Index

a

ABT-719 186
acidic isostere 39
acidity 222
active pharmaceutical ingredient (API) 75
activity 63
– BIOSTER 62
ADMET (absorption, distribution, metabolism, excretion, and toxicity) property 93
α-adrenergic receptor agonist 23
β-adrenergic agonist 23
β-adrenoceptor antagonist
– cardioselective 31
– nonselective 31
alignment 206
aminoheterocycle 32f.
amide/anilide bioisostere 32
analgesics 26
analogue database 58
(+)-anatoxin-a 26
angiotensin antagonist 146
angiotensin II inhibitor
– selective 37
antihistamine H_1 146
antihypertensive drug 17, 70
antineoplastic drug 17
antiseptics 146
antiulcer drug 25
API, *see* active pharmaceutical ingredient
area under the receiver operating characteristic curve (AUC) 161
aromatase (CYP19) inhibitor 23f.
aromatic atom 148
aromaticity 222
arylamine *N*-acetyltransferase family (hNAT1) 163
arylideno-imidazolinonoyl-glycine 74
AT1 receptor 39
atenolol 31ff.
atom
– aromatic 148
– bivalent 17
– conjugated 148
– monovalent 17
– positively charged 148
– tetravalent 19
– trivalent 18
atom description 148
atom environment (AE) 98
atom environment descriptor 98, 124
atom pair descriptor 148
atom type 222
atomic property information 226
atorastatin 143
attachment point 90, 148
AUC, *see* area under the receiver operating characteristic curve

b

BB3 (G-protein-coupled receptor bombesin receptor subtype-3) inhibitor 21
benzazepine D_1/D_5 antagonist 22
benzodioxole 65
1,2,3-benzothiadiazole 65
binding pocket superposition 175
bioanalogue 55
– database 55
bioavailability 33
bioisostere 188, 221
– Cambridge Structural Database (CSD) 61
– classical 15ff.
– conformational aspect 70
– context-specific 177
– drug discovery 219
– finding in the CSD 77
– generation of ideas 173
– historical background 15
– identification 176

Bioisosteres in Medicinal Chemistry, First Edition. Edited by Nathan Brown
© 2012 Wiley-VCH Verlag GmbH & Co. KGaA. Published 2012 by Wiley-VCH Verlag GmbH & Co. KGaA.

– nonbonded interaction 72
– nonclassical 20
– structure-based 174
bioisostere approach 201
bioisostere prediction 221
– quantum chemistry 221
bioisostere replacement 220
– medicinal chemistry 219
bioisosteric analogue
– method for identification 132
bioisosteric fragment 64
bioisosteric fragment replacement 137
bioisosteric group
– identification 136f.
bioisosteric groupings
– lower intrinsic clearance 40
bioisosteric replacement 79, 131, 178, 223
– consequences 31ff.
– context-sensitive 89
bioisosteric substituent 136
bioisosterism 6ff., 16, 55
– classical 16
– Drug Guru project 188
– Friedman's definition 7
– lead optimization 9
– medicinal chemistry 3ff.
– nonclassical 16
– Thornber's parameter 8
– University of Sheffield 224
Bioster 33ff.
– activity 63
– application 69
– citation 62
– component molecule 64
– coverage 59
– database record 60
– description 59
– development 56
– fragment 63
– historical overview 56
– ID code 61
– selection criteria 59
Bioster database 225
BIRB-796 19
bivalent atom 17
bivalent group 17
BLAST 171
blood platelet aggregation inhibitor 218
BMS-488043 19f.
bond cleavage rule 145
bond distance 148
bradykinin B receptor antagonist 42
bradykinin B1 receptor antagonist 219
BROOD program 79, 223

c

Cambridge Crystallographic Data Centre (CCDC) 62
Cambridge Structural Database (CSD) 61ff.
– drug discovery 69
– knowledge-based library 66
cAMP phosphodiesterase III isozyme 217
captopril 70f.
Carbó index 156f.
carbonyl group 20
carboxylate 185
carboxylic acid 21, 36ff., 80
– replacement strategies to aid permeability 35
catechol 22
catechol transformation 189ff.
catecholamine 22f.
cathepsin K inhibitor 25
CATS (chemically advanced template search) 146
CATS descriptor 146f.
CAVEAT program 58, 77, 220
cavity generation 170
CCR5 antagonist 33f.
CDK2 174ff.
centroid connecting path (CCP) 225
chart 98
ChEMBL database 145
chemical database
– mining for context-sensitive bioisosteric replacement 89
chemical transformation
– reaction database 56
cholesterol 18
cholesterol biosynthesis inhibitor 18
CIF, *see* crystallographic information file
cimetidine 25
ciprofloxacin 186
citation
– Bioster 62
clearance
– intrinsic 40
CNS disorder 26
color force field 202
component molecule
– Bioster 64
computational approach
– rational 221
– statistical method 221
conductor-like screening model (*COSMO*) 69
conformational aspect 70
– bioisostere 70
conformational mimicry 80

