



Proposal of the “Parallel and One step” drug design method and simulation study

The new trend of drug design by A-ADME-T-P total prediction

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FUJITSU

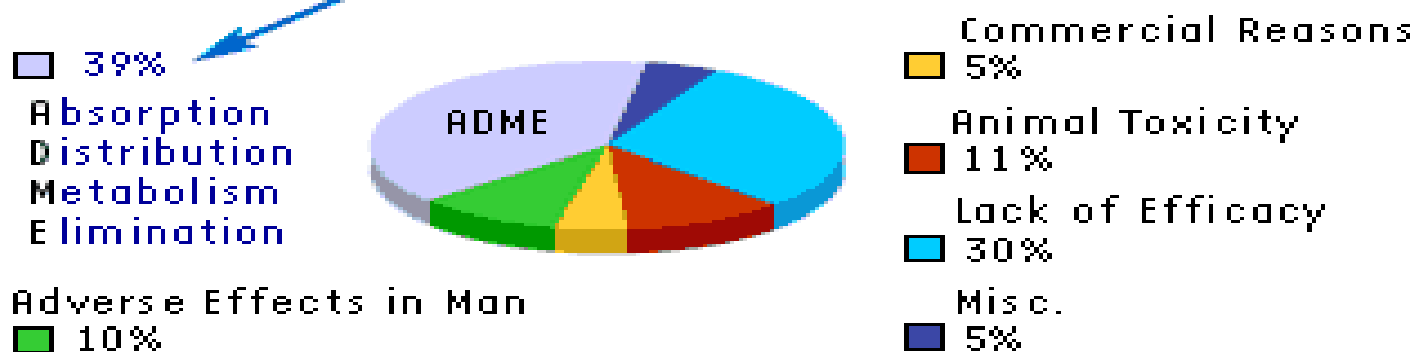
THE POSSIBILITIES ARE INFINITE

Reasons of Drug Development Failure



ADME: Single Largest Cause of Attrition in Drug Development

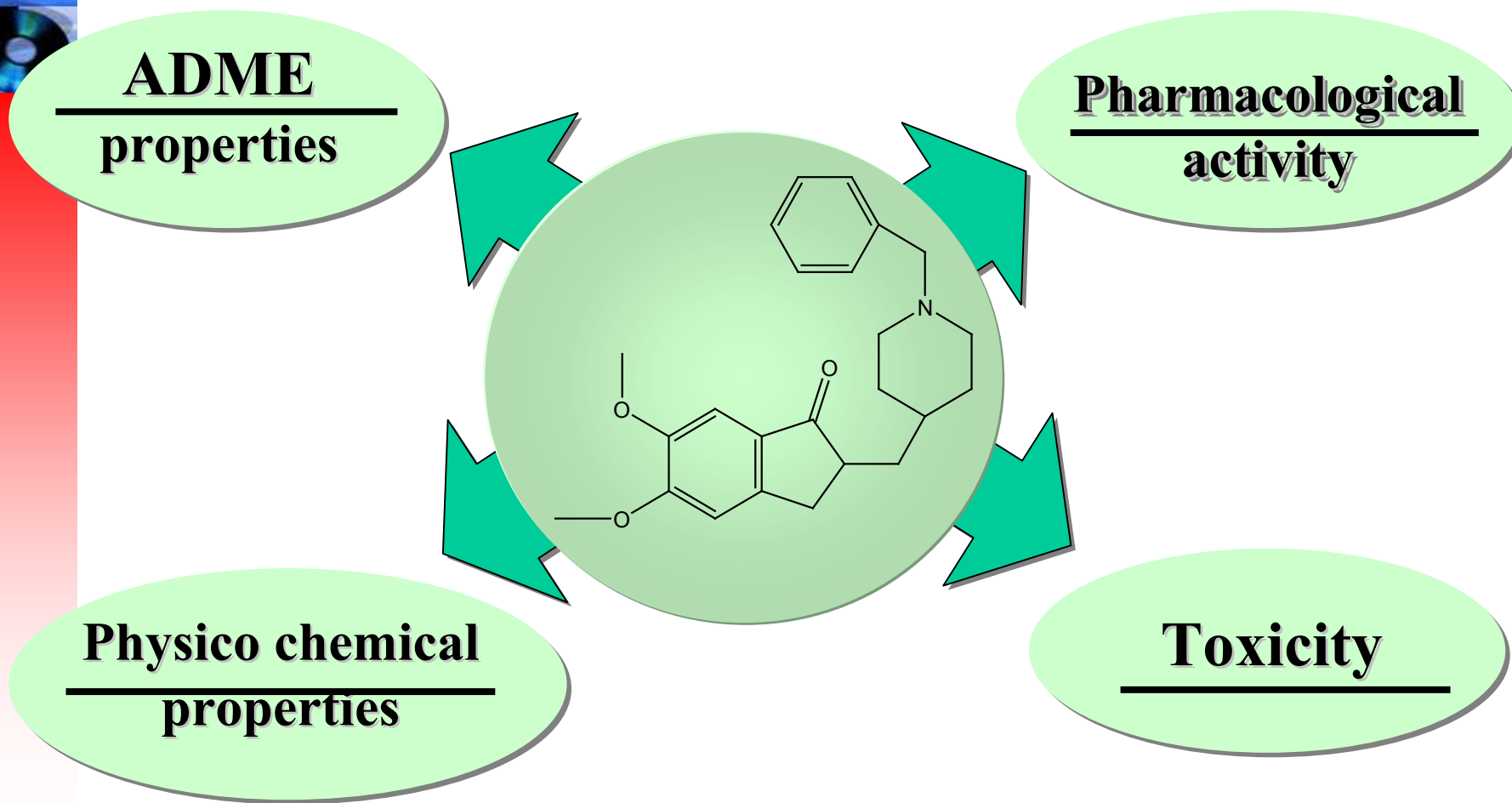
All NCE's (n=198)



