

Index

a

Acacia willardiana 160
N-acetyl galactosamine (GalNac) 321, 359
acid-labile alkyl esters 39
acid-mediated formation of pGlu 50
acidolysis 35
actinomycin D (Dactinomycin[®]) 259, 260
acyclic compounds 135, 136
acyclic triazole peptidomimetics 113–121
– *cis*-amide bond peptidomimetics. 120
– conditions for 120
– exchange of dipeptide fragment with 115
– peptidomimetic inhibitors of HIV-1
 protease 114
– regioselective, sequential Cu-Huisgen
 synthesis of pseudo-nona-
 peptidomimetics 118
– solid-phase Cu-Huisgen backbone and side-
 chain cycloaddition 114
– solution-phase synthesis of triazole
 trimer 116
– synthesis of
– 1,4-and 1,5-triazole dipeptide replacements
 in native protein 119
– β -turn-inducing 1,4-triazole
 peptidomimetics 115
alicyclic β -amino acids
– five-membered alicyclic β -amino
 acids 175–179
– amipurimycin 176
– antifungal activity 177
– cispentacin 176
– structure–activity relationship 178
– synthesis 179
– *in vitro* activity 180–182
– medicinal chemistry 175

– six-membered alicyclic β -amino acids
 179–186
–– structure–activity relationship 185
–– synthesis of tilidine 184
–– tachykinin NK1 receptor antagonists
 185
4-alkylGlu analogs, binding affinities 165
4-alkylidene Glu analogs, binding
 affinities 166, 167
allophenylnorstatine (Apns) 214
Alzheimer's disease 220
Amanita muscaria 160
Amanita pantherina 160
Amanita strobiliformis 160
amastatin 209
 ω -amido group of Asn and Gln 49
– acid-mediated formation of pGlu 50
– ω -amide protections (selected examples) 50
– nitrile and aspartimide from unprotected
 Asn 49
Z-amino acid azides, from methyl esters 41
amino acid-based dendrimers
– peptide dendrimers applications
–– as antimicrobial agents 502–504
–– as DNA/RNA delivery vectors 507–512
–– initial efforts on MAPs 502
–– ion sensors and MRI contrast agents
 505–507
–– as protein/enzyme mimics 504, 505
– peptide dendrimer synthesis 491–502
–– glutamic/aspartic acid, proline, and
 arginine dendrimers 494–497
–– grafted on PAMAM 500–502
–– MAPs synthesis 497–500
–– polylysine dendrimers synthesis 493
amino acids 135, 247

- side-chain functional groups, entail protection 3
- α -amino acids 151
- bioisosterism 159–162
- AMPA, design and synthesis 160, 161
- thioibotenic acid, design and synthesis 161, 162
- conformational restriction 153–159
- ABHD-V and ABHD-VI 159
- DCAN synthesis 156–158
- LY354740 synthesis 158
- glutamic acid 151–153
- structure–activity studies 162–168
- AMPA analogs 162, 163
- 4-substituted Glu analogs 163–168
- aminoacyl-tRNA synthetases 386
- (*2S,4R*)-2-amino-4-(3-(2,2-diphenylethylamine)-3-oxopropyl) pentanedioic acid (DPAG) 168
- 3-amino-2-hydroxydecanoic acid (AHDA) 190, 204, 213
- (*S*)-2-amino-3-(3-hydroxy-7,8-dihydro-6H-cyclohepta [*d*]isoxazol-4-yl)propionic acid (4-AHCP) 163
- 3-amino-2-hydroxymethylhexanoic acid (AHMHA) 197, 202, 210
- 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid (AMPA) receptors 151
- analogs 162, 163
- binding affinities 154, 163
- chemical structures of 163
- design and synthesis 160, 161
- 3-amino-2-hydroxyphenylbutanoic acid (AHPA) 197, 199, 200, 210
- (*S*)-2-amino-3-(3-hydroxy-5-tert-butyl-4-isoxazolyl)propionic acid (ATPA) 163
- functional characterization of 164
- 3-amino-2-oxopropanoate 192
- aminopeptidase P (AP-P) 210
- AP-P inhibitors 210
- aminopeptidases, inhibitors of 207–211
- α -amino protection 2
- non-urethanes 4
- acyl type 4, 5
- alkyl-type groups 11
- benzhydryl groups 12
- diacyl groups 7
- groups cleavable via lactam formation 6
- groups removed by reductive cleavage 8, 9
- monoacyl groups 5
- *N,N*-bis-benzyl protection 12
- phosphine-type groups 10
- phthaloyl (Phth) group 7, 8
- sulfanyl-type groups 13, 14
- sulfonyl-type groups 10, 11
- trifluoroacetyl (*Tfa*) group 5, 6
- triphenylmethyl (Trityl or Trt) group 11, 12
- vinyl groups 12, 13
- urethanes (carbamates/alkyloxycarbonyl groups) 14, 15
- allyloxycarbonyl (Alloc) group 25
- benzylloxycarbonyl (Cbz or Z) group 15–19
- bond, formation of 15
- *tert*-butoxycarbonyl (Boc) group 25–29
- cleaved by β -elimination 19
- cleaved via Michael-type addition 24
- derived from primary alcohols 15
- derived from tertiary alcohols 25
- 9-fluorenylmethoxycarbonyl (Fmoc) group 19–23
- groups derived from secondary alcohols 25
- sulfonylethoxycarbonyl groups 23, 24
- amipurimycin 176
- angiotensin-converting enzyme (ACE) 212
- inhibitors 215
- antibacterial agents 205–207
- antifreeze glycopeptides (AFGPs) 375
- antihyperglyemics
- exendin-4 (*see* Exenatide (Byetta®))
- liraglutide 255
- symlin (pramlintide) 254
- antimicrobial peptides 263–267
- daptomycin 266
- gramicidin S 267
- polymyxin 265, 266
- apstatin 209, 210
- arginine dendrimer, structures 497
- aspartyl proteases inhibitors 211, 212
- BACE-1 inhibitors 224–227
- catalytic mechanism 212
- HIV-1 protease inhibitors 216–220
- HTLV-I inhibitors 220, 221
- plasmeprin II inhibitors 222–224
- renin inhibitors 212–216
- asymmetric epoxidation 191
- (\pm)-2-azanorbornane-3-*exo*,5-*endo*-dicarboxylic acid (DCAN) 153
- *in silico* studies 154
- synthesis 156–158
- azide–alkyne cycloaddition 372
- α -azido acids, as α -amino acid precursors 33
- azido alanine 108
- aziridine-containing peptides 361
- azlactones 7

