J. Pharm. Pharmacol. 1995, 47: 232–236
Received March 18, 1994
Accepted September 6, 1994

Correlation of Pharmacological Properties of a Group of β-Blocker Agents by Molecular Topology

F. J. GARCÍA-MARCH, R. A. CERCÓS-DEL-POZO, F. PÉREZ-GIMÉNEZ, M. T. SALABERT-SALVADOR, J. JAÉN-OLTRA AND G. M. ANTÓN-FOS

Unit of Drug-design and Molecular Connectivity Investigation, Department of Physical Chemistry, Faculty of Pharmacy, University of Valencia, Valencia, Spain

Abstract

The molecular connectivity method has been applied to the study of pharmacological properties, among which are found the angor treatment dose, α-distribution half-life and intravenous LD50 in mouse, of a group of β-blocker agents, verifying its application in the prediction of theoretic values for said pharmacological properties.

To do this, the obtained multiple regression functions of the corresponding connectivity indices were used in relation with the experimental values of the properties, which are accompanied by the statistical parameters used in their selection criteria, as well as the corresponding random and cross-validation studies of said functions, which corroborate the good correlation of the selected equations.

Quantitative structure-activity relationship (QSAR) studies are used to explain or predict the physicochemical (Soler et al 1992) or pharmacological (García et al 1991; Antón-Fos et al 1992) behaviour of drug molecules.

Molecular connectivity is a topological method able to describe the structure of a molecule by means of numbers called indices (χi), calculated starting from the graph of the suppressed hydrogens of the molecule being studied, which subsequently regress in relation with the experimental values of the physical, chemical or biological properties in order to obtain some functions, called connectivity functions (Kier & Hall 1976).

During the last few years, molecular connectivity indices have been used to predict several parameters related to biological activities of drugs (Kier & Hall 1986).

In this study, we examined the relation between different pharmacological properties and the connectivity indices of a group of β-blocker agents.

Obtaining good correlations for the connectivity functions allows their utilization for the prediction of the pharmacological activities of new molecules in the same structural and therapeutic group.

Method of Calculation

Several extensive reviews have been published (Wilson 1972; Trinasjstic 1983; Kier & Hall 1986; García et al 1991) which give detailed descriptions of the theory and method of calculation of all valence and non-valence molecular connectivity indices used in this investigation.

The connectivity indices are defined by the general equation:

Correspondence: F. J. García March, Departamento de Química-Física, Facultad de Farmacia, Avenida Vicente Andrés Estelles s/n, Burjassot 46100 Valencia, Spain.

$$ {}^{m}\chi_t = \sum_{j=1}^{n_m} {}^{m}S_j \quad (1) $$

where m is the order of a subgraph, i.e. number of edges of a subgraph; n_m is the number of type t subgraphs of order m; and ${}^{m}S_j$ is the quantity calculated for each subgraph and defined by:

$$ {}^{m}S_j = \left[\prod_{i=1}^{m+1} (\delta_i) \right]^{\frac{1}{2}} \quad (2) $$

where j denotes the particular set of edges that constitute the subgraph and δ_i is the vertex valence.

The vertex valences, δ^v, of the unsaturated carbon atoms and the heteroatoms (N, S, O) can be calculated using:

$$ \delta^v = Z^v - H \quad (3) $$

where Z^v is the number of valence electrons of the atom and H is the number of hydrogen atoms attached to it. The empirically derived values for the halogens were also used (Kier & Hall 1986).

We used $8\ {}^{m}\chi_t$ indices in our study, ranging from 0 to 4, whose types are: path, cluster and path-cluster.

A single multiple regression analysis was used to find the relationship between the pharmacological properties of β-blocker agents and the connectivity indices, and are calculated from equation 4:

$$ C(\chi) = P = A_0 + \sum_{i=1}^{n} A_i \cdot \chi_t \quad (4) $$

where P is a property and A_0 and A_i represent the regression coefficients of the obtained equation. Once the connectivity function (eqn 4) is established, its value for a specific molecule may be predicted.

The connectivity indices that were used in this study (Table 1) were calculated using equations 1, 2 and 3, and

Table 1. Connectivity indices used in the correlations of a group of β-blocker agents.

