

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
- acceptor capability 379, 382
- N*-acetyltransferases (NATs) 29, 402, 444
- activation energy 151, 266, 267, 271
- ADRs, *see* adverse drug reactions (ADRs)
- adverse drug reactions (ADRs) 7, 58, 59, 337, 403, 404
 - caused by reactive metabolites 8
 - off-target 8
 - on-target 7
- aglycones 420, 421
- AhR/ARNT signaling transduction pathway 466
- AhR-inducible gene battery 461
- ALCHEMY 299
- alcohol consumption 443, 460
- aldosterone synthase 118, 363

b

- algorithms
 - Algorithm Builder (Pharma Algorithms) 379
 - Bayesian classification algorithms 339
 - docking algorithm 246
 - genetic algorithm *k*-nearest neighbor (GA-*k*NN) 388
 - SMART-Cyp's SoM algorithm 67
- amine 299
 - 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
- autoxidation 9
- AZD5438 494
- azole compounds, PXR antagonist model based on 365

- benzodiazepines 6
- benzphetamine 190
- B-factors 179
- 1 β -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
- bupropion 474

- c**
- calcium channel blocker 106, 110, 441
- calculated molar refractivity (CMR) 379, 382, 383
- Cambridge Crystallographic Database (CSD) 225
- capillary electrophoresis (CE) 486
- catechol-O-methyltransferase (COMT) 363
- Caucasian hepatoblastoma 427
- cell-based assays 465
- cetirizine 6
- chemical ionization (CI) 487
- chemical transformations 64, 182, 183, 407
 - achieved by CYPs 134
- 5-chloro-1,3-benzodioxol-4-amine
 - positive ion mass spectrum 489
- chloroperoxidase (CPO) 135
- cholesterol esters 11
- chorismate mutase 192
- circular dichroism (CD) 206
- cisplatin 7
- classification and regression trees (CART) 325
- comparative molecular field analysis (CoMFA) 326
- comparative molecular similarity indices analysis (CoMSIA) 326
- 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
- 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

- 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 Regioselectivity module of Percepta 42
 - RegioSelectivity (RS)-WebPredictor 42
- dealkylation 29
- 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

e

- EC_{50} 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 (MM-GBSA) 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

f

- fadrozole 118
- Fa2N-4 cell line 466
- FAst 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

g

- 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
- gut wall
 - clearance 422
 - metabolism (*see* intestinal metabolism)
 - physiological illustration depicting 416
- h***
 - 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
 - i***
 - ibuprofen 11, 86
 - IC₅₀ inhibition study design 450
 - IC₅₀ values 434
 - idiosyncratic drug reactions (IDRs) 8
 - IDSite 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)
- ketonconazole 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

l

- 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 spectroscopy (LC–MS/MS) 447
 - direct inhibition experimental scheme 448
- liver
 - clearance parameter (CL_H) 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-diiodo-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-glycero-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 (PharmGKB) 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
- polymorphisms 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 approaches 406, 407
- UDP-glucuronosyltransferases (UGTs) 402
- workflow for 399
- P450 regioselectivity module of percepta 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
 - - FAst MEtabolizer (FAME) 42
 - - Metaprint2D 41
 - - P450 Regioselectivity module of Percepta 42
 - - RegioSelectivity (RS)-WebPredictor 42
 - docking 39, 40
 - - IDSite 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 (SRSSs) 82, 83
 - substrate specificity profiles 83
 - sulfation 337, 400, 422, 490
 - sulfotransferases (SULTs) 9, 17, 29, 337, 338, 339, 422
 - sulfoxidation 10, 133
 - SuperCYP database 64
 - supernatant (S9) 446
 - superoxide dismutase (SOD) 9
 - Supersomes 424, 426, 428, 434
 - support vector machine (SVM) 67, 380
 - classification models 334
 - SyGMA (Systematic Generation of potential Metabolites) 34, 45, 297, 311
- t***
- 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
 trovafloxacin 405

u

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

v

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

w

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

x

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

