

Index

a

- absorption 8
- acetaminophen (paracetamol) 61, 298, 299
- acetylcholine 271
- active metabolite (AM) 143–145, 147, 150, 173
- acute coronary syndrome 142, 150, 153, 157
- acute myelogenous leukemia (AML) 119, 125
- acute nociceptive pain models *See also* pain 312
- acute pain *See also* pain 297
- adenosine 5'-diphosphate (ADP) 142
- adenosine triphosphate (ATP) 152
- ADME (absorption, distribution, metabolism and excretion) 38, 39, 92, 104
- ADP-induced platelet aggregation 144, 145, 152
- afimoxifene 168, 171, 175
- agranulocytosis 12, 61, 65
- aldehyde oxidase (AO) 38, 46–48
- allodynia 297
- allopurinol 365, 367, 368
- almotriptan 48, 49
- alogliptin 8
- Ames test 54, 369
- AMG458 60
- aminodiaquine 65–66
- amitriptyline 270, 271
- amoxapine 12, 13
- analogue-based drug discovery (ABDD) 12, 16, 21, 22, 25–27, 167, 176, 180, 288, 320
- analogue drug 3, 16, 22, 25
- anastrozole 24, 25
- angina pectoris 10
- angiotensin-converting enzyme (ACE) 6
- anovulation 170, 171
- antiandrogen effect 6
- anticancer therapy 116
- anticholinergic effect 14
- anticoagulation and treatment 8, 244, 245, 258
- anticonvulsants 299, 300
- antidepressant drug 13, 299, 300
- antidiuretic hormone (ADH) 187
- antiepileptic drug 66
- antiestrogens 176
- antihypertensive therapy 4
- antimalarial agent 65
- antimetabolite 118
- antimigraine drugs 48, 49
- anti-obesity agent 31, 59, 66, 67
- antiplatelet agents 142, 144
- antithrombin (AT) 244
- apixaban 245
- aplastic anemia 61
- apparent intrinsic clearance ($CL_{int,app}$) 39, 40
- aquaretics 197, 203
- arachidonic acid 213, 299
- argatroban 8, 10, 245
- arginine vasopressin (AVP) 187, 188, 203
- ArimidexTM 24
- aromatase inhibitor (AI) 24, 25
- aromatic cyano group 272
- arrhythmias 10
- aspirin (ASA) 142, 149, 256, 298
- aspirin-induced asthma 232
- asthma 51, 212, 230
- atenolol 11
- atherosclerosis 258
- atherothrombosis 142
- atrial fibrillation 246, 258–260
- atypical antipsychotic agents 12
- 5-azacytidine (5-azaC) 118, 119
 - clinical trials 119, 120
 - derivatives 121
 - mechanism of action 119, 120
 - prodrug 120
 - synthesis 120

5-aza-2'-deoxycytidine (5-aza-dC) 118, 119
 – mechanism of action 121
 azumamide E 132

b

baclofen 299
 bazedoxifene 168, 171, 179
 β adrenergic receptor antagonists 10
 β_1 - and β_2 adrenergic receptors 11
 β -adrenergic receptor agonists 212
 17 β -estradiol 166, 167
 bioavailability 9, 99, 122, 179, 195, 223, 224, 277
 bioisosteric replacement 64
 bivalirudin 8, 245
 bleeding liability 143, 144, 150, 156, 259, 260, 300
 blood-brain barrier 314, 330
 blood coagulation cascade 243, 244
 blood pressure 188
 boceprevir (VictrelisTM) 343
 – backup research 352
 – *tert*-butyl urea analogue (boceprevir) 352
 – discovery 344–352, 358
 – hydrogen bonding network with the enzyme 357
 – macrocyclic lead molecule 349
 – optimization of the PK properties by analogues 350
 – truncated analogue of the lead molecule 346
 – undecapeptide lead molecule 344–345
 – X-ray studies 345, 346, 348
 breast cancer 24, 172, 175–178, 322
 – prevention 179
 bromodomain inhibitor 133
 bronchial asthma 11
 bronchoconstriction 213
 buprenorphine 298
 burimamide 5
 burkholdac B (thailandepsin A) 131

c

cabazitaxel (JevtanaTM) 319, 322
 – chemical and physical properties 323
 – clinical studies 330–336
 – preclinical development 328–330
 – structure-activity relationships 323
 – synthesis 325–327
 cachexia 78
 caco-2 assay 97
 calcitonin gene-related peptide 298
 calcium channel blocker 41
 cancer chemotherapeutic drugs 320
 cangrelor 153, 154

