Pergamon

Bioorganic & Medicinal Chemistry, Vol. 3, No. 9, pp. 1255–1262, 1995

0968-0896/95 $9.50 + .00

0968-0896(95)00111-5

Synthesis, Antioxidant Properties, Biological Activity and Molecular Modelling of a Series of Chalcogen Analogues of the 5-Lipoxygenase Inhibitor DuP 654

Lars Engman,[a]* David Stern,[b] Håkan Frisell,[b] Kerstin Vessman,[c] Mats Berglund,[c] Bengt Ek[d] and Carl-Magnus Andersson[e]*

[a]*Uppsala University, Institute of Chemistry, Department of Organic Chemistry, P. O. Box 531, S-751 21 Uppsala, Sweden*

[b]*Department of Chemistry, Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden*

[c]*Department of Analytical Chemistry, Astra Draco AB, P.O. Box 34, S-221 00 Lund, Sweden*

[d]*Department of Biochemistry, Preclinical R&D, Astra Hässle AB, S-431 83 Mölndal, Sweden*

[e]*Organic Chemistry 1, Chemical Center, University of Lund, P. O. Box 124, S-221 00 Lund, Sweden*

Abstract:—2-Phenylsulfenyl- (**1b**), 2-phenylselenenyl- (**1c**) and 2-phenyltellurenyl-1-naphthol (**1d**) were prepared and their antioxidative properties evaluated in comparison with 2-benzyl-1-naphthol (**1a**; DuP 654). 2-Phenyltellurenyl-1-naphthol had a significantly lower (1.00 V versus SCE) oxidation potential than the other three compounds (1.24, 1.27 and 1.25 V, respectively, versus SCE for compounds **1a**, **1b** and **1c**) as determined by cyclic voltammetry. In contrast to the other materials, compound **1d** was able to catalyze the reduction of hydrogen peroxide in the presence of thiols as stoichiometric reducing agents. The organotellurium compound was also the most efficient inhibitor of azo-initiated peroxidation of linoleic acid in a two-phase model system. *Ab initio* geometry optimization at the 3-21G(*) level revealed infinitesimal changes in the molecular conformations of the carbon, sulfur, selenium and tellurium analogues. As judged by their ability to inhibit stimulated LTB_4 biosynthesis in human neutrophils, compounds **1a–1d** all turned out to be highly potent 5-lipoxygenase inhibitors with IC_{50}-values ranging from 0.40 μM for 2-benzyl-1-naphthol (**1a**) to 0.063 μM for 2-phenyltellurenyl-1-naphthol (**1d**).

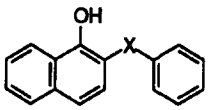
Introduction

Leukotrienes are lipid mediators released from numerous cells in response to inflammatory and allergic stimuli. These substances produce a variety of physiological effects including bronchoconstriction, leukocyte chemotaxis and degranulation, vasoconstriction and vascular permeability. Thus, leukotrienes have been implicated as important mediators in diseases such as asthma, allergy, arthritis, psoriasis and inflammatory bowel disease.[1] The control of the pathophysiological effects of the leukotrienes can be achieved by either antagonizing their actions at their receptors or by preventing their biosynthesis.[2] The production of leukotrienes as well as cyclooxygenase products can be blocked through the inhibition of phospholipase A_2. Regulation of 5-lipoxygenase, though, allows selective inhibition of the biosynthesis of leukotrienes. It has been hypothesized that Ca^{2+} induces the binding of 5-lipoxygenase to a specific integral membrane protein, thus facilitating substrate release from membrane phospholipid stores.[3,4] 5-Lipoxygenase activity is also stimulated by the presence of adenosine triphosphate and hydroperoxy fatty acids. The enzyme is thought to contain a catalytically important iron atom.[1]

Numerous structural analogues of arachidonic acid have been reported as moderately potent inhibitors of 5-lipoxygenase.[5] Hydroxamic acids constitute a more potent class of inhibitors,[6] which, due to their excellent ligand properties (association constants for ferric ion are as high as 10^{12}) have been proposed to bind to active site iron. However, recent results seem to indicate that hydroxamic acids can also act via a redox mechanism.[7] Lipoxygenase activity has been found to be modulated by other redox active compounds. These inhibitors appear to either reduce the active ferric form of the putative iron, or consume hydroperoxides required for enzyme activation. Among antioxidant-based 5-lipoxygenase inhibitors, 2-benzyl-1-naphthol (**1**, DuP 654)[8] has turned out to be particularly efficient (IC_{50} = 0.019 μM in an assay using RBL cells). The material is currently being evaluated as a topical antipsoriatic agent.

We have studied for some time the antioxidative properties of organotellurium compounds. As judged by electrochemical studies[9] and results from several model systems, these compounds are readily oxidized and they can act both as peroxide decomposers[10–13] and as chain-breaking, donating antioxidants.[13–16] Since, according to the present mechanistic view of 5-lipoxygenase inhibition, an inhibitor could be expected to benefit from such properties, we decided to prepare a series of chalcogen analogues **1b–1d** of DuP 654 with

sulfur, selenium and tellurium, respectively, replacing the benzylic methylene group. In the following the synthesis, antioxidant properties, biological activity and molecular modelling of compounds **1a–1d** are described.

