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CNS permeability parameters determination through a statistical analysis driven approach

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INTRODUCTION

With the increasing number of people affected by neurological disorders, new and successful drugs are continually needed [1]. A suitable blood-brain barrier (BBB) penetration is mandatory in the process of drug development although its achievement represents many hurdles. Indeed, the BBB represents a restricted gateway allowing specific nutrients and hormones to selectively permeate. However, this sophisticated protection system has ever hindered the development of molecules able to cross BBB since the standard pharmacokinetic parameters such as oral bioavailability and plasma concentration are not enough to evaluate drug exposure and time course in the brain [2].

Over the years, a number of researchers has attempted to define the features for a successful BBB crossing, using different starting data sets that inevitably had led to different conclusions [3]. Selected studies have considered population distribution, or variation in minimum, maximum and mean of certain parameters of the two BBB set. Other are based on more complex algorithms or quantitative structure-activity relationship analysis [4,5].

AIM OF THE WORK: In the effort to expand the plethora of information collected so far in this field, we are interested in contributing to define a simple set of rules that would prospectively be used for the design or identification of compounds able or not to cross the BBB.

WORKFLOW

1) DATASET GENERATION: The literature was scanned and articles selected weather or not they contained information over chemical compounds ability in crossing BBB. The dataset was split into BBB permeable (BBB^+, logBB >0.0, BB ratio >1.0) and BBB non-permeable (BBB^-, logBB <0.0, BB ratio <1.0), excluding compounds with BB ratio equal to 1.

$$logBB = log\frac{C_{brain}}{C_{blood}}$$

- **BBB^+** 174 compounds
- **BBB^-** 146 compounds

2) MOLECULAR DESCRIPTORS COMPUTATION AND ANALYSIS: For each compound, a series of 15 descriptors was computed with JChem for excel provided by ChemAxon. Therefore, descriptors have been binned in 5 groups giving a large enough sample to provide a statistically valid analysis.

3) 2×5 CONTINGENCY TABLES: BBB "positive/negative" has been crossed by the mean of logBB with a descriptor binned in 5 ranges. Observed and expected distributions were calculated and % deviations (% dev) measured. Conditional probabilities, fold enrichments, and a chi-square contingency table test with Yates correction performed to evaluate the statistical significance of the chi-squared distribution.

RESULTS

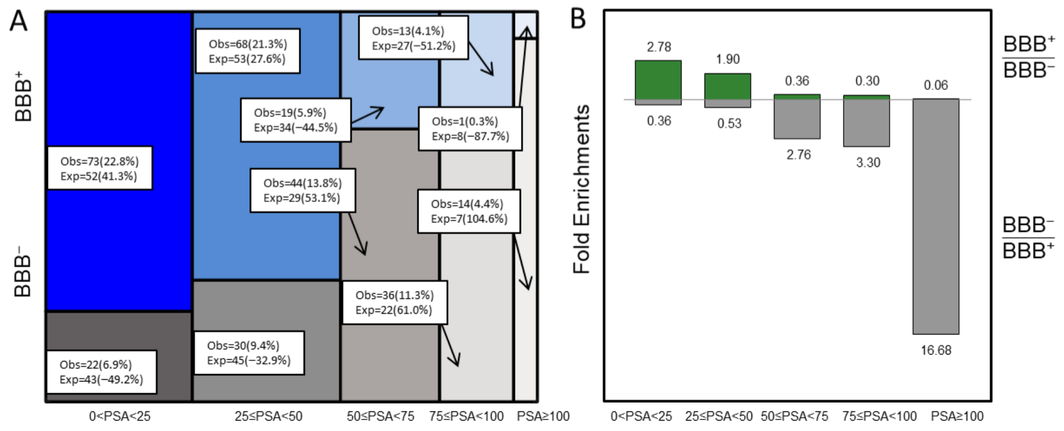
Over 15 descriptors, six resulted to be not significant that means the distribution within the five–descriptor groups and the two logBB set (BBB^+, logBB >0.0, BB ratio >1.0; BBB^-, logBB <0.0, BB ratio <1.0) does not show significant variation.

Descriptor scores

Type	PSA	NOC	logP	NC	logD	OC	IS	HBA	HBD	MW	RC	MR	HAC	AC	RBC
Enrichment	66.79	51.17	47.38	38.29	36.80	35.83	32.02	30.80	29.29	11.18	6.61	6.01	5.68	5.48	4.05
p value	1.08×10^{-13}	2.06×10^{-10}	1.27×10^{-9}	9.77×10^{-8}	1.98×10^{-7}	3.13×10^{-7}	3.19×10^{-7}	3.36×10^{-6}	6.81×10^{-6}	2.46×10^{-2}	1.58×10^{-1}	1.99×10^{-1}	2.24×10^{-1}	2.42×10^{-1}	4.00×10^{-1}
p	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	-	-	-	-	-	-

