

Contents

Contributors	xix
--------------------	-----

1. Models and Mechanisms of Cytochrome P450 Action

John T. Groves

1. Introduction	1
2. Oxygen Activation by Heme-Thiolate Proteins	1
3. Mechanism of Hydroxylation by Cytochrome P450	3
4. Mechanisms and Molecular Trajectories for Hydroxylation by Cytochrome P450	7
5. On the Mechanism of Nitric Oxide Synthase	16
6. Synthetic Oxometalloporphyrins as Models for Cytochrome P450	17
7. Manganese Porphyrins in Catalytic Oxidations	19
8. Metalloporphyrins as Detectors and Decomposition Catalysts of Peroxynitrite	23
9. Synthetic Metalloporphyrins as Stereoselective Catalysts	25
10. Ruthenium Porphyrins in Oxidative Catalysis	26
11. Conclusion	34
Acknowledgments	34
References	34

2. Computational Approaches to Cytochrome P450 Function

Sason Shaik and Samuël P. De Visser

1. Introduction	45
2. Methods	45
3. The Catalytic Cycle of P450	48
3.1. The Resting State (1)	51
3.2. The Pentacoordinate Ferric-Porphyrin (2) and Ferrous-Porphyrin (3) Complexes	52
3.3. The Gating of the Catalytic Cycle	54
3.4. The Ferrous-Dioxygen (4) and Ferric-Dioxygen (5) Complexes	54
3.5. The Protonation Mechanism of Ferric-Dioxygen (5) to Cpd 0 (6)	56
3.6. Cpd 0: The Ferric Peroxide Complex (6)	57
3.7. Protonation of Cpd 0 and Formation of Cpd I (7)	57
3.8. The “Push Effect” on the O–O Cleavage Process	58
3.9. Cpd I (7)	59
3.10. What Makes the Catalytic Cycle Tick? A Summary	63
4. MM and MM/MD Studies of P450 Reactivity Aspects	63
4.1. Studies of Substrate Entrance, Binding, and Product Exit	63
4.2. MM and MM/MD Studies of Regioselectivity	65
5. QM Studies of P450 Reactivity Patterns	66
5.1. Reactivity of Cpd I: General Considerations of the Origins of Two-State Reactivity (TSR) of Cpd I	66
5.2. A Primer to P450 Reactivity: Counting of Electrons	66
5.3. Alkane Hydroxylation	68

5.4. The Rebound Process: More Features than Meet the Eye	72
5.5. Alkene Epoxidation	73
5.6. Hydroxylation of Arenes	75
5.7. Sulfoxidation of Alkyl Sulfides	76
5.8. Can Ferric Peroxide (6) be a Second Oxidant?	77
5.9. Competitive Hydroxylation and Epoxidation in Propene	77
5.10. An Overview of Reactivity Features of Cpd I	79
6. Prospective	80
Acknowledgment	80
References	80

3. Structures of Cytochrome P450 Enzymes

Thomas L. Poulos and Eric F. Johnson

1. Introduction	87
2. Overall Architecture	87
3. P450s from Thermophiles	91
4. Membrane P450s	92
5. Electron Transfer Complexes	95
6. Substrate Complexes	99
7. Conformational Adaptations to Substrates and Inhibitors	100
8. Conformational Dynamics for Substrate Access	102
Acknowledgments	111
References	111

4. Electron Transfer Partners of Cytochrome P450

Mark J.I. Paine, Nigel S. Scrutton, Andrew W. Munro, Aldo Gutierrez, Gordon C.K. Roberts, and C. Roland Wolf

