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(30) 1998/06/22 (09/102,726) US
(54) **ε-CAPROLACTAMES α-AMINO POLYCYCLIQUES ET
COMPOSES CONNEXES**
(54) **POLYCYCLIC α-AMINO-ε-CAPROLACTAMS AND RELATED
COMPOUNDS**

(57) L'invention concerne des ε-caprolactames α-amino polycycliques et des composés connexes, utiles comme intermédiaires synthétiques dans l'élaboration d'inhibiteurs de la libération et/ou de la synthèse des peptides β-amyloïdes.

(57) Disclosed are polycyclic α-amino-ε-caprolactams and related compounds which are useful as synthetic intermediates in the preparation of inhibitors of β-amyloid peptide release and/or its synthesis.

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(21) International Application Number: PCT/US98/22637 (22) International Filing Date: 29 October 1998 (29.10.98) (30) Priority Data: 08/996,422 22 December 1997 (22.12.97) US 09/102,726 22 June 1998 (22.06.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/102,726 (CON) Filed on 22 June 1998 (22.06.98) (71) Applicants (for all designated States except US): ELAN PHARMACEUTICALS, INC. [US/US]; 800 Gateway Boulevard, South San Francisco, CA 94080 (US). ELI LILLY & COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46227 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): AUDIA, James, E. [US/US]; 6449 Lakeside Woods Circle, Indianapolis, IN 46278 (US). MABRY, Thomas, E. [US/US]; 8104 Hi-Vu Drive, Indianapolis, IN 46227 (US). NISSEN, Jeffrey, S. [US/US]; 4348 Oil Creek Drive, Indianapolis, IN 46268		(US). MCDANIEL, Stacey, L. [US/US]; Apartment J, 8650 Bison Lake Circle, Indianapolis, IN 46227 (US). (74) Agents: SWISS, Gerald, F. et al.; Burns, Doane, Swecker & Mathis, L.L.P., P.O. Box 1404, Alexandria, VA 22313-1404 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: POLYCYCLIC α -AMINO- ϵ -CAPROLACTAMS AND RELATED COMPOUNDS		
(57) Abstract Disclosed are polycyclic α -amino- ϵ -caprolactams and related compounds which are useful as synthetic intermediates in the preparation of inhibitors of β -amyloid peptide release and/or its synthesis.		

POLYCYCLIC α -AMINO- ϵ -CAPROLACTAMS AND RELATED COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application No. 08/996,422, filed December 22, 1997 (Attorney Docket No. 002010-062) and entitled "Cycloalkyl, Lactam, Lactone and Related Compounds, Pharmaceutical
5 Compositions Comprising Same, and Methods for Inhibiting β -Amyloid Peptide Release and/or its Synthesis by Use of Such Compounds", which application claims the benefit of U.S. Provisional Application No. 60/064,851, which was converted pursuant to 37 C.F.R. § 1.53(b)(2)(ii) from U.S. Patent Application No. 08/780,025, filed December 23, 1996. Each of these applications are incorporated
10 herein by reference in their entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to polycyclic α -amino- ϵ -caprolactams and related
15 compounds which are useful as synthetic intermediates in the preparation of inhibitors of β -amyloid peptide release and/or its synthesis.

2. References

The following publications, patents and patent applications are cited in this
20 application as superscript numbers:

- ¹ Glenner, et al., *Biochem. Biophys. Res. Commun.* (1984) 120:885-890.
- 25 ² U.S. Patent No. 4,666,829, issued May 19, 1987, to G. G. Glenner et al., entitled "Polypeptide Marker for Alzheimer's Disease and Its Use for Diagnosis."

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- 3 Selkoe, *Neuron*. (1991) 6:487-498.
- 4 Goate, et al., *Nature* (1990) 349:704-706.
- 5 5 Chartier Harlan, et al., *Nature* (1989) 353:844-846.
- 6 Murrell, et al., *Science* (1991) 254:97-99.
- 7 Mullan, et al., *Nature Genet.* (1992) 1:345-347.
- 10 8 T. W. Greene et al., *Protecting Groups in Organic Synthesis*,
Second Edition, Wiley, New York (1991).
- 9 R. F. C. Brown et al., *Tetrahedron Letters* 1971, 8, 667-670.
- 15 10 A. O. King et al., *J. Org. Chem.* 1993, 58, 3384-3386.
- 11 *Tetrahedron Letters* 1993, 34(48), 7685.
- 20 12 U.S. Provisional Application Serial No. 60/019,790, filed June 14,
1996.
- 13 U.S. Patent Application Serial No. 08/996,442, filed December 19,
1997.
- 25 14 R. D. Clark et al., *Tetrahedron* 1993, 49(7), 1351-1356.
- 15 15 Schenk, et al., International Patent Application Publication No. WO
94/10569, "*Methods and Compositions for the Detection of Soluble*
30 *β -Amyloid Peptide*", published 11 May 1994.
- 16 Citron, et al., *Nature* (1992) 360:672-674.
- 17 P. Seubert, *Nature* (1992) 359:325-327.
- 35 18 Hansen, et al., *J. Immun. Meth.*(1989) 119:203-210.
- 19 Games et al., *Nature* (1995) 373:523-527.
- 40 20 Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555.

All of the above publications, patents and patent applications are herein
incorporated by reference in their entirety to the same extent as if each individual

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publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

3. State of the Art

5 Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common
10 medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently
15 known.

The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly
20 amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of
25 individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type (HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

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The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other

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disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of about 39-43 amino acids designated the β -amyloid peptide (β AP) or sometimes $A\beta$, $A\beta$ P or $\beta/A4$. β -Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.¹ The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829².

Molecular biological and protein chemical analyses have shown that the β -amyloid peptide is a small fragment of a much larger precursor protein termed the amyloid precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding APP has demonstrated that β -amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the β -amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the cerebral and meningeal blood vessels is currently unknown.

Several lines of evidence indicate that progressive cerebral deposition of β -amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe³. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with a genetically determined (familial) form of AD (Goate, et al.⁴; Chartier Harlan, et al.⁵; and Murrell, et al.⁶) and is referred to as the Swedish variant. A double mutation changing lysine⁵⁹⁵-methionine⁵⁹⁶ to asparagine⁵⁹⁵-leucine⁵⁹⁶ (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.⁷). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the β -amyloid peptide deposition disease, HCHWA-D, and a change from alanine to glycine at amino

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acid 692 appears to cause a phenotype that resembles AD in some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its β -amyloid peptide fragment can cause AD.

5

Despite the progress which has been made in understanding the underlying mechanisms of AD and other β -amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting β -amyloid peptide release and/or its synthesis *in vivo*.

10

Compounds which inhibit β -amyloid peptide release and/or its synthesis *in vivo* are disclosed in U.S. Patent Application Serial No. 08/996,422, filed December 22, 1997 (Attorney Docket No. 002010-062) and entitled "Cycloalkyl, Lactam, Lactone and Related Compounds, Pharmaceutical Compositions

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Comprising Same, and Methods for Inhibiting β -Amyloid Peptide Release, and/or its Synthesis by Use of Such Compounds," the disclosure of which is incorporated herein by reference in its entirety. The present invention is directed to intermediates useful in the preparation of such compounds.

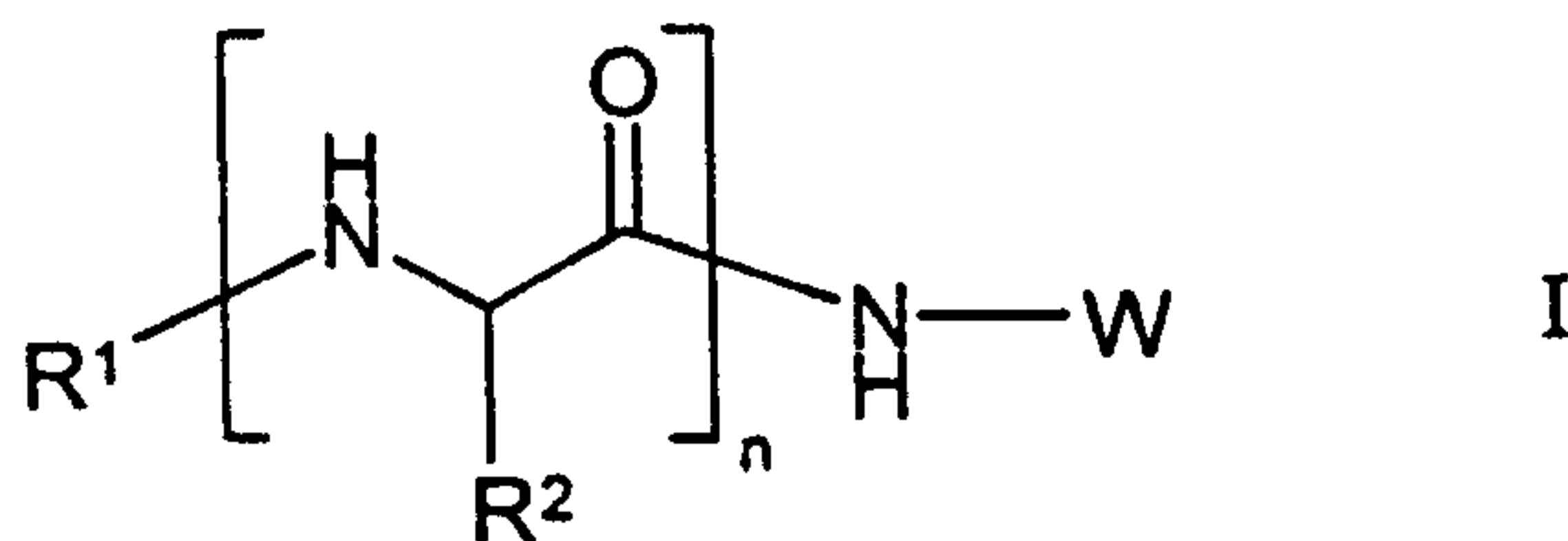
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SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of intermediates which are useful in the preparation the cycloalkyl, lactam, lactone and related compounds described in U.S. Patent Application Serial No. 08/996,422, which compounds inhibit β -amyloid peptide release and/or its synthesis. Accordingly, in one of its composition aspects, this invention is directed to a compound of formula I:

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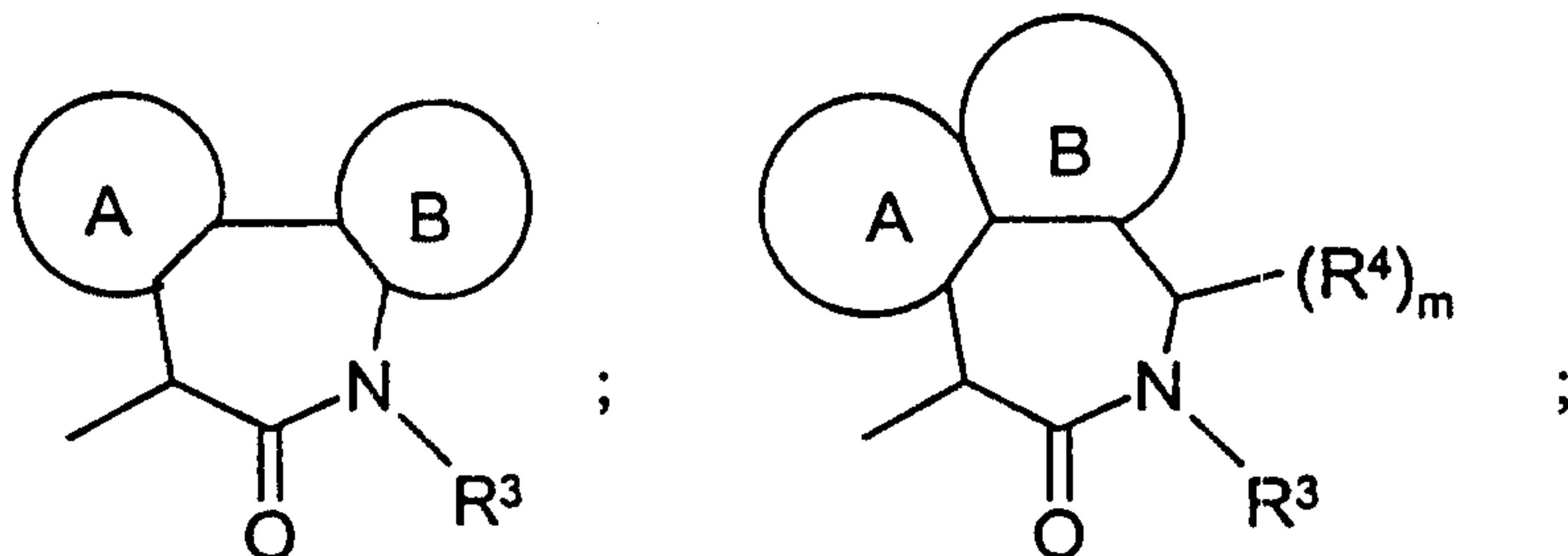


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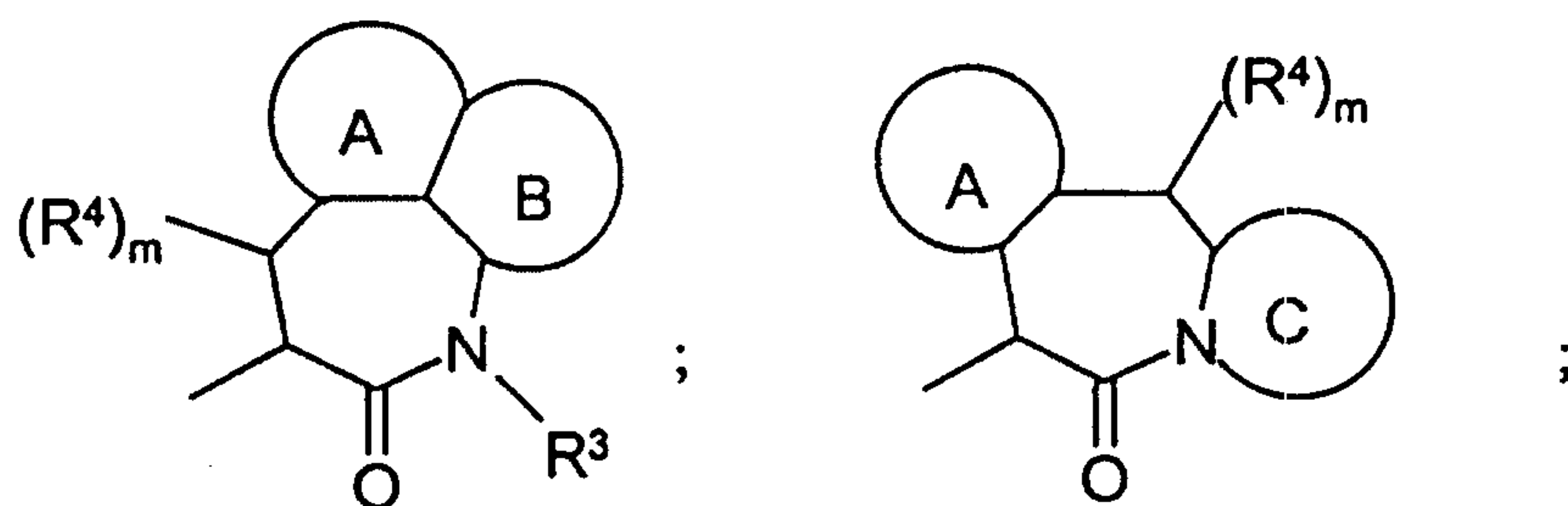
wherein

W is a substituted ϵ -caprolactam selected from the group consisting of:

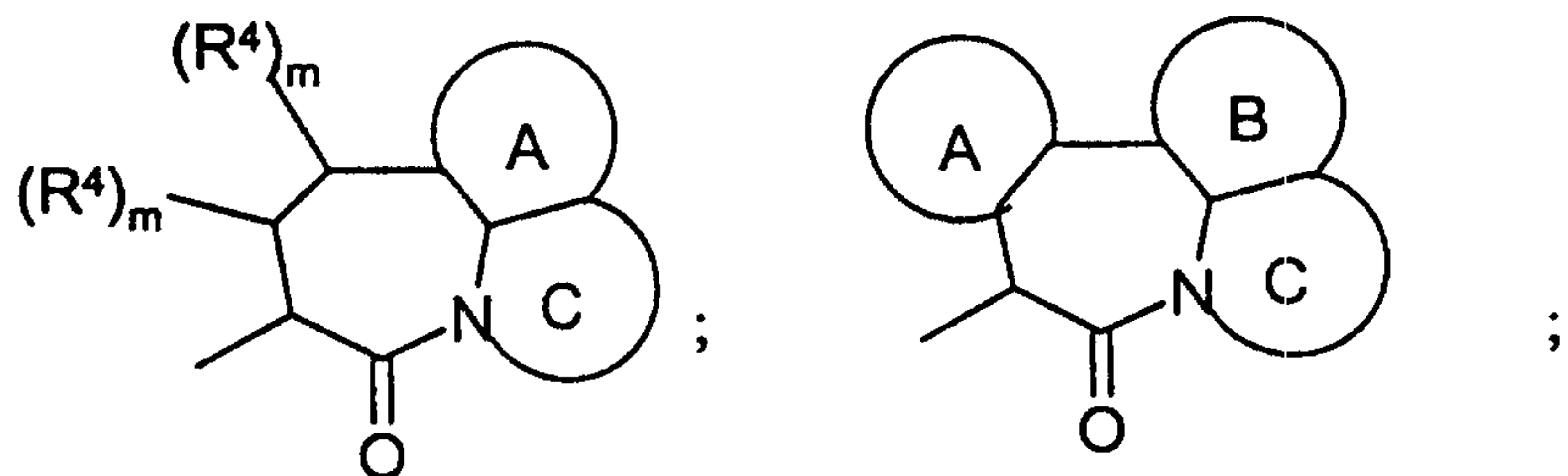
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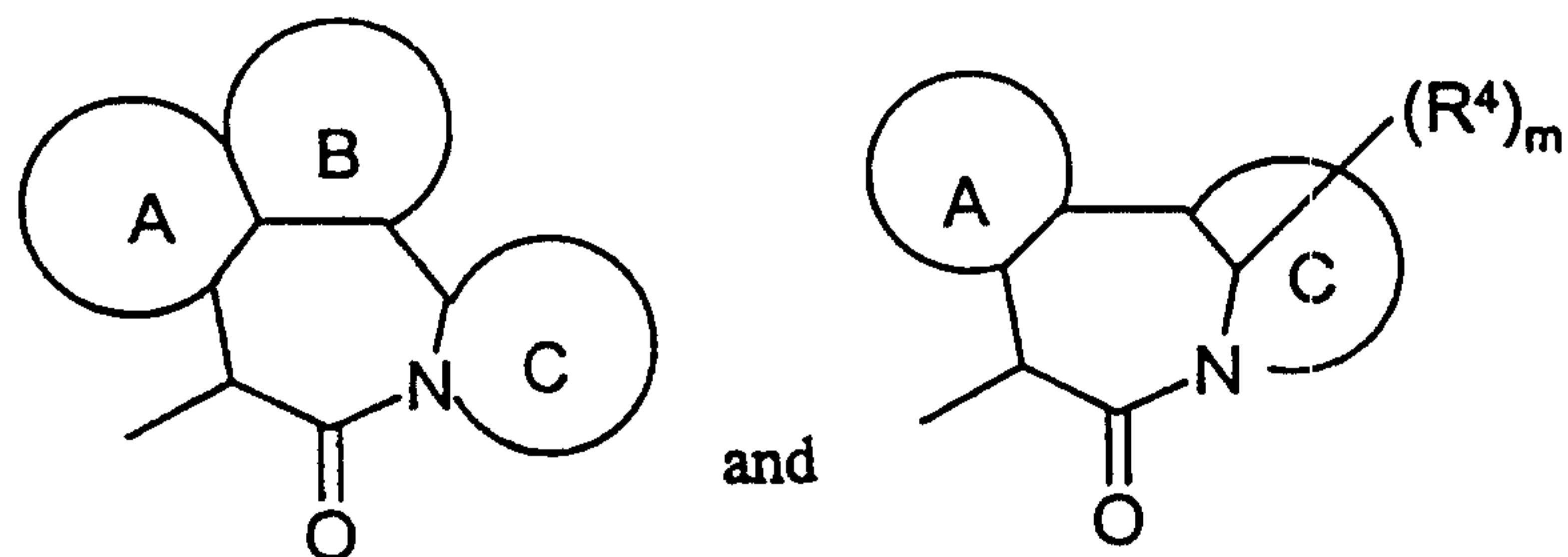
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wherein

ring *A*, together with the atoms of the ϵ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

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ring *B*, together with the atoms of the ϵ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

5 ring *C*, together with the atoms of the ϵ -caprolactam to which it is attached, forms a heteroaryl or heterocyclic ring;

R^1 is selected from the group consisting of hydrogen and an amino-blocking group;

10 each R^2 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heteroaryl and heterocyclic;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

15 each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

20 m is an integer from 0 to 2; n is an integer from 0 to 2; and salts thereof.

Preferably, R^1 is hydrogen, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl, 1-(1'-adamantyl)-1-methylethoxycarbonyl (Acm), allyloxycarbonyl (Aloc), benzyloxymethyl (Bom), 2-*p*-biphenylisopropylloxycarbonyl (Bpoc), *tert*-butyldimethylsilyl (Bsi), benzoyl (Bz), benzyl (Bn), 9-fluorenyl-methyloxycarbonyl (Fmoc), 4-methylbenzyl, 4-methoxybenzyl, 2-nitrophenylsulfenyl (Nps), 3-nitro-2-pyridinesulfenyl (NPys), trifluoroacetyl (Tfa), 2,4,6-trimethoxybenzyl (Tmob), trityl (Trt), and the like. More preferably, R^1 is hydrogen or *tert*-butoxycarbonyl (Boc).

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When n is one or two, each R^2 is preferably (and independently for $n = 2$) selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic.

- 5 Particularly preferred R^2 substituents include, by way of example, hydrogen, methyl, ethyl, n -propyl, isopropyl, n -butyl, isobutyl, *sec*-butyl, *tert*-butyl, $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, 2-methyl- n -butyl, 6-fluoro- n -hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2$ -cyclohexyl, $-\text{CH}_2\text{CH}_2$ -cyclopropyl, $-\text{CH}_2\text{CH}_2$ -cyclohexyl,
 10 $-\text{CH}_2$ -indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH_3)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH_3)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH₂CH₂O)-benzyl, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2$ -imidazol-4-yl,
 15 $-\text{CH}_2$ -(3-tetrahydrofuranyl), $-\text{CH}_2$ -thiophen-2-yl, $-\text{CH}_2$ -(1-methyl)cyclopropyl, $-\text{CH}_2$ -thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, $-\text{CH}_2$ -C(O)O-*t*-butyl, $-\text{CH}_2$ -C(CH_3)₃, $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, 2-methylcyclopentyl, -cyclohex-2-enyl, $-\text{CH}[\text{CH}(\text{CH}_3)_2]\text{COOCH}_3$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}_2$,
 20 $-\text{CH}_2\text{CH}=\text{CHCH}_3$ (cis and trans), $-\text{CH}_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}(\text{O}-t\text{-butyl})\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-(\text{CH}_2)_4\text{NH-Boc}$, $-(\text{CH}_2)_4\text{NH}_2$, $-\text{CH}_2$ -pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), $-\text{CH}_2$ -naphthyl (e.g., 1-naphthyl and 2-naphthyl), $-\text{CH}_2$ -(4-morpholinyl), *p*-(4-morpholinyl-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, thien-2-yl, thien-3-yl, and the like.
- 25

- 30 Preferably, R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl and cycloalkyl.

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Particularly preferred R^3 substituents include, by way of example, hydrogen, methyl, 2-methylpropyl, hexyl, methoxycarbonylmethyl, 3,3-dimethyl-2-oxobutyl, 4-phenylbutyl, cyclopropylmethyl, 2,2,2-trifluoroethyl, cyclohexyl, and the like.

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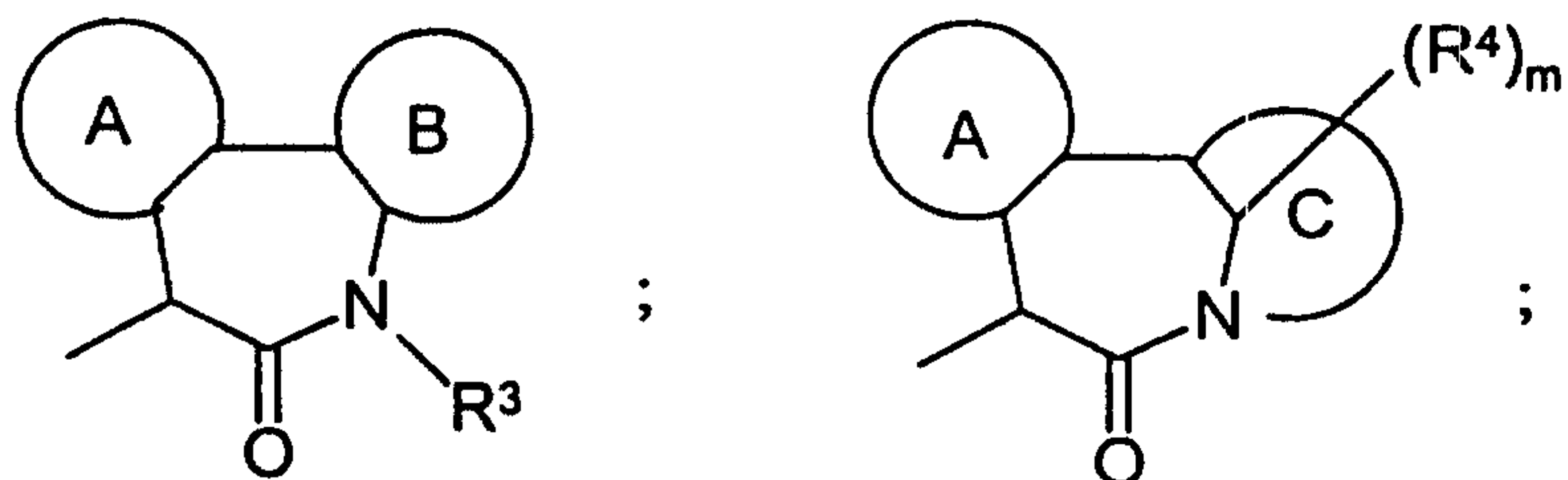
When present, R^4 is preferably alkyl or substituted alkyl.

Preferably, m is 0 or 1. More preferably, m is 0.

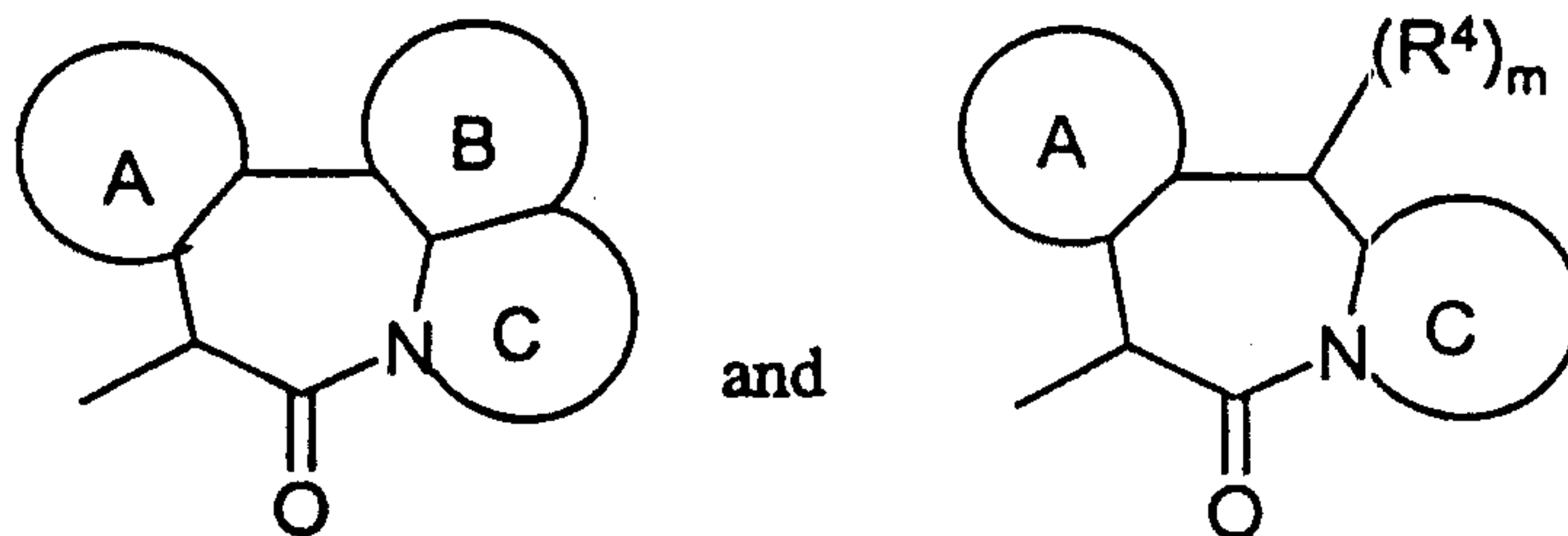
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W is preferably a substituted ϵ -caprolactam selected from the group consisting of:

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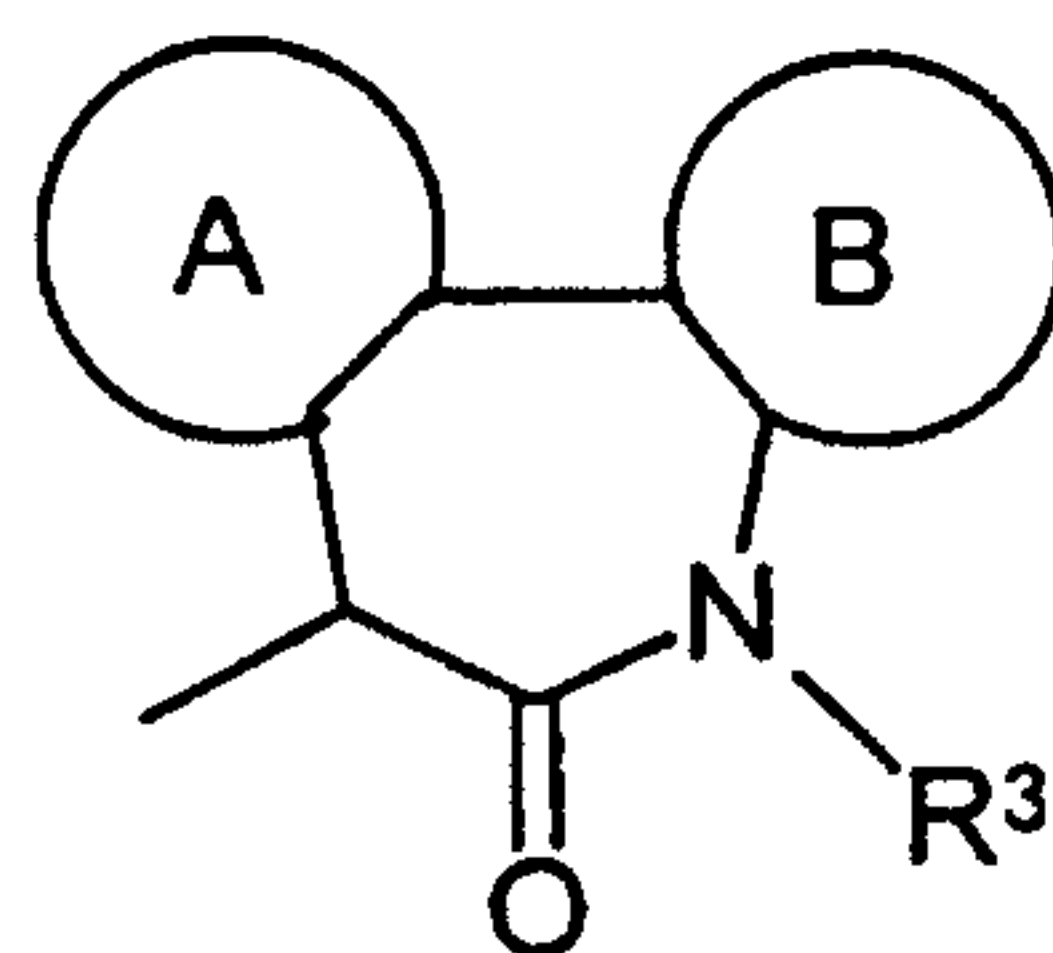
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wherein A , B , R^3 , R^4 and m are as defined herein.

