Supporting Information

Synthesis and Biological Evaluation of a New Series of 2,3,5-Substituted [1,2,4]Thiadiazoles as Modulators of Adenosine A_1 Receptors and their Molecular Mechanism of Action.

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^{13}C NMR Data (5a-5i, 6a-6i, 7a-7i and 8a-8i)

1-Methyl-3-(phenyl-phenyliminomethyl)thiourea (5a). ^{13}C-NMR ($CDCl_3$): δ = 31.7, 121.9, 123.3, 127.8, 128.3, 130.0, 131.5, 146.3, 155.4, 180.7.

1-Ethyl-3-(phenyl-phenyliminomethyl)thiourea (5b). ^{13}C-NMR ($CDCl_3$): δ = 13.6, 40.3, 122.2, 123.5, 127.9, 128.5, 130.3, 131.9, 146.4, 155.5, 189.7.

1-(Phenyl-phenyliminomethyl)-3-propyl-thiourea (5c). ^{13}C-NMR (DMSO-d_6): δ = 11.4, 21.2, 46.5, 120.6, 122.3, 123.1, 129.7, 130.1, 134.3, 140.2, 153.3, 191.7.

1-Butyl-3-(phenyl-phenyliminomethyl)thiourea (5d). ^{13}C-NMR ($CDCl_3$, 600 MHz): δ = 13.7, 20.2, 30.4, 45.6, 122.4, 123.7, 128.0, 128.7, 128.8, 130.5, 132.2, 146.6, 155.6, 179.9.

1-(3-Hydroxypropyl)-3-(phenyl-phenyliminomethyl)thiourea (5e). ^{13}C-NMR ($CDCl_3$): δ = 31.7, 41.9, 58.9, 122.1, 123.6, 127.9, 128.5, 130.3, 131.7, 146.2, 155.2, 180.4, 199.7.

1-Isopropyl-3-(phenyl-phenyliminomethyl)thiourea (5f). ^{13}C-NMR ($CDCl_3$): δ = 21.7, 47.5, 122.2, 123.5, 127.8, 128.5, 130.2, 132.0, 146.3, 155.4, 178.4.

1-Cyclopentyl-3-(phenyl-phenyliminomethyl)thiourea (5g).). ^{13}C-NMR ($CDCl_3$): δ = 23.5, 32.4, 57.1, 122.2, 123.5, 127.8, 128.5, 130.2, 131.9, 146.2, 155.4, 178.8, 199.6.

1-Phenyl-3-(phenyl-phenyliminomethyl)thiourea (5h). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 120.4, 120.9, 122.6, 123.1, 123.5, 124.3, 125.9, 127.5, 128.3, 128.6, 129.4, 129.9, 130.9, 133.6, 134.1, 139.4, 139.9, 156.0, 187.8.

1-Benzyl-3-(phenyl-phenyliminomethyl)thiourea (5i). ^{13}C-NMR (DMSO-d_6): δ = 48.1, 120.6, 120.9, 122.3, 123.3, 126.7, 127.3, 127.8, 128.1, 128.3, 128.5, 130.2, 134.3, 138.9, 140.1, 153.3, 192.3.

1-Methyl-3-(phenyl-3-tolyliminomethyl)thiourea (6a). ^{13}C-NMR ($CDCl_3$): δ = 21.1, 31.9, 119.1, 122.9, 124.4, 128.0, 128.4, 128.6, 130.3, 132.0, 138.4, 146.4, 155.3.

1-Ethyl-3-(phenyl-3-tolyliminomethyl)thiourea (6b). ^{13}C-NMR ($CDCl_3$): δ = 13.6, 21.1, 40.3, 119.1, 122.9, 124.3, 127.9, 128.3, 128.5, 130.2, 132.0, 138.4, 146.3, 155.3, 179.7.

1-(Phenyl-3-tolyliminomethyl)-3-propyl-thiourea (6c). ^{13}C-NMR ($CDCl_3$): δ = 11.4, 21.0, 21.5, 47.3, 119.1, 122.9, 124.3, 127.8, 128.3, 128.5, 130.2, 132.0, 138.4, 146.3, 155.3, 179.8.

1-Butyl-3-(phenyl-3-tolyliminomethyl)thiourea (6d). ^{13}C-NMR (DMSO-d_6): δ = 13.8, 19.6, 21.4, 30.0, 44.3, 117.8, 121.0, 123.9, 127.9, 128.2, 130.0, 134.4, 137.6, 140.1, 153.3, 191.6.

1-(3-Hydroxypropyl)-3-(phenyl-3-tolyliminomethyl)thiourea (6e). ^{13}C-NMR (DMSO-d_6): δ = 21.3, 31.3, 42.0, 58.1, 58.5, 117.9, 121.0, 123.9, 125.2, 125.4, 127.2, 128.0, 128.3, 130.0, 134.3, 137.6, 140.1, 153.6, 161.7, 198.3.

