### Index

**a**
- 6 Å Rule 243–245
  - demonstration 244
  - limitations 245
  - prediction of binding poses 247–249
  - prediction of SoM 244, 245
  - methodological approaches 245–247
  - protein flexibility 249–253
  - validity 245
- abacavir 406
- absolute reasoning domain 307–310
  - relative confidence levels 309
- absorption, distribution, metabolism, and excretion/toxicity (ADME/ADMET) 40, 43, 60, 325, 327, 367, 441
  - ADMET Predictor 42, 47, 65, 70
  - ADMEWORKS Predictor 48
  - data on most FDA-approved drugs 64
  - measurements 321
  - physiological ADMET data for approved drugs 62
  - QikProp, software module for predicting 39
  - acetylation reactions 400
  - E-state index 384
  - rule about demethylation of 299
  - ANOVA (analysis of variance) 325, 326
  - antioxidants 421
  - antiretrovirals 441
  - aprepitant 405
  - area under the curve (AUC) ratios 280, 352, 452, 473, 476
  - aromatic/aliphatic hydroxylation 42
  - artemisinin 405
  - artificial intelligence 19
  - artificial neural network models 334
  - aryl hydrocarbon receptor (AhR) 364, 460
  - aryl hydrocarbon receptor nuclear translocator (ARNT) 460, 466
  - atorvastatin 189
  - ATP hydrolysis 374, 376
  - AutoDock Vina software 31, 40, 285
  - autooxidation 9
  - AZD5438 494
  -azole compounds, PXR antagonist model based on 365

**b**
- basic-helix-loop-helix (bHLH) protein 460
- Bayesian classifiers 334
- BEH C18 column 494
- Bennett acceptance ratio (BAR) 185
benzodiazepines 6
benzphetamine 190
B-factors 179
1β-hydroxytestosterone 203, 204, 207
– space-filling model 207
bile acid esters 11
bile salt export pump (BSEP) 374
bioactivation 7, 406
bioactivity-based mechanistic models 403
bioactivity-mediated toxic compounds
– rationalization of 404
bioavailability (F) 226
biological oxygen demand (BOD) 301
biological system 3
– used in drug metabolism investigations, classification 13
biotransformations 3, 10, 29, 41, 44, 237, 299, 301, 422
black box models 323
blood–brain barrier 70, 374
bomb calorimetry 463
bootstrap aggregation 380
breast cancer resistance protein (BCRP) 374, 375, 427
capillary electrophoresis (CE) 486
catechol-O-methyltransferase (COMT) 363
Caucasian hepatoblastoma 427
cell-based assays 465
cetirizine 6
calculated molar refractivity (CMR) 379, 382, 383
Cambridge Crystallographic Database (CSD) 225
capillary electrophoresis (CE) 486
catechol-O-methyltransferase (COMT) 363
CYP1A2
– expression 471
– inhibition, flavonoid derivatives 333
– isoform 335
– ligands 355
CYP3A
– enzyme family 400
– pregnane X receptor (PXR) 404
CYP3A4
– activity 443, 468
– chronic alcohol consumption 460
– diabetes 460
– fasting 460
– GRID MIFs of 224
– inhibition
– models 334, 360
– quantitative pharmacophore models 360
– inhibitor (see ritonavir)
– isoforms, classification model 335
– MD simulations 164
– mechanism-based inhibitor of 459
– structure 189
– substrate
– models 364
CYP3A5 354, 360, 473
– primary enzyme expressed in 422
CYP1A2 CoMFA model 336
CYP assays
– experimental errors for 323
– high-throughput screening assays 328
CYP2B6 474
– crystal structure 356
– substrates model 355
CYP2C9 40, 43, 47, 78, 86, 92, 93, 95, 123, 249, 329, 354, 357, 457, 469
– activity 406
– heteroactivation model 363
– inhibitors 332, 336, 356, 363
– pharmacophore models 356
– ligands 356, 363, 364
– substrates
– pharmacophore model 357

 Comprehensive expert software packages 16
computer prediction models
– from multiple sources 310–312
confusion matrix 386
conjugation reactions 10, 29, 205, 398, 400
constitutive androstane receptor (CAR) 336, 402, 460
– pharmacophore model 366
cyclohexyl ring, oxidation 297
cyclosporine 87, 106, 122, 378, 441
CYP1A2
– expression 471
– inhibition, flavonoid derivatives 333
– isoform 335
– ligands 355
CYP2C19  83, 126, 329, 333, 334, 358, 444
– inhibitor pharmacophore model  358
– inhibitors  358
CYP2D6
– activity  92, 93, 112, 244, 256, 333, 335, 406, 442
– inhibition models  334
– isoforms
– classification model  335
– pharmacophore model  358
– quantitative model  359
CYP-electron transfer protein interactions  81, 82
