Appendix I. 2-Drug Combinations in Vitro

CompuSyn Report

Example I-A. Enzyme System: Two Drugs

(Adopted from *Table 10 and Appendix III* of Pharmacol Rev 58:621-681, 2006)

CompuSyn Analysis of Yonetani-Theorell Data in Table 10

CompuSyn Generated Report for Drug Combination Data of ADP and O-phenanthroline Data Given in Table 10 Using All Data Points and Partial Data Points were used to demonstrate the flexibility of the method

***I-A-a. All 36 Data Points* are used. (mixed constant and non-constant ratio combinations)**

CompuSyn Report

Experiment Name: APPENDIX III. A: ADP+O-PAL Combinations. Used all data points in Table 10. Overall data analyzed as a non-constant ratio design.
Date: 4/18/2006
File Name: A:\APPENDIX III A.cse
Description ADP+O-phenanthroline, 2drug combo. (Used all 36 data points including a control, in Table 10). This design generate a normalized isobologram and a Fa-CI plot with actural combination data points but without a computer simulation.
(Original data from Yonetani & Theorell, 1964)
Drug: ADP (A) [µM]
Drug: O-PAL (B) [µM]
Drug Combo: ADP+O-PAL (C) (A+B)

Data for Drug: A [µM]

5 data points entered.

Dose	Effect
0.5	0.175
1.0	0.358
1.5	0.492
2.0	0.542
2.5	0.598

X-int: 0.22910
Y-int: -0.2788 +/- 0.02071
m: 1.21678 +/- 0.07607
Dm: 1.69473
r: 0.99419

Data for Drug: B [µM]

5 data points entered.

Dose	Effect
8.7	0.132
17.4	0.267
26.1	0.411
34.8	0.476
43.5	0.548

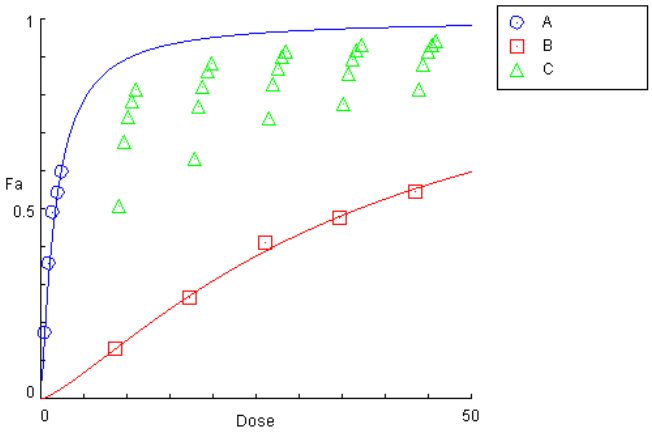
X-int: 1.56589
Y-int: -2.0393 +/- 0.06278
m: 1.30233 +/- 0.04557
Dm: 36.8032
r: 0.99817

Data for Non-Constant Combo: C (A+B)

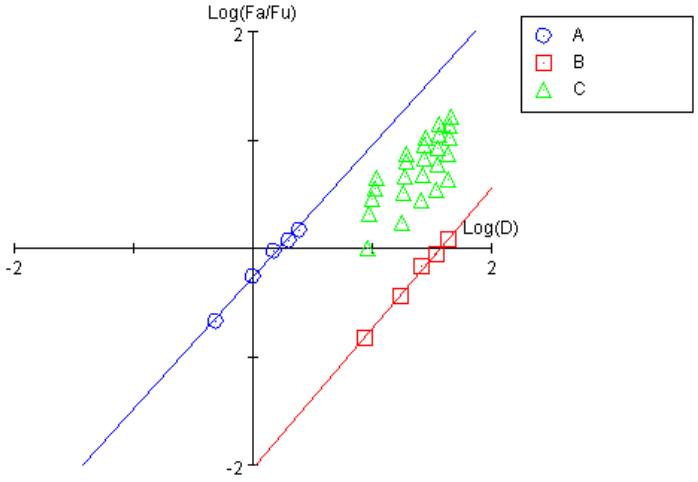
Dose A	Dose B	Effect
0.5	8.7	0.507
1.0	8.7	0.676
1.5	8.7	0.742
2.0	8.7	0.783
2.5	8.7	0.817
0.5	17.4	0.633
1.0	17.4	0.769
1.5	17.4	0.823
2.0	17.4	0.865
2.5	17.4	0.883
0.5	26.1	0.738
1.0	26.1	0.829
1.5	26.1	0.872
2.0	26.1	0.9
2.5	26.1	0.914
0.5	34.8	0.777
1.0	34.8	0.858
1.5	34.8	0.895
2.0	34.8	0.919
2.5	34.8	0.934
0.5	43.5	0.816
1.0	43.5	0.882
1.5	43.5	0.915
2.0	43.5	0.932
2.5	43.5	0.944

25 data points entered.