conjugated atom 148
ConQuest 64ff.
context descriptor 94ff.
corticotropin-releasing factor-1 (CRF1) receptor antagonist 42
Craig plot 135
CREDO 161
Cresset FieldPoint description 210
Cresset FieldPoint representation 205
Cresset FieldScreen technology 203
Cresset representation 204
crystallographic information file (CIF) 62
CRYSTALS package 67
CSD 168
cyclic system 27
cyclopentane 143
CYP19 inhibitor 23
cytochrome P450 inhibitor 63, 195

d
DABE scheme 147
darunavir 168
data analysis module 65
data mining 144
data preprocessing 95
database
– BIOSTER 45ff.
– ligand–protein complex 168
– mining for context-sensitive bioisosteric replacement 89ff.
database molecule preparation 206
database record 60
– BIOSTER 60
Daylight Chemical Information System 187
Daylight fingerprints 149, 171
Daylight Toolkit 92
descriptor 133f., 146ff., 223
– atom pair 148
– CATS 146f.
– context 94ff.
– molecule 97
– properties of substituents and spacers 132
– shape 143
– Similog 147
– whole molecule 97
developability optimization 211
20,25-diazacholesterol 18
trans-diethylstilbestrol 27
3,5-dihydroimidazo[2,1-*b*]quinazolin-2(1*H*)-one 217f.
distributed multipole analysis (DMA) 222
dopamine 178, 183
drug design 137
– random strategy 185
– rational strategy 185
– structure-based 9
drug discovery
– bioisostere 219
– CSD 69
Drug Guru (drug generation using rules) computer programm 186ff.
– Abbott experience 197
– application 194
– bioisosterism 188
– implementation 187
– quantitative assessment of transformation 195
Drug Guru input 193
Drug Guru output 193

e
eccentricity 143
edge 142
– incident 142
– weighted 142
edge density 142
EDULISS (Edinburgh University Ligand Selection System) 161
electrostatic interaction 222
EMIL (example-mediated innovation for lead evolution) 57
end point 94
Endcap group 149
EON 202
epoxide hydrolase inhibitor 33
ErG (extended reduced graph) representation 149f.
estradiol 27
EXP7711 38
extraction of ligand 168

f
FASTA sequence file 171
FBSS (field-based similarity search) 146, 225
FieldPoint 203ff.
FieldPoint pattern 204f.
FieldScreen 207
2D fingerprints 226
flip-flop flag 149
5-fluoro-2′-deoxyuridylic acid (5-fluoro-dUMP) 17
5-fluorouracil 17
FPL 55712 39
fragment
– BIOSTER 62
fragment linking 78
fragmentation method 145

fungicide 146
fuzziness 141

g
G-protein-coupled receptor (GPCR) 162
G-protein-coupled receptor bombesin receptor subtype-3 (BB3) inhibitor 21
Gaussian density 157
Gaussian description 157
Gaussian method 157
graph
– reduced 149
graph matching 144
graph theory 142
Grimm's hydride displacement law 5, 15
group
– bivalent 17
– monovalent 17
– trivalent 18

h
halogen 23
HCV NS3 protease inhibitor 218
hERG 212
hERG binding 195f.
Hert–Willett data set 149
high-throughput screening (HTS) 155
HIV protease 177f.
HIVprotease inhibitor 178
HIV-1 inhibitor 19
human microsomal metabolic stability 95
hydride displacement law 5, 15
hydrogen bond (HB) 133f.
hydrogen bond acceptor 148
hydrogen bond donor 148
hydrogen bonding 222
hydrophobicity 180
hydroxy-to-methoxy transformation 188
hydroxyl group 22
11β-hydroxysteroid dehydrogenase 1 (h11β-HSD1) 163

i
IBIS drug discovery software 69
ICI 204219 40
ID code 60
– BIOSTER 60
IDODEL 78
imatinib 143
indole 74
interaction hot spot 69
intermolecular interaction 80, 172
– identification 172
isopentane 143
isoproterenol 22
IsoStar 67ff.
IsoStar library 69
ISOSTAR knowledge base 225
isostere 16
– based on Grimm's hydride displacement law 16
– defined by Erlenmeyer 16
– defined by Langmuir 5, 16
isosteric quality 193
isosterism 3ff., 55
– Erlenmeyer's addition 6
– Grimm's hydride displacement law 5
– Langmuir definition 4f.

