# Human Health Models

## *in vitro* Mutagenicity Accounting for Metabolic Activation of Chemicals

Laboratory of Mathematical Chemistry, Bulgaria

# The principle (Q)SAR Concept developed in LMC:

## To analyze toxicity as a result of metabolic activation

## Combining on same modeling platform:

- **Toxicokinetics – specific metabolism**
- **Toxicodynamic – interaction with macromolecules**

## TIssue MEtabolism Simulator


1. Mekenyan, O.G., S. Dimitrov, R. Serafimova, E. Thompson, S. Kotov, N. Dimitrova, J. Walker. Identification of the structural requirements for mutagencitiy, by incorporating molecular flexibility and metabolic activation of chemicals I. TA100 Model. *Chem. Res.Toxicol.* 17(6):753-766 (2004).
2. Serafimova, R., M. Todorov, T. Pavlov, S. Kotov, E. Jacob, A. Aptula, and O. Mekenyan, Identification of the Structural Requirements for Mutagencitiy, by Incorporating Molecular Flexibility and Metabolic Activation of Chemicals. II. General Ames Mutagenicity Model Chem. Res. Toxicol. 20 (4), 662–676 (2007).

# Toxicokinetics

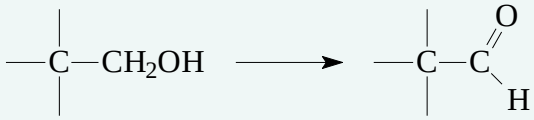
- Prioritized list of non-enzymatic (abiotic) and enzymatic molecular transformations

- Molecular transformations are characterized by:
  - Source and product fragments
  - Inhibiting “masks” preventing the application of metabolic reactions if necessary

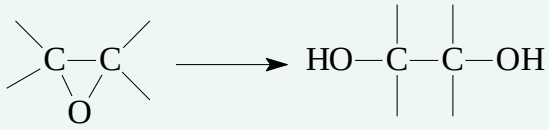
- Substructure-matching software engine applies the simulated biochemical

- Reproduces the documented metabolic pathways and toxicity endpoint resulting from metabolic activation of chemicals

Aliphatic C-oxidation



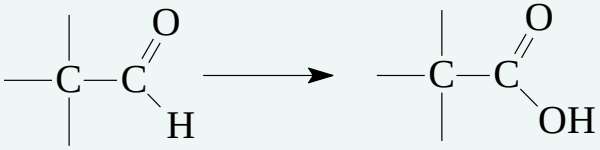
Epoxide Hydration



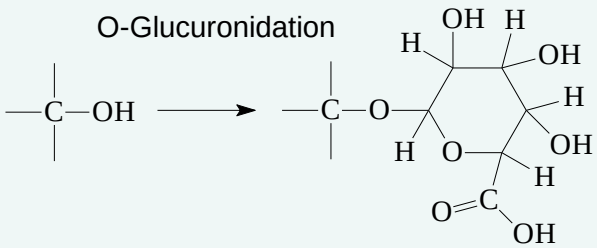
Epoxidation

Aliphatic C-oxidation

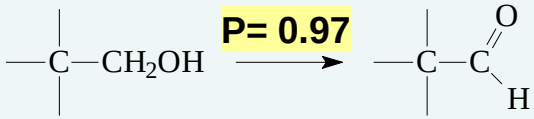
Aliphatic C-oxidation



O-Glucuronidation



Aliphatic C-oxidation

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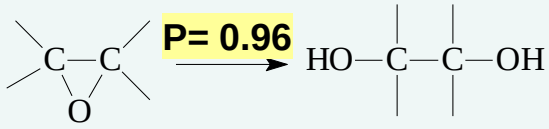


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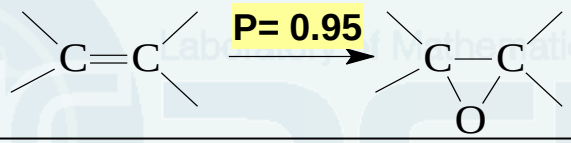
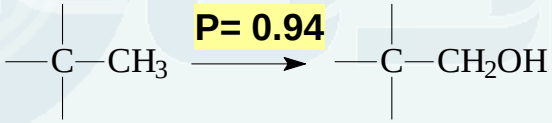



Aliphatic C-oxidation

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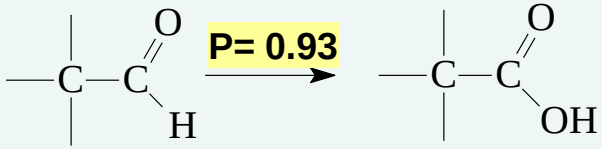
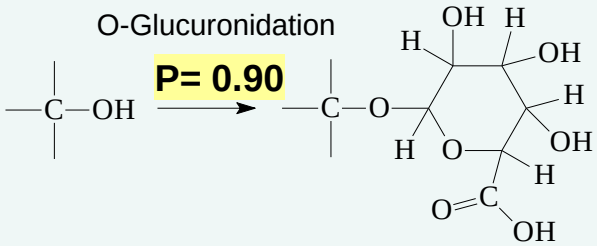
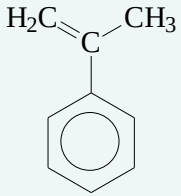