25

More preferably, W is a substituted ϵ -caprolactam of the formula:



-- 10 --

wherein *A*, *B*, and R^3 are as defined herein. In separate preferred embodiments, this invention is also directed to compounds of formula I wherein *W* is independently selected from each of the substituted ϵ -caprolactams illustrated above.

5

Rings *A* and *B* may be the same or different and are preferably independently selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic. More preferably, rings *A* and *B* are independently selected from the group consisting of aryl and cycloalkyl. Still more preferably, rings *A* and *B* are independently aryl.

10

Particularly preferred *A* and *B* rings include, by way of example, phenyl, substituted phenyl, including fluoro-substituted phenyl, cyclohexyl and the like. When the *A* and *B* rings are fused to one another, they preferably form a naphthyl or substituted naphthyl ring.

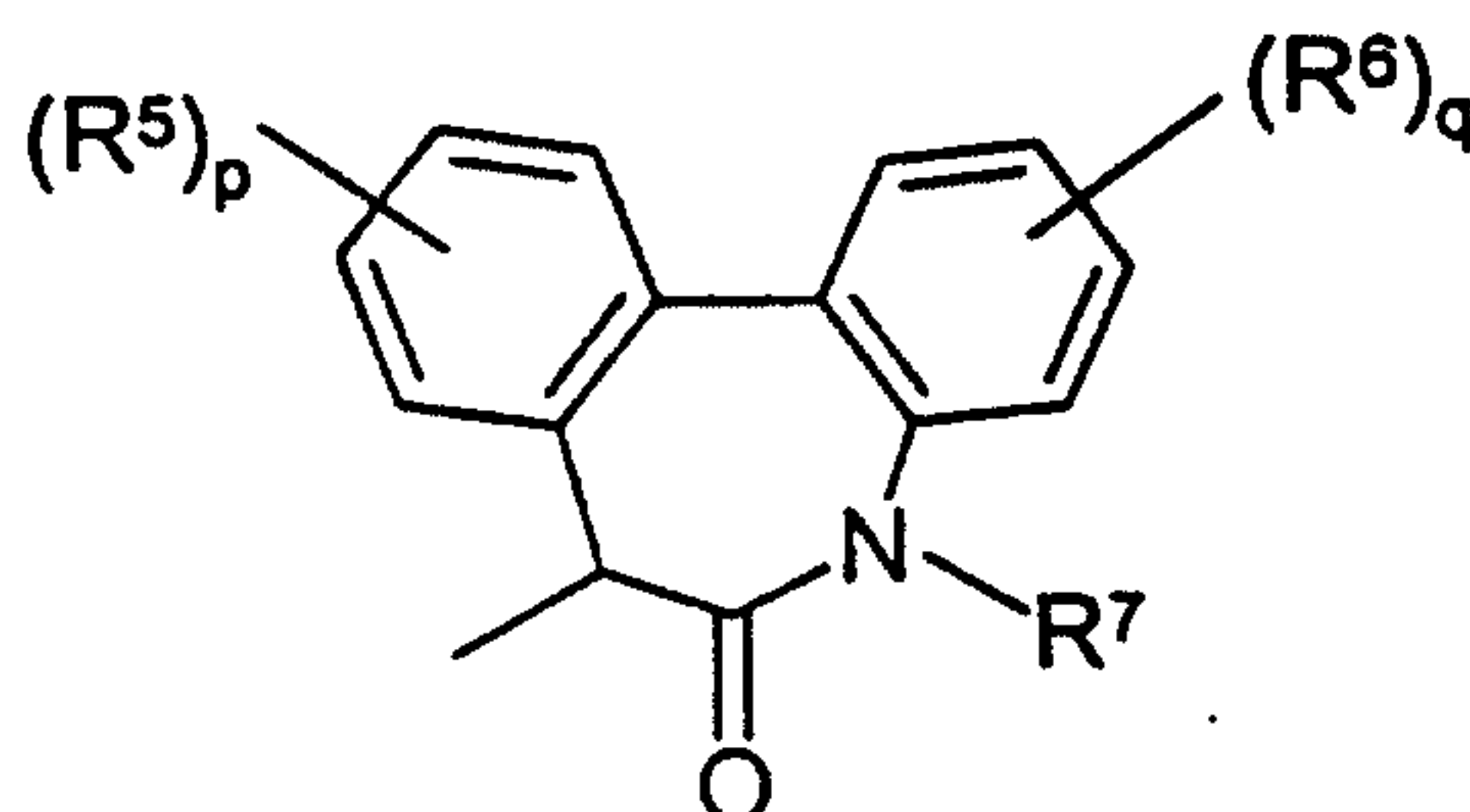
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Particularly preferred *C* rings include, by way of example, pyrrolidinyl, piperidinyl, morpholino and the like.

20

In one preferred embodiment of this invention, *W* is a substituted ϵ -caprolactam of the formula:

25



wherein

30

each R^5 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino,

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aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

5 each R⁶ is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

10 R⁷ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

p is an integer from 0 to 4; *q* is an integer from 0 to 4; and salts thereof.

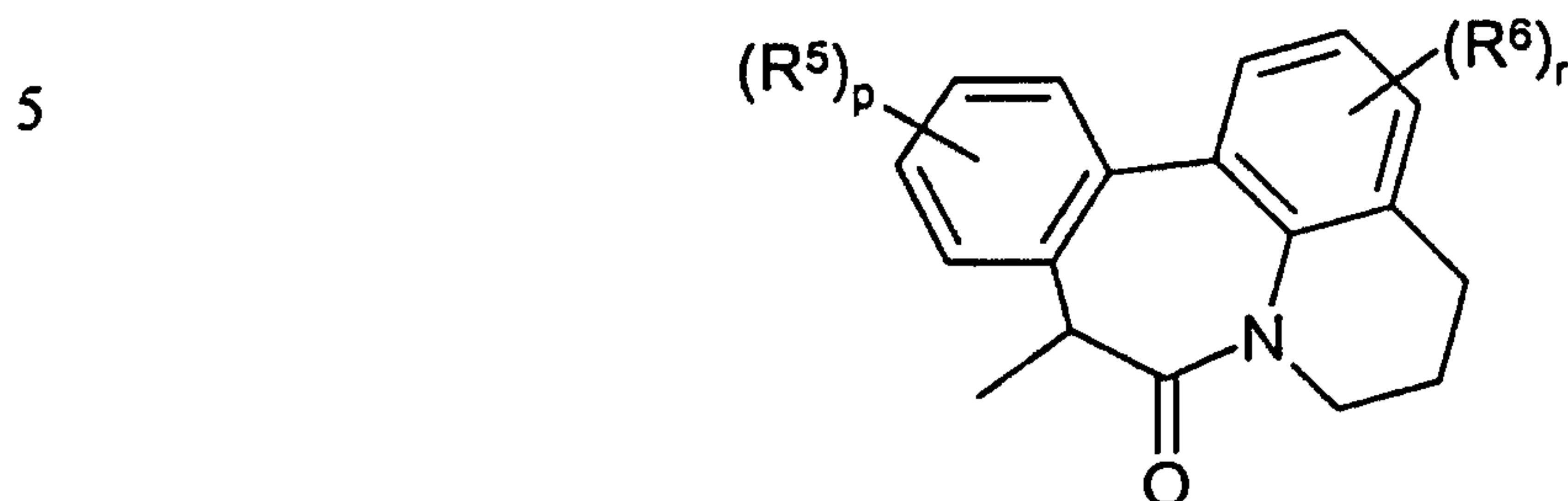
Preferably, R⁵ and R⁶ are independently selected from the group consisting of alkoxy, substituted alkoxy, alkyl, substituted alkyl, amino, substituted amino, 20 carboxyl, carboxyalkyl, cyano, halo, nitro, thioalkoxy and substituted thioalkoxy. More preferably, when present, R⁵ and R⁶ are fluoro.

R⁷ is preferably selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, aryl, cycloalkyl and substituted cycloalkyl. More 25 preferably, R⁷ is selected from the group consisting of hydrogen, alkyl, substituted alkyl and cycloalkyl.

Particularly preferred R⁷ substituents include, by way of example, hydrogen, methyl, 2-methylpropyl, hexyl, methoxycarbonylmethyl, 3,3-dimethyl- 30 2-oxobutyl, 4-phenylbutyl, cyclopropylmethyl, 2,2,2-trifluoroethyl, cyclohexyl, and the like.

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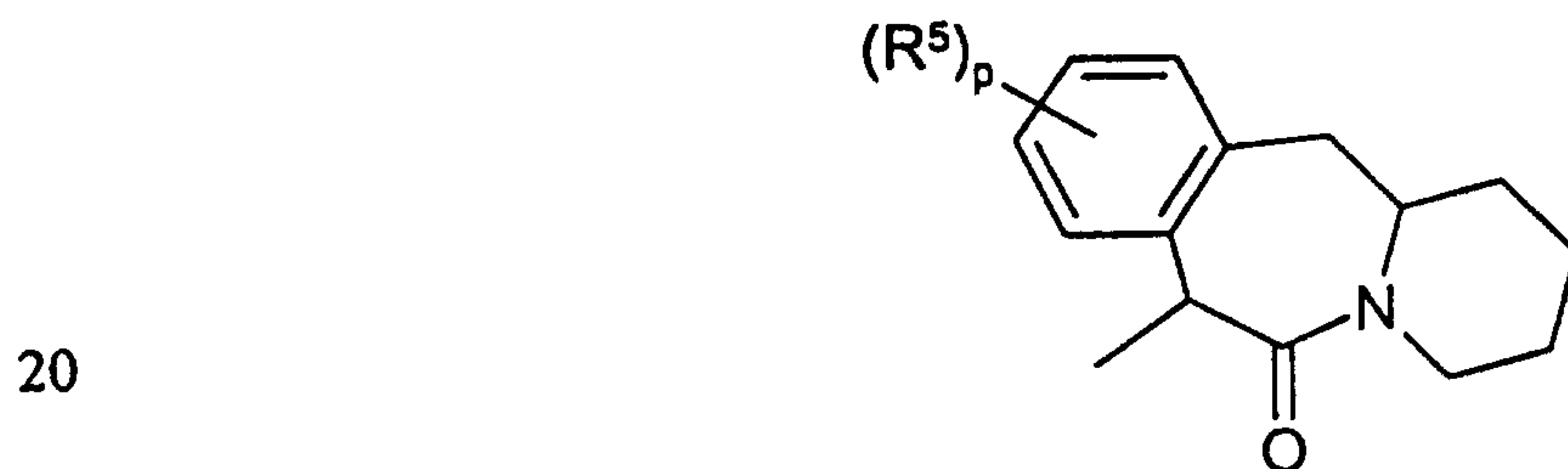
In another preferred embodiment of this invention, *W* is a substituted ϵ -caprolactam of the formula:



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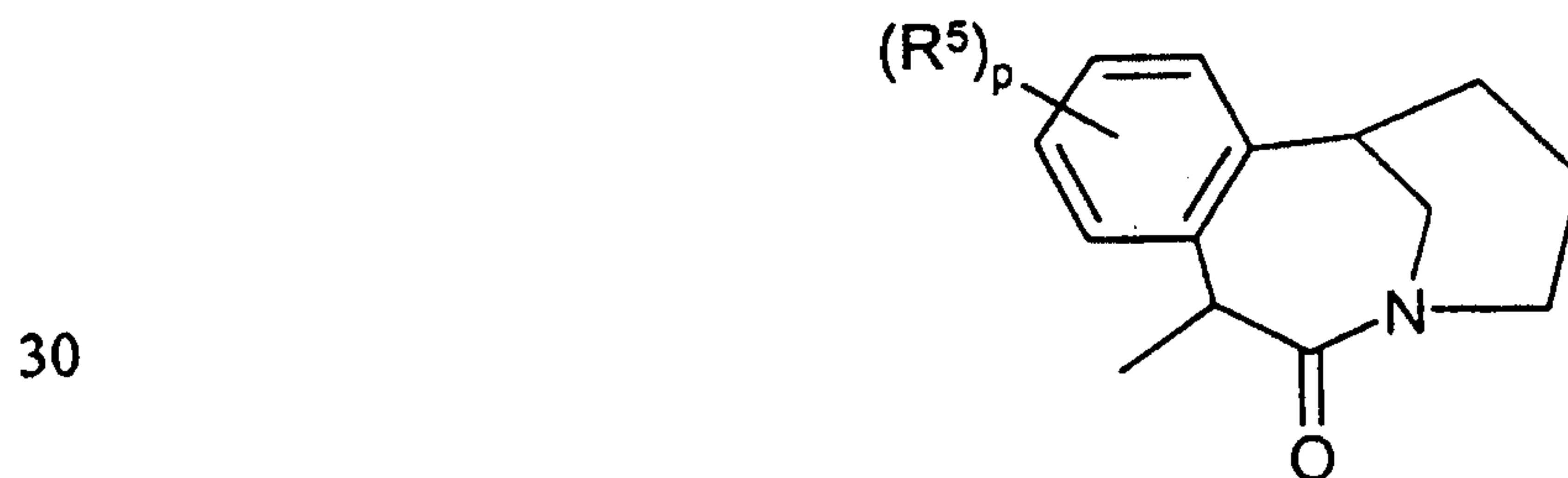
wherein R^5 , R^6 , and p are as defined herein and r is an integer from 0 to 3; and salts thereof.

15 In still another preferred embodiment of this invention, *W* is a substituted ϵ -caprolactam of the formula:



wherein R^5 , and p are as defined herein; and salts thereof.

25 In yet another preferred embodiment of this invention, *W* is a substituted ϵ -caprolactam of the formula:



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wherein R^5 and p are as defined herein; and salts thereof.

Preferred substituted ϵ -caprolactams (i.e., W) include, by way of example, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-(3,3-dimethylbutan-2-onyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl and 7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one-5-yl.

Compounds of this invention include, by way of example, the following:

5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-amino-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-7-(3,3-dimethyl-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-amino-7-(3,3-dimethyl-2-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

-- 14 --

- 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one
- 20 5-(*N*-Boc-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-(*N*-Boc-L-valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-(*N*-Boc-L-*tert*-leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-*tert*-leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-(*N*-Boc-L-alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-(L-alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-(L-alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

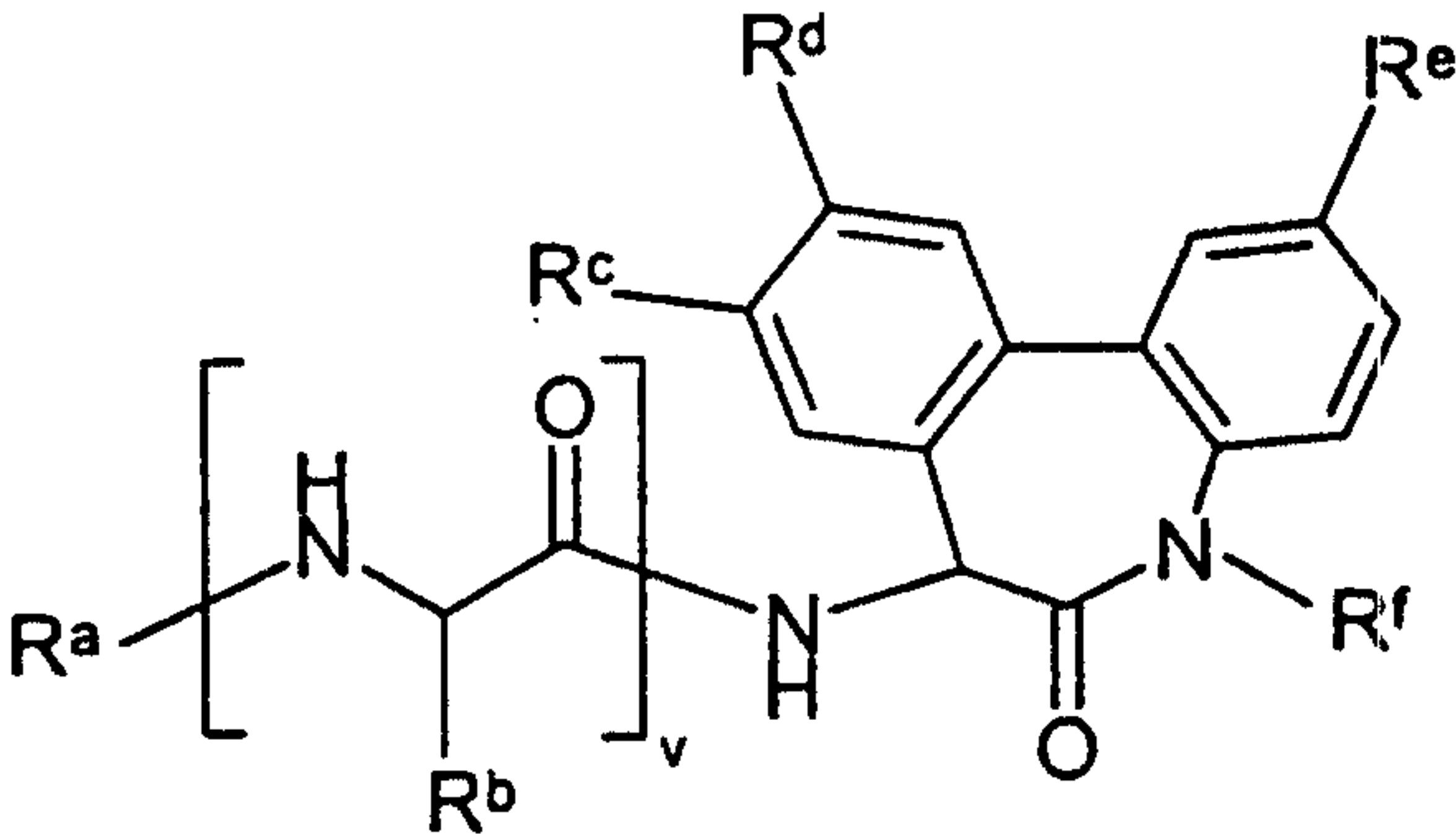
- 5-(*N*-Boc-L-alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-(L-alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-(*N*-Boc-L-alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-(L-alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-(L-alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-(L-valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-(L-valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-(L-valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-(L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-(*N*-Boc-L-valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(*N*-Boc-L-valinyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

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- 5-(L-valinyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-amino-9,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-10,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-aminohexahydropyrido[a]benz[d]azepin-6-one
- 10 9-amino-5,6-Dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one
- 9-(N'-Boc-L-alaninyl)amino-5,6-Dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one
- 15 9-(N'-L-alaninyl)amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one
- 7-amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one
- 20 1-amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 1-(N'-Boc-L-alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 25 1-(N'-L-alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- and salts thereof.
- 30

Preferred compounds include those defined by the formulas as set forth in Tables I, II, III, IV and V below and salts thereof.

Table I



5

10

15

20

R^a	R^b	R^c	R^d	R^e	R^f	v
H-	---	H-	H-	H-	CH_3-	0
Boc- ^a	---	H-	H-	H-	H-	0
Boc-	---	H-	H-	H-	$(CH_3)_2CHCH_2-$	0
H-	---	H-	H-	H-	$(CH_3)_2CHCH_2-$	0
Boc-	---	H-	H-	H-	$CH_3OC(O)CH_2-$	0
H-	---	H-	H-	H-	$CH_3OC(O)CH_2-$	0
Boc-	---	H-	H-	H-	$(CH_3)_3CC(O)CH_2-$	0
H-	---	H-	H-	H-	$(CH_3)_3CC(O)CH_2-$	0
H-	---	H-	H-	H-	$Ph(CH_2)_4-$	0
H-	---	H-	H-	H-	cyclopropyl- CH_2-	0
H-	---	H-	H-	H-	CF_3CH_2-	0
H-	---	H-	H-	H-	cyclohexyl-	0
H-	---	H-	H-	H-	$CH_3(CH_2)_5-$	0
H-	---	F-	H-	H-	CH_3-	0
H-	---	H-	F-	H-	CH_3-	0
H-	---	H-	H-	F-	CH_3-	0
Boc-	CH_3-	H-	H-	H-	CH_3-	1

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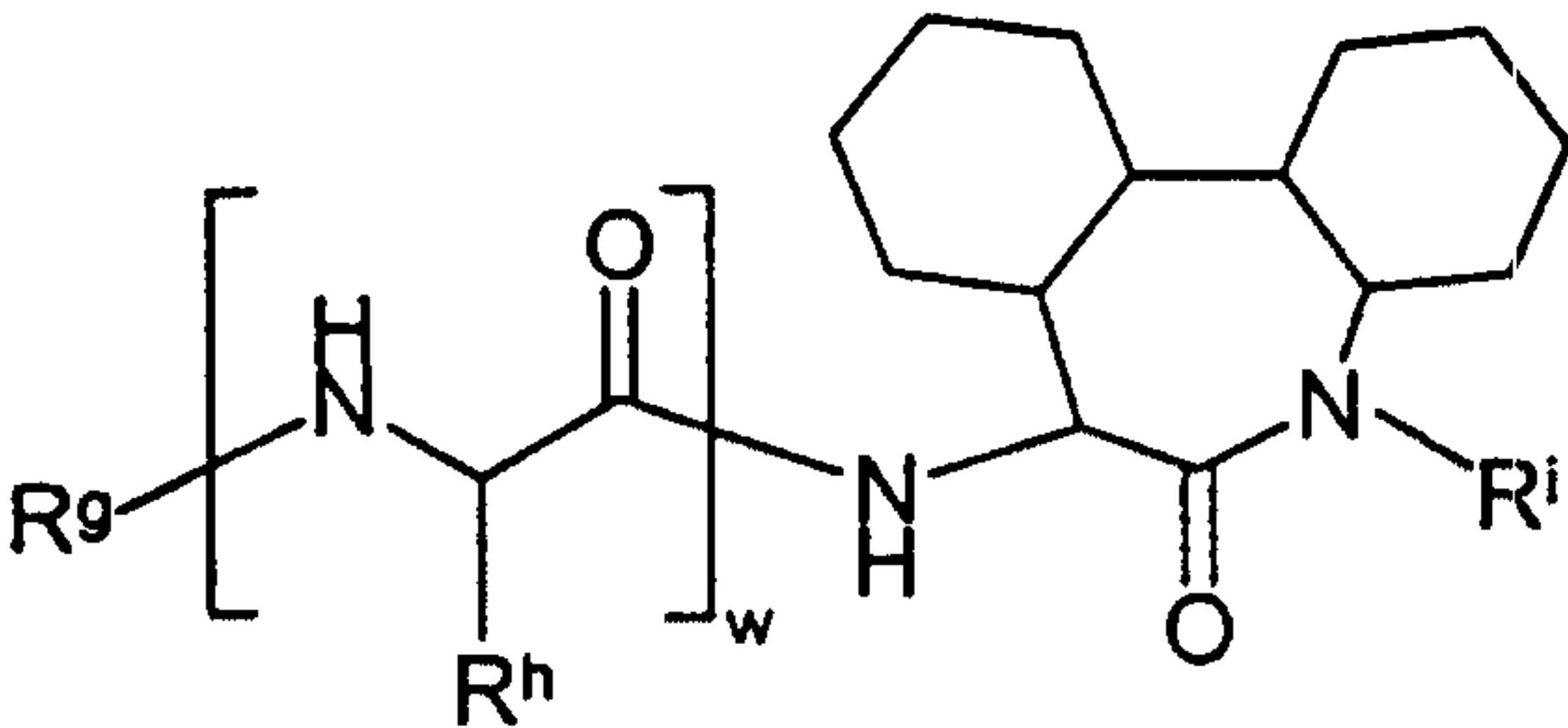
	R ^a	R ^b	R ^c	R ^d	R ^e	R ^f	ν
	H-	CH ₃ -	H-	H-	H-	CH ₃ -	1
	Boc-	(CH ₃) ₂ CH-	H-	H-	H-	CH ₃ -	1
	H-	(CH ₃) ₂ CH-	H-	H-	H-	CH ₃ -	1
	Boc-	(CH ₃) ₃ C-	H-	H-	H-	CH ₃ -	1
5	H-	(CH ₃) ₃ C-	H-	H-	H-	CH ₃ -	1
	Boc-	CH ₃ -	F-	H-	H-	CH ₃ -	1
	H-	CH ₃ -	F-	H-	H-	CH ₃ -	1
	Boc-	CH ₃ -	H-	F-	H-	CH ₃ -	1
	H-	CH ₃ -	H-	F-	H-	CH ₃ -	1
10	Boc-	CH ₃ -	H-	H-	F-	CH ₃ -	1
	H-	CH ₃ -	H-	H-	F-	CH ₃ -	1
	Boc-	CH ₃ -	H-	H-	H-	cyclopropyl-CH ₂ -	1
	H-	CH ₃ -	H-	H-	H-	cyclopropyl-CH ₂ -	1
	Boc-	CH ₃ -	H-	H-	H-	Ph(CH ₂) ₄ -	1
15	H-	CH ₃ -	H-	H-	H-	Ph(CH ₂) ₄ -	1
	Boc-	(CH ₃) ₂ CH-	H-	H-	H-	cyclopropyl-CH ₂ -	1
	H-	(CH ₃) ₂ CH-	H-	H-	H-	cyclopropyl-CH ₂ -	1
	Boc-	(CH ₃) ₂ CH-	H-	H-	H-	Ph(CH ₂) ₄ -	1
	H-	(CH ₃) ₂ CH-	H-	H-	H-	Ph(CH ₂) ₄ -	1
20	Boc-	(CH ₃) ₂ CH-	H-	H-	H-	CH ₃ (CH ₂) ₅ -	1
	H-	(CH ₃) ₂ CH-	H-	H-	H-	CH ₃ (CH ₂) ₅ -	1
	Boc-	(CH ₃) ₂ CH-	F-	H-	H-	CH ₃ -	1
	H-	(CH ₃) ₂ CH-	F-	H-	H-	CH ₃ -	1
	Boc-	(CH ₃) ₂ CH-	H-	F-	H-	CH ₃ -	1
25	H-	(CH ₃) ₂ CH-	H-	F-	H-	CH ₃ -	1
	Boc-	(CH ₃) ₂ CH-	H-	H-	F-	CH ₃ -	1
	H-	(CH ₃) ₂ CH-	H-	H-	F-	CH ₃ -	1
	H-	---	F-	H-	F-	CH ₃ -	0

R ^a	R ^b	R ^c	R ^d	R ^e	R ^f	v
H-	---	H-	F-	F-	CH ₃ -	0

^a Boc = *tert*-butoxycarbonyl = (CH₃)₃COC(O)-

5

Table II

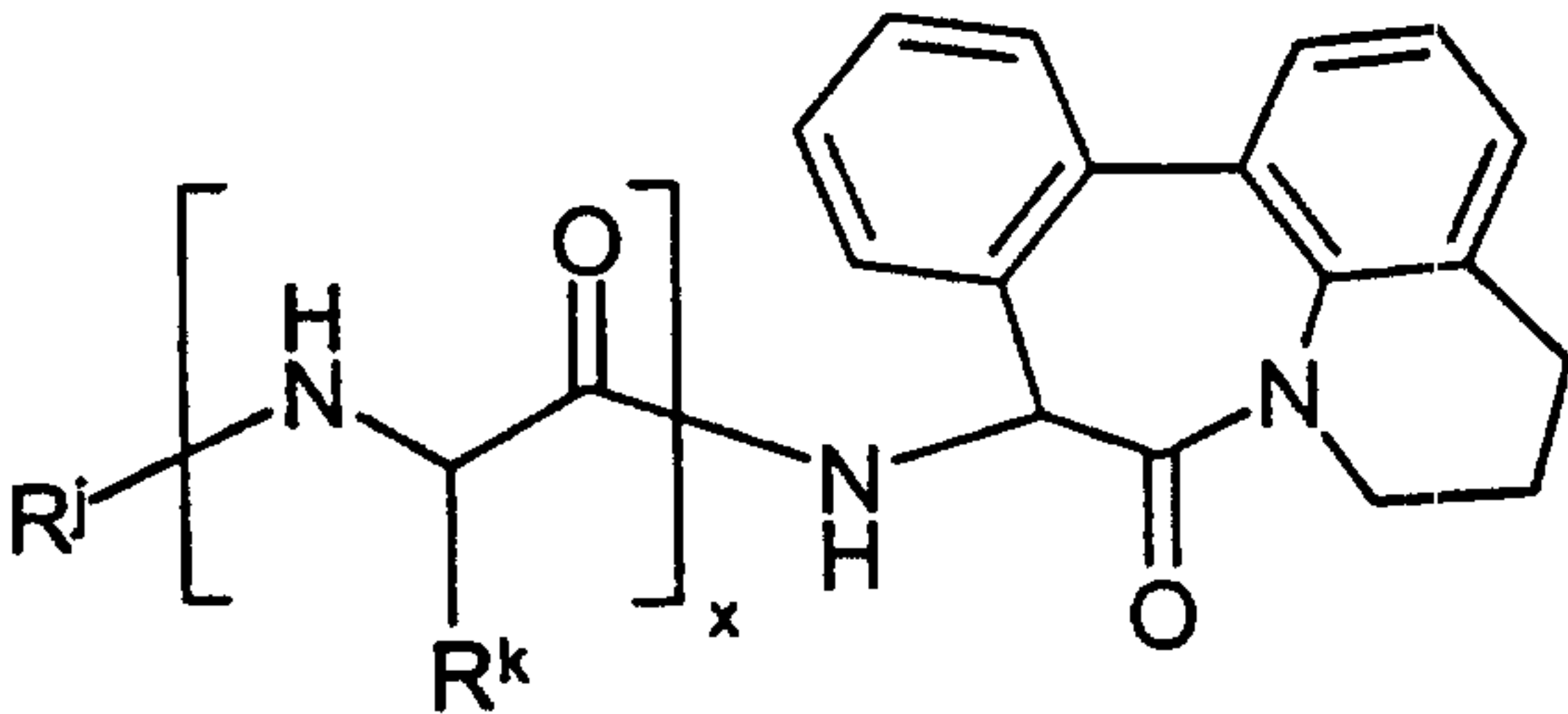


R ^g	R ^h	R ⁱ	w
H-	---	CH ₃ -	0

10

Table III

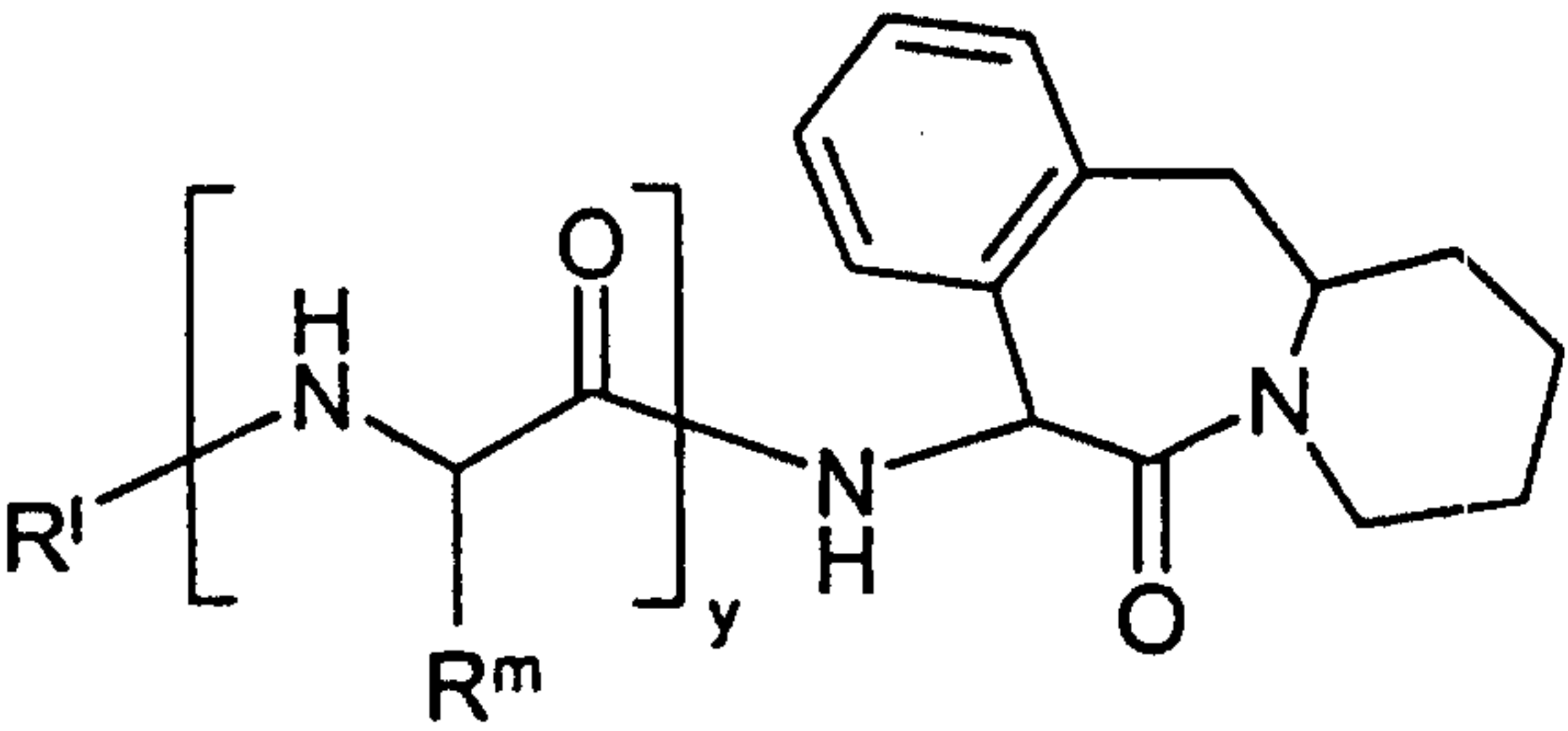
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R ^j	R ^k	x
H-	---	0
H-	CH ₃ -	1

