Supporting Information

Naphtho[1,2-*d*]isothiazole Acetic Acid Derivatives as a Novel Class of Selective Aldose Reductase Inhibitors

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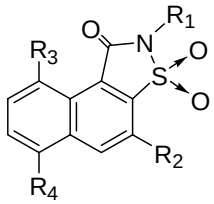
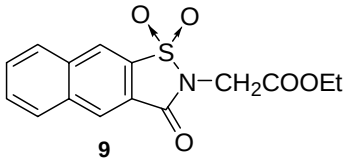
Table 1. Physical Properties of Ester Derivatives **8-10, 15-18, 23, 24, 27, 28.**





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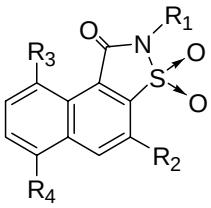
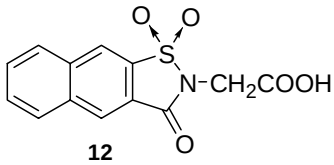
no.	R_1	R_2	R_3	R_4	yield (%)	recryst solv	mp (°C)	formula[a]
8	CH_2COOEt	H	H	H	66	EtOH	150-151	$C_{15}H_{13}NO_5S$
9					71	EtOH	142-144	$C_{15}H_{13}NO_5S$
10	CH_2COOEt	$COOCH_2COOEt$	H	H	75	EtOH	104-105	$C_{20}H_{19}NO_9S$
15	CH_2COOEt	H	NO_2	H	55	EtOH	210-212	$C_{15}H_{12}N_2O_7S$
16	CH_2COOEt	H	H	NO_2	45	EtOH	215-218	$C_{15}H_{12}N_2O_7S$
17	CH_2COOEt	H	NH_2	H	85	EtOH	170-172	$C_{15}H_{14}N_2O_5S$
18	CH_2COOEt	H	H	NH_2	87	AcOEt	236-238	$C_{15}H_{14}N_2O_5S$
23	CH_3	$COOCH_3$	H	H	72	AcOEt	250-251	$C_{14}H_{11}NO_5S$
24	$CH_2C_6H_5$	$COOCH_2C_6H_5$	H	H	87	AcOEt	200-201	$C_{26}H_{19}NO_5S$
27	CH_3	$COOCH_2COOEt$	H	H	40	EtOH	202-204	$C_{17}H_{15}NO_7S$
28	$CH_2C_6H_5$	$COOCH_2COOEt$	H	H	70	EtOH	113-115	$C_{23}H_{19}NO_7S$

[a]Elemental analyses for C, H, N were within ±0.4% of the calculated values.

Table 2. Physical Properties of Acid Derivatives **11-14, 19-22, 25, 26, 29, 30.**





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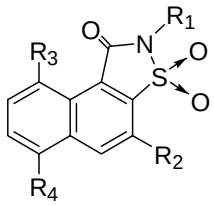
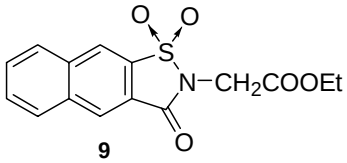
no.	R_1	R_2	R_3	R_4	yield (%)	recryst solv	mp (°C)	formula[a]
11	CH_2COOH	H	H	H	82	EtOH	260-262	$C_{13}H_9NO_5S$
12					86	EtOH	245-246	$C_{13}H_9NO_5S$
13	CH_2COOH	$COOCH_2COOH$	H	H	64	EtOH	230-232	$C_{16}H_{11}NO_9S$
14	CH_2COOH	COOH	H	H	44	^{i}PrOH	234-240 dec.	$C_{14}H_9NO_7S$
19	CH_2COOH	H	NO_2	H	83	AcOH	>300	$C_{13}H_8N_2O_7S$
20	CH_2COOH	H	H	NO_2	79	EtOH	235-240 dec.	$C_{13}H_8N_2O_7S$
21	CH_2COOH	H	NH_2	H	72	EtOH	243-245	$C_{13}H_{10}N_2O_5S$
22	CH_2COOH	H	H	NH_2	74	EtOH	235-237	$C_{13}H_{10}N_2O_5S$
25	CH_3	COOH	H	H	70	EtOH	>300	$C_{13}H_9NO_5S$
26	$CH_2C_6H_5$	COOH	H	H	86	DMF	265-269 dec.	$C_{19}H_{13}NO_5S$
29	CH_3	$COOCH_2COOH$	H	H	60	EtOH	260-262	$C_{15}H_{11}NO_7S$
30	$CH_2C_6H_5$	$COOCH_2COOH$	H	H	89	EtOH	198-200	$C_{21}H_{15}NO_7S$

