Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

Index

absolute free energies, 73-76 FKBP binding calculations for, 75 ligand binding in, 73–74 T4 lysozyme ligand binding, 74-75 negative results for, 74-75 water binding and, 74 absorption/distribution/metabolism/ excretion (ADME) software, 1, 5-7. See also intestinal absorption, in ADME models; metabolism, in ADME models; P-glycoprotein effluxes, in ADME models; solubility, in ADME models BBB penetration and, 169–170 celecoxib, 6-7 for drug discovery, 165-173 administration routes for, 166 clearance in, 172 computational models in, 165 drug-likeness measures in, 165-166 formulation problems with, 165 intestinal absorption and, 168–169 metabolism in, 172–173 P-glycoprotein effluxes and, 170-171 plasma protein binding and, 171-172 proteomic families and, 166 solubility in, 166–168 tissue distribution and, 172 QIKPROP, 5-7 required input, 5 submission to, 5-6 rofecoxib. 6 "rule-of-three," 6 violations, 7 achiral immucillins, 242 acyclic immucillins, 241-242 DATMe. 241-242 ADME software. See absorption/ distribution/metabolism/ excretion software affinity distribution models, for SBDD, 62 - 63basic equations for, 64 Agenerase. See amprenavir AIM theory. See atoms-in-molecules (AIM) theory ALADDIN method, 139 alchemical free-energy calculations, for SBDD, 66, 72-76 absolute free, 73-76 FKBP binding calculations for, 75

ligand binding in, 73-74 T4 lysozyme ligand binding, 74–75 water binding and, 74 negative results from, 76–77 predictive tests for, 76 relative binding free, 72–73 estrogen receptors and, 73 for fructose 1, 6 bisphosphatase, 73 HIV-1 and, 72, 73 for neutrophil elastase inhibitors, 73 solvation free, 76 studies on, 77 with GCMC techniques, 77 alchemical methods, for SBDD, 66 explicit water simulations in, 66 free energy perturbation as, 66 Lennard-Jones parameters for, 69 pathways for, 68-69 WHAM as, 68 Zwanzig relationship, 66 allosteric inhibitors, 94 enzyme binding sites for, 94 monomer cores as target for, 94 protease dimer interfaces in, 94 AMBER force fields, 126 AMP sites, HGLP and, 259-261 AmpC β-lactamase inhibitors, QSAR models for, 161 classification of, 161 amprenavir, 87 analogs, docking scores and, 99 β2-andrenergic receptors, 249 ligand-binding sites in, 249-250 anticancer agents, QSAR models for, 161 anticonvulsive compounds, QSAR models for, 159–161 Maybridge HitFinder library and, 161 APEX-3D method, 139 pharmacore scoring by, 144 applicability domains, in QSAR models, 154-155 confidence index for, 155 definition of, 155 Aptivus. See tipranavir atazanavir, 87 atoms-in-molecules (AIM) theory, 133 azidothymidine (AZT), 87 AZT. See azidothymidine

BACE inhibitors, 187-189 ligand binding affinity and, 184–186 solubility in, 191 BAR. See Bennett Acceptance Ratio BBB penetration. See blood-brain barrier (BBB) penetration, in ADME models Bennett Acceptance Ratio (BAR), 68 **MBAR**, 68 BIEs. See binding isotope effects binding affinity calculations, 129-130 linear scaling and, 130-131 binding isotope effects (BIEs), 238–239, 240 Biochemical and Organic Model Builder (BOMB), for lead generation, 1, 2–3 core binding sites, 2 docking, 3-4 protein hosts, 2-3 results, 3 PDB file, 3 scoring function, 3 small group scans, 10 substituent library, 2 blood-brain barrier (BBB) penetration, in ADME models, 169-170 P-glycoprotein effluxes and, 170-171 BOMB. See Biochemical and Organic Model Builder (BOMB), for lead generation bound pose prediction, with docking, 105-114 with JNK3 proteins, 108-113 aminopyrimidines, 109-110 compound classes in, 109 oximes, 110–111 p38 inhibitors, 110 public structures in, 108–109 pyrazole placement in, 111-113 with SAMPL challenge, 105 manual vs. automated, 113-114 with SAMPL challenge, 105-107 JNK3 structures and, 105 manual process for, 106 semi-automated process for, 106 small-molecule conformations in, 106-107 with urokinase plasminogen activators, 107-108 ligand docking and, 107 public structures in, 107 RMSD-DPI and, 107

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

266 Index

bovine PNP, transition-state structure of, 221-226 immucillins and, 226, 227 crystal structures of, 227-229 inhibitions of, 227 KIEs in, 222–223 inosine arsenolysis interpretation and, 223-224, 226, 230, 238 labeled substrate synthesis in, 221-222 V/KKIEs and, 223 CAPRI. See Critical Assessment of PRedicted Interactions Carbó similarity index (CSI), 133 CASP. See Critical Assessment of Structure Prediction CATALYST method, 138-139 pharmacore scoring with, 143, 144 CATFEE. See Critical Assessment of Techniques for Free Energy Evaluation CAVEAT method, 139 Celebrex. See celecoxib celecoxib, 6-7 charge transfers, 128 chemical shift perturbations (CSP), 123-124 CHEM-X method, 139 pharmacore fingerprinting with, 146 clearance, in drug discovery, 172 cloned proteins, crystallization of, 17 combinatorial libraries, for SBDD, 61 CoMFA. See comparative molecular field analysis comparative molecular field analysis (CoMFA), 132 disadvantages in, 133 comparative molecular similarity indices analysis (CoMSIA), 132 competitive binding methods, of NMR, 49-50 computer-aided drug design, 181–193 BACE optimization in, 187-189 solubility and, 191 challenges in, 181-182 with accuracy, 181 with protein/ligand binding affinities, 181 sampling as, 181-182 development of, 181 with docking, 183-184 ligand binding affinity in, 184-185, 187 BACE inhibitors and, 184-186 with FEP, 184 LIE calculations for, 184 rules for, 189 modeling approaches for, 182 potency and, 189-193 hERG modeling and, 190-192, 193 with protein structures, 182, 183 geometry optimization for, 183 protonation state determination with, 182-183 scoring with, 183-184 CoMSIA. See comparative molecular similarity indices analysis