j
Jmol viewer 65

k
ketoamide 66
KNIME workflow environment 95
knowledge-based library
– CSD 66
kynurenic acid 74

l
L-006235 25
L-873724 25
lead optimization
– bioisosterism 9
LeadIT 220
LeadIT platform 79
leukotriene antagonist 146
liarozole 24
ligand
– assessment 169
– extraction 168
ligand-based topological pharmacophore 146
ligand–protein complex 172
– database 168
LINGO 69
lipophilicity
– effective 37
– intrinsic 37
local environment descriptor 98
losartan 37, 80f.

m
MACCS 160
Maestro 205
Maestro conformation-derived library 207
matched molecular pair (MMP) 59, 90
– context-sensitive analysis 95
– generation 96

– method 89
matched molecular pair analysis (MMPA) 91ff., 226
materials module 65
maximum common subgraph (MCS) isomorphism algorithm 226
maximum common substructure (MCS) 144
maximum common substructure (MCS) extraction 91
MDL Drug Data Report (MDDR) database 91, 144, 226
medicinal chemistry
– bioisostere replacement 219
– bioisosterism 3ff.
– perspectives 217ff.
melanin concentrating hormone receptor 1 (MCHr1) antagonist 162
Mercury program 64
metabolic stability 118ff.
– beneficial transformation 119ff.
– detrimental transformation 119ff.
– neutral transformation 116f.
metabolic stability data set 114
metabolism 8
N-methyl D-aspartate (NMDA) receptor inhibitor 74
metiamide 25
MK-05577 199
MMP, *see* matched molecular pair
MMPA, *see* matched molecular pair analysis
modafinil 20
MOE (molecular operating environment) 201, 220
MOE-derived library 207
Mogul 66ff.
molecular graph 142f.
– example 143
– undirected 142
molecular shape 155ff.
molecular shape complementarity 155
molecular shape similarity 156
– method 156
molecular similarity 222
molecular topology 141ff.
molecular transformation 90
molecule descriptor 97
monomer selection 207
monovalent atom 17
monovalent group 17
MSI 168
multiobjective optimization (MOOP) 12
multiparameter optimization (MPO) 12
Murcko framework 97, 124

n

NAADP EON discovered (Ned) hit 163
NAADP ROCS discovered (Nrd) hit 163
naturally drug-like compound 223
neopentane 143
neuropeptide Y (NPY) 199f.
– bioisosteres of an NPY-Y5 antagonist 199ff.
nicotinic acetylcholine receptor (nAChR) 26
$(\alpha 4)_2(\beta 2)_3$ nicotinic acetylcholine receptor inhibitor 26
nicotinic acid adenine dinucleotide phosphate (NAADP) 163
node 142
– adjacent 142
– colored 142
nonbonded interaction 72
– bioisostere 72
– intermolecular 75
– intramolecular 75
noncyclic system 27
nonhydrogen atom 148
nonsteroidal aromatase inhibitor (NSAI) drug 23f.
norepinephrine 22
NPY-Y5 receptor 199ff.
NPY-Y5 receptor antagonist 200
Nrd hit, *see* NAADP ROCS discovered hit
nuclear receptor (NR) family 162

o

odanacatib 25
olefin-to-amide transformation 195
olefin-to-*o*-phenyl transformation 195
Open Babel molecular toolkit module 98
OpenAstexViewer 65
optimization
– multiobjective 12
oral absorption 38
oxazole 74

p

ΔP distribution
– global 99ff.
ΔP value 98ff.
p38 MAP kinase inhibitor 19
P450 inhibition 63, 195
PDB, *see* Protein Data Bank
PDB ligand database 169
pentane 143
permeability 32ff.
– replacement strategies for carboxylic acids 36

