



# **PRIVILEGED STRUCTURES IN DRUG DISCOVERY**

MEDICINAL CHEMISTRY  
AND SYNTHESIS

LARRY YET

WILEY



## Privileged Structures in Drug Discovery



# Privileged Structures in Drug Discovery

Medicinal Chemistry and Synthesis

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**WILEY**

This edition first published 2018  
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350 Main Street, Malden, MA 02148-5020, USA

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*Library of Congress Cataloging-in-Publication Data*

Names: Yet, Larry, author.

Title: Privileged structures in drug discovery : medicinal chemistry and synthesis / Dr. Larry Yet, University of South Alabama, USA.

Description: Edition 1. | Hoboken, NJ : Wiley, 2018. | Includes bibliographical references and index. |

Identifiers: LCCN 2017047741 (print) | LCCN 2017058921 (ebook) | ISBN 9781118686355 (pdf) | ISBN 9781118686331 (epub) |

ISBN 9781118145661 (cloth)

Subjects: LCSH: Pharmaceutical chemistry. | Drug development--Methodology.

Classification: LCC RS403 (ebook) | LCC RS403 .Y48 2018 (print) | DDC 615.1/9--dc23

LC record available at <https://lcn.loc.gov/2017047741>

Cover Design: Wiley

Cover Image: © MirageC/Gettyimages

Set in 10/12pt Warnock by SPi Global, Pondicherry, India

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

## Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	The Original Definition of Privileged Structures	1
1.2	The Role of Privileged Structures in the Drug Discovery Process	1
1.3	The Loose Definitions of “Privileged Structures”	2
1.4	Synthesis and Biological Activities of Carbocyclic and Heterocyclic Privileged Structures	2
1.4.1	Synthesis and Biological Activities of Three- and Four-Membered Ring Privileged Structures	2
1.4.2	Synthesis and Biological Activities of Five-Membered Ring Privileged Structures	2
1.4.3	Synthesis and Biological Activities of Six-Membered Ring Privileged Structures	4
1.4.4	Synthesis and Biological Activities of Bicyclic 5/5 and 6/5 Ring Privileged Structures	4
1.4.5	Synthesis and Biological Activities of Bicyclic 6/6 and 6/7 Ring Privileged Structures	4
1.4.6	Synthesis and Biological Activities of Tricyclic and Tetracyclic Ring Privileged Structures	4
1.5	Combinatorial Libraries of “Privileged Structures”	4
1.6	Scope of this Monograph	9
	References	10
<b>2</b>	<b>Benzodiazepines</b>	<b>15</b>
2.1	Introduction	15
2.2	Marketed BDZ Drugs	15
2.2.1	1,4-Benzodiazepine Marketed Drugs	15
2.2.2	1,5-Benzodiazepine Marketed Drugs	16
2.2.3	Linearly Fused BDZ Marketed Drugs	16
2.2.4	Angularly Fused-1,4-Benzodiazepine Marketed Drugs	17
2.3	Medicinal Chemistry Case Studies	17
2.3.1	Cardiovascular Applications	17
2.3.2	Central Nervous System Applications	19
2.3.3	Gastrointestinal Applications	23
2.3.4	Infectious Diseases Applications	24
2.3.5	Inflammation Applications	25
2.3.6	Metabolic Diseases Applications	27
2.3.7	Oncology Applications	28
2.4	Synthesis of BDZs	30
2.4.1	Condensation of <i>o</i> -Phenylenediamines to 1,5-Benzodiazepines	31
2.4.1.1	Condensation of <i>o</i> -Phenylenediamines with Ketones	31
2.4.1.2	Condensation of <i>o</i> -Phenylenediamines with $\alpha,\beta$ -Unsaturated Ketones	33
2.4.1.3	Condensation of <i>o</i> -Phenylenediamines with Alkynes	34
2.4.2	Reductive Condensation of $\alpha$ -Substituted Nitrobenzenes with Ketones and $\alpha,\beta$ -Unsaturated Ketones	35
2.4.3	Intramolecular Cyclizations to 1,4-Benzodiazepines	35
2.4.3.1	Intramolecular Cyclizations—Path A	36
2.4.3.2	Intramolecular Cyclizations—Path B	37
2.4.3.3	Intramolecular Cyclizations—Path C	39

2.4.3.4	Intramolecular Cyclizations—Path D	40
2.4.3.5	Intramolecular Cyclizations—Path E	42
2.4.3.6	Intramolecular Cyclizations—Path F	42
2.4.3.7	Intramolecular Cyclizations—Path G	42
2.4.3.8	Intramolecular Cyclizations—Path H	42
2.4.4	Ugi Multicomponent Synthesis	42
2.4.5	Elaboration of 1,4-Benzodiazepines	44
2.4.6	Pyrrolo[2,1- <i>c</i> ]benzodiazepines	45
2.4.7	Fused BDZ Ring Systems	45
2.4.8	Solid-Phase Synthesis of BDZs	47
	References	47
<b>3</b>	<b>1,4-Dihydropyridines</b>	<b>59</b>
3.1	Introduction	59
3.2	Marketed 1,4-Dihydropyridine Drugs	59
3.3	Medicinal Chemistry Case Studies	59
3.3.1	Cardiovascular Applications	59
3.3.2	Central Nervous System Applications	61
3.3.3	Infectious Diseases Applications	62
3.3.4	Inflammation Applications	63
3.3.5	Men's and Women's Health Issues Applications	64
3.3.6	Metabolic Diseases Applications	65
3.3.7	Oncology Applications	65
3.4	Synthesis of 1,4-Dihydropyridines	66
3.4.1	Classical Hantzsch Synthesis	66
3.4.2	Modified Hantzsch Conditions	66
3.4.3	1,4-Disubstituted-1,4-Dihydropyridines	69
3.4.4	Organometallic Additions to Pyridinium Salts	69
3.4.5	From Imines and Enamino Compounds	71
3.4.6	Multicomponent Synthesis	72
3.4.6.1	Three-Component Synthesis of 1,4-Dihydropyridines	72
3.4.6.2	Four-Component Synthesis of 1,4-Dihydropyridines	74
3.4.7	Organocatalytic Synthesis of 1,4-Dihydropyridines	74
3.4.8	Miscellaneous Preparations	75
3.4.9	Elaboration of 1,4-Dihydropyridines	76
	References	77
<b>4</b>	<b>Biaryls</b>	<b>83</b>
4.1	Introduction	83
4.2	Marketed Biaryl Drugs	83
4.3	Medicinal Chemistry Case Studies	87
4.3.1	Cardiovascular Applications	87
4.3.2	Central Nervous System Applications	89
4.3.3	Infectious Diseases Applications	95
4.3.4	Inflammation Applications	98
4.3.5	Men's and Women's Health Issues Applications	102
4.3.6	Metabolic Diseases Applications	103
4.3.7	Oncology Applications	109
4.4	Synthesis of Biaryls	114
4.4.1	Transition Metal-Catalyzed Cross-Coupling Synthesis	114
4.4.1.1	Suzuki–Miyaura Cross-Coupling Reactions with Boronic Acids	114
4.4.1.2	Suzuki–Miyaura Cross-Coupling Reactions with Boronate Esters	114
4.4.1.3	Metal-Catalyzed Homocoupling Reactions	121



4.4.1.4	Uhlmann Coupling Reactions	122
4.4.1.5	Kumada–Tamao–Corriu Cross-Coupling Reactions	123
4.4.1.6	Negishi Cross-Coupling Reactions	124
4.4.1.7	Hiyama Cross-Coupling Reactions	124
4.4.1.8	Stille Cross-Coupling Reactions	125
4.4.1.9	Miscellaneous Cross-Coupling Reactions	126
4.4.1.10	Metal-Catalyzed Functional Group Removal Cross-Coupling Reaction	127
4.4.2	C–H Functionalization Reactions	127
4.4.2.1	Oxidative Coupling Reactions	127
4.4.2.2	Direct C–H Arylations	127
4.4.2.3	C–H Functionalization with Directing Groups	127
4.4.3	Cycloaddition Reactions	132
4.4.3.1	[3+3] Cycloaddition Reactions	132
4.4.3.2	[4+2] Cycloaddition Reactions	132
4.4.3.3	[2+2+2] Cycloaddition Reactions	133
4.4.3.4	Tandem Cycloaddition Reactions	133
4.4.4	Biaryl Phenol Syntheses	133
4.4.5	Miscellaneous Syntheses	134
	References	135
<b>5</b>	<b>4-(Hetero)Arylpiperidines</b>	<b>155</b>
5.1	Introduction	155
5.2	Marketed 4-(Hetero)Arylpiperidine Drugs	155
5.3	Medicinal Chemistry Case Studies	159
5.3.1	Cardiovascular Applications	159
5.3.2	Central Nervous System Applications	159
5.3.3	Infectious Diseases Applications	168
5.3.4	Inflammation Applications	169
5.3.5	Men's and Women's Health Applications	174
5.3.6	Metabolic Diseases Applications	175
5.3.7	Oncology Applications	177
5.4	Synthesis of 4-(Hetero)Arylpiperidines	179
5.4.1	Preparation from 4-Piperidinones	179
5.4.2	Preparation from 4-Prefunctionalized-3-alkenylpiperidines	180
5.4.3	Preparation from Negishi Cross-Coupling of 3-Zincated Piperidines	180
5.4.4	Preparation from 4-Functionalized Piperidines	181
5.4.5	Conjugated Addition to Unsaturated Piperidines	181
5.4.6	Miscellaneous Syntheses	183
	References	185
<b>6</b>	<b>Spiropiperidines</b>	<b>194</b>
6.1	Introduction	194
6.2	Marketed Spiropiperidine Drugs	194
6.3	Medicinal Chemistry Case Studies	195
6.3.1	Cardiovascular Applications	195
6.3.2	Central Nervous System Applications	197
6.3.3	Infectious Diseases Applications	203
6.3.4	Inflammation Applications	205
6.3.5	Men's and Women's Health Applications	210
6.3.6	Metabolic Diseases Applications	211
6.3.7	Oncology Applications	216
6.4	Synthesis of Spiropiperidines	218
6.4.1	Quinolinylnspiropiperidines	218