b

BACE-1 inhibitors 224–227
 – design and structures 225
Bacillus licheniformis 368
 benzyl esters 36, 38
 bestatin 205, 207, 208
 – interactions in active site of MAPs 209
 – synthesis 208
 Bestmann–Ohira reagent 107
 bicyclooctane-2-aza-dicarboxylate (BOAD) 153
 bioisosterism 159–162
 – case studies
 -- AMPA, design and synthesis 160, 161
 -- thioibotenic acid, design and synthesis 161, 162
 – naturally occurring Glu analogs containing 160
 Biopharmaceutics Classification System (BCS) 278
N,N-bis-benzyl amino acids 12
 blood coagulation inhibitors
 – bivalirudin 251
 – integrilin (eptifibatide) 251
N-Boc-protected prolinol 120
N-Boc-(*2S,3S*)-3-amino-2-hydroxy-5-phenylpentanoic acid (AHPPA) 202
 bortezomib (Velcade®) 259
 bovine serum albumin (BSA) 331
 bradykinin 255
 branched peptides
 – as antimicrobials 270
 – solid-phase synthesis of 267
 – as tumor-targeting agents 268–270
N-bromosuccinimide 33
 Brønsted bases 310
 Burgess reagent 5
tert-butyldimethylsilyl (TBS) 346
tert-butyl esters 38, 39

c

calcitonin 256
 calmodulin 459
Campylobacter jejuni 386
 cancer chemotherapy 258
Candida cylindracea lipases (CCL) 192
 carbamate-tethered glycosides 362
 carbocycles, aliphatic and aromatic 136, 137
N-carboxy anhydrides, protection of 31
 ω -carboxy group protection, of asp and glu 55
 – aspartimide formation 55–57
 – ω -esters of asp and glu (selected examples) 59
 carboxymethylcyclodextran 232

carboxy protections 3, 28, 34, 35, 39, 40, 55, 57
 – acid-labile esters 39
 – benzyl ester 36
 -- *tert*-butyl ester 38, 39
 -- cleavage 36
 -- substituted benzyl esters 38
 -- substituted methyl and ethyl esters 37, 38
 – α -carboxy protectors as precursors to 41
 – methyl and ethyl esters 35, 36
 – selected carboxy protections 40
 – substituted methyl and ethyl esters 36
 – temporary α -carboxy protection 39, 41
 cell-based receptor activation assays 284
 central nervous system (CNS) 151
 cerium ammonium nitrate (CAN) 346
 chiral acylchloride strategy 306
m-chloroperbenzoic acid (*m*CPBA) 11
 chymotrypsin 214
 circular dichroism (CD) 114
 cispentacin
 – antifungal activity 175, 177
 – structure 176
 – structure–activity relationship 176
 – *in vitro* activity 180–183
 cleavage
 – of APP by BACE 224
 – conditions for (see carboxy protections; ω -amide protections)
 – by different peptidases 269
 – of ester linker 430
 – of Fmoc group 83
 – groups removed by reductive 8
 – Leu-Pro cleavage site 220
 – mechanism of Na-Bsmoc cleavage 24
 – N^{α} -Dim group, by bromination 13
 – N^{α} -Nps group 14
 – N^{α} -Phth group 8
 – N^{α} protection via lactam formation 6
 – of peptide resins 423
 – of peptides from solid support 400
 – by proteases 409
 – selective, phenacyl ester in presence of 85
 – of *t*Bu-ester 326
 – with TFA 343
 – thiolytic cleavage of N^{α} -Dts protection 9
 – for urethane protections 16
 -- cleaved by β -elimination 19
 coagulation disorders 251
 CODES™ technology 287
 colistin 265
 combinatorial chemistry 395
 computational design, of proteins 473
 confocal microscopy 414
 conformational restriction 153–155

