Supplementary information

Supplementary Material (ESI) for Organic & Biomolecular Chemistry

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Mechanisms of hydrolysis of phenyl- and benzyl 4-nitrophenyl- sulfamate esters

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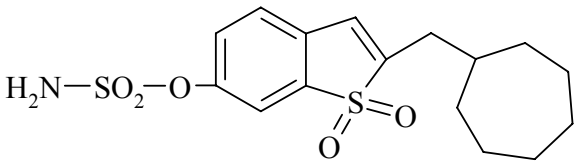

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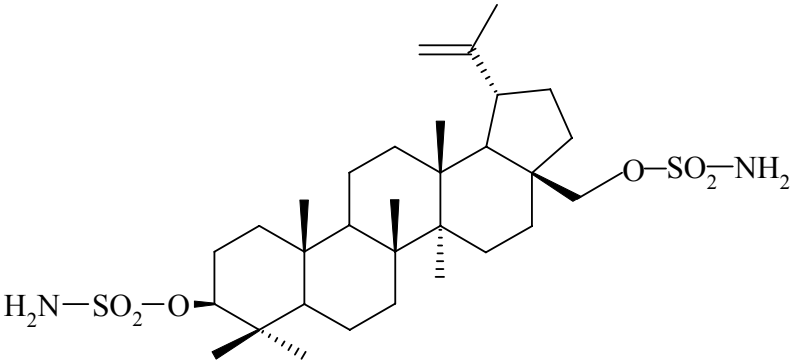
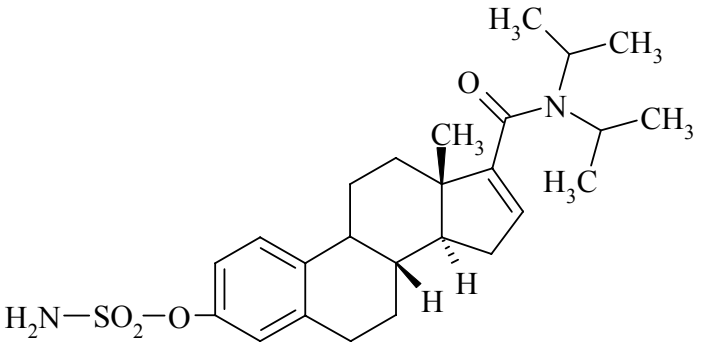


betulinyl-bis-sulfamate



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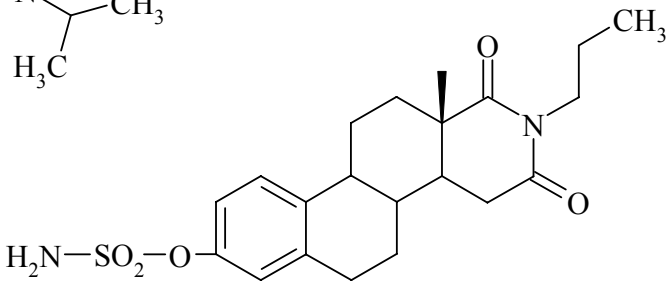

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Fig. **S1** Some newly developed sulfamate-containing inhibitors.

Table S1 Experimental[a] pK_as for the first ionization[b] of compounds **1**.

Compound	Exper. pK_a	Anal. λ (nm)	Hammett σ[d]
1a	7.32	302	0.778
1b	7.40	283	0.71
1c	7.45	253	0.66
1d	7.50	228	0.75
1e	7.66	240	0.56
1f	7.88	229	0.227
1g	7.92	210	0.232
1h	8.15	210	0.062
1i	8.24	216	0
1j	8.34	222	-0.17

[a]Measured in water at 25°C. [b]**1⇆2**. [d]Taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420-427.

Table S2 Experimental[a] pK_as for the second ionization[b] of compounds **1** in ACN

Compound	Exper. pK_a	Hammett σ[c]	Compound	Exper. pK_a	Hammett σ[c]
1a	21.38	0.778	**1h**	22.69	0.062
1f	22.48	0.227	**1i**	22.41	0
1g	22.35	0.232	**1j**	22.71	-0.17

[a] Measured at λ = 340 nm in ACN at 25°C using 4-nitrophenoxide as indicator. [b]**2⇆3**. [c]Taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420-427.

