Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

A statistical analysis of *in-vitro* human microsomal metabolic stability of heterocyclic replacement for di-substituted phenyl in pharmaceutical compounds, identifying iso-steres more likely to have beneficial effects.

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Supplementary Information

Contents

1.0 *In-vitro* human liver microsomal screening protocol
Equipment and Reagents

All Acetonitrile, Formic Acid and Methanol solutions were HPLC grade, supplied by TheromFischer Scientific Ltd (Loughbrough, UK). NADPH was stored at -20 ºC when not in use and was supplied by Sigma Alderich Company Ltd (Dorset, UK). Collagenase A, supplied by Roche Diagnostics (Mannheim, Germany) and Trypsin Inhibitor, also supplied by Sigma, were both stored at 2-8 ºC prior to experimentation. Leibovitz solution supplied by Invitrogen (Paisley, UK) was also stored at this temperature. 0.4% (w/v) Tryphan Blue and DNase were ordered through Sigma and stored at room temperature and -20 ºC respectively.

All HLMs were provided by BD Biosciences and were made up by homogenising liver samples followed by a series of centrifugation steps in which the final pellet consisted of the microsomes. These were stored at -80 ºC. On delivery the HLMs have a protein concentration of 20 mg/ml. These were diluted to 1 mg/ml in 0.1 MINH Phosphate Buffer (pH 7.4) before experimentation. This buffer was made by the in-house Scientific Preparation Team (Alderley Park, AstraZeneca). Rat liver was delivered on ice from the Barriered Animal Breeding Unit (BABU) at AstraZeneca (Alderley Park, UK). These were obtained from 9 week old male Harlan Han-Wistar rats.

The Genesis Workstation 200 used in both assays was provided by Tecan UK Ltd (Reading, UK). Water used to wash the Tecan and in mobile phase mixtures was HPLC grade and supplied by in-house Ultra Purification Units (Marlow, UK). Both Sorval Legend RT (Newport Pagnell) and MSE Centaur 2 (London, UK) centrifuges were used.

1.1 Methods

This assay procedure was conducted using a Genesis Workstation 200 provided by Tecan. All compounds tested were dispensed by the Compound Management Group (CMG) at AstraZeneca at an initial concentration of 10 mM in dimethyl sulfoxide (DMSO) and initial volume of 5 µL. A total of 96 compounds could be tested in one assay, including 6 markers which are used to assess the accuracy and reliability of the generated data. The markers routinely used in this assay were: Phenacetin, Diclofenac, Diazepam, Dextromethorphan and Erythromycin. These specific markers were used because they are the substrates of some of

the major CYP enzymes involved in metabolism and thus provide a clear indication of viability of the HLMs used (Table 1). It should be noted that all marker solutions were pooled together before the assay and were tested as a cocktail.

When 96 compounds were run in any individual assay, two sets of markers were examined on the same plate - one at the front of the plate and one at the back. This was to ensure that there was no variability in the assay procedure throughout each experiment.

Compounds were first diluted 100 fold using acetonitrile followed by the transfer of 3 µL of diluted compound to 270 µL of HLMs. 27 µL of 11.1 mM NADPH was added to initiate the reaction. (HLMs were maintained on a "Te-shake" throughout the assay which was continually shaken at 9000 rpm after the addition of NADPH.) By this stage all compounds are at a concentration 10,000 fold lower than their initial concentration. (i.e. all compounds are now at a concentration of 1 µM). 25 µL of the reaction mixture was removed at time points; 2, 5, 10, 15, 20 and 30 minutes and added to 100 µL Internal Standard and acetonitrile quench solution, thus halting the reaction. Plates containing these samples were then spun at 3000 rpm for 15 minutes at 4 ºC.

Marker	Major CYP Enzymes Responsible for Metabolism In HLMs
Phenacetin	CYP1A1, CYP1A2
Diclofenac	CYP2C9, other CYP2C and CYP3A4 enzymes
Diazepam	CYP3A4
Dextromethotphan	CYP2D6
Erythromycin	CYP3A4

Table 1 – The major CYP enzymes responsible for metabolism of the markers [20-25].