1. Introduction	115
2. NADPH-Cytochrome P450 Reductase and the Diflavin Reductase Family	116
2.1. Background	116
2.2. The Diflavin Reductase Family	117
2.3. CPR Genes	118
2.4. Probing the Physiological Role of CPR	119
2.5. Structure of CPR	120
2.5.1. The FMN-Binding Domain	120
2.5.2. FAD/NADPH-Binding Domain	122
2.6. The Electron Transfer Mechanism	124
2.6.1. Trp676 and FAD Reduction	126
2.6.2. Binding of Two Coenzyme Molecules	127
2.6.3. Internal Electron Transfer	127
2.6.4. Interaction with and Electron Transfer to P450	128
2.7. Cytochrome P450 BM3	131
2.7.1. Electron Transfer Properties of BM3 Reductase	132
2.8. Artificial CPR-P450 Fusion Constructs	133
3. Electron Transfer to P450s from Cytochrome <i>b</i> ₅	133
4. Iron-Sulfur Electron Donors: Adrenodoxin, Putidaredoxin, and their Reductases	134
4.1. General	134
4.2. Interactions with P450	135
5. Novel Redox Systems	138

Acknowledgments	138
References	138

5. Activation of Molecular Oxygen by Cytochrome P450

Thomas M. Makris, Ilia Denisov, Ilme Schlichting, and Stephen G. Sligar

1. Introduction to Oxygen Activation	149
2. General Features of Dioxygen Activation in Heme Enzymes	151
2.1. The Oxidase/Oxygenase Pathway in Cytochrome P450	152
3. Enzymatic Cycle of Cytochrome P450	155
3.1. The Ferrous-Dioxygen Complex	156
3.2. Reduction of Oxy-Ferrous P450 and Formation of Peroxo-Ferric Complexes: Properties, Stability, and Spectroscopy	157
3.3. The Second Branchpoint of P450 Catalysis: Uncoupling with Hydrogen Peroxide Production or Dioxygen Bond Scission	160
4. Structural Input into the Mechanisms of P450-Catalyzed Dioxygen Activation	161
4.1. A "Conserved" Alcohol Side Chain in the Active Site of P450	162
4.2. The "Conserved" Acid Functionality	164
4.3. Crystallographic Studies of P450 Reaction Intermediates	165
4.4. Mechanism-Based Specificity of Proton Transfer	169
4.5. Summary	170
Acknowledgments	170
References	170

6. Substrate Oxidation by Cytochrome P450 Enzymes

Paul R. Ortiz de Montellano and James J. De Voss

1. Introduction	183
2. Activation of Molecular Oxygen	184
3. Hydrocarbon Hydroxylation	186
4. Heteroatom Oxidation and Dealkylation	193
5. Olefin and Acetylene Oxidation	198
6. Oxidation of Aromatic Rings	202
7. Dehydrogenation Reactions	208
8. Carbon–Carbon Bond Cleavage Reactions	211
8.1. Cleavage between Oxygenated Carbons	211
8.2. Cleavage Alpha to Oxygenated Carbon	217
8.3. Cleavage Alpha to Carbon Bearing a Nitrogen Atom	228
9. Conclusions	229
Acknowledgments	230
References	230

7. Inhibition of Cytochrome P450 Enzymes

Maria Almira Correia and Paul R. Ortiz de Montellano

1. Introduction	247
2. Reversible Inhibitors	247
2.1. Coordination to Ferric Heme	248
2.2. Coordination to Ferrous Heme	248
2.3. Heme Coordination and Lipophilic Binding	248

3. Catalysis-Dependent Inhibition	250
3.1. Covalent Binding to the Protein	250
3.1.1. Sulfur and Halogenated Compounds	250
3.1.2. Olefins and Acetylenes	255
3.1.3. Other P450 Protein Modifying Inactivators	259
3.2. Quasi-Irreversible Coordination to the Prosthetic Heme	263
3.2.1. Methylenedioxy Compounds	263
3.2.2. Amines	265
3.2.3. 1,1-Disubstituted and Acyl Hydrazines	266
3.3. Covalent Binding to the Prosthetic Heme	267
3.3.1. Terminal Olefins	267
3.3.2. Acetylenes	269
3.3.3. Dihydropyridines and Dihydroquinolines	272
3.3.4. Alkyl- and Arylhydrazines and Hydrazones	273
3.3.5. Other N–N Functions	275
3.3.6. Other Functionalities	278
3.4. Modification of the P450 Protein by Heme Fragments	280
3.5. Other Modes of P450 Heme Degradation and Protein Denaturation	282
4. P450 Enzyme Specificity	285
5. Inhibitors of Biosynthetic Enzymes	285
5.1. P450 _{sec}	286
5.2. Aromatase	286
5.3. Lanosterol 14-Demethylation	290
5.4. Other Biosynthetic Sterol Hydroxylases	292
5.5. Fatty Acid and Leukotriene Monooxygenases	292
6. Summary	294
Acknowledgment	295
References	295

