Identification and computational characterization of isomers with cis and trans amide bonds in folate and analogues

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(Electronic Supplementary Information)

Table S1: Composition of the model systems for the MD simulations of the studied ligands

Ligand	Isomer	N_{ligand}	N_{H2O}	N_{Na+}	N_{Cl-}
FA	trans	1	4013	13	11
	cis	1	4013	13	11
MTX	trans	1	4013	13	11
	cis	1	4009	13	11
MTHF	trans	1	4011	13	11
	cis	1	4010	13	11
PON	trans	1	4010	12	12
	cis	1	4010	12	12

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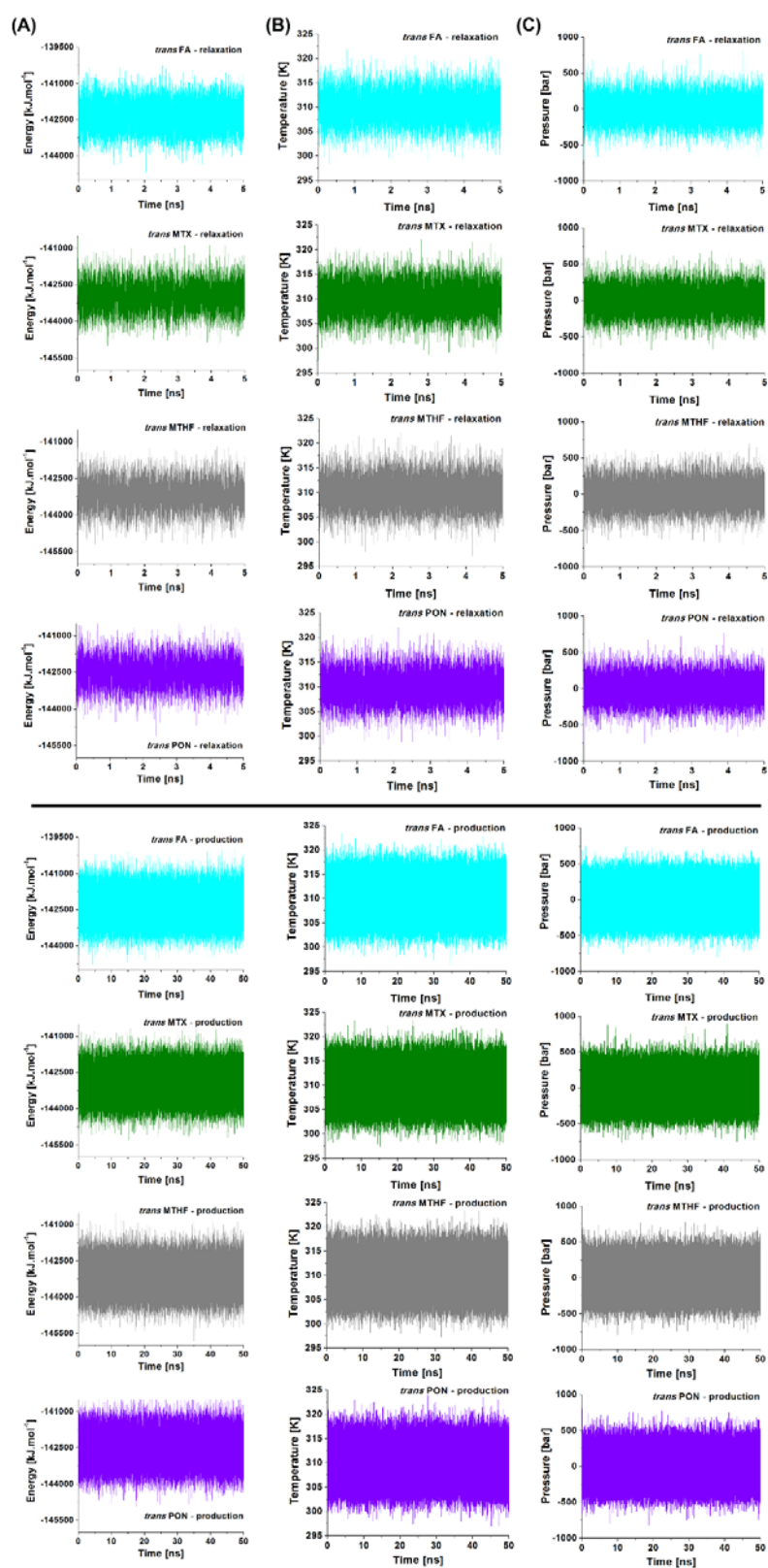
Figure S1: Time evolution of the (A) total energy, (B) temperature, and (C) pressure during the equilibration (top) and the last 50 ns of the production stage (bottom) of the MD simulations of the four studied ligands with *trans* configuration of the amide bond
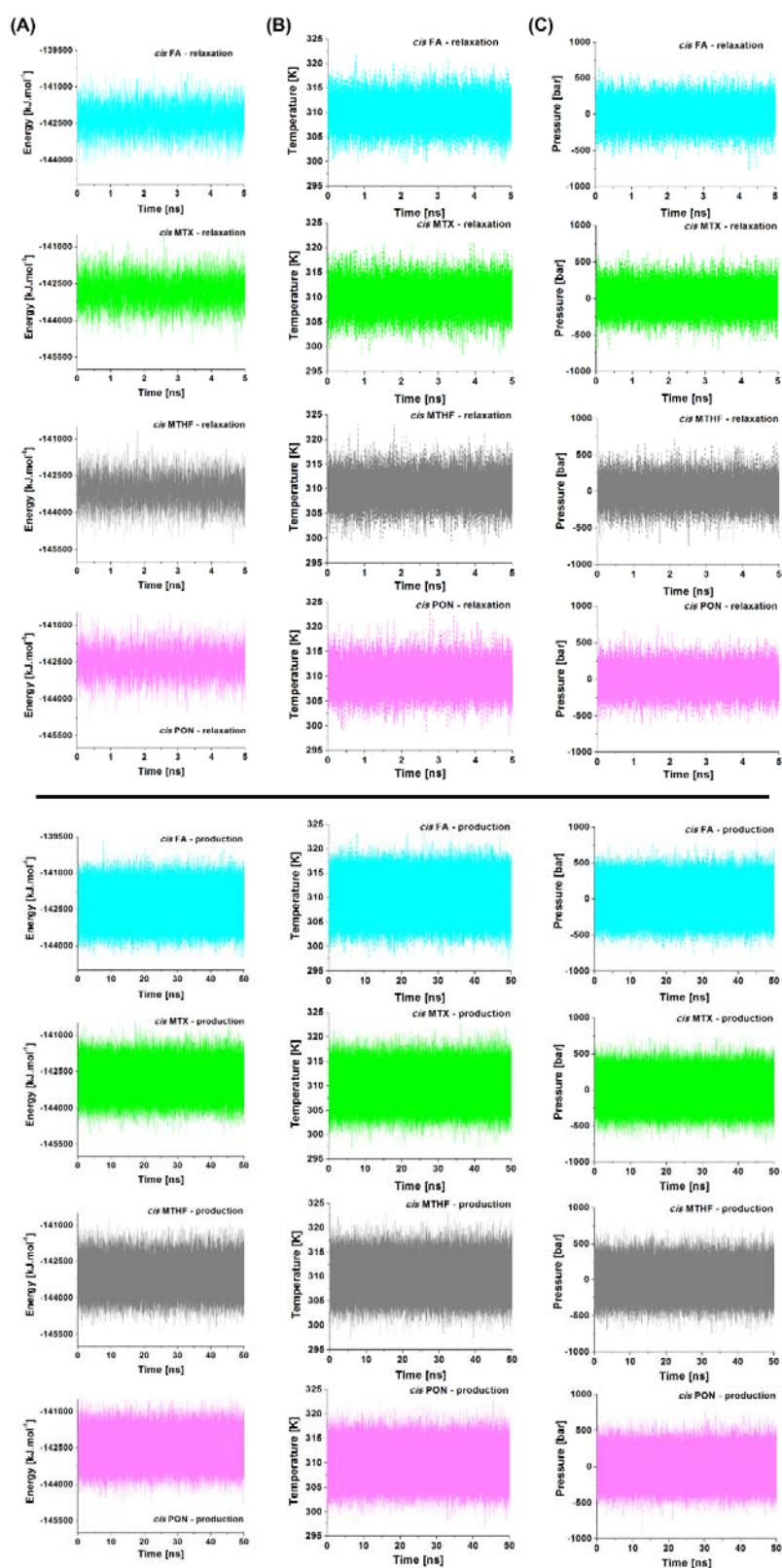
