Srpsko hemijsko društvo

Serbian Chemical Society

XLVIII SAVETOVANJE SRPSKOG HEMIJSKOG DRUŠTVA

KNJIGA RADOVA

48th Meeting of the Serbian Chemical Society

PROCEEDINGS

Novi Sad, 17-18. april 2010.

Novi Sad, April 17-18, 2010

CIP - Каталогизација у публикацији
Народна библиотека Србије, Београд

54(082) (0.034.2)
66(082) (0.034.2)

СРПСКО хемијско друштво (Београд).
Саветовање (48 ; 2010 ; НОВИ САД)
Knjiga radova [Elektronski izvor] = Proceedings / XLVIII savetovanje Srpskog hemijskog društva, Novi Sad, 17-18 april 2010. = 48th Meeting of the Serbian Chemical Society, Novi Sad, April 17-18, 2010 ; [organizator] Srpsko hemijsko društvo = [organized by] The Serbian Chemical Society ; [urednici, editors Rade Marković, Goran Bošković, Aleksandar Dekanski]. - Beograd : Srpsko hemijsko društvo = Serian Chemical Society, 2010 (Novi Sad : Srpsko hemijsko društvo). – 1 elektronski optički disk (CD-ROM) : slika, tekst. ; 12 cm

Sistemski zahtevi: nisu navedeni. - Nasl. sa naslovnog ekrana. - Radovi na srp. i engl. jeziku. – Tekstćir i lat - Tiraž 200. –- Bibliografija uz većinu radova. – Abstracts - Registar.

ISBN 978-86-7132-042-9
1. Српско хемијско друштво (Београд)
а) Хемија – Зборници б) Технологија –Зборници
COBISS. SR-ID 174441996

XLVIII SAVETOVANJE SRPSKOG HEMIJSKOG DRUŠTVA, NOVI SAD 17-18. APRIL 2010.
KNJIGA RADOVA
48TH MEETING OF THE SERBIAN CHEMICAL SOCIETY, NOVI SAD, SERBIA, APRIL 17-18, 2010
PROCEEDINGS

Izdaje / *Published by*
Srpsko hemijsko društvo / *Serbian Chemical Society*
Karnegijeva 4/III, Beograd, Srbija
tel./fax: 011 3370 467; www.shd.org.rs, E-mail: Office@shd.org.rs

Za izdavača / *For Publisher*
Ivanka POPOVIĆ*, predsednik Društva*

Urednici / *Editors*
Rade MARKOVIĆ
Goran BOŠKOVIĆ
Aleksandar DEKANSKI

Dizajn, slog i kompjuterska obrada teksta / *Design, Page Making and Computer Layout*
Aleksandar Dekanski

Tiraž / *Circulation*
200 primeraka / *200 Copy*

Umnožavanje / *Copying*
Srpsko hemijsko društvo / *Serbian Chemical Society - Karnegijeva 4/III, Beograd, Srbija*

ISBN 978-86-7132-042-9

XLVIII savetovanje Srpskog hemijskog društva finansijski su pomogli
48th Meeting of the Serbian Chemical Society is financially supported by

Ministarstvo za nauku i tehnološki razvoj Republike Srbije

Ministry of Science and Technology Development of Republic of Serbia

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GRIND2 – A Second Generation of Alignment-Indipendent Descriptors Derived from Molecular Interaction Fields in Transdermal Delivery. Model Study: Haloperidol.