CYP from a GRID perspective  224–226
CYP inhibition  126, 128, 234, 236, 266, 323, 325, 332, 447
– assays  323
CYP isoforms  32, 33, 35, 36, 111, 189, 281, 321, 329, 334, 358, 431, 434, 473
CYP-mediated site of metabolism prediction
– applications to SoM prediction  280, 281
– isoform-specific models  281–283
– isoform-unspecific models  283, 284
– combinations of structure-based models and reactivity  284, 285
– machine learning methods applied to  278
– atomic descriptors  278, 279
– machine learning methods and optimization criteria  279, 280
– reactivity-based methods applied to  274
– comprehensive methods  276–278
– methods only applicable to carbon atoms  274–276
CYP polymorphism  64, 323
CypScore software  41
CYP model-based prediction, FDA guidance  452
cysteine  496
cytochrome P450 (CYP) enzymes  10, 16, 29, 77, 103, 199, 492. See also various isoforms
– analysis methods  204
– circular dichroism (CD)  206
– HPLC–UV  204, 205
– LC–HRMS  205
– LC–MS  205
– LC–MS/MS  205
– NMR  205–207
– X-ray diffraction  206
– binding site of isoforms  117
– complex CYP products  208–210
– docking for predicting kinetic parameters  120
– challenges  120
– human CYPs classification based on major substrate class  200
– inhibition  321
– assays  491, 492
– issues in predictions  213, 214
– $K_m$ and $k_{cat}$ values
– Michaelis–Menten interpretation  125
– and relationship with substrate and protein structure  124–127
– for various substrate–isoform combinations  121–123
– known substrates of various human CYP isoforms  105, 106
– methods for analysis of products of drugs  203, 204
– molecular dynamics studies  89–91
– number of CYPs present in various species  107
– pathways  400
– protein–ligand crystal structures  119, 120
– SAR of reaction rates  213
– structural data  199
– structural insight into substrate recognition by  107, 108
– CYP2A6  108, 109
– CYP2A13  109, 110
– CYP3A4  115
– CYP8A1  115, 116
– CYP11A1  116–118
– CYP19A1  118, 119
– CYP46A1  119
– CYP1A1, CYP1A2, and CYP1B1  108
– CYP11B2  118
– CYP2C8  110–112
– CYP2C9  112
– CYP2D6  112, 113
– CYP2E1  113
– CYP2R1  113–115
– structure–activity relationships based on products  210, 211
– knowledge-based SAR  212
– SARs based on chemical bond energy  211
– SARs based on docking  211, 212
– structure-based approaches to study metabolism of substrates by  243
– 6 Å Rule  243–245
– substrate binding  199
– substrate identity in various species  104, 106, 107
– substrate properties for various human isoforms  120, 123, 124
– substrate recognition in catalytic cycle 103, 104
– systems for production of reaction products and analysis of systems 200
– membranes from heterologous expression systems 202, 203
– purified CYPs in reconstituted systems 201, 202
– tissue microsomal systems 201
– in vivo systems 201
– untargeted searches for CYP reactions 208
– cytosolic enzyme systems 428

\[d\]
databases 11
– Cambridge Crystallographic Database (CSD) 225
– Human Metabolome Database (HMDB) 59
data mining and machine learning approaches 41, 42
– disadvantage of mining approach 41
– Fast Metabolizer (FAME) 42
– Metaprint2D 41
– P450 Regioslectivity module of Percepta 42
– RegioSelectivity (RS)-WebPredictor 42
deglycosylation 29
dehydrogenases 17
demethylation 299
density functional theory (DFT) 134
desloratadine 6
detoxification 3, 9, 133, 321, 418, 421, 423
diazepam 7
diclofenac 86
dietary component
– bioavailability/elimination, flow chart 417
dietary tyramines
– degradation of 362
dihydrotestosterone
– multistep pathway of oxidation, catalyzed by CYP19A1 210
– sites of oxidation by CYP3A4 212
dimethyl sulfoxide (DMSO)
concentrations 447
dioleoylphosphatidylcholine (DOPC) 96
DME system 436
docking 39, 40
– AutoDock 40
– AutoDock Vina 40
– Glide 40
– GOLD 40
– IDSite 40
– software packages for 40
donor capability 379
dopamine
– mechanism of formation 160–163
3D-QSAR modeling 15
DrugBank 57, 58
– capecitabine drug metabolism pathway 58
drug-drug interaction (DDI) 12, 64, 70, 323, 441
– additional factors influencing drug metabolism 442, 443
– drug metabolism enzymes, in vitro models 463–474
