Electronic Supplementary Material (ESI) for Molecular BioSystems.

Supporting material

Table S1. 12 simulated systems, the Initial and final (after 70 ns of MD simulations) "3P-angles" are shown.

System	Initial "3P-angle" / °	Final "3P-angle" / °
Complex IIa-inhibitor 2 (Mg^{2+} ions included)	114.85	127.62
Complex IIa-inhibitor 2 (without Mg^{2+} ions)	113.70	116.54
Complex IIa-inhibitor 1 (Mg^{2+} ions included)	113.73	138.88
Complex IIa-analogue 3 (Mg^{2+} ions included)	113.25	88.02
Complex mutant I-inhibitor 2 (Mg^{2+} ions included)	118.40	126.12
Complex mutant II-inhibitor 2 (Mg^{2+} ions included)	116.68	122.89
Complex IIa-DAP 6 ("bm1") (Mg^{2+} ions included)	82.13	88.86
Complex IIa-DAP 6 ("bm2") (Mg^{2+} ions included)	80.58	86.33
Free IIa X-ray determined (Mg^{2+} ions included)	113.65	92.12
Free IIa X-ray determined (without Mg^{2+} ions)	115.57	90.77
Free IIa NMR determined (Mg^{2+} ions included)	111.66	87.35
Free IIa NMR determined (without Mg^{2+} ions)	101.72	116.63

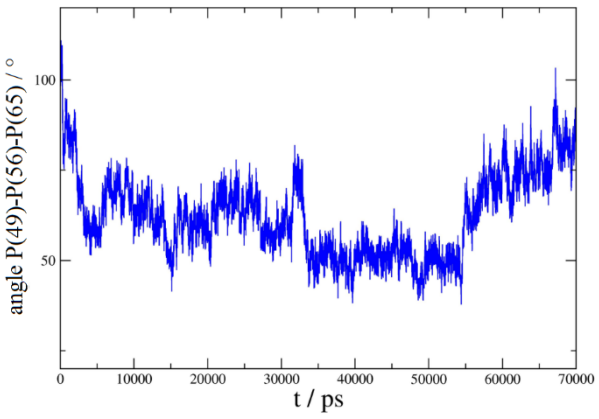


Fig. S1 Changes of the "3P-angle" during MD simulations for the unliganded IIa (the initial structure determined by NMR).