[a]Elemental analyses for C, H, N were within ±0.4% of the calculated values.

Table 3. Spectral Data of Ester Derivatives **8-10, 15-18, 23, 24, 27, 28.**





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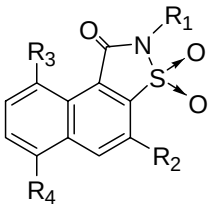
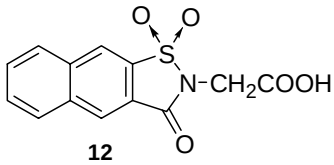
no.	R_1	R_2	R_3	R_4	IR (ν, cm^{-1})	^{1}H-NMR (δ, ppm)	MS (m/e)
8	CH_2COOEt	H	H	H	1740, 1720, 1280, 1140	1.22 (t, 3H, CH_3), 4.20 (q, 2H, OCH_2), 4.64 (s, 2H, NCH_2), 7.87 (t, 1H, H_7), 7.94 (t, 1H, H_8), 8.26 (d, 1H, H_4), 8.27 (d, 1H, H_6), 8.66 (d, 1H, H_5), 9.09 (d, 1H, H_9)	319 [M^+] 246 base
9					1750, 1730, 1320, 1158	1.23 (t, 3H, CH_3), 4.21 (q, 2H, OCH_2), 4.66 (s, 2H, NCH_2), 8.07 (t, 1H, H_6), 8.13 (t, 1H, H_7), 8.67 (d, 1H, H_5), 8.77 (d, 1H, H_8), 9.10 (s, 1H, H_9), 9.23 (s, 1H, H_4)	319 [M^+] 246 base
10	CH_2COOEt	$COOCH_2COOEt$	H	H	1750, 1720, 1280, 1145	1.22 (t, 6H, CH_3), 4.20 (q, 4H, OCH_2), 4.67 (s, 2H, NCH_2), 5.12 (s, 2H, $COCH_2$), 8.00 (t, 1H, H_7), 8.11 (t, 1H, H_8), 8.54 (d, 1H, H_6), 9.28 (d, 1H, H_9), 9.34 (s, 1H, H_5)	449 [M^+] 376 base
15	CH_2COOEt	H	NO_2	H	1740, 1710, 1310, 1190	1.21 (t, 3H, CH_3), 4.16 (q, 2H, OCH_2), 4.61 (s, 2H, NCH_2), 7.99 (t, 1H, H_8), 8.42 (d, 1H, H_4), 8.49 (d, 1H, H_6), 8.57 (d, 1H, H_5), 8.85 (d, 1H, H_8)	364 [M^+] 291 base
16	CH_2COOEt	H	H	NO_2	1745, 1710, 1295, 1195	1.23 (t, 3H, CH_3), 4.21 (q, 2H, OCH_2), 4.68 (s, 2H, NCH_2), 8.08 (t, 1H, H_7), 8.49 (d, 1H, H_4), 8.55 (d, 1H, H_5), 8.94 (d, 1H, H_7), 9.43 (d, 1H, H_9)	364 [M^+] 291 base
17	CH_2COOEt	H	NH_2	H	1740, 1730, 1290, 1200	1.25 (t, 3H, CH_3), 4.21 (q, 2H, OCH_2), 4.60 (s, 2H, NCH_2), 7.00 (d, 1H, H_4), 7.24-7.34 (m, 3H, H_7, NH_2), 7.51 (d, 1H, H_6), 7.99 (d, 1H, H_5), 8.41 (d, 1H, H_8)	334 [M^+] 261 base
18	CH_2COOEt	H	H	NH_2	1740, 1735, 1300, 1220	1.24 (t, 3H, CH_3), 4.22 (q, 2H, OCH_2), 4.65 (s, 2H, NCH_2), 7.02 (d, 1H, H_4), 7.25-7.32 (m, 3H, H_5, NH_2), 7.50 (t, 1H, H_8), 7.98 (d, 1H, H_7), 8.45 (d, 1H, H_9)	334 [M^+] 261 base
23	CH_3	$COOCH_3$	H	H	1717, 1700 1330, 1120	3.23 (s, 3H, NCH_3), 4.02 (s, 2H, OCH_3), 7.94 (t, 1H, H_7), 8.05 (t, 1H, H_8), 8.45 (d, 1H, H_6), 9.18 (s, 1H, H_5), 9.28 (d, 1H, H_9)	305 [M^+] 277 base
24	$CH_2C_6H_5$	$COOCH_2C_6H_5$	H	H	1710, 1644, 1305, 1115	4.99 (s, 2H, NCH_2), 5.53 (s, 2H, OCH_2), 7.32-7.59 (m, 10H, ArH), 7.95 (t, 1H, H_7), 8.06 (t, 1H, H_8), 8.51 (d, 1H, H_6), 9.25 (s, 1H, H_5), 9.30 (d, 1H, H_9)	259 base
27	CH_3	$COOCH_2COOEt$	H	H	1726, 1690, 1300, 1100	1.24 (t, 3H, CH_2CH_3), 3.23 (s, 3H, CH_3), 4.21 (q, 2H, OCH_2), 5.11 (s, 2H, CH_2CO), 7.98 (t, 1H, H_7), 8.09 (t, 1H, H_8), 8.52 (d, 1H, H_6), 9.29 (s, 1H, H_5), 9.33 (d, 1H, H_9)	377 [M^+] 292 base

