Quantitative Structure–Activity Relationships and Eudismic Analyses of the Presynaptic Dopaminergic Activity and Dopamine D2 and σ Receptor Affinities of 3-(3-Hydroxyphenyl)piperidines and Octahydrobenzo[*f*]quinolines

Han Van de Waterbeemd,† Nabil El Tayar,† Bernard Testa,*† Håkan Wikström,‡ and Brian Largent§

School of Pharmacy, University of Lausanne, CH-1005 Lausanne, Switzerland, Organic Chemistry Unit, Department of Pharmacology, University of Göteborg, S-40033 Göteborg, Sweden, and The John Hopkins School of Medicine, Department of Neuroscience, Baltimore, Maryland 21205. *Received May 6, 1987*

Data from the preceding paper[3] were examined by QSAR and eudismic analyses. A fair parabolic relationship was found between the lipophilicity (measured by a RP-HPLC method) and the σ-receptor affinity of 3-(3-hydroxyphenyl)piperidines (3HPP derivatives) and octahydrobenzo[*f*]quinolines (OHBQ derivatives). As far as the dopamine D2 receptor is concerned, the *trans*-7-hydroxy-OHBQ derivatives show a 10-fold higher affinity than the eutomeric *S* enantiomers of 3HPP derivatives, once lipophilicity has been accounted for. This difference in affinity is suggested to correspond to the energy necessary for the 3HPP derivatives to adopt the receptor-bound conformation. The *R* enantiomers of 3HPP derivatives display no apparent increase in D2 affinity with increasing lipophilicity, and indeed the eudismic index in this series increases with affinity (eudismic affinity quotient = 0.70), in agreement with a recent model of the binding of *N*-propyl-3HPP (3PPP) enantiomers to the D2 receptor. The selectivity in σ/D2 affinities was found to depend on both lipophilicity and configuration of the ligands; thus, the selectivity is maximal for log k_w values of ca. 1.7–2.1 and is much larger for the *R* than for the *S* enantiomers of 3HPP derivatives.

The σ receptors are postulated to mediate psychotomimetic effects induced by various opioids, including depersonalization, dysphoria, suspisciousness, and hallucinations.[1] Haloperidol, butaclamol, and thioridazine have good to high affinity for the σ receptors, indicating that these binding sites may have some common features with the dopamine receptors. However, these various receptors are clearly distinct since they have opposed enantioselectivities for butaclamol and since dopamine antagonists such as clozapine and sulpiride do not bind to the σ receptors.[2] It thus appears that the binding of some (but not all) dopamine antagonists to the σ receptors is a potential cause of serious psychic side effects, making it necessary to characterize the structural similarities and differences between σ- and dopamine-receptor ligands.

In the preceding paper, Wikström et al.[3] present a comprehensive structure–activity relationship (SAR) study of 3-(3-hydroxyphenyl)piperidine (3HPP) and octahydrobenzo[*f*]quinoline (OHBQ) derivatives. Their study deals with central effects on dopamine (DA) D2 and opiate σ receptors, reporting in vivo and in vitro data. To take further advantage of these data, we now report their interpretation in terms of QSAR and eudismic analyses. For the QSAR analysis, we have determined the lipophilicity of the compounds by using a RP-HPLC method.[4] The eudismic analysis being a novel approach calls for a brief presentation.

The observation by Pfeiffer[5] that enantiomeric potency ratios increase with potency has been developed into a rigorous analytical treatment of data, called eudismic analysis.[6,7] When two isomers, and particularly two enantiomers, display different potencies or affinities, the more potent isomer is called the eutomer (Eu) and the less potent one the distomer (Dis). Their potency or affinity ratio is called the eudismic ratio (ER); its logarithm is called the *eudismic index* (EI) and is for example calculated according to eq 1. In plots of EI versus pIC_{50}(Eu),

$$EI = pIC_{50}(Eu) - pIC_{50}(Dis) \quad (1)$$

straight lines are usually found with positive slopes between 0.5 and 1.0. The slope has been termed the eudismic affinity quotient (EAQ) and is a measure of the stereoselectivity displayed by a given receptor toward a series of stereoisomeric ligands.

The eudismic analysis has also been extended to compare the stereoselectivity of several receptors toward the same ("promiscuous") ligands. This approach is called the multiple eudismic affinity analysis, whereby several plots of EI versus pIC_{50}(Eu) are combined, and a regression of average EI versus average pIC_{50}(Eu) calculated. It was found that data with significant correlations give slopes of ca. 0.5, i.e. the eudismic ratio increases by ca. three per unit increase of eutomer affinity for the various receptors.[6] In the present study, we have applied eudismic analysis to the D2- and σ-receptor affinities of seven enantiomeric pairs of N-substituted 3HPP derivatives, and of seven diastereoisomeric pairs (cis/trans isomers) of OHBQ derivatives.

QSAR Analysis

The biological activities and apparent lipophilicity (log k_w values at pH 7.5) of the 14 3-(3-hydroxyphenyl)-piperidines (seven pairs of enantiomers) are presented in Table I. The minute difference in lipophilicity between compounds **3** and **4** is devoid of any significance. In the octahydrobenzo[*f*]quinoline series, 29 compounds were examined. They differ in their *N*-alkyl and aromatic substituents and with a few exceptions are racemic cis or trans diastereoisomers. Their affinities and lipophilicities are listed in Table II. Inspection of log k_w values reveal differences between trans and cis isomers ranging from −0.17 to 0.25, but no trend emerges.

I. Intercorrelation between Biological Activities. Presynaptic Dopaminergic Potency (ED_{50}) versus Ligand Affinity at D2 Receptors. The relationship between the presynaptic dopaminergic potency of the drugs, determined in vivo as the effective dose (ED_{50}) required to reduce by 50% the accumulation of DOPA, and their affinity to displace the specific binding of [^{3}H]spiperone at the dopamine D2 receptor (IC_{50}) is shown in

† University of Lausanne.
‡ University of Göteborg.
§ The John Hopkins School of Medicine.

