triphenylphosphine. A solution of **18** (4.8 g, 36 mmol) in CH_2Cl_2 (36 mL) was added at a rate to raise the reaction temperature to 5 °C at the end of the addition. The reaction solution was recooled to −10 °C and the resulting solid collected by filtration and washed with CH_2Cl_2 to give **6**·**HBr** as a blue solid (5.8 g, 58%): mp 112–114 °C.

1,3-Dimethyl-5-[[3-fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]benzimidazolin-2-one (4gg). 5-Bromo-1,3-dimethyl-6-[[3-fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]benzimidazolin-2-one (**4pp**, 190 mg, 0.4 mmol) suspended in DMF (2 mL) was treated with sodium formate (60 mg, 0.88 mmol) and $(PPh_3)_4Pd$ (47 mg) and the mixture heated with stirring at 100 °C for 6 h. The reaction mixture was partitioned between EtOAc and water, the aqueous layer was separated and reextracted with EtOAc, and the combined EtOAc solutions were dried and evaporated. Flash chromatography with EtOAc–toluene (65:35) as eluant gave **4gg** as a white solid (90 mg, 57%). Using this procedure the following were prepared.

6-[[3-Fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]-2-methylisoquinol-1-one (4cc) from 4-bromo derivative (**4nn**) (40%).

6-[[3-Fluoro-5-(4-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-4-yl)phenoxy]methyl]-1-methylquinol-4-one (4ee) from 3-bromo derivative (**4oo**) (36%).

2-Hydroxy-2-[3-(naphth-2-ylmethoxy)phenyl]butan-1-ol (8). 1-[3-(Naphth-2-ylmethoxy)phenyl]propan-1-one (**7**) (6 g, 0.02 mol) dissolved in THF (12 mL) was added to a solution of [(isopropoxydimethylsilyl)methyl]magnesium chloride prepared from (chloromethyl)dimethylisopropoxysilane (8.2 mL, 0.0455 mol), Mg (1.09 g, 0.045 mol), and THF (5 mL). The reaction mixture was stirred at room temperature for 1 h and added to aqueous NH_4Cl, and the organic phase was dried and evaporated. The residue was redissolved in MeOH (60 mL), $NaHCO_3$ (1.73 g, 0.021 mol) and H_2O_2 (30%, 18 mL, 0.18 mol) were added, and the mixture was refluxed overnight. The solvent was evaporated, the residue partitioned between Et_2O and water, and the ethereal phase washed with brine, dried, and evaporated. Chromatography with Me_2CO–CH_2Cl_2 (1:9) as eluant gave **8** as a white solid (5.4 g, 81%): mp 98 °C.

2-Methoxy-2-[3-(naphth-2-ylmethoxy)phenyl]butyl Methyl Ether (9). NaH (50% dispersion in oil, 0.22 g, 4.65 mmol) was added to **8** (0.6 g, 1.85 mmol) dissolved in DMF followed after 5 min by methyl iodide (0.3 mL, 4.65 mmol) and 18-crown-6 (0.06 g, 0.22 mmol). The reaction mixture was stirred overnight and then evaporated, and the residue was partitioned between CH_2Cl_2 and water. The organic phase was washed with brine, dried, and evaporated. Chromatography with Et_2O–CH_2Cl_2 (5:95) gave **9** as white crystals (0.51 g, 87%): mp 47 °C; ^{1}H NMR ($CDCl_3$) δ 7.9–6.6 (11 H, m), 5.2 (2 H, s), 3.6 (2 H, m), 3.3 (3 H, s), 3.1 (3 H, s), 1.8 (2 H, m), 0.75 (3 H, t, J = 7 Hz). Anal. ($C_{23}H_{26}O_3$) C, H.

4-Ethyl-4-[3-(naphth-2-ylmethoxy)phenyl]dioxolane (10). A solution of **8** (1.1 g, 3.3 mmol), paraformaldehyde (1 g), and *p*-TsOH (40 mg) in benzene (15 mL) was refluxed for 3 h. The cooled reaction mixture was washed with aqueous Na_2CO_3, dried, and evaporated. Chromatography with CH_2Cl_2–hexane (4:1) as eluant gave **10** as a white solid (90 mg, 8%): mp 72–3 °C; ^{1}H NMR (CDCl3) δ 8.0–6.8 (11 H, m), 5.25 (2 H, s), 5.15 (1 H, s), 5.0 (1 H, s), 3.95 (2 H, s), 1.9 (2 H, q, J = 7 Hz), 0.8 (3 H, t, J = 7 Hz). Anal. ($C_{22}H_{22}O_3$) C, H.