Figure S2: Time evolution of the (A) total energy, (B) temperature, and (C) pressure during the equilibration (top) and the last 50 ns of the production stage (bottom) of the MD simulations of the four studied ligands with *cis* configuration of the amide bond
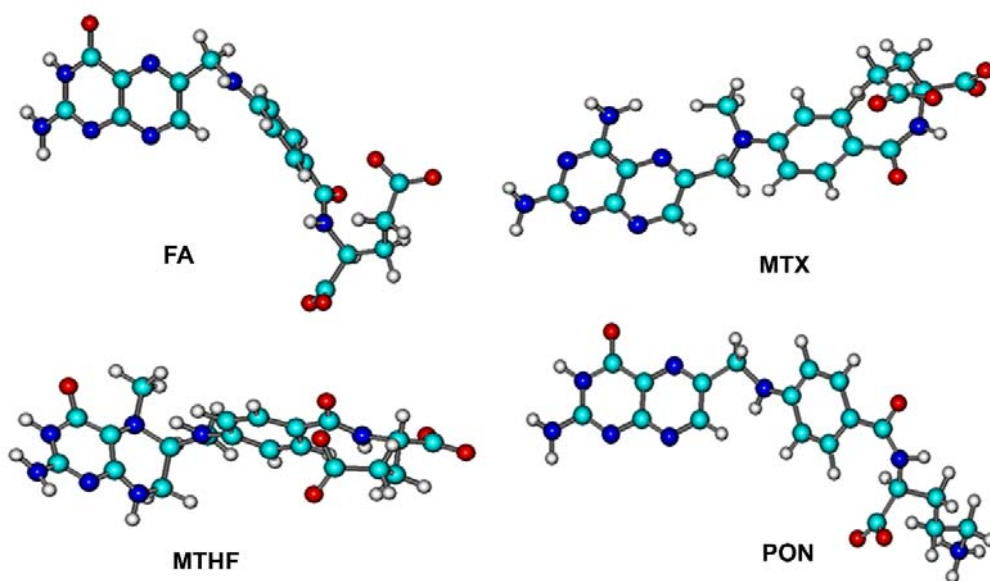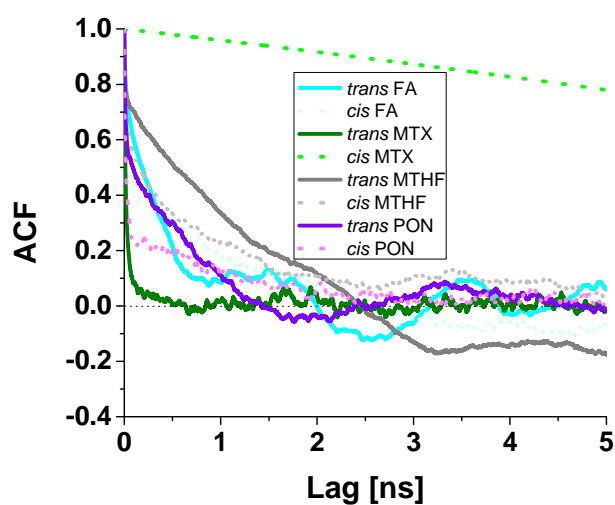
Figure S3: Molecular structures of the most stable conformers from the conformational search of folate, methotrexate, 5-methyl tetrahydrofolate, and pteroyl ornithine

