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# MOLECULAR CONNECTIVITY TO FIND β-BLOCKERS WITH LOW TOXICITY

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**Abstract:** Molecular connectivity has been used to find new β-blocker drugs using linear discriminant analysis and connectivity functions with different topological descriptors. Among the selected compounds stands out the probucol and the β-carotene. Both of them interact with β adrenoceptors. 

Molecular Connectivity is a useful tool to describe molecular structure, and has shown its efficiency to analyze QSAR data. One of the most interesting advantages of molecular topology is the straightforward calculation of the topological descriptors. In this work all of them are derived from the adjacency matrix.

Topological indices have shown their usefulness in the[1] prediction of diverse physical, chemical and biological properties of various types of compounds[1-3]. In recent studies it has been demonstrated through the design of new antivirals[4,5], hypoglycaemics[6] and analgesics[7,8] which can be considered as lead drugs.

In this work we present a β-blocker study. They are effective for hypertension, angina pectoris and arrhythmia. Their application as preventives in post heart attack has been clinically demonstrated for some of them. However, they show secondary effects which may affect the bronchial tubes and the pancreas, due to the presence of β receptors in those organs. This may be important in asthmatic and diabetic patients. All this makes interesting to study this group in order to find new drugs.

The first step is the search of connectivity functions which are able to discriminate whether a particular compound has a β-blocker activity or not. We use stepwise linear discriminant analysis, SLDA, and multilinear regression analysis, MLRA. In a second step, we proceed to the search of chemical structures and their subsequent selection if they pass the discriminant functions. The found compounds should be finally submitted to standard pharmacological tests in order to corroborate their theoretical behaviour.

*Calculation of Topological Descriptors.*

In this work we have used Kier and Hall's connectivity indices[9], the Wiener's number[10] W, as well as the more recently introduced charge[5,11] and geometrical indices[2,7,12]

It is known that the molecular charge distribution plays an important role in many biological and pharmacological activities. It can be assessed through physicochemical parameters such as dipole moment and

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electronic polarizability. In previous papers[5,11] topological charge indices, T.C.I., were defined. Their ability to evaluate global charge transfer was demonstrated by the good correlation obtained between T.C.I. and dipole moment for a heterogeneous set of hydrocarbon compounds[11].

The topological charge indices Gk and Jk are defined as:

$$Gk = \sum_{i=1,j=i+1}^{i=N-1,j=N} |CTij| \delta(k, Dij) \qquad \text{Eq.1}$$

and

$$Jk = \frac{Gk}{(N-1)} \qquad \text{Eq.2}$$

where N= Number of vertices (atoms different to hydrogen) and CTij = mij - mji, where "m" stands for the elements of the M matrix:

$$M = A \times D^{*} \qquad \text{Eq.3}$$

where A = Adjacency N x N matrix, D*= matrix of inverse square distances, in which their diagonal entries are assigned as 0 and $\delta$ = Kronecker's delta.

Hence, Gk represents the sum of all the CTij terms, with Dij = k, Dij being the entries of the topological distance matrix.

Since geometrical factors, such as the molecular shape, may condition the pharmacological activity, a simple set of descriptors named geometrical indices was also introduced[5]. In this work the PR2 descriptor was particularly useful (PR2=number of pairs of ramifications separated by two edges).

Once each β-blocker has been topologically characterized, we proceeded to compile pharmacological information of the group. It can be shown predictive results obtained with the acute toxicity LD50. To obtain the connectivity function between the LD50 and the topological indices we used multiple linear regression.

The election of the connectivity function was carried out following the criterion used habitually with the BMDP 9R package[13], that is, minimization of Malow's Cp parameter,.

