5.8% (n = 6) at 30 nM and 10.6% (n = 6) at 100 nM. The inhibitory effect of AA861 as a reference compound was tested by the standard 5-lipoxygenase assay. An IC_{50} value of 10 μM was obtained, and the value was higher by 1 order of magnitude than the previous value (0.8 μM).[20] The difference of two IC_{50} values may be attributed to the different preparations as described in the text for cirsiliol.

Registry No. **1a**, 134081-23-5; **1b**, 134081-24-6; **1c**, 134081-25-7; **1d**, 134081-26-8; **1e**, 134081-27-9; **1f**, 134081-28-0; **1g**, 134081-29-1; **1h**, 134081-30-4; **2a**, 134081-31-5; **2b**, 134081-32-6; **2c**, 134081-33-7; **2d**, 134081-34-8; **2e**, 134081-35-9; **2f**, 134081-36-0; **2g**, 134081-37-1; **2h**, 134081-38-2; **3a**, 134081-39-3; **3b**, 134081-40-6; **3c**, 134081-41-7; **3d**, 134081-42-8; **3e**, 134081-43-9; **3f**, 134081-44-0; **3g**, 134081-45-1; **3h**, 134081-46-2; **4a**, 134081-47-3; **4b**, 134081-48-4; **4c**, 134081-49-5; **4d**, 134081-50-8; **4e**, 134081-51-9; **4f**, 134081-52-0; **4g**, 134081-53-1; **4h**, 134081-54-2; **5**, 5333-45-9; **7a**, 51379-76-1; **7b**, 134081-63-3; **7c**, 134081-64-4; **7d**, 134081-65-5; **7e**, 134081-66-6; **7f**, 134081-67-7; **7g**, 134081-68-8; **7h**, 134081-69-9; **8a**, 134081-77-9; **8b**, 134081-78-0; **8c**, 134081-79-1; **8d**, 134081-80-4; **8e**, 134081-81-5; **8f**, 134081-82-6; **8g**, 134081-83-7; **8h**, 134081-84-8; **9a**, 134081-85-9; **9b**, 134081-86-0; **9c**, 134081-87-1; **9d**, 134081-88-2; **9e**, 134081-89-3; **9f**, 134081-90-6; **9g**, 134081-91-7; **9h**, 134081-92-8; **10a**, 134081-93-9; **10b**, 134081-94-0; **10c**, 134081-95-1; **10d**, 134081-96-2; **10e**, 134081-97-3; **10f**, 134081-98-4; **10g**, 134081-99-5; **10h**, 134082-00-1; **12a**, 134082-01-2; **12b**, 134082-02-3; **12c**, 134082-03-4; **12d**, 134082-04-5; **12e**, 134082-05-6; **12f**, 134082-06-7; **12g**, 134082-07-8; **12h**, 134082-08-9; **14a**, 52099-20-4; **14b**, 134081-70-2; **14c**, 134081-71-3; **14d**, 134081-72-4; **14e**, 134081-73-5; **14f**, 134081-74-6; **14g**, 134081-75-7; **14h**, 134081-76-8; **15a**, 134082-09-0; **15b**, 134082-10-3; **15c**, 134082-11-4; **15d**, 134082-12-5; **15e**, 134109-93-6; **15f**, 134082-13-6; **15g**, 134082-14-7; **15h**, 134082-15-8; **16a**, 134082-24-9; **16b**, 134082-25-0; **16c**, 134082-26-1; **16d**, 134082-27-2; **16e**, 134082-28-3; **16f**, 134082-29-4; **16g**, 134082-30-7; **16h**, 134082-31-8; **17a**, 134082-16-9; **17b**, 134082-17-0; **17c**, 134082-18-1; **17d**, 134082-19-2; **17e**, 134082-20-5; **17f**, 134082-21-6; **17g**, 134082-22-7; **17h**, 134082-23-8; **18a**, 134082-32-9; **18b**, 134082-33-0; **18c**, 134082-34-1; **18d**, 134082-35-2; **18e**, 134082-36-3; **18f**, 134082-37-4; **18g**, 134109-94-7; **18h**, 134082-38-5; **19**, 134081-55-3; **20**, 134081-56-4; **21**, 134081-57-5; **22**, 134081-58-6; **23**, 134081-59-7; **24**, 134081-60-0; **25**, 134081-61-1; **26**, 134081-62-2; **27**, 7622-60-8; **28**, 116512-06-2; **29**, 134082-46-5; **30**, 134082-39-6; **31**, 134109-95-8; **32**, 134082-40-9; **33**, 134082-41-0; **35**, 24160-94-9; **36**, 134082-42-1; **37**, 134082-43-2; **38**, 124910-02-7; **40**, 134082-44-3; **41**, 134082-45-4; CH_3CH_2COCl, 79-03-8; $CH_3(CH_2)_4COCl$, 142-61-0; $C_6H_{13}CH_2COCl$, 111-64-8; $C_8H_{17}CH_2COCl$, 112-13-0; $C_{10}H_{21}CH_2COCl$, 112-16-3; $C_{12}H_{25}CH_2COCl$, 112-64-1; $C_{14}H_{29}CH_2COCl$, 112-67-4; $C_{16}H_{33}CH_2COCl$, 112-76-5; 3,4-bis(benzyloxy)benzoic anhydride, 1592-48-9; potassium 3,4-bis(benzyloxy)benzoate, 110193-71-0; arachidonate 5-lipoxygenase, 80619-02-9.

(20) Yoshimoto, T.; Yokoyama, C.; Ochi, K.; Yamamoto, S.; Maki, Y.; Ashida, Y.; Terao, S.; Shiraishi, M. *Biochim. Biophys. Acta* **1982**, *713*, 470-473.

(Methoxyalkyl)thiazoles: A New Series of Potent, Selective, and Orally Active 5-Lipoxygenase Inhibitors Displaying High Enantioselectivity[1]

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(Methoxyalkyl)thiazoles are novel 5-lipoxygenase (5-LPO) inhibitors that are neither redox agents nor iron chelators. Consideration of a hypothetical model of the enzyme active site led to this series which is exemplified by 1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-2-yl)propyl methyl ether (**2d**, ICI211965). **2d** inhibits cell-free guinea pig 5-LPO activity, LTC_4 synthesis in plasma free mouse macrophages, and LTB_4 synthesis in rat and human blood (IC_{50}s 0.1 μM, 8 nM, 0.5 μM, and 0.4 μM, respectively) but does not inhibit the synthesis of cyclooxygenase products at concentrations up to 50 μM in macrophages and 100 μM in blood. **2d** is orally active in rat (ex vivo ED_{50} 10 mg/kg in blood taken in 1 h after dosing). SAR studies show that high in vitro potency requires methoxy, thiazolyl, and naphthyl groups and depends critically on the substitution pattern. (Methoxyalkyl)thiazoles are chiral. Resolution of 1-methoxy-6-(naphth-2-ylmethoxy)-1-(thiazol-2-yl)indan (**2j**, ICI216800) shows that (+)-**2j** is 50–150-fold more potent than (−)-**2j** in in vitro assays. Thus, (methoxyalkyl)thiazoles are a new series of orally active, selective 5-LPO inhibitors and represent the first class of inhibitors in which inhibition is mediated by specific, enantioselective interactions with the enzyme.

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 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[2] and the peptidoleukotrienes LTC_4 and LTD_4 are powerful spasmogens in vascular and bronchial tissues.[3] 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. However, only when orally active inhibitors of 5-LPO free from CO inhibitory activity are evaluated clinically will the value of 5-LPO inhibition in the treatment of inflammatory conditions become clear.

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(1) Presented in part at *Inflammation Research Association Fifth International Conference*, Mountain Laurel Resort, White Haven, PA, Sept 23–27, 1990.
(2) McMillan, R. M.; Foster, S. J. *Agents Actions* **1988**, *24*, 114.
(3) O'Donnell, M.; Welton, A. *Therapeutic Approaches to Inflammatory Disease*; Lewis, A. J., Doherty, N. S., Ackerman, N. R., Eds.; Elsevier: New York, 1989; p 169.

0022-2623/91/1834-2176$02.50/0

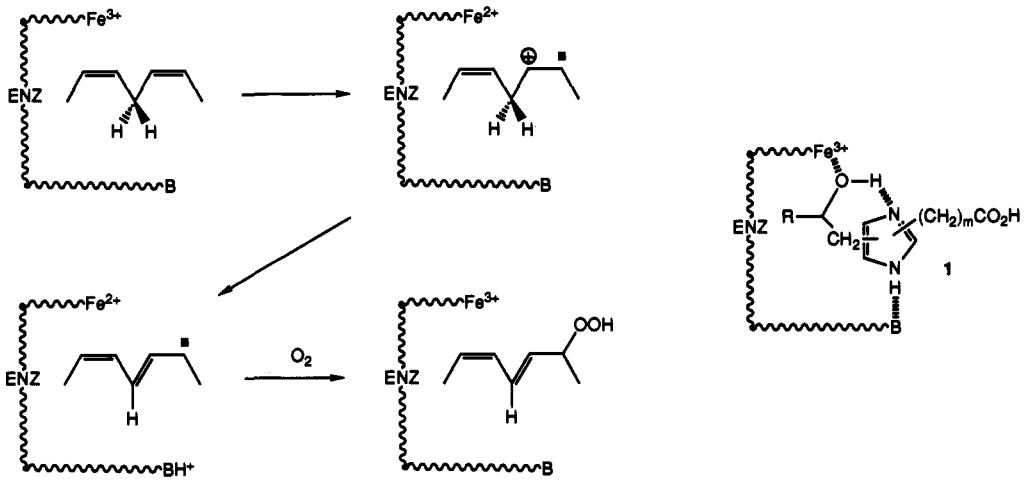

Figure 1.

Although many compounds are known that inhibit 5-LPO, most of these have insufficient 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, methaemoglobin formation has been demonstrated with a number of 5-LPO inhibitors with redox properties.[4]

The target of the current work has been to find orally active inhibitors selective for the 5-LPO pathway and devoid of redox properties. We now report on the successful outcome of this work, which has resulted in the discovery of a novel series of 5-LPO inhibitors, (methoxyalkyl)thiazoles.

Biological Tests

Spectrophotometric Analysis of 5-LPO. Inhibition of cell-free 5-LPO activity was determined spectrophotometrically by the procedure of Aharony and Stein[5] using the high-speed supernatant from either guinea pig PMNs or rat basophilic leukemia (RBL) cells[6] as the enzyme source.