(1) Manallack, D. T.; Beart, P. M.; Gundlach, A. L. *Trends Pharmacol. Sci.* **1986**, *7*, 448.
(2) Tam, S. W. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 6703.
(3) Wikström, H.; Andersson, B.; Elebring, T.; Svensson, K.; Carlsson, A.; Largent, B. *J. Med. Chem.*, previous paper in this issue.
(4) El Tayar, N.; Van de Waterbeemd, H.; Testa, B. *J. Chromatogr.* **1985**, *320*, 293 and 305.
(5) Pfeiffer, C. C. *Science (Washington, D.C.)* **1956**, *124*, 29.
(6) Lehmann, P. A. *Trends Pharmacol. Sci.* **1986**, *7*, 281.
(7) Lehmann, P. A.; Rodrigues de Miranda, J. F.; Ariëns, E. J. *Prog. Drug Res.* **1978**, *20*, 101 and 126.

0022-2623/87/1830-2175$01.50/0

Table I. 3-(3-Hydroxyphenyl)piperidines (3HPP): Apparent Lipophilicity, Affinity Constants for the σ and Dopamine D2 Receptors,[3] Eudismic Indices, and Presynaptic Dopaminergic Potency[3]

				pIC_{50}, μM			EI[c]		D2 pED_{50},[d]
no.	*N*-alkyl	config	log k_w[a]	σ	D2	σ selectivity[b]	σ	D2	μmol/kg
1	H	*R*	(0.41)	−0.66	0.36	−1.02	0.53	0.60	−1.23
2	H	*S*	0.41	−1.19	−0.24	−0.95			<−2
3	Me	*R*	0.96	0.43	−0.61	1.04	0.71	0.32	−0.34
4	Me	*S*	0.94	−0.28	−0.29	0.01			−0.83
5	Et	*R*	0.84	0.95	−0.54	1.49	0.96	0.42	−0.38
6	Et	*S*	(0.84)	−0.01	−0.12	0.11			−0.81
7	*n*-Pr	*R*	1.05	1.52	−0.23	1.75	0.71	0.61	−0.00
8	*n*-Pr	*S*	(1.05)	0.81	0.38	0.43			0.10
9	*i*-Pr	*R*	0.84	0.61	−1.08	1.69	0.07	1.53	−0.83
10	*i*-Pr	*S*	(0.84)	0.68	0.45	0.23			0.43
11	*n*-Bu	*R*	1.41	2.05	−0.43	2.48	0.54	0.99	−0.36
12	*n*-Bu	*S*	(1.41)	1.51	0.56	0.95			0.06
13	$(CH_2)_2Ph$	*R*	2.27	2.10	−0.09	2.19	0.30	1.45	−0.96
14	$(CH_2)_2Ph$	*S*	(2.27)	1.80	1.36	0.44			0.77

[a] Apparent lipophilicity (pH 7.5) measured by RP-HPLC; values in parentheses are estimates. [b] $pIC_{50}(\sigma) - pIC_{50}(D2)$. [c] Eudismic index. [d] Presynaptic dopaminergic potency.

Table II. Octahydrobenzo[*f*]quinolines (OHBQ): Apparent Lipophilicity, Affinity Constants for the σ and Dopamine D2 Receptors,[3] and Presynaptic Potency[3]

					pIC_{50}, μM			D2 pED_{50},[d]
no.	*N*-alkyl	stereochem	OH	log k_w[a]	σ	D2	σ selectivity[b]	μmol/kg
15	H	cis	7	0.34	−1.17	−0.88	−0.29	
16	H	(*R*,*R*)-trans	7	0.17	−0.37	−0.19	−0.18	−1.70
17	H	(*S*,*S*)-trans	7	0.17	−0.56	1.04	−1.60	0.21
18	*n*-Pr	(+)-cis	7	0.70	0.71	<−2.00	>2.71	
19	*n*-Pr	(+)-trans	7	0.95	1.32	0.80	0.52	0.49
20	*n*-Pr	(−)-cis	7	0.70	0.38	−0.32	0.70	
21	*n*-Pr	(−)-trans	7	0.95	0.36	1.47	−1.11	1.85
22	*n*-Pr	cis	8	0.84	1.40	−1.11	2.51	
23	*n*-Pr	trans	8	1.00	2.00	0.14	1.86	0.27
24	H	cis	9	0.50	−1.06	−1.48	0.42	
25	H	trans	9	0.60	−0.29	0.05	−0.34	−1.40
26	*n*-Pr	cis	9	1.20	1.18	−0.83	2.01	
27	*n*-Pr	trans	9	1.15	1.72	1.00	0.72	2.10
28	*n*-Pr	(+)-trans	9	1.15	1.68	1.60	0.08	2.40
29	*n*-Pr	(−)-trans	9	1.15	0.28			0.60
30	*n*-Pr	cis	10	1.04	−0.29	−1.79	1.50	
31	Me	trans	7	0.77	0.21	0.94	−0.73	0.20
32	Et	trans	7	0.83	0.63	0.99	−0.36	0.77
33	*n*-Bu	trans	7	(1.33)	1.64	1.42	0.22	1.10
34	$(CH_2)_2Ph$	trans	7	2.29	1.19	2.22	−1.03	
35	Me	trans	9	0.95		0.58		0.40
36	Et	trans	9	1.04		0.96		1.77
37	*n*-Bu	cis	9	1.58	1.46	−1.02	2.48	
38	*n*-Bu	trans	9	1.57	2.00	−0.48	2.48	
39	Bn	trans	9	2.68	1.96	−0.54	2.50	
40	$(CH_2)_2Ph$	trans	9	(2.80)	1.57	0.00	1.57	
41	*n*-Bu	trans	9[c]	(2.15)	2.30	−0.58	2.88	
42	Bn	trans	9[c]	(3.26)	2.30	−0.74	3.04	
43	$(CH_2)_2Ph$	trans	9[c]	(3.38)	1.85	0.36	1.49	

[a,b,d] See Table I. [c] OMe.