O-Glucuronidation

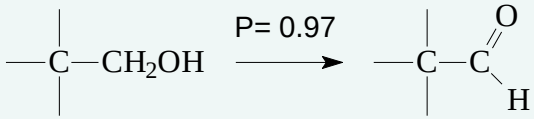


| Substrate | Principle transformations | Metabolites |
|---|---|---|

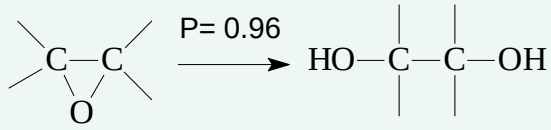
- Isopropenylbenzene



Aliphatic C-oxidation




Epoxide Hydration

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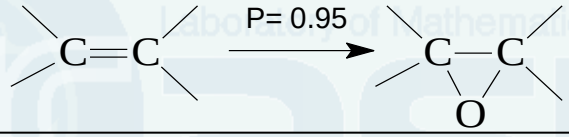
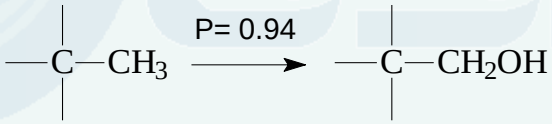
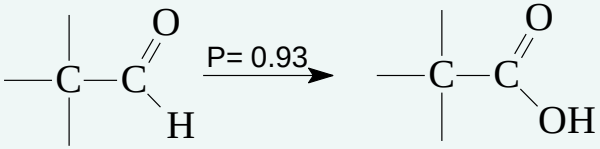


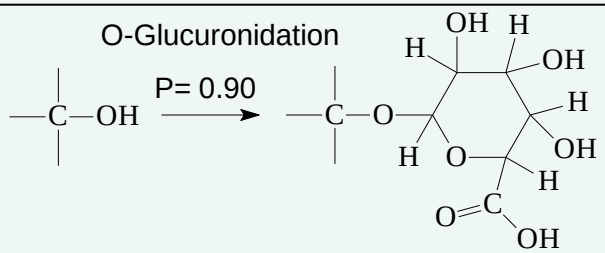

Aliphatic C-oxidation




Aliphatic C-oxidation

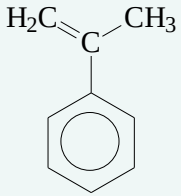



O-Glucuronidation



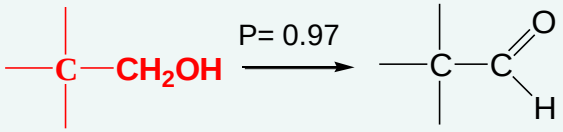
| Substrate | Principle transformations | Metabolites |
|---|---|---|

- Isopropenylbenzene



***Match? - No!***

Aliphatic C-oxidation

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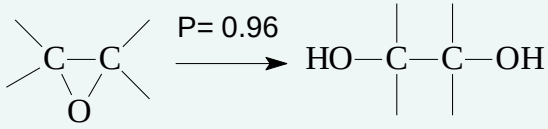


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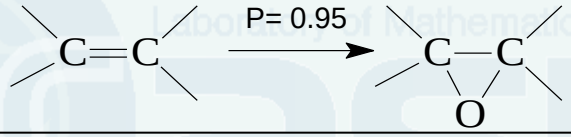
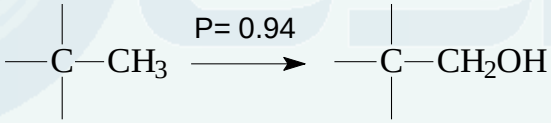
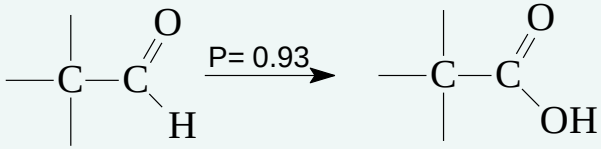