- case studies
 - synthesis of ABHD-V and ABHD-VI 159
 - synthesis of DCAN 156–158
 - synthesis of LY354740 158
 - conformationally restricted Glu analogs 155
 - mechanism of iGluR activation 156
 - coumarin derivatives 233
 - cross-metathesis 378
 - protein modification by transition metals 379
 - sulfur-assisted 380
 - synthesis of neoglycosides via 380
 - CuAAC. *see Cu(I)-catalyzed azide–alkyne click cycloaddition (CuAAC)*
 - Cu-Huisgen cycloaddition reaction 103
 - applications 103
 - mechanism for 104
 - mechanistic consideration for 103–106
 - pseudo-nona-peptidomimetics, regioselective, sequential synthesis 118
 - Cu(I)-catalyzed azide–alkyne click cycloaddition (CuAAC) 372
 - applications 373
 - Danishefsky's glycosyl amino acid syntheses 382
 - pentavalent vaccine construct 383
 - synthetic vaccine against small-cell lung cancer 384
 - vaccine constructs synthesis 381
 - azide–alkyne cycloaddition 372
 - 1,4-disubstituted triazoles as peptide isosteres 373
 - and neoglycoproteins 376–378
 - neoglycoside and neoglycopeptide synthesis via 373–376
 - Curtius rearrangement 176
 - cyclic triazole peptidomimetics 109–113
 - cyclization by Cu-Huisgen cycloaddition, lactamization fail to 113
 - monocyclization vs. cyclodimerization 109
 - self-assembling backbone modified peptidomimetics 112
 - substitution of trans-amide bond in 112
 - VEGFR1 antagonists, synthesis by Cu-Huisgen on-resin cycloaddition 111
 - cyclodimerization 109–111
 - cyclohexylnorstatine 203, 204, 214
 - cyclonorstatine 214
 - cyclooctadiene (COD) ligand 105
 - cyclosporine 22, 24, 257
 - cysteine side-chain modifications 366
 - alkylation 367
- d**
- dehydroalanine (Dha) 361, 368
 - dendrimers. *see peptide dendrimers*
 - 6-deoxy-6-aminohexoses 385
 - deprotection reactions 81
 - cleavage of
 - Boc group with TMS/phenol 84
 - *tert*-butyl ester using $\text{BF}_3\cdot\text{Et}_2\text{O}$ 84, 85
 - Fmoc group 83
 - phenacyl ester in presence of N^α -nosyl group 85
 - conversion of DCHA salt of N^α -protected amino acids into 85, 86
 - deprotection of Pbf group from Z-Arg(Pbf)-OH 85
 - removal of
 - Boc group with TFA 84
 - Nps group 81, 82
 - phenoc group through photolysis 85
 - phth group by hydrazinolysis 81
 - Trt group 85
 - Z group 82, 83
 - selective methyl ester hydrolysis 84
 - transprotection of N^{β} -protecting groups: Fmoc-Met-OH to Boc-Met-OH 84
 - designing modular proteins 474
 - desmopressin 251
 - diaminopropionic acid (Dap) 504
 - 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 112
 - diazacyclohexanones 139
 - dichloromethane (DCM) 5, 104
 - dicyclohexylamine (DCHA) salt 201
 - dicyclohexylcarbodiimide (DCC) 197, 406
 - 2',3'-dideoxykanamycin A 207
 - Diels–Alder reaction 370
 - diethylenetriaminepentaacetic acid (DTPA) 506
 - Digenea simplex* 152
 - N,N*-diisopropylcarbodiimide (DIC) 399
 - diisopropylethylamine (DIPEA) 9, 104, 343
 - 4,5-dimethoxy-2-nitrobenzoyloxycarbonyl (Nvoc) 57
 - 2-(3,5-dimethoxyphenyl)prop-2-yloxycarbonyl (Ddz) 57
 - N,N*-dimethylformamide (DMF) 8, 104
 - 3,5-dimethylpyrazole 197
 - dimethyl (methylthio)sulfonium triflate (DMTST) 340
 - dimethylsulfoxide (DMSO) 104
 - dipeptide
 - formation 30
 - impurities 29
 - synthesis 3

- diphenylmethanimine 5
 disubstituted Fc-peptide dendrimers,
 structures 496
 DNA polymerase 455
 docetaxel 228
 drug discovery 101
Dysidea herbacea 153
- e**
 edeines 205, 206
 electroporation 455
 enfuvirtide. *see* fuzeon
 erythropoietin (EPO) 346
Escherichia coli 210, 376
 estrogen receptor β (ER- β) 341
 – synthesis 341
 1-ethyl-3-(3-dimethylaminopropyl)
 carbodiimide hydrochloride (EDC) 370
 ethyl esters 35, 36
 Evans–Sjögren ketenes 305, 308, 309
 excitatory amino acid transporters
 (EAATs) 152
 exenatide (Byetta[®]) 254, 255
 experimental procedures
 – monitoring and characterizing
 triazoles 121, 122
 – for 1,4-triazoles synthesis using Cu-Huisgen
 cycloaddition 122, 123
 – for 1,4-triazoles synthesis using Ru-Huisgen
 cycloaddition 123
- f**
 factor IXa 184
 factor Xa inhibitors 183
 9-fluorenylmethylpentafluorophenylcarboante
 (Fmoc-OPfp) 33
 Fmoc donors 30
 Fmoc-2-mercaptopbenzothiazole (MBT) 30
 formulation technologies
 – absorption enhancers 284, 285
 – coadministration with protease
 inhibitors 285
 – formulation vehicles 285, 286
 – site-specific delivery 286, 287
 fucosyl-peptide dendrimers 503
 furin 465
 fuzeon 257
- g**
 gadomer structure and computer generated
 model 507
 gene/dendrimer cargo, internalization
 pathway 509
 Gibbs free energy equation 153
 β -glucosidase 459
 glutamatergic neurotransmitter system
 – malfunctioning 152
 – receptor and transporter subtypes in 152
 glutamic acid 151–153
 – dendrimers synthesis 494, 495
 – low-energy conformations 155
 glutathione disulfide 345
 glycoconjugation 364
 glycopeptide 360. *see also* N-glycopeptides; O-
 glycopeptides
 – strategies for synthesis 361
 N-glycopeptides synthesis 342–353
 – erythropoietin N-glycopeptide fragment
 1–28
 -- biantennary dodecasaccharide
 synthesis 346–348
 -- reagents and conditions 347, 348
 – HIV GP120 V3 domain N-glycopeptide,
 chemoenzymatic synthesis
 -- Fmoc-GlcNAc-Asn amino acid building
 block synthesis 351
 -- oxazoline tetrasaccharide donor
 synthesis 350, 351
 -- V3 cyclic GlcNAc peptide and endo A
 coupling with 352, 353
 – N-glycopeptide fragment 1–28 348, 350
 -- reagents and conditions 349
 – RNase C glycoprotein synthesis 343–345
 O-glycopeptides synthesis 324–341
 – estrogen receptor peptides synthesis,
 conformational analysis 340, 341
 – Fmoc-GlcNAc-Ser/Thr amino acids
 synthesis 340
 – mucin-type glycopeptides synthesis
 -- glycopeptide recognition domain, synthesis
 of 331–339
 -- glycopeptide vaccines, synthesis 325–331
 -- tumor-associated glycopeptides,
 synthesis 325–331
 glycoproteins 359
 – enzymatic glycoprotein synthesis 385
 – generation
 O-glycosidic bond 359
 glycosylated cyclic arginine–glycine–aspartate
 (RGD) derivatives 375
 glycosylation 359
 – using Diels–Alder chemistry 370
 – via disulfide formation 367
 gonadotropin-releasing hormone agonists and
 antagonists 251–253
 – cetrorelix 253
 – degarelix 253
 – gonadorelin 251, 252