Tatjana Ž. Verbić✉, Mire Zloh*, Ivan O. Juranić, Branko J. Drakulić**

Faculty of Chemistry, University of Belgrade, P.O. Box 158, 11000 Belgrade, Serbia, ✉tatjanad@chem.bg.ac.rs
**The School of Pharmacy, University of London, 29/39 Brunswick Square*
London WC1N1AX, United Kingdom;
***Department of Chemistry - Institute of Chemistry, Technology and Metallurgy*
University of Belgrade, Njegoševa 12, 11000 Belgrade, Serbia

Introduction

Descriptors derived from molecular interaction fields (MIF)[1] have been proved useful in diverse areas of drug design.[2] Describing potential of the studied target molecule to favorably interact with the chosen probe (well parameterized functional group or an atom), hotspots derived from MIF dependent on isocountour level chosen by the user, or on default filtration procedure, ocassionally represent interaction regions that in real situation cannot be expressed. Similar situation can be found for the first generation of the GRIND,[3] alignment independent descriptors derived from MIFs'. Recently GRIND2, the second generation of the same class of descriptors appeared. New algorithm, AMANDA,[4] is incorporated in program Pentacle.[5] Using empirically derived scaling function on the set of ligand-protein complexes, authors straightforwardly demonstrated that new generation of descriptors is well suited for structure-based drug design, lacking artifacts that appear in the parent class. In this communication we demonstrated alternative usage of GRIND2 on the set of terpenes that acts as a transdermal delivery enhancers for the Haloperidol[6] [HP, (4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidyl]-1-(4-fluorophenyl)-butan-1-one)] (***Figure 1.***) – an old antipsychotic drug used in the treatment of schizophrenia and, more acutely, in the treatment of acute psychotic states and delirium. Due to its strong central antidopaminergic action, HP is classified as a highly potent neuroleptic.

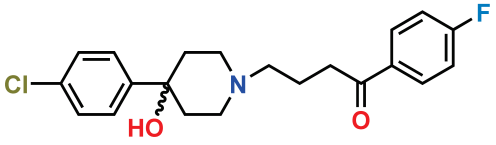


Figure 1. Haloperidol

Transdermal drug delivery offers a variety of advantages over oral and intravenous dosage forms.[6] In many cases, skin penetration enhancers are used to enhance the delivery of these drugs and to reach the desired therapeutic levels. Numerous compounds have been evaluated for penetration enhancing activity.[7] Terpenes represent one of the favourable penetration enhancer groups due to their low toxicity and good irritability profile. They consist of purely hydrocarbon molecules, having unsaturation or not, but also include molecules bearing oxygen functionalities: hydroxyl, keto, carboxyl, ester (including lactones) and ethers (including epoxides) as hydrogen bond acceptor (HBA) or hydrogen bond donor (HBD) groups. Structural diversity of terpenes make them suitable enhancers for both hydrophilic and hydrophobic permeants. It was also proposed that intermolecular complexation between terpens and drugs can play a role in enhacement of transdermal delivery.[8] A set of diverse molecules having strictly defined stereochemistry, different shapes and often, the demanding connectivity (from mono- to bridged tetracyclic systems) represent challenging set for any type of (3D) QSAR methodology. Obtained results strongly suggest that GRIND2 descriptors proved declared selectivity and reliability and could offer good description on structural characteristics that classify molecules according to potentiation ability. To the best of our knowledge, in this communication we demonstrate for the first time application of an alignment independent descriptors, and particularly GRIND2, in the transdermal delivery.

Results and Disscusion

Numerical values of experimentally obtained permeability coefficient of HP through human stratum corneum *in vitro* in the presence of terpenes, were taken from the original reference[6] and given in *Table 1* as negative logarithms (-logK_p). Predicted -logK_p values are given in the same table. Model obtained by PLS analysis in the Pentacle program have reasonable statistical quality ($R^2 = 0.88$), see *Table 2* for details. The PLS plot obtained with 6 latent variables is given in *Figure 2* (variables important for the interpretation of the model are marked by numbers). For the detail description of the methodology, see the original reference.[4]

Tabular representation of the variables most important for model interpretation is given in *Table 3*. Briefly, variable N1-TIP 908 (*Figure 3a*), expressed for the majority of less potent compounds, describes proximity of HBA to alkyl part of the molecule, *i.e.* sterically hindered HBA. Majority of medium sized molecules are less potent; variable O-TIP 826 is expressed for medium sized molecules that have a HBD (mainly –OH group) 10.88 – 11.20 Å away from the terminal part of molecules. Larger molecules have HBD within 12.80 – 13.12 Å, or HBA within 11.84 – 12.16 Å from the distal molecular "end", as described by variables O-TIP 832 (*Figure 3b*) or N1-TIP 928, respectively.