consensus prediction, in QSAR models, 156-159 Critical Assessment of PRedicted Interactions (CAPRI), 79 Critical Assessment of Structure Prediction (CASP), 79 Critical Assessment of Techniques for Free Energy Evaluation (CATFEE), 79 Crixivan. See indinavir crystal packing, 168 crystal structures, 17 diffraction of, 18 electron density map and, 21 patterns for, 18-20 docking and, 99 in GPCRs, 248–250 of human PNP, 234 of immucillins, 227-229 in proposed molecular mechanisms of resistance, for HIV-1, 92-93 proteins as, 17 cloned, 17 docking and, 99 homologous, 17 mammalian, 17 truncation for, 17 scattered beams and, 18 CSI. See Carbó similarity index CSP. See chemical shift perturbations cytochrome analysis, 173 DADMe immucillins, 232-234 enantiomers of, 234–237 human PNP and, 232, 234 pharmacological applications of, 239-241 synthesis of, 232-233 in vivo studies of, 241 DANTE method, 139 pharmacore scoring with, 143 darunavir. 87 data collection, for x-ray crystallography, 18 - 20diffraction and, 18 patterns for, 18-20 quality of, 19–20 as three-dimensional, 18-19 units in, 18 resolution of, 20 with scattered beams, 18 DATMe immucillins, 241–242 DEER. See double electron-electron resonance delavirdine, 87 density functional theory (DFT), 124 DFG-out binding pocket, 201-202 access to, 201-202 DFT. See density functional theory diabetes, HGLP for, 257 diffraction, of crystals, 18 electron density map and, 21 patterns for, 18-20 quality of, 19-20 as three-dimensional, 18-19 units in, 18 diffusion-based methods, of NMR, 48-49 longitudinal relaxation rates of, 48-49

NOEs and, 48-49 sensitivity of, 48 dimethyl sulfoxide (DMSO), 166, 167-168 DISCO method. See DIStance COmparisons (DISCO) method DIStance COmparisons (DISCO) method, 138 in pharmacore identification, 142 docking, 98-114. See also bound pose prediction, with docking bound pose prediction with, 105-114 with JNK3 proteins, 108–113 manual vs. automated, 113–114 with SAMPL challenge, 105–107 with urokinase plasminogen activators, 107-108 censuses for analysis of, 100-102 inhibitors in, 104 potent hits and, 103–104 recommendations for, 102 of screens, 99-100 Wilcoxon-Mann-Whitney nonparametric rank order tests and, 101–102 computer-aided drug design with, 183-184 free-energy calculations and, 98, 99 future applications for, 114 for GPCRs, 251-252 fast, 251–252 manual, 251-252 virtual screening for, 251–252 of HGLP, 257-258, 259-261 lead discovery with, 99-102 methods for SBDD, 61 in pharmacore methods, 140 receptor-based, 144 protein configuration integrals and, 99 protein crystal structures and, 99 in relative proton potential, 128–129 scores. 99 affinity for analogs and, 99 as theory, 98-99 virtual screening for, 3-4, 99-100, 104 - 105Zwanzig relationship and, 98–99 docking screens, census for, 99-100 double electron-electron resonance (DEER), 89 drug design. See also computer-aided drug design; drug discovery and optimization; HIV-1 protease, drug design for; purine nucleoside phosphorylase (PNP), drug design for; structure-based drug design computer-aided, 181-193 BACE optimization in, 187-189 challenges in, 181-182 development of, 181 with docking, 183–184 ligand binding affinity in, 184-187 modeling approaches for, 182 potency and, 189-193 with protein structures, 182–183 scoring with, 183-184

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index More Information

7 Index

for HIV-1 protease, 87-95 allosteric inhibitors in, 94 for HCV, 212 proposed molecular mechanisms of resistance and, 92-94 simulations of, 88-91 structure of, 87-88 unbound structures in, 91-92 viral inhibitors for, 87 LBDD, 120 QSAR methods for, 120 quantum mechanics and, 131 for PNP, 220–239 binding isotope effects and, 238-239, 240 bovine, transition-state structure of, 221-226 human, transition-state structure of, 230 - 234immucillins and, 226-230 kinetic mechanisms for, 220-221 mechanistic implications of, 234-239 remote interactions for, 237–238 third-generation, 241-242 SBDD, 17 catalysis and, 128 combinatorial libraries for, 61 free energy calculations in, 61-79 ITC for, 61 linear scaling in, 130-131 molecular profiles for, 61 parameters of, 120 physics-based models for. 61 quantum mechanics in, 120-127, 128–129, 131, 133 screening methods for, 61 SPR for, 61 transition-state analog, 215–243 drug discovery and optimization, 1-12. See also fragment-based lead discovery; fragment-based structure-guided drug discovery; HIV-1 protease, drug design for; pharmacore methods; SGX FAST fragment-based structure-guided drug discovery ADME properties in, 165-173 administration routes for, 166 clearance in, 172 computational models in, 165 drug-likeness measures in, 165–166 formulation problems with, 165 intestinal absorption and, 168-169 metabolism in, 172-173 P-glycoprotein effluxes and, 170–171 plasma protein binding and, 171-172 proteomic families and, 166 solubility in, 166-168 tissue distribution and, 172 FBLD advantages of, 42 binding efficiency of fragments in, 44 chemical efficiency of fragments in, 42-43 development of, 41 fragment definition in, 41-42 hit-to-lead process in, 44-45

ligand efficiency in, 44 linkage in, 45 NMR in, 41–50, 55 principles of, 42-44 screening in, 41–42 searching efficiency of fragments in, 43-44 validation of fragments in, 44-45 fragment-based structure-guided, 30-39 advantages of, 31 fragment engineering in, 30 fragment libraries for, 31 fragment linkage in, 30 history of, 30 HTS libraries and, 30-31 SGX FAST, 31-39 GPCRs, 1 for HIV-1 protease, 87–95 allosteric inhibitors in, 94 proposed molecular mechanisms of resistance and, 92-94 simulations of, 88–91 structure of, 87–88 unbound structures in, 91-92 viral inhibitors for, 87 HTS. 1 lead generation, 1–5 BOMB, 1, 2–3 GLIDE program, 1 HIV-RT, 1 virtual screening, 3–4 lead optimization, 7–12 complex modeling, 7 conversions, 7 FEP calculations, 7-11 heterocycle scans, 8-10 linker refinement, 11 logistics, 11-12 molecular design calculations, 7–8 protocols, 12 small group scans, 10–11 ligand-based design, 1 with MM-PBSA, 71-72 pharmacore methods for, 137-148 active analog approach in, 137 ALADDIN, 139 APEX-3D, 139 automated perception, from ligand structures, 139-140 CATALYST, 138-139 CAVEAT, 139 CHEM-X, 139 common identification for, 142 DANTE, 139 definition of, 137 **DISCO**, 138 ensemble distance geometry, 138 evolution of, 137-139 excluded volumes in, 145 fingerprints, 146 GALAHAD, 139 GASP, 138-139 HIPHOP, 138–139 history of, 137-139 ligand preparation in, 140-141 manual construction for, 139