The reason why such low substrate concentrations were employed was to ensure that the assay procedure fitted the Michaelis-Menten model, assuming linear first order kinetics [3]. By utilizing substrate concentrations of 1 µM, believed to be well below the Michaelis Constant (K_m) the Michaelis-Menten equation simplifies to $v = (K_{cat}/K_m)[E][S]$, meaning that the rate of clearance is proportional to the concentration of substrate. The situation is avoided where a decrease in substrate has no effect on clearance as all available enzymes are still in use resulting in the maximum rate of clearance.

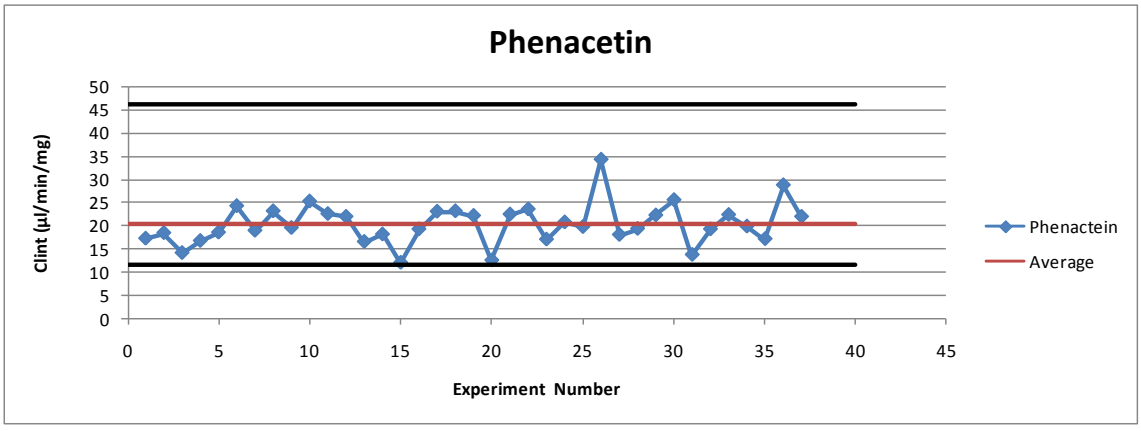
All samples were analysed by HPLC/MS/MS as detailed in section 3.5.