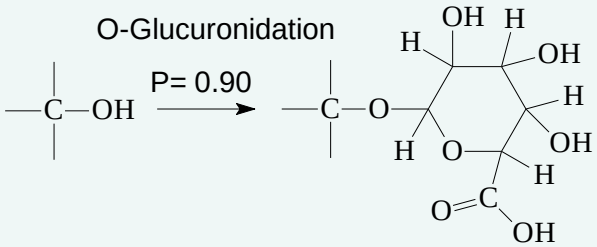

Aliphatic C-oxidation

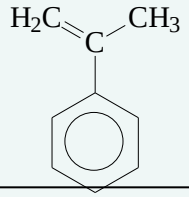
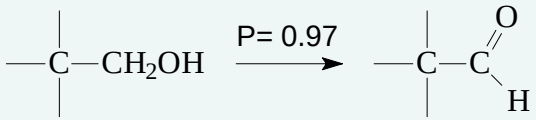
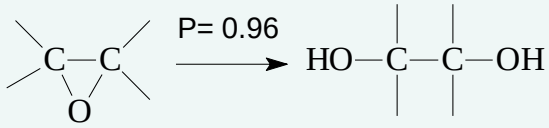
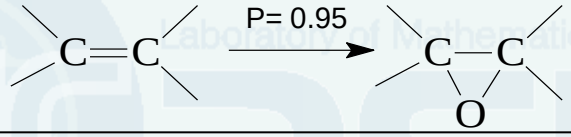
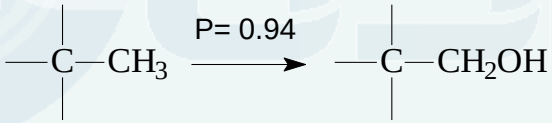
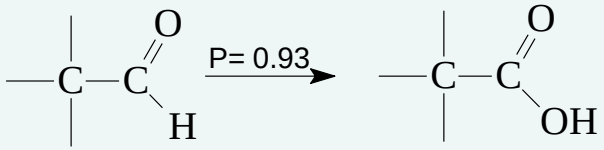
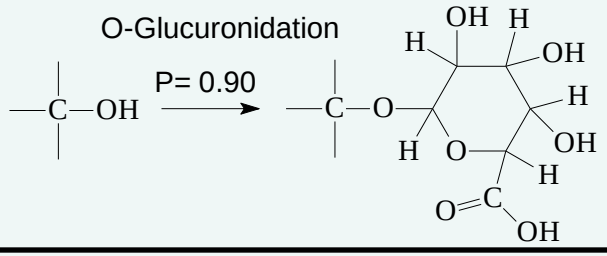


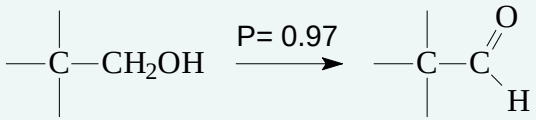
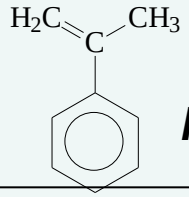
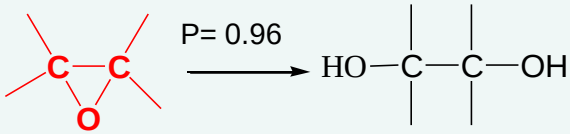
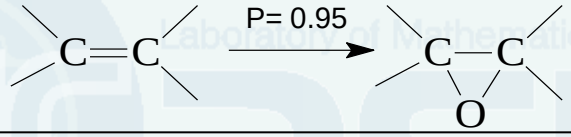
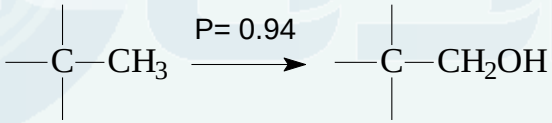
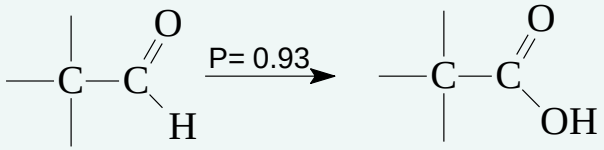
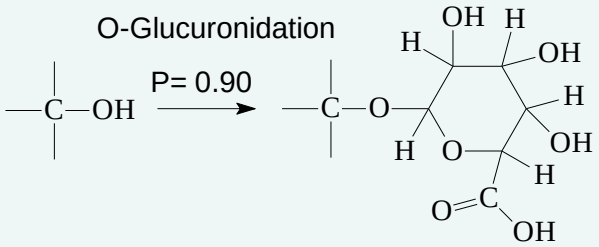

Aliphatic C-oxidation




O-Glucuronidation



| Substrate | Principle transformations | Metabolites |
|---|---|---|
|  | Aliphatic C-oxidation<br>  | |
| | Epoxide Hydration<br>  | |
| | Epoxidation<br>  | |
| | Aliphatic C-oxidation<br>  | |
| | Aliphatic C-oxidation<br>  | |
| | O-Glucuronidation<br>  | |

| Substrate | Principle transformations | Metabolites |
|---|---|---|
| | Aliphatic C-oxidation   | |
|  ***Match? - No!*** | Epoxide Hydration   | |
| | Epoxidation   | |
| | Aliphatic C-oxidation   | |
| | Aliphatic C-oxidation   | |
| | O-Glucuronidation   | |

