

Index

a

- abaloparatid 16–18
- Abilify[®] 89, 103–108
- ABT-737 226–228
- Ac-D-Cys-(D-Arg)_x-NH₂ peptides 135
- acute lymphoblastic leukemia
 - (ALL) 60
- acute myelogenous leukemia/acute myeloid leukemia (AML) 23, 58, 60, 233–235, 238
- acylsulfonamides 229
- Adcetris[®] 57, 62–63, 67–69
- Adlyxin[®] 7
- Adocia 6, 8
- ado-trastuzumab emtansine 57, 62, 67
- Afrezza[®] 5
- Agouron Pharmaceuticals 204, 210, 212
- Aileron Therapeutics 23
- Akt/glycogen synthase kinase 3 (GSK-3) pathway 86
- albiglutide 7
- all-D peptides 135
- all-L enantiomer 135
- amine precursor reuptake and decarboxylation (APRD) cells 85
- 3-aminobenzamide (3-AB) 201, 205, 206
- aminobenzthiazole-based D₂ partial agonists 97
- 2-aminoisobutyric acid (Aib) 7
- 4-amino-1,8-naphthalimide 206
- anaplastic large cell lymphoma (ALCL) tumor cells 62
- anaplastic (ATC) thyroid cancer 162
- ANG 1005 15
- angiogenesis inhibitors 155–163
- anthracycline-based anti-CD22 ADC 75–76
- anti-angiogenic activity 162
- anti-apoptotic proteins 226, 233–235, 238
- antibody-dependent cell mediated cytotoxicity (ADCC) 58, 173
- antibody-dependent cell-mediated phagocytosis (ADCP) 173
- antibody-drug conjugates (ADCs) 14
 - first generation
 - adverse effects 60–62
 - mechanism of action 60
 - molecular design 58–59
 - therapeutic applications 60
 - immunoconjugates 70–74
 - payloads 74–76
 - second generation
 - adverse effects 67–68
 - mechanism of action 63–67
 - molecular design 62–63
 - therapeutic applications 67
 - site specific 69–70
- anticancer drugs 57, 81, 155, 156, 202, 204
- anti-CD22-VC-MMAE 76
- anti conformers*
 - 3-aminobenzamide 205
 - benzoxazole-and benzimidazole-4-carboxamides 206
 - protonated nicotinamide 205

- antigen presenting cells (APCs) 172, 182
- anti-myeloperoxidase 172
- anti-myeloperoxidase autoantibodies (P-ANCA) 178
- anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) 172, 178
- anti-programmed cell death protein-1 (anti-PD-1) therapy 16
- anti-proteinase 3, 172
- antipsychotic drugs 84, 87, 88, 92, 95, 96, 98, 103
- discovery
- β -arrestin-biased D₂ partial agonists 98–99
 - bivalent ligand 98
 - G-protein 99–101
 - traditional D₂ functional screening 96
- antipsychotic mechanisms
- aripiprazole 103–108
 - brexpiprazole 103, 108–111
 - cariprazine 103, 111–115
- antitumor effects of lenvatinib
- RCC 162
 - thyroid cancer 161–162
- AntriaBio 6
- apomorphine 98, 109
- (6*aR*)-apomorphine 90
- apoptosis 57, 225, 226, 233–235
- ArgGlyAsp (RGD) 15
- aripiprazole 101
- affinity and *in vitro* functional activity 104
 - clinical data 107–108
 - drug substance 105
 - functional selectivity and biased ligand signaling 107
 - history 105
 - pharmacokinetics and metabolism 107
 - pharmacology 105–107
 - synthesis of 105
- aripiprazole lauroxil 105, 106
- 2-arylbenzimidazole-4-carboxamides 209, 213
- arylcylohexyl scaffold 92
- arylpiperazines 92, 98–102
- arylsulfonamide 227, 228, 230
- AsnGlyArg (NGR) 15
- atypical antipsychotics 87, 88, 97, 98, 102, 115
- autologous stem cell transplant (ASCT) 67
- aziridinium ions 203
- b**
- Bacillus brevis 9
- base excision repair (BER) pathway 202
- BAX–BAK-dependent apoptosis 232
- B cell lymphoma 2 (BCL-2) protein family 225
- B-cells
- in autoimmunity
 - antigen presentation 172
 - autoantibodies 172
 - cytokines 172
 - neolymphogenesis 172
 - D20-targeting therapeutic antibodies 173
 - in MS 181, 187
 - protective immunity 169
 - rituximab 176
- BCL-2-selective (BCL-X_L-sparing) 227
- BCL-2-selective BH3-only proteins 227
- benzimidazole-4-carboxamides 206–208, 211–213, 218
- benzoxazole-4-carboxamide 207
- Besponsa[®] 58–60
- β -arrestin 86
- “beyond Rule of five” (bRo5) compounds
- chameleonic behaviour 44, 46
 - polar surface area 42–50
- big pharma 204, 209
- Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/WG) 178
- bivalent 5-OH-DPAT ligands 98
- B lymphocyte stimulator (BAFF/BLys) 174, 177, 187