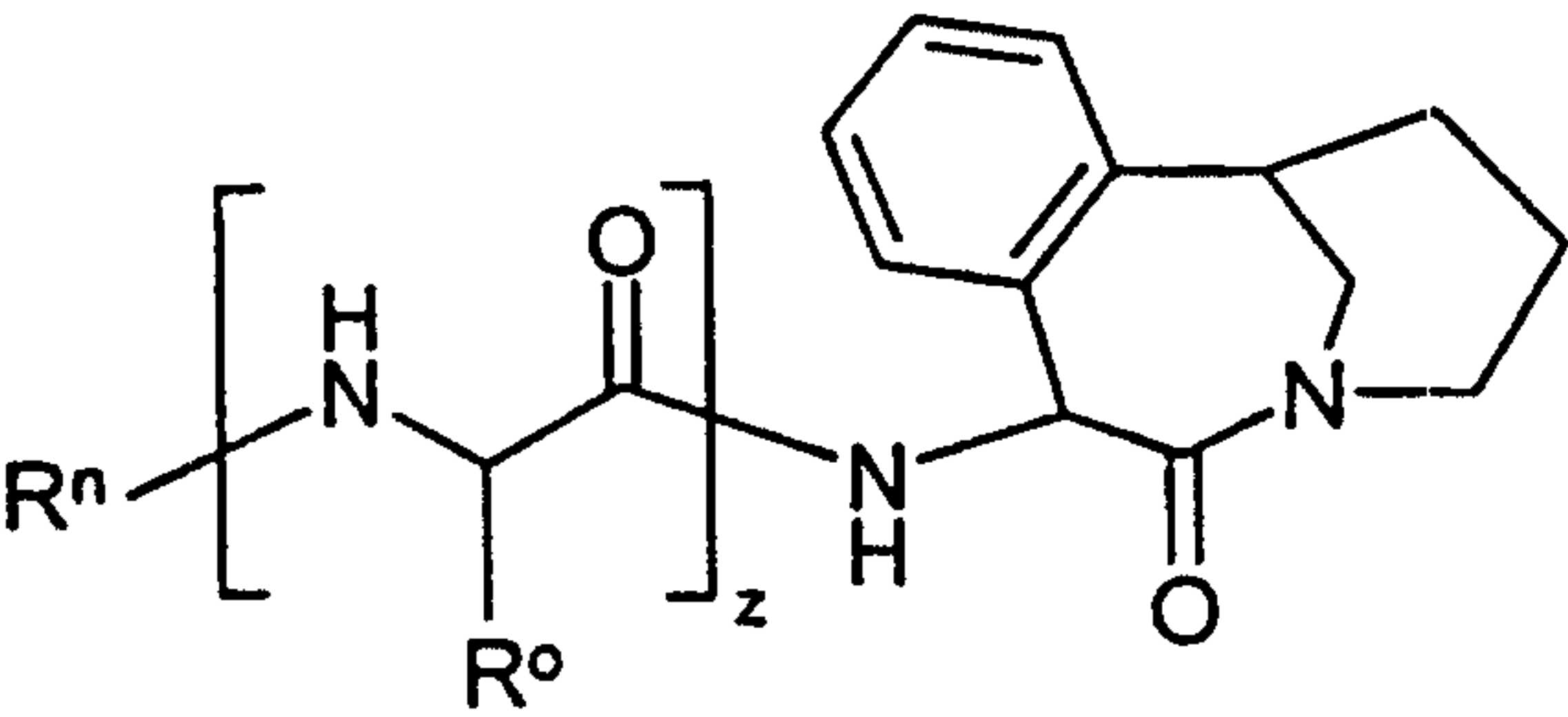
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Table IV



R ^l	R ^m	y
H-	---	0

Table V



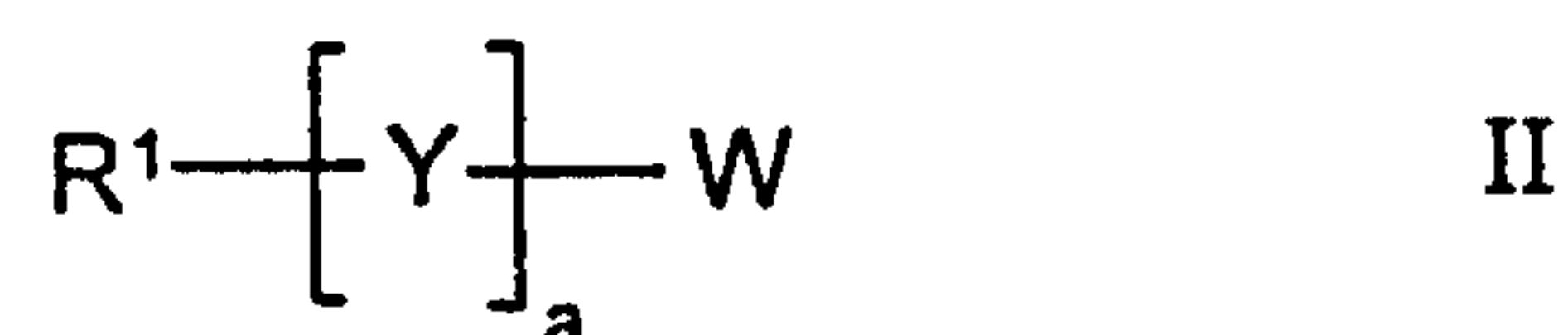
R ⁿ	R ^o	z
H-	---	0
Boc- ^a	CH ₃ -	1
H-	CH ₃ -	1

^a Boc = *tert*-butoxycarbonyl = (CH₃)₃COC(O)-

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Deoxy derivatives of the compounds described in U.S. Patent Application Serial No. 08/996,422 have also been discovered to inhibit β -amyloid peptide release and/or its synthesis *in vivo*. Such compounds are disclosed in U.S. Patent Application Serial No. __/__,__, filed on even date herewith (Attorney Docket
5 No. 002010-136) and entitled "Deoxyamino Acid Compounds, Pharmaceutical Compositions Comprising Same, and Methods for Inhibiting β -Amyloid Peptide Release, and/or its Synthesis by Use of Such Compounds," the disclosure of which is incorporated herein by reference in its entirety.

10 Accordingly, in another of its composition aspects, this invention is directed a compound of formula II:



15

wherein

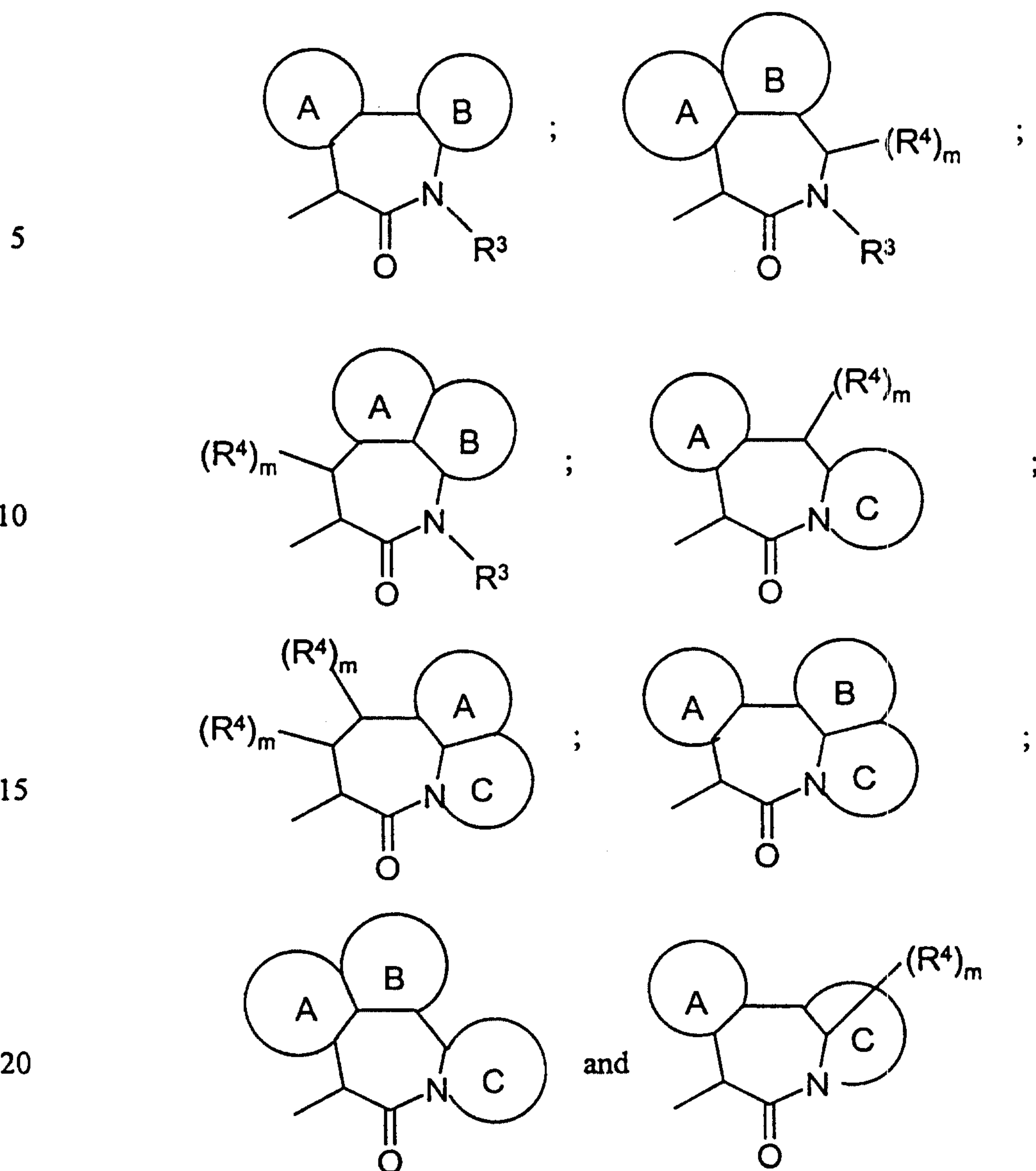
W is a substituted ϵ -caprolactam selected from the group consisting of:

20

25

30

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wherein

25 ring *A*, together with the atoms of the ϵ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

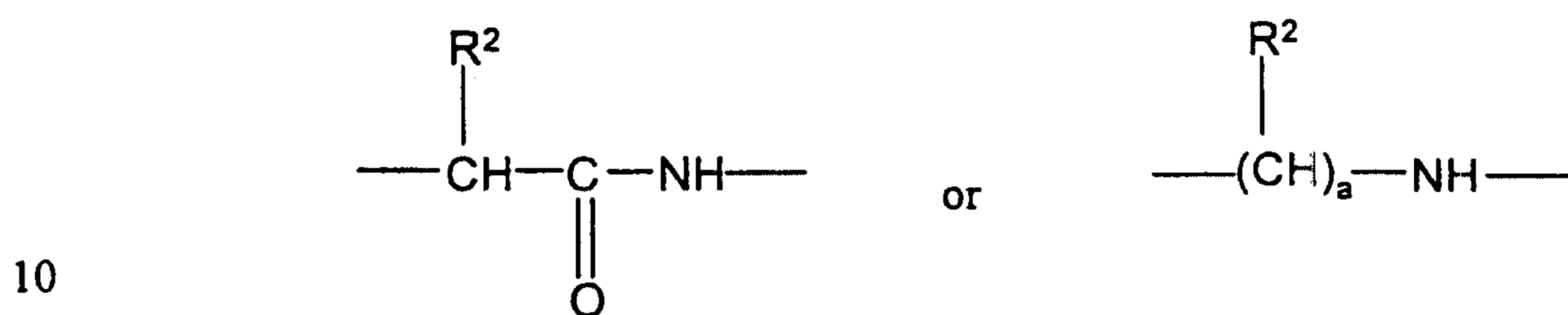
30 ring *B*, together with the atoms of the ϵ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

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ring C, together with the atoms of the ϵ -caprolactam to which it is attached, forms a heteroaryl or heterocyclic ring;

R^1 is selected from the group consisting of hydrogen and an amino-blocking group;

5 Y is represented by the formula:



provided that at least one Y is $-(CHR^2)_a-NH-$;

each R^2 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heteroaryl and heterocyclic;

15

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

20 each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

25 a is an integer from 2 to 6; m is an integer from 0 to 2; n is an integer from 0 to 2; and salts thereof.

When Y in formula II is the group $-(CHR^2)_a-NH-$, the integer a is preferably 2, 3 or 4, more preferably 2 or 4, and still more preferably a is equal to 2. In a preferred embodiment, Y has the formula $-CHR^2-CH_2-NH-$, where R^2 is as defined herein.

30

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The preferred embodiments for R^1 , R^2 , R^3 , R^4 , A , B , C , W , m , n and the like in formula II are the same as those described herein for compounds of formula I.

Compounds of this invention include, by way of example, the following:

5 5-[N'-Boc-2S-aminopropyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

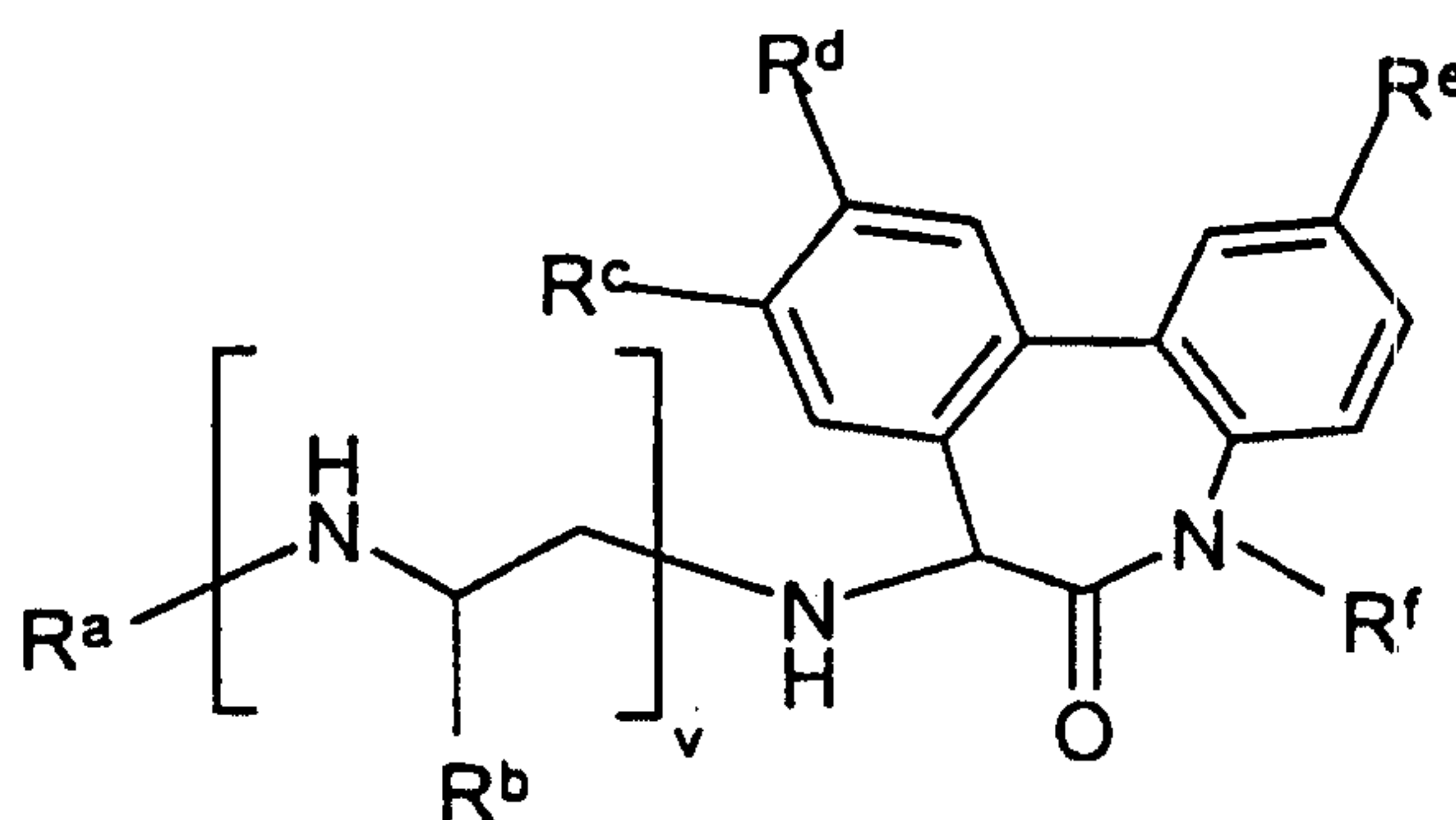
10 5-(2S-aminopropyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

and salts thereof.

Preferred compounds include those defined by the formulas as set forth in Tables VI below and salts thereof.

15

Table VI



20

R^a	R^b	R^c	R^d	R^e	R^f	v
Boc- ^a	CH ₃ -	H-	H-	H-	CH ₃ -	1
H-	CH ₃ -	H-	H-	H-	CH ₃ -	1

^a Boc = *tert*-butoxycarbonyl = (CH₃)₃COC(O)-

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DETAILED DESCRIPTION OF THE INVENTION

For purposes of describing this invention in all its aspects, the following terms have the followings meanings unless otherwise indicated. All other terms have their conventional art-recognized meanings.

5

Definitions

The term "β-amyloid peptide" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kD, which peptide is substantially homologous to the form of the protein described by Glenner, et al.¹ including mutations and post-translational modifications of the normal β-amyloid peptide. In whatever form, the β-amyloid peptide is an approximate 39-43 amino acid fragment of a large membrane-spanning glycoprotein, referred to as the β-amyloid precursor protein (APP). Its 43-amino acid sequence is:

15

1
Asp Ala Glu Phe Arg His Asp Ser Gly Tyr

20

11
Glu Val His His Gln Lys Leu Val Phe Phe

21
Ala Glu Asp Val Gly Ser Asn Lys Gly Ala

25

31
Ile Ile Gly Leu Met Val Gly Gly Val Val

41
Ile Ala Thr (SEQ ID NO: 1)

30

or a sequence which is substantially homologous thereto.

35

"Alkyl" refers to monovalent alkyl groups preferably having from 1 to 20 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, decyl and the like.

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"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 20 carbon atoms, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl.

"Alkylene" refers to divalent alkylene groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene (-CH₂-), ethylene (-CH₂CH₂-), the propylene isomers (e.g., -CH₂CH₂CH₂- and -CH(CH₃)CH₂-) and the like.

"Substituted alkylene" refers to an alkylene group, preferably of from 1 to 10 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused cycloalkyl groups contain from 1 to 3 fused ring structures.

"Alkenylene" refers to divalent alkenylene groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms. This term is

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exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH₂CH=CH- and -C(CH₃)=CH-) and the like.

"Substituted alkenylene" refers to an alkenylene group, preferably of from 2 to 10 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group.

15

"Alkaryl" refers to -alkylene-aryl groups preferably having from 1 to 8 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

20

"Alkoxy" refers to the group "alkyl-O-". Preferred alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

25

"Substituted alkoxy" refers to the group "substituted alkyl-O-" where substituted alkyl is as defined above.

"Alkylalkoxy" refers to the group "-alkylene-O-alkyl" which includes by way of example, methylenemethoxy (-CH₂OCH₃), ethylenemethoxy (-CH₂CH₂OCH₃), *n*-propylene-*iso*-propoxy (-CH₂CH₂CH₂OCH(CH₃)₂), methylene-*t*-butoxy (-CH₂-O-C(CH₃)₃) and the like.

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"Alkylthioalkoxy" refers to the group "-alkylene-S-alkyl" which includes by way of example, methylenethiomethoxy ($-\text{CH}_2\text{SCH}_3$), ethylenethiomethoxy ($-\text{CH}_2\text{CH}_2\text{SCH}_3$), *n*-propylene-thio-*iso*-propoxy ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{SCH}(\text{CH}_3)_2$), methylenethio-*t*-butoxy ($-\text{CH}_2\text{SC}(\text{CH}_3)_3$) and the like.

5

"Alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl ($-\text{CH}=\text{CH}_2$), *n*-propenyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), *iso*-propenyl ($-\text{C}(\text{CH}_3)=\text{CH}_2$), and the like.

10

"Substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy, nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl.

15

20

"Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation. Preferred alkynyl groups include ethynyl ($-\text{C}\equiv\text{CH}$), propargyl ($-\text{CH}_2\text{C}\equiv\text{CH}$) and the like.

25

"Substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkoxy, substituted cycloalkoxyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, heterocycloxy,

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nitro -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl.

"Acyl" refers to the groups alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Acylamino" refers to the group -C(O)NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic and where both R groups are joined to form a heterocyclic group, wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

"Amino" refers to the group -NH₂.

"Substituted amino" refers to the group -N(R)₂ where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, heterocyclic and where both R groups are joined to form a heterocyclic group. When both R groups are hydrogen, -N(R)₂ is an amino group. Examples of substituted amino groups include, by way of illustration, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic, and the like.

The term "amino-blocking group" or "amino-protecting group" refers to any group which, when bound to an amino group, prevents undesired reactions from occurring at the amino group and which may be removed by conventional chemical and/or enzymatic procedures to reestablish the amino group. Any known amino-

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blocking group may be used in this invention. Typically, the amino-blocking group is selected so as to render the resulting blocked-amino group unreactive to the particular reagents and reaction conditions employed in a subsequent pre-determined chemical reaction or series of reactions. After completion of the reaction(s), the amino-blocking group is selectively removed to regenerate the amino group. Examples of suitable amino-blocking groups include, by way of illustration, *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), acetyl, 1-(1'-adamantyl)-1-methylethoxycarbonyl (Acm), allyloxycarbonyl (Aloc), benzyloxymethyl (Bom), 2-*p*-biphenylisopropylloxycarbonyl (Bpoc), *tert*-butyldimethylsilyl (Bsi), benzoyl (Bz), benzyl (Bn), 9-fluorenylmethyloxycarbonyl (Fmoc), 4-methylbenzyl, 4-methoxybenzyl, 2-nitrophenylsulfenyl (Nps), 3-nitro-2-pyridinesulfenyl (NPys), trifluoroacetyl (Tfa), 2,4,6-trimethoxybenzyl (Tmob), trityl (Trt), and the like. If desired, amino-blocking groups covalently attached to a solid support may also be employed.

15

"Aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

20

"Aminoacyloxy" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

25

"Acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

30

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused)

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rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

Unless otherwise constrained by the definition for the aryl substituent, such
5 aryl groups can optionally be substituted with from 1 to 5 substituents selected
from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl,
alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted
alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy,
10 azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heterocyclic,
aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy,
thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl,
-SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl,
-SO₂-heteroaryl and trihalomethyl. Preferred substituents include alkyl, alkoxy,
15 halo, cyano, nitro, trihalomethyl, and thioalkoxy.

"Aryloxy" refers to the group aryl-O- wherein the aryl group is as defined
above including optionally substituted aryl groups as also defined above.

"Carboxyalkyl" refers to the groups "-C(O)Oalkyl" and "-C(O)O-
20 substituted alkyl" where alkyl is as defined above.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 12 carbon atoms
having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups
include, by way of example, single ring structures such as cyclopropyl, cyclobutyl,
25 cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as
adamantanyl, and the like.

"Substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5
(preferably 1 to 3) substituents selected from the group consisting of alkoxy,
30 substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted
cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl,
aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl,

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keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl.

5

"Cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 8 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

10

"Substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl.

15

20

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either fluoro or chloro.

25

"Heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring).

30

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents selected from the group consisting of acyloxy, hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl,

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aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heterocyclic, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, -SO₂-heteroaryl and trihalomethyl. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyll or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

"Heteroaryloxy" refers to the group "-O-heteroaryl".

"Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 15 carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyacylamino, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, keto, thioketo, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of heterocycles and heteroaryls include, but are not limited to, pyrrole, furan, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine,

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carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, indoline, morpholino, piperidinyl, tetrahydrofuranyl, and the like as well as N-alkoxy-nitrogen containing heterocycles.

5

"Heterocyclooxy" refers to the group "-O-heterocycle".

"Keto" or "oxo" refers to the group "=O".

10

"Oxyacylamino" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

15

"Thiol" refers to the group -SH.

"Thioalkoxy" refers to the group -S-alkyl.

"Substituted thioalkoxy" refers to the group -S-substituted alkyl.

20

"Thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

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"Thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

"Thioketo" refers to the group "=S".

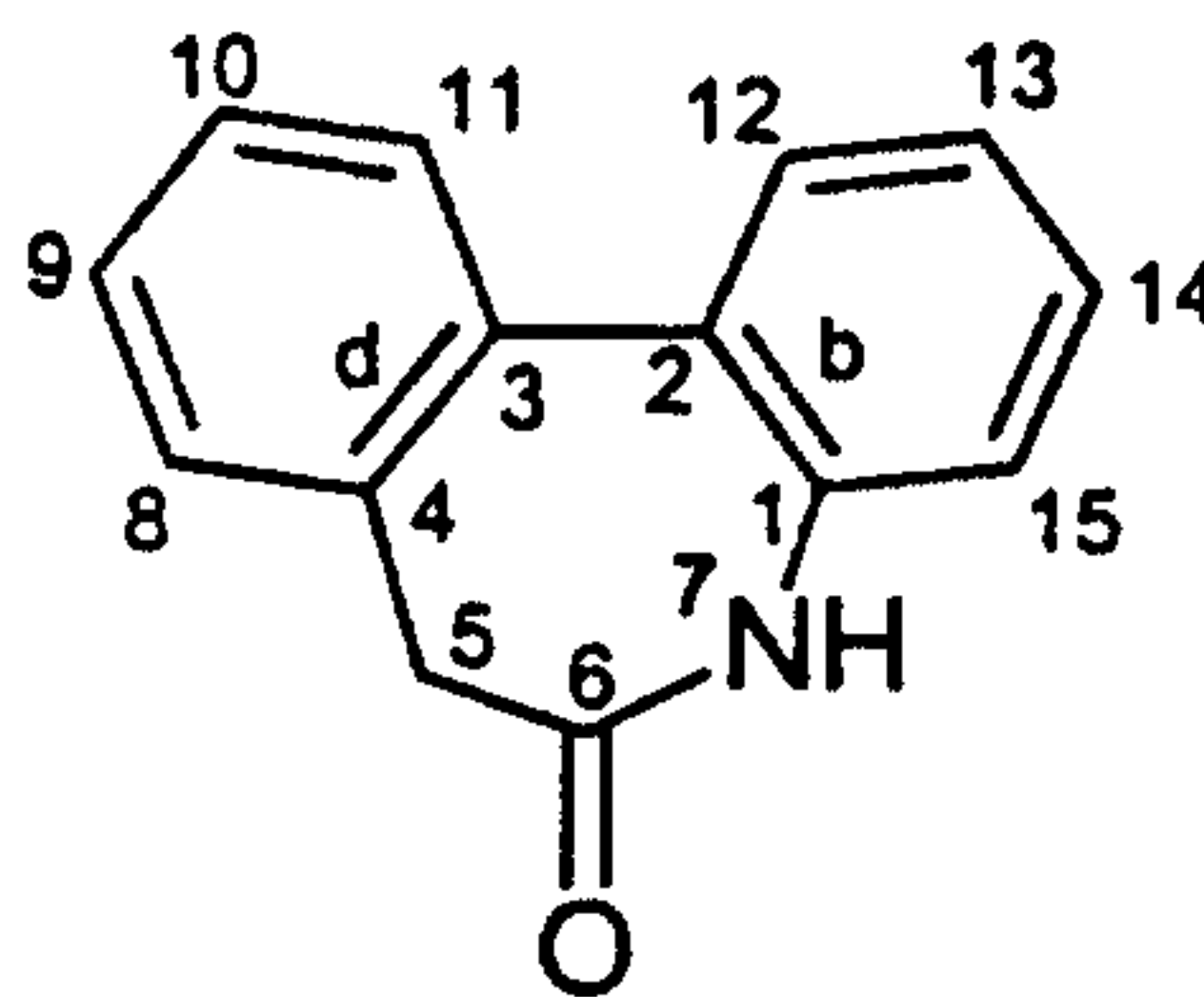
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As to any of the above defined groups which contain 1 or more substituents, it is understood, of course, that such groups do not contain any

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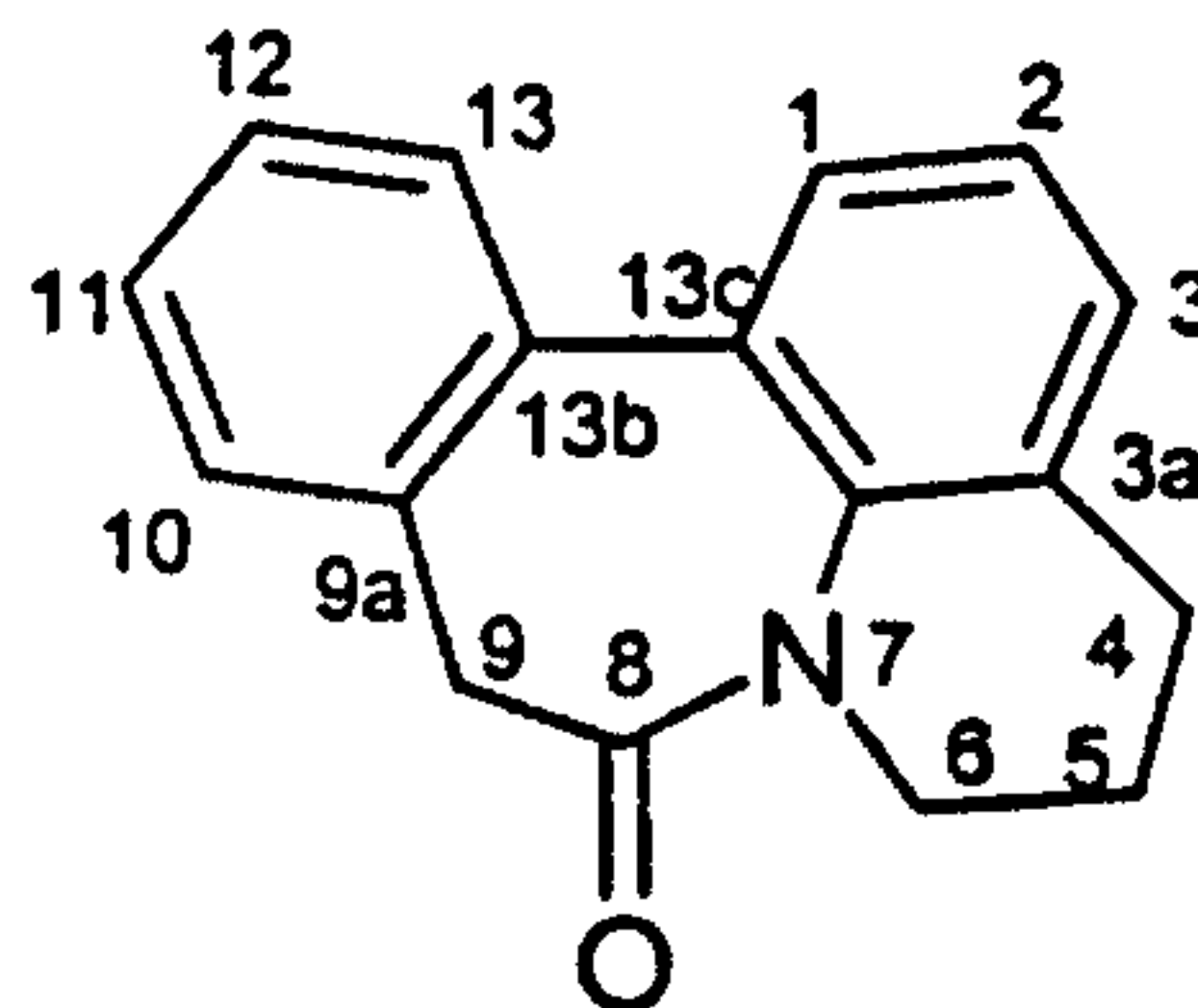
substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible.

