Experimental references

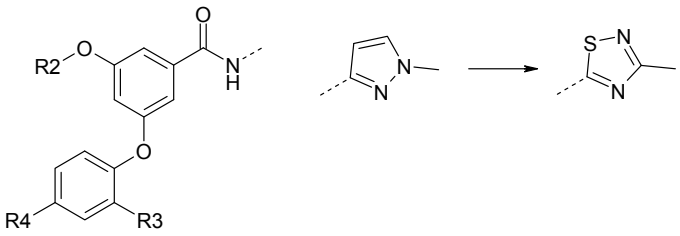
Synthesis of the compounds described in this paper and glucokinase assay protocols are described in WO 2005080359 and WO 2005121110.

Protocols for generating solubility and logD data are described in D. Buttar, N. Colclough, S. Gerhardt, et al. *Bioorg. and Medicinal Chemistry* 2010, **18**, 7486.

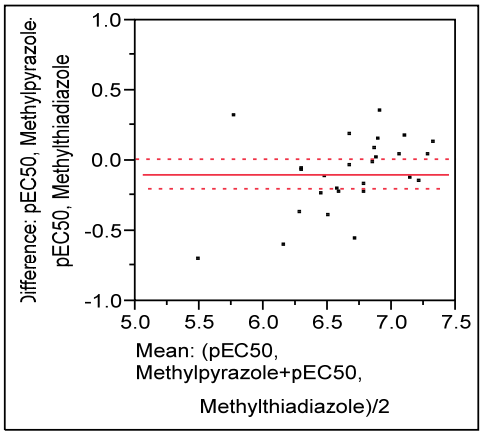
The Caco-2 data were generated as described in Camenisch, J. Alsenz, H. van de Waterbeemd and G. Folkers, *Eur. J. Pharm. Sci*., 1998, **6**, 313.

The hERG assay used to generate the data is described in Bridgland-Taylor, M. H.; Hargreaves, A. C.; Easter, A. et al. *J. Pharmacological and Toxicological Methods* 2006, **54**, 189-199**.**

Matched pair plots



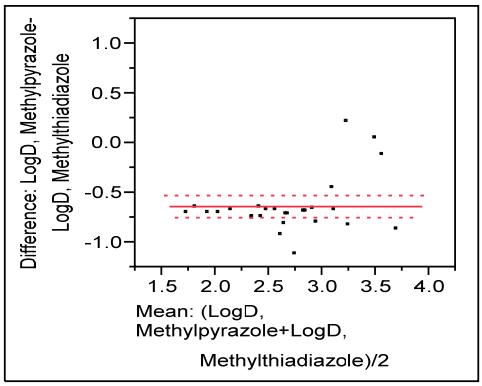
Matched Pairs
Difference: pEC50, Methylpyrazole-pEC50, Methylthiadiazole



pEC50, Methylpyrazole	6.61519
pEC50, Methylthiadiazole	6.71296
Mean Difference	-0.0978
Std Error	0.05081
Upper 95%	0.00666
Lower 95%	-0.2022
N	27

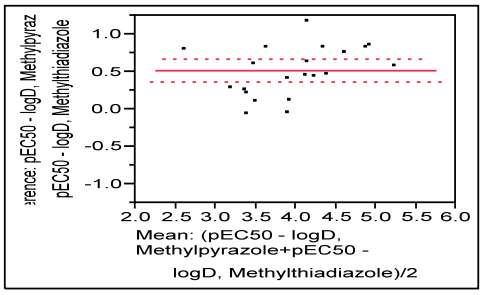
t-Ratio	-1.92452
DF	26
Prob > |t|	0.0653
Prob > t	0.9674
Prob < t	0.0326*

Matched Pairs
Difference: LogD, Methylpyrazole-LogD, Methylthiadiazole



LogD, Methylpyrazole	2.35222	t-Ratio	-11.9432
LogD, Methylthiadiazole	2.99185	DF	26
Mean Difference	-0.6396	Prob > |t|	<.0001*
Std Error	0.05356	Prob > t	1.0000
Upper 95%	-0.5295	Prob < t	<.0001*
Lower 95%	-0.7497		
N	27		
Correlation	0.88202		

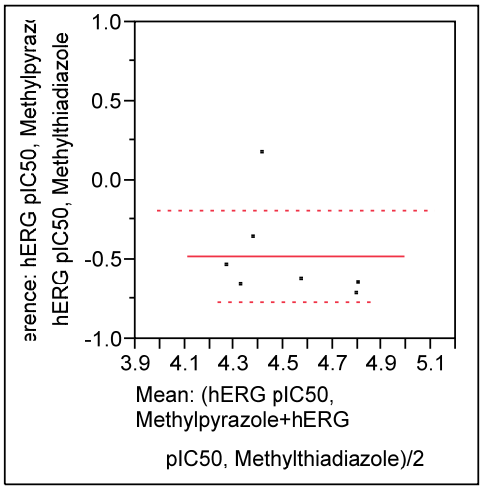
Matched Pairs
Difference: pEC50 - logD, Methylpyrazole-pEC50 - logD, Methylthiadiazole