Dose-Effect Curve



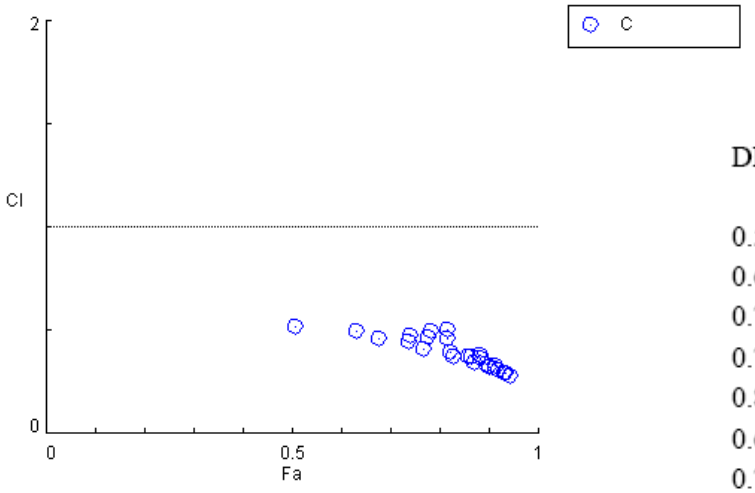
Median-Effect Plot



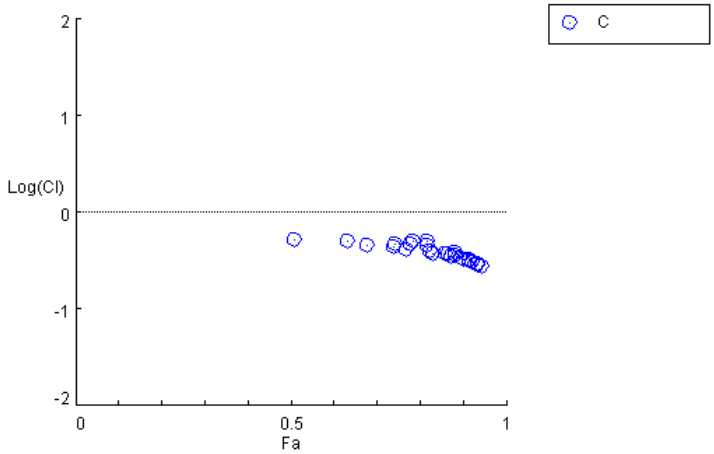
CI Data for Non-Constant Combo: C (A+B)

Dose A	Dose B	Effect	CI
0.5	8.7	0.507	0.51968
1.0	8.7	0.676	0.45680
1.5	8.7	0.742	0.47653
2.0	8.7	0.783	0.49932
2.5	8.7	0.817	0.50629
0.5	17.4	0.633	0.49959
1.0	17.4	0.769	0.40736
1.5	17.4	0.823	0.39558
2.0	17.4	0.865	0.36999
2.5	17.4	0.883	0.38034
0.5	26.1	0.738	0.44615
1.0	26.1	0.829	0.37227
1.5	26.1	0.872	0.34539
2.0	26.1	0.9	0.32518
2.5	26.1	0.914	0.32698
0.5	34.8	0.777	0.46836
1.0	34.8	0.858	0.37215
1.5	34.8	0.895	0.33454
2.0	34.8	0.919	0.30680
2.5	34.8	0.934	0.29074
0.5	43.5	0.816	0.46336
1.0	43.5	0.882	0.36521
1.5	43.5	0.915	0.31618
2.0	43.5	0.932	0.29562
2.5	43.5	0.944	0.27984

Combination Index Plot



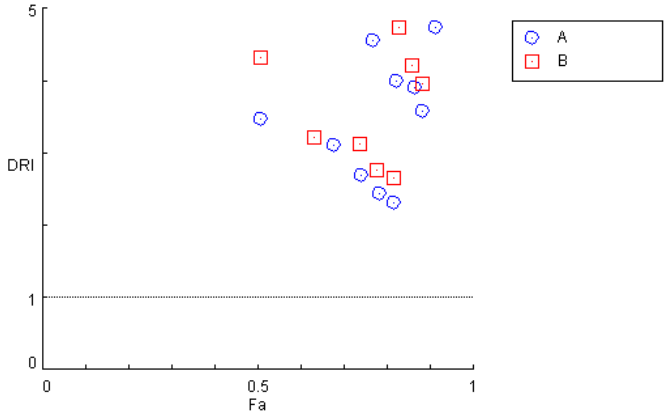
Logarithmic Combination Index Plot



DRI Data for Non-Constant Combo: C (A+B)

Fa	Dose A	Dose B	DRI A	DRI B
0.507	1.73419	37.6031	3.46837	4.32219
0.676	3.10169	64.7351	3.10169	7.44082
0.742	4.03784	82.8258	2.69189	9.52021
0.783	4.86536	98.5855	2.43268	11.3317
0.817	5.79576	116.096	2.31830	13.3443
0.633	2.65254	55.9327	5.30508	3.21452
0.769	4.55366	92.6718	4.55366	5.32597
0.823	5.99267	119.777	3.99511	6.88373
0.865	7.79950	153.215	3.89975	8.80546
0.883	8.92264	173.736	3.56906	9.98483
0.738	3.96944	81.5141	7.93887	3.12314
0.829	6.20186	123.679	6.20186	4.73865
0.872	8.20252	160.600	5.46835	6.15325
0.9	10.3119	198.887	5.15594	7.62019
0.914	11.8217	225.969	4.72867	8.65783
0.777	4.72754	95.9738	9.45508	2.75787
0.858	7.43230	146.465	7.43230	4.20876
0.895	9.86132	190.756	6.57422	5.48149
0.919	12.4740	237.598	6.23699	6.82754
0.934	14.9582	281.538	5.98328	8.09016
0.816	5.76405	115.502	11.5281	2.65522
0.882	8.85220	172.454	8.85220	3.96447
0.915	11.9466	228.199	7.96439	5.24596
0.932	14.5700	274.705	7.28499	6.31505
0.944	17.2713	322.017	6.90850	7.40269