mapping features for, 141-142 model development for, 139 receptor-based, 144-145 SCAMPL 139 scoring of, 143-144 3D chemical features in, 137 3D database screening in, 146-148 torsion angles in, 137–138 QSAR in, 151–162 applicability domains in, 154–155 combinatorial criteria for, 155-156 criticism of, 151-152 development of, 151 Hansch approach to, 152 mechanistic models for, 154 methodologies for, 152-153 model validation in, 153-154 modern data sets in, 152 multiple descriptors in, 152-153 PAHs and, 154 target properties for, 153 SAR, 1 SBDD and, 17 SGX FAST, 31-39 aromatic bromine and, 32 biochemical assays for, 35 complementary biophysical screening, 35 deliverable properties for, 32 end game for, 32, 37 fragment library design in, 31–32, 37 fragment x-ray screening in, 32, 34-35 future prospects for, 38-39 leadlike properties in, 31-32 protein kinases in, 37 SAR optimization in, 35–37 selectivity in, 37 SMERGE program for, 37 SPR screening for, 35 target enabling in, 32, 33-34 X-ray screening in, 35 siRNA, 1 structure-based design, 1 x-ray crystallography and, 17–28 advantages of, 24-25 basic requirements for, 17 data collection for, 18–20 disadvantages of, 25 electron density map for, 20, 21-22 phasing in, 20-21 quantum mechanics in, 120-123 refinement of, 22-24 surface mapping in, 25–28 for water molecules, 26-27 drug potency, computer-aided drug design and, 189-193 hERG modeling and, 190-193 drug resistance, HIV-1 protease and, 87-95 allosteric inhibitors in, 94 proposed molecular mechanisms of resistance and, 92-94 simulations of 88-91 structure of, 87–88 unbound structures in, 91–92 viral inhibitors for, 87 λ-dynamics, as SBDD methodology, 70

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

268

Index

Ehrlich, Paul, 137 electron density map, 20, 21-22 diffraction studies and, 21 display for, 22 interpretation of, 21-22 occupancies in, 22 solvent flattening and, 21 surface mapping and, 25-26 electrostatic potential (ESP) maps, 127-131 relative proton potential and, 127-131 catalysis and, 128 charge transfers in, 128 docking programs in, 128-129 interaction energy decomposition in, 131 linear scaling in, 130-131 point charge models in, 127-128 polarization in, 128 proton affinity in, 128 ZINC database and, 129 energetically restrained refinement (EREF) formalism, 121-122 ensemble distance geometry, 138 enzymatic transition-state formation, 215-216 dynamic coupling in, 216 ground-state destabilization in, 215 NACs and, 216 substrate conformation and, 215-216 EREF formalism. See energetically restrained refinement (EREF) formalism ESP maps. See electrostatic potential (ESP) maps estrogen receptors, 73 expanded ensemble, as SBDD methodology, 70 explicit water simulations, 66 FBLD. See fragment-based lead discovery feature dictionary, for pharmacore features, 141 FEP. See free-energy perturbation FEP calculations, 7-11 azines as NNRTIs, 8 heterocycle scans, 8-10 five-membered heterocyclic core, 205-206 FKBP binding calculations, 75 Fortovase. See saquinavir soft gel fosamprenavir, 87 fragment dictionary, 141-142 fragment fusion, 51 fragment libraries ligand efficiency in, 31 for SGX FAST, 31-32 chemical diversity of, 33 design of, 31-32, 37 properties of, 32-33 size of, 32–33 for structure-guided drug discovery, HTS libraries v., 31 potency for, 31 fragment X-ray screening, 32, 34-35 LIMS and, 34-35 sensitivity of, 35 visualization clarity of, 35

fragment-based lead discovery (FBLD). See also nuclear magnetic resonance (NMR), with FBLD advantages of, 42 binding efficiency of fragments in, 44 chemical efficiency of fragments in, 42-43 development of, 41 fragment definition in, 41-42 for hydrogen bond acceptors, 41 for hydrogen bond donors, 41 molecular classification for, 41 molecular weight in, 41 hit-to-lead process in, 44-45 ligand efficiency in, 44 linkage in, 45 NMR in, 41-50, 55 applications of, 50–55 competitive binding methods of, 49 - 50development of, 41 diffusion-based methods of, 48-49 ligand binding in, 45-46 ligand-directed methods of, 47-50 relaxation-based methods of, 48-49 saturation transfer difference methods of, 47 surface mapping and, 27-28 target-directed methods of, 45-47 WaterLOGSY method in, 47-48 principles of, 42-44 property ranges in, 42 screening in, 41-42 HTS, 42 searching efficiency of fragments in, 43-44 validation of fragments in, 44-45 fragment-based structure-guided drug discovery, 30-39 advantages of, 31 fragment engineering in, 30 fragment libraries for HTS libraries vs., 31 ligand efficiency in, 31 fragment linkage in, 30 history of, 30 HTS libraries and, 30–31 fragment libraries vs., 31 SGX FAST, 31-39 aromatic bromine and, 32 biochemical assays for, 35 complementary biophysical screening, 35 deliverable properties for, 32 end game for, 32, 37 fragment library design in, 31-32, 37 fragment x-ray screening in, 32, 34 - 35future prospects for, 38-39 leadlike properties in, 31-32 protein kinases in, 37 SAR optimization in, 35–37 selectivity in, 37 SMERGE program for, 37 SPR screening for, 35 target enabling in, 32, 33-34 x-ray screening in, 35