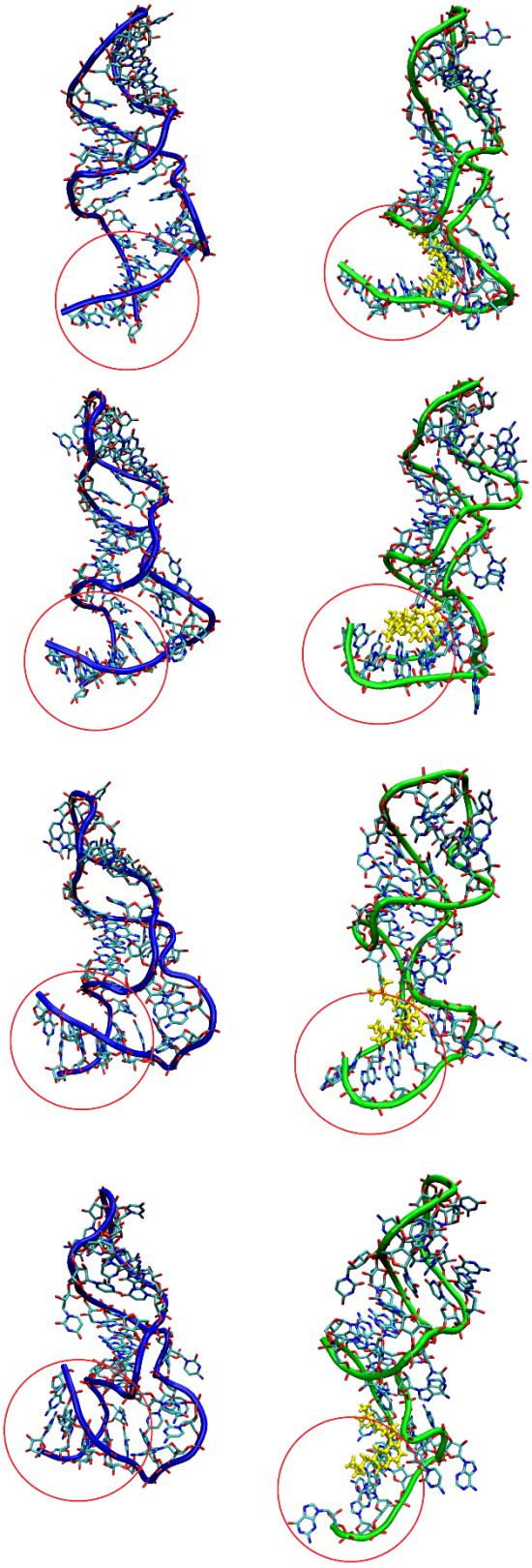


Fig. S2 Several snapshots taken during MD simulations of the, by NMR determined structure, of IIa: ligand free, left, and in the complex with inhibitor **2** (coloured yellow), right. Red cycles are indicating the RBA edge that have folded and unfolded during MD simulations, respectively.

Table S2 Free energies components calculated for the ligand free IIa RNA (initial structure determined by the X-ray method) before and after formation of the L-shaped fold.

Δ Energy (kcal/mol)	Free IIa RNA before folding	Free IIa RNA folded, after 70 ns of MD
ELE	(-4701.4±58.0)	(-4514.1±66.1)
VDW	(-293.1±13.8)	(-282.5±13.8)
PBSUR	(-46.2±0.4)	(-47.4±0.5)
PBSOL	(-7104.7±54.3)	(-7298.4±60.6)
PBTOT	**(-10145.5±28.3)**	**(-10151.4±28.3)**

Table S3 Free energies components calculated for the ligand free IIa RNA (initial structure determined by the NMR method) before and after formation of the L-shaped fold, without the presence of magnesium ions.

Δ Energy (kcal/mol)	Free IIa RNA before folding	Free IIa RNA folded, after 70 ns of MD
