

SUBJECT INDEX

- accABCD* genes, in flavanone synthesis, 177
- Acceptors, of DesVII–Des VIII, 68
- Acceptor specificity, in directed glycosyltransferase evolution, 106
- Acetaldehyde, in ethanol production, 191–192
- Acetaphenone, in flavonoid synthesis, 176
- Acetate kinase (ACK), in malonyl-CoA formation, 179, 180
- Acetic acid, in combinatorial pathway design, 129
- Acetoacetyl-CoA (coenzyme A)
in ethanol production, 192
in MVA pathway, 153, 154
- Acetoacetyl-CoA ligase, in MVA pathway, 154
- Acetoacetyl-CoA thiolase, in MVA pathway, 153
- Acetyl-CoA
in butanol production, 196
in ethanol production, 192
in MVA pathway, 153, 154
polyketides and, 167
- Acetyl-CoA carboxylase (ACC)
in flavanone synthesis, 177–179, 180
in malonyl-CoA formation, 179
- Acetyl-CoA synthase (ACS), in malonyl-CoA formation, 179
- N*-Acetyl-glucosamine, in teicoplanin, 83
- Acetyl phosphate, in malonyl-CoA formation, 179
- 3-Acetylpyridine adenine dinucleotide (APAD), in *Tritrichomonas foetus*, 21
- Acinetobacter bayli* ADP1, in wax ester biosynthesis, 124–125
- Aclacinomycin A, 96
biosynthetic pathway of, 100
molecular structure of, 95
- Aclarubicins, 96
molecular structure of, 95
- Acridone synthase (ACS), in polyketide synthesis, 169
- Actinomycetes, macrolide antibiotics from, 64
- Activation, of inosine 5'-monophosphate dehydrogenase, 36–39
- Acute myelogenous leukemia, enediynes versus, 89
- Acyclic carotenoids, synthesis of, 165
- Acyclic xanthophylls, biosynthesis of, 124
- Acyl carrier protein (ACP)
in combinatorial pathway design, 129
protein–protein interactions and, 133–134
- Acyltransferase (AT) domain
in combinatorial pathway design, 129, 130, 132
protein–protein interactions and, 133
- Adenosine monophosphate (AMP),
biosynthesis of, 2, 3
- Adriamycin, 95–96, 98
molecular structure of, 95
- Aerobacter aerogenes*, IMPDH in, 5, 18, 26
- Aglycones. *See also* Aglycons
anthracyclines and, 98–101
calicheamicin, 91, 92
macrolide glycosyltransferases and, 66
of vicenistatin, 93
- Aglycone substrates, accepted by OleD, 74
- Aglycon exchange reactions
CalG1-catalyzed, 92
CalG4-catalyzed, 93

- Aglycon exchanges, erythromycins
and, 70
- Aglycons. *See also* Aglycones
- anthracyclines and, 98–101
- avermectin and, 76–77
- in natural product glycosylation, 59
- oleandomycin and, 74–75
- in vicenistatin reactions, 94–95
- Aglycon specificity, methymycin and,
66–69
- Agrobacterium tumefaciens*
in artemisinin production, 158
in ubiquinone production, 166–167
- Aklavinone biosynthetic pathway, 72
- AknK glycosyltransferase, 96
mechanism of action of, 99
reactions catalyzed by, 97
- AknS glycosyltransferase, 96, 98,
100–101
mechanism of action of, 99
- aknT* gene, 98
- AknT glycosyltransferase, 98, 100–101
mechanism of action of, 99
- Alanine
cytochrome-P450 enzymes and, 189
in hydroxylated flavonoid synthesis, 190
protein dynamics and, 34
- Alcohol dehydrogenase (*Ec-adhE*), in butanol
production, 196–197
- Alcohol dehydrogenase (*adh*), in ethanol
production, 192
- Aldehydes, in epothilone synthesis, 169
- Alkaloids, in combinatorial pathway design,
128
- α -carotene, in carotenoid biosynthesis, 161,
162
- α -helix
of glycosyltransferases, 61, 62
of IMPDH, 33–34
- α -zearalenol, 94
- Amino acid residues, in polyketide synthesis,
169
- Amino acids
in flavanone synthesis, 177
in glycosyltransferase classification, 60
in purine nucleotide biosynthesis, 2
shikimates and, 173–174
- Amino acid sequences, in glycosyltransferase
design, 101–103
- Aminocoumarins, 86–88
molecular structures of, 87
- Aminomalonyl-ACP extender unit, in
combinatorial pathway design, 129, 130
- Ammonia, in purine nucleotide biosynthesis, 2
- Ammonia-limited conditions, biosynthesis
optimization under, 141–142
- Amorpha-4,11-diene monooxygenase, in
MVA pathway, 154
- Amorphadiene
in artemisinin synthesis, 158
in terpene biosynthesis, 138
- Amorphadiene synthase
in artemisinin synthesis, 158
in MVA pathway, 154
- AmpD1 glycosyltransferase, calicheamicin
and, 93
- AMP-dependent protein kinase (ADPK), 41
- Angiogenesis, flavonols in, 182
- Δ 6,7-Anhydroerythromycin C, synthesis of,
172
- Anomeric kinases, in natural product
glycosylation, 59
- Anthocyanidin synthase (ANS)
in anthocyanin synthesis, 184–185
in flavonoid pathway, 178–179
- Anthocyanins, 175–176, 183–185
medicinal uses of, 183
from plant cell cultures, 155
synthesis of, 178–179
- Anthracyclines, 95–101
mechanism of action of, 96–101
- Anthurium andraeanum*, in anthocyanin
synthesis, 184
- Antibiotics
aminocoumarins as, 86–88
aromatic polyketides as, 95–101
enediynes as, 88–93
glycopeptides as, 78–86
macrolactams as, 93–95
macrolides as, 64–78
nonribosomal peptides as, 78–86
polyketides as, 167

- Anticancer agents/drugs
 anthracyclines as, 96
 terpenoids as, 152
- Antimicrobial agents, terpenoids as, 152
- Antioxidants, ubiquinone, 166–167
- Apiferol, in flavonoid pathway, 178–179
- Apples
 in anthocyanin synthesis, 184
 flavonols from, 182–183
- appY* gene, in carotenoid biosynthesis, 164
- Aquifex aelicus*, peptidoglycan GTs of, 62
- araBAD promoter, carotenoid biosynthesis and, 140
- Arabidopsis thaliana*
 in anthocyanin synthesis, 185
 flavonols from, 182–183
 resveratrol from, 186
- Arabinose, oleandomycin and, 75
- araGT* gene, 101
- AraGT glycosyltransferase, 101
- Aranciamycin, rhamnosylation of, 101
- ArcA regulon, in ethanol production, 193
- Archaea
 IMPDH from, 5, 11
 in KEGG database, 126
- Arginine
 IMPDH ligand binding and, 299
 protein dynamics and, 34–35
 species-selective affinity and, 35
- Aristolochine, optimizing biosynthetic pathway for, 139
- AroE catalysis, in shikimate synthesis, 174, 175
- aro* enzymes, in shikimate synthesis, 174–175
- Aromatic amino acids, shikimates and, 173–174
- Aromatic flavonoid derivatives, 173–190
 from cytochrome-P450, 186–190
 flavonoids, 175–185
 shikimates, 173–175
 stilbenes, 185–186
- Aromatic polyketides, 95–101
- Artemisia annua*
 artemisinin from, 157, 158, 159
 in terpene biosynthesis, 138
- Artemisinic acid, 154
 artemisinin from, 157
 in terpene biosynthesis, 138
- Artemisinic acid pathway, 154
- Artemisinin, 134, 154
 enhanced production of, 157–158
 microbial synthesis of, 158
 from plant cell cultures, 157–158
 synthesis of, 157
 in terpene biosynthesis, 138
 yeast synthesis of, 158–159
- Aryltetrasaccharide, in calicheamicin, 89
- Aspartate, vancomycin Gtf's and, 62
- Aspartate–alanine substitutions, in IMPDH, 24–25
- Astaxanthin
 biosynthesis of, 164
 in carotenoid biosynthesis, 162
- ATP binding, to IMPDH subdomain, 41
- Autosomal dominant retinitis pigmentosa (adRP), 40, 41
- aveBI* gene, 75
- AveBI glycosyltransferase, 75–77
 calicheamicin and, 93
 reactions catalyzed by, 76
- Avermectin, 75–77
 molecular structure of, 57, 76
 reactions of, 76
- AviGT4 glycosyltransferase, 61
- Avilamycin, AviGT4 glycosyltransferase of, 61
- Azepinomycin, as IMPDH inhibitor, 16
- Azithromycin, 64
 molecular structure of, 65
- Baccatin III, in Taxol synthesis, 159
- Bacillus subtilis*, MEP pathway in, 153
- Bacteria. *See also* Microbial synthesis
 as biofuel synthesis biocatalysts, 191
 in butanol production, 196
 carotenoid biosynthesis in, 161–165
 carotenoids in, 160
 enterobactins from, 83–85
 in ethanol production, 191–192
 IMPDH from, 5–8, 11
 in KEGG database, 126
 MEP pathway in, 153–155

- Bacteria. (*Continued*)
terpene cyclases from, 137, 138
ubiquinone from, 166–167
unnatural carotenoids from, 165–166
vancomycin-resistant, 79
- Bacteriophage P1, in shikimate synthesis, 175
- Bacteriophage T5, in astaxanthin synthesis, 165
- Bacteriophage T7
in flavanone synthesis, 177
in Taxol synthesis, 160
- Baker's yeast, in carotenoid biosynthesis, 163
- Barrel fold structure
in IMPDH ligand binding, 27
in IMPDH molecules, 9
- Bateman domains
defined, 40
of inosine 5'-monophosphate dehydrogenase, 37, 39–42
in various proteins, 41–42
- Benzalacetone, medicinal applications of, 168
- Benzalacetone synthase (BAS), in polyketide synthesis, 169
- Benzaldehyde, in flavonoid synthesis, 176
- Benzimidazole NAD analog (BAD), 16
- Berberine, from plant cell cultures, 155
- β -carotene
in astaxanthin biosynthesis, 164, 165
in carotenoid biosynthesis, 161, 162
- β -carotene hydroxylase (*crtZ*)
in astaxanthin biosynthesis, 164
in carotenoid biosynthesis, 162
- β -carotene ketolase (*crtW*)
in astaxanthin biosynthesis, 164
in carotenoid biosynthesis, 162
- β -estradiol, 94
- β -methylene-biphosphonate (β -TAD, β -CH₂-TAD). *See also* Tiazofurin adenine dinucleotide (TAD)
in IMPDH activation, 38
IMPDH crystal structure and, 8, 11, 12
in IMPDH ligand binding, 28
kinetic properties of, 5, 6
NAD analogs of IMPDH and, 16
species-selective affinity and, 35
- β -sheets, of glycosyltransferases, 60, 61
- β -zearalenol, 94
- Binding sites, of inosine 5'-monophosphate dehydrogenase, 26–29
- Biocatalysis database, 127–128
- Biocatalyst-based processes, green chemistry and, 152
- Biocatalysts, microorganisms as, 191
- BioCyc database, 127
- Biodegradation database, 127–128
- Biofuels, 191–197
butanol, 191, 195–197
ethanol, 191–195
microbial synthesis of, 152
utility of, 191
- Bioinformatics
green chemistry and, 152
in polyketide synthesis, 168–169
in protein engineering and pathway design, 123
- Bioreactors, in flavonoid bioproduction, 175
- Biosynthesis, 151–217
of anthocyanins, 184
of aromatic derivatives, 173–190
of biofuels, 191–197
of carotenoids, 160–167
of cell walls, 62
of epothilones, 169, 170–171
of ethanol, 191–195
future of, 142–143
of guanine, 14
of isoflavones, 180–181
of natural products, 197–198
of polyketides, 167–173
of purine nucleotides, 1–4
of terpenoids, 152–160
- Biosynthetic enzymes
in natural product glycosylation, 59
searching for, 124
- Biosynthetic pathways
design of, 128–138
diversification of, 128–138
optimization of, 128, 137, 138–142
- Biosynthetic reaction sequences, combinatorial and evolutionary design of, 121–150