- bone mineral density (BMD) 17
 bone morphogenic proteins (BMPs) 19
 BRCA-mutant ovarian cancer 204
 brentuximab 57, 62
 brentuximab vedotin 57, 62, 64, 67
 brexpiprazole 101
 clinical data 110–111
 drug substance 109
 functional selectivity and biased ligand signaling 110
 history 108
 pharmacokinetics and metabolism 110
 pharmacology 109–110
 synthesis of 108–109
 brimapitide 23
 Bristol-Myers Squibb 102
 Bruton's tyrosine kinase (BTK) 169, 237
 Byetta[®] 6, 7
- C**
- calcimimetics 133, 136, 144, 148
 calcitonin 16–17
 calcium-sensing receptor (CaSR)
 allosteric modulation of 134
 Cys482 lead 144
 extracellular domain of 134
 SAR efforts 134
 calicheamicin 58–60
 carba-NAD⁺ 203
 cariprazine 99
 clinical data 114–115
 drug substance 112
 functional selectivity and biased ligand signaling 113
 history 111–112
 pharmacokinetics 113–114
 pharmacology 112–113
 synthesis of 112
 catecholamine 83
 CD20⁺ B-cells, rituximab in multiple sclerosis patients
 HERMES 183
 HERMES Junior 183
 OLYMPUS study 184
- cell penetrating peptides (CPPs) 3, 22–24
 central nervous system (CNS) 35, 83, 180, 181
 distribution of 38
 lower MW 36
 Ro5 violations for 42
 S+logP 36
 cerebral spinal fluid (CSF) 182
¹⁴C-etelcalcetide 146
 chameleons with molecular dynamics 44–48
 chlorpromazine 83, 87–88, 106
 chronic lymphocytic leukemia (CLL) 174, 226, 236
 Churg–Strauss syndrome 178
 cinacalcet 133–134, 142, 143, 148
 circulating B cells 172, 174, 177
 CKD-mineral bone disorder (CKD-MBD) 133
 clathrin-dependent mechanism 63
 Clinical Global Impression-Severity of Disease (CGI-S)
 assessment 108
 Clinical Global Impressions-Improvement (CGL-I) 107, 108
 clozapine 87–88
 comparative molecular field analysis (COMFA) 103
 complement-dependent cytotoxicity (CDC) 58
 crizotinib 155
 cyclosporine 23
 Cys482 144
 cytokines 15, 172, 182
- d**
- D₂ antagonist chlorpromazine 88
 daptomycin 9
 D₂ autoreceptor agonist activity 92
 dCR₆
 alanine scan of 136–138
 double alanine scan of 138
 defensins 9, 11
 degludec insulin 5, 8
 dibenzylcyclooctyne (DBCO) 69
 dibromomaleimide (DBM) 69, 72