28	$CH_2C_6H_5$	$COOCH_2COOEt$	H	H	1736, 1700, 1300, 1110	1.23 (t, 3H, CH_3), 4.20 (q, 2H, CH_2CH_3), 4.98 (s, 2H, NCH_2), 5.10 (s, 2H, OCH_2), 7.35 (t, 3H, $H_{3'}$,$H_{4'}$,$H_{5'}$), 7.48 (d, 2H, $H_{2'}$,$H_{6'}$), 7.97 (t, 1H, H_7), 8.08 (t, 1H, H_8), 8.52 (d, 1H, H_6), 9.29 (s, 1H, H_5), 9.33 (d, 1H, H_9)	453 [M^+] 285 base

Table 4. Spectral Data of Acid Derivatives **11-14, 19-22, 25, 26, 29, 30.**





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no.	R_1	R_2	R_3	R_4	IR (ν, cm^{-1})	^{1}H-NMR (δ, ppm)	MS (m/e)
11	CH_2COOH	H	H	H	3370, 3170, 1730, 1680, 1290, 1125	4.44 (s, 2H, NCH_2), 7.87 (t, 1H, H_7), 7.94 (t, 1H, H_8), 8.26 (d, 1H, H_4), 8.27 (d, 1H, H_6), 8.66 (d, 1H, H_5), 9.09 (s, 1H, H_9)	291 [M^+] 126 base
12					3350, 3170, 1730, 1690, 1290, 1125	4.50 (s, 2H, NCH_2), 8.07 (t, 1H, H_6), 8.13 (t, 1H, H_7), 8.67 (d, 1H, H_5), 8.77 (d, 1H, H_8), 9.10 (s, 1H, H_9), 9.23 (s, 1H, H_4)	291 [M^+] 126 base
13	CH_2COOH	$COOCH_2COOH$	H	H	3380, 3165, 1762, 1731, 1210, 1120	4.49 (s, 2H, NCH_2), 4.98 (s, 2H, OCH_2), 7.94 (t, 1H, H_7), 8.07 (t, 1H, H_8), 8.45 (d, 1H, H_6), 9.24 (s, 1H, H_5), 9.30 (d, 1H, H_9)	45 base
14	CH_2COOH	COOH	H	H	3457, 3182, 1731, 1697, 1243, 1165	4.51 (s, 2H, NCH_2), 7.95 (t, 1H, H_7), 8.06 (t, 1H, H_8), 8.47 (d, 1H, H_6), 9.20 (s, 1H, H_5), 9.28 (d, 1H, H_9), 13.25 (bs, 1H, COOH, exc), 14.20 (bs, 1H, COOH, exc)	279 base
