PRIVILEGED STRUCTURES IN DRUG DISCOVERY

MEDICINAL CHEMISTRY AND SYNTHESIS

LARRY YET

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Privileged Structures in Drug Discovery

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Medicinal Chemistry and Synthesis

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Contents

1

Introduction

1.1 The Original Definition of Privileged Structures

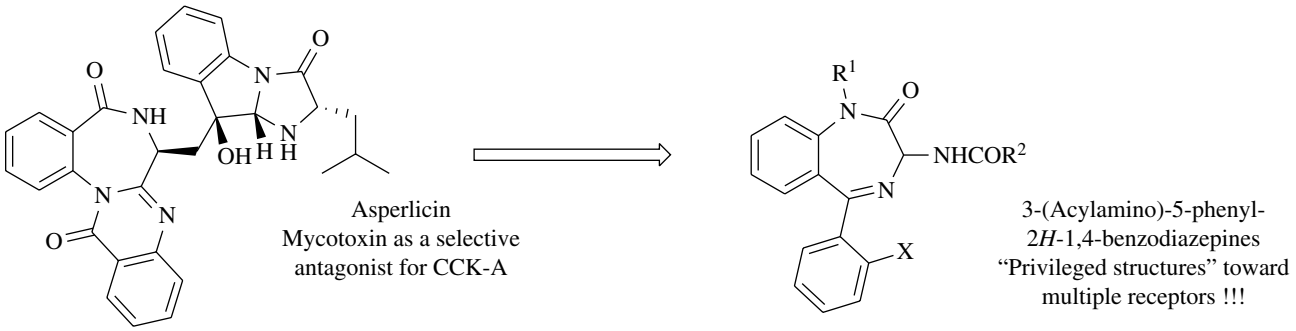
In 1988, Ben Evans and his research team at Merck in their quest for potent, selective, orally effective cholecystokinin (CCK) antagonists studied the prototype 3-(acylamino)-5-phenyl-2*H*-1,4-benzodiazepines as therapeutic agents derived from the natural product lead asperlicin [1]. Evans recognized the core structure exhibited affinity toward central and peripheral benzodiazepine, opiate, CCK-A, α-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



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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

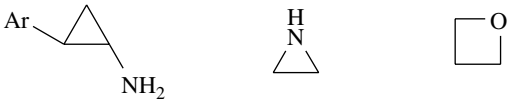
Stockwell assembled one of the most comprehensive listings of privileged scaffolds in tabular forms [38]. We also provide a detailed tabular presentation of the privileged scaffolds based on ring size and fused-ring classifications. The series of tables are based on structures, the titles of the review 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.



1 **2** **3**

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]