- dichlorophenylphenyl piperazine 96
 differentiated (DTC) thyroid cancer 161
 diffuse large B cell lymphoma (DLBCL) 174, 226, 234, 238
 dihydrexidine 95–96
 3,4-dihydro-5-methyl-1(2*H*)-isoquinolinone 206
 1,5-dihydroxyisoquinoline 206
 dipeptidyl peptidase-4 (DDP-IV) 6
 dithiophenylmaleimide (DSPh) 69
 dopamine
 depletion of 84
 dopamine replacement therapy 84
 D₂ partial agonists
 antipsychotic drugs 84, 87, 95
 antipsychotic mechanisms 103
 arylpiperazines 101–102
 cariprazine 103
 dopamine-like scaffolds, classical pharmacophore 89–91
 non-dopamine like scaffolds, “non-classical” pharmacophore 91–92
 risperidone and clozapine 87
 dysregulation of 85
 in motor function 84
 partial agonism 88–89
 periphery 85
 receptors 85
 replacement therapy 84
 substantia nigra 84
 VTA 84
 dopaminergic pathways 84
 dorsal air sac (DAS) 157, 159
 double-alanine dCR₆ 139
 double strand breaks (DSBs) 217
 dulaglutide 7
- e**
 echinocandins 11
 enacarbil 39
 ergoline-aminobenzthiazole-based D₂ partial agonists 97
 etelcalcetide
 clinical studies 145–149
 control/paricalcitol-treated uremic rats 143
 discovery and development of 134
 lead optimization 141
 mechanism of action of 144–145
 PTH in rat models 142
 structure of 134
 thiol conjugates 140–141
 European Medicines Agency (EMA) 103, 204, 236
 everolimus 36, 44, 46, 48, 49, 162
 exenatide 6, 7, 19
 Exondys 51TM 23
 extracellular domain (EDA) of fibronectin 71
 extrapyramidal symptoms (EPS) 83, 87, 88, 115
 extrarenal lupus (EXPLORER) 177
 Exubera[®] 5
- f**
 FAUC 552 98
 Fcγ receptor (FcγR) 58
 FDA approved drugs 2007-2017 36–42
 fibroblast growth factor receptors (FGFR) 155, 157–158, 163
 fibronectin 71
 Finkelstein conditions 108
 first generation ADCs
 adverse effects 60–62
 mechanism of action 60
 molecular design 58–59
 therapeutic applications 60
 fish sperm 4
 follicle-stimulating hormone (FSH) 12
 follicular lymphoma 176, 226, 233, 238
- g**
 gamma butyrolactone’s (GBL) 106
 gastro-enteropancreatic-neuroendocrine tumors (GEP-NETs) 14, 15
 gemtuzumab ozogamicin 57–58, 60
 germinal centers (GC) 171, 172
 glargine insulin 5, 8
 glucagon-like peptide-1 (GLP-1) 4, 6–8
 glucagon-like peptide-2 (GLP-2) 19, 20

glucagon peptide drugs 4
 glucose-dependent insulinotropic polypeptide (GIP) 8, 19
 glycopeptides 9, 11
 G-protein-biased D₂ partial agonists 99
 G protein pathways 86
 granulomatosis with polyangiitis (GPA) 175, 178
 guanylate cyclase-C agonists 20–22
 guanylin 20–21

h

haloperidol 83, 87, 101, 106
 hepatitis C virus (HCV) 36
 HERMES Junior 183
 heterodimeric peptide structure 135
 hexamer complex 5
 homing peptide and tumor-necrosis factor (hTNF) cytokine 15
 5HT_{2A} serotonin receptors 88
 human anti-chimeric antibodies (HACAs) 179
 human cancer cell lines A549 (lung carcinoma) 213
 human ovarian cancer cell line (SK-OV-3) 160
 human serum albumin (HSA) 7
 human umbilical vein endothelial cells (HUVECs) 157, 158
 hydrogen bond acceptor (HBA) 35, 39, 208, 232
 hydrogen bond donor (HBD) 35, 40, 50, 94, 95
 hydrophobic CPPs 22
 5-hydroxy- 209
 7-hydroxy-2-*N,N*-dipropylaminotetralin (7-OH-DPAT) 102
 2-(4-hydroxyphenyl)benzimidazole-4-carboxamide 211
 hypercalcemia 16, 18
 hypoxia-inducible factor (HIF) 162

i

ibritumomab 174–176
 IgG(F8)-SS-DM1 conjugate 71–72
 Ig heavy (IgH) 169

immune complexes (ICs) 172
 incretin peptides 19
 indolinobenzodiazepines (IGN) 74
 inotuzumab ozogamicin 58–60
 insulin 4–6, 8, 14, 20
 intramolecular hydrogen bonds (IMHBs) 44, 206, 209, 212
 irritable bowel syndrome (IBS-C) 21