5 The term "5,7-dihydro-6H-dibenz[b,d]azepin-6-one" refers to a polycyclic ϵ -caprolactam ring system having the formula:



wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

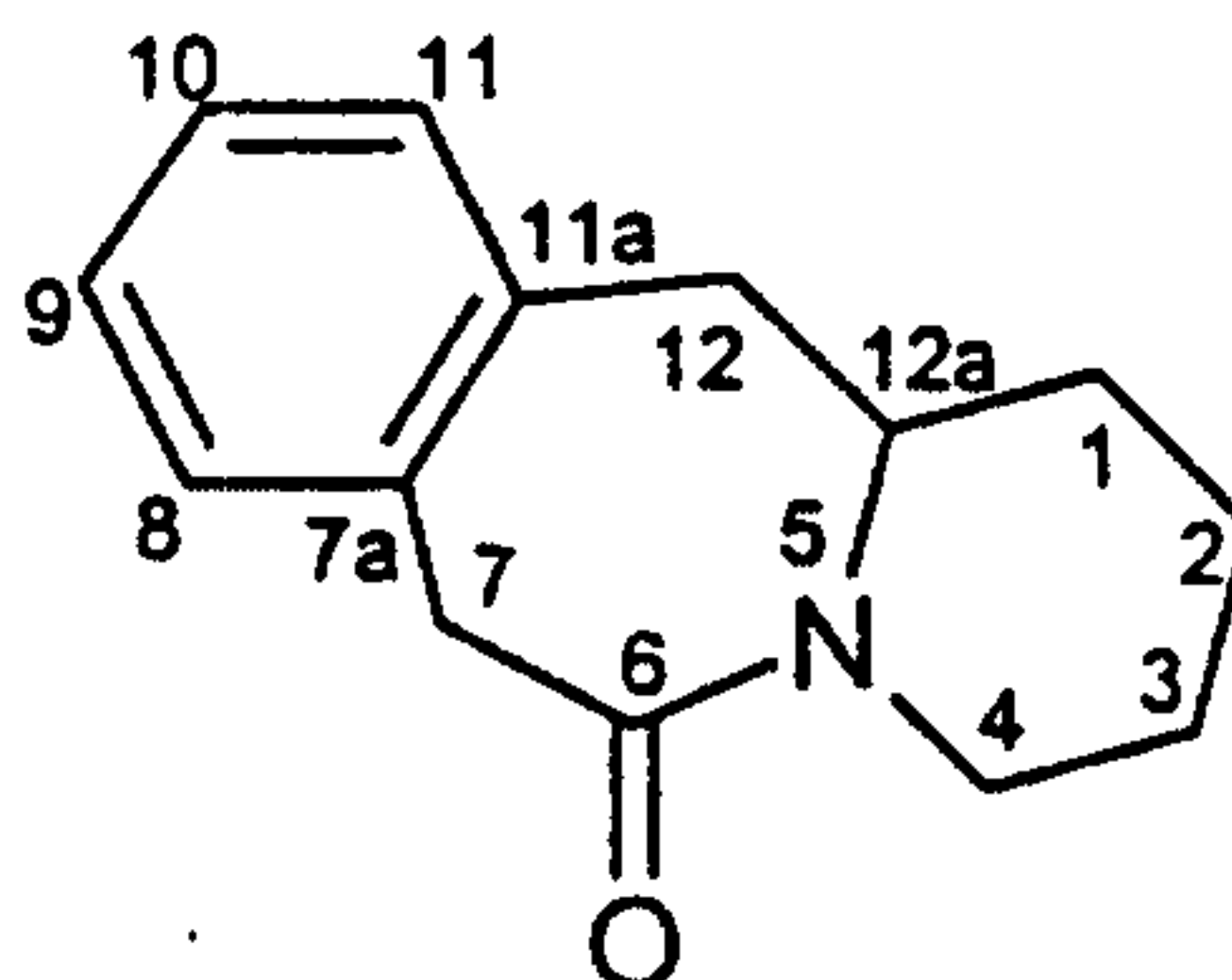
10 The term "5,6-dihydro-4H-quinol[8,1-ab][3]benzazepin-8(9H)-one" refers to a polycyclic ϵ -caprolactam ring system having the formula:



wherein, for nomenclature purposes, the atoms and bonds are numbered and lettered, respectively, as shown.

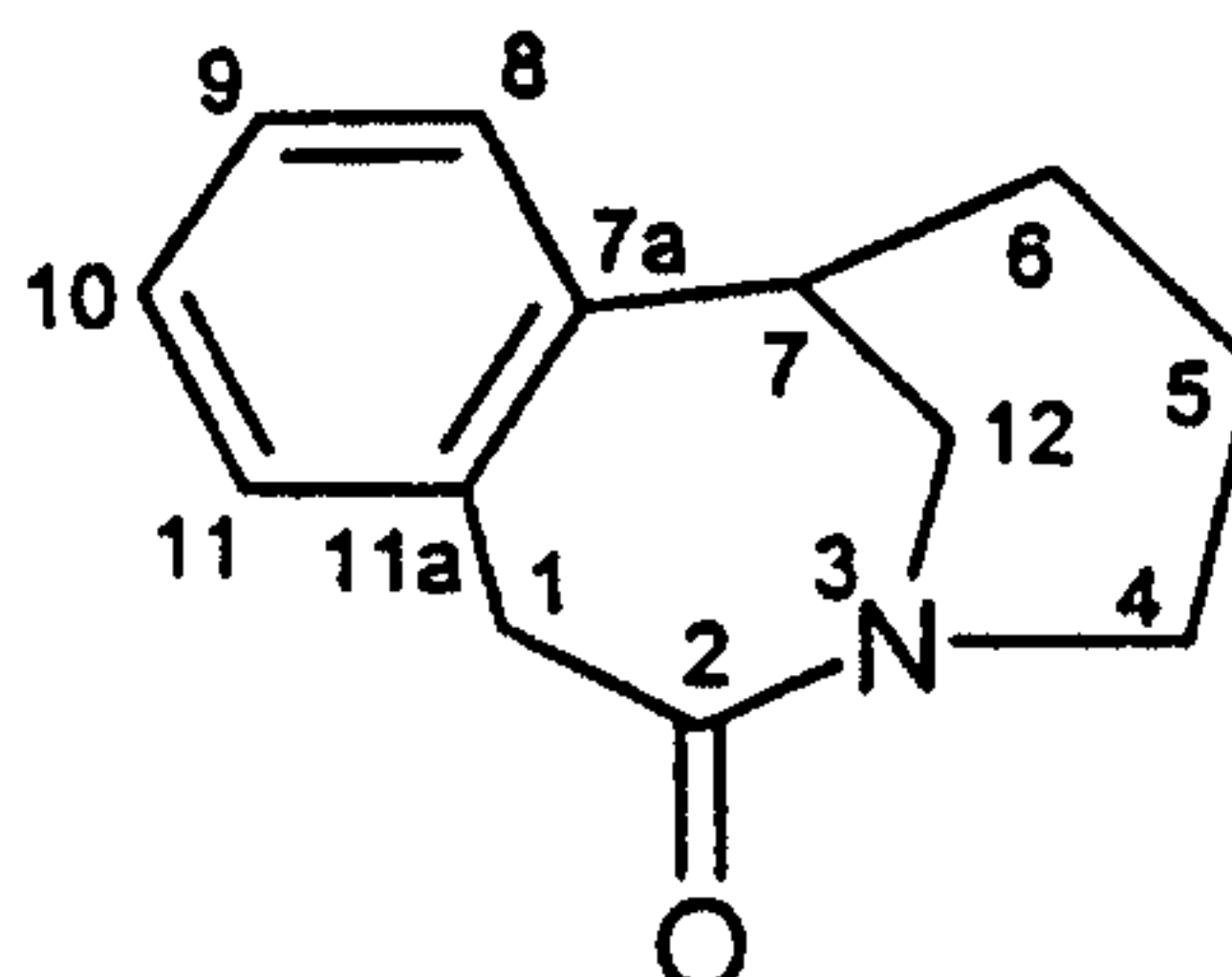
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The term "1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one" refers to a polycyclic ϵ -caprolactam ring system having the formula:



wherein, for nomenclature purposes, the atoms and bonds are numbered and
 5 lettered, respectively, as shown.

The term "4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one" refers to a polycyclic ϵ -caprolactam ring system having the formula:



10 wherein, for nomenclature purposes, the atoms and bonds are numbered and
 lettered, respectively, as shown.

The term "salt(s)" refers to salts of a compound of formula I which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium,
 15 ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

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The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, carboxyl or other protectable functional group of the compound prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical and/or enzymatic steps to reestablish the unprotected functional group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzyldine, phenacyl, *tert*-butyldiphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product.

Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *tert*-butyl, etc. which can be removed by mild hydrolysis conditions compatible with the nature of the product.

Compound Preparation

The polycyclic α -amino- ϵ -caprolactams and related compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts,

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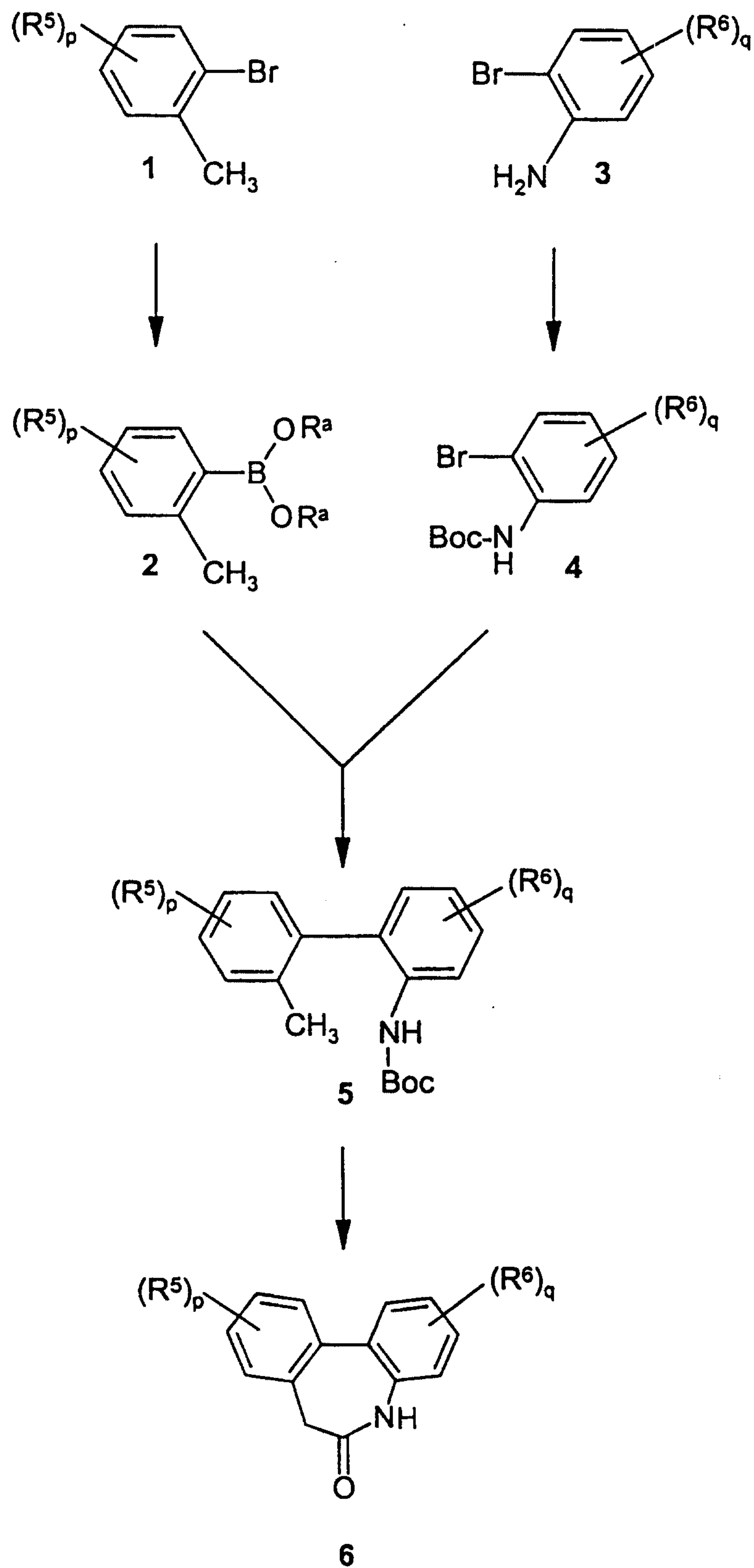
Protecting Groups in Organic Synthesis, Second Edition, Wiley, New York, 1991,⁸ and references cited therein.

5 In a preferred method of synthesis, the compound of this invention are prepared by first aminating a polycyclic ϵ -caprolactam to provide a polycyclic α -amino- ϵ -caprolactam. If desired, the amino group of the polycyclic α -amino- ϵ -caprolactam can then be coupled with a mono- or diamino acid derivative to provide compounds of formula I wherein n is 1 or 2.

10 The polycyclic ϵ -caprolactams employed as starting materials in this invention are either commercially available or can be prepared from commercially available materials using conventional procedures and reagents. For example, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one may be prepared by cyclizing a chloromethyl amide intermediate using the procedures set forth in R. F. C. Brown et al., *Tetrahedron Letters* 1971, 8, 667-670⁹ and references cited
15 therein.

20 Additionally, the synthesis of a representative polycyclic ϵ -caprolactam, i.e., a 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, is illustrated in Scheme 1. As will be readily apparent to those of ordinary skill in the art, the synthetic procedure illustrated in Scheme 1 and the reaction conditions described below can be modified by selecting the appropriate starting materials and reagents to allow the preparation of other polycyclic ϵ -caprolactams.

-- 39 --

Scheme 1

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As shown in Scheme 1, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivatives, 6, wherein R^5 , R^6 , p and q are as defined above, can be readily prepared in several steps from a 2-bromotoluene derivative 1 and a 2-bromoaniline derivative 4. In this synthetic procedure, the 2-bromotoluene derivative, 1, is first converted into the corresponding 2-methylphenylboronate ester, 2. This reaction is typically conducted by treating 1 with about 1.0 to about 2.1 equivalents of an alkyl lithium reagent, preferably *sec*-butyl lithium or *tert*-butyl lithium, in an inert diluent, such as THF, at a temperature ranging from about -80°C to about -60°C for about 0.25 to about 1 hour. The resulting lithium anion is then treated *in situ* with an excess, preferably 1.5 equivalents, of a trialkylborate, such as trimethylborate. This reaction is initially conducted at -80°C to about -60°C and then allowed to warm to about 0°C to about 30°C for about 0.5 to about 3 hours. The resulting methyl boronate ester is typically not isolated, but is preferably converted *in situ* into the pinacol ester by treating the reaction mixture with an excess, preferably about 2.0 equivalents, of pinacol. This reaction is typically conducted at ambient temperature for about 12 to about 24 hours to afford the 2-methylphenylboronate ester, 2, in which both R^a groups are preferably joined together to form $-\text{C}(\text{CH}_3)_2\text{C}(\text{CH}_3)_2-$.

In a separate reaction, the amino group of a 2-bromoaniline derivative, 3, is converted into the *N*-Boc derivative 4 by treating 3 with about 1.0 to about 1.5 equivalents of di-*tert*-butyl-dicarbonate. Typically, this reaction is conducted at a temperature ranging from 25°C to about 100°C for about 12 to 48 hours to afford the *N*-Boc-2-bromoaniline derivative 4.

As further illustrated in Scheme 1, the 2-methylphenylboronate ester, 2, and the *N*-Boc-2-bromoaniline derivative 4 can then be coupled to form the biphenyl derivative 5. This reaction is typically conducted by contacting 4 with about 1.0 to about 1.2 equivalents of 2 and about 1.0 to about 1.2 equivalents of potassium carbonate in the presence of a palladium catalyst, preferably tetrakis(triphenylphosphine)palladium(0). Generally, this coupling reaction is

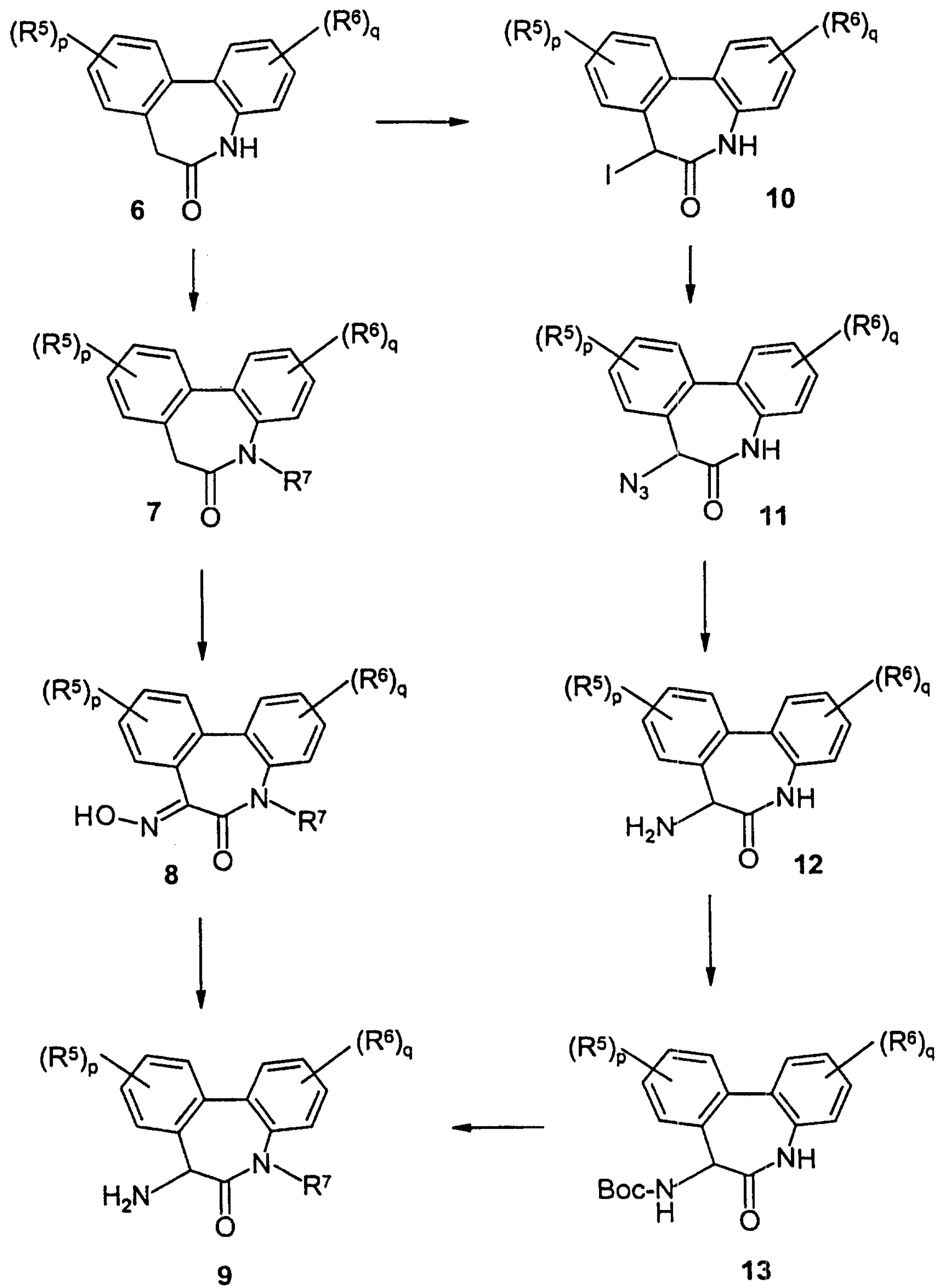
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conducted in a diluent, preferably 20% water/dioxane, under an inert atmosphere at a temperature ranging from about 50°C to about 100°C for about 6 to 24 hours.

Biphenyl derivative 5 is then readily converted into the 5,7-dihydro-6H-dibenz[b,d]azepin-6-one 6 by carboxylation of the 2-methyl group, followed by cyclization to form the ϵ -caprolactam. The carboxylation reaction is typically conducted by contacting 5 with about 2.0 to about 2.5 equivalents of a suitable base, such as *sec*-butyllithium, *tert*-butyllithium and the like, in an inert diluent, such as THF, at a temperature ranging from about -100°C to about -20°C for about 0.5 to 6 hours. The resulting dianion is then treated with excess anhydrous carbon dioxide to form the carboxylate. Treatment of the carboxylate with excess hydrogen chloride in a suitable diluent, such as methanol, at a temperature ranging from about 25°C to about 100°C then affords the 5,7-dihydro-6H-dibenz[b,d]azepin-6-one 6. Various other polycyclic ϵ -caprolactam compounds can be prepared by routine modifications of the above described procedures.

Preferred synthetic procedures for aminating a representative polycyclic ϵ -caprolactam compound are illustrated in Scheme 2. It will be readily apparent to those of ordinary skill in the art that the synthetic procedure illustrated in Scheme 2 and the following reaction conditions can be modified by selecting the appropriate starting materials and reagents to allow the preparation of other polycyclic α -amino- ϵ -caprolactams of this invention.

-- 42 --

Scheme 2

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As shown in Scheme 2, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 6, is optionally *N*-alkylated using conventional reagents and conditions to provide a 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative, 7. Typically, this reaction is conducted by first contacting 6 with about 1.0 to 1.5 equivalents of a suitable base, such as sodium hydride, sodium bis(trimethylsilyl)amide and the like, in an inert diluent, such as DMF, THF and the like, at a temperature ranging from about -78°C to about 50°C for about 0.25 to about 6 hours. The resulting anion is then treated *in situ* with an excess, preferably about 1.1 to about 2.0 equivalents, of an alkyl, substituted alkyl, cycloalkyl halide, etc., typically a chloride, bromide or iodide. This reaction is typically conducted at a temperature ranging from about 0°C to about 60°C for about 1.0 to about 48 hours to afford the 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative, 7.

The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 7 is then oximated by contacting 7 with an excess, preferably with about 1.0 to 1.5 equivalents of a suitable base, such as sodium bis(trimethylsilyl)amide and the like, in the presence of about 1.0 to about 2.0 equivalents of an alkyl nitrite. Suitable alkyl nitrites for use in this reaction include, by way of example, butyl nitrite, isoamyl nitrite and the like. This reaction is typically conducted in an inert diluent, such as THF and the like, at a temperature ranging from about -10°C to about 20°C for about 0.5 to about 6 hours to afford the 7-alkyl-5-oximo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative 8.

Reduction of 8 using conventional reagents and conditions then affords the 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 9. Preferably, this reduction reaction is conducted by hydrogenating the oxime 8 in the presence of a catalyst, such as Raney nickel. This reaction is typically conducted under about 200 psi to about 600 psi of hydrogen at a temperature of about 70°C to about 120°C for about 8 to 48 hours in a diluent, preferably a mixture of ethanol and ammonia (about 20:1). Alternatively, in another preferred procedure, the oxime may be reduced using 10% Pd/C and between about 30 to about 60 psi of hydrogen at a temperature ranging from about 20°C to about 50°C for about 4 hours. The

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resulting 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 9 is generally purified using well known procedures, such as recrystallization and/or chromatography.

5 Alternatively, 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, 9, can be prepared by first forming the 5-iodo derivative 10 of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 6. This reaction is typically conducted as described in A. O. King et al.¹⁰ by treating 6 with an excess, preferably about 1.2 to about 2.5 equivalents, of trimethylsilyl iodide in the presence of an excess of a trialkylamine, 10 such as triethylamine, diisopropylethylamine, TMEDA and the like, at a temperature ranging from about -20°C to about 0°C for about 3 to 30 minutes and then adding about 1.1 to about 2.0 equivalents of iodine (I₂). Typically, after addition of the iodide, the reaction is stirred at a temperature ranging from about 0°C to about 20°C for about 2 to about 4 hours to afford 5-iodo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 10. 15

Displacement of iodide from 10 using an alkali metal azide then affords 5-azido-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 11. Typically, this reaction is conducted by contacting 10 with about 1.1 to about 1.5 equivalents of sodium azide 20 in an inert diluent, such as DMF, at a temperature ranging from about 0°C to about 50°C for about 12 to about 48 hours.

The azido derivative 11 is then reduced to the corresponding amino derivative 12 using conventional procedures and reagents. For example, the azido 25 group is preferably reduced by contacting 11 with an excess, preferably with about 3 equivalents, of triphenylphosphine in a diluent, preferably a mixture of THF and water. This reduction reaction is typically conducted at a temperature ranging from about 0°C to about 50°C for about 12 to 48 hours to afford 5-amino-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 12.

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The amino group of 12 is then protected or blocked using a conventional amino blocking group. Preferably, compound 12 is treated with about 1.0 to about

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1.1 equivalents of di-*tert*-butyl dicarbonate in the presence of an excess, preferably about 2 to about 3 equivalents, of a trialkylamine, such as triethylamine. This reaction is typically conducted in an inert diluent, such as THF, at a temperature ranging from about 0°C to about 50°C for 3 to about 24 hours to provide 5-(*N*-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 13.

Compound 13 is then optionally *N*-alkylated to afford, after de-blocking of the amino group, a 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 9. The *N*-alkylation reaction is typically conducted by treating 13 with about 1.0 to 1.5 equivalents of an alkyl halide, a substituted alkyl halide or a cycloalkyl halide in the presence of about 1.0 to about 1.5 equivalents of a suitable base, such as cesium carbonate and the like. This reaction is generally conducted in an inert diluent, such as DMF and the like, at a temperature ranging from about 25°C to about 100°C for about 12 to about 48 hours.

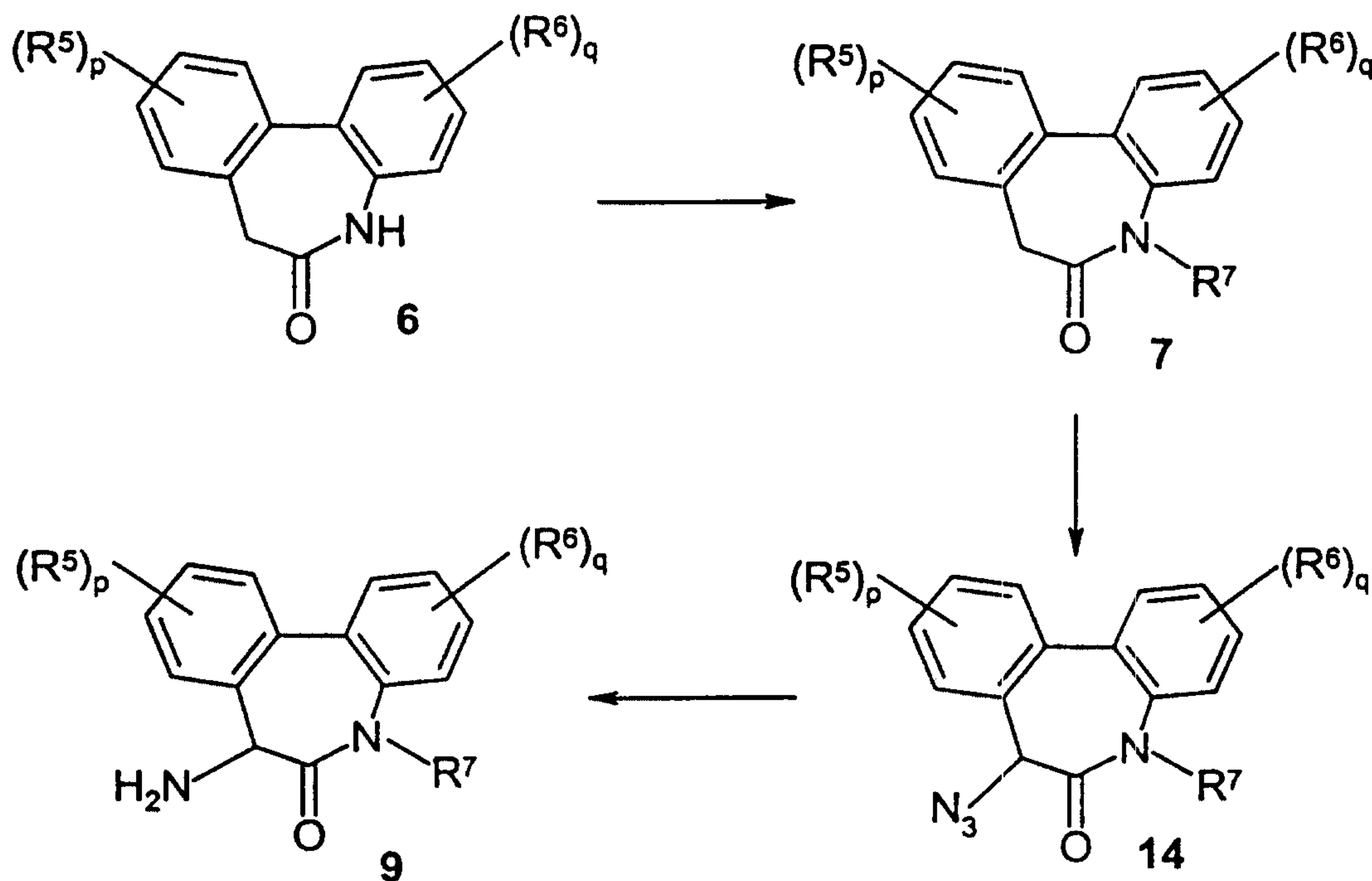
Representative alkyl, substituted alkyl and cycloalkyl halides suitable for use in this *N*-alkylation reaction include, by way of illustration, 1-iodo-2-methylpropane, methyl bromoacetate, 1-chloro-3,3-dimethyl-2-butanone, 1-chloro-4-phenylbutane, bromomethylcyclopropane, 1-bromo-2,2,2-trifluoroethane, bromocyclohexane, 1-bromohexane and the like.