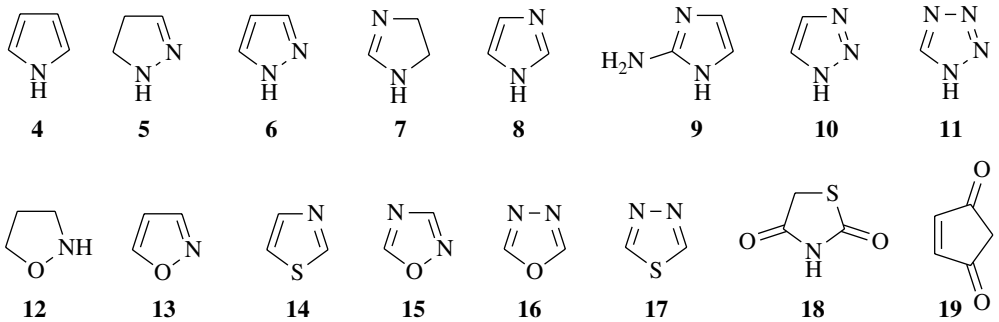


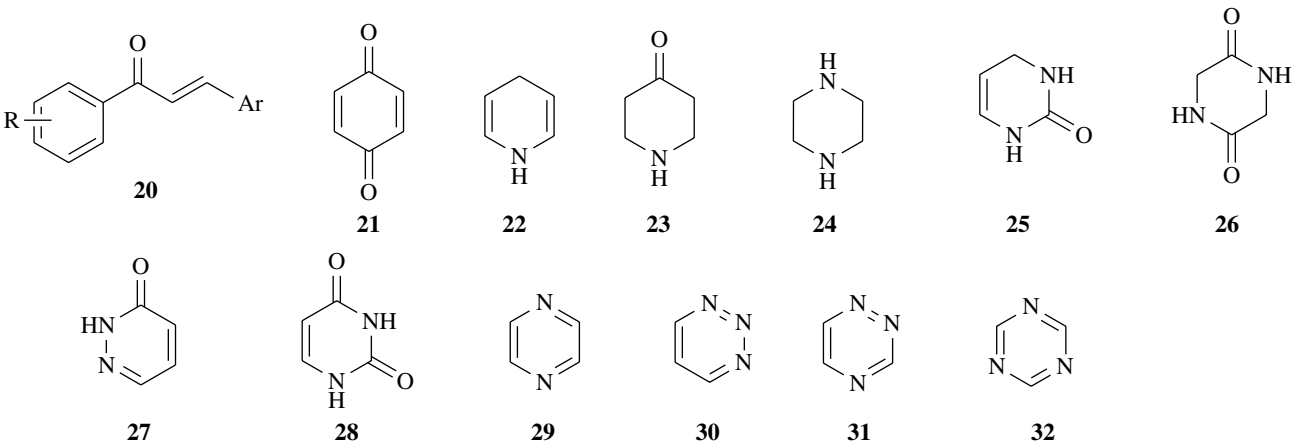
Table 1.2 List of five-membered ring privileged structures reviews.

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**	*In situ* 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*H*-tetrazoles as carboxylic acid isosteres: Medicinal chemistry and synthetic methods	[62]
Tetrazoles	**11**	Tetrazole as a core unit biological evaluation agent	[63]
Isoxazolidines	**12**	Isozazolidine: A privileged scaffold for organic and medicinal chemistry	[64]
Isoxazole	**13**	The isoxazole ring and its *N*-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-Oxiadiazoles: 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]