- Biotin ligase (*BirA*)
in flavanone synthesis, 177–179, 180
in malonyl-CoA formation, 179
- BLAST (Basic Local Alignment Search Tool)
algorithm, 123–124, 128
- Borrelia burgdorferi*, IMPDH from, 5–9,
11–13, 33
- Bovine β -1,4-galactosyltransferase, in
structure-guided glycosyltransferase
design, 104
- Bovine P450 17 α -hydroxylase, cytochrome-
P450 enzymes and, 189
- Breast cancer, flavones versus, 181
- Brefaldin A, 94
- Butanol
as biofuel, 191, 195–197
in ethanol production, 192
physical properties of, 195
- Butanol dehydrogenase (*bdhB*)
in butanol production, 196
in ethanol production, 192
- Butyraldehyde
in butanol production, 196
in ethanol production, 192
- Butyraldehyde dehydrogenase (*adhE*,
Ca-adhE)
in butanol production, 196
in ethanol production, 192
- Butyric acid, in butanol production, 196
- Butyryl-CoA
in butanol production, 196
in ethanol production, 192
- Butyryl-CoA dehydrogenase (*bcd*)
in butanol production, 196
in ethanol production, 192
- Cadinene synthase, in terpene biosynthesis,
137
- Caenorhabditis elegans*, resveratrol effects
in, 185
- Caffeic acid
in flavonoid pathway, 178–179
in resveratrol synthesis, 186
- calG1–4* genes, 89
- CalG1 glycosyltransferase, 89–91
reactions catalyzed by, 90, 91, 92
- CalG2 glycosyltransferase, calicheamicin
and, 93
- CalG3 glycosyltransferase, calicheamicin
and, 93
- CalG4 glycosyltransferase, 93
- Calicheamicin, 88–93
molecular structure of, 57, 89
- Calorimetric studies, of IMPDH, 32
- CAMERA (Cyberinfrastructure for
Advanced Marine Microbial Ecology
Research and Analysis) database, 128
- Cancer. *See also* Acute myelogenous
leukemia; Anticancer agents/drugs;
Breast cancer; Leukemia; Melanoma;
Tumor cells
carotenoids in treating, 161
IMPDH inhibitors versus, 14
- Cancer therapeutics, aminocoumarins as, 86
- Candida albicans*, species-specific drug
selectivity and IMPDH of, 36
- Carbocation migration, in terpene
biosynthesis, 137
- Carbomycin, 64
molecular structure of, 65
- Carbon dioxide (CO₂), in purine nucleotide
biosynthesis, 2
- Carboxylase gene, in erythromycin synthesis,
172
- Carotein. *See* ζ -carotein
- Carotenes, 160–161. *See also* β -carotene
entries
in carotenoid biosynthesis, 161, 162
- Carotenoid cyclases, in unnatural carotenoid
synthesis, 165
- Carotenoid desaturases, 135–136
- Carotenoid end group modifying enzymes,
136
- Carotenoid enzymes, 124, 125
- Carotenoid genes, in biosynthesis
optimization, 141
- Carotenoid oxygenase, 124, 125
- Carotenoid pathways, 161–163
- Carotenoids, 152, 160–167
classic, 161–165
evolutionary biosynthesis of, 135–136
medicinal uses of, 160–161

- Carotenoids (*Continued*)
 optimizing biosynthesis of, 140
 polyketides versus, 167
 as tetraterpenes, 134
 ubiquinone, 166–167
 unnatural, 165–166
- Carotenoid synthases, 136
- Catalytic triads, in glycosyltransferase
 mechanism of action, 62
- Catechins
 in anthocyanin synthesis, 185
 in flavonoid synthesis, 176
- Catharanthus roseus*, in flavone synthesis,
 182, 189–190
- Cation activation, of inosine 5'-mono-
 phosphate dehydrogenase, 36–39
- CAZY database, 60, 78
 in glycosyltransferase classification,
 101–102
- CBS (cysteine β -synthase) domains,
 41–42
 IMPDH, 39–40
- C–C bond formation, in polyketide synthesis,
 167–168
- Cell wall biosynthesis, 62
- Cethromycin, 65
 molecular structure of, 65
- C-GT mechanisms, 86
- Chain elongation, in rearranging and
 modifying PKS assembly line, 132
- Chalcone isomerase (CHI)
 in flavanone synthesis, 177
 in flavone synthesis, 181
 in flavonoid pathway, 178–179
 in isoflavone synthesis, 181
- Chalcones (CHL), 175
 in flavanone synthesis, 177
 in isoflavone synthesis, 181
 synthesis of, 176
- Chalcone synthase (CHS)
 in flavanone synthesis, 177
 in flavone synthesis, 181
 in flavonoid pathway, 178–179
 in polyketide synthesis, 169
- Chemical manufacturing, natural resources
 in, 152
- Chemical mechanisms, of inosine
 5'-monophosphate dehydrogenase, 29–31
- Chemical synthesis
 of epothilones, 169
 of flavonoids, 176
 green chemistry and, 152
 of polyketides, 167–168
- Chemoenzymatic glycorandomization, in
 natural product glycosylation, 58, 59
- Chemotherapeutic agents, purine nucleotide
 targets of, 14
- 6-Chloropurine riboside 5'-monophosphate
 (6-Cl-IMP). *See* 6-Cl-purine riboside
 monophosphate (6-Cl-IMP)
- Chloride ion channels, avermectin and, 75
- Chloroeremomycin, 79–83
- Chloroeremomycin pathway, in glycosyl-
 transferase mechanism of action, 62
- Chlorophyll-containing organisms,
 carotenoids in, 160
- Chloroquine, 157
- Chromosomes, locating genes on, 124
- Chrysanthemic acid, from plant cultures,
 156–157
- Chrysanthemum cinerariaefolium*, pyrethrins
 from, 156–157
- Chrysanthemum coccinum*, pyrethrins from,
 157
- Chrysin, in flavonoid pathway, 178–179
- Cinchona* bark, quinic acid from, 174
- Cinrolone, from plant cultures, 156–157
- Cinnamate 4-hydroxylase (C4H), 188, 189
 in flavone synthesis, 181
- Cinnamoyl-CoA, in flavonoid pathway,
 178–179
- Claisen(Schmidt condensation reaction, in
 flavonoid synthesis, 176
- Clarithromycin, 64
 molecular structure of, 65
- Classic carotenoids, 161–165
- Cleaning products, terpenoids as, 152
- CLM library, of calicheamicin
 variants, 91
- Clostridia, in butanol production, 196
- Clostridium*
 as biofuel synthesis biocatalyst, 191

- in butanol production, 197
- in ethanol production, 192
- Clostridium acetobutyllum*, in butanol production, 196
- 6-Cl-purine riboside monophosphate (6-Cl-IMP), 9, 13, 15, 23–24, 27. *See also* Inosine monophosphate (IMP)
- IMPDH activation and, 37, 38, 39
- IMPDH chemical mechanism and, 30
- IMPDH ligand binding and, 28
- protein dynamics and, 32
- CMP-sialic acid, in directed glycosyltransferase evolution, 105
- CoA-esters, in flavanone synthesis, 177
- Coenzyme-Q10 (CoQ10), in carotenoid biosynthesis, 162, 166–167. *See also* Ubiquinone(s)
- Colchicine, glycosylation of, 56
- Coleus blumei*, terpenoids from, 155
- Colorants, anthocyanins as, 183
- Combinatorial biosynthesis, in natural product glycosylation, 59
- Combinatorial design, of biosynthetic reaction sequences, 121–150
- Combinatorial pathway design, 128
- Comprehensive Microbial Resource (CMR), 124, 125
- Conformation, of IMPDH, 26
- Conformational flexibility, of inosine 5'-monophosphate dehydrogenase, 13, 31–35
- Congenital amaurosis, 40
- Contigs, in KEGG database, 126–127
- Cooperativity, protein dynamics and, 32
- Coptis japonica*, terpenoids from, 155
- 4-Coumaryl-CoA ligase (4CL)
 - in flavanone synthesis, 177
 - in flavone synthesis, 181
 - in flavonoid pathway, 178–179
 - in resveratrol synthesis, 186
- Coumaric acid
 - in flavonoid pathway, 178–179
 - in resveratrol synthesis, 186
- Coumermycin A1, 88
 - molecular structure of, 87
- CouM glycosyltransferase, 88
- crt* gene, in carotenoid biosynthesis, 164
- Crotonase (*crt*, *Ca-crt*)
 - in butanol production, 196
 - in ethanol production, 192
- Crotonyl-CoA, in butanol production, 196
- Crotonyl-CoA reductase, in erythromycin synthesis, 172
- CrtB. *See* Phytoene synthase (*crtB*)
- CrtE. *See* Geranylgeranyldiphosphate synthase (GGPPS, *crtE*)
- crtEBI* operon, in carotenoid biosynthesis, 163
- CrtI. *See* Phytoene desaturase (*crtI*)
- CrtM. *See* Dehydrosqualene synthase (*crtM*)
- CrtM* carotenoid gene, 124, 125
- CrtN. *See* Dehydrosqualene desaturase (*crtN*)
- CrtN* carotenoid gene, 124, 125
- CrtOx homolog, 124, 125
- CrtW. *See* β -carotene ketolase (*crtW*)
- CrtWZYIBE protein, in astaxanthin biosynthesis, 164
- CrtY. *See* Lycopene cyclase (*crtY*)
- crtY* gene, in unnatural carotenoid synthesis, 166
- CrtZ. *See* β -carotene hydroxylase (*crtZ*)
- Cryptosporidium parvum*, IMPDH from, 6
- Crystal structures
 - of IMPDH, 5–8, 9
 - protein dynamics and, 32
- C-terminal domain, in glycosyltransferases, 60–62
- Cyanidin-3-*O*-glucoside, in anthocyanin synthesis, 185
- Cyaninidin, in flavonoid pathway, 178–179
- Cyclases, in unnatural carotenoid synthesis, 165
- Cyclic carotenoids, synthesis of, 165
- Cycloguanile, 157
- Cyclonovobioc acid, 86–87
- CYP71AV1 P450 enzyme, in artemisinin synthesis, 159
- CYP71 P450 enzymes, in terpene biosynthesis, 138
- Cysteine
 - in IMPDH activation, 37
 - in IMPDH ligand binding, 27