- lupron(leuprolide) 252
- G-proteins 463
- Grignard reagents 309
- Grob fragmentation 32
- guanidino group of Arg, protection of 43
 - Arg precursors 45
 - Arg protections (selected examples) 46
 - nitration 44, 45
 - protection through protonation 43
- h***
 - hemolytic index (HI) 502, 503
 - hetero-bifunctional linkers 371
 - hetero Diels–Alder reaction 156
 - hexyl-insulin monoconjugate 2 (HIM2) 283
 - high-performance liquid chromatography (HPLC) 64, 85, 110, 314, 330, 331, 333
 - high-throughput synthesis, of peptides 396.
 - see also* parallel peptide synthesis
 - directed sorting 400–402
 - parallel peptide synthesis 396–400
 - synthesis of peptide arrays 402–405
 - Fodo's technology 402, 403
 - MAS technology instrument 403
 - synthesizers 405
 - technological developments 404
 - histo-aspartyl protease (HAP) 222
 - HIV GP 120 V3 domain *N*-glycopeptide, chemoenzymatic synthesis 352
 - HIV-1 protease 216
 - inhibitors 133, 139
 - design and structure 217
 - potent peptidomimetic inhibitors 114
 - synthesis of 114
 - prodrugs of inhibitors 219
 - HIV reverse transcriptase 459
 - homophenylalanine 202
 - homoserine 108
 - Hoveyda–Grubbs catalyst 379, 380, 382
 - HTLV-I protease inhibitors
 - as anti-AIDS drugs 221
 - design and structures 221
 - Huisgen cycloaddition
 - acyclic triazole peptidomimetics 113–121
 - Cu-Huisgen cycloaddition reaction 103–106
 - applications of 103
 - mechanistic consideration for 103–106
 - cyclic triazole peptidomimetics 109–113
 - [2+3] cycloaddition between azides and acetylenes 102, 103
 - in peptidomimetic chemistry 101
 - Ru-Huisgen cycloadditions, mechanistic consideration for 103–106
 - thermal cycloaddition 102
 - triazole-modified peptidomimetics
 - synthesis, building blocks for 106–109
 - human HeLa cells 512
 - hydrogen bonding, schematic
 - representation 136, 142
 - α -hydroxy- β -amino acids 189
 - occurrence of 189
 - structure of 190
 - from marine organisms 190
 - naturally occurring 190
 - synthesis of 191
 - 3-amino-2-hydroxydecanoic acid and its analogs 204
 - isoserine 191–193
 - isothreonine 193–196
 - norstatines 197–204
 - phenylisoserine 197
 - synthetic demands 205
 - p*-hydroxybestatin 208
 - hydroxy group of Ser, Thr, protection of 54
 - protectors of 54
 - hydroxylsine 359
 - N*-hydroxysuccinimide (NHS) ester 370
 - hypothalamic neurosecretory neurons 250
 - i***
 - ibotenic acid (IBO) 160
 - icatibant (Firazyr[®]) 255, 256
 - iGluR activation, mechanism 156
 - imidazole group of His, protection of 45–48
 - His protections 48
 - N^{α} -Boc-substituted His, preparation of 47
 - unprotected His
 - electrophilic substitution of indole ring of 47
 - racemization of 47
 - imine
 - from chiral aldehydes 298
 - *E/Z* isomerization 297
 - indole group of Trp, protection 48, 49
 - side-reactions of unprotected Trp 48
 - α -integrin receptor 233
 - intestinal drug permeability
 - mechanisms 279
 - N*-iodoacetyl glycosylamines 384
 - isocyanates 363
 - isocyanato peptides, synthesis of 6
 - isoserine 191
 - isothreonine 193–196
 - k***
 - kanamycin 207
 - keyhole limpet hemocyanin (KLH) 381