DRI Plot for Non-Constant Combo: C (A+B)

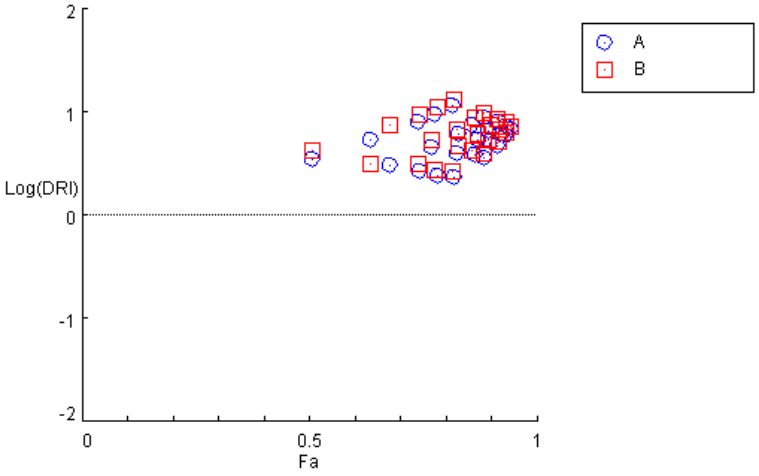


Summary Table

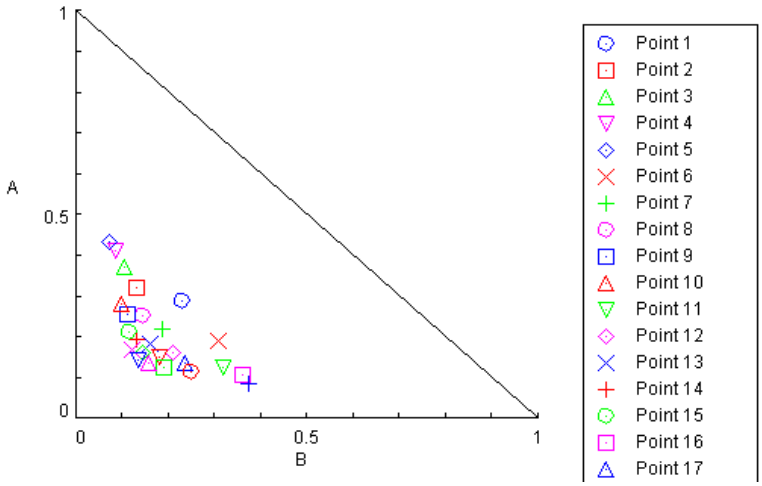
Experiment Name:	APPENDIX III. A: ADP+O-PAL Combinations. Used all data points in Table 10. Overall data analyzed as a non-constant ratio design.
Date:	4/18/2006
File Name:	A:\APPENDIX III A.cse
Description	ADP+O-phenanthroline, 2drug combo. (Used all 36 data points including a control, in Table 10). This design generate a normalized isobologram and a Fa-CI plot with actural combination data points but without a computer simulation. (Original data from Yonetani & Theorell, 1964)
Drug:	ADP (A) [µM]
Drug:	O-PAL (B) [µM]
Drug Combo:	ADP+O-PAL (C) (A+B)

Drug/Combo	Dm	m	r
A	1.69473	1.21678	0.99419
B	36.8032	1.30233	0.99817

Log(DRI) Plot for Non-Constant Combo: C (A+B)



Normalized Isobologram for Combo: C (A+B)



CI values at:

Combo	ED50	ED75	ED90	ED95

Data for Fa = 0.5

Drug/Combo	CI value	Dose A	Dose B
A		1.69473	
B			36.8032

Data for Fa = 0.75

Drug/Combo	CI value	Dose A	Dose B
A		4.18042	
B			85.5551

Data for Fa = 0.9

Drug/Combo	CI value	Dose A	Dose B
A		10.3119	
B			198.887

Data for Fa = 0.95

Drug/Combo	CI value	Dose A	Dose B
A		19.0561	
B			353.008

Data for Fa = 0.97

Drug/Combo	CI value	Dose A	Dose B
A		29.4982	
B			530.982

II-A-b. Constant Combination Ratio in

Diagonal Data Points (table 15 data points)

CompuSyn Report

Experiment Name: APPENDIX III. B: ADP+O-PAL Combinations at a constant ratio. (Data from Table 10, combination data points [1] - [5] used)

Date: 4/18/2006

File Name: A:\APPENDIX III B.cse

Description ADP+O-phenanthroline, 2 drug combo at a constant ratio (1:17.4) (Used only diagonal combination data points). This design will generate a computer simulated Fa-CI plot with the actural combination data points and will also generate a classic isobologram.
(Original data from Yonetani & Theorell, 1964)

Drug: ADP (A) [µM]

Drug: O-PAL (B) [µM]

Drug Combo: ADP+O-PAL (C) (A+B [1:17.4])

Data for Drug: A [µM] — 5 data points entered.

