Sulfonamide/sulfamate switch with a series of piperazinylureido derivatives: synthesis, kinetic and *in silico* evaluation as carbonic anhydrase isoforms I, II, IV, and IX inhibitors.

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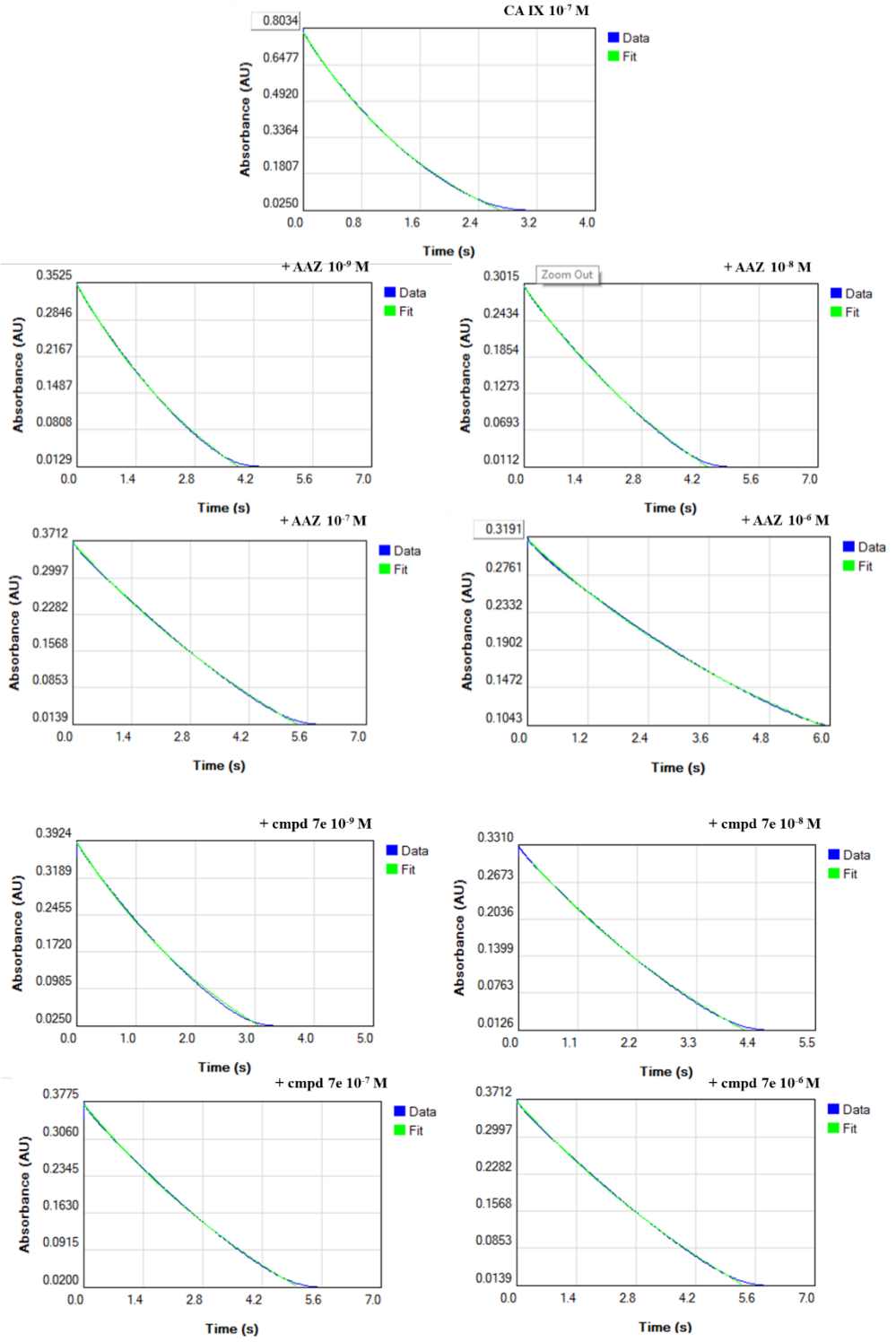
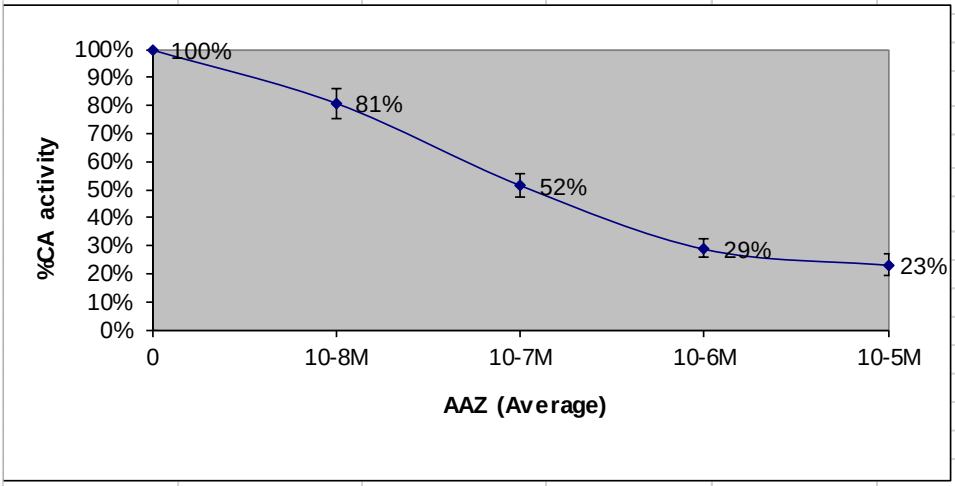
*Examples of absorbance decrease as a function of time for **AAZ** and **21e** with CA IX.*



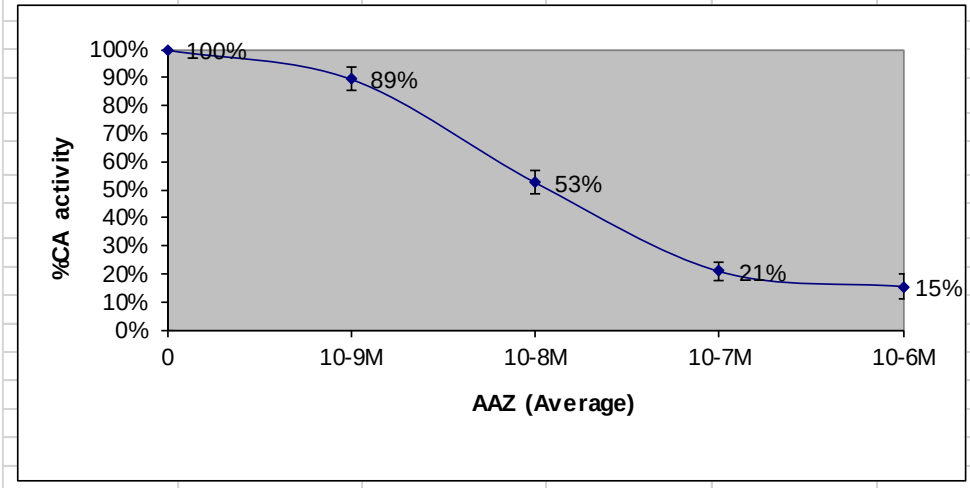
*Examples of CA I, II, IX and XII inhibition % as a function of increasing compound concentration with **AAZ** and **7e**.*

