

INDEX

- AAA proteases, 695–697
ATP-dependent zinc proteases, 695
- Absorption/distribution/metabolism/
excretion (ADME), 647
- Acetazolamide (AAZ), 140, 150, 155, 178,
341, 370, 442, 443, 446–448
complexes, 444, 446–448
Cu(II), 447
structural/biological
characteristics, 444–445
coordination compounds, 443
derivatives, 447
inhibition effect, 141, 370
ionization equilibrium, 442
ligand, 447
lipophilic inhibitors, 448
methazolamide analogues, 178
pharmacokinetics profile, 446
Plasmodium falciparum morphology,
effect on, 348
X-ray crystallography, 443
- Acetohydroxyacid, 60
binding mode, schematic representation
of, 78
interaction between inhibitors 60
- Acetohydroxyacid synthase (AHAS), 938
- Acid extrusion pathways, 229
- Acquired immunodeficiency syndrome
(AIDS), 911
- Activated leukocyte cell adhesion molecule
(ALCAM), 594
- Acute promyelocytic leukemias (APL)
patients, 868
- ADAM, 593, 621, 623
family members, 591, 592
membrane-anchored ADAMs, 591, 592
secreted ADAMTSs, 591, 592
inhibition, 617–618
inhibitors, 619, 625, 632
ADAM-10, 618–621
ADAM-12, 622–623
cyclic *N*-hydroxy-carboxamide, 621
MMP-13 inhibitor, 626, 628, 629
TS, 623
TS4 (aggrecanase-1), 624–630
TS5 (aggrecanase-2), 630–632
prodomain, 618
proteinases, 592
structure, 592
TACE, 593
selective inhibitors, 623
TS proteinases, 605, 623, 624
activity, 623
synthesis, 623
X-ray structures, 624
- Adaptation of fields for molecular
comparison (AFMoC) approach, 388
- Adenomatous Polyp Prevention on Vioxx
trial (APPROVe), 260
- Affinity blotting assay, 420
- Aggrecanases, 632
ADAM-TS4, 632
ADAM-TS5, 632
inhibitor, 579
- Alanine-scanning mutagenesis, 708
- Aliphatic sulfonamides, 113, 114
binding modes, 114
schematic representation, 113

- Alzheimer's disease, 475
- Amine nitrogen, *see* Hydroxamate moiety
- Amino acid, 8, 75, 406
- clusters, 431
 - ligands, 6
 - residue(s), 54, 61, 86, 121, 360, 406
 - sequence alignment, 424
 - side chains, 406
- 5-Amino-1,3,4-thiadiazole-2-sulfonamide (H2ATS) complexes, 451
- structural/biological characteristics, 451
- Amyloid precursor protein (APP)
- cleavage, 593
- Anaerobic metabolism, 229
- Angiogenesis, *in vitro* model, 573
- Angiotensin I/II (AGI/II), 751, 766
- converting enzyme, 751
 - generation, 768
 - hydrolysis, 761
 - Michaelis constant, 766
 - receptor, drugs target, 776
- Angiotensin converting enzyme (ACE), 9, 752
- ACE2, 760
 - open/closet conformations, 760
 - subdomains, 760
 - active site, 776
 - angiotensin I (AGI), 751
 - bradykinin, 753
 - catalysis, 759, 764, 766
 - His513 role, 759
 - mutagenesis studies, 759
 - crystal structures, 777
 - distribution, in tissues/organism, 752
 - domains, 762
 - closet-open conformations, 764
 - in vivo* role, 764
 - Drosophila melanogaster*, 755
 - drug design, 776
 - endothelin-converting enzyme, 762
 - enzyme mechanism, 777
 - germinal form, 752
 - deglycosylation, 762
 - ellipsoid-shaped structure, 756
 - matrix-assisted laser desorption ionization/time-of-flight/mass spectrometry, 762
 - subdomains, 756
 - high-resolution structures, 776
 - hinge-bending motions, 760
 - inhibition, 762, 767
 - kinetic/molecular basis, 762–767
 - pharmacological use, 767
 - like protein, 755
 - ACE3, 755
 - single domain, 755
 - lisinopril-bound structures, 757
 - C-domain vs. N-domain, 757
 - membrane anchoring, 753
 - transmembrane-spanning α -helix role, 753
 - neprilysin, 762
 - nonmammalian species, 754
 - phosphorylation, shedding process, 754
 - physiological role, 752
 - proteolytic cleavage, 754
 - role, 762
 - single domain structures, 777
 - soluble form, role, 754
 - somatic form (sACE), 752
 - deglycosylation, 762
 - internal homology, 753
 - N-domain, 761
 - sequence, 753
 - vs. tACE, 753
 - structural homologues, 766
 - neurolysin, 766
 - protein structures, 754, 755, 757
 - Pyrococcus furiosus*
 - carboxypeptidase, 766
 - resolution, 756
 - structures, 764
 - C-domain vs. N-domain, 765
 - kinetic data, 764
 - three-dimensional, X-ray diffraction, 755–762, 767
 - Xanthomonas axonopodis* pv. *Citri* (XcACE), 755
- Angiotensin converting enzyme
- inhibitors, 751, 752, 753, 763, 764, 769, 770, 772, 775
 - altipril, hydrolysis-resistant masking, 773
 - antihypertensive drugs, 768
 - binding constant, 761, 763
 - biochemical information, 752
 - captopril, 752, 772
 - chemical structure classification, 752, 768

- chloride sites, 761
- dicarboxyl-containing, 770–771, 773–774
 - enalapril, 773
- domain-selective, 769
- first generation, 777
- history, 751
- hydroxamic acid inhibition, 775
- interaction, 768
- ketomethylene derivatives, 775
- natural peptides, 768
- pharmaceutical use, 768
- pharmacokinetic profiles, 769
- phosphorous-containing, 772, 774–775
 - fosinopril, 774
 - role, 774
- rational drug design, 777
- rentiapril, 773
- role, 768
- second generation inhibitors, 777
- side effects, 752
- structures, 759
- sulfhydryl-containing, 769, 772–773
- synthesis, 768
- therapeutic effect, 752
- zofenopril, 773
- Angiotensin receptor blockers (ARBs), 767
- Anion-exchange chromatography, 791
- Anion exchanger (AE) family, 416
 - Ct sequence, truncation mutants, 420
 - ghost membranes, 420
 - mutant, 422
 - proteins, 422
 - wild-type, 422
- Anion translocation pathway, 422
- Anthrax infection, 713
 - antibiotic therapy, 713
 - toxin lethal factor, 712
 - inhibitors, 713
- Antiacid drugs, 369
- Antiangiogenic agent, 578
- Antibacterial agents, 937, 941
 - potential targets, 941
 - AHAS, 941–942
 - HDH, 941–942
- Antibiotic-impregnated collagen shields, 726
- Antibody-dependent cell cytotoxicity (ADCC), 206
- Antibody-directed enzyme prodrug therapy (ADEPT), 691
- Anticancer/antimalarial drugs, 33, 578, 968
- Anticonvulsant, 178
 - aminomethylbenzensulfonamides, 181
 - carbonic anhydrase inhibitors, 109, 178
 - acetazolamide, 178
 - aza analogues, 180
 - in brain, 184
 - drug design of, 109, 185
 - epileptogenesis, 184
 - indanesulfonamides, 183
 - lipophilicity compounds, 179
 - maximal electroshock seizure (MES) test, 179, 180
 - methazolamide (MZA) scaffold, 178, 180
 - model of, 184
 - topiramate analogues, 181–183
 - valproyl/adamantyl moieties, 181
 - drugs, 178, 181
 - GABAergic transmission, 182
 - sugar sulfamates topiramate structures, 46
 - sulfamate inhibitory potency, 178
 - sulfonamide, 178
 - inhibitory potency of, 178
 - sulthiame, schematic representation, 24
- Antiepileptic drugs (AED), 112, 120, 172, 173, 404
 - chemical structures, 172
 - drug-drug interactions, 173
 - first generation, 172
 - mechanism, 173
 - multifactorial mechanism, 120
 - second generation, 172
 - side effects, 173
 - topiramate, 120, 404
 - zonisamide, sulfamoyl group, 112, 172, 174
- Antiglaucoma drug, 33, 141, 144, 146, 448, 465
 - activity correlation, 464
 - dorzolamide, 448
 - human use, 144
 - NO-donating moieties, 146
 - physicochemical properties, 448
 - sulfonamide, 140, 146
- Anti-HIV agents, 985

- Antihypertensive drugs, 776
 inhibitor, rational drug design, 751
 side effects, 776
- Antimalarial drugs, 712
 4-amino-7-chloroquinoline
 substructures, 712
 therapy, 845
- Antiobesity drugs, 9, 242
 CA inhibitors, 9
- Antiviral drugs, 65, 981
- Apicidin, alkyl ketone inhibitors, 872
- Apo *botulinum* neurotoxin serotype B
 catalytic domain (BoNT/B-LC),
 3-dimensional crystal structure,
 707
- Apolipoprotein B mRNA editing enzyme,
 catalytic polypeptide-like 3G
 (APOBEC3G), 982, 984, 981
 active-site loops, 984
 inhibition, 985–986
 structure/catalytic mechanism, 982–985
- Aquifex* enzyme complex, 862
- Artificial neural network (ANN), 388
- Arylacetic acid NSAIDs, chemical
 structures, 258
- Atherosclerotic plaque growth, 504
- Atomic absorption spectroscopy, 959
- ATPase proton pump, 709
- ATP-dependent membrane transport, 171
- Bacillus anthracis*, 712
 receptor-bound protective antigen
 (PA), 712
- Bacillus cereus*, 712
 ADP-ribosylating toxin, 712
- Bacillus thermoproteolyticus*, 680
- Bacterial genome analysis, 10
- Bacterial metalloexopeptidases, 689–690
- Bacterial metalloproteases, 678–679
- Bacterial proteins, 10
 bacterial proteases, 10
Botulinum neurotoxin, 10
Clostridium histolyticum
 collagenase, 10
 tetanus neurotoxin, 10
 role in pathogenesis, 10
 structure, 10
- Bacterial zinc metalloenzymes,
 targeting, 10–11
- α -B antivenom, efficacy, 807
in vitro/in vivo profile, 606–607
- Barrier to autointegration factor (BAF), 925
- BCUT metrics (BCUTs), 385
 3D H-suppressed, 385
- Benzenesulfonamides, 85, 94, 97, 224
 derivatives, 92
 iminodiacetate-Cu²⁺ (IDA-Cu²⁺)
 moiety, 85
 schematic representation, 94
 X-ray crystal structure, 97
- Benzodiazepinone (BZA), 823
- Benzolamide, 457–460
 vs. acetazolamide, 460, 461
 complexes, 457–461
 structural/biological
 characteristics, 459
 ionization equilibrium, 458
 metal complexes, 460
- Benzophenone inhibitors
 based farnesyltransferase, 846, 847
 Schl-5199, hydrophilic/lipophilic, 834
- Benzylester, *in vitro* activity, 844
- Benzyl ketones, 942, 943
 biological activity, 943–944
- Benzyl ring, 579
 MMP-13, 579
ortho/para-chloro substitution, 579
- Bicarbonate (HCO₃⁻), 415
 biochemistry, 415–416
 biological functions, 416
 excretion, renal effect, 157
 transport proteins, 416–419
 classes, 416
- Bicarbonate transporters (BTs), 415, 416,
 426
 family, 417, 426
 Na⁺/HCO₃⁻ cotransporters
 (NBCs), 417
 SLC26A family, 417, 426
 homeostatic mechanism, 416
 metabolon, 415, 419–429
 controversies, 427
 initial characterization, 420–421
 metabolic pathway, 419
 physiological significance, 421–423
 SLC26A/CA interactions, 424–426
- Bicyclic ring systems, 108, 110
- Bidentate ligand(s), 461, 462, 815

- Binding mode, 78–81, 85, 102
 schematic representation, 78, 80, 102
- Binuclear metal center, 966–968
- Biological systems, 4
 animals, 4
 microorganisms, 4
 plants, 4
 zinc catalytic/cocatalytic role, 4–8
- Biosynthetic reactions, 15
 gluconeogenesis, 15
 lipogenesis, 15
 ureagenesis, 15
- Blot overlay assays, 423
- Bond critical point (BCP), 387
- Bone morphogenetic protein-1, 614
- Boron neutron capture therapy, 55
 sulfamide derivatives application, 55
- Bothrops leucurus* venom, 789
 activity, 797
 antiserum, 806
 cross-reactivity studies, 803
 hemorrhagic toxins, 801
 inhibition, 789, 803
 isolation, 789
 leucurolysin-B, 789, 791, 793, 795–797,
 799, 802, 803
 deglycosylated, 796
 fibrin digestion, 799–800
 gelatin zymography analysis, 795, 796
 hemorrhagic effect, 797
 integrins binding, effect on, 802
 metalloproteinase structure, 795
 platelet function, effect on, 802
 proteolytic activity, 797
 purification procedure, 791, 793–797
 SDS-PAGE analyses, 796
 structure-function relationship, 803
 terminal sequence analysis, 791
 metalloproteinases class, 790
 occurrence, 790
 purification, 790
 specificity, 797
 stability properties, 797
 structural chemistry, 791–797
- Botulinum* neurotoxin (BoNT), 705, 707,
 709, 717
 analgesic effect, 717
 catalytic light chain (LC)
 crystal structure, 707
Clostridium botulinum, 705
 controlled studies, 717
 cosmetic use, 716
 efficacy, 716
 mechanisms of action, 717
 serotype A, 706, 712, 716
 catalytic domain, 706
 light chain (LC) inhibitors, 712
 serotype B, 708
 VAMP-2 cleavage, 708
 serotype D, 707
 catalytic domain, 707
 resolution crystal structure, 707
- Botulinum/tetanus neurotoxin* (TeNT)
 protease inhibitors, 709–712
 chelating agents, 709
 captopril, 709
 EDTA, 709
 1,1'-phenanthroline, 709
- Botulism, 705, 709
 causes, 709
 therapeutic agents, 709
- BRGNNR models, physicochemical
 properties, 661
- Brinzolamide (BRZ), 141, 145
 side effects of, 142
- Bristol-Myers Squibb, 829
 drug developers of, 829
 tetrahydrobenzodiazepine-based
 inhibitors
 crystal structure of, 830
- Brucella*, 939, 940
 containing vacuole, 939, 943
 growth curves, 939
 intracellular trafficking, 939–940
 schematic presentation, 940
 virulome mediates adaptation, 940
- Brucellosis treatment
 doxycycline, 938
 rifampicin, 938
 streptomycin, 938
- Budding yeasts, 301
- CA I
 activation of, 476
 catalytic activity of, 480
 dysfunctions of, 480
 hCA I, physiological function of, 476
 L-histidine complex, 476