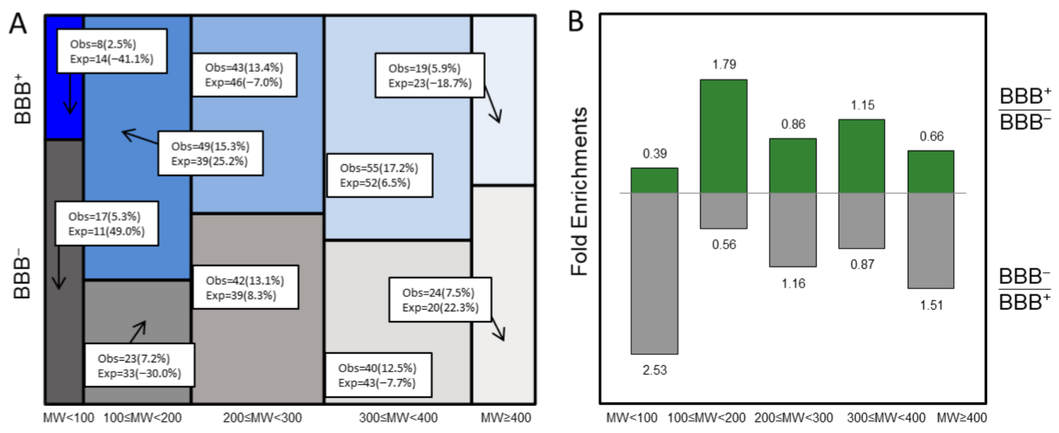
PSA: Polar Surface Area; NOC: Nitrogen and Oxygen Count; NC: Nitrogen Count; OC: Oxygen Count; IS: Ionization State; HBA: Hydrogen Bond Acceptor: HBD: Hydrogen Bond Donor; MW: Molecular Weight; RC: Ring Count; MR: Molar Refractivity; HAC: Heavy Atom Count; AC: Atom Count; RBC: Rotable Bond Count

PSA has demonstrated to be the most significative descriptor within the series with chi-squared enrichment of 66.79 and *p*=1.08 x 10^{-13}.



- In **BBB^+/0<PSA<25** there is a fold enrichment of 2.78 times respect to **BBB^-/0<PSA<25** with 73 observed compounds vs 52 expected (+41.3% dev), and 22 observed compounds vs 43 expected (–49.2% dev) for BBB^- .
- The tendency is kept in **BBB^+/25≤PSA<50** (BBB^+/BBB^- fold enrichment 1.90), with 68 observed compounds vs 53 expected (+27.6% dev), and 30 observed compounds vs 45 expected (–32.9% dev).
- An inverted trend is observed **with higher values of PSA**, representing a prerogative of molecules that do not cross the BBB.

MW (enrichment 11.18; *p*= 2.46 x 10^{-2}) has been found to be a parameter not essential by itself for having a better CNS permeation.

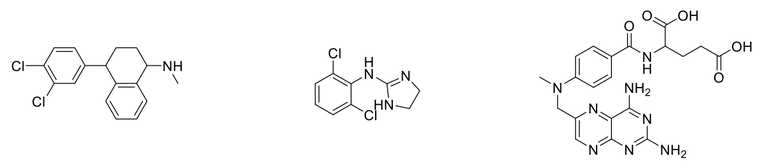


- MW shows a low variation of its chi-squared distribution that resulted to be not significative according to the test.
- The population within the ten quadrants does not provide sufficient variation for correlating MW with a BBB^+/BBB^- variation.
- Also HAC, AC and MR have a not-significative distribution suggesting that parameters describing the mass and size of the molecules do not contribute to a better or worst accumulation within the CNS.

Depending on the combination of multiple descriptors, we set a **three cases probabilistic scenario** attributing a value of**:**

- fold enrichment $BBB^+/BBB^- \geq 1.33$ (green)
- fold enrichment $BBB^-/BBB^+ \geq 1.33$ (red)
- intermediate fold enrichment (yellow)

The not-significative computed descriptors may be considered as BBB^+/BBB^-, since no statistically significant difference between BBB^+ and BBB^- has been found.



Sertraline			
logP	logD	PSA	HBA
5.15	3.02	16.61	1
HBD	NC	OC	NOC
1	1	0	1
IS			
Basic			
logBB=1.6			

Clonidine			
logP	logD	PSA	HBA
2.49	1.66	38.03	3
HBD	NC	OC	NOC
2	3	0	3
IS			
Basic			
logBB=0.11			

Methotrexate			
logP	logD	PSA	HBA
−0.24	−6.56	216.20	12
HBD	NC	OC	NOC
5	8	5	13
IS			
Acid			
logBB=−1.51			

- Sertraline (logBB: +1.6) is a compound with good descriptors distribution having all 9 significative descriptors in the BBB^+ range.
- Clonidine (logBB: +0.11) shows 6 descriptors in BBB^+, 1 in BBB^+/BBB^- and 2 in BBB^-.
- Methotrexate (logBB: −1.51) has a BBB^- distribution for the 9 descriptors. Indeed, methotrexate is a compound with no ability to accumulate within the CNS.

CONCLUSION

The purpose of this work was to create a simple set of rules that could prospectively support the development and identification of CNS, non-CNS or mixed drugs. We statistically analyzed a set of compounds and correlated their logBB with common computed descriptors in order to evaluate significant variations in the properties of the BBB^+ and BBB^- populations. Over the evaluated computed descriptors, nine resulted to be significant for the ability of a molecule to cross the BBB, while six have shown to not influence the BBB permeation. The work has allowed to define a set of rules that would eventually be used to tune the properties for BBB permeation.

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