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A NEW STRUCTURAL ANALOGUE ANTAGONIST OF PEPTIDO-LEUKOTRIENES . THE DISCOVERY OF BAY x7195

T.S. Abram*, H. Böshagen[#], J.E. Butler[#], N.J. Cuthbert, H.P. Francis, P.J. Gardiner, W. Hartwig[#], H.C. Kluender[+], P. Norman, H. Meier[#], U. Rosentreter[#], K.H. Schlemmer[#], S.R. Tudhope and W.A. Taylor.

Bayer plc, Stoke Court, Stoke Poges, SL2 4LY, UK. [#]Bayer AG, D5600 Wuppertal, FRG. [+]Miles Inc., West Haven, USA.

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Abstract: Systematic modification of LTD_4 has led to the discovery of **BAY x7195**, a potent, selective, orally-active peptido-leukotriene antagonist.

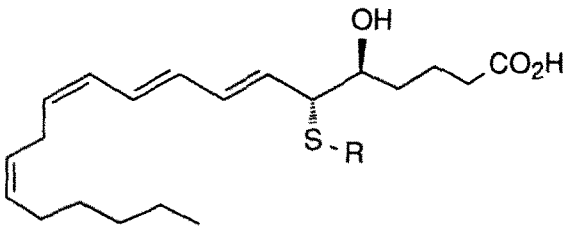
In our search for potent and selective peptido-leukotriene (p-LT) antagonists we decided to concentrate our efforts on p-LT analogues based on modification of the natural agonists LTC_4, LTD_4 and LTE_4. This, we postulated, should maintain receptor selectivity and thereby reduce the possibility of unwanted side-effects. What we wish to report here are the key stages which led to the achievement of this goal and, ultimately, to the discovery of **BAY x7195** - a novel structural analogue antagonist of p-LTs.

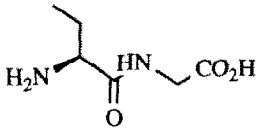
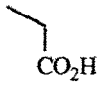
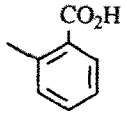
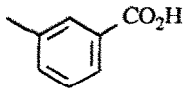
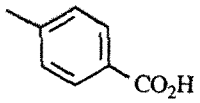
Our initial work concentrated on finding a suitable replacement for the leukotriene amino-acid/peptide unit (-glutathione, -cysteinylglycine, -cysteine). Such compounds, in which the basic back-bone has been conserved, are readily available from LTA_4-methyl ester[1]. We discovered, and reported earlier[2], that this complete unit could be replaced by a simple acetic acid moiety since the resulting compound (Table 1 , entry **1**) retained the potent agonism and receptor affinity of the parent compounds. This had been our first goal, to identify a simplified, yet potent, version of the natural agonists.

Based on this work, we postulated that the amino acid carboxyl group was a key pharmacophore for agonism (all activity was lost if removed [3]) and that the preferred orientation was close to the sulphur atom. We were, therefore, curious to explore the effect of introducing a rigid spacer unit between the sulphur and carboxyl group. We chose a phenyl ring for this purpose and synthesised a series of benzoic acids[1] (Table 1, entries **2** - **4**). The activity of these compounds was striking: compound **3** was a full agonist with activity comparable to LTD_4, compound **2** was a partial agonist, whilst compound **4** was found to be an antagonist of LTD_4-induced contractions of guinea-pig ileum (pA_2 6.3). We have subsequently demonstrated that compound **4**, now known as **BAY u9773**, is an antagonist of LTC_4- and LTD_4-induced contractions in a variety of tissues [4]. Thus, with this rather simple manoeuvre we had achieved our second goal, identifying a novel structural analogue antagonist.

However, compound **4**, **BAY u9773**, contained a number of structural elements (notably the highly unsaturated 'tail' portion) which would have to be replaced if it were to have any drug potential. This task was to prove to be much more complicated than the previous two, especially since we had stressed at the outset the need to have oral activity. In addition, we also recognised that a replacement tail should be stable to ω-oxidation.