Variables DRY-N1 512 and DRY-O 415 describe π system close to HBA/HBD (~5.5 – 6.5 Å). This variable is expressed for the majority of less potent molecules, irrespective of molecular size.

Table 1. Terpenes used in the study, their experimetaly obtained and predicted permeation coeficients, given in negative logarithmic term.

No.	Terpene	logK_p exp.	logK_p calc.	No.	Terpene	logK_p exp.	logK_p calc.
1.	(±)-Nerolidol	-4.59	-5.14	**24.**	(+)-Aromadendrene	-7.40	-6.78
2.	(*S*)-(-)-Citronellal	-4.83	-4.79	**25.**	(+)-Longifolene	-7.42	-7.45
3.	*α*-Phellandrene	-4.96	-5.85	**26.**	Geraniol	-7.43	-7.61
4.	Citral	-5.08	-5.16	**27.**	(*R*)-(-)-Carvone	-7.56	-7.37
5.	Phytol	-5.13	-4.38	**28.**	(-)-α-Santonin	-7.58	-7.91
6.	Octisalate	-5.19	-5.61	**29.**	Eucarvone	-7.60	-7.57
7.	(±)-*α*-Bisabolol	-5.25	-5.50	**30.**	*β*-Citronellol	-7.66	-7.31
8.	(1*R*)-(-)-Myrtenal	-5.29	-5.90	**31.**	Nerol	-7.80	-8.18
9.	Ocimene	-5.41	-5.90	**32.**	(+)-Cedrol	-7.96	-7.96
10.	Myrcene	-5.43	-5.55	**33.**	Cyclohexanemethanol	-8.08	-8.15
11.	(+)-Cedryl acetate	-5.52	-5.30	**34.**	(1*R*)-(-)-Myrtenol	-8.28	-8.63
12.	*α*-Humulene	-6.23	-7.16	**35.**	Thymol	-8.29	-8.40
13.	(*S*)-(-)-Perillaldehyde	-6.59	-6.14	**36.**	(-)-Isopulegol	-8.35	-8.30
14.	(*R*)-(+)-Pulegone	-6.63	-7.26	**37.**	Carvacrol	-8.44	-8.57
15.	Retinol	-6.71	-6.59	**38.**	(-)-*α*-Thujone	-8.52	-7.64
16.	Farnesol	-6.72	-6.64	**39.**	(-)-Isolongifolol	-8.55	-8.27
17.	(-)-Caryophyllene oxide	-6.78	-7.06	**40.**	Squalene	-8.56	-8.84
18.	(-)-*α*-Cedrene	-6.89	-6.72	**41.**	(+)-Dihydrocarveol	-8.71	-8.58
19.	(+)-*β*-Cedrene	-7.01	-6.45	**42.**	Menthone	-8.72	-7.60
20.	Terpinolene	-7.01	-5.98	**43.**	(-)-Dihydrocarveol	-8.87	-8.46
21.	(+)-Dihydrocarvone	-7.17	-7.48	**44.**	(-)-Guaiol	-8.88	-8.75
22.	(-)-*trans*-Caryophyllene	-7.28	-7.15	**45.**	(±)-Linalol	-8.97	-8.87
23.	L-(-)-Menthol	-7.34	-7.77				

variables O-TIP 832 (***Figure 3b***) or N1-TIP 928, respectively. Variables DRY-N1 512 and DRY-O 415 describe π system close to HBA/HBD (~5.5 – 6.5 Å). This variable is expressed for the majority of less potent molecules, irrespective of molecular size.