- Cysteine (*Continued*)
in IMPDH molecules, 9–11, 14, 15
protein dynamics and, 32
- Cytochrome-P450. *See also* P450 entries
in flavone synthesis, 181
in Taxol synthesis, 160
- Cytochrome-P450 enzymes, aromatic
flavonoid derivatives via, 186–190
- Cytochrome-P450 isoflavone synthase (IFS),
in isoflavone synthesis, 180–181
- Cytochrome-P450 reductase (CPR)
in artemisinin synthesis, 159
in flavone synthesis, 182
in flavonoid pathway, 178–179
in hydroxylated flavonoid synthesis, 190
in MVA pathway, 154
in terpene biosynthesis, 138
- Cytotoxicity
of anthracyclines, 96
of avermectins, 75
of enediynes, 88–89
- D₂O, IMPDH chemical mechanism and, 31
- Daidzein, synthesis of, 180
- Dalbavancin, 79
molecular structure of, 80
- Databases
future of, 143
of genomic sequences, 123–126
of metabolic pathways, 126–128
- Daunomycin, 95–96, 97–98
molecular structure of, 95
- Daunorubicin, 95–96
molecular structure of, 95
- Daunosamine, 96–98
- ddsA* gene, in ubiquinone biosynthesis,
167
- 10-Deacetylpaclitaxel, from *Taxus* cell
cultures, 156
- Dehydratase domain, in combinatorial
pathway design, 129
- Dehydration, in rearranging and modifying
PKS assembly line, 132
- Dehydrogenase activity, potassium ion in, 5, 6
- 3-Dehydroquinic acid (DHQ), in shikimate
synthesis, 174, 175
- 3-Dehydroshikimic acid (DHS), in shikimate
synthesis, 174, 175
- Dehydrosqualene desaturase (*crtN*), in
carotenoid biosynthesis, 162, 163
- Dehydrosqualene synthase (*crtM*), in
carotenoid biosynthesis, 162, 163
- 13-Dehydroxybaccatin, from *Taxus* cell
cultures, 156
- Demethylsperidene, biosynthesis of, 165
- 3-Deoxy-D-arabino-heptulosonic acid
7-phosphate (DAHP), in shikimate
synthesis, 174
- 3-Deoxy-D-arabino-heptulosonic acid
7-phosphate synthase (*aroF*), in
shikimate synthesis, 174, 175
- 6-Deoxyerythronolide B (6-DEB, 6dEB)
erythromycins from, 69–70, 171, 172
production of, 131
in rearranging and modifying PKS
assembly line, 132
synthesis of, 167–168
- Deoxyerythronolide B synthase (DEBS), in
erythromycin synthesis, 171–172
- Deoxyfucose, AknK glycosyltransferase and,
96–98
- 2-Deoxyfucosyl-rhodinosaminyl-aklavinone,
98
- Deoxysugars, in polyketide biosynthesis, 132
- Deoxyxylulose-5-phosphate (DXP),
153–154, 155
- Deoxyxylulose-5-phosphate
isomeroreductase, 153–154, 155
- Deoxyxylulose-5-phosphate pathway, 135
- Deoxyxylulose-5-phosphate synthase (DXPS)
in carotenoid biosynthesis, 163
in MEP pathway, 153
in Taxol synthesis, 160
- Deoxyxylulose-P synthase promoter,
carotenoid biosynthesis and, 140
- Desaturases, carotenoid, 135–136
- Desosamine, 70, 72
- desVII/VIII* genes, methymycin and, 66
- DesVII–DesVIII glycosyltransferases
anthracyclines and, 98
erythromycins and, 70
methymycin and, 66–69

- Deuterium kinetic isotope effect (^2H KIE).
See also D_2O
 IMPDH activation and, 38–39
 IMPDH kinetics and, 19–20, 21, 24, 31
 3,4-Dichloroaniline, oleandomycin and, 74
 Digitoxin, glycosylation of, 56
 Dihydro- β -carotenes, biosynthesis of, 165
 Dihydroflavonol 4-reductase (DFR), in
 flavonoid pathway, 178–179
 Dihydroflavonols, in flavonol synthesis, 182
 Dihydrokaempferol
 in hydroxylated flavonoid synthesis, 190
 synthesis of, 183
 Dihydroquercetin
 in hydroxylated flavonoid synthesis, 190
 synthesis of, 183
 1,1'-Dihydroxylicopenone, biosynthesis of, 165
 7,8-Dihydrozeaxanthin, biosynthesis of, 165
 Dimethylallyl diphosphate. *See* Dimethylallyl
 pyrophosphate (DMAPP)
 Dimethylallyl pyrophosphate (DMAPP), 134
 in Taxol synthesis, 159–160
 in terpenoid synthesis, 153, 154, 155
 4-Diphosphocytidyl-2-C-methyl-D-erythritol
 (CDP-ME), in MEP pathway, 154, 155
 Diphospholipid donor-dependent
 peptidoglycan glycosyltransferases, 62
 Diphosphomevalonate decarboxylase, in
 MVA pathway, 154
 Directed evolution
 of carotenoids, 135–136
 of glycosyltransferases, 104–106
 of terpene biosynthesis, 137–138
 Disaccharides, in vancomycin, 56, 57
 Diterpenes, 134
 Diversification, biosynthetic pathway, 128–138
 DNA, anthracycline interactions with, 96
 DNA damage, from enediynes, 88–89
 DNA sequences, BLAST algorithm with,
 123–124
 DNA technologies, future of, 143
 dNDP-D-olivose, urdamycin A and, 102. *See*
also NDP (nucleoside diphosphate)
 donors
 dNDP-L-rhodinose, urdamycin G and, 102
 Domains, protein dynamics and, 31
 Donor/acceptor specificity, of
 glycosyltransferases, 101
 Donor substrates, accepted by OleD, 74
 Double-displacement mechanism, of
 glycosyltransferases, 63–64
 Downstream enzyme promoters, carotenoid
 biosynthesis and, 140
 Doxorubicin, 95–96,
 molecular structure of, 95
Drosophila melanogaster, resveratrol effects
 in, 185
 Drug resistance, in *Saccharomyces*
cerevisiae, 36. *See also* Resistance
 dTDP donor substrates
 erythromycins and, 70
 of DesVII–DesVIII, 68
 vicenistatin and, 93–94, 95
 dTDP-rhodamine, 98
 DXD motif, in glycosyltransferases, 60
dxs gene, carotenoid biosynthesis and, 140,
 164, 165
 EcoCyc database, 127
 EXIMP complex. *See also* Inosine
 monophosphate (IMP)
 in IMPDH kinetics, 17–19
 protein dynamics and, 32
 in *Trichomonas foetus*, 20, 22, 27–28
 Electron transfer proteins (etfAB), in butanol
 production, 196
 Elloramycin, 132
 EXMMP complex. *See also* Mizoribine
 monophosphate (MMP)
 in IMPDH activation, 38
 protein dynamics and, 33, 34
 species-selective affinity and, 35
 EXNAD complex, in *Trichomonas*
foetus, 22. *See also* Nicotinamide
 adenine dinucleotide (NAD)
 Endoplasmic reticulum (ER), cytochrome-
 P450 enzymes and, 186–187, 188
 Enediynes, 88–93
 Engineering. *See also* Genetic engineering;
 Metabolic engineering; Metabolic
 pathway engineering; Pathway
 engineering; Protein engineering

- Engineering. (*Continued*)
of anthocyanin synthesis, 184–185
of biofuels, 191
of flavanone synthesis, 177
of flavonoids, 175–176
of flavonols, 182–183
of hydroxylated flavonoid synthesis, 189–190
of isoprenoid pathways, 134–135
of natural product glycosyltransferases, 101–106
of resveratrol synthesis, 185–186
of unnatural carotenoids, 165–166
- Enolates, synthesis of, 167–168
- Enoyl reductase domain, in combinatorial pathway design, 129, 132
- Enterobactins, 83–86
glucosylation of, 85
molecular structure of, 57, 85
- Enterococci, vancomycin-resistant, 79
- Enterococcus faecium*, vancomycin derivatives versus, 82
- Enthalpy–entropy compensation, protein dynamics and, 32
- Enzyme activity, in biosynthetic pathway regulation, 143
- Enzyme-based reactions, green chemistry and, 152
- Enzyme-dependent approaches, to natural product glycosylation, 58, 59
- Enzyme expression levels, messenger RNA (mRNA) transcript and, 140–141
- Enzyme function, protein dynamics and, 31
- Enzymes
in anthocyanin synthesis, 184
in biosynthetic pathway optimization, 138–139
in butanol production, 196–197
carotenoid end group modifying, 136
cytochrome-P450, 186–190
in ethanol production, 192
in flavanone synthesis, 177
in flavone synthesis, 182
in flavonoid pathway, 178–179
in isoflavone synthesis, 180–181
in medical and industrial compound synthesis, 122, 123
in shikimate synthesis, 174–175
in Taxol synthesis, 159, 160
- epoA* gene, in epothilone biosynthesis, 170
- epo* genes, in epothilone biosynthesis, 170
- EPOSA module, in epothilone biosynthesis, 170
- EPOSP module, in epothilone biosynthesis, 170
- Epothilone A
biosynthesis of, 170, 171
molecular structure of, 168
- Epothilone B
biosynthesis of, 170, 171
molecular structure of, 168
- Epothilone C, biosynthesis of, 170, 171
- Epothilone D, biosynthesis of, 170, 171
- Epothilones, 167, 169–171
biosynthesis of, 169, 170–171
chemical synthesis of, 169
industrial development of, 169–170
molecular structure of, 168, 170
- Epoxidases, in carotenoid biosynthesis, 161, 162
- ERG* genes, in artemisinin synthesis, 158–159
- Ergosterol, 134, 135
in carotenoid biosynthesis, 163
- ERG8* gene, MVA pathway and, 153, 154
- Eriodictyol
in flavonoid pathway, 178–179
synthesis of, 183
- Erwinia*, carotenoid desaturases from, 136
- Erwinia herbicola*, unnatural carotenoids from, 165–166
- Erwinia uredovora*
in carotenoid biosynthesis, 163
unnatural carotenoids from, 165–166
- EryBV glycosyltransferase, 70, 71
calicheamicin and, 93
- EryCII/III glycosyltransferases, 70–72
- eryCIII* gene, 70
- Erythromycin(s), 69–72, 167, 171–172
molecular structure of, 168
oleandomycin and, 75

- Erythromycin A, 64
 biosynthesis of, 69
 molecular structure of, 65, 69
 synthesis of, 167–168
- Erythromycin B, molecular structure and biosynthesis of, 69, 70
- Erythromycin C, molecular structure and biosynthesis of, 69, 70
- Erythromycin D, molecular structure and biosynthesis of, 69, 70
- Erythromycin G, 70
- Erythronolides, 69–70. *See also*
 6-Deoxyerythronolide B entries
- Erythrose 4-phosphate (E4P), in shikimate synthesis, 174
- Escherichia coli*
 anthocyanins from, 184, 185
 aromatic flavonoid derivatives from, 186, 187, 188–189
 in artemisinin synthesis, 158, 159
 in astaxanthin biosynthesis, 164, 165
 as biofuel synthesis biocatalyst, 191
 in butanol production, 196–197
 calicheamicin from, 89
 in carotenoid biosynthesis, 140, 163, 164
 in combinatorial pathway design, 128, 129
 in directed glycosyltransferase evolution, 104–105
 enterobactin and, 85
 epothilones from, 169
 in erythromycin synthesis, 171, 172
 in ethanol production, 191–192, 192–193
 ethanol-tolerant strains of, 193–194, 195
 in flavanone synthesis, 177, 179, 180
 flavones from, 181
 in flavonoid synthesis, 176
 flavonols from, 183
 IMPDH subdomain in, 41
 inosine 5'-monophosphate dehydrogenase from, 6, 9, 12, 15, 22–25, 29, 36, 38–39
 isoflavones from, 181
 isoprenoid pathways engineered in, 134–135
 MEP pathway in, 154, 155
 in natural product biosynthesis, 198
 optimizing biosynthesis in, 141
 patellamide biosynthesis by, 126
 in PCP degradation, 142
 polyketide biosynthesis in, 130–132
 as production organism, 142–143
 resveratrol from, 185–186
 in shikimate synthesis, 174–175
 in Taxol synthesis, 160
 in terpene biosynthesis, 138
 ubiquinone from, 167
 unnatural carotenoids from, 165–166
- Esperamycin-A, shikimates and, 173
- Esters, from plant cultures, 156–157
- Estradiol, 94, 180
- Ethanol, as biofuel, 191–195
- 5-Ethylerythromycin, synthesis of, 172
- Ethylmalonyl-CoA extender unit
 in combinatorial pathway design, 129, 130
- Eucarya (eukaryotes)
 aromatic flavonoid derivatives from, 186
 IMPDH from, 5, 11
 in KEGG database, 126
- Eukaryotic cytochrome-P450, in isoflavone synthesis, 180–181
- Euphorbia milli*, terpenoids from, 155
- Evolutionary design
 of biosynthetic reaction sequences, 121–150
 of glycosyltransferases, 104–106
 in isoprenoid biosynthesis, 134–138
- EXXMP complex. *See also* Xanthosine 5-monophosphate (XMP)
 in IMPDH kinetics, 17–19
 in *Trichomonas foetus*, 21
- E-XMP* hydrolysis
 in *Escherichia coli*, 22, 23–24
 in humans, 25–26
 protein dynamics and, 34–35, 36
- EXXMPXNAD complex. *See also* Nicotinamide adenine dinucleotide (NAD)
 in IMPDH kinetics, 18–19
 in IMPDH ligand binding, 29
 protein dynamics and, 34
- E-XMP* thioimidate, 4
 in IMPDH activation, 37, 39
 IMPDH chemical mechanism and, 29, 30
 in IMPDH kinetics, 17–19

