Supporting Information

Ketones as Building Blocks For Dynamic Combinatorial Libraries: Highly Active Neuraminidase Inhibitors Generated *via* Selection Pressure of the Biological Target.

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Scheme S1. Complete list of ketones used in DCC experiments (see Fig.1 and 2).

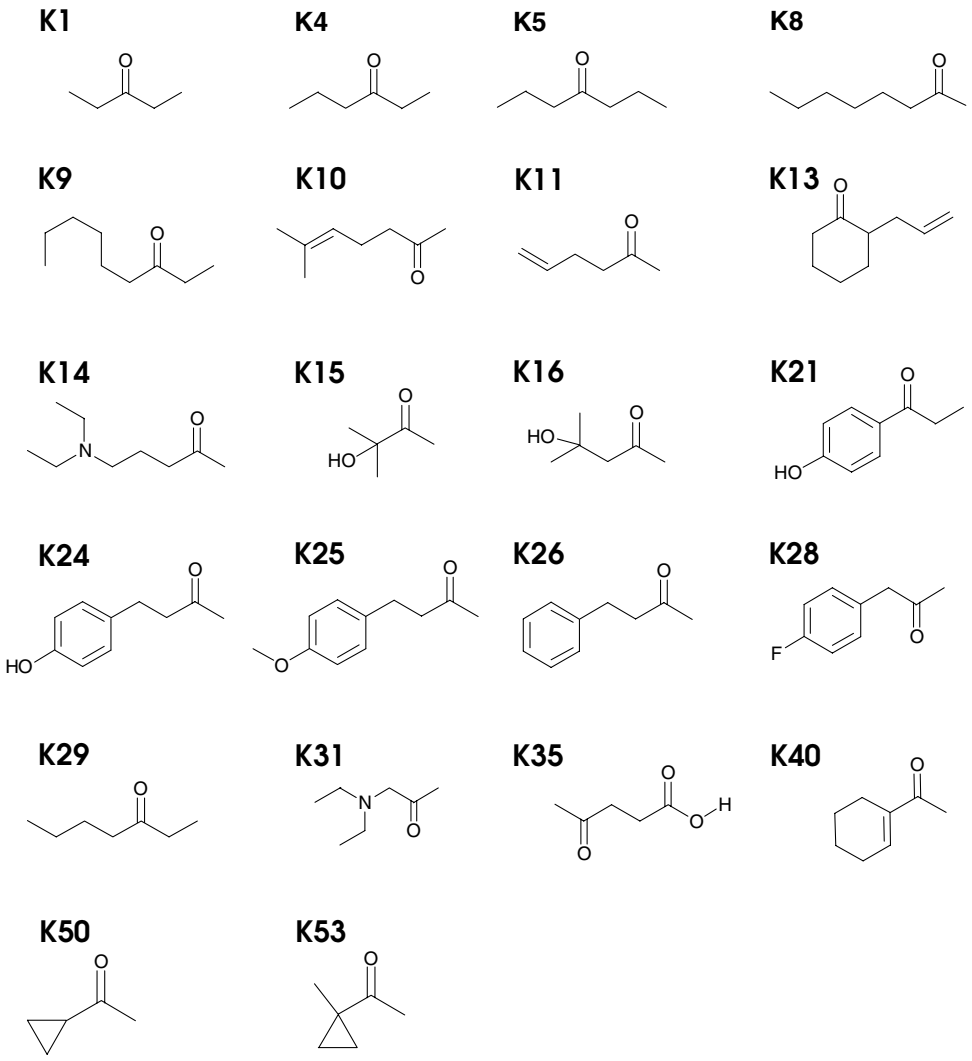

Table S1. *K*i (nM) of resynthesized DCC hits determined for neuraminidases from different virus subtypes.

Neuraminidase source	1	2a	2b	2c	2d	3
B/Victoria/504/2000	9300 ± 500	85 ± 11	232 ± 30	115 ± 1	14000 ± 1000	2,7 ± 0,4
A/Panama/2007/99	34000 ± 4200	4,3 ± 0,6	10 ± 1	25 ±2	9000 ± 1000	0,15 ± 0,04
B/Harbin/7/94	9400 ± 1000	165 ± 17	209 ± 24	328 ± 40	16000 ± 1000	5,8 ± 1,1
A/Johannesburg/33/94	36000 ± 3400	12 ± 0,6	15,7 ± 0,4	117 ± 6	16000 ± 1000	0,37 ± 0,08
cHis-tNA sol	31300 ± 4500	85 ± 5	92 ± 8	696± 70	54000 ± 8000	1,3 ± 0,2
cHis-tNA full	11300 ± 1800	--	46 ± 5	349 ±41	31000 ± 4000	0,9 ± 0,1

