

## Index

### a

absorption-disposition-metabolism-excretion (ADME) studies 137–138, 350, 396

activating mutations 131, 342–344

active pharmaceutical ingredients 42–43

adenosine triphosphate (ATP) mediated autophosphorylation 341

afatinib 9, 10, 77, 80, 345

ALK inhibitors 78, 131–146

all-trans retinoic acid (ATRA) 168, 174

$\alpha$ -glucosidase inhibitor 291, 305

$\alpha$ -hydroxyamide 98

$\alpha$ -methylmilacemide (2-(1-methylpentylamino)acetamide) 391

America Invents Act (AIA) 44

Ames mutagenicity assay 304

amino acid decarboxylase (AADC) inhibitor 320

6-aminouracil 421

analogue approach 7–9

anaplastic lymphoma kinase (ALK)
 

- ALK fusion genes 131
- anaplastic large cell lymphoma (ALCL) 131
- drug design and strategy 134
- lorlatinib 133
- TAE684 131

anilinoquinazolines 9, 341, 343, 345, 346

antibody-dependent cell-mediated cytotoxicity (ADCC) 6, 55, 114, 158, 167, 168, 246–248, 250

antibody-dependent cellular phagocytosis (ADCP) 157–159, 246, 250

antibody drug conjugates (ADC)
 

- design and synthesis 27
- immuno-conjugate development 26
- tumour-associated cleavage 28

antidiabetic agents 293, 305, 311, 312

antidrug antibody (ADA) responses 23, 124

antihistaminics 385

antihyperglycemic agents (AHAs) 291, 293

arginine (L858R) 342

atezolizumab 113, 170, 172, 175, 270

ATP  $K^M$  344

autoimmune disorders 171–173

### b

Bcl-2 inhibitor venetoclax 273

Bcr-Abl inhibitors 72, 74–77, 81

benserazide 320, 332, 333, 386

$\beta$ -amino butanoic acid derivatives 293

$\beta$ -cell apoptosis 291

BIA 9-693 322

bicalutamide (Casodex<sup>®</sup>)
 

- adverse events 99, 101
- hypothalamus pituitary axis 99
- LHRH-A analogue 101

- bicalutamide (Casodex<sup>®</sup>) (*contd.*)
    - monotherapy 100, 101
    - SAR of 100
  - bile acids (BA)
    - farnesoid X receptor (FXR)
      - biosynthesis and enterohepatic cycling 210
      - cholesterol metabolites 211
      - C6-modified CDCA derivatives 214–220
      - coactivator proteins 210
      - metabolic, anti-inflammatory and anti-fibrotic actions 212
  - medicinal chemistry analysis
    - amidation/deconjugation process 206
    - BA bioavailability 210
    - bacterial 7-dehydroxylase 209
    - biliary secretion and metabolism 205
    - C23 and C22 hydroxylated synthetic analogs 208
    - side chain modifications 206
    - 6 $\alpha$ -methyl-ursodeoxycholic acid 206
    - 7 $\alpha$ -analogue 209
    - steroid scaffold modifications 205
    - physiology 200
    - 6 $\alpha$ -ethyl-chenodeoxycholic acid 214
    - structure and properties
      - contiguous hydrophobic area 198
      - hydroxylation pattern 199
      - octanol/water partition coefficient (logP) 199
      - physicochemical properties 200
      - primary, secondary and tertiary BA 198
      - sulfation and glucuronidation reactions 200
    - therapeutic agents 202–204
  - binding detection methods 11, 13
  - biomarkers 31, 193, 229
  - biopharmaceutics 42, 47–56, 59, 60
  - bispecific antibodies (bsAb) 28–30
    - autoimmune diseases 114
    - blinatumomab
      - administration 120–121
      - B cell-derived malignancies 123
      - biological activity 122
      - BiTE<sup>™</sup> antibodies 118
      - CD19-specific therapy 122
      - clinical development 118–120
      - history and design 116–117
      - mAbs 117
      - manufacturing of 118
      - side effects 121–122
    - catumaxomab 114
    - EpCAM/CD3-bispecific catumaxomab 114
    - human IgG1 antibodies 114
    - monoclonal antibody technology 114
    - T cell engaging antibodies 115
  - blinatumomab
    - administration 120–121
    - B cell-derived malignancies 123
    - biological activity 122
    - BiTE<sup>™</sup> antibodies 118, 124
    - vs. CD19 CAR-T cell therapy 125
    - CD19-specific therapy 122
    - clinical development 118–120
    - history and design 116–117
    - mAbs 117
    - manufacturing of 118
    - side effects 121–122
    - ultra-sensitive assays 124
  - bortezomib 163, 168–170, 174, 176
  - bosutinib 74, 77
  - B-Raf inhibitors 79
- C**
- canertinib 345
  - carbidopa 320, 386, 387
  - carfilzomib 163, 169, 170
  - Carlsson, Arvid 385, 386
  - catechol O-methyltransferase (COMT) 319–336, 386, 407
  - catumaxomab 28, 113, 114
  - CD20 antibodies
    - type I 246, 252
    - type II 247, 252
  - CD38 antibody daratumumab 157
    - antibody-dependent cell-mediated cytotoxicity (ADCC) 158