free-energy calculations, in SBDD, 61-79. See also alchemical free-energy calculations, for SBDD; alchemical methods, for SBDD: Molecular Mechanics with Poisson Boltzmann and Surface Area; partition function computation accuracy of, 62-63 for affinity distribution models, 62-63 for binding affinity, 62 alchemical, 66, 72-76 absolute free, 73-76 for fructose 1, 6 bisphosphatase, 73 negative results from, 76-77 predictive tests for, 76 relative binding free, 72–73 solvation free, 76 studies on, 77 docking and, 98, 99 future applications for, 77-79 with CASP, 79 with GAFF, 78 for HIV-1 protease drug design, 93 ligand binding calculations, 70-77 for MM-PBSA, 70-72 methodologies for, 63-70 alchemical methods, 66 for basic equations, 64 expanded ensemble as, 70 Hamiltonian exchanges as, 70 Jarzynski's relationship, 67–68 λ -dynamics, 70 MM-PBSA, 64-65 multiple intermediates, 66-67 multiple ligand simulations, 70 partition function computation, 65-66 pulling methods, 69 umbrella sampling, 69–70 simulation codes for, 78 free-energy perturbation (FEP), 66 with ligand binding affinity, 184 fructose 1, 6 bisphosphatase, 73 fused heterocyclics, 199-201 GAFF. See Generalized Amber Force Field GALAHAD method, 139 GASP method. See Genetic Algorithm Superposition Program method gas-phase potential energies, 64 GCMC techniques. See Grand canonical Monte Carlo (GCMC) techniques Generalized Amber Force Field (GAFF), 78 Genetic Algorithm Superposition Program (GASP) method, 138-139 GLIDE program, for lead generation, 1 filtering, 4 virtual screening, 3, 4–5 GLUE docking program, 173 GPCRs. See G-protein-coupled receptors G-protein-coupled receptors (GPCRs), 1 β_2 -andrenergic, 249 ligand-binding sites in, 249-250 crystal structures in, 248-250 docking studies for, 251-252 fast, 251-252 manual, 251-252 virtual screening for, 251–252

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

Index

as drug target, 248 features of, 248 fragment-based methods for, 253-254 future applications of, 254 modeling for, 248-254 3D, 250-251 molecular dynamic simulations for, 252-253 bilayer and solvent models, 252-253 model building for, 253 rhodopsin, 248–249 ligand-binding sites in, 249–250 SBDD and, 248 3D modeling for, 250-251 with de novo structure prediction, 251 fragment-based methods for, 253-254 with homologies, 250-251 Grand canonical Monte Carlo (GCMC) techniques, 77 GRIND descriptors, 170 Gund, Peter, 137 Hamiltonian exchanges, as SBDD methodology, 70 Hamming, Richard, 165 Hansch QSAR approach, 152 hepatitis C virus (HCV) HIV-1 protease drug design for, 209–213 lead optimization in, 211 modeling for, 209-210 pharmokinetic profiles in, 212 proof of concept in, 211 targets for, 209 virtual medium for, 210 in vitro activity in, 212 incidence rates for, 209 SVR for, 209 hERG. See human ether-à-go-go related gene heterocycle scans, 8-10 polycyclic, 9 HGLP. See human glycogen phosphorylase (HGLP), SBDD for high-throughput screening (HTS), 1 in FBLD, 42 for fragment-based structure-guided drug discovery, 30-31 compliance issues with, 31 disadvantages of, 30 fragment libraries vs., 31 molecule size and, 30-31 for SBDD, 61 HIPHOP method, 138–139 features of, 138 pharmacore scoring with, 143, 144 HIV-1 protease, drug design for, 87-95 allosteric inhibitors in, 94 enzyme binding sites for, 94 monomer cores as target for, 94 protease dimer interfaces in, 94 for HCV, 209–213 lead optimization in, 211 modeling for, 209-210 pharmokinetic profiles in, 212 proof of concept in, 211 targets for, 209 virtual medium for, 210

in vitro activity in, 212 proposed molecular mechanisms of resistance and, 92-94 binding affinity in, 93 crystal packing in, 92–93 entropy change in, 93 free-energy calculations for, 93 microcalorimetric measurements in, 93 wide-open structure for, 92 simulations of, 88–91 with DEER, 89 dihedral angle space constraints in, 91 with EPR method, 89 flap flexibility and, 88–91 with implicit solvent models, 90-91 with multiscale models, 89–90 with NMR, 88-89 structure of, 87-88 flap formation, 87, 88 semi-open, 87, 88, 90 unbound vs. bound, 88 wide-open, 87-88, 91, 92 unbound structures in, 91–92 bound vs., 88 NOESY for, 92 simulations of, 91-92 viral inhibitors for, 87 protease disruption in, 87 receptor binding in, 87 reverse transcription processes for, 87 HIV-1 reverse transcriptase (HIV-RT), 1 relative binding free energies and, 72, 73 HIV-RT. See HIV-1 reverse transcriptase HTS. See high-throughput screening human ether-à-go-go related gene (hERG), 190-192, 193 human glycogen phosphorylase (HGLP), SBDD for, 257–262 AMP sites and, 259-261 design of, 261-262 for diabetes, 257 docking of, 257-258, 259-261 x-ray crystal structures and, 262 energy calculations for, 262 features of, 257 phenyl diacid compounds and, 258, 262 putative binding pocket prediction for, 258-259 characterization of, 261 hydrogen bond contour map and, 261 synthesis of, 261-262 human muscle glycogen phosphorylase (HMGP), SBDD for, 257 human PNP, transition-state structure of, 230-234 crystal structure of, 234 DADMe immucillins and, 232, 234 features of, 230-231 hydrogen bond acceptors, 41 hydrogen bond contour map, 261 hydrogen bond donors, 41

IFPSC. See Industrial Fluid Properties Simulation Collective

immucillins, transition-stage analog design for, 226–230 achiral, 242 acyclic, 241-242 DATMe, 241–242 BIEs and, 238–239 bovine PNP and, 226, 227 crystal structures in, 227-229 inhibition of, 227 clinical trials with, 240 DADMe, 232-234 human PNP and, 232, 234 pharmacological applications of, 239-241 synthesis of, 232-233 in vivo studies of, 241 dissociation constants in, 227, 236, 237, 239 enantiomers of, 234-237 human PNP inhibition by, 231 DADMe immucillins and, 232-234 pharmacological applications of, 239-241 protein dynamics with, 229-230 stoichiometry of, 227 synthesis of, 226–227 in vivo studies on, 239–240 for human T cells, 239-240 for mouse T cells, 240 indinavir, 87 indoles, 204 Industrial Fluid Properties Simulation Collective (IFPSC), 79 inosine arsenolysis interpretation, 223-224, 226, 230, 238 computational modeling for, 225 intestinal absorption, in ADME models, 168-169 classification regression tree, 168 computational models in, 169 descriptors in, 168 intramolecular hydrogen bonds in, 168 - 169PAMPA permeabilities and, 169 Invirase. See saquinavir hard gel ionization identification, in pharmacore methods, 140 isothermal calorimetry (ITC), for SBDD, 61 Jarzynski's relationship, 67-68 BAR in. 68 MBAR in, 68 WHAM in, 68 JNK3 proteins, 108–113 aminopyrimidines, 109-110 compound classes in, 109 oximes, 110-111 p38 inhibitors, 110 public structures in, 108–109 pyrazol placement in, 111–113 with SAMPL challenge, 105 Journal of Information and Modeling, 151, 153