- 6.4.2 Azaspiro[5.5]alkane Systems 218
- 6.4.3 Diazaspiro[5.5]alkane Derivatives 221
- 6.4.4 1,4-Benzodioxinylspiropiperidines 222
- 6.4.5 Spirobenzooxazinylspiropiperidines 223
- 6.4.6 (Iso)Quinolinylnspiropiperidines 223
- 6.4.7 Indenospiropiperidines 225
- 6.4.8 Indolin(on)ylspiropiperidines 225
- 6.4.9 Cyclohexadienonylnspiropiperidines 226
- 6.4.10 Cyclopenta[*b*]pyrrolospiropiperidines 226
- 6.4.11 Chromanylnspiropiperidines 226
- 6.4.12 (Iso)Benzofuran(on)ylspiropiperidines 227
- 6.4.13 Indenospiropiperidines 227
- References 228

## **7 2-Aminopyrimidines 237**

- 7.1 Introduction 237
- 7.2 Marketed 2-Aminopyrimidine Drugs 237
- 7.3 Medicinal Chemistry Case Studies 239
  - 7.3.1 Cardiovascular Applications 239
  - 7.3.2 Central Nervous System Applications 241
  - 7.3.3 Infectious Diseases Applications 245
  - 7.3.4 Inflammation Applications 248
  - 7.3.5 Metabolic Diseases Applications 254
  - 7.3.6 Miscellaneous Applications 255
  - 7.3.7 Oncology Applications 256
- 7.4 Synthesis of 2-Aminopyrimidines 267
  - 7.4.1 Aminations with 2-Halo or 2,4-Dihalopyrimidines 267
  - 7.4.2 Cross-Coupling Reactions with 2-Aminopyrimidines 270
  - 7.4.3 Aminations with 2-Sulfonylpyrimidines 270
  - 7.4.4 Cyclizations with Guanidines 272
- References 272

## **8 2-Aminothiazoles 284**

- 8.1 Introduction 284
- 8.2 Marketed 2-Aminothiazole Drugs 284
- 8.3 Medicinal Chemistry Case Studies 286
  - 8.3.1 Cardiovascular Diseases Applications 286
  - 8.3.2 Central Nervous System Applications 288
  - 8.3.3 Infectious Diseases Applications 292
  - 8.3.4 Inflammation Applications 296
  - 8.3.5 Metabolic Diseases Applications 299
  - 8.3.6 Oncology Applications 301
  - 8.3.7 Miscellaneous Applications 305
- 8.4 Synthesis of 2-Aminothiazoles 306
  - 8.4.1 Hantzsch Synthesis from  $\alpha$ -Functionalized Ketones and Thioureas 306
  - 8.4.2 Hantzsch Synthesis from Ketones and Thioureas 306
  - 8.4.3 Synthesis from  $\alpha$ -Haloketones and Thiocyanates 308
  - 8.4.4 Synthesis from Vinyl Azides and Thiocyanates 308
  - 8.4.5 Synthesis from Amidines and Thiocyanates 309
  - 8.4.6 Synthesis from Alkenyl and Alkynyl Compounds with Thiocyanates or Thioureas 309
  - 8.4.7 Miscellaneous Syntheses 309
  - 8.4.8 Elaboration of 2-Aminothiazoles 311
- References 311

<b>9</b>	<b>2-(Hetero)Arylindoles</b>	<b>321</b>
9.1	Introduction	321
9.2	Marketed 2-Arylindole Drugs	321
9.3	Medicinal Chemistry Case Studies	321
9.3.1	Cardiovascular Applications	321
9.3.2	Central Nervous System Applications	322
9.3.3	Infectious Diseases Applications	323
9.3.4	Inflammation Applications	325
9.3.5	Men's and Women's Health Applications	326
9.3.6	Metabolic Diseases Applications	328
9.3.7	Miscellaneous Applications	328
9.3.8	Oncology Applications	328
9.4	Synthesis of 2-(Hetero)Arylindoles	332
9.4.1	Functionalization to the Preformed Indole System	332
9.4.1.1	2-Functionalized Metallated Indoles with Aryl Halides (Strategy 1)	332
9.4.1.2	2-Halogenated or 2-Triflated Indoles with Functionalized Arenes (Strategy 1)	332
9.4.1.3	Direct Arylation of Indole with Functionalized Arenes (Strategy 2)	334
9.4.1.4	Direct Oxidative Coupling of Indoles with (Hetero)Arenes (Strategy 3)	334
9.4.2	Fischer Indole Synthesis	334
9.4.3	Bischler–Mohlau Indole Synthesis	334
9.4.4	Metal-Catalyzed Approach with Alkynes	334
9.4.4.1	Intramolecular Cyclizations of <i>o</i> -Alkynylanilines (Strategy A)	336
9.4.4.2	Intramolecular Cyclizations of <i>o</i> -Alkynylanilines with Other Groups (Strategy B)	336
9.4.4.3	Intramolecular Cyclizations of <i>o</i> -Haloanilines with Alkynes (Strategy C)	337
9.4.4.4	Intramolecular Cyclizations of <i>o</i> -Alkynylhaloarenes with Primary Amines (Strategy D)	340
9.4.4.5	Miscellaneous Transition Metal-Catalyzed Reactions	340
9.4.4.6	Reductive Cyclizations of <i>o</i> -Nitroalkynylarenes	342
9.4.5	Intramolecular Reductive Cyclizations of <i>o</i> -Nitro (or Azido)alkenylarenes	342
9.4.6	Cyclizations of Arylamido and Arylimine Precursors	343
9.4.7	Cyclizations of <i>o</i> -Vinylaminoarenes	344
9.4.8	Cyclizations with <i>N</i> -Arylenamines or <i>N</i> -Arylenaminones	344
9.4.9	Multicomponent Synthesis	345
9.4.10	Radical Cyclization Reactions	346
9.4.11	Miscellaneous Cyclizations with <i>o</i> -Substituted Anilines	346
	References	348
<b>10</b>	<b>Tetrahydroisoquinolines</b>	<b>356</b>
10.1	Introduction	356
10.2	Marketed THIQ Drugs	356
10.3	Medicinal Chemistry Case Studies	357
10.3.1	Cardiovascular Applications	357
10.3.2	Central Nervous System Applications	359
10.3.3	Infectious Diseases Applications	365
10.3.4	Inflammation Applications	366
10.3.5	Men's and Women's Health Applications	369
10.3.6	Metabolic Diseases Applications	369
10.3.7	Miscellaneous Applications	370
10.3.8	Oncology Applications	372
10.4	Synthesis of THIQs	376
10.4.1	Pictet–Spengler Reactions	376
10.4.1.1	Classical Pictet–Spengler Reactions	376
10.4.1.2	Pictet–Spengler Reactions with Masked Carbonyl Compounds	377
10.4.1.3	Modified Pictet–Spengler Reactions	377
10.4.1.4	Pictet–Spengler-Type Reactions	377