On the other hand, majority of more potent molecules have π system at 12.16 – 12.48 Å from the HBA, or 11.84 – 12.16 Å away from HBD, as described by variables DRY-O 433 (***Figure 3c***) and DRY-N1 512, respectively. This can be clearly seen from the topology, and the width of the DRY-O and DRY-N1 "bands" in ***Figure 4***. For the most potent compounds (top of the bands) DRY-N1 correlograms have a larger end-to-end width than those of the less potent ones (bottom part of the band). Also, there are empty regions for the part of medium or less potent compounds in the DRY-O "band". We can speculate that accessibility of a terpene's HBD allows favourable interactions with the oxygen of the tertiary –OH group of HP, but not with the sterically hindered piperazine nitrogen. Considering the conformational flexibility of

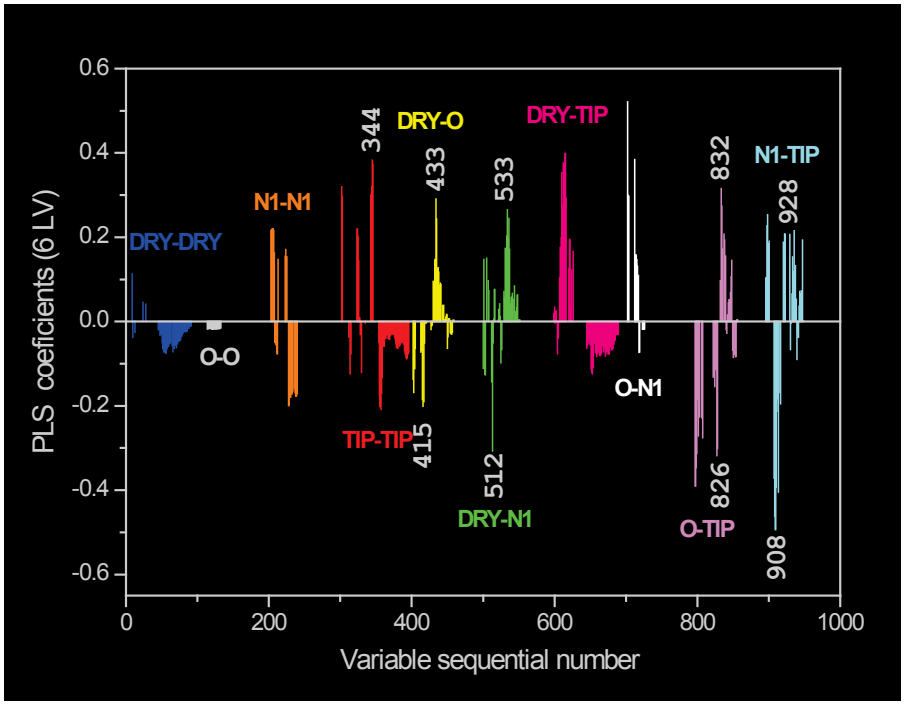


Figure 2. PLS plot obtained by 6LV.

Table 2. Statistics of the model.

Comp.	SSX	SSX_{ac}	SDEC	SDEP	R^2	R^2_{acc}	Q^2_{acc}
1	15.66	15.66	0.83	1.09	0.58	0.58	0.29
2	23.64	39.30	0.68	0.98	0.14	0.73	0.42
3	12.15	51.45	0.60	0.91	0.06	0.79	0.50
4	11.85	63.30	0.56	0.95	0.02	0.81	0.46
5	4.35	67.65	0.49	1.01	0.05	0.86	0.39
6	5.67	73.32	0.45	1.06	0.02	0.88	0.33

Comp. - Number of components; SSX - Percentage of the X sum of squares; SSX_{acc}- Accumulative percentage of the X sum of squares; SDEP- standard deviation error of the predictions.; R^2 - Coefficient of determination; R^2_{acc} - Accumulative coefficient of determination; Q^2_{acc} - Accumulative squared predictive correlation coefficient.

both the HP and the terpenes, the distance of ~12.3 Å between the π system of the aroyl phenyl ring and the tertiary –OH of the haloperidol, corresponds within a reason to the HBA/HBD to π system distance of compounds having significant permeation enhancing potential (variables DRY-O 433 and DRY-N1 512).