Figure 1. A good linear relationship exists for all compounds for which ED_{50} values have been determined, excepting the unsubstituted (NH) ones, which exhibit a separate linear relationship (eq 2 and 3, respectively). In

$$pED_{50} = 1.08\ (\pm 0.32)pIC_{50} - 0.08\ (\pm 0.27)$$
$$n = 22,\ r = 0.844,\ s = 0.538,\ F = 49.6 \qquad (2)$$

$$pED_{50} = 1.60\ (\pm 0.58)pIC_{50} - 1.55\ (\pm 0.29)$$
$$n = 5,\ r = 0.981,\ s = 0.189,\ F = 78.2 \qquad (3)$$

these and all other equations, 95% confidence limits are given in parentheses. Using an indicator H allows N–H ($H = 1$) and N–R ($H = 0$) compounds to be combined into eq 4.

$$pED_{50} = 1.12\ (\pm 0.29)pED_{50} - 1.35\ (\pm 0.52)H - 0.10\ (\pm 0.25)$$
$$n = 27,\ r = 0.903,\ s = 0.507,\ F = 53.1 \qquad (4)$$

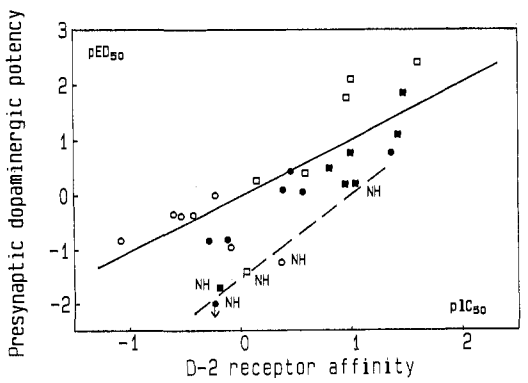

Figure 1. Relationships between in vivo presynaptic potency and in vitro dopamine D2 receptor affinity for N-substituted (eq 2) and N–H compounds (eq 3). The symbols are as follows. 3HPP derivatives: R = ○, S = ●. OHBQ derivatives: *trans*-7-OH = ■, *trans*-9-OH = □.

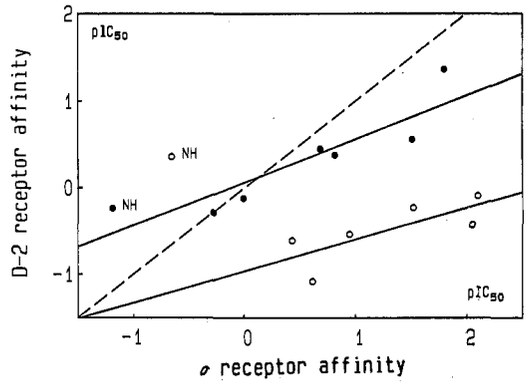

Figure 2. Relationships between D2- and σ-receptor affinities for the enantiomers of 3HPP derivatives (see eq 5 and 6 in the text). The dotted line represents a 1/1 ratio of affinities. Symbols as in Figure 1.

Affinity for σ As Compared to D2 Receptors. For the 3HPP derivatives, D2- and σ-receptor affinities are well correlated. All *S* enantiomers form a straight line (eq 5), as do the *R* enantiomers with the exception of compound 1 (NH). These two lines are shown in Figure 2. Using an indicator *I* allows the *S* and *R* enantiomers (*I* = 0 and 1, respectively) to be combined into eq 6. Figure 2 clearly

$$pIC_{50}(D2) = 0.50\ (\pm 0.28)pIC_{50}(\sigma) + 0.06\ (\pm 0.31)$$
$$n = 7,\ r = 0.897,\ s = 0.282,\ F = 20.7 \qquad (5)$$

$$pIC_{50}(D2) = 0.46\ (\pm 0.19)pIC_{50}(\sigma) - 1.17\ (\pm 0.36)I + 0.08\ (\pm 0.24)$$
$$n = 13,\ r = 0.925,\ s = 0.261,\ F = 29.5 \qquad (6)$$

shows that the *S* enantiomers have a higher affinity for the D2 receptors, while the *R* enantiomers exhibit higher affinity for the σ receptors. The lines for the *R* and *S* enantiomers have identical slopes, but are not parallel to the theoretical line for a 1/1 affinity ratio.

In contrast to the 3HPP derivatives, the OHBQ derivatives do not display any relationship between the σ- and D2-receptor affinities ($r = 0.159$).

II. Biological Activities and Lipophilicity. σ Receptors. Fair parabolic relationships have been found between the affinity to σ receptors (pIC_{50}) and lipophilicity ($\log k_w$) for the 3HPP and OHBQ derivatives as shown by eq 7 (Figure 3a) and eq 8, respectively. Equations 7 and

$$pIC_{50} = -1.17\ (\pm 0.83)(\log k_w)^2 + 4.73\ (\pm 2.36)\ \log k_w - 2.72\ (\pm 1.43)$$
$$n = 14,\ r = 0.908,\ s = 0.460,\ F = 26.0,\ \log k_w(\text{opt}) = 2.02 \qquad (7)$$

$$pIC_{50} = -0.52\ (\pm 0.31)(\log k_w)^2 + 2.64\ (\pm 1.13)\ \log k_w - 1.26\ (\pm 0.79)$$
$$n = 27,\ r = 0.820,\ s = 0.616,\ F = 24.6,\ \log k_w(\text{opt}) = 2.54 \qquad (8)$$

8 are not significantly different, having in particular similar $\log k_w$(opt) values and intercepts. Thus all compounds can be examined together and regressed in a single equation (Figure 3B and eq 9).

$$pIC_{50} = -0.58\ (\pm 0.26)(\log k_w)^2 + 2.92\ (\pm 0.90)\ \log k_w - 1.51\ (\pm 0.62)$$
$$n = 41,\ r = 0.837,\ s = 0.571,\ F = 44.4,\ \log k_w(\text{opt}) = 2.50 \qquad (9)$$

Dopamine D2 Receptors. A global relationship like that found for the σ-receptor affinity (such as eq 9) does not exist for D2 receptors. However, subgroups of compounds show interesting trends. Thus, the *S* enantiomers of 3HPP (eq 10) and the *trans*-7-hydroxy isomers of OHBQ (eq 11) derivatives appear to display lipophilicity-related affinity, although the small number of compounds precludes any firm conclusion. These trends are illustrated in Figure 4.