Compound	$^0\chi^v$	$^1\chi$	$^1\chi^v$	$^3\chi_c$	$^3\chi_c{}^v$	$^4\chi_c{}^v$	$^4\chi_{pc}$	$^4\chi_{pc}{}^v$
Acebutolol	14·180	9·273	7·821	1·343	0·806	0·000	1·831	1·019
Alprenolol	11·225	7·308	6·362	0·901	0·588	0·000	1·208	0·691
Amosualalol	15·088	10·504	8·539	1·971	0·828	0·035	2·616	1·455
Atenolol	11·426	7·692	6·386	1·183	0·687	0·000	1·236	0·685
Betaxolol	13·755	9·710	8·341	1·749	1·420	0·000	1·424	0·834
Bunitrolol	11·104	6·967	5·972	2·024	1·510	0·250	1·575	0·932
Bunolol	13·109	8·656	7·576	2·237	1·671	0·250	2·138	1·377
Bupranolol	12·283	7·339	5·511	2·262	1·778	0·250	1·891	1·275
Clenbuterol	11·871	6·783	6·206	2·275	1·857	0·250	2·362	1·694
Esmolol	12·964	8·753	7·209	1·109	0·663	0·000	1·438	0·768
Labetalol	13·775	9·274	8·052	1·100	0·705	0·000	1·978	1·225
Mabuterol	13·301	8·033	6·421	3·453	1·890	0·263	3·180	1·680
Mepindolol	11·734	7·839	6·686	1·177	0·765	0·000	1·583	0·945
Metipranolol	14·318	8·948	7·554	1·532	1·005	0·000	2·347	1·520
Metoprolol	12·056	8·192	6·736	0·933	0·604	0·000	1·136	0·667
Nadolol	13·542	9·357	7·788	2·613	1·839	0·250	2·972	1·636
Oxprenolol	11·634	7·808	6·501	0·901	0·536	0·000	1·221	0·589
Penbutolol	13·451	8·884	7·570	2·131	1·563	0·250	1·873	1·205
Pindolol	10·811	7·438	6·269	0·973	0·621	0·000	1·393	0·812
Practolol	11·642	7·692	6·390	1·183	0·671	0·000	1·236	0·637
Pronethalol	10·350	6·653	6·067	0·875	0·643	0·000	1·315	0·948
Propranolol	11·466	7·632	6·686	0·954	0·632	0·000	1·342	0·843
Sotalol	11·125	7·366	6·289	2·387	1·017	0·061	1·669	0·892
Timolol	13·430	9·350	7·701	2·179	1·587	0·250	2·064	1·194
Tolamolol	14·274	9·853	8·159	0·913	0·543	0·000	1·631	0·885

computer software developed in our department (Ciudad et al 1987). The connectivity function (eqn 4) was obtained by multilinear regression with the BMDP 9R program of the biostatic package BMDP (Biomedical Computer Programs) (Dixon 1982). To test the quality of the regression equations, the following statistical parameters were used: multiple correlation coefficient (r), standard error of estimate (s.e.), F-Snedecor function values (F), Mallow's CP and Student's *t*-test (statistical significance), as well as the corresponding cross-validation studies of the selected functions.

Random and cross-validation studies were performed on the selected equations which are described as follows.

Randomness was achieved by randomly modifying the value of the independent variables which intervene in the equation, subsequently modifying the value of the dependent (property), also done randomly, after each modification the BMDP 9R was executed, passing on to compare the calculated correlation coefficient with the one obtained for the selected equation (Topliss & Costello 1972).

Cross validation was assessed using the jackknife method of Gray & Shucany (1972). The elimination of n observations was effected, by means of a random process, and a regression program was executed, repeating the process as many times as was necessary until all the observations had been eliminated a minimum of one time and a maximum of four times, finally comparing the coefficients of the calculated independent variables, the correlation coefficients, standard deviations and the residuals, with those obtained in the selected equation.

The following pharmacological properties were investigated: angor treatment dose (mg day^{-1}), α-distribution half-life ($t^{\frac{1}{2}}_{\alpha}$) (h), and intravenous LD50 in mice (mg kg^{-1}). The experimental values for these properties were obtained from different bibliographic sources (Shing & Jewitt 1974; Opie 1980; Wood 1984; Benfield et al 1986; Lennard et al 1986).

Results and Discussion

The molecular connectivity indices and the experimental values of the pharmacological properties for a group of β-blocker agents, are shown in Tables 1 and 2, respectively.

Good correlation equations were verified for most pharmacological properties. Both the order and number of connectivity indices were varied.

Table 2. Experimental values for several pharmacological properties of β-blocker agents using the molecular connectivity method.