- antibody-dependent cellular phagocytosis (ADCP) 158, 159
- complement-dependent cytotoxicity (CDC) 157
- discovery of 156
- enzymatic modulation 159
- expression, in cancer 155
- expression, in normal tissue 155
- functions 154
- immunomodulation 160
- in multiple myeloma
- autoimmune diseases 172, 173
  - clinical combination therapies, 168–170
  - clinical laboratory assays 165
  - hematologic malignancies 171
  - monotherapy studies 163, 164
  - plasma cell dyscrasias 164
  - preclinical combination therapies 167, 168
  - responders and non-responders 164
  - solid tumors 171
  - subcutaneous delivery 165
  - programmed cell death (PCD) 159
  - therapeutic target 154
- CDK inhibitor 80
- ceritinib 78
- clinical phase I evaluation 143
  - clinical trials 145
  - crizotinib-resistance mutations 140, 141
  - crizotinib-resistant xenograft tumors models 141, 142
- drug design of 134
- in vitro* ADME evaluation 137
  - in vitro* evaluation 136–137
  - in vivo* evaluation 138–140
  - pre-clinical pharmacokinetic evaluation 138
  - synthesis of 135–136
- Chinese hamster ovary (CHO) cells 24, 118, 123, 156, 248
- 5-chloro-4-*N*-methylindole 350
- 2, 4-(4-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3-yl)benzene-1,2,3-triol, BIA 9-693) 322
- 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine hydrochloride 371
- Cholbam™ 203
- Clinical Global Impression–Severity of Illness (CGI-S) 405–407
- C6-modified CDCA derivatives
- Arg328 side chain 218
  - axial 7 $\alpha$ -hydroxy moiety 217
  - C-terminal H12 217
  - rFXR-LBD 217
  - SAR analysis 217
- Committee for Orphan Medicinal Products (COMP) 373
- complement-dependent cytotoxicity (CDC) 6, 122, 157–158, 246, 249
- COMT inhibitors 320–322, 333, 335, 386, 407
- crizotinib 78, 131–146
- cyclic adenosine diphosphate ribose (cADPR) 155, 159
- d**
- dabrafenib 79
- dacomitinib 345
- damage-associated molecular patterns (DAMPs) 249
- daratumumab (Darzalex®), 4, 21, 153–176, 195 *see also* CD38 antibody daratumumab
- desmethyl indole 350
- dexamethasone 153, 168–170, 176
- diazabicyclic heterocycles 349
- 5 $\alpha$ -dihydrotestosterone (DHT) 95, 100, 103
- dithiothreitol (DTT) 166
- divisional applications, patent application 60
- dopamine agonists (DA) 319, 386
- dopamine precursor levodopa (L-DOPA) 319–321, 332–334, 385–387, 406–407