8. Induction of Cytochrome P450 Enzymes

Susanne N. Williams, Elizabeth Dunham, and Christopher A. Bradfield

1. Introduction	323
1.1. Cytochrome P450 Enzymes and the Adaptive Response	323
1.2. Overview of Nuclear Receptors	323
2. The Pregnenol X Receptor	324
2.1. Introduction	324
2.2. The PXR	325
2.3. PXR Ligands and Species Differences	325
2.4. Activation of Transcription	325
2.5. Mouse Models	326
2.6. Future Research	327
3. The Constitutive Androstane Receptor	328
3.1. Introduction	328
3.2. The Nuclear Receptor CAR	328
3.3. Mediators of CAR Activity	328
3.4. Activation of Transcription	330
3.5. Mouse Models	330
3.6. Future Directions	331
4. The Peroxisome Proliferator Activated Receptor α	331

4.1. Introduction	331
4.2. PPAR Isoforms	332
4.3. PPAR α Ligands	332
4.4. Activation of Transcription	332
4.5. Species Differences	334
4.6. Mouse Models	334
4.7. Future Directions	334
5. The Aryl Hydrocarbon Receptor	335
5.1. Introduction	335
5.2. The AHR	335
5.3. AHR Ligands	336
5.4. Activation of Transcription	337
5.5. Mouse Models	338
5.6. Future Directions	338
5.7. Conclusions	339
Acknowledgments	339
References	339

9. Hormonal Regulation of Liver Cytochrome P450 Enzymes

David J. Waxman and Thomas K.H. Chang

1. Introduction	347
2. Steroid Hormones as Substrates for Sex-Dependent Liver P450s	348
3. Developmental Regulation of Sex-Dependent Rat Liver P450s	348
4. Hormonal Control of Liver P450 Expression	350
4.1. Regulation by Gonadal Hormones	350
4.1.1. Testosterone	350
4.1.1.1. Distinct Effects of Neonatal Androgen and Adult Androgen	350
4.1.1.2. Testosterone Suppression of Female Enzymes	350
4.1.1.3. Mechanisms of Testosterone Regulation	351
4.1.2. Estrogen	351
4.2. Regulation by Growth Hormone	351
4.2.1. Sex-Dependent GH Secretory Profiles	351
4.2.2. Transcriptional Effects of GH on CYP Genes	354
4.2.3. Cellular Mechanisms of GH Signaling	354
4.2.3.1. Significance of GH Pulse Frequency	355
4.2.3.2. Role of GH Receptor (GHR)	355
4.2.4. Role of STAT5b in Sex-Dependent CYP Expression	356
4.2.4.1. GH Signaling Pathways Involving STAT Transcription Factors	356
4.2.4.2. STAT5b Gene Knockout Mouse Model	359
4.2.4.3. Interaction of GH-Responsive CYP Promoters with GH-Activated STAT5b	360
4.2.4.4. Interactions between STAT5b and Liver Transcription Factors Regulating Sex-Specific CYPs	361
4.2.4.5. Downregulation of Hepatic STAT5b Signaling	361
4.3. Regulation by Thyroid Hormone	362
4.3.1. Cytochromes P450	362
4.3.2. NADPH-Cytochrome P450 Reductase	362
5. Alteration of Liver P450 Expression by Hormonal Perturbation	362
5.1. Modulation by Drugs	362