Compound	LD50 (mg kg^{-1})	Angor treatment dose (mg day^{-1})	$t^{\frac{1}{2}}_{\alpha}$ (h)
Acebutolol	—	800	0·450
Alprenolol	23	—	—
Amosualalol	—	—	0·260
Atenolol	—	100	0·330
Betaxolol	—	—	3·600
Bunitrolol	48	—	—
Bunolol	46	—	—
Bupranolol	45	—	—
Clenbuterol	—	—	1·000
Esmolol	—	—	0·030
Labetalol	—	300	—
Mabuterol	120	—	1·120
Mepindolol	—	—	0·184
Metipranolol	31	—	0·330
Metoprolol	—	200	0·200
Nadolol	—	100	—
Oxprenolol	20	160	0·300
Penbutolol	44	—	2·050
Pindolol	26	10	0·085
Practolol	95	—	0·083
Pronethalol	31	—	—
Propranolol	24	120	0·160
Sotalol	166	240	0·560
Timolol	36	15	—
Tolamolol	—	—	0·116

Table 3. Correlation coefficients computed from random number variables for a three-variable model of β-blocker agents: angor treatment dose, $t^{l}_{i\alpha}$ and LD50 value data.

Range of r	Modification variable					
	Independent (100 runs)			Dependent (100 runs)		
	Number of values			Number of values		
	Angor treatment dose	$t^{l}_{i\alpha}$	LD50	Angor treatment dose	$t^{l}_{i\alpha}$	LD50
< 0·1	2	1	0	4	0	3
0·1–0·2	9	5	2	12	10	3
0·2–0·3	16	17	9	16	14	15
0·3–0·4	19	29	20	22	20	30
0·4–0·5	18	26	27	19	25	25
0·5–0·6	21	13	19	12	17	14
0·6–0·7	13	9	16	7	11	5
0·7–0·8	1	0	6	6	3	4
0·8–0·9	1	0	1	2	0	1
> 0·9	0	0	0	0	0	0

The selected equation for the angor treatment dose (ATD) of the compounds studied was:

$$ATD = (799{\cdot}99 \pm 107{\cdot}93)\,{}^{0}\chi^{v} - (1034{\cdot}24 \pm 155{\cdot}43)\,{}^{1}\chi - (1047{\cdot}00 \pm 268{\cdot}92) \quad (5)$$

The statistical parameters for equation 5 were: n = 10; r = 0·949; s.e. = 81·30; DF = 9; F = 32·04; CP = 4 and $P < 0{\cdot}001$. For ${}^{0}\chi^{v}$, $t = 7{\cdot}41$ ($P < 0{\cdot}001$) and for ${}^{1}\chi$ $t = 6{\cdot}65$ ($P < 0{\cdot}001$).

For the α-distribution half-life ($t^{l}_{i\alpha}$) values, the best regression equation was:

$$t^{l}_{i\alpha} (0{\cdot}61 \pm 0{\cdot}10)\,{}^{1}\chi^{v} + (2{\cdot}75 + 0{\cdot}26)\,{}^{3}\chi^{v}_{c} - (2{\cdot}28 \pm 0{\cdot}32)\,{}^{4}\chi_{pc}v - (3{\cdot}97 \pm 0{\cdot}69) \quad (6)$$

The statistical parameters for equation 6 were: n = 17; r = 0·955; s.e. = 0·30; DF = 16; F = 45·31; CP = 4; and $P < 0{\cdot}001$. For ${}^{1}\chi^{v}$, $t = 6{\cdot}20$ ($P < 0{\cdot}001$), for ${}^{1}\chi^{v}_{c}$, $t = 10{\cdot}70$ ($P < 0{\cdot}001$), and for ${}^{4}\chi_{pc}v$, $t = 7{\cdot}07$ ($P < 0{\cdot}001$).

The selected equation for the intravenous LD50 in mouse was:

$$LD50 = (133{\cdot}64 \pm 11{\cdot}25)\,{}^{3}\chi_{c} - (428{\cdot}07 \pm 47{\cdot}21)\,{}^{4}\chi^{v}_{c} - (72{\cdot}19 \pm 11{\cdot}48)\,{}^{4}\chi_{pc} - (0{\cdot}84 \pm 11{\cdot}65) \quad (7)$$

The statistical parameters for equation 7 were: n = 14; r = 0·971; s.e. = 11·81; DF = 13; F = 54·13; CP = 4; and $P < 0{\cdot}001$. For ${}^{3}\chi_{c}$, $t = 11{\cdot}88$ ($P < 0{\cdot}001$), for, ${}^{4}\chi^{v}_{c}$, $t = 9{\cdot}07$ ($P < 0{\cdot}001$), and for, ${}^{4}\chi_{pc}$, $t = 6{\cdot}29$ ($P < 0{\cdot}001$).