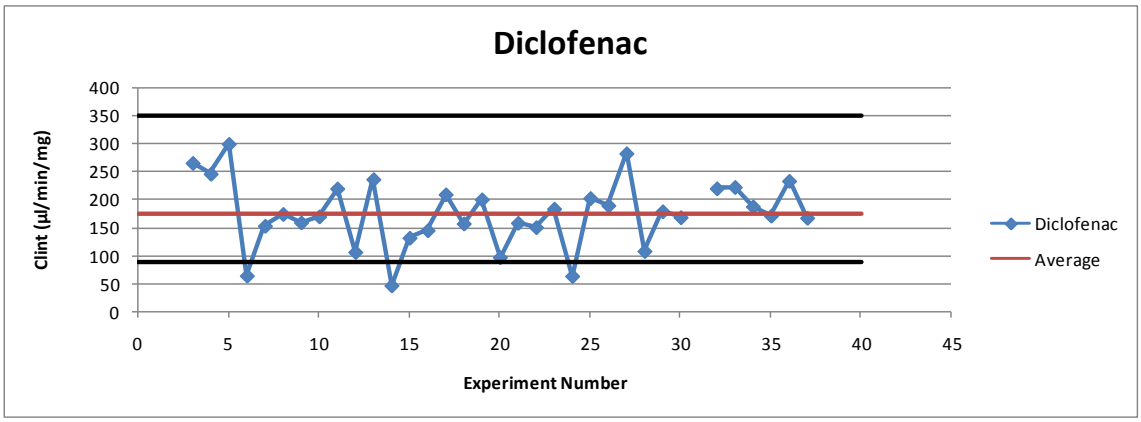
1.2 Calculations

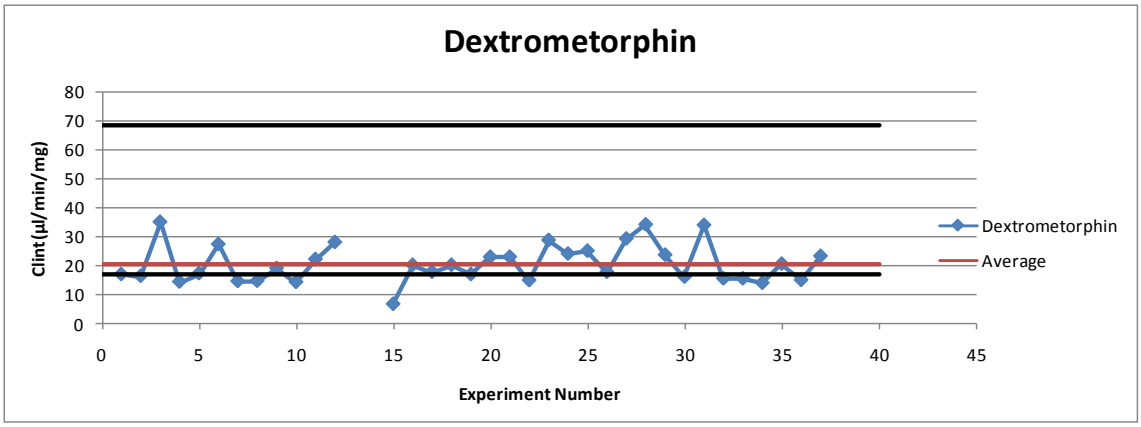
All incubations were analysed using QuanLynx^{Tm} browser. A "response" value was calculated for each compound at each time point by dividing the peak area of the Analyte peak on the chromatogram by the peak area of the Internal Standard [29]. These values were converted to percentages, with the highest response value equating to 100%.

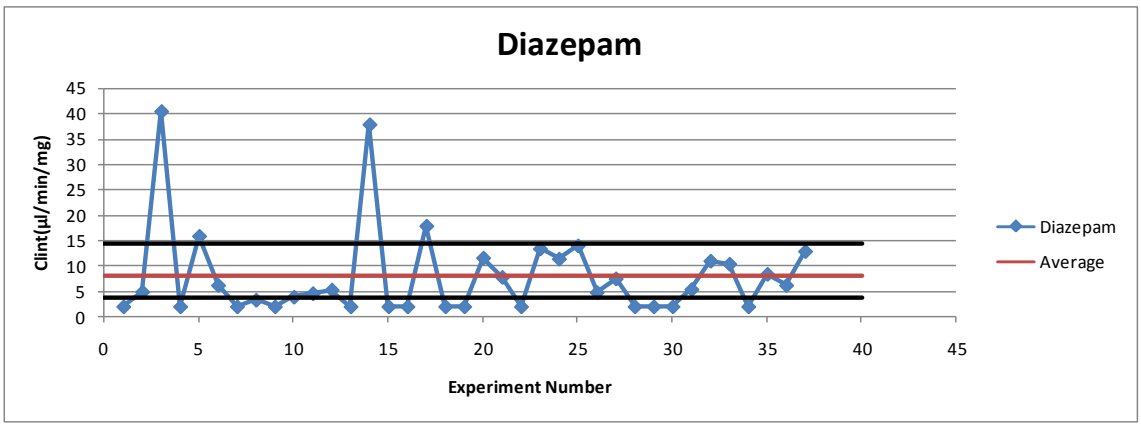
The Internal Standard was monitored throughout the course of each experiment, as large variations in Internal Standard may lead to inaccurate responses. For each compound a plot of "Percentage of Un-Metabolized Compound" vs Incubation time was plotted and the initial gradient determined (proportional to the initial rate of the reaction). This is equivalent to the negative form of the first order rate constant (k). This can also be calculated by: $LN(2)/T_{1/2}$. The rate constant was subsequently multiplied by 1000 as the concentration of protein in the microsomes was at 1 mg/mL. All Cl_{int} values therefore had units of µL/min/mg.