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.[7]

Eicosanoid Generation in Whole Blood. The potency and selectivity of 5-LPO inhibitors were evaluated by studying eicosanoid generation in heparinised rat or human blood as described by Foster et al.[7] with the following modification. 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 methyl cellulose 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.

Statistical Analysis. IC_{50} and ED_{50} values were calculated on an IBM-PC using an iterative, four-parameter curve-fitting program. 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.

Chemistry

(Methoxyalkyl)thiazoles are a series of 5-LPO inhibitors represented by the general structure **2** (Het = thiazolyl, Scheme I). The (methoxyalkyl)thiazole feature was generated by alkylation (route E) of the corresponding (hydroxyalkyl)thiazoles **3** (Het = thiazolyl), which in turn were assembled by routes B–D using Grignard or organolithium chemistry shown in Scheme I. Alternatively, the phenol **11** with the (methoxyalkyl)thiazolyl group preformed was alkylated (route A). For acetylene-linked compounds the propargyl derivative **13** was coupled to iodotoluenes using Pd catalysis. Phenol **11** was synthesized by either of the routes shown in Scheme II. (Hydroxyalkyl)imidazoles were prepared similarly to route B using the protected imidazole derivative **18** (Scheme III). Finally, **19** and **20** were prepared as shown in Scheme IV.

Lead Generation

Our starting point was a consideration of the groups likely to be present at the active site of 5-LPO. Although the sequences of various LPOs are known,[8] no three-dimensional structure information has yet been reported. Therefore, we developed a hypothetical model of the active site and in this we were influenced by the mechanism proposed by Gibian and Galaway[9] for the soyabean LPO reaction. Briefly, this envisages transfer of an electron from the pentadienyl unit of the substrate to Fe(III) to generate a radical cation. A basic group abstracts a proton from the radical cation to produce the pentadienyl radical (Figure 1). This mechanism requires an iron atom and a base at or close to the active site of the enzyme. In addition, the structure of the substrate suggests further lipophilic and carboxylate binding regions. It was with these groups that our inhibitors were designed to interact. The Fe(III) ion is oxophilic, and alcohols are known to be ligands.[10] The binding of the hydroxyl to iron is improved

(4) Albert, D. H.; Machinist, J.; Young, P. R.; Dyer, R.; Bouska, J.; Brooks, D. W.; Carter, G. W. *FASEB J.* **1989**, *3*, A735, Abs 2954.
(5) Aharony, D.; Stein, R. L. *J. Biol. Chem.* **1986**, *261*, 11512.
(6) McMillan, R. M.; Masters, D. J.; Vickers, V. C.; Dicken, M. P.; Jacobs, V. N. *Biochim. Biophys. Acta* **1989**, *1005*, 170.
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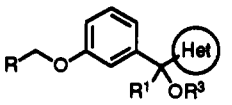
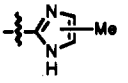
(10) Cotton, S. A. *Coord. Chem. Rev.* **1972**, *8*, 185. Slappendel, S.; Aasa, R.; Mallmström, B. G.; Verhagen, J.; Veldik, G. A.; Vliegenthart, J. F. G. *Biochim. Biophys. Acta* **1982**, *708*, 259.

Table I. Evolution of **2d** from Initial Hypothesis[a]



	R	R¹	R³	Het	guinea pig 5-LPO IC_{50} (μM)	mouse mø 5-LPO IC_{50} (μM)	whole blood 5-LPO rat IC_{50} (μM)	whole blood 5-LPO human IC_{50} (μM)
3z	n-C_9H_{19}	H	H		6.3 ± 0.8 (2)		>30 (2)	
3aa	4-biphenylyl	H	H		7.0 (1)			
3bb	2-naphthyl	H	H		7.6 ± 0.9 (5)		>30 (2)	
3a	2-naphthyl	H	H		5.1 ± 1.9 (3)		30 ± 0 (2)	
2a	2-naphthyl	H	Me		12 ± 4.3 (7)	0.3 ± 0.06 (51)	6 ± 2.0 (4)	7 ± 3.2 (2)
2b	2-naphthyl	Me	Me		0.5 ± 0.2 (2)	0.005 (1)	0.8 ± 0 (2)	0.5 (1)
2d	2-naphthyl	Et	Me		0.1 ± 0.04 (3)[b]	0.008 (1)	0.5 ± 0.2 (3)	0.4 ± 0.2 (3)

[a] IC_{50}s ± SE (number of determinations). [b] IC_{50} 0.2 μM (1) vs RBL 5-LPO.

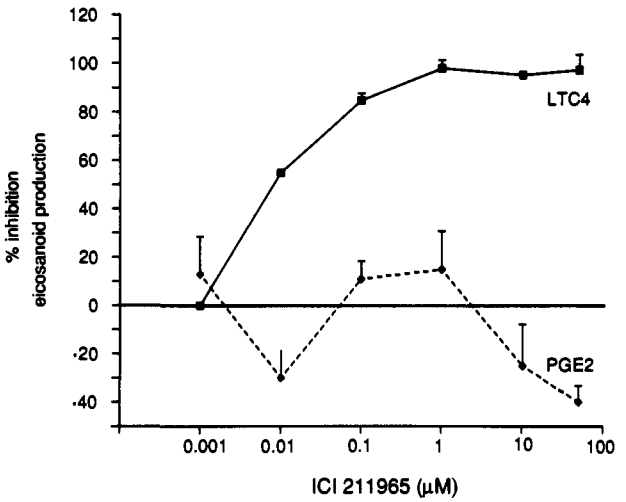


Figure 2. Effect of ICI211965 on LTC_4 and PGE_2 synthesis in mouse peritoneal macrophages in vitro. Results are mean values.

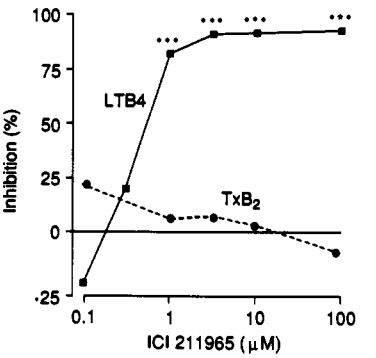


Figure 3. Effect of ICI211965 on LTB_4 and TXB_2 synthesis in human blood in vitro. Results are the means of triplicates. (*** = $p < 0.001$).

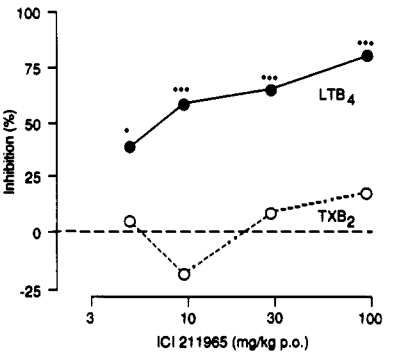


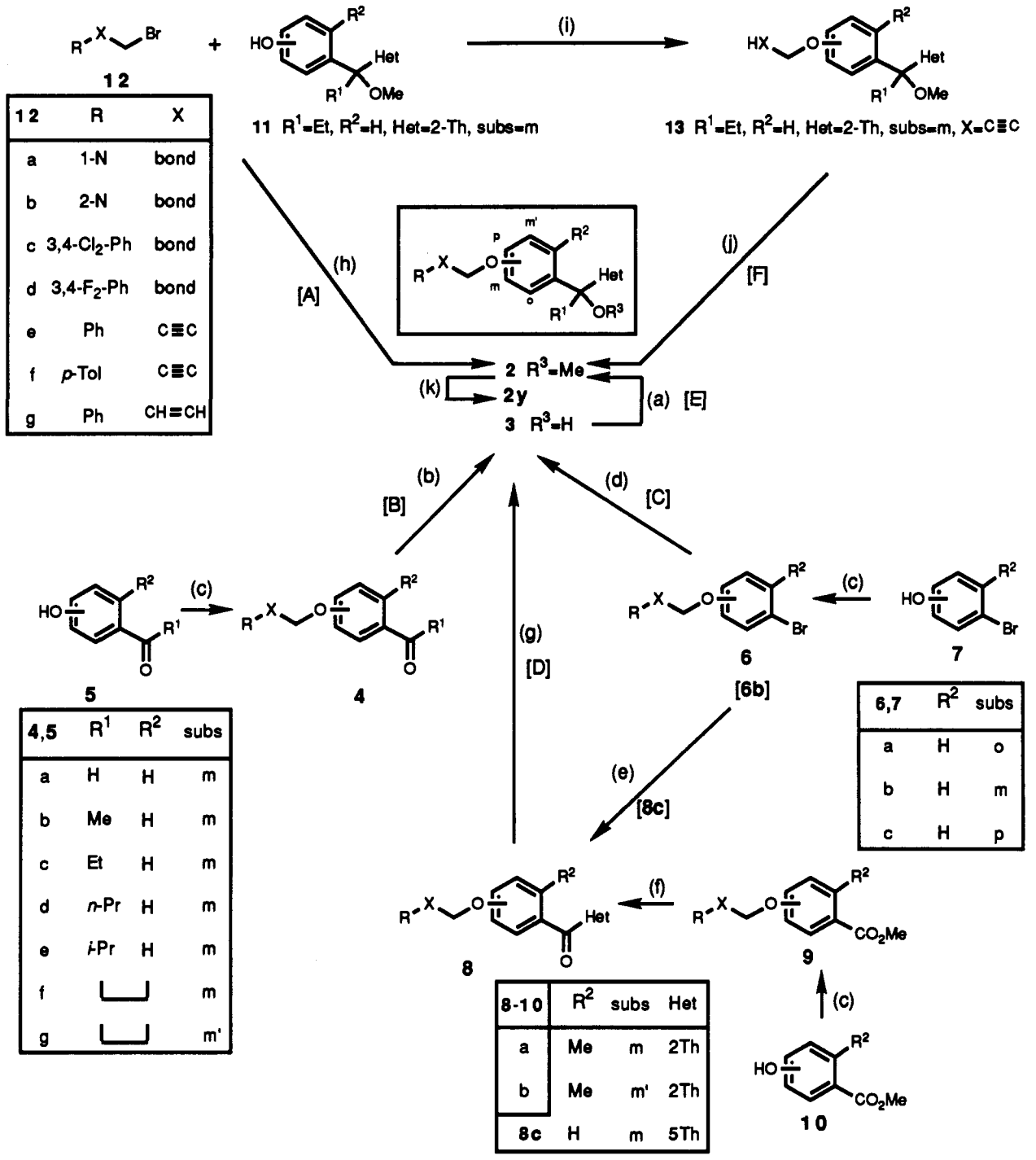
Figure 4. Effect of ICI211965 on LTB_4 and TXB_2 synthesis by rat blood ex vivo. Compound or vehicle were administered orally, and 1 h later animals were killed and bled. Points represent mean values (n = 5). (* = $p < 0.05$; *** = $p < 0.001$).

when a pendant group is capable of hydrogen bonding to the hydroxyl proton.[11] We have therefore studied hydroxyimidazoles corresponding to general structure **1** in which the hydroxy group, hydrogen bonded to imidazole as shown, would provide a ligand to iron. Further, the imidazole N-H has the possibility to interact with a basic group on the enzyme. Activity against the isolated enzyme was found in a series of substituted phenylimidazolylcarbinols **3z**, **3aa**, and **3bb** (Table I).