10.4.1.5	Pictet–Spengler Synthesis of Tic	378
10.4.2	Transition Metal-Catalyzed Reactions	379
10.4.2.1	Intramolecular $\alpha$ -Arylation Reactions	379
10.4.2.2	Intramolecular Cyclizations of <i>N</i> -Propargylbenzylamines	379
10.4.2.3	Intramolecular Heck Cyclizations	379
10.4.2.4	Intramolecular Nucleophilic Additions	379
10.4.2.5	One-Pot Multistep Metal-Catalyzed Cyclization Reactions	380
10.4.3	Multicomponent Synthesis of THIQs	382
10.4.4	Synthesis of 3-Aryltetrahydroisoquinolines	382
10.4.5	Synthesis of 4-Aryltetrahydroisoquinolines	383
10.4.6	Miscellaneous Intramolecular Cyclizations	386
10.4.7	Asymmetric Reduction of 1-Substituted-3,4-Dihydroisoquinolines	387
10.4.7.1	Iridium-Catalyzed Hydrogenations of Dihydroisoquinolines, Isoquinoline Salts, and Isoquinolines	388
10.4.7.2	Ruthenium- and Rhodium-Catalyzed Reductions of Dihydroisoquinolines	389
10.4.7.3	Asymmetric Additions to Dihydroisoquinolines, Dihydroisoquinoline Salts, and Dihydroisoquinoline <i>N</i> -Oxides	389
10.4.7.4	Asymmetric Intramolecular Cyclizations	391
10.4.7.5	Asymmetric Intramolecular Cyclizations with Chiral Sulfoxides	391
10.4.7.6	Miscellaneous Asymmetric Preparations	392
10.4.8	Arylations of THIQs	393
10.4.9	C–H Functionalization of THIQs	395
10.4.9.1	Direct C-1 (Hetero)Arylations of THIQs	395
10.4.9.2	Oxidative C-1 CDC Reactions	395
10.4.9.3	Oxidative C-1 CDC with $\beta$ -Ketoesters	396
10.4.9.4	Oxidative C-1 CDC with Ketones	397
10.4.9.5	Oxidative C-1 CDC with Indoles	397
10.4.9.6	Oxidative C-1 CDC with Aliphatic Nitro Compounds	398
10.4.9.7	Oxidative C-1 CDC with Alkynes	399
10.4.9.8	Oxidative C-1 CDC with Alkenes	399
10.4.9.9	Oxidative C-1 Cross-Dehydrogenative Phosphonations	400
10.4.9.10	Miscellaneous Oxidative C-1 CDC Reactions	400
	References	401
<b>11</b>	<b>2,2-Dimethylbenzopyrans</b>	<b>414</b>
11.1	Introduction	414
11.2	Marketed 2,2-Dimethylpyran Drugs	414
11.3	Medicinal Chemistry Case Studies	415
11.3.1	Cardiovascular Applications	415
11.3.2	Central Nervous System Applications	416
11.3.3	Infectious Diseases Applications	418
11.3.4	Inflammation Applications	419
11.3.5	Metabolic Diseases Applications	419
11.3.6	Oncology Applications	419
11.3.7	Cannabinoid Receptors	421
11.4	Synthesis of 2,2-Dimethylbenzopyrans	423
11.4.1	Annulations of Phenol Derivatives with Unsaturated Systems	423
11.4.1.1	Annulations of Phenol Derivatives with Simple Alkenes	423
11.4.1.2	Annulations of Phenol Derivatives with $\alpha,\beta$ -Unsaturated Systems	424
11.4.1.3	Annulations of Phenol Derivatives with Nitroalkenes	424
11.4.1.4	Annulations of Phenol Derivatives with Allylic Alcohols	424
11.4.1.5	Annulations of Phenol Derivatives with Propargyl Alcohols	425
11.4.2	Replacement of the Methyl Group of 2,2-Dimethylbenzopyrans	425

11.4.3	Functionalization of 2,2-Dimethylbenzopyrans	426
11.4.4	Fused 2,2-Dimethylbenzopyran Ring Systems	428
11.4.5	Solid-Phase Synthesis of 2,2-Dimethylbenzopyrans	428
	References	429
<b>12</b>	<b>Hydroxamates</b>	<b>435</b>
12.1	Introduction	435
12.2	Marketed Hydroxame Drugs	435
12.3	Medicinal Chemistry Case Studies	436
12.3.1	Central Nervous System Applications	436
12.3.2	Infectious Diseases Applications	436
12.3.3	Inflammation Applications	439
12.3.4	Men's and Women's Health Applications	452
12.3.5	Metabolic Diseases Applications	453
12.3.6	Oncology Applications	453
12.4	Synthesis of Hydroxamates	466
12.4.1	Synthesis of Hydroxamates from Carboxylic Acids	466
12.4.2	Synthesis of Hydroxamates from Carboxylic Acid Derivatives	466
12.4.2.1	Synthesis of Hydroxamates from Esters	466
12.4.2.2	Synthesis of Hydroxamates from Acid Chlorides	468
12.4.2.3	Synthesis of Hydroxamates from Oxazolidinones	468
12.4.3	Miscellaneous Syntheses of Hydroxamates	469
12.4.4	Solid-Phase Synthesis of Hydroxamates	469
	References	470
<b>13</b>	<b>Bicyclic Pyridines Containing Ring-Junction Nitrogen</b>	<b>481</b>
13.1	Introduction	481
13.2	Marketed Bicyclic Ring-Junction Pyridine Drugs	481
13.3	Medicinal Chemistry Case Studies	482
13.3.1	Cardiovascular Applications	482
13.3.2	Central Nervous System Applications	483
13.3.3	Gastrointestinal Applications	487
13.3.4	Infectious Diseases Applications	488
13.3.5	Inflammation Applications	491
13.3.6	Metabolic Diseases Applications	493
13.3.7	Miscellaneous Applications	494
13.3.8	Oncology Applications	494
13.4	Synthesis of Pyrazolo[1,5- <i>a</i> ]pyridines	498
13.4.1	[3+2] Dipolar Cycloadditions	498
13.4.2	Intramolecular Cyclizations	499
13.4.3	From <i>N</i> -Aminopyridinium Ylides	500
13.4.4	From 2-Substituted Pyridines	500
13.4.5	Thermal and Radical Cyclizations	500
13.5	Synthesis of Imidazo[1,5- <i>a</i> ]pyridines	501
13.5.1	From 2-Methylaminopyridines	501
13.5.2	From 2-Methylaminopyridine Amides	502
13.5.3	From 2-Methylaminopyridine Thioamides or Thioureas	503
13.5.4	From Pyridine-2-Carbaldehydes (Picolinaldehydes)	503
13.5.5	From 2-Cyanopyridines	503
13.5.6	From Pyridine-2-Esters	504
13.5.7	From Di-2-Pyridyl Ketones	504
13.5.8	From Pyridotriazoles	504
13.5.9	Miscellaneous Syntheses	504

13.5.10	Chemical Elaborations of Imidazo[1,5- <i>a</i> ]pyridines	505
13.6	Synthesis of Imidazo[1,2- <i>a</i> ]pyridines	507
13.6.1	Ugi Three-Component Reactions	507
13.6.1.1	Classical Ugi Three-Component Reactions of 2-Aminopyridines, Aldehydes, and (Iso)Nitriles	507
13.6.1.2	Modified Ugi Three-Component Reactions	507
13.6.2	From 2-Aminopyridines and Carbonyl Compounds	509
13.6.2.1	From 2-Aminopyridines and Methyl Ketones	509
13.6.2.2	From 2-Aminopyridines and $\beta$ -Ketoesters	509
13.6.2.3	From 2-Aminopyridines and Miscellaneous Ketones	510
13.6.2.4	From Pyridines and 2-Aminopyridines with $\alpha$ -Haloketones or $\alpha$ -Haloaldehydes	511
13.6.3	From 2-Aminopyridines and Alkynes	512
13.6.3.1	From 2-Aminopyridines and Alkynes	512
13.6.3.2	From 2-Aminopyridines, Alkynes, and Aldehydes	513
13.6.4	From 2-Aminopyridines and $\alpha,\beta$ -Unsaturated Systems	513
13.6.5	From 2-Aminopyridines and Nitroolefins	515
13.6.6	Cyclizations from 2-Aminopropargylpyridines	515
13.6.7	Cyclizations from Pyridyl Enamines(ones)	517
13.6.8	From Other Heterocycles	517
13.6.9	Miscellaneous Syntheses	518
13.6.10	Chemical Elaboration of Imidazo[1,2- <i>a</i> ]pyridines	520
13.6.10.1	Cross-Coupling Reactions of Pre-functionalized Imidazo[1,2- <i>a</i> ]pyridines	520
13.6.10.2	C—H Functionalization of Imidazo[1,2- <i>a</i> ]pyridines	521
13.6.11	Fused Imidazo[1,2- <i>a</i> ]pyridine Ring Systems	523
	References	525

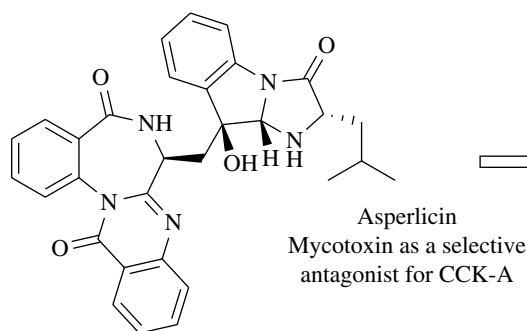
<b>Index</b>	536
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## Introduction

### 1.1 The Original Definition of Privileged Structures

In 1988, Ben Evans and his research team at Merck in their quest for potent, selective, orally effective cholecystokinin (CCK) antagonists studied the prototype 3-(acylamino)-5-phenyl-2*H*-1,4-benzodiazepines as therapeutic agents derived from the natural product lead asperlicin [1]. Evans recognized the core structure exhibited affinity toward central and peripheral benzodiazepine, opiate, CCK-A,  $\alpha$ -adrenergic, serotonin, muscarinic, and angiotensin I receptors. To quote verbatim from the words of Ben Evans in this seminal publication, which set in force the term “privileged structures” for the next three decades in two different paragraphs:

Thus, this single ring system, the 5-phenyl-1,4-benzodiazepine ring, provided ligands for a surprisingly diverse collection of receptors, the natural ligands for which appear to bear little resemblance to one another or to the benzodiazepines in question. The only obvious similarity is among the benzodiazepine structures themselves. These structures appear to contain common features which facilitate binding to various proteinaceous receptor surfaces, perhaps through binding elements different from those employed for binding of the natural ligands.