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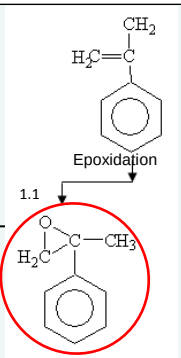
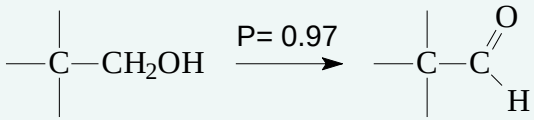
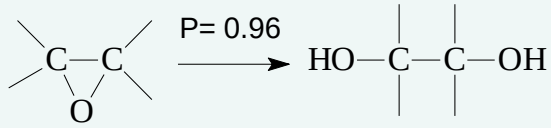
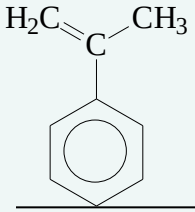



Aliphatic C-oxidation



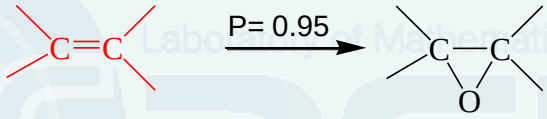

Epoxide Hydration



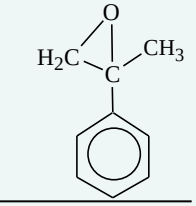



***Match? - Yes!***

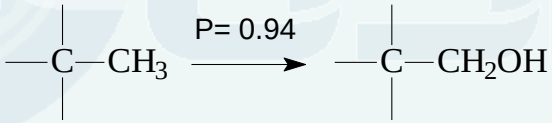
Epoxidation



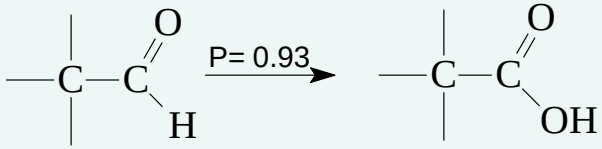

**RESULT**



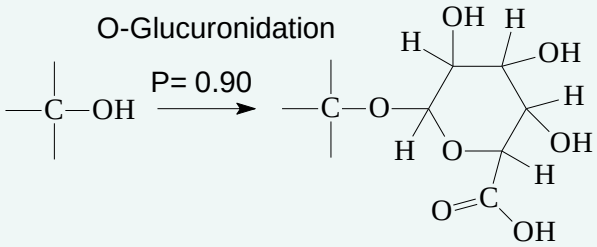
Aliphatic C-oxidation




Aliphatic C-oxidation

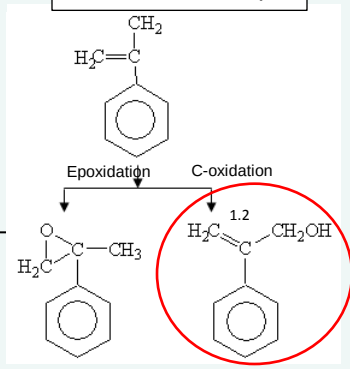



O-Glucuronidation

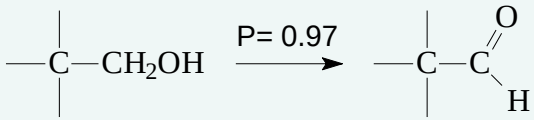


Substrate | Principle transformations | Metabolites

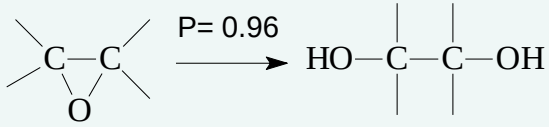
Generated map



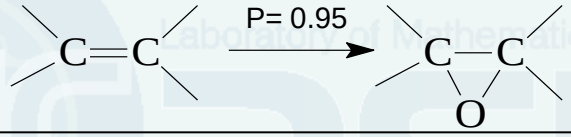

Aliphatic C-oxidation

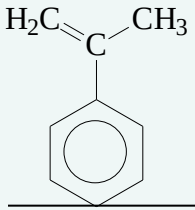



Epoxide Hydration



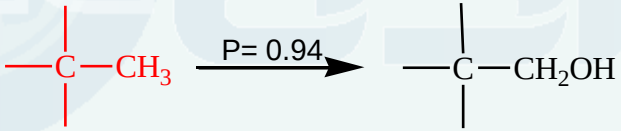