No activity was observed, however, in the rat whole blood system. A wider SAR study was undertaken based on these structures and the thiazolyl derivative **3a** (Table I) was found to be a weak inhibitor (IC_{50} 30 μM) in rat whole blood. The *O*-methyl derivative **2a** showed increased potency in rat blood, and this was improved further in all four in vitro systems by introduction of methyl (**2b**) or ethyl (**2d**) at the benzylic carbon.[12] Thus **2d** was a potent inhibitor of isolated guinea pig 5-LPO (IC_{50} 0.1 μM) and of LT synthesis in plasma-free mouse macrophages (IC_{50} 0.008 μM). The difference in potency of **2d** in these two assays may be related to the absence of 5-LPO activating protein in the isolated enzyme assay.[13,14] In rat and human whole blood **2d** was equally effective (IC_{50}s 0.5 and 0.4 μM, respectively) but less potent than in the macrophage assay, probably due to plasma protein binding. Further, **2d** (ICI211965) was selective for the 5-LPO pathway in both macrophages (Figure 2) and rat and human blood (Figure 3, only data in human blood shown) in which the synthesis of CO products was unaffected up to 50 μM in macrophages and 100 μM in either blood system. In addition to potent in vitro inhibition, **2d** was orally active with an ED_{50} of 10 mg/kg in an ex vivo determination in rat blood taken 1 h after dosing (Figure 4) without effect on CO products at 100 mg/kg. Such selectivity is representative of this series of (methoxyalkyl)thiazoles, and no further data will be presented regarding the CO enzyme. Although (methoxyalkyl)thiazoles can no longer inhibit the enzyme in the manner proposed in our initial hypothesis, in the event the original rationale has led us on to a selective and orally active series of 5-LPO inhibitors.[15]

(11) Behere, D. V.; Goff, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 4945.
(12) The redox potential of **2a** was 1.69 V measured in MeCN by cyclic voltammetry using the method previously described.[7] Under these conditions the redox potential of ICI207968 was 0.45 V.
(13) Rouzer, C. A.; Ford-Hutchinson, A. W.; Morton, H. E.; Gillard, J. W. *J. Biol. Chem.* **1990**, *265*, 1436.
(14) We have observed this effect in various series of 5-LPO inhibitors, including redox-based inhibitors.

Scheme I[a]



[a] Notes: Generic elements of **2** and **3** are specified in Table VI. Subs refers to substitution pattern in central phenyl ring as indicated in **2**. In **4**, **6**, **8**, and **9**, R = 2-naphthyl and X = direct bond. 1-N = 1-naphthyl. Th = thiazolyl. Reagents: (a) NaH, MeI, THF, room temperature (−10 to −5 °C for **2f**); (b) *n*-BuLi, thiazole, THF, −70 to room temperature (4-methylthiazole for **4c** to **2m**, 5-methylthiazole for **4b** to **2n**); (c) 2-(bromomethyl)naphthalene, K_2CO_3, DMF, room temperature; (d) Mg, THF, ethyl(2-thiazolyl)methanone reflux (ethyl(4-thiazolyl)methanone for **6b** to **3e**); (e) Mg, THF, inverse addition to 5-thiazolyl-C(O)OCO_2Et (from 5-thiazolecarboxylic acid, $ClCO_2Et$, Et_3N, −10 to −15 °C THF), −30 °C to room temperature; (f) *n*-BuLi, 2-bromothiazole, THF, inverse addition, −70 °C; (g) EtMgBr, THF, reflux for **2f**; MeLi, THF, room temperature for **2o,p**; (h) K_2CO_3, DMF, room temperature; (i) propargyl bromide, K_2CO_3, acetone; (j) $(PPh_3)_2PdCl_2$, CuI, Et_3N, MeCN, 55 °C, *o*-tolyl iodide for **2n**, *m*-tolyl iodide for **2v**; (k) 10% $Pd/CaCO_3$, H_2, MeOH.

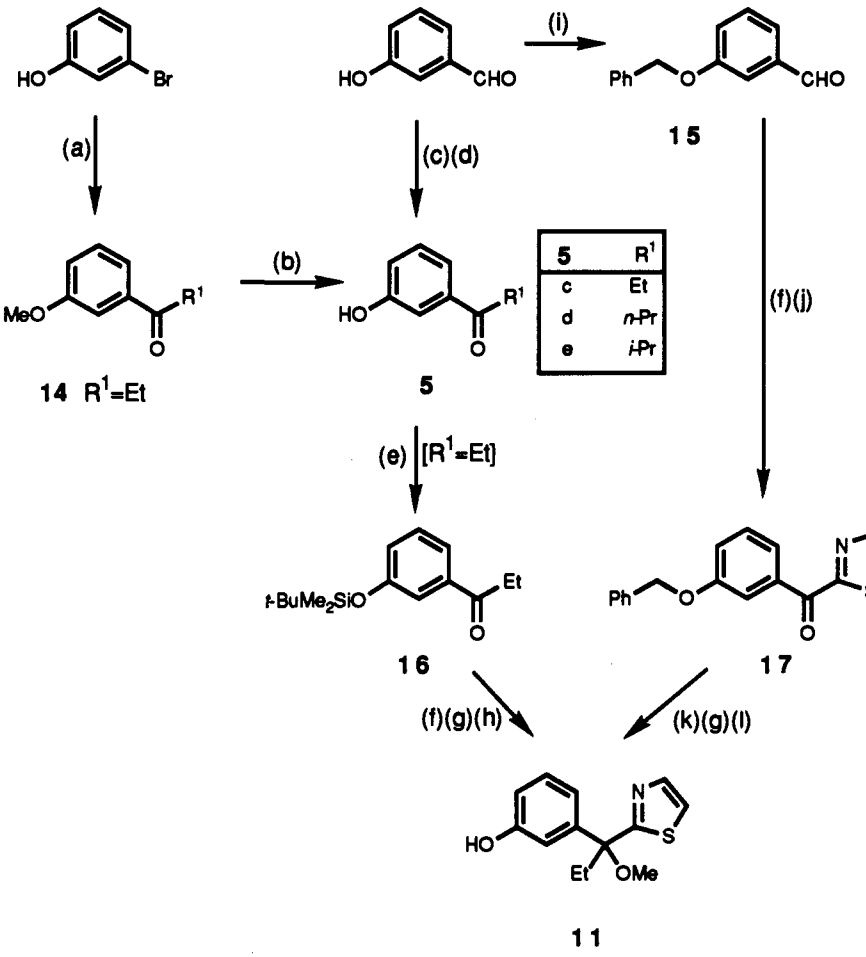
Further SAR

In many reports on 5-LPO inhibitors, structural changes resulting in increased potency can be correlated with increased lipophilicity.[16] In order to evaluate the scope of (methoxyalkyl)thiazoles for improvements in potency by rational drug design we sought evidence of specific interactions with the enzyme. We did this by modifying the

(15) (Methoxyalkyl)thiazoles do not chelate iron. The UV spectrum of **2d** was unchanged upon addition of $FeCl_3$. Under identical conditions the hydroxamic acid BWA4C showed a shift in its UV spectrum.

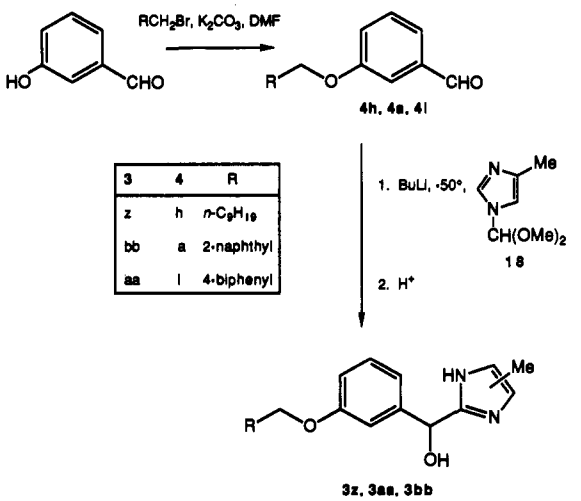
(16) E.g.: Hammond, M. L.; Kopka, I. E.; Zambias, R. A.; Caldwell, C. G.; Boger, J.; Baker, F.; Bach, T.; Luell, S.; MacIntyre, D. E. *J. Med. Chem.* **1989**, *32*, 1006.

Scheme II[a]

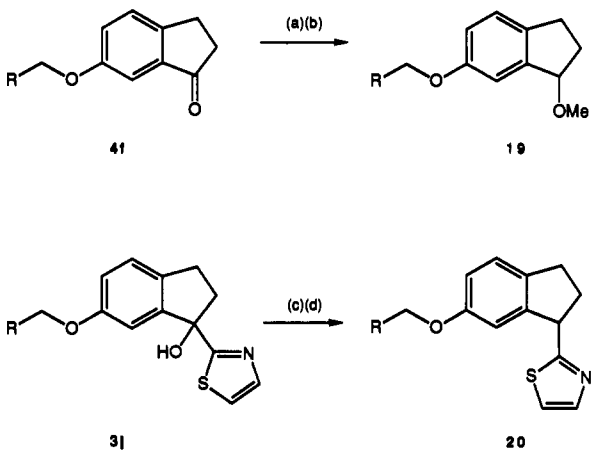


[a] Reagents: (a) Mg, THF, inverse addition to $Et(CO)_2O$, Et_2O, −70 °C to room temperature; (b) py·HCl, 210 °C; (c) R^1MgBr, Et_2O, reflux; (d) DDQ, dioxane, room temperature; (e) t-$BuMe_2SiCl$, imidazole, DMF, room temperature; (f) n-BuLi, thiazole or 2-bromothiazole, THF, −70 °C to room temperature; (g) NaH, MeI, THF, room temperature; (h) n-Bu_4NF, THF, room temperature; (i) $PhCH_2Br$, K_2CO_3, DMF, room temperature; (j) $(COCl)_2$, DMSO, Et_3N, −50 to 10 °C; (k) EtMgBr, THF, reflux; (l) 30% Pd/C, H_2, EtOAc.