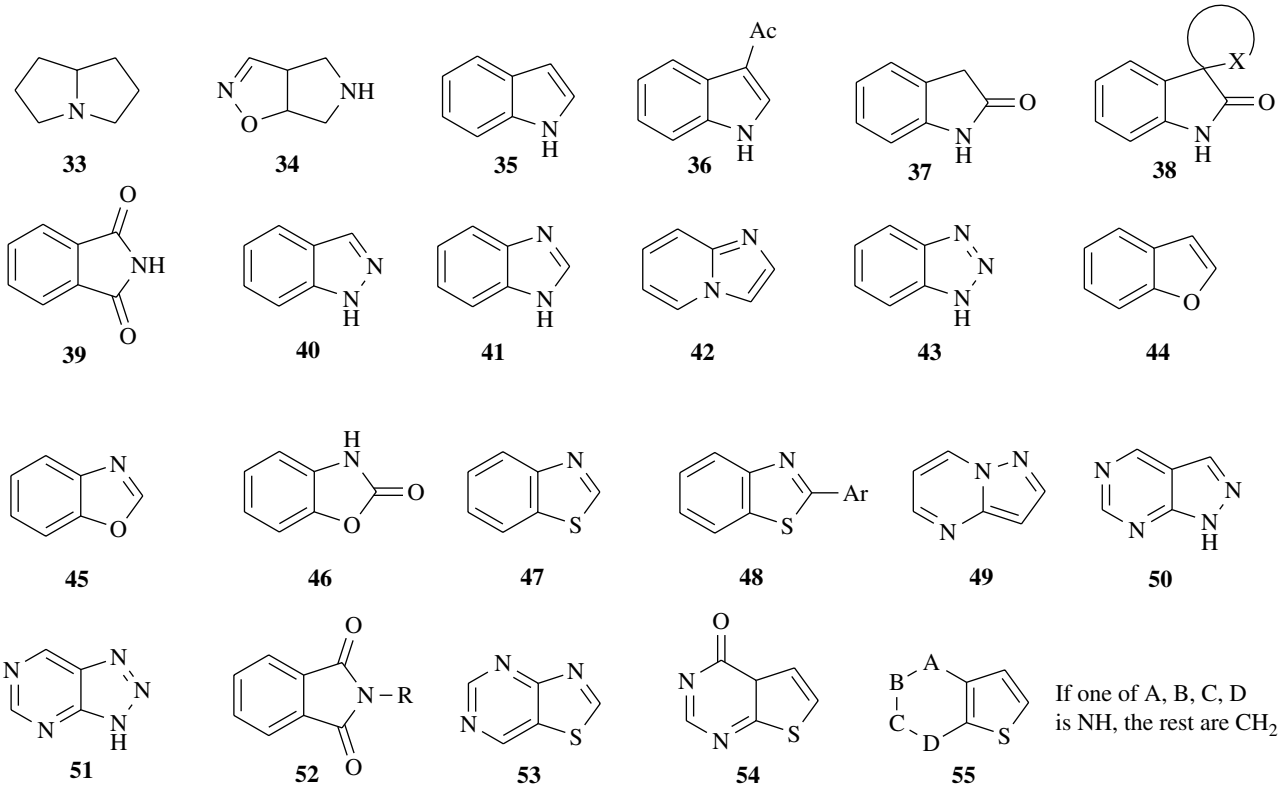
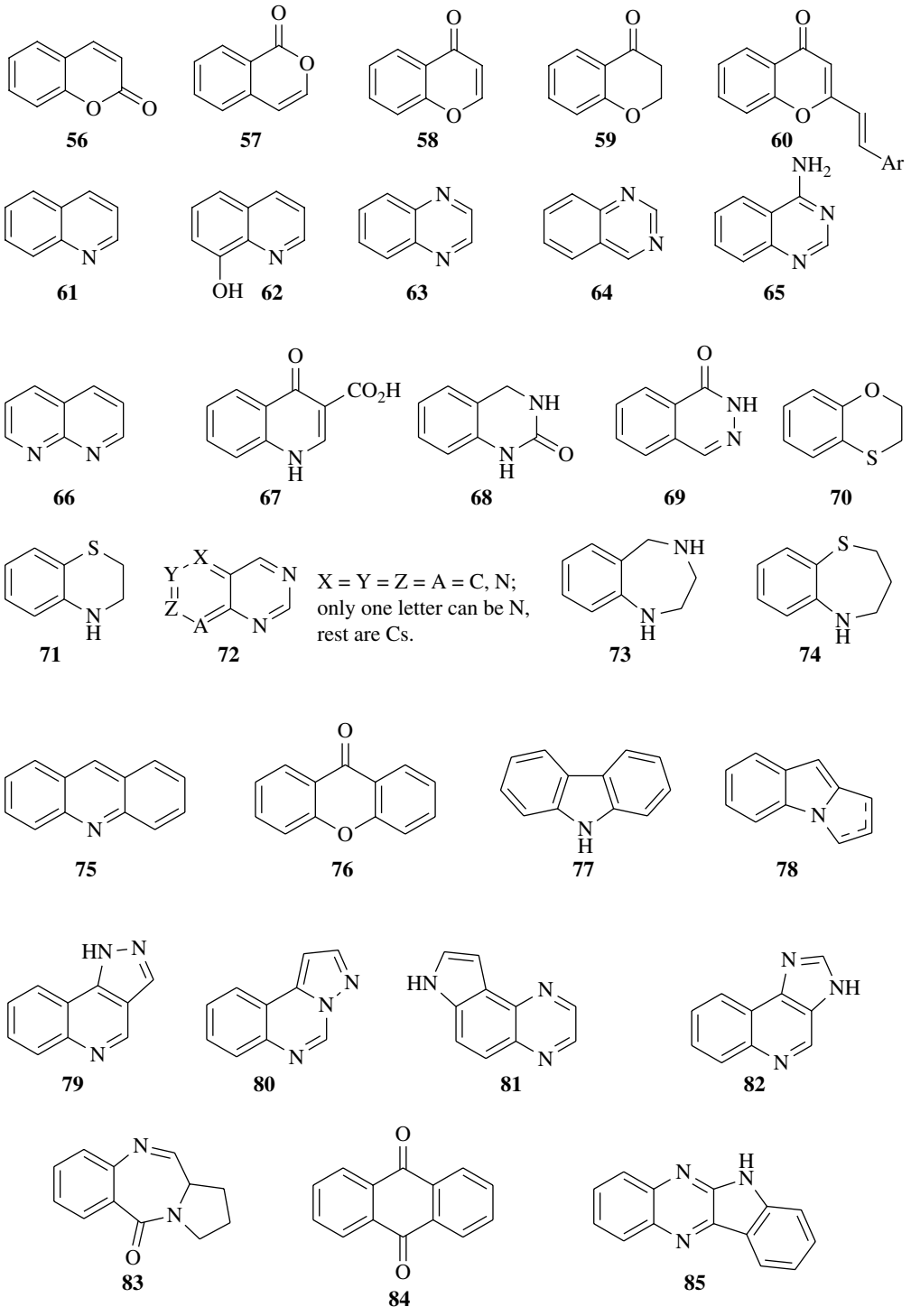