Epoxidation



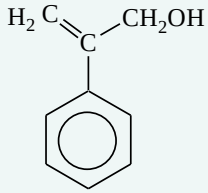



Aliphatic C-oxidation

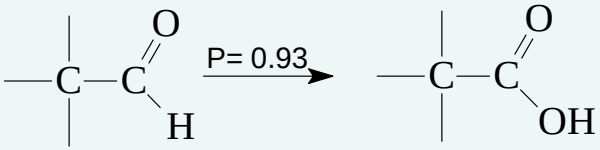
***Match? - Yes!***



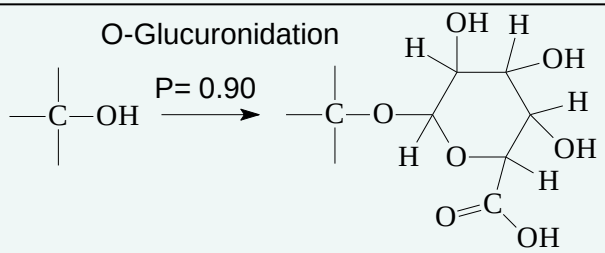

**RESULT**



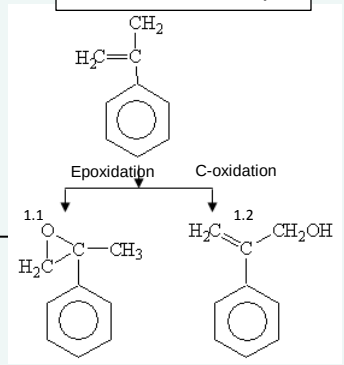
Aliphatic C-oxidation



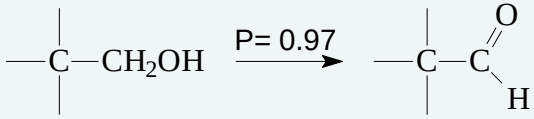

O-Glucuronidation



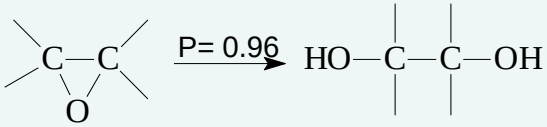
Generated map



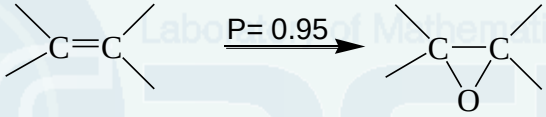

Aliphatic C-oxidation



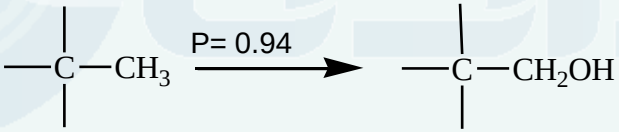

Epoxide Hydration

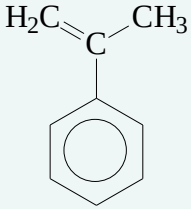



Epoxidation



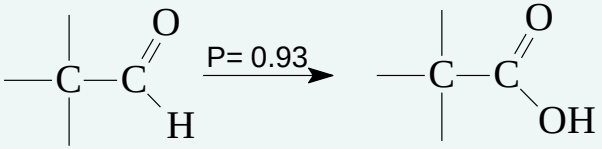

Aliphatic C-oxidation



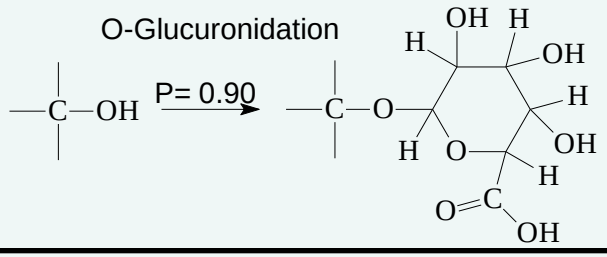



***Match? - No!***

Aliphatic C-oxidation

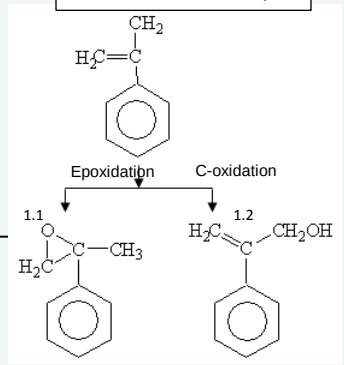



O-Glucuronidation

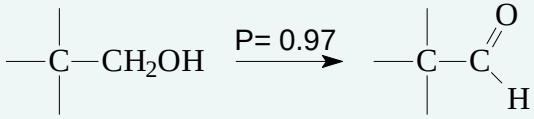


| Substrate | Principle transformations | Metabolites |
|---|---|---|

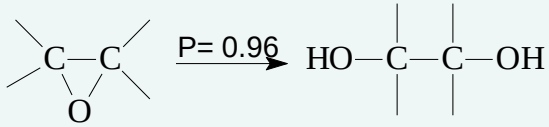
Generated map