Scheme III



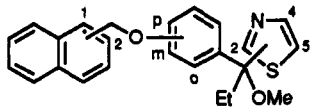
Scheme IV[a]



[a] R = 2-naphthyl. Reagents: (a) $NaBH_4$, EtOH, RT; (b) NaH, MeI, THF, room temperature; (c) p-TsOH, CH_2Cl_2, reflux; (d) PtO_2, AcOH, EtOAc, MeOH, 75 psi of H_2.

spatial arrangement of the groups comprising **2d** in structures largely isolipophilic with **2d**. For example, changing the point of attachment of the naphthalene ring from β to α resulted in a 10-fold loss of potency in the human whole blood assay (**2d** vs **2c**, Table II). Further, modification of the substitution pattern of the central aromatic ring from meta to either ortho (**2g**) or para (**2h**) led to at least a 100-fold drop in potency. Similarly, the point of attachment of the thiazole could be changed from 2 to 4 without appreciable loss in potency (**2d** vs **2e**), but 5-thiazolyl (**2f**) was 1 order of magnitude less potent. The spatial requirements of the methoxy and thiazolyl fragments were demonstrated by comparison of the conformationally constrained indan analogues **2i** and **2j** (Table

Table II. Dependence of in Vitro Potency of **2d** upon Substitution Pattern[a]



	points of attachment			human whole blood
	naphthyl	phenyl	thiazolyl	5-LPO IC_{50} (μM)
2c	1	m	2	4.8 ± 0.8 (2)
2d	2	m	2	0.4 ± 0.1 (3)
2g	2	o	2	>40 (1)
2h	2	p	2	~40 (1)
2e	2	m	4	0.6 ± 0.1 (2)
2f	2	m	5	6.3 (1)

[a] IC_{50}s ± SE (number of determinations).

III). Whereas in the latter potency similar to **2d** was maintained in both macrophage and human blood in vitro systems, the isomer **2i** was 1000-fold less potent in macrophages and showed no inhibition up to 40 μM in blood. Using the indan framework of **2j** we showed that both the methoxy and thiazolyl groups were needed for inhibition. Neither **19**, in which thiazolyl is absent, nor **20**, which lacks methoxy, showed inhibition below 40 μM. Finally we used the asymmetry of **2j** to test the chiral nature of the interaction. All chiral compounds described so far were tested as racemic mixtures. Racemic **2j** was separated into its enantiomers and inhibition was shown to be due almost entirely to the (+)-isomer with inhibitory properties essentially absent in the (−)-isomer.[17]

Encouraged by these results we delineated further what structural variation was possible while maintaining high potency. The jump in potency achieved between **2a** and **2b** or **2d** was associated with substitution on the benzylic carbon. Further substitution, however, led to loss of potency. Thus when R^1 = *n*-Pr (**2k**) (Table IV) the potency was reduced about 10-fold in macrophages and 20-fold in blood and when R^1 = *i*-Pr (**2l**) the potency was some 100-fold worse in both systems. These results indicated both steric and conformational constraints were limiting binding at this region on the enzyme. Substitution in the 2-thiazolyl ring was also detrimental. Methyl substitutions at the 4-position (**2m**) or 5-position (**2n**) each led to loss of potency.

We have studied substitution in the central aromatic ring in which R^2 = Me (Table IV). Potent inhibition was maintained with the (naphthylmethyl)oxy group at the m′ position (**2p** vs **2b**) but reduced at least 100-fold in macrophages and blood when (naphthylmethyl)oxy was at the m position (**2o** and **2b**). The minimum-energy conformation of these *o*-tolyl derivatives about the quarternary center had the aromatic methyl intersecting the methoxy and thiazolyl groups.[18] Therefore, with regard to the spatial arrangement of methoxy, thiazolyl, central phenyl ring, and (naphthylmethyl)oxy groups, **2p** was equivalent to **2j** and **2o** to **2i**, and the potencies of each pair were consistent with this analysis.

Variations we have made to the naphthyl fragment of **2d** showed that occupancy of the region occupied by ring A (furthest ring from point of attachment) on the enzyme is essential for potent inhibition. For example, the phenyl derivative **2q**, which lacks ring A, was 100-fold less effective in human whole blood. However, insertion of spacer groups such as ethynyl (**2t**) or 1,2-ethenyl (**2x**) between the phenyl ring and the methyleneoxy fragment restored potency virtually to the same level as **2d**. These spacer groups to some extent fill the space occupied by ring B (ring bearing point of attachment) but principally they place the phenyl ring at the ring A region on the enzyme. A 1,2-ethylenyl spacer group (**2y**) would also serve the same purpose but **2y** was 1 order of magnitude less potent. This compound is, however, more flexible, and the loss of rotational freedom on binding to the enzyme will make a negative contribution to the binding energy. The ring A space could also be filled by substitution on the phenyl ring of **2q**. Thus, 3,4-dichlorophenyl (**2r**) was almost equivalent to naphthyl (**2d**) but 3,4-difluorophenyl (**2s**) was less effective. We have also investigated the effect of methyl substitution on the phenyl ring of the acetylenic compound **2t**. Potency decreased in the order ortho > meta > para (**2u** vs **2v** vs **2w**).

Conclusions

Most 5-lipoxygenase inhibitors have the potential to participate in redox processes or to chelate iron and may therefore act through relatively nonspecific mechanisms. With these types of inhibitors it has seldom proved possible to achieve high degrees of selectivity for 5-LPO with respect to CO. In addition, in vitro potency of such classes of compounds is often determined by lipophilicity with little indication of specific interactions with the enzyme.

In this series of (methoxyalkyl)thiazoles inhibition due to redox or iron chelating properties is unlikely. Inhibitory potency for 5-LPO attained the nanomolar level in whole cells and selectivity for 5-LPO over CO exceeded 5000. Some examples were orally active, the most potent being **2d**, which had an ED_{50} of 10 mg/kg. Table V shows a comparison of **2d** (ICI211965) with other reported 5-LPO inhibitors. In vitro **2d** was more potent than all the other inhibitors shown with the exception of BWA4C with which it was comparable. However, only **2d** combined high in vitro potency with high selectivity for 5-LPO. Ex vivo **2d** was 2-fold less potent in rat blood taken 1 h after dosing than A-64077, which is under clinical investigation,[19] and 3-fold less potent than ICI207968.[7]

(Methoxyalkyl)thiazoles exhibit convincing SAR in which large differences in potency are observed between essentially isolipophilic molecules. Moreover, a pair of enantiomers shows a separation of in vitro potency of 2 orders of magnitude. This is the first time, as far as we are aware, in any series of 5-LPO inhibitors that inhibition has been shown to be highly enantioselective. These observations lead us to conclude that inhibition of 5-LPO by (methoxyalkyl)thiazoles derives from specific and enantioselective interactions between inhibitor and enzyme. For these reasons the results presented in this paper should enable more potent and specific inhibitors of 5-LPO to be found based on rational drug design.

Experimental Section

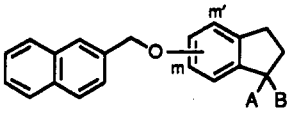
All reactions (excluding catalytic hydrogenations) were performed in an argon atmosphere. THF was dried and distilled from sodium and benzophenone under argon. Aqueous NH_4Cl refers to a saturated aqueous solution. Unless stated otherwise, organic solutions were dried over $MgSO_4$. All evaporations were carried out in vacuo with Buchi rotary evaporators. Chromatography refers to column chromatography on silica (E. Merck, 70–230 or

(17) At the time of writing the absolute configuration of these enantiomers has not been assigned. An X-ray determination on (+)-**2j** was not resolved sufficiently to assign absolute configuration.

(18) MNDO calculations support this analysis.

(19) Rubin, P. *Inflammation Research Association Fifth International Conference*, Mountain Laurel Resort, White Haven, PA, Sept 23–27, 1990.

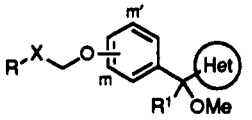
Table III. In Vitro Potency and Enantioselectivity of Indan Analogues[a]



	A	B	subs	RBL 5-LPO IC_{50} (μM)	mouse mø 5-LPO IC_{50} (μM)	human whole blood 5-LPO IC_{50} (μM)
2i	OMe	2-Th	m'		13 (1)	>40 (1)
(±)-**2j**	OMe	2-Th	m	0.8 (1)	0.014 ±0.008 (2)	0.7 ± 0.2 (4)
(+)-**2j**	OMe	2-Th	m	0.13 (1)	<0.03 (1)	0.5 ± 0.2 (3)
(−)-**2j**	2-Th	OMe	m	>20 (1)	1.5 ± 0.3 (2)	>40 (3)
19	H	OMe	m			>40 (2)
20	H	2-Th	m			>40 (2)

[a] Th = thiazolyl; IC_{50}s ± SE (number of determinations).

Table IV. Wider SAR[a]



	R	X	R^1	R^2	subs	Het	mouse mø 5-LPO IC_{50} (μM)	human whole blood 5-LPO IC_{50} (μM)
2k	2-N	bond	*n*-Pr	H	m	2-Th	0.08 (1)	8.8 ± 2.2 (3)
2l	2-N	bond	*i*-Pr	H	m	2-Th	1.0 (1)	40 (2)
2m	2-N	bond	Et	H	m	4-Me-2-Th	0.82 (1)	~40 (1)
2n	2-N	bond	Me	H	m	5-Me-2-Th		~40 (1)
2o	2-N	bond	Me	Me	m	2-Th	2.0 (1)	~40 (1)
2p	2-N	bond	Me	Me	m'	2-Th	0.03 (1)	0.7 ± 0.3 (2)
2q	Ph	bond	Et	H	m	2-Th		~40 (1)
2r	3,4-Cl_2Ph	bond	Et	H	m	2-Th		1.1 (1)
2s	3,4-F_2Ph	bond	Et	H	m	2-Th	0.8 (1)	40 (1)
2t	Ph	C≡C	Et	H	m	2-Th	0.03 (1)	1.0 ± 0.07 (2)
2u	*o*-Tol	C≡C	Et	H	m	2-Th		0.6 ± 0.2 (2)
2v	*m*-Tol	C≡C	Et	H	m	2-Th		2.5 (1)
2w	*p*-Tol	C≡C	Et	H	m	2-Th		22 (1)
2x	Ph	CH=CH	Et	H	m	2-Th	0.006 (1)	0.8 ± 0.3 (2)
2y	Ph	$(CH_2)_2$	Et	H	m	2-Th		11 ± 3.0 (3)

[a] N = naphthyl, Th = thiazolyl; IC_{50}s ± SE (number of determinations).