Dose	Effect
0.5	0.175
1.0	0.358
1.5	0.492
2.0	0.542
2.5	0.598

X-int: 0.22910
Y-int: -0.2788 +/- 0.02071
m: 1.21678 +/- 0.07607
Dm: 1.69473
r: 0.99419

Data for Drug: B [µM] — 5 data points entered.

Dose	Effect
8.7	0.132
17.4	0.267
26.1	0.411
34.8	0.476
43.5	0.548

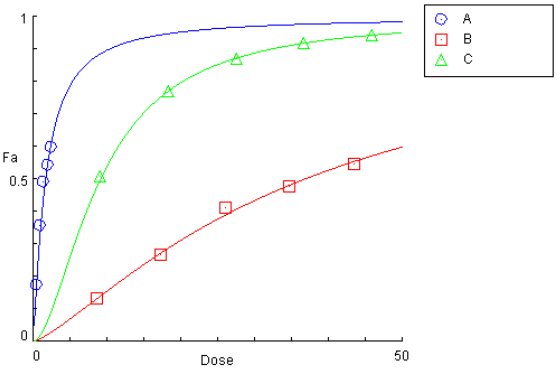
X-int: 1.56589
Y-int: -2.0393 +/- 0.06278
m: 1.30233 +/- 0.04557
Dm: 36.8032
r: 0.99817

Data for Drug Combo: C (A+B [1:17.4]) — 5 data points entered.

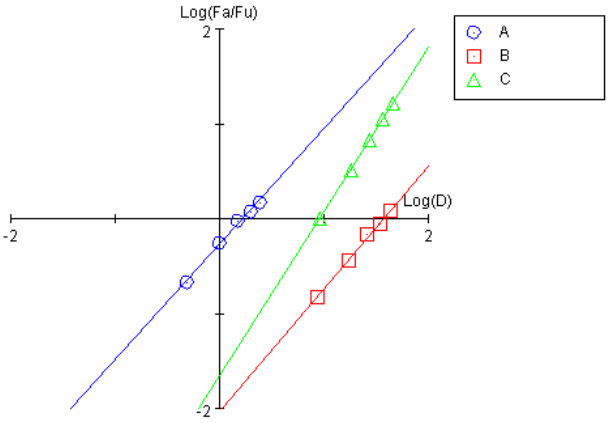
Dose A	Effect
0.5+	0.507
1.0+	0.769
1.50000+	0.872
2.0+	0.919
2.50000+	0.944

X-int: 0.95987
Y-int: -1.6691 +/- 0.0163
m: 1.73884 +/- 0.0116
Dm: 9.11747
r: 0.99993

Dose-Effect Curve



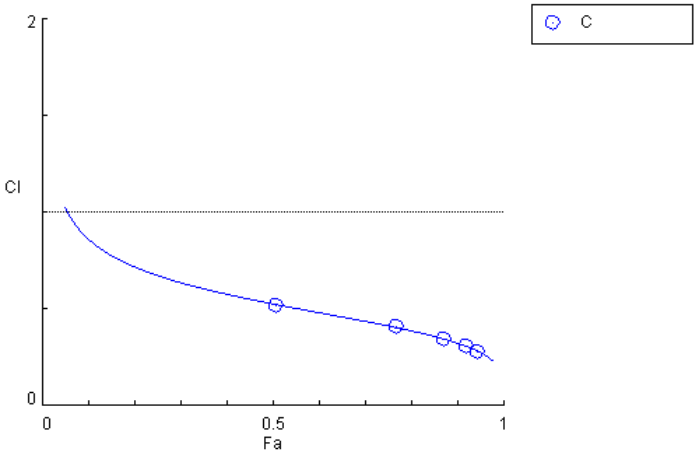
Median-Effect Plot



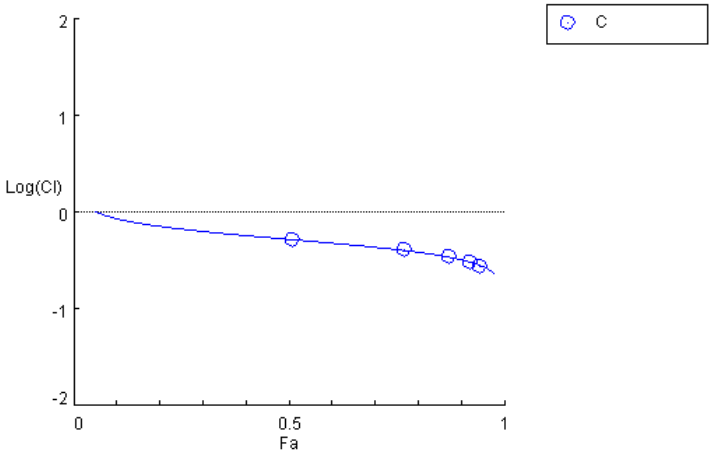
CI Data for Drug Combo: C (A+B [1:17.4])

