Supplementary

Multitargeting the Action of 5-HT$_6$ Serotonin Receptor Ligands by Additional Modulation of Kinases in the Search for a New Therapy for Alzheimer's Disease: Can It Work from a Molecular Point of View?

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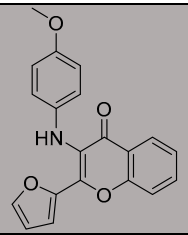
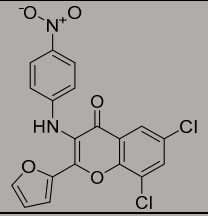
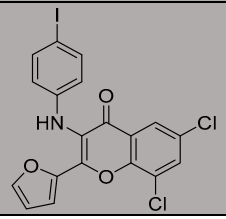
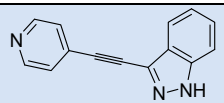
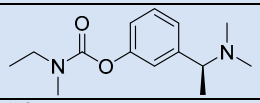
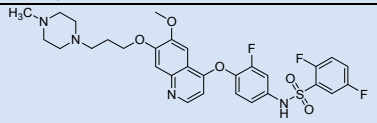
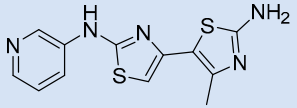
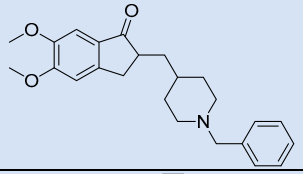
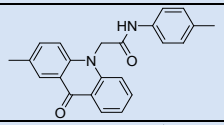
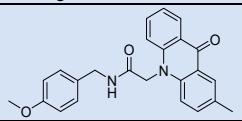
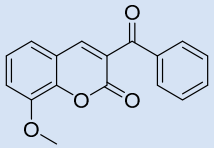
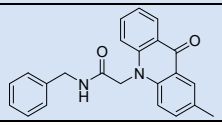
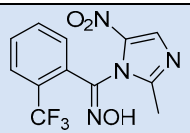
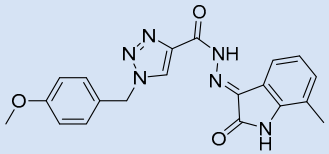
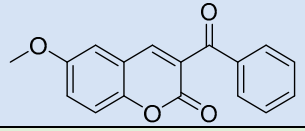
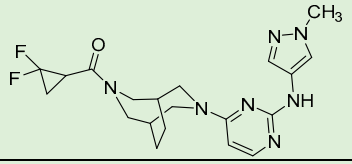
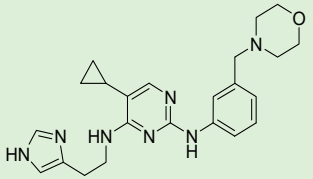
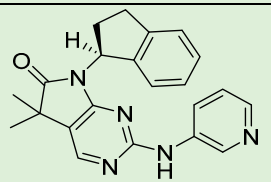
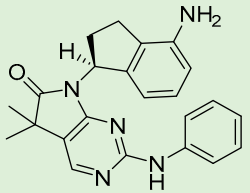
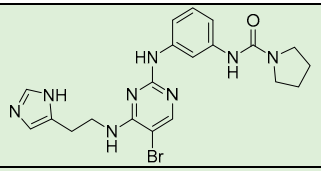
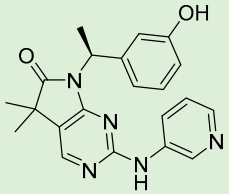
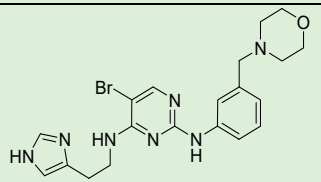
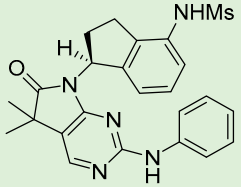
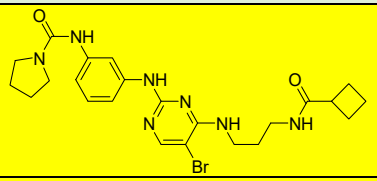
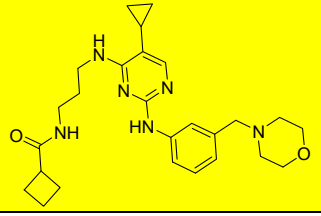
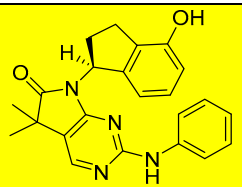
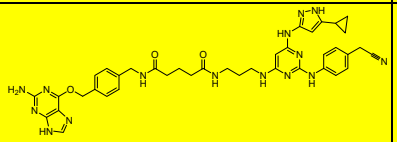
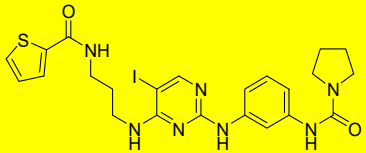
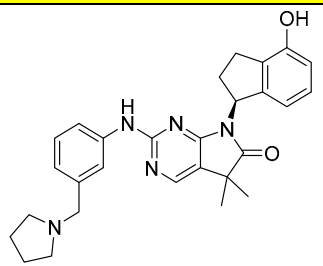
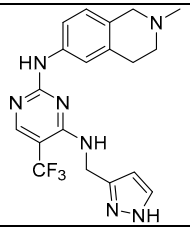
Table S1. MARK4 inhibitors described in literature