Table 1.4 List of bicyclic 5/5 and 6/5 ring privileged structures reviews.

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**	Spiroxoindoles: 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-*a*]pyridines	**42**	Recent progress in the pharmacology of imidazo[1,2-*a*]pyridines	[114]
Imidazo[1,2-*a*]pyridines	**42**	Imidazo[1,2-*a*]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 derivates: 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*H*)-Benzoxazolones	**46**	2(3*H*)-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-*a*]pyrimidines	**49**	An insight on synthetic and medicinal aspects of pyrazolo[1,5-*a*]pyrimidine scaffold	[125]
Pyrazolo[3,4-*d*]pyrimidines	**50**	4-Amino-substituted pyrazolo[4,3-*d*]pyrimidines: Synthesis and biological properties	[126]
Pyrazolo[3,4-*d*]pyrimidines	**50**	Biologically driven synthesis of pyrazolo[3,4-*d*]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**	Thialidomide as a multi-template for development of biologically active compounds	[129]
Thiazolo[4,5-*d*]pyrimidines	**53**	Thiazolo[4,5-*d*]pyrimidines as a privileged scaffold in drug discovery	[130]
Thieno[2,3-*d*] pyrimidin-4-ones	**54**	Recent developments regarding the use of thieno[2,3-*d*]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*H*)-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]
Xanthones	**76**	Recent insight into the biological activities of synthetic xanthone derivatives	[163]
Carbazoles	**77**	Biological potential of carbazole derivatives	[164]
Pyrrolo[1,2-*a*]indoles	**78**	Synthesis and some biological properties of pyrrolo[1,2-*a*]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*H*-indolo[2,3-*b*] quinoxalines	**85**	6*H*-indolo[2,3-*b*]quinoxalines: DNA and protein interacting scaffold for pharmacological studies	[173]

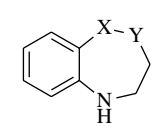
Table 1.7 Combinatorial synthesis of privileged structures reviews.

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]

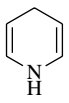
Many of the information in the annual surveys show original library syntheses based on privileged structures. Table 1.7 shows combinatorial synthetic reviews on privileged structures.