Kaletra. *See* lopinavir-ritonavir KIEs. *See* kinetic isotope effects

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

270 Index

kinetic isotope effects (KIEs), 217-220 in bovine PNP, 222–223 inosine arsenolysis interpretation and, 223–224, 226, 230, 238 V/KKIEs and, 223 computational modeling for, 219-220 features of, 218 inhibitor design approach to, 220 for inosine arsenolysis interpretation, 223–224, 226, 230, 238 as intrinsic, 219 kinetic mechanisms, for PNP drug design, 220-221 laboratory information management system (LIMS), 33 fragment X-ray screening and, 34-35 LBDD. See ligand-based drug design lead generation, 1-5 BOMB, 1, 2-3 core binding sites, 2 docking, 3-4 protein hosts, 2-3 results. 3 scoring function, 3 substituent library, 2 GLIDE program, 1 filtering, 4 virtual screening, 3, 4-5 HIV-RT, 1 virtual screening, 3-4 docking, 3-4 GLIDE program, 3, 4–5 NNRTIs, 3-4 ZINC database, 4 lead optimization, 7-12 complex modeling, 7 conversions, 7 FEP calculations, 7-11 azines as NNRTIs, 8 heterocycle scans, 8-10 in HCV drug design, 211 macrocyclization approach to, 212-213 heterocycle scans, 8-10 linker refinement, 11 logistics, 11-12 molecular design calculations, 7–8 FEP, 7-11 protocols, 12 small group scans, 10-11 **BOMB**, 10 Lennard-Jones parameters, for SBDD, 69 Lexiva. See fosamprenavir libraries. See combinatorial libraries, for SBDD; fragment libraries LIE calculations. See linear interaction energy calculations ligand binding affinity, 184–185, 187 BACE inhibitors and, 184-186 with FEP, 184 LIE calculations for, 184 ligand binding calculations, for SBDD, 70-77 absolute free energies and, 73-74 MM-PBSA as, 70-72 computational costs of, 70

MSE values for, 70-71 positive/negative partitioning in, 71 scores for, 71 ligand preparation, in pharmacore methods, 140-141 docking and, 140 ionization identification for, 140 with MCMM, 140 with MMFF, 140 model development in, 140 with OPLS, 140 sampling methods for, 140 tautomerization in, 140 ligand-based drug design (LBDD), 120 OSAR methods for, 120 quantum mechanics and, 131 with QSAR, 131-132 ligand-directed methods, of NMR, 47-50 advantages of, 47 disadvantages of, 47 ligands, in drug discovery and optimization design for, 1 in FBLD, 44 NMR and, 45-46 in fragment libraries, efficiency of, 31 quantum mechanics and, 123-125 SAR optimization and, 36 LIGANDSCOUT model, 144–145 LIMS. See laboratory information management system linear interaction energy (LIE) calculations, 184 linear scaling, 130-131 MOZYME program for, 130 technology development for, 130-131 with water molecules, 130 Lipinski's rules, 31 lopinavir-ritonavir. 87 LUDI interaction map, 144 mammalian proteins, crystallization of, 17 mapping. See also surface mapping of pharmacore features, 141-142 feature dictionary for, 141 fragment dictionary for, 141–142 of interaction sites, 141 of ionic groups, 141 Martin, Yvonne, 138 matched molecular pairs analysis, 167 Maybridge HitFinder library, 4 anticonvulsive models and, 161 MBAR. See multistate Bennett Acceptance Ratio MCMM. See Monte Carlo Multiple Model Merck Molecular Force Field (MMFF), 140 metabolism, in ADME models, 172-173 aromatic hydroxylation extraction and, 172 cytochrome analysis and, 173 GLUE docking program for, 173 MetaSite program for, 173 QSAR models, 173 quantum mechanics and, 172 MetaSite program, 173 Mining Minima method, 66

MMFF. See Merck Molecular Force Field

Area molecular design calculations, 7-11 molecular dynamic simulations, for GPCRs, 252-253 bilayer and solvent models explicit, 252-253 implicit, 253 model building for, 253 Molecular Mechanics with Poisson Boltzmann and Surface Area (MM-PBSA), 64-65 bound/unbound stimulation and, 64-65 coordinate sampling in, 64 in drug discovery, 71–72 dynamic trajectory analysis in, 65 entropic costs with, 65 gas-phase potential energies in, 64 as ligand binding calculation, 70-72 computational costs of, 70 MSE values for, 70-71 solute entropy change in, 64 solvation energy term in, 64-65 structure generation in, 64 molecular quantum similarity, 133 molecular replacement, 20 Monte Carlo Multiple Model (MCMM), 140 MOZYME program, 130 multiple intermediates, as SBDD methodology, 66-67 double-wide sampling in, 67 thermodynamic integration in, 67 curvature from, 67 slow growth simulation in, 67 Zwanzig relationship expansion in, 67 multistate Bennett Acceptance Ratio (MBAR), 68 NACs. See near-attack conformers near-attack conformers (NACs), 216 neutrophil elastase inhibitors, 73 nevirapin, 87 NNRTIs FEP calculations, 8 virtual screening, 3–4 NOEs. See nuclear Overhauser effects NOESY. See nuclear Overhauser effect spectroscopy Norvir. See ritonavir nuclear magnetic resonance (NMR), with FBLD, 41-50, 55 applications of, 50-55 fragment fusion in, 51 fragment linking in, 51–52 variation and elaboration in, 53-55 competitive binding methods of, 49-50 diffusion-based methods of, 48-49 for HIV-1 protease, 88-89 ligand binding in, 45-46 ligand-directed methods of, 47-50 advantages of, 47 disadvantages of, 47 quantum mechanics in, 123-125 CSP in, 123–124