The study of randomness of these equations (Table 3) demonstrates their non-randomness.

In the case of angor treatment dose, one correlation coefficient > 0·8 is obtained when the independent variable is studied and two correlation coefficients > 0·8 when the dependent variable is studied; therefore, the probability (P) that a correlation coefficient > 0·9 can be obtained is < 0·01 and < 0·02, respectively. For the $t^{l}_{i\alpha}$, nine correlation coefficients > 0·6 are obtained when the independent variable is studied and three correlation coefficients > 0·7 when the dependent variable is studied; therefore, the probability that a correlation coefficient > 0·9 may be obtained is > 0·09 and > 0·03, respectively. In the case of the LD50, one correlation coefficient > 0·8 is obtained when the independent variable is studied and one correlation coefficient > 0·8 when the dependent variable is studied; therefore, the probability that a correlation coefficient > 0·9 can be obtained is < 0·01 and < 0·01, respectively.

The cross-validation study of the selected equations was

Table 4. Statistical stability test information of the regression model for values of β-blocker agents.

	Original model (no deletions)		One deletion per run (10 runs)	
	Regression value	Standard deviation	Regression value	Standard deviation
Correlation coefficient	0·949		0·947	0·024
Standard deviation	81·296		79·263	11.285
Coefficient of ${}^{0}\chi^{v}$	799.984	107·930	782·935	95·152
Coefficient of ${}^{1}\chi$	− 1034·230	155·426	− 1012·238	122·204
Constant	− 1047·330	268·926	− 1022·301	189.373
Average residual	55·310	13·196	56·793	
Residuals less than one standard deviation	70·00%		66·00%	
Residuals between one and two standard deviations	30·00%		33·00%	
Residuals greater than two standard deviations	0%		1·00%	

Table 5. Statistical stability test information of the regression model for $t^{l}_{\frac{1}{2}\alpha}$ values of β-blocker agents.

	Original model (no deletions)		Two deletions per run (17 runs)	
	Regression value	Standard deviation	Regression value	Standard deviation
Correlation coefficient	0·955		0·954	0·009
Standard deviation	0·301		0·285	0·045
Coefficient of $^{1}\chi^{v}$	0·610	0·098	0·554	0·113
Coefficient of $^{3}\chi_{c}{}^{v}$	2·751	0·257	2·597	0·347
Coefficient of $^{4}\chi_{pc}{}^{v}$	−2·278	0·322	−2·095	0·412
Constant	−3·967	0·694	−3·624	0·671
Average residual	0·223	0·035	0·225	
Residuals less than one standard deviation	70·59%		72·32%	
Residuals between one and two standard deviations	29·41%		26·30%	
Residuals greater than two standard deviations	0%		1·38%	

carried out varying the number of eliminations made and the number of runs for each property in particular, observing that by raising the number of eliminations the model was made more unstable; this was to be expected because the degrees of freedom were considerably diminished. Thus, in the case of the angor treatment dose, $t^{l}_{\frac{1}{2}\alpha}$ and LD50 the corresponding stability of one, two, and two eliminations was chosen which was repeated a total of 10, 17 and 14 runs, respectively, corresponding in all cases, to approximately 10% of the eliminated observations, a value recommended by some authors (Kier & Hall 1986) (Tables 4, 5, 6). The comparison of the results between the obtained values for the selected model and the model of one- or two-eliminations, depending on which cases, show that the selected equations are very stable as is made patent by the equality of the obtained terms, as well as by the low standard deviations in each one of them. The analysis of the obtained residuals for the selected model as well as for the one or two elimination model, manifest minimum discrepancies in the measures as well as in their standard deviation, an aspect of the study which strengthens the predictive quality of the model.

