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QSAR STUDY OF ORTHO-PHENYLPHENOL LEUKOTRIENE B_4 RECEPTOR ANTAGONISTS

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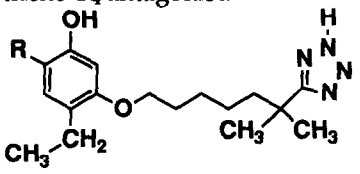
Abstract.
QSAR models for a series of o-phenylphenol LTB_4 receptor antagonist have been developed with regression analysis. These models related specific features, electronic, size and shape, of the substituent with biological activity. The models have predictive value and may be useful in assisting future synthetic direction within this series of compounds.

Leukotriene B_4 (LTB_4) is a metabolite of the arachidonic acid pathway. LTB_4 is believed to be an important mediator in the inflammatory processes of several diseases such as asthma, inflammatory bowel disease and arthritis and has also been implicated in ARDS.[1] LTB_4 is a potent mediator of polymorphonuclear leukocyte (PMN) chemotaxis, aggregation, lysosomal enzyme release and superoxide generation.[2] It also modulates vasculature permeability.[3]

In asthmatics, high levels of LTB_4 have been detected in bronchial alveolar lavage fluids These levels have been correlated with a large influx of PMNs and eosinophilis (EOs) into the lung.[4] Leukotriene B_4 has been implicated as a mediator involved in the inflammatory cell influx which may be associated with the hypersensitivity observed in some asthmatics.[5] Early work at Lilly led to LY255283 (I, R=CH3CO), an acetophenone LTB_4 antagonist, and LY223982 (II), a benzophenone LTB_4 antagonist.[6] Although these compounds had potency, they lacked significant oral activity. Therefore, we were interested in developing highly potent and orally active competitive antagonist of LTB_4 receptors as therapeutics for asthma. The discovery of LY280748 (I, R=Ph) provided an exceptionally potent orally active and structurally novel LTB_4 antagonist.[7] This compound provided the first example of a biphenyl lipophilic moiety in a leukotriene B_4 antagonist.



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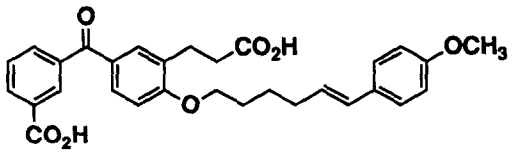

II

The SAR to date has shown that the intrinsic potency and oral activity of the biphenyl series of antagonists is linked to the substituent on the appended phenyl ring. The present QSAR is directed toward the identification of the physicochemical properties that control the intrinsic potency in the biphenyl series.

The compound dataset consisted of 11 compounds represented by structure I (R=substituted phenyl), with variations in the phenyl ring substituent at the ortho, meta, and para positions (Table I). Biological activity was defined as the ability of the compound to inhibit the specific binding of [^{3}H]LTB_4 to guinea pig lung membranes. The activity (pKi) was expressed

as the negative logarithm of the affinity of the compound for the LTB_4 receptor on guinea pig lung membranes (Table I). Published substituent constants were used for the groups on the phenyl ring.[8] These parameters included values for electronic (σ, F, R), lipophilic (π), and size (MR, molar refractivity in milliliters). Several substituent shape descriptors, the Sterimol terms (L1, B1, B2, B3, B4), as defined by Verloop were also included as part of the descriptors. [9] The term L1 defines the length (Å) of the substituent along its longest axis. The term B1 is the minimum width while terms B2, B3, and B4 measure the width in four rectangular directions. The B4 term generally represents the maximum width. The biological activity data and the complete set of parameters for QSAR are given in Table I. The correlation coefficient matrix of pertinent parameters is shown in Table II. Regression analysis was performed on a Apple Macintosh IIcx using the program JMP, a statistical visualization program from the SAS Institute. In the QSAR equations the numbers in parentheses are the standard errors, n is the number of observations, r is the correlation coefficient, and F is a measure for significance.