– drug metabolism, inhibition of 441
– metabolic 441
– metabolism, transcriptional regulation 460–463
– pharmacokinetics (PKs) 441
– primary hepatocyte culture models 459
drug–food interactions 64, 70
drug metabolism enzymes
– drug’s clearance 441
drug metabolism enzymes, in vitro models
– cellular models, gene expression 471–474
– control/test compounds, treatment 470, 471
– gene reporter assays 465, 466
– induction assays, in cellular models 468–470
– induction studies, cellular models for 466–468
– ligand binding assays 463–465
drug metabolism, factors affecting 12
– epigenetic mechanisms 13
– intra-individual factors 13
– pharmacodynamic/pharmacokinetic drug responses 12
drug metabolism, inhibition of 441
– cytosol 456, 457
– human liver microsomes (HLMs) 445–456
– predicting inhibition, in vitro models 444, 445
– primary hepatocytes 458, 459
– recombinant enzymes 457, 458
– S9 fraction 456, 457
drug metabolism, pharmacokinetics (DMPK) 321
drug-metabolizing enzymes, in vitro inducers 470
drug’s fate in body 5
dynamics of CYPs 88
active site access and egress pathways 93–95
active site flexibility 88, 92, 93
active site solvation 93
EC₅₀ values 324, 434, 464, 465, 473
efflux ratio (ER) 377, 378
electron impact (EI) 487
electrophiles 8
electrophoresis-based separation 486
electrospray ionization (ESI) 487
electrostatic effect 163
encainide 7
encoding rules in a knowledge base 299
endoplasmatic reticulum (ER) 423
endoxifen 7
endpoint methods 186
linear interaction energy 187
molecular mechanics-generalized Born surface area 186, 187
QM endpoint methods 187
epoxidation 113, 133, 209, 266, 283
aromatic and double bonded carbon atoms 271, 272
ergodic hypothesis 181
estradiol 10, 105, 106
estrone 10, 11
experimental drug metabolism 18
expert software packages 11
exponential averaging (EXP) 185
fadrozole 118
Fa2N-4 cell line 466
FAd METabolizer (FAME) 42
fatty acids 77
felodipine 106, 110, 441
fexofenadine 106, 444
flavin-containing monooxygenases 17, 444
catalyzed N-oxygenation of tertiary amines 10
flavonols
glucuronidation of 361
UGT1A9 pharmacophore model 361, 362
flurbiprofen 43
ligands 357
food bioactives
bioavailability (BA) 416
first-pass metabolism 418
intestinal absorption 416–418
metabolism, in vitro models classification 418, 419
Fourier transform ion cyclotron resonance (FT-ICR) instruments 487
free energy cycle 184
free energy methods 183
endpoint methods 186
linear interaction energy 187
molecular mechanics-generalized Born surface area 186, 187
QM endpoint methods 187
pathway methods 183, 184
Bennett acceptance ratio 185
free energy perturbation 185
pathway planning 184, 185
thermodynamic integration 185, 186
free energy perturbation 185
free radicals 9
FuFo actives
bioavailability 415
high concentrations 422
ingredients 415
pharmacokinetics (PK) of 415
functional proteins 4, 12, 13, 16
GALAS modeling approach 42
gas chromatography (GC) 204, 486
gas chromatography–mass spectrometry (GC–MS) 302
gene expression 12
GeneGo pathway 405
gene products 12
regulatory 12
genetic algorithm k-nearest neighbor (GA-kNN) 388
genetic polymorphisms 13
Gibbs energy 182
Gilbert’s syndrome 442
GIT enzymes 416
Glide software 40
glucuronidation 6, 9, 10, 29, 295, 337, 354, 361, 362, 422, 442, 443, 493
glutathione (GSH) 9, 496
hepatic 400
trapping 235
glutathione S-transferases 9, 17, 29, 422
glycosylated flavonoids 421
GOLD software 31, 40, 248, 254
graphical processing unit (GPU) technologies 179
GRID/GOLPE QSAR methodology 337
GRID software 223
gut microflora
complex intestinal models (TIM-2) 421
exposure time 419
fecal slurry 421
isolated pure bacterial cultures 421
modifications 419
several microbial enzymes 420
in vitro models 420, 421

HepaRG cell culture model 467, 468, 471
hepatic clearance 423
hepatic enzyme leakage 471
hepatic metabolism
cryopreserved hepatocytes vs. microsomes 428, 429
FuFo ingredients, pharmacokinetics 423
hepatocyte cell lines 426, 427
hepatocytes, in culture 429–431
microsomes 424
physiological illustration depicting 416
primary cultures 427, 428
S9 fractions 426
supersomes 424