The contribution of the index $^{0}\chi^{v}$ (eqn 5) to the value of the property is positive, which means that molecules with a high value of this index will possess high treatment dose values, for example acebutolol ($^{0}\chi^{v} = 14{\cdot}18$ and ATD = 800 mg day^{-1}) and labetalol ($^{0}\chi^{v} = 13{\cdot}77$ and ATD = 300 mg day^{-1}). Other molecules, such as timolol and nadolol, present a low value for the property (ATD = 15 and 100 mg day^{-1}, respectively), even when having a high $^{0}\chi^{v}$ index value (13·43 and 13·54, respectively); in these cases, index $^{1}\chi$, which contributes negatively to the regression equation, also possesses a high value (9·35 and 9·36, respectively). Molecules with low $^{0}\chi^{v}$ values, such as pindolol ($^{0}\chi^{v} = 10{\cdot}81$) have low values for this property (ATD = 10 mg day^{-1}).

The greatest contribution in equation 6 comes from the index $^{3}\chi_{c}^{v}$, a structural parameter which gives information about the ramifications of the molecules. Molecules with high index values such as betaxolol ($^{3}\chi_{c}^{v} = 1{\cdot}42$), clenbuterol ($^{3}\chi_{c}^{v} = 1{\cdot}86$), mabuterol ($^{3}\chi_{c}^{v} = 1{\cdot}89$) and penbutolol ($^{3}\chi_{c}^{v} = 1{\cdot}56$) are expected to have high $t^{l}_{\frac{1}{2}\alpha}$ values, and effectively this is what occurs (3·60, 1·00, 1·12 and 2·05 h, respectively).

Of the indices that appear in equation, index $^{3}\chi_{c}$ is the one with the greatest contribution to the value of the property. This means that the molecules with a high value of this index, as its contribution is positive, will have high LD50 values in mouse, as is confirmed by the values corresponding to mabuterol ($^{3}\chi_{c} = 3{\cdot}45$, LD50 = 120 mg kg^{-1}) and sotalol ($^{3}\chi_{c} = 2{\cdot}39$, LD50 = 166 mg kg^{-1}). Molecules with a low $^{3}\chi_{c}$ index such as alprenolol ($^{3}\chi_{c} = 0{\cdot}90$), oxprenolol ($^{3}\chi_{c} = 0{\cdot}90$) or pro-

Table 6. Statistical stability test information of the regression model for LD50 values of β-blocker agents.

	Original model (no deletions)		Two deletions per run (14 runs)	
	Regression value	Standard deviation	Regression value	Standard deviation
Correlation coefficient	0·971		0·972	0·017
Standard deviation	11·810		11·004	2·378
Coefficient of $^{3}\chi_{c}$	133·637	11·246	134·865	9·147
Coefficient of $^{4}\chi_{c}{}^{v}$	−427·067	47·207	−431·127	33·867
Coefficient of $^{4}\chi_{pc}$	−72·194	11·475	−73·045	7·747
Constant	−0·842	11·648	−1·193	12·644
Average residual	7·418	1·852	7·734	
Residuals less than one standard deviation	85·71%		77·04%	
Residuals between one and two standard deviations	7·14%		16·33%	
Residuals greater than two standard deviations	7·14%		6·63%	

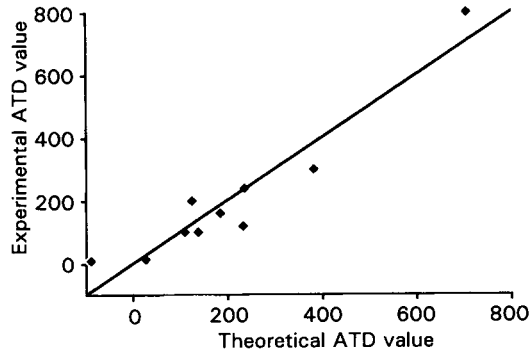

FIG. 1. Correlation between experimental and calculated values (eqn 5) corresponding to the angor treatment dose (mg day^{-1}).

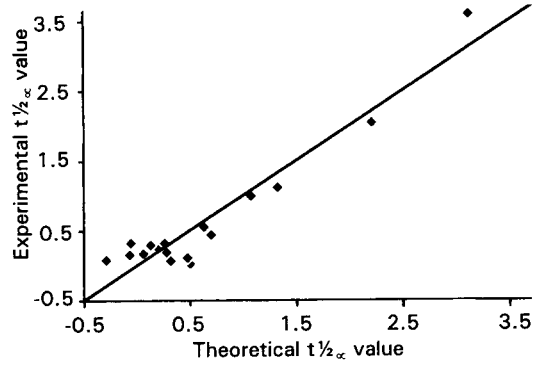

FIG. 2. Correlation between experimental and calculated values (eqn 6) corresponding to the $t_{\frac{1}{2}\alpha}$ (h).