The connectivity functions chosen were:

$$1/\log LD50iv = 2.31 - 0.32\,(^{1}\chi - {}^{1}\chi^{v}) - 1.89\,{}^{1}\chi\,{}^{1}\chi^{v} - 0.28\,{}^{3}\chi_{c}\,{}^{3}\chi_{c}^{v} - 0.51\,({}^{4}\chi_{p} - {}^{4}\chi_{p}^{v}) \qquad \text{Eq.4}$$

N = 18 r = 0.9164 SE = 0.049 F = 17.1 p<0.0001

$$\log LD50or = 1.56 + 1.79\,{}^{1}\chi - 1.81\,{}^{1}\chi^{v} + 0.36\,{}^{2}\chi_{c} + 2.37\,{}^{4}\chi_{p}^{v} - 2.76\,{}^{4}\chi_{p} \qquad \text{Eq.5}$$

N = 17 r = 0.9052 SE = 0.208 F = 10.1 p = 0.0008

Table 1 shows the predicted results for this property LD50iv (intravenous) and LD50or (oral) both in mice. The accuracy of prediction for LD50 is quite acceptable considering the wide range of the property value (117<LD50or<4500), therefore Eq.4 and Eq.5 provide excellent discrimination between toxic compounds (low LD50 values) and innocuous compounds (high LD50 values). In addition, these functions allow to predict the values of LD50 with compounds which have not been included in the regressions (see test group in table 1).

Table 1.- Results of the LD50, (mg/kg in mice) and predicted values, for a set of compounds showing β-blocker activity.

| Compound | LD50iv[a] | LD50iv[b] | Residual | LD50or[a] | LD50or[c] | Residual |
|---|---|---|---|---|---|---|
| | | | Training Group | | | |
| Acebutolol | 76.0[d] | 82.2 | -6.2 | - | - | - |
| Alprenolol | - | - | - | 278.0 | 415.1 | -137.1 |
| Arotinolol | 86.0 | 57.8 | 28.2 | - | - | - |
| Atenolol | 98.7 | 84.5 | 14.2 | 2000.0 | 1993.6 | 6.3 |
| Befunolol | 102.0 | 75.1 | 26.8 | - | - | - |
| Betaxolol | 37.0 | 38.0 | -1.0 | 944.0 | 624.8 | 319.2 |
| Bufetolol | - | - | - | 409.0 | 237.7 | 171.2 |
| Bufuralol | 29.7 | 25.9 | 3.8 | 117.0 | 272.9 | -155.9 |
| Bunitrolol | - | - | - | 1349.0 | 998.3 | 350.7 |
| Butidrine | 20.2 | 24.6 | -4.4 | 235.0 | 211.7 | 23.3 |
| Carteolol | 54.5 | 39.4 | 15.1 | 810.0 | 656.1 | 153.9 |
| Indenolol | 26.0 | 32.4 | -6.4 | - | - | - |
| Labetanol | 47.0 | 51.1 | -4.1 | 1450.0 | 1373.5 | 76.5 |
| Metipranolol | 31.0 | 38.8 | -7.8 | - | - | - |
| Metoprolol | 118.0 | 292.1 | -174.1 | 2090.0 | 3060.6 | -970.6 |
| Nadolol | - | - | - | 4500.0 | 2708.1 | 1791.9 |
| Nadoxolol | 180.0 | 119.0 | 61.0 | 1000.0 | 710.3 | 289.7 |
| Nipradilol | 74.0 | 63.6 | 10.4 | 540.0 | 742.2 | -202.2 |
| Pronethanol | 46.0 | 38.0 | 8.0 | 512.0 | 486.4 | 25.6 |
| Propranolol | 22.0 | 34.1 | -12.1 | 565.0 | 403.7 | 161.3 |
| Sotalol | - | - | - | 2600.0 | 2631.6 | -31.6 |
| Talinolol | 25.0 | 25.8 | -.8 | 593.0 | 1048.5 | -455.5 |
| Tertatolol | 37.0 | 34.1 | 2.9 | - | - | - |
| | | | Test Group | | | |
| Bopindolol | 17.0 | 15.9 | 1.1 | - | - | - |
| Bucumolol | 33.1 | 46.8 | -13.7 | 676.0 | 827.6 | -151.6 |
| Celiprolol | 56.2 | 42.8 | 13.4 | 1834.0 | 1768.5 | 65.5 |
| Levobunolol | 25.0 | 37.7 | -12.7 | 700.0 | 797.9 | -97.9 |
| Timolol | - | - | - | 1190.0[d] | 1464.5 | -274.5 |

[a] Values taken from reference 21.
[b] Values calculated from Eq. 5
[c] Values calculated from Eq. 6
[d] Values taken from reference 22.

