CORRELATON BETWEEN ANISOTROPIC LIPOPHILICITY AND IN SILICO PREDICTED HUMAN DISTRIBUTION OF 1-ARYL-3 METHYL SUCCINIMIDE DERIVATES

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INTRODUCTION:

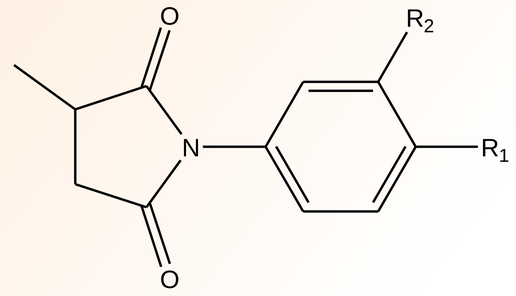
Lipophilicity of drug candidates is used in quantitative structure−activity relationship (QSAR) studies, as molecular descriptor in ADME-tox predictions and as structural information about their biological effects. The distribution of drugs in the body depends mainly on their lipophilicity and their potential to bind to plasma proteins.

OBJECTIVES:

To analyze the influence of lipophilicity on the distribution of newly synthesized succinimide derivates in the human body based on in silico predicted volume of distribution and affinity to bind to the plasma proteins.

METHOD / DESIGN:

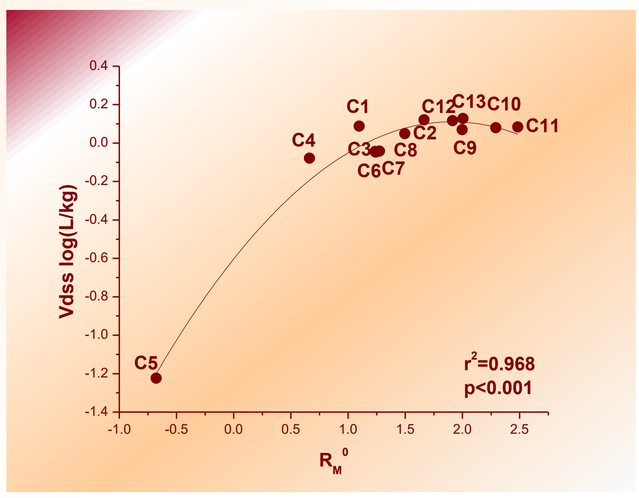
Thirteen newly synthesized 1-aryl-3-methyl succinimide derivates were studied by reversed chromatography and their anisotropic lipophilicity was determined. Precoated RP-18W/UV 254 plates (Macherey-Nagel GMBH and Co., Düren, Germany) was used as stationary phase while binary solutions of methanol and water with a varying volume fraction of organic solvent were applied as the mobile phase. The spots were detected at 254 nm with UV lamp. Software package i-lab 2.0 (https://ilab.acdlabs.com/iLab2/) was used for determining volume of distribution (Vd) while pkCSM (http://biosig.unimelb.edu.au/pkcsm/) was applied for predicting the volume of distribution in stationary state (Vdss) and the fraction of the drug unbound to plasma protein (%unbound) based on the structure of the molecules. Finally, the percent of the drug bound to plasma proteins (PPB) was calculated by PreAdmet software (https://preadmet.bmdrc.kr/adme/) for all compounds observed.