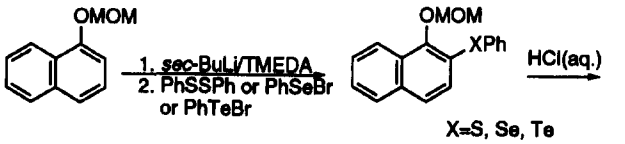


1 a X=CH_2
b X=S
c X=Se
d X=Te

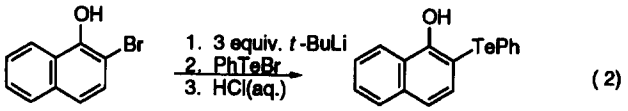
Synthesis

2-Phenylsulfenyl-1-naphthol (**1b**) has previously been prepared in low yield by acid-promoted decomposition of benzenesulfenanilides in the presence of 1-naphthol[17] or by dehydrogenative phenylsulfenylation of α-tetralone.[18] The compound has also been prepared, in 75% yield, from phthalide anion and a vinylsilane.[19] 2-Phenylselenenyl-1-naphthol (**1c**) has been obtained in low yield by oxidation of α-tetralone with benzeneseleninic anhydride.[20] In an effort to prepare compounds **1b–1d** from a common precursor, 1-naphthyl methoxymethyl ether was *ortho*-lithiated with *sec*-butyllithium and treated with diphenyl disulfide, phenylselenenyl bromide or phenyltellurenyl bromide. After deprotection, compounds **1b** and **1c** were obtained in 75 and 61% overall yields, respectively (Eq. 1). However, it was not possible to find deprotection conditions where compound **1d** was stable.

This compound was instead prepared in low and variable yield (23–39%) by treatment of 2-bromo-1-naphthol with three equivalents of *tert*-butyllithium followed by addition of *in situ* prepared phenyltellurenyl bromide (Eq. 2). Compound **1d** was purified by flash chromatography in small portions (≈50 mg) to avoid decomposition on the column.



(1)



(2)

Antioxidant Properties

The electrochemical oxidation of compounds **1a–1d** was carried out in dichloromethane, containing tetrabutylammonium perchlorate as the electrolyte, using a scan rate of 100 mV s^{-1}. For all compounds, an irreversible first oxidation peak was observed in the cyclic voltammogram. The peak oxidation potentials versus SCE, E_p, are reported in Table 1. Except for the organotellurium compound **1d** (E_p = 1.0 V), the oxidation potentials of the compounds were close to 1.25 V.

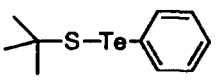
The capacity of compounds **1a–1d** to decompose hydrogen peroxide in the presence of thiols (glutathione peroxidase-like activity) was assessed by using a ^1H NMR method previously developed in our laboratory.[10,12] In this assay, thiols are oxidized to the corresponding disulfides in CD_3OD or CD_3OD:D_2O in the presence of hydrogen peroxide and a catalytic amount of the compound to be evaluated. The time required to reduce the thiol concentration by 50%, t_{50}, is determined as a measure of the peroxide decomposing activity of the catalyst. Thiols useful in this assay must

Table 1. Oxidation potentials and antioxidant and 5-lipoxygenase inhibiting capacity of compounds **1a–1d**

Compound	Oxidation potential E_p (V)*	^1H NMR model t_{50}-values (min)†			Lipid peroxidation model		LTB_4-assay
		N-acetyl-cysteine system	*tert*-butyl-mercaptan system	1-octyl-mercaptan system	R_{inh} (μM h^{-1})‡	T_{inh} (h)§	IC_{50} (μM)‖
1a	1.24	inactive	inactive	inactive	297	1.0	0.40
1b	1.27	inactive	inactive	inactive	680	1.6	0.25
1c	1.25	inactive	inactive	inactive	484	1.5	0.079
1d	1.00	60	717	15	65	2.6	0.063

*Versus SCE.
†Time required to reduce the thiol concentration by 50%.
‡Rate of peroxidation during the inhibited phase.
§Duration of the inhibited phase of peroxidation.
‖Concentration of test substance required to inhibit 50% of the LTB_4 production observed in the control experiment.