Inhibition profile of AAZ

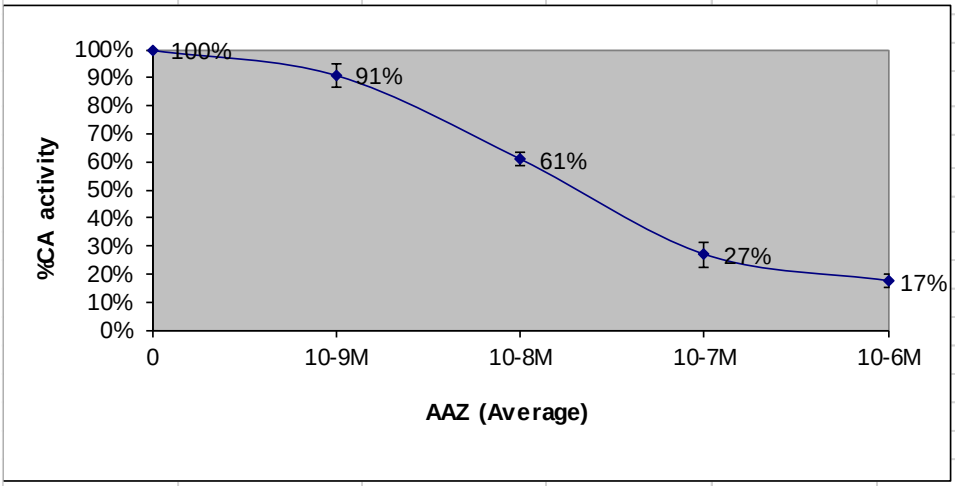
Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA I 10-7M	0	0.4923	100%	0%	0.0E+00
AAZ	10-8M	0.3985	81%	19%	1.0E-08
AAZ	10-7M	0.2541	52%	48%	1.0E-07
AAZ	10-6M	0.1423	29%	71%	1.0E-06
AAZ	10-5M	0.1142	23%	77%	1.0E-05



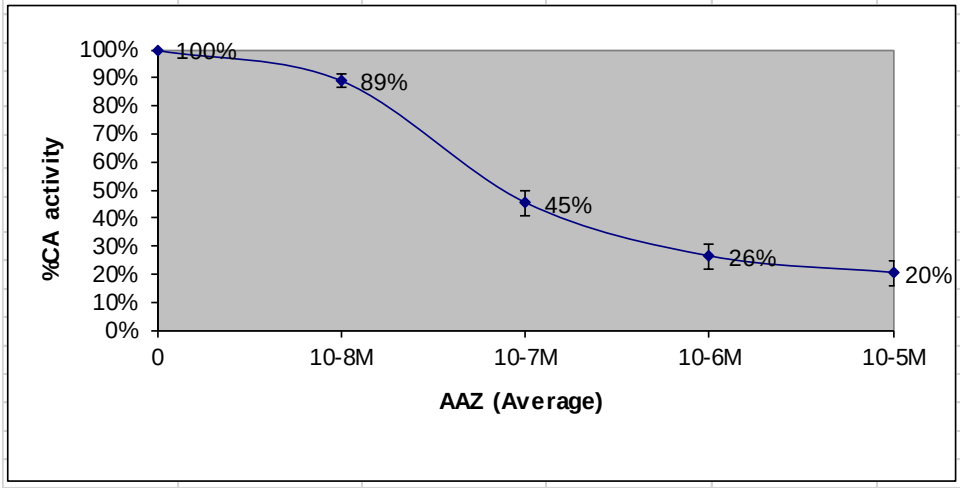
Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA II 10-7M	0	1.4531	100%	0%	0.0E+00
AAZ	10-9M	1.3005	89%	11%	1.0E-09
AAZ	10-8M	0.7635	53%	47%	1.0E-08
AAZ	10-7M	0.3029	21%	79%	1.0E-07
AAZ	10-6M	0.2248	15%	85%	1.0E-06



Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA IV 10-7M	0	1.124	100%	0%	0.0E+00
AAZ	10-9M	1.0223	91%	9%	1.0E-09
AAZ	10-8M	0.6854	61%	39%	1.0E-08
AAZ	10-7M	0.3025	27%	73%	1.0E-07
AAZ	10-6M	0.1963	17%	83%	1.0E-06

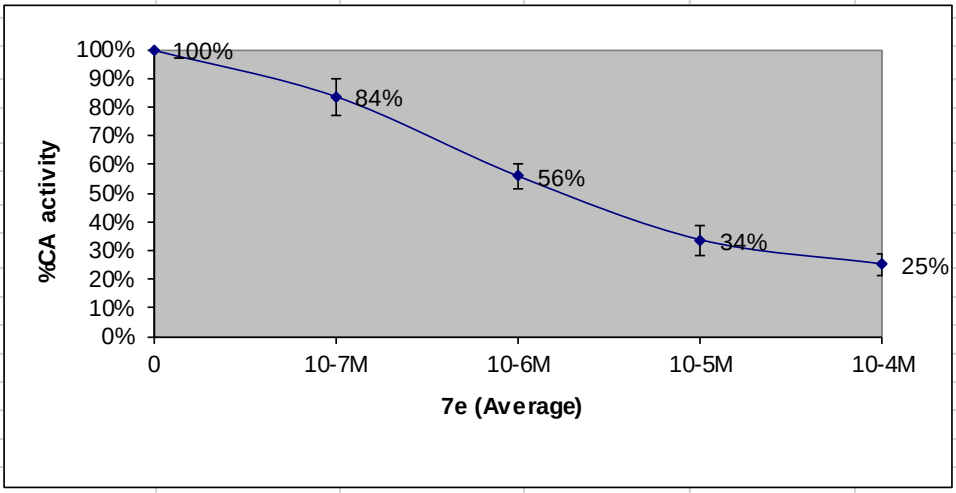


Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA IX 10-7M	0	0.4752	100%	0%	0.0E+00
AAZ	10-8M	0.4231	89%	11%	1.0E-08
AAZ	10-7M	0.2154	45%	55%	1.0E-07
AAZ	10-6M	0.1245	26%	74%	1.0E-06
AAZ	10-5M	0.0963	20%	80%	1.0E-05