1.6 Scope of this Monograph

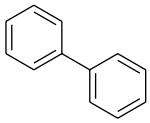
The author's inspiration for this monograph occurred years ago when three pivotal reviews in the literature appeared on the topic of privileged structures in drug discovery. Stockwell's [38] monumental and comprehensive tables of privileged scaffolds for library design and Fraga's [37], DeSimone's [39], 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 β-lactams, (benz)imidazoles, pyrazoles, quinolones, isoquinolines, rhodanines, coumarins, xanthones, 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



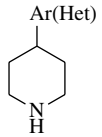
X = CH_2, Y = NH
1,4-Benzodiazepines
X = NH, Y = CH_2
1,5-Benzodiazepines



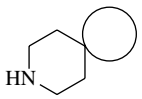
1,4-Dihydropyridines



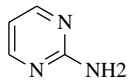
Biphenyls



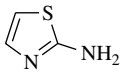
4-(Hetero)aryl-piperidines



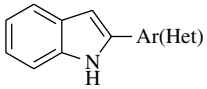
Spiropiperidines



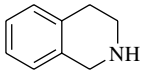
2-Aminopyrimidines



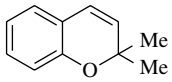
2-Aminothiazoles



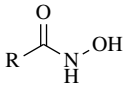
2-(Hetero)aryl-indoles



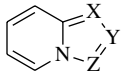
Tetrahydroisoquinolines



2,2-Dimethylbenzopyrans



Hydroxamates



X = N, Y = Z = CH
Imidazo[1,2-*a*]pyridines
X = CH, Y = N, Z = CH
Imidazo[1,5-*a*]pyridines
X = Y = CH, Z = N
Pyrazolo[1,5-*a*]pyridines

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.

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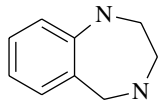
2

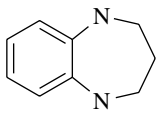
Benzodiazepines

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, α-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 core



1,5-Benzodiazepene core

2.2 Marketed BDZ Drugs

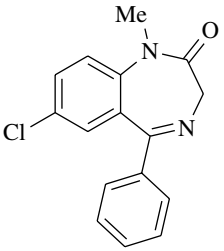
Many of the BDZ drugs that have been marketed over the last half century are of central nervous system therapeutic value. The marketed drugs are organized in the following sections in relation to their 1,4- or 1,5-benzodiazepine systems.

2.2.1 1,4-Benzodiazepine Marketed Drugs

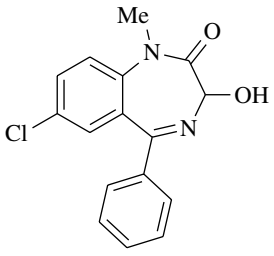
Diazepam, marketed as Valium™ by Roche, is a BDZ with anticonvulsant, anxiolytic, sedative, muscle relaxant, and amnesic properties and has a long duration of action [2, 3]. It is used in the treatment of severe anxiety disorders, as a hypnotic in the short-term management of insomnia, as a sedative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

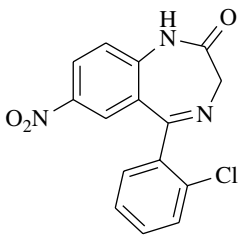
Clonazepam, sold under the trade name Klonopin™, is an anticonvulsant used for several types of seizures, including myotonic or atonic seizures, photosensitive epilepsy, and absence seizures, although tolerance may develop [5, 6]. It is seldom effective in generalized tonic–clonic or partial seizures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



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

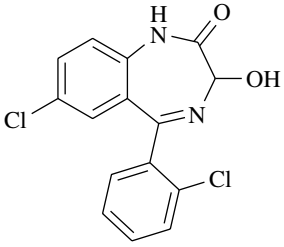


Temazepam
Trade Name: Restoril™
Mallinckrodt
Launched: 1981
MW = 300.74

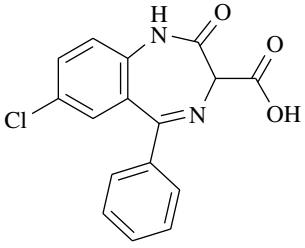


Clonazepam
Trade Name: Klonopin™
Roche
Launched: 1975
MW = 315.72

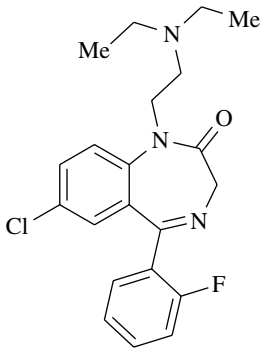
Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis, First Edition. Larry Yet.