Conclusion

In summary, less potent compounds have a sterically hindered HBD and the smaller distance between HBD/HBA and the π system of molecules than more potent compounds. Larger molecules with HBD ~12 – 13.5 Å from the one of molecular termini (irrespective of overall molecular dimensions) exert significant enhancement abilty. Thus, it can be supposed that more active terpens, due to favourable HBD/HBD to π system distance, as well as molecular size, might form complex with HP, which might enhance its permeation through human skin. Further modelling study aimed to support this hypothesis is in progress.

Table 3. Description of MIF hot spots, encoded in variables, associated to structural elements of molecules imporatnat for the model interpretation.

Probe block	Variable No.	Distance (Å)	Impact	Description
TIP-TIP	344	15.04 – 15.36	+	edge-to-edge distance in a few medium sized molecules that have significant enhacement potency toward HP.
DRY-O	415	6.08 – 6.40	–	HBD and π system of the terpenoid moiety, in a majority of less potent molecules.
DRY-O	433	11.84 – 12.16	+	HBD and π system of the terpenoid moiety, inherent to more potent molecules.
DRY-N1	512	5.44 – 5.76	–	similar to variable 415, HBD and π system that are positioned within the particular distance; associated to majority of less potent molecules.
DRY-N1	533	12.16 – 12.48	+	similar to variable 433, HBD and π system positioned within the particular distance; inherent to more potent molecules.
O-TIP	826	10.88 – 11.20	–	present for the majority of less potent molecules that have HBD and terminal moiety within defined spatial distance.
O-TIP	832	12.80 – 13.12	+	describes distance through molecule, from HBD to terminal alkyl group.
N1-TIP	908	5.44 – 5.76	–	similar to variable 827, present for the majority of less potent molecules that have HBD and terminal moiety within defined spatial distance.
N1-TIP	928	11.84 – 5.76	+	similar to variable 832, describes distance through molecule from HBD to terminal alkyl group.

Experimental: All 3D structures (**1**-**45** and haloperidol) were generated by OMEGA[9] from SMILES notation, using MMFF,[10] taking into account all erroneously depicted structures given in the original reference. For the flexible molecules 20 conformations were generated and those with the minimal heat of formation were used for further optimisation. All structures were minimized by the semiempirical MO PM6[11] method using MOPAC2009[12] in implicit solvent (water), to root mean square gradient below 0.01. The VegaZZ 2.3.1[13] was used as GUI. Prepared 3D structures were imported into Pentacle 1.0.1[4,5] and final model was obtained using 6LV and four random groups of the approximately same size for internal crossvalidation (Q^2), as described in the text. Retinoic acid, *β*-carotene, (-)-carveol and (-)-epiglobulol were excluded from the set as the outliers. The first two compounds are grouped away from the rest of the set, exert insignificant enhancement potency, and influence on statistical reliability of the model. We cannot yet offer valuable explanation why the later two *compounds are outliers.*

Acknowledgment: The Ministry of Science and Technological Development of Serbia support this work. Grant 142010.

