Supporting Information

Nor-piperidine Imidazo-azepines as a New Class of Potent and Selective H_1 Antihistamines

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^{1}H and ^{13}C NMR data of intermediates

Compound 7:
^{1}H NMR (400 MHz) δ 1.24 (t, *J*=7.1 Hz, 3 H), 1.52 (qd, *J*=12.4, 4.3 Hz, 2 H), 1.81 (br.d, *J*=13.2 Hz, 2 H), 2.90 (br.t, *J*=12.5 Hz, 2 H), 3.83 (tt, *J*=11.5, 3.7 Hz, 1 H), 4.13 (br.s, 2 H), 4.11 (q, *J*=7.1 Hz, 2 H), 6.89 (d, *J*=1.1 Hz, 1 H), 7.04 (m, 4 H), 7.15 (d, *J*=1.1 Hz, 1 H), 7.33 (m, 6 H), 7.78 (s, 1 H)
^{13}C NMR (101 MHz) δ 14.7, 27.9, 43.2, 44.3, 61.2, 64.6, 125.1, 128.2, 128.8, 128.9, 139.2, 142.2, 155.5, 194.2

Compound 8b:
^{1}H NMR (360 MHz) δ 1.84 (qd, *J*=12.4, 3.8 Hz, 2 H), 1.98 (br.d, *J*=12.4 Hz, 2 H), 2.12 (td, *J*=11.9, 2.6 Hz, 2 H), 2.31 (s, 3 H), 2.97 (dt, *J*=11.7, 3.3 Hz, 2 H), 3.55 (tt, *J*=11.6, 3.9 Hz, 1 H), 7.26 (br.d, *J*=12.0 Hz, 2 H)
^{13}C NMR (91 MHz) δ 28.2, 42.8, 46.3, 55.0, 120.5, 131.2, 144.6, 194.2

Compound 10:
^{1}H NMR (360 MHz) δ 1.79 (qd, *J*=12.3, 3.8 Hz, 2 H), 1.91 (br.d, *J*=12.3 Hz, 2 H), 2.09 (td, *J*=11.8, 2.7 Hz, 2 H), 2.30 (s, 3 H), 2.92 (br.dt, *J*=11.7, 3.2 Hz, 2 H), 3.01 (t, *J*=7.2 Hz, 2 H), 3.42 (s, 3 H), 3.62 (tt, *J*=11.6, 3.9 Hz, 1 H), 4.56 (t, *J*=7.2 Hz, 2 H), 5.87 (dd, *J*=3.6, 1.8 Hz, 1 H), 6.03 (t, *J*=3.1 Hz, 1 H), 6.52 (dd, *J*=2.7, 1.8 Hz, 1 H), 6.87 (d, *J*=1.0 Hz, 1 H), 7.11 (d, *J*=1.0 Hz, 1 H)

Compound 11a
^{1}H NMR (360 MHz) δ 2.27 (s, 3 H), 2.38 (br.s, 2 H), 2.45 (br.s, 2 H), 2.70 (t, *J*=5.8 Hz, 2 H), 2.82 (t, *J*=5.8 Hz, 2 H), 2.90 (t, *J*=5.8 Hz, 2 H), 3.44 (s, 3 H), 4.32 (t, *J*=5.8 Hz, 2 H), 6.06 (d, *J*=2.8 Hz, 1 H), 6.50 (d, *J*=2.8 Hz, 1 H), 6.85 (d, *J*=1.3 Hz, 1 H), 6.92 (d, *J*=1.3 Hz, 1 H)
^{13}C NMR (91 MHz) δ 27.3, 31.0, 31.4, 33.6, 42.9, 46.1, 56.8, 57.1, 109.3, 117.2, 118.2, 118.3, 120.0, 126.2, 126.5, 139.9, 150.3

Compound 11b
^{1}H NMR (360 MHz) δ 1.26 (t, *J*=7.1 Hz, 3 H), 2.64 (t, *J*=5.9 Hz, 2 H), 2.76 (t, *J*=5.9 Hz, 2 H), 2.91 (t, *J*=5.8 Hz, 2 H), 3.45 (m, 5 H), 3.53 (br.t, *J*=5.7 Hz, 2 H), 4.15 (q, *J*=7.1 Hz, 2 H), 4.32 (t, *J*=5.8 Hz, 2 H), 6.02 (d, *J*=2.8 Hz, 1 H), 6.51 (d, *J*=2.8 Hz, 1 H), 6.87 (d, *J*=1.3 Hz, 1 H), 6.93 (d, *J*=1.3 Hz, 1 H)
^{13}C NMR (91 MHz) δ 14.7, 27.3, 30.8, 31.1, 33.7, 42.9, 44.6, 45.0, 61.2, 109.2, 116.9, 118.4, 119.6, 120.2, 126.4, 126.6, 138.9, 149.9, 155.5