The *N*-Boc protecting group is then removed using conventional procedures and reagents to afford the 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 9. This deblocking reaction is typically conducted by treating the *N*-Boc compound 13 with anhydrous hydrogen chloride in an inert diluent, such as 1,4-dioxane, at a temperature ranging from about 0°C to about 50°C for about 2 to about 8 hours. The resulting 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 9 is generally purified using well known procedures, such as recrystallization and/or chromatography.

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The 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, 9, can also be prepared via an azide transfer reaction as illustrated in Scheme 3.

Scheme 3

5 As shown in Scheme 3, 5,7-dihydro-6H-dibenz[b,d]azepin-6-one, 6, is first *N*-alkylated as described above using conventional reagents and conditions to provide a 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative, 7.

10 The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 7 is then reacted with an azide transfer reagent to afford 5-azido-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 14. Typically, this reaction is conducted by first contacting 7 with an excess, preferably with about 1.0 to 1.5 equivalents of a suitable base, such as lithium diisopropylamine and the like, in an inert diluent such as THF, at a temperature ranging from about -90°C to about -60°C for about 15 0.25 to about 2.0 hours. The resulting anion is then treated with an excess, preferably with about 1.1 to about 1.2 equivalents, of an azide transfer reagent, such as 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide). This reaction is

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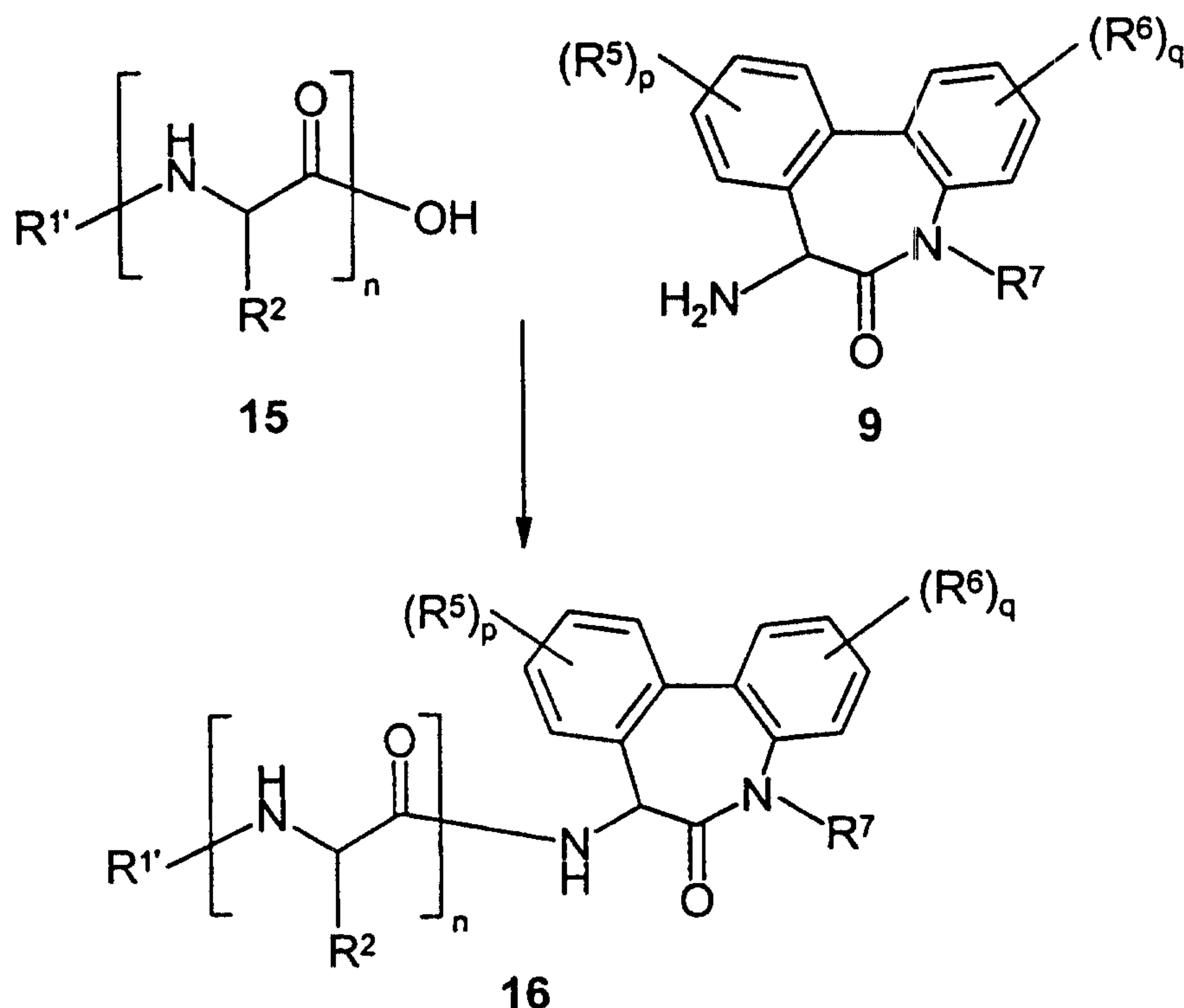
typically conducted at a temperature ranging from about -90°C to about -60°C for about 0.25 to about 2.0 hours. The reaction mixture is then typically treated with an excess of glacial acetic acid and the mixture is allowed to warm to ambient temperature and then heated at about 35°C to about 50°C for about 2 to 4 hours to afford the 5-azido-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one derivative 14. Reduction of 14 as described above using conventional reagents and conditions then affords the 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one 9.

If desired, the aryl rings of 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, 9, and related compounds may be partially or fully saturated by treatment with hydrogen in the presence of a hydrogenation catalyst. Typically, this reaction is conducted by treating 9 with hydrogen at a pressure of about 10 to about 100 psi in the presence of a catalyst, such as rhodium on carbon. This reaction is typically conducted at a temperature ranging from about 20°C to about 100°C for about 12 to 96 hours in a suitable diluent, such as ethyl acetate/acetic acid (1:1) and the like.

After preparing the polycyclic α -amino- ϵ -caprolactam, the α -amino group may be coupled with a mono- or dipeptide derivative (i.e., an amino acid derivative) to prepared compounds of formula I, wherein n is 1 or 2. Scheme 4 illustrates the coupling of a representative polycyclic α -amino- ϵ -caprolactam, i.e., 9, with a mono- or dipeptide derivative 15, wherein R^2 and n are as defined above and R^1 is an amino-blocking group.

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Scheme 4



As illustrated in Scheme 4, the coupling of 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones, 9, with a mono- or dipeptide 15 affords the amide 16. This reaction is typically conducted by reacting at least a stoichiometric amount of the amino compound 9 and the mono- or dipeptide 15 with a standard coupling reagent, typically in the presence of a trialkylamine, such as ethyldiisopropylamine, under conventional coupling reaction conditions.

Optionally, well-known coupling promoters, such as *N*-hydroxysuccinimide, 1-hydroxybenzotriazole and the like, may be employed in this reaction. Typically, this coupling reaction is conducted at a temperature ranging from about 0°C to about 60°C for about 1 to about 72 hours in an inert diluent, such as THF, to afford the amide 16.

Suitable coupling reagents include, by way of example, carbodiimides, such as ethyl-3-(3-dimethylamino)propylcarbodiimide (EDC), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC) and the like, and other well-known

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coupling reagents, such as N,N'-carbonyldiimidazole, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) and the like. The coupling reagent may also be bound to a solid support. For example, a polymer supported form of EDC is described in *Tetrahedron Letters* 1993, 34(48), 7685.¹¹ Additionally, 1-(3-(1-pyrrolidiny)propyl-3-ethylcarbodiimide (PEPC) and its corresponding polymer supported forms may be used as a coupling reagent. Briefly, PEPC can be prepared by first reacting ethyl isocyanate with 1-(3-aminopropyl)pyrrolidine. The resulting urea is treated with 4-toluenesulfonyl chloride to provide PEPC. The polymer supported form is prepared by reacting PEPC with an appropriate resin, such as chloromethylated styrene/divinylbenzene resins (Merrifield's resins) under standard conditions to give the desired reagent. Such methods are described more fully in U.S. Provisional Application Serial No. 60/019,790, filed June 14, 1996,¹² which application is incorporated herein by reference in its entirety.

The mono- or dipeptide derivatives employed in the coupling reaction are commercially available or can be prepared using conventional procedures and reagents from commercially available starting materials. The mono- and dipeptide derivatives may be derived from naturally-occurring and non-natural amino acids. For example, suitable mono-peptide derivatives (i.e., amino acid derivatives) include, by way of illustration, *N*-Boc-glycine, *N*-Boc-L-alanine, *N*-Boc-L-valine, *N*-Boc-L-leucine, *N*-Boc-L-isoleucine, *N*-Boc-*tert*-L-leucine, *N*-Boc-L-methionine, *N*-Boc-L-phenylalanine, *N*-Boc-L-phenylglycine, *N*-Boc-L-aspartic acid β -*tert*-butyl ester, *N*-Boc-L-glutamic acid β -*tert*-butyl ester, *N*-Boc-N ϵ -Cbz-L-lysine, *N*-Boc-norleucine and the like. Exemplary dipeptides include, for purposes of illustration only, *N*-Boc-glyciny-L-alanine, *N*-Boc-L-alaniny-L-alanine, *N*-Boc-L-alaniny-L-valine, *N*-Boc-glyciny-L-phenylglycine, *N*-Boc-L-phenylglyciny-L-valine and the like.

After forming amide 16, the amino-blocking group R^{1'}, is typically removed to reestablish the amino group. For example, when R^{1'} is a *tert*-

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butoxycarbonyl group, the *N*-Boc group can be removed by treating 16 with anhydrous hydrogen chloride in an inert diluent, such as 1,4-dioxane. This reaction is typically conducted at a temperature ranging from about -10°C to about 15°C while hydrogen chloride gas is introduced into the reaction mixture, and then at a
5 temperature ranging from about 10°C to about 60°C for about 1 to about 24 hours. Other amino-blocking groups can be removed using well-known art recognized procedures.

If desired, the deoxy derivatives of formula II can also be prepared using
10 conventional reagents and procedures. The synthesis of such compounds is described more fully in U.S. Patent Application Serial No. __/__,__, filed on even date herewith (Attorney Docket No. 002010-136) and entitled "Deoxyamino Acid Compounds, Pharmaceutical Compositions Comprising Same, and Methods for Inhibiting β -Amyloid Peptide Release, and/or its Synthesis by Use of Such
15 Compounds," the disclosure of which is incorporated herein by reference in its entirety, and in the Examples set forth below.

As will be apparent to those skilled in the art, the polycyclic α -amino- ϵ -caprolactams of this invention may contain one or more chiral centers. Typically,
20 such compounds will be prepared as a racemic mixture. If desired, however, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or diastereomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) of the polycyclic α -amino- ϵ -caprolactams of formula I are included within the scope of this invention. Pure stereoisomers (or
25 enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

30 Utility

The compounds of the invention are useful as synthetic intermediates in the preparation of inhibitors of β -amyloid peptide release and/or its synthesis.

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Accordingly, the intermediates of this inventions have utility in the preparation of compounds which are useful, for example, for diagnosing and treating Alzheimer's disease in mammals, including humans.

5 For example, the use of various compounds of this invention in the preparation of inhibitors of β -amyloid peptide release and/or its synthesis is described in U.S. Patent Application No. 08/996,422, filed December 19, 1997,¹³ the disclosure of which is incorporated herein by reference in its entirety.

10 The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

EXAMPLES

15 In the examples below, the following abbreviations have the following meanings, unless otherwise indicated. All other abbreviations have their generally accepted meaning.

20	BEMP	=	2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
	Boc	=	<i>tert</i> -butoxycarbonyl
	BOP	=	benzotriazol-1-yloxy-tris-(dimethylamino)phosphonium hexafluorophosphate
	bd	=	broad doublet (spectral)
25	bs	=	broad singlet (spectral)
	°C	=	degrees Celsius
	calcd	=	calculated
	δ	=	chemical shift in parts per million downfield from tetramethylsilane
30	d	=	doublet (spectral)
	dd	=	doublet of doublets (spectral)
	DIC	=	diisopropylcarbodiimide
	DIPEA	=	diisopropylethylamine
	DMF	=	dimethylformamide
35	DMAP	=	dimethylaminopyridine
	DMSO	=	dimethyl sulfoxide
	EDC	=	ethyl-1-(3-dimethylaminopropyl)carbodiimide
	ee	=	enantiomeric excess
	eq.	=	equivalents

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	Et	=	ethyl
	EtOAc	=	ethyl acetate
	g	=	gram(s)
	h	=	hour(s)
5	HMDS	=	1,1,1,3,3,3-hexamethyldisilazane or bis(trimethylsilyl)amine
	HOAc	=	acetic acid
	HOBt	=	1-hydroxybenzotriazole hydrate
10	HPLC	=	high-performance liquid chromatography
	Hunig's base	=	diisopropylethylamine
	IPA	=	isopropyl alcohol
	L	=	liter
	m	=	multiplet (spectral)
	M	=	moles per liter
15	max	=	maximum
	Me	=	methyl
	meq	=	milliequivalent
	mg	=	milligram
	mL	=	milliliter
20	mm	=	millimeter
	mmol	=	millimole
	MW	=	molecular weight
	N	=	normal
	ng	=	nanogram
25	nm	=	nanometers
	NMR	=	nuclear magnetic resonance
	OD	=	optical density
	PEPC	=	1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide
	PP-HOBT	=	piperidine-piperidine-1-hydroxybenzotriazole
30	psi	=	pounds per square inch
	ϕ	=	phenyl
	q	=	quartet (spectral)
	quint.	=	quintet (spectral)
	rpm	=	rotations per minute
35	s	=	singlet (spectral)
	t	=	triplet (spectral)
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	tlc or TLC	=	thin layer chromatography
40	μ L	=	microliter
	UV	=	ultraviolet

Additionally, the following abbreviations are used to indicate the commercial source for certain compounds and reagents:

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	Aldrich	=	Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233 USA
5	Fluka	=	Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779 USA
	Lancaster	=	Lancaster Synthesis, Inc., P.O. Box 100 Windham, NH 03087 USA
10	Sigma	=	Sigma, P.O. Box 14508, St. Louis MO 63178 USA
15	Bachem	=	Bachem Biosciences Inc., 3700 Horizon Drive, Renaissance at Gulph Mills, King of Prussia, PA 19406 USA
20	Novabiochem	=	Calbiochem-Novabiochem Corp. 10933 North Torrey Pines Road, P.O. Box 12087, La Jolla CA 92039-2087

In the examples below, all temperatures are in degrees Celsius (unless otherwise indicated). The following General Procedures were used as indicated to prepare the compounds set forth in the examples below.

25

GENERAL PROCEDURE A

Preparation of 5-Amino-7-alkyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Derivatives

30 Step A: To a stirred solution of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (30 mmol) in DMF (150 mL) was added in portions 97% NaH (1.08g, 45 mmol). Bubbling occurred immediately and was followed by heavy precipitation. After 10 min., an alkyl halide (33 mmol) was added. The precipitate dissolved quickly and in about 10 min. a clear solution was obtained. The reaction mixture was stirred

35 overnight and then evaporated as completely as possible on a rotovap at 30°C. Ethyl acetate (100 mL) was added to the residue and this mixture was washed with water, brine, and dried over magnesium sulfate. After filtration and concentration, the residue was typically chromatographed to provide the 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one.

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Step B: The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq.) from Step A was dissolved in THF and isoamyl nitrite (1.2 eq.) was added. The mixture was cooled to 0°C in an ice bath. NaHMDS (1.1 eq., 1M in THF) was added dropwise. After stirring for 1 hour or until the reaction was complete, the mixture
5 was concentrated then acidified with 1N HCl and extracted with EtOAc. The organic portion was dried and concentrated to yield a crude product which was purified by silica gel chromatography.

Step C: The resulting oxime from Step B was dissolved in EtOH/NH₃
10 (20:1) and hydrogenated in a bomb using Raney nickel and hydrogen (500 psi) at 100°C for 10 hours. The resulting mixture was filtered and concentrated to provide a crude product which was purified by silica gel chromatography to yield the title compound.

15

GENERAL PROCEDURE B

Preparation of
Fluoro-Substituted 5,7-Dihydro-6H-
dibenz[b,d]azepin-6-one Derivatives

A modification of the procedure of Robin D. Clark and Jahangir,
20 *Tetrahedron* 1993, 49(7), 1351-1356¹⁴ was used. Specifically, an appropriately substituted *N*-Boc-2-amino-2'-methylbiphenyl was dissolved in THF and cooled to -78°C. *sec*-Butyllithium (1.3M in cyclohexane, 2.2 eq.) was added slowly so that the temperature remained below -65°C. The resulting mixture was allowed to warm to -25°C and was stirred at that temperature for 1 hour. The mixture was
25 cooled to -78°C. Dry CO₂ was bubbled through the mixture for 30 seconds. The mixture was allowed to warm to ambient temperature then was carefully quenched with water. The mixture was concentrated under reduced pressure then was adjusted to pH 3 with 1N HCl. The mixture was extracted with EtOAc and the organic portion was dried and concentrated to yield a crude material. The crude
30 material was dissolved in methanol and the solution was saturated with HCl. The mixture was heated at reflux for 12 hours then was allowed to cool. The mixture

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was concentrated to provide crude lactam which was purified by chromatography or crystallization.

GENERAL PROCEDURE C

5

Resolution of 5-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

In a round bottom flask was added the racemic freebase amine (1.0 eq.) in methanol followed by di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.). The mixture was concentrated *in vacuo* to a residue and redissolved in a moderate
10 volume of methanol and allowed to stir at room temperature open to the atmosphere (8-72 hours). The solid was removed by filtration. The enantiomeric excess was determined by chiral HPLC (Chiracel ODR) using 15% acetonitrile and 85% H₂O with 0.1% trifluoroacetic acid and a flow rate of 1.0 mL/min at 35°C. The resolved di-*p*-toluoyl-D-tartaric salt was then dissolved in EtOAc and saturated
15 NaHCO₃ until pH 9-10 was reached. The layers were separated and the organic layer was washed again with saturated NaHCO₃, H₂O, and brine. The organic layer was dried over MgSO₄ and the drying agent was removed by filtration. The filtrate was concentrated *in vacuo*. The free amine was dissolved in MeOH and HCl (12M, 1.0 eq.) was added. The salt was concentrated *in vacuo* and the resulting
20 film was triturated with EtOAc. The HCl salt was filtered and rinsed with EtOAc. The ee was determined by chiral HPLC. This General Procedure can also be used to resolve other 5-amino-7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones.

GENERAL PROCEDURE D

25

EDC Coupling Procedure

A round bottom flask was charged with a carboxylic acid (1.0 eq.), hydroxybenzotriazole hydrate (1.1 eq.) and an amine (1.0 eq.) in THF under nitrogen atmosphere. An appropriate amount (1.1 eq for free amines and 2.2 eq. for hydrochloride amine salts) of base, such as Hunig's base was added to the well
30 stirred mixture followed by EDC (1.1 eq.). After stirring from 4 to 17 hours at room temperature the solvent was removed at reduced pressure, the residue taken up in ethyl acetate (or similar solvent) and water, washed with saturated aqueous

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sodium bicarbonate solution, 1N HCl, brine, dried over anhydrous sodium sulfate and the solvent removed at reduced pressure to provide the product.

GENERAL PROCEDURE E

5

N-Boc Removal Procedure

A stream of anhydrous HCl gas was passed through a stirred solution of the N-Boc compound in 1,4-dioxane (0.03-0.09 M), chilled in a ice bath to ~10°C under N₂, for 10-15 minutes. The cooling bath removed and the solution was allowed to warm to room temperature with stirring for 2-24 hours, monitoring by
10 TLC for the consumption of starting material. The solution was concentrated (and in some instances dissolved in CH₂Cl₂ then re-concentrated and placed in vacuum oven at 60-70°C to remove most of the residual dioxane). The residue was typically used without further purification.

15

GENERAL PROCEDURE F

Reduction of Pyridines and Subsequent Acylation

Step A - Reduction of Pyridines

A substituted pyridine hydrochloride was dissolved in ethanol. Rhodium on alumina was added and the mixture was shaken under 60 psi atmosphere of
20 hydrogen at 40°C for 6 to 18 hours. The mixture was filtered and concentrated to provide a crude product used in Step B.

Step B - Acylation of Piperidines

The crude product from Step A was vigorously stirred in a mixture of
25 chloroform and saturated aqueous sodium bicarbonate. Chloroacetyl chloride (about 1.1 equivalents) was added dropwise. The resulting mixture was stirred for one hour. The organic portion was separated, dried and concentrated to provide a crude product which was purified by silica gel chromatography.

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GENERAL PROCEDURE G

Fridel-Crafts Alkylation

An appropriately substituted chloroacetamide (1 equivalent) and aluminum trichloride (2.4 equivalents) were stirred in *o*-dichlorobenzene. The mixture was heated to between 150°C and the refluxing temperature for between one and four hours. The mixture was allowed to cool and then was poured onto ice. The mixture was extracted with methylene chloride and the organic portion was dried and concentrated to yield a crude product which was purified either by crystallization or by chromatography.

GENERAL PROCEDURE H

Azide Transfer

The lactam starting material was dissolved in THF and the stirred solution was cooled to -78°C. An appropriate base, such as lithium diisopropylamine (1.1 eq.), was slowly added. The mixture was stirred for 30 minutes. A solution of trisyl azide (1.1 eq.) in THF was added dropwise. The resulting mixture was stirred at -78°C for 30 minutes. Glacial acetic acid (4.2 eq.) was added and the mixture was allowed to warm to room temperature. The mixture was heated to 40°C and stirred at that temperature for between 2 and 4 hours. Water was added and the mixture was extracted with ethyl acetate. The organic portion was dried and concentrated to provide a crude product which was purified by silica gel chromatography.

GENERAL PROCEDURE I

Azide Reduction

The azide starting material (1 eq.) was dissolved in 4% water/THF. Triphenylphosphine (2.8 eq.) was added and the mixture was stirred at ambient temperature for 16 hours. The mixture was extracted with dilute aqueous hydrochloric acid. The aqueous portion was washed with ether and then adjusted to pH 9 - 10 with aqueous sodium hydroxide. The mixture was extracted with methylene chloride. The organic portion was dried and concentrated to provide the crude amine which was purified by silica gel chromatography.

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Example 1

Synthesis of
5-Amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride

5 Step A - Synthesis of 7-Methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A round bottom flask was charged with sodium hydride (0.295 g, 7.46 mmol) in 9.0 mL of DMF and treated with 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.3 g, 6.22 mmol) (CAS # 20011-90-9, prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* 1971, 8, 667-670⁹ and references cited therein). After stirring at 60°C for 1 h, the solution was treated with methyl iodide (1.16 mL, 18.6 mmol) and stirring continued for 17 h with the exclusion of light. After cooling, the reaction was diluted with CH₂Cl₂/H₂O, washed with NaHSO₄ solution, H₂O, and dried over Na₂SO₄. Evaporation and flash chromatography (SiO₂, CHCl₃) gave 0.885 g (63%) of the title compound as a colorless solid.

Physical data were as follows:

¹H-NMR (CDCl₃): δ = 7.62 (d, 2H), 7.26-7.47 (m, 6H), 3.51 (m, 2H), 3.32 (s, 3H).

C₁₅H₁₃NO (MW = 223.27); mass spectroscopy (MH⁺) 223.

20 Anal. Calcd for C₁₅H₁₃NO; C, 80.69 H, 5.87 N, 6.27. Found: C, 80.11 H, 5.95 N, 6.23.

Step B - Synthesis of 7-Methyl-5-oximo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 The product from Step A (0.700 g, 3.14 mmol) was dissolved in 20 mL of toluene and treated with butyl nitrite (0.733 mL, 6.28 mmol). The reaction temperature was lowered to 0°C and the solution was treated with KHMDS (9.42 mL, 0.5 M) under N₂ atmosphere. After stirring for 1 h the reaction was quenched with a saturated solution of NaHSO₄, diluted with CH₂Cl₂ and separated. The organic layer was dried over Na₂SO₄ and the title compound purified by chromatography (SiO₂, 98:2 CHCl₃/MeOH) giving 0.59 g (80 %) as a colorless solid.

Physical data were as follows:

NMR data was as follows:

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¹H-NMR (CDCl₃): δ = 9.39 (s, 2H), 7.75-7.42 (m, 8H), 4.80 (s, 1H), 3.30 (s, 3H).

C₁₅H₁₅ClN₂O (MW = 274.75); mass spectroscopy (MH⁺) 239.1.

Anal Calcd for C₁₅H₁₅ClN₂O₃; C, 65.57; H, 5.50; N, 10.20; Found: C, 65.51, H, 5.61; N, 10.01.

Example 3

Synthesis of

5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

10 Step A - Synthesis of 5-Iodo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 g, 4.77 mmol) (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* 1971, 8, 667-670⁹ and references cited therein) and Et₃N (2.66 mL, 19.12 mmol) were stirred
15 for 5.0 minutes at -15°C in CH₂Cl₂ and treated with TMSI (1.36 mL, 9.54 mmol). After stirring for 15 minutes, I₂ (1.81 g, 7.16 mmol) was added in a single portion and the reaction allowed to warm to 5-10°C over 3 h. The reaction was quenched with sat. Na₂SO₃, diluted with CH₂Cl₂ and separated. The organics were washed with Na₂SO₃ and NaHSO₃ and dried over MgSO₄. After filtration, the organics
20 were concentrated to approximately 20 mL and diluted with an additional 20 mL of hexanes. The title compound was isolated as a tan precipitate by filtration or could be chromatographed (SiO₂, CHCl₃/MeOH, 99:1) to provide a yellow solid.

Physical data were as follows:

¹H-nmr (CDCl₃): δ = 8.05 (bs, 1H), 7.64-7.58 (m, 2H), 7.52-7.45 (m, 2H),
25 7.38-7.32 (m, 3H), 7.11 (d, 1H), 5.79 (s, 1H).

C₁₄H₁₀INO (MW = 335.139); mass spectroscopy (MH⁺) 336.

Anal. Calcd for C₁₄H₁₀INO; C, 50.17 H, 3.01 N, 4.18. Found: C, 49.97 H, 3.01 N, 4.06. .

30 Step B - Synthesis of 5-Azido-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

The product from Step A was dissolved in DMF and treated with 1.2 equivalents of NaN₃. After stirring 17 h at 23°C, the mixture was diluted with

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EtOAc/H₂O, separated, washed with brine and dried over MgSO₄. Trituration from hot EtOAc provided the title compound as a tan powder.

Physical data were as follows:

¹H-nmr (DMSO-*d*₆): δ = 10.51 (s, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.48 (m, 4H), 7.30 (m, 1H), 7.24 (m, 1H) 5.27 (s, 1H).

C₁₄H₁₀N₄O (MW = 250.13); mass spectroscopy (MH⁺) 251.

Step C - Synthesis of 5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

The product from Step B was dissolved in THF/H₂O and stirred at 23°C for 17 h in the presence of 3.0 equivalents of Ph₃P. The reaction was diluted with 50 % HOAc/toluene, separated, the aqueous layer extracted with toluene and evaporated to an oily residue. The pH of the residue was adjusted to pH 7.0 by the addition of 1N NaOH and the resulting HOAc salt was collected and vacuum dried. This salt was treated with di-*tert*-butyl dicarbonate (1.05 equivalents) (Aldrich) and Et₃N (2.1 equivalents) in THF. After stirring for 5 h at 23°C, the reaction was filtered and the title compound was isolated as a colorless powder.

Physical data were as follows:

¹H-nmr (CDCl₃): δ = 7.69-7.31 (m, 8H), 7.11 (m, 1H), 6.22 (m, 1H), 5.12 (m, 1H), 1.47 (s, 9H).

C₁₉H₂₀N₂O₃ (MW = 324.16); mass spectroscopy (MH⁺) 325.

Example 4

**Synthesis of
5-Amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Step A - Synthesis of 5-(N-Boc-Amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2g, 0.617 mmol) (Example 3) in DMF was treated with Cs₂CO₃ (0.22 g, 0.678 mmol) and warmed to 60°C. To the reaction mixture was added 1-iodo-2-methylpropane (0.078 mL, 0.678 mmol) and stirring continued for 17 h. After cooling to 23°C, the mixture was diluted with CH₂Cl₂, washed with several

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portions of brine and dried over Na_2SO_4 . The title compound was purified by chromatography (SiO_2 , $\text{CHCl}_3/\text{MeOH}$ 9:1).

Physical data were as follows:

$\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3$ (MW = 380.41); mass spectroscopy (MH+) 381.

5 Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3$; C, 72.61 H, 7.42 N, 7.36. Found: C, 72.31 H, 7.64 N, 7.17.

Step B - Synthesis of 5-Amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

10 The product from Step A was deprotected using General Procedure E to provide the title compound as a slightly colored solid after neutralization and extraction with ethyl acetate, drying over Na_2SO_4 and vacuum drying.

Physical data were as follows:

15 ^1H -nmr (CDCl_3): δ = 7.63-7.31 (m, 8H), 4.35 (bs, 1H), 4.27 (m, 1H), 3.30 (m, 1H), 2.02 (bs, 2H), 0.55 (d, 3H), 0.29 (d, 3H).

$\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$ (MW = 280.17); mass spectroscopy (MH+) 281.

Example 5

20 **Synthesis of**
5-Amino-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A- Synthesis of 5-(N-Boc-Amino)-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.03, 3.08 mmol) (Example 3) in DMF was treated with Cs_2CO_3 (1.10 g, 3.39 mmol) and warmed to 60°C. To this reaction mixture was added methyl bromoacetate (0.321 mL, 3.39 mmol) (Aldrich) and stirring was continued for 17 h. After cooling to 23°C, the mixture was diluted with CH_2Cl_2 , washed with several portions of brine and dried over Na_2SO_4 . The title compound was purified
30 by chromatography (SiO_2 , CHCl_3).

Physical data were as follows:

$\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_5$ (MW = 396.44); mass spectroscopy (MH+) 397

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Anal. Calcd for $C_{22}H_{24}N_2O_5$; C, 66.65 H, 6.10 N, 7.07. Found: C, 66.28 H, 5.72 N, 6.50.

5 Step B - Synthesis of 5-Amino-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The product from Step A was deprotected using General Procedure E to provide the title compound as a colorless solid after evaporation and vacuum drying.

Physical data were as follows:

10 ^1H -nmr (DMSO- d_6): δ = 7.72-7.42 (m, 8H), 4.92 (s, 1H), 4.53 (m, 2H), 3.52 (s, 3H).

$C_{17}H_{16}N_2O_3 \cdot \text{HCl}$ (MW = 332.78); mass spectroscopy (MH⁺ free base) 297.

Example 6

15 **Synthesis of**
 5-Amino-7-(3,3-dimethyl-2-butanonyl)-
 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

 Step A- Synthesis of 5-(N-Boc-Amino)-7-(3,3-dimethyl-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20 A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2 g, 0.617 mmol) (Example 3) in DMF was treated with Cs_2CO_3 (0.3 g, 0.925 mmol) and warmed to 60°C. To this reaction mixture was added 1-chloro-3,3-dimethyl-2-butanone (0.096 mL, 0.74 mmol) (Aldrich) and stirring was continued for 17 h. After cooling to 23°C, the mixture was diluted with CH_2Cl_2 , washed with
25 several portions of brine and dried over Na_2SO_4 . The title compound was isolated as a colorless solid.

