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

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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 basolatoral 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.