MM-PBSA. See Molecular Mechanics with

Poisson Boltzmann and Surface

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

1 Index

DFT and, 124 NOE in, 123 screening methods for, 123 relaxation-based methods of, 48-49 saturation transfer difference methods of, 47 with spectroscopy, 47 surface mapping and, 27-28 target-directed methods of, 45-47 chemical shift perturbation in, 46 ligand binding in, 45–46 WaterLOGSY method in, 47-48 nuclear Overhauser effect spectroscopy (NOESY), 92 nuclear Overhauser effects (NOEs), 48-49, 123 OPLS. See Optimized Potential for Liquid Simulation Optimized Potential for Liquid Simulation (OPLS), 140 PAHs. See polycyclic aromatic hydrocarbons PAMPA. See parallel artificial membrane permeability assay parallel artificial membrane permeability assay (PAMPA), 169 partition function computation, 65-66 Mining Minima method, 66 mode integration in, 66 Patchett, Arthur, 165 Pauling, Linus, 215 PDB file. See Protein Data Bank (PDB) file Pearlman, David, 72 P-glycoprotein effluxes, in ADME models, 170-171 BBB penetration and, 170-171 pharmacores for, 170 QSAR models for, 170 3D-QSAR for, 170 GRIND descriptors in, 170 TOPS-MODE descriptors in, 170 pharmacore methods, 137-148 active analog approach in, 137 ALADDIN, 139 APEX-3D, 139 automated perception, from ligand structures, 139-140 CATALYST, 138-139 CAVEAT, 139 CHEM-X, 139 common identification for, 142 with DISCO, 142 DANTE, 139 definition of, 137 **DISCO**, 138 ensemble distance geometry, 138 evolution of, 137-139 excluded volumes in, 145 crystallographic receptor structure as, 145 inactive structures and, 145 shrink-wrap method for, 145 fingerprints, 146 with CHEM-X software, 146 creation of, 146

with 3D database screening, 146 for triplet sets, 146 GALAHAD, 139 GASP 138-139 HIPHOP, 138–139 features of, 138 history of, 137-139 ligand preparation in, 140-141 docking and, 140 ionization identification for, 140 with MCMM, 140 with MMFF, 140 model development in, 140 with OPLS, 140 sampling methods for, 140 tautomerization in, 140 manual construction for, 139 with Seeman model, 139 mapping features for, 141-142 feature dictionary for, 141 fragment dictionary for, 141-142 of interaction sites, 141 of ionic groups, 141 model development for, 139 for P-glycoprotein effluxes, 170 receptor-based, 144-145 development of, 144 docking in, 144 with LIGANDSCOUT model, 144-145 with LUDI interaction map, 144 SCAMPI, 139 scoring of, 143–144 with APEX-3D, 144 with CATALYST, 143, 144 with DANTE, 143 with HIPHOP, 143, 144 with PHASE method, 143, 144 with SCAMPI, 144 3D chemical features in, 137 3D database screening in, 146-148 automated perception in, 147 hits in, 146 information returns with, 148 partial matching in, 147 as point-based, 147 precomputed conformers in, 146 torsion angles in, 137-138 PHASE method, pharmacore scoring by, 143, 144 phasing, in x-ray crystallography, 20–21 electron density map for, 20, 21-22 molecular replacement and, 20 structure determination from, 20-21 for protein models, 21 waves and, 20 phenyl diacid compounds, 258, 262 plasma protein binding, 171–172 PNP. See purine nucleoside phosphorylase (PNP), drug design for point charge models, 127-128 polycyclic aromatic hydrocarbons (PAHs), 154 polycyclic heterocycle scans, 9 predictive tests, 76 Prezista. See darunavir protease dimer interfaces, 94 protein(s)

computer-aided drug design with, 182, 183 geometry optimization for, 183 protonation state determination with, 182-183 configuration integrals for, 99 crystallization of, 17 cloned, 17 docking and, 99 homologous, 17 mammalian, 17 refinement data for, 26 truncation for, 17 INK3, 108-113 aminopyrimidines, 109-110 compound classes in, 109 oximes, 110–111 p38 inhibitors, 110 public structures in, 108-109 pyrazole placement in, 111-113 with SAMPL challenge, 105 phasing and, 21 quantum mechanics and, structure modeling of, 125-127 AMBER force fields in, 126 geometry validation in, 125 native discrimination in, 126–127 semiempirical geometry approximations in, 125-126 protein configuration integrals, 99 Protein Data Bank (PDB) file, 3 in SGX FAST, 33 p38, SBDD for, 197-206 DFG-out binding pocket and, 201–202 access to, 201-202 five-membered heterocyclic core, 205-206 trisubstituted imidazole, 205 fused heterocyclics and, 199-201 indoles and, 204 with pyrazolopyrimidines, 202 with pyrimidines, 197–199 with thiazoles, 202-204 with triazines, 197-199 purine nucleoside phosphorylase (PNP), drug design for, 220–239. See also immucillins, transition-stage analog design for binding isotope effects and, 238-239, 240 bovine, transition-state structure of, 221-226 immucillins and, 226, 227 KIEs and, 222-223 labeled substrate synthesis in, 221-222 V/KKIEs and, 223 human, transition-state structure of, 230-234 crystal structure of, 234 features of, 230-231 immucillin inhibition of, 231 immucillins and, 226-230 achiral, 242 acyclic, 241–242 BIEs and, 238-239 bovine PNP and, 226, 227 clinical trials with, 240 DADMe, 232-234

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

272 Index

purine nucleoside phosphorylase (cont.) dissociation constants in, 227, 236, 237, 239 enantiomers of, 234-237 human PNP inhibition by, 231 pharmacological applications of, 239-241 protein dynamics with, 229-230 stoichiometry of, 227 synthesis of, 226-227 in vivo studies on, 239-240 kinetic mechanisms for, 220-221 mechanistic implications of, 234-239 enantiomers as, 234-237 transition-state discrimination as, 234 remote interactions for, 237-238 third-generation, 241-242 pyrazolopyrimidines, 202 pyrimidines, 197-199 pyrazolopyrimidines, 202 OIKPROP, 5-7 required input, 5 submission to, 5-6 QSAR. See quantitative structure/activity relationship QSM. See quantum similarity measure QTMS. See quantum topological molecular similarity quantitative structure/activity relationship (QSAR). See also quantitative structure/activity relationship (QSAR) models in drug discovery, 151-162 applicability domains in, 154-155 combinatorial criteria for, 155–156 criticism of, 151-152 development of, 151 Hansch approach to, 152 mechanistic models for, 154 methodologies for, 152-153 model validation in, 153-154 modern data sets in, 152 multiple descriptors in, 152-153 PAHs and, 154 target properties for, 153 LBDD and, 120, 131-132 models for, 157 acceptability criteria for, 155-156 for AmpC β-lactamase inhibitors, 161 for anticancer agents, 161 for anticonvulsive compounds, 159-161 applicability domains in, 154-155 consensus prediction in, 156-159 future research for, 161–162 good practices in, 156-159 mechanistic, 154 predictive workflow, 159 statistical figures of merit for, 156–157 toxicity results for, 158 validation of, 153-154 virtual screening for, 159 quantum mechanics and, 131-132 3D model, 131–132 spectroscopic, 132