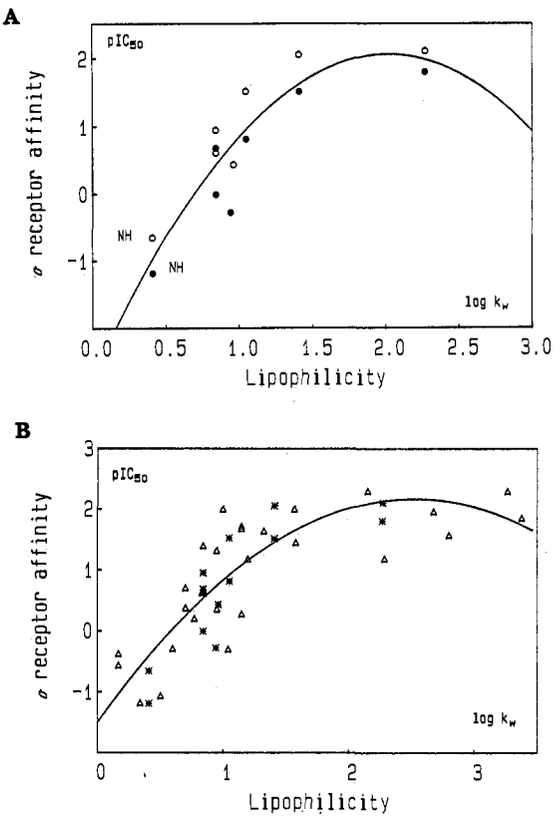

Figure 3. Relationships between apparent lipophilicity at pH 7.5 ($\log k_w$) and σ-receptor affinity for 3HPP derivatives (Figure 3A, eq 7) and all compounds in this study (Figure 3B, eq 9). The symbols are as follows. 3HPP derivatives: *R* = ○, *S* = ●, all = *; all OHBQ derivatives = △.

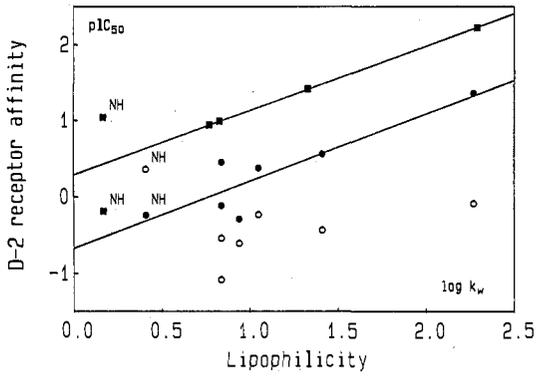

Figure 4. Relationships between lipophilicity and D2-receptor affinity for *trans*-7-hydroxy-OHBQ derivatives and the *R* and *S* enantiomers of 3HPP derivatives. Symbols as in Figure 1.

$$pIC_{50} = 0.88\ (\pm 0.50)\ \log k_w - 0.68\ (\pm 0.62)$$
$$n = 7,\ r = 0.896,\ s = 0.284,\ F = 20.3 \qquad (10)$$

$$pIC_{50} = 0.85\ (\pm 0.68)\ \log k_w + 0.28\ (\pm 0.80)$$
$$n = 6,\ r = 0.867,\ s = 0.435,\ F = 12.2 \qquad (11)$$

The (*S*)-3HPP and the *trans*-(4a*S*,10b*S*)-7-hydroxy-OHBQ derivatives have superimposable N and OH groups in a two-dimensional representation.[8] It is thus interesting

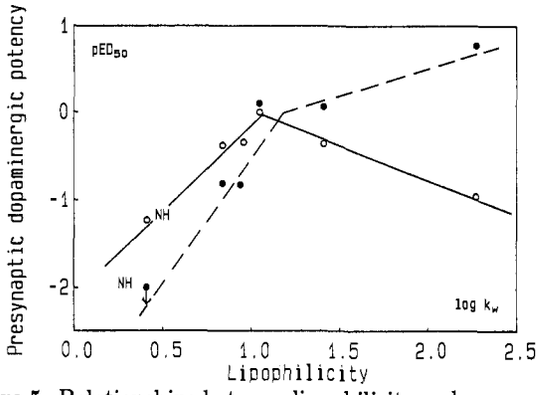

Figure 5. Relationships between lipophilicity and presynaptic dopaminergic potency for N–H and *N*-*n*-alkyl 3HPP derivatives. The lines are not calculated ones, but are merely indicative. Symbols as in Figure 1.

to note that the more rigid *trans*-7-hydroxy-OHBQ derivatives show a 10-fold higher D2-receptor affinity than the more flexible 3HPP derivatives, once lipophilicity has been accounted for. Indeed, the slopes of eq 10 and 11 are not statistically different, and one line is ca. 1 pIC_{50} unit above the other. This effect points to three-dimensional topographical differences, as discussed later. In contrast to the above, a systematic difference is not seen in the affinity of the same compounds to the σ receptors.

Figure 4 also suggests another interesting feature, namely that the *R* enantiomers of 3HPP derivatives display a D2-receptor affinity that is practically not influenced by lipophilicity. However, a closer inspection of the data falsifies this preliminary conclusion (see Discussion).

Presynaptic Dopaminergic Potency. A plot of the presynaptic dopaminergic potency of 3HPP derivatives versus their lipophilicity shows no overall relationship, but reveals partial trends. Excluding the *N*-isopropyl derivatives, two distinct bilinear relationships are apparent for the *R* and *S* enantiomeric series (Figure 5), but no equation can be calculated due to an insufficient number of compounds.

When the OHBQ derivatives are similarly examined, a fair relationship exists for the 14 compounds (eq 12).

$$pED_{50} = 2.44\ (\pm 1.51)\ \log k_w - 1.48\ (\pm 1.41)$$
$$n = 14,\ r = 0.712,\ s = 0.870,\ F = 12.4 \qquad (12)$$

III. Receptor Selectivity as a Function of Lipophilicity. Plotting the receptor selectivity versus lipophilicity for the seven enantiomeric pairs of 3HPP derivatives yields the interesting result shown in Figure 6A. It appears that the receptor selectivity is dependent on both lipophilicity and configuration. Despite the limited number of observations, both *R* and *S* series each fit an apparent parabolic relationship ($n = 7$, $r = 0.97$; and $n = 7$, $r = 0.95$, respectively), with a maximum σ/D2 selectivity for $\log k_w = 1.7$ in both series.