Fa	CI Value	Total Dose
0.05	1.01787	1.67675
0.1	0.86064	2.57688
0.15	0.77587	3.36232
0.2	0.71767	4.10802
0.25	0.67296	4.84712
0.3	0.63621	5.60083
0.35	0.60460	6.38649
0.4	0.57647	7.22113
0.45	0.55074	8.12371
0.5	0.52666	9.11747
0.55	0.50364	10.2328
0.6	0.48121	11.5118
0.65	0.45889	13.0162
0.7	0.43619	14.8421
0.75	0.41252	17.1500
0.8	0.38702	20.2356
0.85	0.35827	24.7235
0.9	0.32340	32.2592
0.95	0.27420	49.5769
0.97	0.24388	67.3080

Combination Index Plot



Logarithmic Combination Index Plot



CI values for actual experimental points:

Total Dose	Fa	CI Value
9.2	0.507	0.51968
18.4	0.769	0.40736
27.6	0.872	0.34539
36.8	0.919	0.30680
46.0	0.944	0.27984

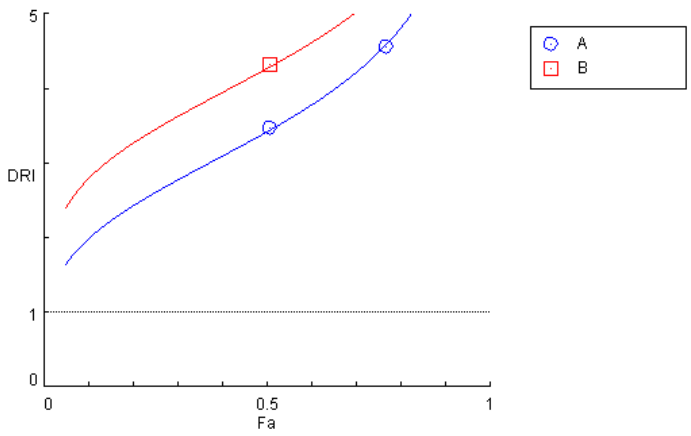
DRI Data for Drug Combo: C (A+B [1:17.4])

Fa	Dose A	Dose B	DRI A	DRI B
0.05	0.15072	3.83695	1.65393	2.41984
0.1	0.27853	6.81027	1.98879	2.79473
0.15	0.40737	9.71490	2.22927	3.05540
0.2	0.54238	12.6938	2.42934	3.26758
0.25	0.68704	15.8316	2.60805	3.45390
0.3	0.84466	19.2014	2.77490	3.62534
0.35	1.01895	22.8797	2.93568	3.78841
0.4	1.21446	26.9571	3.09453	3.94763
0.45	1.43707	31.5476	3.25492	4.10658
0.5	1.69473	36.8032	3.42015	4.26854
0.55	1.99859	42.9343	3.59376	4.43689
0.6	2.36494	50.2456	3.78003	4.61555
0.65	2.81870	59.1998	3.98457	4.80953
0.7	3.40032	70.5405	4.21543	5.02587
0.75	4.18042	85.5551	4.48511	5.27534
0.8	5.29541	106.704	4.81506	5.57614
0.85	7.05046	139.422	5.24718	5.96337
0.9	10.3119	198.887	5.88168	6.51959
0.95	19.0561	353.008	7.07251	7.52963
0.97	29.4982	530.982	8.06393	8.34222

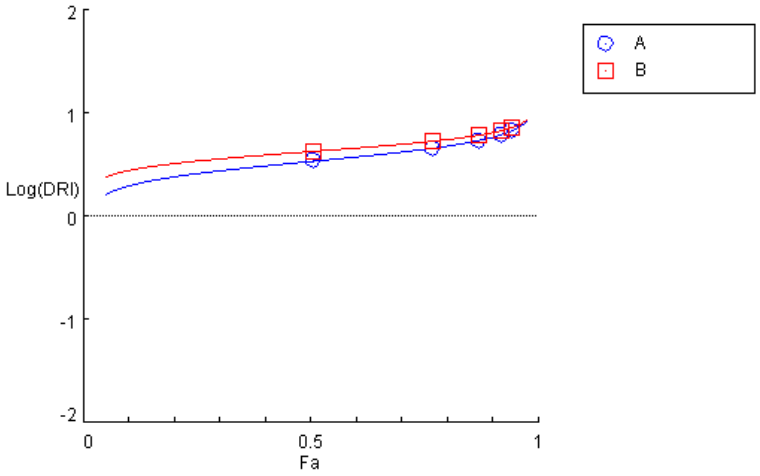
DRI values calculated at experimental points

Fa	Dose A	Dose B	DRI A	DRI B
0.507	1.73419	37.6031	3.46837	4.32219
0.769	4.55366	92.6718	4.55366	5.32597
0.872	8.20252	160.600	5.46835	6.15325
0.919	12.4740	237.598	6.23699	6.82754
0.944	17.2713	322.017	6.90850	7.40269

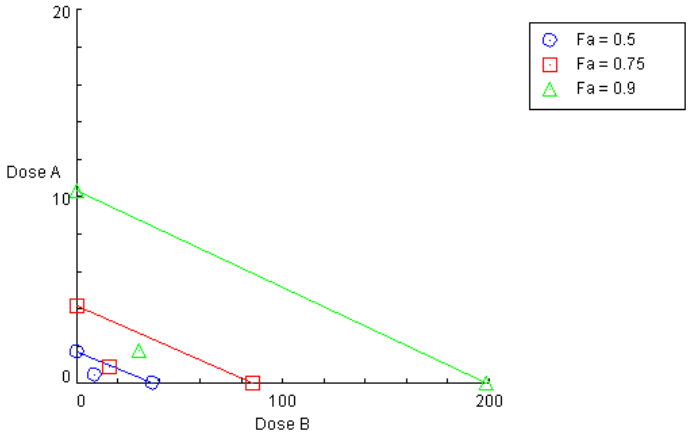
DRI Plot for Combo: C (A+B [1:17.4])