Regression analysis yielded significant correlations between the biological response (pKi) and the Sterimol descriptors **B2** and **B3** (Equations 1 and 2). These terms are correlated as indicated in the correlation matrix (Table II). This high degree of correlation is unusual in our experience.[10] The high correlation suggest these terms may be describing the same feature of the substituent and thus the two models may not be different. These terms are shape descriptors of the substituent width (Å).

QSAR Equation 1:

Predicted pKi = 9.53(±0.34) - 1.01 (±0.18) **B2**

n=11 r=0.88 F=30.68 p=0.000

QSAR Equation 2

Predicted pKi = 8.33(±0.35) - 0.89 (±0.19) **B3**

n=11 r=0.85 F=23.03 p=0.001

Regression analysis of pKi with Sterimol descriptors **B4** and **L1** were moderately significant (Equations 3 and 4). These terms describe the width (Å) about the widest axis and the length (Å) about the longest axis of substitution. These were correlated to a higher degree than usual in our experience and support the model above suggesting the importance of substituent size and shape.[10]

QSAR Equation 3

Predicted pKi = 8.81(±0.34) - 0.53(±0.15) **B4**

n=11 r=0.75 F=12.02 p=0.007

QSAR Equation 4

Predicted pKi = 9.19(±0.62) - 0.46(±0.19) **L1**

n=11 r=0.64 F=6.21 p=0.034

Using multiple regression a model was found with the combined terms for the substituent electronic effects, **R**, and the size term **MR** (Equation 5).[11]

Table I. QSAR Parameters and Data

Serial#	R-phenyl	pKi[a]	MR	F	R	pi	L1	B1
280748	H	8.46 (±0.08) (n=15)	1.03	0.00	0.00	0.00	2.06	1.00
287407	p-Fluoro	8.52 (±0.11) (n=7)	0.92	0.43	-0.34	0.14	2.65	1.35
285268	m-Methyl	7.21 (±0.12) (n=6)	5.65	-0.04	-0.13	0.56	3.00	1.52
287406	m-Fluoro	8.33 (±0.13) (n=7)	0.92	0.43	-0.34	0.14	2.65	1.35
287442	m-Methoxy	7.79 (±0.15) (n=7)	7.87	0.26	-0.51	-0.02	3.98	1.35
285058	p-Methyl	7.47 (±0.11) (n=5)	5.65	-0.04	-0.13	0.56	3.00	1.52
287776	p-Methoxy	7.42 (±0.14) (n=7)	7.87	0.26	-0.51	-0.02	3.98	1.35
285902	o-Methyl	7.23 (±0.12) (n=7)	5.65	-0.04	-0.13	0.56	3.00	1.52
292691	p-(CH3)2N	7.20 (±0.12) (n=6)	15.55	0.10	-0.92	0.18	3.53	1.50
292692	m-CF3	7.18 (±0.10) (n=6)	5.02	0.38	0.19	0.88	4.57	1.35
293980	p-Cl	7.69 (±0.21) (n=3)	6.03	0.41	-0.15	0.71	3.52	1.80

a) Negative logarithm of the affinity of the compound for the LTB4 receptor on guinea pig lung m
Numbers in parentheses are standard errors.

Table II. Correlation Matrix

	MR	F	R	PI	L1	B1	B2	B3	B4
MR	1.00	-0.24	-0.66	0.01	0.54	0.40	0.81	0.85	0.69
F		1.00	-0.07	-0.05	0.34	0.08	-0.07	-0.09	0.07
R			1.00	0.61	-0.11	-0.11	-0.26	-0.34	-0.23
PI				1.00	0.31	0.59	0.45	0.39	0.22
L1					1.00	0.31	0.79	0.74	0.94
B1						1.00	0.48	0.46	0.20
B2							1.00	0.99	0.88
B3								1.00	0.85
B4									1.00

