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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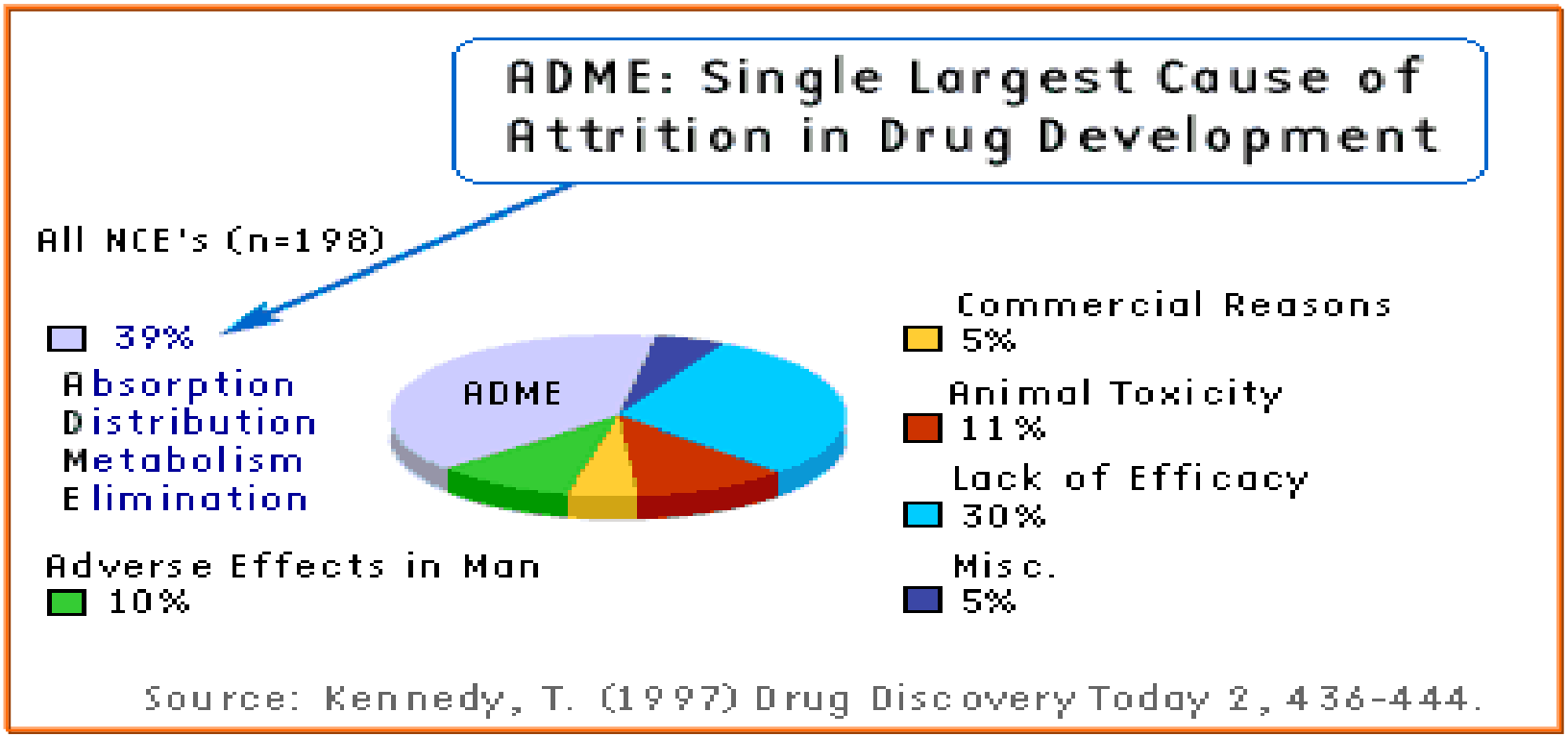
FUJITSU