in vitro liver metabolism models
advantages/disadvantages of 425, 426
in vitro models 424
hepatocyte nuclear factor 4 α 353
hepatocytes 11, 13, 373, 423, 427–429, 433, 445, 446, 458, 463, 468, 470, 475, 491
hERG potassium channel 404
heterologous expression systems 202
membranes from 202
insect cell systems 202
mammalian cells 202
microbial membrane systems 202, 203
heteronuclear multiple bond correlation (HMBC) 206
heteronuclear single quantum coherence (HSQC) 206
high-performance computing (HPC) facilities 180
high-performance liquid chromatography (HPLC) 203, 204, 434
high-resolution mass spectrometry (HRMS) 205
human CYPs 78
based on major substrate class 200
genes encoding 77
structural features 78–81
three-dimensional structures 78

human endogenous steroid biosynthesis 363
human ether-a-go-go-related gene (hERG) 321
human hepatoma cell line HepG2 465
human liver microsomal stability
QSAR models of 339
human liver microsomes (HLMs) 445–456
CYP inhibitors 449
direct inhibition 447–452
liver S9 fractions 456, 458
time-dependent inhibition 452–456
time-dependent inhibition experimental design 454
in vitro to in vivo extrapolation (IV/IVE) 449
Human Metabolome Database (HMDB) 59
human organic cation transporter 1 (hOCT1) 375
hydrogen bonding 85, 110, 134, 151, 224, 249, 382, 391
capacity 385
hydrolases 16, 17
3-hydroxylated benzodiazepines 6
hydroxylation 29
of aliphatic carbon atoms 268
aromatic and double bonded carbon atoms 271, 272
hydroxymethylbenzene 293
4-hydroxytamoxifen 7, 405
ibuprofen 11, 86
IC50 inhibition study design 450
IC50 values 434
idiosyncratic drug reactions (IDRs) 8
IDSsite 40
indomethacin 86
inducer models 363
hetero/autoactivation 363
CYP3A4 substrate model 364
CYP2C9 heteroactivation model 363, 364
nuclear receptors 364
CAR ligands 366
pregnane X receptor 364–366
inhibition assays 329
inhibitor concentrations (IC50) curve 447
interactions with metabolizing enzymes
methods for predicting 31–36
inter-individual factors 12
intestinal metabolism 421
FuFo actives 422
subcellular/cellular models 423
tissue intact models 423
in vitro models 422, 423
in vitro hepatocyte variation. 430
in vitro liver metabolism models
– advantages and disadvantages of 425, 426
in vitro metabolism models
– mathematical models for 432, 433
– measurement methodology 432
– pharmacokinetic analysis 431, 432
isothermal titration calorimetry (ITC) 180
K
KBS, see knowledge-based system (KBS) 462, 463
kinetic isotope effects (KIEs) 213, 214
knowledge-based application 299
knowledge-based software 16, 37–39
knowledge-based system (KBS) 37–39, 44, 45, 293, 313, 407
– absolute and relative reasoning 307–310
– basic structure of 294
– building/maintaining 295–299
– encoding rules 299, 300
– logic of argumentation 303–307
– MYCIN 295
– performance, validation/assessment of 312–314
– predictions from multiple sources 310–312
– ways of working 301, 302
Kupffer cells 445
I
lactase phlorizin hydrolase (LPH) 421
L-742 694 compound 405
lead optimization 226
– challenges 226
leave-many-out (LMO) 326
leave-one-out (LOO) 326
level of quantification (LOQ) 434
libraries 53, 447
– precalculated fragment-based 37
ligand-based approach 30, 48, 351, 355
ligand binding assays 463–465
ligand-derived models 37
ligand parameterization 188, 189
ligand–protein interactions 223, 225, 248
linear interaction energy (LIE) 247
linking experiment and simulation 180
lipid peroxidation 9, 10
lipophilic
– anionic substrates 86, 95, 97
– drugs 8
– interactions 79
metabolites 11
– xenobiotics 353
liquid chromatography–mass spectrometry (LC–MS) 302
liquid chromatography–mass spectroscopy/mass spectrometry (LC–MS/MS) 447
– direct inhibition experimental scheme 448
liver
– clearance parameter (CLH) 431
– cytosol 457
– microsomes 339
– toxicity 496
– in vitro cellular models 446
logic of argumentation, usage 303–307
loratadine 6
lorazepam 6
luciferase 464–466
m
machine learning approaches 41, 42
major histocompatibility complex (MHC) 406
MassMetaSite 236–239
mass spectrometry (MS) 485
Matthews correlation coefficient (MCC) 327, 334, 387