- double mutant, EGFR 345, 346
  - drug discovery
    - affinity maturation 25
    - analogue approach 9
    - antibody drug conjugates (ADC) 26–28
    - antibody production and physicochemical properties 24–25
    - bispecific antibodies (bsAb) 28–30
    - cancer treatments 4
    - clinical efficacy 30
    - CNS diseases 6
    - diabetes 6
    - dinutuximab (Unituxin<sup>®</sup>) 4
      - DMPK investigations 17–18
      - enhanced lead generation strategies 7–16
      - epigenetic targets 6
      - FcγR binding 26
      - fragment-based lead discovery (FBLD) 13
      - G-protein coupled receptors (GPCR) 6
      - hematological supplement therapies 3
      - hereditary orotic aciduria 4
      - high throughput screening (HTS) 9–11
      - immune response to antibodies 23
      - library sharing 15
      - multi-drug resistant infections 6
      - NCEs 7
      - neurodegenerative diseases 6
      - new biological entities (NBE) 19–23
      - new molecular entities (NMEs) 3
      - non-small cell lung cancer 6
      - pancreatic cancer therapy 6
      - physicochemical parameters 18
      - probe compounds 15
      - protein-protein interactions 6
      - repositioning 14
    - sebelipase α (Kanuma<sup>®</sup>) 4
      - structure-based design 11–12
      - target product profiles 5
      - therapeutic armamentarium 5
      - tolerability assessment 19
      - virtual screening 12–13
- e**
- elotuzumab (Empliciti<sup>®</sup>) 4, 163
  - enzalutamide (Xtandi<sup>®</sup>) 185–89
    - anti-androgen withdrawal response 102
    - metastatic castration resistant prostate cancer (mCRPC) 104
    - resistance mechanisms 102
    - structural modifications 103
  - entacapone 320, 321, 334, 335
  - epidermal growth factor receptor (EGFR) 341
    - kinase domain 342, 343
    - tyrosine kinase inhibitor (TKI) therapy 353
  - Epworth Sleepiness Scale (ESS) score 374
  - ErbB-1 77, 341
  - ErbB family inhibitors 73
  - European Patent Convention (EPC) 47, 58
  - Exon19 del 342
- f**
- Fasted state simulated intestinal fluid (FaSSIF) solubility 19
  - FcγR binding 249–250
  - first-generation inhibitors 320
  - flavin adenine dinucleotide (FAD)-dependent mitochondrial enzyme 386
  - fluorodeoxyuridine monophosphate (FdUMP) 419, 427
  - 3-fluoro-omargetin 297
  - fluoropyrimidine prodrugs 420
  - 5-fluorouracil (5-FU)
    - antitumor effect 417, 419–420
    - side effects 417
    - systematic drug degradation 417

- fluorouridine triphosphate (FUTP) 419  
 flutamide (Eulexin<sup>®</sup>) 96–98  
 Food, Drug and Cosmetic Act 50  
 fragment-based drug discovery 8  
 fragment-based lead discovery (FBLD) 13–14  
 FTC-092 (1-(3-*O*-benzyl-2-deoxy- $\beta$ -D-ribofuranosyl)-5-trifluoromethyl-2,4(1H,3H)-pyrimidinedione) 420
- g**
- gastric inhibitory polypeptide (GIP) 291  
 gastrointestinal adverse events 143  
 gastrointestinal toxicities 433  
 gefitinib 77, 341, 344  
 Gilotrif<sup>™</sup> 345  
 gimeracil 420  
 glimepiride 308–310  
 Global Impression of Change (CGI-C) 334, 335, 406  
 glucagon-like peptide-1 (GLP-1) 21, 291, 303, 305  
 glutathione (GSH) 134, 135  
 glycoengineering 26, 247, 248, 250  
 GlycoMab technology 247  
 glycosylated hemoglobin 291, 311  
 G-protein coupled receptors (GPCR) 6, 202
- h**
- Hatch–Waxman Act 54  
 hematologic malignancies 166, 171  
 hematologic toxicity 433  
 HER1 341  
 heteroreceptors 360  
 high throughput screening (HTS) 8–11, 371  
 histamine H<sub>1</sub>-receptor 359  
 histamine H<sub>3</sub> receptor 359–375  
 histaminergic neuronal pathways 359  
 histaminergic presynaptic auto-inhibitory receptor 359–360  
 Hornykiewicz, Oleh 385
- H<sup>3</sup>-receptor selective ligands 360  
 human equilibrative nucleoside transporter 1 (hENT1) 429  
 human leukocyte antigen-C (HLA-C) molecules 167  
 human or horse TP inhibitors 421  
 hydroxyflutamide 96–98, 100  
 hypoparathyroidism 21  
 hypophosphatasia 4, 21
- i**
- ibrutinib 72, 80, 270, 273  
 icotinib 76, 81  
 immunofixation (IFE) gels 165–166  
 immunomodulation 160, 170, 173  
 indirect antiglobulin tests (IATs) 166  
 indole substituted inhibitors 351  
 insulin-like growth factor receptor tyrosine kinase 1 (IGF1R) 346, 349–351  
 irreversible anilinoquinazoline based EGFR inhibitors 345  
 isatuximab 175  
 2-(*isopropylsulfonyl*)aniline 135  
 ivacaftor 5  
 ixazomib (Ninlaro<sup>®</sup>) 4
- k**
- kainic acid-induced multifocal status epilepticus 400  
 kinase dysfunction 67  
 kinase inhibitor drugs  
   approved kinase inhibitor drugs 68  
   approved ROCK kinase inhibitors 76  
   ATP-binding pocket 67  
   cellular activities 67  
   FDA approved covalent small molecule kinase inhibitors  
     ibrutinib 80  
   FDA approved non-covalent small molecule kinase inhibitors 73, 75  
   ALK inhibitors 78  
   B-Raf inhibitors 79  
   CDK Inhibitor 80  
   ErbB family inhibitors 73

