

## Volume 7

*A survey of  
the biotransformations  
of drugs and chemicals  
in animals*

**Edited by D. R. Hawkins**

# Biotransformations

*A survey of the biotransformations  
of drugs and chemicals in animals*

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Huntingdon Life Sciences



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**Biotransformations**

**Volume 7**

# Preface

This series encompasses biotransformations of chemical entities whether they are pharmaceuticals, agrochemicals food additives, or environmental or industrial chemicals in vertebrates within the animal kingdom, a group which includes mammals, birds and fish. Each of the previous volumes has generally included material published during a calendar year, the sixth volume covering mainly 1992. It has now been considered appropriate to adopt a degree of selectivity in the material included based mainly on the extent of contribution to the knowledge database. This volume contains material selected from publications appearing in 1993 and 1994. An attempt has been made to include a comprehensive coverage of the scientific literature but due to the great diversity of journals where reports on biotransformations appear there will undoubtedly be some omissions. Any notable omissions communicated to the Editor could be included in a subsequent volume. The incorporation of cumulative indexes first introduced in Volume 3 is being continued in this and subsequent volumes, a feature which will facilitate access to key information on structurally related compounds.

A long term goal was to produce a computerized version of the material in this series with appropriate automatic search facilities. In conjunction with Synopsys Scientific Systems Ltd development of this type of product including a CD-ROM version has been in progress and release is expected in late 1996.

## Arrangement of material and access

An overview chapter has been prepared which contains highlights such as novel biotransformation, mechanisms of toxicity and notable species differences. The abstracts are arranged according to compound class, although there may be cases where allocation to one or another class is somewhat subjective. It has been considered valuable to be able to access information on the biotransformation of compounds with similar structural features. For this purpose the concept of key functional groups have been selected where biotransformation has been shown to occur but in addition group have also been included where biotransformation has not taken place. The same functional groups may not necessarily be included in all abstracts of the same compound since some papers may be confined to specific aspects of biotransformation and here only the relevant groups are included. A list of the functional groups follows which may be referred to before proceedings to the corresponding index. Two other indexes have been included containing compound names and types of biotransformation processes respectively.

In the precis for each compound certain key information has been included when available. Where radiolabelled compounds have been used the position(s) of labelling have been indicated on the structure. Comments on the source of metabolites and information on the quantitative importance of individual metabolites such as percentage

material in the sample of percentage administered dose are given where possible. Also in order to provide a perspective on the criteria for identification the procedures used for separation and isolation of metabolites and structural assignments such as chromatographic and physico-chemical techniques and use of reference compounds have been discussed.

D. R. Hawkins

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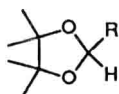
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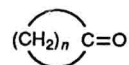
# Key Functional Groups

R may be any unspecified group including H. Where two or more R groups are indicated these may be the same or different groups. Where aromatic rings or other cyclic systems are shown they may also contain substituents when they are not specified as part of the key functional group.

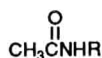
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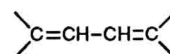
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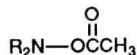
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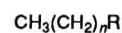
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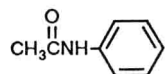
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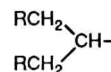
Alkane



N-Acetyl aryl amine



iso-Alkane



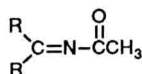
Acetylene



Alkene



N-Acetylimine



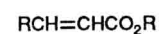
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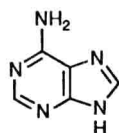
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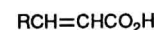
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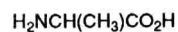
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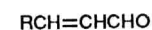
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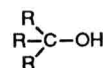
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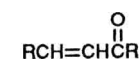
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tert-Alcohol

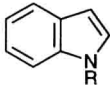
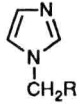


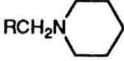
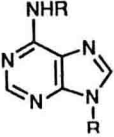
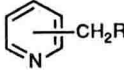
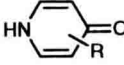
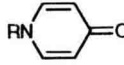
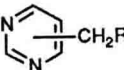