be clearly distinguishable by ^{1}H NMR from their corresponding disulfides and also unreactive towards hydrogen peroxide in the uncatalyzed reaction. *N*-Acetylcysteine was studied in a 4:1 mixture of D_2O:CD_3OD under acidic conditions (aqueous pH ≈2) whereas the other two thiols used, *tert*-butyl mercaptan and 1-octyl mercaptan, were studied in CD_3OD. The t_{50}-data for compounds **1a–1d** are presented in Table 1. Of the compounds tested, only the organotellurium compound **1d** was able to act as a catalytic peroxide decomposer. This is probably because it is readily oxidized by hydrogen peroxide to the corresponding telluroxide and this species is reduced to the divalent state by the thiol present. In contrast to many other diaryl tellurides tested in this system,[12] t_{50}-values for compound **1d** in the *tert*-butyl mercaptan (717 min) and 1-octyl mercaptan (15 min) systems differed considerably. By inspection of the aromatic portion of the ^{1}H NMR spectrum during a peroxidation experiment (a three-fold excess of catalyst was used as compared to the standard conditions) it was concluded that the divalent (telluride) state was the resting state of the catalyst in the 1-octyl mercaptan system. A similar experiment in the *tert*-butyl mercaptan system revealed that the catalyst was decomposed under the experimental conditions. In this case, *tert*-butylthio phenyltelluride (**2**) was identified (by comparison with an authentic sample[10]) as one of the decomposition products. A low peroxide-decomposing activity of this compound has previously been observed.[10]



2

Compounds **1a–1d** were also assessed for their capacity to inhibit azo-initiated peroxidation of linoleic acid in a water:chlorobenzene two-phase system containing a thiol reducing agent in the aqueous phase.[13] In the procedure used, autoxidation was initiated in chlorobenzene at 42 °C by thermolysis of 2,2'-azobis(2,4-dimethylvaleronitrile), AMVN. The chlorobenzene layer, which also contained the test substance, was vigorously stirred with an equal volume of an aqueous solution containing *N*-acetylcysteine. The progress of peroxidation in the organic phase was monitored by HPLC with UV detection at 234 nm. For comparison of antioxidant efficiency, the inhibited rate of peroxidation, R_{inh}, was determined by least squares methods from absorbance/time plots during the first hour after addition of the initiator. The progress of peroxidation was then monitored for another 3 h and the duration of the inhibited phase, T_{inh}, determined graphically as the cross-point for the inhibited and the uninhibited lines.[13] The R_{inh} and T_{inh} values for compounds **1a–1d** under the experimental conditions used (test substance 40 μM, *N*-acetylcysteine 1 mM, linoleic acid 34 mM, AMVN 1.4 mM) are shown in Table 1. As compared with the uninhibited reaction (R_{inh} ≈1800 μM h^{-1}), all compounds inhibited peroxidation of linoleic acid. The most active compound, **1d**, inhibited peroxidation as efficiently as Trolox (R_{inh} = 67 μM h^{-1}, Ref. 13) but the duration of the inhibited phase was considerably longer (2.6 h as compared to 1.5 h for Trolox[13]). The organotellurium compound is likely to act as a catalytic inhibitor of lipid peroxidation, the duration of the inhibited phase being related to the amount of thiol in the aqueous phase.[13]

Biological Activity

Compounds **1a–1d** were assessed for their ability to inhibit the production of LTB_4 in A 23187 activated human neutrophils. In this assay, cells were preincubated with the test substance prior to the activation with 1 μM A 23187 and the formation of LTB_4 determined after ethyl acetate extraction by HPLC with UV detection at 235 nm. The inhibitory potency, IC_{50}, was estimated from concentration response curves by least squares nonlinear regression analysis. The results are presented in Table 1. All four compounds tested potently inhibited LTB_4 production. The sulfur analogue **1b** was almost equipotent with compound **1a** whereas the selenium and tellurium analogues **1c** and **1d** were almost one order of magnitude more potent than the parent.

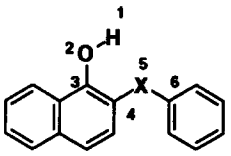
Molecular Modelling

In order to study the influence of increasing chalcogen substitution on electrostatic charge, electric dipole moment and conformation of compounds **1a–1d**, PM3 calculations were initially carried out.[21,22] Although PM3 geometry optimization has previously been used for organotellurium compounds,[23] the results with compound **1d** did not seem trustworthy. In contrast to the other three compounds investigated, a planar lowest energy conformation was predicted for compound **1d** with a positive electrostatic charge (0.16) at tellurium. In sulfide **1b** and selenide **1c** the heteroatom charges calculated were –0.30 and –0.23, respectively. Furthermore, a PM3 calculation on 4-ethoxyphenyl 2(2-pyridyl)phenyl telluride[24] also predicted a planar structure. This is not in agreement with the X-ray diffraction structure of the material obtained from the Cambridge Crystallographic Database. On the other hand, a PM3 calculation on an organoselenium compound, bis(3,4-dimethoxyphenyl) selenide, showed good agreement with the corresponding X-ray diffraction structure.[25]

In order to obtain reliable electrostatic charge, dipole moment and conformational data on all compounds, an *ab initio* geometry optimization at the 3-21G(*) level was carried out.[26] As crude starting geometries for these calculations, the lowest energy conformations from MM3 (Molecular Mechanics Program 3)[27] calculations were used. In order to use the MM3 program, missing bond-, angle-, torsional- and out of plane bending parameters were added to the existing force field. These

new parameters were based on existing X-ray data, and similar parameters already published for selenium and tellurium compounds.[28] The MM3 parameters are given in the Experimental.