Cpd	Structure	SMILES	MARK4 inhibition				FA
			IC$_{50}$ (μM)	% (1 μM)	% (10 μM)	Kd (μM)	
S1		O=C1C(NC2=CC=C(OC)C=C2)=C(C3=CC=CO3)OC4=C1C=CC=C4	5560				2.26
S2		O=C1C(NC2=CC=C([N+]([O-])=O)C=C2)=C(C3=CC=CO3)OC4=C1C=C(Cl)C=C4Cl	2120				2.67
S3		O=C1C(NC2=CC=C(I)C=C2)=C(C3=CC=CO3)OC4=C1C=C(Cl)C=C4Cl	1980				2.7

S4		C1(C#CC3=CC=NC=C3)=NNC2=C1C=CC=C2			>50		**5**
S5		CCN(C(OC1=CC=CC([C@@H](N(C)C)C)=C1)=O)C	6.94				**5.16**
S6		O=S(C1=CC(F)=CC=C1F)(NC2=CC=C(OC4=C3C=C(OC)C(OCCCN5CCN(C)CC5)=CC3=NC=C4)C(F)=C2)=O				5.975	**5.22**
S7		CC(N=C(N)S1)=C1C2=CSC(NC3=CN=CC=C3)=N2			83		5.22
S8		O=C1C(CC2=CC(OC)=C(OC)C=C21)CC3CCN(CC3)CC4=CC=CC=C4	5.3				**5.28**
S9		O=C(NC2=CC=C(C)C=C2)CN(C4=C3C=CC=C4)C1=CC=C(C)C=C1C3=O	4.5				**5.35**
S10		O=C(NCC2=CC=C(OC)C=C2)CN(C4=C3C=CC=C4)C1=CC=C(C)C=C1C3=O	2.20				**5.66**
S11		O=C1OC2=C(OC)C=CC=C2C=C1C(C3=CC=CC=C3)=O	2.09				**5.68**
S12		O=C(NCC2=CC=CC=C2)CN(C4=C3C=CC=C4)C1=CC=C(C)C=C1C3=O	1.8				**5.75**

S13		CC1=NC=C([N+]([O-])=O)N1C(C2=C(C(F)(F)F)C=CC=C2)=NO	1.74				**5.76**
S14		O=C(C1=CN(CC2=CC=C(OC)C=C2)N=N1)N/N=C3C(NC4=C/3C=CC=C4C)=O	1.54				5.81
S15		O=C1OC2=CC=C(OC)C=C2C=C1C(C3=CC=CC=C3)=O	1.3				**5.89**
S16		CN(N=C1)C=C1NC2=NC=CC(N3CC(CN(C(C4C(F)(F)C4)=O)C5)CCC5C3)=N2		59%			6.07
S17		C1(NC2=CC=CC(CN4CCOCC4)=C2)=NC=C(C5CC5)C(NCCC3=CNC=N3)=N1	0.808				6.09
S18		O=C(C1(C)C)N([C@]2([H])C(C=CC=C3)=C3CC2)C4=C1C=NC(NC5=CN=CC=C5)=N4	0.520				6.28
S19		O=C(C1(C)C)N([C@]2([H])C(C=CC=C3N)=C3CC2)C4=C1C=NC(NC5=CC=CC=C5)=N4	0.450				6.35