Molecule	τ_c, ns	R^2
trans FA	0.42	0.840
cis FA	1.69	0.970
trans MTX	0.03	0.821
cis MTX	>5[#]	---
trans MTHF	1.75	0.985
cis MTHF	>5[#]	---
trans PON	0.50	0.909
cis PON	4.34*	0.870

[#]The ACF does not reach zero within 5 ns lag.

*The value is extracted from a three-exponential-decay fit.

Figure S4: (left) Autocorrelation functions of the RMSD values of the atomic coordinates of the ligands and (right) characteristic times for substructure transitions; the R^2 values of the single-exponential-decay fits of the first 10 % of the ACF are also provided
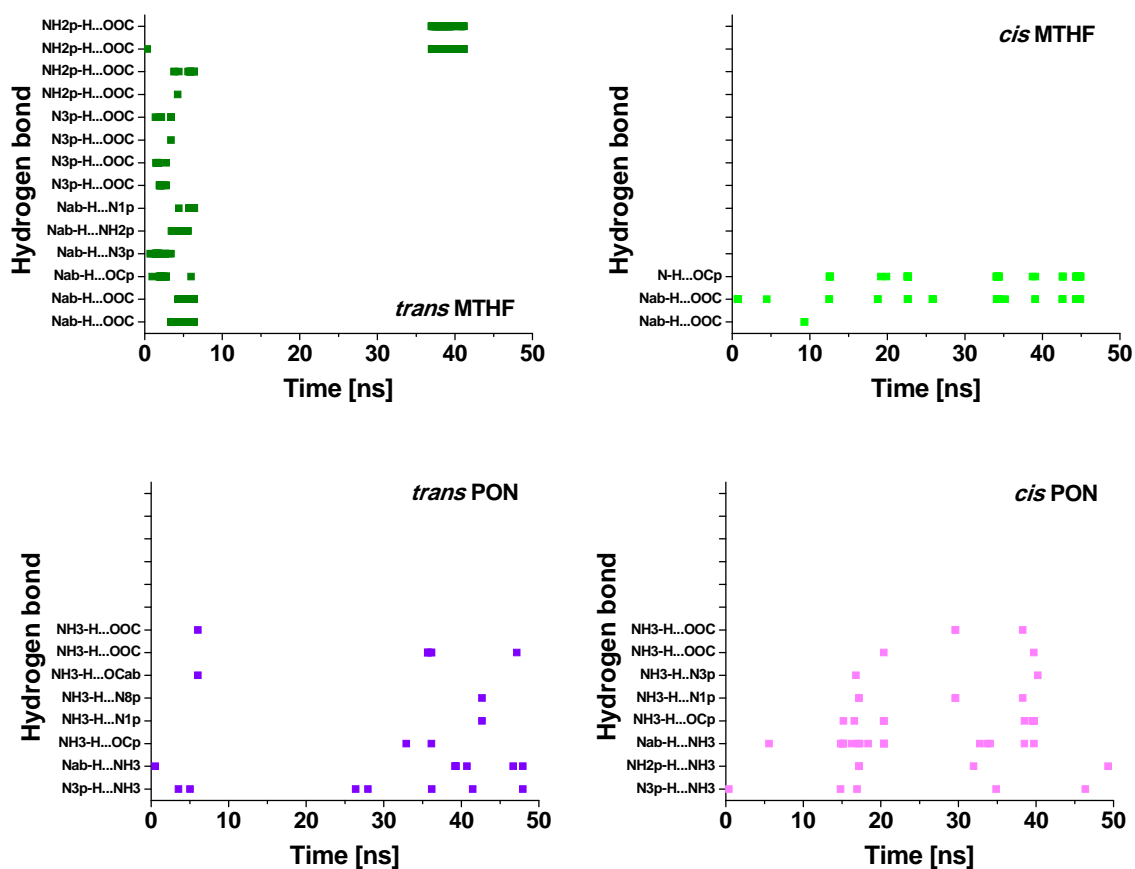
Figure S5: Existence maps of the intramolecular hydrogen bonds formed in (left) *trans* and (right) *cis* MTHF (top) and PON (bottom) during the last 50 ns of the MD simulations; only the bonds with lifetime > 5 ps are shown; the abbreviation 'ab' stands for amide bond and 'p' – for pterin

Table S2: Summed up NBO charges of the fragments of the ligands aside from the amide bond calculated with the two quantum chemical methods for the most populated MD geometries; R denotes the part of the molecules containing pteroyl, linker, and phenyl, while R' stands for the glutamate (ornithine) terminus past the amide bond

