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# QUANTITATIVE STRUCTURE – ACTIVITY RELATIONSHIP IN ANTIDIABETIC DRUGS BY USING TOPOLOGICAL DESCRIPTORS

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The quantitative structure – activity relationship in antidiabetic oral drugs has been analyzed on the basis of topological indices that allow to discriminate the structure of different molecules either small or large. The overall correlation structure – activity allows to find the best antidiabetic drugs and to predict the activity of new compound proposed as oral antidiabetic. The screened procedure based on topological indices prevents the expensive and long testing of a high number of compounds.

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## 1. Introduction

One of the most important problems in the pharmakinetics and pharmadynamics of the drugs is the relation between the structure of the molecular units and activity of the drug.

The prediction of the properties of synthetic molecule that could lay at the basis of a drug is challenging. The best approach is to determine the precise structure of the molecule (atomic coordination) and to apply quantum mechanical calculation with wave function and specialized methods in order to get the shapes and energies of the electron charge distribution from which many molecular properties can be obtained. Another approach is to determine the properties of the basical fragments of the molecule and to combine them in a proper way to get the whole molecular configuration and properties.

The most simple but powerful approach is to use the graph of the molecule and calculate the topological index of the whole molecule. Many studies evidenced that the mathematically calculated index is correlated with a number of physical properties of a given substance. One of the most popular index is the Randič index [1] called also Randič molecular – connectivity index.

A lot of topological indices have been introduced recently for explaining different aspects of large molecules as e.g. fullerenes and nanotubes [2-13].

As well known, the biological response is triggered when an appropriate simulating molecule docks with a receptor on the surface of the cell. In many cases the specific shape of the triggering molecule is not as important as its volume or surface area. The topological index could be ideal for evidencing the ability of the molecule to induce a particular biological response because it is well correlated with the surface area and volume. The superiority of the Randič index ($I_R$ a branching index) over the other molecular – connectivity indices has been shown in many papers [14].

Even the Randič index seems to be not entirely correct because it does not take into account the whole molecular structure because it neglects the hydrogen atoms. It is not possible to

discriminate between molecules having comparable skeleton but very different numbers of hydrogen atoms.

A new index ($I_P$) that overcomes these problems has been introduced by Popescu [15]. The new index is the sum of two components. The first one is the Randič index applied to molecular skeleton. The second one is calculated as the ratio of the number of hydrogen atoms to the number of atoms of the skeleton. The sum is normalized to the number of the atoms of the molecule.

A strong correlation between this new index and the anticancer activity of polycyclic hydrocarbons has been already revealed [15].

In this paper we report the calculation of the Randic normalized index and of the Popescu normalized index for a large number of antidiabetic drugs in order to show that these indices can discriminate between different classes of drugs and to correlate their values with the antidiabetic efficiency. We tried also to point out the correlation between structure and activity for some oral antidiabetic drugs whose hierarchy of the activity in reducing glucose has been already ascertained experimentally.

## 2. Methods and experimental data

The branching index R can be easily calculated for a molecule using simple software and minimum computer resources.

To calculate the index one assigns to each edge of a molecule (hydrogen suppressed) a value witch depends on the degrees of the vertices the edge connects. The degree of any vertex is equal to the number of other vertices to which it is linked.

The value is the product of the reciprocals of the square roots of the degrees of the vertices it joins. The sum of all values gives the Randič index of the molecule:

$$I_R = \sum (m \cdot n)^{-0.5} \tag{1}$$

where *m* and *n* are the valences of adjacent vertices joined by an edge.

The Popescu index was calculated on the basis of $I_R$ index. The ratio between the number of hydrogen and the total number of atoms was calculated and to this result was added the $I_R$ index. Finally, the sum was normalized to the total number of atoms in the molecule.

The topological index, $I_P$, was calculated for a series of antidiabetic drugs in the classes: Sulfonylureas, Alfa glucosidase inhibitors, Meglitinides, Biguanides and Thiazolidinediones.

Repaglinide is a new oral blood glucose lowering agent, a member of the carbamoylmethyl benzoic acid family [16]. Its mechanism of action is partly similar to that of sulfonylurea: the release of insulin from the pancreatic beta cells is stimulated by closure of ATP-dependent potassium channels. However, repaglinide regulates these channels via a different binding site on the beta cell than glibenclamide, and the drug does not cause insulin release in the absence of glucose, or during voltage – clamping.

Among the calculated sulfonylureases is glipizide. The glipizide was compared to repaglinide [17]. Changing in fasting blood glucose (FBG) and HbAlc during the 12 months of treatment showed a significant difference in favour of repaglinide. In oral hypoglycalmic agents (OHA) – naive patients, HbAlc decreased in the repaglinide and glipizide groups by $1.5\%$ and 0.3% respectively, ($P < 0.05$ between groups). Fasting blood glucose decreased in the repaglinide group by $2 mmol/l$ and increased in the glipizide group by $1.0 mmol/l$ ($P < 0.05$ between groups). In the study of population as a whole, repaglinide was able to maintain glicemic control (HbAlc level) during the 1- year study period, whereas control deteriorated significantly with glipizide group compared with the repaglinide group ($P < 0.05$). Repaglinide, given as a prandial glucose regulator, is shown to be an effective and safe treatment of patients with type 2 diabetes, and is better than glipizide in controlling HbAlc and FBG levels.