Table V. Comparison of **2d** (ICI211965) with Standard 5-LPO Inhibitors

	in vitro IC_{50} (μM)						ex vivo rat ED_{50} (mg/kg po) LTB_4
	mouse mø		blood: rat		blood: human		
	LTC_4	PGE_2	LTB_4	PGE_2	LTB_4	TXB_2	
ICI207968	3.2	>1000	1.5	600	1.5	470	3
A-64077	1.2	27	2	25	2.0	25	5
WY-50295	NT[a]	NT	NT	NT	>40	NT	NT
BWA4C	0.006	0.8	0.3	7	0.4	7.2	10
ICI211965	0.008	>50	0.3	>100	0.4	>100	10

[a] NT = not tested.

230–400 mesh). Flash chromatography was performed as described.[20] 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, or WM400 or JEOL FX90Q instruments and are reported as δ values (parts per million) relative to Me_4Si as internal standard. Optical rotations were measured on a Thorn NPL 243 polarimeter. 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 immediate precursors are shown in Table VI where this data is not given in the Experimental Section.

1-(3-Methoxyphenyl)propan-1-one (14). A solution of (3-methoxyphenyl)magnesium bromide, prepared from 3-methoxyphenyl bromide (187 g, 1 mol), magnesium (24 g, 1 mol), and THF (500 mL), was added over 1.5 h to a stirred solution of propionic anhydride (260 g, 2 mol) in ether (500 mL) cooled to −70 °C. Aqueous NH_4Cl (500 mL) was added, and the mixture was allowed to warm to room temperature overnight. The organic phase was separated, washed with 10% aqueous NaOH (4 × 500 mL) and brine (500 mL), dried, and evaporated. Distillation gave 14 (160 g, 97%): bp 70–76 °C (0.05 mmHg).

1-Hydroxy-1-(3-hydroxyphenyl)propane (21). 3-Hydroxybenzaldehyde (76 g, 0.62 mol) dissolved in ether (1 L) was added during 1 h to a stirred solution of ethylmagnesium bromide, prepared from ethyl bromide (149 mL, 2 mol), magnesium (48.6 g, 2 mol), and ether (550 mL), cooled in an ice–salt bath. The reaction mixture was stirred vigorously for 1 h after the addition, allowed to warm to room temperature, and added cautiously to 2 N HCl (1 L) and ice (1 L). The layers were separated, and the aqueous layer was extracted with ether (750 mL). The combined ether solutions were washed with brine (500 mL), dried, and evaporated. Recrystallization (EtOAc–hexane)

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table VI.[a] Physical and Synthetic Data for **2a–y, 3a–q, 3z, 3aa, 3bb, 19,** and **20**

	R	X	R^1	R^2	R^3	Ph subs	Het	formula	anal.[b]	mp, °C	synthetic procedure[c] (yield,[d] %)
2a	2-naphthyl	bond	H	H	Me	m	2-thiazolyl	$C_{22}H_{19}NO_2S$	CHNS	72–4	E (85)
2b	2-naphthyl	bond	Me	H	Me	m	2-thiazolyl	$C_{23}H_{21}NO_2S$	CHN	90–1	E (70)
2c	1-naphthyl	bond	Et	H	Me	m	2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	87–9	A (85)
2d	2-naphthyl	bond	Et	H	Me	m	2-thiazolyl	$C_{24}H_{23}NO_2S$	CHNS	93.5	A (80)
2e	2-naphthyl	bond	Et	H	Me	m	4-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	93–4	E (71)
2f	2-naphthyl	bond	Et	H	Me	m	5-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	88–90	E (79)
2g	2-naphthyl	bond	Et	H	Me	o	2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	oil	E (48)
2h	2-naphthyl	bond	Et	H	Me	p	2-thiazolyl	$C_{24}H_{23}NO_2S$	CH;N[e]	98–100	E (49)
2i	2-naphthyl	bond	$-CH_2CH_2-$		Me	m′	2-thiazolyl	$C_{24}H_{21}NO_2S \cdot 0.1CH_2Cl_2$	CHN	109–10	E (80)
2j	2-naphthyl	bond	$-CH_2CH_2-$		Me	m	2-thiazolyl	$C_{24}H_{21}NO_2S$	CHN	96–96.5	E (75)
(+)-2j	2-naphthyl	bond	$-CH_2CH_2-$		Me	m	2-thiazolyl	$C_{24}H_{21}NO_2S$			*f*
(−)-2j	2-naphthyl	bond	$-CH_2CH_2-$		Me	m	2-thiazolyl	$C_{24}H_{21}NO_2S$			*f*
2k	2-naphthyl	bond	*n*-Pr	H	Me	m	2-thiazolyl	$C_{25}H_{25}NO_2S$	CHN	64–6	E (100)
2l	2-naphthyl	bond	*i*-Pr	H	Me	m	2-thiazolyl	$C_{25}H_{25}NO_2S$	CHN	64–7	E (79)
2m	2-naphthyl	bond	Et	H	Me	m	4-methyl-2-thiazolyl	$C_{25}H_{25}NO_2S$	CHN	83.5–85	E (88)
2n	2-naphthyl	bond	Me	H	Me	m	5-methyl-2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	103–4	E (94)
2o	2-naphthyl	bond	Me	Me	Me	m	2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	95–6	E (48)
2p	2-naphthyl	bond	Me	Me	Me	m′	2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	101–2	E (81)
2q	Ph	bond	Et	H	Me	m	2-thiazolyl	$C_{20}H_{21}NO_2S \cdot 0.1H_2O$	CHN	oil	*f*
2r	3,4-Cl_2Ph	bond	Et	H	Me	m	2-thiazolyl	$C_{20}H_{19}Cl_2NO_2S$	CHN	60–1	A (73)
2s	3,4-F_2Ph	bond	Et	H	Me	m	2-thiazolyl	$C_{20}H_{19}F_2NO_2S \cdot 0.1H_2O$	CHN	58–9	A (87)
2t	Ph	C≡C	Et	H	Me	m	2-thiazolyl	$C_{22}H_{21}NO_2S$	CHN	oil	A (100)
2u	*o*-tolyl	C≡C	Et	H	Me	m	2-thiazolyl	$C_{23}H_{23}NO_2S \cdot 0.25H_2O$	CHN	oil	F (29)
2v	*m*-tolyl	C≡C	Et	H	Me	m	2-thiazolyl	$C_{23}H_{23}NO_2S \cdot 0.1EtOAc$	CHN	oil	F
2w	*p*-tolyl	C≡C	Et	H	Me	m	2-thiazolyl	$C_{23}H_{23}NO_2S$	CHN	oil	A (70)
2x	Ph	CH=CH	Et	H	Me	m	2-thiazolyl	$C_{22}H_{23}NO_2S$	CHN	61–2	A (55)
2y	Ph	$(CH_2)_2$	Et	H	Me	m	2-thiazolyl	$C_{22}H_{25}NO_2S$	CHN	oil	*f*
3a	2-naphthyl	bond	H	H	H	m	2-thiazolyl	$C_{21}H_{17}NO_2S$	CHN	105–6	B (37)
3b	2-naphthyl	bond	Me	H	H	m	2-thiazolyl	$C_{22}H_{19}NO_2S$	CHN	114–5	B (69)
3d	2-naphthyl	bond	Et	H	H	m	2-thiazolyl	$C_{23}H_{21}NO_2S$	CHN	110–113	B (63)
3e	2-naphthyl	bond	Et	H	H	m	4-thiazolyl	$C_{23}H_{21}NO_2S$	*g*		C (50)
3f	2-naphthyl	bond	Et	H	H	m	5-thiazolyl	$C_{23}H_{21}NO_2S$	C[h];HN	foam	D (43)
3g	2-naphthyl	bond	Et	H	H	o	2-thiazolyl	$C_{23}H_{21}NO_2S$	*g*		C (41)
3h	2-naphthyl	bond	Et	H	H	p	2-thiazolyl	$C_{23}H_{21}NO_2S$	*g*		C (20)
3i	2-naphthyl	bond	$-CH_2CH_2-$		H	m′	2-thiazolyl	$C_{23}H_{19}NO_2S$	CHN	foam	B (41)
3j	2-naphthyl	bond	$-CH_2CH_2-$		H	m	2-thiazolyl	$C_{23}H_{19}NO_2S$	CHN	43–4	B (73)
3k	2-naphthyl	bond	*n*-Pr	H	H	m	2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	102–3	B (85)
3l	2-naphthyl	bond	*i*-Pr	H	H	m	2-thiazolyl	$C_{24}H_{23}NO_2S \cdot 0.25H_2O$	CHN	102–3	B (84)
3m	2-naphthyl	bond	Et	H	H	m	4-methyl-2-thiazolyl	$C_{24}H_{23}NO_2S$	CHN	98	B (75)
3n	2-naphthyl	bond	Me	H	H	m	5-methyl-2-thiazolyl	$C_{23}H_{21}NO_2S$	CHN	122.5–123.5	B (69)
3o	2-naphthyl	bond	Me	Me	H	m	2-thiazolyl	$C_{23}H_{21}NO_2S$	*g*		D (90)
3p	2-naphthyl	bond	Me	Me	H	m′	2-thiazolyl	$C_{23}H_{21}NO_2S$	*g*		D (69)
3q	Ph	bond	Et	H	H	m	2-thiazolyl	$C_{19}H_{19}NO_2S$	*g*		*f*
3z	*n*-C_9H_{19}	bond	H	H	H	m	4(5)-methyl-2-imidazolyl	$C_{21}H_{32}N_2O_2$	CH;N[i]	105–7	G (8)
3aa	4-biphenylyl	bond	H	H	H	m	4(5)-methyl-2-imidazolyl	$C_{24}H_{22}N_2O_2 \cdot 0.25H_2O$	CHN	192–3	G (27)
3bb	2-naphthyl	bond	H	H	H	m	4(5)-methyl-2-imidazolyl	$C_{22}H_{20}N_2O_2$	CHN	120–3	G (56)
19	2-naphthyl	bond	$-CH_2CH_2-$		Me	m	H	$C_{21}H_{20}O_2$	CHN	41.5–43	E (58)
20	2-naphthyl	bond	$-CH_2CH_2-$		[OR^3 = H]	m	2-thiazolyl	$C_{23}H_{19}NOS$	CHN	100–2	*f*

[a] See **2** and **3** in Scheme I for definition of substituents; **19** and **20** are in Scheme IV. [b] Elemental analyses were within ±0.4% of the calculated value except where indicated otherwise. [c] Procedure described in Experimental Section and indicated in Scheme I (A–F) and Scheme IV (G). [d] Yield of final step. [e] N: calcd, 3.6; found, 3.1. [f] Synthesis described in Experimental Section. [g] Used directly in next step. [h] C: calcd, 72.6; found 72.0. [i] N: calcd, 8.1; found 7.6.

gave **21** (55 g, 58%): mp 105–7 °C. Anal. ($C_9H_{12}O_2$) C, H.