ELE	(4435.6±148.1)	(4351.9±191.2)
VDW	(-334.3±11.5)	(-331.2±12.9)
PBSUR	(53.7±0.4)	(53.4±0.4)
PBSOL	(-13997.9±138.7)	(-13921.5±184.9)
PBTOT	**(-7867.7±24.8)**	**(-7870.9±27.4)**

Table S4 Free energies components calculated for the ligand free IIa RNA (initial structure determined by NMR) before and after formation of the L-shaped fold, with included Mg^{2+} ions.

Δ Energy (kcal/mol)	Free IIa RNA before folding (Mg^{2+} included)	Free IIa RNA folded after 70 ns of MD (Mg^{2+} included)
ELE	(-13855.8±65.1)	(-13810.3±50.7)
VDW	(-142.2±17.2)	(-142.3±16.6)
PBSUR	(-51.1±0.8)	(-52.0±0.6)
PBSOL	(-4186.5±69.1)	(-4261.9±52.6)
PBTOT	**(-16114.1±33.9)**	**(-16150.8±32.0)**

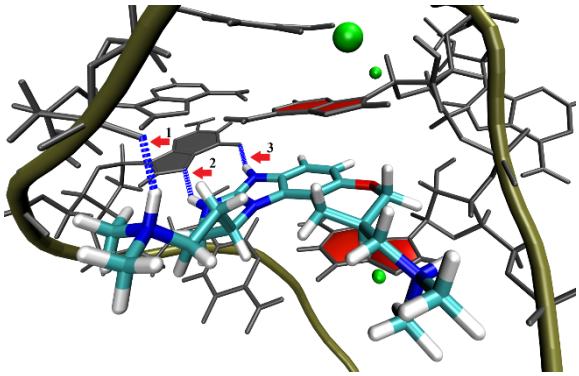


Fig. S3 The ligand **1** binding site (after 70 ns of MD simulations). Inhibitor **1** is intercalated between two bases (above A53, below G52, shown in red). Mg^{2+} ions are shown in green. Intermolecular hydrogen bonds formed between: 1) HN(**1**)-O2P(A109), 2) HN03(**1**)-N7(G110) and 3) H01(**1**)-O6(G110) are shown as blue dashed lines and indicated by red arrows.