Log(DRI) Plot for Combo: C (A+B [1:17.4])



Isobologram for Combo: C (A+B [1:17.4])



Summary Table

Experiment Name: APPENDIX III. B: ADP+O-PAL Combinations at a constant ratio. (Data from Table 10, combination data points [1] - [5] used)

Date: 4/18/2006

File Name: A:\APPENDIX III B.cse

Description ADP+O-phenanthroline, 2 drug combo at a constant ratio (1:17.4) (Used only diagonal combination data points). This design will generate a computer simulated Fa-CI plot with the actural combination data points and will also generate a classic isobologram.
(Original data from Yonetani & Theorell, 1964)

Drug: ADP (A) [µM]

Drug: O-PAL (B) [µM]

Drug Combo: ADP+O-PAL (C) (A+B [1:17.4])

Drug/Combo	Dm	m	r
A	1.69473	1.21678	0.99419
B	36.8032	1.30233	0.99817
C	9.11747	1.73884	0.99993

CI values at:

Combo	ED50	ED75	ED90	ED95
C	0.52666	0.41252	0.32340	0.27420

Data for Fa = 0.5

Drug/Combo	CI value	Dose A	Dose B
A		1.69473	
B			36.8032
C	0.52666	0.49551	8.62195

Data for Fa = 0.75

Drug/Combo	CI value	Dose A	Dose B
A		4.18042	
B			85.5551
C	0.41252	0.93207	16.2179

Data for Fa = 0.9

Drug/Combo	CI value	Dose A	Dose B
A		10.3119	
B			198.887
C	0.32340	1.75322	30.5060

Data for Fa = 0.95

Drug/Combo	CI value	Dose A	Dose B
A		19.0561	
B			353.008
C	0.27420	2.69439	46.8825

Data for Fa = 0.97

Drug/Combo	CI value	Dose A	Dose B
A		29.4982	
B			530.982
C	0.24388	3.65804	63.6499

I-A-c. Partial Data Points with *Non-Constant Combination Ratios in The Two Triangles in the Data Table (total 30 data points)*

CompuSyn Report

Experiment Name: APPENDIX III.C: ADP+O-PAL Combinations at non-constant ratios. (Data from Table 10, used combination data points in triangles only)

Date: 4/18/2006

File Name: A:\APPENDIX III C.cse

Description ADP+O-phenanthroline, 2 drug combo. non-constant ratios (Used combination data points in triangles only [without constant ratios]). This design will generate a normalized isobologram and will generate a Fa-CI plot with actual combination data points but without a computer simulation.
(Original data from Yonetani & Theorell, 1964)

Drug: ADP (A) [µM]

Drug: O-PAL (B) [µM]

Drug Combo: ADP+O-PAL (C) (A+B)

Data for Drug: A [µM]

5 data points entered.

Dose	Effect
0.5	0.175
1.0	0.358
1.5	0.492
2.0	0.542
2.5	0.598

X-int: 0.22910
Y-int: -0.2788 +/- 0.02071
m: 1.21678 +/- 0.07607
Dm: 1.69473
r: 0.99419

Data for Drug: B [µM]

5 data points entered.

Dose	Effect
8.7	0.132
17.4	0.267
26.1	0.411
34.8	0.476
43.5	0.548

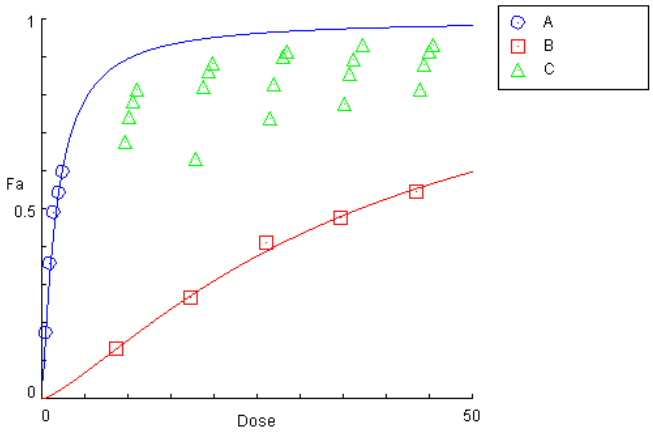
X-int: 1.56589
Y-int: -2.0393 +/- 0.06278
m: 1.30233 +/- 0.04557
Dm: 36.8032
r: 0.99817

Data for Non-Constant Combo: C (A+B)