Synthesis

NMR spectra were recorded at 250 MHz (^{1}H) or 62.9 MHz (^{13}C) on a Bruker Avance 250 spectrometer. Coupling constants are in hertz. Mass spectra were recorded on a Bruker Esquire 3000 mass spectrometer. The synthesis of the amines (**2a**, **2b**, **2c**) derived from DCC hits and of amine **2d** was conducted as previously described,[13] with the exception that the reductive amination of an appropriately protected derivative of amine **1** with the ketones was performed in MeOH in the presence of $NaCNBH_3$.[S1] Compound **3** was pepared as described in the literature.[S2]

(3*R*, 4*R*, 5*S*)-4-acetamido-5-amino-3-(1-ethylpropyl)amino-1-cyclohexene-1-carboxylic Acid Hydochloride (2a)

^{1}H NMR (D_2O) δ 6.91 (s, 1H), 4.49-4.46 (m, 1H), 4.42 (t, 1H, *J* = 9.7), 3.79 (ddd, 1H, *J* = 5.4, 10.8), 3.41 (q, 1H, *J* = 5.9), 3.10 (d, 1H, *J* = 5.2, 17.5), 2.70-2.56 (m, 1H), 2.12 (s, 3H), 1.87-1.73 (m, 4H), 1.05-0.98 (m, 6H); ^{13}C NMR (D_2O) δ 176.2, 168.3, 133.2, 129.7, 60.2, 56.2, 49.7, 28.4, 23.3, 22.8, 22.0, 9.0, 8.2; LRMS (ESI^+) *m/z* 284 ($[M+H]^+$).

(3*R*, 4*R*, 5*S*)-4-acetamido-5-amino-3-(1-(*R*/*S*)-ethylbutyl)amino-1-cyclohexene-1-carboxylic Acid Hydochloride (2b)

(1:1 diastereomeric mixture); ^{1}H NMR (D_2O) δ 6.91 (s, 1H), 4.52-4.47 (m, 1H), 4.43 (t, 1H, *J* = 10.5), 3.85-3.74 (m, 1H), 3.53-3.41 (m, 1H), 3.10 (dd, 1H, *J* = 5.3, 17.5), 2.70-2.53 (m, 1H), 2.18 (s, 3H), 1.82-1.68 (m, 4H), 1.47-1.33 (m, 2H), 1.05-0.92 (m, 6H); ^{13}C NMR (D_2O) δ 176.2, 168.1, 133.1, 129.9, 59.3, 58.9, 56.2, 49.7, 32.3, 31.3, 28.3, 23.9, 22.9, 22.5, 18.4, 17.8, 13.4, 9.1, 8.2; LRMS (ESI^+) *m/z* 298 ($[M+H]^+$).

(3*R*, 4*R*, 5*S*)-4-acetamido-5-amino-3-[3-(4-hydroxyphenyl)-1-(*R*/*S*)-methylpropyl]amino-1-cyclohexene1-carboxylic Acid Hydochloride (2c)

(3:2 diastereomeric mixture); ^{1}H NMR (D_2O) δ 7.22-7.19 (m, 2H), 6.92-6.70 (m, 3H), 4.48-4.28 (m, 2H), 3.80-3.67 (m, 1H), 3.55-3.32 (m, 1H), 3.13-3.00 (m, 1H), 2.88-2.45 (m, 3H), 2.11-1.97 (m, 5H), 1.47-1.39 (m, 3H); ^{13}C NMR (D_2O) δ 176.2, 168.0, 154.3, 133.0, 132.6, 132.4, 130.2, 130.1, 129.8, 115.9, 55.8, 53.0, 49.6, 49.5, 35.3, 30.2, 28.4, 22.8, 15.6; LRMS (ESI^+) *m/z* 362 ($[M+H]^+$).

(3*R*, 4*R*, 5*S*)-4-acetamido-5-amino-3-[(4-diethylamino-1-(*R*/*S*)-methylbutyl]amino-1-cyclohexene-1-carboxylic Acid Hydochloride (2d)

(3:2 diastereomeric mixture); ^{1}H NMR (D_2O) δ 6.91-6.88 (m, 1H), 4.53-4.36 (m, 2H), 3.81-3.60 (m, 2H), 3.27-3.02 (m, 7H), 2.62-2.50 (m, 1H), 2.12 (s, 3H), 1.89-1.72 (m, 4H), 1.43-1.23 (m, 9H); LRMS (ESI^+) *m/z* 355 ($[M+H]^+$).

References

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(S2) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681-690.