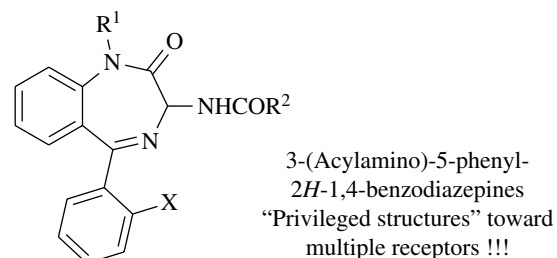


Arguments have been constructed to suggest that structures with high affinity for a given receptor may be more numerous, but at the same time more difficult to pinpoint than has heretofore been appreciated. The development of the compounds described here has illustrated an approach to that end having potentially wider utility, selective modification of “privileged structures” known to have provided ligands for diverse receptors in the past.

IUPAC has provided a structural definition of privileged structures—“Substructural feature which confers desirable (often drug-like) properties on compounds containing that feature. Often consists of a semi-rigid *scaffold* which is able to present multiple hydrophobic *residues* without undergoing hydrophobic collapse” [2].

### 1.2 The Role of Privileged Structures in the Drug Discovery Process

There are many steps in the drug discovery process to deliver a drug from initial chemical hits, lead optimization, chemical development and scale-ups, clinical trials, and FDA approvals to the market. Nowadays, it takes an average of 12–15 years and almost 800 million to 1 billion dollars of investment to deliver a single therapeutic drug to the market [3]. The lead optimization strategies are key steps for the medicinal chemists, and for this to occur, chemical



hits for specific targets need to be validated. There are many strategies that have been employed in the search for chemical hits such as high-throughput screening of corporate compound libraries [4–6], virtual screening [7–10], and natural products as sources of new drugs [11–13]. Once the chemical hits are discovered, “medicinal chemistry” tools such as fragment-based drug design [14, 15], analogue-based drug design [16–18], Lipinski’s Rule of Five [19], bioisosteric replacements [20–22], “repurposing” old drugs [23–25], computer-aided drug design (CADD) [7, 26–29], scaffold hopping [30, 31], selective optimization of side activities (SOSA approach) [32], and early ADME pharmacokinetic analyses [33, 34] are employed in the lead optimization stages of the drug discovery process.

The use of privileged structures is a viable strategy in the discovery of new medicines at the lead optimization stages of the drug discovery process. There are several published reviews which find that “privileged structures” are useful concepts for the rational design of new lead drug candidates [35–40]. These “privileged structures” tend to provide highly favorable characteristics in which alterations to the core structures lead to different levels of potency and specificity. Using these privileged structures as starting points for drug discovery, thousands of molecules can be synthesized for a range of therapeutic biological targets of interest. Furthermore, privileged structures typically exhibit drug-like properties, which could lead to viable leads for further development. One must be careful and thoughtful in the drug discovery process that sometimes there are no true explanations why certain structures are privileged or why they are active against a particular group of targets. Though numerous repeated frameworks appear in biologically active molecules, no clear explanations exist for their privileged nature.

### 1.3 The Loose Definitions of “Privileged Structures”

Since the original definition of “privileged structures” coined by Evans in 1988, the definition has gone through several reiterations [39]. Privileged structures are liberally referred nowadays in many different terms such as privileged scaffolds, chemotypes, molecular fragments,

privileged structural motifs, and molecular scaffolds. There are no rigorous rules that define a structure as “privileged,” but typically they contain two or three ring systems that are connected by single bonds or by ring-fusion. The structures that results from such arrangements are usually rigid frameworks that can show the appended functionality in a well-defined fashion that is desirable for molecular recognition of the biological target, and it is usually the variable nature of these functionalities that define the selectivity on a privileged core for a particular target.

### 1.4 Synthesis and Biological Activities of Carbocyclic and Heterocyclic Privileged Structures

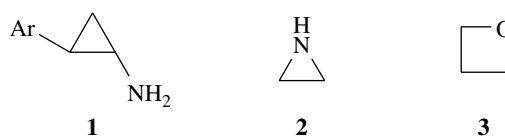
Stockwell assembled one of the most comprehensive listings of privileged scaffolds in tabular forms [38]. We also provide a detailed tabular presentation of the privileged scaffolds based on ring size and fused-ring classifications. The series of tables are based on structures, the titles of the review article, and the reference numbers in each table under the appropriate listings. We hope it will be a useful source of inspiration for the drug discovery community of organic and medicinal chemists.

#### 1.4.1 Synthesis and Biological Activities of Three- and Four-Membered Ring Privileged Structures

There are only a few reviews published on the three- and four-membered ring privileged structures and they are listed in Table 1.1.

#### 1.4.2 Synthesis and Biological Activities of Five-Membered Ring Privileged Structures

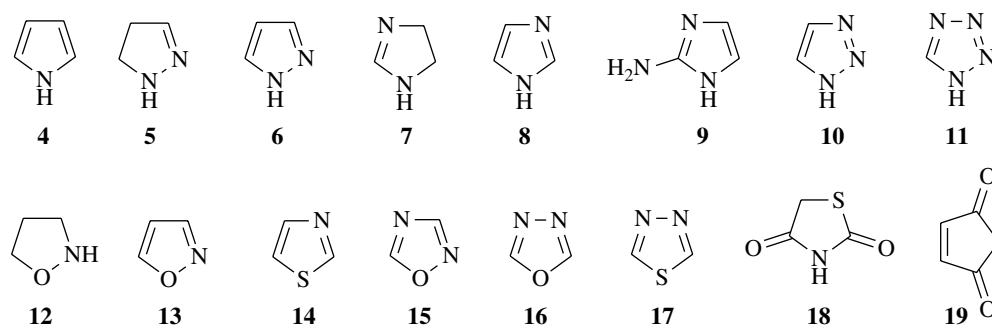
Numerous reviews on the synthesis and biological activities of five-membered ring privileged structures are outlined in Table 1.2.



**Table 1.1** List of three- and four-membered ring privileged structures reviews.

Structure	Number	Review title	Reference
Phenylcyclopropylamines	1	An overview of phenylcyclopropylamine derivatives: Biochemical and biological significance and recent developments	[41]
Aziridines	2	Synthetic aziridines in medicinal chemistry: A mini-review	[42]
Oxetanes	3	Oxetanes: Recent advances in synthesis, reactivity, and medicinal chemistry	[43]
Oxetanes	3	Oxetanes as versatile elements in drug discovery and synthesis	[44]





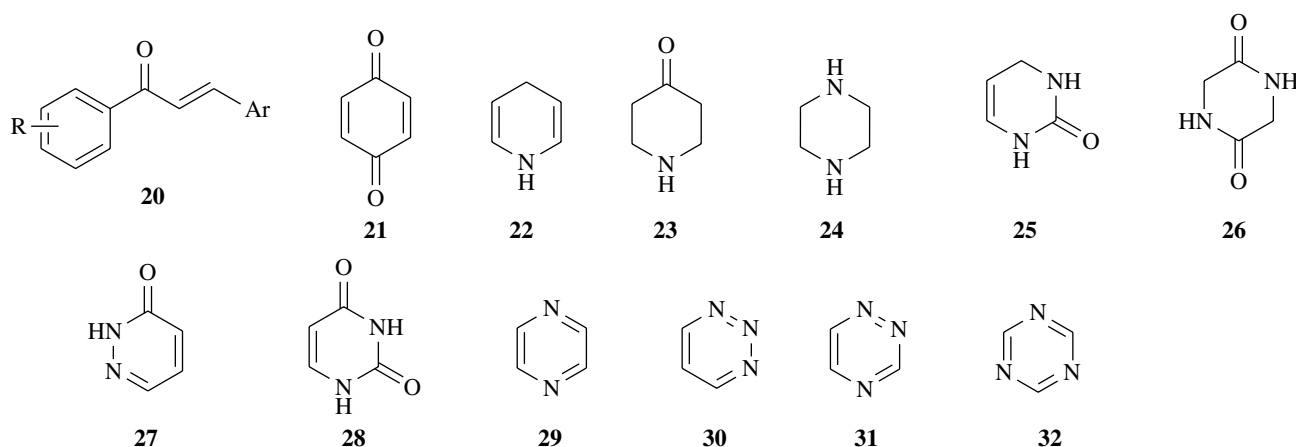
**Table 1.2** List of five-membered ring privileged structures reviews.