k

Kadcyla[®] 62, 63, 66–68, 74

l

lactate dehydrogenase (LDH) 236
 lanreotide 14
 lantibiotics 11
 LASSBio-579 97
 Lente insulin 4
 lenvatinib mesylate (lenvatinib) drug targeting VEGFR 157–158
 FGFR 157–158
 molecular targeted anticancer agents 155–156
 novel type V kinase-binding mode 158–161
 renal cell cancer 162–163
 thyroid cancer 161–162
 tumor angiogenesis 156
 VEGF-targeting drugs 156–157
 linacotide 21
 Lipoprotein receptor-related protein 1 (LRP-1) 15
 liver alcohol dehydrogenase (LADH) 202
 lixisenatide 7, 8
 long-acting/basal insulins 5
 LoVo (colon cancer) 213
 lupus nephritis (LN) (LUNAR) 177
 luteinizing hormone releasing hormone (LHRH) 12–13
 (5*R*),(8*R*)-lysergic acid diethylamide (LSD) 90
 Lyxumia[®] 7

m

macimorelin 39
 macrocyclic peptides 23

- “magic bullet” cancer therapy 14
 - major histocompatibility complex (MHC) 16, 171
 - mantle cell lymphoma (MCL) 233
 - Massachusetts
 - General
 - Hospital-Cognitive 111
 - median progression-free survival (mPFS) 237
 - medullary thyroid cancer (MTC) 161
 - metabolic diseases
 - GLP-1 6–8
 - glucagon 8
 - insulin 4–6
 - degludec plus liraglutide 8
 - glargine plus lixisenatide 8
 - 5-methoxy-2-(4-methoxyphenyl)benzimidazole-4-carboxamide 209
 - 2-(3-methoxyphenyl)benzimidazole-4-carboxamide 208, 211, 213, 216
 - 2-(4-methoxyphenyl)benzimidazole-4-carboxamide 209
 - 5-(3-methyl-1-triazeno)imidazole-4-carboxamide (MTIC) 204
 - microscopic polyangiitis (MPA) 175
 - mipsagargin 15
 - model amphipathic peptide (MAP) 22
 - molecular dynamics,
 - chameleons 44–48
 - monomethyl auristatin E (MMAE) 62
 - Montgomery-Asberg Depression Rating Scale (MADRS) 108
 - multiple sclerosis (MS)
 - anti-CD20 mAb experience,
 - rituximab 183–184
 - classification of 181
 - clinical-pathological features 181
 - neurological symptoms 180
 - ocrelizumab
 - OPERA 185–186
 - ORATORIO study 186–187
 - phenotypic disease patterns 181
 - myelodysplastic syndrome 23, 238
 - Mylotarg[®] 57–60
- n**
- navitoclax 226–228, 230, 232, 233, 238
 - neuroleptic drugs 83
 - Neutral Protamine Hagedorn (NPH) 4
 - NeuvaxTM 15
 - N*-hydroxysuccinimide ester 59
 - nicotinamide adenine dinucleotide (NAD⁺) 201–203
 - nigrostriatal pathway 84
 - niraparib 218
 - 2-nitro-6(5*H*)-phenanthridone 206
 - N*-methylation 207
 - N*-methyl-D-aspartate (NMDA) 106
 - N*¹-methyl-2-(4-methoxyphenyl)benzimidazole-4-carboxamide 209
 - N,N'*-dimethylethylenediamine (DEA) 76
 - n*-octane for simeprevir 48, 50
 - non-circulating B cells 174
 - non-classical D₂ partial agonists 91
 - non-cleavable linker (NCL) 63
 - blood-brain barrier 36
 - distribution of 38
 - HBA 39
 - HBD 40
 - Ro5 violations for 42
 - non-Hodgkins lymphoma (NHL) 173
 - tumor cell lines 233
 - non-ribosomally synthesized 9–11
 - N_{pyridinium}-C_{ribose} bond 206
 - 5/6Nx rat model 142
- o**
- obinutuzumab 174–177, 234, 237
 - ocrelizumab
 - four Phase III RA trials 179–180
 - LN in the BELONG study 180
 - in multiple sclerosis 176
 - OPERA 185–186
 - ORATORIO study 186–187
 - relapsed/refractory NHL 179
 - octreotide 14, 15
 - ofatumumab 174, 175
 - olaparib 218
 - oligoclonal bands (OCBs) 181–182