- CA II, 277, 432
activation of, 477
 L-adrenaline complex, 481–482
 L/D histidine complexes, 477–479
 L/D phenylalanine complexes,
 480–481
binding motif, 425
catalytic activity, 432, 480
crystal structure, 421
dysfunctions of, 480
inhibition, docking-based 3D-QSAR
 model, 391
inhibitors, 109, 386
injected oocytes, 432
support vector machines (SVM), 386
- CA IV cDNA, 426
- CA VII inhibitors, 184
 in brain, 184
 3D structure, 184
 isozymes, 184
- CA IX, 194, 208, 392, 424. *See also*
 Carbonic anhydrase
 breast and lung cancer, 202
 CA12 gene, 200
 cancer detection and therapy, 205
 catalyzes hydration of, 204
 celecoxib/valdecoxib, nanomolar
 concentrations of, 207
 clinical value of, 201–202
 colonic epithelium, 197
 3D-QSAR model, 392
 enzyme function, 208
 expression, regulation of, 199
 gene coding for, 198
 glycoprotein, 195
 homology model of, 196
 human CAs, 196
 isoenzymes, domain composition, 195
 MDCK, 229
 values of, 230
 MN protein, 194, 195
 monoclonal antibodies, 206
 N-terminal PG domain, 194
 post-translational level, 200
 renal carcinoma cells, 205
 role, 424
 selective inhibitors, 409
 spin-labeled sulfonamide, 230–235
 benzenesulfonamide moiety, 232
 bovine CA B, 231
 EPR measurements, 233–235
 EPR signals of, 234, 235
 EPR technique, 230
 inhibition test, 233–235
 pyrrolidine/piperidine ring, 231
 structures of, 231, 232
 tempo, design of, 232
 tissue distribution, 197
 transcriptional activation of, 204
 tumor cells, roles of, 203–205
- CA IX inhibitors, 224
 fluorescent sulfonamide, 224
 benzene sulfonamides, 224
 biological evaluation, 228–230
 fluorescent sulfonamides, design
 of, 224
 inhibition test, 225–228
 X-ray diffraction, 225
 QSAR model, 385
- CA XII, 194, 208. *See also* Carbonic
 anhydrase
 cancer biology, role of, 205
 cDNA sequence, 196, 223
 celecoxib/valdecoxib, nanomolar
 concentrations of, 207
 clinical value of, 201–202
 enzyme function, 208
 expression, regulation of, 199
 hypoxia/pvhl pathway, 202
 isoenzymes, domain composition, 195
 isoform, 202
 target of pVHL tumor suppressor
 protein, 196
 tissue distribution, 197
 transmembrane domain, 196
 tumor cells, roles of, 203–205
 tumor types, 197
- CA XIII, 274, 276, 277
 catalytic activity, 274–276
 characterization, 274
 cytosolic enzyme, 274
 expression, 274
 inhibition, 274–276
- CA XV, 279
 catalytic activity, 279–280
 characterization, 278–279
 expression, 278–279
 inhibition, 279–280

- CaaX prenyltransferases, 813, 826
 structure, 815
 farnesyltransferase reaction, 815
 mechanism, 815
- CaaX-prenyltransferase inhibitors, 813, 823
 antiproliferative activity of, 813
 bisubstrate analogue inhibitors, 838–840
 farnesyltransferase inhibitors, 838, 840
 GGPP-competitive inhibitors, 839
 competitive inhibitors, 823–836
 AstraZeneca, 825
 BDZ-2b, 824
 benzophenone inhibitor Schl-5199, 834
 Bristol–Myers Squibb, 829
 CaaX tetrapeptide substrate, 823
 farnesyltransferase inhibitors, 826, 835
 FTI-276, 824
 Merck inhibitors, 828
 nonthiol farnesyltransferase inhibitors, 827
 R115777-like inhibitors, 833
 SCH 66336, 832
 tetrahydrobenzodiazepine-based inhibitors, 830
 tricyclic benzoocycloheptapyridine inhibitors, 831
 FPP competitive inhibitors, 836–838
 farnesyltransferase inhibitors, 838
 GGTase inhibitors, 837
 peptide substrate binding, 836
 GGTase-I inhibitors, 836
 natural products, 840
- CaaX tetrapeptide
 CVIM, 823
 substrate, 815, 832,
 binding, 832
 conformational change, 823
 diphosphate moiety, 816
 farnesyl substrate-binding site, 816
 thiolate of, 815
 transfer of, 815
- Cab active site, stereoview, 292
- Cab/Cam inhibitors, 296
 anions, 296
 sulfonamides, 296
- Cadmium-containing enzyme, 29
- Caenorhabditis elegans* carbonic anhydrases, 301
- CAH-4b/CAH-4a, carbonic anhydrase activities, 313
- Calcium pentosan polysulfate, 631
- Camelysin, 683
- cAMP-dependent PKA
 phosphorylation, 427
- Can2 core
 N-terminal subdomain, 326
 structural analysis, 331
- Candida albicans*, 30
- Candida neoformans*, capsule biosynthesis, 30
- Canine kidney epithelial cells (MDCK), 229
 CA isoforms, 229
 immunofluorescence analysis, 229
- Canonical subclass CA (Cab), 291
- Captopril, 892
- Carbamoylphosphate synthase (CPSase), 302
- Carbamoylphosphate synthesis, 350
- Carbamoylphosphate synthetase II (CPS II), 344
- Carbon dioxide (CO₂)
Candida albicans morphology, 306
 concentrating mechanism, 32
 hydration ester hydrolysis, 63
 hydration reaction, 16, 362
 catalyzed by α -CA isozymes, 16, 362
 kinetic parameters, 16, 362
 sensing system, 326
- Carbonic anhydrase inhibitors (CAIs), 19,
 39, 30, 40, 41, 42, 43, 44, 46, 49, 52,
 53, 54, 56, 60, 63, 67, 73, 74, 75, 79,
 87, 101, 111, 123, 124, 125, 126, 139,
 140, 261, 295–296, 344, 345, 375,
 377, 400, 409, 410, 431, 440, 450, 452,
 461, 464
- acetazolamide (AAZ), 156, 369, 370, 371
 inhibitory effect, 369
- adducts, X-ray crystallography, 66
- amino acids residues, 184
- antibiotics/ antifungals, 30
- anticancer drugs, hypoxic tumor cells, 208
- anticonvulsant, 46, 174, 178, 185
 activity, 46
 agents, 174
 drug design of, 185, 178
- as antifungals, 309–310
- antiglaucoma agents, 119, 143, 146

- Carbonic anhydrase (*Continued*)
- antimalarial properties, 348–349
 - aqueous humor secretion, 146
 - aromatic/heterocyclic sulfonamide structures, 345
 - benzenesulfonamide, 82
 - benzolamide, 157
 - boron neutron capture therapy (BNTC), 208
 - bumethanide, 165
 - 6-chloro-4-amino-benzene-1,3-disulfonamide, 93
 - chlorthalidone, 165
 - classes, 440
 - classical sulfonamide, 166
 - clinical evaluation, 370
 - clinical use, overview of, 174
 - conception of, 40
 - conventional chemotherapeutic drugs, 208
 - data, 262
 - with COX-2 selective inhibitors, 262
 - with sulfonamide inhibitors, 262
 - designing of, 40, 49
 - selectivity issues, 399
 - sulfamate group, 44
 - sulfamide motif, 53
 - zinc binding functions, 39
 - diabetic retinopathy, 149
 - dichlorophenamide, 93
 - dominant ZBG, 325
 - bioisosteres, 325
 - sulfonamides, 325
 - dorzolamide/brinzolamide, 143
 - 3D-QSAR models, 389–390
 - effect, 46
 - 6-ethoxy-2-benzothiazole-sulfonamide (EZA), 428
 - ethoxzolamide, 431
 - facile synthesis, 125
 - furosemide, 165
 - importance in drug design, 73
 - indapamide, 165
 - inhibition profile, 166
 - in vitro* study, 370
 - in vivo* NO precursor arginine, 146
 - isoform-specific, 40
 - isozyme-specific, 40, 74
 - kidneys, 156
 - lipophilicity compounds, 179
 - adamantyl moieties, 181
 - valpropyl, 181
 - macular degeneration, 149
 - macular edema, treatment of, 148, 150
 - malaria parasite, 344–348
 - mechanism, 80, 82
 - by generic benzenesulfonamide inhibitor, 82
 - by generic sulfonamide inhibitor, 80
 - membrane-impermeant designing, 90, 408
 - mammalian eye, 146
 - metal complexes, 464
 - methazolamide (MZA), 370, 452
 - metholazone, 165
 - nematode parasitic disease, treatment option, 316
 - N*-(*p*-sulfamoylphenyl)- α -D-glycopyranosylamines, 145, 146
 - NO-donating moieties, 146
 - ophthalmologists, 141
 - phosphate-phosphonate-based, 63
 - physiological processes, 156
 - profiles, 450
 - properties, 446, 450
 - QSAR models scaffold, 376–382
 - impact on drug design, 375
 - role, 440
 - saliva, 142
 - side effects, 140
 - structure, 42, 43, 52, 174, 401, 403
 - sugar moieties, 120
 - sulfonamide COX-2 inhibitors
 - clinical impact, 265
 - pharmacological evidences, 262–263
 - structural evidences, 263–265
 - sulfonamide drug, 41, 56, 139, 400
 - diuretics, 158
 - effect of, 145
 - 1,3,4-thiadiazole-2-sulfonamide, 144, 155
 - thioureido moiety, 87
 - triazinyl structure, 410
 - 6-trifluoromethyl-4-amino-benzene-1,3-disulfonamide, 93
 - X-ray crystallography, 73

- Carbonic anhydrases (CAs), 7, 9, 15, 30, 32, 39, 40, 72, 139, 193, 261, 336, 360, 375, 399, 406, 419, 423, 429, 439
- active isoforms, 400
- active site, 24, 43, 81, 86, 111, 117, 123
- activity, 400
- adducts, X-ray crystallographic structures, 339
- amino acids, isoforms I and II, 475
- anticancer drugs, 206
- bicarbonate transport metabolon, 419
- binding site, 420
- biochemical features of, 194
- Akt kinase, 195
 - bacteria, 196
 - cDNA encoding, 194
 - cDNA sequencing, 196
 - cytoplasmic, 195
 - glycoprotein, 195
 - isoenzymes, domain composition of, 195
 - MN gene codes, 194
 - MN protein, 194
 - monoclonal antibody, 194
 - proton transfer rate, 196
 - recombinant protein, 195
 - single disulfidic bridge, 196
- biosynthetic processes, 244
- biosynthetic reactions, 473
- blood-brain barrier, 175
- blood vessels, 166
- bone resorption, 193
- brain expression of, 175
- CA-related proteins, 15
- α -class, 15, 17, 39, 73, 74, 337, 341, 350, 375, 399
- active site structure, 41
 - catalyzed CO₂ hydration catalytic mechanism, 18
 - catalyzed reactions, 17
 - cone-shaped cavity, 74
 - 3D structure, 74, 76
 - human, 73
 - inhibition data, 346
 - isoenzymes, 73, 74, 155, 324, 400
 - kinetic mechanism, 338
 - malaria parasite, 341–344, 350, 351
 - sequence alignment, 76
- β -class, 15, 26, 39, 73, 289–295, 325, 327, 375, 399
- bacterial sequential components, 361
 - Can2 active site, 327–329
 - Can2 structure of, 326–327
 - canonical subclass, 289–293
 - noncanonical subclass, 289, 293–295
 - plant/cab-type, 27
 - Zn(II) coordination sphere, 27
- γ -class, 15, 28, 39, 73, 286, 375, 399
- active sites, 286–289
 - Cam, 28
 - catalytic mechanism, 29, 286–289
 - zinc hydroxide mechanism, 29
- δ -class, 15, 29, 39, 73, 375
- ϵ -class, 375, 399
- ξ -class, 15, 39
- cancer, mutations and epigenetic changes, 194
- catalysis, 336–339
- catalytic active forms, 399
- catalytic/inhibition mechanisms, 17, 40
- catalyzed CO₂ hydration, catalytic mechanism, 77
- catalyzed reaction, 324, 338
- catalytic mechanism, 338
- cerebral capillaries, luminal membrane of, 175
- classes, introduction, 285–286
- clinical relevance, 9
- clinical value of, 201
- cDNA microarray, 202
 - hypoxic tumor cells, 201
 - mRNA expression, 202
 - renal cell carcinomas, 202
- computational research, 393
- convulsions, links, 176–178
- crude human red cell enzyme, activation of, 473
- de novo* lipogenesis, 245
- directed pharmacological agents, 74
- distribution, 30
- DNA clones, 360
- 3D-QSAR models, 376, 388
- drug targets, 325–326
- carbonic anhydrase inhibitors, 325
 - targeting β -CAs, 325–326