2-(Benzyloxy)-1-[3-(benzyloxy)phenyl]ethanone (19). (Benzyloxy)acetonitrile (1.36 g, 9.2 mmol) was added to [3-(benzyloxy)phenyl]magnesium bromide, prepared from 3-(benzyloxy)phenyl bromide (2.55 g, 9.7 mmol), Mg powder (0.23 g, 9.7 mmol), and THF (20 mL), and heated at 60 °C for 1 h. After cooling to room temperature, Et_2O (20 mL) was added followed by dropwise addition of 1 N HCl (50 mL) and the mixture stirred for 20 min. The organic layer was separated, washed with water

(20 mL) and then brine (20 mL), dried, and evaporated. Chromatography with CH_2Cl_2 as eluant gave **19** as an oil (2.1 g, 65%): ^1H NMR ($CDCl_3$) δ 7.6–7.1 (14 H, m), 5.1 (2 H, s), 4.75 (2 H, s), 4.7 (2 H, s).

3-(Benzyloxy)-2-[3-(benzyloxy)phenyl]-2-hydroxypropan-1-ol (20). The procedure used to prepare **8** applied to **19** gave **20** as an oil (87%): ^1H NMR ($CDCl_3$) δ 7.5–6.7 (14 H, m), 5.05 (2 H, s), 4.55 (2 H, s), 4.0–3.5 (4 H, m), 3.3 (1 H, s), 2.3 (1 H, m).

[3-(Benzyloxy)-2-[3-(benzyloxy)phenyl]-2-hydroxy-1-propoxy]-*tert*-butyldimethylsilane (21). A solution of **20** (2 g, 5.5 mmol), imidazole (0.45 g, 6.6 mmol), *tert*-butyldimethylchlorosilane (0.99 g, 6.6 mmol), and DMF (10 mL) was heated overnight at 60 °C, cooled to room temperature, and diluted with EtOAc and water. The organic phase was separated, washed with water and then brine, dried, and evaporated. Chromatography with CH_2Cl_2 as eluant gave **21** as an oil (2.1 g, 81%): ^1H NMR (DMSO-d_6) δ 7.5–6.8 (14 H, m), 5.05 (2 H, s), 4.9 (1 H, s), 4.5 (2 H, s), 3.65 (2 H, m), 3.6 (2 H, s), 0.8 (9 H, s), 0.0 (6 H, s).

[3-(Benzyloxy)-2-[3-(benzyloxy)phenyl]-2-methoxy-1-propoxy]-*tert*-butyldimethylsilane (22). Method B applied to **21** gave **22** as an oil (92%).

3-(Benzyloxy)-2-[3-(benzyloxy)phenyl]-2-methoxypropan-1-ol (23). Tetra-*n*-butylammonium fluoride (1 M in THF, 9 mL, 0.17 mmol) was added to **22** (2 g, 4.1 mmol) dissolved in THF (20 mL) and left overnight at room temperature. The solution was evaporated, the residue partitioned between EtOAc and water, and the organic phase separated, washed with brine, dried, and evaporated. Chromatography with Et_2O–CH_2Cl_2 (1:9) as eluant gave **23** as an oil (1.5 g, 99%).

2-(3-Hydroxyphenyl)-2-methoxypropane-1,3-diol (24). The procedure used to prepare **5b** applied to **23** gave **24** as an oil (82%): ^1H NMR (DMSO-d_6) δ 9.2 (1 H, s), 7.25–6.5 (4 H, m), 4.5 (2 H, m), 3.7 (4 H, m), 3.2 (3 H, s).

2-[3-(Naphth-2-ylmethoxy)phenyl]-2-methoxypropane-1,3-diol (25). Method C applied to **24** and 2-(bromomethyl)-naphthalene gave **25** as a white solid (60%): mp 129 °C; ^1H NMR (DMSO-d_6) δ 8.05–6.85 (11 H, m), 5.25 (2 H, s), 4.55 (2 H, d, J = 5 Hz), 3.75 (4 H, d, J = 5 Hz), 3.1 (3 H, s). Anal. ($C_{21}H_{22}O_4$) C, H.