quantitative structure/activity relationship (QSAR) models, 157 acceptability criteria for, 155-156 for AmpC β-lactamase inhibitors, 161 classification of, 161 for anticancer agents, 161 for anticonvulsive compounds, 159–161 Maybridge HitFinder library and, 161 applicability domains in, 154-155 confidence index for, 155 definition of, 155 consensus prediction in, 156-159 future research for, 161–162 good practices in, 156–159 mechanistic, 154 for metabolism, in ADME models, 173 for P-glycoprotein effluxes, 170 predictive workflow, 159 for lead optimization, 159–161 statistical figures of merit for, 156-157 toxicity results for, 158 validation of, 153-154 virtual screening for, 159 quantum mechanics, in SBDD, 120-131, 133. See also electrostatic potential (ESP) maps catalysis and, 128 CoMFA method in, 132 disadvantages in, 133 CoMSIA method in, 132 ESP maps and, 127-131 relative proton potential and, 127-131 interaction energy decomposition in, 131 LBDD and, 131 with QSAR, 131-132 linear scaling in, 130-131 MOZYME program for, 130 technology development for, 130-131 with water molecules, 130 metabolism and, 172 molecular quantum similarity and, 133 AIM theory and, 133 in NMR refinement, 123–125 CSP in, 123-124 DFT and, 124 NOE in, 123 screening methods for, 123 protein structure modeling with, 125-127 AMBER force fields in, 126 geometry validation in, 125 native discrimination in, 126-127 semiempirical geometry approximations in, 125-126 QSAR and, 131-132 QSM for, 133 spectroscopic, 132 3D model, 131–132 QTMS and, 133 in RBDD qualitative uses of, 127 quantitative uses of, 128-129 in x-ray refinement, 120-123 EREF formalism for, 121-122 quantum similarity measure (QSM), 133 CSI for, 133 quantum topological molecular similarity (QTMS), 133

R factor, 23 RBDD linear scaling in, 130-131 quantum mechanics in qualitative uses of, 127 ESP maps and, 127–131 quantitative uses of, 128-129 relative proton potential and, 127-131 receptor-based pharmacore methods, 144 - 145development of, 144 docking in, 144 with LIGANDSCOUT model, 144-145 with LUDI interaction map, 144 recursive partitioning, in ADME models, 167 relative binding free energies, 72-73 estrogen receptors and, 73 for fructose 1, 6 bisphosphatase, 73 HIV-1 and, 72, 73 for neutrophil elastase inhibitors, 73 relative proton potential, 127-131 catalysis and, 128 charge transfers in, 128 docking programs in, 128-129 interaction energy decomposition in, 131 linear scaling in, 130-131 MOZYME program for, 130 technology development for, 130-131 with water molecules, 130 point charge models in, 127-128 polarization in, 128 proton affinity in, 128 ZINC database and, 129 relaxation-based methods, of NMR, 48-49 Reviews in Computational Chemistry, 151 Revataz. See atazanavir rhodopsin, 248-249 ligand-binding sites in, 249-250 ritonavir, 87 rofecoxib, 6 SAMPL. See Statistical Assessment of the Modeling of Proteins and Ligands saquinavir hard gel, 87 saquinavir soft gel, 87 SAR. See structure/activity relationships saturation transfer difference methods, of NMR, 47 with spectroscopy, 47 SBDD. See structure-based drug design Scaffold MErging via Recursive Graph Exploration (SMERGE) program, 37 SCAMPI. See Statistical Classification of Activities of Molecules for Pharmacore Identification scans heterocycle, 8-10 small group, 10-11 BOMB, 10 scattered beams, crystal structures and, 18 Science, 7 scoring, with computer-aided drug design, 183-184 screening for docking, censuses for, 99-100

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

Index

for drug discovery and optimization in FBLD, 41-42 for lead generation, 3-4 with fragment X-rays, 32, 34-35 LIMS and, 34-35 sensitivity of, 35 for GLIDE program, for lead generation, 3, 4–5 HTS 1 42 in FBLD, 42 for fragment-based structure-guided drug discovery, 30-31 for SBDD, 61 for NNRTIs, 3–4 for SGX FAST complementary biophysical screening, 35 fragment x-ray screening in, 32, 34-35 with fragment x-rays, 32, 34-35 with SPR, 35 with x-rays, 35 with SPR, 35 virtual for docking, 3-4, 99-100, 104-105 GLIDE program and, 3, 4–5 ZINC database in, 4 Seeman model, 139 SGX FAST fragment-based structure-guided drug discovery aromatic bromine and, 32 biochemical assays for, 35 complementary biophysical screening, 35 with SPR, 35 deliverable properties for, 32 end game for, 32, 37 fragment library design in, 31–32, 37 chemical diversity of, 33 Lipinski's rules and, 31 properties of, 32-33 size of, 32–33 fragment x-ray screening in, 32, 34–35 LIMS and, 34-35 sensitivity of, 35 visualization clarity of, 35 future prospects for, 38-39 leadlike properties in, 31-32 protein kinases in, 37 SAR optimization in, 35–37 binding sites in, 36, 38 fragment choice in, 36 fragment engineering in, 36 goals for, 36 ligand efficiency in, 36 in target enabling, 32 selectivity in, 37 SMERGE program for, 37 SPR screening for, 35 with complementary biophysical screening, 35 target enabling in, 32, 33-34 LIMS in, 33 modular robotics in, 33-34 PDB domains in, 33 SAR optimization in, 32 x-ray screening in, 35