Structure	Number	Review title	Reference
Pyrroles	4	Pyrrole: An emerging scaffold for construction of valuable therapeutic agents	[45]
Pyrazolines	5	Synthesis and biological activity of chiral dihydropyrazole: Potential lead for drug design	[46]
Pyrazolines	5	Pyrazolines: A biological review	[47]
Pyrazoles	6	Recent advances in bioactive pyrazoles	[48]
Pyrazoles	6	The therapeutic voyage of pyrazole and its analogs: A review	[49]
Pyrazoles	6	Pyrazoles as promising scaffold for the synthesis of anti-inflammatory and/or antimicrobial agents: A review	[50]
Pyrazoles	6	Pyrazole derivatives as antitumor, anti-inflammatory and antibacterial agents	[51]
Pyrazoles	6	Recent progress on pyrazole scaffold-based antimycobacterial agents	[52]
2-Imidazolines	7	Biologically active compounds based on the privileged 2-imidazoline scaffold: The world beyond adrenergic/imidazoline receptor modulators	[53]
Imidazoles	8	Imidazoles as promising scaffolds for antibacterial activity: A review	[54]
Imidazoles	8	Imidazoles as potential antifungal agents: A review	[55]
Imidazoles	8	Comprehensive review in current developments of imidazole-based medicinal chemistry	[56]
2-Aminoimidazoles	9	2-Aminoimidazoles in medicinal chemistry	[57]
1,2,3-Triazoles	10	Click chemistry for drug development and diverse chemical-biology applications	[58]
1,2,3-Triazoles	10	1,2,3-Triazole in heterocyclic chemistry, endowed with biological activity, through 1,3-dipolar cycloadditions	[59]
1,2,3-Triazoles	10	<i>In situ</i> click chemistry: probing the binding landscapes of biological molecules	[60]
Tetrazoles	11	Potential pharmacological activities of tetrazoles in the new millennium	[61]
Tetrazoles	11	5-Substituted-1 <i>H</i> -tetrazoles as carboxylic acid isosteres: Medicinal chemistry and synthetic methods	[62]
Tetrazoles	11	Tetrazole as a core unit biological evaluation agent	[63]
Isoxazolidines	12	Isoxazolidine: A privileged scaffold for organic and medicinal chemistry	[64]
Isoxazole	13	The isoxazole ring and its <i>N</i> -oxide: A privileged core structure in neuropsychiatric therapeutics	[65]
Thiazoles	14	Recent applications of 1,3-thiazole core structures in the identification of new lead compounds and drug discovery	[66]
Thiazoles	14	Bioactive thiazole and benzothiazole derivatives	[67]
Oxadiazoles	15, 16	Recent updates on biological activities of oxadiazoles	[68]
Oxadiazoles	15, 16	Synthesis and biological activities of oxadiazole derivatives: A review	[69]
1,2,4-Oxadiazoles	15	[1,2,4]-Oxadiazoles: Synthesis and biological applications	[70]

(Continued)

Table 1.2 (Continued)

Structure	Number	Review title	Reference
1,3,4-Oxadiazoles	16	1,3,4-Oxadiazoles: An emerging scaffold to target growth factors, enzymes and kinases as anticancer agents	[71]
1,3,4-Oxadiazoles	16	1,3,4-Oxadiazole: A privileged structure in antiviral agents	[72]
1,3,4-Oxadiazoles	16	1,3,4-Oxadiazole: A biologically active scaffold	[73]
1,3,4-Oxadiazoles	16	1,3,4-Oxadiazole derivatives as potential biological agents	[74]
1,3,4-Oxadiazoles	16	Oxadiazoles as privileged motifs for promising anticancer leads: Recent advances and future prospects	[75]
1,3,4-Thiadiazoles	17	Biological and pharmacological activities of 1,3,4-thiadiazole based compounds	[76]
1,3,4-Thiadiazoles	17	Thiadiazole—a promising structure in medicinal chemistry	[77]
2,4-Thiazolidinediones	18	Therapeutic journey of 2,4-thiazolidinediones as a versatile scaffold: An insight into structure–activity relationship	[78]
Cyclopentenediones	19	Chemical properties and biological activities of cyclopentenediones	[79]



#### 1.4.3 Synthesis and Biological Activities of Six-Membered Ring Privileged Structures

Plenty of reviews are available for the synthesis and biological activities of six-membered ring privileged structures listed in Table 1.3.

#### 1.4.4 Synthesis and Biological Activities of Bicyclic 5/5 and 6/5 Ring Privileged Structures

There is no shortage of synthesis and biological activities of bicyclic 5/5 and 6/5 ring privileged structures reviews listed in Table 1.4.

#### 1.4.5 Synthesis and Biological Activities of Bicyclic 6/6 and 6/7 Ring Privileged Structures

Again, there is no shortage of synthesis and biological activities of the popular bicyclic 6/6 ring privileged structures reviews listed in Table 1.5.

#### 1.4.6 Synthesis and Biological Activities of Tricyclic and Tetracyclic Ring Privileged Structures

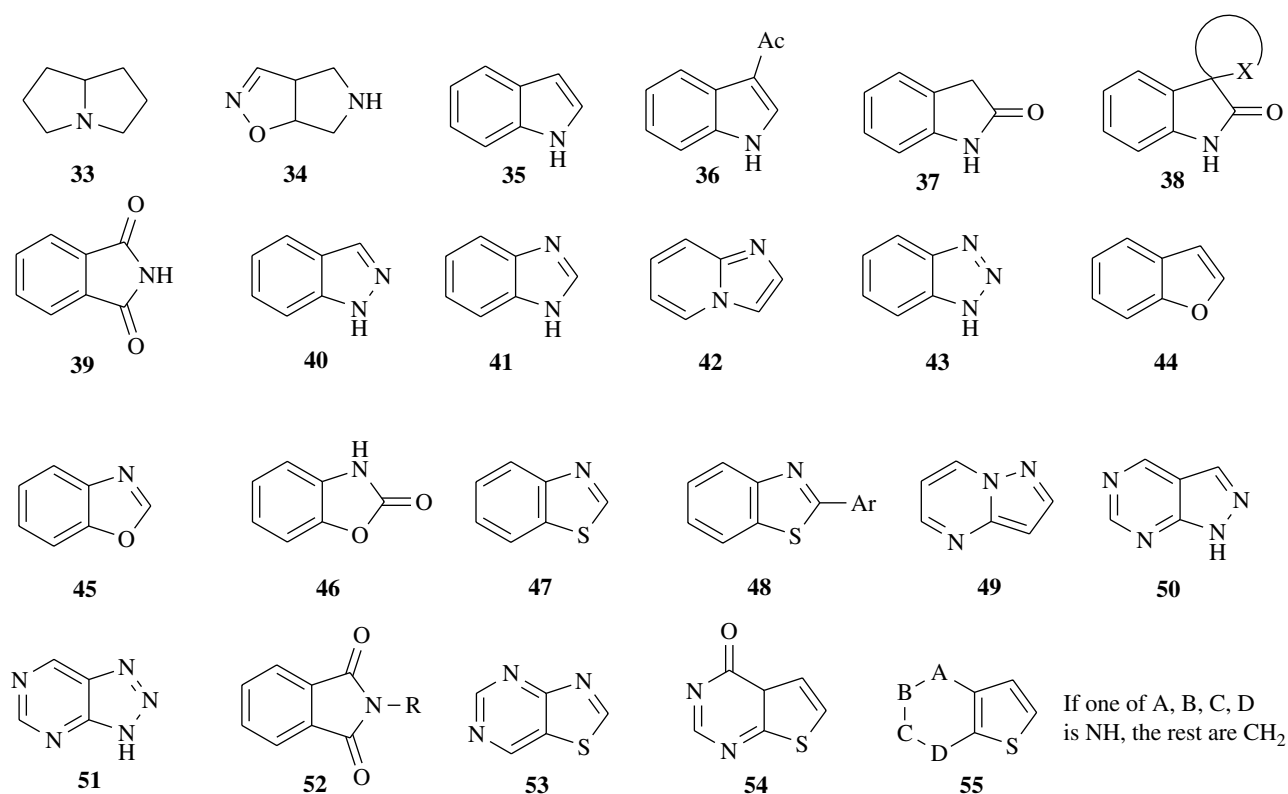
A general review on the use of tricyclic structures in medicinal chemistry appeared a decade ago [162]. Table 1.6 outlines recent reviews on the use of specific tricyclic and tetracyclic structures employed in medicinal chemistry programs.

### 1.5 Combinatorial Libraries of “Privileged Structures”

If we entertained the idea of “privileged structures” as core structures for low molecular weight compounds, analogous to the fragment-based method of drug discovery, combinatorial chemistry protocols can be