S20		BrC1=CN=C(NC2=CC(NC(N3CCCC3)=O)=CC=C2)N=C1NCCC4=CN=CN4	0.338				6.47
S21		O=C(C1(C)C)N([C@@H](C)C2=CC=CC(O)=C2)C3=C1C=NC(NC4=CN=CC=C4)=N3	0.270				6.56
S22		BrC1=CN=C(NC3=CC=CC(CN4CCOCC4)=C3)N=C1NCCC2=CNC=N2	0.214				**6.69**
S23		O=C(C1(C)C)N([C@]2([H])C(C=CC=C3NS(C)(=O)=O)=C3CC2)C4=C1C=NC(NC5=CC=CC=C5)=N4	0.180				6.75
S24		O=C(N2CCCC2)NC1=CC=CC(NC3=NC=C(Br)C(NCCCNC(C4CCC4)=O)=N3)=C1	0.072				**7.14**
S25		O=C(C3CCC3)NCCCNC1=NC(NC4=CC=CC(CN5CCOCC5)=C4)=NC=C1C2CC2	0.041				**7.39**

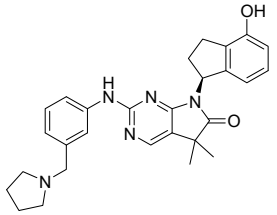
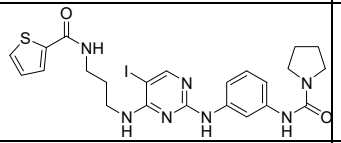
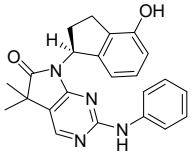
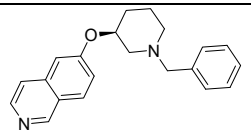
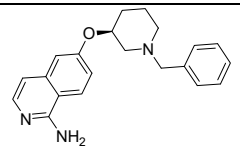
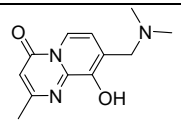
S26		O=C(C1(C)C)N([C@]2([H])C(C=CC=C3O)=C3CC2)C4=C1C=NC(NC5=CC=CC=C5)=N4	0.021				7.68
S27		O=C(CCCC(NCC5=CC=C(COC6=NC(N)=NC7=C6N=CN7)C=C5)=O)NCCCNC1=CC(NC2=NNC(C4CC4)=C2)=NC(NC3=CC=C(CC#N)C=C3)=N1	0.021				**7.68**
S28		O=C(N2CCCC2)NC1=CC=CC(NC3=NC=C(I)C(NCCCNC(C4=CC=CS4)=O)=N3)=C1	0.019				**7.72**
S29		CC(C(N1[C@H]2CCC3=C2C=CC=C3O)=O)(C)C(C1=N4)=CN=C4NC5=CC=CC(CN6CCCC6)=C5	0.002				**8.70**
S30		CN1CCC2=CC(NC3=NC=C(C(F)(F)F)C(NCC4=NNC=C4)=N3)=CC=C2C1	0.00201				**8.7**

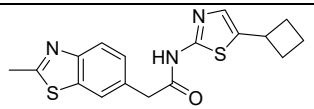
The range of activity (FA range) is discriminated with different colors.

Formal activity (FA) descriptor of the inhibiting action, calculated according to the data provided [1-13], as follows:

a) FA = pIC_{50}
b) FA= pKd
c) FA = p(the given concentration/0.02 x %inhibition)

Table S2. Selected ADMET properties calculated with pkCSM software (http://biosig.unimelb.edu.au/pkcsm/prediction) [14] for the most active kinase inhibitors fitted in pharmacophore features of the 5-HT$_6$R ligands

		Absrorption		Distribution	Toxicity	
Cpd	**Structure**	**[1]Caco-2 permeability**	**[2]Intestinal absorption [%]**	**[3]CNS Permeability**	**hERG I inhibitor**	**[4]Oral Rat Acute Toxicity (LD_{50})**
23		0.848	88.83	-2.11	No	3.207
24		0.592	75.89	-2.553	No	2.344
25		0.685	92.87	-1.933	No	2.628
31		1.66	94.376	-1.257	No	3.069
32		1.184	90.671	-1.908	No	2.802
44		1.115	100	-3,317	No	2.623

47		1.388	89.803	-1,886	No	2.974
Ref.	**Donepezil**	1.001	93.076	-1.933	No	2.886

[1]Caco-2 > 0.9 for high permeable compounds; [2]poor intestinal absorption < 30%; [3]CNS permeability: logPS> -2 (high), -3≤ logPS ≤-2 (moderate), logPS< -3 unable; [4]LD_{50} [mol/kg b.w.]. [5]Ref.