- Carbonic anhydrases (CAs) (*Continued*)
- expression, regulation of, 199
 - CA12 gene, 200
 - CA9 transcription, 199
 - estrogen receptor alpha, 200
 - hypoxia response element, 199
 - extracellular, 429
 - family, classes, 323
 - functions, 30
 - glutamate receptors, excitatory activity of, 176
 - hypothetical roles of, 176
 - hypoxic cells, pH regulation, 207
 - immunohistochemical detection, 205
 - inhibition mechanisms, 9, 40
 - inhibitor complexes, 124
 - X-ray structural data, 123
 - inhibitory effect, 92
 - inhibitory properties, 105, 111
 - interactions, 418, 426
 - Na⁺-coupled HCO₃⁻ transporters, 426
 - intracellular, 429
 - introduction, 273
 - isoforms, 43, 156, 477
 - activation of, 477
 - drug, therapeutic applications of, 160
 - human brain, activation of, 482–483
 - kidneys, 156
 - mitochondria, 244
 - physiological processes, 156
 - transmembrane tumor-associated CA IX, 43
 - tumor-associated, 161
 - isozymes, 26, 42, 50, 51, 53, 64, 65, 99, 108, 125, 156, 157, 160, 174, 402, 406, 448, 454, 457
 - active site architecture, 402
 - CA I/II/IV, 99, 454
 - CA inhibition data, 64
 - calcium/magnesium ions, excretion of, 156
 - clinically used, 42
 - discovery of, 174
 - drug, therapeutic effects, 160
 - hCA I, *N*-tetradecyl sulfamate, 51
 - hCA II, *N*-decyl sulfamate, 51
 - hCA IX, 51
 - His64 role in catalysis, 402
 - inhibition study, 64
 - inhibitors classes, 402
 - inhibitory properties, 50
 - locations in cell model, 401
 - proximal tubule, 156
 - role, 457
 - schematic localization of, 175
 - X-ray crystal structure, 65
 - kidneys, 166
 - ligands, 376
 - mammalian, X-ray crystal structures, 125
 - membrane-anchored, interactions, 423
 - membrane-associated, 90
 - membrane-bound
 - isozyme IV, 407
 - isozyme IX, 409
 - selective inhibition, 406
 - metabolons, 429
 - CA II, 429, 431, 432
 - monocarboxylate transporter1 (MCT1), 431
 - Na⁺/H⁺ exchanger, 429
 - noncatalytic role, 432
 - N*-type sodium-dependent neutral amino acid transporter isoform 3 (SNAT3), 432
 - metalloenzymes, 193, 244, 323
 - monoclonal antibodies, 205
 - chimeric G250, 206
 - immunohistochemical detection, 205
 - immunotherapeutic tools, 206
 - PG region, 205
 - multiple sequence alignment, 311
 - nanomolar concentrations of, 207
 - normoxic cells, 198
 - obesity, treatment of, 244–245
 - phylogenetic tree, 244
 - physiological
 - pathological roles, 9
 - physiopathological functions, 32, 399
 - processes involvement, 400
 - proton transfer reaction, 483
 - of protozoa/helminthes, 336
 - related proteins, 73, 155, 261, 399
 - role, 360
 - sugar moieties, 120
 - sulfonamides, 79, 208
 - crystal structures, 79
 - NH⁻ moiety, 79

- tissue distribution of, 197
 carcinomas of renal clear cell, 197
 cervical cancer, 197
 hypoxia-induced transcriptional
 activation, mechanism of, 198
 renal cell carcinomas, 197
- tumor cells, roles of, 203
 bicarbonate import mechanism, 203
 bicarbonate transporters, 204
 glucose transporters, 203
 hypoxic cells, 204
 hypoxia triggers, 203
 ion movement, 203
 pH regulation, 203
 signal transduction, 205
- ubiquitous, 375
 X-ray structures, 157, 388
 Zn²⁺-containing enzyme, 261
- Carbonic anhydrases activators (CAAs), 32, 474
 amine/amino acid, chemical structure
 of, 474
 drug design, 475–476, 483
 hCA I, physiological function of, 476
 His64, 481
 isozymes, binding of, 474
 L-histidine complex, hCA I, binding
 affinity of, 476
 molecular structure, 475–476
- Carboxylate analogues, enantiomers of, 581
- Carboxylate-based inhibitors, 331
- Carboxylic acid
 analogues, 566
 inhibitor, structure of, 580
- Carboxypeptidase A, 3D structures, 756
- Carboxypeptidase G2, 691
- Carboxypeptidase T (CPT), 689
- Carcinogenic compound, 574
- Cardiac hypertrophy, 622
- Cardiovascular risk, 259
 cyclooxygenase inhibition 259–260
 type II diabetes, 155
- Catalysis process, 7, 19, 765
 proton transfer, 19
 rate-limiting step, 19
 zinc-bound water molecule role, 8
- Catalytically active isozymes, 39
- Catalytic core domain, enzyme active
 site, 914, 984
- Catalytic proton shuttle, inhibition, 86
- Catalytic zinc atom, hydroxamate binders
 of, 558
- cDNA sequence, 753
- Celecoxib long-term arthritis safety
 (CLASS), 260
- Cell-based ADAM-12 activity assay, 622
- Cell-based assays, 618
- Cell surface integrins, binding motif, 803
- Cellular signal transduction, proteins,
 813
- Central nervous system (CNS), 175, 176
 CAs, expression of, 175
 CAs, localization of, 175
 palmitoylated protein, 706
- Chelating agents, EDTA/BAPTA, 804
- Chinese hamster ovary (CHO) cells, 753
- Chlamydomonas reinhardtii*, 31
- 5-Chloroacetamido-1,3,4-thiadiazole-2-
 sulfonamide (H₂CZA)
 complexes, 449
 structural/biological characteristics, 449
- 5-(2-Chlorophenyl)-1,3,4-thiadiazole-2-
 sulfonamide (HCTS), 450
- Chlorthalidone, 160
- Cholera, 681
- Ciliary process isozymes, bicarbonate-rich
 aqueous humor secretion, 32
- Cinnamic acid-containing inhibitors,
 PXD101 structures, 866
- Classical NSAIDs, 257, 260
- Clathrin-dependent pathway, 594
- Clinical pharmacological agents, 40
- Clostridium* Collagenase (ChC), 721, 722,
 723, 726
 application, 726
 catalytic domain, 722
 Co(II)-substituted, electronic
 spectroscopic studies, 722
 3D structure, 722
 inhibition, with sulfonated
 hydroxamates, 723
- inhibitors, 723, 724, 725
 activity, 501
 applications, 726–727
 fatty acids, 725
 hydroxamates, sulfonated amino
 acid, 723
 potent class, 723

- Clostridium* Collagenase (ChC) (*Continued*)
 sulfonlated hydroxamate, QSAR study, 724
 1,3,4-thiadiazole-2-thiones, 724
 MMPs, 725
 inhibition, with thiadiazoles, 725
 segments, 721
 substrate hydrolysis, 798
- Clostridium histolyticum*, 721, 724, 727
 bacterial collagenases, 727
 infections causes, 721
 neurotoxins, catalytic pathway, 708
- Clostridium perfringens*, 727
 food poisoning, 727
 human gas gangrene, 727
- Coccolysin, *see* Gelatinase
- Cocrystallization experiments, 331
- Collagen(s)
 components of, 490
 degrading microorganisms, 734
 induced platelet aggregation, 803
- CoMFA model, 665, 666
- Comparative structural analysis, 105
- Computational neural network (CNN)
 committee, 386
- CoMSIA models, 390, 392
 analysis, statistical results, 391
- Conformationally restrained P1-P2' sulfonamides, 561
 hydroxamates, 561
 SAR, 561
- Connective tissue pathologies, 623
- Convulsions, 171
 CA, hypothetical roles of, 176
 neurological disorders, 171
- Corneal collagen shields, 726
- Coronary heart disease, 260
- Correlation coefficient, 383, 384, 385, 387, 390
 cross-validation, 384, 385, 387, 390
- Crassulacean acid metabolism (CAM)
 plants, 32
- Cryptococcus neoformans*, 296, 305, 326, 328, 329
 Can2, active site features, 328
 carbon dioxide sensing, 305
- Crystallographic analysis, 90
- CsoSCA enzyme, 292
 active site, stereoview, 293
- C-terminal domain, 430, 914
 DNA binding, 914
 oligomerization, 914
- CVIM substrate peptide, 819
 binding of, 819
 polar interactions, 819
- Cyclic adenosine 3', 5'-monophosphate (cAMP), 30
- α,α -Cyclic- β -aminohydroxamic acids, 605
 β,β -Cyclic- β -aminohydroxamic acids, 606
- Cyclic TNF- α converting enzyme (TACE)
 inhibitors, 604
- Cyclic urea derivatives, 615
- Cyclodextrin-sulfonamide complexes, 144
- Cyclooxygenase (COX) isoenzymes, 256, 257, 259
 COX-1, 257, 259
 derived mucosal prostanoids, 257
 mediated TXA₂, 259
 mRNA variant, 257
 COX-2, 257, 259, 261
 expression, 257
 inhibitors, 260-265
 selective inhibitors, 255, 257
 sulfonamide-containing inhibitors, 262
 isoforms, 257, 259
 pathway, 256
- Cyclopropyl hydroxamic acids, 613
- Cysteine
 based inhibitors, 561
 rich domains, 797
 switch box, 617
- CysteinyI residues, 796, 797
 disintegrin-like domain, 797
- Cystoid macular edema, 149
- Cytidine deaminases, 983, 984
 deamination catalysis, 983
- Cytoplasmic carbonic anhydrase
 isoform, 402
- Cytoplasmic domain, 416
- Cytoplasmic pH buffering system, 369
- Cytosolic isoforms, 53, 61
- Cytosolic isozymes, 55, 65, 86, 88
 hCA I/II, 55, 65, 86
 micro-nanomolar inhibitors, 55
- Cytosolic isozymes *vs.* CA II, 402
 selective inhibition, 402
 CA active site, 404
 CA isozyme I, 402

- CA isozyme III, 404
 CO₂ hydration activity, 404
- D-amino acids, 74
 Dansylsulfonamide, 420
 Decapeptide angiotensin I (AGI), 751
de novo biosynthesis pathway, 952
 enzymes, 952
 structural features, 952
de novo lipogenesis, 244, 245
 6-Deoxy-6-demethyl-4-
 dedimethylaminotetracycline
 (CMT-3) structure, 737
 DFT-based quantum mechanical
 descriptors, 387
 D-His adduct, amino acid residues, 479
 DHO/CA-asp interactions, 962
 Dichlorophenamide, 140
 Dihydroorotase (DHOase), 951, 952, 953,
 955, 956, 961, 967, 959
 catalytic mechanism, 967
 crystal structures, 956–957
 folding, schematic presentation, 960
 HDDP, 970, 973
 hydrolysis, 967
 inhibitor complexes, 968–970
 metal content, 958
 molar ratio, 963
 occurrence/evolution, 953
 phylogenetic analysis, 953
 purification properties, 954
 structure, 959–962
 Thermus thermophilus, structure, 964
 Dimethylcasein
 assay, 797
 proteolytic activity, 791
 Disintegrin/cysteine-rich domains, 617
 Distal renal tubular acidosis (dRTA), 416
 Distomer, *in vitro* activity, 563
 Diuretic sulfonamide, potential novel
 applications of, 165
 DNA phosphodiester bond, 914
 D986NDD acidic cluster, role, 427
 Domain interactions, analysis of, 918
 σ donor ligand, 441
 Door-keepers, *see* Amino acid residues
 Dorzolamide, 145
 Dorzolamide hydrochloride, 144
 Dorzolamide treatment, 141
- hCA II, 143
 side effects, 142
 Double-action inhibition mechanism,
 443
 Drug designing, 721, 775
 application, 726–727
 Clostridium histolyticum collagenase
 inhibitors, 721
 perspectives, 775–776
 Drug-resistant strains, 981
 DrugScore, knowledge-based scoring
 function, 388
 Drug targets, 3, 4, 8, 15
 carbonic anhydrases, 15
 categories, 4
 definition, 3
 zinc enzymes, 3
 zinc metalloproteins, 8–11
 D-tryptophan inhibitors, 574
 Dual-action mechanism, 441
 Dual aromatase-steroid sulfatase inhibitors
 (DASIs), 117, 118
 schematic representation, 118
 Dual prenylation inhibitors, 828
 L-778, 828
 Dual STS-CA inhibitors, structures, 48
- Edema factor (EF), *see* Lethal factor
 Edge-to-face interaction, 106
 EDTA-inactivated proteinases, 803
 Elapid venoms, 796
 kaouthiagin, 796
 ohagin, 796
 Electron-withdrawing effect, 441
 Electropray ionization mass
 spectrometry, 683
 Engelbreth-Holm-Swarm (EHS)
 tumors, 802
Enterococcus faecalis, 680, 681
 enzyme, crystal structure, 693
 etiologic agent, 680
 hp α CA, 360
 Enzyme (s)
 catalyze, 156
 Enterococcus faecalis, 693
 generating factors, 789
 inhibitor affinity, 92, 105, 107
 inhibitor complexes, 123
 Enzyme inhibitors, 22