The results of the *ab initio* calculations for compounds **1a–1d** are presented in Table 2 (selected electrostatic charges), Table 3 (electric dipole moments) and Table 4 (selected bonds and angles). It can be concluded from these data that the lowest energy conformation for all compounds in the series are very similar. Concerning charges, there is a smooth decrease in negative charge at the heteroatom as one traverses the series from sulfur (–0.30), selenium (–0.18) to tellurium (–0.11). There is also a smooth decrease in dipole moment as one moves from the carbon analogue (2.08 D) via the sulfur (1.40 D) and selenium (1.24 D) compounds to the tellurium derivative (1.15 D). A systematic decrease in the bond angle 4-X-6 (for index see structure **3**) is also apparent as X is changed: carbon (111.22°), sulfur (103.99°), selenium (100.81°), tellurium (97.97°). However, in contrast to the sulfur, selenium and tellurium analogues, the hydrogen atom of the hydroxyl group is pointing away from the connecting atom X in the carbon analogue **1a**.



3

Conclusions

2-Substituted 1-naphthols are among the most potent 5-lipoxygenase inhibitors known. An evaluation[8] of a series of compounds obtained by structural variation in the 2-substituent, the 1-hydroxyl group, the naphthalene ring substituents and the 1,2-disubstituted naphthalene

Table 2. Calculated electrostatic charges at the HF/3-21G(*) level for compounds **1a–1d**

Compound	Atom index (as in structure **3**)	Electrostatic charge 3-21G(*)[a]
1a	5 (Carbon)	–0.10
	4 (Csp^2)	–0.06
	3 (Csp^2)	0.35
	6 (Csp^2)	0.18
	2 (Osp^3)	–0.62
	1 (H)	0.44
1b	5 (Sulfur)	–0.30
	4 (Csp^2)	0.29
	3 (Csp^2)	0.24
	6 (Csp^2)	0.24
	2 (Osp^3)	–0.56
	1 (H)	0.40
1c	5 (Selenium)	–0.18
	4 (Csp^2)	0.11
	3 (Csp^2)	0.31
	6 (Csp^2)	0.11
	2 (Osp^3)	–0.54
	1 (H)	0.36
1d	5 (Tellurium)	–0.11
	4 (Csp^2)	0.17
	3 (Csp^2)	0.25
	6 (Csp^2)	0.07
	2 (Osp^3)	–0.50
	1 (H)	0.32

[a]Electrostatic charges were calculated on 3-21G(*) geometry optimized structures.

Table 3. HF/3-21G(*) calculated dipole moments for compounds **1a–1d**

Compound	Calculated dipole moment 3-21G(*)[a], μ (Debye)
1a	2.075
1b	1.405
1c	1.245
1d	1.154

[a]Calculated for the lowest energy conformation in each case.

Table 4. Important structural features of compounds **1a–1d** obtained by HF/3-21G(*) calculations

Compound	Structural parameter:	
	Bond	
1a	4(Csp^2)-C(Csp^3)	1.517 Å
1a	6(Csp^2)-C(Csp^3)	1.524 Å
1a	H-C(Csp^3)	3.302 Å[a]
1b	4(Csp^2)-S	1.767 Å
1b	6(Csp^2)-S	1.787 Å
1b	H-S	2.521 Å
1c	4(Csp^2)-Se	1.911 Å
1c	6(Csp^2)-Se	1.931 Å
1c	H-Se	2.551 Å
1d	4(Csp^2)-Te	2.132 Å
1d	6(Csp^2)-Te	2.154 Å
1d	H-Te	2.746 Å
	Angle	
1a	4(Csp^2)-C(Csp^3)-6(Csp^2)	111.215 (degrees)
1b	4(Csp^2)-S-6(Csp^2)	103.988 (degrees)
1c	4(Csp^2)-Se-6(Csp^2)	100.808 (degrees)
1d	4(Csp^2)-Te-6(Csp^2)	97.974 (degrees)
	Dihedral angle	
1a	3(Csp^2)-4(Csp^2)-C(Csp^3)-6(Csp^2)	92.657 (degrees)
1b	3(Csp^2)-4(Csp^2)-S-6(Csp^2)	94.427 (degrees)
1c	3(Csp^2)-4(Csp^2)-Se-6(Csp^2)	89.680 (degrees)
1d	3(Csp^2)-4(Csp^2)-Te-6(Csp^2)	91.625 (degrees)

[a]The hydrogen is pointing away from the chalcogen atom.

unit itself suggested that 2-benzyl-1-naphthol (**1a**) was the most interesting compound for clinical trials[29–32] as a topical antipsoriatic agent. In the present study, a series of DuP 654 analogues **1b–1d**, with the benzylic group replaced by sulfur, selenium and tellurium, respectively, were prepared. By this variation of the structure, it was hoped to modify the antioxidant profile and the 5-lipoxygenase inhibiting activity of the parent compound **1a**. *Ab initio* geometry optimization at the 3-21G(*) level revealed only minimal changes in the molecular conformation with increasing chalcogen substitution. However, slight variations in electrostatic charges and dipole moments were observed as expected.