Maximum Unbiased Validation (MUV) database 352
McGowans characteristic volume 382
MD simulations 247, 248
– CYPs in lipid bilayers 96
MetabolExpert software 15, 16, 301
metabolic
– enzymes, phase I 362, 363
– intermediate complex 360
– profiling, toxicological effects 353
– stability 491, 492
– toxification 7
– mechanisms of toxicity, parameters 437
metabolism
– transcriptional regulation
– gene induction pathways 460–462
– gene repression/suppression 462, 463
Metabolite Database 41
metabolite detection/profiling 485–496
– chromatography 486, 487
– cytochrome P450 inhibition assays 491, 492
– liquid chromatography–mass spectrometry 487–490
– metabolic stability 491, 492
– reactive metabolite detection 496
– sample preparation for 490, 491
– sample preparation for LC–MS 490, 491
– in vivo/in vitro studies, identification 492–495
metabolite identification (MetID) 224
metabolites
– classification of drugs without/with active 7
– detection and profiling (see metabolite detection/profiling)
– discrepancy between numbers of observed and possible metabolites 298
– formation
– vs. substrate depletion 432
– major determinants of metabolite formation 267
– metabolite predictors 66
– methods for predicting SoMs, structures of 31–36
– online databases 55
– predicting toxic effects (see predicting toxic metabolites)
– software for predicting (see software for predicting metabolites)
– spectroscopy 206–208
– structure prediction 30
– methods for 31–36
– of toluene (methylbenzene) 293
Metabolizer 45, 65, 297
MetaPred server 68
MetaPrint2D 41, 66, 67, 68
MetaPrint2D-React 66, 401
MetaSite software 15, 16, 39, 226, 227
– accessibility function 227–229
– automated metabolite identification (see MassMetaSite)
– prediction for PH-302 CYP3A4 inhibition 237
– prediction of CYP inhibition 234–236
– reactivity function 229, 230
– site of metabolism prediction 230, 231
– validation 231
META software 15, 16, 44
METEOR software 15, 16, 302
3-methoxy-O-desmethyl encainide 7
2-methyl-3-(3,5-diodo-4-hydroxybenzoyl)benzofuran 356
4-methyl(hydroxymethyl)benzene 293
MEXAlert software 39
Michaelis–Menten constant 424, 431
micronutrients 415
midazolam 474
MIF-based SoM predictor 46
MIF-based technologies 224
MIF discretization 227
MIFs, see molecular interaction fields (MIFs)
molecular docking 69. See also docking
molecular dynamics (MD) 78, 179
– simulations 37
molecular interaction fields (MIFs) 39, 46, 223
molecular orbital (MO) methods 16
monoamine oxidase (MAO) 362
morphine 7
morphine 6-O-glucuronide 7
multidrug resistance (MDR) 374, 375, 378
multidrug resistance–associated proteins 374
multiple linear regression (MLR) 323
– CYP2C9 substrates 329
mutations 78, 86, 91, 256
– analysis of CYP2B4 82
– CYP1A2 T124S 85
– CYP2D6 F483A 192
– effect of 256–258
– predicting substrate formation and 258
n
N-acetyltransferases (NATs) 29
NADPH-regenerating system 447
naproxen 85, 86, 105
negative predictive value (NPV) 386
Netherlands Cancer Institute (NKI) 378
nicotinamide adenine dinucleotide phosphate oxidase 445
NMR relaxation 179
N/O-dealkylation 42
non-CYP oxidoreductases 16
nordazepam 7, 60
nuclear magnetic resonance (NMR) spectroscopy 248, 486
nuclear overhauser correlated spectroscopy (NOESY) spectra 206
nuclear receptors (NRs) 353
– CYP induction 353
nucleophiles 8
O
O-desmethyl encainide 7
O-desmethyltramadol 7, 60
omeprazole 358
online drug metabolism databases 53, 54, 56, 57
– categories 56
– DrugBank database 57, 58
– Human Metabolome Database 59
– PharmGKB 59, 60
– PubChem 61
– specialized databases 63
-- PK/DB 64
-- PKKB 64
-- SuperCYP 64
-- UM-BBD 63
– synoptic databases 61
-- BindingDB 63
-- ChEBI 62
-- ChEMBL 62
-- KEGG 62, 63
-- Wikipedia 60, 61

online drug metabolism prediction servers 65
– ADMET predictors 70
– metabolite predictors 66
– SoM predictors 66–68
– specialized predictors 68–70
oral contraceptives 441
organic anion transporters (OATs) 374, 427
organic anion transporting polypeptides
(OATPs) 427
organic cation transporters (OCTs)
373, 427
oxazepam 6, 7
oxidative hydroxylation 299
oxidative stress 8, 9
oxidoreductases 8, 9, 16

\(P\)