5.2. Modulation by Polycyclic Aromatic Hydrocarbons	363
5.3. Modulation by Pathophysiological State	363
5.3.1. Diabetes	363
5.3.2. Liver Cirrhosis	364
5.4. Modulation by Ethanol and Dietary Factors	364
5.5. Impact on Drug Metabolism and Procarcinogen Activation	365
6. Conclusion	365
Acknowledgment	366
References	366

10. Human Cytochrome P450 Enzymes

F. Peter Guengerich

1. Background and History of Development of the Field	377
2. General Issues of Variability and Polymorphism	383
3. Approaches to Defining Catalytic Specificity of Human P450s	388
3.1. Inhibitors	389
3.2. Correlations	389
3.3. Antibody Inhibition	390
3.4. Demonstration of Reaction with Recombinant P450	392
4. Relevance of P450s in <i>In Vivo</i> Drug Metabolism	392
5. Relevance of P450s in Toxicology and Cancer Risk	395
6. Individual Human P450 Enzymes	396
6.1. P450 1A1	396
6.1.1. Sites of Expression and Abundance	396
6.1.2. Regulation and Polymorphism	397
6.1.3. Substrates and Reactions	397
6.1.4. Knowledge about Active Site	397
6.1.5. Inhibitors	398
6.1.6. Clinical Issues	398
6.2. P450 1A2	398
6.2.1. Sites of Expression and Abundance	398
6.2.2. Regulation and Polymorphism	398
6.2.3. Substrates and Reactions	399
6.2.4. Knowledge about Active Site	399
6.2.5. Inhibitors	399
6.2.6. Clinical Issues	400
6.3. P450 1B1	400
6.3.1. Sites of Expression and Abundance	400
6.3.2. Regulation and Polymorphism	400
6.3.3. Substrates and Reactions	400
6.3.4. Knowledge of Active Site	402
6.3.5. Inhibitors	402
6.3.6. Clinical Issues	402
6.4. P450 2A6	402
6.4.1. Sites of Expression and Abundance	402
6.4.2. Regulation and Polymorphism	402
6.4.3. Substrates and Reactions	403
6.4.4. Knowledge about Active Site	403
6.4.5. Inhibitors	404
6.4.6. Clinical Issues	404

6.5. P450 2A7	404
6.6. P450 2A13	404
6.6.1. Sites of Expression and Abundance	404
6.6.2. Regulation and Polymorphism	405
6.6.3. Substrates and Reactions	405
6.6.4. Knowledge about Active Site	405
6.6.5. Inhibitors	405
6.6.6. Clinical Issues	405
6.7. P450 2B6	405
6.7.1. Sites of Expression and Abundance	405
6.7.2. Regulation and Polymorphism	405
6.7.3. Substrates and Reactions	406
6.7.4. Knowledge about Active Site	406
6.7.5. Inhibitors	406
6.7.6. Clinical Issues	406
6.8. P450 2C8	407
6.8.1. Sites of Expression and Abundance	407
6.8.2. Regulation and Polymorphism	407
6.8.3. Substrates and Reactions	407
6.8.4. Knowledge about Active Site	407
6.8.5. Inhibitors	408
6.8.6. Clinical Issues	408
6.9. P450 2C9	408
6.9.1. Sites of Expression and Abundance	408
6.9.2. Regulation and Polymorphism	408
6.9.3. Substrates and Reactions	409
6.9.4. Knowledge about Active Site	409
6.9.5. Inhibitors	410
6.9.6. Clinical Issues	410
6.10. P450 2C18	411
6.10.1. Sites of Expression and Abundance	411
6.10.2. Regulation and Polymorphism	411
6.10.3. Substrates and Reactions	411
6.10.4. Knowledge about Active Site	411
6.10.5. Inhibitors	411
6.10.6. Clinical Issues	412
6.11. P450 2C19	412
6.11.1. Sites of Expression and Abundance	412
6.11.2. Regulation and Polymorphism	412
6.11.3. Substrates and Reactions	412
6.11.4. Knowledge about Active Site	413
6.11.5. Inhibitors	413
6.11.6. Clinical Issues	413
6.12. P450 2D6	413
6.12.1. Sites of Expression and Abundance	413
6.12.2. Regulation and Polymorphism	413
6.12.3. Substrates and Reactions	414
6.12.4. Knowledge about Active Site	416
6.12.5. Inhibitors	417
6.12.6. Clinical Issues	418
6.13. P450 2E1	418