Concerning the antioxidant profile, it was found that the organotellurium derivative **1d** had a significantly lower oxidation potential than the other materials. Also, the organotellurium compound showed much improved antioxidant properties as compared with the parent. In the presence of a stoichiometric amount of a thiol reducing agent, compound **1d** was shown to act both as a catalytic peroxide decomposer and as a catalytic chain-breaking antioxidant. As judged by their ability to inhibit stimulated LTB_4 biosynthesis in human neutrophils, compounds **1a–1d** were potent 5-lipoxygenase inhibitors, the organotellurium and organoselenium derivatives being more potent than the other compounds. Considering the similar *in vitro* biological activity of all materials but superior antioxidative properties of compound **1d**, it must be concluded that the latter either cannot be properly expressed in the model used or they are irrelevant. The pharmacological relevance of such additional antioxidant behaviour might be better assessed in more complex inflammation models.

Experimental

Melting points are uncorrected. ^1H NMR spectra were obtained at 250 MHz in $CDCl_3$ solutions containing Me_4Si as internal standard. Tetrahydrofuran was freshly distilled from potassium. 2-Benzyl-1-naphthol (**1a**),[8] 1-naphthyl methoxymethyl ether[33] and 2-bromo-1-naphthol[34] were prepared according to literature methods. Elemental analyses were performed by Analytical Laboratories, Gummersbach, Germany. All electrochemical measurements were performed at 25 °C under argon in a thermostated, undivided IBM cell with a platinum-button working electrode and platinum wire counter electrode with an SCE reference electrode. The cell was controlled with a PAR 173 galvanostat equipped with a 175 programmer and a 179 calorimeter. The scan rate was 100 mV s^{-1} and the substrate concentration 1 mM in a 0.13 M Bu_4NClO_4 solution in dry dichloromethane (freshly distilled from calcium hydride). Oxidation potentials were calibrated against ferrocene, with $E_{1/2}$ (ferrocene/ferrocenium ion) = 310 mV. The determination of t_{50}-values by ^1H NMR spectroscopy in the *N*-acetylcysteine, *tert*-butyl mercaptan and 1-octylmercaptan systems was carried out as previously described[10,12] using 2.7×10^{-7} mol of the catalyst.

2-(Phenylsulfenyl)-1-naphthol (1b)

To a solution of 1-naphthyl methoxymethyl ether (0.3 g, 1.6 mmol) in THF (25 mL) containing TMEDA (0.27 mL, 1.76 mmol), *sec*-BuLi (1.4 mL 1.2 M, 1.68 mmol) was added dropwise at –78 °C and stirring continued for 25 min. A solution of diphenyl disulfide (0.77 g, 3.51 mmol) in THF (4 mL) was then added and stirring continued at –78 °C for 1 h. After addition of water (5 mL) the temperature was allowed to rise to ambient. The reaction mixture was extracted with CH_2Cl_2 (2 × 25-mL) and the combined extracts dried over $MgSO_4$. Gradient chromatography[35] (hexanes–EtOAc) afforded an inseparable 1:4 mixture of starting material and 2-(phenylsulphenyl)-1-naphthyl methoxymethyl ether as an oil (0.450 g) as determined by ^1H NMR. Some characteristic peaks in the ^1H NMR of 2-(phenylsulfenyl)-1-naphthyl methoxymethyl ether are reported below: 5.31 (*s*, 2H), 3.72 (*s*, 3H). The mixture was dissolved in THF:isopropanol (15 mL of each) and cooled in an ice-bath while a stream of freshly generated HCl (from NaCl and sulfuric acid) was bubbled through the stirred solution for 6 h. Extractive work-up as described above followed by gradient chromatography (hexanes–EtOAc) afforded 0.30 g (75%) of colourless crystals, mp 40 °C (hexanes). ^1H NMR: 8.29 (*d*, 1H), 7.82 (*d*, 1H), 7.50–7.58 (several peaks, 3H), 7.42 (*d*, 1H), 7.07–7.22 (several peaks, 6H). Anal. calcd for $C_{16}H_{12}OS$: C, 76.16; H, 4.79. Found: C, 76.22; H, 4.69.