- E-XMP* (*Continued*)
 IMPDH ligand binding and, 26, 27, 28, 29
 species-selective affinity and, 35
 in *Trichomonas foetus*, 21–22
- Extender units, in combinatorial pathway design, 129, 130, 131
- Farnesyl diphosphate (FPP), 135, 136
 in biosynthetic pathway optimization, 139
 in carotenoid biosynthesis, 162, 163
 in MVA pathway, 153, 154
- Farnesyl diphosphate synthase. *See* Farnesyl pyrophosphate synthase (FPPS)
- Farnesyl pyrophosphate synthase (FPPS)
 in artemisinin synthesis, 158
 in carotenoid biosynthesis, 163
 in MVA pathway, 154
- Far-ultraviolet (UV) dichroism spectrum,
 protein dynamics and, 32
- Fe(III). *See* Iron [Fe(III)]
- Fermentation
 in biosynthesis optimization, 142
 in butanol production, 197
 in erythromycin synthesis, 172
 in ethanol production, 191–192
 in terpene biosynthesis, 138
- FK506 immunosuppressant, shikimates and,
 173
- Flanking domain, in IMPDH molecules, 9
- Flap structures
 in IMPDH ligand binding, 27
 in IMPDH molecule, 4, 9, 11, 12,
 13, 20
 protein dynamics and, 31, 32, 33–34
- Flavanone 3 β -hydroxylase (FHT)
 in flavonoid pathway, 178–179
 in flavonol synthesis, 182
- Flavanones, 175, 177–180
 in flavone synthesis, 181
 in flavonol synthesis, 182
 synthesis of, 176, 177–180
- Flavones, 175, 181–182
 medicinal applications of, 181
 synthesis of, 176, 178–179
- Flavone synthases (FSI, FSII)
 in flavone synthesis, 182
 in flavonoid pathway, 178–179
 cytochrome-P450 enzymes and, 189–190
 in flavonoid pathway, 178–179
- Flavonoid 3'-hydroxylase (F3'H),
 cytochrome-P450 enzymes and, 189–190
- Flavonoid glycosyltransferases, mechanisms
 of action of, 62
- Flavonoid pathways, 178–179
 in combinatorial pathway design, 129
- Flavonoids, 175–185
 anthocyanins, 183–185
 in directed glycosyltransferase evolution,
 105–106
 flavanones, 177–180
 flavones, 181–182
 flavonols, 182–183
 isoflavones, 180–181
 polyketides versus, 167
- Flavonols, 175, 182–183
 synthesis of, 176, 178–179
- Flavonol synthase (FLS)
 in flavonoid pathway, 178–179
 in flavonol synthesis, 182
- Flexibility, of inosine 5'-monophosphate
 dehydrogenase molecule, 13, 31–35
- Fluorescent-activated cell sorting (FACS),
 in directed glycosyltransferase
 evolution, 105
- FNR regulatory function, in ethanol
 production, 193
- Fold structures
 in glycosyltransferase mechanism of
 action, 62–63
 in glycosyltransferases, 60, 61–62
- FPP genes, in artemisinin synthesis, 158–159
- Fragaria*, in anthocyanin synthesis, 185
- Fragrances, terpenoids as, 152
- Front-face mechanism, of
 glycosyltransferases, 64
- Fruits
 anthocyanins in, 183
 flavonoids from, 175
 improving carotenoid content of, 161
- Fucose, AknK glycosyltransferase and,
 96–98

- Fuel, in chemical manufacturing, 152
- Fumarate reductase (*frd*, *frdBC*)
in butanol production, 196–197
in ethanol production, 192
- Fungi, carotenoids in, 160. *See also* Yeast
- Galactose, oleandomycin and, 74–75
- β -1,4-Galactosyltransferase, in structure-guided glycosyltransferase design, 104
- Gasoline, butanol and, 195
- GenBank, 124
- Gene assignments, in genomes, 123–124
- Gene cassettes, in natural product glycosylation, 58
- Gene clusters, 124
methymycin and, 66
in tylosin synthesis, 173
- Gene deletions, in carotenoid biosynthesis, 163–164
- Gene expression, in biosynthetic pathway regulation, 143
- Genes
in biosynthesis optimization, 141
in butanol production, 196
in epothilone biosynthesis, 170
in erythromycin synthesis, 171–172
locating on chromosomes, 124
plant biosynthetic, 137
- Genetic engineering, green chemistry and, 152. *See also* Engineering
- Genetic manipulations, in improving carotenoid content of plants, 161
- Genistein
in flavonoid pathway, 178–179
synthesis of, 180
- Genkwanin, in flavonoid pathway, 178–179
- Genome shuffling, in biosynthesis optimization, 142
- Genomics, 123
- Genomic sequences, 123–126
databases of, 123–126
in medical and industrial compound synthesis, 122
- Geranyl diphosphate (GPP)
in MVA pathway, 153, 154
in Taxol synthesis, 159
- Geranylgeranyl diphosphate (GGDP, GGPP), 135, 136
in carotenoid biosynthesis, 161, 162
in Taxol synthesis, 160
- Geranylgeranyldiphosphate synthase (GGPPS, *crtE*)
in carotenoid biosynthesis, 140, 161, 162, 163
in Taxol synthesis, 159, 160
in unnatural carotenoid synthesis, 165–166
- Gerbera*, in anthocyanin synthesis, 185
- Gibberellins, 152
- Gluconobacter suboxydans*, ubiquinone from, 167
- Glucosaminyltransferases, 83
- Glucose
calicheamicin and, 89
NovM glycosyltransferase and, 88
- Glucose metabolism, in shikimate synthesis, 174
- Glucosylase, carotenoid, 136
- Glutamic acid (glutamate)
cytochrome-P450 enzymes and, 188
in IMPDH activation, 37
species-selective affinity and, 35
- D-Glyceraldehyde 3-phosphate (G3P)
in carotenoid biosynthesis, 161, 164
in isoprenoid production, 135
in MEP pathway, 153
- Glycerol-limited conditions, biosynthesis optimization under, 141–142
- Glycidol, in epothilone synthesis, 169
- Glycine
cytochrome-P450 enzymes and, 189
in IMPDH activation, 37
- Glycine metabolism, in ethanol production, 193
- Glycodiversification, strategies for, 56–58, 59
- Glycopeptide antibiotics, 78–86
- Glycosylation, of 6-DEB, 131–132
- Glycosyltransferases (GTs), 55–119
aminocoumarins, 86–88
aromatic polyketides, 95–101
in carotenoid biosynthesis, 163
chemical mechanisms of, 62–64

- Glycosyltransferases (*Continued*)
in combinatorial pathway design, 129
enediynes, 88–93
engineering, 101–106
importance of natural product, 56–58,
59, 107
in vitro characterization of natural product,
64–101
macrolactams, 93–95
macrolides, 64–78
nonribosomal peptides, 78–86
in polyketide biosynthesis, 132
sequence classification of, 58–60
structural classification of, 60–62
- GMP reductase, molecular structure of, 9. *See also* Guanosine monophosphate (GMP)
- GOLD database, 123
- Grains, anthocyanins in, 183
- Gram-negative bacteria, MEP pathway in, 153
- Grapes. *See also* *Vitis vinifera*
anthocyanins from, 183
resveratrol from, 185
- “Green/amber/red assay,” in oleandomycin
studies, 73–74
- Green chemistry, 152
- Growth processes, biosynthesis optimization
and, 141–142
- Grubbs catalyst, in epothilone synthesis, 169
- GT-A fold structure
in directed glycosyltransferase evolution,
104–105
in glycosyltransferase mechanism of
action, 62–63
in glycosyltransferases, 60, 61, 62
in structure-guided glycosyltransferase
design, 103–104
- GT-B fold structure
in directed glycosyltransferase evolution,
105–106
in glycosyltransferase mechanism of
action, 62–63, 86
in glycosyltransferases, 60, 61–62, 78
in structure-guided glycosyltransferase
design, 104
- GtfA glycosyltransferase, chloroeremomycin
and, 79–82
- GtfB glycosyltransferase
calicheamicin and, 93
chloroeremomycin and, 79–82
- GtfC glycosyltransferase, chloroeremomycin
and, 79–82
- GtfD glycosyltransferase, 61
calicheamicin and, 93
vancomycin and, 79–83
- GtfE glycosyltransferase, vancomycin and,
79–82
- Guanacastepenes, 152
- Guanine biosynthesis, 14
- Guanosine monophosphate (GMP),
biosynthesis of, 2, 3. *See also* GMP
reductase
- Haematococcus pluvialis*, in carotenoid
biosynthesis, 164
- Halogenases, in combinatorial pathway
design, 129
- Halo-purine nucleotides, IMPDH chemical
mechanism and, 30
- Hamsters. *See* Mammals
- Heart disease, carotenoids in treating, 161
- Heavy water (D₂O), IMPDH chemical
mechanism and, 31
- Hedamycin, 86
- HedL glycosyltransferase, 86
- Hemoglobin, in astaxanthin synthesis,
164–165
- Herbs, flavonoids from, 175
- Heterologous hosts
optimizing biosynthesis in, 141
polyketide production in, 131–132
as production organisms, 142–143
in terpene biosynthesis, 137–138
- Hsp90 glycosyltransferase, 86
- Humans
flavonoids for, 175
IMPDH subdomain in, 41
inosine 5'-monophosphate dehydrogenase
from, 5–9, 25–27, 29, 37–39
medicinal benefits of carotenoids to, 161
resveratrol effects in, 185
- Hybrid genomes, in combinatorial pathway
design, 129

- Hydride transfer, IMPDH activation and, 38
- Hydrogen bonding
in IMPDH ligand binding, 29
vicenistatin reactions and, 94
- Hydrolysis
of E-XMP* thioimidate, 4
IMPDH chemical mechanism and, 30
- 1-Hydroxy-2-methyl-2-(*E*)-butenyl
4-diphosphate (HMBPP), in MEP
pathway, 154, 155
- 3-Hydroxy-3-methylglutaryl-coenzyme A
(HMG-CoA), in MVA pathway, 153, 154
- 3-Hydroxy-3-methylglutaryl-coenzyme A
reductase
in artemisinin synthesis, 158
in MVA pathway, 153, 154
- 3-Hydroxy- β -zeacarotene, biosynthesis of,
165
- 3-Hydroxybutyryl-CoA, in ethanol
production, 192
- 3-Hydroxybutyryl-CoA dehydrogenase (*hbd*)
in butanol production, 196
in ethanol production, 192
- 1'-Hydroxy- γ -carotene, biosynthesis of, 165
- Hydroxylases
carotenoid, 136
in carotenoid biosynthesis, 161, 162
- Hydroxylated flavonoids, synthesis of,
189–190
- 1-Hydroxylycopene, biosynthesis of, 165
- Hydroxymalonyl-ACP extender unit, in
combinatorial pathway design,
129, 130
- 1-Hydroxyneurosporine, biosynthesis of, 165
- Hypericins, from plant cell cultures, 155
- Hypericum perforatum*, terpenoids from, 155
- Hypoxanthine, in purine nucleotide
biosynthetic pathways, 2
- Idarubicin, 98
- idi* gene
in astaxanthin synthesis, 165
carotenoid biosynthesis and, 140
- Illicium*, shikimic acid from, 174
- IMD2/4* genes, in *Saccharomyces cerevisiae*,
36
- IMP analogs, of IMPDH, 15, 16. *See also*
Inosine monophosphate (IMP)
- IMP binding site, of IMPDH, 26–28
- IMP dehydrogenases, 15
- IMPDH inhibitors, 4. *See also* Inosine
5'-monophosphate dehydrogenase
(IMPDH)
medicinal applications of, 14–16
- IMPDH monomer, 4
- Industrial compounds, synthesis of, 122
- Ingenol, 152
- Inhibitors, of inosine 5'-monophosphate
dehydrogenase, 14–16, 17
- Inosine 5'-monophosphate dehydrogenase
(IMPDH), 1–53. *See also* IMPDH
entries
active site of, 23–24
Bateman domain of, 37, 39–42
chemical mechanism of, 29–31
crystal structure of, 5–8
effects of mutations of, 25
from *Escherichia coli*, 6, 9, 12, 15,
22–25, 29
human, 5–9, 25–26
IMP analogs of, 15, 16
isozymes of, 3–4
kinetic mechanism of, 17–26
kinetic properties of, 5, 6
ligand binding of, 26–29
medicinal applications of inhibitors of,
14–16
molecular structure of, 9–13
monovalent cation activation of, 36–39
NAD analogs of, 15–16
natural product inhibitors of, 16
novel synthetic inhibitors of, 17
prominent features of, 4–5, 6, 7
protein conformational flexibility of, 13,
31–35
protein structures of, 5–13
purification of, 5
in purine nucleotide biosynthesis, 1–4
sequence comparisons among isozymes
of, 12
species-specific drug selectivity of, 35–36
subdomain of, 9, 13, 37, 39–42