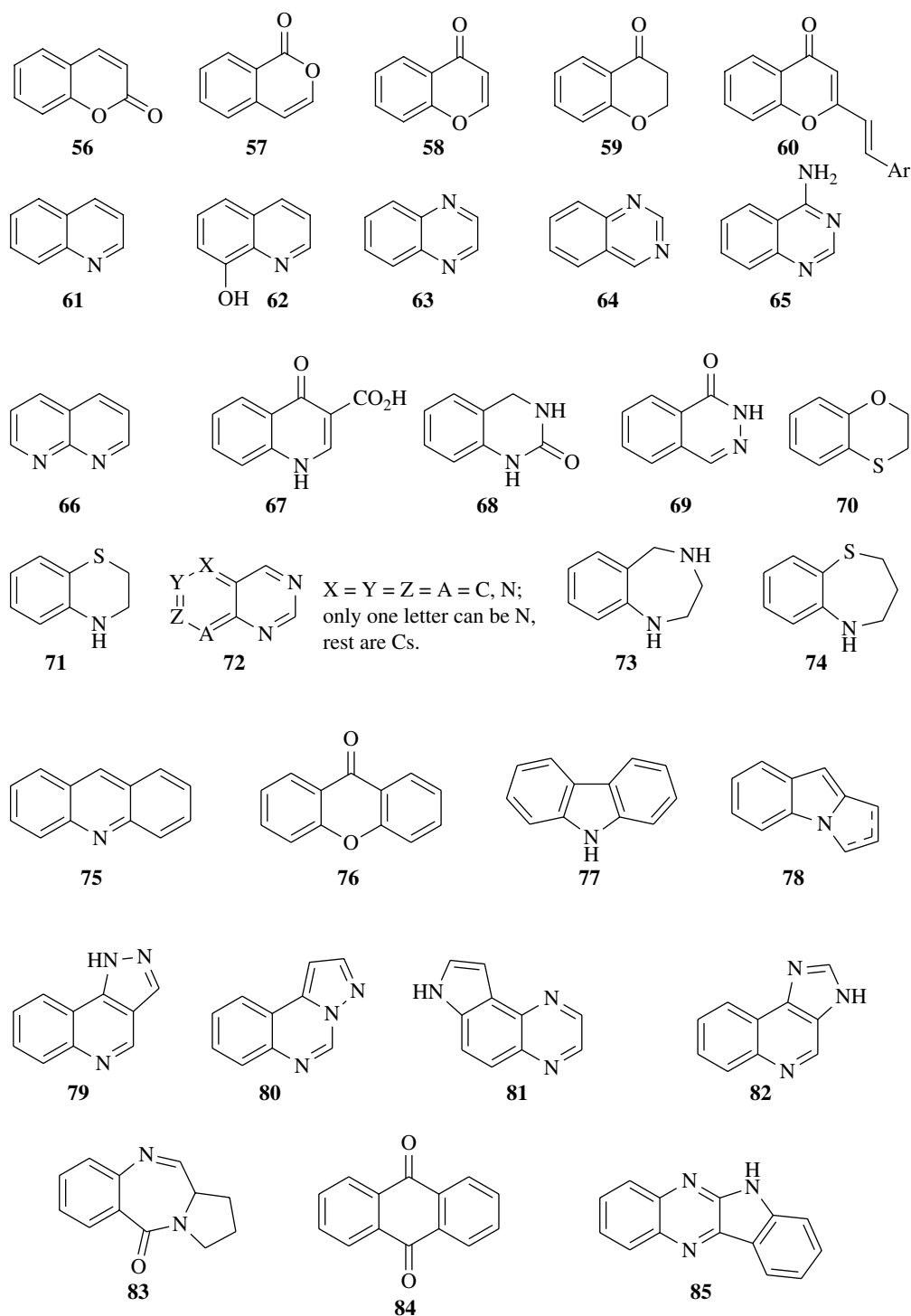
**Table 1.3** List of six-membered ring privileged structures reviews.

Structure	Number	Review title	Reference
Chalcones	20	Anti-cancer chalcones: Structural and molecular target perspectives	[80]
Chalcones	20	Exploring pharmacological significance of chalcone scaffold: A review	[81]
Chalcones	20	Chalcone: A privileged structure in medicinal chemistry	[82]
Benzoquinones	21	Perspectives on medicinal properties of benzoquinone compounds	[83]
1,4-Dihydropyridines	22	1,4-Dihydropyridines: A class of pharmacologically important molecules	[84]
1,4-Dihydropyridines	22	1,4-Dihydropyridines as calcium channel ligands and privileged structures	[85]
1,4-Dihydropyridines	22	Dihydropyridines: Evaluation of their current and future pharmacological applications	[86]
Piperidin-4-ones	23	Piperidin-4-one: The potential pharmacophore	[87]
Piperazines	24	Piperazine scaffold: A remarkable tool in generation of diverse pharmacological agents	[88]
Piperazines	24	An evolving role of piperazine moieties in drug design and discovery	[89]
Dihydropyrimidinones	25	Recent advances in the pharmacology of dihydropyrimidinones	[90]
Dihydropyrimidinones	25	Recent synthetic and medicinal perspectives of dihydropyrimidinones: A review	[91]
2,5-Diketopiperazines	26	2,5-Diketopiperazines as neuroprotective agents	[92]
Pyridazinones	27	The therapeutic journey of pyridazinone	[93]
Uracils	28	In search of uracil derivatives as bioactive agents. Uracils and fused uracils: Synthesis, biological activity and applications	[94]
Pyrazines	29	Unequivocal role of pyrazine ring in medicinally important compounds: A review	[95]
1,2,3-Triazines	30	1,2,3-Triazine scaffold as a potent biologically active moiety: A mini-review	[96]
1,2,3-Triazines	30	Triazine as a promising scaffold for its versatile biological behavior	[97]
1,2,4-Triazines	31	1,2,4-Triazine analogs as novel class of therapeutic agents	[98]
1,3,5-Triazines	32	Medicinal chemistry discoveries among 1,3,5-triazines: recent advances (2000–2013) as antimicrobial, anti-TB and antimalarials	[99]
1,3,5-Triazines	32	1,3,5-Triazine-based analogues of purines: From isosteres to privileged scaffolds in medicinal chemistry	[100]



**Table 1.4** List of bicyclic 5/5 and 6/5 ring privileged structures reviews.

Structure	Number	Review title	Reference
Pyrrolizines	33	An integrated overview on pyrrolizines as potential anti-inflammatory, analgesic and antipyretic agents	[101]
Pyrroloisoxazoles	34	Pyrroloisoxazole: A key molecule with diverse biological actions	[102]
Indoles	35	From nature to drug discovery: The indole scaffold as a “privileged structure”	[103]
Indoles	35	Indoles as therapeutics of interest in medicinal chemistry: Bird’s eye view	[104]
Indoles/indazoles	35/40	Chemistry and biology of indoles and indazoles	[105]
3-Acetylindoles	36	3-Acetylindoles: Synthesis, reactions and biological activities	[106]
Oxindoles	37	Oxindole: A chemical prism carrying plethora of therapeutic benefits	[107]
Oxindoles	37	Indolinones as promising scaffold as kinase inhibitors	[108]
Spirooxindoles	38	Spirooxindoles: Promising scaffolds for anticancer agents	[109]
Phthalimides	39	Recent advances in the chemistry of phthalimide analogues and their therapeutic potential	[110]
Benzimidazoles	41	Comprehensive review in current developments of benzimidazole-based medicinal chemistry	[111]
Benzimidazoles	41	Functionalized benzimidazole scaffolds: Privileged heterocycle for drug design in therapeutic medicine	[112]
Benzimidazoles	41	Benzimidazoles: An ideal privileged drug scaffold for the design of multitargeted anti-inflammatory ligands	[113]
Imidazo[1,2- <i>a</i> ]pyridines	42	Recent progress in the pharmacology of imidazo[1,2- <i>a</i> ]pyridines	[114]
Imidazo[1,2- <i>a</i> ]pyridines	42	Imidazo[1,2- <i>a</i> ]pyridine scaffold as prospective therapeutic agents	[115]
Benzotriazoles	43	Benzotriazole: An overview on its versatile biological behavior	[116]
Benzofurans	44	Bioactive benzofuran derivatives: An insight on lead developments, radioligands and advances of the last decade	[117]
Benzofurans	44	Bioactive benzofuran derivatives: A review	[118]
Benzofurans	44	Biological and medicinal significance of benzofuran	[119]
Benzoxazoles	45	Recent advances in the development of pharmacologically active compounds that contain a benzoxazole scaffold	[120]
Benzoxazoles	45	Benzoxazoles and oxazolopyridines in medicinal chemistry studies	[121]
2(3 <i>H</i> )-Benzoxazolones	46	2(3 <i>H</i> )-Benzoxazolone and bioisosteres as “privileged scaffold” in the design of pharmacological probes	[122]
Benzothiazoles	47	Recent advances in the chemistry and biology of benzothiazoles	[123]
2-Arylbenzothiazoles	48	2-Arylbenzothiazole as a privileged scaffold in drug discovery	[124]
Pyrazolo[1,5- <i>a</i> ]pyrimidines	49	An insight on synthetic and medicinal aspects of pyrazolo[1,5- <i>a</i> ]pyrimidine scaffold	[125]
Pyrazolo[3,4- <i>d</i> ]pyrimidines	50	4-Amino-substituted pyrazolo[4,3- <i>d</i> ]pyrimidines: Synthesis and biological properties	[126]
Pyrazolo[3,4- <i>d</i> ]pyrimidines	50	Biologically driven synthesis of pyrazolo[3,4- <i>d</i> ]pyrimidines as protein kinase inhibitors: An old scaffold as a new tool for medicinal chemistry and chemical biology studies	[127]
8-Azapurines	51	8-Azapurine nucleus: A versatile scaffold for different targets	[128]
Thalidomides	52	Thalidomide as a multi-template for development of biologically active compounds	[129]
Thiazolo[4,5- <i>d</i> ]pyrimidines	53	Thiazolo[4,5- <i>d</i> ]pyrimidines as a privileged scaffold in drug discovery	[130]
Thieno[2,3- <i>d</i> ]pyrimidin-4-ones	54	Recent developments regarding the use of thieno[2,3- <i>d</i> ]pyrimidin-4-one derivatives in medicinal chemistry, with a focus on their synthesis and anticancer properties	[131]
Tetrahydrothieno-pyridines	55	Synthesis and biological activity of substituted-4,5,6,7-tetrahydrothienopyridines: A review	[132]



established for privileged structures, with their inherent affinity for diverse biological receptors, represent an ideal source of core scaffolds and capping fragments for the design and synthesis of combinatorial libraries to enable numerous targets to be processed simultaneously across different therapeutic areas

[174]. The majority of privileged structures contain multiple sites for diversification by chemical modifications to achieve a huge number of possible pharmacological profiles.