6.13.1. Sites of Expression and Abundance	418
6.13.2. Regulation and Polymorphism	419
6.13.3. Substrates and Reactions	420
6.13.4. Knowledge about Active Site	420
6.13.5. Inhibitors	421
6.13.6. Clinical Issues	421
6.14. P450 2F1	422
6.15. P450 2J2	422
6.16. P450 2R1	423
6.17. P450 2S1	423
6.18. P450 2U1	423
6.19. P450 2W1	423
6.20. P450 3A4	423
6.20.1. Sites of Expression and Abundance	424
6.20.2. Regulation and Polymorphism	424
6.20.3. Substrates and Reactions	425
6.20.4. Knowledge about Active Site	426
6.20.5. Inhibitors	430
6.20.6. Clinical Issues	430
6.21. P450 3A5	431
6.21.1. Sites of Expression and Abundance	431
6.21.2. Regulation and Polymorphism	431
6.21.3. Substrates and Reactions	432
6.21.4. Knowledge about Active Site	432
6.21.5. Inhibitors	432
6.21.6. Clinical Issues	432
6.22. P450 3A7	432
6.22.1. Sites of Expression and Abundance	432
6.22.2. Regulation and Polymorphism	433
6.22.3. Substrates and Reactions	433
6.22.4. Knowledge about Active Site	433
6.22.5. Inhibitors	433
6.22.6. Clinical Issues	434
6.23. P450 3A43	434
6.24. P450 4A11	434
6.24.1. Sites of Expression and Abundance	434
6.24.2. Regulation and Polymorphism	434
6.24.3. Substrates and Reactions	434
6.24.4. Knowledge about Active Site	434
6.24.5. Inhibitors	435
6.24.6. Clinical Relevance	435
6.25. P450 4A22	435
6.26. P450 4B1	435
6.26.1. Sites of Expression and Abundance	435
6.26.2. Regulation and Polymorphism	435
6.26.3. Substrates and Reactions	435
6.26.4. Knowledge about Active Site	436
6.26.5. Inhibitors	436
6.26.6. Clinical Issues	436
6.27. P450 4F2	436
6.28. P450 4F3	436

6.29. P450 4F8	437
6.30. P450 4F11	437
6.31. P450 4F12	437
6.32. P450 4F22	437
6.33. P450 4V2	437
6.34. P450 4X1	437
6.35. P450 4Z1	437
6.36. P450 5A1	437
6.36.1. Sites of Expression and Abundance	437
6.36.2. Regulation and Polymorphism	438
6.36.3. Substrates and Reactions	438
6.36.4. Knowledge about Active Site	439
6.36.5. Inhibitors	439
6.36.6. Clinical Issues	439
6.37. P450 7A1	439
6.37.1. Sites of Expression	439
6.37.2. Regulation and Polymorphism	439
6.37.3. Substrates and Reactions	440
6.37.4. Knowledge about Active Site	441
6.37.5. Inhibitors	441
6.37.6. Clinical Issues	441
6.38. P450 7B1	441
6.39. P450 8A1	441
6.39.1. Sites of Expression and Abundance	442
6.39.2. Regulation and Polymorphism	442
6.39.3. Substrates and Reactions	442
6.39.4. Knowledge about Active Site	442
6.39.5. Inhibitors	442
6.39.6. Clinical Issues	443
6.40. P450 8B1	443
6.41. P450 11A1	443
6.41.1. Sites of Expression	443
6.41.2. Regulation and Polymorphism	445
6.41.3. Substrates and Reaction	445
6.41.4. Knowledge about Active Site	445
6.41.5. Inhibitors	445
6.41.6. Clinical Issues	446
6.42. P450 11B1	446
6.42.1. Sites of Expression	446
6.42.2. Regulation and Polymorphism	446
6.42.3. Substrates and Reactions	446
6.42.4. Knowledge about Active Site	447
6.42.5. Inhibitors	447
6.42.6. Clinical Issues	447
6.43. P450 11B2	447
6.43.1. Sites of Expression	447
6.43.2. Regulation and Polymorphism	447
6.43.3. Substrates and Reactions	448
6.43.4. Knowledge about Active Site	448
6.43.5. Inhibitors	448
6.43.6. Clinical Issues	448

