J. Pharm. Pharmacol. 1988, 40: 609–612
Received April 26, 1988

Influence of Lipophilicity and Chirality on the Selectivity of Ligands for β_1- and β_2-Adrenoceptors

NABIL EL TAYAR, BERNARD TESTA, HAN VAN DE WATERBEEMD, PIERRE-ALAIN CARRUPT AND ALBERTO J. KAUMANN*

*School of Pharmacy, University of Lausanne, Place du Château 3, CH-1005 Lausanne, Switzerland, and *Smith Kline and French Research Ltd, Welwyn AL6 9AR, UK*

Abstract—Eudismic and QSAR analyses are reported for the β_1- and β_2-adrenoceptor affinities and β_1-selectivity of 10 enantiomeric pairs of ligands with only *N*-isopropyl or *N*-t-butyl groups. For both receptors, the eudismic index (ratio of affinity) increases with the affinity of the eutomers. However, the affinity of the distomers for the β_2-adrenoceptor is relatively high, suggesting additional hydrophobic interactions. This is confirmed by various correlations between affinities and lipophilicities, showing that the affinity for β_2-adrenoceptors is slightly more dependent on lipophilicity than that for β_1-adrenoceptors. As a result, the β_1-selectivity of the investigated β_1-adrenoceptor ligands is strongly and negatively correlated with their lipophilicity ($r = -0.942$).

β-Adrenoceptors, like most pharmacological receptors, display a high degree of enantioselectivity. Thus, they are activated or blocked by chiral neurotransmitters or drugs which are laevorotatory and have in their side-chain a chiral centre of constant absolute configuration designated as (*R*) for arylethanolamine derivatives and (*S*) for aryloxypropanolamine derivatives (Easson & Stedman 1933; Luduena et al 1949; Kaumann & Birnbaumer 1974; Patil et al 1975; Morris & Kaumann 1984).

The subdivision of β-adrenoceptors into β_1 and β_2 subtypes originally proposed by Lands et al (1967) has since then received abundant experimental support and the selectivity of many agonists or antagonists has been established (Rugg et al 1978; Minneman et al 1979; Stiles et al 1983). Peptide maps have been used to establish structural differences between mammalian β_1- and β_2-adrenoceptors (Dixon et al 1986) which must at least in part account for the β_1/β_2 selectivity of many β-adrenoceptor agonists and antagonists. Initially, β_1-selectivity was equated with cardioselectivity. While this concept was valid in the days when heart β-adrenoceptors were considered to be only β_1, this is no longer true because β_1- and β_2-adrenoceptors coexist in most mammalian hearts. For example, the β_2-selective agonist fenoterol is as potent as the non-selective adrenaline in guinea-pig sinoatrial node (Lemoine et al 1985).

Structural differences between β-adrenoceptor subtypes have been deduced by Morris & Kaumann (1984). Using ten pairs of enantiomeric drugs, they showed that β_1-adrenoceptors in heart tissues exhibit higher affinity ratios for enantiomers than β_2-adrenoceptors in lung tissues. In other words, Morris & Kaumann showed that the configuration of β-adrenoceptor agonists and antagonists is a structural factor influencing both affinity and receptor selectivity. The conclusion was thus drawn that the steric requirements of β_1-adrenoceptors are more stringent than those of β_2-adrenoceptors.

Another important structural property influencing the affinity of antagonists to β-adrenoceptors is their lipophilic character (Ban et al 1985; IJzerman et al 1985; Bree et al 1986). As an approximate and qualitative rule, it has been found in a number of studies that many β_1-selective antagonists are relatively hydrophilic while the β_2-selective antagonists are more lipophilic (Smith 1978; Machin et al 1984). Presently, however, the qualitative nature of this rule does not allow conclusions to be drawn regarding differential requirements of β-adrenoceptor subtypes. This is all the more true since the receptor subtype selectivity of β-adrenoceptor agonists and antagonists is also known to be partly influenced in-vivo by selective tissue distribution (Cruickshank 1982; Kenakin 1986), a markedly lipophilicity-dependent phenomenon. In addition, β_1-selectivity can be improved by proper substitution on the *para* position of the aryl aromatic ring and/or by substitution on the side-chain amino group. However, the selectivities due to both types of substituents are not additive and probably result from different binding modes (Rzeszotarski et al 1983).