The SLDA is an useful technique to find discriminant functions with ability to distinguish between the compounds with β-blocker activity and inactive compounds. The method used for descriptor selection was the F-Snedecor parameter. The classification criterion used was the minimum value of Mahalanobis. The quality of the discriminate function is evaluated through the Wilk's U-statistical parameter.

The discriminant function chosen was:

$$D = -22.96 - 2.26\,{}^{1}\chi^{v} + 6.48\,{}^{2}\chi - 5.74\,{}^{4}\chi_{pc} - 4.01 G_{4}{}^{v} + 147.67\,J_{4} - 1.06\,{}^{4}\chi_{c}{}^{4}\chi_{c}{}^{v} - 0.0005\,W - 0.404\,PR2 \quad \text{Eq.6}$$

(6.5) (61.0) (29.8) (17.0) (38.1) (8.85) (13.2) (12.7)

N = 81 F = 23.4 U-statistics (Wilks' λ) = 0.28

Table 2.- Results obtained applying the stepwise linear discriminate analysis to β-blockers.

| Active group | | | Inactive group | | |
|---|---|---|---|---|---|
| Compound | D | Class | Compound | D | Class |
| | | Training group | | | |
| Acebutolol | 4.60 | + | Acipimox | -3.75 | - |
| Arotinolol | 3.95 | + | Aminopyrine | -11.50 | - |
| Atenolol | 4.14 | + | Antrafenine | -9.39 | - |
| Befunolol | 8.09 | + | Azacitidine | -5.54 | - |
| Betaxolol | 9.18 | + | Beclobrate | -6.34 | - |
| Bevantolol | 4.95 | + | Bezafibrate | -4.91 | - |
| Bisoprolol | 10.30 | + | Bromosalicychloranilide | 1.12 | + |
| Bopindolol | 7.80 | + | Buclosamide | -1.47 | - |
| Bucumolol | 8.23 | + | Candicidin | -7.21 | - |
| Bufetolol | 9.72 | + | Carboquone | -1.18 | - |
| Bufuralol | 3.74 | + | Carmustine | -10.13 | - |
| Bunitrolol | 3.45 | + | Chlorambucil | 0.64 | + |
| Bupranolol | 5.61 | + | Chlordantoin | -2.22 | - |
| Butidrine | -3.25 | - | Chlormidazole | -7.59 | - |
| Butofilol | 8.15 | + | Diamthazole | -2.60 | - |
| Carazolol | 4.52 | + | Diflunisal | 0.47 | + |
| Carteolol | 6.44 | + | Doxorubicin | -4.61 | - |
| Carvedilol | 7.19 | + | Econazole | -0.57 | - |
| Celiprolol | 9.66 | + | Enilconazole | -3.17 | - |
| Cetamolol | 5.57 | + | Etofibrate | -4.58 | - |
| Cloranol | 6.13 | + | Fenofibrate | -6.17 | - |
| Dilevalol | 4.92 | + | Gemfibrozil | -6.75 | - |
| Epanolol | 3.30 | + | Glafenine | -0.34 | - |
| Esmolol | 3.16 | + | Idoxurine | -6.17 | - |
| Indenolol | 2.79 | + | Improsulfan | 0.58 | + |
| Labetalol | 2.39 | + | Indomethacin | -5.67 | - |
| Levobunolol | 4.77 | + | Metampicillin | -11.85 | - |
| Metipranolol | 4.53 | + | Minocycline | -9.15 | - |
| Metoprolol | 5.63 | + | Oxytetracycline | -5.92 | - |
| Moprolol | 1.84 | + | Pirifibrate | -4.57 | - |
| Nadolol | 10.28 | + | Ramifenazone | -8.32 | - |
| Nifenalol | 3.93 | + | Ribavirin | -4.88 | - |
| Oxprenolol | 1.94 | + | Rolitetracycline | -6.65 | - |
| Pindolol | 4.26 | + | Ronifibrate | -5.15 | - |
| Practolol | 3.59 | + | Salsalate | -6.70 | - |
| Pronethanol | -1.25 | - | Sancycline | -10.27 | - |
| Propranolol | 1.76 | + | Tetracycline | -8.31 | - |
| Sotalol | 5.17 | + | Vidarabine | -2.58 | - |
| Sulfinalol | 6.25 | + | Zidovudine | -4.34 | - |
| Talinolol | 8.96 | + | | | |
| Timolol | 3.42 | + | | | |
| Xibenolol | 3.44 | + | | | |
| | | Test group | | | |
| Alprenolol | 0.15 | + | Acedapsone | -4.01 | - |
| Amosulalol | 1.84 | + | Bufexamac | -4.24 | - |
| Mepindolol | 6.31 | + | Butoconazole | -1.80 | - |
| Nadoxolol | 0.42 | + | Cefotiam | -0.81 | - |
| Nipradilol | 11.26 | + | Cytarabine | -5.16 | - |
| Penbutolol | 5.91 | + | Dermostatin | 13.99 | + |
| Tertalolol | 4.95 | + | Fenoprofen | -9.29 | - |
| Toliprolol | 1.07 | + | Naproxen | -5.21 | - |
| | | | 1-Deoxy-1-2-(OHethylamino)-D-glucitol* | -7.39 | - |
| | | | 1-Deoxy-1-(octylamino)-D-glucitol* | -4.65 | - |
| | | | N-methyl glucamine* | -10.28 | - |
| | | | 1-(N-3 allyloxy-2-OHpropyl)-2-amino ethyl- imidazolidinone* | -3.82 | - |