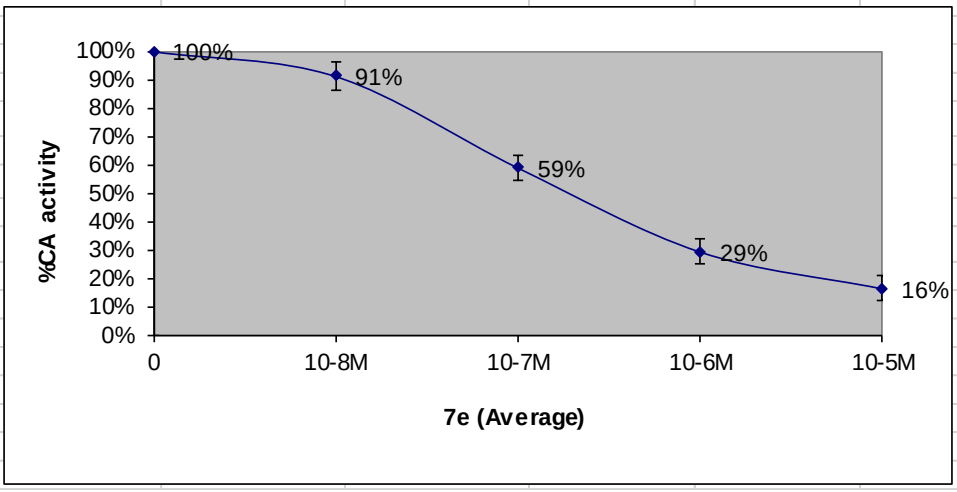


Inhibition profile of 7e.

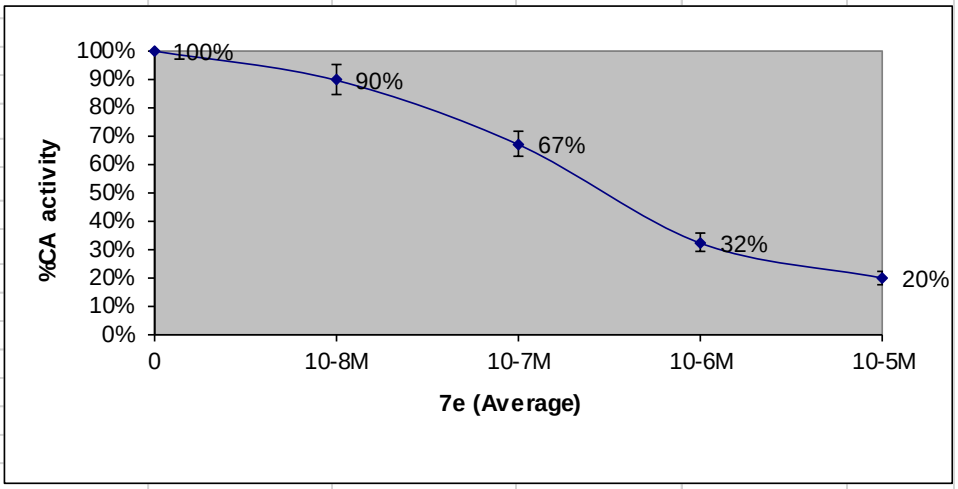
Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA I 10-7M	0	0.4923	100%	0%	0.0E+00
7e	10-7M	0.4123	84%	16%	1.0E-07
7e	10-6M	0.2753	56%	44%	1.0E-06
7e	10-5M	0.1655	34%	66%	1.0E-05
7e	10-4M	0.1236	25%	75%	1.0E-04



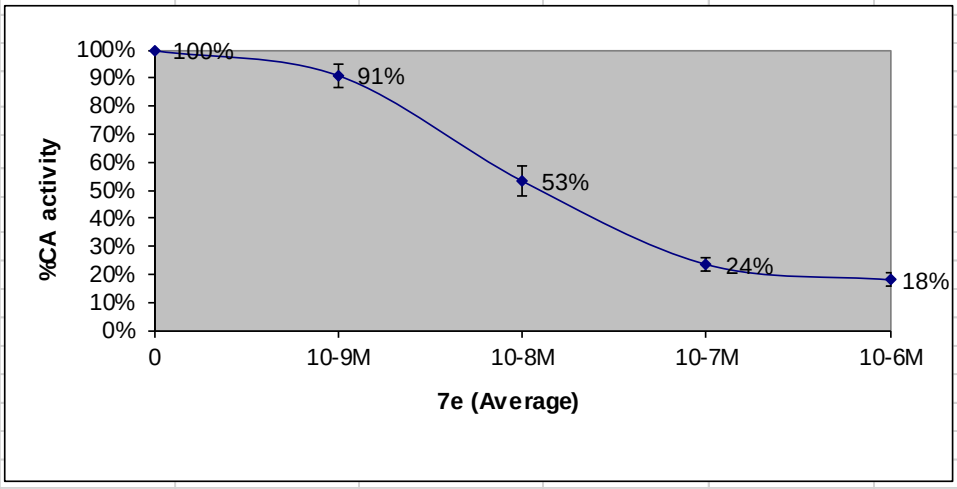
Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA II 10-7M	0	1.4531	100%	0%	0.0E+00
7e	10-8M	1.3254	91%	9%	1.0E-08
7e	10-7M	0.8563	59%	41%	1.0E-07
7e	10-6M	0.4253	29%	71%	1.0E-06
7e	10-5M	0.2365	16%	84%	1.0E-05



Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA IV 10-7M	0	1.124	100%	0%	0.0E+00
7e	10-8M	1.008	90%	10%	1.0E-08
7e	10-7M	0.7532	67%	33%	1.0E-07
7e	10-6M	0.3625	32%	68%	1.0E-06
7e	10-5M	0.2239	20%	80%	1.0E-05



Compound	Inhibitor concentration	Slope	%Free Enzyme	%Inhibition	
CA IX 10-7M	0	0.4752	100%	0%	0.0E+00
7e	10-9M	0.4326	91%	9%	1.0E-09
7e	10-8M	0.2536	53%	47%	1.0E-08
7e	10-7M	0.1125	24%	76%	1.0E-07
7e	10-6M	0.0865	18%	82%	1.0E-06