1-palmitoyl-2-oleoyl-sn-glycro-3-
phosphocholine (POPC) 94, 96
paracetamol 6, 400, 407
parameterization
– ligand 188
– linear interaction energy 187
partial least-squares discriminant analysis
(PLS-DA) 332
PASS (prediction of the activity spectra of
substances) 403
pathways-based information 404
PBPK models 452
Percepta module 42
peroxidases 9, 17
P-glycoprotein (P-gp) 418, 427
P-gp Predictor 69
pharmacodynamic (PD) effects 5
Pharmacogenomics Knowledge Base
(ParmGKB) 59
pharmacokinetic (PK) effects 5
pharmacokinetic–pharmacodynamic (PKPD)
modeling 5
pharmacophore-based methods
– CYP induction, nuclear receptors 353
– definitions of 352
– determination of chemical features 354
– inducer models 363–366
– qualitative models 352
– substrate and inhibitor 354–363
pharmacophore models 15, 284, 340, 352,
353
– substrate and inhibitor 354–363
phase space 181
phenacetin 6, 474
phenobarbital 462
N-(1-phenylcyclohexyl)-2-
ethoxyethanamine 296
3’-phosphoadenosine-5’-phosphosulfate
(PAPS) 338
phosphoglycoprotein (P-gp)-mediated
disposition 6, 373, 374
– adenosine triphosphate (ATP) 374
– ATPase binding cassette (ABC) 373
– compound structure, influence 380–385
– cytochrome P450 3A4 (CYP3A4) 375
– drug discovery, application 388–391
– drug transporter 374
– QSAR models (see QSAR models)
– QSAR prediction 376
– solute carrier (SLC) superfamilies 373
– substrate identification 389
– in vitro/in silico approaches 374
physiologically based pharmacokinetics
(PBPK) 392, 451, 452
pioglitazone 235
– GSH adducts 235
– inhibition for CYP isoforms 235, 236
polymerizations 17, 77
polyunsaturated fatty acids 9
positive predictive value (PPV) 386
potential energy surface (PES) 183
PreADMET 70
predicting toxic metabolites 397, 401
– absolute metabolism likelihoods and
rates 401, 402
– anticipating toxic effects of 398
– bioactivity-based mechanistic models 403,
404
– CYPs, polymorphisms 402
– cytochrome P450 (CYP) pathways 400
– endogenous/exogenous substances 397
– hepatic glutathione (GSH) 400
– incorporating pathway information
404–406
– knowledge-based systems 407
– MetaPrint2D-React 401
– pharmacogenetic data 402
– political developments 408
– reactive metabolites 407, 408
– relative and absolute rates 399, 401, 402
– in silico methods 397
– toxic effects 402
– bioactivity-based mechanistic models 402, 403
– incorporating pathway information 404–406
– knowledge-based systems 407
– reactive metabolites 407, 408
– toxicogenetic/pharmacogenomic approaches 406, 407
– toxicogenetic/pharmacogenomic models 402, 403
– incorporating pathway information 404–406
– knowledge-based systems 407
– reactive metabolites 407, 408
– toxicogenetic/pharmacogenomic approaches 406, 407
– UDP-glucuronosyltransferases (UGTs) 402
– workflow for 399
P450 regioselectivity module of perceive 42
pregnane X receptor (PXR) 336, 364, 402, 427, 460
procarcinogens 77
prodrugs 6, 7
propranolol 493
prostaglandins 77, 115
Protein Data Bank (PDB) 225, 355
protein flexibility 249–253
protein–ligand complexes 37, 107, 354
protein–ligand crystal structures 119, 120
protein–ligand interactions 39
PubChem 61
purified CYPs in reconstituted systems 201, 202
pyrazoles 294

q
QikProp software 39
QM/MM studies 135
– applications to cytochrome P450 enzymes 144–146
– conversion of Cpd 0 into Cpd I in T252X mutants 148–151
– Cpd I species of different cytochrome P450s 154, 155
– formation of Cpd I from Cpd 0 146–148
– mechanism of cytochrome P450 StaP 155–160
– mechanism of dopamine formation 160–163
– properties of Cpd I 151–154
– methodological issues in studies 136
– electrostatic QM/MM interactions 139
– MM methods 138
– QM methods 137, 138
– QM/MM boundary treatments 139, 140
– QM/MM energy versus free energy calculations 141
– QM/MM geometry optimization 140
– QM/MM molecular dynamics and free energy calculations 140, 141
– QM/MM partitioning 136, 137
– subtractive versus additive QM/MM schemes 139
– practical issues in studies 141
– accuracy of QM/MM results 143
– extracting insights from QM/MM calculations 144
– QM/MM geometry optimization 143, 144
– QM/MM setup 142, 143
– QM/MM software 141, 142
