Supporting Information

4-Oxo-β-lactams (azetidine-2,4-diones) are potent and selective inhibitors of human leukocyte elastase

Jalmira Mulchande,[a] Rudi Oliveira,[a] Marta Carrasco,[a] Luís Gouveia,[a] Rita C. Guedes,[a] Jim Iley,[b] Rui Moreira,[a*]

[a] iMed.UL, Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto, 1649-003 Lisbon, Portugal; [b] Department of Chemistry & Analytical Sciences, The Open University, Milton Keynes, MK7 6AA, UK

To whom correspondence should be addressed: e-mail rmoreira@ff.ul.pt

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Analytical data for compounds 3 and 6

Table SI.1. Elemental analysis for compounds **3** and **6**.

Compd	Formula	C, H, N Calculated				C,H,N Found			
		C	H	N	S	C	H	N	S
3f	$C_{14}H_{17}NO_2$	72.70	7.41	6.06	-	72.12	7.45	5.88	-
3g	$C_{12}H_{14}N_2O_2$	66.04	6.47	12.84	-	66.29	6.53	13.07	-
3h	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	-	66.81	6.85	11.71	-
3i	$C_{17}H_{17}NO_2$	76.38	6.41	5.24	-	76.31	6.34	5.23	-
3l	$C_{15}H_{19}NO_2$	73.44	7.81	5.71	-	72.99	7.88	5.67	-
3m	$C_{15}H_{19}NO_2$	73.44	7.81	5.71	-	73.36	8.19	5.48	-
3n	$C_{18}H_{17}NO_2$	77.40	6.13	5.01	-.	77.22	6.08	5.08	-
3o	$C_{17}H_{15}NO_2$	76.96	5.70	5.28	-	76.88	5.59	5.24	-
3p	$C_{11}H_{11}NO_2$	69.83	5.86	7.40	-	70.15	6.37	7.75	-
6a	$C_{21}H_{20}N_2O_2S_2$	63.61	5.08	7.06	16.17	63.55	5.18	6.85	
6b	$C_{21}H_{20}N_2O_3S$	66.29	5.30	7.36	8.43	66.54	5.35	7.26	8.45
6c	$C_{22}H_{21}N_3O_3S$	64.85	5.19	10.31	7.87	64.41	5.29	9.92	7.55
6d	$C_{18}H_{21}N_3O_2S$	62.95	6.16	12.23	9.34	62.82	6.98	11.76	8.87
6e	$C_{21}H_{20}N_2O_2S_2$	63.61	5.08	7.06	16.17	63.32	5.11	6.92	16.12
6f	$C_{21}H_{20}N_2O_3S$	66.29	5.30	7.36	8.43	65.98	4.88	7.23	8.13
6g	$C_{22}H_{20}N_2O_5S$	62.25	4.75	6.60	7.55	61.87	4.66	6.30	7.21
6h	$C_{22}H_{21}N_3O_3S$	64.85	5.19	10.31	7.87	64.66	5.17	10.41	7.91
6i	$C_{20}H_{19}N_3O_2S_2$	60.43	4.82	10.57	16.13	60.01	5.03	10.22	
6j	$C_{20}H_{21}NO_2S$	70.77	6.24	4.13	9.45	70.32	6.14	4.00	9.11

Infrared and mass spectra for compounds 3 and 5

3f ν_{max} (film) 1868, 1740; EI-MS *m/z* 231 $[M]^+$ 11.97 %, 98 $[(CH_3CH_2)_2C{=}C{=}O]^{\cdot+}$ 100.0%.

3g ν_{max} (film) 1869, 1743; EI-MS *m/z* 218 $[M]^+$ 16.44%; 98 $[(CH_3CH_2)_2C{=}C{=}O]^{\cdot+}$ 75.5%.