The racemic *cis*- and *trans*-9-hydroxy derivatives of OHBQ also show an apparent parabolic relationship ($n = 8$, $r = 0.88$), with $\log k_w(\text{opt}) = 2.08$ (Figure 6B). No distinct relationship is seen for the other OHBQ derivatives.

Eudismic Analysis of Receptor Affinities

The eudismic indices of the enantiomers of 3HPP derivatives are given in Table I. For the OHBQ derivatives (Table II), pairs of cis–trans isomers were available for eudismic analysis, but the fact that some of these isomers

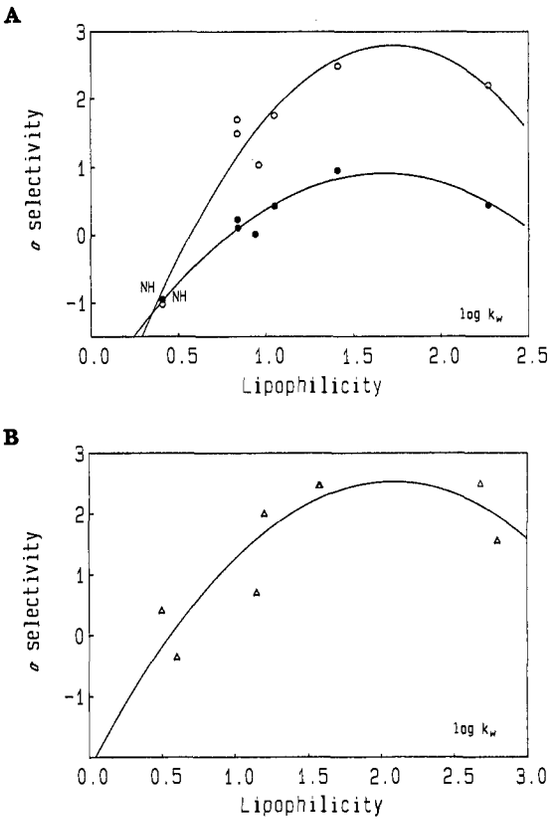

Figure 6. Relationships between σ-/D2-receptor selectivity and lipophilicity for the *R* and *S* enantiomers of 3HPP derivatives (Figure 6A) and for the racemic *cis*- and *trans*-9-hydroxy derivatives of *OHBQ* (Figure 6B). Symbols as in Figure 3.

were used as racemates while others were resolved into their enantiomers poses a most serious problem. A preliminary investigation showed the prohibitive difficulty of applying an eudismic analysis to such a stereochemically heterogeneous set of data. As a consequence, the eudismic analysis to follow deals only with 3HPP derivatives. Plots of eutomer versus distomer affinities are presented in Figure 7. For the dopamine D2 receptor (Figure 7A), six out of the seven enantiomeric pairs of 3HPP derivatives fit a straight line given by eq 13, the *N*-isopropyl derivative being excluded. Interestingly, the plot shows that the

$$pIC_{50}(\text{Eu}) = 2.49\ (\pm 2.02)pIC_{50}(\text{Dis}) + 1.26\ (\pm 0.81)$$
$$n = 6,\ r = 0.863,\ s = 0.328,\ F = 11.7 \qquad (13)$$

distomer of the *N*-isopropyl pair is far less active than expected, whereas the affinity of its eutomer falls within the expected range. Steric hindrance at the receptor of the N-substituent is thus implicated for the (*R*)- but not for the (*S*)-*N*-isopropyl analogue, suggesting different modes of interaction for the two enantiomers,[8,9] as discussed later.

When the σ-receptor affinities of the seven pairs of enantiomers (3HPP derivatives) are plotted in Figure 7B, a single straight line can be calculated (eq 14). Interestingly,

$$pIC_{50}(\text{Eu}) = 0.90\ (\pm 0.30)pIC_{50}(\text{Dis}) + 0.59\ (\pm 0.32)$$
$$n = 7,\ r = 0.960,\ s = 0.300,\ F = 59.1 \qquad (14)$$

the slope of eq 14 is close to unity, in marked contrast with eq 13, suggesting in a first approximation that stereoselectivity does not increase with affinity. Globally, however,

(8) Liljefors, T.; Wikström, H. *J. Med. Chem.* **1986**, *29*, 1896.

(9) Wikström, H.; Andersson, B.; Sanchez, D.; Lindberg, P.; Arvidsson, L.-E.; Johansson, A. M.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1985**, *28*, 215.

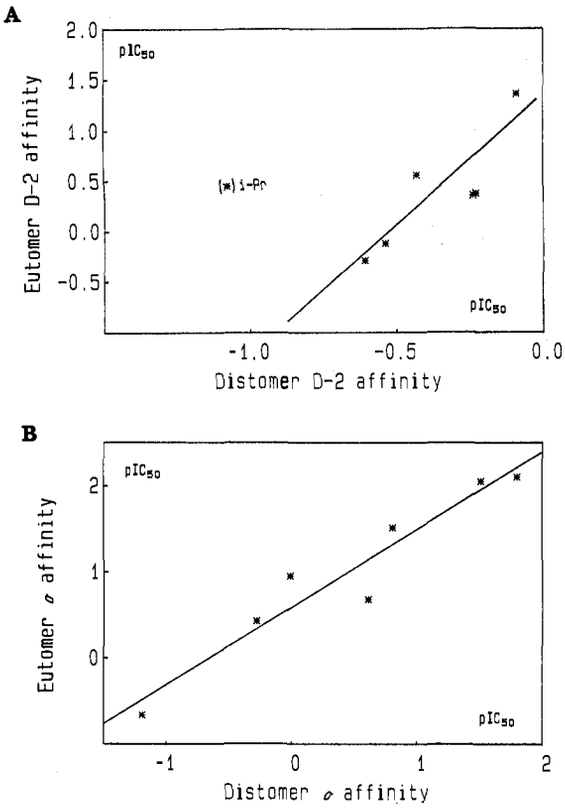

Figure 7. Eutomer affinity versus distomer affinity of the 3HPP enantiomeric pairs for D2 receptors (Figure 7A) (eq 13) and for σ receptors (Figure 7B) (eq 14).