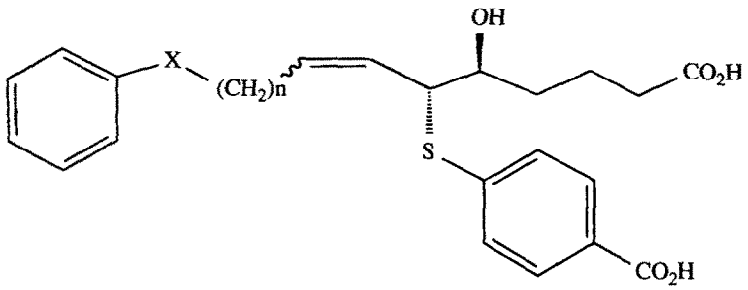
Table 1



Compound[12]	R	pD_2[a]	pK_i[b]
LTD_4		8.4 ± 0.1	9.0 ± 0.1
1		8.5 ± 0.1	8.7 ± 0.1
2		6.9 ± 0.1	7.6 ± 0.1
3		8.2 ± 0.5	8.7 ± 0.1
4		6.3 ± 0.1[c]	7.0 ± 0.1

a) Agonist activity was determined on guinea-pig ileum and shown as the negative logarithm of the ED_{50} value ± S.E.M. b) Binding affinities were determined as previously described [2]. c) Antagonist affinity determined on guinea-pig ileum against LTD_4, the pA_2 value shown was obtained from the resultant Schild plot (slope = -1.1 ± 0.3 , n= 6).

Table 2



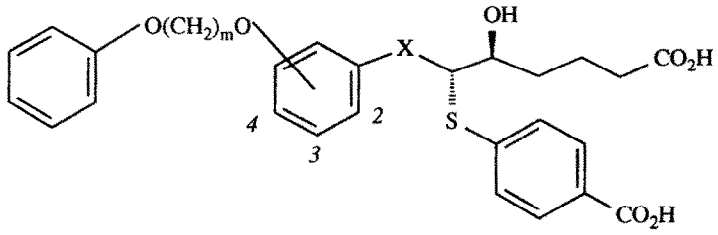
Compound[12]	X	n	Z/E[a]	pK_i[b]
5	CH_2	1	Z	<4
6	CH_2	1	E	<4
7	CH_2	2	Z	<4
8	CH_2	2	E	<4
9	CH_2	4	Z	4.7 ± 0.2
10	CH_2	7	Z	6.5 ± 0.1
11	CH_2	8	Z	6.6 ± 0.1
12	O	8	Z	6.2 ± 0.2
13	O	9	Z	6.5 ± 0.1
14	CH_2	10	Z	5.9 ± 0.1
15	CH_2	12	Z	5.3 ± 0.2

a) Double bond geometry. b) Inhibition of [^{3}H]-LTD_4 binding to guinea-pig lung membranes was determined as previously described [2]. Values are shown as the mean ± S.E.M.

For the next series of compounds we retained the chirality of the natural agonists by employing methyl 7-oxo-5(S),6(R)-oxidoheptanoate as the common intermediate in the synthesis of the LTA_4 analogues[5]. We tackled ω-oxidation by simply terminating the tail with either a phenyl or a phenoxy group. A series of **BAY u9773** analogues with simple tails containing a single double-bond between carbons 7 and 8 were prepared (Table 2, entries **5-15**). These went someway towards defining the preferred overall tail length (entries **10-13**). However, there was an unacceptable drop off in activity, probably due to the partial removal of unsaturation.

The requirement for further unsaturation, we felt, would be best satisfied by the incorporation of an additional phenyl or phenoxy unit. This, however, introduced the possibility of many different positional and regioisomers, the synthesis of which was facilitated by the incorporation of two phenoxy linkages [5]. Several such examples are illustrated in Table 3. It is clear from these results that a suitable replacement tail was rather elusive and only the unconjugated compound **22** possessed the desired in vitro potency. This compound was a more potent antagonist of LTD_4- induced contractions of guinea-pig trachea (GPT) than **BAY u9773**. Furthermore, compound **22** was also active in vivo following oral administration (ID_{50} ≈ 3mg/kg versus i.v. LTD_4 in a ventilated guinea-pig model). Thus, we had achieved our third goal, identifying a more acceptable tail unit, and in addition, had demonstrated good oral activity.