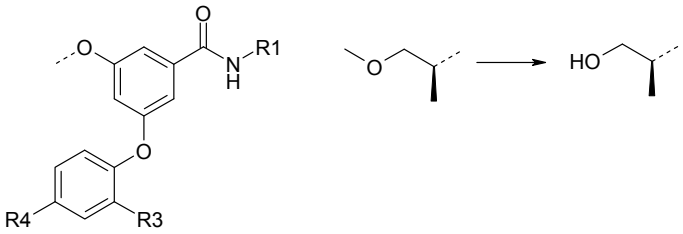
pEC50 - logD, Methylpyrazole	4.20952	t-Ratio	6.997316
pEC50 - logD, Methylthiadiazole	3.70095	DF	20

Mean Difference	0.50857	Prob > |t|	<.0001*
Std Error	0.07268	Prob > t	<.0001*
Upper 95%	0.66018	Prob < t	1.0000
Lower 95%	0.35696		
N	21		
Correlation	0.89036		

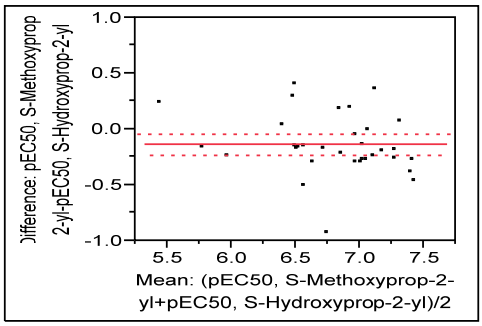
Matched Pairs
Difference: hERG pIC50, Methylpyrazole-hERG pIC50, Methylthiadiazole



hERG pIC50, Methylpyrazole	4.26871	t-Ratio	-4.09099
hERG pIC50, Methylthiadiazole	4.74817	DF	6
Mean Difference	-0.4795	Prob > |t|	0.0064*
Std Error	0.1172	Prob > t	0.9968
Upper 95%	-0.1927	Prob < t	0.0032*
Lower 95%	-0.7662		
N	7		
Correlation	0.35408		

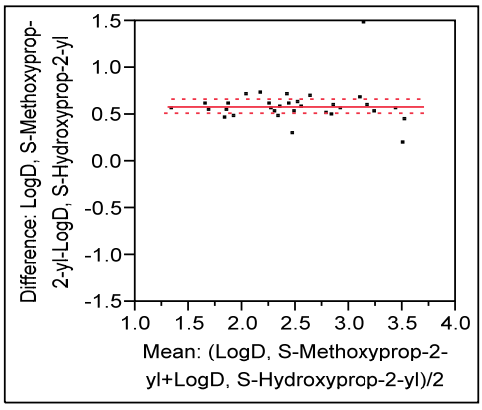


Matched Pairs
Difference: pEC50, S-Methoxyprop-2-yl-pEC50, S-Hydroxyprop-2-yl



pEC50, S-Methoxyprop-2-yl	6.72833	t-Ratio	-2.92292
pEC50, S-Hydroxyprop-2-yl	6.8647	DF	32
Mean Difference	-0.1364	Prob > |t|	0.0063*
Std Error	0.04665	Prob > t	0.9968
Upper 95%	-0.0413	Prob < t	0.0032*
Lower 95%	-0.2314		
N	33		
Correlation	0.8526		

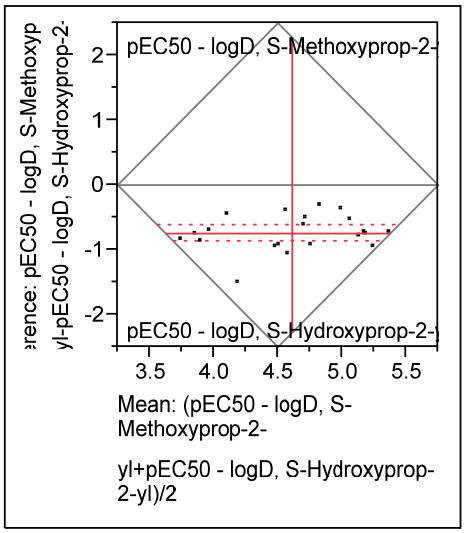
Matched Pairs
Difference: LogD, S-Methoxyprop-2-yl-LogD, S-Hydroxyprop-2-yl