19	CH_2COOH	H	NO_2	H	3445, 3130, 1725, 1690, 1310, 1190	4.54 (s, 2H, NCH_2), 8.08 (t, 1H, H_7), 8.48 (d, 1H, H_4), 8.59 (d, 1H, H_6), 9.00 (d, 1H, H_5), 9.48 (d, 1H, H_8)	336 [M^+] 126 base
20	CH_2COOH	H	H	NO_2	3440, 3125, 1720, 1695, 1290, 1190	4.61 (s, 2H, NCH_2), 8.07 (t, 1H, H_8), 8.53 (d, 1H, H_4), 9.11 (d, 1H, H_5), 9.31 (d, 1H, H_7), 9.70 (d, 1H, H_9)	336 [M^+] 126 base
21	CH_2COOH	H	NH_2	H	3450, 3100, 1725, 1690, 1310, 1190	4.44 (s, 2H, NCH_2), 6.95 (d, 1H, H_4), 7.55 (t, 1H, H_7), 7.97 (d, 1H, H_6), 8.27 (d, 1H, H_5), 9.77 (d, 1H, H_8)	306 [M^+] 45 base
22	CH_2COOH	H	H	NH_2	3454, 3105, 1710, 1697, 1290, 1190	4.54 (s, 2H, NCH_2), 6.99 (t, 1H, H_8), 7.64 (d, 1H, H_4), 7.98 (d, 1H, H_5), 8.22 (d, 1H, H_7), 8.79 (d, 1H, H_9)	306 [M^+] 45 base
25	CH_3	COOH	H	H	3424, 3175, 1717, 1707, 1296, 1194	3.19 (s, 3H, CH_3), 7.96 (t, 1H, H_7), 8.08 (t, 1H, H_8), 8.47 (d, 1H, H_6), 9.20 (s, 1H, H_5), 9.28 (d, 1H, H_9), 14.18 (bs, 1H, COOH, exc)	291 [M^+] 177 base
26	$CH_2C_6H_5$	COOH	H	H	3411, 3175, 1710, 1613, 1310, 1120	4.97 (s, 2H, CH_2), 7.35 (t, 3H, $H_{3'}$,$H_{4'}$,$H_{5'}$), 7.48 (d, 2H, $H_{2'}$,$H_{6'}$), 7.93 (t, 1H, H_7), 8.04 (t, 1H, H_8), 9.46 (d, 1H, H_6), 9.18 (s, 1H, H_5), 9.30 (d, 1H, H_9)	367 [M^+] 91 base
29	CH_3	$COOCH_2COOH$	H	H	3385, 2723 1713, 1650, 1310, 1110	3.23 (s, 3H, CH_3), 5.01 (s, 2H, CH_2), 7.96 (t, 1H, H_7), 8.07 (t, 1H, H_8), 8.49 (d, 1H, H_6), 9.25 (s, 1H, H_5), 9.29 (d, 1H, H_9), 13.40 (bs, 1H, COOH, exc)	349 [M^+] 292 base