Source: Kennedy, T. (1997) Drug Discovery Today 2, 436-444.

ADME, Toxicity (60%) > Activity (30%)

Drug properties and compound structure

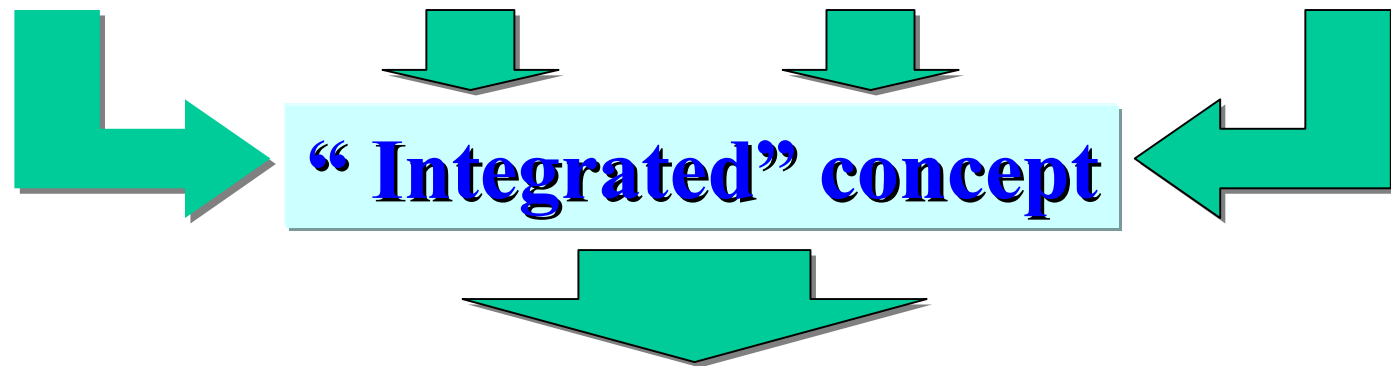


“Integrated” concept for drug development



Activity + ADME + Toxicity + Property

All drug properties shall be considered at the same time

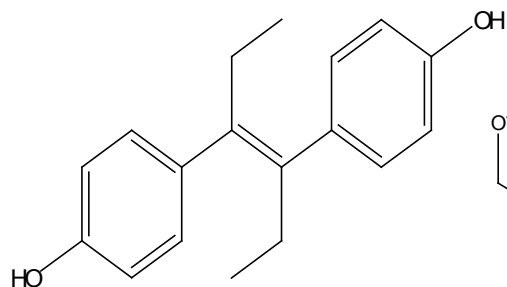


“Integrated” in silico screening & drug design

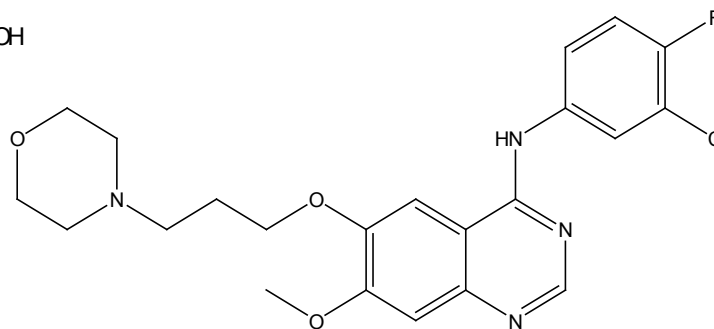
Drugs which possesses **Side-Effect**



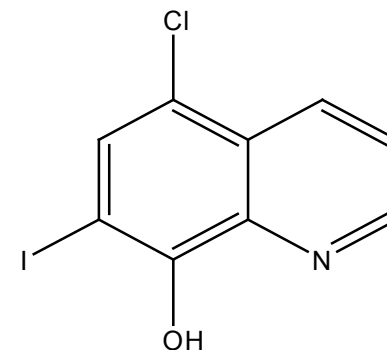
DESPLEX



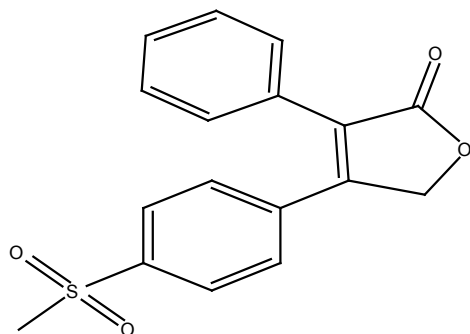
IRESSA



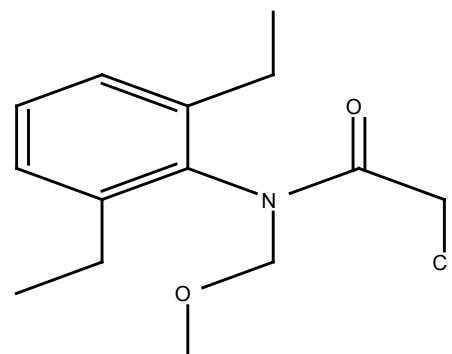
CLIOQUINOL



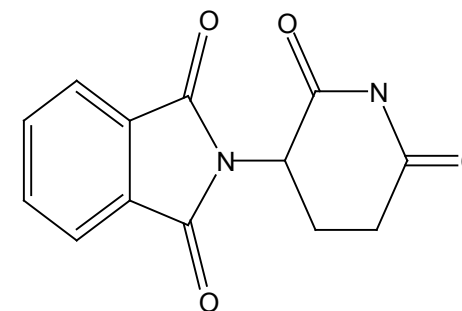
VIOXX



ALACHLOR



ISOMIN



Prediction Results on Side-Effect Drugs

ADMEWORKS: Worksheet - Microsoft Internet Explorer

Side-Effects Drugs have Wrong **CYP3A4** Property

Worksheet: **adverse 7 comps**

Selected Page: 1/1

View: **CYP3A4(INHIBITOR/LIGAND)**
 CARCINOGENICITY(FN/FP MODELS)
 Ames TEST (TA98 & TA100)

	ID	Name	3A4 Inhibitor	Carcinogenicity-FN	Carcinogenicity-FP	AMES-TA98	AMES-TA100
<input type="checkbox"/>	1	CLIOQUINOL	+	-*	-*	+	+
<input type="checkbox"/>	2	DESPLEX	+	+	-	-	-
<input type="checkbox"/>	3	IRESSA	+	-	-	+	+
<input type="checkbox"/>	4	ISOMIN	+	-	-	-	-