2-(Phenylselenenyl)-1-naphthol (1c)

To a solution of 1-naphthyl methoxymethyl ether (0.45 g, 2.37 mmol), in THF (20 mL) containing TMEDA (0.39 mL, 2.6 mmol), *sec*-BuLi (1.9 mL 1.3 M, 2.49 mmol) was added dropwise at –78 °C and stirring continued for 1 h. A solution of phenylselenenyl bromide (0.61 g, 2.6 mmol) in THF (5 mL) was then added and stirring continued at –78 °C for 1 h. After addition of water (5 mL) the temperature was allowed to rise to ambient. The reaction mixture was extracted with CH_2Cl_2 (2 × 25-mL) and the combined extracts dried over $MgSO_4$. Gradient chromatography (hexanes–EtOAc) afforded an inseparable 1:4 mixture of starting material and 2-(phenylselenenyl)-1-naphthyl methoxymethyl ether as an oil (0.87 g) as determined by ^1H NMR. Some characteristic peaks in the ^1H NMR spectrum of 2-(phenylselenenyl)-1-naphthyl methoxymethyl ether are reported below: 5.29 (*s*, 2H), 3.75 (*s*, 3H). The mixture was then dissolved in THF:isopropanol (15 mL of each) and cooled in an ice-bath while a stream of freshly generated HCl (from NaCl and sulfuric acid) was bubbled through the stirred solution for 1 h. Extractive work-up as described above followed by gradient chromatography (hexanes–EtOAc) afforded 0.44 g (61%) of the title compound as colourless crystals, mp 66.5 °C (hexanes), lit.[20] mp 61–62 °C. ^1H NMR: 8.30 (*dd*, 1H), 7.82 (*dd*, 1H), 7.64 (*d*, 1H), 7.52–7.57 (several peaks, 2H), 7.39 (*d*, 1H), 7.17–7.24 (several peaks, 5H), 7.08 (*s*, 1H).

2-(Phenyltellurenyl)-1-naphthol (1d)

To a solution of 2-bromo-1-naphthol (1.0 g, 4.48 mmol) in THF (30 mL), *t*-BuLi (9.35 mL 1.52 M, 14.2 mmol) was added dropwise at –78 °C and stirring continued for 30 min. A solution of phenyltellurenyl bromide (1.28 g, 4.48 mmol) in THF (13 mL), prepared by addition of bromine (0.72 g, 4.48 mmol) in hexanes to phenyltellurenyl lithium [prepared from bromobenzene (0.7 g, 4.48 mmol), *t*-BuLi (7.94 mL 1.7 M, 13.5 mmol) and elemental tellurium (0.57 g, 4.48 mmol)], was then added dropwise at –78 °C and stirring continued for 15 min at –78 °C and 15 min at ambient temperature. After hydrolysis at –78 °C, work up with CH_2Cl_2:H_2O and flash chromatography of 1/8 of the crude product, 0.044–0.075 g (23–39%) of the title compound, mp 65 °C (hexanes), was obtained. Attempts to purify larger amounts of the material resulted in drastically reduced yields due to decomposition on the column. ^1H NMR: 8.29 (*dd*, 1H), 7.87 (*d*, 1H), 7.79–7.83 (*m*, 1H), 7.40–7.55 (several peaks, 4H), 7.13–7.33 (several peaks, 4H), 6.84 (*s*, 1H). Anal. calcd for $C_{16}H_{12}OTe$: C, 55.24; H, 3.48. Found: C, 55.10; H, 3.46.

Peroxidation assay.[13] A HPLC (Waters 600) equipped with an autoinjector (5 μL samples were withdrawn every 16.5 min) with a sample holder at 42.0 °C (Gilson 231 with thermostated sample rack), UV detector (Kratos 757) and a Nelson 6000 chromatography data system was used for the peroxidation studies. In a typical experiment, linoleic acid in chlorobenzene (7.5 mL, 36.2 mM) was stirred (1500 rpm) in a 20 mL thermostated reaction vessel. To this solution the inhibitor, in *n*-butanol (107 μL, 3.0 mM; 40 μM final concentration), was added by syringe followed by an aqueous thermostated solution of *N*-acetyl cysteine (8.0 mL, 1.0 mM). Finally, a thermostated solution of AMVN in chlorobenzene (0.5 mL, 22.4 mM) was added. Samples were withdrawn (after interruption of the stirring and phase separation) from the lower chlorobenzene layer and injected onto a Waters Resolve Silica 90 Å column (5 μM, 3.9 × 150 mm) eluted with heptane:ethanol (95:5) at a flow rate of 1.0 mL min^{-1}. After sampling, stirring was immediately resumed allowing for an overall 79% mixing time during an experiment. The formation of conjugated dienes (retention time 3.8–4.3 min) was monitored at 234 nm and the concentration determined by integration using an experimentally determined response factor. This was based on the amount of triphenylphosphine oxide formed in the reaction of linoleic acid hydroperoxides with excess triphenylphosphine.

Each of the three first additions of reactants to the reaction vessel were arranged to occur immediately before the automatic sampling. Then, after another three samplings, the initiator was added followed by 15 more analyses during the next 4 h. The inhibited rate of peroxidation, R_{inh} (Table 1), was calculated by least squares methods during the first hour (four injections) after addition of the initiator. In the absence of in-

hibitor, the rate of peroxidation was 1800–1900 μM h^{-1}. T_{inh}-values were determined graphically as the cross-point for the inhibited and the uninhibited lines.

