

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

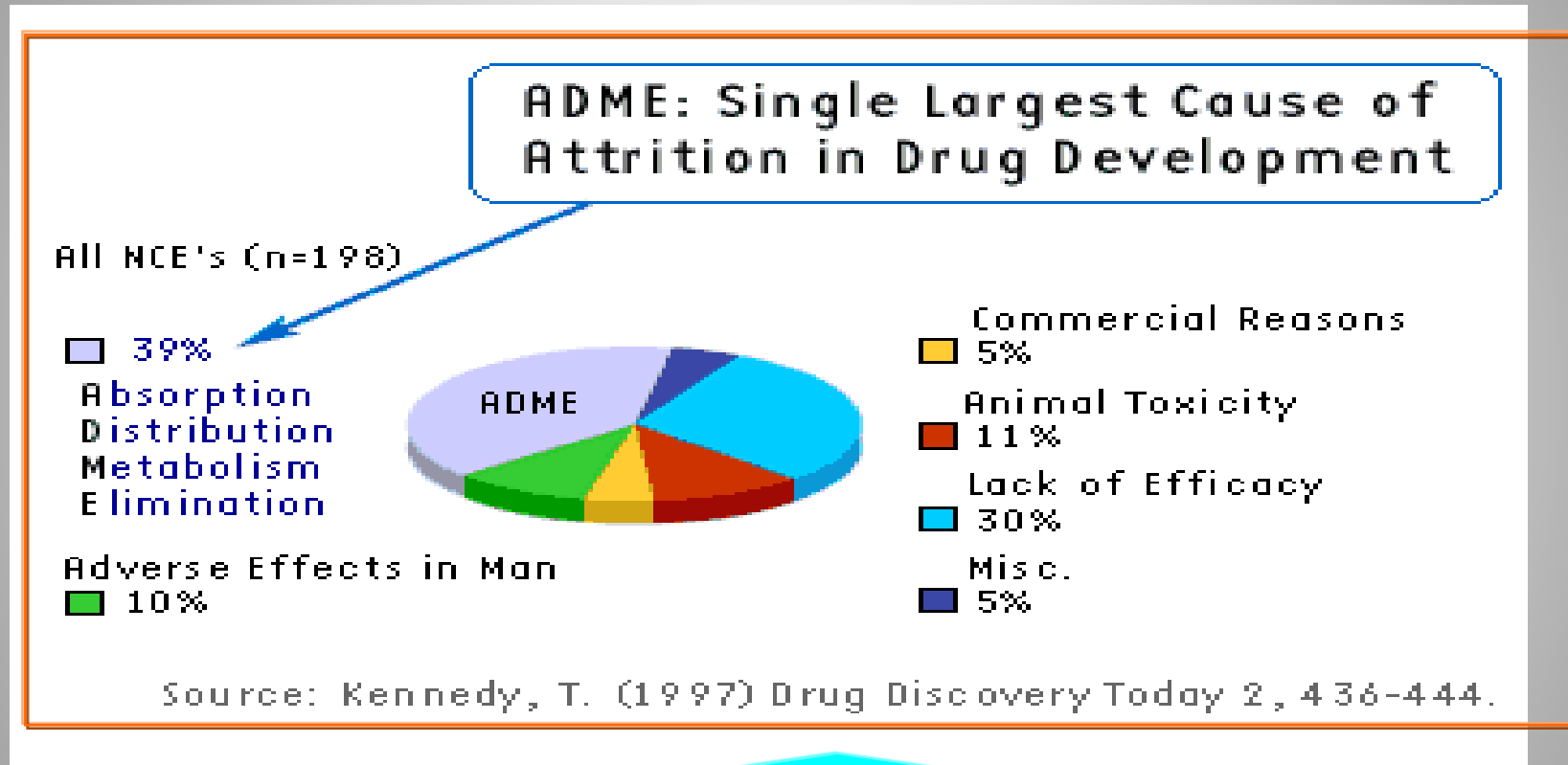
## **The new trend of drug design by A-ADME-T-P total prediction**

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# Reasons of Drug Development Failure