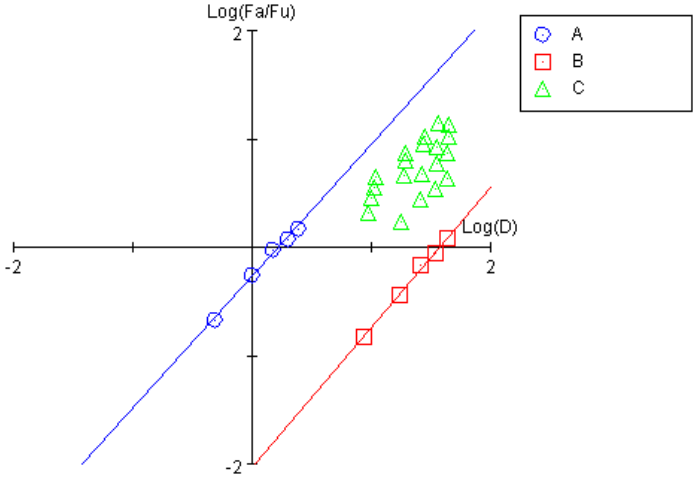
Dose A	Dose B	Effect
1.0	8.7	0.676
1.5	8.7	0.742
2.0	8.7	0.783
2.5	8.7	0.817
0.5	17.4	0.633
1.5	17.4	0.823
2.0	17.4	0.865
2.5	17.4	0.883
0.5	26.1	0.738
1.0	26.1	0.829
2.0	26.1	0.9
2.5	26.1	0.914
0.5	34.8	0.777
1.0	34.8	0.858
1.5	34.8	0.895
2.5	34.8	0.934
0.5	43.5	0.816
1.0	43.5	0.882
1.5	43.5	0.915
2.0	43.5	0.932

20 data points entered.

Dose-Effect Curve



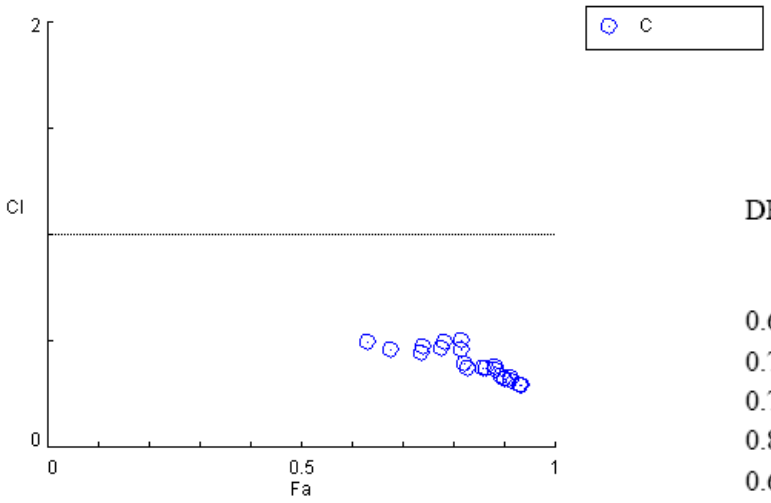
Median-Effect Plot



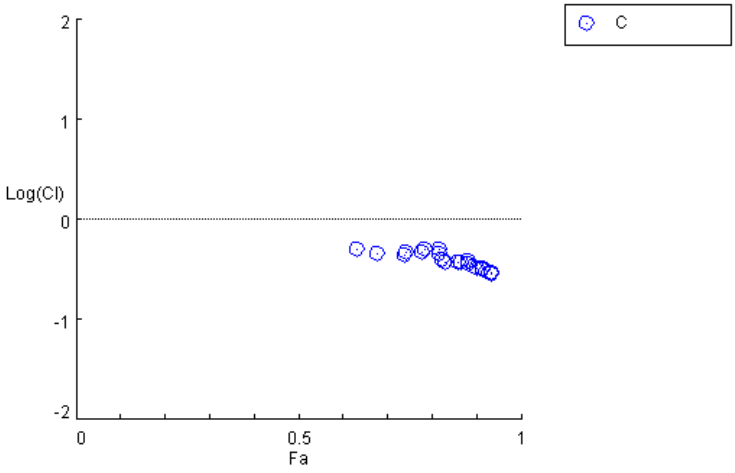
CI Data for Non-Constant Combo: C (A+B)

Dose A	Dose B	Effect	CI
1.0	8.7	0.676	0.45680
1.5	8.7	0.742	0.47653
2.0	8.7	0.783	0.49932
2.5	8.7	0.817	0.50629
0.5	17.4	0.633	0.49959
1.5	17.4	0.823	0.39558
2.0	17.4	0.865	0.36999
2.5	17.4	0.883	0.38034
0.5	26.1	0.738	0.44615
1.0	26.1	0.829	0.37227
2.0	26.1	0.9	0.32518
2.5	26.1	0.914	0.32698
0.5	34.8	0.777	0.46836
1.0	34.8	0.858	0.37215
1.5	34.8	0.895	0.33454
2.5	34.8	0.934	0.29074
0.5	43.5	0.816	0.46336
1.0	43.5	0.882	0.36521
1.5	43.5	0.915	0.31618
2.0	43.5	0.932	0.29562