THE POSSIBILITIES ARE INFINITE

Reasons of Drug Development Failure

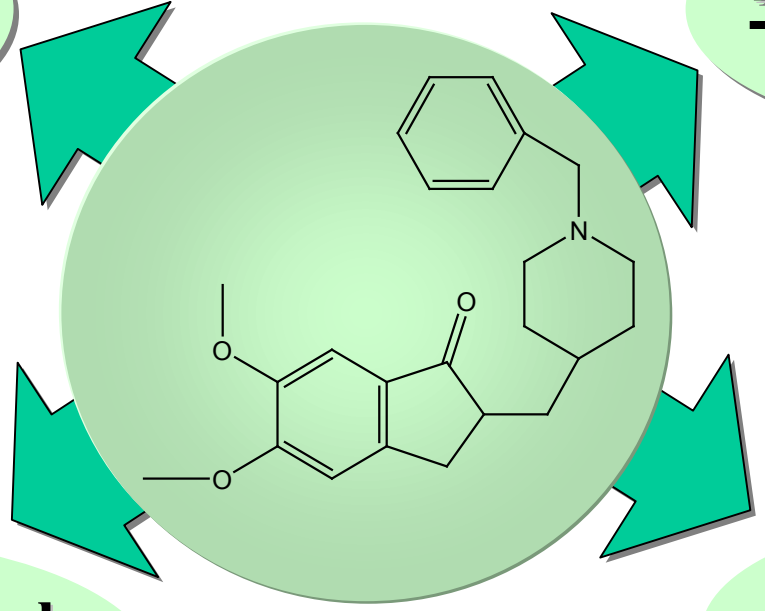


ADME, Toxicity (60%) > Activity (30%)

Drug properties and compound structure

ADME properties

Pharmacological activity



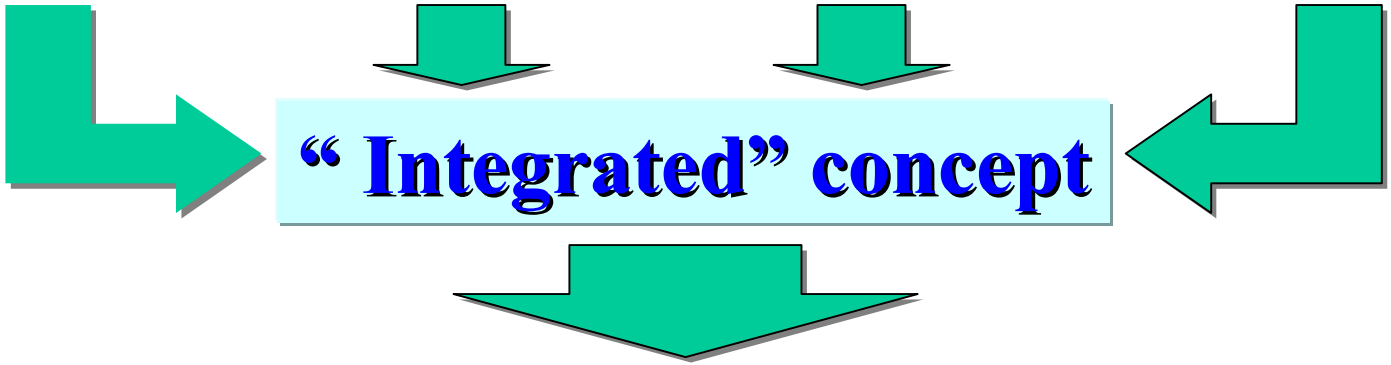
Physico chemical properties

Toxicity

“Integrated” concept for drug development

Activity + ADME + Toxicity + Property

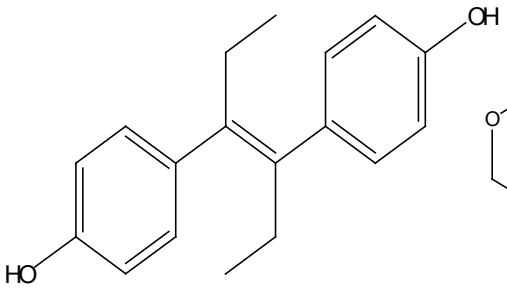
All drug properties shall be considered at the same time



“ Integrated” in silico screening & drug design

Drugs which possesses Side-Effect

DESPLEX



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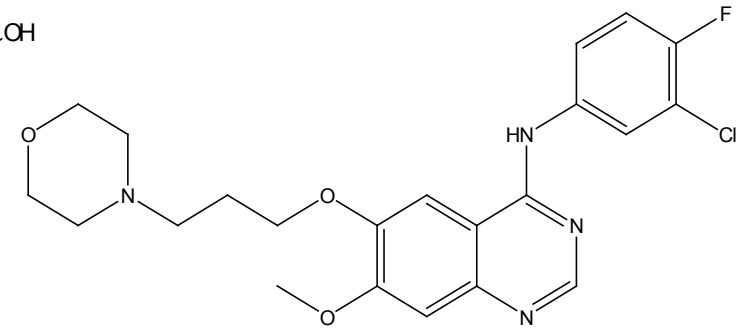
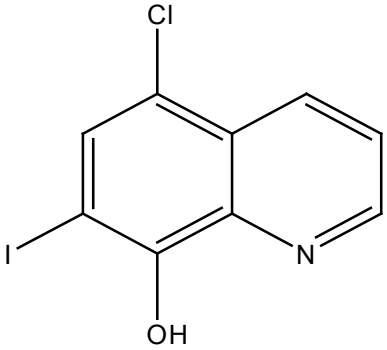
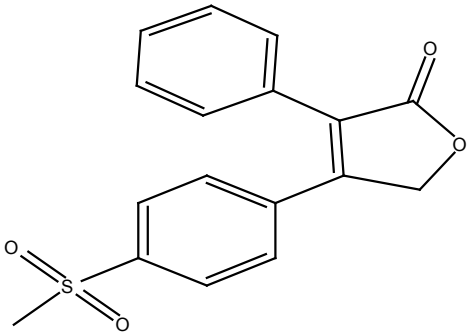