QSAR models 322, 353, 375, 405
– applicability domains 328
– assessment and validation 327, 328
– black box models 323
– classical 326, 329–333
– conjugative metabolizing enzymes 337
– for cytochrome P450 328
– SARs 328, 329
– 3D models 335, 336
– 3D QSAR methods 340
– enzyme induction 336, 337
– of human hepatic microsomal intrinsic clearance 340
– local vs. global 325, 326
– machine learning 327, 333
– models 325
– MLR-based 326
– models, classification 334, 335
– molecular descriptors 324
– multiple linear regression (MLR) 323
– predictive ability 327
– SAR 326
– in silico 324
– prediction 324
– sulfotransferases 338, 339
– training SAR 325
– uridine diphosphate glucosyltransferase (UGT) 338
– in vitro clearance 339, 340
QSAR prediction
– experimental data/assays 376–378
– phosphoglycoprotein (P-gp)-mediated disposition 376, 380, 385–388
– substrate identification 378–380
quantitative reverse transcription polymerase chain reaction (qRT-PCR) 473
quantitative structure–activity relationship (QSAR), see QSAR models
quantum mechanical (QM)
  – calculations 37
  – tool 134
quenching 9
quinone reductases 9

**r**
random forest (RF) 335, 380
reactive nitrogen species (RNSs) 9
reactive oxygen species (ROSs) 8, 9
reactivity models 40, 41
  – for CYP reactions 268
  – -- combined carbon atom models 273
  – -- comprehensive models 273, 274
  – -- epoxidation of aromatic and double bonded carbon atoms 271, 272
  – -- hydroxylation
  -- -- aliphatic carbon atoms 268–270
  -- -- aromatic and double bonded carbon atoms 271, 272
-- CypScore 41
-- SMARTCyp 40
-- software for 40, 41
-- StarDrop 40, 41
receiver operating characteristic (ROC) curves 38, 312
recombinant enzymes 232, 233, 238, 457, 458
recursive partitioning (RP) 335, 380
regioselectivity
  -- P450 Regioselectivity module of Percepta 42
  -- RegioSelectivity (RS)-WebPredictor 42, 67, 281
registration, evaluation, and authorization of chemicals (REACH) 323
reliability index (RI) 42
retinoid X receptor (RXR) 461
reversed-phase (RP) chromatography 487, 494
rhodamine-123 375
rifampicin 365, 441, 461, 469, 470
ritonavir 87, 88, 105, 106, 115, 122, 453, 459, 469, 470
root mean square error (RMSE) 324
rosiglitazone 235
  -- GSH adducts 235
  -- **in vivo** liver toxicity 235
RS-WebPredictor 42, 67, 68
s
sandwich culture model 429
SAR, see structure-activity relationship (SAR)
*Scutellaria baicalensis* 359
shape-focused approaches 42, 43
single-nucleotide polymorphisms (SNPs) 456
site of metabolism (SoM) prediction 30, 38
  – competition between different SoMs with regard to 267
-- Metabolism module of ADMET Predictor 42
  -- methods for 31–36
  -- software 38
-- SoM predictors 56, 66
-- structure-based predictions 243
SMARTCyp approach 45, 67, 248
  -- for CYP isoforms 2D6 and 2C9 248
  -- for descriptor calculation 42
  -- software 40
SMIRKS rules 267
sodium taurocholate cotransporting polypeptide (NTCP) 373
soft drugs 6
software for predicting interactions of small molecules
  -- ADMET Predictor Metabolism module 47
  -- ADMEWORKS Predictor 48
  -- isoCyp 47
  -- with metabolizing enzymes 46–48
  -- MetaDrug 47
  -- MetaPred 47
  -- PASS 48
  -- Percepta software package 46, 47
  -- VirtualToxLab 48
  -- WhichCyp 47
software for predicting metabolites 43
  -- data mining and machine learning approaches 46
  -- -- MetaPrint2D-React 46
  -- -- knowledge-based systems 44, 45
  -- -- JChem Metabolizer 45
  -- -- META 44
  -- -- MetabolExpert 44
  -- -- MetaDrug 45
  -- -- Meteor 44, 45
  -- -- SyGMA 45
  -- -- TIMES 45
  -- -- UM-PPS 45
  -- molecular interaction fields 46
  -- -- MetaSite 46
software for predicting sites of metabolism 38
– data mining and machine learning approaches 41, 42
– FAs MEtabolizer (FAME) 42
– Metaprint2D 41
– P450 Regioselectivity module of Percepta 42
– RegioSelectivity (RS)-WebPredictor 42
docking 39, 40
– IDs 40
– knowledge-based systems 38, 39
– MEXAlert 39
– QikProp 39
– molecular interaction fields 39
– MetaSite 39
reactivity models 40, 41
– CypScore 41
– SMARTCyp 40
– StarDrop 40
– shape-focused approaches 42, 43
– ROCS 43