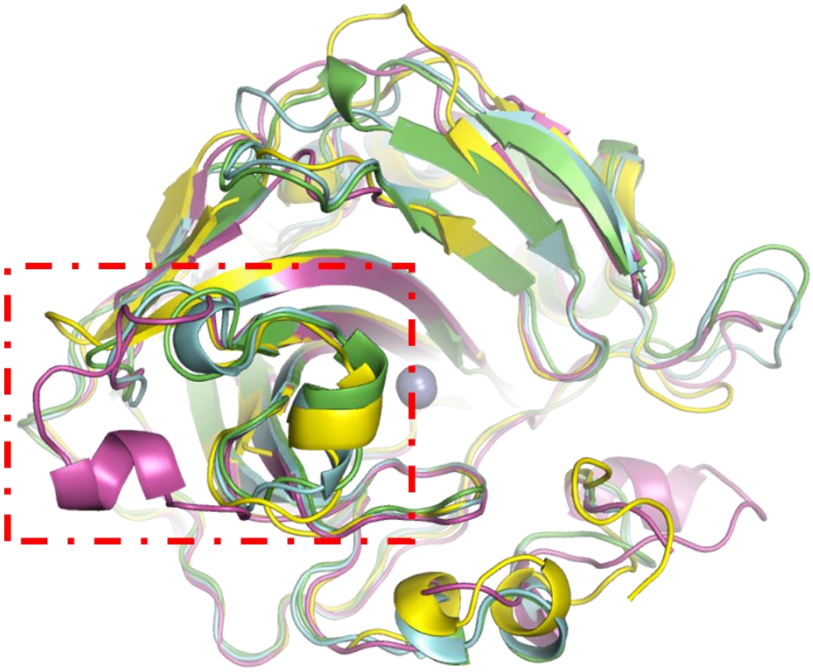
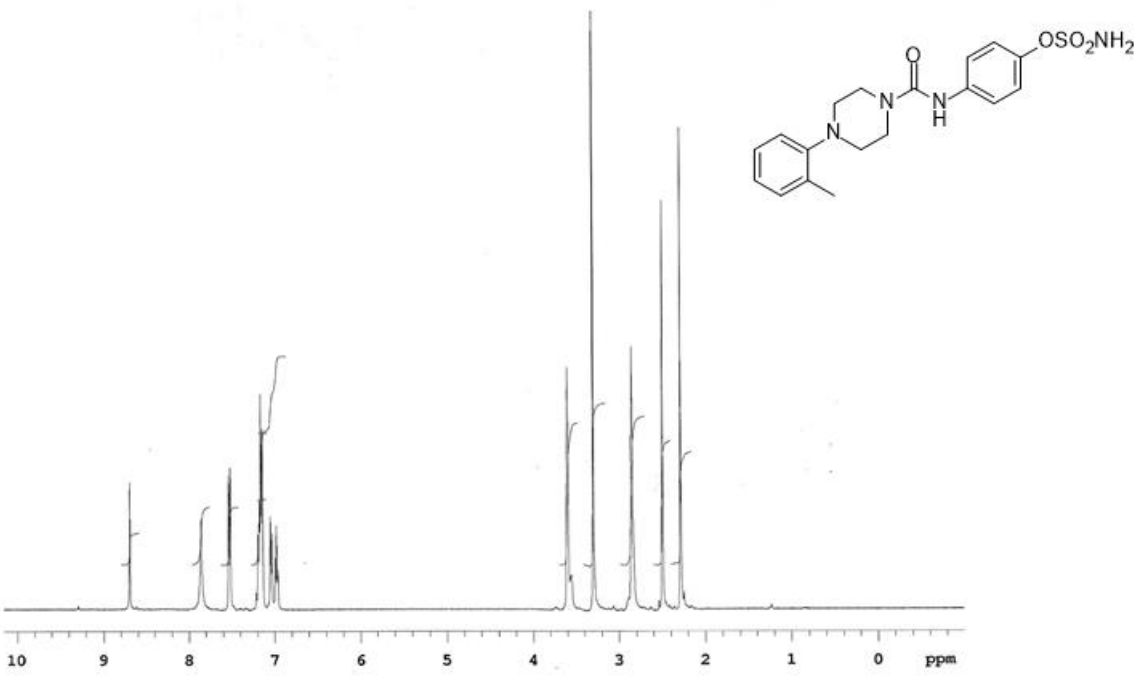
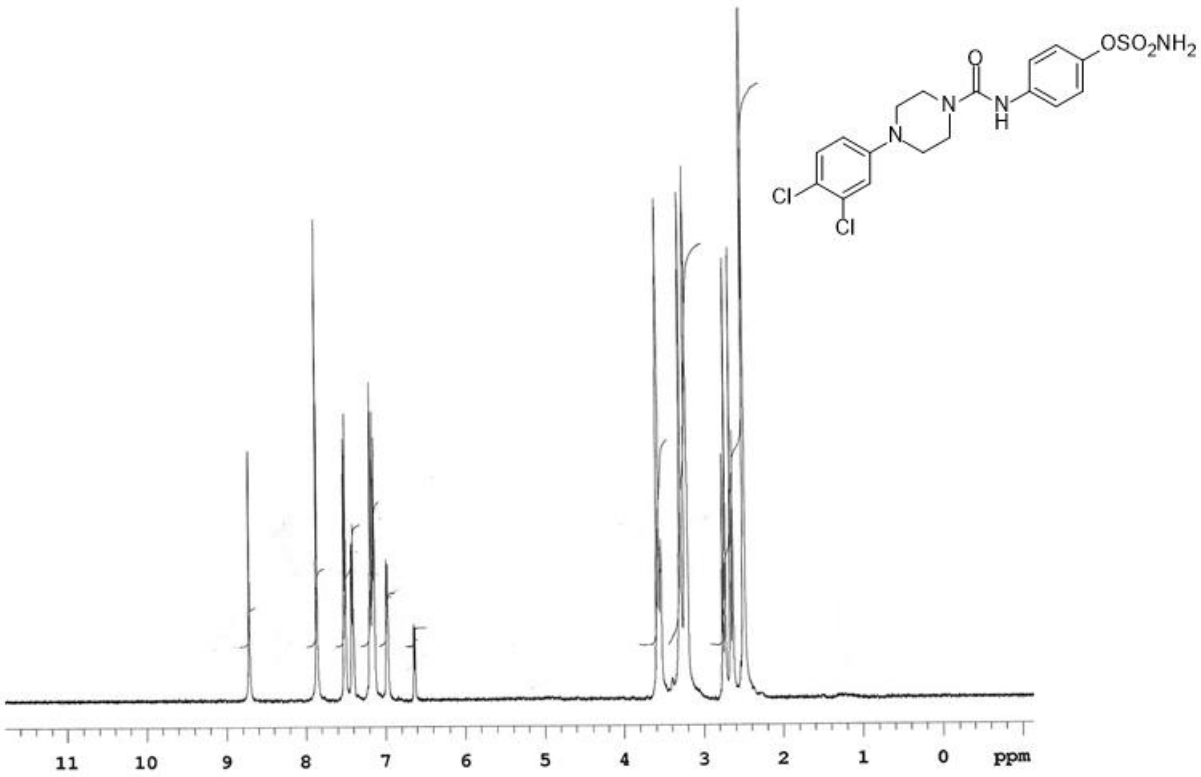


Figure 1S. Focus on the different position of the loop between residues 126-136 in CA IV (magenta, PDBID: 5jn8) respect the other isoforms CA I (green, PDBID: 3w6h), CA II (cyan, PDBID: 4g0c) and CA IX (yellow, PDBID: 3iai).