1-Isopropyl-3-(phenyl-3-tolyliminomethyl)thiourea (6f). ^{13}C-NMR (DMSO-d_6): δ = 21.3, 21.8, 46.3, 117.7, 120.8, 123.8, 127.8, 128.2, 128.3, 130.0, 134.4, 137.5, 140.2, 153.3, 190.5.

1-Cyclopentyl-3-(phenyl-3-tolyliminomethyl)thiourea (6g). ^{13}C-NMR (DMSO-d_6): δ = 21.4, 23.5, 31.3, 38.3, 56.2, 117.7, 120.8, 123.8, 127.8, 128.1, 128.3, 129.9, 134.4, 137.5, 140.2, 153.3, 191.1.

1-Phenyl-3-(phenyl-3-tolyliminomethyl)thiourea (6h). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 21.3, 118.3, 120.2, 120.6, 121.6, 122.6, 123.6, 124.5, 125.1, 127.7, 128.4, 128.8, 130.0, 130.5, 130.9, 131.6, 133.7, 134.2, 137.8, 139.3, 139.5, 140.0, 154.7, 156.3, 187.9, 190.5.

1-Benzyl-3-(phenyl-3-tolyliminomethyl)thiourea (6i). ^{13}C-NMR (DMSO-d_6): δ = 21.4, 48.1, 117.9, 121.0, 124.0, 126.7, 127.2, 127.5, 127.7, 128.1, 128.3, 130.1, 134.4, 137.6, 138.5, 140.1, 153.4, 192.3.

2,3-Diphenyl-5-*N*-methylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7a). ^{13}C-NMR (DMSO-d_6): δ = 31.5, 126.6, 127.6, 128.6, 130.1, 130.6, 132.4, 134.5, 164.6, 175.6.

2,3-Diphenyl-5-*N*-ethylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7b). ^{13}C-NMR (DMSO-d_6): δ = 14.1, 40.0, 126.7, 127.7, 128.7, 130.3, 130.7, 132.6, 134.6, 164.9, 175.0.

2,3-Diphenyl-5-*N*-propylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7c). ^{13}C-NMR (DMSO-d_6): δ = 11.4, 21.8, 46.6, 126.7, 127.7, 128.7, 130.3, 130.7, 132.6, 134.7, 164.7, 175.1.

2,3-Diphenyl-5-*N*-butylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7d). ^{13}C-NMR (DMSO-d_6): δ = 13.6, 19.5, 30.5, 44.7, 126.6, 127.7, 128.7, 130.9, 132.7, 134.4, 166.0, 175.7.

2,3-Diphenyl-5-*N*-(3-hydroxypropyl)imino-*2H*-[1,2,4]thiadiazole hydrobromide (7e). ^{13}C-NMR (DMSO-d_6, 400MHz): δ = 31.4, 58.0, 61.5, 126.6, 127.6, 128.6, 130.2, 130.7, 132.5, 134.5, 165.1, 175.2.

2,3-Diphenyl-5-*N*-isopropylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7f). ^{13}C-NMR (DMSO-d_6, 600MHz): δ = 21.8, 48.0, 126.5, 127.6, 128.0, 128.4, 128.5, 128.6, 129.4, 130.2, 130.2, 130.8, 132.6, 134.3, 165.9, 174.5.

2,3-Diphenyl-5-*N*-cyclopentylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7g). ^{13}C-NMR ($CDCl_3$): δ = 23.5, 32.6, 58.0, 125.7, 126.9, 128.8, 130.9, 133.1, 134.1, 165.5, 174.2.

2,3-Diphenyl-5-*N*-phenylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7h). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 117.7, 120.0, 120.3, 121.3, 121.7, 122.5, 123.3, 123.6, 124.9,

125.8, 126.3, 126.6, 127.3, 128.0, 128.3, 128.9, 129.4, 130.7, 131.1, 131.5, 132.5, 133.2, 133.9, 137.0, 172.5.

2,3-Diphenyl-5-*N*-benzylimino-*2H*-[1,2,4]thiadiazole hydrobromide (7i). ^{13}C-NMR (DMSO-d_6): δ = 48.1, 126.6, 127.7, 127.9, 128.7, 130.4, 130.9, 132.8, 134.4, 136.7, 175.8.

5-*N*-Methylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8a). ^{13}C-NMR (DMSO-d_6): δ = 20.7, 31.5, 124.7, 126.6, 127.6, 128.6, 129.9, 130.2, 131.3, 132.5, 134.4, 140.1, 164.5, 175.6.

5-*N*-Ethylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8b). ^{13}C-NMR (DMSO-d_6): δ = 14.1, 20.7, 39.9, 124.6, 126.6, 127.6, 128.6, 129.9, 130.1, 131.2, 132.5, 134.4, 140.0, 164.4, 174.8.