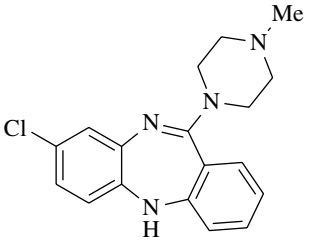
Lorazepam
Trade Name: Ativan™
Actavis
Launched: 1977
MW = 321.16



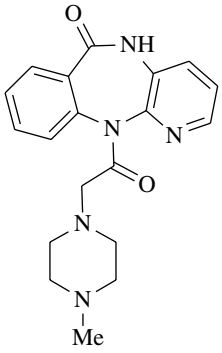
Clorazepate
Trade Name: Tranxene™
Hoffmann La Roche
Launched: 1972
MW = 314.72



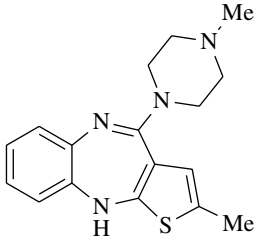
Flurazepam
Trade Name: Dalmane™
Hoffmann La Roche
Launched: 1970
MW = 387.88



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



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

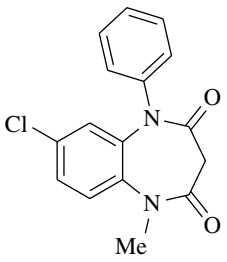


Olanzapine
Trade Name: Zyprexa™
Lilly
Launched: 1996
MW = 312.44

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.

Pirenzepine, sold as Gastrozepin™ by Valley Forge Pharmaceuticals, is a muscarinic M_1 selective receptor antagonist used in the treatment of peptic ulcers by reducing gastric acid secretion and reducing muscle spasm [18, 19]. It promotes the healing of duodenal ulcers and due to its cytoprotective actions it is beneficial in the prevention of duodenal ulcer recurrence.

Olanzapine, marketed under the trade name Zyprexa™ by Lilly, is an atypical antipsychotic, approved by the FDA for the treatment of schizophrenia and bipolar disorder [20–22]. Olanzapine is structurally similar to clozapine, but it is classified as a thienobenzodiazepine. Recently, the radiosynthesis and lipophilicity of [^{11}C]-olanzapine as a new potential PET 5-HT_2 and D_2 receptor radioligand were reported [23]. An interesting multistep continuous flow preparation of olanzapine with high-frequency inductive heating [IH(hf)] was disclosed [24].

2.2.4 Angularly Fused-1,4-Benzodiazepine Marketed Drugs

Estazolam, marketed under the brand name ProSom™, is a BDZ derivative drug developed by Upjohn in the 1970s, which possesses anxiolytic, anticonvulsant, sedative, and skeletal muscle relaxant properties [25]. Estazolam is an intermediate-acting oral BDZ and it is commonly prescribed for short-term treatment of insomnia [26].

Alprazolam, sold as Xanax™ by Pharmacia and Upjohn, is a BDZ class of psychoactive drugs with anxiolytic, sedative, hypnotic, skeletal muscle relaxant, anticonvulsant, and amnestic properties [27–29]. Alprazolam, like other BDZs, binds to specific sites on the $GABA_A$ receptor. Alprazolam is commonly used and FDA approved for the medical treatment of panic disorder and anxiety disorders, such as generalized anxiety disorder (GAD) or social anxiety disorder (SAD).