LTB_4-assay. Whole blood was collected from healthy donors. Following centrifugation (1000 × *g*, 10 min), the platelet-rich plasma was removed and the buffy coat, including white cells, collected. Red cells were lysed by exposing them to water for 1 min followed by centrifugation in 0.9% NaCl (250 × *g* for 5 min). The remaining white cells were put on top of the bilayered Percoll^R solution (of 1.0063 g cm^{-3} and 1.0075 g cm^{-3}) and the gradient centrifuged (850 × *g* for 10 min). The neutrophils in between the two density layers were collected, diluted with 0.9% NaCl and centrifuged (100 × *g*, 10 min). The pellet was resuspended in phosphate buffered saline with Ca^{2+} and Mg^{2+}, and 5.6 mM glucose was added.

The reaction assay contained 2 mL of cells (5 × 10^6 cells mL^{-1}). The cells were preincubated for 10 min at 37 °C with the test compound prior to the activation with 1 μM of the calcium ionophore A 23187 (Calbiochem, La Jolla, CA, U.S.A.) for 10 min. The test compounds were dissolved in ethanol and given in a volume of 5 μL. After incubation, the arachidonic acid metabolite production was stopped by addition of ethyl acetate and the metabolites were extracted at pH 3. Analysis of LTB_4 formation was performed by reversed-phase liquid chromatography using a Nucleosil 120-3 C18 (Machery-Nagel, Germany) column. The mobile phase consisted of methanol:water:acetic acid (72:28:0.1 by volume). LTB_4 was detected by its UV absorbance at 235 nm and peak heights were measured in mV units by a Kontron MT2 chromatography data system. The identity of the product was confirmed by comparison with an authentic sample (Cayman Chemical Company, Ann Arbor, MI, U.S.A.). The inhibitory potency (IC_{50}) of each compound was estimated by computer-assisted least-square nonlinear regression. Each value represents the mean of duplicate estimations.

Molecular modelling. Semiempirical PM3[20] and *ab initio* 3-21G(*) calculations were performed using the Spartan program package (version 3.1)[36] on an Indigo xz Graphics computer. A Macintosh Quadra 800 computer was used for the MM3(92) calculations together with the Mac Mimic 2 program package.[37]

Parameters used in the MM3 calculations of compounds **1a–1d** are shown below.

Bond stretching parameters.

Atom types	k_s (mdyn Å^{-1})	l_0 (Å)	m (Debye)
C_{Ar}-S	3.20	1.815	1.20
C_{Ar}-Se	2.90	1.930	–1.10
C_{Ar}-Te	2.95	2.130	–1.00

Angle parameters.

Angle type	k_b (mdyn Å rad^{-2})	θ_0 (degrees)
C_{Ar}-S-C_{Ar}	0.80	98.0
C_{Ar}-C_{Ar}-S	0.45	118.0
C_{Ar}-Se-C_{Ar}	0.70	98.0
C_{Ar}-C_{Ar}-Se	0.45	119.0
C_{Ar}-Te-C_{Ar}	0.70	96.0
C_{Ar}-C_{Ar}-Te	0.45	120.0

Out-of-plane bending parameters.

Angle type	k_b (mdyn Å rad^{-2})
C_{Ar}-S	0.10
C_{Ar}-Se	0.10
C_{Ar}-Te	0.10

Torsional parameters.

Dihedral angle type	v_1 (kcal mol^{-1})	v_2 (kcal mol^{-1})	v_3 (kcal mol^{-1})
C_{Ar}-C_{Ar}-C_{Ar}-S	0	15.0	0
H-C_{Ar}-C_{Ar}-S	0	15.0	0
C_{Ar}-C_{Ar}-S-C_{Ar}	–0.60	0.60	–0.40
C_{Ar}-C_{Ar}-C_{Ar}-Se	0	15.0	0
H-C_{Ar}-C_{Ar}-Se	0	15.0	0
C_{Ar}-C_{Ar}-Se-C_{Ar}	–0.60	0.60	–0.40
C_{Ar}-C_{Ar}-C_{Ar}-Te	0	15.0	0
H-C_{Ar}-C_{Ar}-Te	0	15.0	0
C_{Ar}-C_{Ar}-Te-C_{Ar}	–0.60	0.60	–0.40

Acknowledgements

Financial support by the Swedish Natural Science Research Council and the Swedish National Board for Industrial and Technical Development is gratefully acknowledged.

References and Notes

1. Summers, J. B. *Drug News Persp.* **1990**, *3*, 517.

2. Fitzsimmons, B. J.; Rokach, J. In *Bioactive Molecules*; Rokach, J., Ed.; Elsevier: Amsterdam, 1989; Vol. 11, Chapter 6.