siRNA. See small interfering RNA small group scans, 10-11 BOMB, 10 small interfering RNA (siRNA), 1 SMERGE program. See Scaffold MErging via **Recursive Graph Exploration** (SMERGE) program solubility, in ADME models, 166-168 in BACE ligands, 191 crystal packing and, 168 in DMSO stock, 166, 167-168 Gaussian process for, 167 matched molecular pairs analysis and, 167 minimum accepted level for, 167 prediction of, 167 recursive partitioning in, 167 solute entropy change, 64 solvation energy terms, 64-65 free, 76 solvent flattening, 21 spectroscopic 3D-QSAR, 132 SPR. See surface plasmon resonance Statistical Assessment of the Modeling of Proteins and Ligands (SAMPL), 79 docking and, 105-107 JNK3 structures and, 105 manual process for, 106 semi-automated process for, 106 small-molecule conformations in, 106-107 Statistical Classification of Activities of Molecules for Pharmacore Identification (SCAMPI), 139 pharmacore scoring by, 144 structure/activity relationships (SAR), 1 ligand efficiency and, 36 QSAR, LBDD and, 120 in SGX FAST fragment-based structure-guided drug discovery, 35-37 binding sites in, 36, 38 fragment choice in, 36 fragment engineering in, 36 goals for, 36 ligand efficiency in, 36 in target enabling, 32 structure-based drug design (SBDD), 17. See also free energy calculations, in SBDD; quantum mechanics, in SBDD catalysis and, 128 combinatorial libraries for, 61 free-energy calculations in, 61-79 accuracy of, 62-63 alchemical, 66, 72-76 future applications for, 77-79 ligand binding calculations, 70-77 methodologies for, 63-70 simulation codes for, 78 GPCRs and, 248 for HGLP, 257-262 AMP sites and, 259–261 design of, 261-262 for diabetes, 257 docking of, 257-258, 259-261

energy calculations for, 262 features of, 257 phenyl diacid compounds and, 258, 262 putative binding pocket prediction for, 258-259 synthesis of, 261-262 for HMGP, 257 ITC for, 61 linear scaling in, 130-131 molecular profiles for, 61 HST screening for, 61 for p38, 197–206 DFG-out binding pocket and, 201–202 five-membered heterocyclic core, 205-206 fused heterocyclics and, 199-201 indoles and, 204 pyrazolopyrimidines and, 202 with pyrimidines, 197-199 with thiazoles, 202-204 with triazines, 197–199 parameters of, 120 physics-based models for, 61 quantum mechanics in, 120-127, 128–129, 131, 133 catalysis and, 128 CoMFA method in, 132 CoMSIA method in, 132 ESP maps and, 127-131 interaction energy decomposition in, 131 LBDD and, 131 linear scaling in, 130-131 molecular quantum similarity and, 133 in NMR refinement, 123-125 protein structure modeling with, 125-127 QSAR and, 131-132 QTMS and, 133 in x-ray refinement, 120-123 screening methods for docking, 61 with HST, 61 SPR for, 61 surface mapping, 25–28 electron density in. 25-26 molecular binding in, 27 NMR and, 27–28 regional association in, 27-28 substructure decomposition and, 27 for water molecules, 26-27 surface plasmon resonance (SPR), 35 with complementary biophysical screening, 35 for SBDD, 61 sustained virologic response (SVR), for HCV, 209 SVR. See sustained virologic response (SVR), for HCV T4 lysozyme ligand binding, 74-75 negative results for, 77 target-directed methods, of NMR, 45-47 chemical shift perturbation in, 46

ligand binding in, 45–46

Cambridge University Press & Assessment 978-0-521-88723-6 — Drug Design Edited by Kenneth M. Merz, Jr, Dagmar Ringe, Charles H. Reynolds Index <u>More Information</u>

274 Index

tautomerization, in pharmacore methods, 140 thermodynamic integration, in SBDD, 67 curvature from, 67 slow growth simulation in, 67 Zwanzig relationship expansion in, 67 thiazoles, 202-204 3D database screening, in pharmacore method, 146-148 automated perception in, 147 hits in, 146 information returns with, 148 partial matching in, 147 for pharmacore fingerprinting, 146 as point-based, 147 precomputed conformers in, 146 3D quantitative structure/activity relationship (3D-QSAR), 131-132 descriptor categories of, 131-132 for P-glycoprotein effluxes, 170 spectroscopic, 132 3D-QSAR. See 3D quantitative structure/activity relationship tipranavir, 87 topological substructural molecular design (TOPS-MODE) descriptors, 170 TOPS-MODE descriptors. See topological substructural molecular design (TOPS-MODE) descriptors transition-state analog drug design, 215-243 enzymatic formation in, 215-216 dynamic coupling in, 216 ground-state destabilization in, 215 NACs and, 216 substrate conformation and, 215-216 KIEs and, 217-220 computational modeling for, 219-220 features of, 218 inhibitor design approach to, 220 as intrinsic, 219

mimicry in, 217 for PNP, 220–239 triazines, 197–199 trisubstituted imidazole, 205

umbrella sampling, for SBDD, 69–70 urokinase plasminogen activators, 107–108 ligand docking and, 107 public structures in, 107 RMSD-DPI and, 107

Vioxx. *See* rofecoxib Viracept, 87 virtual screening for docking, 3–4, 99–100, 104–105 GLIDE program, 3, 4–5 for GPCRs, 251–252 NNRTIs, 3–4 for QSAR models, 159 ZINC database, 4

water binding free energy, 74 water molecules, in x-ray crystallography, 23–24 surface mapping for, 26–27 Water/Ligand Observed via Gradient SpectroscopY (WaterLOGSY) method, in NMR, 47–48 WaterLOGSY method. *See* Water/Ligand Observed via Gradient SpectroscopY (WaterLOGSY) method, in NMR weighted histogram analysis method (WHAM), 68 WHAM. *See* weighted histogram analysis method

Wilcoxon-Mann-Whitney nonparametric rank-order tests, 101–102 William the Conqueror, 98

x-ray crystallography, drug discovery and, 17–28

advantages of, 24-25 basic requirements for, 17 for proteins, 17 data collection for, 18–20 diffraction and, 18 resolution of, 20 with scattered beams, 18 disadvantages of, 25 strategies against, 25 electron density map for, 20, 21-22 diffraction studies and, 21 display for, 22 interpretation of, 21-22 occupancies in, 22 solvent flattening and, 21 with HGLP, 262 phasing in, 20-21 electron density map for, 20 molecular replacement and, 20 structure determination from, 20-21 waves and, 20 quantum mechanics in, 120-123 EREF formalism for, 121–122 refinement of, in SBDD, 22-24, 123 misinterpretation measures and, 24 protein data and, 24-26 quantum mechanics and, 120–123 R factor in. 23 surface mapping in, 25-28 electron density in, 25-26 molecular binding in, 27 NMR and, 27-28 regional association in, 27-28 substructure decomposition and, 27 for water molecules, 26-27 water molecules and, 23-24 surface mapping for, 26-27

ZINC database, 129 Zwanzig relationship, 66 docking and, 98–99 in thermodynamic integration, 67