Compound 14 (fumarate salt (1:1))
^{1}H NMR (400 MHz, DMSO-d_6, 70°C) δ 1.08 (t, *J*=7.2 Hz, 3 H), 2.58 (m, 6 H), 2.68 (m, 2 H), 2.75 (m, 2 H), 2.86 (t, *J*=5.8 Hz, 2 H), 3.42 (s, 3 H), 4.28 (m, 2 H), 5.89 (d, *J*=2.8 Hz, 1 H), 6.57 (s, 2 H), 6.62 (d, *J*=2.8 Hz, 1 H), 6.75 (d, *J*=1.2 Hz, 1 H), 7.09 (d, *J*=1.3 Hz, 1 H)
^{13}C NMR (101 MHz, DMSO-d_6) δ 10.6, 26.3, 29.1, 29.5, 32.9, 42.0, 50.6, 52.6, 52.8, 107.7, 115.7, 118.8, 119.1, 119.9, 125.1, 126.8, 134.0, 136.4, 148.8, 166.4

Compound 16
^{1}H NMR (400 MHz) δ 1.38 (qd, *J*=12.2, 4.0 Hz, 1 H), 1.54 (m, 2 H), 1.80 (m, *J*=11.8, 11.8, 8.4, 3.7, 3.7 Hz, 1 H), 1.94 (m, 3 H), 2.88 (m, 1 H), 2.96 (m, 1 H), 3.49 (s, 2 H), 3.60 (s, 3 H), 3.62 (d, *J*=8.4 Hz, 1 H), 6.07 (dd, *J*=3.7, 2.7 Hz, 1 H), 6.11 (dd, *J*=3.7, 1.8 Hz, 1 H), 6.57 (dd, *J*=2.7, 1.8 Hz, 1 H), 7.28 (m, 5 H)
^{13}C NMR (101 MHz) δ 30.0, 30.4, 34.1, 35.5, 39.6, 53.1, 63.0, 107.4, 109.3, 118.8, 123.4, 124.2, 127.0, 128.2, 129.0, 138.2

Compound 17 (fumarate salt (1:1))
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.71 (m, 4 H), 2.30 (m, 2 H), 2.98 (dt, *J*=11.5, 3.3 Hz, 2 H), 3.14 (m, 1 H), 3.68 (s, 2 H), 3.84 (s, 3 H), 6.11 (m, 1 H), 6.60 (s, 2 H), 7.12 (m, 2 H), 7.32 (m, 5 H)
^{13}C NMR (101 MHz, DMSO-d_6) δ 28.2, 37.1, 42.9, 51.9, 61.4, 107.8, 119.2, 127.5, 128.3, 129.1, 129.4, 131.9, 134.3, 136.2, 166.6, 192.5

Compound 18
^{1}H NMR (400 MHz) δ 1.78 (br.d, *J*=12.6 Hz, 2 H), 1.88 (qd, *J*=12.1, 3.8 Hz, 2 H), 2.07 (td, *J*=11.5, 2.8 Hz, 2 H), 2.85 (tt, *J*=11.3, 4.0 Hz, 1 H), 2.95 (dt, *J*=11.6, 3.4 Hz, 2 H), 3.53 (s, 2 H), 3.67 (s, 3 H), 6.56 (m, 2 H), 7.24 (m, 2 H), 7.31 (m, 4 H)
^{13}C NMR (101 MHz) δ 29.0, 36.5, 45.4, 53.3, 63.2, 109.4, 123.2, 124.8, 126.4, 126.9, 128.1, 129.0, 138.5, 198.2

Compound 20a
^{1}H NMR (360 MHz) δ 2.47 (m, 4 H), 2.56 (t, *J*=5.7 Hz, 2 H), 3.03 (t, *J*=5.7 Hz, 2 H), 3.51 (s, 2 H), 3.61 (s, 3 H), 5.96 (dd, *J*=2.6, 1.7 Hz, 1 H), 6.42 (t, *J*=2.0 Hz, 1 H), 6.56 (t, *J*=2.4 Hz, 1 H), 6.96 (br.s, 2 H), 7.27 (m, 5 H), 8.97 (br.s, 1 H)