peroxisome proliferator-activated receptor (PPAR) 162
– PPAR-γ 79
Pfizer metabolism index parameter, *see* PMI parameter
pharmacokinetics 8, 34
pharmacophore 158
– ligand-based topological 146
3D pharmacophore searching 201
phenol bioisosteres 64
phenyl/pyridine bioisosteric replacement 20
PHT ((±)-pyrido[3,4-*b*]homotropane) 26
piperonyl butoxide 65
PMI (Pfizer metabolism index) parameter 94
polar surface area (PSA) 200f.
positively charged atom 148
PPAR (peroxisome proliferator-activated receptor) 162
PPAR-γ (peroxisome proliferator-activated receptor gamma) 79
practolol 31f.
precedence rules 151
propranolol 31
protein criteria 169
Protein Data Bank (PDB) 71ff., 167ff.
– pocket 179
protein structure 167ff.
PSA, *see* polar surface area
pseudoatom 5
Pub3D 161
pyridine 26
(±)-pyrido[3,4-*b*]homotropane, *see* PHT

q

QSAR (quantitative structure–activity relationship) 91
quantum chemical topology (QCT) 222
quantum chemistry
– bioisostere prediction 221
Quantum Isostere Database (QID) 137, 222

r

R-group descriptor 69
rapid overlay of chemical structures, *see* ROCS
RCSB web site 168
RDKit molecular toolkit 96
reaction database 56
– chemical transformation 56
RECAP, *see* retrosynthetic combinatorial analysis procedure
receptor interaction 8
ReCore 77, 220f.
reduced graph 149
reduced graph node 151
ReLiBase 168
remove–Cl transformation 195f.
replacement 10
– bioisosteric, *see* bioisosteric replacement
– consequences of bioisosteric replacement 31ff.
retrosynthetic combinatorial analysis procedure (RECAP) 93, 145
RG generation algorithm 150
rilmenidine 17f.
ring equivalent 19
ring system 149
ROCS (rapid overlay of chemical structures) 148ff., 192, 200f.
ROCS shape searching 202

s

SAR, *see* structure–activity relationship
scaffold hopping 77, 224f.
SCH 23390 22
SCH 39166 22
SciFinder database 162
scoring 206
screening 208
3D SD format 168
γ-secretase inhibitor 42
sequence search 175
SFK 38393 22
shape descriptor 143
shape similarity method
– choosing 160
– superposition-based 156
– superposition-free 158
shape similarity tool 158
sigma profile 137
sildenafil 143, 186
silicon bioisosteric replacement 19
similarity
– tools to identify bioisosteric group 136
Similog descriptor 147
simplified molecular input line entry system (SMILES) 95f., 168, 187, 206
SMARTS pattern 187
SMILES string
– generation and validation 170
SMIRKS system 187ff.
spacer 132
spirocarbamate 209
SPLICE 77
structural moiety 8
structure–activity relationship (SAR) 124, 158, 211
structure-based drug design 9

subpocket hydrophobicity 180
substituent space
– classical method for navigation 135
substructure search 173
sulfonamide groupings 40
SuMo 168
SuperStar 67ff.
surface property 137
SURFNET algorithm 170

t
T-ANALYZE 91
T-MORPH 91
Tanimoto similarity coefficient 171
template molecule preparation 204
tetravalent atom 19
tetrazolate 82f.
tetrazole 36, 158, 169f., 175
1*H*-tetrazole 80ff.
thiourea 25
thrombin inhibitor 41
topological descriptor 142
topological pharmacophore 146
– ligand-based 146
topological representation 141
torsional barrier 222
transformation 90ff., 193
– beneficial 119ff.
– context-sensitive 122
– detrimental 119ff.
– metabolic stability 116ff.
– neutral 116
– quantitative assessment of Drug Guru transformation 195
Tripos SYBYL atom type 98
trivalent atom 18
trivalent group 18

u
UFSRAT (ultrafast shape recognition with atom types) 160ff.
ultrafast shape recognition (USR) 159ff.
UNITY 2D fingerprints 146
USR::OptIso 160

v
vardenafil 186
velneperit 199
vertices 142
VLA-4 antagonist 33
vorozole 24

w
WebCSD 65
WENDI (web engine for non-obvious drug information) 161
WOMBAT database 69, 226

x
XED 203
XED force field 206
XedView software 207

z
zafirlukast 40
Zagreb index 144
– first 144
– second 144
zero-order Gaussians 158
ZINC 163