Table S3 Spectrophotometric[a] and kinetic[b] pK_as for the ionization[c] of compounds **4a-g**

Compound	pK_a^{spectr}	pK_a^{kin}	Hammett σ[d]
4a	7.83	7.75	0.73[e]
4b	8.11	7.79	0.227
4c	7.89	7.80	0.50[e]
4d	8.04	7.91	0.062
4e	8.26	8.01	0
4f	8.22	8.07	-0.17
4g	8.26	8.12	-0.27

[a]Measured spectrophotometrically in water at 25°C at constant ionic strength(μ)=1.0 M KCl. Analytical wavelength was 302 nm for all substrates. [b]Calculated by fitting the pH-rate profile data to eqn 1 with the Fig.P® program. [c]**4⇆5**. [d] Taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420-427. [e]The σ value for 2-chloro is from M. T. Tribble and J. G. Traynham, *J. Am. Chem. Soc.*, 1969, **91**, 379-388.

Table S4 pH-Rate profile data[a,b] for the hydrolysis of compound **4a** in water at 25°C

pH	$-\log k_{obs}$ /s	pH	$-\log k_{obs}$ /s
6.37	3.98	9.95	2.58
7.10	3.29	10.8	2.58
7.62	2.93	12.0	2.55
8.15	2.71	13.0	2.56
8.47	2.65	14.0	2.47
9.14	2.68		

[a]Measured spectrophotometrically in water at 25°C at (μ)=1.0 M KCl. Analytical wavelength was 400 nm.[b] The following buffers were used to control pH in the ranges shown: pH from 6.37-7.62 phosphate (0.005 – 0.1 M); pH 8.15-9.14 borate (0.01 – 0.2 M; pH 9.95-10.8 carbonate (0.05 – 0.2 M) and pH 12-14 hydroxide (0.01 – 1 M).

Table S5 pH-Rate profile data[a] for the hydrolysis of compound **1a** in water at 50°C.

H_o/pH	-logk_{obs}/s	H_o/pH	-logk_{obs}/s
-1.05	3.87[b]	5.00	3.37[c,d]
-0.83	3.83[b]	5.47	3.01[c,d]
-0.69	3.82[b]	6.05	2.64[c,d]
-0.44	3.79[b]	6.59	2.00[c,d]
0	3.79[c]	6.71	1.91[c,d]
0.3	3.76[c]	7.14	1.60[c,d]
0.8	3.71[c]	7.30	1.59[c,d]
1.0	3.65[c]	7.80	1.41[c,d]
2.33	3.54[c]	8.60	0.83[c,d]
3.8	3.49[c,d]	8.78	0.72[c,d]

[a]Conditions: Substrate concentration was 1 x 10^{-4}M. Runs were followed by the production of 4-nitrophenol at 265 nm or 4-nitrophenoxide at 410 nm and were carried out for at least 4 half-lives and done in triplicate. Runs were generally reproducible to within ± 5% except those at pHs 7.8, 8.6 and 8.78 which were reproducible to within ± 9%. [b]Constant ionic strength (μ)=3.0 M KCl. [c](μ)=1.0 M KCl. [d]Carried out using 0.01 M TRIS-cacodylate buffer.

Table S6 Logk_{obs} for the hydrolysis[a] of compounds **1a** and **1f-j** in water at 50°C at pH = 2.0, the pK_a of the leaving phenols[b] and literature Hammett σ value[c]

Compound	-logk_{obs}/s	Anal. λ (nm)	pK_a	Hammett σ
1a	3.60	325	7.15	0.778
1f	4.50	290	9.41	0.232
1g	4.46	275	9.37	0.227
1h	4.78	280	9.89	0.062
1i	4.69	275	9.99	0

1j	4.90	280	10.26	-0.17

[a]At μ=1.0 M KCl. [b]In water at 25°C. Values were taken from A. Albert and E. P. Serjeant, *The Determination of Ionization Constants*, third ed., Chapman and Hall, London, 1984, p.145. [c]Taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420-427.

Table S7 Hydrolysis of compound **1a** in aqueous organic solvent mixtures[a] of identical ionizing power (Y_{OTs}) but differing nucleophilicities (N_{OTs}).

Solvent system	N_{OTs}	Y_{OTs}	$logk_{obs}$ /s	Rate ratio $k_{solvent\ mixture}/k_{97\%\ TFE\ or\ 97\%\ HFIP}$
44.8% EtOH	-0.19	1.83	-3.39	95[b]
52.4% MeOH	-0.17	1.83	-3.45	84[b]
36% ACN	-1.16	1.83	-3.52	71[b]
97% TFE	-3.25	1.83	-5.37	-
10% EtOH	-0.41	3.78	-3.46	22[c]
10% MeOH	-0.41	3.78	-3.47	21[c]
10% ACN	-1.29	3.60	-3.47	21[c]
97% HFIP	-4.27	3.60	-4.79	-

[a]At 50 °C using v/v mixtures except for 97% TFE and 97% HFIP which were w/w. [b]Compared with the rate in 97% TFE. [c]Compared with the rate in 97%HFIP.