LogD, S-Methoxyprop-2-yl	2.78781	t-Ratio	16.98298

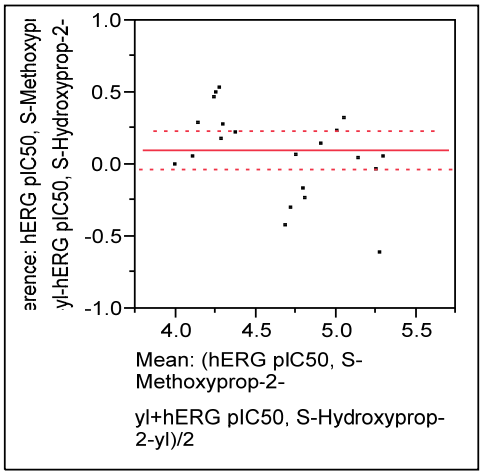
LogD, S-Hydroxyprop-2-yl	2.19797	DF	31
Mean Difference	0.58984	Prob > |t|	<.0001*
Std Error	0.03473	Prob > t	<.0001*
Upper 95%	0.66068	Prob < t	1.0000
Lower 95%	0.51901		
N	32		
Correlation	0.94215		

Matched Pairs
Difference: pEC50 - logD, S-Methoxyprop-2-yl-pEC50 - logD, S-Hydroxyprop-2-yl

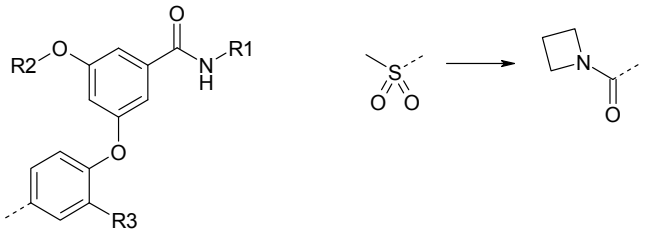


pEC50 - logD, S-Methoxyprop-2-yl	4.24333	t-Ratio	-12.2266
pEC50 - logD, S-Hydroxyprop-2-yl	4.98381	DF	20
Mean Difference	-0.7405	Prob > |t|	<.0001*
Std Error	0.06056	Prob > t	1.0000
Upper 95%	-0.6141	Prob < t	<.0001*
Lower 95%	-0.8668		
N	21		
Correlation	0.86258		

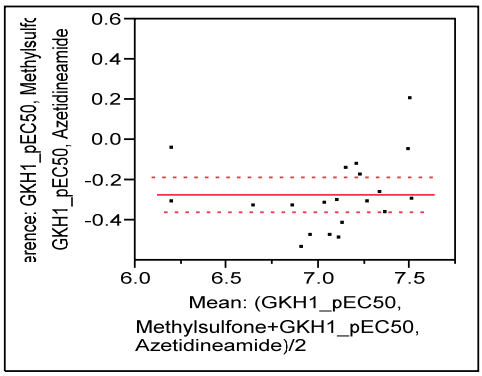
Matched Pairs
Difference: hERG pIC50, S-Methoxyprop-2-yl-hERG pIC50, S-Hydroxyprop-2-yl



hERG pIC50, S-Methoxyprop-2-yl	4.67939	t-Ratio	1.49932
hERG pIC50, S-Hydroxyprop-2-yl	4.58181	DF	21
Mean Difference	0.09758	Prob > |t|	0.1487
Std Error	0.06508	Prob > t	0.0743
Upper 95%	0.23293	Prob < t	0.9257
Lower 95%	-0.0378		
N	22		
Correlation	0.80961		

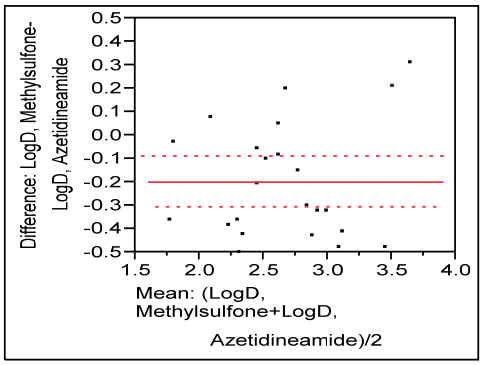


Matched Pairs
Difference: GKH1_pEC50, Methylsulfone-GKH1_pEC50, Azetidineamide



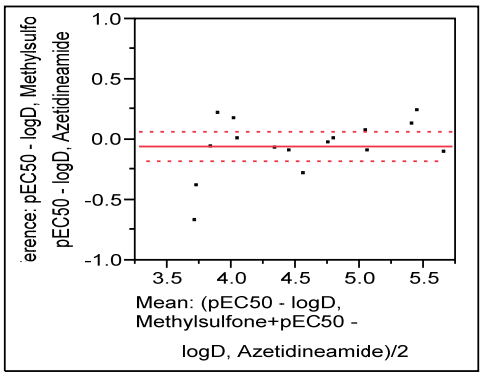
GKH1_pEC50, Methylsulfone	6.92295	t-Ratio	-6.77081
GKH1_pEC50, Azetidineamide	7.197	DF	19
Mean Difference	-0.274	Prob > |t|	<.0001*
Std Error	0.04048	Prob > t	1.0000
Upper 95%	-0.1893	Prob < t	<.0001*
Lower 95%	-0.3588		
N	20		
Correlation	0.88992		