30	$CH_2C_6H_5$	$COOCH_2COOH$	H	H	3446, 2724, 1716, 1654, 1310, 1125	4.98 (s, 2H, NCH_2), 5.10 (s, 2H, OCH_2), 7.35 (t, 3H, $H_{3'}$,$H_{4'}$,$H_{5'}$), 7.48 (d, 2H, $H_{2'}$, $H_{6'}$), 7.97 (t, 1H, H_7), 8.08 (t, 1H, H_8), 8.52 (d, 1H, H_6), 9.29 (s, 1H, H_5), 9.33 (d, 1H, H_9), 14.22 (s, 1H, COOH exc)	149 base

ANALYTICAL DATA

no.	formula	Calcd. %			Found %		
		C	H	N	C	H	N
2	$C_{15}H_{17}NO_4S$	58.61	5.57	4.56	58.55	5.56	4.67
3	$C_{15}H_{17}NO_4S$	58.61	5.57	4.56	58.55	5.44	4.72
4	$C_{16}H_{17}NO_6S$	54.69	4.88	3.99	54.79	4.89	4.02
5	$C_{11}H_7NO_3S$	56.64	3.02	6.01	56.60	3.00	5.89
6	$C_{11}H_7NO_3S$	56.64	3.02	6.01	56.56	2.98	6.00
7	$C_{12}H_7NO_5S$	51.98	2.54	5.05	51.73	2.50	5.00
8	$C_{15}H_{13}NO_5S$	56.42	4.10	4.39	56.44	4.01	4.22
9	$C_{15}H_{13}NO_5S$	56.42	4.10	4.39	56.34	4.12	4.18
10	$C_{20}H_{19}NO_9S$	53.45	4.26	3.12	53.24	4.42	3.22
11	$C_{13}H_9NO_5S$	53.60	3.11	4.81	53.41	3.06	4.73
12	$C_{13}H_9NO_5S$	53.60	3.11	4.81	53.45	3.01	4.99
13	$C_{16}H_{11}NO_9S$	48.86	2.82	3.56	48.53	2.68	3.50
14	$C_{14}H_9NO_7S$	50.15	2.71	4.18	50.00	2.71	4.00
15	$C_{15}H_{12}N_2O_7S$	49.45	3.32	7.69	49.32	3.22	7.56
16	$C_{15}H_{12}N_2O_7S$	49.45	3.32	7.69	49.25	3.22	7.56
17	$C_{15}H_{14}N_2O_5S$	53.88	4.22	8.38	53.61	4.21	8.63
18	$C_{15}H_{14}N_2O_5S$	53.88	4.22	8.38	53.53	4.20	8.22
19	$C_{13}H_8N_2O_7S$	46.43	2.40	8.33	46.21	2.33	8.11
20	$C_{13}H_8N_2O_7S$	46.43	2.40	8.33	46.29	2.27	8.56
21	$C_{13}H_{10}N_2O_5S$	50.98	3.29	9.15	50.71	3.09	9.01
22	$C_{13}H_{10}N_2O_5S$	50.98	3.29	9.15	50.67	3.00	9.04
23	$C_{14}H_{11}NO_5S$	55.08	3.63	4.59	55.01	3.59	4.44
24	$C_{26}H_{19}NO_5S$	68.26	4.19	3.06	68.22	4.26	3.01
25	$C_{13}H_9NO_5S$	53.60	3.11	4.81	53.53	3.07	4.69
26	$C_{19}H_{13}NO_5S$	62.12	3.57	3.81	62.32	3.49	3.55
27	$C_{17}H_{15}NO_7S$	54.11	4.01	3.71	54.06	4.32	3.93
28	$C_{23}H_{19}NO_7S$	60.92	4.22	3.09	60.83	4.12	3.03
29	$C_{15}H_{11}NO_7S$	51.58	3.17	4.01	51.44	3.12	4.06
30	$C_{21}H_{15}NO_7S$	59.29	3.55	3.29	59.09	3.23	3.09

31	$C_{20}H_{21}NO_7S$	57.27	5.05	3.34	57.21	4.97	2.99