cannabinoid receptor 1 antagonists (CB₁ antagonists) 28–32, 66, 67
 capecitabine 333
 captopril 6, 7
 carbamazepine 299
 celecoxib 45, 299
 CelexaTM *see* citalopram 272
 chemical named entity recognition (NER) 25
 chlorothiazide 4
 chlorotrianisene (TACE) 167
 chlorpromazine 12–14
 chromatine 114, 116, 117
Chromobacterium violaceum 128
 chromosome 114
 chronic constriction injury neuropathy pain (CCI) *See also* pain 313
 chronic heart failure 203
 chronic lower back pain *See also* pain 312
 chronic neuropathic pain models
 See also pain 312
 chronic pain *See also* pain 297
 Churg-Strauss syndrome (CSS) 231
 cimetidine 5, 6
 CiprallexTM *see* escitalopram
 CipramilTM *see* citalopram
 cisapride 79
 citalopram 14, 15, 269, 271, 288
 – binding of the enantiomers to the SERT 280
 – clinical efficacy 277
 – discovery 272–277
 – metabolism of the enantiomers 280
 – pharmacological profile 276
 – *R*-citalopram's inhibition of escitalopram 279, 280
 – synthesis 275
 clearance 45, 48, 58, 92, 94
 clogP 32, 89, 103
 clomiphen 167–171, 180
 clomipramine 284
 clonidine 299
 clopidogrel 143, 145, 149, 154
 clorgyline 48
 clozapine 12, 13, 62, 63
 cocaine 296
 codeine 298, 301
 colorectal distension-induced visceral pain model (rat) *See also* pain 313
 combinatorial chemistry 79
 competition 21, 22, 25, 26, 216
 conivaptan 199–201
 constipation 12, 78
 contraceptives *See* non-steroidal contraceptives 171, 172
 controlled-release formulations 314

- Controlled Substances Act (CSA) 296
coronary artery disease (CAD) 155
corticosteroids 212
corticotropin-releasing factor-1
 antagonists 62–64
covalent adduct 123
cyclic adenosine monophosphate (cAMP) 188
CTP-347 56–58
cutaneous T-cell lymphoma (CTCL) 133
cyclooxygenases (COX-1 and COX-2) 299
CYP1A2 48, 147, 314
CYP3A 147
CYP2B6 145, 147, 302
CYP2C9 147, 314
CYP2C19 145, 147, 150
CYP2D6 46, 48, 56, 174, 302, 314
CYP3A4 39–41, 45, 47, 48, 54, 58–60, 155, 302, 314
cysteinyl leukotrienes (CysLTs, LTC₄, LTD₄ and LTE₄) 213, 215
 – *See also* leukotrienes
cysteinyl leukotriene 1 receptor (CysLT₁R)
 antagonists 211, 212, 217, 225, 229
cytochrome P450 (CYP) enzymes 6, 38, 42, 46, 174
 – mechanism-based inactivation 38
 – time-dependent inactivation 56, 58
cytosine 114, 116, 117
cytosine phosphate guanine dinucleotide (CpG) 116
cytotoxicity 82, 121, 122
- d**
- dabigatran etexilate 9, 10, 243, 246–264
 – clinical studies and indications 258
 – double prodrug 254
 – *in vitro* and *in vivo* activity 252
 – log P 252
 – preclinical pharmacology 254
 – selectivity profile 253
10-deacetylbaccatin III (10-DAB) 321, 325
deep venous thrombosis (DVT)
 prophylaxis 259
delta opioid receptor (DOR) 311
depression treatment 270
desipramine 271, 284, 312
N-desmethyltamoxifen 174
O-desmethyltramadol 302
deuterated paroxetine analogue 56, 57
deuteration 58
dextromethorphan 58
diabetes, type 2 7
diabetic gastroparesis 92
diabetic neuropathy 298, 312
diabetic polyneuropathy pain model (rat) 313
diazepam 6
diclofenac 299
diethylstilbestrol (DES) 167
dihydro-5-azacytidine 122
diltiazem 41
dipeptidyl peptidase IV (DPP IV) inhibitor 7
diphenhydramine 14, 15
direct-acting P2Y₁₂ antagonists 152
direct analogue 4
direct thrombin inhibitors *See also* thrombin 8, 9, 245
 – bivalent 8
 – univalent 8
DMPK (distribution, metabolism, and pharmacokinetics) 230, 277
DNA 52, 114
DNA methyltransferases (DNMTs) 116, 117
DNMT inhibitors 118, 121–124
docetaxel (TaxotereTM) 321, 322
DOPA decarboxylase 4
dopamine 78, 311
dopamine transporter (DAT) inhibition 272
double prodrug *See also* prodrug 9, 253
drug class 3, 16, 22
drug-drug interactions (DDIs) 51, 54, 56, 58, 59, 61, 99, 245, 277, 314, 333
“drug-like” molecules 38, 79, 103
drug metabolizing enzymes (DMEs) 38
drug types 3
dual-acting drugs 10, 11, 301, 311, 315
dual antiplatelet therapy 142, 145
duloxetine 287, 299
duration of action 41
dyspnea 154, 156, 158
- e**
- early-phase analogues 8, 16
edoxaban 245
electrophilic compounds 60
eletriptan 48, 49
elinogrel 157
enalapril 7
enclomiphene 169
endogenous estrogen 167
endorphins 299, 300
endoxifen 173
enkephalins 299
enoxaparin 259
eosinophilia 231
epigallocatechin gallate 123
epigenetic code 115
epigenetic modulation 116
epigenetics 114, 133