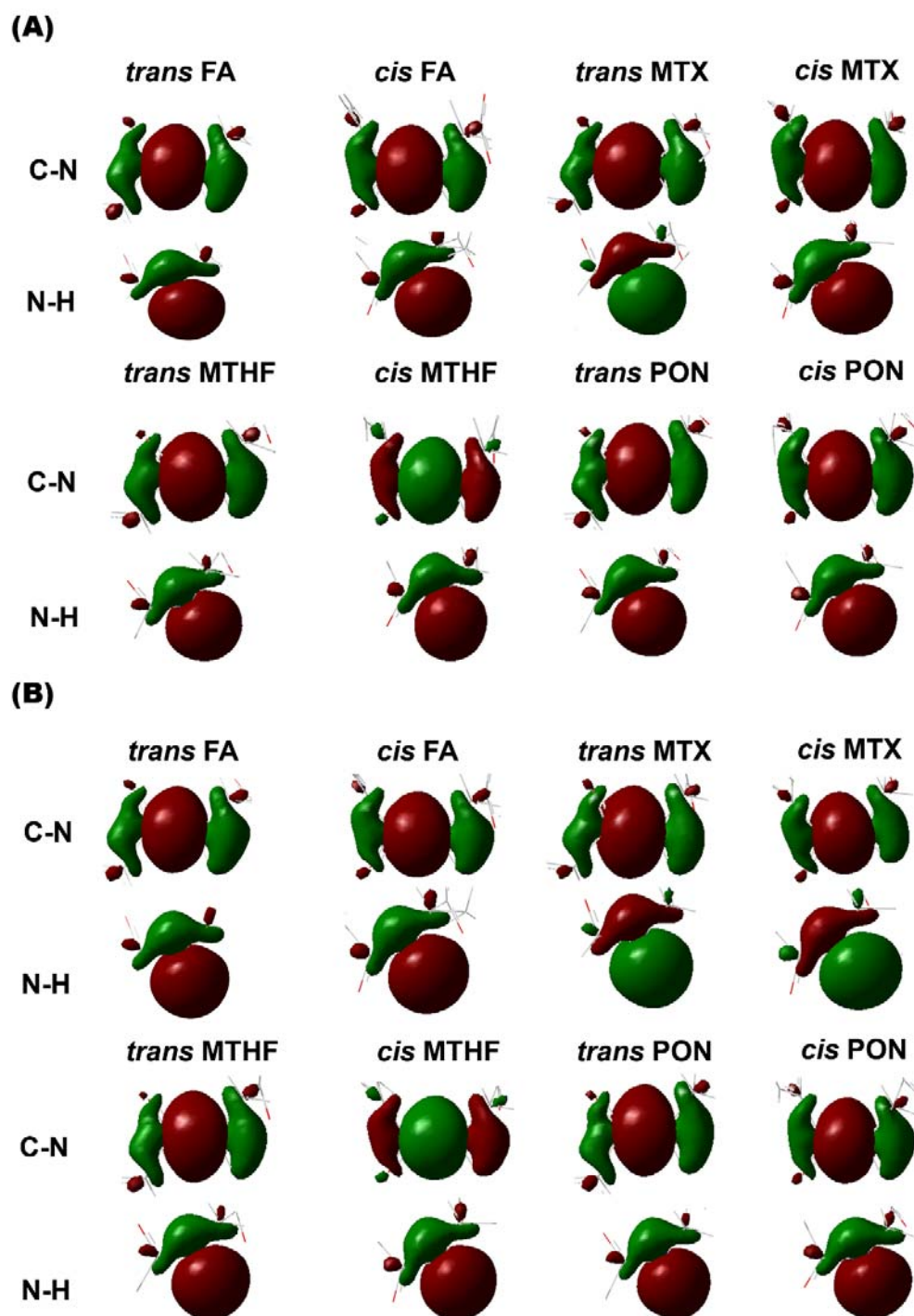| Ligand	Isomer	B3LYP		MP2	
		R	R'	R	R'
FA	trans	0.030	-1.766	0.029	-1.761
	cis	-0.026	-1.762	-0.021	-1.759
MTX	trans	0.029	-1.758	0.024	-1.742
	cis	0.015	-1.779	0.011	-1.770
MTHF	trans	0.044	-1.769	0.035	-1.762
	cis	-0.006	-1.772	-0.008	-1.764
PON	trans	0.033	0.238	0.024	0.254
	cis	-0.026	0.241	-0.021	0.248

Figure S6: NBOs encompassing the atoms from the N-H and C-N bonds in the two forms of all ligands calculated with (A) B3LYP/6-311+G** or (B) MP2/6-311+G** for the most populated structure from the MD simulations (Figure 5 of the main manuscript)

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