<input type="checkbox"/>	5	ALACHLOR	+	+	-	-	+
<input type="checkbox"/>	6	VIOXX	+	-*	-*	-*	+

イントラネット

Structure Modification Introduce Mutagenicity in spite of the “CYP3A4” Property have no changed

The screenshot displays the ADMETWORKS software interface. At the top, a menu bar includes options like 'ファイル(E)', '編集(E)', '表示(V)', 'お気に入り(A)', 'ツール(T)', and 'ヘルプ(H)'. Below the menu is a toolbar with navigation icons. The main workspace is divided into two panes: 'ISOMIN.mol' on the left and 'ISOMIN 2' on the right. A large green arrow points from the 'Original Structure' (ISOMIN) to the 'Modified Structure' (ISOMIN 2). Below the structures is a table comparing various properties for different compounds. The table has columns for 'ID', 'Name', '3A4 Inhibitor', 'Carcinogenicity-FN', 'Carcinogenicity-FP', 'AMES-TA98', and 'AMES-TA100'. The 'ISOMIN' row (ID 4) is highlighted with a blue border, and the 'ISOMIN 2' row (ID 9) is highlighted with a red border. A yellow arrow points to the '3A4 Inhibitor' column for ISOMIN 2, and a red arrow points to the 'Carcinogenicity-FN' column for ISOMIN 2. A black arrow points from the 'Original Structure' to the 'ISOMIN' row, and a blue arrow points from the 'Modified Structure' to the 'ISOMIN 2' row.