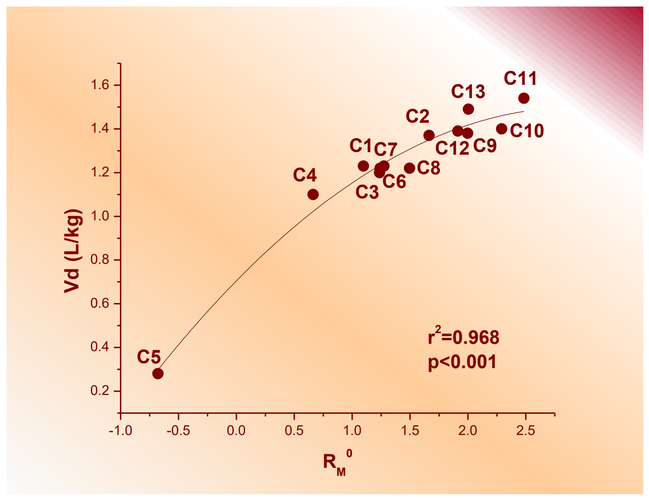


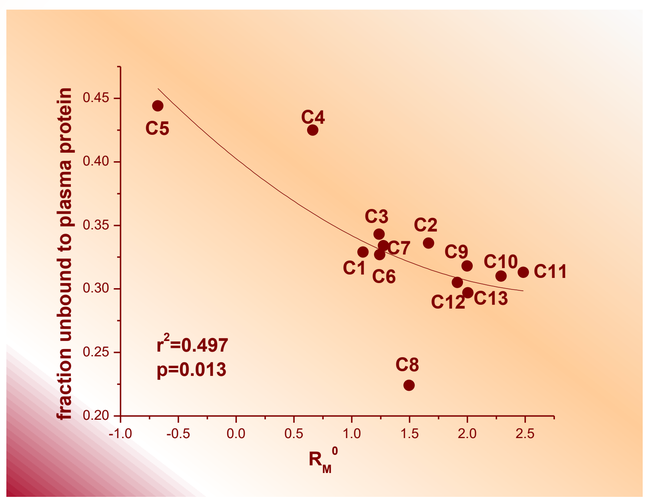
Compound	R_1	R_2
C1	-H	-H
C2	$-CH_3$	-H
C3	$-OCH_3$	-H
C4	-OH	-H
C5	-COOH	-H
C6	-H	$-COCH_3$
C7	$-COCH_3$	-H
C8	$-NO_2$	-H
C9	-Cl	-H
C10	-Br	-H
C11	-I	-H
C12	-H	-Cl
C13	-H	-Br

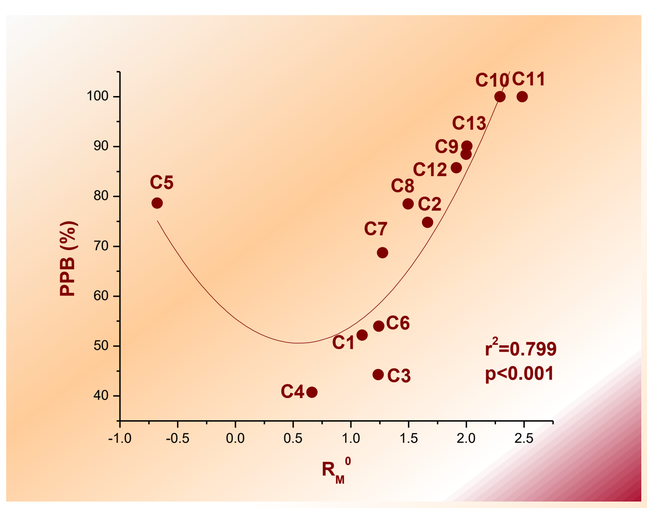
RESULTS:

Retention constants, R_M^0 for 13 newly synthesized 1-aryl-3-methyl succinimide derivates obtained by using thin-layer reversed-phase chromatography were applied as measurement of anisotropic lipophilicity. The values of the volume of distribution and plasma protein binding affinity varied depending on the software applied. Nevertheless, statistically significant parabolic correlation (r^2=0.968, p<0.001) was described between volume of distribution (i-lab 2.0 software) and anisotropic lipophilicity followed by also statistically significant parabolic association (r^2=0.965, p<0.001) between volume of distribution in stationary state Vdss (pkCSM software) and experimentally determined anisotropic lipophilicity, R_M^0 for the analyzed compounds. Furthermore, the fraction of the drug unbound to plasma proteins (calculated with pkCSM software) was correlated with anisotropic lipophilicity of the analyzed compounds and parabolic association was obtained with high statistical quality (r^2=0.497, p=0.013). In addition, the percent of the drug bound to plasma proteins, PPB (PreAdmet software) was associated with anisotropic lipophilicity for observed series of succinimide derivatives with statistical significance (r^2=0.799, p<0.001).









CONCLUSIONS:

Lipophilicity is the primary underlying structural property that governs the distribution of 1-aryl-3-methyl succinimide derivates and their affinity to bind to plasma proteins. Introducing more lipophilic substituent in the 1-aryl-3-methyl succinimide core, the higher volume of distribution is expected followed by enhanced plasma protein affinity. One should be careful when making structural modifications that change lipophilicity in order to adjust an ADMET property since other properties that are also affected by lipophilicity may be altered as well and should be monitored.