Triazolam, marketed under the brand name Halcion™, is a BDZ drug which possesses pharmacological properties similar to that of other BDZs, but it is generally only used as a sedative to treat severe insomnia [30]. In addition to the hypnotic properties triazolam possesses, amnesic, anxiolytic, sedative, anticonvulsant, and muscle relaxant properties are also present. Due to its short half-life, triazolam is not effective for patients that suffer from frequent awakenings or early wakening.

Adinazolam, sold as Deracyn™ by Upjohn Company, is triazolobenzodiazpine, which possesses anxiolytic, anticonvulsant, sedative, and antidepressant properties [31, 32]. Adinazolam was developed to enhance the antidepressant properties of alprazolam.

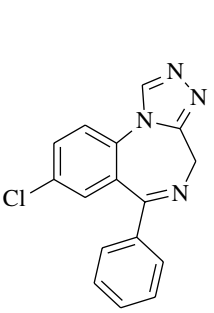
Midazolam, marketed under the trade name Versed™, is a short-acting drug in the BDZ class developed by Hoffmann-La Roche in the 1970s [33–35]. The drug is used for the treatment of acute seizures, moderate-to-severe insomnia, and for inducing sedation and amnesia before medical procedures. It possesses profoundly potent anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties. Midazolam has a fast recovery time and is the most commonly used BDZ as a premedication for sedation; less commonly it is used for induction and maintenance of anesthesia.

2.3 Medicinal Chemistry Case Studies

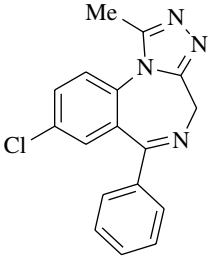
The 1,4-benzodiazepine scaffold is of particular interest in drug design due to a balanced ensemble of beneficial physicochemical properties, including a semi-rigid and compact diazepine ring with spatial placements of several substituents, combined with low number of rotatable bonds, hydrogen bond donors and acceptors, and intermediate lipophilicity [36]. The BDZs no doubt has its very first applications as central system indications but now has expanded into all therapeutic areas in the last decade or two.

2.3.1 Cardiovascular Applications

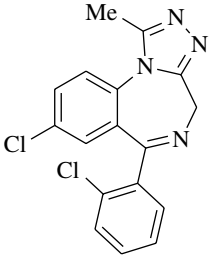
Arginine vasopressin (AVP) is a cyclic non-peptide that exerts its action by binding to three membrane-bound G-protein–coupled receptor (GCPR) subtypes, V_{1a}, V_2,



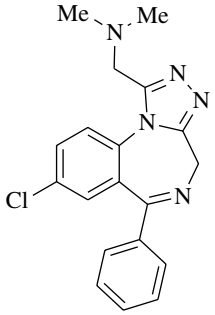
Estazolam
Trade Name: Prosom™
Abbott
Launched: 1990
MW = 294.70



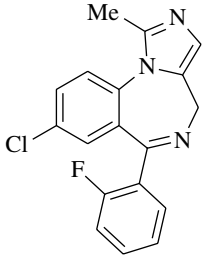
Alprazolam
Trade Name: Xanax™
Pharmacia and Upjohn
Launched: 1981
MW = 308.77



Triazolam
Trade Name: Halcion™
Pharmacia and Upjohn
Launched: 1982
MW = 343.20



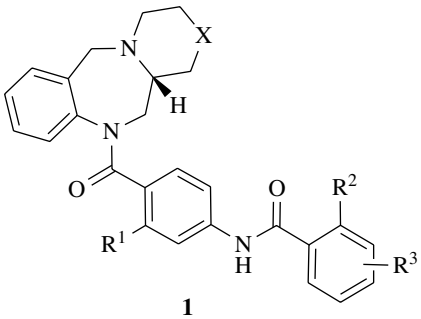
Adinazolam
Trade Name: Deracyn™
Upjohn
Launched: 1980
MW = 351.83



Midazolam
Trade Name: Versed™
Roche
Launched: 1998
MW = 325.78

and V_3 [37–40]. The V_2 receptor is primarily located in the principal cells of the renal collecting ducts and is involved in such important physiological responses such as reabsorption of water in the kidneys and mediates AVP-induced antidiuresis to preserve normal plasma osmolality. Selective non-peptide vasopressin V_2 receptor antagonists have received attention for their potential use in treating diseases of excessive renal reabsorption of water [41]. Johnson and Johnson Pharmaceutical researchers reported non-peptide vasopression V_2 receptor antagonists based on oxazino- and thiazino[1,4]benzodiazepine templates **1** [42] and Japanese workers disclosed pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) V_2 receptor antagonists **2** [43]. The two noted compounds of type **1** showed pronounced aquaretic activity in rats on oral administration.

