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Original paper

Auxins, auxin transport inhibitors, and competitors for auxin receptors do not show statistically significant differences in 212 molecular descriptors

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Abstract This study compares 212 molecular descriptors of four auxins (indolebutyric acid; indoleacetic acid; 2,4-dichlorophenoxyacetic acid; 1-naphthaleneacetic acid), three auxin transport inhibitors [2-(naphthalen-1-ylcarbamoyl)benzoic acid; 2,3,5-triiodobenzoic acid; 9-hydroxy-9H-fluorene-9-carboxylic acid], and five competitors for auxin receptors [2-(2,4,6-trichlorophenoxy)acetic acid; 2-(4-chlorophenoxy)-2-methylpropanoic acid; 3-phenylpropanoic acid; 3-(2-chlorophenoxy)butanoic acid; 2-amino-3-(5-methyl-1H-indol-3yl) propanoic acid]. The analysed compounds did not show statistically significant differences in any of those descriptors, suggesting that chemical and structural differences, *per se*, do not determine their functional diversities. We propose that combination with other, yet unknown chemical groups confers the specificity necessary for these molecules to act as auxins, as auxin transport inhibitors or auxin receptor competitors

Keywords Chemo-informatics, mathematical chemistry, molecular descriptors, plant growth regulators

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Introduction

Auxins are one of the most important groups of substances for regulating growth and morphogenesis in plant cell, tissue and organ culture (F.B. SALISBURY & C.W. ROSS 1992 [1]; I. MACHAKOVA & al. 2008 [2]; J.VAN STADEN & al. 2008 [3]). Among hundreds of published examples, we can mention, for instance, that in vitro rooting was enhanced in *Nicotiana benthamiana* by the auxin indoleacetic acid (IAA) (S.ESSERTI& al. 2017 [4]). Indolebutyric acid (IBA) has been recommended for shoot and root organogenesis of *Eriocephalus africanus*, a medicinal and aromatic plant species (O. MADZIKANE-MLUNGWANA & al. 2017 [5]). Naphthaleneacetic acid (NAA) significantly increased the number of bulblets developed on leaf explants of *Scadoxus puniceus* (G. NAIDOO 2010 [6]). Callus cultures from leaves and young shoots of *Taxus globosa* were produced with 2,4-dichlorophenoxiacetic acid (2,4-D) (N.TAPIA & al. 2013 [7]).

Regarding polar transport of auxins, it can be inhibited for example by 2-(naphthalen-1-ylcarbamoyl)benzoic acid (Naptalam), 2,3,5-triiodobenzoic acid, and 9-hydroxy-9H-fuorene-9-carboxylic acid (Flurenol) (I. MACHAKOVA & al. 2008 [2]). Moreover, Naptalam has been shown to disrupt the tropic growth as an inhibitor of polar auxin transport (W. TEALE & PALME 2017 [8]). The latter compound, as well as 2,3,5-triiodobenzoic acid, induced pseudonodules in legume species forming indeterminate nodules, such as *Medicagotruncatula*, but failed to elicit such structures in *Lotus japonicus* and other species forming determinate nodules (J.NG & MATHESIUS 2018 [9]); both compounds also altered somatic embryogenesis in carrot, blocking morphological transitions between successive developmental stages, for example generating enlarged globular embryos (F.M. SCHIAVONE & COOKE 1987 [10]).

Other auxin analogues have been reported to compete for auxin receptors, thus interfering with auxin functions (I. MACHAKOVA & al. 2008 [2]). They include, for example: 2-(2,4,6-trichlorophenoxy)acetic acid; 2-(4-chlorophenoxy)-2-methylpropanoic acid (Clofibric acid); 3-phenylpropanoic acid; 3-(2-chlorophenoxy)butanoic acid; and 2-amino-3-(5-methyl-1H-indol-3yl)propanoic acid (5-methyltryptophan).

Despite the important physiological effects of auxins and related compounds acting as auxin transport inhibitors, or competitors for auxin receptors, the specific differences in chemical and structural features of these molecules that could be responsible for their distinct biological functions remain unknown. Those differences could be revealed by the determination and analysis of molecular descriptors for some compounds of each functional group. A 'molecular descriptor' has been defined as "the final result of a logical and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment" (R. TODESCHINI & CONSONNI 2009 [11]).