Dolle published very comprehensive surveys of combinatorial libraries annually for over a decade [175–187].

**Table 1.5** List of bicyclic 6/6 and 6/7 ring privileged structures reviews.

Structure	Number	Review title	Reference
Coumarins	56	Biological importance of structurally diversified chromenes	[133]
Coumarins	56	Current developments of coumarin-based anti-cancer agents in medicinal chemistry	[134]
Coumarins	56	Coumarin: A privileged scaffold for the design and development of antineurodegenerative agents	[135]
Coumarins	56	Benzocoumarins: Isolation, synthesis, and biological activities	[136]
Isocoumarins	57	Isocoumarins, miraculous natural products blessed with diverse pharmacological activities	[137]
Chromones	58	Chromone: A valid scaffold in medicinal chemistry	[138]
Chroman-4-ones	59	Recent advances of chroman-4-one derivatives: Synthetic approaches and bioactivities	[139]
2-Styrylchromones	60	Biological activities of 2-styrylchromones	[140]
2-Styrylchromones	60	An overview of 2-styrylchromones: Natural occurrence, synthesis, reactivity and biological properties	[141]
Quinolines	61	The concept of privileged structures in rational drug design: Focus on acridine and quinoline scaffolds in neurodegenerative and protozoan diseases	[142]
Quinolines	61	Biological activities of quinoline derivatives	[143]
Quinolines	61	Quinoline as a privileged scaffold in cancer drug discovery	[144]
Quinolines	61	A review on anticancer potential of bioactive heterocycle quinolone	[145]
8-Hydroxyquinolines	62	8-Hydroxyquinolines in medicinal chemistry: A structural perspective	[146]
8-Hydroxyquinolines	62	8-Hydroxyquinoline: A privileged structure with a broad-ranging pharmacological potential	[147]
Quinoxalines	63	Quinoxaline, its derivatives and applications: A state of the art review	[148]
Quinoxalines	63	Quinoxaline-based scaffolds targeting tyrosine kinases and their potential anticancer activity	[149]
Quinazolines	64	Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification	[150]
4-Aminoquinazolines	65	4-Aminoquinazoline analogs: A novel class of anticancer agents	[151]
1,8-Naphthyridines	66	1,8-Naphthyridine derivatives: A review of multiple biological activities	[152]
4-Quinolone-3-carboxylic acids	67	The 4-quinolone-3-carboxylic acid motif as a multivalent scaffold in medicinal chemistry	[153]
Dihydroquinazolinones	68	Synthetic strategy with representation on mechanistic pathway for the therapeutic applications of dihydroquinazolinones	[154]
Phthalazinones	69	Phthalazin-1(2 <i>H</i> )-one as a remarkable scaffold in drug discovery	[155]
Dihydrobenzo[1,4]-oxathiines	70	Dihydrobenzo[1,4]oxathiine: A multi-potent pharmacophoric heterocyclic nucleus	[156]
1,4-Benzothiazines	71	Functionalized 1,4-benzothiazine: A versatile scaffold with diverse biological properties	[157]
Pyridopyrimidines	72	Recent advances in the chemistry and biology of pyridopyrimidines	[158]
1,4-Benzodiazepine	73	Recent development in [1,4]benzodiazepines as potent anticancer agents: A review	[159]
1,4-Benzodiazepine	73	Benzo- and thienobenzodiazepines: Multi-target drugs for CNS disorders	[160]
1,5-Benzothiazepine	74	1,5-Benzothiazepine, a versatile pharmacophore: A review	[161]

**Table 1.6** List of tricyclic and tetracyclic ring privileged structures reviews.

Structure	Number	Review title	Reference
Acridines	75	The concept of privileged structures in rational drug design: Focus on acridine and quinolone scaffolds in neurodegenerative and protozoan diseases	[142]
Xanthenes	76	Recent insight into the biological activities of synthetic xanthone derivatives	[163]
Carbazoles	77	Biological potential of carbazole derivatives	[164]
Pyrrolo[1,2- <i>a</i> ]indoles	78	Synthesis and some biological properties of pyrrolo[1,2- <i>a</i> ]indoles	[165]
Pyrazoloquinolines	79	An overview on synthetic methodologies and biological activities of pyrazoloquinolines	[166]
Pyrazoloquinazolines	80	Pyrazoloquinazolines: Synthetic strategies and bioactivities	[167]
Pyrroloquinazolines	81	The chemistry and pharmacology of privileged pyrroloquinazolines	[168]
Pyrroloquinoxalines	81	Recent progress in biological activities and synthetic methodologies of pyrroloquinoxalines	[169]
Imidazoquinolines	82	Imidazoquinolines: Recent developments in anticancer activity	[170]
Pyrrolobenzodiazepines	83	Biosynthesis, synthesis, and biological activities of pyrrolobenzodiazepines	[171]
Anthraquinones	84	Anthraquinones as pharmacological tools and drugs	[172]
6 <i>H</i> -indolo[2,3- <i>b</i> ]quinoxalines	85	6 <i>H</i> -indolo[2,3- <i>b</i> ]quinoxalines: DNA and protein interacting scaffold for pharmacological studies	[173]

**Table 1.7** Combinatorial synthesis of privileged structures reviews.

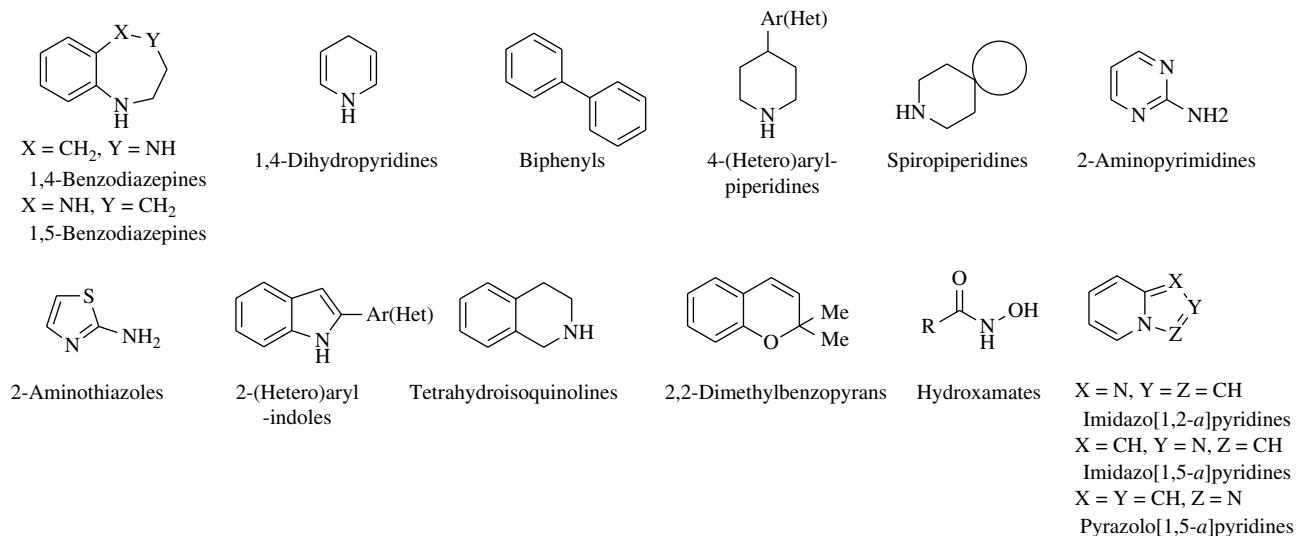
Review title	Reference
Recent advances in the solid-phase combinatorial synthetic strategies for the quinoxaline, quinazoline and benzimidazole based privileged structures	[188]
The combinatorial synthesis of bicyclic privileged structures or privileged substructures	[189]
Privileged scaffolds for library design and drug discovery	[38]
Recent advances in the solid-phase combinatorial synthetic strategies for the benzodiazepine based privileged structures	[190]
Exploring privileged structures: the combinatorial synthesis of cyclic peptides	[191]
Libraries from natural product-like scaffolds	[192]
Privileged structure-based combinatorial libraries targeting G protein-coupled receptors	[193]
Nitrogen containing privileged structures and their solid phase combinatorial synthesis	[194]
Design, synthesis, and evaluation of small-molecule libraries	[195]
Advances in solution- and solid-phase synthesis toward the generation of natural product-like libraries	[196]

Many of the information in the annual surveys show original library syntheses based on privileged structures. Table 1.7 shows combinatorial synthetic reviews on privileged structures.