- OPC-4392 105
 ortho-nitrophenol 206
 Otsuka Pharmaceuticals 102, 105
 oxazole 208
- p**
- Paget's disease 16
 para-nitrophenol 206
 parathyroid hormone (PTH) 141
 (1-34) 17–18
 parathyroid related protein
 (PTHrP) 18
 parkinsonism-like symptoms 87
 P2-binding moiety 230
 PD 128483 88, 89
 peptide-based therapy, ESRD
 patients 134
 peptide-drug conjugates
 (PDCs) 14–15
 peptides
 antibiotics
 non-ribosomally
 synthesized 9–11
 ribosomally synthesized 11–12
 in bone diseases
 BMPs 19
 calcitonin 16–17
 incretin peptides 19
 PTH (1-34) 17
 PTHrP 18
 in cancer
 luteinizing hormone releasing
 hormone (LHRH) 12–13
 PDC 15
 somatostatin 13–14
 vaccines 15–16
 CPPs 22–23
 in gastrointestinal diseases
 GC-C 20–22
 GLP-2 19–20
 macrocytic peptides 23
 in metabolic diseases
 GLP-1 6–8
 glucagon 8
 insulin 4–6
 insulin degludec plus liraglutide 8
 insulin glargine plus lixisenatide 8
 6(5*H*)-phenanthridone 206
 2-phenylbenzimidazole-4-
 carboxamide 208, 211, 212
 phenylpiperazine analog 92
 Physical Functioning
 Questionnaire 111
 plecanatide 21, 22
 PNU-159682 76
 poly (ADP-ribose) polymerase (PARP)
 benzimidazole-carboxamides 212
 benzoxazole-/
 benzimidazole-
 carboxamides 205–212
 clinical studies 217–218
 DNA-damaging drugs 203
 in DNA repair 201
 2-(3-methoxyphenyl)
 benzimidazole-4-
 carboxamide 216
 NAD⁺ 201–202
 quinazolinones 205–212
 radiopotentiators 212
 single agent therapy 216–217
 structure activity relationships 213
 tricyclic benzimidazoles 212–215
 polycationic compounds 136
 polycationic peptides 134
 polymyxins 9
 polyphor 23
 Positive and Negative Symptom Scale
 (PANSS) 107, 110, 111
 positron emission topography
 (PET) 113
 postsynaptic D₂ receptors 89, 92, 95,
 106
 (*S*)-(-)-3-PPP 89
 pre-B cell receptor (pre-BCR) 169
 presynaptic D₂ autoreceptors 95
 primed for death 226, 234, 235
 progressive relapsing MS
 (PRMS) 181
 prostate-specific membrane antigen
 (PSMA) 15
 protein kinase C (PKC) 135
 2-pyridylpiperazine derivative 92
 pyrrolobenzodiazepine (PBD)
 dimers 69, 74

q

quetiapine 87–88
 quinazolinones 205–212, 218
 quinpirole 88, 89

r

radius of gyration (R_{gy}) 48, 49
 Ra Pharma 23
 relapsed or refractory (R/R) CLL 60,
 174, 175, 227
 relapsing-remitting MS (RRMS) 181
 renal cell cancer/renal cell carcinoma
 (RCC) 155, 162
 resistance-modifier 203
 reticuloendothelial system (RES) 173
 Reviva Pharmaceuticals 96
 Rexulti[®] 89, 102, 103, 108–111
 RGH-188 103
 rheumatoid arthritis (RA)
 synovia 172
 ribonucleic acids (RNAs) 16
 ribosomally synthesized 11–12
 risperidone 87–88, 101, 114
 rituximab
 AAV and autoimmune
 disorders 178–179
 antibodies and autoantibodies 178
 chimeric anti-CD20 mAb 175
 first anti-CD20 mAb experience
 autoimmunity 176–178
 in multiple sclerosis 183–184
 HACAs 179
 roxindole 91
 RP-5063 96
 rucaparib (Rubraca) 201–218
 Rule of five (Ro5) 35, 104, 108, 111,
 232

s

sandwich tube formation (sTF)
 assay 157
 Sarepta Therapeutics 23
 schizophrenia 83, 85–89, 95–97, 103,
 105–111, 114, 116
 SDX 208-912 91
 SDZ 208-911 91
 secondary hyperparathyroidism (SHPT)