epigenome 114, 115
 epothilone 320
 eraser enzymes 115
 escitalopram (CipralexTM, LexaproTM) 15, 269, 271, 288
 – allosteric binding site at SERT 273, 274, 280, 282, 284–286
 – anxiolytic-like activity 280
 – clinical efficacy 287
 – derivatives 284
 – pharmacological profile 279, 281–285
 – positron emission tomography (PET) 282
 – synthesis 278
 estrogen receptor (ER) 166
 ethamoxxytriphetol (MER-26) 167
 – antifertility action in animals 167
 etoricoxib 299
 euchromatin 114
 eukaryots 114
 extended-release formulation 296
 extrapyramidal side effects (EPS) 12
 ezetimibe 44, 45

f

factor Xa (FXa) 244, 245
 fadrozole 24
 famotidine 6
 fazarabine 122
 febuxostat 365
 – discovery 369–373
 – lead optimization 369, 370
 – mixed-type inhibition 371
 – 2-phenyl-4-methyl-5-thiazolecarboxylic (lead compound) 369
 – selectivity 372
 – use in patients with renal impairment 372
 – X-ray of febuxostat-bound bovine XOR 370
 felbamate 66, 67
 FemaraTM 24
 fentanyl 296, 298, 300
 fibrin 244, 258
 fibrinogen 244, 258
 fibromyalgia 301
 FK228 (romidepsin, IstodaxTM) 129
 – bacterial fermentation 129
 – total synthesis 130
 flavin-containing monooxygenase (FMO) 174
 fluorine substitution 42–44
 fluorofelbamate 67
 5-fluoro-2'-deoxycytidine 122
 5-fluorouracil 118
 fluoxetine 14, 15, 276, 283
 focal adhesion kinase inhibitors 58
 formalin model 313

FPL-55712 212, 213, 215, 219, 220, 228
 frovatriptan 48, 49
 Fukuyama-Mitsunobu reaction 81
 fulvestrant 166, 167, 171
 functional dyspepsia 78

g

gabapentin 299
 gastric cancer 322
 gastric hyperacidity 5
 gastrointestinal (GI) motility 77–79, 100
 gastroparesis 78
 gene expression 114, 116
 gene mutation 114
 genetic polymorphism 147, 156, 174
 genome 114, 124
 genotoxicity 38, 51, 52, 54, 61
 genotype 114
 GERD (gastroesophageal reflux disease) 79
 ghrelin 77, 78
 ghrelin agonists 77
 ghrelin receptor (GRLN) 82
 GI (gastrointestinal) prokinetic agent 79
 glucuronidation 50, 51
 glutamate 298
 glutathione (GSH) 51, 52, 58, 60–67, 77, 78
 gonadotropin releasing hormone (GnRH) 169
 gout 365, 371–373
 G-protein-coupled receptors (GPCRs) 25, 26, 187
 granulocytopenia 5
 green tea 123
 growth hormone (GH) 77
 growth hormone secretagogues (GHS) 77, 78
 guinea-pig ileum strips 216
 guinea-pig labored abdominal breathing model 222
 guinea-pig tracheal spirals 216
 gynecomastia 6