Müller et al. [18] have revealed a marked ranking in the ratios of plasma insulin – increasing and blood glucose decreasing activity between the different sulfonylureas (glimepiride < glipizide < gliclazide <glibenclamide). Glimepiride reduced blood glucose in hyperglycemic mice by 40%, plasma insulin by 50% and HbAlc by 33%, whereas glibenclamide and gliclazide had no effect on these parameters [19].

Taken into account the above described data we have taken a scale of activity of the antidiabetic drugs with equal distance between components. Although this supposition is not entirely correct it allows to have an idea regarding the correlation of the drug activity with the topological index.

Fig. 1 shows the plot of the topological index versus the drug activity in reducing blood glucose. It is observed that the effect on the blood glucose reduction is higher for low topological index values of the drug molecule.

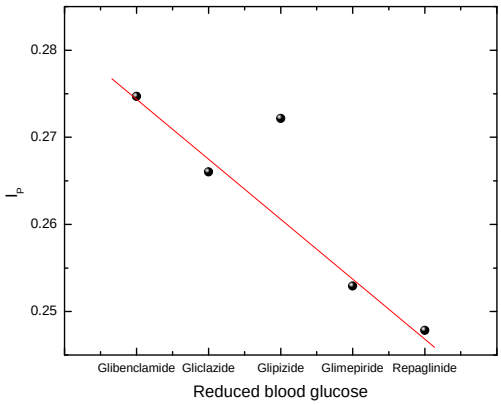


*Fig. 1. The $I_P$ topological index versus molecular activity against blood glucose*

It is interesting to remark that the usual Metformin drug has an intermediary activity, while a new drug, full of hopes, Sitagliptin, seems to be not effective against blood glucose.

In order to have a general image on the antidiabetic drug we have plotted the Randič index versus Popescu index for all the investigated substances. Figure 2 and Table 1 shows the results. The distribution of the points shows that some drugs are situated in the narrow range of the low values topological indices. It is remarkable that Rosiglitazone, which is suspected to play a leading role in the vascular accidents occurring in patients, is characterized by high value of the topological index. It is advised, according to the clinical studies, that possible adverse effects must be taken into account for Rosiglitazone and Pioglitazone: fluid retention and congestive heart failure, hepatic disturbances, weight gain and anemia.

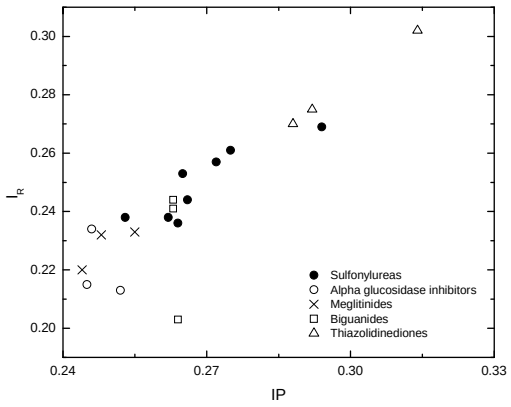


*Fig. 2 The plot of Randic index versus Popescu index for the antidiabetic drugs. Sulfonylureas (1-Chlorpropamide, 2-Tolazamide, 3-Glipizide, 4-Gliclazide, 5-Gliquidine, 6-Glimepiride, 7-Tolbutamide, 8-Glibenclamide) Alpha glucosidase inhibitors (9-Acarbose, 10-Miglitol, 11-Voglibose) Meglitinides (12 – Nateglinide, 13 – Repaglinide, 14 – Mitiglinide) Biguanides (15-Metformin, 16-Ciglitazone, 17-Yohimbine) Thiazolidinediones (18-Pioglitazone,19-Sitagliptin,20-Rosiglitazone (Avandia))*

*Table 1: Randic index and Popescu index for the antidiabetic drugs from Figure 2*

| Drug | $I_R$ | $I_P$ |
|---|---|---|
| **Sulfonylureas** | | |
| Chlorpropamide | 0.26866 | 0.29415 |
| Tolazamide | 0.23854 | 0.26235 |
| Glipizide | 0.25715 | 0.27217 |
| Gliclazide | 0.24383 | 0.26603 |
| Gliquidone | 0.25284 | 0.26559 |
| Glimepiride | 0.23821 | 0.25291 |
| Tolbutamide | 0.23614 | 0.26391 |
| Glibenclamide | 0.26079 | 0.27470 |
| **Alpha glucosidase inhibitors** | | |
| Acarbose | 0.23441 | 0.24590 |
| Miglitol | 0.21331 | 0.25248 |
| Voglibose | 0.21514 | 0.24505 |
| **Meglitinides** | | |
| Nateglinide | 0.22004 | 0.24352 |
| Repaglinide | 0.23204 | 0.24785 |
| Mitiglinide | 0.23258 | 0.25523 |
| **Biguanides** | | |
| Metformin | 0.20323 | 0.26435 |
| Ciglitazone | 0.24087 | 0.26261 |
| Yohimbine | 0.24362 | 0.26285 |
| **Thiazolidinediones** | | |
| Pioglitazone | 0.27034 | 0.28812 |
| Sitagliptin | 0.30182 | 0.31428 |
| Rosiglitazone | 0.27499 | 0.29226 |

## 3. Conclusions

Using topological descriptors we have correlated their values with the activity of some oral antidiabetic drugs. It was established a negative correlation. The drug activity seems to be higher for lower values of the topological descriptors. For accurate correlation of the topological indices with the drug activity, a quantitative scale of the efficacity of various drugs is necessary.

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