

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

HT Caco-2 permeability: the dominant role played by solutes' hydrogen bonding donor properties

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1508134> since 2015-10-09T08:00:53Z

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

HT Caco-2 permeability: the dominant role played by solutes' hydrogen bonding donor properties

T. Potter ^{a)}, G. Ermondi ^{b)}, G. Newbury ^{a)} and G. Caron ^{b)}

a) Cyprotex Discovery Limited, 15 Beech Lane, Macclesfield, SK10 2DR, UK.

b) Molecular Biotechnology and Health Sciences Dept., University of Torino, via Quarelo 15, 10135 Torino, Italy.

Email: giulia.caron@unito.it; Web sites: www.cassmedchem.unito.it, www.cyprotex.com

Aim

To obtain a mechanistic understanding of high throughput (HT) Caco-2 permeability data.

Methods

P_{app} was determined in Caco-2 cells using a standard HT procedure: Caco-2 cells were seeded onto Millicell 96 well plates and cultured for 20 days for confluent monolayer formation. Test compounds were dosed in the apical compartment, and after 2 hours the apical and basolateral plates were separated, and samples diluted for analysis by LC/MS/MS against an 8-point calibration curve.

VS+ (v. 1.0.7, <http://www.moldiscovery.com>) using default settings and four probes (OH2, DRY N1 and O probes that mimic respectively water, hydrophobic, HBA and HBD properties of the environment) were used to build a PLS model. The Block Relevance (BR) analysis was performed as described elsewhere (*MedChemComm*, 2013, 4, 1376).

Results

Experimental log P_{app} values of the compounds belonging to the training set (n = 54) were imported into VS+ as response variables (Y) and a relation between Y and the 82 VS+ descriptors (X) was sought using the PLS algorithm. A model was found. Internal and external validations (for the test set n = 31) were performed. A mechanistic interpretation was obtained by the BR analysis which enables the organization of the VS+ descriptors in six blocks (Size, Water, Hydrophobicity, O, N1 and Others).

BR analysis outlined the major role (about 35% of the weight of all blocks) played by HBD solute properties to govern Caco-2 permeability. The role of HBA solute groups by contrast is modest and similar to all remaining blocks.

Conclusion

BR analysis is a new tool that facilitates the mechanistic interpretation of PLS models; it can replace solvation equations and go beyond them since the nature of VS+ descriptors introduces the 3rd dimension and the ionization in the models.