1.3 The Markers









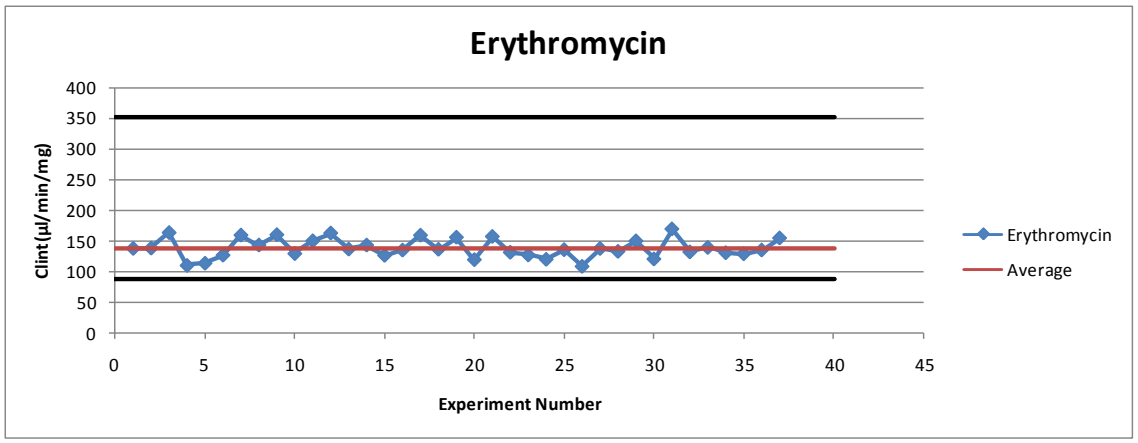


Figure - Graphs showing the variation in Cl_{int} for the markers used in HLM experiments: (a) Phenacetin (b) Diclofenac (c) Dextrometorphin (d) Diazepam (e) Erythromycin, over the course of the experimental procedure. The red line present on each graph indicates the average Cl_{int} of that maker. The black lines present on each graph indicate a 2 fold range either side of the expected Cl_{int}.

The 5 markers, Phenacetin, Diclofenac, Dextrometorphin, Diazepam and Erythromycin were run routinely with each HLM assay and their Cl_{int}s monitored over the experimental procedure. Each experiment was only considered to pass when the 3 out of 5 markers fell within 2 fold to the expected Cl_{int} for that marker. The expected Cl_{int}s were calculated from IBIS by calculating the mean of all compounds tested in previous experiments.

1.4 Triplicate testing variation.

Three results for each compound were determined and recorded below (Table 2). Variation was determined by finding Log10 of HLM Cl_{int} result and calculating the global mean (1.40), standard deviation (0.67), standard error for the data set (0.0047), and so the variance at 0.45. Of the 248 data points below 48 were outside 2 fold from each mean, which was 19% of the data. Plots 1 and 2 indicate the degree of variability for each compound, illustrating the assay is quite reproducible.