A compound is classified as active (+) if $D > 0$ and as inactive (-) if $D < 0$

*Compounds with the substructure $R_1$-CHOH-$CH_2$-NH-$R_2$

The numbers in parenthesis below the coefficients are the F-statistic values for each variable for the Eq.6.

Table 2 summarizes the classification results obtained after applying the discriminant function to each molecule. A compound will be selected as active if D >0 or as inactive if D <0. In the training group, we get an average measure of correct prediction close to 92.4% (6 errors out of 81), while in the test group this increases to approximately 95%.

In spite of the fact that the training active group compounds have the same substructure, ($R_1$-CHOH-$CH_2$-NH-$R_2$, where $R_1$ and $R_2$ are any heavy group) we have checked the discriminant capacity of the Eq.6, introducing in the inactive test group, compounds with this typical substructure of β-blockers. As it can be observed, the discriminant function, Eq.6, classifies correctly all of them. The rest of compounds of the test group were selected randomly by BMDP 7M program.

This function, Eq.6, has been applied to an extensive group of compounds, some with therapeutic use in humans. Among the compounds which show positive values of the discriminant function, D, stands out the probucol (hypolipidemic), filipin III (antifungal), clidanac (analgesic) and β-carotene (provitamin A). Table 3 shows the values of discriminant function D and the acute toxicity for each compound.

Table 3.- Values of discriminant function D and toxicity (LD50iv and LD50or), for the compounds with theoretical β-blocker activity.

| Compound | D | LD50iv[a] (mg/kg) | LD50iv (mg/kg) | LD50or[b] (mg/kg) | LD50or (mg/kg) |
|---|---|---|---|---|---|
| Probucol | 11.8 | 25 | - | 44922 | >5000 |
| Filipin III | 10.7 | 5 | - | 18 | - |
| Clidanac | 1.4 | 34 | - | 252 | 41 |
| β-carotene | 5.1 | 26 | - | 6749 | - |

[a] Values calculated from Eq.4 ; [b] Values calculated from Eq.5

After an extensive bibliographic research, we have verified that all of them interact with the β adrenoceptors[14-18]. It has been proved that probucol increases QTc electrocardiogram interval such as sotalol makes[14,15]. In the same way, both filipin and propranolol interact with the β-adrenoceptors precoupled to Gs in chicken erythrocyte membranes[16]. In a recent study, it has been showed the efficacy of β–carotene to have a protective effect on the development of coronary heart disease, specially in myocardial infarction. This study has revealed that supplemental administration of 50 mg of β–carotene led a 50% reduction of incidence in a group of sick volunteers[18].