QSAR Equation 5

Predicted pKi = 8.18(±0.13) - 1.32(±0.36) **R** - 0.15(±0.03) **MR**

n=11	r=0.90	F=17.22	p=0.001
	R term	F=13.53	p=0.006
	MR term	F=34.37	p=0.000

The results of this QSAR study suggest the importance of the size, shape and electronic character of the aromatic ring substituent. The four physicochemical properties which correlated most with the biological activity were the Sterimol descriptors of the substituent length (**L1**) and descriptors of substituent width in different directions (**B2, B3,** and **B4**), exclusive of the descriptor of narrowest width (**B1**). The general descriptor of substituent bulk, **MR**, was not highly significant as a single descriptor, but was significant when combined with the electronic descriptor **R**. These descriptors are useful from a predictive point since many values may be obtained from a table in a textbook or within a database. Therefore, it is possible to use any of the QSAR equations to prioritize or suggest possible substituents. As an example Equation 5 was used for this purpose using the values for the descriptors **MR** and **R**.[12] Using QSAR Equation 5, 129 substituents were screened and the results for the predicted biological activity were sorted. A partial list is presented in Table III . Examination of the data suggest that near optimum activity may reside with the hydrogen or fluoro substituent. Other small substituents appear in the list and may be worth consideration for reasons other than intrinsic potency described by the present QSAR. Other factors, such as adsorption, distribution and metabolism, are important in developing a useful drug . The substituents of possible interest must be considered with respect to their effects on these important factors.

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10. Using 129 substituents we find the correlation of **B2** and **B3** to be 0.66. The correlation of L1 and B4 is 0.45. However these results are dependent on the particular set of substituents chosen.

11. Following a suggestion of a reviewer, we used multiple regression analysis to examine possible models using the Sterimol descriptors (**L1, B1, B2, B3, B4**) with either **R** or **MR**. We found two statistically valid models using **MR** combined with either **L1** or **B4**. In these models the significance of the individual terms were less than those found in the model defined by Equation 5. We found no valid models involving **R** and the Sterimol descriptors.

Predicted pKi = 8.40(±0.25) - 0.04(±0.03) **MR** - 0.35(±0.15) **B4**

n=11 r=0.87 F=12.45 p=0.004

MR term F=2.39 p=0.16

B4 term F=5.55 p=0.046

Predicted pKi = 8.59(±0.42) - 0.06(±0.03) **MR** - 0.25(±0.14) **L1**

n=11 r=0.84 F=9.39 p=0.008

MR term F=5.72 p=0.044

L1 term F=3.03 p=0.12

12. The descriptors **MR** and **R** are positional independent terms. Based upon our data, we concluded that the position of the substituent has little effect on the biological response as a LTB4 receptor antagonist in these assays.

Table III. Predicted biological activity using Equation 5.

substituent	R	MR	predicted pKi
OH	-0.64	2.85	8.59
F	-0.34	0.92	8.49
NH2	-0.68	5.42	8.26
H	0	1.03	8.02
p-OCH3	-0.51	7.87	7.66
NH(OH)	-0.4	7.22	7.62
NHCH3	-0.74	10.33	7.59
CH3	-0.13	5.65	7.50
Cl	-0.15	6.03	7.47
CF3	0.19	5.02	7.17
OCHF2	-0.14	7.86	7.18
CO2-	0.13	6.05	7.09
CH2OH	0	7.19	7.09
Br	-0.17	8.88	7.06
CN	0.19	6.33	6.97
OCF3	0	7.86	6.99
CHO	0.13	6.88	6.97
CO2H	0.15	6.93	6.94
N(CH3)2	-0.92	15.55	7.04
CH2NH2	-0.1	9.09	6.94
SH	-0.11	9.22	6.93
NHCHO	-0.23	10.31	6.92
CH2CN	-0.18	10.11	6.89
OCH2CH3	-0.44	12.47	6.87
CH=NOH (t)	-0.13	10.28	6.80

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