In the present paper, the influence of configuration and lipophilicity on the affinity and receptor selectivity of ten enantiomeric pairs of β-adrenoceptor agonists, partial antagonists and antagonists is quantitatively assessed using eudismic analysis and classical regression analysis. The binding data used in this study were obtained from the paper of Morris & Kaumann (1984) while lipophilicity data (apparent *N*-octanol/water partition coefficient at pH 7·4) were collected from Woods & Robinson (1981), and Bree et al (1986). It must be stressed that the receptor selectivity of all β-antagonists investigated here is influenced only by the nature of the aromatic ring and its substituents and not by the amino group substituent, which is an isopropyl or t-butyl group.

Methods

Eudismic analysis

In recent years, an elegant theoretical method called *eudismic analysis* has been developed to quantitate the stereoselectivity displayed by a given receptor towards series of stereoisomeric ligands (Lehmann et al 1976; Lehmann 1987). Briefly, when two stereoisomers 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*, its logarithm being

Correspondence to: B. Testa, School of Pharmacy, University of Lausanne, Place du Château 3, CH-1005 Lausanne, Switzerland.

the *eudismic index* (EI). When affinities are considered, EI is calculated according to:

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

where K is the equilibrium dissociation constant. In plots of EI vs pK_{Eu}, straight lines with a positive slope are usually found. This slope has been termed the *eudismic affinity quotient* (EAQ) and is taken as a quantitative measure of the stereoselectivity of the receptor.

Statistical calculations

Linear regression analyses and plots were performed using the Graph-Pad program operating on an IBM PC/AT microcomputer. In regression equations, the values given in parenthesis are 95% confidence limits.

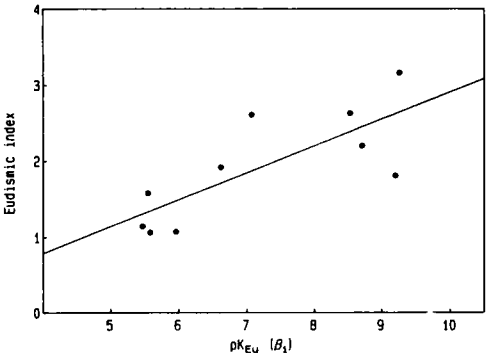

FIG. 1. Eudismic analysis (plots of EI vs pK_{Eu}) for the affinity of enantiomers to the β_1-adrenoceptors (eqn 2).

Results and Discussion

Table 1 reports the affinities of the eutomers and distomers of 10 enantiomeric pairs of β-adrenoceptor agonists and antagonists, as well as their eudismic indices and apparent lipophilicity at pH 7·4. The relationships between eudismic indices (EI) and affinity constants of the eutomers (pK_{Eu}) for β_1- and β_2-adrenoceptors are expressed by equations 2 and 3 and are depicted in Figs 1 and 2, respectively.

$$EI(\beta_1) = 0{\cdot}35(\pm 0{\cdot}24)\ pK_{Eu} - 0{\cdot}63(\pm 1{\cdot}77)$$
$$n = 10;\ r = 0{\cdot}767;\ s = 0{\cdot}50;\ F = 11{\cdot}4 \quad (2)$$

$$EI(\beta_2) = 0{\cdot}21(\pm 0{\cdot}16)\ pK_{Eu} - 0{\cdot}13(\pm 1{\cdot}24)$$
$$n = 10;\ r = 0{\cdot}715;\ s = 0{\cdot}40;\ F = 8{\cdot}36 \quad (3)$$