6.44. P450 17A1	448
6.44.1. Sites of Expression	448
6.44.2. Regulation and Polymorphism	449
6.44.3. Substrates and Reactions	449
6.44.4. Knowledge about Active Site	450
6.44.5. Inhibitors	450
6.44.6. Clinical Issues	450
6.45. P450 19A1	450
6.45.1. Sites of Expression	451
6.45.2. Regulation and Polymorphism	451
6.45.3. Substrates and Reactions	452
6.45.4. Knowledge about Active Site	452
6.45.5. Inhibitors	452
6.45.6. Clinical Issues	452
6.46. P450 20A1	452
6.47. P450 21A2	453
6.47.1. Sites of Expression	453
6.47.2. Regulation and Polymorphism	453
6.47.3. Substrates and Reactions	453
6.47.4. Knowledge about Active Site	453
6.47.5. Inhibitors	453
6.47.6. Clinical Issues	453
6.48. P450 24A1	454
6.48.1. Sites of Expression and Abundance	454
6.48.2. Regulation and Polymorphism	454
6.48.3. Substrates and Reactions	455
6.48.4. Knowledge about Active Site	455
6.48.5. Inhibitors	455
6.48.6. Clinical Issues	455
6.49. P450 26A1	455
6.50. P450 26B1	456
6.51. P450 26C1	456
6.52. P450 27A1	456
6.52.1. Sites of Expression and Abundance	456
6.52.2. Regulation and Induction	456
6.52.3. Substrates and Reactions	458
6.52.4. Knowledge about Active Site	458
6.52.5. Inhibitors	458
6.52.6. Clinical Issues	458
6.53. P450 27B1	459
6.53.1. Sites of Expression and Abundance	459
6.53.2. Regulation and Polymorphism	459
6.53.3. Substrates and Reactions	460
6.53.4. Knowledge about Active Site	460
6.53.5. Inhibitors	460
6.53.6. Clinical Issues	460
6.54. P450 27C1	460
6.55. P450 39A1	460
6.56. P450 46A1	461
6.57. P450 51A1	461
6.57.1. Sites of Expression and Abundance	461

6.57.2. Regulation and Polymorphism	461
6.57.3. Substrates and Reactions	462
6.57.4. Knowledge about Active Site	462
6.57.5. Inhibitors	462
6.57.6. Clinical Issues	462
7. Concluding Remarks	462
Acknowledgments	463
References	463