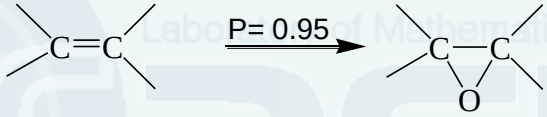

Aliphatic C-oxidation



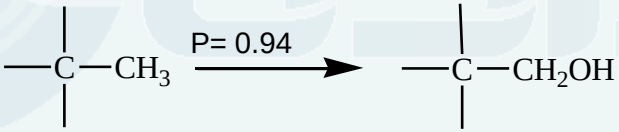

Epoxide Hydration



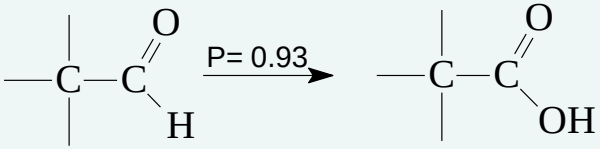

Epoxidation

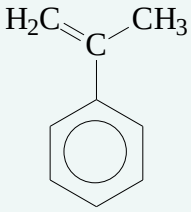



Aliphatic C-oxidation



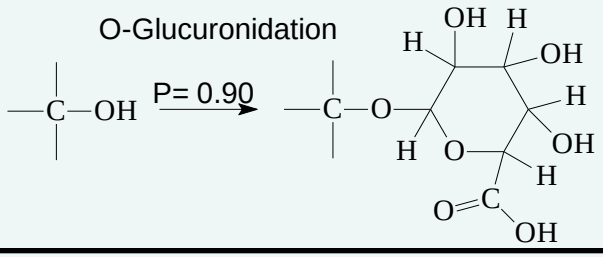

Aliphatic C-oxidation



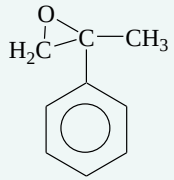



***Match? - No!***

O-Glucuronidation

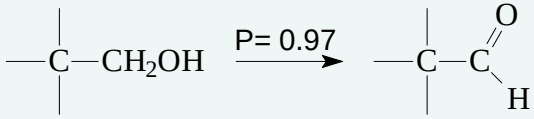


- Metabolite 1.1

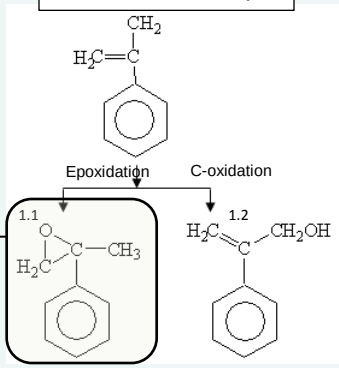


***Match? - No!***

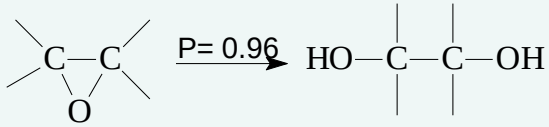
Aliphatic C-oxidation



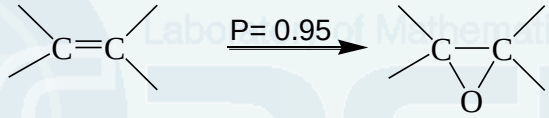

Generated map



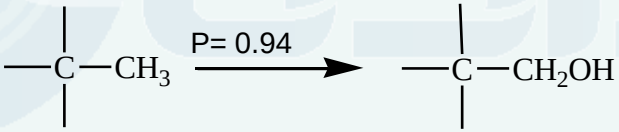

Epoxide Hydration



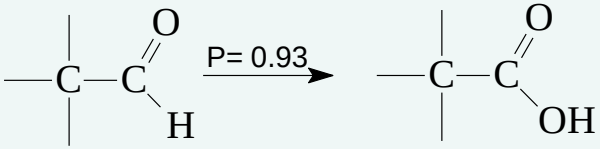

Epoxidation



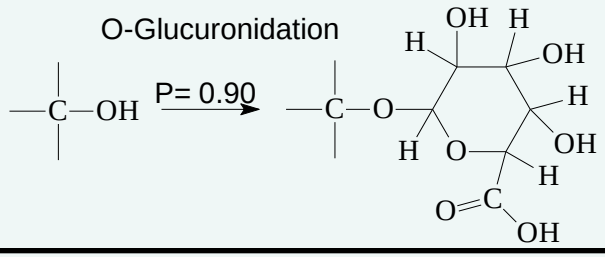

Aliphatic C-oxidation




Aliphatic C-oxidation

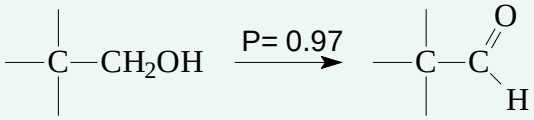


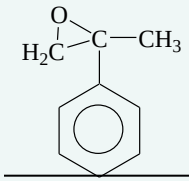

O-Glucuronidation