In an analogous manner the following were prepared.

1-Hydroxy-1-(3-hydroxyphenyl)butane (22) (85%): mp 115–6 °C. Anal. ($C_{10}H_{14}O_2$) C, H.

1-Hydroxy-1-(3-hydroxyphenyl)-2-methylpropane (23) (76%): mp 132–4 °C. Anal. ($C_{10}H_{14}O_2$) C, H.

1-(3-Hydroxyphenyl)propan-1-one (5c). Method a. Pyridine (242 mL, 3 mol) and concentrated HCl (272 mL) were distilled until the temperature of the distillate reached 210 °C. **14** (160 g, 0.975 mol) was added, and the reaction mixture was stirred at 210 °C for 0.5 h and poured onto ice. The resulting solid was collected and dried to give **5c** (125 g, 85%): mp 76–7 °C. Anal. ($C_9H_{10}O_2$) C, H.

Method b. To a stirred solution of **21** (276 g, 1.82 mol) in dioxane (9.8 L) was added DDQ (442 g, 1.95 mol). After 72 h the reaction mixture was filtered and the filtrate evaporated. Flash chromatography with EtOAc–Tol (15:85) as eluant gave **5c** (264 g, 97 %).

In an analogous manner to method b the following were prepared.

1-(3-Hydroxyphenyl)butan-1-one (24) (88%): mp 57–9 °C.

1-(3-Hydroxyphenyl)-2-methylpropan-1-one (25) was used directly to prepare 4e.

1-[3-[(*tert*-Butyldimethylsilyl)oxy]phenyl]propan-1-one (16). A solution of **5a** (125 g, 0.83 mol), imidazole (142 g, 2.08 mol), and *tert*-butyldimethylchlorosilane (150 g, 1 mol) in DMF (330 mL) was stirred for 18 h at room temperature. The reaction mixture was partitioned between ether (500 mL) and ice-cold water (500 mL), and the ether layer was washed with water (4 × 50 mL), dried, and evaporated. Distillation gave **16** (186 g, 95%): bp 114–18 °C (0.01 mmHg).

1-Hydroxy-1-[3-[(*tert*-butyldimethylsilyl)oxy]phenyl]-1-(thiazol-2-yl)propane (26). 2-Bromothiazole (66 mL, 0.735 mol) in ether (150 mL) was added over 0.75 h to a stirred solution of *n*-BuLi in hexane (1.6 M, 460 mL, 0.735 mol) at −70 °C. A solution of **16** (186 g, 0.7 mol) in ether (350 mL) was added during 0.75 h at −70 °C, and the reaction mixture was allowed to warm to room temperature. Aqueous NH_4Cl (500 mL) was added, and the ether layer was separated, washed with water (2 × 100 mL) and brine (100 mL), dried, and evaporated to give **26** as an oil (245 g, 100%): ^1H NMR ($CDCl_3$) δ 7.7 (1 H, d, J = 3 Hz), 7.25 (1 H, d, J = 3 Hz), 7.16 (2 H, m), 7.06 (1 H, m), 6.7 (1 H, m), 2.35 (2 H, m), 0.95 (9 H, s), 0.9 (3 H, t, J = 6 Hz), 0.15 (6 H, s). Anal. ($C_{18}H_{29}NO_2SiS$) C, H, N.

1-[3-[(*tert*-Butyldimethylsilyl)oxy]phenyl]-1-(thiazol-2-yl)propyl Methyl Ether (27) (Procedure E). A solution of **26** (245 g, 0.7 mol) in THF (500 mL) was added dropwise to a stirred suspension of NaH (from 55% dispersion in oil, 30.6 g, 0.7 mol) in THF (500 mL). When hydrogen evolution had ceased methyl iodide (87 mL, 1.5 mol) was added and stirring was continued for 2 h. Aqueous NH_4Cl (500 mL) was added, and the THF layer was separated, evaporated, recombined with the aqueous layer, and extracted with ether (2 × 500 mL). The ether solutions were washed with brine (2 × 100 mL), dried, and evaporated. Flash chromatography with EtOAc–Tol (5:95) as eluant gave **27** as an oil (250 g, 98%): ^1H NMR ($CDCl_3$) δ 7.7 (1 H, d, J = 3 Hz), 7.25 (1 H, d, J = 3 Hz), 7.15 (1 H, t, J = 7 Hz), 7.05 (1 H, m), 6.9 (1 H, m), 6.7 (1 H, m), 3.2 (3 H, s), 2.66 (1 H, sext), 2.4 (1 H, sext), 0.92 (9 H, s), 0.75 (3 H, t, J = 6.5 Hz), 0.1 (6 H, s). Anal. ($C_{19}H_{29}NO_2SiS$) C, H, N.

[3-(Benzyloxy)phenyl]thiazol-2-ylmethanol (28) (Procedure B). To a stirred solution of thiazole (16.7 mL, 0.235 mol) in THF (200 mL) at −70 °C was added *n*-BuLi (1.5 M in hexane, 156 mL, 0.235 mol) during 1 h. A solution of **15** in THF (200 mL) was added dropwise, and the reaction temperature was maintained at −70 °C for 1 h and then allowed to reach room temperature during 1.5 h. The reaction mixture was added to aqueous NH_4Cl (1 L). The THF layer was separated, evaporated, recombined with the aqueous layer, and extracted with EtOAc (2 × 500 mL). The EtOAc solutions were washed with brine (100 mL), dried, and evaporated. Crystallization (EtOAc–hexane) gave **28** (55.5 g, 79%): ^1H NMR (DMSO-d_6) δ 7.65 (1 H, d, J = 2.6 Hz), 7.55 (1 H, d, J = 2.6 Hz), 7.5–6.8 (9 H, m), 5.85 (1 H, m), 5.02 (2 H, m).

[3-(Benzyloxy)phenyl] Thiazol-2-yl Ketone (17). A solution of DMSO (28.1 mL, 0.395 mol) was added dropwise to a rapidly stirred solution of oxalyl chloride (17.3 mL, 0.198 mol) maintained between −50 °C and −55 °C. After 5 min **28** (55 g, 0.185 mol) dissolved in CH_2Cl_2 (150 mL) and DMSO (20 mL) was added dropwise, and 15 min after the end of the addition triethylamine (139 mL, 1 mol) was added during 0.5 h. The reaction mixture was allowed to warm to 10 °C, washed with water (30 mL), 2 N HCl (150 mL), and brine (30 mL), and dried. Evaporation gave **17** as an oil (55 g, 100%): ^1H NMR (DMSO-d_6) δ 8.27 (1 H, d, J = 3 Hz), 8.23 (1 H, d, J = 3 Hz), 8.05 (2 H, m), 7.55–7.3 (8 H, m), 5.2 (2 H, s).

1-[3-(Benzyloxy)phenyl]-1-hydroxy-1-(thiazol-2-yl)propane (3q) (Procedure D). To a stirred solution of **17** (19 g, 64 mmol) in ether (50 mL) at room temperature was added dropwise ethylmagnesium iodide, prepared from ethyl iodide (10.3 mL, 128 mmol), magnesium (3.12 g, 128 mmol), and ether (40 mL). After 1 h the reaction mixture was added to 2 N HCl (100 mL), the organic phase was separated, and the aqueous phase was extracted with EtOAc (100 mL). The combined organic solutions were washed with brine and dried. Evaporation gave **3q** (19 g, 91%).

1-[3-(Benzyloxy)phenyl]-1-(thiazol-2-yl)propyl Methyl Ether (2q). In an analogous manner to **27**, **3q** was converted to **2q** (52%).

1-(3-Hydroxyphenyl)-1-(thiazol-2-yl)propyl Methyl Ether (11). Method a. To a stirred solution of **27** (250 g, 0.69 mol) in THF (500 mL) was added tetrabutylammonium fluoride (1 M in THF, 760 mL, 0.76 mol). After 2 h the solvent was evaporated and the residue was partitioned between EtOAc (500 mL) and aqueous NH_4Cl (500 mL). The aqueous phase was separated and reextracted with EtOAc (200 mL), and the combined EtOAc solutions were washed with brine (100 mL), dried, and evaporated. Recrystallization (EtOH–hexane) gave **11** (130 g, 76%): mp 112–13 °C. Anal. ($C_{13}H_{15}NO_2S$) C, H, N.

Method b. A solution of **2q** (4.9 g, 14.4 mmol) was hydrogenated over 30% Pd/C (3.5 g) until hydrogen uptake ceased (ca. 24 h). After filtration the solvent was evaporated. Flash chromatography with EtOAc–Tol (20:80) as eluant gave **11** (2.7 g, 76%): mp 112–3 °C.