Kinugasa reaction 314, 315

– catalysts for 315

– with Cu (II) catalyst 316

Kochetkov anomeric amination 348

Kochetkov method 343

Koenigs-Knorr reaction 364

I

β -lactamase 459

β -lactams, asymmetric synthesis

– arenechromium imines 302

– by azaferrocene catalyst 314

– bis-aldimines 308

– *N*-bis(trimethylsilyl)methyl imines 306

– *N*-Boc- α -aminoimines 300

– catalysts influence on stereoselectivity 309–317

–– β -lactams 106 with proton sponge 312

–– Kinugasa reaction with Cu (II) catalyst 316

–– tandem nucleophile/Lewis acid-promoted synthesis 312–314

–– trans- β -lactams 113, catalytic asymmetric synthesis of 314–316

– with chiral catalysts 312

– chiral imines 302

– chiral substituents influence on stereoselectivity 298

– double asymmetric cycloinduction 308, 309

– Evans-Sjögren ketenes 309

– imine 301, 303, 304

– component, asymmetric induction 298–305

– geometry influence on stereoselectivity 294, 295

– isomerization influence, nucleophilic attack onto ketene stereoselectivity 296, 297

– ketene 301, 303, 304

– component, asymmetric induction 305–308

– Lewis acid/nucleophile synthesis 313

– order of addition influence of reactants 297, 298

– solvent polarity influence on stereoselectivity 296

– symmetrical/unsymmetrical ketimines 307

– unsubstituted imines 307
– via Staudinger reaction (*see* Staudinger reaction)

Lansbury method, for glycopeptides 342

β -letosulfide 201

leucine aminopeptidase 208

ligand-binding domain (LBD) 155

lipid dendrimer 508, 510

lysine side-chains modifications 368–370

m

macrocyclic human renin inhibitors 215

macrocyclic peptidomimetics 133–135

macro-lactonization strategy 113

magnetic resonance imaging (MRI) 505, 506, 513

matrix-assisted laser desorption ionization (MALDI)-MS 413

membrane-bound glycoprotein mucin 1 (MUC1) 325

4-mercaptophenylacetic acid 378

O-mesitylenesulfonylhydroxylamine (MSH) 368

metalloaminopeptidases (MAPs) 208

metallopeptidases 208

metalloproteases 465

methanethiosulfonate (MTS) 367

p-methoxy benzyl (PMB) 346

4-methoxyphenacyloxycarboxyl (Phenoc) 57

N-methyl- α -amino acids (NMAs) 7, 22

4-methylbenzhydrylamine (MBHA)

resin 110

p-methylbestatin 208

methyl (*S*)-Boc- δ -azido-norvalinate synthesis 109

N-methyl-D-aspartic acid (NMDA) receptors 151

methyl esters 35, 36

– group, structure–activity relationship 185

N-methylmorpholine (NMM) 31, 203, 233, 363

4-methylpiperidine 399

methylsulfonyl triflate (MeSOTf) 326

7-methyl,5,7-triaza-bicyclo[4.4.0]dec-5-ene (MTBD) 34

Michael acceptor 368

Michael addition–cyclization process 304, 305

Michaelis–Menten kinetics 504

microsclerodermin A 190

Mitsunobu reaction 108

monocyclization 110

mucin-type glycopeptides synthesis

– glycopeptide vaccines synthesis 325–331

– MUC1-OVA glycopeptide vaccines 330

– reagents and conditions 326–329

– P-selectin glycoprotein ligand-1 synthesis, glycopeptide recognition domain 331–339

– PSGL-1 glycopeptides 337–339

– reagents and conditions 334, 335

- sialyl-T antigen–BSA conjugate 332, 333
- T antigen–BSA conjugate 332, 333
- structure 322, 323
- tumor-associated glycopeptides 325–331
- reagents and conditions 326–329
- mucosal cell permeability 278
- MUC1–OVA glycopeptide vaccines, synthesis 330
- multicomponent reactions (MCRs) 5
- multidrug-resistant (MDR) gram-negative pathogens 266
- multiple antigenic peptides (MAPs) synthesis 497–500
- designs 500
- initial efforts on 502
- ligating unprotected peptides, chemoselective methods for 499
- schematic diagram for 498
- multivalency effect, thermodynamic model 499

- n**
- N^{α} -Dts-protected amino acids 9
- N^{α} -Dts protection, thiolytic cleavage of 9
- N^{α},N^{α} -bis-protected amino acids 32
- N^{α} -Nps-protected amino acids 13
- N^{α} -Phth-amino acids 7
- N^{α} -protected peptide acid 3
- N^{α} -protecting groups 32
 - in synthesis of NMAs 33, 34
- N^{α} protection. *see* α -amino protection
- N^{α} -sub-amino acids 12
- native chemical ligation (NCL) 343
- N^{α} -Trt-protected amino acids 12
- natural peptides, degradation 248
- natural proteins 473
- N^{α} -urethane protections, interconversion of 31
- neoglycopeptide 360, 361
 - application, as synthetic vaccines 380–384
- C-glycosides 365
- C=N linkage 365, 366
- N-glycosides 362–364
- O-glycosides 364
- S-glycosides 361, 362
- via CuAAC 373–376
- neoglycoproteins 361
 - CuAAC and 376–378
- nesiritide (Natrecor[®]) 249
- neurotensin
 - structure 270
 - tetra-branched forms 269
- p*-nitrobestatin 208
- p*-nitrophenyl anthranilate (PNPA) 371
- nonsymmetric dendrimers 507
- nuclear magnetic resonance (NMR) spectroscopy 116, 120, 133