- Metabolite 1.1

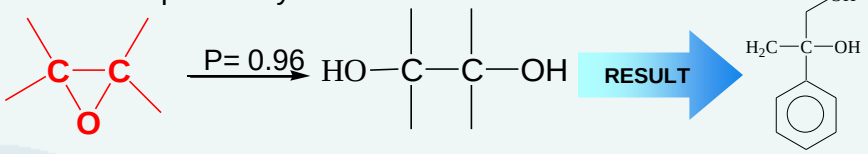
Aliphatic C-oxidation



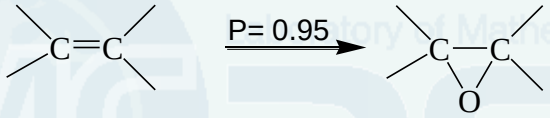



***Match?- Yes!***

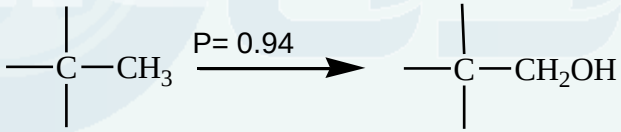
Epoxide Hydration



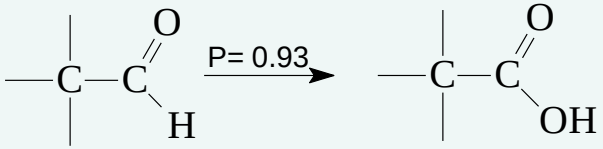

Epoxidation



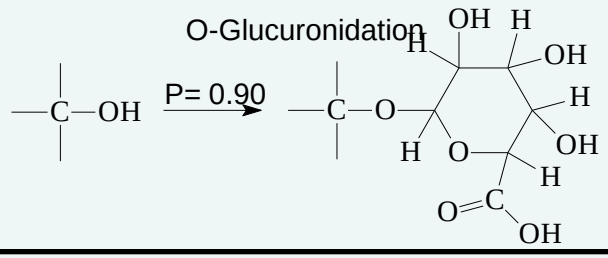

Aliphatic C-oxidation



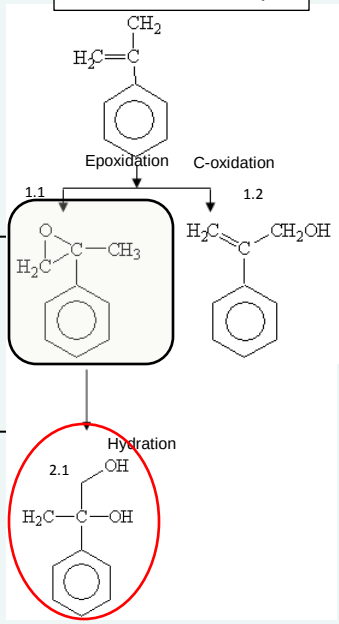

Aliphatic C-oxidation




O-Glucuronidation




Generated map



# Toxicodynamics

1. Identification of alerting groups in parent structures responsible for interactions with DNA

2. Predicting metabolic activation of chemicals by combining alerting groups with metabolic simulator

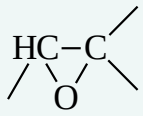
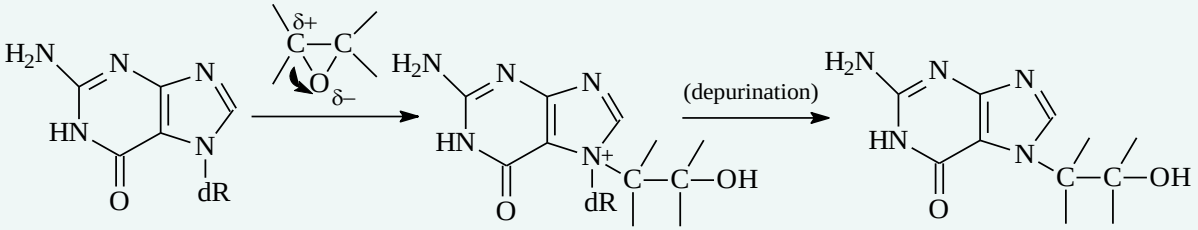
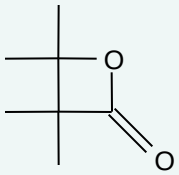
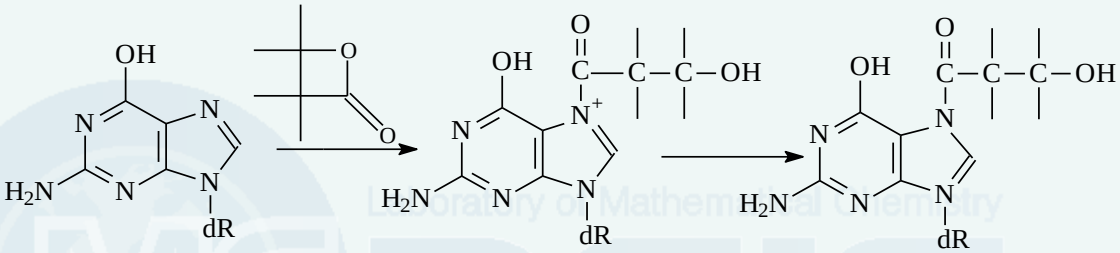
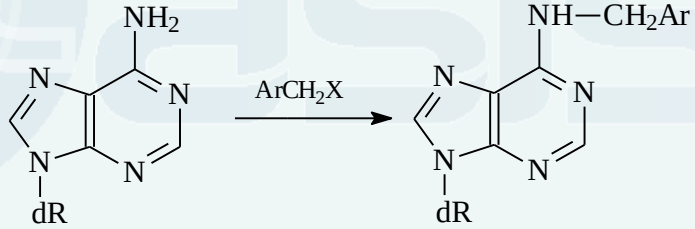
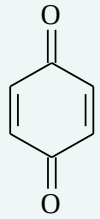
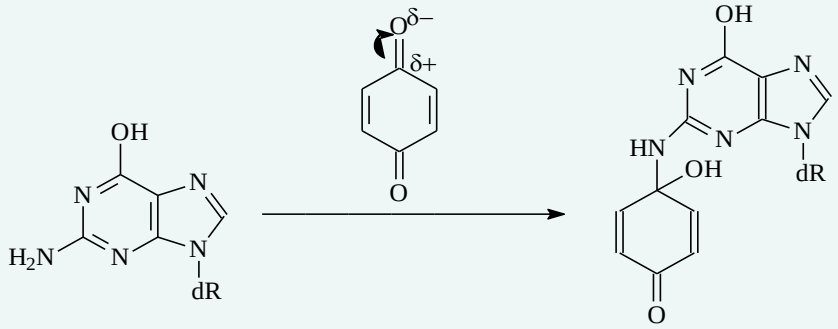
# Toxicodynamics