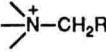
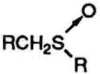
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
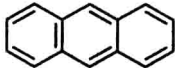
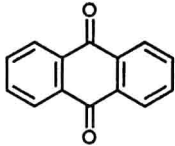
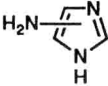
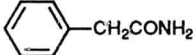
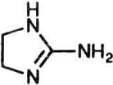
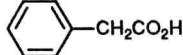
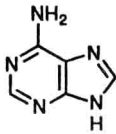
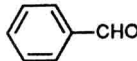
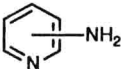
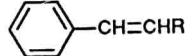
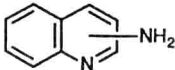
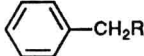

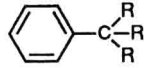
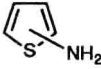
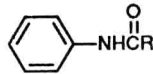
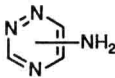
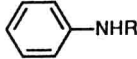
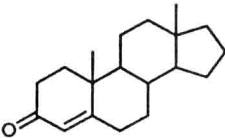
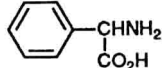
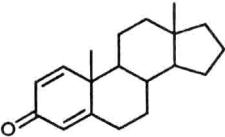
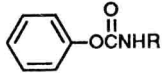
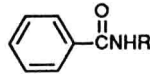


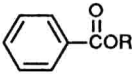
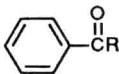
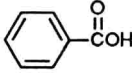
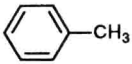
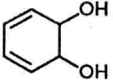
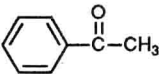
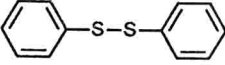
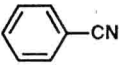
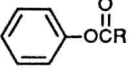
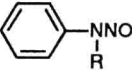
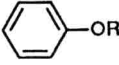
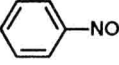
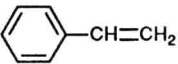
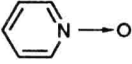
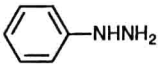
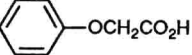
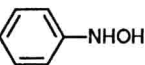
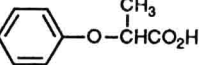
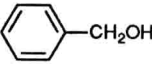
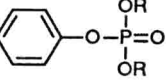
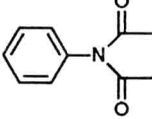
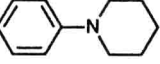
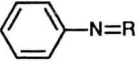
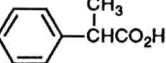
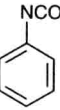
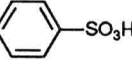


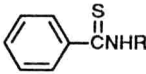
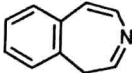
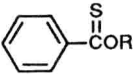
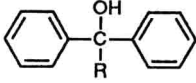
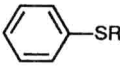
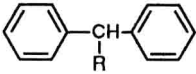
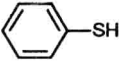
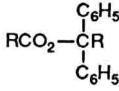
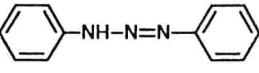
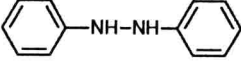

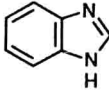
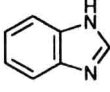