Table 2

Compound	HLM Clint run 1_ul/min/kg	HLM Clint run 2_ul/min/kg	HLM Clint run 3_ul/min/kg	Log10_HLMCLint_Run1	Log10_HLMCLint_Run2	Log10_HLMCLint_Run3	Mean(Log10HLMCLint)	Std Dev(Log10HLMCLint)	Variance(Log10HLMCLint)
AZ1	.	70.5	74.8	.	1.85	1.87	1.86	0.02	0.0003
AZ2	215.6	185.7	105.9	2.33	2.27	2.02	2.21	0.16	0.0265
AZ3	.	60.3	71.3	.	1.78	1.85	1.82	0.05	0.0026
AZ4	39	.	7.5	1.59	.	0.88	1.23	0.51	0.2563
AZ5	88.4	78.1	88.3	1.95	1.89	1.95	1.93	0.03	0.0010
AZ6	.	.	6.2	.	.	0.79	0.79	.	.
AZ7	33.4	4.5	2.4	1.52	0.65	0.38	0.85	0.60	0.3567
AZ8	347	151.6	139.9	2.54	2.18	2.15	2.29	0.22	0.0477
AZ9	9.3	15.6	20.5	0.97	1.19	1.31	1.16	0.17	0.0304
AZ10	.	2	2	.	0.30	0.30	0.30	0.00	0.0000
AZ11	35.4	29.2	6.3	1.55	1.47	0.80	1.27	0.41	0.1688
AZ12	40.6	25.5	4.6	1.61	1.41	0.66	1.23	0.50	0.2481
AZ13	.	2	2	.	0.30	0.30	0.30	0.00	0.0000
AZ14	.	3.9	2.8	.	0.59	0.45	0.52	0.10	0.0104
AZ15	.	4.1	2	.	0.61	0.30	0.46	0.22	0.0486
AZ16	.	7.2	6.1	.	0.86	0.79	0.82	0.05	0.0026
AZ17	6.5	13.6	12.6	0.81	1.13	1.10	1.02	0.18	0.0311
AZ18	5.2	2	13.8	0.72	0.30	1.14	0.72	0.42	0.1759
AZ19	.	319.3	.	.	2.50	.	2.50	.	.
AZ20	.	139.1	83	.	2.14	1.92	2.03	0.16	0.0251
AZ21	.	7.5	34.1	.	0.88	1.53	1.20	0.47	0.2163
AZ22	.	14.1	146.7	.	1.15	2.17	1.66	0.72	0.5174
AZ23	136	70.5	30.2	2.13	1.85	1.48	1.82	0.33	0.1073
AZ24	.	347	347	.	2.54	2.54	2.54	0.00	0.0000
AZ25	123	75.1	73.4	2.09	1.88	1.87	1.94	0.13	0.0160
AZ26	13.8	42.7	50.2	1.14	1.63	1.70	1.49	0.31	0.0934
AZ27	159.6	133.8	143.5	2.20	2.13	2.16	2.16	0.04	0.0015
AZ28	35.2	24.7	11.8	1.55	1.39	1.07	1.34	0.24	0.0586
AZ29	.	103.4	.	.	2.01	.	2.01	.	.
AZ30	37.5	29.8	29	1.57	1.47	1.46	1.50	0.06	0.0038
AZ31	252.4	186	149.3	2.40	2.27	2.17	2.28	0.11	0.0131
AZ32	60	86.9	90.9	1.78	1.94	1.96	1.89	0.10	0.0098
AZ33	.	92.6	103.6	.	1.97	2.02	1.99	0.03	0.0012
AZ34	93.9	94.7	71.5	1.97	1.98	1.85	1.93	0.07	0.0048