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

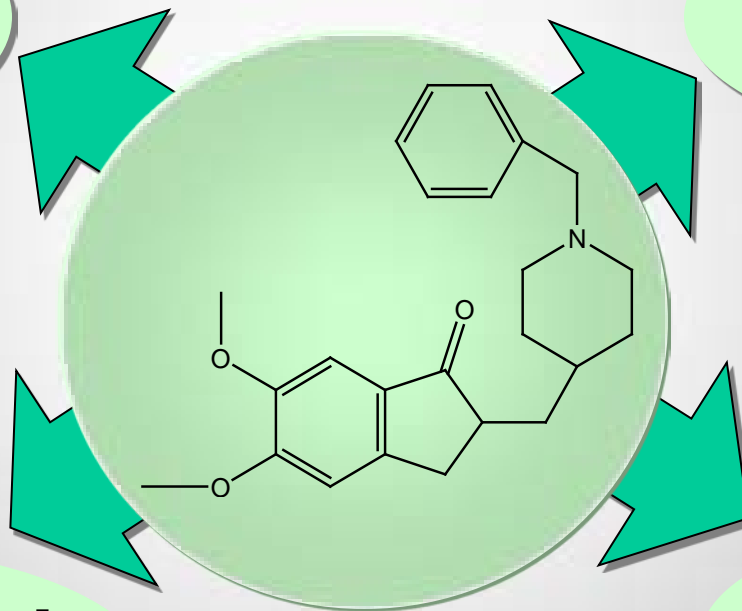
# Drug properties and compound structure

ADME  
properties

Pharmacological  
activity

Physico chemical  
properties

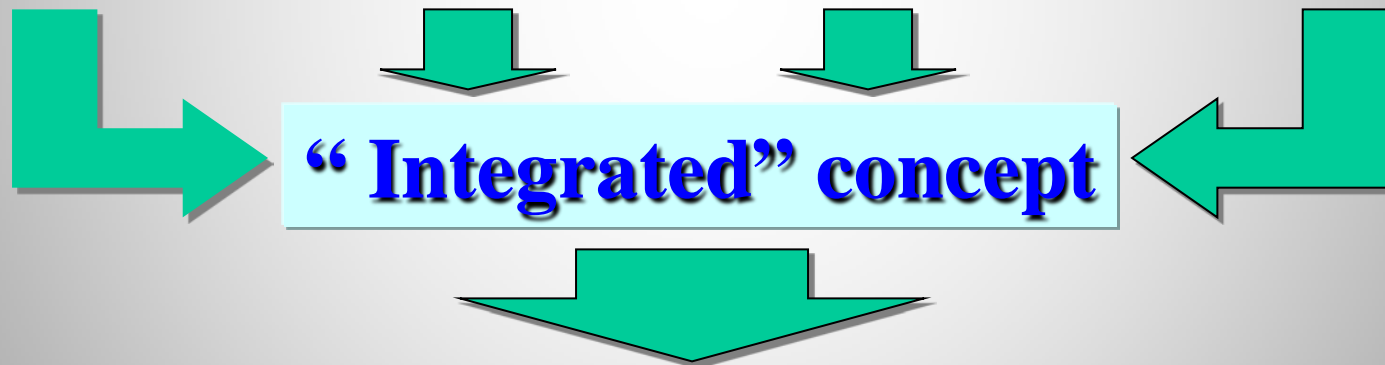
Toxicity



# “Integrated” concept for drug development

Activity + ADME + Toxicity + Property

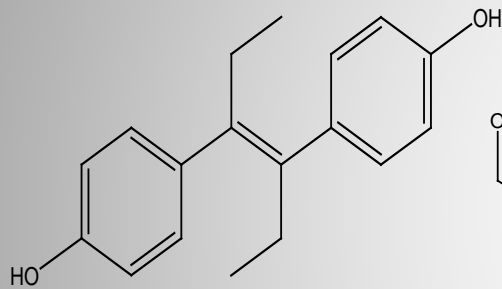
All drug properties shall be considered at the same time