These two equations display a fair correlation coefficient while their constant term is not significantly different from zero. The slopes of these lines (i.e. the eudismic affinity quotient, see above) are positive in agreement with the findings of Lehmann (1987). Interestingly, the eudismic affinity quotient of the β_1-adrenoceptors (eqn 2) is marginally but not significantly (in statistical terms) higher than that of the β_2-adrenoceptors (eqn 3). This would suggest that the β_1-adrenoceptor might exhibit somewhat stricter stereochemical (and more generally steric) requirements than the β_2-adrenoceptors, as qualitatively concluded by Morris & Kaumann (1984). In fact, a closer inspection of data in Table 1 reveals that the consistently lower eudismic index of β_2-adrenoceptors has its origin in significantly higher $pK_{Dis}(\beta_2)$ vs $pK_{Dis}(\beta_1)$ values, in agreement with other studies (Lemoine & Kaumann 1983; Quast & Vollmer 1984; Walter et al 1984).

Table 1. Receptor affinity and selectivity of 10 enantiomeric pairs of β-adrenoceptor ligands.

Ligand	β_2-adrenoceptors[a] pK_{Eu}	pK_{Dis}	E.I.[d]	β_1-Adrenoceptors[a] pK_{Eu}	pK_{Dis}	E.I.[d]	β_1-Selectivity[b]	Lipophilicity[c] log $P_{7.4}$
Isoprenaline	6·82	4·90	1·92	7·07	4·46	2·61	0·25	−1·93
Adrenaline	5·91	4·80	1·11	5·47	4·33	1·14	−0·44	−2·50
Noradrenaline	5·04	3·80	1·24	5·55	3·97	1·58	0·51	−2·86
Prenalterol	6·49	5·29	1·20	6·62	4·70	1·92	0·13	−0·28
Practolol	5·38	4·81	0·57	5·58	4·52	1·06	0·20	−1·31
Alprenolol	8·90	7·56	1·34	8·53	5·90	2·63	−0·37	0·36
Pindolol	9·45	7·15	2·30	9·26	6·10	3·16	−0·19	−0·09
Atenolol	5·46	4·68	0·78	5·96	4·89	1·07	0·50	−1·88
Bupranolol	9·47	8·03	1·44	9·20	7·39	1·81	−0·27	1·08
Propranolol	9·16	7·20	1·96	8·71	6·51	2·20	−0·45	1·31

(a) Values from Morris & Kaumann (1984).
(b) Values calculated as $pK_{Eu}(\beta_1)$ minus the $pK_{Eu}(\beta_2)$.
(c) Apparent n-octanol/water partition coefficient measured at pH 7·4; data from Woods & Robinson (1981).
(d) E.I. correspond to the affinity ratio of the stereoisomers (Eudismic Index).

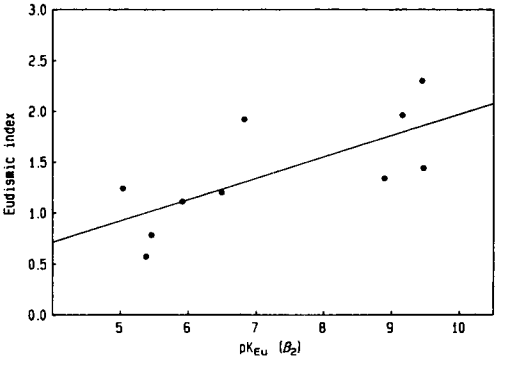

FIG. 2. Eudismic analysis (plots of EI vs pK_{Eu}) for the affinity of enantiomers to the β_2-adrenoceptors (eqn 3).