AZ35	46.2	.	22.7	1.66	.	1.36	1.51	0.22	0.0476
AZ36	.	119.2	135	.	2.08	2.13	2.10	0.04	0.0015
AZ37	2	2	2	0.30	0.30	0.30	0.30	0.00	0.0000
AZ38	.	2	7	.	0.30	0.85	0.57	0.38	0.1480
AZ39	23.7	8.3	8.6	1.37	0.92	0.93	1.08	0.26	0.0669
AZ40	128	132.6	145.2	2.11	2.12	2.16	2.13	0.03	0.0008
AZ41	.	142.7	97.2	.	2.15	1.99	2.07	0.12	0.0139
AZ42	19	17.7	13	1.28	1.25	1.11	1.21	0.09	0.0077
AZ43	.	.	147.7	.	.	2.17	2.17	.	.
AZ44	.	195	179.2	.	2.29	2.25	2.27	0.03	0.0007
AZ45	.	.	.	.	.	.	2.27	0.03	0.0007
AZ46	347	205.8	148.5	2.54	2.31	2.17	2.34	0.19	0.0346
AZ47	7.1	8.6	2	0.85	0.93	0.30	0.70	0.34	0.1185
AZ48	64.6	49.8	36	1.81	1.70	1.56	1.69	0.13	0.0162
AZ49	2	.	143.6	0.30	.	2.16	1.23	1.31	1.7226
AZ50	14.8	20.9	2	1.17	1.32	0.30	0.93	0.55	0.3028
AZ51	192.7	234.4	136.7	2.28	2.37	2.14	2.26	0.12	0.0141
AZ52	.	185.1	135.5	.	2.27	2.13	2.20	0.10	0.0092
AZ53	7.7	3.8	4.1	0.89	0.58	0.61	0.69	0.17	0.0283
AZ54	21.4	3	2	1.33	0.48	0.30	0.70	0.55	0.3031
AZ55	.	5.2	.	.	0.72	.	0.72	.	.
AZ56	2	2	2	0.30	0.30	0.30	0.30	0.00	0.0000
AZ57	24	26	31.1	1.38	1.41	1.49	1.43	0.06	0.0033
AZ58	8.3	4.7	2	0.92	0.67	0.30	0.63	0.31	0.0968
AZ59	18.7	16.3	4.4	1.27	1.21	0.64	1.04	0.35	0.1203
AZ60	56.8	57	41.7	1.75	1.76	1.62	1.71	0.08	0.0061
AZ61	6.6	.	2	0.82	.	0.30	0.56	0.37	0.1344
AZ62	2	2	2	0.30	0.30	0.30	0.30	0.00	0.0000
AZ63	7.5	6.8	9.5	0.88	0.83	0.98	0.90	0.07	0.0056
AZ64	32	2	2	1.51	0.30	0.30	0.70	0.70	0.4833
AZ65	25.5	32.7	34.7	1.41	1.51	1.54	1.49	0.07	0.0050
AZ66	2	2	2.5	0.30	0.30	0.40	0.33	0.06	0.0031
AZ67	.	16.5	11	.	1.22	1.04	1.13	0.12	0.0155
AZ68	49.2	46.3	52.4	1.69	1.67	1.72	1.69	0.03	0.0007
AZ69	326.2	112.3	159	2.51	2.05	2.20	2.26	0.24	0.0558
AZ70	6.3	2	4.4	0.80	0.30	0.64	0.58	0.25	0.0650
AZ71	7.7	5.3	2	0.89	0.72	0.30	0.64	0.30	0.0914
AZ72	69.3	52.6	45.2	1.84	1.72	1.66	1.74	0.09	0.0089
AZ73	124.8	126.8	51.6	2.10	2.10	1.71	1.97	0.22	0.0499
AZ74	.	107.3	147.6	.	2.03	2.17	2.10	0.10	0.0096
AZ75	136.8	108.2	111.6	2.14	2.03	2.05	2.07	0.06	0.0031
AZ76	23.7	24.6	26.7	1.37	1.39	1.43	1.40	0.03	0.0007
AZ77	25.4	26.3	3.8	1.40	1.42	0.58	1.13	0.48	0.2311
AZ78	41.1	56.8	.	1.61	1.75	.	1.60	0.14	0.0193

AZ79	41.1	.	26.1	1.61	.	1.42	1.60	0.14	0.0193
AZ80	18.3	75.6	66.2	1.26	1.88	1.82	1.65	0.34	0.1158
AZ81	100.7	81.5	75.7	2.00	1.91	1.88	1.93	0.06	0.0041
AZ82	38.9	41.8	58.6	1.59	1.62	1.77	1.66	0.10	0.0090