Matched Pairs
Difference: LogD, Methylsulfone-LogD, Azetidineamide



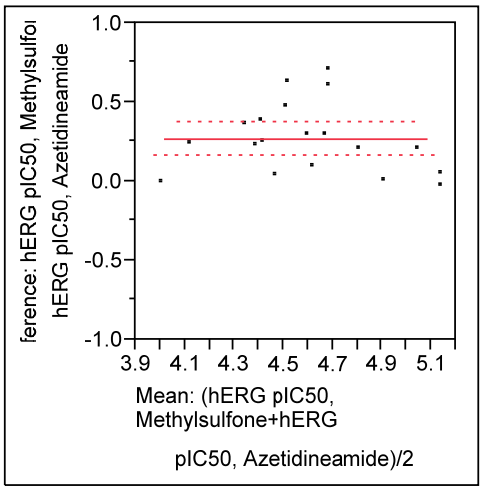
LogD, Methylsulfone	2.56529	t-Ratio	-3.86383
LogD, Azetidineamide	2.76283	DF	22
Mean Difference	-0.1975	Prob > |t|	0.0008*
Std Error	0.05112	Prob > t	0.9996
Upper 95%	-0.0915	Prob < t	0.0004*
Lower 95%	-0.3036		
N	23		
Correlation	0.88859		

Matched Pairs
Difference: pEC50 - logD, Methylsulfone-pEC50 - logD, Azetidineamide



pEC50 - logD, Methylsulfone	4.51625	t-Ratio	-0.95814
pEC50 - logD, Azetidineamide	4.57219	DF	15
Mean Difference	-0.0559	Prob > |t|	0.3532
Std Error	0.05838	Prob > t	0.8234
Upper 95%	0.0685	Prob < t	0.1766
Lower 95%	-0.1804		
N	16		
Correlation	0.94581		

Matched Pairs
Difference: hERG pIC50, Methylsulfone-hERG pIC50, Azetidineamide



hERG pIC50, Methylsulfone	4.73461	t-Ratio	5.350568
hERG pIC50, Azetidineamide	4.46484	DF	18
Mean Difference	0.26977	Prob > |t|	<.0001*
Std Error	0.05042	Prob > t	<.0001*
Upper 95%	0.3757	Prob < t	1.0000
Lower 95%	0.16384		
N	19		
Correlation	0.78018		

SMILES strings for the 70 compounds made in the matrix campaign

Cc1nc(sn1)NC(=O)c2cc(cc(c2)O[C@@H](C)COC)Oc3ccc(cc3)C(=O)NC4CCN(CC4)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3nc(cs3)CNC

CC(C)N1CCN(CC1)Cc2csc(n2)NC(=O)c3cc(cc(c3)O[C@@H](C)COC)Oc4ccc(cc4)S(=O)(=O)C

CC(C)N1CCC(CC1)NC(=O)c2ccc(cc2)Oc3cc(cc(c3)O[C@@H](C)COC)C(=O)Nc4ccn(n4)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)NC3CCN(CC3)C)C(=O)Nc4ccn(n4)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3cc[nH]n3

Cc1nc(sn1)NC(=O)c2cc(cc(c2)O[C@@H](C)COC)Oc3ccc(cc3)C(=O)N(C)C4CCN(CC4)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C3CC3)C4CCN(CC4)C)C(=O)Nc5nccs5

CC(C)N1CCN(CC1)Cc2cnc(s2)NC(=O)c3cc(cc(c3)O[C@@H](C)COC)Oc4ccc(cc4)S(=O)(=O)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3ncc(s3)CNCC4CC4

CC(C)N1CCC(CC1)NC(=O)c2ccc(c(c2)Cl)Oc3cc(cc(c3)O[C@@H](C)COC)C(=O)Nc4ccn(n4)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3ncc(s3)CSCCN(C)C

Cc1nc(sn1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)S(=O)(=O)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C)C(=O)Nc3ccn(n3)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)NC3CCN(CC3)C)C(=O)Nc4ccn(n4)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C3CCN(CC3)C)C(=O)Nc4ccn(n4)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N3CCCN(CC3)C)C(=O)Nc4ccn(n4)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)CC(=O)N(C)C)C(=O)Nc3ccn(n3)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C3CCN(C3)C)C(=O)Nc4ccn(n4)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)NCCN3CCCC3)C(=O)Nc4ccn(n4)C