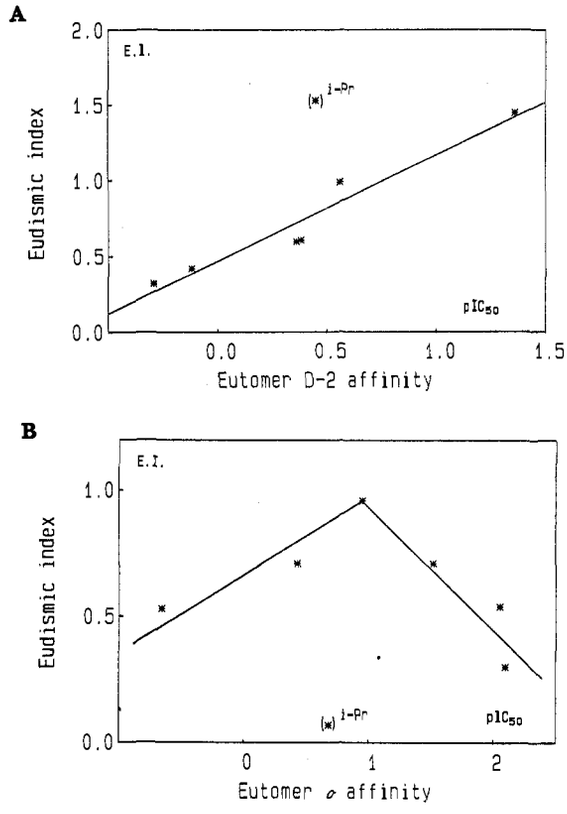

Figure 8. Eudismic analysis [plots of EI versus pIC_{50}(Eu)] for the binding of 3HPP enantiomers to the D2 receptor (Figure 8A) (eq 15) and to the σ receptor (Figure 8B, where the lines are merely indicative and not calculated).

such plots are not very informative and are even misleading, as shown below by eudismic analysis.

A plot of EI versus pIC_{50}(Eu) is shown in Figure 8A for the binding of the 3HPP derivatives to the D2 receptor. The *N*-isopropyl analogue is again an outlier, its EI being far too large as compared with that of other analogues. The other six pairs of enantiomers can be linearily regressed, yielding eq 15. In agreement with the findings

$$\mathbf{EI}(D2) = 0.70\ (\pm 0.24)pIC_{50}(Eu) - 0.47\ (\pm 0.16)$$
$$n = 6,\ r = 0.970,\ s = 0.114,\ F = 63.9 \qquad (15)$$

of Lehmann,[6] the slope of this line is positive, with a value between 0.5 and 1.0. The eudismic affinity quotient (EAQ) of the D2 receptor toward *N*-*n*-alkyl-3HPP derivatives is thus 0.70.

When the affinity of the same compounds for the σ receptor is examined by eudismic analysis (Figure 8B), an interesting plot is obtained. Indeed, the N–H, N–Me, and N–Et homologues define a straight line (r = 0.96). The slope of this line (EAQ = 0.25) is *positive*, but its value is markedly smaller than 0.5, indicating little stereoselectivity in this limited subseries of ligands. Much more intriguing is the fact that the N–Et, N–Pr, N–Bu, and N–$(CH_2)_2$Ph analogues define a straight line (r = –0.95) with a *negative* slope (**EAQ** = –0.49). This is a quite rare occurrence of an *anti-Pfeiffer's rule* behavior, as discussed later.

Discussion

A traditional QSAR approach using a number of parameters was attempted but failed to yield significant results, as did a Free–Wilson analysis. In contrast, some valuable rationalizations emerge from a number of plots and correlations. It first appears that all compounds tested display in vivo presynaptic dopaminergic activity and that this activity is fairly well correlated with in vitro D2-receptor affinity (eq 2–4, Figure 1). The behavior of secondary amines is peculiar, since the compounds are ca. 10 times less active in vivo than expected from their in vitro affinity (see regressor of indicator value in eq 4). The reason for this difference is not known but could be due to pharmacokinetic factors, i.e. the tertiary amines cross the blood–brain barrier better than secondary amines.

A search for relationships between receptor affinity and lipophilicity reveal differences between D2 and σ receptors. For σ receptors, all compounds investigated (n = 41) display a single parabolic relationship between affinity and lipophilicity (eq 9). While the statistics of this equation are not particularly good, they nevertheless are fair and lead to the conclusion that, within the two chemical series investigated, the σ receptors are not highly structure-selective.

In contrast, dopamine D2 receptors appear more discriminative. The *S* enantiomers of 3HPP derivatives display D2-receptor affinities, which increase with lipophilicity (eq 10), while the affinities of *R* enantiomers show little variation from one analogue to the other and in a first approximation appear essentially uninfluenced by lipophilicity. However, close inspection of Figure 4 shows that for the *N*-methyl, *N*-ethyl, and *N*-*n*-propyl homologues in the *R* series, D2-receptor affinity does increase with lipophilicity, but does not increase further for the *N*-butyl and *N*-(phenylethyl) analogues. A limitation of plots like those in Figure 4 is that they are not very revealing in terms of the receptor's enantioselectivity. This is when eudismic analysis becomes useful by correlating enantioselectivity and affinity independently of any structural property of the ligands.

The differences in D2-receptor affinity between the *R* and *S* enantiomers of 3HPP derivatives fully confirm a recent topographical model[8] for the interaction of (*R*)- and

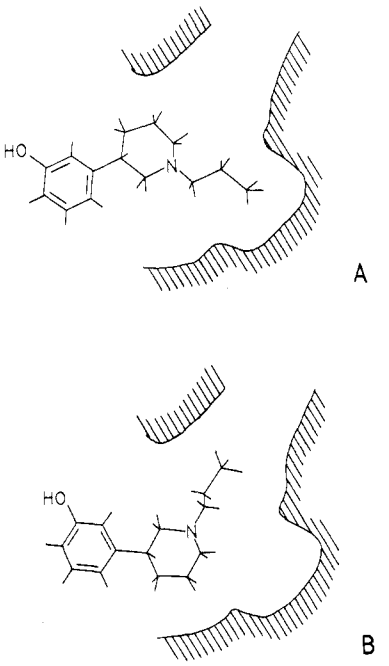

Figure 9. Modification of the dopamine D2 receptor model of Liljefors and Wikström[8] to show the different binding modes and *N*-alkyl structure–binding relationships of 3HPP derivatives. Figure 9A, distomeric *R* enantiomers; Figure 9B, eutomeric *S* enantiomers.