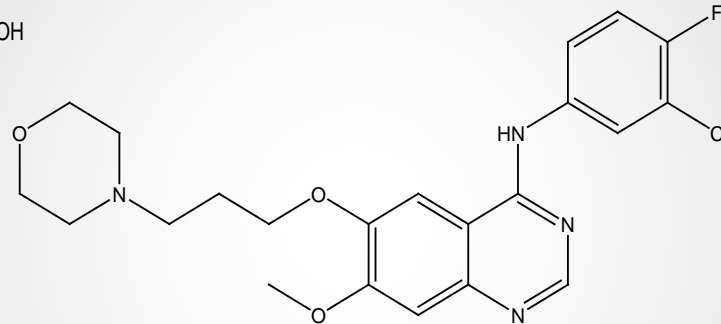
“Integrated” in silico screening & drug design

# Drugs which possesses **Side-Effect**

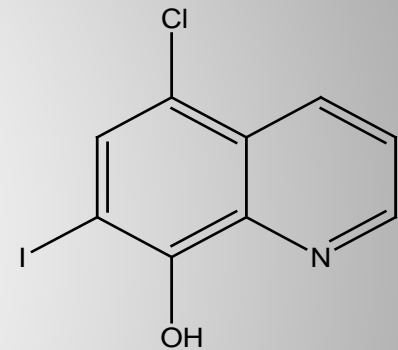
**DESPLEX**



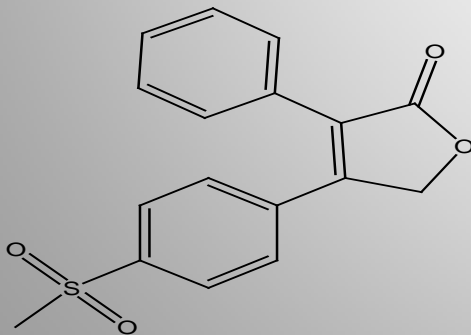
**IRESSA**



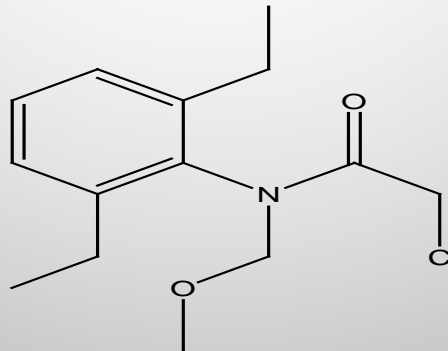
**CLIOQUINOL**



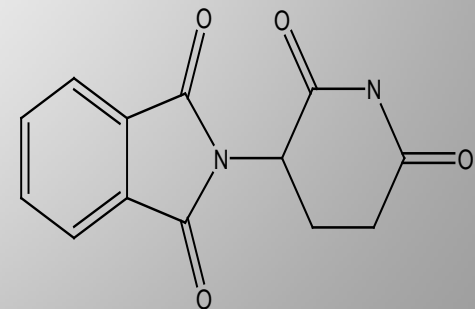
**VIOXX**



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

View: All

	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	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	+	-	-	-	+

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

The screenshot displays the ADMEWORKS interface. On the left, the 'Original Structure' is shown as a 3D ball-and-stick model. A large green arrow points to the 'Modified Structure' on the right, which is a similar molecule with a different side chain. Below these structures is a table with columns for various ADME/Tox properties. A blue box highlights the 'ISOMIN' row, and a red box highlights the 'ISOMIN 2' row. A yellow arrow points from the 'ISOMIN' row to the 'ISOMIN 2' row, indicating the transition. A red arrow points to the 'Carcinogenicity-FN' column for 'ISOMIN 2', and another red arrow points to the 'AMES-TA100' column for 'ISOMIN 2'.