Cc1cc(n[nH]1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)S(=O)(=O)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)N3CCC3)C(=O)Nc4ccn(n4)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)O)C(=O)Nc3nccs3

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N3CCC3)C(=O)Nc4ccn(n4)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2Cl)C(=O)N(C)C)C(=O)Nc3ccn(n3)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C)C(=O)Nc3ccn(n3)C

Cc1nc(sn1)NC(=O)c2cc(cc(c2)OC(C)C)Oc3ccc(cc3)C(=O)N(C)CC(=O)N(C)C

Cc1nc(sn1)NC(=O)c2cc(cc(c2)OC(C)C)Oc3ccc(cc3)C(=O)N(C)CCO

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2Cl)S(=O)(=O)C)C(=O)Nc3ccn(n3)C

Cc1nc(sn1)NC(=O)c2cc(cc(c2)O[C@@H](C)COC)Oc3ccc(cc3)C(=O)N4CC(C4)O

Cc1nc(sn1)NC(=O)c2cc(cc(c2)O[C@@H](C)COC)Oc3ccc(cc3)C(=O)N4CCCN(CC4)CCO

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(CCOC)C3CCN(CC3)C(=O)C)C(=O)Nc4ccn(n4)C

CC(C)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C3CC3)C4CCN(CC4)C(=O)C)C(=O)Nc5ccn(n5)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C)C(=O)Nc3cc[nH]n3

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)N(C)C)C(=O)Nc3ccn(n3)C

CC[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3ccn(n3)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N3CCCC3)C(=O)Nc4ccn(n4)C

Cn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H]3CCC[C@H]3O)Oc4ccc(cc4)S(=O)(=O)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3ncccn3

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)N3CCCC3)C(=O)Nc4ccn(n4)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)C)C(=O)Nc3cc[nH]n3

CCn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)S(=O)(=O)C

CCn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3F)S(=O)(=O)C

CCn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3F)C(=O)N(C)C

CCS(=O)(=O)c1ccc(c(c1)F)Oc2cc(cc(c2)O[C@@H](C)CO)C(=O)Nc3ccn(n3)C

CCn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3F)C(=O)N4CCC4

CCn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)C(=O)N4CCC4

CC[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3ccn(n3)C

Cc1cc(nn1C)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)S(=O)(=O)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2F)S(=O)(=O)C)C(=O)Nc3ccon3

CCS(=O)(=O)c1ccc(cc1)Oc2cc(cc(c2)O[C@@H](C)CO)C(=O)Nc3ccn(n3)C

CC[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)N3CCC3)C(=O)Nc4ccn(n4)C

CC[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2F)S(=O)(=O)C)C(=O)Nc3ccn(n3)C

CCn1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)C(=O)N(C)C

CC[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N3CCC3)C(=O)Nc4ccn(n4)C

CC[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C)C(=O)Nc3ccn(n3)CC

CCS(=O)(=O)c1ccc(c(c1)F)Oc2cc(cc(c2)O[C@@H](C)CO)C(=O)Nc3cnc(cn3)C

CC[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N(C)C)C(=O)Nc3ccn(n3)C

CC(C)n1ccc(n1)NC(=O)c2cc(cc(c2)O[C@@H](C)CO)Oc3ccc(cc3)S(=O)(=O)C

C[C@@H](COC)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)N(C)C)C(=O)Nc3cc[nH]n3

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N3CCC3)C(=O)Nc4cc[nH]n4

C[C@H]([C@@H](C)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C)C(=O)Nc3ccn(n3)C)O

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)N3CCOCC3)C(=O)Nc4ccn(n4)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)C(=O)NC3CC3)C(=O)Nc4ccn(n4)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2F)C(=O)N3CCOCC3)C(=O)Nc4ccn(n4)C

CC1CCN1C(=O)c2ccc(c(c2)F)Oc3cc(cc(c3)O[C@@H](C)CO)C(=O)Nc4ccn(n4)C

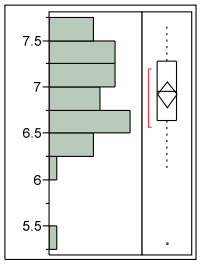
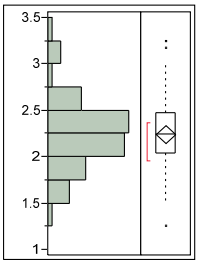
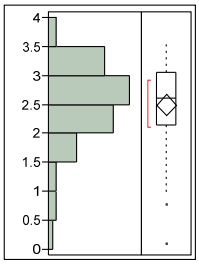
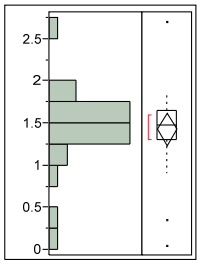
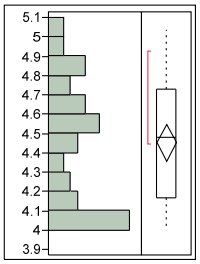
C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)N3CCOCC3)C(=O)Nc4ccn(n4)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)N3CCC3)C(=O)Nc4ccn(n4)C