3. Wong, A.; Hwang, S. M.; Cook, M. N.; Hogaboom, G. K.; Crooke, S. T. *Biochemistry* **1988**, *27*, 6763.

4. Wong, A.; Cook, M. N.; Foley, J. J.; Sarau, H. M.; Marshall, P.; Hwang, S. M. *Biochemistry* **1991**, *30*, 9346.

5. Cashman, J. R. *Pharm. Res.* **1985**, *2*, 253.

6. Summers, J. B.; Gunn, B. P.; Martin, J. G.; Martin, M. B.; Mazdiyasni, H.; Stewart, A. O.; Young, P. R.; Bouska, J. B.; Goetze, A. M.; Dyer, R. D.; Brooks, D. W.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1960.

7. Nelson, M. J.; Batt, D. G.; Thompson, J. S.; Wright, S. W. *J. Biol. Chem.* **1991**, *266*, 8225.

8. Batt, D. G.; Maynard, G. D.; Petraitis, J. J.; Shaw, J. E.; Galbraith, W.; Harris, R. R. *J. Med. Chem.* **1990**, *33*, 360.

9. Engman, L.; Persson, J.; Andersson, C. M.; Berglund, M. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1309.

10. Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 9737.

11. Andersson, C. M.; Hallberg, A.; Brattsand, R.; Cotgreave, I. A.; Engman, L.; Persson, J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2553.

12. Engman, L.; Stern, D.; Pelcman, M.; Andersson, C. M. *J. Org. Chem.* **1994**, *59*, 1973.

13. Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C. M.; Engman, L. *J. Org. Chem.* **1995**, *60*, 4461.

14. Cotgreave, I. A.; Moldéus, P.; Engman, L.; Hallberg, A. *Biochem. Pharmacol.* **1991**, *42*, 1481.

15. Andersson, C. M.; Brattsand, R.; Hallberg, A.; Engman, L.; Persson, J.; Moldéus, P.; Cotgreave, I. A. *Free Rad. Res.* **1994**, *20*, 401.

16. Engman, L.; Persson, J.; Vessman, K.; Ekström, M.; Berglund, M.; Andersson, C. *Free Rad. Biol. Med.* in press.

17. Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2261.

18. Trost, B. M.; Rigby, J. H. *Tetrahedron Lett.* **1978**, 1667.

19. Date, M.; Watanabe, M.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 902.

20. Barton, D. H. R.; Brewster, A. G.; Ley, S. V.; Read, C. M.; Rosenfeld, M. N. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1473.

21. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

22. Stewart, J. J. P. *J. Comput. Chem.* **1991**, *12*, 320.

23. Amato, M. E.; Grassi, A.; Irgolic, K. J.; Pappalardo, G. C.; Radics, L. *Organometallics* **1993**, *12*, 775.

24. Al-Salim, N.; West, A. A.; McWhinnie, W. R.; Hamor, T. A. *J. Chem. Soc. Dalton Trans.* **1988**, 2363.

25. Schiffling, C.; Klar, G. *J. Chem. Research (S)* **1989**, 2.

26. Herle, W. J.; Random, L.; Pople, J. A. *Ab Initio Molecular Orbital Theory;* Wiley: New York, 1986.

27. Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551.

28. Allinger, N. L.; Allinger, J. A.; Yan, L. Q. *J. Mol. Struct. (Theochem)* **1989**, *201*, 363.

29. Harris, R. R.; Batt, D. G.; Galbraith, W.; Ackerman, N. R. *Agents Actions* **1989**, *27*, 297.

30. Harris, R. R.; Mackin, W. M.; Batt, D. G.; Rakich, S. M.; Collins, R. J.; Bruin, E. M.; Ackerman, N. R. *Skin Pharmacol.* **1990**, *3*, 29.

31. Kerr, J. S.; Batt, D. G.; Pinto, D. J.; Stampfli, H. F. *Res. Comm. Chem. Pathol. Pharmacol.* **1992**, *77*, 77.

32. Arenberger, P.; Raap, A.; Armah, B.; Kemény, L.; Ruzicka, T. *Skin Pharmacol.* **1993**, *6*, 148.

33. Harvey, R. G.; Hahn, J.-T.; Bukowska, M.; Jackson, H. *J. Org. Chem.* **1990**, *55*, 6161.

34. Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.

35. Baeckström, P.; Stridh, K.; Li, L.; Norin, T. *Acta Chem. Scand.* **1987**, *41B*, 442.

36. The Spartan program package can be purchased from Wavefunction, Inc., 18401, Von Karman Avenue, Suite 370, Irvine, CA 92715, U.S.A.

37. The version of MM3 used is the MM3(92) program, implemented for Macintosh computers in a program package called Mac Mimic 2 by InStar Software AB, IDEON Research Park, S-223 70 Lund, Sweden. MM3 versions for platforms other than Macintosh are available from the Quantum Chemistry Program Exchange, University of Indiana, Bloomington, IN 47405, U.S.A.

(*Received in U.S.A.* 7 *March* 1995; *accepted* 29 *April* 1995)