Compound 21
^{1}H NMR (360 MHz) δ 2.23 (m, 2 H), 2.76 (m, 6 H), 3.53 (m, 2 H), 3.89 (s, 3 H), 4.51 (d, *J*=15.7 Hz, 1 H), 4.87 (d, *J*=15.7 Hz, 1 H), 6.10 (d, *J*=2.6 Hz, 1 H), 6.77 (d, *J*=2.6 Hz, 1 H), 6.90 (d, *J*=1.3 Hz, 1 H), 6.95 (d, *J*=1.3 Hz, 1 H), 7.27 (m, 5 H)

Compound 22
^{1}H NMR (360 MHz) δ 2.21 (m, 2 H), 2.72 (m, 6 H), 3.53 (m, 2 H), 3.63 (s, 3 H), 4.49 (d, *J*=15.6 Hz, 1 H), 4.87 (d, *J*=15.6 Hz, 1 H), 6.48 (d, *J*=2.3 Hz, 1 H), 6.87 (d, *J*=1.3 Hz, 1 H), 6.95 (d, *J*=1.3 Hz, 1 H), 7.28 (m, 6 H)

Compound 23 (fumarate salt (1:1))
^{1}H NMR (360 MHz, DMSO-d_6) δ 1.28 (br.d, *J*=13.5 Hz, 1 H), 1.42 (m, 2 H), 1.64 (br.d, *J*=13.3 Hz, 1 H), 2.27 (qt, *J*=11.0, 3.5 Hz, 1 H), 2.72 (m, 2 H), 3.20 (m, 2 H), 3.83 (s, 3 H), 3.90 (d, *J*=11.2 Hz, 1 H), 4.84 (d, *J*=17.5 Hz, 1 H), 5.30 (d, *J*=17.5 Hz, 1 H), 6.18 (d, *J*=2.4 Hz, 1 H), 6.45 (s, 2 H), 6.71 (d, *J*=1.2 Hz, 1 H), 7.18 (d, *J*=2.4 Hz, 1 H), 7.22 (d, *J*=1.2 Hz, 1 H)

Compound 24
^{1}H NMR (360 MHz) δ 1.74 (br.d, *J*=13.3 Hz, 2 H), 2.22 (td, *J*=12.6, 4.3 Hz, 2 H), 2.42 (td, *J*=11.5, 2.5 Hz, 2 H), 2.65 (m, 3 H), 3.04 (t, *J*=7.5 Hz, 2 H), 3.52 (s, 2 H), 4.44 (dd, *J*=8.3, 6.7 Hz, 2 H), 6.79 (m, 1 H), 6.84 (m, 1 H), 7.09 (m, 2 H), 7.28 (m, 8 H)

Compound 25a
^{1}H NMR (400 MHz, 70°C) δ 2.42 (ddd, *J*=13.1, 8.7, 3.7 Hz, 2 H), 2.65 (m, 4 H), 2.84 (m, 2 H), 3.41 (t, *J*=6.7 Hz, 2 H), 3.45 (s, 2 H), 4.23 (t, *J*=6.7 Hz, 2 H), 6.73 (d, *J*=1.3 Hz, 1 H), 6.92 (d, *J*=1.3 Hz, 1 H), 7.11 (dd, *J*=7.4, 1.8 Hz, 1 H), 7.15 (td, *J*=7.3, 1.3 Hz, 1 H), 7.21 (m, 2 H), 7.29 (m, 4 H), 7.50 (dd, *J*=7.9, 1.3 Hz, 1 H)

Compound 25b (base)
^{1}H NMR (400 MHz) δ 2.38 (ddd, *J*=13.5, 8.6, 3.3 Hz, 2 H), 2.76 (ddd, *J*=13.5, 7.0, 3.2 Hz, 2 H), 3.00 (ddd, *J*=12.7, 7.0, 3.3 Hz, 2 H), 3.17 (ddd, *J*=12.7, 8.6, 3.1 Hz, 2 H), 3.45 (t, *J*=6.6 Hz, 2 H), 4.26 (t, *J*=6.6 Hz, 2 H), 6.77 (d, *J*=1.3 Hz, 1 H), 6.93 (d, *J*=1.2 Hz, 1 H), 7.15 (dd, *J*=7.3, 1.6 Hz, 1 H), 7.19 (td, *J*=7.3, 1.3 Hz, 1 H), 7.26 (td, *J*=7.5, 1.9 Hz, 1 H), 7.52 (d, *J*=7.8 Hz, 1 H)