Vasopressin V_2 receptor selective agonists are a class of antidiuretics with the potential to be useful in the treatment of diseases characterized by the production of large volumes of diluted urine or inadequate levels of AVP, such as central and nephrogenic diabetes insipidus, enuresis, and nocturia [44]. Researchers at Wyeth reported



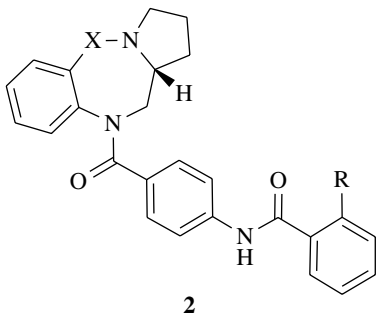
1

X = S, R^1 = H, R^2 = Ph, R^3 = H

V_2 K_i = 3.2 nM; V_1 K_i = 84 nM

X = O, R^1 = Cl, R^2 = Ph, R^3 = H

V_2 K_i = 0.90 nM; V_1 K_i = 24 nM



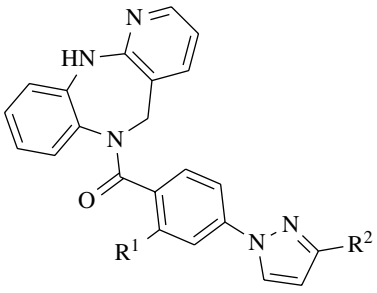
2

X = CH_2, R = Ph

V_2 IC_{50} = 1.2 nM; V_1 IC_{50} = 127 nM

X = C(O), R = Ph

V_2 IC_{50} = 0.22 nM; V_1 = 15.8% inhib. at 10 μM

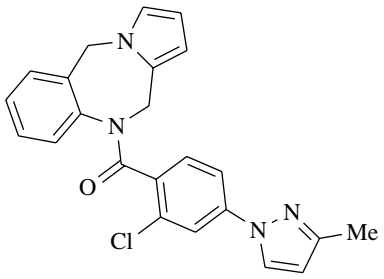


3

R^1 = Cl, R^2 = Me

V_2 binding IC_{50} = 493 nM

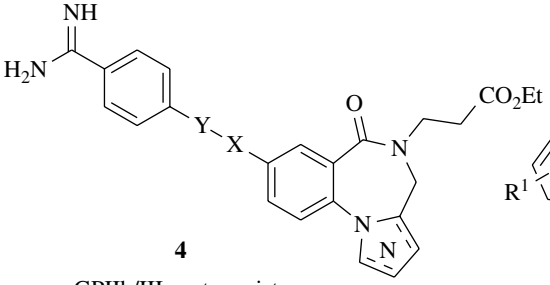
V_1 binding IC_{50} = 5954 nM



WAY-151932 (VNA-932)

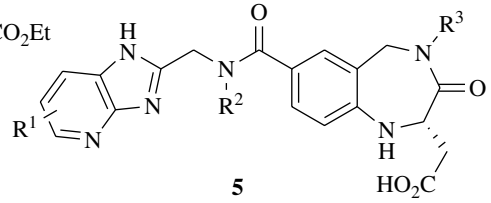
V_2 binding IC_{50} = 80 nM

V_1 binding IC_{50} = 778 nM



4

GPIIb/IIIa antagonists



5

Vitronectin receptor
($\alpha\nu\beta3$) antagonists