According to the concept of complementarity (Ariëns 1983) between a ligand and its specific receptor sites, a high affinity ratio of stereoisomers (i.e. eudismic index) is expected for chiral molecules whose centre of chirality plays a

determining role in the receptor-ligand fit or complementarity. In contrast, a small affinity ratio is expected for stereoisomers with low affinity and hence with relatively poor complementarity. This type of relationship appears to be common for many types of bioactive agents and is often called Pfeiffer's rule (1956). Exceptions exist (Van de Waterbeemd et al 1987) such that a low affinity ratio is observed for stereoisomers with high affinity. This "anti-Pfeiffer" behaviour is believed to result from increased affinity of the distomers when they display additional weak bonds with the receptor (mainly hydrophobic interactions) not occurring with the eutomers (Van de Waterbeemd et al 1987). Such additional interactions may well account for the fact that the enantiomers of the highly lipophilic, β_2-selective agent IPS 339 display almost identical affinities (Main & Tucker 1985).

In the same manner, we postulate that the lower eudismic index observed for β_2-adrenoceptors compared with β_1-adrenoceptors is due to a more important role played by hydrophobic interactions in β_2-adrenoceptor binding. To test this hypothesis, the role of lipophilicity in influencing affinity and β-adrenoceptor selectivity was investigated. The relationships between the receptor affinities or β_1-selectivity of these compounds with their lipophilic character were calculated, yielding equations 4–8:

β_2-adrenoceptors

$$pK_{Eu} = 1{\cdot}08(\pm 0{\cdot}49)\ \log P_{7{\cdot}4} + 8{\cdot}08(\pm 0{\cdot}79)$$
$$n = 10;\ r = 0{\cdot}874;\ s = 0{\cdot}94;\ F = 26{\cdot}0 \qquad (4)$$

$$pK_{Dis} = 0{\cdot}92(\pm 0{\cdot}32)\ \log P_{7{\cdot}4} + 6{\cdot}57(\pm 0{\cdot}52)$$
$$n = 10;\ r = 0{\cdot}920;\ s = 0{\cdot}62;\ F = 43{\cdot}8 \qquad (5)$$

β_1-adrenoceptors

$$pK_{Eu} = 0{\cdot}92 \pm (0{\cdot}44)\ \log P_{7{\cdot}4} + 7{\cdot}94(\pm 0{\cdot}71)$$
$$n = 10;\ r = 0{\cdot}863;\ s = 0{\cdot}85;\ F = 23{\cdot}4 \qquad (6)$$

$$pK_{Dis} = 0{\cdot}68(\pm 0{\cdot}26)\ \log P_{7{\cdot}4} + 5{\cdot}83(\pm 0{\cdot}43)$$
$$n = 10;\ r = 0{\cdot}904;\ s = 0{\cdot}51;\ F = 35{\cdot}6 \qquad (7)$$

β_1-selectivity

$$pK_{Eu}(\beta_1) - pK_{Eu}(\beta_2) = -0{\cdot}24(\pm 0{\cdot}08)\ \log P_{7{\cdot}4} - 0{\cdot}11(\pm 0{\cdot}11)$$
$$n = 9;\ r = -0{\cdot}942;\ s = 0{\cdot}13;\ F = 54{\cdot}8 \qquad (8)$$

Examination of equations (4–7) confirms that hydrophobic interactions play an important role in the affinity of stereoisomers at both β_1- and β_2-adrenoceptors. As postulated above, the affinity for β_2-adrenoceptors is slightly more dependent on lipophilicity, at least for the distomers. Indeed, a t-test shows that the correlation coefficients of equations 5 and 7 are significantly different ($t = 2{\cdot}49$, $P < 0{\cdot}05$) and hence that log P explains a greater percentage of the variance in equation 5 than in equation 7. This trend becomes clearer in equation 8, where an inverse linear relationship is observed between β_1-selectivity and lipophilicity of eutomers. Thus, a decrease in lipophilicity is associated with an increase in β_1-selectivity, as shown in Fig. 3. A confirmation of this hypothesis can be found in the high lipophilicity and β_2-selectivity of compounds IPS 339 and ICI 118 551 (Bree et al 1986; Main & Tucker 1985). This rule however may not be a general one being seemingly restricted to β-adrenoceptor ligands displaying an isopropyl or t-butyl amino substituent. Changing this substituent to bulkier and more lipophilic groups can also improve β_1-selectivity, in which cases the above rule no longer applies. An example is the lipophilic β_1-selective agent CGP 20712 A, 2-hydroxy-5-{2-[hydroxy-3-(4-[(1-methyl-4-trifluoromethyl)-1H-imidazol-2-yl]phenoxy)-propyl]aminoethoxyl}-benzamide (Kaumann 1986; Kaumann & Lemoine 1987).