Compound 25c
^{1}H NMR (360 MHz) δ 1.45 (s, 9 H), 2.32 (ddd, *J*=13.7, 7.0, 5.8 Hz, 2 H), 2.79 (br.s, 2 H), 3.53 (br.m, 6 H), 4.27 (br.s, 2 H), 6.79 (d, *J*=1.3 Hz, 1 H), 6.92 (d, *J*=1.3 Hz, 1 H), 7.19 (m, 2 H), 7.25 (td, *J*=7.3, 2.3 Hz, 1 H), 7.47 (dd, *J*=7.7, 1.4 Hz, 1 H)

Compound 26a
^{1}H NMR (360 MHz) δ 1.44 (s, 9 H), 2.28 (ddd, *J*=13.6, 9.5, 3.8 Hz, 2 H), 2.79 (br.s, 2 H), 2.77 (t, *J*=6.0 Hz, 1 H), 3.55 (br.m, 6 H), 4.34 (br.m, 2 H), 4.42 (d, *J*=5.7 Hz, 2 H), 6.43 (s, 1 H), 7.21 (m, 3 H), 7.44 (dd, *J*=7.7, 1.3 Hz, 1 H)

Compound 27
^{1}H NMR (360 MHz, DMSO-d_6) δ 1.39 (s, 9 H), 2.10 (ddd, *J*=13.7, 9.8, 3.8 Hz, 2 H), 2.74 (br.d, *J*=13.7 Hz, 2 H), 3.39 (br.s, 2 H), 3.44 (t, *J*=6.7 Hz, 2 H), 3.60 (dt, *J*=13.6, 4.6 Hz, 2 H), 4.26 (m, 4 H), 4.43 (d, *J*=5.5 Hz, 2 H), 4.57 (t, *J*=5.5 Hz, 1 H), 4.84 (t, *J*=5.5 Hz, 1 H), 7.21 (m, 3 H), 7.41 (m, 1 H)

Compound 26b
^{1}H NMR (360 MHz) δ 1.46 (s, 9 H), 2.35 (ddd, *J*=13.7, 9.5, 3.7 Hz, 2 H), 2.85 (br.d, *J*=13.7 Hz, 2 H), 3.51 (m, 4 H), 3.73 (ddd, *J*=13.4, 6.4, 3.6 Hz, 2 H), 4.78 (t, *J*=6.5 Hz, 2 H), 7.19 (dd, *J*=7.3, 2.0 Hz, 1 H), 7.25 (m, 2 H), 7.46 (dd, *J*=7.6, 1.6 Hz, 1 H), 7.69 (s, 1 H), 9.64 (s, 1 H)

Compound 26d

^{1}H NMR (400 MHz, 55°C) δ 1.45 (s, 9 H), 2.32 (ddd, *J*=13.8, 9.8, 3.7 Hz, 2 H), 2.86 (br.d, *J*=14.0 Hz, 2 H), 3.42 (t, *J*=6.7 Hz, 2 H), 3.49 (br.t, *J*=11.7 Hz, 2 H), 3.77 (ddd, *J*=13.5, 6.0, 3.6 Hz, 2 H), 4.79 (t, *J*=6.7 Hz, 2 H), 7.14 (dd, *J*=7.4, 1.9 Hz, 1 H), 7.19 (td, *J*=7.3, 1.5 Hz, 1 H), 7.23 (td, *J*=7.4, 1.9 Hz, 1 H), 7.45 (dd, *J*=7.8, 1.5 Hz, 1 H), 7.80 (s, 1 H)

^{13}C NMR (101 MHz, 55°C) δ 28.5, 33.5, 36.0, 41.2 (br.s), 43.8, 45.2, 79.6, 123.1, 126.6, 127.3, 127.6, 131.9, 137.1, 137.4, 141.1, 155.0, 156.0, 163.4

Compound 26e

^{1}H NMR (360 MHz) δ 1.45 (s, 9 H), 2.29 (ddd, *J*=13.9, 10.1, 3.8 Hz, 2 H), 2.84 (br.d, *J*=13.9 Hz, 2 H), 3.43 (m, 4 H), 3.81 (dt, *J*=13.7, 4.6 Hz, 2 H), 4.84 (t, *J*=6.7 Hz, 2 H), 5.65 (br.s, 2 H), 7.15 (dd, *J*=7.4, 2.0 Hz, 1 H), 7.21 (m, 2 H), 7.39 (s, 1 H), 7.45 (dd, *J*=7.7, 1.6 Hz, 1 H)

Compound 28a (fumarate salt (1:1))