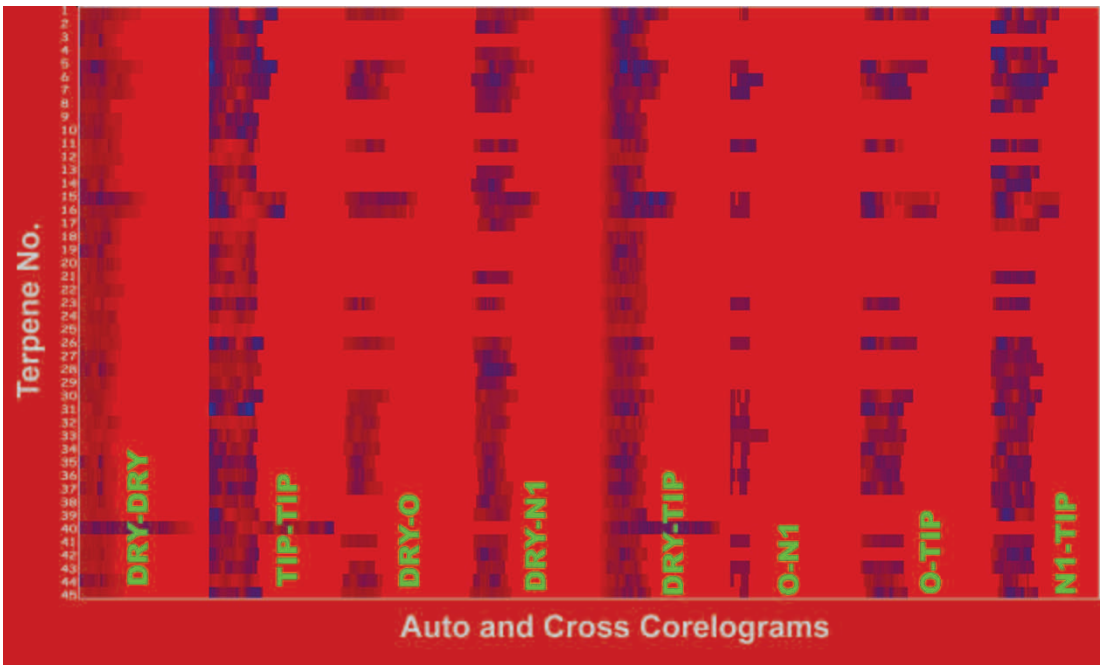
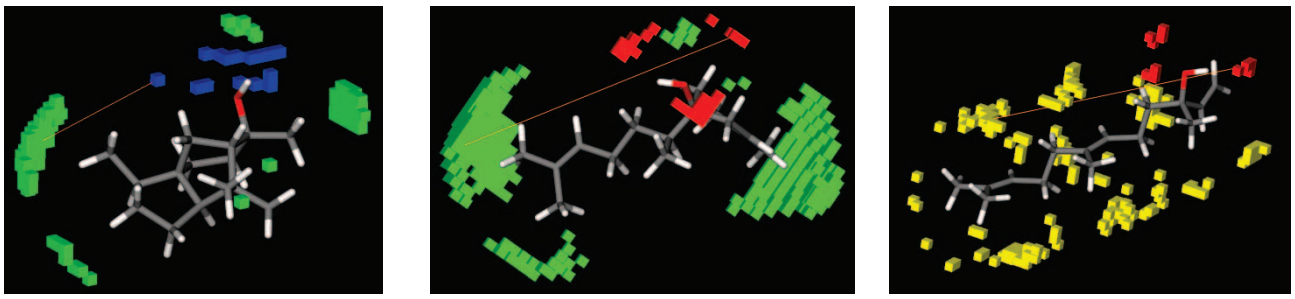


Figure 3. Auto- and crosscorelograms for the 1-45. O-O and N1-N1 autocorelograms that describes a few variables are excluded for clarity. Compounds are arranged from the top to the bottom by their decresing penetration enhacement abbility.



a) **b)** **c)**

Figure 4. a) Variable N1-TIP 908 for compound 32, b) variable O-TIP 832 for compound 8, c) variable DRY-N1 433 for compound 1.

ГРИНД2 – Друга генерација дескриптора независних од поравнавања молекула изведених из поља молекулских интеракција у трансдермалном ослобађању лека. Модел студија: халоперидол.

У саопштењу је описана примена друге генерације дескриптора изведних из поља молекулских интеракција на примеру употребе терпена за побољшање трансдермалне испоруке антипсихотичког лека Халоперидол. Испитивани сет садржи 45 терпена са дефинисаном стереохемијом. Добијени резултати показују да је друга генерација дескриптора далеко селективнија у односу на прву генерацију; осим тога, у оквиру испитиваног сета рационализовани су структурни захтеви за високу јачину дејства терпена као поспешивача проласка Халоперидола кроз кожу. Дискутовани су структурни детаљи одговорни за јачину дејства испитиваних једињења и претпостављен је механизам њиховог дејства.

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