Physical data were as follows:

$C_{25}H_{30}N_2O_4$ (MW = 422.522); mass spectroscopy (MH⁺) 423.

Anal. Calcd for $C_{25}H_{30}N_2O_4 \cdot 0.6825 \text{ mol H}_2\text{O}$; C, 69.05 H, 7.27 N, 6.44.

30 Found: C, 69.03 H, 7.27 N, 6.60.

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Step B - Synthesis of 5-Amino-7-(3,3-dimethyl-2-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The product from Step A was deprotected using General Procedure E to provide the title compound as a colorless solid after evaporation and vacuum drying.

Physical data were as follows:

¹H-nmr (DMSO-*d*₆): δ = 9.14 (bs, 3H), 7.76-7.32 (m, 8H), 4.99 (d, 1H), 4.98 (s, 1H), 4.69 (d, 1H), 1.15 (s, 9H).

C₂₀H₂₂N₂O₂ HCl (MW = 358); mass spectroscopy (MH⁺ free base) 323.

Example 7

Synthesis of
5-Amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., *Tetrahedron Letters*, No. 8, 667-670, (1971) and references cited therein) and 1-chloro-4-phenylbutane (Aldrich), the title compound was prepared.

Physical data were as follows:

Step B: Synthesis of 5-Hydroxyimino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 2.37 (m, 2H), 3.65 (m, 1H), 4.50 (m, 1H).

C₁₅H₁₃NO (MW = 370.45); mass spectroscopy (MH⁺) 371.2.

Step C: Synthesis of 5-Amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 2.27 (m, 2H), 3.55 (m, 1H), 4.33 (m, 1H).

(MW = 356.47); mass spectroscopy (MH⁺) 357.3.

Example 8

Synthesis of
5-Amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al.,

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Tetrahedron Letters 1971, 8, 667-670⁹ and references cited therein) and (bromomethyl)cyclopropane (Aldrich), the title compound was prepared.

Physical data were as follows:

Step B: Synthesis of 5-Hydroxyimino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.6 (m, 1H), 4.15 (m, 1H).

(MW = 292.34); mass spectroscopy (MH⁺) 293.2.

Example 9

Synthesis of

5-Amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* 1971, 8, 667-670⁹ and references cited therein) and 1-bromo-2,2,2-trifluoroethane (Aldrich), the title compound was prepared.

Physical data were as follows:

Step A: Synthesis of 7-(2',2',2'-Trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.46 (d, 1H), 3.63 (d, 1H), 4.07 (m, 1H), 5.06 (m, 1H).

Step B: Synthesis of 5-Hydroxyimino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 4.13 (m, 1H), 5.27 (m, 1H).

(MW = 320.27); mass spectroscopy (MH⁺) 321.2.

Example 10

Synthesis of

5-Amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* 1971, 8, 667-670⁹ and references cited therein) and bromocyclohexane (Aldrich), the title compound was prepared.

Physical data were as follows:

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Step A: Synthesis of 7-Cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.35 (d,1H), 3.47 (d,1H), 4.03 (m, 1H).

5

Example 11

Synthesis of 5-Amino-7-hexyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in R. F. C. Brown, et. al., *Tetrahedron Letters* 1971, 8, 667-670⁹ and references cited therein) and 1-bromohexane (Aldrich), the title compound was prepared.

15

Example 12

Synthesis of 5-Amino-9-fluoro-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A - Synthesis of 4-Fluoro-2-methylphenylboronate Pinacol Ester
2-Bromo-5-fluorotoluene (1.0 eq.) (Aldrich) was stirred in THF at -78°C.

20 *sec*-Butyllithium (1.05 eq., 1.3 M in cyclohexane) was slowly added and the mixture was stirred for 45 minutes. Trimethylborate (1.5 eq) (Aldrich) was then added and the mixture was allowed to warm to ambient temperature. After stirring for 1 hour, pinacol (2 eq.) (Aldrich) was added. The mixture was stirred for 16 hours then was concentrated under reduced pressure. The resulting residue was
25 slurried in CH₂Cl₂ and filtered through Celite. The filtrate was concentrated to yield an oil which was purified by chromatography on deactivated silica gel (Et₃N) to yield the title compound.

Step B - Synthesis of *N*-Boc-2-bromoaniline

30

2-Bromoaniline (1 eq.) (Aldrich) and di-*tert*-butyl-dicarbonate (1.1 eq.) (Aldrich) were stirred at 80°C for 20 hours. The resulting mixture was allowed to cool and was directly distilled using house vacuum to provide the title compound.

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Step C - Synthesis of N-Boc-2-amino-4'-fluoro-2'-methylbiphenyl

N-Boc-2-bromoaniline (1 eq.) (Step B), the arylboronate ester (1.1 eq.) (Step A), K_2CO_3 (1.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (0.02 eq.) were stirred in 20% water/dioxane under nitrogen. The solution was heated at reflux for 10 hours. The mixture was allowed to cool then was concentrated. The resulting residue was partitioned between water and chloroform. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography using 1:1 CH_2Cl_2 /hexanes.

Step D - Synthesis of 9-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure B and using the product from Step C, the title compound was prepared.

Physical data were as follows:

(MW = 227.24); mass spectroscopy (MH+) 228.0.

Step E - Synthesis of 9-Fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

9-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq.) (Step D), cesium carbonate (1.1 eq.) (Aldrich) and methyl iodide (1.1 eq.) (Aldrich) were stirred in dry DMF at ambient temperature for 16 hours. The mixture was concentrated under reduced pressure to provide a residue which was partitioned between EtOAc and water. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography to provide the title compound.

Physical data were as follows:

^1H -nmr ($CDCl_3$): δ = 3.33 (s, 3H), 3.42 (d, 1H), 3.54 (d, 1H).

(MW = 241.27); mass spectroscopy (MH+) 242.0.

Step F - Synthesis of 5-Amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure A, Steps B and C, and using the product from Step E, the title compound was prepared.

Physical data were as follows:

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Gen. Proc. A/Step B: Synthesis of 5-Hydroxyimino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.44, 3.47 (singlets, 3H) .

(MW = 270.26); mass spectroscopy (MH⁺) 271.4.

5 Gen. Proc. A/Step C: Synthesis of 5-Amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 2.08 (s,2H); 3.34 (s,3H); 4.30 (s,1H).

(MW =256.3); mass spectroscopy (MH⁺) 257.0.

10 Example 13

Synthesis of

5-Amino-10-fluoro-7-methyl-

5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following the procedure of Example 12 and using 2-bromo-4-fluorotoluene

15 (Lancaster) in Step A, the title compound was prepared.

Physical data were as follows:

Step D: Synthesis of 10-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃/DMSO-*d*₆): δ = 3.34 (q,2h); 9.91(s,1H).

20 (MW = 227.24); mass spectroscopy (MH⁺) 228.0.

Step E: Synthesis of 10-Fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.33 (s,3H), 3.42 (d,1H), 3.57 (d, 1H).

(MW = 241.27); mass spectroscopy (MH⁺) 242.0.

25 Step F: Synthesis of 5-Amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Gen. Proc. A/Step B: Synthesis of 5-Hydroxyimino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.43, 3.47 (singlets, 3H).

(MW = 270.26); mass spectroscopy (MH⁺) 271.4.

Gen. Proc. A/Step C: Synthesis of 5-Amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

35 ¹H-nmr (CDCl₃): δ = 2.06 (s, 2H); 3.34 (s,3H); 4.28 (s, 1H).

(MW = 256.3); mass spectroscopy (MH⁺) 257.0.

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Example 14

Synthesis of

5-Amino-13-fluoro-7-methyl-

5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

5 Following the procedure of Example 12 and using 2-bromo-4-fluoroaniline (Lancaster) in Step B, and *o*-tolylboronic acid (Aldrich) in Step C, the title compound was prepared.

Physical data were as follows:

10 Step D: Synthesis of 13-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 3.5 (bm, 2H).

(MW = 227.24); mass spectroscopy (MH⁺) 227.8.

Step E: Synthesis of 13-Fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15 ¹H-nmr (DMSO-*d*₆): δ = 3.33 (s, 3H), 3.35 (d, 1H), 3.52 (d, 1H).

(MW = 241.27); mass spectroscopy (MH⁺) 241.8.

Step F: Synthesis of 5-Amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20 Gen. Proc. A/Step B: Synthesis of 5-Hydroxyimino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): d = 3.39, 3.44 (singlets, 3H) .

(MW = 270.26); mass spectroscopy (M⁺) 270.1.

25 Gen. Proc. A/Step C: Synthesis of 5-Amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 2.06 (bs, 2H); 3.33 (s, 3H); 4.35 (s, 1H).

R_f (5% methanol/chloroform) = 0.3.

Example 15

Synthesis of

5-Amino-7-methyl-1,2,3,4,5,7-hexahydro-

6H-dicyclohexyl[b,d]azepin-6-one

30 5-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride

(Example 1) was dissolved in a 1:1 mixture of EtOAc/HOAc. Rhodium on carbon

35 (5%) was added and the mixture was stirred at 60°C under 60 psi of hydrogen for 3 days. The reaction mixture was then filtered and the filtrate was concentrated to

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provide an oil which was purified by SCX-cation exchange chromatography to yield the title compound.

Physical data were as follows:

(MW = 250.38); mass spectroscopy (MH⁺) 251.3.

5

Example 16

Synthesis of

(S)- and (R)-5-(L-Alaninyl)amino-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

10

Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-Alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15

N-Boc-L-Alanine (0.429 g, 2.26 mmol) (Aldrich) was dissolved in THF and treated with HOBt hydrate (0.305 g, 2.26 mmol), and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.45 g, 1.89 mmol) (Example 1). The temperature was lowered to 0°C and the reaction mixture was treated with EDC (0.449 g, 2.26 mmol) (Alrich) and stirred for 17 hours under N₂. The reaction mixture was then evaporated and the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over Na₂SO₄. The resulting diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 mL/minute.

20

Isomer 1: Retention time 3.37 minutes.

NMR data was as follows:

¹H-NMR (CDCl₃): δ = 7.62-7.33 (m, 9H), 5.26 (d, 1H), 5.08 (m, 1H), 4.34 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.40 (d, 3H).

25

Optical Rotation: [α]₂₀ = -96 @ 589 nm (c = 1, MeOH).

C₂₃H₂₇N₃O₄ (MW = 409.489); mass spectroscopy (MH⁺) 409.

Anal. Calcd for C₂₃H₂₇N₃O₄; C, 67.46 H, 6.64 N, 10.26. Found: C, 68.42 H, 7.02 N, 9.81.

Isomer 2: Retention time 6.08 minutes.

30

NMR data was as follows:

¹H-NMR (CDCl₃): δ = 7.74 (bd, 1H), 7.62-7.32 (m, 8H), 5.28 (d, 1H), 4.99 (m, 1H), 4.36 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.46 (d, 3H).

Optical Rotation: [α]₂₀ = 69 @ 589 nm (c = 1, MeOH).

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$C_{23}H_{27}N_3O_4$ (MW = 409.489); mass spectroscopy (MH+) 409.

Anal. Calcd for $C_{23}H_{27}N_3O_4$; C, 67.46 H, 6.64 N, 10.26. Found: C, 67.40 H, 6.62 N, 10.02.

5 Step B - Synthesis of (S)- and (R)-5-(L-Alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

In separate reaction flasks, each isomer from Step A was dissolved in dioxane and treated with excess HCl(g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

10 Isomer 1:

$C_{18}H_{19}N_3O_2 \cdot HCl$ (MW = 345.832); mass spectroscopy (MH+ free base) 309.

Optical Rotation: $[\alpha]_{20} = -55$ @ 589 nm (c = 1, MeOH).

Isomer 2:

15 $C_{18}H_{19}N_3O_2 \cdot HCl$ (MW = 345.832); mass spectroscopy (MH+ free base) 309.

Optical Rotation: $[\alpha]_{20} = +80$ @ 589 nm (c = 1, MeOH).

Example 17

20 **Synthesis of
(S)- and (R)-5-(L-Valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-Valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 N-Boc-L-Valine (0.656 g, 3.02 mmol) (Aldrich) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), DIPEA (1.05 mL, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (0.75 g, 2.75 mmol) (Example 1). The temperature was lowered to 0°C and the reaction mixture was treated with EDC (0.601 g, 3.02 mmol) (Alrich) and stirred for 17
30 hours under N₂. The reaction mixture was then evaporated and the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over Na₂SO₄. The resulting diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 mL/minute.

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Isomer 1: Retention time 3.23 minutes.

Optical Rotation: $[\alpha]_{20} = -120$ @ 589 nm ($c = 1$, MeOH).

$C_{25}H_{31}N_3O_4$ (MW = 437.544); mass spectroscopy (MH+) 438

Isomer 2: Retention time 6.64 minutes.

5 Optical Rotation: $[\alpha]_{20} = +50$ @ 589 nm ($c = 1$, MeOH).

$C_{25}H_{31}N_3O_4$ (MW = 437.544); mass spectroscopy (MH+) 438

Step B - Synthesis of (S)- and (R)-5-(L-Valinyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

10 In separate reaction flasks, each of the isomers from Step A was dissolved in dioxane and treated with excess HCl(g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

$C_{20}H_{23}N_3O_2 \cdot HCl$ (MW = 373.88); mass spectroscopy (MH+ free base) 338.

15 Optical Rotation: $[\alpha]_{20} = -38$ @ 589 nm ($c = 1$, MeOH).

Isomer 2:

$C_{20}H_{23}N_3O_2 \cdot HCl$ (MW = 373.88); mass spectroscopy (MH+ free base) 338.

Optical Rotation: $[\alpha]_{20} = +97$ @ 589 nm ($c = 1$, MeOH).

20 Example 18

**Synthesis of
(S)- and (R)-5-(L-*tert*-Leucinyl)amino-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

25 Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-*tert*-Leucinyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

30 N-Boc-L-*tert*-Leucine (0.698 g, 3.02 mmol) (Fluka) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), DIPEA (1.05 mL, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (0.75 g, 2.75 mmol) (Example 1). The temperature was lowered to 0°C and the reaction mixture was treated with EDC (0.601 g, 3.02 mmol) (Alrich) and stirred for 17 hours under N₂. The reaction mixture was then evaporated and the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over

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Na₂SO₄. The diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 mL/minute.

Isomer 1: Retention time 3.28 minutes.

Optical Rotation: $[\alpha]_{20} = -128$ @ 589 nm (c = 1, MeOH).

5 C₂₆H₃₃N₃O₄ (MW = 451.571); mass spectroscopy (MH⁺) 452

Isomer 2: Retention time 5.52 minutes.

Optical Rotation: $[\alpha]_{20} = +26$ @ 589 nm (c = 1, MeOH).

C₂₆H₃₃N₃O₄ (MW = 451.571); mass spectroscopy (MH⁺) 452

10 Step B - Synthesis of (S)- and (R)-5-(L-*tert*-Leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

In separate reaction flasks, each of the isomers from Step A was dissolved in dioxane and treated with excess HCl(g). After stirring for 17 hours, the title
15 compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

C₂₁H₂₅N₃O₂•HCl (MW = 387.91); mass spectroscopy (MH⁺ free base) 352.

Optical Rotation: $[\alpha]_{20} = -34$ @ 589 nm (c = 1, MeOH).

Isomer 2:

20 C₂₁H₂₅N₃O₂•HCl (MW = 387.91); mass spectroscopy (MH⁺ free base) 352.

Optical Rotation: $[\alpha]_{20} = +108$ @ 589 nm (c = 1, MeOH).

Example 19

25 **Synthesis of
5-(L-Alaniny)amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

Step A - Synthesis of 5-(N-Boc-L-Alaniny)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-Boc-L-alanine (Aldrich) and
30 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 1), the title compound was prepared.

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Step B - Synthesis of 5-(L-Alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

5

Example 20

Synthesis of 5-(L-Valinyl)amino-7-methyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Hydrochloride

10 Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-Boc-L-valine (Aldrich) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 1), the title compound was prepared.

15

Step B - Synthesis of 5-(L-Valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

20

Example 21

Synthesis of 5-(L-Alaninyl)amino-9-fluoro-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

25 Step A - Synthesis of 5-(N-Boc-L-Alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using N-Boc-L-alanine (Aldrich) and 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 12), the title compound was prepared.

30

Step B - Synthesis of 5-(L-Alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

35

-- 75 --

Example 22

Synthesis of

**5-(L-Alaninyl)amino-10-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Step A - Synthesis of 5-(N-Boc-L-Alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 13), the title compound was prepared.

10

Step B - Synthesis of 5-(L-Alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

15

Example 23

Synthesis of

**5-(L-Alaninyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20 Step A - Synthesis of 5-(N-Boc-L-Alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 14), the title compound was prepared.

25

Step B - Synthesis of 5-(L-Alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

30

Example 24

Synthesis of

**5-(L-Alaninyl)amino-7-cyclopropylmethyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Synthesis of 5-(N-Boc-L-Alaninyl)amino-7-
cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 8), the title compound was prepared.

10

Step B - Synthesis of 5-(L-Alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

15

Example 25

Synthesis of

**5-(L-Alaninyl)amino-7-phenbutyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Step A - Synthesis of 5-(N-Boc-L-Alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-alanine (Aldrich) and 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7), the title compound was prepared.

25

Step B - Synthesis of 5-(L-Alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

30

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Example 26

**Synthesis of
5-(L-Valinyl)amino-7-cyclopropylmethyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 8), the title compound was prepared.

10

Step B - Synthesis of 5-(L-Valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

15

Example 27

**Synthesis of
5-(L-Valinyl)amino-7-phenbutyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

20 Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7), the title compound was prepared.

25

Step B - Synthesis of 5-(L-Valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

30

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Example 28

**Synthesis of
5-(L-Valinyl)amino-7-hexyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 11), the title compound was prepared.

10

Step B - Synthesis of 5-(L-Valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

15

Physical data were as follows:

¹H-nmr (DMSO-*d*₆): δ = 2.17 (bm, 1H); 3.98, 4.07 (doublets, 1H); 4.27 (m, 1H); 5.24, 5.33 (doublets, 1H).

(MW = 407.55, free base); mass spectroscopy (MH⁺) 408.1.

20

Example 29

**Synthesis of
5-(L-Valinyl)amino-9-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

25 Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 12), the title compound was prepared.

30

Step B - Synthesis of 5-(L-Valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

Physical data were as follows:

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¹H-nmr (DMSO-*d*₆): δ = 2.05 - 2.27 (bm, 1H); 3.96, 4.07 (doublets, 1H); 5.26, 5.32 (doublets, 1H).

(MW = 355.41, free base); mass spectroscopy (MH⁺) 356.3.

Anal. Calcd for C₂₀H₂₂FN₃O₂.HCl; C, 61.30 H, 5.92 N, 10.72. Found: C, 61.15 H, 6.22 N, 10.69.

Example 30

Synthesis of

5-(L-Valinyl)amino-10-fluoro-7-methyl- 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 13), the title compound was prepared.

Step B - Synthesis of 5-(L-Valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

Physical data were as follows:

¹H-nmr (DMSO-*d*₆): δ = 2.05 - 2.30 (bm, 1H); 3.97, 4.06 (doublets, 1H); 5.23, 5.32 (doublets, 1H).

(MW = 355.41, free base); mass spectroscopy (MH⁺) 356.3.

Anal. Calcd for C₂₀H₂₂FN₃O₂.HCl; C, 61.30 H, 5.92 N, 10.72. Found: C, 61.04 H, 5.90 N, 11.01.

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Example 31

**Synthesis of
5-(L-Valinyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Step A - Synthesis of 5-(N-Boc-L-Valinyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Following General Procedure D and using *N*-Boc-L-valine (Aldrich) and 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 14), the title compound was prepared.

10

Step B - Synthesis of 5-(L-Valinyl)amino-13-fluoro-7-methyl-5,7-
dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

15

Physical data were as follows:

¹H-nmr (DMSO-*d*₆): δ = 2.05 - 2.28 (bm, 1H); 3.98, 4.07 (doublets, 1H);
5.27, 5.34 (doublets, 1H).

(MW = 355.41, free base); mass spectroscopy (MH⁺) 356.4.

Anal. Calcd for C₂₀H₂₂FN₃O₂·HCl; C, 61.30 H, 5.92 N, 10.72. Found: C,
20 61.24 H, 6.07 N, 10.86.

Example 32

**Synthesis of
5-Amino-9,13-difluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

25

Following the procedure of Example 12 and using 2-bromo-4-fluoroaniline (Lancaster) in Step B, the title compound was prepared.

Physical data were as follows:

30 Step D: Synthesis of 9,13-Difluoro-5,7-dihydro-6H-
dibenz[b,d]azepin-6-one
(MW = 245.23); mass spectroscopy (MH⁺) 246.0.

Step F: Synthesis of 5-Amino-9,13-difluoro-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one

¹H-nmr (CDCl₃): δ = 2.14 (s, 2H); 3.31 (s, 3H); 4.32 (s, 1H).

35

(MW = 274.3); mass spectroscopy (MH⁺) 275.0.

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Step B - Synthesis of 8-Phenyl-1,2,3,4-tetrahydroquinoline

The product from Step A (0.99 g, 4.82 mmol) was hydrogenated according to the procedure described by Honel, M., et. al., J.C.S. Perkin I, (1980), 1933-1938.

Physical data were as follows:

5 ^1H -nmr (CDCl_3): δ = 7.46 (m, 3H), 7.38 (m, 2H), 6.98 (m, 2H), 6.70 (m, 1H), 3.27 (t, 2H), 2.86 (t, 2H), 1.96 (m, 2H).

$\text{C}_{15}\text{H}_{15}\text{N}$ (MW = 209); mass spectroscopy (MH^+) 210.

10 Step C - Synthesis of 1-Chloromethylacetyl-8-phenyl-1,2,3,4-tetrahydroquinoline

The product from Step B (1.0 g, 4.78 mmol) was dissolved in CH_2Cl_2 (20 mL)/ H_2O (20 mL) and treated with NaHCO_3 (0.602 g, 7.18 mmol) followed by chloroacetyl chloride (0.478 ml, 5.26 mmol). After stirring for 17 h at 23°C , the reaction was diluted with CH_2Cl_2 , washed with saturated NaHCO_3 , dried over
15 Na_2SO_4 and purified by SiO_2 chromatography (CHCl_3 /Hexanes 9:1). The product was isolated as a colorless solid.

Physical data were as follows:

$\text{C}_{17}\text{H}_{16}\text{ClNO}$ (MW = 286.77); mass spectroscopy (MH^+) 287.

Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{ClNO}$; C, 71.45 H, 5.64 N, 4.90. Found: C, 71.63 H,
20 5.60 N, 4.87.

Step D - Synthesis of 5,6-Dihydro-4H-quinolo[8,1-ab][3]benzazepin-8(9H)-one

The product from Step C (0.89 g, 3.11 mmol) was mixed thoroughly with
25 AlCl_3 (0.87 g, 6.54 mmol) at 23°C and the mixture heated neat at 100°C for 5-7 minutes. After vigorous gas evolution, the molten mixture was allowed to cool and extracted with several portions of CH_2Cl_2 / NaHCO_3 (sat). The combined organic layers were dried over Na_2SO_4 and the title compound was purified by chromatography (SiO_2 , CHCl_3 /hexanes 9:1), yielding a colorless oil which
30 solidified upon standing.

Physical data were as follows:

$\text{C}_{17}\text{H}_{15}\text{NO}$ (MW = 249.312); mass spectroscopy (MH^+) 250.

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Anal. Calcd for $C_{17}H_{15}NO$; C, 81.90 H, 6.06 N, 5.62. Found: C, 81.75 H, 6.11 N, 5.86.

5 Step E - Synthesis of 9-Oximo-5,6-Dihydro-4H-quinol[8,1-ab][3]benzazepin-8(9H)-one

10 The product from Step D (0.490 g, 1.97 mmol) was dissolved in THF and butyl nitrite (0.46 mL, 3.93 mmol) and treated with KHMDS (0.5 M, 4.52 mL, 2.26 mmol) at 0°C. After stirring for 1 h, the reaction was quenched with cold 1 N HCl, extracted with EtOAc, the combined organic layers dried over Na_2SO_4 and the product purified by SiO_2 chromatography ($CHCl_3/MeOH$, 99:1). The title compound was isolated as a colorless solid.

Physical data were as follows:

$C_{17}H_{14}N_2O_2$ (MW = 278.3); mass spectroscopy (MH⁺) 279.

Anal. Calcd for $C_{17}H_{14}N_2O_2 \cdot 0.3317$ mol H_2O ; C, 71.82 H, 5.19 N, 9.85.

15 Found: C, 71.85 H, 5.09 N, 9.59.

 Step F - Synthesis of 9-Amino-5,6-Dihydro-4H-quinol[8,1-ab][3]benzazepin-8(9H)-one

20 The product from Step E (0.360 g, 1.29 mmol) was hydrogenated over Ra/Ni (0.05 g) in EtOH (50 mL)/ NH_3 (anhydrous) (5.0 mL) at 100°C and 500 psi for 10 h. The catalyst was removed by filtration and the resulting filtrate chromatographed over SiO_2 ($CHCl_3/MeOH$, 98:2) yielding the titled compound as a colorless oil which solidified upon standing.

Physical data were as follows:

25 $C_{17}H_{16}N_2O$ (MW = 264.326); mass spectroscopy (MH⁺) 266.

Anal. Calcd for $C_{17}H_{16}N_2O$; C, 77.25 H, 6.10 N, 10.60. Found: C, 77.23 H, 6.15 N, 10.49.

30

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Example 35

**Synthesis of
9-(N'-L-Alaninyl)amino-5,6-dihydro-
4H-quino[8,1-ab][3]benzazepin-8(9H)-one Hydrochloride**

5

Step A - Synthesis of 9-(N'-Boc-L-Alaninyl)amino-5,6-Dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one

Following General Procedure D and using N-Boc-Alanine (Aldrich) and 9-amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one (from Example 34), the title compound was prepared.

10

Physical data were as follows:

$C_{25}H_{29}N_3O_4$ (MW = 435.521); mass spectroscopy (MH⁺) 436.

Anal. Calcd for $C_{25}H_{29}N_3O_4 \cdot 0.4102$ mol H₂O; C, 67.79 H, 6.79 N, 9.49;

Found: C, 67.83 H, 6.91 N, 9.29.

15

Step B - Synthesis of 9-(N'-L-Alaninyl)amino-5,6-dihydro-4H-quino[8,1-ab][3]benzazepin-8(9H)-one Hydrochloride

Following General Procedure E and using the product from Step A, the title compound was prepared.

20

Physical data were as follows:

$C_{20}H_{21}N_3O_2 \cdot HCl$ (MW = 371.6); mass spectroscopy (MH⁺ free base) 335.

Example 36

**Synthesis of
7-Amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one**

25

Step A - Synthesis of N-Chloroacetyl-2-benzylpiperidine

Following General Procedure F and using 2-benzylpyridine, the title compound was prepared.

Physical data were as follows:

30

(MW = 251.8); mass spectroscopy (MH⁺) 252.0.

Step B - Synthesis of 1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one

35

Following General Procedure G and using N-chloroacetyl-2-benzylpiperidine, the title compound was prepared.

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Physical data were as follows:

¹H-nmr (CDCl₃): δ = 1.3-1.9 (6H); 2.42 (t, 1H); 3.08 (m, 2H); 3.47 (m, 1H); 3.96 (q, 2H); 4.66 (d, 1H); 7.2 (m, 4H).
(MW = 215.3); mass spectroscopy (MH⁺) 216.1.

5

Step C - Synthesis of 7-Oximo-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one

Following General Procedure A (Step B) and using 1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one (from Step B), the title
10 compound was prepared.

Physical data were as follows:

(MW = 244.3); mass spectroscopy (MH⁺) 245.0.

15

Step D - Synthesis of 7-Amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one

Following General Procedure A (Step C) and using 7-oximo-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one (from Step C), the
title compound was prepared.

Physical data were as follows:

20 ¹H-nmr (CDCl₃): δ = 1.3-1.9 (6H); 2.42 (t, 1H); 3.08 (m, 2H); 3.47 (m, 1H); 3.96 (q, 2H); 4.66 (d, 1H); 7.2 (m, 4H).
(MW = 230.3); mass spectroscopy (MH⁺) 231.1.

Example 37

25

Synthesis of 1-(N'-L-Alaninyl)amino-4,5,6,7-tetrahydro- 3,7-methano-3H-3-benzazonin-2(1H)-one

Step A - Synthesis of N-Chloroacetyl-3-phenylpiperidine

Following General Procedure F and using 3-phenylpyridine hydrochloride
30 (Aldrich), the title compound was prepared.

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Step B - Synthesis of 4,5,6,7-Tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure G and using *N*-chloroacetyl-3-phenylpiperidine, the title compound was prepared.

5 Physical data were as follows:

¹H-nmr (CDCl₃): δ = 1.32-1.57 (2H); 2.08 (m, 2H); 2.81 (t, 1H); 3.13 (bs, 1H); 3.37 (m, 2H); 4.36 (m, 2H); 4.50 (d, 1H).

(MW = 201.3); mass spectroscopy (MH⁺) 202.1.

10 Step C - Synthesis of 1-Oximo-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure A (Step B) and using the product from Step B, the title compound was prepared.

15 Step D - Synthesis of 1-Amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure A (Step C) and using the product from Step C', the title compound was prepared.

Physical data were as follows:

20 ¹H-nmr (CDCl₃): δ = 2.86 (t, 1H); 3.17 (bs, 1H); 3.39 (dd, 1H); 4.40 (d, 1H); 4.50 (d, 1H); 5.39 (s, 1H).

(MW = 216.3); mass spectroscopy (MH⁺) 217.4.

25 Step E - Synthesis of 1-(N'-Boc-L-Alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure D and using *N*-tert-Boc-L-alanine (Aldrich) and the product from Step D, the title compound was prepared.

Physical data were as follows:

(MW = 387.48); mass spectroscopy (MH⁺) 388.1.

30

Step F - Synthesis of 1-(N'-L-Alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one

Following General Procedure E and using the product from Step E, the title compound was prepared.

35 Physical data were as follows:

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¹H-nmr (CDCl₃): δ = 2.85 (t, 1H); 3.16 (bs, 1H); 3.40 (dd, 1H); 3.67 (m, 1H); 4.35 (d, 1H); 4.56 (d, 1H); 6.40 (d, 1H).

(MW = 287.4); mass spectroscopy (MH⁺) 288.1.

5

Example 38

Synthesis of

5S-[N'-(2S-hydroxy-3-methylbutyryl)-2S-aminopropyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

10

Step A - Synthesis of N-Boc-L-Alaninal

Methylene chloride (50 mL) was added to a flask equipped with an addition funnel and cooled to -78°C before adding 1.6 mL oxalyl chloride (18.3 mmol, 2.4 eq). This was stirred for 5 minutes, at which time 1.8 mL dimethyl sulfoxide (25.4 mmol, 3.3 eq) dissolved in 20 mL CH₂Cl₂ was added over 5 minutes. This was stirred for an additional 5 minutes before adding 1.4 g N-Boc-L-alaninol (7.8 mmol, 1.0 eq) in 20 mL CH₂Cl₂. The reaction mixture was stirred for 5 minutes before 6.5 mL triethylamine (46.6 mmol, 6.0 eq) was added and the reaction warmed to room temperature for 10 minutes. The reaction was quenched with 200 mL 0.1 N aqueous HCl, and this was extracted with 2 x 100 mL CH₂Cl₂. The combined organic layers were washed with 100 mL saturated NaHCO₃ followed by 100 mL saturated NaCl, then dried over Na₂SO₄ and removed *in vacuo*. The remaining oil was passed through a silica gel plug with ethyl acetate (EtOAc). The solvent was removed *in vacuo* to yield 1.14 g (85%) of the desired product.