3-Methoxy-3-[3-(naphth-2-ylmethoxy)phenyl]oxetane (4c). To a stirred solution of **25** (0.34 g, 1 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 0.63 mL, 1 mmol) followed by TosCl (0.2 g, 1 mmol) dissolved in THF (1 mL). After 0.5 h, further *n*-BuLi (0.63 mL, 1 mmol) was added and the reaction heated at 60 °C for 4 h. The solvent was evaporated and the residue partitioned between Et_2O and water. The ethereal layer was washed with brine, dried, and evaporated. Chromatography with Et_2O–CH_2Cl_2 (2:98) as eluant gave **4c** as a white solid (0.12 g, 22%): ^1H NMR ($CDCl_3$) δ 8.0–6.9 (11 H, m), 5.25 (2 H, s), 4.9 (2 H, d, J = 6 Hz), 4.75 (2 H, d, J = 6 Hz), 3.1 (3 H, s).

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Registry No. 2b, 130722-44-0; **3e**, 130722-29-1; **3f**, 130722-34-8; **3h**, 141376-37-6; **3k**, 130722-28-0; **3kk**, 141376-38-7; **3ll**, 141376-39-8; **3o**, 130723-89-6; **3q**, 141376-40-1; **3qq**, 133739-86-3; **3rr**, 130723-10-3; **4a** (isomer 1), 141376-41-2; **4a** (isomer 2), 130768-12-6; **4aa**, 133739-13-6; **4b**, 130722-35-9; **4bb**, 133739-14-7; **4c**, 130722-86-0; **4cc**, 141376-42-3; **4d**, 130722-39-3; **4dd**, 141376-43-4; **4e**, 130722-38-2; **4ee**, 141376-44-5; **4f**, 130722-32-6; **4ff**, 139486-99-0; **4g**, 130722-83-7; **4gg**, 139486-96-7; **4h**, 130768-11-5; **4hh**, 139486-94-5; **4i**, 130767-90-7; **4ii**, 139486-93-4; **4j**, 141376-45-6; **4jj**, 141376-46-7; **4k**, 130722-37-1; **4kk**, 130768-26-2; **4l**, 130724-92-4; **4ll**, 141376-47-8; **4m**, 130724-93-5; **4mm**, 133739-66-9; **4n**, 130722-51-9; **4nn**, 141396-42-1; **4o**, 130723-90-9; **4oo**, 141376-48-9; **4p**, 141376-49-0; **4pp**, 139486-95-6; **4q**, 141376-50-3; **4qq**, 141376-51-4; **4r**, 133739-01-2; **4rr**, 130723-11-4; **4s**, 133739-19-2; **4t**, 133739-18-1; **4u**, 133739-03-4; **4v**, 133739-04-5; **4w**, 141376-52-5; **4x**, 141376-53-6; **4y**, 140841-32-3; **4z**, 133739-11-4; **5a**, 130722-57-5; **5b**, 130723-09-0; **6**·HBr, 54256-35-8; **7**, 129425-69-0; **8**, 131341-17-8; **9**, 131480-49-4; **10**, 131340-70-0; **16**, 133739-68-1; **17**, 133739-67-0; **18**, 29768-03-4; **19**, 141376-54-7; **20**, 130722-89-3; **21**, 130742-82-4; **22**, 130722-90-6; **23**, 130722-91-7; **24**, 130722-92-8; **25**, 130722-85-9; 5-LPO, 80619-02-9; 3,4,5,6-tetrahydro-2*H*-pyran-4-one, 29943-42-8; 3-(benzyloxy)phenyl bromide, 53087-13-1; 6-(bromomethyl)quinoline, 53967-21-8; 6-methylquinol-2(1*H*)-one, 4053-34-3; chloromethyl pivalate, 18997-19-8; 2-bromopyridine, 109-04-6; propargyl alcohol, 107-19-7; [(isopropoxydimethylsilyl)methyl]magnesium chloride, 122588-50-5; (benzyloxy)acetonitrile, 13620-31-0; *tert*-butyldimethylchlorosilane, 18162-48-6.