(*S*)-3-(3-hydroxyphenyl)-*N*-*n*-propylpiperidine (3PPP) with the dopamine receptor. Indeed, Liljefors and Wikström concluded from pharmacological and conformational data that (*R*)-3PPP (the distomer) binds with its *N*-propyl group filling a "propyl cleft", while the same group in (*S*)-3PPP (the eutomer) points in a sterically "unrestricted upward" direction (see Figure 9). The present data (e.g., Figure 4) indicate that in the distomeric *R* enantiomers, C_nH_m fragments prolonging the *N*-propyl group do not contribute to the binding energy and must therefore lie outside the cleft. Perhaps such fragments escape perpendicularly from the cleft, i.e. by pointing either toward or away from the observer of Figure 9A. In regard to the eutomeric *S* enantiomers, their affinity increases with increasing chain length; this suggests an addition to the receptor model of Liljefors and Wikström in that the "unrestricted upward direction" they defined must in fact be a cleft of undefined length binding the N-substituent (Figure 9B). Such a hypothesis may explain why eutomer affinity increases faster in the 3HPP series than distomer affinity (Figure 7A); in other words, it offers a molecular explanation for the positive eudismic affinity quotient (eq 15 and Figure 8A).

Another interesting finding to emerge from Figure 4 is the fact that the more rigid *trans*-7-hydroxy-OHQB derivatives show a 10-fold higher D2 affinity than the more flexible 3HPP derivatives, once lipophilicity has been accounted for. This difference is believed to be caused by conformational factors. Indeed, a difference of 1 unit in pIC_{50} values corresponds approximately to a difference of 1.4 kcal/mol in binding energies.[10] The energy necessary to bring 3PPP from its preferred conformation to a conformer superimposable on *trans*-7-hydroxy-OHBQ is 2.4 kcal/mol, and the fair correspondence between the two energy differences supports the ideas presented by Liljefors and Wikström.[8] Furthermore, *trans*-7-hydroxy-OHBQ derivatives display a relationship between affinity and lipophilicity similar to that of (*S*)-3HPP derivatives, suggesting a mode of binding comparable to that shown in Figure 9B, in agreement with other studies.[9]

When the presynaptic dopaminergic potency of the 3HPP derivatives is examined as a function of lipophilicity (Figure 5), unexpected variations become apparent between enantiomers. In particular, the S/R ratio is smaller than one for the lower homologues, reaches a value close to one for 3PPP itself, and grows larger than one for the *N*-butyl and *N*-(phenylethyl) derivatives. There are thus marked differences in the way lipophilicity is related to D2 receptor affinity on one side (Figure 4) and presynaptic dopaminergic potency on the other (Figure 5). Such differences remain masked in Figure 1, and an eudismic analysis (not reported) did not uncover additional information.

The σ-receptor affinity, when examined globally, is comparatively influenced by lipophilicity in both series of 3HPP and OHBQ derivatives (Figure 3). In addition, eudismic analysis is of marked interest here in that it reveals the strong influence of configurational factors. Indeed, Table I shows that for the 3HPP derivatives, the EI has smaller values for the more bulky N-substituents. While Figure 7B suggests an approximately proportional increase in affinity for eutomers and distomers, Figure 8B shows that the eudismic index of the 3HPP enantiomers increases with increasing affinity only up to the *N*-ethyl enantiomers. For 3PPP itself and its higher homologues, the eudismic index decreases markedly with increasing affinity, implying that in this subseries the affinity of distomers increases faster than that of eutomers. In terms of drug–receptor interactions, we interpret this anti-Pfeiffer's rule behavior to indicate that a bulky N-substituent (3 C or more) in the distomeric *S* enantiomers is able to reach, and bind to, a hydrophobic pocket in the σ receptor inaccessible to the eutomers. The *N*-isopropyl derivative in the 3HPP series displays a peculiar behavior in that its eudismic index is close to zero, with the *S* enantiomer being the eutomer in this case. Clearly the N-substituent plays a marked role in receptor binding and in influencing the eudismic index.

One of the questions addressed in this work concerns the structural similarities and differences characterizing ligands of the D_2 and σ receptors. Figure 2 shows that in the 3HPP series, good correlations exist between the two affinities, a clear enantioselectivity being seen. The *S* enantiomers display little σ-receptor selectivity (average value 0.36 when excluding the N–H derivative, see Table I), while the *R* enantiomers have a marked σ-receptor selectivity (average value 1.77 when excluding the N–H derivative, see Table I). The configuration of 3HPP derivatives is thus one of the structural factors influencing σ-/D_2-receptor selectivity.

For a number of *trans*-OHBQ derivatives with an OH group in the 7-, 8-, or 9-position, the σ-receptor selectivity ranges from −1.60 to 3.04. No structure–selectivity relationships are readily apparent, except that small *N*-alkyl groups seem to be associated with some D2 selectivity while the analogues with large N-substituents are markedly σ selective (see Table II). Plotting the receptor selectivity versus lipophilicity (Figure 6) extracts more information from the data. The already noted σ-receptor selectivity of *R* enantiomers of 3HPP derivatives is seen more clearly in Figure 6A than in Figure 2, revealing also that the selectivity itself is lipophilicity-dependent and reaches its highest value for $\log k_w = 1.7$. For the 9-hydroxy-OHBQ analogues, the selectivity can also be expressed as a parabolic function of lipophilicity (Figure 6B), confirming that

(10) Andrews, P. *Trends Pharmacol. Sci.* **1986**, *7*, 148.

the highest σ selectivity is reached for log k_w values close to 2.

