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QSAR prediction of pharmacological classification using principal components analysis

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For a drug to produce an appropriate biological response, it must possess the right physico-chemical and structural properties to allow it to reach the desired receptor site readily and to bind to that receptor in a particular manner. It follows that the *type* of response, as well as its magnitude, must depend on these properties. Hence QSAR can, in principle, be used to predict pharmacological classification. There have been several studies based on this approach (e.g. Henry & Block 1979, Garreau et al 1982, Petrusewicz et al 1993, Nasal et al 1997). We have used the data-set of Nasal et al for the study reported here; the data-set comprised 83 drugs from five pharmacological classes, namely psychotropics and inactive phenothiazines (class 1), drugs acting on α-adrenoceptors(class 2), β-adrenolytics (class 3), histamine H_1-antagonists (class 4) and histamine H_2-antagonists (class 5). Nasal et al used only HPLC capacity factors determined in eight different systems as physico-chemical properties. Using principal components analysis (PCA), they were able to obtain reasonable - although far from complete - separation of the different pharmacological classes.

We believe that the data of Nasal et al could be weighted too much towards hydrophobicity. In addition their system cannot be used to predict pharmacological classification of drugs that are not available (e.g. because they have not yet been synthesised). We therefore decided to calculate a wide range of properties for the drugs in the data-set of Nasal et al, and to use PCA to determine to what extent we could achieve separation between the classes.

Physico-chemical parameters were calculated using the ClogP for Windows (Biobyte Inc., Claremont CA) and MOPAC6 (QCPE, Bloomington IN) software; for the latter, molecules were first constructed and energy-minimised in NEMESIS (Oxford Molecular Ltd.). Topological parameters were generated using MOLCONN-X2 (Hall Associates, Quincy MA). A total of 79 descriptors was generated with these packages, for 81 drugs. (We were unable to confirm the structures of two of the drugs in the data-set of Nasal et al). Statistical analysis was carried out using MINITAB ver. 10.1.

Initially we used all 79 descriptors to generate PCs, and found that a plot of PC1 against PC2 gave a clean separation into two clusters, one comprising classes 3 and 5,and the other comprising classes 1, 2 and 4. The number of descriptors was reduced until further reduction resulted in incomplete separation; the key descriptors were found to be the topological descriptors ${}^2\kappa_\alpha$, ${}^3\kappa_\alpha$ and the Wiener number, together with the number of H bond donor groups. The same approach enabled us to obtain total separation between classes 3 and 5 in a plot of PC2 against PC3 (key descriptors ${}^4\chi_{pc}$, ${}^4\chi_c$ and ${}^5\chi_p$), between class 2 and classes 1 and 4 in a plot of PC1 against PC2 (key descriptors ${}^5\chi_{ch}$, ${}^6\chi_{ch}$, ${}^5\chi^v_{ch}$, ${}^0\kappa_\alpha$, Fujita H bond indicator variable, number of H bond acceptor groups and number of H bond donor groups), and finally between classes 1 and 4 in a plot of PC1 against PC3 (key descriptors ${}^5\chi_{ch}$, ${}^6\chi_{ch}$, ${}^3\kappa$, ${}^4\chi_c$ and ${}^6\chi^v_{ch}$). 100% separation was achieved in all cases.

In order to validate the above analysis, we selected ten further drugs, two from each of the classes. The model correctly classified nine out of the ten, with only the H_2-receptor antagonist zolantidine falling outside the boundary determined from the training set. However, it should be noted that zolantidine did not fall within the boundary of any other class, so perhaps it is fairer to say that it was not fully correctly classified.

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