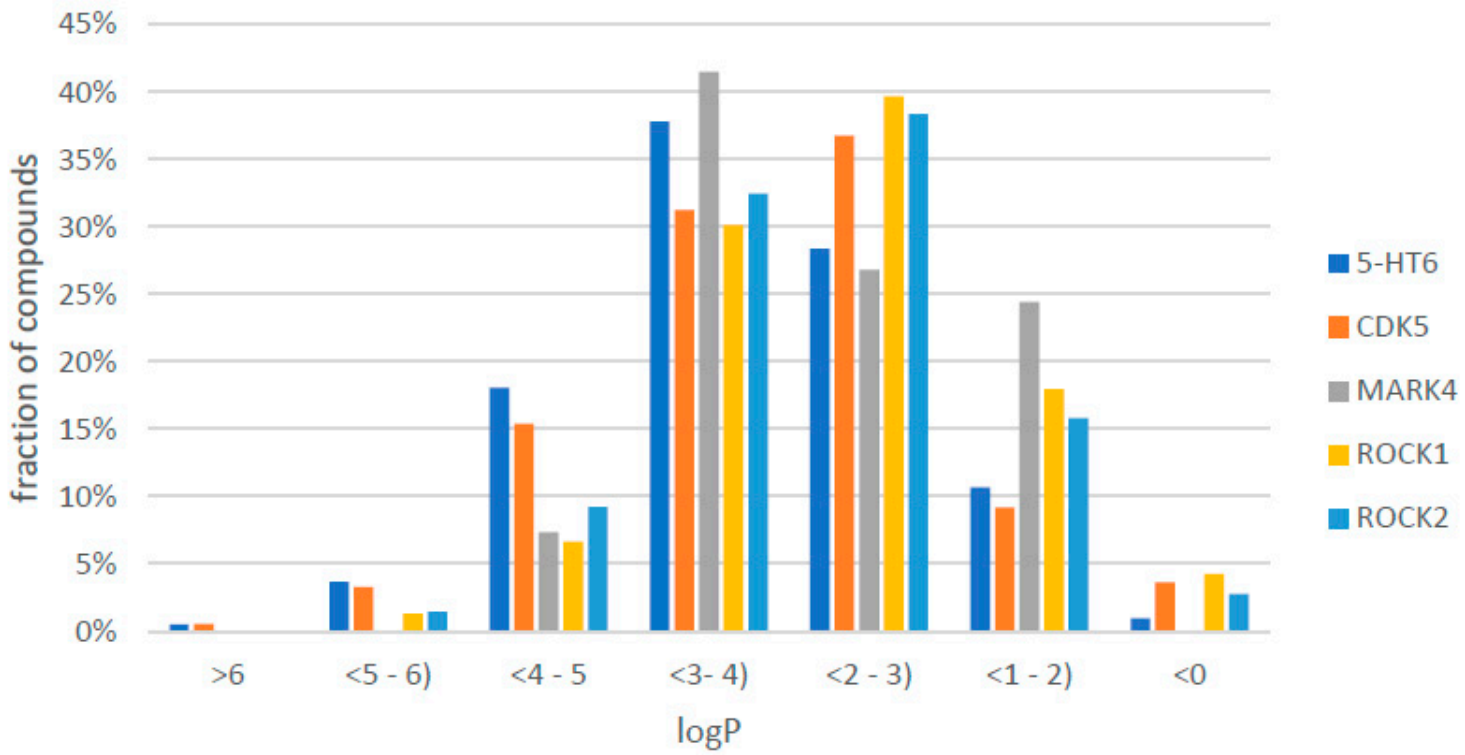


Figure S1. Distribution of logP values for the examined ligands.

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References

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4. Peerzada, M.N.; Khan, P.; Khan, N.S.; Avecilla, F.; Siddiqui, S.M.; Hassan, Md.I.; Azam, A. Design and Development of Small-Molecule Arylaldoxime/5-Nitroimidazole Hybrids as Potent Inhibitors of MARK4: A Promising Approach for Target-Based Cancer Therapy. *ACS Omega* **2020**, *5*, 22759–22771, doi:10.1021/acsomega.0c01703.

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