LIPOPHILICITY AS KEY FACTOR FOR ORAL BIOAVAILABILITY OF 1-ARYL-3 METHYL SUCCINIMIDE DERIVATES

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INTRODUCTION:

Prediction of bioavailability of a drug candidate in the early stage of drug design and development followed by the selection of compounds with favorable structural properties are the key for later clinical efficiency of the potential therapeutic molecule. Lipophilicity is the pivotal physico-chemical property affecting permeability through biological barriers, potency, distribution and elimination of a drug in the body. Since lipophilicity influence many biological properties, it is the most frequently applied parameter in drug discovery SAR studies.
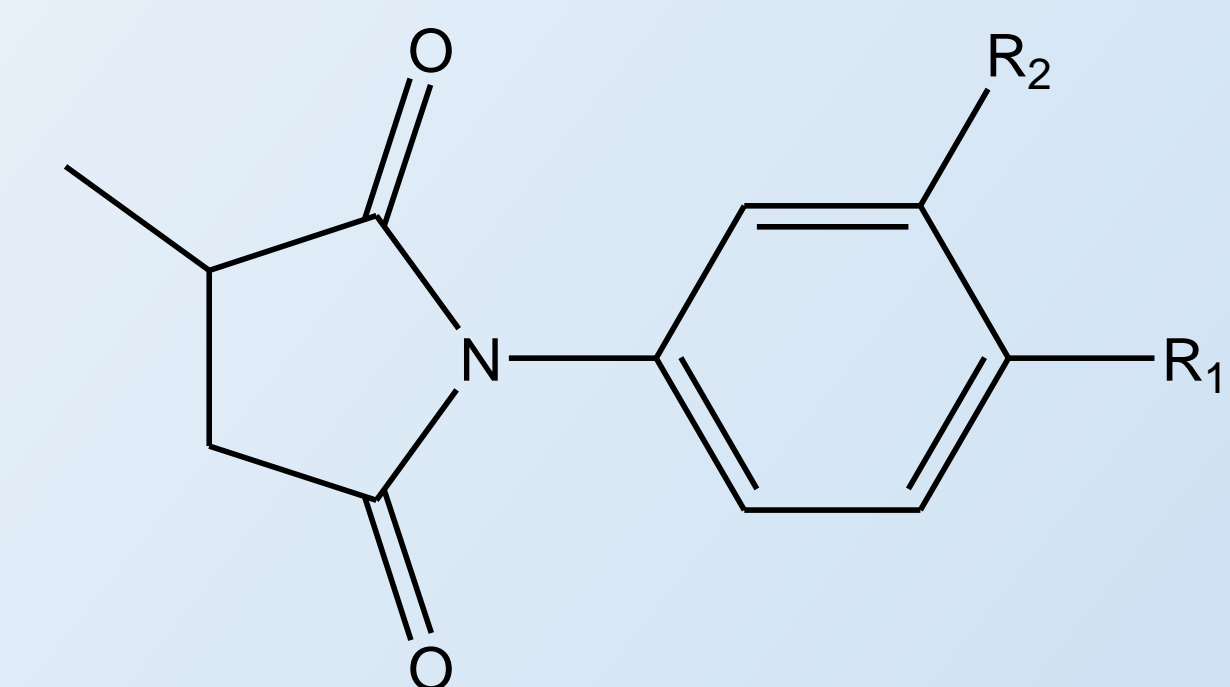
OBJECTIVES:

To assess the influence of lipophilicity on the oral absorption of newly synthesized 1-aryl-3-methyl succinimide derivates which is determined in silico as Caco-2 permeability, absorption constant and percent of absorbed molecules.
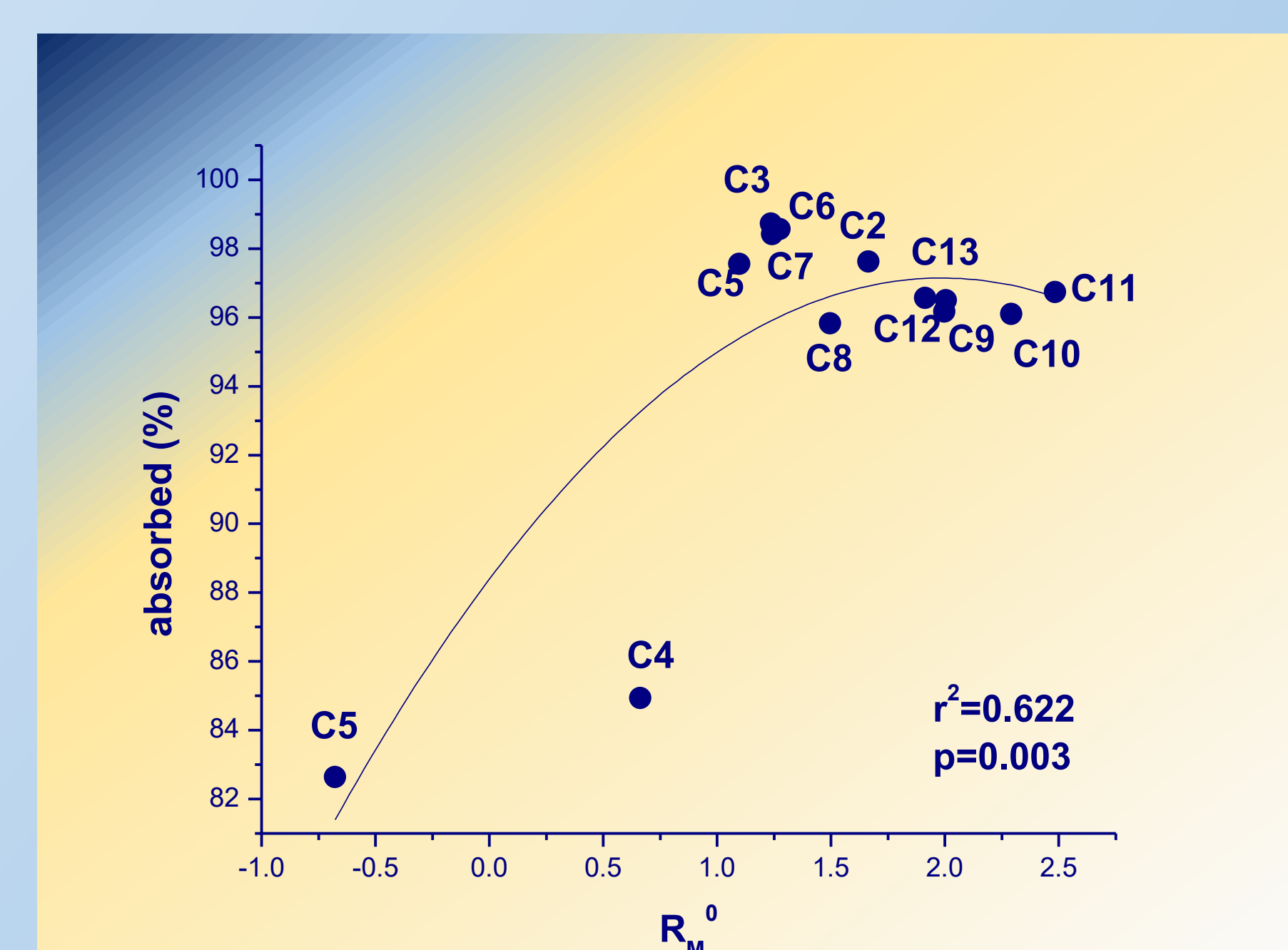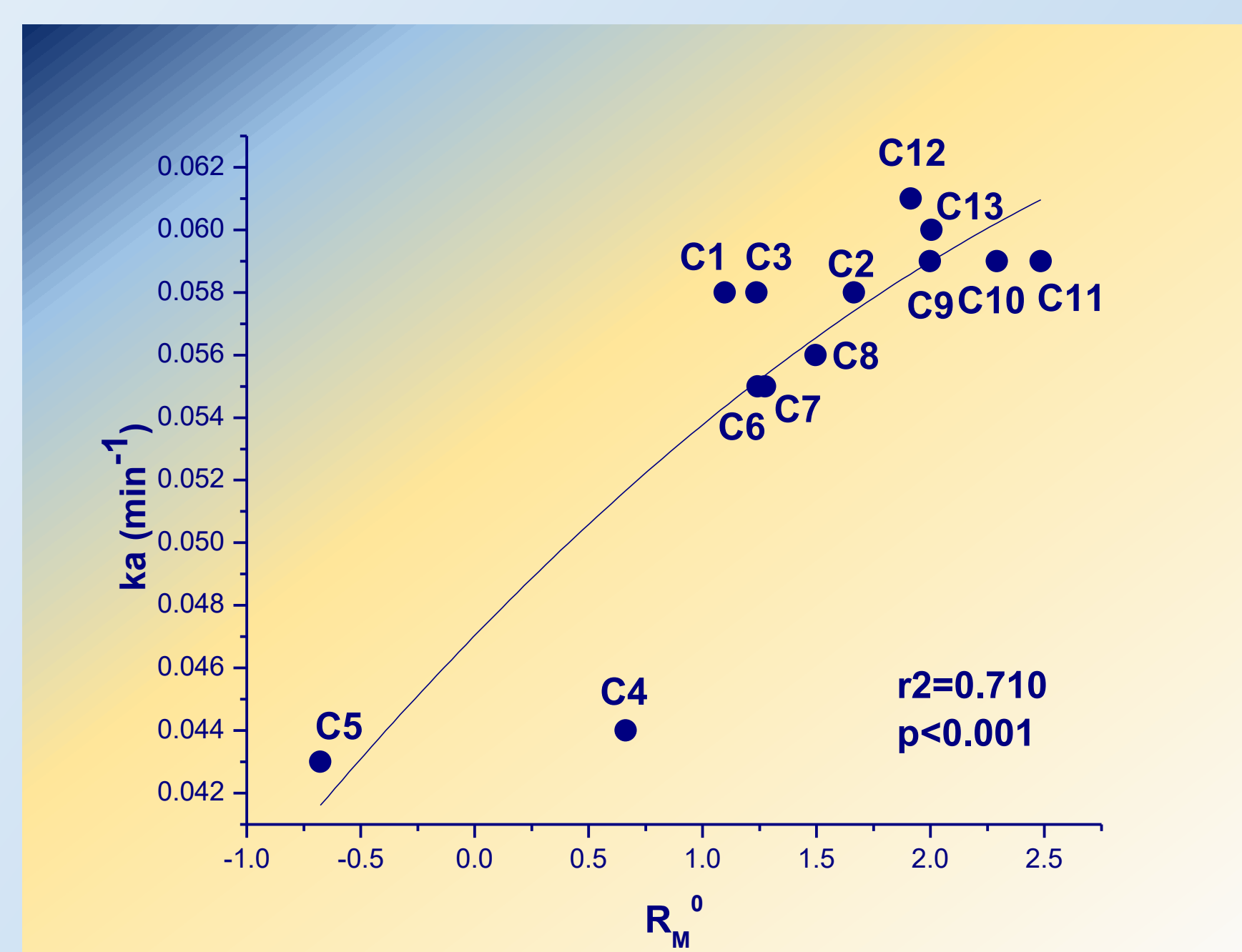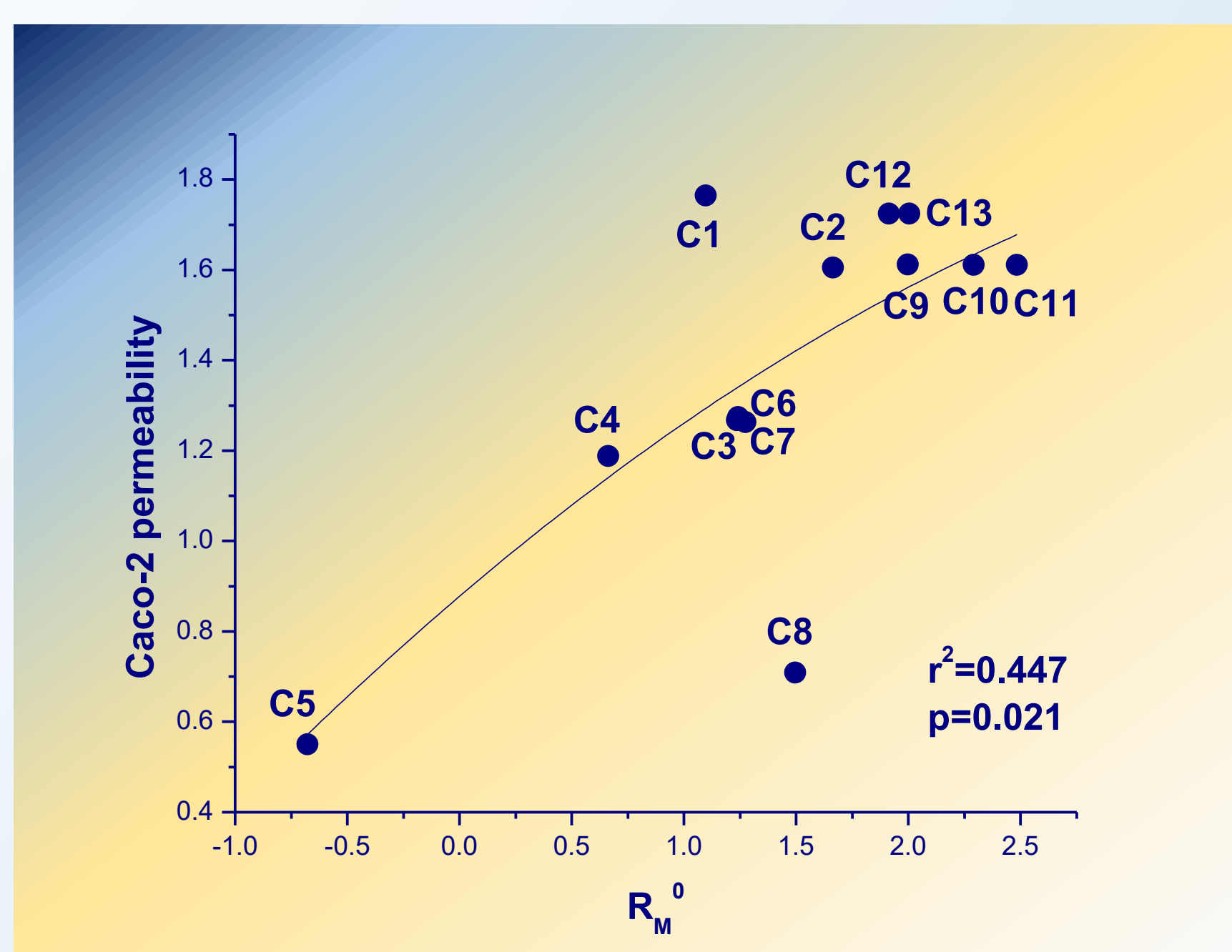
METHOD / DESIGN:

Reversed chromatography was applied to determine experimentally the anisotropic lipophilicity of thirteen newly synthesized 1-aryl-3-methyl succinimide derivates. The mobile phase was mixture of water and methanol with a varying fraction of the organic solvent while as the stationary phase precoated RP-18W/UV 254 plates (Macherey-Nagel GMBH and Co., Düren, Germany) were applied. After development, the spots were detected at 254 nm with UV lamp. Software package i-lab 2.0 (https://ilab.acdlabs.com/iLab2/) was applied for determining absorption constant, ka, while Caco-2 permeability and percent of the absorbed molecules (%absorbed) was predicted with pkCSM software (http://biosig.unimelb.edu.au/pkcsm/) for all compounds observed based on their structure.

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:

Anisotropic lipophilicity was quantified with retention constants, R_M^0 obtained by applying thin-layer reversed-phase chromatography for 13 newly synthesized 1-aryl-3-methyl succinimide derivates. All observed compounds are expected to have favorable Caco-2 permeability except compound 5 with carboxylic group. For all analyzed succinimide derivates small absorption constants and short absorption times are expected as ell as high absorption rate. Statistically significant parabolic correlation ($r^2=0.447$, $p=0.021$) was determined between Caco-2 permeability (calculated with pkCSM software) and anisotropic lipophilicity. Moreover, statistically significant parabolic association ($r^2=0.710$, $p<0.001$) was obtained between absorption constant, ka (i-lab 2.0) and experimentally determined anisotropic lipophilicity, R_M^0 for the observed compounds. Finally, the percent of the absorbed molecules, %absorbed (pkCSM software) was influenced by anisotropic lipophilicity with statistical significance ($r^2=0.622$, $p=0.003$) and described with parabolic function.

CONCLUSIONS:

Lipophilicity is a key characteristic in transport processes, including intestinal absorption and membrane permeability of 1-aryl-3-methyl-succinimide derivates. The increment of lipophilicity of the 1-aryl-3methyl succinimide core results in enhanced permeability, elevated absorption constant and enlarged bioavailability. However, the augmentation of the permeability through membranes and intestinal absorption as result of increased lipophilicity is limited probably due to consequent solubility decrement of the studied compounds.