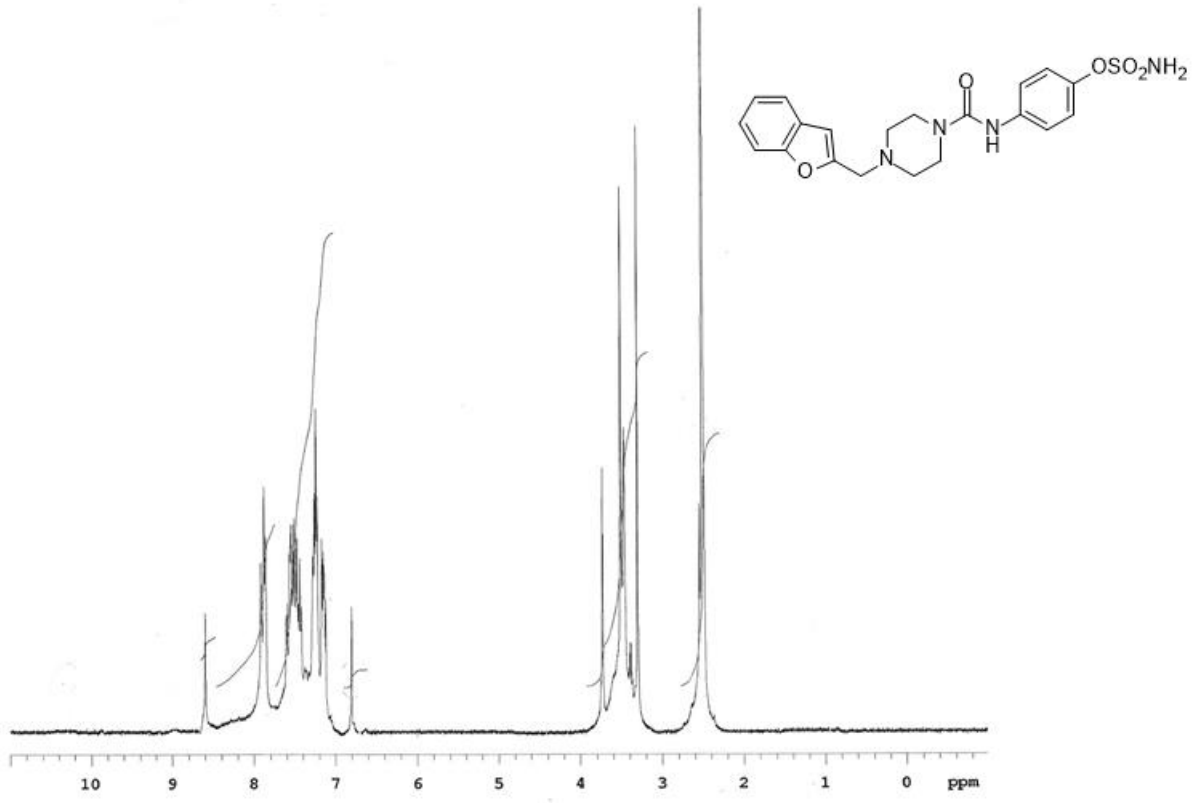
^{1}H NMR of compound **3b**



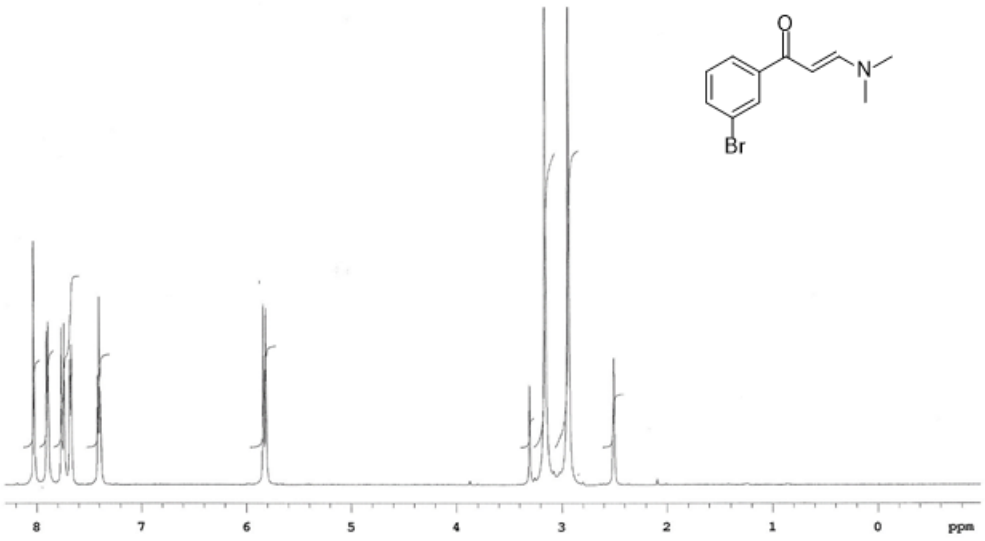
^{1}H NMR of compound **3g**



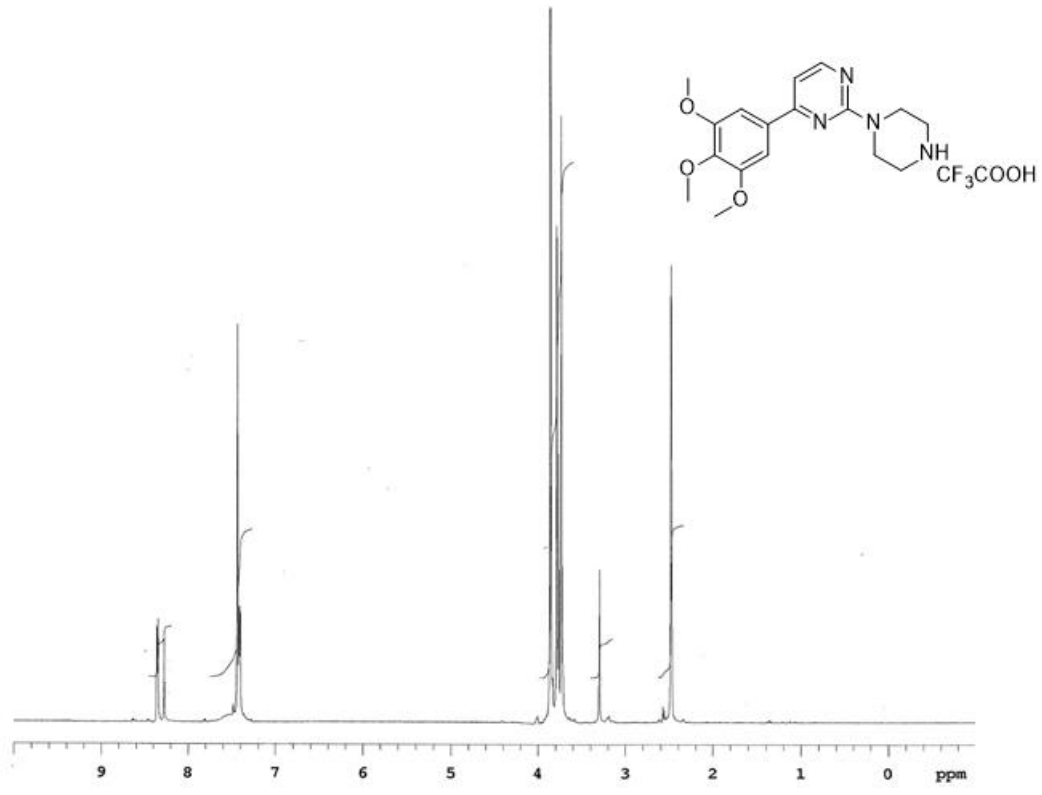