- Inosine (*Continued*)
substrate interactions of, 17–20
from *Trichomonas foetus*, 6–8, 9–11, 12, 13, 16, 20–22, 27–28, 29
water activation mechanism of, 31–35
- Inosine monophosphate (IMP). *See also* EXIMP complex; IMP entries; 6-Cl-purine riboside monophosphate (6-Cl-IMP)
binding of, 4, 26–28
in *Escherichia coli*, 22–25
in humans, 25–26
in IMPDH activation, 37, 38
IMPDH chemical mechanism and, 29, 30, 31
IMPDH inhibitors and, 14, 15, 16
in IMPDH kinetics, 18–19
kinetic properties of, 5, 6
molecular structure of, 3
protein dynamics and, 32
in purine nucleotide biosynthetic pathways, 2, 3
in *Trichomonas foetus*, 20–22
- Insecticides, pyrethrins as, 156–157
- Institute for Genomic Research, The (TIGR), 124, 125
- Inverting enzymes, in glycosyltransferase classification, 60
- Inverting glycosyltransferases, mechanism of action of, 62–63
- In vitro evolution, of carotenoid functions, 135
- IPP–DMAPP isomerase, in MVA pathway, 154. *See also* Dimethylallyl pyrophosphate (DMAPP); Isopentenyl pyrophosphate (IPP)
- IPP isomerase
in artemisinin synthesis, 158
in Taxol synthesis, 159–160
- iroB* gene, 85
- IroB glycosyltransferase, 85–86
- Iron [Fe(III)], enterobactins and, 83–85
- Isoflavones, 175, 180–181
- Isoflavone synthase (IFS)
in flavonoid pathway, 178–179
in isoflavone synthesis, 180–181
- Isoflavonoids, 180
synthesis of, 178–179
- Isolemonene, artemisinin from, 157
- Isoleucine, IMPDH ligand binding and, 299
- Isopentenyl diphosphate. *See* Isopentenyl pyrophosphate (IPP)
- Isopentenyl diphosphate isomerase (*Idi*), in carotenoid biosynthesis, 163
- Isopentenyl pyrophosphate (IPP), 134. *See also* IPP entries
in biosynthetic pathway optimization, 139
in carotenoid biosynthesis, 161, 162, 163
in Taxol synthesis, 159–160
in terpenoid synthesis, 153, 154, 155
- Isopentenyl pyrophosphate isomerase
promoter, carotenoid biosynthesis and, 140
- Isoprene units
in terpenoid synthesis, 153, 154, 155
in ubiquinone synthesis, 166
- Isoprenoid biosynthesis, evolutionary design in, 134–138
- Isoprenoids, 134, 152. *See also* Terpenoids
- Isoprenoid wax esters, microbial synthesis of, 124–125
- Isorawsonol, as IMPDH inhibitor, 16
- Isozymes, IMPDH, 3–4, 5–13
- ispB* gene, in astaxanthin synthesis, 165
- ispD* gene, carotenoid biosynthesis and, 140
- ispDispF* gene, in astaxanthin synthesis, 165
- ispF* gene, carotenoid biosynthesis and, 140
- ispH* gene, in MEP pathway, 154, 155
- Ivermectins, 75–76
molecular structure of, 76
- Jasmolone, from plant cultures, 156–157
- J. Craig Venter Institute, metagenomic database at, 128
- Kaempferol
in flavonoid pathway, 178–179
in hydroxylated flavonoid synthesis, 190
oleandomycin and, 75
synthesis of, 183
- KEGG (Kyoto Encyclopedia of Genes and Genomes) databases, 126–127
- Ketoacids, in epothilone synthesis, 169
- Ketolase, carotenoid, 136

- Ketolides, 64–65
- Ketoreductase (KR) domain, in combinatorial pathway design, 129, 130, 132
- Ketosynthase (KS) domain
in combinatorial pathway design, 129, 130, 132–133
protein–protein interactions and, 133–134
- Kinetic analysis, of vancomycin derivatives, 79
- Kinetic isotope effect (KIE), IMPDH kinetics and, 19–20, 21, 24, 31
- Kinetic mechanisms, of inosine 5'-monophosphate dehydrogenase, 17–20, 20–22, 22–26
- Kinetics
of IMPDH, 5, 6
of IMPDH chemical mechanism, 30–31, 32–35, 37, 38–39
of IMPDH ligand binding, 26–29
of IMP, MMP, RMP, MPA, and TAD, 5, 6
of *Trichomonas foetus* IMPDH, 19
- Klebsiella oxytoca*, in ethanol production, 192
- KO11 *Escherichia coli*, in ethanol production, 192–193
- lac* promoter, in artemisinin synthesis, 158
- Lactate dehydrogenase (*ldhA*), in butanol production, 196–197
- Lactobacillus*, in low pH environments, 142
- Lactococcus lactis*, IMPDH Bateman domain in, 41–42
- Lactone aglycones, macrolide glycosyltransferases and, 66
- lacZ* gene, 188, 189
- Landomycin oligosaccharide, 75
- LanGT1 glycosyltransferase, 75
- LanGT4 glycosyltransferase, 75
- Leber congenital amaurosis, 40
- Leucine, in hydroxylated flavonoid synthesis, 190
- Leucoanthocyanidins
in anthocyanin synthesis, 185
in flavonoid synthesis, 176
- Leucoanthocyanin synthase (LAR), in flavonoid pathway, 178–179
- Leucocyanidin, in flavonoid pathway, 178–179
- Leucodelphinidin, in flavonoid pathway, 178–179
- Leucopelargonidin, in flavonoid pathway, 178–179
- Leukemia
enediynes versus, 89
IMPDH isozymes and, 4
- Lewis acids, in glycosyltransferase mechanism of action, 63, 64
- LgtC glycosyltransferase, 60, 61
- Library, of calicheamicin variants, 91
- Ligand binding
of inosine 5'-monophosphate dehydrogenase, 26–29
protein dynamics and, 31, 32
- Ligands, in KEGG database, 126–127
- Limonene, 134
- Limonene hydroxylase, 187–188
- Lindleyin, medicinal applications of, 168
- Lipophilic antioxidants, ubiquinone, 166–167
- Loop structures
in IMPDH ligand binding, 27
in IMPDH molecules, 9–11, 12, 13, 20
protein dynamics and, 31, 32
- Low dissolved-oxygen (DO) levels, in astaxanthin synthesis, 165
- Luteolin, in flavonoid pathway, 178–179
- Lycopene, carotenoid biosynthesis and, 140, 161, 162, 163, 164
- Lycopene cyclase (*eryY*)
in carotenoid biosynthesis, 161, 162, 163
in unnatural carotenoid synthesis, 166
- Lycopene production genes, in biosynthesis optimization, 141
- Lymphocytes, IMPDH expression in, 14
- Macrocyclic lactone aglycones, macrolide glycosyltransferases and, 66
- Macrolactams, 93–95
- Macrolactone ring, in combinatorial pathway design, 129
- Macrolactones, in enterobactin, 85

- Macrolides, 64–78
 avermectin, 75–77
 classification and development of, 64–66
 erythromycin, 69–72
 methymycin, 66–69
 oleandomycin, 72–75
 OleD glycosyltransferase of, 61
 sorangicin, 77–78
- Malaria, artemisinin versus, 157
- Malonic acid, in combinatorial pathway design, 129
- Malonyl-CoA
 in flavanone synthesis, 177
 in flavonoid pathway, 178–179
 formation of, 179
 polyketides and, 167
- Malonyl-CoA extender unit, in combinatorial pathway design, 129, 130, 131
- Malus domestica*, in anthocyanin synthesis, 184. *See also* Apples
- Mammalian cells, IMPDH expression in, 14
- Mammals, IMPDH from, 5, 12, 26, 27, 37
- Mannosylglycerate synthase (MGS), 60, 61
- Marinobacter*, peptide sequence of, 125
- Marinobacter aqualei*, peptide sequence of, 125
- Marinobacter hydrocarbonoclasticus*, wax esters from, 124–125
- Mass production, of flavonoids, 175–176
- Mass spectrometry, in oleandomycin studies, 73–74
- Maximum production, in medical and industrial compound synthesis, 123
- Mechanisms of action
 in glycosyltransferase classification, 60
 of glycotransferases, 62–64
- Medicago trunculata*, in structure-guided glycosyltransferase design, 104
- Medical compounds, synthesis of, 122–123
- Medicinal applications, of inosine 5'-monophosphate dehydrogenase, 14–16
- Megalomicins
 molecular structure of, 57
 naturally occurring, 65–66
- Melanoma, flavones versus, 181
- MEP cytidyltransferase, in MEP pathway, 154, 155. *See also* 2-C-Methyl-D-erythritol-4-phosphate (MEP)
- MEP pathway, in terpenoid synthesis, 153–155
- 6-Mercaptopurine, IMPDH inhibitors and, 14
- Messenger RNA (mRNA), cytochrome-P450 enzymes and, 189
- Messenger RNA transcript, in tuning enzyme expression levels, 140–141
- Metabolic engineering, in medical and industrial compound synthesis, 122–123
- Metabolic pathway engineering, 128–138
 in natural product glycosylation, 58, 59
- Metabolic pathways, databases of, 126–128
- Metabolic traits, in biosynthesis optimization, 141
- MetaCyc database, 127
- Metagenomic approaches, 123–128
 in medical and industrial compound synthesis, 122
- Metal ions, in IMPDH activation, 38–39
- Methoxyluteolin, in flavonoid pathway, 178–179
- Methoxymalonyl-ACP extender unit, in combinatorial pathway design, 129, 130
- 2-C-Methyl-D-erythritol 2,4-cyclodiphosphate (MECDP) synthase, in MEP pathway, 154, 155
- 2-C-Methyl-D-erythritol-4-phosphate (MEP), 153–154, 155
- β -Methylene-biphosphonate (β -TAD, β -CH₂-TAD). *See also* Tiazofurin adenine dinucleotide (TAD)
 in IMPDH activation, 38
 IMPDH crystal structure and, 8, 11, 12
 in IMPDH ligand binding, 28
 kinetic properties of, 5, 6
 NAD analogs of IMPDH and, 16
 species-selective affinity and, 35e
 dinucleotide (TAD)
- Methylmalonyl-CoA
 in erythromycin synthesis, 171, 172
 polyketides and, 167