5-*N*-Propylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8c). ^{13}C-NMR (DMSO-d_6): δ = 11.3, 20.8, 21.9, 46.7, 124.8, 126.6, 127.8, 128.7, 130.1, 130.4, 131.6, 132.7, 134.3, 140.2, 165.7, 175.6.

5-*N*-Butylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8d). ^{13}C-NMR (DMSO-d_6): δ = 13.6, 19.5, 20.8, 30.5, 44.5, 124.8, 126.7, 127.8, 128.7, 130.0, 130.3, 131.4, 132.6, 134.6, 140.1, 164.6, 175.0.

5-*N*-(3-Hydroxypropyl)imino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8e). ^{13}C-NMR (DMSO-d_6): δ = 20.8, 31.6, 42.3, 58.0, 124.8, 126.7, 127.8, 128.7, 130.0, 130.3, 131.4, 132.6, 134.5, 140.2, 164.7, 175.1.

5-*N*-Isopropylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8f). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 20.3, 21.5, 47.6, 124.3, 126.4, 127.4, 128.3, 129.6, 129.8, 130.9, 132.2, 134.2, 139.8, 164.5, 173.9.

5-*N*-Cyclopentylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8g). ^{13}C-NMR (DMSO-d_6): δ = 20.8, 23.2, 28.3, 32.3, 57.0, 124.8, 126.7, 127.8, 128.7, 129.1, 130.0, 130.3, 131.4, 132.7, 134.5, 140.2, 174.2.

5-*N*-Phenylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8h). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ = 20.3, 112.3, 119.9, 124.3, 125.7, 126.2, 127.3, 128.4, 128.7, 129.3, 129.6, 130.0, 131.3, 132.4, 133.8, 139.9, 141.0, 148.4, 157.7, 164.7, 168.3.

5-*N*-Benzylimino-2-(3-methylphenyl)-3-phenyl-*2H*-[1,2,4]thiadiazole hydrobromide (8i). ^{13}C-NMR (DMSO-d_6): δ = 20.8, 48.1, 124.7, 126.6, 127.9, 128.8, 130.1, 130.4, 131.5, 132.7, 134.4, 136.7, 140.2, 164.8, 175.5.

Elemental Analyses

Compd	Theoretical in %			Experimental in %			Deviation in %			Molecular Formula
	C	H	N	C	H	N	C	H	N	
7c	54.26	4.82	11.17	54.04	4.77	11.42	0.22	0.05	-0.25	$C_{17}H_{17}N_3S{\cdot}HBr$
7d	55.39	5.16	10.76	55.18	4.99	10.55	0.21	0.17	0.21	$C_{18}H_{19}N_3S{\cdot}HBr$
7e	51.54	4.98	10.27	51.52	4.96	10.27	0.02	0.02	0.00	$C_{17}H_{17}N_3OS{\cdot}HBr{\cdot}0.3\ H_2O$
7f	53.72	4.89	11.06	53.75	4.99	10.96	-0.03	-0.10	0.10	$C_{17}H_{17}N_3S{\cdot}HBr{\cdot}0.3\ H_2O$
7g	56.72	5.01	10.44	56.77	5.22	10.45	-0.05	-0.21	-0.01	$C_{19}H_{19}N_3S{\cdot}HBr$
7h	57.28	4.09	10.02	57.55	3.97	10.12	-0.27	0.12	-0.10	$C_{20}H_{15}N_3S{\cdot}HBr{\cdot}0.3\ H_2O$
7i	59.44	4.28	9.90	59.43	4.28	9.88	0.01	0.00	0.02	$C_{21}H_{17}N_3S{\cdot}HBr$
8c	55.39	5.16	10.76	55.38	5.02	10.81	0.01	0.14	-0.05	$C_{18}H_{19}N_3S{\cdot}HBr$
8d	56.44	5.48	10.39	56.11	5.45	10.40	0.33	0.03	-0.01	$C_{19}H_{21}N_3S{\cdot}HBr$
8e	53.21	4.96	10.34	52.85	4.88	10.25	0.36	0.08	0.09	$C_{18}H_{19}N_3S{\cdot}HBr$
8f	54.73	5.24	10.64	54.70	5.55	10.97	0.03	-0.31	-0.33	$C_{18}H_{19}N_3S{\cdot}HBr{\cdot}0.3\ H_2O$
8g	57.69	5.33	10.09	57.30	5.60	10.39	0.39	-0.27	-0.30	$C_{20}H_{21}N_3S{\cdot}HBr$
8h	57.48	4.50	9.58	57.47	4.26	9.74	0.01	0.24	-0.16	$C_{21}H_{17}N_3S{\cdot}HBr{\cdot}0.7\ H_2O$
8i	59.78	4.65	9.51	59.84	4.86	9.82	-0.06	-0.21	-0.31	$C_{22}H_{19}N_3S{\cdot}HBr{\cdot}0.1\ H_2O$