^{1}H NMR of compound **3j**



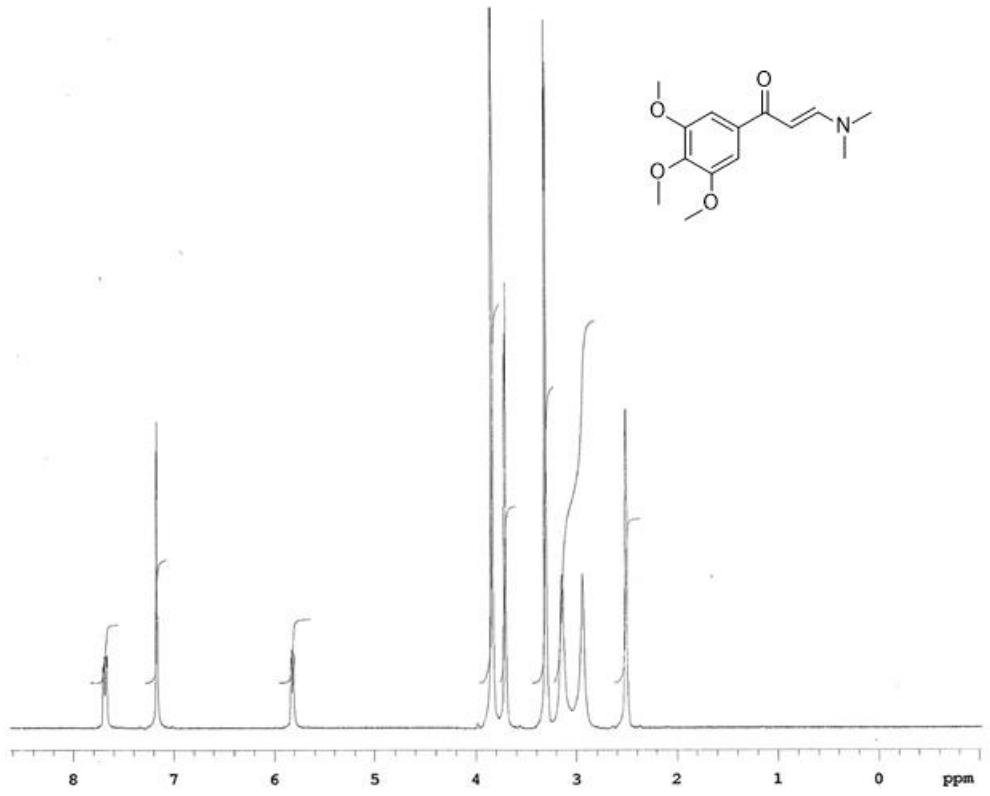
^{1}H NMR of compound **5e**



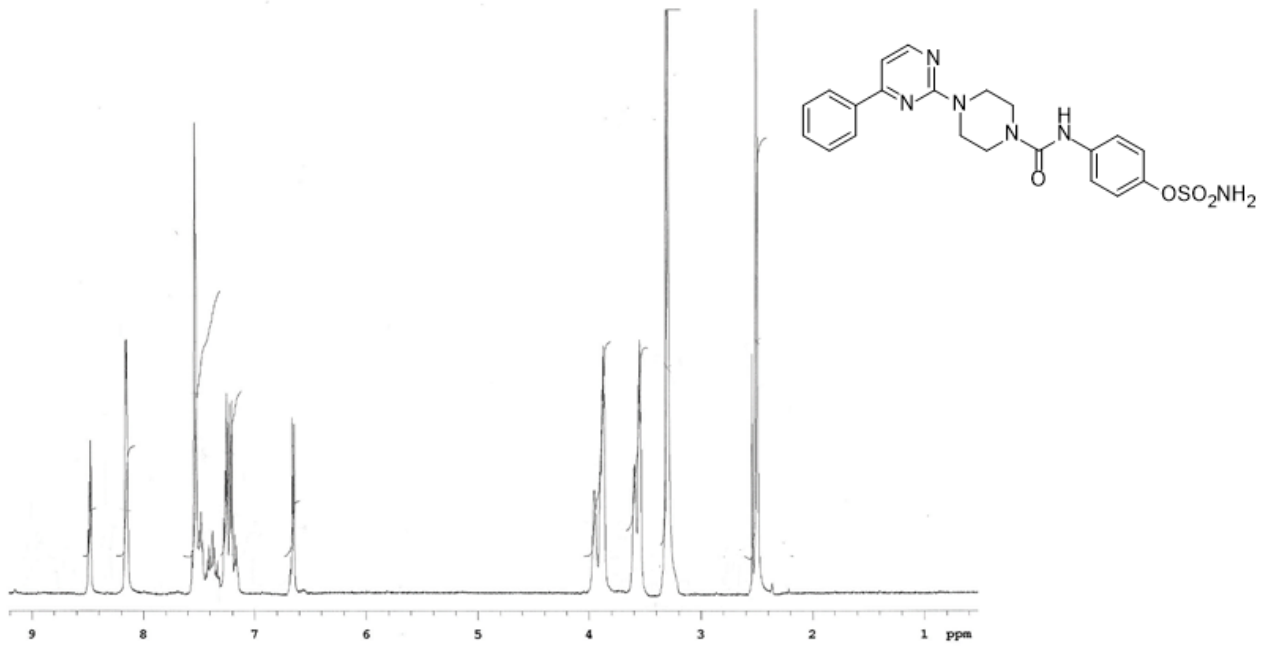
^{1}H NMR of compound **6h**