- Enzyme-linked immunosorbent assay (ELISA), 428
 binding assays, 803
 BTs/Cas, physical interaction, 428
- Enzymes containing metals, *see* Metalloenzymes
- Epidermal growth factor (EGF), 594, 622
- Epidermal growth factor receptor (EGFR), 593
- Epilepsy, ketogenic diet, 172
- Epinephrine, 481
- Erythrocyte plasma membrane (eAE1), 416
- Escherichia coli*, 737, 738, 756, 914
 DHOase, 971
 enterohemorrhagic, 738
 expression system, 362
 HEXXH motif, 737
 IgA1 protease, 737
 inhibitors interaction, 971
 StcE protease, 738
 structural homology, 756
- Estrone 3-O-sulfamate (EMATE), 115
 ring system, 115
 side effects, 115
- Ethoxzolamide (HEZA) complexes, 140, 454–457
 CA inhibitory properties, 454
 coordination behavior, 457
 coordination compounds, 454
 geometries of, 454
 metal ions, 454
 structural/biological characteristics, 455–456
- Ethylene glycol (EG) units, 85
- Eukaryotic cells, DNA, 859
- European medicines agency (EMA), 260
- Exit groove, 823
- Expressed sequence tag (EST) database, 754
- Expression systems, 776
- Extracellular matrix (ECM)
 components, 801, 802
in vitro proteolysis, 802
in vivo models, 801
 proteolytic degradation, 808
 proteins, 790, 801, 803
 amino acid motifs, 803
 hemorrhage induction mechanism, 801
 SVMPs action, 801
- Extracellular pH (pHe), 229
 hypoxic vs. normoxic, 229
 immunofluorescence analysis, 230
- Extracellular stilbene-disulfonate inhibitor (DIDS), 420
- Face-to-face stacking interaction,
 Phe131, 91, 99, 264
- Fagus silvatica*, 629
- Farnesylated proteins, 814
 antiproliferative activity, 814
 prenylation of, 843
- Farnesyltransferase inhibitor(s), 814, 826, 830, 835, 840, 845, 848
 amino acid, 926
 anticancer therapy, 843
 anti-infective agents, 843
 African sleeping sickness, 846–847
 amebiasis, 848
 American trypanosomiasis, 847–848
 antifungal agents, 849
 antiviral agents, 848–849
 eukaryotic organisms, 843
 leishmaniasis, 848
 malaria, 844–846
 toxoplasmosis, 848
 antimalarial properties, 845
 antiproliferative activity, 814
 farnesylated proteins, 814
 clinical activity, 842–843
 anticancer drugs, 842
 dose limiting toxicities, 843
 dual prenylation inhibitor, 842
 side effects, 843
- GGTIs, 842
 human tumor cell lines, 840
 MEK kinase inhibitor, 842
N/K-Ras-driven tumors, 840
 natural sources, 841
 preclinical activity, 840–842
 toxicity levels, 845
- Fatal spastic paralysis, 705
- Filarial pathogen, life cycle, 316
- First-line eradication triple therapy, 359
- FITC-labeled inhibitors, 313
- Flavobacterium meningosepticum*, 688
- FlexS
 alignment procedure, 392
 construction algorithm, 392
- Fluorescein, X-ray crystal structure, 88

- Fluorescent DNA dyes, 368
 membrane-impermeant, 368
 membrane-permeant, 368
- Fluorescent inhibitors, 225
 chemical structures of, 225
 inhibition constant, 226
 mechanism of, 226
- Fluorescent sulfonamides, 225, 228
 aminofluorescein derivative, 87
 CA IX inhibitors
 biological evaluation, 228–230
 design of, 224–225
 X-ray diffraction studies, 225–228
 HCA IX, 228
- Folate hydrolase 1 (FOLH1), 881
- Foscarnet, inhibition constant, 65
- FPP competitive inhibitors, 836
 farnesyl residue, structural variations
 of, 837–838
 farnesyltransferase inhibitors, 838
 library screening, 838–839
 peptide substrate binding, 836
- Fractional factorial design (FFD), 665
- Fragilysin, 688
- FTase, 817
 a₂-binding site of, 821
 binding site of, 820, 821
 bulky side chains of, 816
 CaaX peptide, 822
 FPP complex, 818
 FPP CVIM complex, 818
 GGTase-I, 818
 prenyl-binding sites of, 819
 RhoB to function, 822
 L-778,123, crystal structure of, 829
 piperazine-based, 829
 reaction path, schematic representation
 of, 817, 818
 RhoB, CKVL sequence of, 822
- FtsH, 695, 696, 697
- Fungal carbonic anhydrases, 301–309
Aspergillus, 308
Candida albicans NCE103, 306–307
 functionality, 307
 identification, 306
 regulation, 307
Candida glabrata, 307
Cryptococcus neoformans
 CAN2, 303–305
 functionality, 303
 identification, 303
 regulation, 305
 introduction, 301
Saccharomyces cerevisiae
 NCE103, 301–303
 discovery, 302
 functionality, 302
 transcriptional analysis, 302
- Fungal β-CAs inhibition, 329
 Can2 inhibition, 329–330
 by sulfonamides/sulfamates, 329–330
 product analogue acetate, 330–331
- Fungal CO₂-sensing systems, 328
- Furin recognition site, RXXR sequence, 592
- Furosemide, 161
- GABA_A receptor, mechanisms of, 177
- GABA binds, 177
- GABAergic excitations, 176
- Gastroduodenal diseases, 359
 CA inhibitors, therapeutic usage
 of, 369–371
Helicobacter pylori eradication, 359
- GCPII-based substrates, 900
 anticancer agents, 901
 polypeptide conjugates, 901
 therapeutic/diagnostic, 900
- GCPII inhibitors, development, 886
 arginine patch, 889
 bioisosteres of, 898
 blood-brain barrier (BBB), 887
 glutamate moiety of, 898
 hydrophobic interaction, 889
 hydroxamate acid, 887
in vitro fluorescent microscopy, 890
 phosphoramidate/phosphoramidate-
 based, 889
 phosphonate
 analogues, 886
 based optical imaging agents, 890
 based radiotracers, 891
 phosphite, 888
 2-PMPA, active site of, 887
 structure-activity relationship (SAR), 887
 tunnel region, 899
 urea-based, 899
- Gelatinase(s), 579, 681
- Gel overlay assays, 430

- Gem*-dimethyl group, 563
- Genetic algorithm (GA), 385
- artificial neural network (ANN), 388
 - CNN, routines, 386
 - kernel partial least square (KPLS), 388
 - application, 388
 - nonlinear feature, 388
- Geranylgeranyl-transferase-I inhibitor (GGTI)- 825
- GGPP-competitive inhibitors, 839
- GGTase-I, 820
- a_2 -binding site of, 821
 - FTase
 - binding sites of, 820
 - prenyl-binding sites of, 819
 - inhibitors, 837
 - methionine/glutamine, 820
 - hydrophobic/polar side chains of, 820
 - prenylation inhibitors, 836
 - reaction, 817
 - substrates, 818
- Glaucoma, 139
- animal models, *in vivo* efficacy, 83
 - blindness, 139
 - eye disease, 140
 - IOP, 140
 - treatment for, 139, 140
 - sulfonamides, 140
- Gluconeogenesis, 156
- Glucosamine sulfate, 549
- Glutamate bioisostere analogues, 899
- Glutamate carboxypeptidase II (GCPII), 881
- central nervous system (CNS), 882
 - crystal structure of, 897
 - 3D ectodomain structure, 884
 - genetic sequence of, 885
 - glutamate bioisosteres, 897
 - glutamate-sensor, 882
 - hydrophobic region, 884
 - N*-acetyl- α -linked acidic dipeptidase (NAALADase), 881
 - natural substrates, catabolism of, 883
 - phosphonate-based inhibitors, 892
 - quisqualic acid, 897
 - stereochemistry, effect of, 894
 - substrates/inhibitors, 884
 - 3-carboxybenzyl group, 884
 - glutamate bioisostere, 897–900
 - in vitro* assay methods, 885
 - phosphite-based inhibitors, 894
 - thiol-based, 892–894
 - urea-based, 894–897
 - tunnel region, 884, 897
 - type II transmembrane metalloenzyme, 881
 - urea-based SPECT imaging agents, 897
 - X-ray crystal structure, 896
 - zinc metalloenzyme, 882
- Glutamate carboxypeptidases (GCPs), 690
- Glutamate-glutamine cycle, 432
- Glutathione S-transferase (GST)
- pull-down assays, 426, 430
- Glycopeptide antibiotic, 692
- Glycoprotein(s), 761
- bands, SDS-PAGE, 793
 - nidogen/enactin, 802
 - oligosaccharides, roles, 761
- Glycosylphosphatidylinositol (GPI), 278
- anchored carbonic anhydrase IV (CA IV), 423
 - MMPs, 491
 - N*-glycosylated proteins, 278
- Golgi software, 665
- G-protein-coupled receptors (GPCRs), 767
- Gram-negative spiral bacterium, 359
- Helicobacter pylori*, 359
- Gram-positive cell wall anchor motif, 737
- HEXXH motif, 737
 - LPXTG, 737
- GRID interaction energies, 665
- Group III metabotropic glutamate receptors (mGlu3), 881
- Haemophilus influenzae* enzyme, 294, 327
- structures of, 293
- Hageman factor-dependent kinase system, 682
- Halothiobacillus neapolitans*, 289
- Hammett's δ constant, 376
- hCA I
- catalytic activity, 360
 - inhibitors, 49
 - L-His complex, 478
 - overall view of, 478
 - n*-octyl sulfamate, 49
 - phenyl sulfamate, 49
 - inhibition data, 50

- hCA II, 75, 78, 89, 91, 97, 99, 120, 161, 360, 406, 474
- active site, 77, 89, 97, 99, 100, 102, 104, 264
 - stereoview, 264
 - X-ray crystallography, 102
 - Zn²⁺ ion ligands, 77
 - adducts, 45, 475
 - X-ray crystallographical data, 337
 - X-ray crystallographical structures, 81, 474–475
 - benzene sulfonamides structures, 163
 - brinzolamide adduct, 108
 - celecocixib adduct, structure, 263
 - celecocixib-6, schematic drawing, 263
 - dichlorophenamide, 163
 - EMATE adduct, ribbon diagram, 49
 - high-resolution X-ray crystal structure, 44, 120
 - histamine adduct, 476
 - histamine, superposition of, 482
 - housekeeping enzyme, 163
 - indapamide, binding of, 161
 - X-ray crystal structure, 161
 - indapamide complex, 162
 - inhibitor adducts, 95, 101, 108, 110, 112, 113, 114, 118, 122
 - binding affinity of, 406
 - structural analysis, 101
 - superposition, 95, 108, 110, 112, 114, 118, 122
 - inhibitor complexes, 120
 - L-adrenaline complexes, superposition of, 482
 - L/D-His complexes, 479
 - magenta/green, superposition of, 477
 - superposition of, 479
 - X-ray structure of, 479
 - L/D-Phe, superposition of, 480
 - metal ion, 162
 - N*-(4-sulfamoylphenyl)- α -D-glucopyranosylamine, 44
 - ribbon diagram, 75
 - role, 360
 - solvent accessible surface, 91
 - sulfamates adducts, structural analysis, 119
 - sulfonamide/sulfamate/sulfamide complexes, 161, 163, 226
 - TPM, active site region, 247
 - valdecoxib adduct structure, 263
 - X-ray crystal structure, 78, 83, 406
- hCA II/inhibitor complexes, 75
- aliphatic sulfonamides, 111
 - 3D structures, 75
 - inorganic anions binding, 79
 - sulfonamide/sulfamate/sulfamide inhibitors Binding, 79–123
 - benzenesulfonamides, 81–100
 - containing ring systems, 109
 - containing sugar moieties, 119
 - heterocyclic sulfonamides, 100
 - steroid sulfatase inhibitors, 115
 - ureates/hydroxamates binding, 75–79
- hCAVII inhibitors, binding of, 184
- hCA IX
- amino acid characteristic, active site, 88
 - inhibitory properties, 52
 - polar and hydrophobic interactions, 227
 - tumor cells, expression, 224
 - tumor tissues, isoform, 224
- hCA XIII, 275, 277
- AZA complex, 278
 - 3D structure, 276–278
- HCO₃ flux, 429
- Heart failure, 156
- Heat-shock sigma factor, sigma-32, 696
- HEK293 cells, 421, 424, 426
- Helicobacter pylori*, 93, 359, 360, 361, 362, 364, 365, 367, 369, 370, 371
- acid acclimation, 369
 - α/β carbonic anhydrase, 30, 359, 364, 365
 - alignment, 361
 - amino acid sequence, 363
 - biological function, 367
 - catalytic activity, 360, 362
 - deletion mutant, 369
 - DNA clones, 362
 - inhibition data, 362, 364, 365
 - inhibitory activity, 363
 - kinetic/inhibition properties, 362
 - molecular nature, 360
 - oligomerization, 361
 - pH regulation, 368
 - subcellular localization, 367
 - zinc binding core, 361
- CAs role, 371
- cytosolic hpbCA, biological roles, 367
 - genome projects, 360