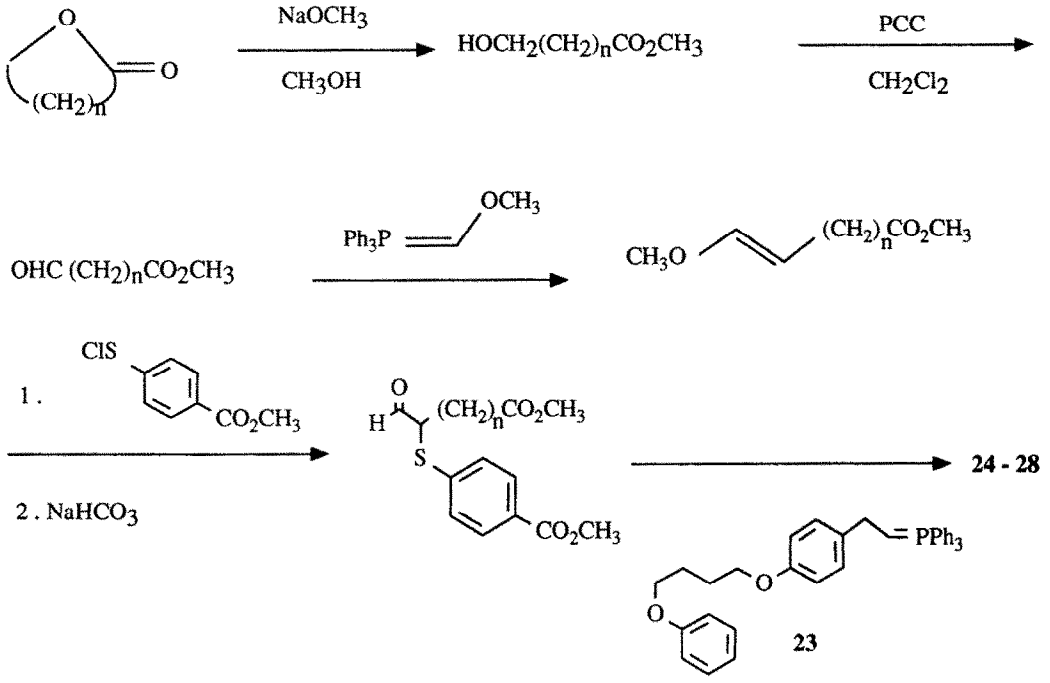
Table 3



Compound[12]	X	m	Tail Attachment	pK_B[a]
16	CH=CH	4	4	6.5 ± 0.3
17	CH=CH	4	3	< 5
18	CH=CH	4	3	6.8 ± 0.2
19	CH=CH	4	2	< 5
20	CH_2CH=CH	3	2	< 5
21	CH_2CH=CH	3	3	< 5
22	CH_2CH=CH	4	4	8.3 ± 0.3

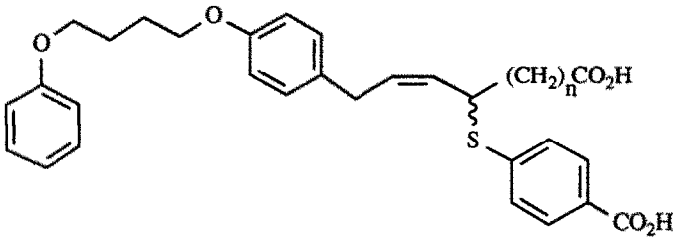
a) Antagonist affinity was determined at 10 μM on GPT rings against LTD_4. Values are shown as the mean ± S.E.M.

Scheme 1



Since the two chiral centres (5S and 6R) and the 'head' portion were the last vestiges of the natural molecule, it was to these components that we then directed our attention to see if 'fine tuning' in this area would further enhance the potency. We decided to omit the 5-hydroxyl function, which had the potential for oxidation in vivo, and to explore the effect of varying the 'head' length. To further simplify the synthesis we initially prepared the racemates as outlined in Scheme 1. It is clear from Table 4 that the antagonist activity peaks when n is either 2 or 4 (entries **26** and **28**, respectively). It also appears that the activity is unaltered by the omission of the hydroxyl function. Surprisingly, however, whilst compounds **26** and **28** had comparable activity on GPT only **26** displayed the desired potency against LTD_4 on human bronchial muscle (**26** pK_B 8.0, **28** pK_B 6.8).