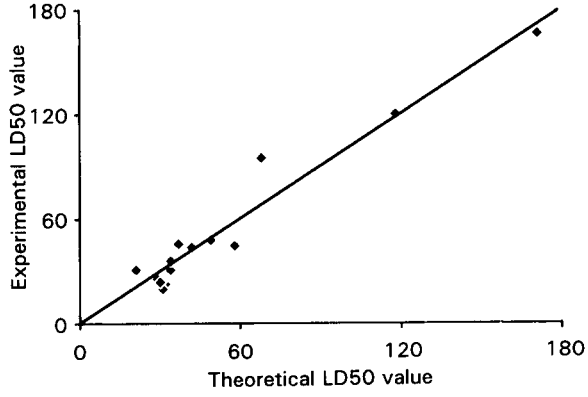

FIG. 3. Correlation between experimental and calculated values (eqn 7) corresponding to the intravenous LD50 in mouse (mg kg^{-1}).

nethalol ($^3\chi_c = 0{\cdot}87$) will also have low values for this property (23, 20 and 31 mg kg^{-1}, respectively).

The comparison between experimental and theoretical values for this property following equations 5, 6 and 7 are given in Figs 1, 2 and 3, respectively.

Conclusion

The molecular connectivity method has been applied to the correlation of different pharmacological properties of a group of β-blocker agents, obtaining good agreement between experimental and theoretical values, as well as a favourable response to the random and cross-validation studies carried out. This would seem to allow the use of such equations as models for prediction of structures with relevant pharmacological activity.

Acknowledgements

The authors wish to thank Comision Interministerial de Cienca y Tecnologia, SAF92-0684 (Spanish Ministry of Science and Education) for its economical support of their effort.

References

Antón-Fos, G. M., Garcia-Doménech, R., Pérez-Giménez, F., Garcia-March, F. J., Soler-Roca, R. M., Salabert-Salvador, M. T., Gálvez-Alvarez, J. (1992) Estudios de prección de propiedades farmacocinéticas de hipoglucemiantes orales utilizando relaciones Q.S.A.R. An. Real Acad. Farm. 58: 551–562

Benfield, P., Clissold, S. P., Brogden, R. N. (1986) Metoprolol, an updated review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. Drugs 31: 376–429

Ciudad, J., García, R., Gálvez, J. (1987) Algoritmo para el cálculo de los indices de conectividad. Su aplicación a la determinación de la refracción molar de un grupo de moleculas. An. Quim. 83: 385–389

Dixon, W. J. (1982) BMD Manual: Biomedical Computer Programs. University of California Press, Los Angeles, CA

Garcia, R., Gálvez, J., Moliner, R., Garcia, F. J. (1991) Prediction and interpretation of some pharmacological properties of cephalosporins using molecular connectivity. Drug Invest. 3: 344–350

Gray, H. L., Shucany, W. R. (1972) The Generalized Jackknife Statistic. Marcel-Dekker, Inc., New York

Kier, L. B., Hall, L. H. (1976) Molecular Connectivity in Chemistry and Drug Research. Academic Press, New York

Kier, L. B., Hall, L. H. (1986) Molecular Connectivity in Structure-Activity Analysis. Research Studies Press, Letchworth

Lennard, K. S., Tucker, G. T., Wood, H. F. (1986) The polymorphic oxidation of β-adrenoceptor antagonist. Clinical pharmacokinetic considerations. Clin. Pharmacokinet. 11: 1–17

Opie, L. H. (1980) Drugs and the heart I. Beta blocking agents. The Lancet 1: 693–698

Shing, B. N., Jewitt, D. E. (1974) Beta adrenergic receptor blocking drugs in cardiaca arrhytmias. Drugs 7: 426–461

Soler, R. M., García, F. J., Antón, G. M., García, R., Pérez, F., Gálvez, J. (1992) Molecular topology and chromatographic retention parameters for benzodiazepines. J. Chromatogr. 607: 91–95

Topliss, J., Costello, R. (1972) Chance factors in studies on quantitative structure-activity relationships. J. Med. Chem. 15: 1066–1072

Trinasjstic, N. (1983) Chemical Graph Theory. CRC Press, Boca Ratón, FL

Wilson, R. (1972) Introduction to Graph Theory. Academic Press, New York

Wood, A. J. J. (1984) Pharmacologic differents between β-blockers. Am. Heart. J. 108: 1070–1077