Fig. 3 shows that adrenaline is an outlier in this relationship, and it was not included in the final equation 8. This exception is difficult to explain. An inspection of Table 1 shows that the decreased β_1-selectivity of adrenaline (in other words the ratio of β_1/β_2 affinities) relative to that of, e.g. noradrenaline or isoprenaline, is due essentially to an increased β_2-affinity of the former. These data are consistent with a particular preference of adrenaline for β_2-adrenoceptors as noted by others (Ariëns & Simonis 1983; Misu & Kubo 1986; Kaumann & Lemoine 1987). What remains unexplained, however, is the reason for this particular β_2-selectivity. Because lipophilicity cannot account for this behaviour, other structural and presumably stereoelectronic features must play a determining role. Their assessment requires further structure-activity relationship studies.

Conclusion

Interactions between ligands and receptors are so complex that they cannot be expressed in terms of a single structural factor (Van de Waterbeemd & Testa 1987). Furthermore, various ligands may display different modes of binding to a given receptor, for example phenoxypropanolamines have been suggested to bind more into the interior of β_2-adrenoceptors than do phenylethanolamines (Donné-Op den Kelder et al 1986). Similarly, it was concluded that the *N*-alkyl group in eutomeric and distomeric *N*-alkyl-3-(3-hydroxyphenyl)piperidines binds to different regions of the dopamine D_2 receptor (Van de Waterbeemd et al 1987).

From the analysis in this study, we conclude that it may be equivocal to assume "steric" differences between β_1- and β_2-adrenoceptors. In our opinion, the apparent "steric" differences between the two β-adrenoceptors subtypes arise mainly from a stronger hydrophobic component in the binding to β_2-adrenoceptors. This difference is particularly felt with the distomers for which the geometrical fit between ligand and receptor is not as good as that of the eutomers, allowing non-directional (hydrophobic) interactions to

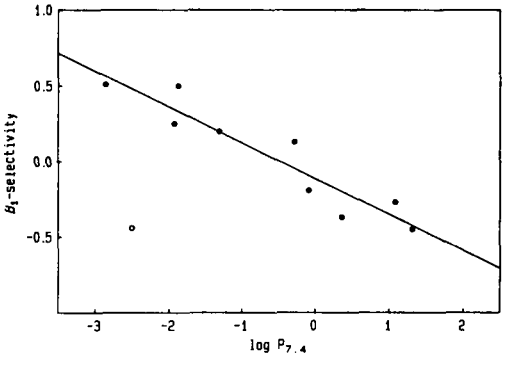

FIG. 3. Relationship between lipophilicity (log $P_{7{\cdot}4}$) and β_1-selectivity for the eutomers in Table 1 (eqn 8). Adrenaline is an outlier in this relationship.

make a proportionally larger contribution to binding energy. Another, more far-reaching implication is that the environment of the β_2-adrenoceptors might be more lipophilic than that of β_1-adrenoceptors.

Acknowledgements

BT, HVDW, PAC & NET are indebted to the Swiss National Science Foundation for research grant 3.539–0.83 and 3.508–0.86.