Combination Index Plot



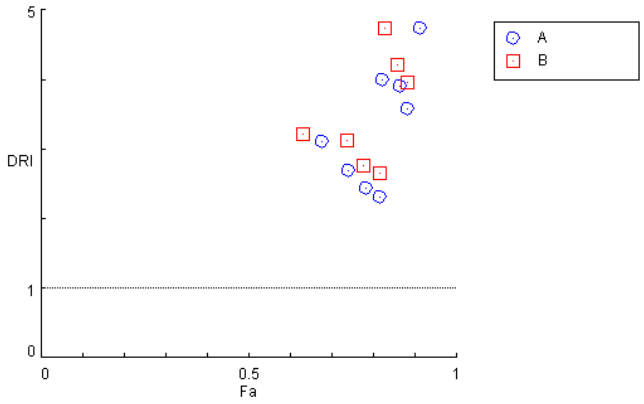
Logarithmic Combination Index Plot



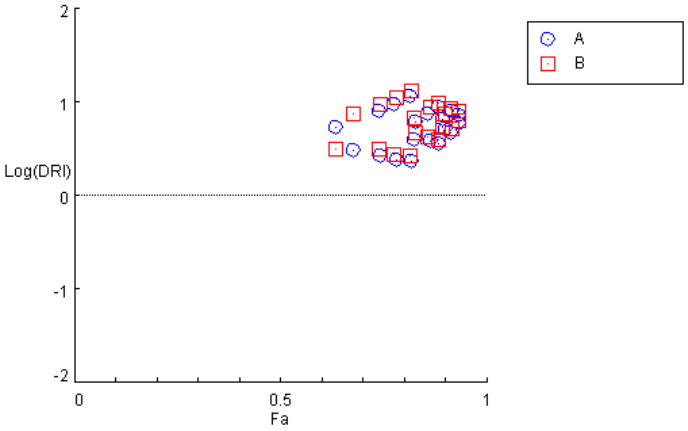
DRI Data for Non-Constant Combo: C (A+B)

Fa	Dose A	Dose B	DRI A	DRI B
0.676	3.10169	64.7351	3.10169	7.44082
0.742	4.03784	82.8258	2.69189	9.52021
0.783	4.86536	98.5855	2.43268	11.3317
0.817	5.79576	116.096	2.31830	13.3443
0.633	2.65254	55.9327	5.30508	3.21452
0.823	5.99267	119.777	3.99511	6.88373
0.865	7.79950	153.215	3.89975	8.80546
0.883	8.92264	173.736	3.56906	9.98483
0.738	3.96944	81.5141	7.93887	3.12314
0.829	6.20186	123.679	6.20186	4.73865
0.9	10.3119	198.887	5.15594	7.62019
0.914	11.8217	225.969	4.72867	8.65783
0.777	4.72754	95.9738	9.45508	2.75787
0.858	7.43230	146.465	7.43230	4.20876
0.895	9.86132	190.756	6.57422	5.48149
0.934	14.9582	281.538	5.98328	8.09016
0.816	5.76405	115.502	11.5281	2.65522
0.882	8.85220	172.454	8.85220	3.96447
0.915	11.9466	228.199	7.96439	5.24596
0.932	14.5700	274.705	7.28499	6.31505

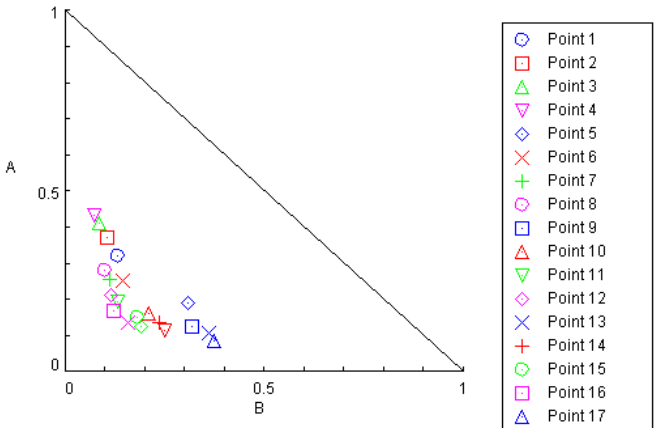
DRI Plot for Non-Constant Combo: C (A+B)



Log(DRI) Plot for Non-Constant Combo: C (A+B)



Normalized Isobologram for Combo: C (A+B)



Summary Table

Experiment Name: APPENDIX III.C: ADP+O-PAL Combinations at non-constant ratios. (Data from Table 10, used combination data points in triangles only)

Date: 4/18/2006

File Name: A:\APPENDIX III C.cse

Description ADP+O-phenanthroline, 2 drug combo. non-constant ratios (Used combination data points in triangles only [without constant ratios]). This design will generate a normalized isobologram and will generate a Fa-CI plot with actual combination data points but without a computer simulation.
(Original data from Yonetani & Theorell, 1964)

Drug: ADP (A) [µM]

Drug: O-PAL (B) [µM]

Drug Combo: ADP+O-PAL (C) (A+B)

Drug/Combo	Dm	m	r
A	1.69473	1.21678	0.99419
B	36.8032	1.30233	0.99817

CI values at:

Combo	ED50	ED75	ED90	ED95

Data for Fa = 0.5

Drug/Combo	CI value	Dose A	Dose B
A		1.69473	
B			36.8032

Data for Fa = 0.75

Drug/Combo	CI value	Dose A	Dose B
A		4.18042	
B			85.5551

Data for Fa = 0.9

Drug/Combo	CI value	Dose A	Dose B
A		10.3119	
B			198.887

Data for Fa = 0.95

Drug/Combo	CI value	Dose A	Dose B
A		19.0561	
B			353.008

Data for Fa = 0.97

Drug/Combo	CI value	Dose A	Dose B
A		29.4982	
B			530.982