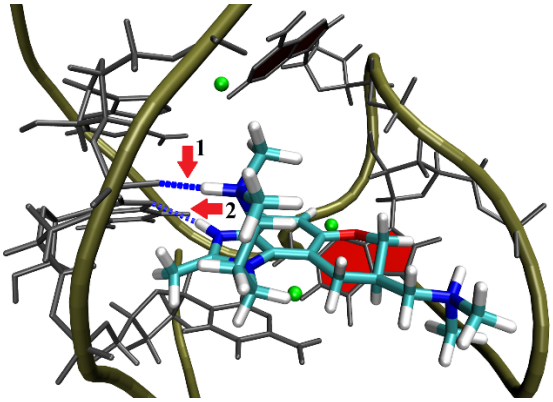


Fig. S4 The analogue **3** binding site (after 70 ns of MD simulations). Bases A53 and G52 are shown in red. Mg^{2+} ions are shown as green balls. Intermolecular hydrogen bonds formed between: 1) HN(**3**)-O2P(G110) and 2) H01(**3**)-N7(G110) are shown as blue dashed lines and indicated by red arrows.

Fig. S5 Superposition of the subdomain IIa structures obtained during simulations with and without ligand: The initial structure of the IIa-inhibitor **2** complex is coloured orange, the final structure of the IIa-inhibitor **2** complex, blue, and the final free IIa RNA structure, black.