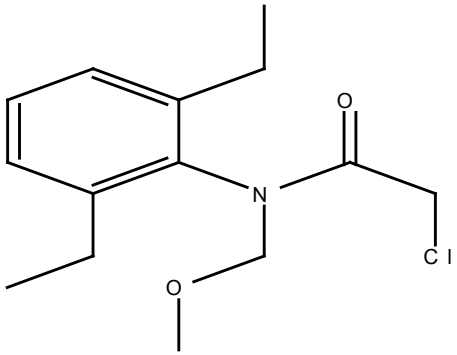
CLIOQUINOL



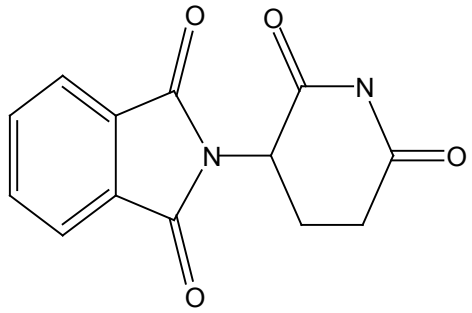
VIOXX



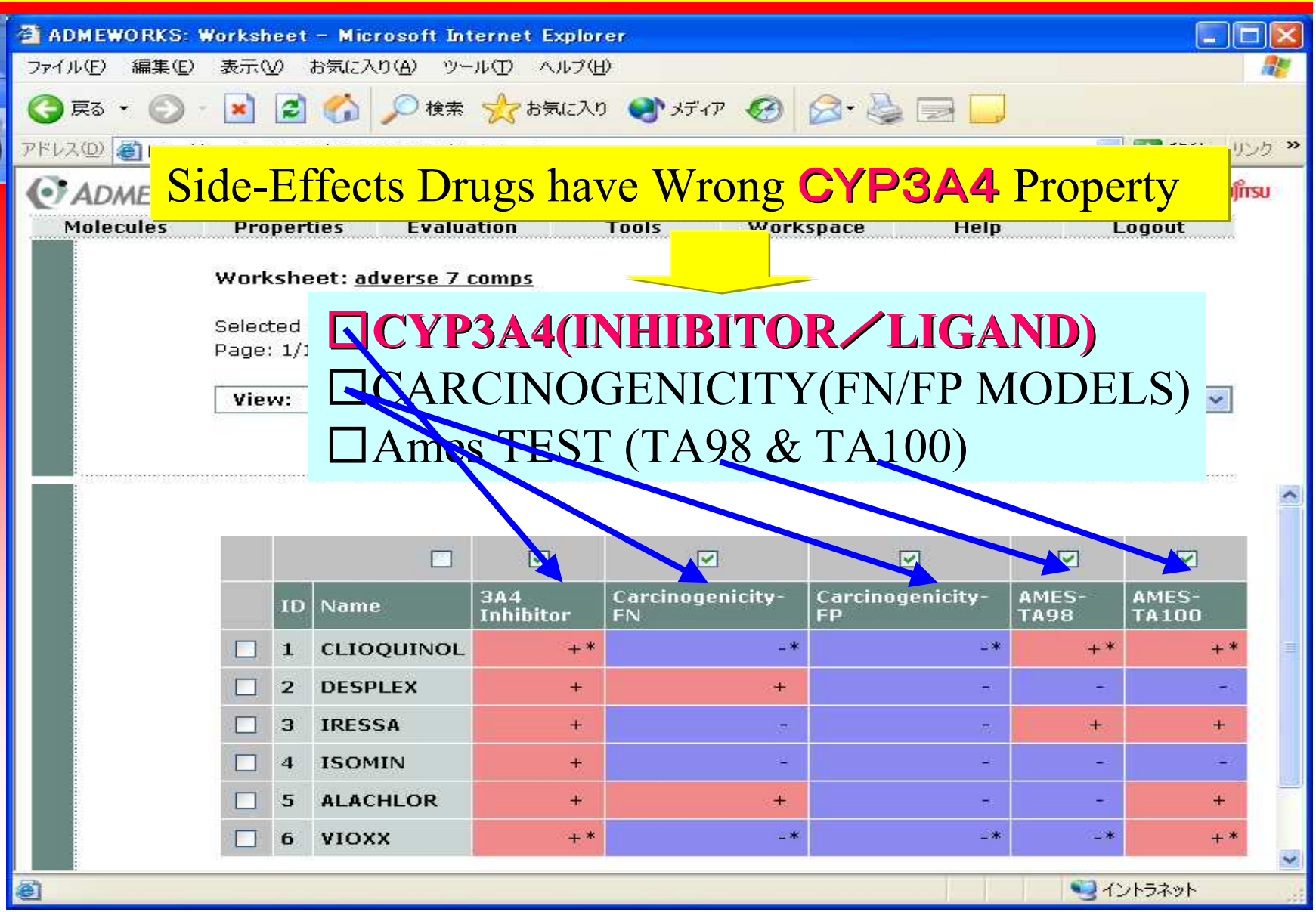
ALACHLOR



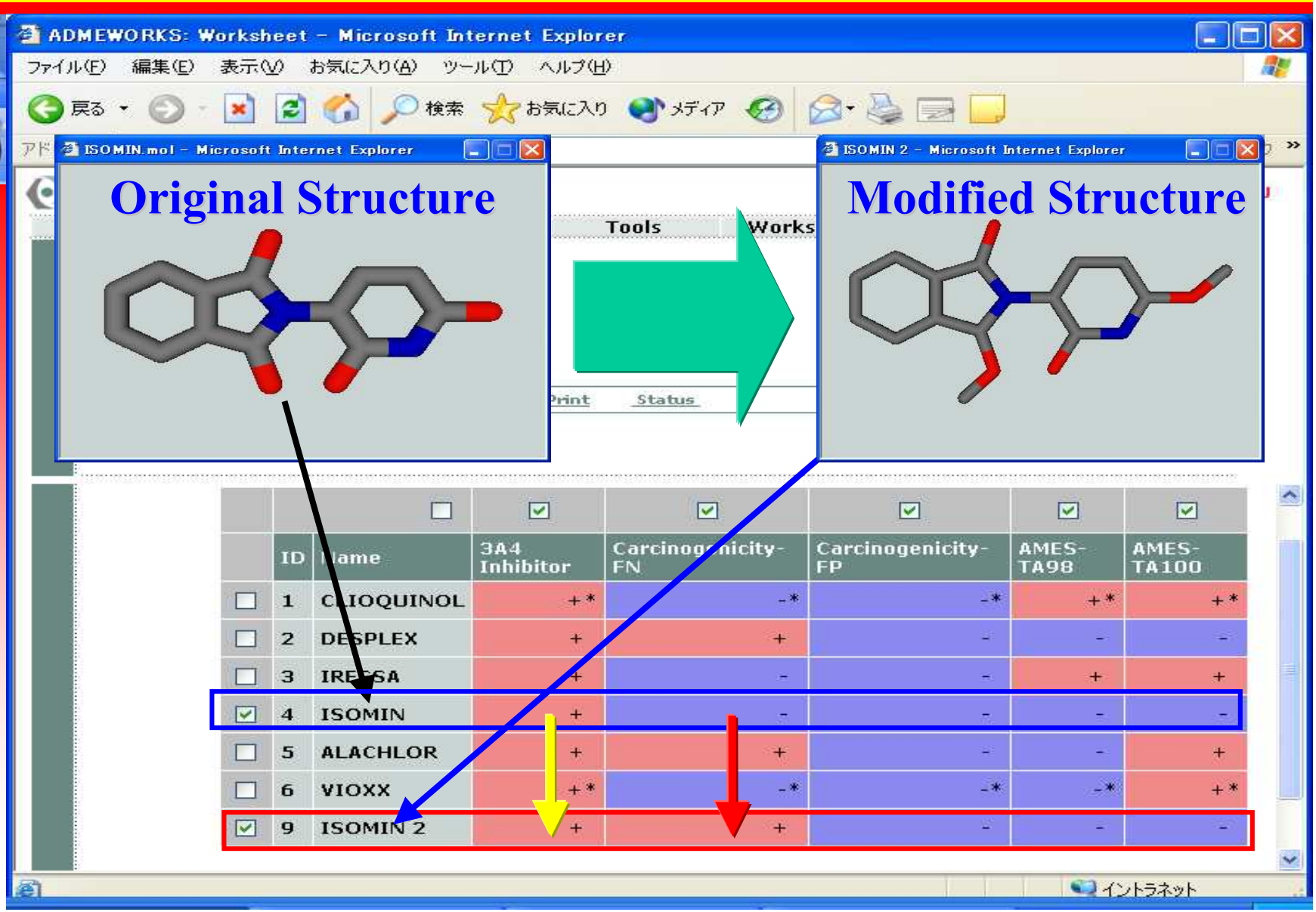
ISOMIN