- Helicobacter pylori* (Continued)
infection, 371
killing effect, 371
periplasmic hpaCA, biological roles, 367
susceptibility to sulpiride (SLP), 370
- Hemagglutinin/protease, 681
- Hematological cancer, 843
- Hemostatic system, metallopeptidases
class, 790
- Heparin binding epidermal growth
factor, 622
- Hepatitis C virus (HCV), 848
replication, 849
RNA replication, 848
- HEPES buffer, 27, 428
- Heterocycles, five-membered sulphur-
containing, 124
- Heterocyclic inhibitors, *gem*-dimethyl
group, 563
- Heterocyclic sulfonamide, 101, 565
- Heterogeneous glycosylation, 793
- Highest occupied molecular orbital energy
(Ehomo), 383
- Highly active antiretroviral combination
therapy (HAART), 911, 981
associated drug resistance, 919
HIV infection, 919
strand transfer inhibitors, 920
raltegravir, structure of, 920
- Hinge region, *see* Linker region
- His-Glu-Xaa-Xaa-His (HEXXH)
motif, 680, 686, 692
- His-His-Cys-Cys (HHCC) motif, 915
prototypic zinc finger, 916
retroviral integrases, 916
zinc coordination of, 926
- Histamine, 475
HCA II, 475
hydrogen bonds, 475
X-ray crystallographic structure, 475
- Histidine biosynthesis, 941
HDH catalyzing, 941
L-histidinol dehydrogenase, 941
- Histidine cluster, 277
- Histidine residue(s), 465, 759, 765
active site, 759
zinc metal binding, 311
- Histidinol dehydrogenase (HDH), 938, 942
- anti-infectious agents, 938
enzymatic reaction catalyzed, 942
inhibitors, 937, 938, 941, 944, 945
- Histone deacetylases (HDACs)
inhibitors, 860, 861, 866
2-aminophenylamide, thiol, and
ketone, 868
anticancer agents, 870
aromatic hydroxamate, 866
Asp-His charge-relay systems, 862
belinostat, 869
cellular/tissue distribution of, 861
electrophilic ketones, 867
enzyme assays, 870
enzyme family, 860
eubacteria, 860
in humans, 860
anti-inflammatory drugs, 871
DNA methyltransferase, 870
multiprotein complexes, 860
natural product, 861–862
structures of, 862
non-sirtuin, classes, 860
Plasmodium berghei malaria, 872
Plasmodium falciparum, 872
preclinical profile, 869
protein databank (PDB), 864
structural information, 862–864
synthetic hydroxamic acids, 564–568
therapeutic applications, 868–873
cancer, 868–871
isoform selectivity profile, 872–873
therapeutic area, 871–872
tumor cell proliferation, 868
zinc binding group, 864, 873
- Histone deacetylase-like protein
(HDLP), 862
- HDAC enzyme homologue, 862
SAHA, crystal structure of, 864
TSA, binding site of, 863
- Histone(s), 859
acetylation of, 860
acetylome, 860
chromatin structure, 850–860
classes of, 859
deacetylase enzymes, 860
gene expression, regulation of, 860
nuclear proteins, 861

- posttranslational modifications, 859
 - proteins, 859
- Homo sapiens, aqueous humor formation, 140
- Homology modeling, 125
- Hormone-dependent tumors, 117
- Host cell genome, 912
- HpCA inhibitors, 31
- Hpx domain, feature of, 500
- Human carbonic anhydrase (hCA), 160, 360, 364, 406
 - adducts, 164
 - amino acid sequences, 406
 - bumethanide, 161
 - chlorthalidone, 160
 - dichlorophenamide, 164
 - family, 123
 - furosemide, 161
 - hydrochlorothiazide, 158
 - hydroflumethiazide, 158
 - indapamide, 160, 164
 - inhibition data, 364
 - inhibitors, 58, 64, 160, 163
 - activity, 65
 - inhibition, 58, 64
 - isoforms, 158
 - isoenzymes I–III, 160, 313, 314
 - activation of, 478
 - inhibitory constants, 314
 - enzymatic activities comparison, 313
 - metolazone, 160
 - quinethazone, 160
 - sulpiride, 164
 - superposition of, 164
 - weak/strong inhibitor, 163, 165
 - XIII enzymes, 274
- Human ADAMTS family, 593
- Human bicarbonate transporter genes, 417
 - cytoplasmic domain, 417
 - phylogenetic tree, 417
 - transmembrane domain, 417
- Human brain
 - Alzheimer's diseases, 480
 - carbonic anhydrase isoforms, activation of, 482–483
 - isozymes, 482
 - Parkinson's diseases, 480
- Human genome, 3, 4
 - derived proteins, 3
 - enzymes role, 4
- Human immunodeficiency virus (HIV), 911, 983
 - CD4+ blood cell, 911
 - infection, 10, 981
 - integrase inhibitors, 10
 - reverse transcriptase, 981
 - RNA level, 911
- Human immunodeficiency virus type 1 (HIV-1), 911
 - cadmium, 916
 - integrase (IN), 912
 - catalytic core domain, 924
 - D77, binding site of, 924
 - DDE motif, 912
 - drug discovery, 919
 - HHCC motif, 917
 - insolubility of, 913
 - metalloenzyme, 912
 - molecular docking, 924
 - NMR spectroscopy, 916
 - polynucleotidyl transferases, 912
 - ribbon diagram of, 915
 - structural information, 916
 - viral cDNA, 913
 - Zn²⁺ 917
 - monomeric zinc finger domain, 917
 - nucleocapsid protein NCp7, 915
 - Vif protein, 983, 985
 - axis, 986
- Human immunoglobulin A1, 736
- Human isozyme CA II, 18
 - Zn(II) ion coordination, 18
- Human (α_2 -macroglobin, glycoprotein, 501
- Human macrophage-like THP-1 cells, 944
- Human matrix metalloproteinase
 - domains, structure of, 521
 - MMP-9, role, 738
- Human proMMP-2-TIMP-2 complex, 3D
 - structure of, 497
- Human proteome, structure-based drug design, 3
- Human whole blood assay, 612
- Human zinc metalloenzymes, targeting, 8–10
- Huntington's disease, 871
- Hydration energy (HE), 384

- Hydroflumethiazide, 158
- Hydrogen bond(s), 26, 43, 45, 46, 54, 61, 62, 66, 78, 79, 98, 101, 105, 114, 360, 496, 581, 706, 759, 764, 766
- Ala160 amide nitrogen, 581
- Ala160 carbonyl, 581
- C-terminal X amino acid, 816
- cysteine switch, 496
- His143, 863
- interactions, 17, 765, 961
- network, 81
- oxygen atoms, 863
- pentacoordination of, 863
- Rap2a protein, Asn, 816
- role, 759
- sulfonamide nitrogen, 581
- sulfonamide oxygen, 581
- ZBF moiety, 26
- Hydrolytic processes, 17
- Hydrophilic binding pocket, 46
- Hydrophobic amino acid, 421
- Hydrophobic effect, ligand binding, 764
- Hydrophobic pocket, 27
- Hydroxamate(s) moiety, 537, 714
- based inhibitors, 505
- drawbacks, 714
- Hydroxamic acid, 573, 566
- in vitro* activity, 566
- Hydroxypropyl- β -cyclodextrin (HP β CD), 144
- Hydroxypyridinone tertiary sulfonamide, 582, 583
- Hypertension, 751, 777
- effective drugs, 751, 777
- risk factor, 751
- Hypoxia, 95, 96
- activable CAIs, 98
- activable prodrugs, 96
- Hypoxia inducible factor 1 (HIF-1), 312
- Hypoxia response element (HRE), 199
- Hypoxic cells, 409
- Hypoxic tumor(s), 50, 88, 201
- cDNA microarray, 202
- cells, 201
- isoform CAIX, 88
- metabolism, oncogenic alterations, 201
- Hytrosial, 921
- N*-terminal domain, 921
- structure of, 921
- Imidazolidinedione, subnanomolar activity, 835
- Iminodiacetic-hydroxamate (IDA-HA) inhibitors, 537
- MMPIs, development of, 537
- N*-substituent groups, 537
- succinyl-HA, schematic representation, 537
- Immunofluorescence experiments, 420
- Immunoglobulin (IgA) proteinases, 695
- IgA1 proteases, 737
- Immunoprecipitation experiments, 424
- IN inhibitors drug discovery, 919
- allosteric inhibitors, 921
- β -diketo acids, 919
- block HIV replication, 921
- LEDGF, 922
- multimerization process, 922
- N*-terminal HHCC motif, 921
- oligomerization process, 922
- potential targets for, 919
- viral enzyme, 919
- viral DNA integration, 922
- IN-LEDGF interaction, molecular mechanism of, 923
- IN oligomeric structure, 926
- In vitro* CA inhibition, 179
- In vitro* HCV replication, 849
- In vivo* anticonvulsant properties, 179
- In vivo* hydroxylamine, 574
- Indane ring plane, bulky substituent, 110
- Indanesulfonamides, inhibition activities of, 183
- Indapamide, 160
- Inhibitor(s), 52, 53, 55, 57, 59, 62, 66, 96, 103, 105, 107, 109, 112, 113, 121, 122, 401
- binding mode, 112
- design, implications, 972–977
- HCA II active site, 103
- heterocyclic rings, 113
- IN, drug discovery, 919
- vs.* interaction, 66
- isozyme-specific, 401
- NH moiety, 62
- organ-selective, 401
- schematic representation, 96, 103, 105, 107, 109, 121, 122
- structures, 52, 53, 55, 57, 59

- Integrin, structure-function analyses, 803
 Interglobular domain (IGD), 624
 International union of biochemistry, 4
 estradiol-3,17-bis-sulfamate, 53
 resorciny-1,3-bis-sulfamate, 53
 4-tert-butyl-1,2-phenylene-bis-sulfamate, 53
 Intraocular pressure (IOP), 139, 261, 140.
 See also Ocular hypertension
 cornea, 143
 cyclodextrin-sulfonamide complexes, 144
 glaucoma, 140
 animal model, 144
 of hypertensive albino rabbits, 145
 hypertensive/normotensive albino rabbits, 148
 dorzolamide (DZA), 148
 sulfonamide, 148
 timolol, 149
 NO donors arginine, effect of, 147
 normotensive rabbits, 142
 sodium nitroprusside, effect of, 147
 Iodophenyl ring, 896
 Isoprenylcysteine carboxymethyltransferase (ICMT), 814
 Isosteric acetohydroxamic acid, 79
 Isothermal titration calorimetry (ITC), 763, 764
 displacement method, 763
 tight binding process, 764
 Isothiocyanatosulfonamides, thioureas, 86
 Isozyme(s), 62, 83, 90, 93, 404, 407
 active site, 407
 bacterial/archaeal, 93
 characteristic feature, 407
 inhibition, 404, 407
 in vitro affinity, 83
 mammalian, 93
 membrane-associated, 90
 selective CA IX inhibitors, 88
 selective compounds, 90
 selective inhibitors, 26
 specific CA inhibitors (CAIs), 344
 Ketoconazole, 832
 antifungal 14- α -demethylase inhibitor, 832
 Kier' s first-order valence molecular connectivity index, 376
 Kier shape index, 383
k-nearest neighbor (*k*NN) analysis, 386
Lachesis muta muta venom, coagulant effect, 807
 β -Lactam, 731
 antibiotics, 731
 carba-penems, 731
 lethal action, 731
 third-generation cephalosporins, 731
 critical role, 731
 four-membered ring, 731
 L-Adrenaline complex, *see* Epinephrine
 hydrogen bonds, 481
 Laser photocoagulation, 149
 Latanoprost, 144
 Latent variables (LVs), 387
 LDADD motif, 423
 L/D Phenylalanine complexes, 480
 Leave-one-out (LOO), 383, 385
 cross-validation method, 385, 662
Legionella pneumophila, 733
 Legionnaire's disease, 683
Leishmania spp. 848
 Lens epithelium-derived growth factor (LEDGF), 922
 Lethal factor (LF), 712
 crystal structure, 712
 inhibitors, 713, 715
 design, 713
 noncompetitive, 715
 Leuc-B', neutralization, 806
 Leucurolysin-B (Leuc-B), 804–807
 amino acid sequence analysis, 807
 anti-antibodies, 805
 DMC hydrolyzing activity, 806
 inhibition stoichiometry, 805
 by α 2-macroglobulin, 805
 protein inhibitors, 803
 proteolytic activity
 inhibition, 807
 reagents effect, 804
 resistance, 805
 Leucyl aminopeptidases (LAPs), 689
 induced TNF- α 605
 mouse model, 605
 stimulated human WBA, 601