- kinase inhibitor drugs (*contd.*)
- JAK family inhibitors 78
  - MEK inhibitors 79
  - MET inhibitors 78
  - PI3K inhibitor 79
  - VEGFR family inhibitors 77
  - FDA approved rapalogs 80
  - history of
    - in 1980s 70
    - in 1990s 71
  - icotinib 81
  - noncovalent kinase inhibitors 69
  - noncovalent SMKIs 67
  - prototype kinase inhibitors 72
  - radotinib 81
  - ripiasudil 81
  - ROCK inhibitors 81
  - two-lobe kinase domain 67
  - type II inhibitors 69
  - type III and IV inhibitors 69
- I**
- lenalidomide 9, 158, 163, 167–170, 174, 269, 270
  - Lewy bodies 384
  - ligand-based virtual screening 8, 12
  - ligand binding domain (LBD) 95, 98, 210, 214, 217, 220, 341
  - lipophilic ligand efficiency (LLE) 348–350, 354
  - Lonsurf™ *see* trifluridine (FTD) and tipiracil hydrochloride (TPI)
  - luteinizing hormone-releasing hormone (LHRH) 97
  - lysosomal acid lipase deficiency 4
- m**
- mAb cancer therapies 122
  - maximal electroshock test (MES) 391, 396, 400
  - MEK inhibitors 79
  - membrane-attack complexes (MAC) 156, 157
  - membrane-bound (MB-COMT) 125, 247, 320
  - metformin 307–311
  - MET inhibitors 78–79
  - Micromet, Inc 119
  - milacemide (2-(*n*-pentylamino)acetamide) 388
  - minimal residual disease (MRD) 117, 169, 262
  - minimum anticipated biological effect level (MABEL) 124
  - monoamine oxidase-B (MAO-B) 319, 386, 388–390, 396–398
  - morpholine 330
  - M-protein 160, 165, 166
  - mTOR activity 81
  - mutations 67, 77, 79, 102, 140–141, 342, 343, 384
- n**
- natural killer (NK) cells 114, 115, 155, 250
  - natural products 9, 10, 70, 214
  - nicotinic acid-adenine dinucleotide phosphate (NAADP) 155, 159
  - nilutamide (Anandron®) 96, 98–99
  - nimotuzumab 55
  - nitrocatechol pharmacophore 321, 325
  - nivolumab 113, 170, 172, 175
  - non-Hodgkin's lymphoma (NHL) 26, 119, 167, 171, 253, 260
  - non-human primates (NHPs) 18, 118, 124
  - non-small cell lung cancer (NSCLC) 9, 77, 131–146, 341–354
  - non-steroidal androgen receptor antagonists
    - bicalutamide (Casodex®) 99–102
    - enzalutamide (Xtandi®) 102–105
    - flutamide (Eulexin®) 96–98
    - nilutamide (Anandron®) 98–99
  - N*<sup>α</sup>-(4-Phenylbutyl)histamine 366
  - N*-phenyl substituted pyrazole compounds 325
  - N*-tele-methylhistamine 360, 367, 372
  - nucleoside antimetabolites 417, 418