References

Ariëns, E. J. (1983) Stereoselectivity of bioactive agents: General aspects. In: Ariëns, E. J., Soudijn, W., Timmermans, P. B. M. W. M. (eds) Stereoselectivity and Biological Activity of Drugs. Blackwell Scientific Publications, Oxford, pp 11–32

Ariëns, E. J., Simonis, A. M. (1983) Physiological and pharmacological aspects of adrenergic receptor classification. Biochem. Pharmacol. 32: 1539–1545

Ban, T., Sada, S., Takahashi, Y., Sada, H., Fujita, T. (1985) Effects of para-substituted beta-adrenoceptor blocking agents and methyl-substituted phenoxypropanolamine derivatives on maximum upstroke velocity of action potential in guinea-pig papillary muscles. N. S. Arch. Pharmacol. 329: 77–85

Bree, F., El Tayar, N., Van de Waterbeemd, H., Testa, B., Tillement, J.-P. (1986) The binding of agonists and antagonists to rat lung beta-adrenergic receptors as investigated by thermodynamics and structure-activity relationships. J. Receptor Res. 6: 381–409

Cruickshank, J. M. (1982) The clinical implications of hydrophilicity and cardioselectivity in beta-blockers. Int. J. Clin. Pharm. Res. 11: 185–189

Dixon, R. A. F., Kobilka, B. R., Strader, D. J., Benovic, J. L., Dohlman, H. G., Frielle, T., Bolanowski, M. A., Bennett, C. D., Rands, E., Diehl, R. E., Mumford, R. A., Slater, E. E., Sigal, I. S., Caron, M. C., Lefkowitz, R. J., Strader, C. D. (1986) Cloning of the gene and cDNA for mammalian beta-adrenergic receptor and homology with rhodopsin. Nature 321: 75–79

Donné-Op den Kelder, G. M., Bijloo, G. J., Bultsma, T. (1986) 3-D receptor mapping of the skeletal muscle β_2-adrenoceptor. Eur. J. Med. Chem. 21: 475–485

Easson, L. H., Stedman, E. (1933) Studies on the relationship between chemical constitution and physiological action. V. Molecular dissymmetry and physiological activity. Biochem. J. 27: 1257–1266

IJzerman, A. P., Aué, G. H. J., Bultsma, T., Linschoten, M. R., Timmerman, H. (1985) Quantitative evaluation of the β_2-adrenoceptor affinity of phenoxypropanolamines and phenylethanolamines. J. Med. Chem. 28: 1328–1334

Kaumann, A. J. (1986) The β_1-adrenoceptor antagonist CGP 20712 A unmasks β_2-adrenoceptors activated by (−)-adrenaline in rat sinoatrial node. N. S. Arch. Pharmacol. 332: 406–409

Kaumann, A. J., Birnbaumer, L. (1974) Studies on receptor-mediated activation of adenylyl cyclases. Stereo specificity and determination of apparent affinity constants for beta-blockers. J. Biol. Chem. 249: 7874–7885

Kaumann, A. J., Lemoine, H. (1987) β_2-Adrenoceptor-mediated positive inotropic effect of adrenaline in human ventricular myocardium. Quantitative discrepancies with binding and adenylate cyclase stimulation. N. S. Arch. Pharmacol. 335: 403–411

Kenakin, T. P. (1986) Tissue and receptor selectivity: Similarities and differences. In: Testa, B. (ed) Advances in Drug Research. vol. 15, Academic Press, London, pp 71–109

Lands, A. M., Arnold, A., McAuliff, J. P., Luduena, F. P., Brown, T. G. (1967) Differentiation of receptor systems activated by sympatomimetic amines. Nature 214: 597–598

Lehmann, P. A. (1987) A quantitative stereo-structure activity relationship. Analysis of the binding of promiscuous chiral ligands to different receptors. Quant. Struct.-Act. Relat. 6: 57–65

Lehmann, P. A., Rodriques de Miranda, J. F., Ariëns, E. J. (1976) Stereoselectivity and affinity in molecular pharmacology. In: Jucker, E. (ed) Progress in Drug Research. vol. 20 Birkhäuser Verlag, Basel, pp 101–126

Lemoine, H., Kaumann, A. J. (1983) A model for the interaction of competitive antagonists with two receptor-subtypes characterized by a Schild-plot with apparent slope unity. Agonist-dependent enantiomeric affinity ratios for bupranolol in trachea but not in right atria of guinea pigs. N. S. Arch Pharmacol. 322: 111–120