h

half-life 8, 45, 46, 48, 51, 92, 94, 179, 277, 302, 314
 haloperidol 12
 HCV NS3 protease inhibitors 344–359
 head cancer 322
 heat shock protein (HSP) 166, 178
 heparin 244, 259
 – *See also* low molecular weight heparin
 heparin-induced thrombocytopenia 245
 hepatic side effects 9
 – alanine aminotransferase 9
 – bilirubin 9

hepatitis C virus (HCV) 343
 – bloodborne pathogen 344
 – epidemic 343
 – viral life cycle 343
 hepatocellular carcinoma 343
 hepatocytes 51
 hepatotoxicity 61, 62, 65, 66, 232, 245
 heterochromatin 114
 hexamethylene bisacetamide 125, 126
 high-throughput screening (HTS) 82
 hirudin 8
 histamine 212, 271
 histamine H₁-receptor antagonist 14
 histamine H₂-receptor antagonist 5
 histone deacetylase (HDAC) 124
 – catalytic reaction mechanism 125
 – selectivity 125
 – X-ray structure 124
 – zinc-dependent and inhibitors 124–132
 histone proteins 114, 115
 HIV-1 protease inhibitor 41
 hormone refractory metastatic prostate cancer (mHRPC) 323, 336
 hormone replacement therapy (HRT) 180
 hot plate model (mouse) 313
 HPLC (high-pressure liquid chromatography) 278
 human carboxyl esterases (hCEs) 147, 150
 human immunodeficiency virus (HIV) 40
 human liver cytosol 47, 51
 human liver microsomes (HLMs) 37–40, 42, 58, 64, 97
 hydralazine 123
 hydrochlorothiazide 4
 5-hydroxyindoleacetic acid (5-HIAA) 277
 5-hydroxytryptamine 2C receptor agonist 52
 hyperalgesia 297
 hypertension 10
 hyperuricemia 157, 372, 373
 hyponatremia 198, 201

i

ibuprofen 299, 312
 ICI 198615 223
 ICI 198707 223
 idiosyncratic toxicity 38, 56, 61, 63
 idoxifene 175
 imipramine 13–15, 270, 271
 immature rat uterotrophic assay 176
 immediate-release formulation 296, 301
 indinavir 40
 indoleacetic acid metabolite 48
 inhalers 214
 intracranial glioblastomas 336

intraocular pressure (IOP) 23
 intravenous (i.v.) administration 92
 iproniazid 270
 irritable bowel syndrome (IBS) 78, 79

j

Jevtana™ *see* cabazitaxel

k

Kaposi's sarcoma 322
 kappa opioid receptor (KOR) 311
 ketobemidone 298

l

L-648051 225, 230
 L-649923 225
 L-695499 226
 largazole 131
 larotaxel 322
 lasofoxifene 168, 171
 latanoprost 23
 lead compound 14, 15, 24, 50, 125, 225, 227, 249, 369
 lead optimization 197, 344, 345, 369
 letrozole 24, 25
 leukotrienes *See also* cysteinyl
 leukotrienes 213, 215, 216
 levodopa 3
 levomethadone 298
 Lexapro™ *see* escitalopram
 ligand efficiency 304, 345, 350
 linagliptin 8
 lipophilicity 39, 48
 5-lipoxygenase (5-LO) 50, 51, 213, 214
 5-lipoxygenase activating protein (FLAP) 215
 liver cirrhosis 343
 liver transplantation 343
 lixivaptan 201
 loop diuretics 199
 loperamide 298, 300
 loxapine 62, 63
 low molecular weight heparin (LMWH) 244, 246, 259
 LTD₄ binding assays 217
 LTD₄-derived compounds 220
 LTD₄ molecular modeling 219
 lung cancer 322
 LY-171883 223, 227, 230

m

macrocycles in drug design 77, 79, 80
 major depressive disorder 277, 287
 MAO-A 48, 49
 MAO-B 48