In a recent study (I.ANDÚJAR & al. 2018 [12]), we calculated 212 descriptors of auxins, cytokinins and gibberellins, and 49 of them showed statistically significant differences between the analysed groups of compounds. Some of these differences can be described as follows: i) gibberellins contain terminal tertiary C (sp3), terminal quaternary C (sp3), ring secondary C (sp3), ring tertiary C (sp3), and ring quaternary C (sp3) that are not present either in cytokinins or auxins; ii) gibberellins are also relatively rich in terminal secondary C (sp3) and 10-membered rings, which are absent in cytokinins; iii) cytokinins have 10 times more nitrogen atoms than auxins but this atom is not present in gibberellins; iv) auxins have 10 times more substituted benzene C (sp2) and 5 times more benzene-like rings than cytokinins, but these structures are not present in gibberellins. These data were used to generate a dendrogram in which auxins, cytokinins and gibberellins were correctly classified in three independent branches (I. ANDÚJAR & al. 2018 [12]).

Following this approach, the present study compared the same 212 molecular descriptors of the molecules mentioned above: four auxins, three auxin transport inhibitors, and five competitors for auxin receptors (formulas shown in Fig. 1). We expected to be able to identify molecular descriptors specifically associated with each group of compounds that could be used for their functional classification.

Materials and Methods

DRAGON software (version 5.5, 2007) and CambridgeSoftChemOffice (version 12, 2010) including ChemDraw and Chem3D, were used to calculate 212 molecular descriptors (I. ANDÚJAR & al. 2018 [12]) of the studied compounds (Fig. 1). These descriptors were classified into three categories: constitutional descriptors, functional group counts, and molecular properties. All data were statistically evaluated using SPSS (Version 8.0 for Windows, SPSS Inc., New York, NY) to perform one-way ANOVA ($p=0.05$). A hierarchical cluster analysis using the molecular descriptors for auxins, auxin transport inhibitors, and auxin receptor competitors was performed. The dendrogram was built using average linkage (between groups). Variables were standardised to vary from 0 to 1 according to M. KANTARDZIC, 2003 [13].

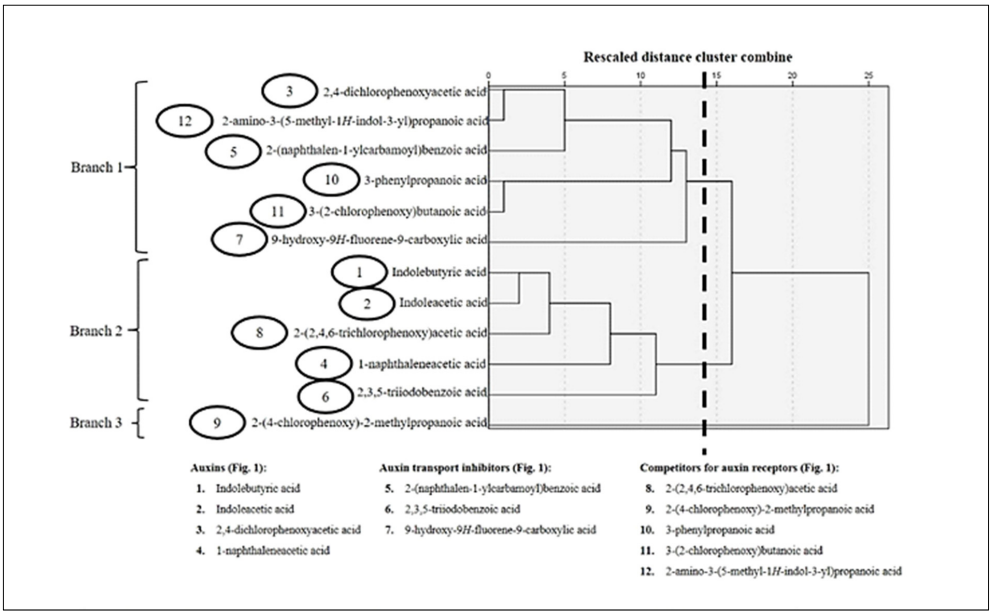

Figure 2. Hierarchical cluster analysis using 212 molecular descriptors for auxins, auxin transport inhibitors, and competitors for auxin receptors. Statistical significant differences among groups of regulators were not observed (one-way ANOVA, $p>0.05$). The dendrogram was built using average linkage (between groups). Variables were standardised to vary from 0 to 1 according to M. KANTARDZIC, 2003 [13].