- Methylmalonyl-CoA extender unit, in combinatorial pathway design, 129, 130, 131
- N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine (NTG) in ubiquinone biosynthesis, 166–167
- Methylomonas*, in astaxanthin synthesis, 164
- 7-*O*-Methyltransferase (7OMT) in flavone synthesis, 182 in flavonoid pathway, 178–179
- Methyl transferases, in carotenoid biosynthesis, 163
- Methymycin, 66–69 molecular structure and biosynthesis of, 67
- Mevalonate (MVA) kinase in artemisinin synthesis, 158 in MVA pathway, 153, 154
- Mevalonate pathway, in terpenoid synthesis, 153, 154
- Mevalonate pyrophosphate decarboxylase, in artemisinin synthesis, 158
- MGT (macrolide glycosyltransferase), 72, 73. *See also* OleD glycosyltransferase
- Michaelis complexes, IMPDH chemical mechanism and, 29
- Microbial Biocatalytic Reactions and Biodegradation (UM-BBD) Pathway Database, 127–128
- Microbial genomics, advances in, 122–123
- Microbial synthesis of anthocyanins, 184 of biofuels, 152 of classic carotenoids, 161–165 of epothilones, 169–170 of flavonoids, 176–177 of natural products, 152 of polyketides, 167–173 of resveratrol, 185–186 of terpenoids, 152–153, 158–160 of ubiquinone, 166–167 of unnatural carotenoids, 165–166
- Micromonospora megalomicea*, megalomicins from, 65–66
- Microorganisms as biofuel synthesis biocatalysts, 191 in medical and industrial compound synthesis, 122–123
- Misfolded proteins, studies of, 188
- Mizoribine as IMPDH inhibitor, 14 molecular structure of, 7
- Mizoribine monophosphate (MMP). *See also* EXMMP complex IMP analogs of IMPDH and, 15 in IMPDH activation, 38 kinetic properties of, 5, 6 resistance to, 36
- Monoxygenase, carotenoid, 136
- Monoterpene esters, from plant cultures, 156–157
- Monoterpenes, 134
- Monovalent cation activation, of inosine 5'-monophosphate dehydrogenase, 36–39
- Mutagenesis in astaxanthin biosynthesis, 164 in biosynthesis optimization, 141, 142 as glycosyltransferase mechanism of action, 62 in carotenoid biosynthesis, 163 in tylosin synthesis, 173
- Mutagenesis study, of human IMPDH, 26–27
- Mutasythesis, in natural product glycosylation, 59
- Mutations in biosynthesis optimization, 141–142 carotenoid biosynthesis and, 140 cytochrome-P450 enzymes and, 187, 188, 189 in directed glycosyltransferase evolution, 105 in ethanol production, 193–194, 194–195 IMPDH subdomain, 40–41 in ubiquinone biosynthesis, 166–167
- Mycarose, 70
- Mycophenolic acid (MPA) in humans, 25 IMPDH activation and, 37–39 IMPDH inhibitors and, 14, 15–16 in IMPDH ligand binding, 28, 29 kinetic properties of, 5, 6 molecular structure of, 7 protein dynamics and, 32 species-selective affinity of, 35–36

- Mylotarg, 89
- Myrcene, 134
- Myricetin
in flavonoid pathway, 178–179
in hydroxylated flavonoid synthesis, 190
- Myxococcus xanthus*, in epothilone biosynthesis, 171
- N*-acetyl-glucosamine, in teicoplanin, 83
- NAD analogs. *See also* Nicotinamide adenine dinucleotide (NAD)
of human IMPDH, 25–26
of IMPDH, 15–16
- NAD binding site, of IMPDH, 28–29
- NADH cofactor, in butanol production, 196.
See also Reduced nicotinamide adenine dinucleotide (NADH)
- NADPH–cytochrome-P450 reductase, in terpene biosynthesis, 138
- Narbomycin, molecular structure and biosynthesis of, 67
- Naringenin
in flavonoid pathway, 178–179
in hydroxylated flavonoid synthesis, 190
synthesis of, 183
- National Center for Biotechnology Information (NCBI), bioinformatics databases at, 123–124
- Natural product biosynthesis, future of, 197–198
- Natural product glycosylation, development of, 56–58, 59
- Natural product glycosyltransferases (GTs), 55–119
engineering of, 101–106
importance of, 56–58, 107
in vitro characterization of, 64–101
structural chemistry of, 58–64
- Natural product inhibitors, of IMPDH, 16
- Natural products, microbial synthesis of, 152
- Natural resources, in chemical manufacturing, 152
- NDP (nucleoside diphosphate) donors.
See also dNDP entries
in natural product glycosylation, 59
in vicenistatin reactions, 95
- NDP donor specificity, in directed glycosyltransferase evolution, 106
- Negative cooperativity, protein dynamics and, 32
- Neisseria meningitidis*, glycosyltransferases of, 60
- Neomethymycin, molecular structure and biosynthesis of, 67
- Neuraminidase inhibitors, shikimates and, 173
- Nicotiana tabacum*, resveratrol from, 186
- Nicotinamide adenine dinucleotide (NAD)
in *Escherichia coli*, 22, 23–24
in humans, 25–26
in IMPDH activation, 38
IMPDH binding of, 28–29
IMPDH chemical mechanism and, 30, 31
IMPDH inhibitors and, 14, 15–16
in IMPDH kinetics, 17–19
IMPDH ligand binding and, 27
molecular structure of, 3
protein dynamics and, 32, 33–34
in purine nucleotide biosynthetic pathways, 2, 3
species-selective affinity and, 35
in *Tritrichomonas foetus*, 20, 21, 22
- Nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome-P450 enzymes and, 186, 187
- Nicotinamide ring, in IMPDH ligand binding, 28
- Niddamycin, synthesis of, 172
- Nitrosoguanidine, in tylosin synthesis, 173
- N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (NTG), in ubiquinone biosynthesis, 166–167
- Noncovalent complexes, IMPDH chemical mechanism and, 29
- Nonribosomal peptides, 78–86
- Nonribosomal peptide synthases (NRPSs), 126
in combinatorial pathway design, 128, 129
- nov* gene cluster, 86
- Noviose, 86, 88
- NovM glycosyltransferase, 86–88
- Novobiocin, 86–88

- molecular structure of, 57
- NRP pathway, in combinatorial pathway design, 128–129
- N-terminal domain, in glycosyltransferases, 60, 61
- Nuclear magnetic resonance (NMR)
 - methods, in IMPDH conformation studies, 26, 28
- Nucleotidyltransferases, in natural product glycosylation, 59
- Nutraceutical supplements, flavonoids as, 175
- NysD1 glycosyltransferase, calicheamicin and, 93
- ole1* gene, 72
- Oleandomycin, 72–75
 - in directed glycosyltransferase evolution, 105
 - molecular structure and glycosylation of, 73
- Oleandrose, 70, 71, 75, 76
- Oleandrosides, 70, 71
- OleD glycosyltransferase, 61, 72–75
- OleD mutations, in directed glycosyltransferase evolution, 105–106
- oleG1* gene, 72
- oleG2* gene, 72
- OleI glycosyltransferase, 72–75
- OleR glucosidase, 72
- Olivose, urdamycin A and, 102
- Open reading frames (ORFs), 123–124
- Operons, 124
 - in artemisinin synthesis, 158
- Optimization, of biosynthetic pathways, 128, 137, 138–142
- Orf3* glycosyltransferase, teicoplanin and, 83
- Organelle genomes, in KEGG database, 126–127
- Oritavancin, 79
 - molecular structure of, 80
- Oxidation reactions, in terpene biosynthesis, 138
- Oxygenases, in combinatorial pathway design, 129
- Oxygen availability, in astaxanthin synthesis, 164–165
- P1 phage, in shikimate synthesis, 175
- P67T mutation, in directed glycosyltransferase evolution, 105
- P450 17 α -hydroxylase, cytochrome-P450 enzymes and, 189. *See also* Cytochrome-P450 entries
- P450 enzymes
 - in artemisinin synthesis, 159
 - in Taxol synthesis, 160
 - in terpene biosynthesis, 137–138
- P450 epoxidase, in epothilone biosynthesis, 170
- P450 proteins, 187
- P450 reductases, aromatic flavonoid derivatives via, 186, 187
- Paclitaxel, from *Taxus* cell cultures, 156
- pACYC184 plasmid, in ubiquinone biosynthesis, 167
- Pantheinylation, in erythromycin synthesis, 171
- Paracoccus denitrificans*, ubiquinone from, 166
- Paracoccus haeundaensis*, in astaxanthin biosynthesis, 164
- Patellamide A, 126
- Patellamide C, 126
- Pathway design, bioinformatics in, 123
- Pathway engineering, 128–138
 - in natural product glycosylation, 58, 59
- Pathway Prediction System (PPS), 127–128
- Pathways
 - databases of, 126–128
 - in medical and industrial compound synthesis, 122, 123
- pcc* gene, in erythromycin synthesis, 172
- Pelargonidin, in flavonoid pathway, 178–179
- Pentachlorophenol (PCP), degradation of, 142
- Peptide sequences, BLAST algorithm with, 123–124
- Peptidoglycan glycosyltransferases, 62
- Perilla frutescens*, terpenoids from, 155
- Petroleum-based synthesis, of medical and industrial compounds, 122
- Petroselinum crispum*, in flavanone synthesis, 177

- Petunia*, in anthocyanin synthesis, 184
- Pharmaceuticals
polyketides as, 167
terpenoids as, 152
- Pharmacokinetics, glycosyltransferases
in, 56
- Pharmacology, glycosyltransferases in, 56
- Phenol, optimizing biosynthesis of, 141
- Phenotypic screening, in ethanol production,
193–195
- Phenylalanine
IMPDH ligand binding and, 299
in flavanone synthesis, 177
in flavonoid pathway, 178–179
in polyketide synthesis, 169
protein dynamics and, 34
- Phenylalanine ammonia lyase (PAL)
in anthocyanin synthesis, 184
in flavonoid pathway, 178–179
- Phenylalanine/tyrosine ammonia lyase (PAL/
TAL), in flavanone synthesis, 177
- Phenylpropanoic acids, in flavanone
synthesis, 177
- pH gradient, in biosynthesis optimization,
142
- Phosphoenolpyruvate (PEP), in shikimate
synthesis, 174
- Phosphoenolpyruvate synthase, in
astaxanthin synthesis, 164
- Phosphomevalonate kinase
in artemisinin synthesis, 158
in MVA pathway, 154
- Phosphopantetheinyl transferase, in
erythromycin synthesis, 171
- 5-Phosphoribosyl-1-pyrophosphate (PRPP),
in purine nucleotide biosynthetic
pathways, 2
- Phosphotransacetylase (PTA), in
malonyl-CoA formation, 179, 180
- Photorhabditis luminescens*, in flavanone
synthesis, 177–179
- pH–rate studies, of IMPDH chemical
mechanism, 30–31
- Phytochemicals, anthocyanins as, 183
- Phytochrome-activating light, in anthocyanin
synthesis, 184
- Phytoene, in carotenoid biosynthesis, 161,
162
- Phytoene desaturase (*crtI*), in carotenoid
biosynthesis, 161, 162, 163
- Phytoene synthase (*crtB*)
in carotenoid biosynthesis, 161, 162, 163
in unnatural carotenoid synthesis, 165
- Phytoestrogens, 180. *See also* Isoflavones
- Phytohormones, in improving carotenoid
content of plants, 161
- Piceatannol, in resveratrol synthesis, 186
- PikC hydroxylase, methymycin and, 67
- Pikromycin, molecular structure and
biosynthesis of, 67
- Pikromycin PKS gene cluster, 173
- Pinoembrin, in flavonoid pathway, 178–179
- PKS assembly line. *See also* Polyketide
synthases (PKSs)
protein–protein interactions and, 133–134
rearranging and modifying, 132–133
in synthetic biology, 143
- PKS biosynthetic gene cluster, in
combinatorial pathway design, 129–134
- PKS gene cluster, 173
- PKS megasynthases, 131
- pK values, of IMPDH chemical mechanism,
31, 34–35
- Plant cell cultures
anthocyanins from, 183–184
in flavonoid synthesis, 176–177
terpenoids from, 155, 156–158
- Plant extraction, terpenoid production via,
152–153
- Plant P450, in flavone synthesis, 181
- Plant PKSs, in polyketide synthesis, 168–169
- Plants
anthocyanins from, 183–184
cytochrome-P450 enzymes from, 188
flavones from, 182
flavonoids from, 175–176
improving carotenoid content of, 161
isoflavones in, 180
MEP pathway in, 153–155
polyketides from, 168–169
resveratrol from, 185–186
terpene cyclases from, 136–137