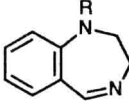
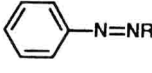
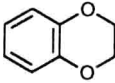
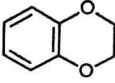
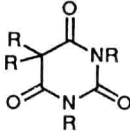
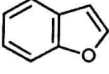
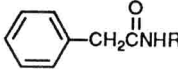
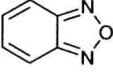
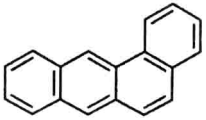
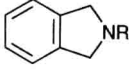
Alkoxyphenyl	$\text{RCH}_2\text{O}-\text{C}_6\text{H}_5$	Alkyl aryl amine	$\text{R}-\text{N}(\text{CH}_2\text{R})-\text{C}_6\text{H}_5$
Alkyl alcohol	$\text{RCH}_2\text{OH}$	iso-Alkyl aryl amine	$\text{R}-\text{N}(\text{CH}(\text{R})_2)-\text{C}_6\text{H}_5$
sec-Alkyl alcohol	$\text{R}-\text{CH}(\text{R})-\text{OH}$	sec-Alkyl aryl amine	$\text{R}-\text{N}(\text{CH}_2\text{CH}(\text{R})_2)-\text{C}_6\text{H}_5$
tert-Alkyl alcohol	$\text{R}-\text{C}(\text{R})_2-\text{OH}$	Alkyl aryl ether	$\text{RCH}_2\text{O}-\text{C}_6\text{H}_5$
Alkyl aldehyde	$\text{RCH}_2\text{CHO}$	Alkyl aryl sulfoxide	$\text{RCH}_2\text{S}(=\text{O})-\text{C}_6\text{H}_5$
Alkyl amide	$\text{RC}(=\text{O})\text{NHCH}_2\text{R}$	Alkyl aryl thioether	$\text{RCH}_2\text{S}-\text{C}_6\text{H}_5$
Alkyl amine	$\text{RCH}_2\text{NH}_2$	Alkylazoxy	$\text{RCH}_2\text{S}-\text{C}_6\text{H}_5$
Alkyl tert-amine	$\text{R}-\text{N}(\text{R})_2$	Alkyl carbamate	$\text{RCH}_2\text{OC}(=\text{O})\text{NHR}$
sec-Alkyl amine	$\text{R}-\text{CH}(\text{R})-\text{NHR}$	Alkyl carbonate	$\text{RCH}_2\text{OC}(=\text{O})\text{OR}$
tert-Alkyl amine	$\text{R}-\text{C}(\text{R})_2-\text{NHR}$	Alkyl carboxamide	$\text{RCH}_2\text{C}(=\text{O})\text{NHR}$
Alkylamino	$\text{RCH}_2\text{NH}-$	iso-Alkyl carboxamide	$\text{R}-\text{CH}(\text{R})\text{C}(=\text{O})\text{NHR}$
iso-Alkylamino/iso-alkylamine	$\text{R}-\text{CH}(\text{R})\text{NH}-$	Alkyl carboxylate	$\text{RCH}_2\text{CO}_2\text{R}$
Alkyl aryl amide	$\text{R}-\text{C}(=\text{O})-\text{N}(\text{CH}_2\text{R})-\text{C}_6\text{H}_5$	tert-Alkyl carboxylate	$\text{R}-\text{C}(\text{R})_2-\text{CO}_2\text{R}$

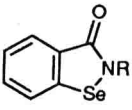
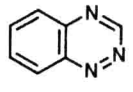
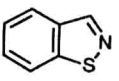
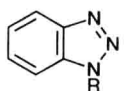
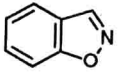
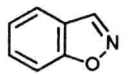
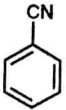
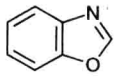
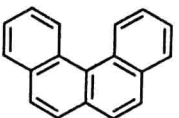
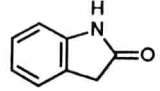
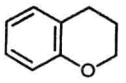
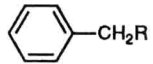
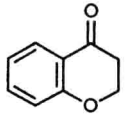
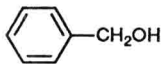
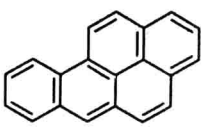
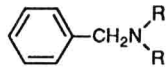
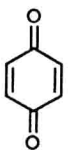
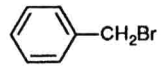
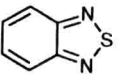
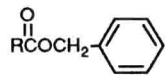
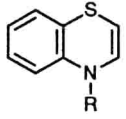
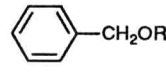
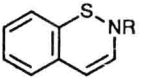
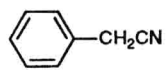
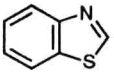
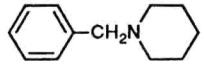
Alkyl carboxylic acid	$\text{RCH}_2\text{C}(=\text{O})\text{COH}$	<i>N</i> -Alkylimine	$\text{R}-\text{CH}=\text{N}-\text{R}$
iso-Alkyl carboxylic acid	$\begin{array}{c} \text{R} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{R} \end{array} \text{C}(=\text{O})\text{COH}$	<i>N</i> -Alkylindole	
<i>N</i> -Alkyl cycloalkylamine	$(\text{CH}_2)_n-\text{NHCH}_2\text{R}$	Alkyl ketone	$\text{RCH}_2\text{C}(=\text{O})\text{CR}$
Alkylcyclohexane	$\text{RCH}_2-\text{C}_6\text{H}_{11}$	<i>N</i> -Alkylmorpholine	$\text{RCH}_2-\text{N}(\text{C}_2\text{H}_4)_2$
Alkyl cyclopentane	$\text{RCH}_2-\text{C}_5\text{H}_9$	Alkyl nitrate	$\text{RCH}_2\text{ONO}_2$
Alkyl ester	$\text{RCOCH}_2\text{R}$	Alkyl nitrile	$\text{RCH}_2\text{CN}$
iso-Alkyl ester	$\begin{array}{c} \text{R} \\ \diagup \\ \text{COCH} \\ \diagdown \\ \text{R} \end{array}$	Alkyl <i>N</i> -oxide	$\begin{array}{c} \text{RCH}_2 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{RCH}_2 \end{array} \text{CH}_2\text{R} \quad \text{O}$
Alkyl ether	$\text{RCH}_2\text{OR}$	Alkyl peroxide	$\text{RCH}_2\text{O}-\text{OCH}_2\text{R}$
Alkyl hydrazide	$\text{RCNHNHR}$	Alkylphenyl	$\text{RCH}_2-\text{C}_6\text{H}_5$
Alkyl hydrazine	$\text{RCH}_2\text{NHNHR}$	iso-Alkyl phenyl	$\begin{array}{c} \text{R} \\ \diagup \\ \text{CH} \\ \diagdown \\ \text{R} \end{array} -\text{C}_6\text{H}_5$
<i>N</i> -Alkylimidazole		Alkyl phosphate	$\text{RCH}_2\text{OP}(=\text{O})(\text{OR})_2$
Alkyl imide	$\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{RCH}_2\text{CNCCH}_2\text{R} \\   \\ \text{R} \end{array}$	Alkyl phosphine	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{P}-\text{R} \\   \\ \text{R} \end{array}$
<i>N</i> -Alkyl imide	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C} \\   \\ \text{R}-\text{C} \\ \parallel \\ \text{O} \end{array} \text{N}-\text{CH}_2\text{R}$	<i>N</i> -Alkylpiperazine	$\text{RN}(\text{C}_4\text{H}_8)\text{NCH}_2\text{R}$