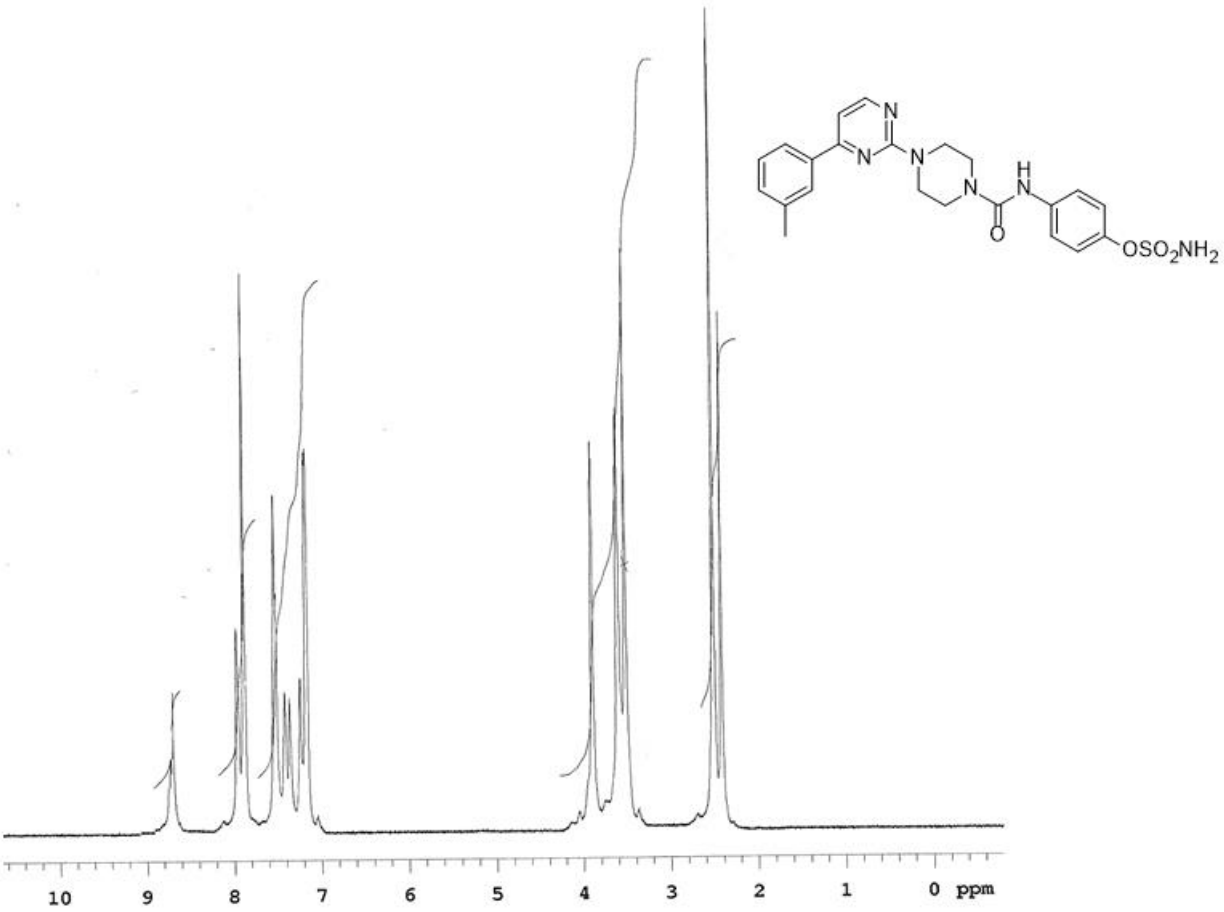
^{1}H NMR of compound **5h**



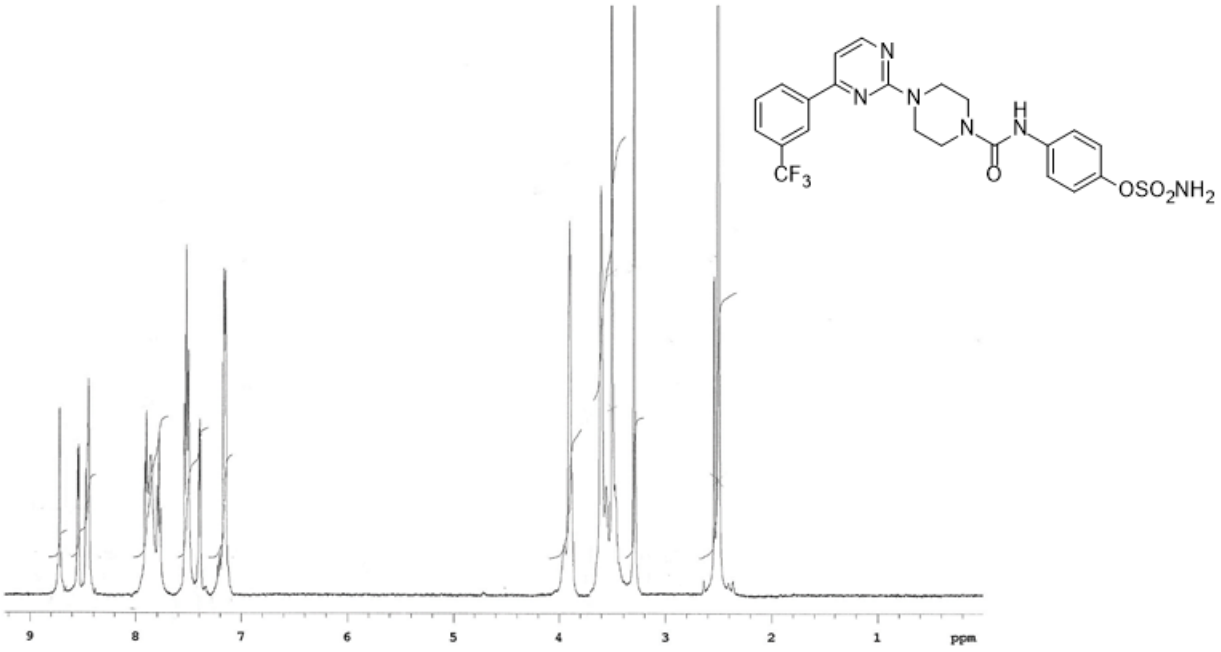
^{1}H NMR of compound **7a**



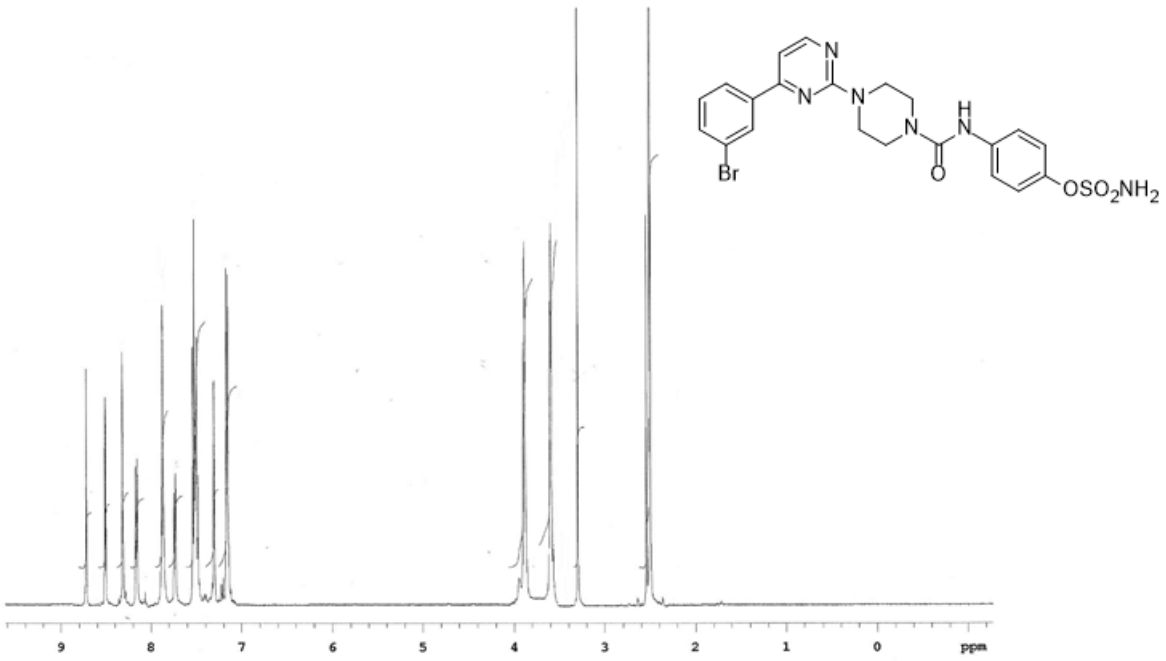