- Plasmids
 in artemisinin synthesis, 158
 in tylosin synthesis, 173
 in ubiquinone biosynthesis, 167
Plasmodium, artemisinin versus, 157
“Plug-and-play” gene cassettes, in natural product glycosylation, 58
Polyketide biosynthesis
 in *Escherichia coli*, 130–132
 in heterologous hosts, 131–132
Polyketide chain, in combinatorial pathway design, 129, 130
Polyketides, 167–173
 biosynthesis of, 129–134
 in combinatorial pathway design, 129
 epothilones, 167, 169–171
 erythromycins, 167, 171–172
 molecular structures of, 168
 pharmaceutical applications of, 167
 from plants, 168–169
 total chemical synthesis of, 167–168
 tylosins, 172–173
Polyketide synthases (PKSs). *See also* PKS entries
 in combinatorial pathway design, 128, 132–133
 in epothilone synthesis, 169–170
 in erythromycin synthesis, 171, 172
 in flavanone synthesis, 177
 polyketides and, 167, 168–169
 protein–protein interactions and biosynthesis of, 133–134
 in tylosin synthesis, 173
Polymerase chain reactions (PCRs)
 in directed glycosyltransferase evolution, 105
 in ethanol production, 193, 194
 in terpene biosynthesis, 137
Potassium ion (K^+)
 in dehydrogenase activity, 5, 6
 IMPDH and, 12
 in IMPDH activation, 36–39
 in IMPDH kinetics, 18, 19, 22
Precursor-directed biosynthesis, in natural product glycosylation, 59
Precursors
 in carotenoid biosynthesis, 161
 of terpenoids, 153, 154, 155
Precursor supply, in biosynthetic pathway regulation, 143
Pregnenolone, 94
Prenyl chains, in terpene biosynthesis, 136–137
Primary metabolites, terpenoids as, 152, 154–155
Prochloron didemni, patellamide biosynthesis by, 126
Proficiency, in directed glycosyltransferase evolution, 105
Promiscuity, in directed glycosyltransferase evolution, 105
Promiscuous glycosyltransferases
 in natural product glycosylation, 59
 among vancomycin derivatives, 82–83
Propionyl-CoA
 in erythromycin synthesis, 171, 172
 polyketides and, 167
Propionyl-CoA carbonylase, 131
 in erythromycin synthesis, 172
Propionyl-CoA ligase, 131
Protein conformation, of inosine 5'-monophosphate dehydrogenase, 13, 31–35
Protein Data Bank (PDB), 10–11, 12
Protein dynamics, enzyme function and, 31
Protein engineering
 advances in, 122–123
 bioinformatics in, 123
Protein expression, in hydroxylated flavonoid synthesis, 190
Protein–IMP interactions, 27
Protein–protein interactions, in PKS biosynthesis, 133–134
Proteins
 Bateman domains in, 41–42
 in biosynthetic pathway optimization, 139
 CBS domains in, 39–40
 IMPDH, 5–7, 9
 in KEGG database, 126–127
 studies of misfolded, 188
Protein structures, of inosine 5'-monophosphate dehydrogenase, 5–13

- Proteolysis data, protein dynamics and, 32
- Protoplast fusion, in biosynthesis optimization, 142
- Provitamin D2, in carotenoid biosynthesis, 163
- prpE* gene, in erythromycin synthesis, 171–172
- prpRBCD* operon, in erythromycin synthesis, 171
- Pseudomonas putida*
optimizing biosynthesis in, 141–142
polyketide biosynthesis in, 131
- pta* gene, in butanol production, 197
- pUC19 plasmid, in ubiquinone biosynthesis, 167
- Pulegone, artemisinin from, 157
- Purine nucleotides
biosynthesis of, 1–4
as chemotherapeutic agent targets, 14
- Pyrethric acid, from plant cultures, 156–157
- Pyrethrins, from plant cultures, 156–157
- Pyrethrolone, from plant cultures, 156–157
- 2-Pyrone synthase (2-PS), in polyketide synthesis, 169
- Pyruvate. *See also* Pyruvic acid
in carotenoid biosynthesis, 161, 164
in MEP pathway, 153
- Pyruvate decarboxylase (*pcd*), in ethanol production, 192
- Pyruvate kinase, molecular structure of, 9
- Pyruvic acid, in ethanol production, 192.
See also Pyruvate
- Quercetin, 104
in flavonoid pathway, 178–179
in hydroxylated flavonoid synthesis, 190
synthesis of, 183
- Quinic acid, 173–174, 175
- Quinones, 135
- Radiochromatography, cytochrome-P450 enzymes and, 189
- Rate-limiting carotenoid genes, in biosynthesis optimization, 141
- Rational protein engineering, of terpene biosynthesis, 137–138
- Rational sequence-guided design, of glycosyltransferases, 101–103, 103–104
- Rebeccamycin, molecular structure of, 57
- Recombinant DNA (rDNA), in ubiquinone biosynthesis, 167
- Recombinant DNA technologies
in medical and industrial compound synthesis, 122
in natural product biosynthesis, 197–198
- Recombinant *Escherichia coli*, in combinatorial pathway design, 128
- Recombinant RNA methyltransferase, in polyketide biosynthesis, 131
- Recombinant terpene biosynthesis, optimization and diversification of, 137–138
- Reduced nicotinamide adenine dinucleotide (NADH)
in *Escherichia coli*, 22, 24
in humans, 26
in IMPDH kinetics, 19
in IMPDH ligand binding, 28
molecular structure of, 3
protein dynamics and, 32–34
in purine nucleotide biosynthetic pathways, 2–4
in *Trichomonas foetus*, 20, 21–22
- Reduction reactions, in terpene biosynthesis, 138
- Red wine
anthocyanins in, 183
resveratrol in, 185
- Regional Display Viewer, 124
- Regioselective glycosylation, 58
- Relavancin, 79
molecular structure of, 80
- Replication processes, biosynthesis optimization and, 141–142
- Resiniferatoxin, 152
- Resistance
to antimalarial agents, 157
in *Saccharomyces cerevisiae*, 36
to vancomycin, 79

- Resveratrol
 in flavonoid pathway, 178–179
 synthesis of, 176, 185–186
- Retaining double-displacement mechanism,
 of glycosyltransferases, 63–64
- Retaining S_N-1-like mechanism, of
 glycosyltransferases, 63, 64
- Retinitis pigmentosa, 40, 41
- Retinoids, in improving carotenoid content of
 plants, 161
- Retinopathy, 40
- Rhamnose
 calicheamicin and, 89
 NovM glycosyltransferase and, 88
- Rhamnosylation, of aranciamycin, 101
- Rhodinose, urdamycin G and, 102
- Rhodobacter*, unnatural carotenoids from,
 165
- Rhodobacter sphaeroides*, ubiquinone from,
 166
- Ribavirin
 IMPDH crystal structure and, 8
 as IMPDH inhibitor, 14
 molecular structure of, 7
- Ribavirin monophosphate (RMP)
 in IMPDH ligand binding, 27
 kinetic properties of, 5, 6
- Ribosome binding sequences, in tuning
 enzyme expression levels, 140–141
- Rifampicin, sorangicin and, 77
- RNA polymerase, 188
- RNase cleavage sites, in tuning enzyme
 expression levels, 140–141
- Rosmarinic acid, from plant cell cultures, 155
- Rossmann-like domains, in
 glycosyltransferases, 60
- RP10 retinitis pigmentosa, 40
- rpoD* gene, in ethanol production, 193
- rpoS* gene, in carotenoid biosynthesis, 164
- rssB* gene, in carotenoid biosynthesis, 163
- Saccharomyces cerevisiae*
 anthocyanins from, 184
 in carotenoid biosynthesis, 163
 in ethanol production, 191
 in flavanone synthesis, 177
 in flavonoid synthesis, 176
 isoflavones from, 181
 isoprenoid pathways engineered in,
 134–135
 in natural product biosynthesis, 198
 resveratrol from, 185, 186
 species-specific drug selectivity and
 IMPDH of, 36
 in Taxol synthesis, 160
 in terpenoid synthesis, 158
- Saccharopolyspora erythraea*, erythromycin
 from, 171, 172
- SaGT4a glycosyltransferase, 103
- Salmochelin, 85
- Salmonella enterica*, enterobactin and,
 85
- SARP family, in tylosin synthesis, 173
- Secondary metabolites, terpenoids as, 152,
 154–155
- Selection, in biosynthesis optimization, 141,
 142
- Selenazole adenine dinucleotide (SAD)
 in *Escherichia coli*, 23
 in IMPDH activation, 38
 IMPDH crystal structure and, 8, 9
 in IMPDH ligand binding, 28, 29
 NAD analogs of IMPDH and, 15–16
- Sequence-guided design, of
 glycosyltransferases, 101–103
- Serine, enterobactins and, 85
- Sesquiterpenes, 134
- sfp* gene, in erythromycin synthesis, 171
- Shikimate kinase (*aroKL*), in shikimate
 synthesis, 174
- Shikimates, 173–175
- Shikimic acid (shikimate), 173–174, 175
- Shikonin, from plant cell cultures, 155
- Sialic acid, in directed glycosyltransferase
 evolution, 105
- Sialyltransferases (STs), in directed
 glycosyltransferase evolution,
 104–105
- Sigma 70 factor, in ethanol production,
 193, 195
- S_N-1-like mechanism, of
 glycosyltransferases, 63, 64

- Social concerns, in chemical manufacturing, 152
- Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), 187–188
- Sodium ion (Na⁺), in IMPDH activation, 37
- Solanum aculeatissimum*, glycosyltransferases from, 103
- Sorangicin, 77–78
molecular structure and analogs of, 77
- Sorangium cellulosum*
in epothilone biosynthesis, 170, 171
sorangicin from, 77
- sorF* gene, 77
- SorF glycosyltransferase, 77–78
- Species-specific drug selectivity, of inosine 5'-monophosphate dehydrogenase, 35–36
- Sphingobium chlorophenicum*, in PCP degradation, 142
- Sphingomonas*, in astaxanthin biosynthesis, 164
- SPT15 mutant, in ethanol production, 194–195
- Squalene synthase, in MVA pathway, 154
- Standardization, of synthetic biology, 143
- Staphylococcus aureus*
carotenoid desaturase and synthase from, 136
aminocoumarins from, 86
genome of, 124, 125
peptidoglycan GTs of, 62
vancomycin derivatives versus, 82
vancomycin-resistant, 79
- Starter domain, in combinatorial pathway design, 130, 131, 132
- Stereoselective aldol reactions, in polyketide synthesis, 167–168
- Stereoselective C–C bond formation, in polyketide synthesis, 167–168
- Stereoselective glycosylation, 58
- Sterol biosynthetic genes, in artemisinin synthesis, 158–159
- Sterols, 152
- Stilbenes, 185–186
synthesis of, 176, 178–179
- Stilbene synthase (STS)
in flavonoid pathway, 178–179
in polyketide synthesis, 169
in resveratrol synthesis, 186
- Strain improvement, in biosynthesis optimization, 141, 142
- Streptococcus pyogenes*
IMPDH from, 6–9, 10–11, 12, 13, 37, 38
IMPDH subdomain in, 39–40
- Streptomyces*
aminocoumarins from, 86
in erythromycin synthesis, 171
in tylosin synthesis, 173
- Streptomyces antibioticus*, oleandomycin from, 72
- Streptomyces avermectinius*, avermectin from, 75
- Streptomyces coelicolor*
in epothilone biosynthesis, 170–171
in erythromycin synthesis, 171
- Streptomyces echinatus*, anthracyclines from, 101
- Streptomyces fradiae*, tylosin from, 173
- Streptomyces halstedii*, vicenistatin from, 93
- Streptomyces spheroides*, novobiocin from, 86
- Streptomyces venezuelae*
methymycin from, 66
tylosin from, 173
- Structure-guided design, of glycosyltransferases, 103–104
- StSGT glycosyltransferases, 103
- Subdomains
of inosine 5'-monophosphate dehydrogenase, 9, 13, 37, 39–42
protein dynamics and, 31
- Substrate interactions, of inosine 5'-monophosphate dehydrogenase, 17–20
- Substrate recognition, in rearranging and modifying PKS assembly line, 133
- Sugar biosynthesis, in natural product glycosylation, 59
- Sugar donors, in natural product glycosylation, 58, 59
- Sugar exchange reactions, CalG1-catalyzed, 90, 91