Lemoine, H., Ehle, B., Kaumann, A. J. (1985) Direct labelling of β_2-adrenoceptors. Comparison of binding potency of ^{3}H-ICI 118 551 and blocking potency of ICI 118 551. Ibid. 331: 40–51

Luduena, F. B., Ananenko, E., Siegmund, O. H., Miller, L. C. (1949) Comparative pharmacology of the optical isomers of arterenol. J. Pharmacol. Exp. Ther. 95: 155–170

Machin, P. J., Hurst, D. N., Bradshaw, R. M., Blaber, L. C., Burden, D. T., Melarange, R. A. (1984) β_1-Selective adrenoceptor antagonists. 3. 4-Azolyl-linked phenoxypropanolamines. J. Med. Chem. 27: 503–509

Main, B. G., Tucker, H. (1985) Recent advances in β-adrenergic blocking agents. Progr. Med. Chem. 22: 121–164

Minneman, K. P., Hegstrand, L. R., Molinoff, P. B. (1979) Simultaneous determination of beta-1 and beta-2 adrenergic receptors in tissues containing both receptor subtypes. Mol. Pharmacol. 16: 34–46

Misu, Y., Kubo, T. (1986) Presynaptic β-adrenoceptors. Med. Res. Rev. 6: 197–225

Morris, T. H., Kaumann, A. J. (1984) Different steric characteristics of β_1- and β_2-adrenoceptors. N. S. Arch. Pharmacol. 327: 176–179

Patil, P. N., Miller, D. D., Trendelenburg, U. (1975) Molecular geometry and adrenergic drug activity. Pharmacol. Rev. 26: 323–392

Pfeiffer, C. C. (1956) Optical isomerism and pharmacological action. Science 124: 29–31

Quast, U., Vollmer, K. O. (1984) Binding of β-adrenoceptor antagonists to rat and rabbit lung: Special reference to levobunolol. Drug Res. 34: 579–586

Rzeszotarski, W. J., Gibson, R. E., Simms, D. A., Jagoda, E. M., Vaughan, J. N., Eckelman, W. C. (1983) Cardioselectivity of β-adrenoceptor blocking agents. 2. Role of the amino group substituent. J. Med. Chem. 26: 644–648

Rugg, E. L., Barnett, D. B., Nahorski, S. R. (1978) Coexistence of beta$_1$ and beta$_2$ adrenoceptors in mammalian lung: Evidence from direct binding studies. Mol. Pharmacol. 14: 996–1005

Smith, L. H. (1978) Cardio-selective β-adrenergic blocking agents. J. Appl. Chem. Biotechnol. 28: 201–212

Stiles, G. L., Strasser, R. H. Caron, M. C., Lefkowitz, R. J. (1983) Mammalian β-adrenergic receptors. Structural differences in β_1 and β_2 subtypes revealed by peptide maps. J. Biol. Chem. 258: 10689–10694

Van de Waterbeemd, H., Testa, B. (1987) The parametrization of lipophilicity and other structural properties in drug design. In: Testa, B. (ed) Advances in Drug Research. vol. 16, Academic Press, London, p. 85–225

Van de Waterbeemd, H., El Tayar, N., Testa, B., Wikström, H., Largent, B. (1987) Quantitative structure-activity relationships and eudismic analyses of the presynaptic dopaminergic activity and dopamine D2 and sigma receptor affinities of 3-(3-hydroxyphenyl)piperidine and octahydrobenzo(f)quinolines. J. Med. Chem. 30: 2175–2181

Walter, M., Lemoine, H., Kaumann A.J. (1984) Stimulation and blocking effects of optical isomers of pindolol on the sinoatrial node and trachea of guinea pig. Role of β-adrenoceptor subtypes in the dissociation between blockade and stimulation. N. S. Arch Pharmacol. 327: 159–175

Woods, P. B., Robinson, M. L. (1981) An investigation of the comparative liposolubilities of β-adrenoceptor blocking agents. J. Pharm. Pharmacol. 33: 172–173