Results and Discussions

Contrary to our initial expectations, no statistically significant differences were found in any of the 212 molecular descriptors, when comparing the analysed auxins, auxin transport inhibitors and competitors for auxin receptors. The dendrogram generated from all calculated data (Fig. 2) showed three clearly defined branches but did not allow the classification of the analysed compounds according to their physiological roles. Branch 3 included a single molecule, the competitor for auxin receptors, 2-(4-chlorophenoxy)-2-methylpropanoic acid (Clofibric acid), which was clearly separated from the rest of the chemicals. Branch 2 in the dendrogram was constituted by three auxins (IBA, IAA and NAA), one auxin transport inhibitor (2,3,5-triiodobenzoic acid) and the competitor for auxin receptors 2-(2,4,6-trichlorophenoxy)acetic acid.Finally, branch 1 included the auxin 2,4-D, two auxin transport inhibitors, namely 2-(naphthalene-1-ylcarbamoyl)benzoic acid (Naptalam) and 9-hydroxy-9H-fluorene-9-carboxylic acid (Flurenol), and three auxin analogues described as receptor competitors: 3-phenylpropanoic acid, 3-(2-chlorophenoxy)butanoic acid, and 2-amino-3-(5-methyl-1H-indol-3-yl)propanoic acid (Fig. 2).

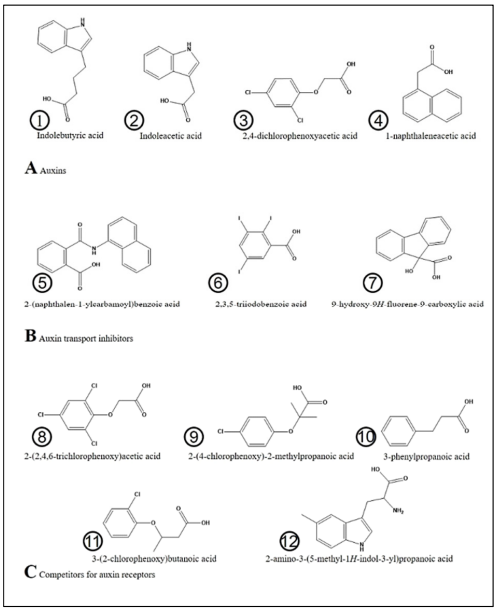

Figure 1. Auxins, auxin transport inhibitors and competitors for auxin receptors compared in this work

Molecular descriptors have been applied in many studies to define biological activities of a wide range of biochemicals (R.ARIMOTO & al. 2005 [14]; G.M. CASAÑOLA-MARTIN & al. 2007 [15]; J.L. FAULON & al. 2008 [16]; D.C. KOMBO & al. 2013 [17]; A. LAVECCHIA & CERCHIA 2016 [18]; T. RODRIGUES & al. 2016 [19]; K. DIEGUEZ-SANTANA & al. 2017 [20]; H. PHAM-THE & al. 2017 [21]). We have previously established that this chemo-informatic methodology is effective to differentiate auxins, cytokinins, cytokinin antagonists, gibberellins and antigibberellins (partially published in I. ANDÚJAR & al. 2018 [12]). The use of the same 212 descriptors in the present work, however, did not allow identifying significant differences among the selected auxins, auxin transport inhibitors and receptor competitors. Considering the large number of chemical indicators included in the analysis, it seems extremely unlikely that additional molecular descriptors, specific for each functional group of molecules, could be found.

Other factors, apart from specific chemical or structural differences, appear to determine the functional diversities of these groups of molecules.For instance, it is possible that the structures shown in Fig. 1 need to combine with other (unknown) chemical groups to acquire their specific roles as auxins, transport inhibitors or receptor competitors. It would be very interesting to confirm this hypothesis, identifying those putative auxin-interacting molecules, and thus strengthen our knowledge on the mechanisms of action of these essential plant growth regulators.