solid-phase extraction (SPE) 491
S-oxidation 42
specificity (sp) 386
StarDrop software 40, 41
statins 441
statistical mechanics 180
steroids 77
structural variability 83, 97
– CYP1A2 83–85
– CYP2A6 85
– CYP3A4 87, 88
– CYP2C9 85, 86
– CYP2D6 86
– CYP2E1 87
structure-activity relationship (SAR) 39, 322
– based on chemical bond energy 211
– based on docking 211, 212
– based on products 210, 211
– knowledge-based SAR 212
– SARs based on chemical bond energy 211
– SARs based on docking 211, 212
– CYP inhibitor
– SAR, related to ionization state 330
– SAR, related to molecular size 331
– 3D-QSAR modeling 15
– GRID/GOLPE QSAR methodology 337
– knowledge-based 212
– PLS-based QSAR model 340
– reaction rates 213
– SAR of reaction rates 213
– training SAR 325
structure-based methods 37
– molecular docking (see molecular docking)
– for predicting metabolism 30
– for predicting sites and products of metabolism (see 6 Å Rule; protein flexibility)
structure-based prediction 40
structure–function relationships 77
structure–metabolism relationships (SMRs) 30
substrate and inhibitor pharmacophore models
cytochrome P450 enzymes 354
– CYP3A5 inhibitors 360
– CYP3A7 inhibitors 360
– CYP3A4 substrate pharmacophore model 359, 360
– CYP1A2, substrates/inhibitors 354, 355
– CYP2B6 substrates 355, 356
– CYP2C9 ligands 356, 357
– CYP2C19, substrates 357, 358
– CYP2D6 model 358, 359
– interference with phase I metabolic enzymes 362, 363
– UDP-glucuronosyltransferases (UGTs) 9, 29, 361, 402, 422
– UGT1A1 substrates 361
– UGT1A4 substrates 361
– UGT1A9 substrates 361, 362
– UGT2B7 substrates 362
substrate recognition sites (SRSs) 82, 83
substrate specificity profiles 83
sulfation 337, 400, 422, 490
sulfotransferases (SULTs) 9, 17, 29, 337, 338, 339, 422
tamoxifen 7, 105, 106
temazepam 6
terfenadine 444
testosterone 164, 203
– hydroxylation 201
– sites of oxidation by CYP3A4 212
tetrachlorodibenzo-p-dioxin (TCDD) 460
thermodynamic integration 185
thin layer chromatography (TLC) 486
time-dependent inhibition (TDI) 266
time-of-flight (TOF) 238, 487, 488
TIMES (Tissue Metabolism Simulator) 34, 45, 301
tissue microsomal systems 201
TNO developed Intestinal Model (TIM-2) 421
total free energy 249
toxicity pathways 408
toxicophores 9
toxification 3, 7–9
toxophores 9
ToxTree software 267
tramadol 7
transactivation assays 465
transcription factor activators 464
– in vitro screening methods 464
transferases 16
transferase–transporter coupling 10
transition state theory (TST) 183
trapping assays 496
trichloroacetic acid (TCA) 491
troglitazone 105, 111, 112, 122, 234, 235
trovofloxacin 405

UDP-glucuronosyltransferases 17, 444
UGT1A1 enzyme 442, 446
UGT1A gene 473
UM-BBD database 45, 69
UM-PPS web server 45, 69
uridine diphosphate glucosyltransferases (UGTs) 337

validation 30
– assay validation
–– analytics 434
–– reference compounds, selection 433, 434
–– in vitro model, theoretical steps 434, 435
– maximum unbiased validation (MUV) database 352
– MetaSite 231
– model validation 312–314, 327
van der Waals (vdW) interactions 185
very low-density lipoprotein (VLDL) 437
vitamin K epoxide reductase complex (VKORC1) 406
VolSurf descriptors 380, 384, 388

warfarin 441
– crystal structure 363
– ligands 357
water 254
– computational studies 254
– effect of crystallographic water molecule in CYP1A2 254
– effect of water molecules
–– on predicted docking poses 255
––– SoM predictions, effects sorted in classes 255
–– and protein structures 256
– entropic effect 254
– x-ray structure of CYP1A2 254
web-accessible databases 54
web servers 53, 54, 71
well-stirred model 432
whole-cell hepatocyte assays 339
Wikipedia 53
WikiProjects 60
World Wide Web 53

xenobiotics 104, 415, 417
– classification of human CYPs based on 200
– CYPs induction 336
– definition 415
– detoxification process 418
– drug’s clearance 441
– harmful 367
– metabolism 3, 30
–– enzymes expression of 459, 460, 463
–– factors influencing 18
–– genes, mRNA expression of 471
–– principal metabolic proteins 322
– metabolite prediction 66
– response elements (XREs) 460
XMetDB database 266
x-ray diffraction 206