CKD/ESRD patients 134
 peptide-based therapy 134
 vascular calcification 143
 secondary progressive MS (SPMS) 181
 second generation ADCs
 adverse effects 67–68
 mechanism of action 63–67
 molecular design 62–63
 therapeutic applications 67
 Sheenan Disability Scale 111
 sialic acid binding Ig-like lectin
 (Siglec) 58
 single-strand breaks (SSBs) 202
 SIP(F8)-SS-DM1 71–72
 site specific ADCs
 bioconjugation of engineered
 amino-acids 69
 enzyme mediated bioconjugation 69
 linker-based bioconjugation 69
 Sjogren's syndrome 172
 skin infection 9, 12
 skin secretions 12
 S+logP 36
 small immunoprotein (SIP) format 71
 solvent-accessible surface area
 (SASA) 48–49
 sorafenib 158, 160
 stem cells 19, 85, 169, 173
 stochastic bioconjugation
 techniques 68
 strain-promoted alkyne-azide
 cycloaddition (SPAAC) 69
 structure-activity relationship by
 nuclear magnetic resonance
 (SAR-by-NMR) 226
 structure-activity relationships
 (SAR) 134
 alanine residues, Ac-carrar-NH₂ and
 Ac-crrrar-NH₂ 138
 CaSR 134
 cationic charge
 optimization 135–136
 dCR₆
 alanine scan of 136–138
 double alanine scan of 138
 thiol conjugates 140–141
 thiol residue 140

- sunitinib 158
 Suzuki–Miyaura reaction 212
 SW620 (colon cancer) 213
 syn conformers
 3-aminobenzamide 205
 benzoxazole-and benzimidazole-4-carboxamides 206
 protonated nicotinamide 205
 systemic lupus erythematosus (SLE) 172, 177
- t**
- talipexole 88, 89
 T-cell 171
 Technosphere® 6
 teduglutide 20
 teicoplanin 11
 telavancin 10–11
 teriparatide 16–18
 tetrahydroquinolinones 97
 three rapid-acting insulin 5
 throat infection 9
 thymidylate synthase inhibitor 212
 thyroid cancer 161–162
 topological polar surface area (TPSA) 38
 molecular dynamics (MD) analysis 45
 molecular weight 40
 vs. MW for oral drugs 41
 vs. number of rotatable bonds for oral drugs 41
 polar surface area 38, 42–50
 Veber rule 40
 tositumomab 174, 175
 trans-activating transcriptional activator (TAT) 22
 trans-dihydrochloride (TDHL) 90
 Transmembrane Activator and Calcium-modulator and cyclophilin-ligand Interactor-Ig (TACI-Ig) 187
 transportan 22
 trastuzumab 57, 58, 62–64, 67, 73
 tricyclic benzimidazoles 212–215
 tricyclic PARP-1 inhibitors 213
 tuberoinfundibular pathway 85, 87
- tumor angiogenesis 156, 157, 159, 162
 tumor lysis syndrome (TLS) 236
 tumor vasculature 15, 157
 type 1 diabetes mellitus (T1DM) 4, 179
 type 2 diabetes mellitus (T2DM) 4
 type I CaSR agonist 144
 “typical” antipsychotics 87, 88, 106, 115
 tyrothricin 9
- u**
- U-68553 89
 UNC9444 101
 UNC9994 98, 99
 uroguanylin 20–21
- v**
- vancomycin 9–11, 23
 vascular calcification 133, 143, 149
 vascular endothelial growth factor receptors (VEGFR) 155–163
 vascular permeability factor (VPF) 156
 Veber rule 40
 VEGFR2 155, 158–162
 veliparib 218
 vemurafenib 155
 venetoclax
 clinical studies 236–238
 discovery of 227–232
 mechanism of action 232–233
 predictive biomarkers 233–234
 targeted agents/
 chemotherapeutics 234–235
 ventral tegmental area (VTA) 84
 vilazodone 39
- w**
- Wegener’s granulomatosis 175, 178
- x**
- X-linked agammaglobulinemia (XLA) 169
- y**
- Young Mania Rating Scale (YMRS) 107