- Linker region, 491
 Lipophilic binding pocket, 942
 Lipophilicity compounds, 179, 464
 Lipophilic residue, 826
 Lisinopril, 758, 759, 767
 coordinates, 759
 lysyl moiety, 758
 phenyl moiety, 759
Listeria monocytogenes, 680
 Liver enzymes, 504
 Lonafarnib, 831
 Lowest unoccupied molecular orbital energy (Elumo), 383
 Low molecular mass (LMM), 983
 Lung disease, 157
Lysobacter enzymogenes, 693
 Lysostaphin, 693. *See also* Staphylolysin
 LytM, autolysin, 694
- Malaria parasite, 335, 339
 cell biology/biochemistry, 339–341
 genomes, 340
 introduction, 335–336
 Malonyl hydroxamates, 534
 Malta fever, 938
 Mammalian CA isozymes, 33, 278, 325
 CA I/III, 33
 CARPs, 33
 kinetics/inhibition/subcellular localization, 278
 MAPK kinases, 712
 Marimastat model, 597
 Matrix-assisted laser desorption ionization time-of-flight mass spectrometry, 683, 762
 Matrix metalloproteinases (MMPs), 5, 59, 489, 685, 721, 723, 790
 Batimastat, 526
 binding site architecture, 524
 catalytic domain, 3D structures of, 496
 catalytic domain, 497–498
 fibronectin type II (Fn II) domain, 498–499
 Hpx domain, 499
 linker region, 499
 prodomain, 496–497
 cDNA cloning, 491
 chicken enzyme, 495
 collagenases, 492–493
 conformationally restrained tertiary sulfonamides, 560
 distomer, 563
 domain structure of, 492
 3D-QSAR models, 664, 648, 663
 CoMFA technique, 663
 CoMSIA technique, 663
 on MMP inhibitors, 664
 studies, 663–668
 enamelysin, 495
 endogenous inhibitors, 501
 anticollagenase activity, 501
 human (α_2 -macroglobin, 501
 TIMPs, inhibition mechanism of, 502–504
 epilysin, 496
 extracellular matrix (ECM) molecules, 489
 family members, 490, 520
 collagens, 490
 metzincin group, 519
 found in, 489
 gelatinases, 493–494
 hemopexin domain, 495
 hypochlorous acid (HOCl), 496
 Ilomastat, 532
 imidazole group, 532
 inhibition, 723
 with sulfonylated hydroxamates, 723
 -inhibitors (MMPIs), 804
 action mechanism, 552–554
 active site and binding, 522–524
 analogous succinyl hydroxamic acid, 533
 β -arylsulfonyl-based, 577
 Batimastat, 534, 537
 benzenesulfonamido-glycylhydroxamates, SAR, 557
 benzhydryl, 532
 binding regions, 554
 bulky aromatic sulfonamides, 567–568
 compounds, generation of, 551
 crystal structures and NMR, 522
 crystallographic data, 554
 C-terminal amide group, 532
 C-terminal ketone, 533
 design, representation of, 523
 3D-QSAR models, 664
 drugs launch on market, 549

- gem*-dimethyl group/ring size, effect of, 562
- general structure of, 580
- hydroxamate inhibitors, graphical summary of, 539–540
- hydroxamate peptidomimetic, 525
- ilomastat, 530
- influencing parameters, 559
- literature, analysis of, 550
- malonic acid base hydroxamate inhibitor, 534
- Marimastat, 532, 537
- on market, 550
- mechanism-based thiirane inhibitors, 579
- metastatic disease, 569
- NMR methods, 524
- N*-*O* alkyl tertiary sulfonamido-based, development of, 572
- non-prime side, 522
- nonsubstrate-like binding mode, 534
- P'*₂/*P'*₃ groups, 530
- peptidic succinic hydroxamate inhibitors, 539
- peptidomimetic inhibitors, class of, 533
- peptidyl, 3-substituted 1-hydroxy-urea, 533
- phosphodiesterase type 4 (PDE4), 576
- prinomastat, 569
- properties, 59
- ring size and ring heteroatom, effect of, 562
- SB-3CT, 551
- secondary sulfonamido-based, 573
- stereochemical features of, 581
- structures of, 522, 539, 559, 570, 575, 577
- substrate-inhibitor interactions, 804
- succinyl analogues, 535
- sulfonamido-based, 583, 588
- sulfone-based, 576–581
- sultam hydroxamates, 570
- TACE inhibitory activity, 530, 536, 570
- tertiary *N*-*O*-alkylsulfonamido-based, 572
- tertiary sulfonamido-based, 572, 577
- therapeutic inefficacy of, 524
- TIMPs, *in vivo* effects of, 524
- X-ray crystallography, 524, 530
- ZBGs, sulfonamido-based inhibitors, 581–583
- zinc-binding group (ZBG), 520, 522, 554, 581–583
- zucchini hydroxamate, 526
- isoenzymes possess, 521
- mammalian, 493
- Marimastat, 526
- matrilysins, 494
- MMP-13/MMP-2 inhibitor, structure of, 575, 576
- N*-arylsulfonamide-based inhibitor, 538
- NMR analysis, 523
- nomenclature, 490–492
- numbering system, 490
- peptidic/nonpeptidic inhibitors, 535
- iminodiacetyl hydroxamate inhibitors, 537–539
- N*-sulfonyl aminoacid hydroxamate inhibitors, 539
- succinyl hydroxamate inhibitors, 535
- peptidomimetic hydroxamate inhibitors, 526
- malonyl hydroxamate inhibitors, 534–535
- succinyl hydroxamate inhibitors, 526–534
- phosphonamide inhibitors, binding mode, 610
- physiological levels of, 549
- protein class I-IV, 790
- QSAR studies, evaluation, 660
- S1' pocket, 565
- short-pocket, 724
- site cleft, activity of, 521, 498
- stromelysins, 494, 495
- subgroup, 495
- substrate specificity, 499
- multidomain metalloproteinases, 500
- noncatalytic domains, 500
- proteins/peptide substrates, 499
- succinyl hydroxamate inhibitors, 527
- enzyme, 528
- structure-activity relationship (SAR), 527–528
- succinyl inhibitors, structure of, 526
- Batimastat BB-94, 526
- Marimastat BB-2516, 526

- Matrix metalloproteinases (*Continued*)
- sulfonyl-based compounds, design of, 554
 - 1OV0 complex, 556
 - CGS 27023A analogues, 556
 - secondary sulfonamido-based, 573–576
 - sulfonamides, 554
 - sulfonylated, 556
 - tertiary sulfonamido-based, 555
 - ZBGs, 555
 - synthetic inhibitors of, 504–505
 - thiazepine, 564
 - in vitro* inhibitory profile, 564–565, 567
 - ZBG, modification of, 567
 - tissue endogenous inhibitors, 521
 - transmembrane proteins, 494
 - X-ray crystallography, 532
- Matrixins, *see* Matrix metalloproteinases
- Maximal electroshock seizure (MES)
- model, 454
 - mice, 182
- MDCK
- CA IX cells, 229
 - immunofluorescence analysis of, 229
 - pH_e, values of, 230
 - fluorescent derivatives, 229
- Membrane-anchoring hydrophobic sequence, 756
- Membrane-associated isozyme, HCA IV, 67
- Membrane-bound isozymes, 15
- Membrane-permeant compounds, 423
- Mercaptan-thermolysin complex, 739
- Merck inhibitors, based on, 828
- Metal-bound hydroxide ion, 78
- Metal-bound water ligands, 29
- Metal chelators, 680, 682, 683, 688
- DTPA, 688
 - EDTA, 680, 682, 683, 688
 - EGTA, 680, 682, 683
 - 1,10-phenanthroline, 683
- Metal cofactors, catalytic role of, 912
- Metallo-carboxypeptidases, 689
- Metallo-dependent hydrolase, 957
- Metalloenzymes, 4, 6, 325, 336. *See also* HDH
- role of, 8
 - zinc, 10
- Metallo-β-lactamases, 732, 733
- classes, 732
 - Zn²⁺ ligands, 732
 - X-ray crystallography, 732
 - zinc binding sites, 732
- Metalloprotein(s), 4, 9
- high-resolution X-ray crystal structures, 4
 - metalloenzymes, 4, 6, 7, 8, 73
 - carbonic anhydrase, 8, 73
 - catalytic zinc binding sites, 7
 - chloride-dependent, 751
 - role, 8
 - structural zinc binding sites, 6
 - metallopeptidase, 733
 - Legionella pneumophila*, 733
 - metal ion chelators, 733
 - MspA, 733
 - ProA, 733
- metalloprotease (MPRs), 677, 680, 684, 721, 790
- active site, 710
 - activity inhibitors, 711
 - BoNT serotype A light chain (BoNT/A LC), 711
 - cysteine-rich domain, 790
 - high-throughput assay, 711
 - inhibitors, 724, 892
 - M9 family, 684–686
 - thermolysin family (M4), 680–684
- metalloproteinases (MMPs), 490, 505, 595, 591, 733, 789, 801
- ADAMs, 789, 795
 - bacterial serralysin, 491
 - cancer therapy, 579
 - cDNA cloning, 490
 - cysteinyll residues, 795
 - domain, HEXGH sequence, 592
 - fragilysin, 688
 - hemorrhagic toxins, 801
 - N-terminal inhibitory domains, 503
 - SVMPs, 795
 - types of, 578
 - Vibrio cholerae*, 733
 - zinc enzymes, 4
- Methanobacterium thermoautotrophicum*, 26, 291, 327
- canonical subclass CA (Cab), 291
 - DHOase, 956
 - enzyme, 27, 292
- Methanosarcina thermophila*, 286, 325
- γ-class Cam, 287, 288
 - active site, 287
 - catalytic mechanism, 288

- Methazolamide (MZA) complex, 140, 370, 452–454
 bidentate binding, 452
 coordination abilities, 452
 inhibition effect, 370
 ionization equilibrium, 452
 monodentate binding, 452
 Ni(II)/Zn(II) complexes, 454
 structural/biological characteristics, 453
 X-ray crystallography, 452
- Methotrexate therapy, 691
- Methylsulfone COX-2 inhibitors, chemical structures, 258
- Metolazone, 160
- Metzincins, 491
- Microtiter plate assay, 422
 binding assay, 420, 421
 GST-AE1Ct, 421, 422
- Middle cerebral artery occlusion (MCAO), 888
- Midwest center, structural genomics, 964
- Mitochondrial respiratory oxidation, waste product, 416
- Molecular dynamics (MD) simulations, 682
- Molecular field analysis (MFA) model, 667
- Molecular interaction fields (MIFs), 648
- Molecular signaling processes, isozymes involved, 33
- Monocarboxylate transporters (MCTs), 431
- Monodentate ligand, 442
- MonoMac-6 cells, 597
- Mononuclear metal center, 965
- Mouse CA (mCA)
 inhibition data, 275
 isozymes, 274
 sulfonamide inhibitors, 275
 XV, inhibition constant, 279
- Mouse proximal convoluted tubule cell line (mPCT), 426
- MPR(s), 706, 713, 726
 glutamate residue, 706
 HEXXH motif, 713
 histidine residues, 706
 inhibitors, ChC inhibitory properties, 723
 serrallysin, 687
- Multiple linear regression (MLR)
 techniques, 660, 661, 647
 analysis (MLRA), 383
 QSAR models, 647
 structure–activity relationships, 660
- Multi-zinc-containing enzymes, cocatalytic zinc sites, 8
- Murine leukemia virus (MLV), 984
- Musculo-skeletal syndrome (MSS), 569
- Mutagenesis, carboxylate docking, 758
- Mycobacterium tuberculosis*, 289
 Rv1284 29, active site structures, 291
 Rv3588c CA, 295, 327
 crystal structure, 295
- N*-acetylaspartate (NAA), 881
- N*-acyl-homoserine lactone (AHL) signal molecules, 684
- Na⁺/H⁺ exchangers (NHEs), 429
- N*-alkyl-substituted hydroxamic acid, *in vitro* activity, 566
- NBCe1-associated current (I_{NBC}), 427
- NBCe1, 428
 CA II-enhanced activity, 428
 expressing oocytes, 428
- NCp7, zinc ion of, 926
- Nematode carbonic anhydrases, 310
Caenorhabditis elegans carbonic anhydrases, 310–314
 characterization, 312
 introduction, 301
 parasitic nematodes, 314–315
- Nephron, 156
- Neural endopeptidase (NEP), 774
- Neural networks (NN), 647
- Neurodegenerative diseases, 871
- Neurological disorders, 171, 177
 clinical medicine, 171
 convulsions, 171
 epilepsy, 9
 treatment of, 93
- Neuron seizures, causes of, 171
- Neuronal excitability, 184
 alkalosis, 174
 bicarbonate anion, 184
- Neuronal transmission, *see* GABAergic excitation
- NHE1, 430, 431
 phosphorylation, 430, 431
 transfected cells, 430