Table S8 $Logk_{obs}$ for the hydrolysis of **1a** in 50% aqueous ACN at 25°C at high pH.

pH	$logk_{obs}$/s	Anal. λ nm	pH	$logk_{obs}$/s	Anal. λ nm
8.7	-4.71	325[a]	11.7	0.921	400[b,c]
9.7	-4.46	400[b]	12.7	2.068	400[b,c]
10.7	-1.67	400[b]			

[a]Appearance of 4-nitrophenol. [b]Appearance of 4-nitrophenoxide. [c]Rates determined using stopped-flow apparatus.

Table S9 Logk_{obs} for the hydrolysis of compounds **1a** and **1g-j** at pH = 11.7 at 25°C in 50% aqueous ACN, the pK_a of the leaving phenols and literature Hammett σ values.

Compound	logk_{obs} /s	Anal. λ (nm)	pK_a	Hammett σ
1a	0.921	325	7.15	0.778
1g	-2.39	275	9.37	0.232
1h	-3.47	280	9.89	0.062
1i	-3.52	275	9.99	0
1j	-4.26	280	10.26	-0.17

[a]In water at 25°C. Values were taken from A. Albert and E. P. Serjeant, *The Determination of Ionization Constants*, 3rd ed., Chapman and Hall, London, 1984, p.145. [b]Taken from D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420-427.

Table S10 Logk_a for the hydrolysis of compounds **4a-g i**n water[a] at 25°C and Hammett σ values[b]

Compound	-logk_a /s	Hammett σ
4a	2.57	0.73[c]
4b	2.46	0.227
4c	2.56	0.50[c]
4d	2.43	0.062
4e	2.40	0
4f	2.33	-0.17
4g	2.33	-0.27

[a]μ = 1.0 M (KCl). Analytical wavelength was 400 nm for each substrate. [b]See Table S3, footnote d. [c]The σ value for 2-chloro is from M. T. Tribble and J. G. Traynham, *J. Am. Chem. Soc.*, 1969, **91**, 379-388.

Table S11 pH-rate profile data for the hydrolysis of compounds **4b–g**.[a]

Compound	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
pH	- logk_{obs} /s					
6.37	3.82	3.82	3.96	3.92	3.96	4.03
7.10	3.27	3.38	3.31	3.44	3.39	3.40
7.62	2.91	2.99	2.92	2.95	2.96	2.97
8.15	2.65	2.74	2.65	2.66	2.63	2.64
8.47	2.55	2.65	2.54	2.54	2.48	2.50
9.14	2.47	2.59	2.45	2.43	2.37	2.35
9.95	2.45	2.55	2.42	2.40	2.32	2.32
10.77	2.47	2.57	2.44	2.41	2.34	2.35
12.0	2.45	2.54	2.42	2.38	2.31	2.30
13.0	2.42	2.52	2.41	2.37	2.31	2.30
14.0	2.33	2.44	2.33	2.29	2.23	2.19

[a]Conditions are the same as those reported in Table 2 for compound **4a**.

Table S12 Effect of acetate buffer on the hydrolysis of **1a** in water at 25°C

Buffer	Buffer conc. (M)	pH	10^5 k_{obs} /s
Acetate	0.09	4.63	1.21
Acetate	0.018	4.65	1.28
Acetate	0.036	4.65	1.27

T**able S13** Physical and analytical data for compounds **4a-g**

Compound	m.p. (°C)	Calculated (%)			Found (%)		
		C	H	N	C	H	N
4a	111 – 112	41.35	2.67	7.43	41.61	2.78	7.36

4b	106 – 107	45.56	3.23	8.17	45.79	3.21	8.28
4c	84 – 85	45.56	3.23	8.17	45.56	3.21	8.08
4d	100 – 101	47.85	3.40	8.56	48.02	3.42	8.68
4e	109 – 110	50.64	3.92	9.09	50.81	3.87	9.10
4f	113 – 114	52.17	4.38	8.69	52.58	4.54	8.75
4g	103 - 104	49.70	4.17	8.30	50.64	4.22	8.25