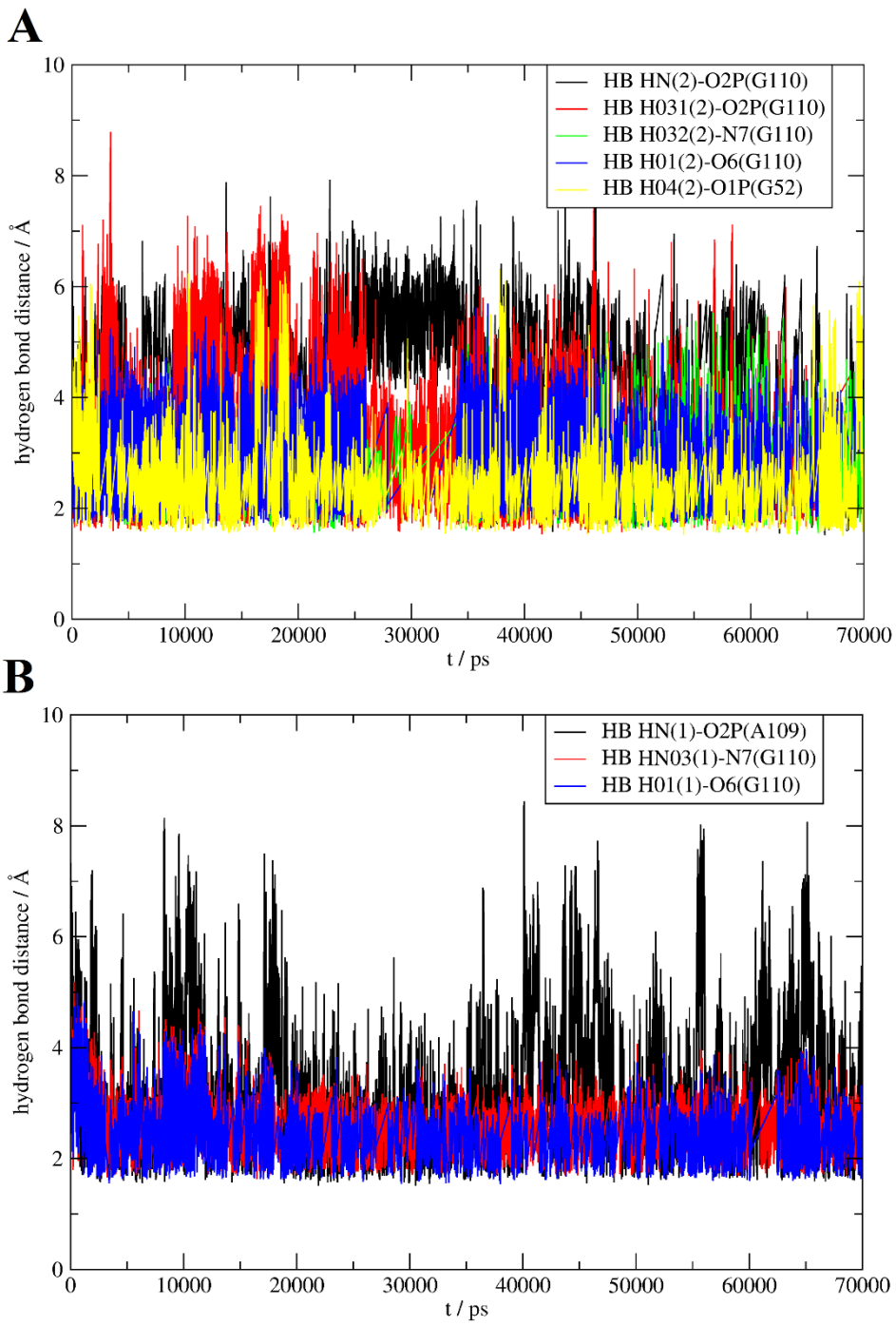


Fig. S6 The time dependent plots of the RNA - inhibitors (**1** and **2**) hydrogen bond (HB) distances (sampled during 70 ns long MD simulations). (A) IIa-**2** complex, (B) IIa-**1** complex. The time averaged values of the HB distances are: d[HN(**2**)-O2P(G110)]=(2.90±0.24)Å, d[H031(**2**)-O2P(G110)]=(2.97±0.26)Å, d[H032(**2**)-N7(G110)]=(3.01±0.19) Å, d[H01(**2**)-O6(G110)]=(3.06±0.23)Å, d[H04(**2**)-O1P(G110)]=(2.87±0.21)Å. (B) IIa-**1** complex. Averaged values of HB distances are: d[HN(**1**)-O2P(A109)]=(2.89±0.20)Å, d[HN03(**1**)-N7(G110)]=(3.00±0.19)Å, d[H01(1)-O6(G110)]=(2.92±0.20)Å.

Table S5 The MM_PBSA binding free energies components calculated for complexes after 70 ns of MD simulations (Mg^{2+} ions are part of the receptor in the calculations).

Δ Energy (kcal/mol)	Complex IIa-inhibitor 2	Complex IIa-inhibitor 1	Complex IIa-analogue 3	Complex mutant I-inhibitor 2	Complex mutant II-inhibitor 2
ELE	(-1508.5±19.0)	(-1482.8±30.1)	(-1431.9±28.0)	(-1437.2±18.3)	(-1461.2±18.8)
VDW	(-42.6±3.3)	(-43.2±2.3)	(-31.9±2.6)	(-45.2±2.7)	(-47.2±3.0)
PBSUR	(-4.8±0.2)	(-4.8±0.2)	(-4.1±0.2)	(-4.8±0.1)	(-5.4±0.1)
PBSOL	(1501.1±16.5)	(1479.5±28.4)	(1428.7±27.1)	(1449.5±18.0)	(1473.4±20.1)
PBTOT	**(-50.0±8.6)**	**(-46.5±6.6)**	**(-35.2±5.4)**	**(-32.9±6.7)**	**(-35.0±8.9)**

Table S6 The binding free energies components calculated for two binding modes of the complex IIa–DAP **6**.