- matrix metalloproteinases 124
 - mechanism-based CYP inactivation 38
 - melagatran 9
 - melanocortin-4 receptor 59, 60
 - melitracen 270, 271
 - meloxicam 62, 63
 - mercaptopurine 118
 - metabolic soft spots 44
 - metabolic stability 97, 345
 - metabolism sites 43
 - metamizol (dipyrone) 299
 - metastatic breast cancer 333, 336
 - metastatic castration-resistant prostate cancer (mCRPC) 323, 336
 - methamphetamine 296
 - N-methylacetamide 125, 126
 - methyl dopa 3, 4
 - methylphenidate 296
 - metiamide 5
 - metoclopramide 79
 - 5-methylcytosine 114, 118
 - methyl binding domains (MBDs) 116
 - MI complex (metabolite-intermediate complex) 56, 59
 - mibefradil 54
 - Michael addition 122, 123
 - microdialysis 280
 - microtubules 320
 - midazolam 58
 - mitoxantrone 323, 334, 336
 - MK-0571 226, 230
 - MK-0679 231
 - mode of action (MoA) 22, 23, 142, 152
 - dual mode of action 296
 - MOE (molecular operating environment) drug discovery software 192, 194
 - molecular weight (MW) 103
 - molibdopterin 368
 - monoamine oxidases (MAO) *See also* MAO-A and MAO-II 38, 46, 48
 - monoamine oxidase inhibitor (MAOI) 270
 - monotarget drugs 5
 - montelukast sodium (MK-0476) 211, 212, 214, 229, 232
 - discovery 224–227
 - morphine 11, 296, 297, 300, 301, 311, 312, 314
 - mosavaptan (OPC-31260, Physuline™) 197
 - mucous secretion 213
 - multitarget drugs 12
 - mu (μ) opioid receptor (MOP) agonists 11, 296, 300, 301, 315
 - mustard oil visceral pain model (rat)
 - See also* pain 313
 - mutagenicity 51, 369
 - myelodysplastic syndromes (MDS) 119–121, 125
- n**
- nafoxidine 168
 - naloxone 301
 - nanaomycin A 123
 - NAPAP and analogues 246–248
 - NAPQI (N-acetyl-p-benzoquinone imine) 62
 - naratriptan 48, 49
 - narlaprevir 343
 - boceprevir analogues 352
 - discovery of narleprevir 355–359
 - improving cellular activities of analogues 353
 - X-ray studies 353, 356
 - natural products 119, 123, 126, 131, 132, 320
 - nebulizers 214
 - neck cancer 322
 - nelivaptan (SSR 149415) 199
 - neuropathic lower back pain 314
 - neuropathic pain 297, 298, 300
 - neutropenia 144, 332, 334
 - neutrophils 51
 - nisoxetine 283
 - nociceptive pain *see also* pain 297, 298
 - nonsteroidal anti-inflammatory drugs (NSAIDs) 299, 300, 312, 314
 - nonsteroidal contraceptives 171, 172
 - nonsteroidal estrogen 167
 - norepinephrine (NE) 271, 299, 311
 - norepinephrine transporter (NET) inhibition 272
 - norepinephrine reuptake inhibitor 296, 301, 311, 315
 - nortriptyline 270, 271
 - nucleosome 114
 - nutraceuticals 133
- o**
- obsessive compulsive disorder 277, 287
 - olanzapine 12
 - onset time 314
 - OPC-18549 189
 - OPC-21268 192
 - ophena 168
 - opioid drugs 11, 299, 300
 - opioid receptors 311
 - oral bioavailability 92, 122
 - ORL1 (NOP, nociceptinreceptor) receptor 311
 - ormeloxifene 168, 171
 - orthopedic surgery 245, 246, 259
 - ospemifene 171, 175

osteoarthritis 297
 osteoporosis 45, 58, 175
 ovarian cancer 58, 322
 ovulation induction 169
 oxipurinol 367, 372
 2-oxo-clopidogrel 146, 147
 2-oxo-ticlopidine 145
 oxycodone 12, 296, 298, 312, 313
 oxytocin 188

