Supplementary Material 1

Design, synthesis and antimycobacterial activity of hybrid molecules combining pyrazinamide with 4-phenylthiazol-2-amine scaffold

Jan Zitko, Ondřej Janďourek, Pavla Paterová, Lucie Navrátilová, Jiří Kuneš, Jarmila Vinšová, Martin Doležal

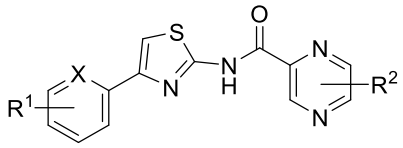
MycPermCheck – prediction *of M. tuberculosis* permeability

Structures were drawn manually in Maestro, Schrödinger Suite (Release 2014-2; Schrödinger, Inc.) , converted to 3D and prepared using LigPrep (energy minimization using OPLS_2005 force field, generation of possible states at pH 7.0 ± 2.0 using Epic, without generation of tautomers). QikProp module was used to calculate molecular descriptors of the compounds. The resulting CSV file was used as an input for online application MycPermCheck v1.1.[1,2]

Table 1. Summary of QikProp descriptors used for the calculation and their optimal values derived from permeable compounds (values taken from ref[1], see the reference for detailed explanation.)

Descriptor	Definition	Optimal value for permeable compounds
FOSA	Hydrophobic component of the SASA (saturated carbon and attached hydrogen).	90.8–272.23 Å^2
QPlogPo/w	Predicted octanol/water partition coefficient.	2.779–4.479
PISA	The π-interacting part of the solvent accessible surface area (carbon and attached hydrogen).	205.16–355.49 Å^2
accptHB	Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution, Values are averages taken over a number of configurations, so they can be non-integer.	3.750–6.000
glob	Globularity descriptor, where r is the radius of a sphere with a volume equal to the molecular volume. Globularity is 1.0 for a spherical molecule.	0.794–0.839

Table 2. MycPermCheck v1.1 results



Compound					QikProp Descriptors				
No.	**R^1**	**X**	**R^2**	**Prob.**	**FOSA**	**QPlogPo/w**	**PISA**	**accptHB**	**glob**
7a	H	CH	H	**0.628**	0	2.143	381.05	6.50	0.83684
7b	4-F	CH	H	**0.627**	0	2.626	333.45	6.50	0.82706
7c	4-Cl	CH	H	**0.614**	0	2.375	343.05	6.50	0.83286
7d	4-OCH_3	CH	H	**0.516**	92.712	2.225	325.34	7.25	0.82597
7e	3,4-$(OCH_3)_2$	CH	H	**0.435**	175.997	2.340	290.70	8.00	0.80552
7f	H	N	H	**0.539**	0	1.560	363.17	7.50	0.83650
8a	H	CH	5-Cl	**0.663**	0	2.878	336.24	6.00	0.82578
8b	4-F	CH	5-Cl	**0.65**	0	3.111	298.24	6.00	0.82200
8c	4-Cl	CH	5-Cl	**0.662**	0	3.365	288.65	6.00	0.81649
8d	4-OCH_3	CH	5-Cl	**0.553**	92.712	2.963	280.53	6.75	0.81542
8e	3,4-$(OCH_3)_2$	CH	5-Cl	**0.475**	176.028	3.129	245.81	7.50	0.79600
8f	H	N	5-Cl	**0.576**	0	2.290	318.36	7.00	0.82548
9a	H	CH	6-Cl	**0.634**	0	2.674	336.32	6.50	0.82574
9b	4-F	CH	6-Cl	**0.62**	0	2.907	298.31	6.50	0.82196
9c	4-Cl	CH	6-Cl	**0.633**	0	3.159	288.72	6.50	0.81645
9d	4-OCH_3	CH	6-Cl	**0.521**	92.715	2.752	280.65	7.25	0.81532
9e	3,4-$(OCH_3)_2$	CH	6-Cl	**0.443**	176.006	2.921	245.94	8.00	0.79593
9f	H	N	6-Cl	**0.545**	0	2.087	318.44	7.50	0.82544

impermeable (prob. < 0.52)
intermediate permeability
permeable (prob. > 0.60)

blue-scale: the darker colour, the further is the value from optimum for permeation derived from the active (permeable) training set of the MycPermCheck model

References:

1. Merget, B.; Zilian, D.; Muller, T.; Sotriffer, C. A. *Bioinformatics* **2013,** *29*, 62.
2. MycPermCheck. Available online at http://www.mycpermcheck.aksotriffer.pharmazie.uni-wuerzburg.de/. (Accessed March 24, 2017).