## O

- obeticholic acid (Ocaliva™)
  - biliary secretion and
    - pharmacokinetics 224
  - choleretic effect 224
  - intraduodenal and intravenous
    - administration 224
  - pharmacokinetics and metabolism 223
  - physicochemical properties 223
  - preclinical models, of liver diseases 225–228
  - primary biliary cholangitis treatment 228
  - synthesis of 220
- obinutuzumab
  - ADCC potency 250
  - CD20 binding 248
  - chronic lymphocytic leukemia
    - chemotherapy-free regimens 273
    - CLL11 study 272
    - combinational therapy studies 271
    - GAUSS and GAUGUIN studies 271
    - GREEN study 272–273
    - obinutuzumab single-agent studies 270
    - single-agent studies 271
  - complement-dependent cytotoxicity 249
  - direct cell death induction 249
  - Fab fragment 248
  - FcγR binding 249
  - glycoengineering, concept of 247
  - human xenograft models, of B-cell lymphoma 251–252
  - non-Hodgkin lymphoma
    - chemotherapy-free regimens 269
    - combination therapy studies 260, 261
    - GADOLIN study 262, 267
    - GALLIUM study 267
    - GOYA study 268, 269
    - single-agent studies 253, 260
  - non-tumor indications 273–274
  - phagocytic activity 250
  - whole blood B-cell depletion 250
- O-debenzylated safinamide 403
- olanzapine 46
- omarigliptin (MARIZEV™, MK-3102)
  - add-on therapy
    - glimepiride 310
    - metformin and sitagliptin 308–310
    - safety and tolerability 311
  - bioisosteres 294
  - clinical data 305–308
  - hERG selectivity 294
  - in vitro* pharmacology
    - pharmacokinetics 303
    - preclinical species 302
  - in vivo* pharmacokinetic parameters 297
  - pharmaceutical properties 304
  - physicochemical properties 304
  - pre-clinical safety pharmacology 304
  - pyrroloimidazole analogues 294
  - pyrrolopyrimidine metabolite 294
  - synthesis of 298, 300
  - in type 2 diabetes mellitus 306
  - X-ray and modelling studies 297
- opicapone
  - central heterocyclic core 325, 327
  - COMT inhibitors 320, 321
  - early pyrazole analogues 322, 325
  - identification of 330
  - optimization of oxadiazolyl
    - nitrocatechols 327, 330
  - Parkinson's disease 319, 320
  - phase I and phase II studies 333, 334
  - phase III studies 334, 335
  - preclinical profile 332, 333
- orexins 372, 373
- orotate phosphoribosyltransferase (OPRT) activity 430
- Orphan Drug Act (ODA) 54
- osimertinib 4, 5, 77, 80, 341–354
- oxadiazolyl nitrocatechols 327–330

**p**

- palbociclib 4, 5, 80
- pancreatic  $\beta$ -cells 291
- panobinostat (Farydak<sup>®</sup>) 4
- Paris Convention for the Protection of Industrial Property 45
- Parkinson's disease (PD) 319, 320
  - antihistaminics 385
  - etiology 384
  - management of 385
  - meta-analysis 383
  - 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 384
  - monoamine oxidase (MAO) inhibitor 385
  - non-human primates 384
  - pharmacotherapy 386–387
  - primary motor signs 383
  - reserpine 385
  - safinamide *see safinamide*
  - synthetic antimuscarinics 385
- Patent Cooperation Treaty (PCT) 45
- patent eligibility
  - biopharmaceutics 47
  - definition 43
  - DNA sequence 44
  - inventive step/non-obviousness 47
  - monoclonal antibodies 46
    - antibody sequence claims 48
    - biological targets 48
    - nucleic acid based therapeutics 49
  - novelty 44
  - small molecules and peptides 44
  - TRIPS agreement 43
  - USPTO 44
- patent lifecycle management
  - combination products 57
  - formulations and/or galenics 57
  - 2nd or higher medical indication patent 58
- patent lifetime
  - patent term adjustment (PTA) 50
  - patent term extension (PTE) 50
  - pediatric investigations (EU) 50, 52
    - supplementary protection certificates (SPC) 50
- Patent Protection and Affordable Care Act 54
- Patient's Global Impression of Change (PGI-C) 334, 335
- pediatric investigation plan (PIP) 52, 53
- pediatric use marketing authorization (PUMA) 54
- pembrolizumab 113
- peripheral blood mononuclear cells (PBMCs) 158, 167
- phage display techniques 24
- pharmaceutical industry, role of patents 41–42
- phenotypic screening 8, 11
- PI3K inhibitor 72, 79–80
- pioglitazone 307, 311
- piperazine derivative 349
- pitolisant 359–375
- plasma cell dyscrasias 164–165
- pomalidomide 163, 169, 170
- programmed cell death (PCD) 157, 159, 170
- Property Forecast Index (PFI) 19
- prostate cancer
  - androgen receptor (AR) signaling 95
  - bicalutamide (Casodex<sup>®</sup>) 99–102
- pyrazolopyridine 348
- pyrazolopyrimidine 349
- pyridinyl isosteres of thioperamide 361
- pyrimidine/xanthine analogues 293
- pyrrolidine analogues 293
- 6-[(1-pyrrolidinyl)methyl]-5-bromouracil 424
- 6-[(1-pyrrolidinyl)methyl]-5-chlorouracil hydrochloride 422

**r**

- radotinib 76, 81
- Raman spectroscopy 18
- rapalogs 67, 76, 80–81
- rapamycin 72, 80