Δ Energy (kcal/mol)	IIa–DAP 6 („bm1“)	IIa–DAP 6 („bm2“)
ELE	(-201.6±7.7)	(-496.2±30.0)
VDW	(-26.5±3.5)	(-9.3±0.5)
PBSUR	(-4.3±0.2)	(-4.3±0.1)
PBSOL	(68.2±6.7)	(358.5±27.0)
PBTOT	**(-159.9±4.7)**	**(-126.2±1.2)**

Table S7 ESP charges determined with the QM approach for the inhibitor **2** modelled with PCM and with the QM/MM approach (ME and EE) for complex with IIa, with and without the presence of Mg^{2+} ions.

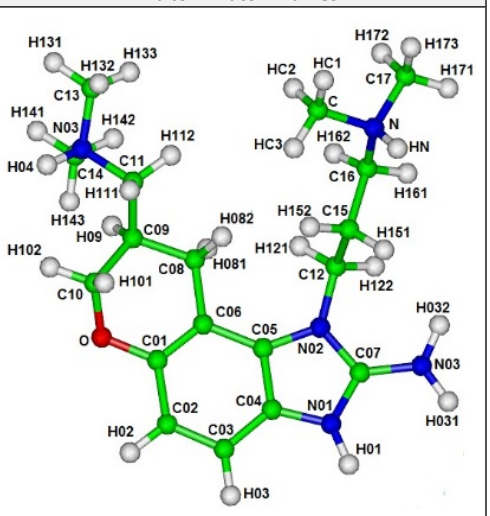
ESP charges / unit charge (e^+)				Inhibitor 2 - atom names
atom	inhibitor **2** modelled with PCM	inhibitor **2** from the complex with IIa **EE (ME)**	inhibitor **2** from the complex with IIa and Mg^{2+} **EE (ME)**	
N03	-0.943	-1.082 (-0.825)	-1.089 (-0.826)	
H031	0.492	0.543 (0.414)	0.553 (0.414)	
H032	0.495	0.522 (0.470)	0.519 (0.470)	
C07	0.660	0.689 (0.477)	0.827 (0.480)	
N01	-0.487	-0.495 (-0.410)	-0.569 (-0.413)	
H01	0.443	0.460 (0.428)	0.485 (0.429)	
C04	0.150	0.169 (0.118)	0.118 (0.121)	
C03	-0.181	-0.187 (-0.124)	-0.182 (-0.125)	
H03	0.200	0.233 (0.205)	0.217 (0.205)	
C02	-0.359	-0.254 (-0.232)	-0.435 (-0.232)	
H02	0.201	0.241 (0.219)	0.241 (0.219)	
C01	0.463	0.514 (0.418)	0.647 (0.424)	
O	-0.535	-0.610 (-0.438)	-0.568 (-0.441)	
C10	0.222	0.463 (0.260)	0.418 (0.267)	
H101	0.055	0.033 (-0.006)	0.009 (-0.008)	
H102	0.064	0.086 (0.103)	0.088 (0.103)	
C09	0.152	-0.345 (-0.218)	-0.400 (-0.233)	
C11	-0.461	-0.035 (-0.139)	-0.014 (-0.135)	
N04	0.235	-0.144 (-0.010)	-0.152 (-0.015)	
C13	-0.408	-0.250 (-0.358)	-0.350 (-0.356)	
H131	0.206	0.128 (0.161)	0.161 (0.160)	
H132	0.181	0.142 (0.212)	0.163 (0.211)	
HI33	0.185	0.273 (0.180)	0.198 (0.180)	
C14	-0.463	-0.261 (-0.318)	-0.350 (-0.314)	
H141	0.199	0.161 (0.150)	0.185 (0.149)	
H142	0.212	0.179 (0.193)	0.201 (0.192)	
H143	0.192	0.146 (0.197)	0.171 (0.197)	
H04	0.332	0.328 (0.339)	0.365 (0.340)	
H111	0.182	0.044 (0.126)	0.152 (0.125)	
H112	0.203	0.171 (0.160)	0.151 (0.160)	
H09	0.054	0.155 (0.159)	0.212 (0.160)	
C08	0.011	0.176 (0.140)	0.278 (0.169)	
H081	0.038	0.081 (0.049)	0.070 (0.044)	
H082	0.080	0.038 (0.001)	0.035 (-0.003)	
C06	-0.223	-0.319 (-0.183)	-0.518 (-0.200)	
C05	0.054	-0.003 (-0.086)	0.278 (-0.081)	
N02	-0.079	-0.035 (0.129)	-0.359 (0.121)	
C12	-0.196	-0.165 (-0.459)	0.217 (-0.445)	
H121	0.131	0.074 (0.165)	0.040 (0.161)	
H122	0.159	0.123 (0.222)	0.059 (0.217)	
C15	0.128	-0.164 (-0.007)	-0.349 (0.004)	
H151	0.039	0.178 (0.116)	0.223 (0.112)	
H152	0.032	0.099 (0.090)	0.098 (0.087)	
C16	-0.300	-0.188 (-0.245)	-0.159 (-0.251)	
H161	0.195	0.178 (0.200)	0.173 (0.201)	
H162	0.160	0.116 (0.147)	0.113 (0.148)	
N	0.157	0.090 (0.069)	0.083 (0.066)	
C17	-0.390	-0.407 (-0.380)	-0.358 (-0.380)	
H171	0.194	0.166 (0.229)	0.164 (0.229)	
H172	0.185	0.204 (0.202)	0.214 (0.202)	
H173	0.175	0.226 (0.168)	0.178 (0.168)	
HN	0.334	0.3802 (0.323)	0.356 (0.323)	
C	-0.380	-0.434 (-0.449)	-0.448 (-0.445)	
HC1	0.189	0.196 (0.194)	0.245 (0.193)	
HC2	0.182	0.232 (0.208)	0.234 (0.208)	
HC3	0.178	0.142 (0.244)	0.162 (0.243)	