Experimental Section

Lipophilicity. The apparent lipophilicity of most compounds was measured at pH 7.5 by a RP-HPLC method previously described.[4] The method yields capacity factors extrapolated to 0% methanol, i.e. log k_w values that are taken as a direct measure of apparent lipophilicity.[11] Missing values were estimated from derived fragmental values and are given in parentheses.

Correction for ionization (to yield "true" lipophilicity) was not undertaken. Indeed, the compounds exist as neutral molecules, zwitterions, cations (N^+), and anions (O^-), suggesting complex ionization schemes. We have measured with previously described methods[12] the pK_a values of 3PPP. The two macroscopic pK_a values, 9.77 (± 0.08) and 9.33 (± 0.06), as obtained by potentiometry, could be attributed to the functional groups N and OH, respectively, by studying the UV spectra of 3PPP as a function of pH to establish the pK_a value of the phenolic group. The corresponding pK_a values of dopamine are 8.57 (N) and 10.08 (OH)[13] and for apomorphine 7.20 (N) and 8.92 (OH).[14]

In all correlation equations, the regression coefficients are reported together with their 95% confidence limits.

Acknowledgment. We thank Agneta Fougberg and Maria Lindbäck for performing most of the HPLC lipophilicity measurements. This study was supported by the Swiss National Science Foundation (Grant 3.539-0.83 to B.T. and H.v.d.W.).

(11) Braumann, T. *J. Chromatogr.* **1986**, *373*, 191.
(12) Marrel, C.; Boss, G.; Van de Waterbeemd, H.; Testa, B.; Cooper, D.; Jenner, P.; Marsden, C. D. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 459.
(13) Schüsler-Van Hees, M. T. I. W.; Beijersbergen van Henegouwen, G. M. J.; Driever, M. F. J. *Pharm. Weekbl., Sci. Ed.* **1983**, *5*, 102.
(14) Newton, D. W.; Kluza, R. B. *Drug Intell. Clin. Pharm.* **1978**, *12*, 546.

Antitumor Activity of Bis(diphenylphosphino)alkanes, Their Gold(I) Coordination Complexes, and Related Compounds[1]

Christopher K. Mirabelli,*† David T. Hill,‡ Leo F. Faucette,† Francis L. McCabe,† Gerald R. Girard,‡ Deborah B. Bryan,‡ Blaine M. Sutton,‡ Joan O'Leary Bartus,† Stanley T. Crooke,† and Randall K. Johnson†

Departments of Molecular Pharmacology and Medicinal Chemistry, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received April 6, 1987*

Bisphosphines related to bis(diphenylphosphino)ethane (dppe) and their gold complexes are described that are active in a spectrum of transplantable tumor models. When administered ip on days 1–5 at its maximally tolerated dose (MTD) of 40 μmol/kg, dppe reproducibly gives 100% increase in life span (ILS) in mice bearing ip P388 leukemia. Coordination of chlorogold(I) to each phosphine in dppe gave a complex that had similar activity but at a much lower dose level than dppe; the MTD for the gold(I) complex was 7 μmol/kg. Among other metal complexes of dppe, the Au(III) complex was active (>50% ILS) whereas Ag(I), Ni(II), Pt(II), Pd(II), and Rh(I) complexes were inactive. Among dppe analogues, replacement of phenyl groups with ethyl or benzyl groups resulted in inactivity for both ligands and the corresponding gold complexes whereas substitution with cyclohexyl or heterocyclic ring systems yielded ligands and/or gold complexes with antitumor activity. Among substituted-phenyl dppe and dppe$(AuCl)_2$ analogues, 3-fluoro, 4-fluoro, perdeuterio, 4-methylthio, and 2-methylthio analogues were active; 4-methyl, 3-methyl, 4-methoxy, 4-dimethylamino, and 4-trifluoromethyl analogues were marginal or inactive. Analogues in which the ethane bridge of dppe or dppe$(AuCl)_2$ was varied between one and six carbons, unsaturated or substituted, revealed that activity was maximal with ethane or *cis*-ethylene. Compounds with good P388 activity were also active in other animal tumor models.

There has been widespread interest in the potential antineoplastic activity of transition-metal complexes for the past decade following the serendipitous discovery of the antitumor activity of cisplatin in the late 1960s.[2] Cisplatin was developed to clinical trial on the basis of its activity in animal tumor models, primarily L1210 leukemia, P388 leukemia, and B16 melanoma. The drug has subsequently been shown to have a broad spectrum of activity in animal tumor models and in a number of human solid tumors, particularly in genitourinary carcinomas. On the basis of the activity of platinum complexes, other transition metal containing complexes have been investigated as potential antitumor agents. Rhodium and palladium complexes have been the most thoroughly evaluated, but none of the complexes of metals other than platinum has, to date, shown sufficient activity to warrant development to clinical trial.

Until recently, there has been minimal evaluation of gold complexes in animal tumor models. However, in 1981 Simon et al. reported that auranofin, (1-thio-β-D-glucopyranose 2,3,4,6-tetraacetato-*S*)(triethylphosphine)gold, a gold-containing complex used in the treatment of rheumatoid arthritis, possessed significant antitumor effects in animals bearing ip P388 leukemia.[3] We have subse-

†Department of Molecular Pharmacology.
‡Department of Medicinal Chemistry.
*To whom reprint request should be sent.

(1) Presented in part at the following: (a) Proceedings of the American Association of Cancer Research, Houston, TX, May 1985; Abstracts 1001, 1007, 1008. (b) Proceedings of the American Association for Cancer Research, Los Angeles, CA, May 1986; Abstracts 1114, 1115. (c) 190th National Meeting of the American Chemical Society, Chicago, IL, Sept 1985; paper MEDI 14. (d) 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 1986; paper INORG 11.
(2) Rosenberg, B.; VanCamp, J.; Trosko, E.; Mansour, V. *Nature (London)* **1969**, *222*, 385. *Cisplatin: Current Status and New Developments*; Prestayko, A. W., Crooke, S. T., Carter, S. K., Eds.; Academic: New York, 1980. Cleare, M. J.; Hydes, P. C. In *Metal Ions in Biological Systems*; Sigel, H., Ed.; Marcel Dekker: New York, Vol. 11, p 1.

0022-2623/87/1830-2181$01.50/0