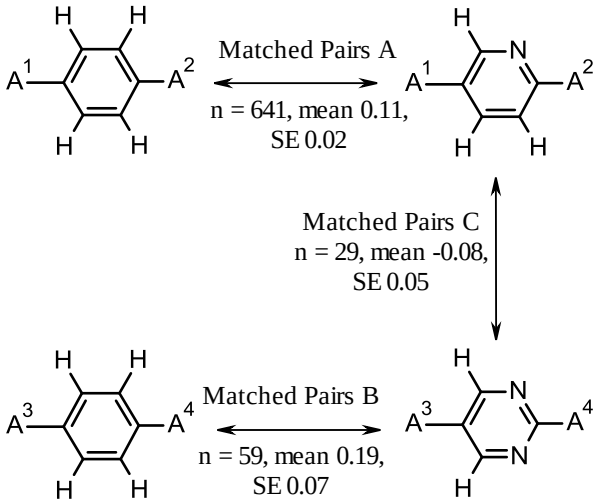
2.0 Computational Procedures and Matched Pair Analysis

Matched pairs for a given transform were found from the global *in-vitro* HLM dataset by using in-house proprietry software (‘ThricePairs’), to yield a total of 1680 matched pairs. For those transforms without data (the bulk of 5-membered heterocycles) compound pairs were identified from the corporate collection using the same software in batch mode. This yielded 750 compounds to test in the *in-vitro* HLM assay. Testing began with a random subset of compounds and each compound tested three times to test variability of the assay – 86 compounds – see selection 1.4. Results were processed by removing out-of-range values for statistical evaluation yielding 2323 matched pairs in total. Compound diversity was examined by considering the mean Tanimoto distance across each group, which was determined by in-house program 'alfi' and the Tanimoto distances calculated using the program 'snailflush'. Only 6 matched pair groups were found to have a mean Tanimoto below 0.6 (where 0.0 maybe an exact match and 1.0 highly diverse) and all data have been included in Table 1 in the manuscript as there may still be useful information to interpret from them. Matched pair analysis was performed using SAS JMP version 8.0 and p-values reported in Table 1. These corresponded with the mean ΔLog_{10} HLM Cl_{int} greater than 2 × SE for the distribution. As described above the total dataset of 2323 matched pairs was used to find frequency greater than or equal to 0.5 ΔLog_{10} HLM Cl_{int} increase in stability [F(0.5)] and less than –0.5 ΔLog_{10} HLM Cl_{int} (i.e. decrease in stability) [F(-0.5)]. The subtraction of Log terms in this fashion (Log_{10} (benzene) – Log_{10} (heterocycle)) was performed such that an increase in stability was a positive value to aid clarity for the reader. After examining several ‘cut-offs’, and considering the proposals and probabilities published by others, we proposed that 0.5 Log_{10} unit of change in HLM level was reasonable (i.e. 3.2 fold).

Matched triplicate testing.

It could be incorrect to directly compare two distributions from two transforms as they do not necessarily contain the same core structures (Scheme 2 – A1/A2 may not equal A3/A4).

However from within the dataset we extracted matched pairs C for the transform ((2,5)-pyridine to (2,5)-pyrimidine) and found n = 29, and a mean of -0.08 ΔLog_{10} HLM (SE 0.05), thus confirming that within SE the comparison can be made between these transform matched pairs.



Scheme 2 – Illustration of how the matched pair analysis was performed for the paper. For matched pairs A:- A1=A1 and A2=A2, matched pairs B A3=A3 and A4=A4, however A groups may overlap for some pairs. For matched pairs C A1=A3 and A2=A4.

2.1 SMARTS and atom mapping used to find matches.

Table 3

Those transforms coloured red – no matched pairs founds in the AstraZeneca corporate collection.

Transform	Smart1	Smart2	Atom Mapping
(1,2)-Bn_(2,3)-pyrazine	[c!H]1[c!H][n][cH][cH][n]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,2)-Bn_(2,3)-pyridine	[c!H]1[c!H][n][cH][cH][cH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,2)-Bn_(3,4)-pyrazine	[c!H]1[c!H][n][n][cH][cH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,2)-Bn_(3,4)-pyridine	[c!H]1[c!H][cH][n][cH][cH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,2)-Bn_(4,5)-pyrimidine	[c!H]1[c!H][n][cH][n][cH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,3)-Bn_(2,4)-pyrimidine	[c!H]1[n][c!H][n][cH][cH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4 5=56 =6
(1,3)-Bn_(2,4)-pyridine	[c!H]1[cH][c!H][n][cH][cH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,3)-Bn_(2,6)-pyrimidine	c!H]1[cH][c!H][n][cH][n]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,3)-Bn_(2,6)-pyridine	[c!H]1[n][c!H][cH][cH][cH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,3)-Bn_(3,5)-pyrazine	[c!H]1[n][c!H][cH][n][cH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,3)-Bn_(3,5)-pyridine	[c!H]1[cH][c!H][cH][n][cH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,4)-Bn_(2,5)_pyrazine	[c!H]1[n][cH][c!H][n][cH]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4