- Sugar moieties, in glycopeptide antibiotics, 78, 80
- Sugar nucleotide libraries, in natural product glycosylation, 58
- Sugars
- anthracycline interactions with, 96
 - in biosynthetic pathway optimization, 138–139
 - glycosyltransferases and, 56–58, 59
 - in vicenistatin reactions, 94–95
- Sugar substrate specificity, methymycin and, 66–69
- Sulfadoxin, 157
- Synthases, carotenoid, 136
- Synthesis. *See also* Biosynthesis; Chemical synthesis; Microbial synthesis; Sugar biosynthesis
- of flavones, 181–182
 - of isoflavones, 180–181
 - of stilbenes, 185–186
 - of terpenoids, 152–155
 - via cytochrome-P450 enzymes, 186–190
- Synthetic biology
- future of, 142–143
 - standardization of, 143
- Synthetic inhibitors, of inosine 5'-monophosphate dehydrogenase, 17
- Systems biology, 143
-
- T5 promoter, in astaxanthin synthesis, 165
- T7 phage promoter
- in flavanone synthesis, 177
 - in Taxol synthesis, 160
- TAF25 mutant, in ethanol production, 194–195
- Tagetes erecta*, pyrethrins from, 157
- TATA-binding protein, in ethanol production, 194
- Taxadiene
- microbial synthesis of, 159–160
 - from *Taxus* cell cultures, 156
- Taxadiene hydroxylases, in Taxol synthesis, 159
- Taxadiene synthase (TS), in Taxol synthesis, 159
- Taxane derivatives, from *Taxus* cell cultures, 156
- Taxane hydroxylases, in Taxol synthesis, 159
- Taxoids, from *Taxus* cell cultures, 156
- Taxol, 134, 138
- microbial synthesis of, 158–160
 - from *Taxus* cell cultures, 156
- Taxol pathway engineering, in terpene biosynthesis, 138
- Taxus*
- in terpene biosynthesis, 138
 - terpenoids from cell cultures of, 156
- Taxus brevifolia*
- Taxol from, 159–160
 - terpenoids from cell cultures of, 156
- Taxus chinensis*, terpenoids from cell cultures of, 156
- Taxuyunnanine C, from *Taxus* cell cultures, 156
- TDP-vicenisamine, 94
- Teicoplanin, 83
- biosynthesis of, 84
 - as glycopeptide antibiotic, 78–79
 - molecular structure of, 78, 84
- tei* gene cluster, 83
- Telithromycin, 65
- molecular structure of, 65
- Terpene biosynthesis, optimization and diversification of, 137–138
- Terpene cyclases, 136–137
- in terpene biosynthesis, 137, 138
- Terpenes, 134
- evolutionary biosynthesis of, 136–138
- Terpenoids, 152–160. *See also* Isoprenoids
- applications of, 152
 - described, 152–155
 - microbial synthesis of, 152–153, 158–160
 - from plant cell cultures, 155, 156–158
- Tetracenomycin, 132
- Tetramers, of IMPDH proteins, 5–7
- Tetraterpenes, 134
- tGtfA glycosyltransferase, 83
- in teicoplanin biosynthesis, 84
- tGtfB glycosyltransferase, 83
- in teicoplanin biosynthesis, 84
- Thalictrum minor*, terpenoids from, 155

- The Institute for Genomic Research (TIGR), 124, 125
- Thioesterase (TE) domain, in combinatorial pathway design, 130, 131
- Thiolase (*thi*)
in butanol production, 196
in ethanol production, 192
- Thio-NAD, in humans, 26
- Tiazofurin, 5
as IMPDH inhibitor, 14, 15–16
molecular structure of, 7
species-selective affinity and, 35
- Tiazofurin adenine dinucleotide (TAD). *See also* β -methylene-biphosphonate (β -TAD, β -CH₃-TAD)
in *Escherichia coli*, 22
IMPDH inhibitors and, 14
in IMPDH ligand binding, 28, 29
kinetic properties of, 5, 6
species-selective affinity and, 35
- Topoisomerase II inhibitors, anthracyclines as, 96
- Torulene, in unnatural carotenoid synthesis, 166
- Toxicity stresses, in biosynthesis
optimization, 142
- Toxic solvents, green chemistry and, 152
- Transferred-NOE NMR methods, in IMPDH conformation studies, 26, 28
- Tricarboxylic acid (TCA) cycle, in butanol production, 196
- Trichomonas foetus*. *See Tritrichomonas foetus*
- Triose phosphate isomerase (TIM), molecular structure of, 9
- Triterpenes, 134
- Tritrichomonas foetus*
IMPDH inhibitors and, 14
IMPDH kinetics in, 19
IMPDH subdomain in, 40, 41
inosine 5'-monophosphate dehydrogenase from, 6, 7, 8, 9–11, 12, 13, 16, 20–22, 27–28, 29, 33–35, 37, 38
species-specific drug selectivity and IMPDH of, 35
- Tryptophan
IMPDH ligand binding and, 29
in IMPDH molecules, 11
Tryptophan fluorescence, 20
- Tubulin polymerization, glycosylation and, 56
- Tumor cells, IMPDH expression in, 14
- Tuning enzyme expression levels, messenger RNA (mRNA) transcript in, 140–141
- Two-phase partitioning bioreactor (TPPB), in artemisinin synthesis, 158
- Tylosins, 172–173
molecular structure of, 168
oleandomycin and, 75
- TyIP protein, in tylosin synthesis, 173
- TyIR protein, in tylosin synthesis, 173
- TyIS protein, in tylosin synthesis, 173
- TyIU protein, in tylosin synthesis, 173
- Type I polyketide synthases, in combinatorial pathway design, 128, 130, 132–133
- Tyrosine
in flavanone synthesis, 177
in flavonoid pathway, 178–179
IMPDH ligand binding and, 299
protein dynamics and, 34
- Tyrosine ammonia lyase (TAL), in flavonoid pathway, 178–179
- Tyrosine phenol lyase, in optimizing phenol biosynthesis, 141
- Ubiquinone(s), 135, 166–167. *See also* Coenzyme-Q10 (CoQ10)
in carotenoid biosynthesis, 162
medicinal value of, 166
- UDP (uridine diphosphate)-galactose, glycosyltransferases and, 103
- UDP-glucose, glycosyltransferases and, 103
- UDP-glucose(flavonoid 3-O-glucosyltransferase (3GT)
in anthocyanin synthesis, 184
in flavonoid pathway, 178–179
- UDPGT signature motif, glycosyltransferases and, 103
- UDP-N-acetyl-glucosaminyltransferases, 83
- Ultraviolet (UV) dichroism spectrum, protein dynamics and, 32
- Ultraviolet irradiation
in anthocyanin synthesis, 184
in tylosin synthesis, 173

- United States
 ethanol biofuel production in, 191
 natural product biosynthesis in,
 197–198
 pyrethrin production/marketing in,
 156–157
- Universal carotenoid pathway, 161–163
- Universal precursors, of terpenoids, 153, 154,
 155
- University of Minnesota, biocatalysis/
 biodegradation database at, 127–128
- Unnatural aglycone substrates, accepted by
 OleD, 74
- Unnatural carotenoids, synthesis of, 165–166
- Unnatural polyketides, synthesis of, 172
- upc2-1* gene, in artemisinin synthesis, 158
- Urdamycin, 86
- Urdamycin A, 102
- Urdamycin G, 102
- UrdGT1b glycosyltransferase, 102–103
- UrdGT1c glycosyltransferase, 102–103
- UrdGT2 glycosyltransferase, 86
- UrdGT glycosyltransferases, 103
- Uridine diphosphate (UDP). *See* UDP entries
- VanA glycosyltransferase, 79
- VanB glycosyltransferase, 79
- Vancomycin, 79–83
 calicheamicin and, 91
 disaccharide moiety of, 56
 as glycopeptide antibiotic, 78–79
 GtfD glycosyltransferase of, 61–62
 molecular structure of, 57, 78
- Vancomycin aglycon, 79, 81, 82
- Vancomycin pseudoaglycon, 79, 81
- Vancomycin-resistant enterococci (VRE), 79
- Vancomycin-resistant *Staphylococcus aureus*
 (VRSA), 79
- Vancosamines, 81–82
 molecular structures of, 81
- Vancosaminy1-D-glucose disaccharide, of
 vancomycin, 79
- Vegetables
 anthocyanins in, 183
 flavonoids from, 175
 improving carotenoid content of, 161
- Vicenisamine, 93
- Vicenistatin, 93–95
- VinC glycosyltransferase, 93–94
 reactions catalyzed by, 93, 94
- Vitis vinifera*, resveratrol from, 186. *See also*
 Grapes
- Viruses, flavones versus, 181
- Vitis*, terpenoids from, 155
- VvGT1 glycosyltransferase, in directed
 glycosyltransferase evolution, 105–106
- VX-497, as IMPDH inhibitor, 17
- Water activation, of inosine 5'-
 monophosphate dehydrogenase, 31–35
- Wax esters, microbial synthesis of, 124–125
- Wax ester synthase/diacyl glycerol
 acyltransferase (WS/DGAT), 124–125
- Xanthophylls, 160–161
 biosynthesis of, 124
- Xanthosine 5-monophosphate (XMP).
 See also EXXMP entries
 in *Escherichia coli*, 22
 in humans, 25–26
 in IMPDH activation, 37
 IMPDH chemical mechanism and, 29, 30
 IMPDH inhibitors and, 14, 15
 in IMPDH kinetics, 18–19
 IMPDH ligand binding and, 26, 28
 molecular structure of, 3
 protein dynamics and, 32, 33
 in purine nucleotide biosynthetic
 pathways, 2, 3
 release of, 4
 in *Tritrichomonas foetus*, 21
- Xylose
 NovM glycosyltransferase and, 88
 oleandomycin and, 75
- Xylosylation, oleandomycin and, 75
- Y289L mutation, in structure-guided
 glycosyltransferase design, 104
- Yeast
 in anthocyanin synthesis, 185
 aromatic flavonoid derivatives from, 186
 in artemisinin synthesis, 158–159

- Yeast (*Continued*)
- in carotenoid biosynthesis, 163
 - ethanol-tolerant strains of, 194–195
 - flavones from, 182
 - in flavonoid synthesis, 176–177
 - in isoflavone synthesis, 181
 - isoprenoid pathways engineered in, 135
 - MVA pathway in, 153
 - polyketide biosynthesis in, 130–131
 - as production organism, 142–143
 - terpene cyclases from, 137, 138
- YifP protein, in carotenoid biosynthesis, 163
- YjiD protein, in carotenoid biosynthesis, 163
- Zearalenols, 94
- ζ-carotein, in carotenoid biosynthesis, 161, 162
- Zingiberine, 134
- Zymomonas mobilis*, in ethanol production, 191–192