p

paclitaxel (TaxolTM) 320–322
 pain 11, 296, 297, 299, 300
 – acute noniceptive pain models 312
 – acute pain 297
 – chronic constriction injury neuropathic pain (CCI) 313
 – chronic lower back pain 312
 – chronic pain 297
 – colorectal distension-induced visceral pain model (rat) 313
 – mustard oil visceral pain model (rat) 313
 – visceral pain model 312
 panic disorders 277, 287
 paracetamol *see* acetaminophen
 Parkinson's disease 42
 paroxetine 56, 57, 276, 283, 287
 patents 21
 peg-interferon 343
 peptic ulcer 5
 percutaneous coronary artery intervention (PCI) 144, 150, 153, 157
 peroxisome proliferator-activated receptor- γ (PPAR- γ) 49
 “personalized medicine” 216
 pethidine 298
 PF-562271 58
 permeability glycoprotein (P-gp) 32, 97, 129
 – inhibitor 259
 – overexpression 322
 pharmacological analogue 6, 215, 229, 230
 phenotype 114
 phenylquinone-induced writhing model 313
 phenytoin 299
 pioglitazone 49, 50
 pioneer drug 3, 4, 6, 8, 10, 13, 16, 21, 22, 25
 piroxycam 299
 plasma protein binding *see* PPB
 platelet 142
 polar surface area (PSA) 103
 polycystic ovarian syndrome (PCOS) 170
 polypharmacy 300
 postoperative ileus (POI) 78
 poststroke depression 277

poststroke pain 298
 posttranslational modifications 115
 post-traumatic stress disorder 277
 PPB (plasma protein binding) 230, 250, 277, 314
 pranlukast (ONO-1078) 211, 212, 214
 – discovery 227–229
 prasugrel 143, 145, 147–149, 152
 prednisolone 323, 333
 prednisone 323, 333
 procainamide 123
 prodrug 24, 123, 131, 143, 172, 174, 252
 – *See also* double prodrug
 profertility drugs 169
 proinflammatory prostaglandins 299
 pronethalol 10
 propranolol 6, 10, 11
 prostaglandin $F_{2\alpha}$ (PGF $_{2\alpha}$) 23, 24
 prostate cancer 322
 protease-activated receptors (PARs) 244
 protein kinases 25, 286
 prothrombin 244
 purinergic receptors (P2Y $_1$ and P2Y $_{12}$) 142, 143
 P2Y $_{12}$ receptor antagonists 142

q

quetiapine 12, 13, 62, 63

r

raloxifene (keoxifene, EvistaTM) 168, 171, 175–180
 ranitidine 6
 rat arteriovenous shunt thrombosis model 148
 reactive metabolite (RM) 38, 51, 52, 54, 60, 62, 64–68
 reactive oxygen species 368
 reader enzymes 115
 regulatory agencies 52
 relcovaptan (SR 49059) 199
 reperfusion injury 368
 ResculaTM 23
 respiratory depression 12
 restless legs syndrome 301
 REV-5901 225
 reversible inhibitor 8
 RG108 123
 rhinitis 232
 ribavirin 343
 rimonabant 28–32
 rivaroxaban 245
 rizatriptan 48, 49
 RNA methyltransferases 117
 romidepsin *see* FK228