1-[3-(2-Naphthyloxy)phenyl]-1-(thiazol-2-yl)propyl Methyl Ether (2d) (Procedure A). To a solution of **11** (4.52 g, 18.2 mmol) and 2-(bromomethyl)naphthalene (4.2 g, 19 mmol) in DMF (30 mL) was added potassium carbonate (3.76 g, 27.2 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was added to water (200 mL) and extracted with EtOAc (3 × 50 mL). The EtOAc solutions were dried and evaporated. Flash chromatography with EtOAc–Tol (5:95) as eluant gave **2d** (5.4 g): ^1H NMR (DMSO-d_6) δ 7.95 (4 H, m), 7.7 (1 H, d, J = 3 Hz), 7.62 (1 H, d, J = 3 Hz), 7.55 (3 H, m), 7.28 (1 H, t, J = 7 Hz), 7.06 (1 H, m), 6.98 (2 H, m), 5.25 (2 H, s), 3.12 (3 H, s), 2.6 (1 H, sext), 2.4 (1 H, sext), 0.65 (3 H, t, J = 6 Hz).

Using procedure A the following were prepared.

3-(Naphth-2-ylmethoxy)benzaldehyde (4a) (87%): mp 108–10 °C. Anal. ($C_{18}H_{14}O_2$) C, H.

1-[3-(Naphth-2-ylmethoxy)phenyl]ethanone (4b) (86%): mp 89–90 °C. Anal. ($C_{19}H_{16}O_2$) C, H.

1-[3-(Naphth-2-ylmethoxy)phenyl]propan-1-one (4c) (85%): mp 57–8 °C. Anal. ($C_{20}H_{18}O_2$) C, H.

1-[3-(Naphth-2-ylmethoxy)phenyl]butan-1-one (4d) (80%): mp 49–51 °C. Anal. ($C_{21}H_{20}O_2$·0.25Tol) C, H.

1-[3-(Naphth-2-ylmethoxy)phenyl]-2-methylpropan-1-one (4e) (52%): oil; ^1H NMR ($CDCl_3$) δ 7.9–7.8 (4 H, m), 7.65–7.15 (7 H, m), 5.3 (2 H, s), 3.6–3.4 (1 H, m), 1.2 (6 H, d).

6-(Naphth-2-ylmethoxy)indan-1-one (4f) (77%): mp 121 °C. Anal. ($C_{20}H_{16}O_2$) C, H.

4-(Naphth-2-ylmethoxy)indan-1-one (4g) (85%): mp 120–1 °C.

3-(*n*-Decyloxy)benzaldehyde (4h) (37%) was used directly in next step.

3-[(4-Biphenylylmethyl)oxy]benzaldehyde (4i) (49%): mp 115–7 °C.

2-(Naphth-2-ylmethoxy)phenyl bromide (6a) (78%): mp 83–4 °C. Anal. ($C_{17}H_{13}BrO$) C, H, Br.

3-(Naphth-2-ylmethoxy)phenyl bromide (6b) (98%): mp 111.5–12 °C. Anal. ($C_{17}H_{13}BrO$) C, H.

4-(Naphth-2-ylmethoxy)phenyl bromide (6c) (99%): mp 104–6 °C.

Methyl 2-methyl-5-(naphth-2-ylmethoxy)benzoate (9a) (89%): mp 73–4 °C. Anal. ($C_{20}H_{18}O_3$) C, H.

Methyl 2-methyl-3-(naphth-2-ylmethoxy)benzoate (9b) (70%): mp 47 °C. Anal. ($C_{20}H_{18}O_3$) C, H.

3-(Benzyloxy)benzaldehyde (15) (93%): mp 54–6 °C.

1-(Thiazol-4-yl)propan-1-one (30). *N*,*N*-Dimethylthiazole-4-carboxamide (936 mg, 3 mmol) in solution in THF (10 mL) was treated dropwise at 0 °C with ethylmagnesium bromide (2 M in THF, 4 mL, 8 mmol). After the addition water (5 mL) was added, the pH was adjusted to 2, and the product was extracted into ether (10 mL), which was dried and evaporated. Chromatography with CH_2Cl_2 as eluant gave **30** (230 mg, 27%): ^1H NMR ($CDCl_3$) δ 8.8 (1 H, d, J = 3 Hz), 8.2 (1 H, d, J = 3 Hz), 3.15 (2 H, q, J = 7.5 Hz), 1.25 (3 H, t, J = 7.5 Hz).

1-Hydroxy-1-[3-(naphth-2-ylmethoxy)phenyl]-1-(thiazol-4-yl)propane (3e). (Procedure C). To a solution of **6b** (625 mg, 2 mmol) in THF (5 mL) was added powdered magnesium (48 mg, 2 mmol) and a crystal of iodine. The mixture was heated to 50 °C to initiate reaction and then stirred without heating until all the magnesium had been consumed. A solution of **30** (230 mg, 1.6 mmol) dissolved in THF (5 mL) was added, and after 5 min the reaction was quenched with water (3 mL), adjusted to pH 2 with 2 N HCl, and extracted with ether (60 mL). The ether solution was dried and evaporated. Chromatography with ether–CH_2Cl_2 (5:95) as eluant and then crystallization from ether–pentane gave **3e** (300 mg): ^{1}H NMR ($CDCl_3$) δ 8.7 (1 H, d, J = 2 Hz), 8.0–6.8 (12 H, m), 5.2 (2 H, s), 3.2 (1 H, s), 2.5–2.0 (2 H, m), 1.85 (3 H, t, J = 8 Hz).

1-(Thiazol-2-yl)propan-1-one (29). 2-Bromothiazole (8.2 g, 0.05 mol) dissolved in ether (100 mL) was added dropwise to stirred *n*-BuLi (1.5 M in hexane, 33.3 mL, 0.05 mol) at −70 °C. After 1.5 h this solution was added via a cannula to a stirred solution of *N*,*N*-dimethylpropionamide (5 g, 0.05 mol) in ether (100 mL) maintained at −70 °C during the addition. The reaction was kept at −70 °C for 1 h and allowed to warm to room temperature overnight. Aqueous NH_4Cl was added, and the ether layer was separated, washed with brine, and dried. Evaporation gave **29** as an oil (6.99 g, 99%): ^{1}H NMR ($CDCl_3$) δ 8.0 (1 H, d, J = 3 Hz), 7.65 (1 H, d, J = 3 Hz), 3.2 (2 H, q, J = 7 Hz), 1.25 (3 H, t, J = 7 Hz).

[3-(Naphth-2-ylmethoxy)phenyl]thiazol-5-ylmethanone (8c). To a stirred solution of thiazole-5-carboxylic acid (1.8 g, 14 mmol) and triethylamine (2.04 mL, 14.5 mmol) in THF (30 mL) cooled between −10 °C and −20 °C was added dropwise ethyl chloroformate (1.36 mL, 14.5 mmol), and stirring was continued for a further 20 min. This solution was cooled to −40 °C, and to it was added a cooled (0 °C) Grignard solution prepared from **6b** (5 g, 16 mmol), magnesium (440 mg, 18 mmol), and THF (20 mL). The reaction mixture was stirred at −40 °C for 1 h and 0 °C for 2 h, added to ice-cold 2 N HCl, and extracted with ether. The ether solution was dried and evaporated. Flash chromatography, with EtOAc–Tol (10:90) as eluant gave **8c** (1.78 g, 37%): mp 109–10 °C; ^{1}H NMR (DMSO-d_6) δ 9.5 (1 H, s), 8.4 (1 H, s), 8.0–7.9 (4 H, m), 7.6–7.4 (7 H, m), 5.4 (2 H, s). Anal. ($C_{21}H_{15}NO_2S$) C, H, N.

[2-Methyl-3-(naphth-2-ylmethoxy)phenyl]thiazol-2-ylmethanone (8b). To a stirred solution of 2-bromothiazole (0.98 g, 6 mmol) in ether (15 mL) was added *n*-BuLi (1.55 M in hexane, 3.87 mL, 6 mmol) at −70 °C. After 0.5 h this solution was added to a solution of **9b** (1.85 g, 6 mmol) in THF (60 mL) at −70 °C. The reaction mixture was stirred a further 0.5 h at −70 °C, quenched with aqueous NH_4Cl (100 mL), allowed to warm to room temperature, and extracted with ether. The ether solution was dried and evaporated. Flash chromatography with EtOAc–Tol (2:98) as eluant gave **8b** as an oil (1.7 g, 78%): ^{1}H NMR ($CDCl_3$) δ 8.05 (1 H, d, J = 3 Hz), 7.85 (4 H, m), 7.7 (1 H, d, J = 3 Hz), 2.5 (3 H, m), 7.25 (2 H, m), 7.1 (1 H, m), 5.3 (2 H, s), 2.35 (3 H, s).

[2-Methyl-5-(naphth-2-ylmethoxy)phenyl]thiazol-2-ylmethanone (8a). In an analogous manner to **8b**, **8a** was prepared as an oil (78%) and used directly in next step.

1-[3-(Prop-2-yn-1-yloxy)phenyl]-1-(thiazol-2-yl)propyl Methyl Ether (13). Compound 11 (31 g, 0.124 mol), potassium carbonate (48 g, 0.35 mol), propargyl bromide (80 wt % solution in toluene, 48 mL, 0.32 mol), and acetone (375 mL) were refluxed for 18 h. The reaction mixture was cooled and filtered, and the filtrate was evaporated. The residue was partitioned between ether and water, and the ether layer was dried and evaporated. Flash chromatography with EtOAc–hexane (1:3) as eluant gave **13** as an oil (34 g, 94%): ^{1}H NMR ($CDCl_3$) δ 7.7 (1 H, d, J = 3 Hz), 7.25 (2 H, m), 7.1 (2 H, m), 6.85 (2 H, m), 4.67 (2 H, d, J = 2.5 Hz), 3.2 (3 H, s), 2.7 (1 H, sext), 2.5 (1 H, t, J = 2.5 Hz), 2.45 (1 H, sext), 0.8 (3 H, t, J = 6.5 Hz). Anal. ($C_{16}H_{17}NO_2S$) C, H, N.

1-[3-[[3-(3-Methylphenyl)prop-2-yn-1-yl]oxy]phenyl]-1-(thiazol-2-yl)propyl Methyl Ether (2v) (Procedure F). Triethylamine (0.42 mL, 3 mmol), $(PPh_3)_2PdCl_2$ (30 mg), and cuprous chloride (30 mg) were added to a stirred solution of 3-iodotoluene (0.385 mL, 3 mmol) in MeCN (15 mL) followed by a solution of **13** (861 mg, 3 mmol) in MeCN (5 mL), and the reaction mixture was heated at 55–60 °C for 2 h. The cooled mixture was filtered, and solvent was evaporated. The residue was partitioned between ether and aqueous $NaHCO_3$, and the ether layer was washed with water and brine, dried, and evaporated. Flash chromatography with EtOAc–hexane (1:5) as eluant gave **2v** as an oil (410 mg, 36%): ^{1}H NMR ($CDCl_3$) δ 7.7 (1 H, d, J = 3 Hz), 7.3–7.1 (8 H, m), 6.9 (1 H, m), 4.9 (2 H, s), 3.2 (3 H, s), 2.5 (1 H, sext), 2.45 (1 H, sext), 2.3 (3 H, s), 0.8 (3 H, t, J = 7 Hz).