- ¹⁵N-heteronuclear single-quantum correlation spectra (¹⁵N-HSQC), 661
- N*-hydroxyformamide, *see* Reverse hydroxamate
- N*-hydroxysulfamide(s), 61, 62
 - CA inhibitory activity, 61
 - inhibitory activity, 62
- N*-hydroxyurea, 60, 533
 - hydroxamate functionality, 78
 - inhibition study, 60
 - interaction b/w inhibitors, 60
- Nitrogen atoms, 475
- N/K-Ras-driven tumors, 840
- N*-L-histidinylphenylsulfonil hydrazide
 - histidinol dehydrogenase inhibitors, 945
- No binder inhibitors (NBIs), 552
- Nonclassical QSAR methods, 661–663
- Non-COX-2-dependent mechanism(s), 261, 265
- Nonprotein zinc ligand, 19
- Nonpyrophosphate substructures, 837, 839
- Nonradioactive/radioactive iodine atoms, 891
- Nonspecific dipeptidase, *see* Angiotensin converting enzyme (ACE)
- Nonsteroidal anti-inflammatory agents, 255
 - celecoxib, 255
 - rofe-coxib, 255
 - valdecoxib, 255
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 99, 100, 256–259
 - cardiovascular side effects, 260
 - cyclooxygenase inhibition, 256–259
 - nonspecific, 259
- Nonsulfonamide COX-2 inhibitor SC-560, 262
- Nonthiol farnesyltransferase inhibitors, 827
 - 4-aminopiperidine scaffolds, 827
 - cyanobenzylimidazole cysteine replacement, 827–827
 - tetrahydroisoquinoline carboxylic acid, 827
- Nonthiol prenylation inhibitors, 830
 - benzoylleucine substructure, 830–831
 - benzoylmethione substructure, 830–831
- N*-terminal domain, 504, 915
 - Can2, role of, 331
 - carbamylation of, 504
 - histidine, 915
 - membrane domain, 430
 - proteoglycan-like domain, 424
 - ribbon diagram of, 918
 - TIMPs, amino group of, 504
 - transmembrane domain, 495
 - zinc ion, 915
- Nucleosome, 859
- Nucleotides, 951
 - de novo* pathway, 951
 - salvage pathways, 951
- Numbness, 140
- Obesity, 241
 - antiobesity carbonic anhydrase inhibitors, 246
 - drug design of, 246
 - topiramate (TPM), 246
 - zonisamide (ZNS), 248
 - antiobesity drugs, 242
 - orlistat, 243
 - phentermine, 242
 - rimonabant, 243
 - sibutramine, 243
 - carbonic anhydrases, treatment of, 244
 - energy expenditure, 241
 - energy intake, 241
 - fatty acid biosynthesis, 245
 - carbonic anhydrase isozymes, role of, 245
 - food and drug administration (FDA), 243
 - risk factor, 241
- Ocular hypertension, 140
- Oligoethylene glycol units, 84
- Oligosaccharide glycoproteins, 761
 - oligonucleotide binding (OB), 502
- Organic phosphonates/phosphates, inhibition constants, 67
- Organ-selective inhibitors, 40
- Orphan drug, benzolamide, 457
- O*-sialoglycoprotein endopeptidase, 693
- Osteoarthritis (OA), 624
- Ovarian epithelial cancer (EOC) cells, 594
- Oxazolidine ring, 898
- Oxyaminic oxygen, 573
- Oxygen species, 496

- Pappalysins metalloproteinase, 591
 pregnancy-associated plasma protein-A1 (PAPP-A1), 591
 pregnancy-associated plasma protein-A2, 592
- Paramagnetic systems, 53
¹H-NMR spectroscopy, 53
- Para*-substituted phenyl hydroxamic acids, 865
- Parkinson's disease, 717
- Partial least squares (PLS)
 algorithms, 648
 coefficients, 662
 FFD-based variable selection, 665
 model, 665
 regressions, 661
- Partition coefficient, 376
- Pathogenic microorganisms, 736
- Pearson cross-validated square correlation, 384
- Peptide inhibitors, 824
- Peptide-mimetic backbone, 595
- Peptidic succinic hydroxamate inhibitors, 525
 generic structure for, 525
 MMP inhibitors, 539
- Peptidomimetic hydroxamate inhibitors, 526
 malonyl hydroxamate inhibitors, 534–535
 succinyl hydroxamate inhibitors, 526
 batimastat and marimastat, 526–527
 isosteric analogues, 533–534
 P'_2 - P'_3 amide bond, 532–533
 variations, 527–532
- Peptidomimetic inhibitors, 824, 825
- Peptidyl-dipeptidase A, *see* Angiotensin I converting enzyme
- pH-dependent electronic absorption spectrum, 686, 722
- Pharmacoforic model, 613
- Pharmacological agents, 33
 antibacterials, 33
 anticonvulsants, 33
 antifungals, 33
 antiglaucoma drugs, 33
 antiobesity agents, 33
 development of, 31
 drug design, 33
 enzyme binding capacity of, 40
- Phentermine, catecholaminergic drug, 242
- Phenyl, carboxylic acid group, 893
- Phorbol 12-myristate 13-acetate ester (PMA) stimulation, 595
- Phosphinate inhibitor, structure, 740
- Phosphinic acid, 968
- Phosphinic inhibitor, RXPA380, 774
- Phosphoenolpyruvate (PEP) carboxylase, 32
- Phosphonamide
 derivatives, 609, 611
 design, 611
in vitro profile, 609
 MMP inhibitors, structures, 608
- Phosphonate inhibitor, 581
 enantiomers of, 581
 MMP-8 inhibitor, 582
 structure of, 582
- Ping-pong mechanism, 286
- Pisum sativum*, 26, 289
 B-CAs, 26
 CA, mechanism, 290
 enzyme, 294
 structure, 26
- Pivaloyl derivative, coordination properties, 448
- PKA phosphorylation site, 427
- Plasma membrane expression, 421
- Plasma proteins, 801, 808
 Fg, 801
 FN, 801, 802
 digestion pattern, 802
 role, 802
 proteolytic degradation, 808
 protease inhibitors (PIs), 675, 676, 804
 α 2-macroglobulin, 804
- Plasma vitronectin, 802
 blood clot formation, 802
 platelet stimulation, 802
- Plasmodium berghei*, 845
- Plasmodium falciparum*, 31, 843
 CA isozymes, 341
 α -CAs, 31
 inhibitory properties, 347
 malarial parasite enzyme, 31
PfCAI gene encoding, 342
 sulfonamides, 346
- Plasmodium* species, 339
- Plastic lenses, implantation of, 149

- Platelet aggregation inhibitors, 790
 cysteine-rich domains, 790
 noncatalytic disintegrin-like, 790
- P*-methoxyphenyl group, 566
- Porcine TACE (pTACE) assay, 601
- Porphyridium purpureum*, 26, 325
 enzyme, 291, 292
 noncanonical subclass, 292
- Porphyromonas gingivalis*
 amino acid sequence of, 964
 DHOase, structure, 956, 964
- Potential drug targets, 731
 bacterial zinc peptidases, 731
 metallo- β -lactamase, 731
- Prenylated peptide, thioether of, 815
- Prenyl transfer reaction, schematic
 representation of, 822
- Prinomastat, 551, 561
- Procollagen C-proteinase (PCP), *see* Bone
 morphogenetic protein-1
- Prokaryotic β -CA, catalytic mechanism, 28
- Pro-MMPs activation, 553
 substrate hydrolysis, catalytic mechanism
 of, 553
- Prostacyclin biosynthesis, 260
- Prostaglandin (PG), 257
 biosynthesis of, 257
 cyclooxygenase enzyme, 256
- Prostate cancer, 896
 positron emission tomography (PET), 896
 SPECT imaging agents, 896
 urea-based PET, 896
- Prostate-specific antigen (PSA), 886
 androgen receptor (AR), 886
- Prostate-specific membrane antigen
 (PSMA), 9, 881
 androgen regulation, 886
 binding molecules, 902
 binding molecules, 902
 cDNA sequences, 885
 expression, 886
 homodimers, 902
 macromolecular, ligands, 901
 ProstaScintTM 902
 protein levels, 886
 RNA aptamers, 902
 R5-XC1 peptide, 902
 small interfering RNAs (siRNAs), 903
 tumor target specificity, 898
 sixty minute image, 898
- Protease activity, 705, 706
 H chain, 706
 B-trefoil fold, 706
 lectin-like domain, 706
 L chain, 706
 critical role, 706
- Protease inhibitors (PIs), 675
- Protein, 795
 3D folding, 676
 farnesylation, pathogenic fungi, 849
 functional activity, 795
 inhibitor interactions, 121
 ligand interaction(s), 662, 663
 metal partnership, 439
 proteases (PRs), 675, 686, 690, 706
 fragments, X-ray crystal structures, 706
 introduction, 675–680
 M12 family, 686–688
 M19, M20, M22, M23, M26, and M27
 families, 691–695
 proteinase-proteinase inhibitor
 equilibrium, 677
 protein binding interaction, 5, 707, 814
- Protein kinase C (PKC), 425
 broad-spectrum, 425
 chelerythrine (CHE), 425
 phosphorylation site, 426
- Protein prenyl transferases, 813
 farnesyltransferase (FTase), 813
 geranylgeranyltransferases-I (GGTase-I), 813
 geranylgeranyltransferases-II (GGTase-II), 813
- Proteins termination, 814
 CaaX sequence, 813
 posttranslational modification of, 814
 GGTase-I, 813
- Proteoglycanase, 490
- Prothrombotic risk, 259
- Proton pump inhibitor (PPI), 359
- Proton shuttle, 440
- Proton transfer process, 19
- Prototypical matrix metalloproteases, 596
- Pseudolysin, 682
- Pseudomonas aeruginosa*, 681, 687
- Pseudomonas fluorescens*, 956
- Pseudomonas keratitis*, rabbit model, 726
- Psoriasis, skin disease, 871

- Purine auxotroph, 341
- Putative carbonic anhydrases, sequence alignment, 308
- pVHL tumor suppressor protein, 199
- Pyrimidine biosynthetic pathway, 344, 350
- Pyrrolidione based inhibitor, 828
- Pz peptidase, 735, 736
 - critical regions, 735
 - amino acid sequence alignments, 735
 - Geobacillus collagenovorans*, 736
 - X-ray data, 736
 - homologues, 736
 - Pro-Leu-Gly-Pro-D-Arg, 734
- Quantitative structure-activity relationship (QSAR) models, 376, 383, 384, 386, 387, 388, 391, 392, 393
 - analysis, 375, 383
 - binary, 384, 385
 - BCUT improvement, 385
 - vs. SVM, 386
 - variable selection method, 385
 - CA isoenzyme, 384
 - 2D, QSAR equations, 384
 - 3D, 388, 392, 393
 - CA inhibitors scaffold, 391
 - docking-based, 391
 - Golpe software, 392
 - test sets, 392
 - development, 662
 - using LUDI scoring functions, 662
 - using MOE scoring functions, 662
 - hCA I/II, 383
 - hCA XIV inhibitors, 384
 - introduction, 647–648
 - ligand binding, 661
 - ¹⁵N and ¹H amide chemical shift, 661
 - MMP inhibitors, 649–659
 - parameters, 648
 - predictivity, 383, 392
 - quality, 647
 - quantum topological molecular similarity (QTMS) approach, 387
 - studies, 376
 - 3D-studies, 388
 - nonclassical, 385
 - topological indexes, 376
 - validity, 383
- Quantum mechanical parameters, 383
- Quantum topological molecular similarity (QTMS)
 - quantum chemical topology (QCT), 387
- Quinethazone, 160
- Quorum-sensing (QS) systems, 684
- R115777, 833
 - crystal structure of, 833
 - like inhibitors, 833
- Racemic mixtures, 740
- Randic connectivity index, 376
- Rap2a protein, 816
- Ras converting enzyme 1 (Rce1), 814
- Rate-limiting proton transfer, 290
- Rational drug design, 751
- Receptor surface analysis (RSA)
 - methodologies, 667
- Recombinant mCA XV, 279
- Renal carbonic anhydrase, 265
- Renal physiology, 155
- Renin-angiotensin-aldosterone neurohormonal system (RAS), 767
- Renin-angiotensin system, 767–768
- Reprolysin family, SVMPs, 789
- Retinal photoreceptors, 150
- Reverse hydroxamate, 596
- Rheumatoid arthritis (RA), 519, 603
 - patients, human synovium tissue explants, 611
- RIKEN structural genomics/proteomics initiative, 964
- Ring system, 40, 46
- RNA, 310, 983
 - mediated interference, 310
 - protein complexes, 983
- Saccharin (HSAC) complexes, structural / biological characteristics, 463
- Saccharomyces cerevisiae*, see Budding yeasts
- S-acyl-2-mercaptobenzamide thioesters, chemotype of, 927
- SCH, 66336, 832
 - benzocycloheptapyridyl tricycle of, 832
 - crystal structure of, 832
- Schiff bases, 54, 407
- SDS-digested freeze-fracture immunogold labeling, 367