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

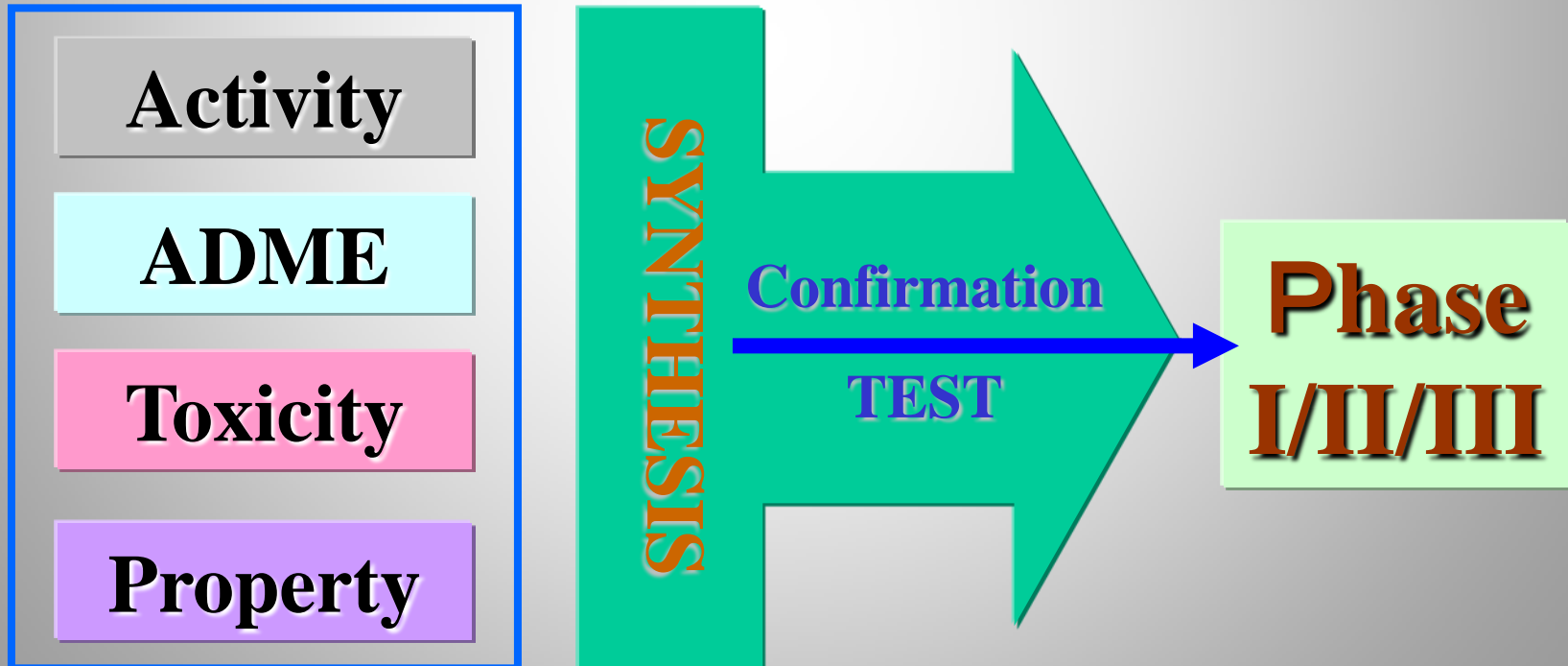
# Flow of the “Parallel & One Step” D.D.

## “Parallel & One Step” D.D.

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In Silico prediction

Wet Experiment





## 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 PhaseI

## Parallel Approach:

**Efficiency  
Ratio**

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

## Case2 : Three Times Feedback Screening to reach PhaseI

### Parallel Approach:

**Efficiency  
 Ratio**

<p><b>1. Prediction Ratio 100%</b>                      ADME-T In Silico Screening = 1.0000</p>	→	$\frac{1.0000}{59 \text{ E-}9}$	= <b>16858005</b> times
<p><b>2. Prediction Ratio 90%</b>                      ADME-T In Silico Screening = 0.4308</p>	→	$\frac{0.4308}{59 \text{ E-}9}$	= <b>1347824</b> times
<p><b>3. Prediction Ratio 80%</b>                      ADME-T In Silico Screening = 0.1678</p>	→	$\frac{0.1678}{59 \text{ E-}9}$	= <b>79649</b> times
<p><b>4. Prediction Ratio 70%</b>                      ADME-T In Silico Screening = 0.0576</p>	→	$\frac{0.0576}{59 \text{ E-}9}$	= <b>3221</b> times

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

## ■ Screening Test ( 8 Items)

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

### 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.



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