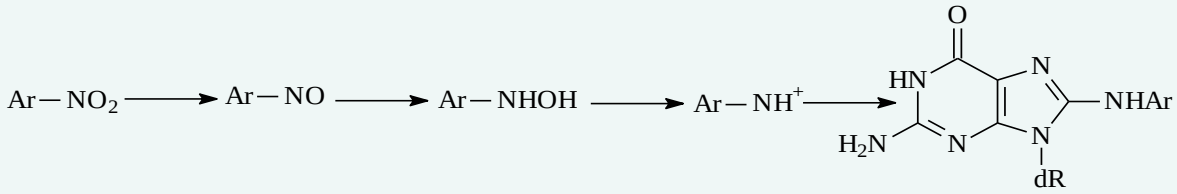
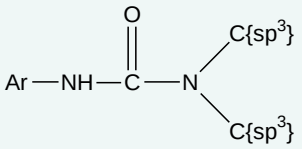
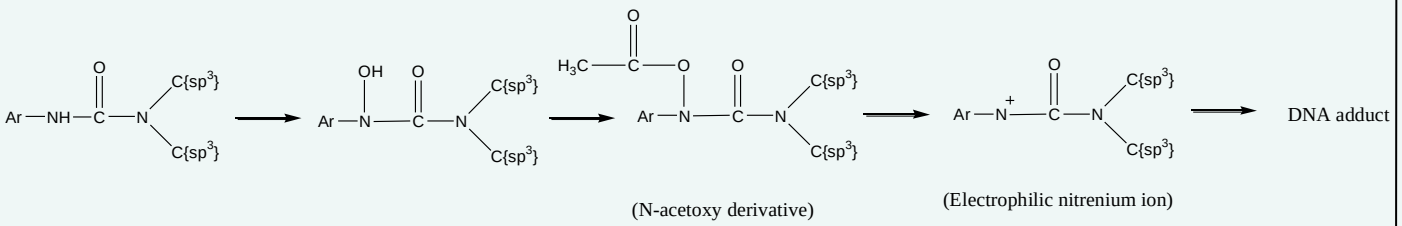
1. Identification of alerting groups in parent structures responsible for interactions with DNA

2. Predicting metabolic activation of chemicals by combining alerting groups with metabolic simulator

## Alerting Groups

## Mechanism: Direct-Acting Mutagens

| | |
|---|---|
|  Epoxides |  |
|  Lactones |  |
| $ArCH_2X$ X= Cl, Br, I Benzyl halides |  |
|  Quinones |  |

| Alerting Groups | Mechanism: Alerts acting after bacterial enzymatic activation |
|---|---|
| —$NO_2$ Nitro group |  |
| —NO Nitroso grou | NHAr |
| Ar—$NH_2$ Aromatic ami | HAr |
|  Urea derivatives |  |

- These transformations belong to inherent mutagenicity.
- They are assumed and not simulated.
- The simulated metabolism in TIMES models is conditioned by external metabolic machinery (S9) only.

# Toxicodynamics

1. Identification of alerting groups in parent structures responsible for interactions with DNA

2. Predicting metabolic activation of chemicals by combining alerting groups with metabolic simulator

# Simulating liver metabolism and interaction with DNA