			5=5 6=6
(1,4)-Bn_(2,5)_pyrimidine	[c!H]1[n][cH][c!H][cH][n]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,4)-Bn_(2,5)_pyridine	[c!H]1[n][cH][c!H][cH][cH]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,4)-Bn_(2,6)_pyridazine	[c!H]1[n][n][c!H][cH][cH]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
(1,4)-Bn_(*N*,*N*)-piperazine	[N!H]1[CH2][CH2][N!H][CH2][CH2]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4 5=5 6=6
5memberedheterocycles			
(1,2)-Bn_(2,3)-thiophene	[c!H][c!H][cH][cH][s]	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-thiazole	[c!H][c!H]n[cH][s]	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-thiadiazole	[c!H][c!H]nns	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-isothiazole	[c!H][c!H][cH]n[s]	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(2,3)-1H-pyrrole	[c!H]1[c!H][cH][cH][nH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)- 1H-imidazole	[c!H]1[c!H]n[cH][nH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)- 1H-triazole	[c!H]1[c!H]nn[nH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-pyrazole	[c!H]1[c!H][cH]n[nH]1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(2,3)-furan	[c!H]1[c!H][cH][cH]o1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-oxazole	[c!H]1[c!H]n[cH]o1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-oxadiazole	[c!H]1[c!H]nno1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,2)-Bn_(4,5)-isooxazole	[c!H]1[c!H][cH]no1	[c!H][c!H][cH][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-thiophene	[c!H]1[cH][c!H][cH][s]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-thiazole	[c!H]1n[c!H][cH][s]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-thiadiazole	[c!H]1n[c!H]ns1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-isothiazole	[c!H]1[cH][c!H]n[s]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-1H-pyrrole	[c!H]1[cH][c!H][cH][nH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-1H-imidazole	[c!H]1n[c!H][cH][nH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-1H-triazole	[c!H]1n[c!H]n[nH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-1H-pyrazole	[c!H]1[cH][c!H]n[nH]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-furan	[c!H]1[cH][c!H][cH][o]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-oxazole	[c!H]1n[c!H][cH][o]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-oxadiazole	[c!H]1n[c!H]n[o]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,3)-Bn_(2,4)-isoxazole	[c!H]1[cH][c!H]n[o]1	[c!H][cH][c!H][cH][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-thiophene	[c!H]1[cH][cH][c!H][s]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-thiazole	[c!H]1n[cH][c!H][s]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-thiadiazole	[c!H]1nn[c!H][s]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-1H-pyrrole	[c!H]1[cH][cH][c!H][nH]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-1H-imdiazole	[c!H]1n[cH][c!H][nH]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-1H-triazole	[c!H]1nn[c!H][nH]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-furan	[c!H]1[cH][cH][c!H][o]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-oxazole	[c!H]1n[cH][c!H][o]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4
(1,4)-Bn_(2,5)-oxadiazole	[c!H]1nn[c!H][o]1	[c!H][cH][cH][c!H][cH][cH]	1=1 2=2 3=3 4=4

For this table Bn = benzene

No matched pairs were found for the following transforms:-

(1,2)-Bn_(4,5)-isothiazole,
(1,2)-Bn_(4,5)-triazole,
(1,2)-Bn_(4,5)-oxadiazole,
(1,3)-Bn_(2,4)-thiadiazole,
(1,3)-Bn_(2,4)-pyrrole,
(1,4)-Bn_(2,5)-1H-triazole.