Table S8 ESP charges determined with the QM approach for the analogue **3** modelled with PCM and with the QM/MM approach (ME and EE) for complex with IIa, with and without the presence of Mg^{2+} ions.

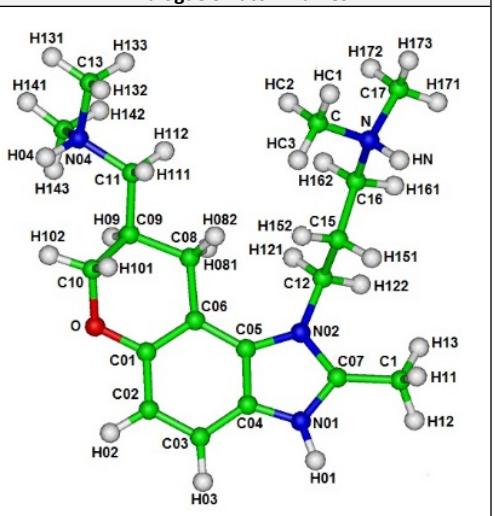
ESP charges / unit charge (e^+)				Analogue 3 - atom names
atom	analogue **3** modelled with PCM	analogue **3** from the complex with IIa **EE (ME)**	analogue **3** from the complex with IIa and Mg^{2+} **EE (ME)**	
C1	-0.458	-0.471 (-0.501)	-0.393 (-0.524)	
H11	0.183	0.119 (0.229)	0.145 (0.227)	
H12	0.173	0.160 (0.203)	0.215 (0.194)	
H13	0.192	0.225 (0.187)	0.221 (0.207)	
C07	0.378	0.376 (0.342)	0.286 (0.444)	
N01	-0.401	-0.432 (-0.380)	-0.498 (-0.408)	
H01	0.435	0.501 (0.422)	0.455 (0.410)	
C04	0.143	0.196 (0.092)	0.517 (0.166)	
C03	-0.165	-0.133 (-0.073)	-0.419 (-0.162)	
H03	0.199	0.246 (0.192)	0.268 (0.218)	
C02	-0.300	-0.292 (-0.316)	-0.266 (-0.278)	
H02	0.192	0.262 (0.248)	0.191 (0.238)	
C01	0.456	0.534 (0.519)	0.447 (0.527)	
O	-0.468	-0.511 (-0.436)	-0.454 (-0.491)	
C10	0.111	0.215 (0.086)	-0.142 (0.248)	
H101	0.099	0.146 (0.120)	0.200 (0.099)	
H102	0.096	0.073 (0.119)	0.118 (0.086)	
C09	-0.011	-0.234 (-0.167)	0.221 (-0.329)	
C11	-0.468	0.064 (-0.038)	0.011 (0.082)	
N04	0.114	-0.203 (-0.180)	0.076 (-0.140)	
C13	-0.367	-0.289 (-0.322)	-0.535 (-0.335)	
H131	0.199	0.181 (0.195)	0.238 (0.201)	
HI32	0.173	0.199 (0.173)	0.209 (0.185)	
H133	0.181	0.218 (0.202)	0.190 (0.206)	
C14	-0.344	-0.305 (-0.208)	-0.329 (-0.272)	
H141	0.170	0.140 (0.183)	0.163 (0.193)	
H142	0.192	0.202 (0.160)	0.185 (0.167)	
H143	0.172	0.080 (0.113)	0.098 (0.115)	
H04	0.358	0.467 (0.391)	0.414 (0.373)	
H111	0.208	0.168 (0.152)	0.106 (0.122)	
H112	0.232	0.082 (0.105)	0.053 (0.080)	
H09	0.113	0.073 (0.057)	0.008 (0.080)	
C08	0.132	0.326 (0.449)	0.044 (0.472)	
H081	0.048	-0.006 (-0.008)	0.078 (0.017)	
H082	0.074	-0.081 (-0.033)	-0.010 (-0.112)	
C06	-0.273	-0.335 (-0.370)	-0.201 (-0.430)	
C05	0.029	-0.058 (0.051)	-0.193 (0.121)	
N02	-0.012	0.001 (0.067)	0.186 (-0.132)	
C12	-0.001	-0.187 (-0.376)	-0.265 (-0.084)	
H121	0.087	0.124 (0.197)	0.173 (0.090)	
H122	0.102	0.072 (0.191)	0.138 (0.142)	
C15	-0.045	0.071 (0.260)	0.028 (-0.032)	
H151	0.084	0.030 (-0.155)	0.074 (0.080)	
H152	0.051	0.055 (0.093)	0.055 (0.111)	
C16	-0.114	-0.246 (-0.275)	-0.297 (-0.228)	
H161	0.155	0.137 (0.107)	0.128 (0.087)	
H162	0.133	0.184 (0.181)	0.186 (0.166)	
N	0.005	0.056 (0.067)	0.030 (0.173)	
C17	-0.396	0.445 (-0.470)	-0.244 (-0.445)	
H171	0.206	0.228 (0.216)	0.145 (0.201)	
H172	0.189	0.236 (0.206)	0.214 (0.199)	
H173	0.182	0.206 (0.221)	0.102 (0.216)	
HN	0.385	0.343 (0.365)	0.430 (0.308)	
C	-0.379	-0.326 (-0.227)	-0.464 (-0.275)	
HC1	0.179	0.186 (0.093)	0.229 (0.166)	
HC2	0.187	0.159 (0.164)	0.236 (0.133)	
HC3	0.196	0.209 (0.114)	0.195 (0.128)	

Table S9 ONIOM energies obtained for the IIa–inhibitor **2** and for the IIa–analogue **3** complexes, with and without Mg^{2+} ions present.

	E^{ONIOM} / (kcal/mol)			
	IIa–inhibitor **2**	IIa–inhibitor **2** (Mg^{2+} included)	IIa-analogue **3**	IIa-analogue **3** (Mg^{2+} included)
ME	-658447.9	-666645.6	-648291.3	-654405.6
EE	-658462.7	-666684.7	-648294.1	-654409.4