NMR data was as follows:

25

¹H NMR (300 MHz, CDCl₃): δ = 9.56 (s, 1H, CHO), 5.06 (bs, 1H, NH), 4.24 (bq, 1H, CH), 1.45 (s, 9H, C(CH₃)₃), 1.33 (d, 3H, J = 7.2 Hz, CHCH₃).

M⁺ (ionspray) Calcd for C₈H₁₅NO₃ 173.2, Obs. 174.2 (M + 1H).

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Step B - Synthesis of 5S-[N'-(tert-butyloxycarbonyl)-2S-aminopropyl]-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

To a solution of 620 mg of 5S-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (2.6 mmol, 1.0 eq) (from Example 1) in 50 mL methanol was added 653 mg of N-Boc-L-alaninal (3.8 mmol, 1.4 eq) (from Step A), followed

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by 74 mg of sodium cyanoborohydride (1.2 mmol, 0.5 eq). This was stirred at room temperature for 1 hour after which the solvent was removed. The resulting solid was dissolved in 50 mL methylene chloride and washed with 50 mL aqueous saturated NaHCO₃. The aqueous layer was re-extracted with 50 mL methylene chloride. The combined organic solvents were dried over Na₂SO₄ and removed *in vacuo*. The crude product was purified by flash chromatography (1:1 hexanes:ethyl acetate) to yield 309 mg (30%) of the desired product.

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.64-7.31 (m, 8H, aromatic Hs), 4.04 (bs, 1H, CHN), 3.73 (bs, 1H, CHCH₃), 3.34 (s, 3H, NCH₃), 2.78 (dd, 1H, *J* = 4.9, 12.0 Hz, CHHN), 2.48 (dd, 1H, *J* = 6.8, 12.0 Hz, CHHN), 1.43 (s, 9H, CCH₃), 1.17 (d, 3H, *J* = 6.8 Hz, CHCH₃).

M⁺ (ionspray) Calcd for C₂₃H₂₉N₃O₃ 395.5, Obs. 396.1 (M + 1H).

15 Step C - Synthesis of 5S-(2S-aminopropyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

HCl (g) was bubbled through a solution of 317 mg of 5S-[N'-(tert-butyloxycarbonyl)-2S-aminopropyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.8 mmol) (from Step B) in 30 mL dioxane for 15 minutes. This was stirred at room temperature for 17 hours at which time the solvent was removed *in vacuo* to yield 248 mg (94 %) of a white solid. This was used without further purification.

NMR data was as follows:

¹H NMR (300 MHz, CD₃OD) 7.73-7.45 (m, 8H, aromatic Hs), 3.76 (m, 1H, CHCH₃), 3.38 (m, 5H, NCH₃ and CH₂N), 1.46 (d, 3H, *J* = 6.4 Hz, CHCH₃).

M⁺ (ionspray) Calcd for C₁₈H₂₁N₃O 295.4, Obs. 296.4 (M + 1H).

30 Step D - Synthesis of 5S-[N'-(2S-hydroxy-3-methylbutyryl)-2S-aminopropyl]amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

To a solution of 240 mg 5S-(2S-aminopropyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.8 mmol, 1.0 eq) (from Step C) in 25 mL 4:1 tetrahydrofuran (THF): dimethylformamide (DMF) was added 125 mg of 2-

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hydroxy-3-methylbutyric acid (1.1 mmol, 1.3 eq), 184 mg of N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide (1.0 mmol, 1.2 eq), 139 mg 1-hydroxybenzotriazole hydrate (0.9 mmol, 1.1 eq), and 0.5 mL of diisopropylethylamine (2.9 mmol, 3.5 eq). The reaction mixture was stirred at room temperature for 20 hours. The solvent was removed and the remaining oil diluted with 30 mL CH₂Cl₂ and washed with 25 mL 0.1 N aqueous HCl. The aqueous layer was back extracted with 25 mL CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and removed *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to yield 38 mg (12 %) of the desired product as a white solid.

NMR data was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.62-7.37 (m, 8H, aromatic Hs), 6.67 (d, 1H, *J* = 9.0 Hz, NHCO) 4.61 (m, 1H, CHCH₃), 4.40 (bs, 1H, CHNH), 4.13 (d, 1H, *J* = 3.8 Hz, CHOH), 3.38 (s, 3H, NCH₃), 2.95 (m, 2H, CH₂NH), 2.10 (m, 1H, CH(CH₃)₂), 1.26 (d, 3H, *J* = 6.4 Hz, CHCH₃), 1.06 (d, 3H, *J* = 6.8 Hz, CH(CH₃)₂), 0.93 (d, 3H, *J* = 6.8 Hz, CH(CH₃)₂).

M⁺ (ionspray) Calcd for C₂₃H₂₉N₃O₃ 395.5, Obs. 396.1 (M + 1H).

Anal. Calcd for C₂₃H₂₉N₃O₃ C, 69.85; H, 7.39; N, 10.62. Found: C, 69.63; H, 7.44; N, 10.32.

The following examples illustrate how a compound prepared from a synthetic intermediate of this invention could be assayed to determine its ability to inhibit β-amyloid production in a cell or tested to determine its ability to suppress β-amyloid release and/or synthesis *in vivo*.

Example 39

Cellular Screen for the Detection of Inhibitors of β-Amyloid Production

Using the procedure of this example, compounds can be assayed for their ability to inhibit β-amyloid production in a cell line possessing the Swedish mutation. This screening assay employs cells (K293 = human kidney cell line) which are stably transfected with the gene for amyloid precursor protein 751 (APP751) containing the double mutation Lys₆₅₁Met₆₅₂ to Asn₆₅₁Leu₆₅₂ (APP751

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numbering) in the manner described in International Patent Application Publication No. 94/10569¹⁵ and Citron et al.¹⁶. This mutation is commonly called the Swedish mutation and the cells, designated as "293 751 SWE", are plated in Corning 96-well plates at $2-4 \times 10^4$ cells per well in Dulbecco's minimal essential media (Sigma, St. Louis, MO) plus 10% fetal bovine serum. Cell number is important in order to achieve β -amyloid ELISA results within the linear range of the assay (~ 0.2 to 2.5 ng per mL).

Following overnight incubation at 37°C in an incubator equilibrated with 10% carbon dioxide, media are removed and replaced with 200 μ L of a compound to be tested (drug) containing media per well for a two hour pretreatment period and cells are incubated as above. Drug stocks are prepared in 100% dimethyl sulfoxide such that at the final drug concentration used in the treatment, the concentration of dimethyl sulfoxide does not exceed 0.5% and, in fact, usually equals 0.1%.

At the end of the pretreatment period, the media are again removed and replaced with fresh drug containing media as above and cells are incubated for an additional two hours. After treatment, plates are centrifuged in a Beckman GPR at 1200 rpm for five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, 100 μ L of conditioned media or appropriate dilutions thereof are transferred into an ELISA plate precoated with antibody 266 [P. Seubert, *Nature* (1992) 359:325-327¹⁷] against amino acids 13-28 of β -amyloid peptide as described in International Patent Application Publication No. 94/10569¹⁵ and stored at 4°C overnight. An ELISA assay employing labeled antibody 3D6 [P. Seubert, *Nature* (1992) 359:325-327¹⁷] against amino acids 1-5 of β -amyloid peptide is run the next day to measure the amount of β -amyloid peptide produced.

Cytotoxic effects of the compounds are measured by a modification of the method of Hansen, et al.¹⁸. To the cells remaining in the tissue culture plate is added 25 μ L of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, St. Louis, MO) stock solution (5 mg/mL) to a final concentration

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of 1 mg/mL. Cells are incubated at 37°C for one hour, and cellular activity is stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylsulfate in 50% dimethylformamide, pH 4.7). Complete extraction is achieved by overnight shaking at room temperature. The difference in the OD_{562nm} and the OD_{650nm} is measured in a Molecular Device's UV_{max} microplate reader as an indicator of the cellular viability.

The results of the β -amyloid peptide ELISA are fit to a standard curve and expressed as ng/mL β -amyloid peptide. In order to normalize for cytotoxicity, these results are divided by the MTT results and expressed as a percentage of the results from a drug free control. All results are the mean and standard deviation of at least six replicate assays.

The test compounds are assayed for β -amyloid peptide production inhibition activity in cells using this assay. The results of this assay can be used to demonstrate that the compounds prepared from the intermediates of this invention inhibit β -amyloid peptide production by at least 30% as compared to control when employed at 10 μ g/mL.

Example 40

***In Vivo* Suppression of β -Amyloid Release and/or Synthesis**

This example illustrates how the compounds prepared from the intermediate compounds of this invention could be tested for *in vivo* suppression of β -amyloid release and/or synthesis. For these experiments, 3 to 4 month old PDAPP mice are used [Games et al., (1995) *Nature* 373:523-527¹⁹]. Depending upon which compound is being tested, the compound is usually formulated at between 1 and 10 mg/mL. Because of the low solubility factors of the compounds, they may be formulated with various vehicles, such as corn oil (Safeway, South San Francisco, CA); 10% ethanol in corn oil; 2-hydroxypropyl- β -cyclodextrin (Research Biochemicals International, Natick MA); and carboxy-methyl-cellulose (Sigma Chemical Co., St. Louis MO).

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The mice are dosed subcutaneously with a 26 gauge needle and 3 hours later the animals are euthanized via CO₂ narcosis and blood is taken by cardiac puncture using a 1 cc 25G 5/8" tuberculin syringe/needle coated with solution of 0.5 M EDTA, pH 8.0. The blood is placed in a Becton-Dickinson vacutainer tube containing EDTA and spun down for 15 minutes at 1500 xg at 5°C. The brains of the mice are then removed and the cortex and hippocampus are dissected out and placed on ice.

1. Brain Assay

To prepare hippocampal and cortical tissue for enzyme-linked immunosorbent assays (ELISAs) each brain region is homogenized in 10 volumes of ice cold guanidine buffer (5.0 M guanidine-HCl, 50 mM Tris-HCl, pH 8.0) using a Kontes motorized pestle (Fisher, Pittsburgh PA). The homogenates are gently rocked on a rotating platform for three to four hours at room temperature and stored at -20°C prior to quantitation of β -amyloid.

The brain homogenates are diluted 1:10 with ice-cold casein buffer [0.25% casein, phosphate buffered saline (PBS), 0.05% sodium azide, 20 μ g/mL aprotinin, 5 mM EDTA, pH 8.0, 10 μ g/mL leupeptin], thereby reducing the final concentration of guanidine to 0.5 M, before centrifugation at 16,000 xg for 20 minutes at 4°C. Samples are further diluted, if necessary, to achieve an optimal range for the ELISA measurements by the addition of casein buffer with 0.5 M guanidine hydrochloride added. The β -amyloid standards (1-40 or 1-42 amino acids) were prepared such that the final composition equaled 0.5 M guanidine in the presence of 0.1% bovine serum albumin (BSA).

The total β -amyloid sandwich ELISA, quantitating both β -amyloid (aa 1-40) and β -amyloid (aa 1-42) consists of two monoclonal antibodies (mAb) to β -amyloid. The capture antibody, 266 [P. Seubert, *Nature* (1992) 359:325-327¹⁷], is specific to amino acids 13 - 28 of β -amyloid. The antibody 3D6 [Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555²⁰], which is specific to amino acids 1 - 5 of β -amyloid, is biotinylated and served as the reporter antibody in the assay. The 3D6

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biotinylation procedure employs the manufacturer's (Pierce, Rockford IL) protocol for NHS-biotin labeling of immunoglobulins except that 100 mM sodium bicarbonate, pH 8.5 buffer is used. The 3D6 antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP but detects only β -amyloid species with an amino terminal aspartic acid. The assay has a lower limit of sensitivity of ~50 pg/mL (11 pM) and shows no cross-reactivity to the endogenous murine β -amyloid peptide at concentrations up to 1 ng/mL.

The configuration of the sandwich ELISA quantitating the level of β -amyloid (aa 1-42) employs the mAb 21F12 [Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555²⁰] (which recognizes amino acids 33-42 of β -amyloid) as the capture antibody. Biotinylated 3D6 is also the reporter antibody in this assay which has a lower limit of sensitivity of ~125 pg/mL (28 pM).

The 266 and 21F12 capture mAbs are coated at 10 μ g/mL into 96 well immunoassay plates (Costar, Cambridge MA) overnight at room temperature. The plates are then aspirated and blocked with 0.25% human serum albumin in PBS buffer for at least 1 hour at room temperature, then stored desiccated at 4°C until use. The plates are rehydrated with wash buffer (Tris-buffered saline, 0.05% Tween 20) prior to use. The samples and standards are added to the plates and incubated overnight at 4°C. The plates are washed ≥ 3 times with wash buffer between each step of the assay. The biotinylated 3D6, diluted to 0.5 μ g/mL in casein incubation buffer (0.25% casein, PBS, 0.05% Tween 20, pH 7.4) is incubated in the well for 1 hour at room temperature. Avidin-HRP (Vector, Burlingame CA) diluted 1:4000 in casein incubation buffer is added to the wells for 1 hour at room temperature. The colorimetric substrate, Slow TMB-ELISA (Pierce, Cambridge MA), is added and allowed to react for 15 minutes, after which the enzymatic reaction is stopped with addition of 2 N H₂SO₄. Reaction product is quantified using a Molecular Devices Vmax (Molecular Devices, Menlo Park CA) measuring the difference in absorbance at 450 nm and 650 nm.

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2. Blood Assay

The EDTA plasma is diluted 1:1 in specimen diluent (0.2 gm/l sodium phosphate•H₂O (monobasic), 2.16 gm/l sodium phosphate•7H₂O (dibasic), 0.5gm/l thimerosal, 8.5 gm/l sodium chloride, 0.5 mL Triton X-405, 6.0 g/l globulin-free bovine serum albumin; and water). The samples and standards in specimen diluent are assayed using the total β-amyloid assay (266 capture/3D6 reporter) described above for the brain assay except the specimen diluent was used instead of the casein diluents described.

Formulations other than those described above can also be used for oral delivery and intravenous delivery to a mammal. For oral delivery, the compound can be mixed with either 100% corn oil or, alternatively, in a solution containing 80% corn oil, 19.5% oleic acid and 0.5% labrafil. The compound can be mixed with the above solutions in concentrations ranging from 1 mg/mL to 10 mg/mL. The compound in solution is preferably administered orally to the mammal at a dose volume of 5 mL/kg of body weight. For IV delivery, the compound is preferably mixed with a solution of 3% ethanol, 3% solutol HS-15 and 94% saline. The compound is preferably mixed with the above solution in concentrations ranging from 0.25 mg/mL to 5 mg/mL. The compound in solution is preferably administered by IV to the mammal at a dose volume of 2 mL/kg of body weight.

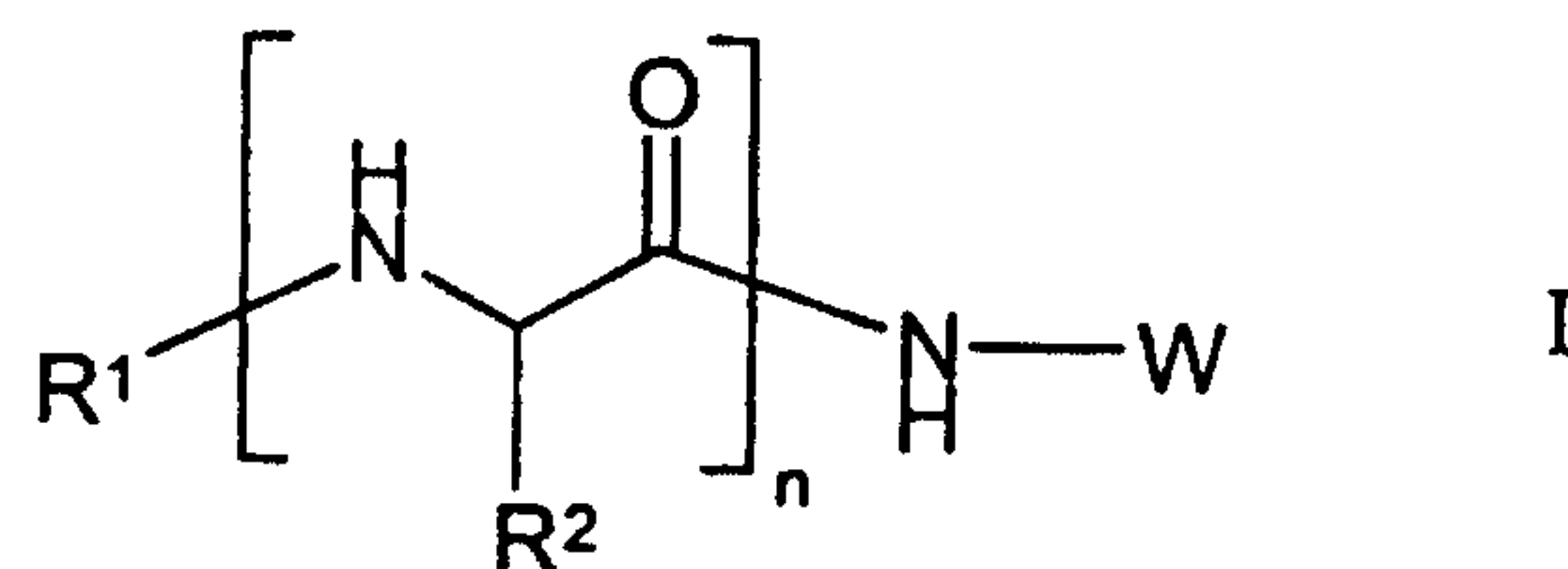
From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

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WHAT IS CLAIMED IS:

1. A compound of formula I:

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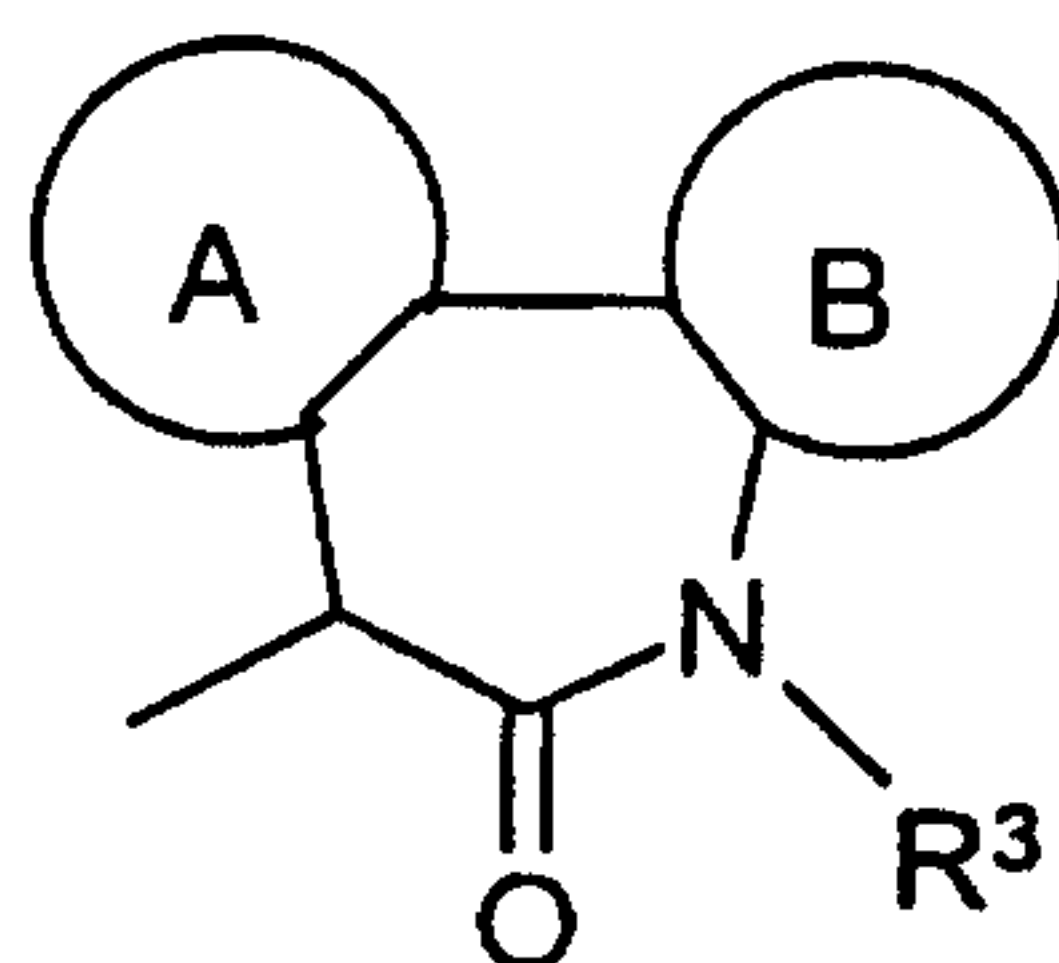


wherein

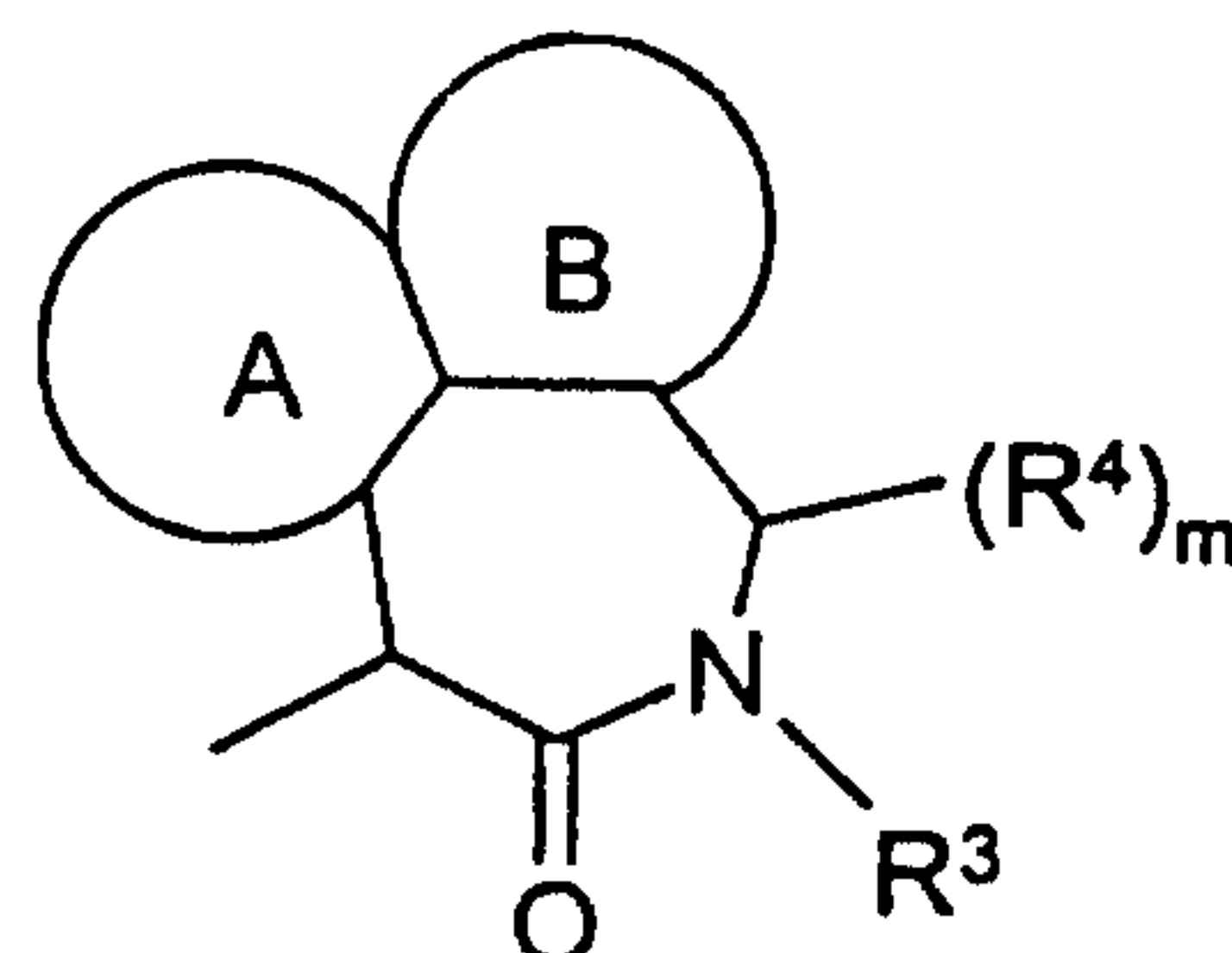
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W is a substituted ϵ -caprolactam selected from the group consisting of:

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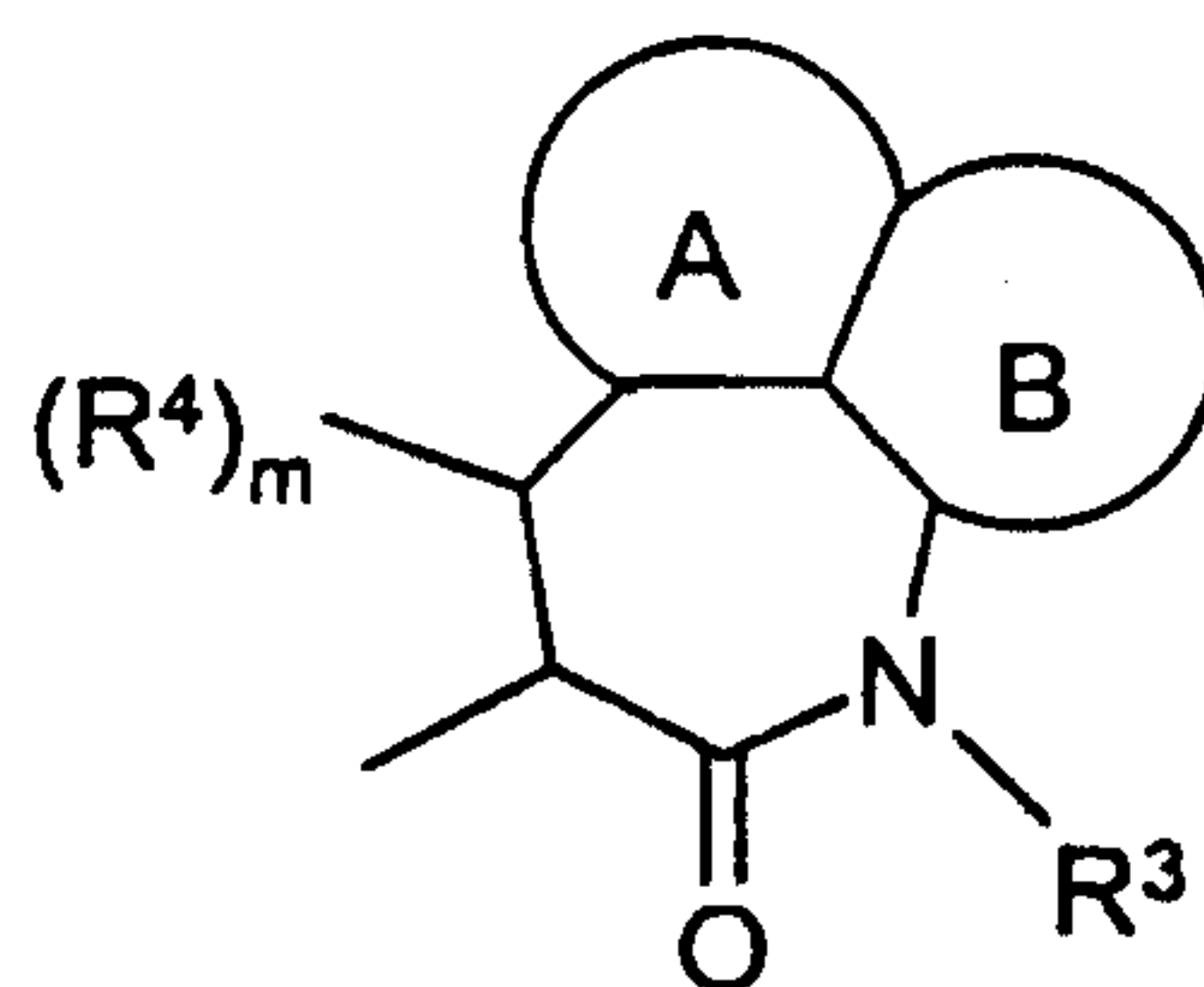


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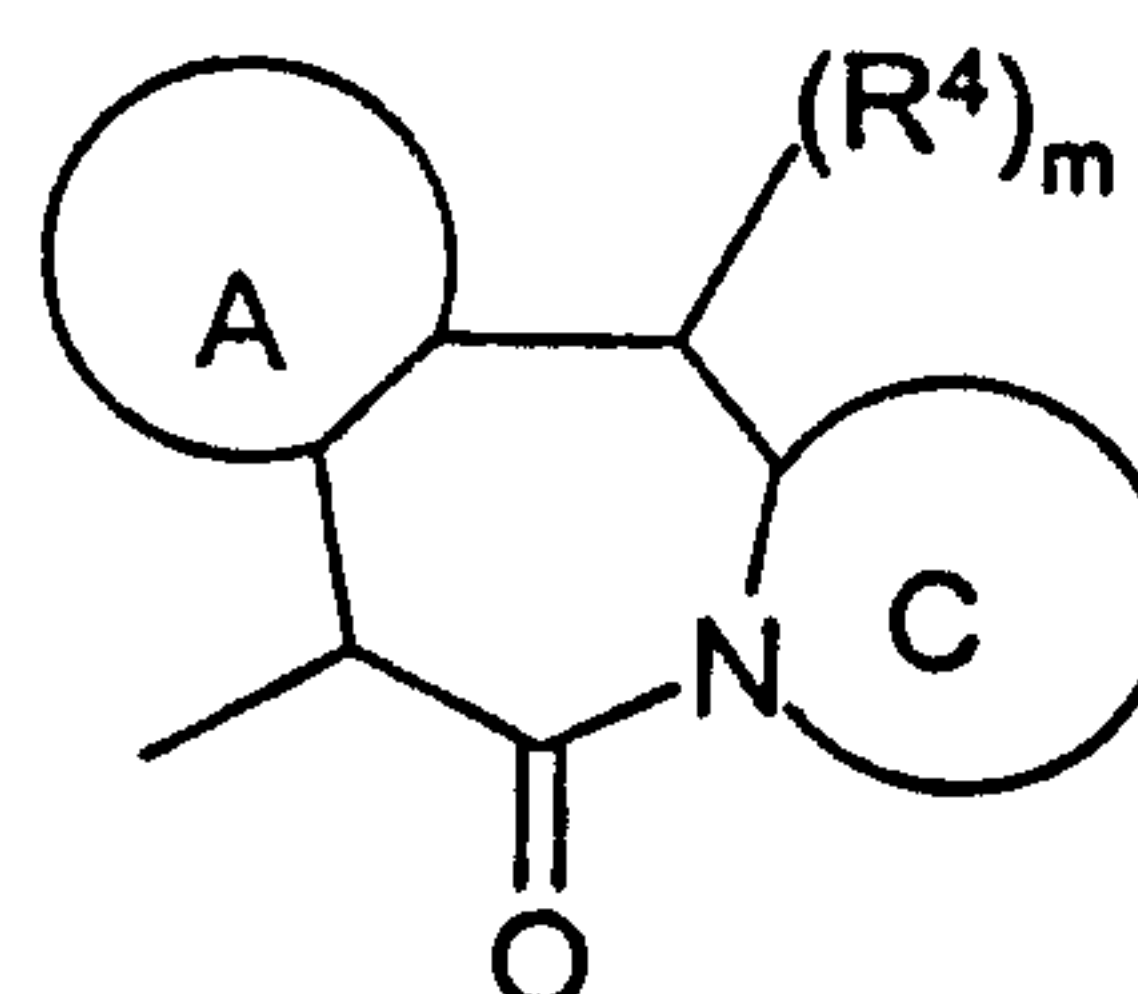