3h ν_{max} (film) 1862, 1741; EI-MS *m/z* 232 $[M]^+$ 33.14%; 98 $[(CH_3CH_2)_2C{=}C{=}O]^{\cdot+}$ 100.0%.

3i ν_{max} (film) 1868, 1739; EI-MS *m/z* 267 $[M]^+$ 10.41%; 169 $[C_{10}H_7N{=}C{=}O]^{\cdot+}$ 100.0%.

3l ν_{max} (film) 1860, 1737; EI-MS *m/z* 245 $[M]^+$ 6.87%, 125 $[(CH_3CH_2)CH_2CH(CH_3)_2C{=}C{=}O]^{\cdot+}$ 100.0%.

3m ν_{max} (film) 1861, 1741; EI-MS *m/z* 245 $[M]^+$ 4.38 %; 98 $[(CH_3CH_2)_2C{=}C{=}O]^{\cdot+}$ 100.0%.

3n ν_{max} (film) 1855, 1733; EI-MS *m/z* 279 $[M]^+$ 75.54%; 160 $[(CH_3CH_2)(CH_2C_6H_5)C{=}C{=}O]^{\cdot+}$ 100.0%.

3o ν_{max} (film) 1852, 1740; EI-MS *m/z* 265 $[M]^+$ 81.34%; 146 $[(CH_3)(CH_2C_6H_5)C=C=O]^{\cdot+}$ 98.0%.

3p ν_{max} (film) 1858, 1737; EI-MS *m/z* 189 $[M]^+$ 22.37%; 70 $[(CH_3)_2C=C=O]^{\cdot+}$ 100.0%.

6a ν_{max} (film) 1868, 1738; EI-MS *m/z* 396 $[M]^+$ 32.99%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6b ν_{max} (film) 1868, 1740; EI-MS *m/z* 380 $[M]^+$ 29.76%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6c ν_{max} (film) 1857, 1740; EI-MS *m/z* 407 $[M]^+$ 11.73%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6d ν_{max} (film) 1870, 1738; EI-MS *m/z* 343 $[M]^+$ 14.24%, 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6e ν_{max} (film) 1861, 1737; EI-MS *m/z* 396 $[M]^+$ 16.55%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6f ν_{max} (film) 1857, 1738; EI-MS *m/z* 380 $[M]^+$ 57.89%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6g ν_{max} (film) 1855, 1733, 1683, 2500-4000 (large); EI-MS *m/z* 424 $[M]^+$ 1.37%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6h ν_{max} (film) 1855, 1735; EI-MS *m/z* 407 $[M]^+$ 39.01%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

6i ν_{max} (film) 1868, 1741; EI-MS *m/z* 397 $[M]^+$ 62.79%; 299 2-((5-isocyanatopyridin-2-yl)methylthio)benzothiazole $[C_{14}H_9N_3OS_2]^{\cdot+}$ 100.0%.

6j ν_{max} (film) 1849, 1736; EI-MS *m/z* 339 $[M]^+$ 2.37%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 100.0%.

Synthesis of compounds 5

1-(2-(Bromomethyl)phenyl)-3,3-diethylazetidine-2,4-dione, 5a. A mixture of **3f** (0.282 mmol), *N*-bromosuccinimide (NBS) (0.310 mmol) and benzoyl peroxide (0.0282 mmol) in tetrachloromethane was heated under reflux for 12h, the reaction being monitored by TLC. Benzoic acid was removed by filtration and the solvent removed under reduced pressure. Attempted purification by column chromatography failed as it was found that the product and the remaining **3f** have the same R_f. Consequently, the mixture of **3f** and **5a (**66%) was used without further purification; ν_{max} (film) 1869, 1740; δ ^{1}H-NMR 1.19 (6H, t, *J* = 7.6); 1.97 (4H, q, *J* =7.6); 4.64 (2H, s); 7.35-7.44 (3H, m); 7.49 (1H, dd, *J* =7.6, 2.0); EI-MS *m/z* 310 $[M]^+$ 1.41%; 312 $[M]^{2+}$ 1.39%; 132 $[C_7H_6N=C=O]^{\cdot+}$ 12.45%; 98 $[(CH_3CH_2)_2C=C=O]^{\cdot+}$ 100.00%.