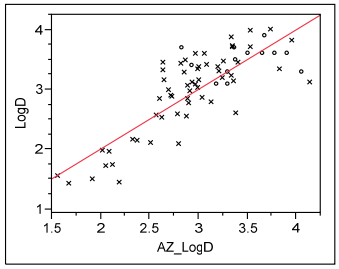
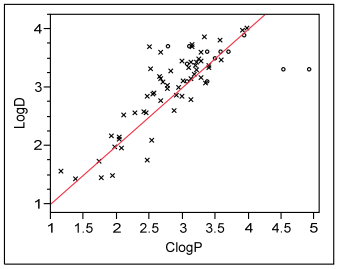
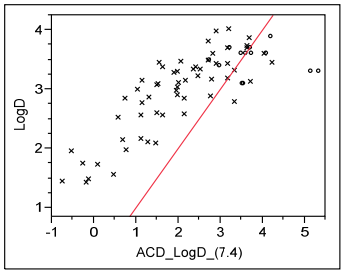
CC(C)OC1CN(C1)C(=O)c2ccc(c(c2)F)Oc3cc(cc(c3)O[C@@H](C)CO)C(=O)Nc4ccn(n4)C

C[C@@H](CO)Oc1cc(cc(c1)Oc2ccc(cc2)S(=O)(=O)C3CCC3)C(=O)Nc4ccn(n4)C

Data distributions for the compounds listed above

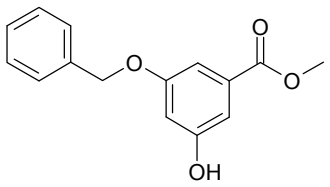
Glucokinase pEC_{50}	LogD	Log µM Solubility	Log Caco-2 A to B	hERG pIC_{50}
				
Median 7.0, mean 6.9	Median 2.2, mean 2.2	Median 2.6, mean 2.5	Median 1.5, mean 1.4	Median 4.5, mean 4.5

X-y plot of predicted vs measured logD for neutral compounds using AZlogD, clogP and ACD logD. Points marked with circles are out of the dynamic range of the measured data and are excluded from the statistics.

AZlogD	clogP	ACDlogD
		
RMSE = 0.39	RMSE = 0.47	RMSE = 1.2
mean bias = 0.04	mean bias = 0.13	mean bias = 1.0
n=58		

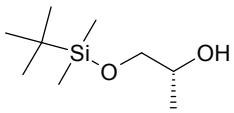
Synthesis of AZD1092

Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate



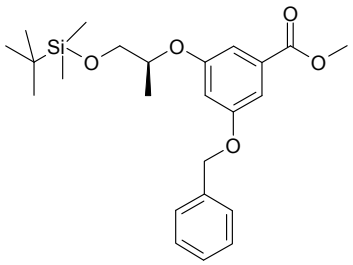
To a stirred solution of methyl 3,5-dihydroxybenzoate (1.00 kg, 5.95 mol) in DMF (6 L) was added potassium carbonate (892 g, 9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (1.44 kg, 8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with dichloromethane (1 × 3 L and 2 × 5 L). The combined extracts were washed with water (10 L) and dried overnight ($MgSO_4$). The solution was evaporated in *vacuo*, and the crude product was purified by flash column chromatography in 3 batches (3 × 2 kg silica, eluting with a gradient consisting of hexane containing 10% DCM, to neat DCM, to DCM containing 50% ethyl acetate) to eliminate starting material. The resulting material was further purified by high pressure liquid chromatography (HPLC) in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to afford the title compound (323 g, 21%). ^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H)

(2*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}propan-2-ol



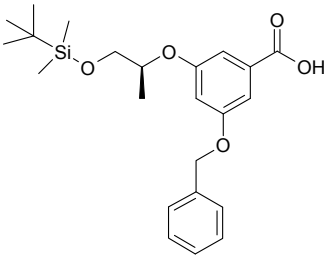
tert-Butyl(dimethyl)silyl chloride (5.90 g, 39.5 mmol) was added to a solution of (2*R*)-propane-1,2-diol (3.00 g, 39.5 mmol) in DCM (100 mL) followed by diisopropylethylamine (DIPEA) (7.10 g, 55.3 mmol) and the reaction was stirred under argon for 72 h. The reaction was diluted with diethylether (500 mL) and water (140 mL) and the organic layer was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography on silica (eluting with 1:15 to 1:10 ethyl acetate: hexane) to afford the title compound as a colourless oil (6.00 g, 80%). ^{1}H NMR δ ($CDCl_3$) 0.10 (m, 6H), 0.92 (s, 9H), 1.14 (d, 3H), 2.42 (d, 1H), 3.38 (dd, 1H), 3.60 (dd, 1H), 3.82 (m, 1H)
The data are consistent with those reported in the literature (*J. Org. Chem*., **1998**, *53*, 2300).