- SDS-PAGE, 753, 793, 797
analyses, 791, 802
- Second-line quadruple therapy, 359
- Selective COX-2 inhibition, 259
- Selective enzyme expression, *see* Hypoxia
- Semi therapeutic collagen-induced arthritis model, 611
- Serine protease inhibitors, 676, 738
- Serratia proteamaculans*, 687
- Sezolamide/dorzolamide complexes, structural/biological characteristics, 462
- Shield matrix, 726
- Signal transduction pathways, 618
- Single chain protoxins, 705
- Single photon emission computed tomography (SPECT), 892
- Site-directed mutagenesis, 965
- Small-molecule drugs, 8
- Snake venoms, 789, 795, 802, 807
immunological reactivity, 807
Mr hemorrhagins, 795
proteins, 802
- Solid-phase binding assays, 420, 430, 428
ELISA, 428
SPR, 428
- Solute carrier 4A family (SLC4A)
proteins, 416, 422
Cl⁻/HCO₃⁻ exchange activity, 422
- Solute carrier 26A family (SLC26) proteins, chloride-losing diarrhea, 417
- Spin-labeled inhibitors, 232
EPR measurements, 233–235
EPR signals of, 234
hCA II, EPR signals of, 235
structures of, 232
- Stage-dependent α -carbonic anhydrase activity, 342
- Standard deviation of errors of prediction (SDEP), 385
- Staphylolysin, 693, 694. *See also* Lysostaphin
- Steering effect, 85
- Steroid sulfatase (STS), 115
estrone-3-sulfate (E1S) to estrone (E1) catalysis, 115
inhibitors, 48, 50, 117
antitumor properties, 50
bis-sulfamate, 48
coumarin sulfamate, 48
667COUMATE, 48
EMATE, X-ray crystal structure, 48
sulfamate-based, schematic representation, 116
role, 115
- Stoichiometry, PKA-induced shift, 427
- Strand transfer inhibitors, 920
raltegravir, structure of, 920
- Streptococcus pneumoniae*, 736
disease caused, 736
immunoglobulin A1 proteinase, 736
zinc metalloproteases, human immunoglobulin A1, 736
- Streptomyces griseus* aminopeptidase (SGAP), 677
- Structural classification of proteins (SCOP) database, 957
- Structure-activity relationship (SAR), 346, 600
approaches, 660
Bayesian-regularized genetic neural network (BRGNN), 660
MLR, 660
data, 49
- Structure-assisted drug development, 331
for Can2/NCE103, 331–332
- Structure-based virtual screening, 622
- Structure-stabilizing motifs, 5
- Suberoylanilide hydroxamic acid (SAHA), 864
antiproliferative activity, 867
structures of, 865
- Substrate protein, Ca₁a₂X tetrapeptide of, 816
- Sugar-derivative moieties, 123
- Sulfamates, 25, 45, 51, 178
bianionic species, 45
CA inhibitor, 25
binding, 25
EMATE, 25
inhibition data, 51
methyl moiety, 48
- Sulfamides, 55, 61
adduct, 53
hCA II-inhibitor, space fill/stick model, 54
analogue, 122, 404
X-ray crystallography, 405

- inhibition, 56
- N,N*-disubstituted, 55
- N*-substituted, 55
- X-ray crystal structure, 53
- Sulfamoyl moieties, role, 93–95
- 4-Sulfamoyl-phenyl-ethyl (SPE) group, 538
- Sulfanilyl-derived compounds, 275
- Sulfonamides, 22, 41, 60, 63, 87, 101, 108, 159, 178, 225, 363, 402, 407, 408, 409, 439, 709
 - aliphatic/aromatic, 407, 709
 - aromatic/heterocyclic, 60, 363, 365–367, 408, 440
 - bicyclic, 108
 - α -CA inhibition mechanism, 22
 - cationic, structure, 408
 - CGS 27023A, 572
 - as complexing agents, 440
 - containing CA inhibitors, 31, 264
 - COX-2 inhibitors, 42, 255, 265
 - chemical structures, 258
 - clinically used, 42
 - derivatives, 19
 - CA inhibitory properties, 19–21
 - drug, 139, 157
 - physiologic effects, 157
 - as dual carbonic anhydrase inhibitors, 439
 - fluorescent, 87, 409
 - function, 41
 - inhibition data, 402
 - inhibition properties of, 225
 - inhibitors, 24, 43
 - X-ray crystallographic structures, 43
 - isozymes, inhibition data, 159
 - metal complexes, 439, 441
 - methylene carbon atom, 573
 - moieties, 40, 43, 710
 - aliphatic/aromatic, 710
 - motif, 67
 - phosphoryl structures, 63
 - thiophene/thiadiazole derivatives, 101
 - tumor cell growth inhibitory properties, 409
 - type of, 572
- Sulfonamido-based MMPI, 555
 - secondary sulfonamido, 573
 - tertiary sulfonamido, 555
 - CGS 27023A analogues, 556
 - conformationally restrained tertiary sulfonamido-based hydroxamates, 560
 - N-O* alkyl sulfonamides, 555
 - reversed tertiary sulfonamido-based hydroxamates, 571
- Sulfonamido-based thiomorpholines, structure, 612
- Sulfonamido moieties, 57, 58
 - bulky substituents, 57
- β -Sulfone hydroxamic acid structure, 613
- α -Sulfone piperidine structure, 613
- Sulfonylated amino acid hydroxamates, catalytic zinc ions, 59
- Sulfonylhydrazide moiety, 945
- Sulphone-based 3,3-piperidines, structure, 612
- Superoxide dismutases (SOD), 8
- Support vector machines (SVM) model, 386, 387
 - leave-one-out (LOO) cross-validation accuracy, 387
- Surface plasmon resonance (SPR), 428
- SVMPs, 789, 791, 798, 790, 802, 805, 806
 - anti-leuc-B antibodies, cross-reactivity, 806
 - fibrinolytic effect, 798
 - hemorrhagic effect, 798
 - inhibitory effects, 802
 - on oxidized insulin B-Chain, proteolytic specificity, 798
- Synaptic vesicles, 709
 - protein, 707
- Synaptobrevin proteolysis mechanism, 707
- Synergetic inhibition effect, 441
- Synthetic hydroxamic acids, 864
 - HDAC inhibitors, 864
 - suberoylanilide hydroxamic acid, 864
- Synthetic matrix metalloproteinase (MMP) inhibitors, 552
 - action mechanism, 552–554
 - classification of, 552
- Szeged (Sz) indexes, 383
- Targeting Zn²⁺ ion, 925
 - DNA, 925
 - IN-specific inhibitors interfere, 925
 - N*-terminal domain, 926
 - structural peptidomimetic inhibitors, 926
 - zinc ejectors, 926

- TBLASTN, bioinformatics approach, 342
t-butyloxycarbonylamido ligand, 447
Tetanus neurotoxin (TeNT), 705, 706, 708
 Clostridium tetani, 705
 proteolytic activity, active site, 708
 proteolytic substrate, 706
 serotypes, 705
 therapeutic agents, 709
 VAMP-2 cleavage, 708
Tetrahydroquinolines, 845
Thalassiosira weissflogii CA (TWCA1), 29
 native PAGE, 29
 radiolabeled, 29
Therapeutic arthritis research and
 gastrointestinal event trial
 (TARGET), 260
Thermolysin, 756, 765
 active site residues role, 765
 catalytic activity, 804
 catalytic mechanism, ACE
 based, 766–767
 structures, 756, 765
Thiadiazole ring, structure, 461
Thiazepine, *in vitro* inhibition, 567
Thiazide diuretics, 155
Thienothiopyran sulfonamide
 complexes, 461–462
Thiirane-containing inhibitors, 579
 mechanism of action, 580
Thimet oligopeptidases (TOPs), X-ray
 crystallographic analysis, 736
Thioesters mechanism, 927
Thioetheral group, insertion of, 559
Thiol
 based derivatives, 616
 based GCPII inhibitors, 893
 modifying reagents, 618
 4-aminophenylmercuric acetate, 618
 octylthioglucoside, 618
 sulfone-based selective TACE
 inhibitors, 617
Thiophene ring, 462
Three domains spanning residues, schematic
 diagram of, 912
Thrombospondin motifs, 593
Thrombotic cardiovascular events, 260
Thromboxane synthase
 prostaglyclin balance, shift, 259
 prostaglandins, 256
Tissue inhibitors of metalloproteinases
 (TIMPs), 500, 519, 593
 superimposition of, 503
Titration experiments, 805
Topiramate (TPM), 123, 181, 182, 246,
 405
 adducts structure, 405
 binding mode, schematic
 representation, 47
 chemical structures, 246
 GABAergic transmission, 182
 hCA II, active site region, 247
 isomer, 48
 structural analogue, 123
 sugar sulfamate, 246
 sulfamate fructopyranose, 181
 sulfamate moiety, 246
 sulfamide analogue, 25, 55, 405
 binding, 25
 endocyclic sugar oxygen, 405
 structure/inhibitory activities/schematic
 representation, 405
 X-ray crystal structure, 55
 ZNS chemical structures, 246
TopoTarget, 865
Transferrin receptor (TfR), 689, 882
Transforming growth factor β (TGF- β),
 881
Transmembrane tumor-associated isozyme,
 HCA IX, 65
Trichostatin A (TSA), 861
Tricyclic benzocycloheptapyridine
 inhibitors, 831
Trimeresurus flavoviridis, 795
Trypanosoma brucei, 843, 846
 farnesyltransferase (*TbFTase*), 846
Tumor-associated CA isoforms, IX/XII,
 465
Tumor-associated isozyme, 49, 63, 86, 98,
 409
 CA IX, 409
 hCA IX, 86
Tumor necrosis factor- α converting enzyme
 (TACE), 529, 578, 593–596, 598
 docking model, 611
 downstream domains, 595
 cysteine rich, 595
 disintegrin, 595
 inhibitors, 596, 597, 604, 617

- cyclopropyl hydroxamic acids, 613–615
- novel nonhydroxamate inhibitors, 615–617
- peptidomimetic/sulfonamide hydroxamate CGS27023A, 596
- phosphonamido-based TACE inhibitors, 608–610
- semirigid succinamides/cyclic amides, 599–608
- succinyl hydroxamate marimastat, 596
- sulfonamido-/sulfone-based TACE inhibitors, 611–613
- γ -lactam inhibitors, 599
- prodomain, properties, 618
- properties, 618
- Tumor necrosis factor (TNF), 529
- mediated inflammatory autoimmune diseases, 612
- related activation-induced cytokine (TRANCE), 594
- Tumor-specific drug, 96, 599, 618
- Two-metal-ion catalysis mechanism, 913
- Two-prong approach, 86, 465
- Two-prong inhibitor, interactions, 85
- Ubiquitin-proteasome pathway, 983
- Ubiquitous proteases, characterization, 10
- Ubiquitous zinc enzymes, carbonic anhydrases, 15
- Urease, role, 360
- Valproic acid (VPA), 862
- Valproyl/adamantyl moieties, aromatic/heterocyclic sulfonamides, 181
- Vancomycin, 738, 739
- D-alanyl-D-alanine dipeptidase, resistant enterococci, 738
- resistance, 739
- VanX gene, 739, 692
- aggregates, 739
- D-alanyl-D-alanine dipeptidase inhibition mechanism, 740, 741
- inhibition constants, 739
- inhibitors, 693
- X-ray crystallographic analysis, 739
- van der Waals interactions, 43, 112, 115, 406
- residues, 226
- Vasopressor angiotensin II (AGII), 751
- Venom glands, 796
- Venom peptides, structure-activity studies, 752
- Vesicle-associated membrane protein (VAMP), 706–708
- cellubrevin, 706
- VAMP-1, 706
- VAMP-2, 706
- SNARE recognition motif, 707
- Vibrio cholerae* strains, 681, 733
- cholera, 733
- hemagglutinin/protease (HAPA), 733
- 3D structures, 734
- homology modeling, 734
- Zn-metalloprotease, 733
- Vioxx gastrointestinal outcomes research (VIGOR) trial, 260
- Viral DNA, 3'/5'-end, 913
- Voltage-dependent sodium channels, dysfunction of, 171
- Vorinostat, *see* Suberoylanilide hydroxamic acid
- Whole blood assay (WBA), 596
- Wild-type CA II cDNA, 422
- Wild-type orthorhombic crystals, 963
- X activator from *Vipera lebetina* (VLFXA), 790
- Xenograft model, tumor growth inhibition, 867
- Xenopus* oocytes, 422, 427, 428, 431, 432
- MCT1 expression, 431
- transcription factor III A (TFIIIA), 916
- X-ray absorption spectroscopy, 29
- X-ray crystallography techniques, 125, 440, 442, 446
- data, 63
- X-ray structure, S1' cavity analysis, 566
- Zinc, 7, 815
- amphoteric properties, 7
- binding domains, enzyme proteins, 915
- binding histidine residues, 956, 958
- binding motif, 694
- bound hydroxide, 287, 293
- bridging ligands, 958
- complex structure, 452

Zinc (*Continued*)

- containing enzymes, 9
 - dimeric enzyme, 291
 - diversity, 9
 - importance, 9
- coordination sphere, 226, 2277
 - amino acid residues, 226
 - stereoview of, 227
- ejecting compounds, 926, 927
- endopeptidases, 591
- enzymes, biomedical research, 11
- finger-containing proteins, biological functions, 5
- hydroxide mechanism, 27
- metalloendopeptidases, 489
- metalloproteases, 683, 915
- pentacoordination of, 863
- prenyltransferase's activity, 815
- PRs, exopeptidases, 677
- sites, 6
 - protein interface, 6
 - role, 6
- Zinc binder inhibitors (ZBIs), 552
- Zinc binding functions (ZBFs) model, 24, 40, 41, 67
- Zinc-binding groups (ZBGs), 41, 123–126, 505, 525, 551
 - exploration, 41
 - HDAC inhibitors, 864, 873
 - hydroxamate inhibitors, 525
 - hydroxamic acid, 873
 - methyl ketone, 873
 - natural product apicidin, 867
 - piperidine spirocycle adjacent, 578
 - sulfonamido-based inhibitors, 581
 - triazolyl, 583
 - trifluoromethyl, 873
- Zinc metalloproteins, 9, 10, 375, 399
 - ADAM inhibitors, 9
 - angiotensin-converting enzyme (ACE), 9
 - carbonic anhydrases, 375, 399
 - histone deacetylase, 9, 859, 860
 - identification, 10
 - medical relevance, 9
 - metalloproteinases, *see* Metzincins
 - MMPs inhibitors, role, 9
 - prostate-specific membrane antigen (PSMA), 9
 - protein farnesyltransferase, 9
 - zinc endopeptidases, 9
- Zonisamide (ZNS), 248
 - antiepileptic drug, 248
 - HCA II, active site region, 249
 - X-ray crystal structure, 248