3-(4-Methylphenyl)prop-2-ynol (31). By using procedure F, **31** was prepared as an oil and used directly in the following preparation.

3-(4-Methylphenyl)prop-2-yn-1-yl Bromide (12f). Bromine (1.92 g, 0.012 mol) was added to a solution of triphenylphosphine (3.46 g, 0.0132 mol) in CH_2Cl_2 (40 mL) at 0 °C followed by a cooled (0 °C) solution of **31** (1.75 g, 0.012 mol) in CH_2Cl_2 (40 mL). Solvent was evaporated and flash chromatography gave **12f** (2.26 g, 90%) as an oil, which was used directly in the preparation of **2w**.

Methyl 5-Amino-2-methylbenzoate (32). Methyl 2-methyl-5-nitrobenzoate (23 g, 0.118 mol) dissolved in ethanol (400 mL) was hydrogenated in the presence of 10% Pd/C (1.2 g) at 2–3 atm during 2 h. The catalyst was removed by filtration, and the filtrate was concentrated. Distillation (Kuegelrohr apparatus, oven temperature 150 °C) at 0.05 mmHg gave **32** as an oil (18.3 g, 94%): ^{1}H NMR ($CDCl_3$) δ 7.2 (1 H, d, J = 2 Hz), 6.95 (1 H, d, J = 7 Hz), 6.65 (1 H, dd, J_1 = 7 Hz, J_2 = 2 Hz), 3.8 (3 H, s), 3.55 (2 H, s), 2.4 (3 H, s). Anal. ($C_9H_{11}NO_2$) C, H, N.

Methyl 5-Hydroxy-2-methylbenzoate (33). A stirred solution of **32** (19.95 g, 0.12 mol) in 5.4 vol % H_2SO_4 (350 mL) was treated dropwise at 0–5 °C with sodium nitrite (8.3 g, 0.12 mol) dissolved in water (28 mL). At the end of the addition the cooling bath was removed, and the reaction was allowed to warm to room temperature and then refluxed for 0.5 h. On cooling crystals were deposited which were collected and distilled (Kuegelrohr, oven temperature 150 °C), at 0.05 mmHg to give **33** (12.8 g, 64%): mp 74–6 °C.

1-[3-(2-Phenylethoxy)phenyl]-1-(thiazol-2-yl)propyl Methyl Ether (2y). Compound **2t** (250 mg, 0.69 mmol) in MeOH (5 mL) was hydrogenated over 10% Pd/$CaCO_3$ (30 mg). When the theoretical volume of hydrogen had been absorbed the catalyst was filtered and solvent evaporated. Chromatography with ether–CH_2Cl_2 (5:95) as eluant gave **2y** (220 mg, 87%).

1-(Diethoxymethyl)-4-methylimidazole (18). 4(5)-Methylimidazole (25 g, 0.3 mol), triethyl orthoformate (210 mL, 1.26 mol) and *p*-TsOH (1.5 g, 0.008 mol) were heated with stirring at 150 °C. When ethanol ceased distilling excess triethyl orthoformate was evaporated and potassium carbonate (2 g) added. Distillation gave **18** (30.6 g, 55%): bp 82–5 °C (0.15 mmHg).

[3-(Naphth-2-ylmethoxy)phenyl][4(5)-methylimidazol-2-yl]methanol (3bb) (Procedure G). *n*-BuLi (1.5 M in hexane, 6.7 mL, 10 mmol) was added dropwise to a stirred solution of **18** (1.84 g, 10 mmol) in THF (17 mL) at −40 °C. After 0.5 h **4a** (2.2 g, 8.3 mmol) dissolved in THF (10 mL) was added during 1 min, and after 0.5 h the cooling bath was removed. The reaction mixture was allowed to warm to room temperature, added to water (100 mL), and extracted with ether (2 × 100 mL). The ether solution was extracted with 0.2 N HCl (5 × 20 mL), and the combined aqueous extracts were adjusted to pH 7 with $NaHCO_3$ and salt saturated. Extraction with EtOAc (3 × 50 mL), drying, and evaporation gave **3bb**, which was recrystallized from $CHCl_3$–hexane (1.79 g): ^{1}H NMR ($CDCl_3$) δ 7.84 (4 H, m), 7.5 (3 H, m), 7.15 (2 H, m), 6.96 (1 H, d, J = 7 Hz), 6.87 (1 H, d, J = 7 Hz), 6.8 (1 H, br), 6.55 (1 H, s), 5.82 (1 H, s), 5.15 (2 H, s), 2.72 (3 H, s).

6-(Naphth-2-ylmethoxy)indan-1-ol (34). A solution of **4f** (576 mg, 2 mmol) in EtOH (10 mL) was stirred with $NaBH_4$ (88 mg, 2.4 mmol) for 2 h. The reaction was diluted with 2 N HCl and extracted with EtOAc, and the EtOAc solution was washed with brine and dried. Evaporation gave **34** as an oil (530 mg, 91%): ^{1}H NMR ($CDCl_3$) δ 8.0–6.75 (10 H, m), 5.22 (3 H, s), 3.2–1.5 (4 H, m).

6-(Naphth-2-ylmethoxy)-1-(thiazol-2-yl)ind-1-ene (35). A solution of **3j** (746 mg, 210 mmol) and *p*-TsOH (75 mg) in CH_2Cl_2 (10 mL) was heated at reflux for 0.25 h. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The EtOAc layer was separated, washed with aqueous $NaHCO_3$

and brine, dried, and evaporated. Chromatography with CH_2Cl_2 as eluant gave **35** as a yellow solid (504 mg, 54%): mp 124–5 °C; ^1H NMR ($CDCl_3$) δ 8.2–6.92 (13 H, m), 7.1 (1 H, d, J = 2 Hz), 5.32 (2 H, s), 3.5 (2 H, d, J = 2 Hz). Anal. ($C_{23}H_{17}NOS$) C, H, N.

6-(Naphth-2-ylmethoxy)-1-(thiazol-2-yl)indan (20). A solution of **35** (606 mg, 1.7 mmol) in EtOAc (55 mL), AcOH (55 mL), and MeOH (55 mL) was hydrogenated over PtO_2 (90 mg) at 70 psi for 72 h. The catalyst was filtered and the solvent was evaporated. The residue was partitioned between ether and water, and the ether layer was separated, dried, and evaporated. Chromatography with ether–CH_2Cl_2 (5:95) as eluant gave **20** (500 mg): ^1H NMR ($CDCl_3$) δ 8.0–6.9 (12 H, m), 5.2 (2 H, s), 4.8 (1 H, t, J = 8 Hz), 3.2–2.2 (4 H, m).

Resolution of (±)-2j. Racemic **2j** was resolved by using preparative HPLC on a Pirkle chiral column (ionic form) with (*S*)-(+)-(3,5-dinitrobenzoyl)phenylglycine [(*S*)-(+)-DNBPG] as chiral support.[21] Elution with dioxane–hexane (3:97) provided (+)-**2j**, mp 83–4 °C. The opposite enantiomer (−)-**2j**, $[\alpha]_D$ −5 ± 0.5°, was obtained under identical conditions with a preparative (*R*)-(−)-DNBPG column. Optical purity was assessed as ≥95% by analytical HPLC with an (*R*)-(−)-DNBPG column.

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Novel Thiophene-, Pyrrole-, Furan-, and Benzenecarboxamidotetrazoles as Potential Antiallergy Agents

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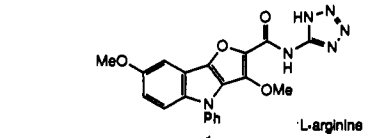
The synthesis and antiallergic activity of a series of novel thiophene-, pyrrole-, furan-, and benzenecarboxamidotetrazoles are described. A number of compounds inhibit the release of histamine from anti-IgE-stimulated human basophils. Optimal inhibition is exhibited in compounds with a 3-alkoxy, a 4-halo, and a 5-methyl, 5-methoxy, or 5-bromo on a thiophene-2-carboxamidotetrazole.

Introduction

Inflammatory mediators such as histamine, leukotrienes, prostaglandins, proteases, and chemotactic factors released by various cells are responsible for the symptoms of allergic diseases.[1] Thus, inhibition of mediator release has been an attractive approach for the development of antiallergic drugs. Historically, the passive cutaneous anaphylaxis (PCA) model in the rat has been the primary allergic model for characterizing mast cell stabilizers. To date, the use of this model has failed to provide therapeutically useful agents.[2] Although drugs currently used as antiallergic agents have been found to inhibit mediator release from various cells, it is not clear that this is their primary mode of action since high concentrations are required for this effect.

Our strategy for the discovery of well-defined inhibitors of mediator release for the prophylactic treatment of allergic diseases employed the inhibition of IgE-dependent histamine release from human basophils as an initial in vitro screen.[3]

Recently, the antiallergic activities of series of furo[3,2-*b*]indoles,[3c,4,5] indoles,[5a] and benzo[*b*]thiophenes[5b] have been described. These series contained potent inhibitors of mediator release in the basophil assay, i.e., CI-922 (**1**),[3c,5] CI-949 (**2a**),[5a] and CI-959 (**2b**).[5b] Conceptually, **2** was derived from **1** by removing the furan ring in **1**. As a result of this modification **2a** and **2b** are more water soluble (Table III) and can be prepared by shorter synthetic routes than **1**. In an attempt to further increase water solubility and synthetic accessibility and to further decrease the lipophilicity of the carboxamidotetrazoles, another ring was removed from **2** to give the monocyclic compounds **3**.



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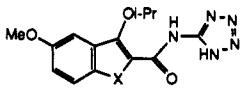

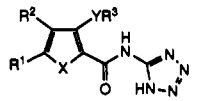

3

2a X = NPh; L-arginine salt

2b X = S; sodium salt

X = S, NR^5, O, CR^6=CH

Y = O, S

R^3 = Me, Et, i-Pr, CH_2Ph

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