Methyl 3-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethoxy)-5-[(phenylmethyl)oxy] benzoate



(2*R*)-1-{[*tert*-Butyl(dimethyl)silyl]oxy}propan-2-ol (3.31 g, 17.4 mmol) was added to a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (3.00 g, 11.6 mmol) in tetrahydrofuran (THF) (50 mL) at 0°C followed by addition of triphenylphosphine (4.57 g, 17.4 mmol) then di-*iso*-propylazodicarboxylate (3.43 mL, 17.4 mmol) and the reaction was warmed to RT and stirred for 16 h. The reaction was quenched with water (100 mL) and diethylether (400 mL) and the organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica (eluting with 1:15 to 1:5 ethyl acetate:hexane) to afford the title compound as a colourless oil (4.00 g, 80%). ^{1}H NMR δ ($CDCl_3$) 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.29 (d, 3H), 3.63 (dd, 1H), 3.78 (dd, 1H), 3.92 (s, 3H), 4.44 (m, 1H), 5.08 (s, 2H), 6.77 (m, 1H), 7.40 (m, 7H)

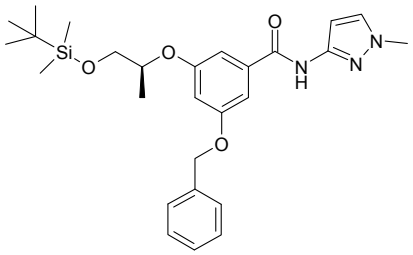
3-{(Phenylmethyl)oxy}-5-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethoxy) benzoic acid



Methyl 3-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethoxy)-5-[(phenylmethyl)oxy]benzoate (3.0 g, 6.98 mmol) was dissolved in THF (50 mL) and water (10mL) and lithium hydroxide monohydrate (586 mg, 13.95 mmol) added. The resultant mixture was heated with stirring at 45ºC for 2 hours, then at ambient temperature for 16 hours, and at 45ºC for a further 4 hours. Water (40 mL) was added and the solvent removed

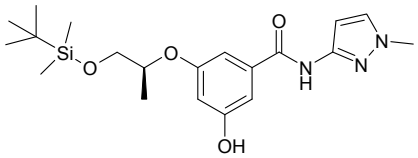
in vacuo. The resultant solution was acidified carefully with 1M citric acid (2 equivalents), washed with water and brine then dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the title compound as a colourless gum (2.58 g, 89%). ^{1}H NMR δ (d_6-DMSO) 0.02 (d, 6H), 0.84 (s, 9H), 1.17 (d, 3H), 3.66 (m, 2H), 4.43 (m, 1H), 5.05 (s, 2H), 6.56 (br s, 1H), 7.10 (br s, 1H), 7.17 (br s, 1H), 7.25-7.44 (m, 5H), 7.60 (br s, 1H)

3-((1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyloxy)-5-(phenylmethyl) oxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



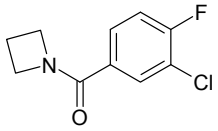
DIPEA (4.06 g, 23.4 mmol) was added to a suspension of 3-{(phenylmethyl)oxy}-5-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethoxy) benzoic acid (2.43 g, 5.84 mmol), 1-methyl-1H-pyrazole-3-amine (0.85 g, 8.76 mmol) and O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexofluorophosphate (HATU) (4.66 g, 12.3 mmol) in N,N-dimethylformamide (DMF) (50 mL) and stirred at ambient temperature for 16 hours. The resultant mixture was partially reduced *in vacuo*, poured into water (100 mL) and extracted with diethylether (2 × 50 mL). The extracts were washed with water and brine then dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (eluting with 0-100% ethyl acetate in isohexane) to afford the title compound as a colourless oil (1.87 g, 65%). ^{1}H NMR δ (d_6-DMSO) 0.02 (d, 6H), 0.84 (s, 9H), 1.21 (d, 3H), 3.68 (d, 2H), 3.76 (s, 3H), 4.58 (m, 1H), 5.13 (s, 2H), 6.56 (m, 1H), 6.70 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.29-7.46 (m, 5H), 7.57 (m, 1H), 10.74 (br s, 1H); *m/z* 496 $(M+H)^+$