- o**
- OctreoscanTM 262, 263
- octreotide 260, 261
- Ojima–Holton β -lactam coupling method 197
- oligopeptides 1, 2
 - as antibacterial agents 205
 - binds to α,β_3 integrins 506
 - formation, during introduction of N^{α} -urethane protections 30
 - reaction mechanism for formation of 30
 - transporter (PEPT1) 281
- one-pot N^{α} protection 33
- oxazolidinone 34
- oxytocin 249, 250
- ozonolysis 364

- p**
- paclitaxel
 - analogs, clinical trials 231
 - and derivatives 228
 - DAB 228
 - docetaxel 228
 - plasmin-sensitive prodrug 233
 - prodrugs in advanced, clinical trials 232
 - structure of 228
 - synthesis
 - of IDN 5109 and SB-T-1214 229
 - of isotaxel and release mechanism of paclitaxel 231
 - of 3'-N-acetyl-paclitaxel analogs 230
 - and release mechanism of paclitaxel plasmin-sensitive prodrug 233
 - route for paclitaxel analogs 229, 231
 - parallel peptide synthesis 396
 - diketopiperazine linker release 398
 - Frank's synthesis on paper circles 396
 - Geysen's pin synthesis 397
 - use of lanterns 397
 - Houghten's technique of tea-bag synthesis 397
 - new instruments 398–400
 - centrifugal DNA and peptide synthesizer 399
 - TetrasTM 398
 - peptide cleavage from solid support 397, 398
- parathyroid hormone 256, 257

- peptide dendrimers. *see also* amino acid-based dendrimers
- applications
 - as antimicrobial agents 502–504
 - as DNA/RNA delivery vectors 507–512
 - initial efforts on MAPs 502
 - ion sensors and MRI contrast agents 505–507
 - as protein/enzyme mimics 504, 505
 - catalysis of ester hydrolysis 504
 - synthesis 491–502
 - of cyclic peptide dendrimers 500
 - glutamic/aspartic acid, proline, and arginine dendrimers 494–497
 - grafted on PAMAM 500–502
 - MAPs synthesis 497–500
 - polylysine dendrimers synthesis 493
- peptide drugs
- antimicrobial peptides 263–267
 - Daptomycin 266
 - Gramicidin S 267
 - Polymyxin 265, 266
 - availability in market 249–258
 - antihyperglycemics 254, 255
 - blood coagulation inhibitors 251
 - calcitonin 256
 - cyclosporine 257
 - desmopressin 251
 - fuzeron 257, 258
 - gonadotropin-releasing hormone agonists and antagonists 251–253
 - icatibant 255, 256
 - natriuretic peptide (Nesiritide) 249
 - oxytocin 249, 250
 - parathyroid hormone 256, 257
 - sermorelin 256
 - vasopressin 250
 - intestinal absorption, fundamental considerations 277–279
 - oncology, approved peptides in 258–263
 - actinomycin D 259, 260
 - bortezomib 259
 - narimastat 260
 - Octreoscan™ 262, 263
 - octreotide 260, 261
 - vapreotide 261, 262
 - oral bioavailability 277
 - formulation technologies 284–287
 - improvement strategies 280–287
 - limiting barriers 279–280
 - perspectives 267–270
 - branched peptides as antimicrobials 270
 - branched peptides as tumor-targeting agents 268–270
 - peptide libraries
 - future of 421
 - omission libraries 408
 - orthogonal libraries 408, 409
 - peptide mixtures, synthesis of 406–409
 - positional scanning libraries 406
 - solution-based screening, of OBOC libraries 418–421
 - synthesis of peptides, on mixture of particles 409–416
 - automated bead picking system 414
 - bead sorting instrument for OBOC 413
 - determination of structure of peptide on 416–418
 - hit isolation through magnetic bead sorting 412
 - one-bead-one-compound (OBOC) technology 409, 410, 415
 - one-bead–two-compounds assay 411
 - synthesis of hexapeptide library 416
 - validation 413
 - synthetic protocols 421
 - dual-layer beads, preparation of 425, 426
 - library of libraries, preparation of 426
 - OBOC libraries for testing in solution, preparation of 426–431
 - pin synthesis 421, 422
 - split-and-mix synthesis of OBOC noncleavable libraries 424, 425
 - SPOT synthesis 422
 - synthesis in tea-bags 422, 423
 - synthesis on cotton 423, 424
 - peptides 1, 11, 20, 29, 35, 38
 - antimicrobial 263, 264, 270, 502, 503
 - biostability of 249
 - cationic 265, 270
 - combinatorial 458, 459, 461, 465
 - containing difficult sequences as useful tool for 220
 - crude 423
 - dendrimeric 502
 - as drugs 249
 - library (*see* peptide libraries)
 - natural 248
 - oligo-branched 268
 - synthesis using cystine as self-protected Cys 51–53
 - tetra-branched neurotensin 270
 - therapeutic 264
 - Z group-protected 82
- peptidomimetic drugs