Now we can apply Eq.4 and Eq.5 to predict the toxicity in mice of these four compounds: β-carotene gives a value for LD50iv of 26, while LD50or is 6749, no experimental data were found. Probucol gives respectively 25 and 44922, the datum found in the bibliography is LD50or > 5000 mg/Kg both in rats and

mice[19]. The Eq.5 predicted successfully low toxicity in these cases while Eq.4 predicted acceptable values. Filipin III gives respectively 5 and 18 these values predict high toxicity, it is known that filipin induces arthritis in rabbits[20]. Clidanac gives 34 and 252 respectively, while the only datum found is LD50or = 41 mg/Kg in rats[21]. Probably clidanac acts as β-blocker but its toxicity is something underestimated by Eqs. 4 and 5.

This work demonstrates that by an adequate choice of topological descriptors it is possible not only to predict roughly pharmacological properties but also to discriminate the β-blocker activity of a compound through discriminant equation, with a surprising level of efficiency, especially considering the simplicity of the calculations.

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**References**

1. Kier, L. B.; Hall, L. H. Molecular Connectivity in Structure-Activity Analysis, Research Studies Press. Letchworth, England, 1986; pp 225-246.
2. García, R ; Gálvez, J.; Moliner, R.; García, F. Drug Invest. **1991**, *3*, 344.
3. Julián-Ortiz, J. V. de ; García-Domenech, R.; Galvez, J. J. Chromatogr. **1996**, *719*, 37.
4. Muñoz, C.; Julian-Ortiz, J. V. de ; Gimeno, C.; Catalán, V.; Galvez, J. Rev. Esp. Quimioter. **1994**, *7*, 279.
5. Gálvez, J.; Garcia, R.; Julian-Ortiz, J. V. de ; Soler, R. J. Chem. Inf. Comput. Sci. **1995**, *35*, 272.
6. Antón-Fos, G. M.; García-Domenech, R.; Perez-Gimenez, F.; Peris-Ribera, J. E.; García-March, F. J.; Salabert-Salvador, M. T. Arzneim-Forsch/Drug Res. **1994**, *44*, 821.
7. Gálvez, J.; Garcia, R.; Julián-Ortiz, J. V. de ; Soler, R. J. Chem. Inf. Comput. Sci. **1994**, *34*, 1198.
8. García-Domenech, R.; García-March, F. J.; Soler, R.; Galvez, J.; Antón-Fos, G. M.; Julián-Ortiz, J. V. de Quant. Struct.-Act. Relat. **1996**, *15*, 201.
9. Kier, L. B.; Hall, L. H. Eur. J. Med. Chem. **1977**, *12*, 313.
10. Wiener, H. J. Am. Chem. Soc. **1947**, *69*, 2636.
11. Galvez, J.; García-Domenech, R.; Salabert, M. T.; Soler, R. J. Chem. Inf. Comput. Sci. **1994**, *34*, 520.
12. Moliner, R.; García, F.; Gálvez, J.; García-Domenech, R.; Serrano, C. An. R. Acad. Farm. **1991**, *57*, 287.
13. Dixon, W. J.: BMDP Statistical Software. Berkeley, University of California, USA 1990.
14. Cobbe, S. M.; Alexopoulos, D. Eur. Heart. J. **1988**, *9*, 24.
15. Sasaki, N.; Saku, K. Artery. **1993**, *20*, 115.
16. Murray, R.; Keenan, A. K. Cell-Signal. **1989**, *1*, 173.
17. Gilligan, D. M.; Sack, M. N. J. Am. Coll. Cardiol. **1994**, *24*, 1611.
18. Curt, D. Pharmedicum **1996**, *4*, 15.
19. Lebeau, J. E. Nouv. Presse Med. **1980**, *9*, 3001.
20. Weissmann, G.; Pras, M.; Rosenberg, L. Arthritis Reum. **1967**, *10*, 325.
21. The Merck Index., Merck & CO., Inc. Rahway, N. J. USA, Eleventh Edition, 1989.
22. AHES Drug Information, American Hospital Formulary Service, Bethesda, 1993, pp 896.

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