- RECOURSE study 432, 433  
 regulatory data exclusivity and/or  
     market exclusivity  
     Article 39 (3) of the TRIPS agreement 53  
     monopoly rights 55  
     orphan drugs 54  
     PUMA 54  
 repositioning 9, 14–15  
 reserpine 385  
 Restless Legs Syndrome (RLS) 400, 407  
 reversible covalent binding 82  
 rituximab 26, 122, 174, 245, 248–251, 253, 262, 267, 268, 273  
 rociletinib 80  
 rosiglitazone 311
- S**
- safinamide 387  
     blocks voltage-dependent sodium channels 398  
     clinical PKM and safety 403  
     clinical studies  
       in advanced PD 406–407  
       in early PD 403–405  
     clinical trials  
       and marketing authorizat 408  
       for other indications 407  
     inhibits glutamate release 399  
     *in vivo* antiepileptic efficacy  
       assessment 395  
     MAO-B 396–398  
     milacemide 388–391  
     modulates voltage-dependent calcium channels 399  
     preclinical epilepsy models 400–401  
     preclinical PD models 401–402  
     preclinical PKM 402–403  
     safety and tolerability in clinical studies 408  
     SAR efforts 391–395  
 saxagliptin 305  
 SCID mice bearing H1975 xenografts 349  
 sebelipase  $\alpha$  (Kanuma<sup>®</sup>) 4
- second-generation COMT inhibitors 320  
 semiquantitative LC-MS analysis 134  
 serum protein electrophoresis (SPEP) 165  
 sirolimus 80  
 sitagliptin 52, 293, 297, 308–311  
 solid tumors 125, 171–172, 175, 417, 431  
 soluble form (S-COMT) 222, 320, 333, 334  
 sorafenib 72, 77, 81  
 Structural Genomics Consortium (SGC) 15  
 structure based de-novo ligand design 8  
 structure-based virtual screening (SBVS) 12, 13  
 sugammadex (Bridion<sup>®</sup>) 4  
 synthetic antimuscarinics 385  
 synuclein alpha (SNCA) 384
- t**
- TAGRISSO<sup>™</sup> 341–354  
 T877A mutation 98  
 target product profiles (TPP) 5  
 tegafur 420  
 tegafur–gimeracil–potassium oxonate (TS-1) 417–418, 420  
 thiazolidinediones 291, 311  
 thioperamide  
     chemical background 360–363  
     clinical development studies 373–374  
     generation of a chemical lead 362–366  
     generation of pitolisant 369–371  
     pharmacological screening methods 366–367  
     preclinical development studies 371–373  
     structure-activity optimisation 367–369  
 threonine 790, 344  
 thymidine kinase 1 (TK1) 429  
 T790M mutation-positive non-small cell lung cancer (NSCLC) 353

- tolcapone 320, 321
  - Tovok™ 345
  - trametinib 72, 79
  - trifluoro-deoxy thymidine mono-phosphate (F<sup>3</sup>dTMP) 427
  - trifluoro-deoxy thymidine triphosphate (F<sup>3</sup>dTTP) 427
  - trifluridine (FTD) and tipiracil hydrochloride (TPI) 417
    - anti-tumor effect of 427–429
    - clinical development 417
    - clinical efficacy, safety, and approval 432–434
    - medicinal chemistry, *in vitro* and pharmacokinetic studies 420–425
    - nucleoside antimetabolites 417, 418
    - optimal dosing scheme 430–432
    - pharmacologic effect of 429–430
    - preclinical *in vivo* efficacy studies 425–427
    - structure of 417, 419
  - tripolisant (USAN) 371
  - TRIPS agreement, Article 39 (3) of 53
  - trogocytosis 164, 167
  - Type I CD20 antibodies 246–247, 250, 252
  - Type II CD20 antibodies 246–249
  - Type 2 diabetes mellitus (T2DM) 291–293, 305–308
- u**
- U.S. Patent Act 58
  - ursodeoxycholic acid (UDCA) 197, 204
- v**
- VEGFR family inhibitors 77–78
  - virtual screening 8, 12–13
- w**
- Wakix™ 374, 375
  - wearing off phenomenon 386, 401
  - whole blood B-cell depletion 250–251
  - wild type EGFR 80, 348, 352, 353
- x**
- Xadago™ 408
  - X-ray analysis 13
  - X-ray crystallography 11, 218
  - X-ray powder diffraction 18, 304
- y**
- Yahr, Melvin 386