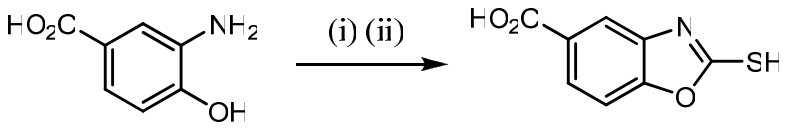
1-(4-(Bromomethyl)phenyl)-3,3-diethylazetidine-2,4-dione, 5b. Prepared as described for **5a**, by reaction of **3b** (0.346 mmol) with NBS (0.364 mmol) and benzoyl peroxide (0.0346 mmol), and purified using hexane-ethyl acetate 9.5:0.5, to yield white crystals (71%), m.p. 71-72 ºC, ν_{max} (film) 1865, 1740; δ ^{1}H-NMR 1.08 (6H, t, *J* = 7.6); 1.88 (4H, q, *J* =7.6); 4.50 (2H, s); 7.47

(2H, dd, *J* =7.2, 2.0); 7.86 (2H, dd, *J* =7.2, 2.0); δ ^{13}C-NMR 9.25, 23.98, 32.62, 72.35, 119.45, 130.01, 133.73, 136.27, 172.06; EI-MS *m/z* 310 $[M]^+$ 3.42%; 312 $[M+2]^+$ 3.40%; 132 $[C_7H_6N{=}C{=}O]^{\cdot+}$ 100.00%.

1-(6-(Bromomethyl)pyridin-3-yl)-3,3-diethylazetidine-2,4-dione, 5c. Prepared as described for **5a**, by reaction of **3h** (0.522 mmol) with NBS (0.549 mmol) and benzoyl peroxide (0.0522 mmol), and purified using dichloromethane as eluant, to yield a pink oil (36%), ν_{max} (film) 1868, 1741; δ ^{1}H-NMR 1.10 (6H, t, *J* = 7.6); 1.91 (4H, q, *J* =7.6); 4.61 (2H, s); 7.56 (1H, d, *J* =8.4); 8.23 (1H, dd, *J* =8.4, 2.8); 9.13 (1H, d, *J* = 2.8); δ ^{13}C-NMR 9.25, 23.96, 32.45, 72.66, 128.46, 130.10, 130.95, 141.42, 148.94, 171.43; EI-MS *m/z* 311 $[M]^+$ 8.30%; 313 $[M+2]^+$ 8.27%; 98 $[(CH_3CH_2)_2C{=}C{=}O]^{\cdot+}$ 100.00%.

2-Mercaptobenzoxazole-5-carboxylic acid, 9. A mixture of 3-amino-4-hydroxybenzoic acid (5 mmol) and potassium ethyl xanthate in ethanol 95%-water (6:1) was refluxed for 3h. The reaction mixture was concentrated, acidified to pH 2 with stirring, and cooled. The product separated as grey crystals (53%) which were filtered-off, dried and used without any further purification; ν_{max} (film) 3216 (large); 1699; δ ^{1}H-NMR 7.53 (1H, d, *J* = 8,8); 7.74 (1H, d, *J* = 1.2); 7.85 (1H, dd, *J* = 8,4; 1,2); δ ^{13}C-NMR 109.93; 111.24; 125.84; 127.42; 131.22; 150.93; 166.61; 180.58.

Scheme SI.1 – Synthesis of 2-mercaptobenzo[d]oxazole-5-carboxylic acid 9



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(i) $EtOCS_2K$, EtOH 95%, H_2O, reflux; (ii) HCl, H_2O

Complete ref. 60:

30. Gaussian 03, Revision C.02, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.