3-((1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



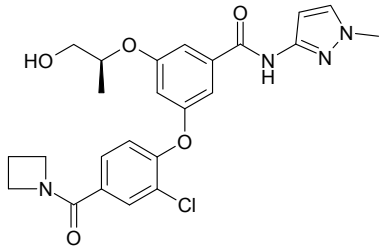
3-((1*S*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyloxy)-5-(phenylmethyl) oxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1.8 g, 3.64 mmol) was dissolved in methanol (50 mL) and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (0.2 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, and the filtrate concentrated *in vacuo* to give the desired compound (1.45 g, 98%). ^{1}H NMR δ (d_6-DMSO) 0.02 (d, 6H), 0.83 (s, 9H), 1.18 (d, 3H), 3.66 (m, 2H), 3.72 (s, 3H), 4.51 (m, 1H), 6.42 (m, 1H), 6.52 (m, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.55 (m, 1H), 9.58 (br s, 1H), 10.59 (br s, 1H); *m/z* 406 $(M+H)^+$

1-(3-Chloro-4-fluorobenzoyl)azetidine



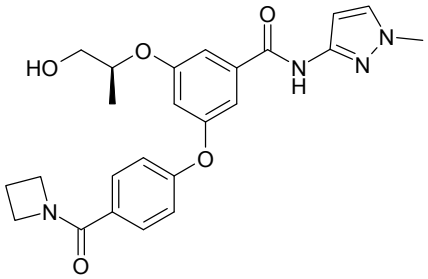
To a solution of 3-chloro-4-fluorobenzoic acid (1.74 g, 10.0 mmol) in DCM (50 mL) was added oxalyl chloride (1.05 mL, 12.0 mmol) and DMF (1 drop). The mixture was stirred at ambient temperature for 16 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride and azetidine hydrochloride (1.12 g, 12 mmol) were taken up in DCM (25 mL) and triethylamine (4.18 mL, 30 mmol) added to the mixture, which was stirred at ambient temperature for 2 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated. The residue was crystallized from ethyl acetate / isohexane to give the title compound (1.64 g, 77%). ^{1}H NMR δ ($CDCl_3$) 2.4 (m, 2H), 4.2-4.4 (m, 4H), 7.2 (m, 1H), 7.55 (m, 1H), 7.7 (m, 1H)

3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



To a mixture of 3-((1*S*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}-1-methylethyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (215 mg, 0.53 mmol) and 1-(3-chloro-4-fluorobenzoyl) azetidine (135 mg, 0.63 mmol) in DMF (2.0 mL) was added potassium carbonate (146 mg, 1.06 mmol) and the stirred mixture heated at 160°C under microwave heating for 120 minutes. The mixture was allowed to reach ambient temperature and pressure then evaporated. The residue was purified by flash chromatography (eluting with 0-20% methanol in DCM) to afford the title compound (130 mg, 51%). ^{1}H NMR δ ($CDCl_3$) 1.22 (d, 3H), 2.14 (m, 2H), 3.50 (m, 2H), 3.76 (s, 3H), 4.05 (m, 2H), 4.33 (m, 2H), 4.56 (m, 1H), 4.84 (t, 1H), 6.53 (d, 1H), 6.78 (m, 1H), 7.12 (m, 2H), 7.42 (s, 1H), 7.59 (m, 2H), 7.80 (m, 1H), 10.84 (br s, 1H); *m/z* 485/487 $(M+H)^+$

AZD1092: 3-{[4-(Azetidin-1-ylcarbonyl)phenyl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-{[4-(Azetidin-1-ylcarbonyl)-2-chlorophenyl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (104 mg, 0.215 mmol) was dissolved in methanol (3 mL) and THF (3 mL). Triethylamine (65 mg, 0.644 mmol) was added and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (25 mg) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 16 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, the filtrate concentrated *in vacuo* and dissolved in ethyl acetate (10 mL), washed with water (2 × 10mL,

saturated aqueous sodium chloride solution (10 mL) and dried ($MgSO_4$) to give the title compound (95 mg, 98%). ^{1}H NMR δ (d_6-DMSO) 1.22 (d, 3H), 2.24 (m, 2H), 3.51 (m, 2H), 3.76 (s, 3H), 4.02 (m, 2H), 4.30 (br s, 2H), 4.56 (m, 1H), 4.84 (t, 1H), 6.53 (d, 1H), 6.80 (m, 1H), 7.06 (d, 2H), 7.21 (m, 1H), 7.43 (m, 1H), 7.57 (m, 1H), 7.66 (d, 2H), 10.83 (br s, 1H); *m/z* 451 $(M+H)^+$

The material can be crystallised from an ethylacetate and toluene mixture after purification by chromatography (on silica and then /or on neutral alumina) and, where necessary, treatment with activated charcoal; mpt 131ºC. The material was >99% pure by LC and >95% enantiomeric excess by chiral HPLC.