- intestinal absorption, fundamental considerations 277–279
- oral bioavailability 277
- limiting barriers 279, 280
- Perlman's catalyst 306
- Peyer's patches 286
- phage vectors 452
- combinatorial peptide libraries, generation of 455–458
- Kunkel mutagenesis approach 457
- modified protocol 456, 457
- M13 bacteriophage 452, 453
- phage-displayed combinatorial peptide libraries
- advantages 452
- alanine scanning for 460
- disadvantages 452
- identifying peptide ligands
 - binding to cell surfaces 463, 464
 - to surfaces of inert materials 465
- mapping protease specificity 464, 465
- mapping protein–protein interactions 461–463
- phage ELISA 461
- screening, for peptide ligands to target proteins 458–460
- phage-display particles, types of 453
- type 3 or 8 displaying, combinatorial peptides 453, 454
- phebestin 210, 211
- phenolic group of Tyr, protection 54
- protectors of 55
- phenylisoserine 197
- phenylnorstatine 197
- phenylthiosulfonate (PTS) 367
- phosphoadenosyl phosphosulfate (PAPS) 336
- photocleavable carboxy protectors 57
- photocleavable protections 57
 - advantages of 57
- phthaloylating reagents 8
- plasmeprin II inhibitors 222–224
- Plasmodium falciparum* 222
- poly(amido amine) (PAMAM)
 - dendrimers 491, 500, 501
 - synthesis 501
- polylysine dendrimers synthesis 493
- Polymyxins 265, 266
- polypeptides 1
 - linear 513
 - N^{α} -deprotection 14
- polypropylene imine (PPI) 491
- post-translational modifications 1
- probestin 211
- prodrug approach, for oral bioavailability of peptide-based drugs 280, 281
- prostate-specific antigen 465
- protease inhibitors 285
- protease–ligand complexes 132
- proteases 462, 464
- protection reactions 2, 59
 - general procedure, for preparation of 59
- amino acid benzyl ester *p*-toluenesulfonate salts 70, 71
- amino acid ethyl esters 69, 70
- amino acid methyl ester hydrochloride salts 68, 69
- amino acids using pentafluorophenyl carbonate 80, 81
- *tert*-butyl esters of N^{α} -unprotected amino acids 71–80
- N^{α} -Aloc-amino acids 65
- N^{α} -Boc-amino acids 65–67
- N^{α} -Bpoc-amino acids 67, 68
- N^{α} -Bsmoc-amino acids 64, 65
- N^{α} -Fmoc-amino acids 62–64
- N^{α} -Ns-amino acids 60
- N^{α} -Nsc-amino acids 64
- N^{α} -phthaloyl amino acids using *N*-(ethoxycarbonyl)phthalimide 59
- N^{α} -Trt-amino acids 59, 60
- N^{α} -Z-amino acids 61
- Tfa-Arg-OH 59
- protectors
 - of hydroxy group of Ser/Thr 54
 - of phenolic function of Tyr 55
- protein design methods 475, 476
 - computational design 476, 477
 - computational enzyme design 477, 478
 - results of computational design experiments 478–480
 - β -barrel 478, 479
 - β -sheets 478, 479
 - TIM-barrel 478, 479
 - top7 479
 - directed evolution methods 480
 - expression systems and assays 481, 482
 - randomization strategies 480, 481
- protein design, protocol for 484–486
 - RosettaDesign 485, 486
 - RosettaHoles method 486
- protein interfaces, design of 482–484
- proteinogenic amino acid 2
- protein–protein interactions 461, 463
- protein side-chain modifications 366
 - modifications of
 - cysteine side-chains 366–368

-- fluorescent anthranilamide-linked glycoconjugate 371
 -- hetero-bifunctional linkers 371
 -- lysine side-chains 368–370
 protein structure databases 474
 P-selectin glycoprotein ligand-1 (PSGL-1) 331
 – chemoenzymatic synthesis 338, 339
 – synthesis 337
Pseudomonas aeruginosa 503
 pyridinium chlorochromate (PCC) 201

q

(*S*)-quisqualic acid (QUIS) 160
Quisqualis indica 160

r

racemization 6, 7
 – and β -elimination in S-protected Cys residues 53
 – of N^{α} -acyl- α -amino acid derivatives 7
 recombinant DNA technology 248
 reductive amination 364
 regioselectively addressable functionalized templates (RAFTs) 365
 renin–angiotensin system (RAS) 212
 restriction process 153
 retro-synthetic analysis 155
 ribosomes 1, 205
 RNase C enzyme 345
 RNase C glycoprotein
 – synthesis 344, 345
 -- fragments 344
 -- through NCL 345
 RNase fragment 344
 rotating-frame Overhauser spectroscopy (ROESY) 137
 ruthenium-catalyzed Huisgen cycloaddition 103
 – mechanistic consideration for 103–106
 – Ru-catalysts, synthesis of 105

s

Schlerochiton ilicifolius 153
 scytovemin A 190, 191
 secondary amide bond 1
 self-assembling backbone modified peptidomimetics 112
 serine 108, 321, 326, 340, 359, 381, 407, 421
 serine proteases 465
 sermorelin 256
 severe combined immunodeficiency (SCID) 186

sialic acid 321
 sialyl-T antigen–BSA conjugate
 – synthesis 332, 333
 side-chain protection
 – ω -amido group of Asn and Gln 49, 50
 – ω -amino group of diamino acids 41–44
 – guanidino group of Arg 43
 -- Arg precursors 45
 -- nitration 44, 45
 -- protection through protonation 43
 – imidazole group of His 45–48
 – indole group of Trp 48, 49
 – β -thiol group of Cys 50, 51
 silyl ester protection 41
 solid-phase chemistry 395
 solid-phase peptide synthesis (SPPS) 4, 360, 395
 solid-phase synthesis 104, 116
 split-and-mix combinatorial peptide dendrimer library 505
 S-protected cys derivatives, common
 – side-reactions with 51
 – ω -carboxy group of Asp and Glu 55
 -- aspartimide formation 55–57
 – β -elimination 51
 – hydroxy group of Ser, Thr, and phenolic group of Tyr 54
 -- protectors of the hydroxy group of Ser/Thr 54
 -- protectors of the phenolic function of Tyr 55
 – oxidation 51
 – racemization 51
 – synthesis of peptides using cystine as self-protected Cys 51–53
 – thioether group of Met 53, 54
 standard Kaiser test 122
 Staudinger reaction 293, 294. *see also*
 – β -lactams, asymmetric synthesis
 – asymmetric induction
 -- from imine component 298–305
 -- from ketene component 305–308
 – chiral catalysts for 311
 – diastereoisomeric excess 296
 – double asymmetric cycloinduction 308, 309
 – influence of
 -- catalysts on stereoselectivity 309–312
 -- chiral substituents on 298
 -- geometry of imine on stereoselectivity in 294, 295
 -- isomerization of imine 296, 297
 -- polarity of solvent on 296