ID	Name	3A4 Inhibitor	Carcinogenicity-FN	Carcinogenicity-FP	AMES-TA98	AMES-TA100
<input type="checkbox"/>	1 C. IOQUINOL	+	-	-	+	+
<input type="checkbox"/>	2 DESPLEX	+	+	-	-	-
<input type="checkbox"/>	3 IREPSA	+	-	-	+	+
<input checked="" type="checkbox"/>	4 ISOMIN	+	-	-	-	-
<input type="checkbox"/>	5 ALACHLOR	+	+	-	-	+
<input type="checkbox"/>	6 VIOXX	+	-	-	-	+
<input checked="" type="checkbox"/>	9 ISOMIN 2	+	+	-	-	-

Flow of the “Parallel & One Step” D.D.

“Parallel & One Step” D.D.

In Silico prediction

Wet Experiment

Activity

ADME

Toxicity

Property

SYNTHESIS

Confirmation

TEST

Phase
I/II/III

Comparative Simulation Test of “Parallel D.D.” and “Step by Step D.D.” Approach



■ “Parallel D.D.”

1. In Silico Screening of ADME-T Property.
2. Prediction Ratio will be Changed from 70%, 80%, 90% and 100%.

■ “Step by Step D.D.”

1. Screening by Wet Experiment of ADME-T Property.
2. Success Rate of Experiment will be Fixed to 50%.

Used Monitoring Parameter of Comparative Simulation Test of D.D.

■ Efficiency Ratio by Parallel D.D.


$$\text{Efficiency Ratio} = \frac{\text{'Parallel' Drug Design}}{\text{'Step by Step' Drug Design}}$$

Condition 1: Number of test: Total 8

ADME related test = 5 Items

Toxicity related test = 3 Items

Condition 2: Prediction Ratio **100%, 90%, 80%, 70%**

'Step by Step' Method was Fixed on **50%**

Condition 3: Number of Redesign Process

The case1; 1 trial (Pass through by 1 trial)

The case2; 3 trial (Pass through by 3 trials)

Case1 : Only One Time Screening to reach Phase I



Parallel Approach:

			Efficiency Ratio
1. Prediction Ratio 100% ADME-T In Silico Screening = 1.0000	→	$\frac{1.0000}{0.0039}$	= 256 times
2. Prediction Ratio 90% ADME-T In Silico Screening = 0.4308	→	$\frac{0.4308}{0.0039}$	= 111 times
3. Prediction Ratio 80% ADME-T In Silico Screening = 0.1678	→	$\frac{0.1678}{0.0039}$	= 43 times
4. Prediction Ratio 70% ADME-T In Silico Screening = 0.0576	→	$\frac{0.0576}{0.0039}$	= 15 times

Case2 : Three Times Feedback Screening to reach Phase1



Parallel Approach:

1. Prediction Ratio **100%**

ADME-T In Silico Screening = 1.0000



$$\frac{1.0000}{59 \text{ E-}9}$$

= **16858005**
times

2. Prediction Ratio **90%**

ADME-T In Silico Screening = 0.4308



$$\frac{0.4308}{59 \text{ E-}9}$$

= **1347824**
times

3. Prediction Ratio **80%**

ADME-T In Silico Screening = 0.1678



$$\frac{0.1678}{59 \text{ E-}9}$$

= **79649**
times

4. Prediction Ratio **70%**

ADME-T In Silico Screening = 0.0576



$$\frac{0.0576}{59 \text{ E-}9}$$

= **3221**
times

Results of Simulation Test of “Parallel & One Step” Drug Design

■ Screening Test (8 Items)

	“Parallel D.D.”		“Step by Step D.D.”
Efficiency Ratio of Pre-clinical Stage			
Case 1	15 Times	~	256 Times
Case 2	3,221 Times	~	16,858,005 Times

Case 1:

Drug Development is cleared only one time in silico screening and ADME-T wet screening process.

Case 2:

Drug Development is cleared by three time in silico screening and ADME-T wet screening processes.