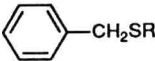
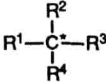
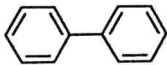
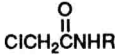





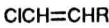
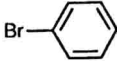

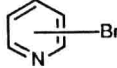

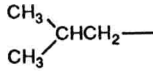
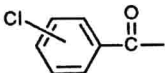
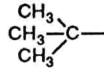
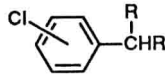
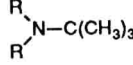
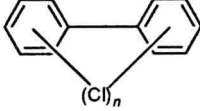


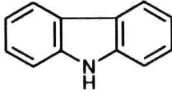
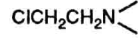
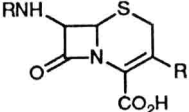
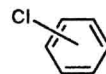
<i>N</i> -Alkylpiperidine		<i>S</i> -Alkyl thiocarbamate	$\text{RCH}_2\text{SCONHR}$
<i>N</i> -Alkylpurine		Alkyl thiocarboxylate	$\text{RCH}_2\text{C}(=\text{O})\text{SR}$
Alkylpyridine		Alkyl thioester	$\text{RC}(=\text{O})\text{SCH}_2\text{R}$
Alkylpyridone		Alkyl thioether	$\text{RCH}_2\text{SR}$
<i>N</i> -Alkylpyridone		Alkyl thiol	$\text{RCH}_2\text{SH}$
Alkylpyrimidine		Alkylurea	$\text{RNHC}(=\text{O})\text{NHCH}_2\text{R}$
<i>N</i> -Alkylpyrrolidine		Alkyne	$\text{RC}\equiv\text{CR}$
Alkyl quaternary ammonium		Allyl	$\text{RCH}_2-\text{CH}=\text{CH}_2$
Alkyl sulfamate	$\text{RCH}_2\text{OSO}_2\text{NHR}$	Allyl amine	$\text{RCH}=\text{CH}-\text{NH}_2$
Alkyl sulfate	$\text{RCH}_2\text{OSO}_3\text{H}$	Allylic alcohol	$\text{RCH}=\text{CH}\overset{\text{R}}{\underset{ }{\text{C}}}\text{HOH}$
Alkyl sulfonate	$\text{RCH}_2\text{OSO}_2\text{R}$	Allylic methyl	$\text{CH}_3\text{CH}=\text{CHR}$
Alkyl sulfonic acid	$\text{RCH}_2\text{SO}_3\text{H}$	Amidine	$\text{RC}(=\text{NR})\text{NR}_2$
Alkyl sulfoxide		Amidoxime	$\text{RC}(=\text{NOH})\text{NH}_2$