- rosiglitazone 49, 50
- rotatable bond count 103
- rule breaker 89
- “rule of 5” 230, 231
- S**
- S-adenosyl-methionine (SAM) 116–118
- salicylates 299
- Salmonella* reverse mutation assay 52
- sativaptan (SR 121463) 199
- saxagliptin 8
- sedative effect 14
- selective estrogen receptor modulator (SERM) 166, 167
- selective norepinephrine reuptake inhibitor (SNRI) 271, 287
- selective serotonin reuptake inhibitors (SSRI) 13, 14, 56, 271, 272
- serendipity 12, 13, 288, 303
- serotonin (5-hydroxytryptamine, 5-HT) 78, 270, 271, 299, 311
- serotonin reuptake inhibitor 301
- serotonin transporter (SERT) 276
- sertraline 276
- SGI-1027 123
- simulated moving bed (SMB) technology 278
- sirtuins (SIRT6) 124
- sitagliptin 7, 8
- SK&F 102922 226
- skin rashes 61
- slow onset time 245
- social anxiety disorder 287
- social phobia 277
- solid-phase synthesis 83
- solid tumors 332
- solution-phase synthesis 87
- spinal cord injury 298
- spinal nerve ligation neuropathic pain model (rat) 313
- SRS-A 212, 213, 215, 217
- stability 122
- stand-alone drug 4
- steady-state platelet inhibition 144
- stent placement 144
- Streptovorticillium ladakanus* 119
- streptozotocin (STZ) – induced heat hyperalgesia 312
- stroke prevention 144, 246, 259, 260
- structure-activity relationship (SAR) 38, 44, 46, 50, 58, 68, 83–92, 144, 167, 190, 193, 194, 219, 250, 251, 272, 273–69, 303, 304, 323, 351
- structure-based drug design 343, 344
 - limitations 357, 358
- suberoylanilide hydroxamic acid (SAHA) 125, 126
- substance P 298
- substrate analogue 7, 118
- sudoxicam 62, 63
- sulfotransferases (SULTs) 49
- sumatriptan 48, 49
- sustained-release formulations 301
- syndrome of inappropriate antidiuretic hormone (SIADH) 197
- synergistic analgesic effect 302
- T**
- tacedinaline 132
- tail flick model (rat, mouse, dog) 313
- talopram 14, 15, 271
- talsupram (Lu 05-003) 271
- tamoxifen 168, 171, 172–175, 178, 180
 - metabolic pathways 173
- tapentadol (PalexiaTM) 11, 12, 295, 297
 - chemical structure 296
 - discovery 296–318
 - pharmacokinetics and drug-drug interactions 314
 - preclinical and clinical profile 310–314
 - reduced gastrointestinal (GI) side effects 313
 - synergistic dual mechanism of action 311
 - synthesis 306–310
- taranabant 66, 67
- tardive dyskinesia 79
- taxoids 320
- TaxolTM see paclitaxel
- Taxus baccata* (European yew) 322
- Taxus brevifolia* (Pacific yew tree) 321
- tegaserod 79
- telaprevir (IncivekTM) 343
- teprotide 6, 7
- tesetaxel 321, 322
- “tether” 80, 92, 93
- theophylline 6
- thienopyridines 143
- thrombin 243–245
 - X-ray crystal structure of thrombin-dabigatran-complex 252–253
 - X-ray crystal structure of thrombin-NAPAP-complex 246
- thrombin inhibitors 8, 43
- thrombopoietin receptor agonists 64
- thrombosis 8, 243
- thrombosis prevention 246
- thrombotic thrombocytopenic purpura 144
- thromboxane A₂ (TXA₂) 142
- ticagrelor 154–157
- ticlopidine 143, 144, 149

- tilidine 298
 tolvaptan (SamscaTM) 198
 tomoxetine 283
 tooth pulp stimulation (rabbit) 313
 toremifene 168, 171, 175
 tramadol 11, 296, 297, 300–303
 transcription 114, 116
 trichostatin A 126
 tricyclic antidepressant (TCA) 270, 277, 284
 triptan class 48, 49
 troglizazone 49, 50
 tumor resistance 322
 TZP-102 92
- u**
- U19052 220, 221
 ulimorelin 77, 93, 94
 – C¹⁴-labeled 98
 – clinical investigations 101–103
 – conformational rigidity 95
 – gastric emptying data 100
 – human cytochrome P450 profile 99, 100
 – intramolecular H-bond 95
 – NMR spectroscopy 95
 – pharmacokinetic data 99
 – protein binding 98
 – synthesis 96
 – X-ray crystallography 95
 ultrasonic vocalization model 280
 unoprostone 23
 uric acid 365
 uridine glucuronosyl transferases (UGTs) 38, 49
- v**
- validated hits 82
 van der Waals interaction 250, 346, 347, 351
 vascular endothelial growth factor-2 receptor 50
 vasopressin V_{1a} receptor binding affinities 190–193
 vasopressin V_{1a} receptor cloning 192
 vasopressin V₂ receptor antagonists 187, 188, 193–203
 venlafaxine 287
 venous thromboembolism (VTE) 244, 259
 verapamil 259
 verlukast (MK-0679) 226
 vildagliptin 7, 8
 vincristine polyneuropathy model (rat) 313
 visceral pain model *See also* pain 312
 vitamin K antagonist (VKA) 245, 258
 vorinostat (SAHA, ZolinzaTM) 127
 – analogues 127, 128
 – synthesis 127
- w**
- warfarin 6, 245, 246, 259, 260
 writer enzymes 115
- x**
- XalatanTM 23
 xanthines 212
 xanthine dehydrogenase (XDH) 368
 xanthine oxidase (XO) 368
 xanthine oxidoreductase (XOR) 365
 xenobiotics 51, 54, 147
 ximelagatran 9, 10, 245
- y**
- YM-17690 229
 yeast model (rat) 313
 yew tree species (*Taxus* spp.) 320
- z**
- zafirlukast (ICI 204219) 211, 212, 214, 231, 232
 – discovery 218–224, 229, 230
 zeburaline 122
 zileuton 51, 232
 zimelidine 14, 15
 zolmitriptan 48, 49
 zuclophene 169