- mechanism 294, 311
- reduction approach 122
- stereochemistry of 295
- β-strand mimetics**
 - acyclic compounds 135, 136
 - aliphatic and aromatic carbocycles 136, 137
 - ligands containing
 - one/multiple rings with one heteroatom 138, 139
 - one ring with one heteroatom 137, 138
 - one ring with two heteroatoms 139
 - one ring with two/three heteroatoms 140
 - two rings with one heteroatom 140, 141
 - two rings with two/three heteroatoms 141, 142
 - macrocyclic peptidomimetics 133–135
 - recent advances in 129
 - β-sheets 130
 - β-strands 129
 - composed of Ala residues 130
 - strand/sheet/turn/helix recognition, differences in 130, 131
 - towards β-strand mimetics 131–133
- Streptomyces olivoreticuli* 207
- structure–activity studies 162–168, 178
 - case studies
 - AMPA analogs 162, 163
 - 4-substituted Glu analogs 163–168
 - binding affinities of 4-alkylGlu analogs at native iGluRs and 165–167
 - DPAG, selective inhibitor of the EAAT2 subtype 168
 - substituted benzyl esters 38
- sulfosuccinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) 370
- synthesized peptides, sequences and structures 509
- synthetic glycopeptides 324
- synthetic peptides 2

- t**
- tachykinin NK1 receptor antagonists 185
- target protein 247
- L-tartaric acid 204
- Taxus baccata* 228
- T cells 383
- temporary α acarboxy protection 39, 41
- tetrahydrofuran (THF) 104, 343
- tetra-*n*-butylammonium fluoride (TBAF) 333
- tetrathiomolybdate salt 32
- tetravalent RAFT glyoclusters 366
- thermal Huisgen cycloaddition 102
- thioether group of Met, protection 53
 - through oxidation 53
- N*-thioformyl glycosides 363
- thiobiotenic acid (TIBO)
 - chemical structures of 161
 - design and synthesis 161, 162
- β-thiol protections of Cys 52
- threonine 359
 - mutant dendrimer 505
- tilidine synthesis 184
- tissue-type plasminogen activator 465
- transesterification 200
- triazoles 101
 - ^1H -triazole-CH NMR resonances 121
 - linked AFGP analogs 376
 - modified peptidomimetics synthesis, building blocks for 106–109
 - as peptide bond isosteres 102
 - peptidomimetic, synthesis 117
 - 1,4-triazoles
 - β-turn-induced 115
 - use of 111
 - trimer, solution-phase synthesis 116
 - uses of 116
- triethylamine (TEA) 9, 191, 421
- trifluoroacetic acid (TFA) 5, 157, 215, 326, 419, 493
- trifluoroacetic anhydride (TFAA) 5, 7, 59
- tris-[(1-benzyl-1*H*-1,2,3-triazol-4-yl) methyl] amine (TBTA) 104
- tris(2-carboxyethyl)phosphine (TCEP) 344, 345, 350, 378
- trypsin variants 465
- tumor-targeting agents 258
- tumor-targeting drugs 268
- tyrosine 331, 336, 359, 421

- u**
- ubenimex 205, 209
- ubiquitin 484
- unprotected amino acids 1
- urea-linked glycosides 363
- urethanes
 - bond formation 15–17
 - cleavage 17–19
 - by β-elimination 19
 - derived from primary alcohols 15
 - allyloxycarbonyl (Alloc) group 25
 - benzoyloxycarbonyl (Cbz or Z) group 15–19
 - cleaved by b-elimination 19–24
 - cleaved via Michael-type addition 24
 - derived from, secondary alcohols 25

- derived from, tertiary alcohols 25
 - Boc analogs 28, 29
 - *tert*-butoxycarbonyl (Boc) group 25, 26
 - deprotection 27
 - lewis acids 28
 - organosilanes 28
 - oxidizing agent 28
 - preparation 26, 27
 - protic acids 27
 - removal of Boc groups 28
 - modes of fission 15
 - protected NCAs 31
 - protectors
 - formation of dipeptide impurities during 29, 30
 - nitrogen of α -amino acid *N*-carboxy anhydrides (NCAs), protection of 31
 - urethanes via transprotection, introduction of 30, 31
 - structure 15
- US Food and Drug Administration (FDA) 253, 256, 260, 264, 266

v

- vapreotide 261
- vascular endothelial growth factor receptor 1 (VEGFR1) 110
- potential VEGFR1 antagonists, synthesis of 111
- vasopressin 250
- Veber–Hirschmann cyclic hexapeptide cyclo (-PFwKTF-) 283

w

- Wang resin 329
- Weinreb amide derivatives 108
- (*S*)-willardiine (WILLA) 160
- Willebrand factor 251

x

- X-ray crystallography 177, 461
- X-ray crystal structure analysis 101
 - of peptidomimetics 115

z

- zwitterionic intermediate 295