^{1}H NMR of compound **7b**



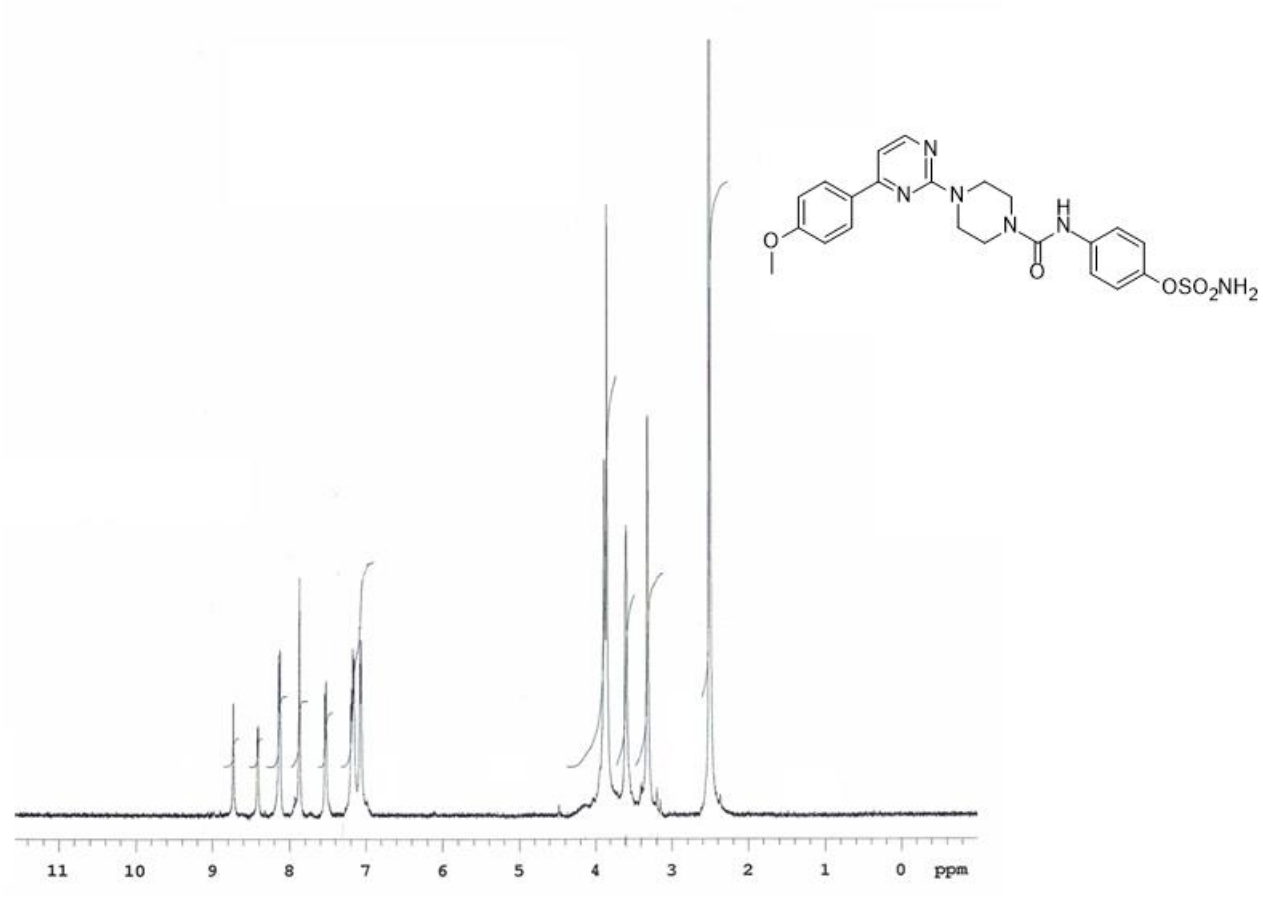
^{1}H NMR of compound **7c**



^{1}H NMR of compound **7e**



^{1}H NMR of compound **7g**



^{1}H NMR of compound **7h**