Table 4



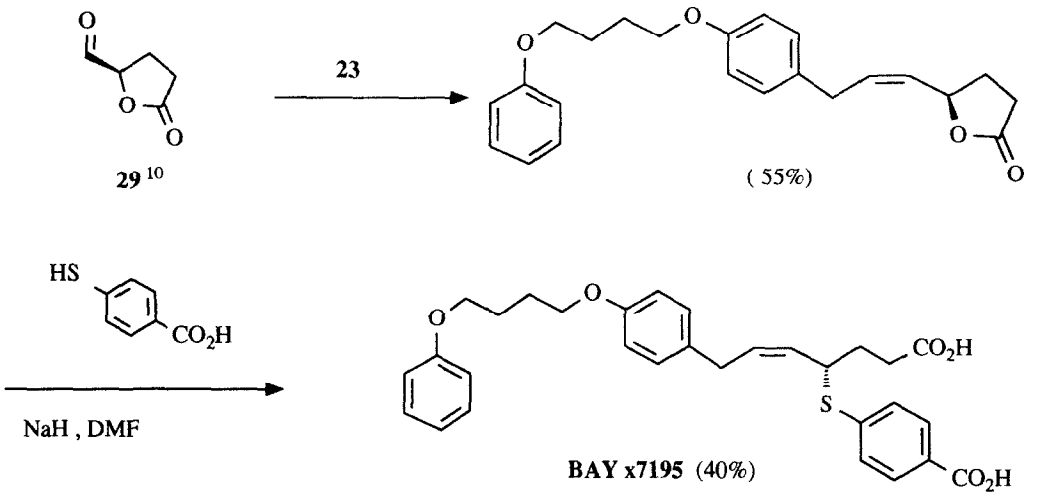
Compound[12]	n	pK_B[a]
24	0	6.4 ± 0.2
25	1	6.9 ± 0.3
26	2	8.4[b] ± 0.2
27	3	7.0 ± 0.4
28	4	8.3[b] ± 0.7

a) Antagonist affinity was determined at 1μM on GPT rings against LTD_4 unless otherwise indicated. b) At 0.1μM antagonist.

Compound **26** was resolved by chiral chromatography (enantiomeric excess ≥ 99%)[6] and the bulk of the activity was found to reside with the (+)-enantiomer (pA_2 8.4 on GPT) rather than with the (-)-enantiomer (pA_2 7.0 on GPT). The absolute configuration of the (+)-enantiomer was confirmed, by chiral synthesis (see Scheme 2[7,12]), as the S-enantiomer. This compound, now known as **BAY x7195**, is a potent and selective[8] p-LT antagonist with good oral activity (ID_{50} ≈ 2mg/kg against LTD_4 in spontaneously-breathing guinea-pigs)[9].

Thus, we had achieved our goal of designing a structural analogue p-LT antagonist by systematically modifying the natural p-LT agonist. The resulting compound, **BAY x7195**, is well-tolerated by animals and man and so our expectation that such an approach might lead to selective and well-tolerated compounds, has been realised. **BAY x7195** is currently undergoing clinical evaluation and should assist in defining the role of p-LTs in asthma.

Scheme 2



References and notes

1. Synthesis involved treating LTA_4-methyl ester[5] with the corresponding thiol and triethylamine in methanol, followed by hydrolysis of the ester functions by treating with aqueous lithium hydroxide in acetonitrile.

2. Norman, P.; Abram, T.S.; Cuthbert, N.J.; Gardiner, P.J. *European J. Pharmacol.* **1990**, *182*, 301.

3. For example, replacement of the peptide with cysteamine leads to complete loss of activity on the guinea-pig ileum.

4. Cuthbert, N.J.; Tudhope, S.R.; Gardiner, P.J.; Abram, T.S.; Norman, P.; Thompson, A.M.; Maxey, R.M.; Jennings, M.A. *Ann. N.Y. Acad. Sci.* **1991**, *629*,402 . Labat, C.; Ortiz, J.L.; Norel, X.; Gorenne, I.; Verley, J.; Abram, T.S.; Cuthbert, N.J.; Tudhope, S.R.; Norman, P.; Gardiner, P.J.; Brink, C. *J. Pharmacol. Exp. Ther.* **1992** , *263* , *800* .

5. The substances were prepared from the corresponding epoxide in a like manner to that described in note 1 above. The epoxide resulted from the Wittig reaction between methyl 7-oxo-5(S), 6(R)-oxidoheptanoate[11] and an appropriate triphenylphosphorane.

6. Analytical details: Chiralcel OD (4.6 x 250mm): hexane : *n*-propanol (98:2) 1mL min^{-1}, UV detection (280nm), retention times (-)29.6 min, (+) 32.8 min.

7. Full synthetic details will be published later.

8. **BAY x7195** (1μM) was inactive against a range of contractile agonists (e.g. carbachol, U46619, $PGF_{2\alpha}$ and histamine) on the guinea-pig trachea.

9. Full data will be reported in another communication.

10. Tumlinson, J.H.; Klein, M.G.; Doolittle, R.E.; Ladd, T.L.; Proveaux, A.T. *Science* **1977**, *197*, 789.

11. Rokach, J.; Zamboni, R.; Lau, C.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2759.

12. The compounds described were all fully characterised.