11. Cytochrome P450 and the Metabolism and Bioactivation of Arachidonic Acid and Eicosanoids

Jorge H. Capdevila, Vijaykumar R. Holla, and John R. Falck

1. Introduction	531
2. Metabolism of Eicosanoids	532
2.1. NADPH-Independent Reactions	532
2.2. NADPH-Dependent Reactions	533
2.2.1. $\omega/\omega-1$ Oxidation of Prostanoids	533
2.2.2. $\omega/\omega-1$ Oxidation of Leukotrienes and Other Eicosanoids	534
3. Metabolism of Arachidonic Acid: The Arachidonic Acid Monooxygenase	535
3.1. bis-Allylic Oxidation (Lipoxygenase-Like Reactions)	536
3.2. Hydroxylation at C ₁₆ –C ₂₀ ($\omega/\omega-1$ Hydroxylase Reactions)	536
3.2.1. Introduction	536
3.2.2. Enzymology, Isoform Specificity	537
3.3. Olefin Epoxidation (Epoxygenase Reactions)	539
3.3.1. Introduction	539
3.3.2. Enzymology, Isoform Specificity	539
3.3.3. P450 Arachidonic Acid Epoxygenase: A Member of the Arachidonic Acid Metabolic Cascade	541
3.4. Functional Roles of the P450 Arachidonic Acid Monooxygenase	542
3.4.1. Vascular Reactivity; Ion Channel Regulation	542
3.4.2. Blood Pressure Control and Hypertension	543
4. Conclusion	545
Acknowledgments	545
References	545

12. Cytochrome P450s in Plants

Kirsten Annette Nielsen and Birger Lindberg Møller

1. Introduction	553
1.1. Natural Products	553
1.2. Chemical Warfare	553
1.3. Chemical Communication	553
1.4. Medicinal Agents	554
2. The P450 Superfamily in Plants	554
2.1. Nomenclature	554
3. Tools Available to Identify Biological Functions	555
3.1. Phylogenetic Relationships	555
3.2. Mutant Collections in <i>A. thaliana</i>	556

3.3. Reverse Genetics	556
3.4. Heterologous Expression in Microorganisms	556
3.5. Isolation of Enzymes	557
3.6. Homology-Based Cloning	557
4. Non-A-Type P450s Mediating Steroid Biosynthesis	557
4.1. CYP90s	558
4.2. CYP85s	560
5. A-Type P450s Mediating Plant Protection	560
5.1. Broad Defense: Cyanogenic Glucosides	560
5.1.1. Biosynthesis	561
5.1.2. Substrate Channeling and Metabolon Formation	563
5.1.3. Substrate Specificities	564
5.2. Functional Uniformity within the CYP79 Family	564
5.3. Functional Diversity among CYP71S	566
5.3.1. CYP71A and CYP71B Subfamilies	566
5.3.2. CYP71C Subfamily: Grass-Specific Defense Compounds	566
5.3.3. CYP71D, -F, and -R Subfamilies	568
5.4. Specialized Defense—Isoflavonoids in Legumes	569
6. P450 Mediated Production of Alkaloids with Medicinal Importance	571
7. Future Prospects: Crosstalk and Metabolic Engineering	573
References	575

13. The Diversity and Importance of Microbial Cytochromes P450

*Steven L. Kelly, Diane E. Kelly, Colin J. Jackson, Andrew G.S. Warrilow,
and David C. Lamb*

1. Introduction to Microbial CYPs	585
2. Classes of Microbial CYPs	587
3. Considering the Origins and Relatedness of Microbial CYPs	589
3.1. CYP51 and Evolution of the Superfamily	590
3.2. Bacterial CYP51	592
4. Archetypal Bacterial CYPs	594
5. Biodiversity of Bacterial CYPs and the Actinomycetes	596
5.1. Mycobacterial CYPs	596
5.2. Biodiversity in Streptomycetes	598
5.3. CYP Biodiversity in Archaeabacteria	601
6. Fungal CYPs	601
7. Azole Antifungals and the Evolution of New Resistant Genes	603
7.1. The Fungal CYP51 System	603
7.2. Azole Activity and Resistance in Fungi	605
8. Conclusions	610
Acknowledgments	610
References	610

Appendix: Human and Rat Liver Cytochromes P450: Functional Markers, Diagnostic Inhibitor Probes, and Parameters Frequently Used in P450 Studies

619

Maria Almira Correia

Index	659
-------------	-----