## 1.6 Scope of this Monograph

The author's inspiration for this monograph occurred years ago when three pivotal reviews in the literature appeared on the topic of privileged structures in drug discovery. Stockwell's [38] monumental and comprehensive tables of privileged scaffolds for library design and Fraga's

[37], DeSimone's [39], and Costantino's [40] reviews on selected privileged structures case studies spurred the author's motivation to pursue a monograph on this topic of "privileged structures." During the preparation of this monograph, Bräse edited a book titled *Privileged Scaffolds in Medicinal Chemistry – Design, Synthesis, Evaluation* in 2016 from different viewpoints [197]. Chapters included  $\beta$ -lactams, (benz)imidazoles, pyrazoles, quinolones, isoquinolines, rhodanines, coumarins, xanthenes, spirocycles, and cyclic peptides as privileged scaffolds in medicinal chemistry. Other key chapters included heterocycles containing nitrogen and sulfur as potent biologically active scaffolds, thiirane class of gelatinase inhibitors



as a privileged template that crosses the blood–brain barrier, natural product scaffolds of value in medicinal chemistry, and ergot alkaloids. *We will keep the nomenclature of “privileged structures” for the rest of the book !!!*

The author has selected a dozen privileged structures such as the benzodiazepines, 1,4-dihydropyridines, biphenyls, 4-arylpiperidines, spiropiperidines, 2-aminopyrimidines, 2-aminothiazoles, 2-arylindoles, tetrahydroisoquinolines, 2,2-dimethylbenzopyrans,

hydroxamates, and imidazopyridines to showcase the use of these structures in drug discovery programs. Each chapter will have a listing of the FDA-approved marketed drug with that “privileged structure,” followed by detailed sections of medicinal chemistry case studies across multiple therapeutic areas and finally comprehensive sections on the syntheses of the structures employing classical and state-of-the-art organic chemistry reactions.

## References

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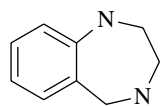
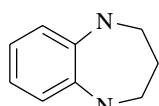
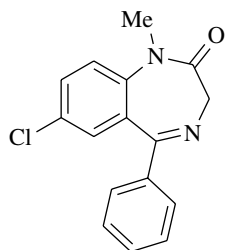
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## 2

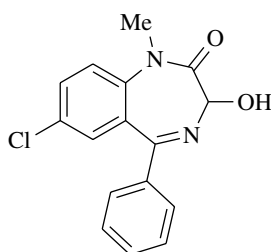
## Benzodiazepines

## 2.1 Introduction

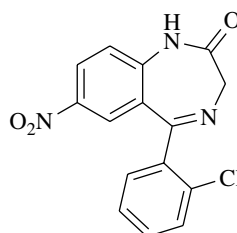
Benzodiazepine (BDZ) privileged structures are represented as the 1,4-benzodiazepene or the 1,5-benzodiazepine cores and it should be fitting that we start with this class of structures as it is where Evans and his research team coined the original term of “privileged structures” in 1988 when they studied potent, selective, orally effective 1,4- benzodiazepine (CCK antagonists as therapeutic agents from the natural product lead asperlicin [1]. Evans recognized the 1,4-benzodiazepine core structures exhibited affinity toward central and peripheral BDZ, opiate, CCK-A,  $\alpha$ -adrenergic, serotonin, muscarinic, and angiotensin I receptors. As mentioned in the Chapter 1, each chapter will have a short introduction, followed by a list of marketed drugs containing the “privileged structures,” then medicinal chemistry case studies, and the classical and state-of-the-art chemical syntheses of the “privileged structures” will round out the rest of the chapter.

1,4-Benzodiazepene  
core1,5-Benzodiazepene  
core**Diazepam**

Trade Name: Valium™  
Roche  
Launched: 1963  
MW = 284.70

**Temazepam**

Trade Name: Restoril™  
Mallinckrodt  
Launched: 1981  
MW = 300.74

**Clonazepam**

Trade Name: Klonopin™  
Roche  
Launched: 1975  
MW = 315.72

## 2.2 Marketed BDZ Drugs

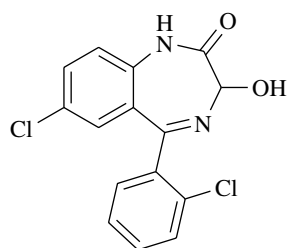
Many of the BDZ drugs that have been marketed over the last half century are of central nervous system therapeutic value. The marketed drugs are organized in the following sections in relation to their 1,4- or 1,5-benzodiazepine systems.

## 2.2.1 1,4-Benzodiazepine Marketed Drugs

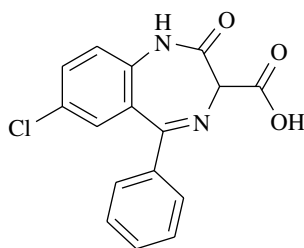
Diazepam, marketed as Valium™ by Roche, is a BDZ with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnesic properties and has a long duration of action [2, 3]. It is used in the treatment of severe anxiety disorders, as a hypnotic in the short-term management of insomnia, as a sedative and premedicant, as an anticonvulsant, and in the management of alcohol withdrawal syndrome.

Temazepam, marketed as Restoril™ by Mallinckrodt, is a 3-hydroxy analog of diazepam and is one of diazepam's primary active metabolites and is approved for the short-term use of insomnia [4].

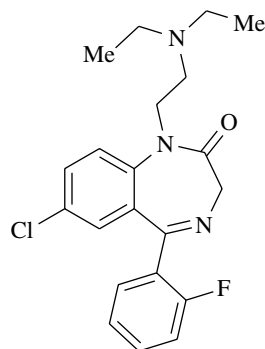
Clonazepam, sold under the trade name Klonopin™, is an anticonvulsant used for several types of seizures, including myotonic or atonic seizures, photosensitive epilepsy, and absence seizures, although tolerance may develop [5, 6]. It is seldom effective in generalized tonic-clonic or partial seizures [4].

**Lorazepam**

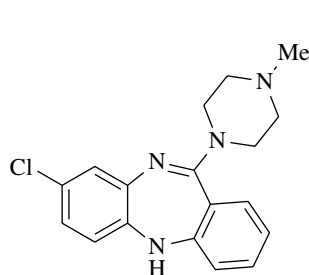
Trade Name: Ativan™  
 Actavis  
 Launched: 1977  
 MW = 321.16

**Clorazepate**

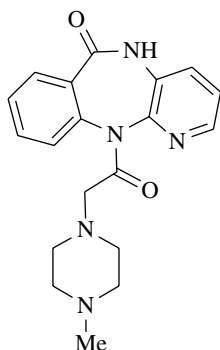
Trade Name: Tranxene™  
 Hoffmann La Roche  
 Launched: 1972  
 MW = 314.72

**Flurazepam**

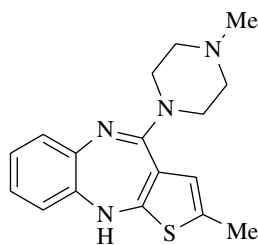
Trade Name: Dalmane™  
 Hoffmann La Roche  
 Launched: 1970  
 MW = 387.88

**Clozapine**

Trade Name: Clozaril™  
 Novartis  
 Launched: 1989  
 MW = 326.82

**Pirenzepine**

Trade Name: Gastrozepin™  
 Valley Forge Pharmaceuticals  
 Launched: 1980s  
 MW = 351.40

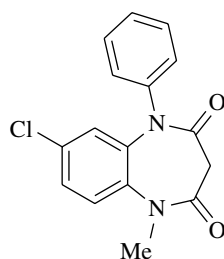
**Olanzapine**

Trade Name: Zyprexa™  
 Lilly  
 Launched: 1996  
 MW = 312.44

Lorazepam, marketed as Ativan™ by Actavis, is a BDZ used to treat anxiety disorders or anxiety associated with depression [7, 8]. Clorazepate, sold as Tranxene™, is a BDZ derivative that has anxiolytic, anticonvulsant, sedative, hypnotic, and skeletal muscle relaxant properties [9, 10]. Flurazepam, marketed as Dalmane™, is BDZ derivative which also possesses anxiolytic, anticonvulsant, sedative, and skeletal muscle relaxant properties [11]. Flurazepam produces a metabolite with a very long half-life for 40–250 h, which may stay in the bloodstream for up to 4 days and thus is used in patients who have difficulty in maintaining sleep.

## 2.2.2 1,5-Benzodiazepine Marketed Drugs

Clobazam, marketed under the brand name Onfi™, is a BDZ drug with anxiolytic properties since 1975 and as an anticonvulsant since 1984 [12, 13]. Clobazam was approved in 2011 for the treatment of seizures and for adjunctive therapy for epilepsy in patients who have not responded to first-line drugs and in children who are refractory to first-line drugs [14].

**Clobazam**

Trade Name: Onfi™  
 Lundbeck  
 Launched: 1975  
 MW = 300.74

## 2.2.3 Linearly Fused BDZ Marketed Drugs

Clozapine, marketed by Novartis as Clozaril™, is an atypical antipsychotic medication used in the treatment of schizophrenia and is also used off-label in the treatment of bipolar disorder [15–17]. Clozapine is classified as an atypical antipsychotic drug because of its profile of binding to serotonin as well as dopamine receptors. Clozapine is usually used as a last resort in patients that have not responded to other antipsychotic treatments due to its danger of causing agranulocytosis as well as the costs of having to have blood tests continually during treatment. It is, however, one of the very effective antipsychotic treatment choices.