Prediction Results on Side-Effect Drugs

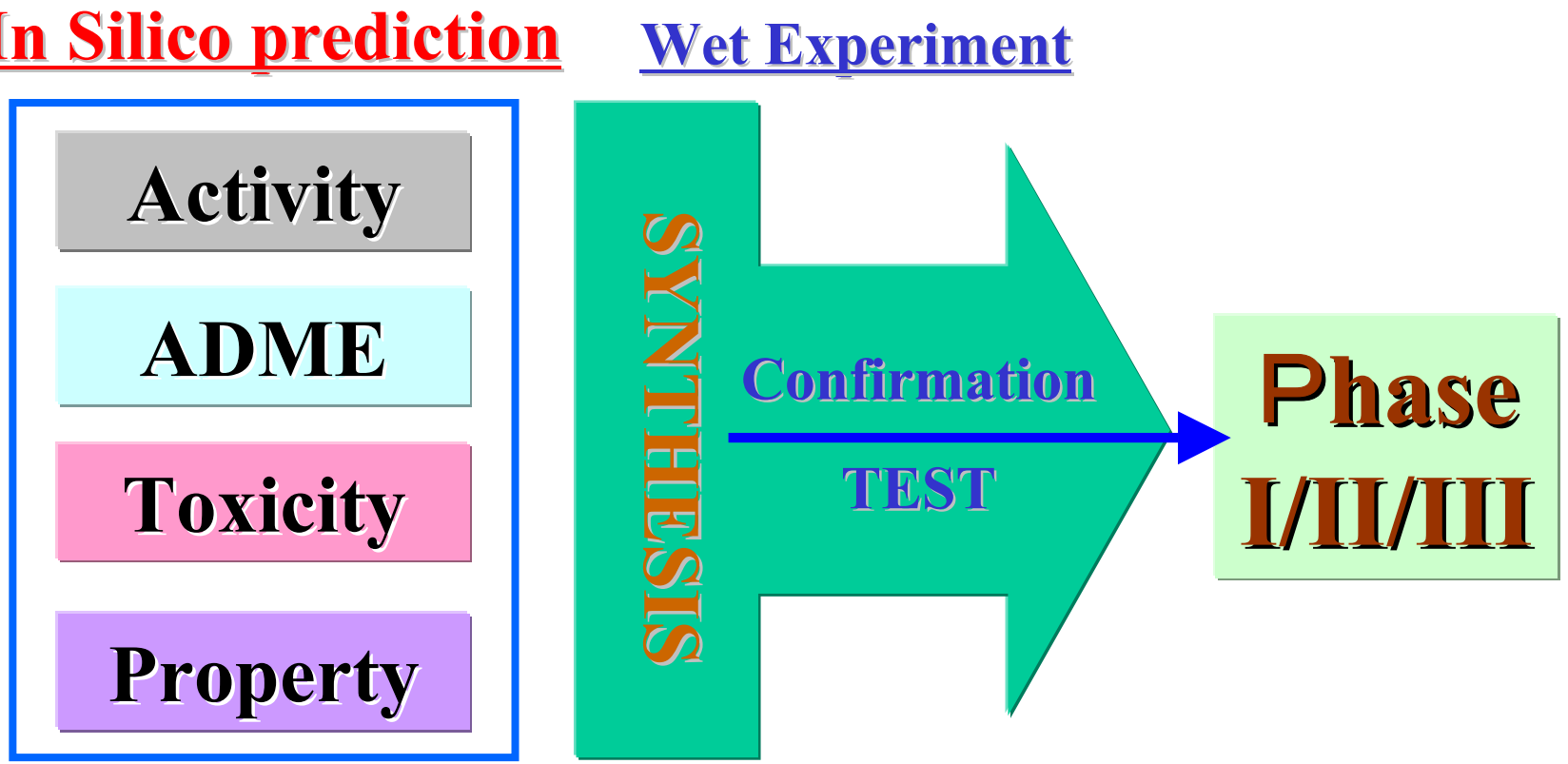


Structure Modification Introduce Mutagenicity in spite of the "CYP3A4" Property have no changed



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

“Parallel & One Step” D.D.



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
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 PhaseI

Parallel Approach:

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