Amino acid		Anthracene	
Aminoglycoside	—	Anthraquinone	
Aminoimidazole		Aryl acetamide	
Aminoimidazoline		Aryl acetic acid	
Aminopurine		Aryl aldehyde	
Aminopyridine		Arylalkene	
Aminoquinoline		Arylalkyl	
Aminothiazole		Aryl tert-alkyl	
Aminothiophene		Aryl amide	
Aminotriazine		Aryl amine	
Androstadienone		Aryl amino acid	
Androsten-3-one		Aryl carbamate	
		Aryl carboxamide	

Aryl carboxylate		Aryl ketone	
Aryl carboxylic acid		Arylmethyl	
Aryl dihydrodiol		Aryl methyl ketone	
Aryl disulfide		Aryl nitrile	
Aryl ester		N-Arylnitrosamine	
Aryl ether		Arylnitroso	
Arylethylene		Aryl N-oxide	
Aryl hydrazine		Aryloxacetic acid	
Arylhydroxylamine		Aryloxypropionic acid	
Arylhydroxymethyl		Aryl phosphate	
N-Arylimide		Arylpiperidine	
N-Arylimine		Aryl propionic acid	
Aryl isocyanate		Aryl sulfonic acid	

Aryl thiocarboxymide		Benzazepine	
Aryl thiocarboxylate		Benzhydrol	
Aryl thioether		Benzhydryl	
Aryl thiol		Benzhydryl carboxylate	
Aryl triazene		Benzidine	
Azetidine		Benzimidazole	
Azide	$R-N=N=N$	Benzimidazoline	
Aziridine		Benzodiazepine	
Azobenzene		Benzodioxane	
Azoxy	$R-N=N-O$	Benzodioxin	
Barbiturate		Benzofuran	
Benzamide		Benzofurazan	
Benzanthracene		Benzoindoline	

Benzoisoselenazolone		Benzotriazine	
Benzoisothiazole		Benzotriazole	
Benzoisoxazole		1,2-Benzoxazole	
Benzonitrile		1,3-Benzoxazole	
Benzo[c]phenanthrene		Benzoxazoline	
Benzopyran		Benzyl	
Benzopyranone		Benzyl alcohol	
Benzo[a]pyrene		Benzyl amine	
Benzoquinone		Benzyl bromide	
Benzothiadiazole		Benzyl ester	
Benzothiazine		Benzyl ether	
		Benzyl nitrile	
Benzothiazole		N-Benzylpiperidine	

Benzyl thioether		Chiral carbon	
Biphenyl		Chloroacetamide	
Bromoacetyl		Chloroacetyl	
Bromoalkane		Chloroalkane	
Bromoalkyl		Chloroalkene	
Bromophenyl		Chloroalkyne	
Bromopyridine		Chloroalkyl	
iso-Butyl		Chlorobenzoyl	
tert-Butyl		Chlorobenzyl	
N-tert-Butyl		Chlorobiphenyl	
Carbamate		Chlorocyclopropane	
Carbazole		N-Chloroethyl	
Cephalosporin		Chlorophenyl	



Chloropyridazinone		Cycloalkene	
Chloropyridine		Cycloalkylamine	
Chlorotriazine		Cycloalkyl amine	
Chlorouracil		Cycloalkyl ester	
Cholanic acid		Cyclohexadienone	
Cholestenone		Cyclohexane/cyclohexyl	
Chrysene		Cyclohexanol	
Coumarin		Cyclohexanone	
Cyanamide	$\text{RNHCN}$	Cyclohexene	
N-Cyanoguanidine	$\text{RNHCNHR}$ $\text{  }$ $\text{NCN}$	Cyclohexenol	
Cycloalkane/cycloalkyl		Cyclohexenone	
		Cyclohexyl amide	
		Cyclopentene	