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References

1. F.B. SALISBURY, C.W. ROSS, Plant Physiology (In Spanish) Wadsworth Publishing, California (1992).
2. I. MACHAKOVA, E. ZAZIMALOVA, E.F. GEORGE, Plant growth regulators I: Introduction; auxins, their analogues and inhibitors. In: Plant Propagation by Tissue Culture, E.F. GEORGE, M.A. HALL, G.J. DE KERK, eds. Springer, Dordrecht, 2008, pp. 175-204.
3. J. VAN STADEN, E. ZAZIMALOVA, E.F. GEORGE, Plant growth regulators II: cytokinins, their analogues and antagonists. In: Plant Propagation by Tissue Culture, E.F. GEORGE, M.A. HALL, G.J. DE KERK, eds. Springer, Dordrecht, 2008, pp. 205-226.
4. S. ESSERTI, M. FAIZE, L.A. RIFAI, A, SMAILI, M. BELFAIZA, L. FAIZE, N. ALBURQUERQUE, L. BURGOS, T. KOUSSA, K. MAKROUM, Media derived from brown seaweeds Cystoseiramyriophylloides and Fucus spiralis for in vitro plant tissue culture. Plant Cell Tiss. Org. Cult., 128: 437-446 (2017).
5. O. MADZIKANE-MLUNGWANA, M. MOYO, A.O. AREMU, L. PLÍHALOVÁ, K. DOLEŽAL, J. VAN STADEN, J.F. FINNIE, Differential responses to isoprenoid, N 6-substituted aromatic cytokinins and indole-3-butyric acid in direct plant regeneration of Eriocephalusafricanus. Plant Grow Reg., 82: 103-110 (2017).
6. G. NAIDOO, Ecophysiological differences between fringe and dwarf Avicennia marina mangroves. Trees, 24: 667-673 (2010).
7. N. TAPIA, A. ZAMILPA, M. BONFILL, E. VENTURA, D. CRUZ-VEGA, A. DEL VILLAR, F- CRUZ-SOSA, L. OSUNA, Effect of the culture medium and biotic stimulation on taxane production in TaxusglobosaSchltdl in vitro cultures. Acta Physiol. Plant., 35: 3447-3455 (2013).
8. W. TEALE, K. PALME, Naphthylphthalamic acid and the mechanism of polar auxin transport. J. Exp. Bot., 69: 303-312 (2017).
9. J. NG, U. MATHESIUS, Acropetal auxin transport inhibition is involved in indeterminate but not determinate nodule formation. Front. Plant Sci., 9: 169 (2018).
10. F.M. SCHIAVONE, T.J. COOKE, Unusual patterns of somatic embryogenesis in the domesticated carrot: developmental effects of exogenous auxins and auxin transport inhibitors. Cell Differ., 21: 53-62 (1987).
11. R. TODESCHINI, V. CONSONNI, Molecular descriptors for chemoinformatics Wiley-VCH (2009).
12. I. ANDÚJAR, D. GÓMEZ, L. PÉREZ, J.C. LORENZO, Use of chemo-informatics to identify molecular descriptors of auxins, cytokinins and gibberellins. J. Appl. Bioinforma. Comput. Biol., doi: 104172/2329-95331000151 7 (2018).
13. M. KANTARDZIC, Data mining: Concepts, models, methods and algorithms Wiley, New Jersey (2003).
14. R. ARIMOTO, M.A. PRASAD, E.M. GIFFORD, Development of CYP3A4 inhibition models: comparisons of machine-learning techniques and molecular descriptors. J. Biomol. Screen., 10: 197-205 (2005).
15. G.M. CASAÑOLA-MARTIN, M.T.H. KHAN, Y. MARRERO-PONCE, A. ATHER, S. SULTAN, F. TORRENS, R. ROTONDO, TOMOCOMD-CARDD descriptors-based virtual screening of tyrosinase inhibitors. 1. Evaluation of different classification model combinations using group, atom-

type and total bilinear indices. Bioorg. Med. Chem., 15: 1483-1503 (2007).

16. J.L. FAULON, M. MISRA, S. MARTIN, K. SALE, R. SAPRA, Genome scale enzyme–metabolite and drug–target interaction predictions using the signature molecular descriptor. Bioinformatics, 24: 225-233 (2008).
17. D.C. KOMBO, K. TALLAPRAGADA, R. JAIN, J. CHEWNING, A.A. MAZUROV, J.D. SPEAKE, T.A. HAUSER, S. TOLER, 3D molecular descriptors important for clinical success. J. Chem. Inf. Model., 53(2): 327-342 (2013).
18. A. LAVECCHIA, C. CERCHIA, In silico methods to address polypharmacology: current status, applications and future perspectives. Drug Disc. Today, 21(2): 288-298 (2016).
19. T. RODRIGUES, D. REKER, P. SCHNEIDER, G. SCHNEIDER, Counting on natural products for drug design. Nat. Chem., 8(6): 531-541 (2016).
20. K. DIEGUEZ-SANTANA, H. PHAM-THE, O.M. RIVERA-BORROTO, A. PURIS, H.L. THI-THU, G.M. CASAÑOLA-MARTIN, A two QSAR way for antidiabetic agents targeting using α-amylase and α-glucosidase inhibitors: model parameters settings in artificial intelligence techniques. Lett.Drug.Des. Disc., 14: 862-868 (2017).
21. H. PHAM-THE, G.M. CASAÑOLA-MARTIN, K. DIEGUEZ-SANTANA, N.N. HAI, N.T. NGOC, L.V. DUC, H.L. THI-THU, Quantitative structure-activity relationship analysis and virtual screening studies for identifying HDAC2 inhibitors from known HDAC bioactive chemical libraries. SAR QSAR Environ. Res., 28: 199-220 (2017).