^{1}H NMR (360 MHz, DMSO-d_6) δ 2.35 (m, 2 H), 2.78 (m, 6 H), 3.46 (t, *J*=6.8 Hz, 2 H), 3.67 (s, 2 H), 4.14 (t, *J*=6.8 Hz, 2 H), 6.58 (s, 2 H), 6.95 (s, 1 H), 7.24 (m, 3 H), 7.33 (m, 5 H), 7.42 (m, 1 H)

Compound 28b (fumarate salt (1:1))

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (t, *J*=11.5 Hz, 2 H), 2.62 (t, *J*=10.6 Hz, 2 H), 2.82 (m, 4 H), 3.33 (t, *J*=6.9 Hz, 2 H), 3.59 (s, 2 H), 4.81 (t, *J*=6.9 Hz, 2 H), 6.59 (m, 2 H), 7.19 (m, 4 H), 7.31 (m, 5 H), 7.43 (d, *J*=7.5 Hz, 1 H), 7.49 (s, 1 H), 7.68 (br.s, 1 H) (contains 0.4 eq. ethanol)

^{13}C NMR (101 MHz, DMSO-d_6) δ 32.4, 34.5, 42.6, 42.7, 50.3, 61.3, 125.7, 126.2, 126.7, 127.0, 127.4, 128.2, 129.4, 130.7, 132.0, 134.3, 136.5, 137.2, 141.5, 153.2, 162.0, 166.5;

Appendix: Elemental analyses

Compound	Molecular formula	Calcd			Found		
		C	H	N	C	H	N
1	$C_{16}H_{20}N_4$	71.61	7.51	20.88	71.22	7.50	20.67
2a	$C_{16}H_{18}N_4O.C_4H_4O_4$	60.29	5.57	14.06	60.43	5.72	13.91
3a	$C_{17}H_{20}N_4O.2HCl$	53.98	6.13	14.81	54.21	6.02	14.60
7	$C_{25}H_{27}N_3O_3$	71.92	6.52	10.06	72.04	6.56	10.07
8b	$C_{10}H_{15}N_3O$	62.15	7.82	21.74	61.76	8.01	21.55
10	$C_{17}H_{24}N_4O$	67.97	8.05	18.65	68.06	8.14	18.94
11a	$C_{17}H_{22}N_4$	72.31	7.85	19.84	72.10	7.87	19.89
11b	$C_{19}H_{24}N_4O_2$	67.04	7.11	16.46	66.38	7.14	16.33
14	$C_{18}H_{24}N_4.C_4H_4O_4$	64.06	6.84	13.58	63.34	6.88	13.31
16	$C_{19}H_{23}N_3$	77.78	7.90	14.32	77.49	8.02	14.33
17	$C_{18}H_{22}N_2O.C_4H_4O_4$	66.32	6.58	7.03	65.82	6.53	6.99
18	$C_{18}H_{22}N_2O$	76.56	7.85	9.92	76.39	7.94	9.85
20a	$C_{21}H_{24}N_4$	75.87	7.28	16.85	75.78	7.32	16.89
21	$C_{23}H_{24}N_4O$	74.17	6.49	15.04	74.44	6.63	15.08
22	$C_{23}H_{24}N_4O$	74.17	6.49	15.04	73.93	6.67	14.93
23	$C_{16}H_{20}N_4O.C_4H_4O_4$	59.99	6.04	13.99	59.53	6.12	13.90
24	$C_{23}H_{27}N_3O$	76.42	7.53	11.62	76.24	7.61	11.70
25a	$C_{23}H_{25}N_3$	80.43	7.34	12.23	80.41	7.71	12.60
25b	$C_{16}H_{19}N_3.HCl$	66.31	6.96	14.50	66.20	7.00	14.44
25c	$C_{21}H_{27}N_3O_2$	71.36	7.70	11.89	71.56	7.90	11.99
26a	$C_{22}H_{29}N_3O_3$	68.90	7.62	10.96	68.92	7.87	11.14
26b	$C_{22}H_{27}N_3O_3$	69.27	7.13	11.02	69.07	7.16	10.89
26d	$C_{22}H_{27}N_3O_4$	66.48	6.85	10.57	65.42	6.74	10.74
26e	$C_{22}H_{28}N_4O_3$	66.65	7.12	14.13	66.72	7.15	14.33
27	$C_{23}H_{31}N_3O_4$	66.81	7.56	10.16	66.55	7.38	10.10
28a	$C_{23}H_{24}BrN_3.C_4H_4O_4$	60.23	5.24	7.80	59.97	5.28	7.76
28b	$C_{24}H_{26}N_4O.C_4H_4O_4.H_2O.0.4C_2H_6O$	64.16	6.44	10.39	63.74	6.35	10.59