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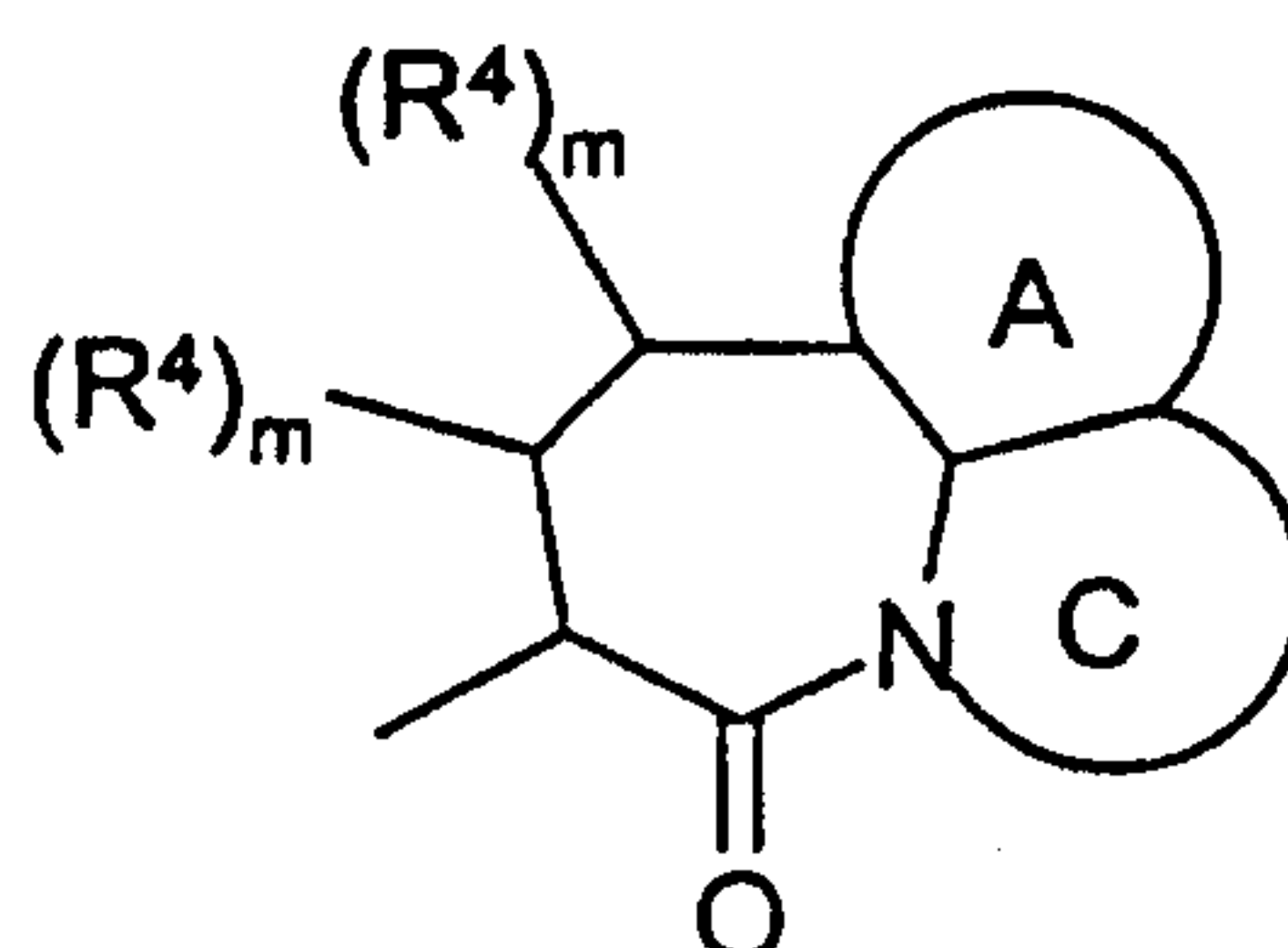


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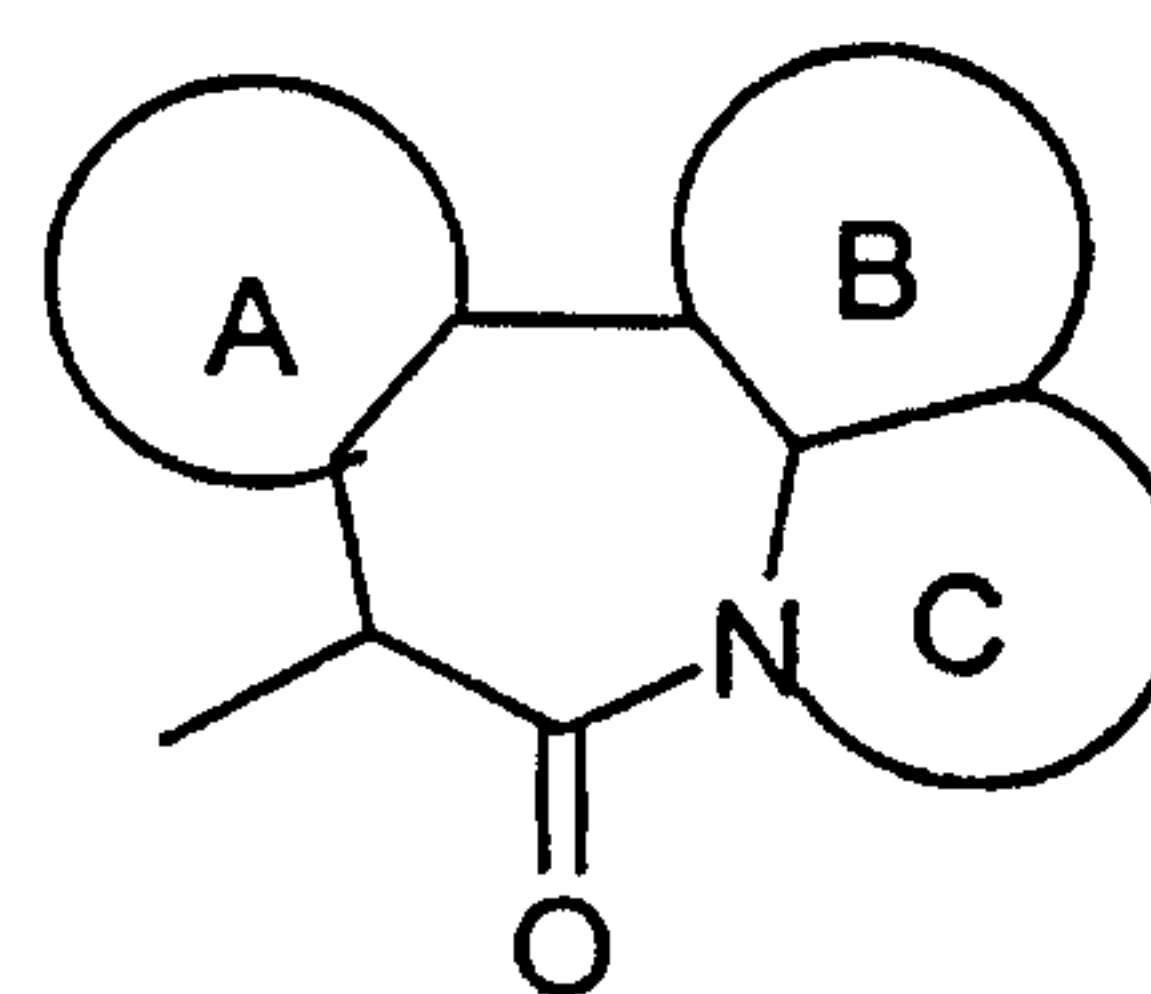


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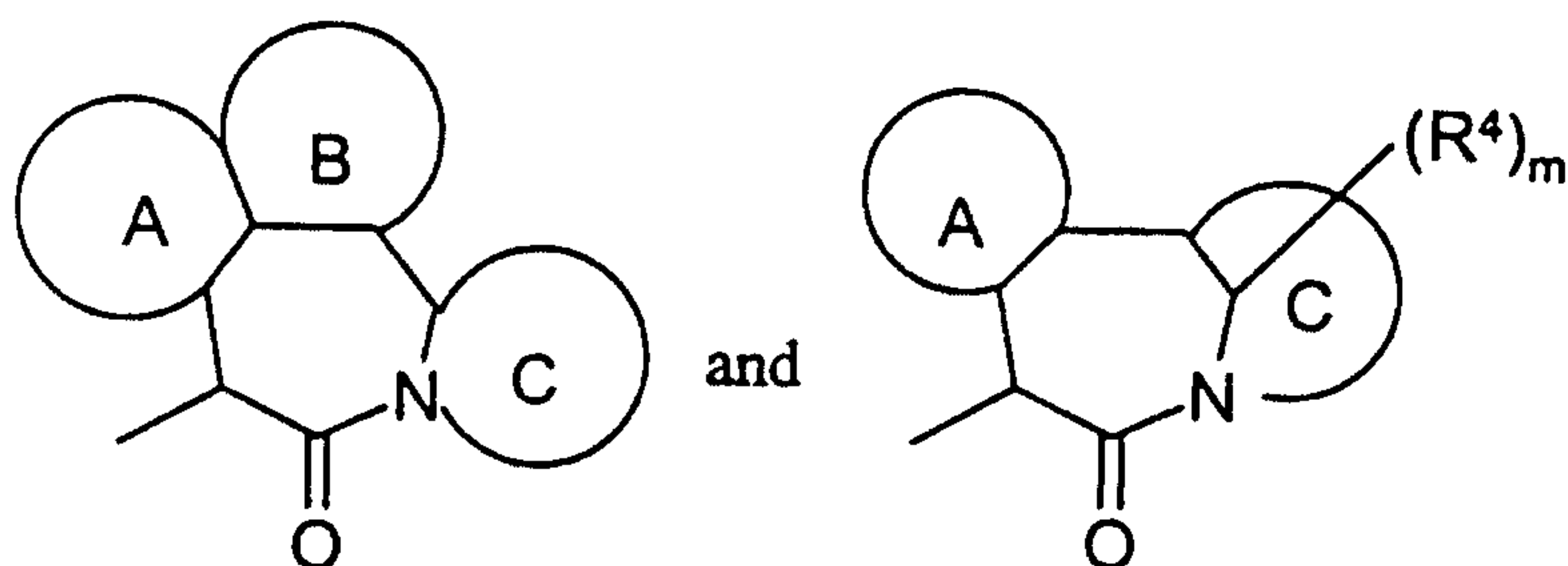


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wherein

10 ring A, together with the atoms of the ϵ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

15 ring B, together with the atoms of the ϵ -caprolactam to which it is attached, forms a carbocyclic or heterocyclic ring selected from the group consisting of aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

ring C, together with the atoms of the ϵ -caprolactam to which it is attached, forms a heteroaryl or heterocyclic ring;

20 R^1 is selected from the group consisting of hydrogen and an amino-blocking group;

each R^2 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heteroaryl and heterocyclic;

25 R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

30 each R^4 is independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

m is an integer from 0 to 2; n is an integer from 0 to 2; and salts thereof.

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2. The compound of Claim 1 wherein R¹ is selected from the group consisting of hydrogen, *tert*-butoxycarbonyl, benzyloxycarbonyl, acetyl, 1-(1'-adamantyl)-1-methylethoxycarbonyl, allyloxycarbonyl, benzyloxymethyl, 2-*p*-biphenylisopropylloxycarbonyl, *tert*-butyldimethylsilyl, benzoyl, benzyl, 9-fluorenylmethyloxycarbonyl, 4-methylbenzyl, 4-methoxybenzyl, 2-nitrophenylsulfenyl, 3-nitro-2-pyridinesulfenyl, trifluoroacetyl, 2,4,6-trimethoxybenzyl and trityl.

3. The compound of Claim 2 wherein R¹ is selected from the group consisting of hydrogen and *tert*-butoxycarbonyl.

4. The compound of Claim 1 wherein each R² is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic.

5. The compound of Claim 4 wherein each R² is independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, -2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃, -CH₂OH,

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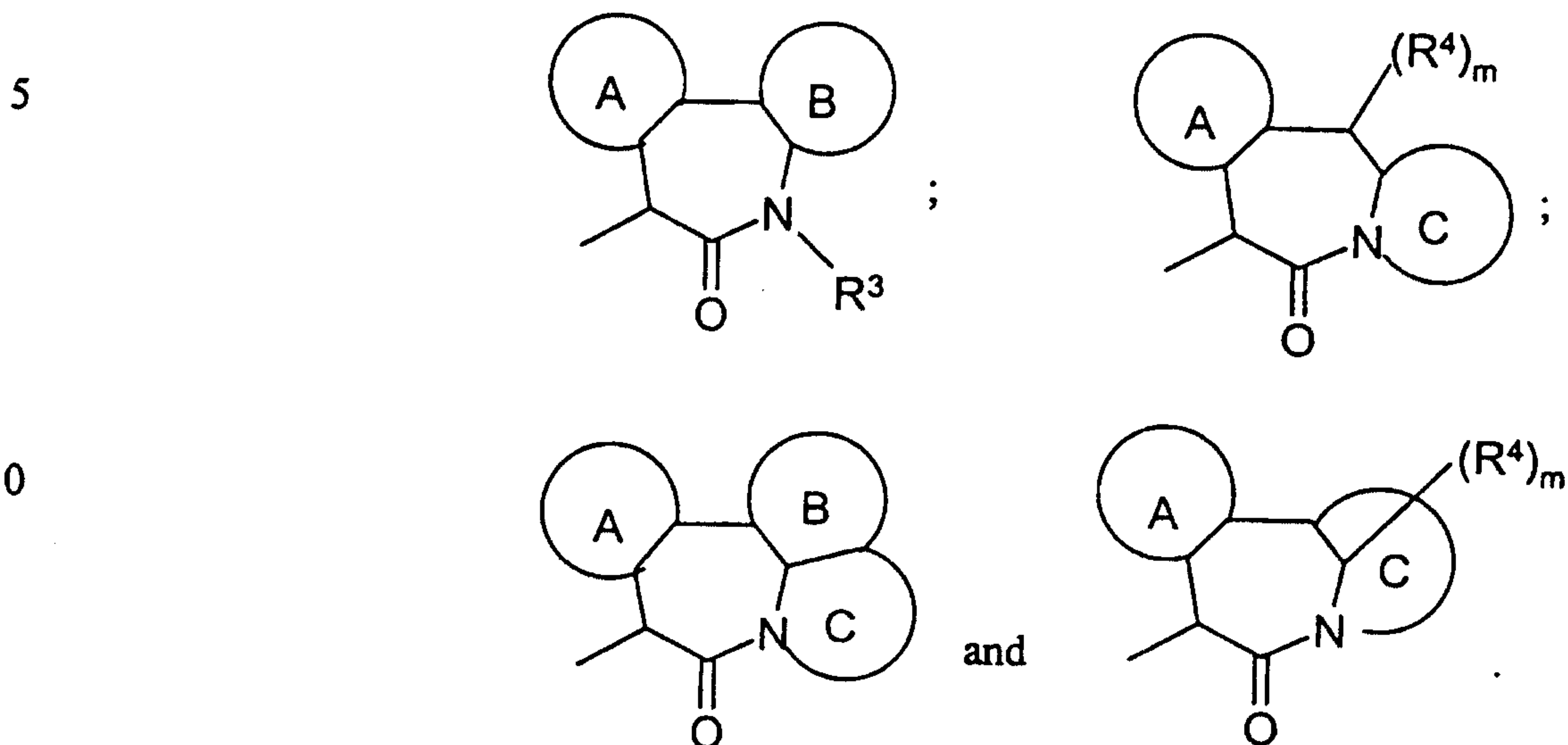
-CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc,
-(CH₂)₄NH₂, -CH₂-pyridyl, pyridyl, -CH₂-naphthyl,
-CH₂-(4-morpholinyl), *p*-(4-morpholinyl-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-
yl, 5-chlorobenzo[b]thiophen-2-yl,
5 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl,
5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,
6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl and thien-3-yl.

6. The compound of Claim 1 wherein R³ is selected from the group
10 consisting of hydrogen, alkyl, substituted alkyl and cycloalkyl.

7. The compound of Claim 6 wherein R³ is selected from the group
consisting of hydrogen, methyl, 2-methylpropyl, hexyl, methoxycarbonylmethyl,
3,3-dimethyl-2-oxobutyl, 4-phenylbutyl, cyclopropylmethyl, 2,2,2-trifluoroethyl
15 and cyclohexyl.

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8. The compound of Claim 1 wherein *W* is a substituted ϵ -caprolactam selected from the group consisting of:

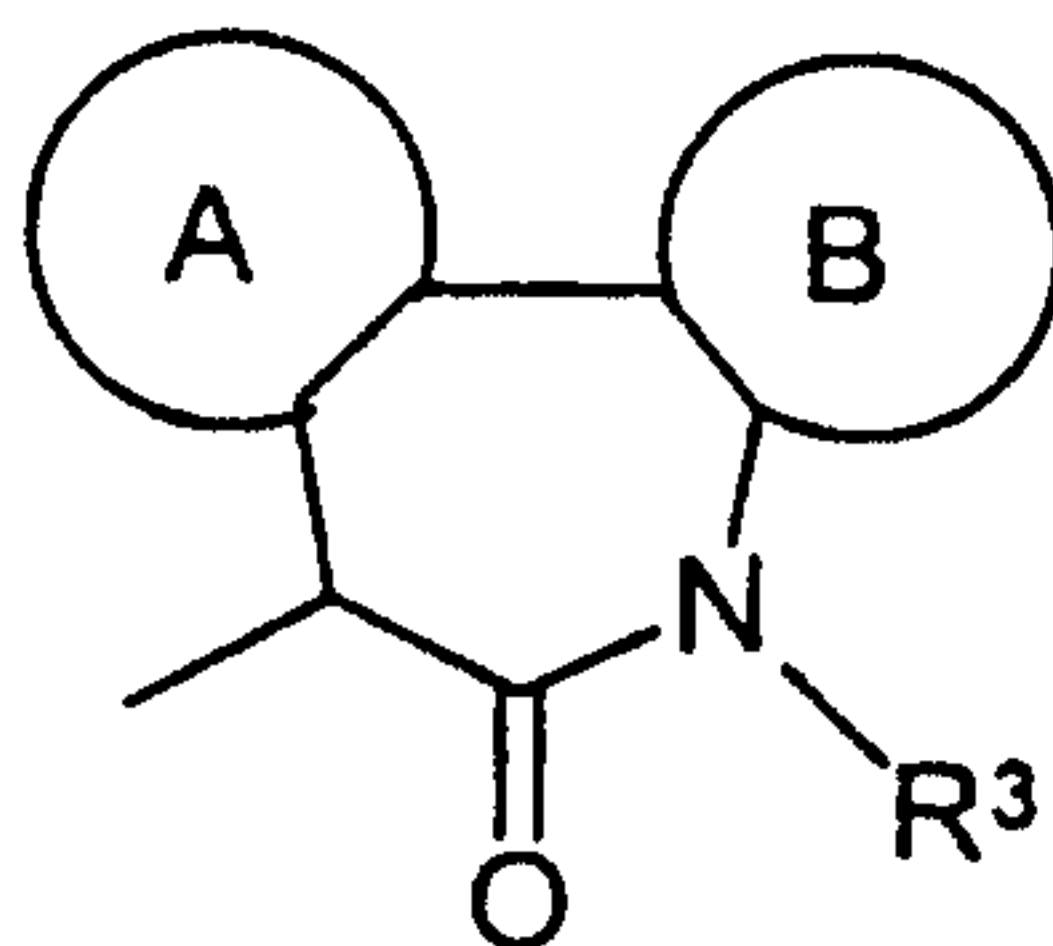


9. The compound of Claim 8 wherein rings *A* and *B* are the same or different and each is independently selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic.

20 10. The compound of Claim 9 wherein rings *A* and *B* are independently selected from the group consisting of aryl and cycloalkyl.

25 11. The compound of Claim 10 wherein rings *A* and *B* are independently aryl.

12. The compound of Claim 8 wherein *W* is a substituted ϵ -caprolactam of the formula:



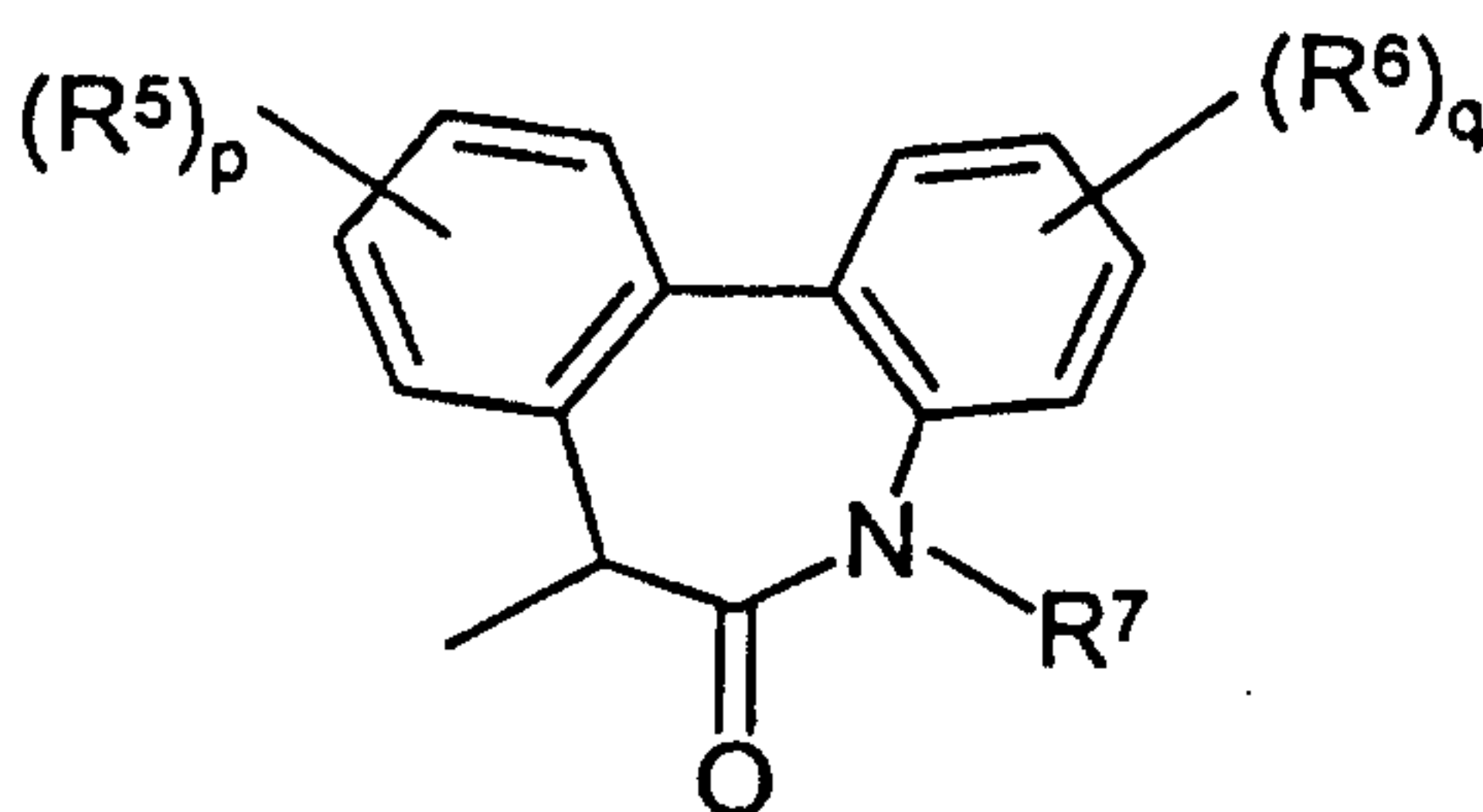
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13. The compound of Claim 12 wherein rings *A* and *B* are the same or different and each is independently selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic.

14. The compound of Claim 13 wherein rings *A* and *B* are independently selected from the group consisting of aryl and cycloalkyl.

15. The compound of Claim 14 wherein rings *A* and *B* are independently aryl.

16. The compound of Claim 12 wherein *W* is a substituted ϵ -caprolactam of the formula:



wherein

each R^5 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

each R^6 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted

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cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

R⁷ is selected from the group consisting of hydrogen, alkyl, substituted
5 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl and heterocyclic;

p is an integer from 0 to 4; *q* is an integer from 0 to 4; and salts thereof.

10 17. The compound of Claim 16 wherein R⁵ and R⁶ are independently selected from the group consisting of alkoxy, substituted alkoxy, alkyl, substituted alkyl, amino, substituted amino, carboxyl, carboxyalkyl, cyano, halo, nitro, thioalkoxy and substituted thioalkoxy.

15 18. The compound of Claim 16 wherein R⁷ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, acyl, aryl, cycloalkyl and substituted cycloalkyl.

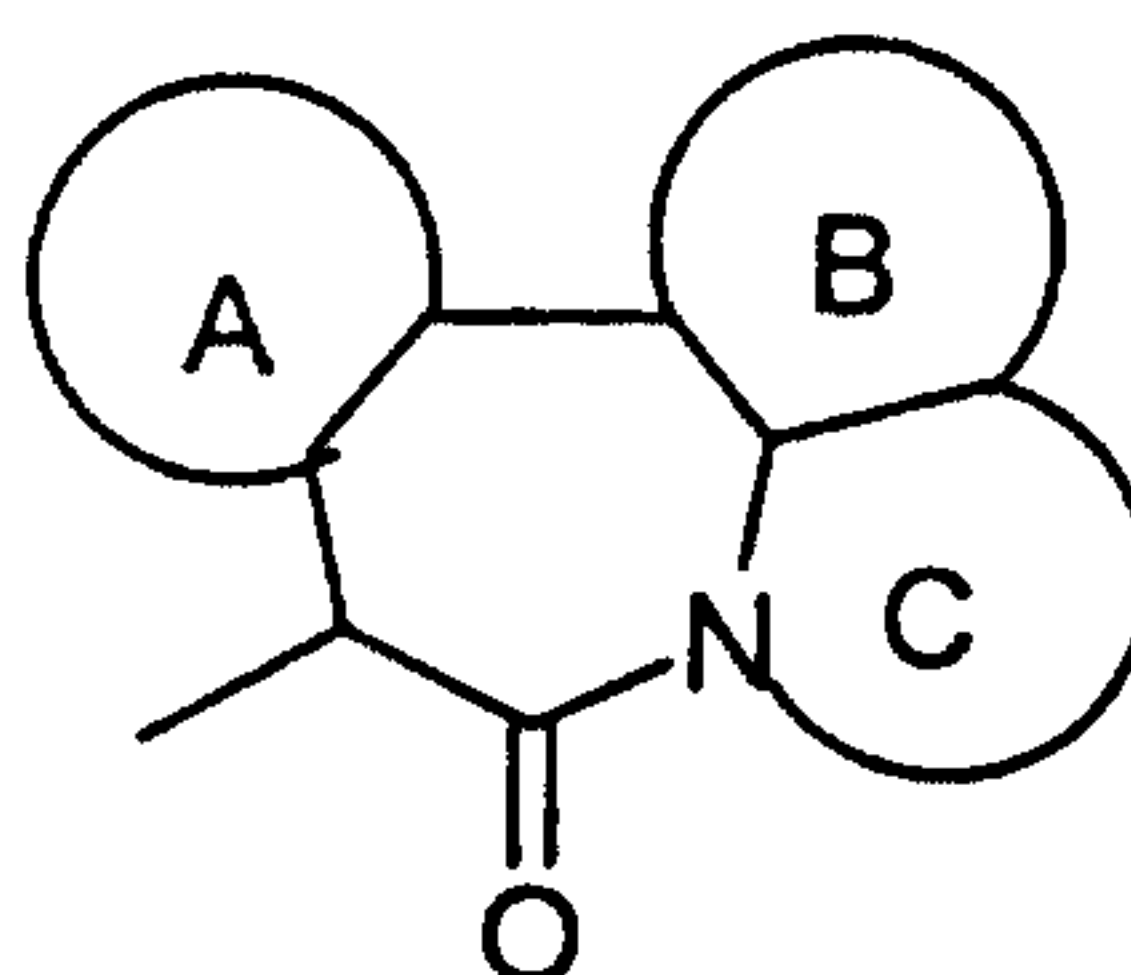
20 19. The compound of Claim 18 wherein R⁷ is selected from the group consisting of hydrogen, methyl, 2-methylpropyl, hexyl, methoxycarbonylmethyl, 3,3-dimethyl-2-oxobutyl, 4-phenylbutyl, cyclopropylmethyl, 2,2,2-trifluoroethyl and cyclohexyl.

25 20. The compound of Claim 16 wherein *W* is a substituted ϵ -caprolactam selected from the group consisting of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 7-(3,3-dimethylbutan-2-onyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-phenbutyl-30 5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-yl, 7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-

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one-5-yl, 7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl, 13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one-5-yl and 7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one-5-yl.

21. The compound of Claim 8 wherein *W* is a substituted ϵ -caprolactam of the formula:



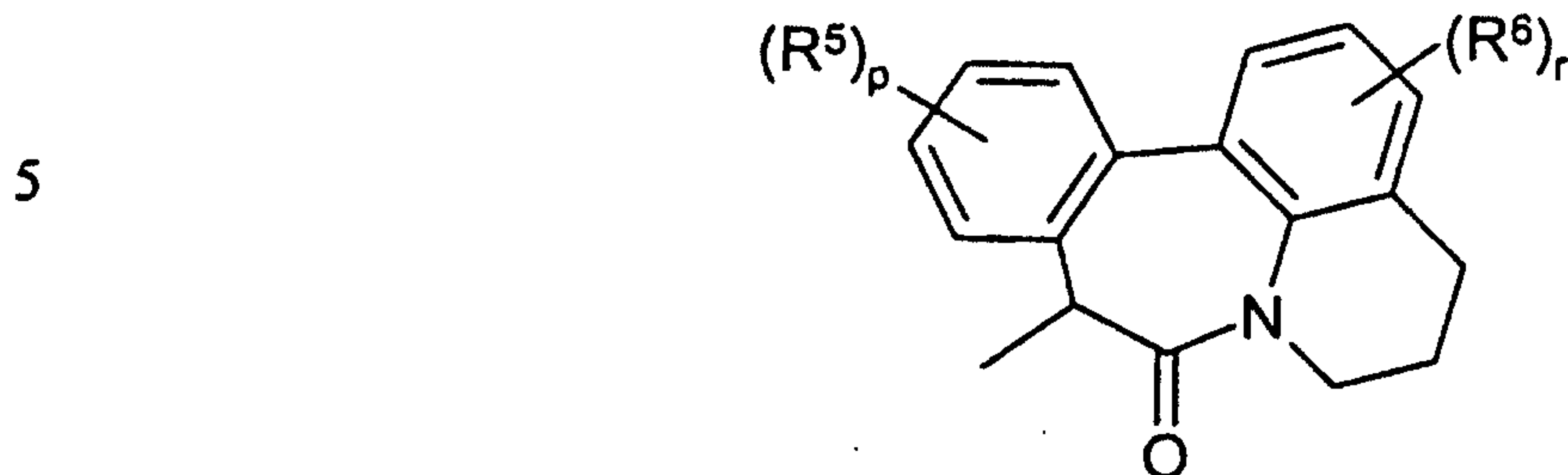
22. The compound of Claim 21 wherein rings *A* and *B* are the same or different and each is independently selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic.

23. The compound of Claim 22 wherein rings *A* and *B* are independently selected from the group consisting of aryl and cycloalkyl.

24. The compound of Claim 23 wherein rings *A* and *B* are independently aryl.

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25. The compound of Claim 24 wherein W is a substituted ϵ -caprolactam of the formula:



10 wherein

each R^5 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

15

each R^6 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

20

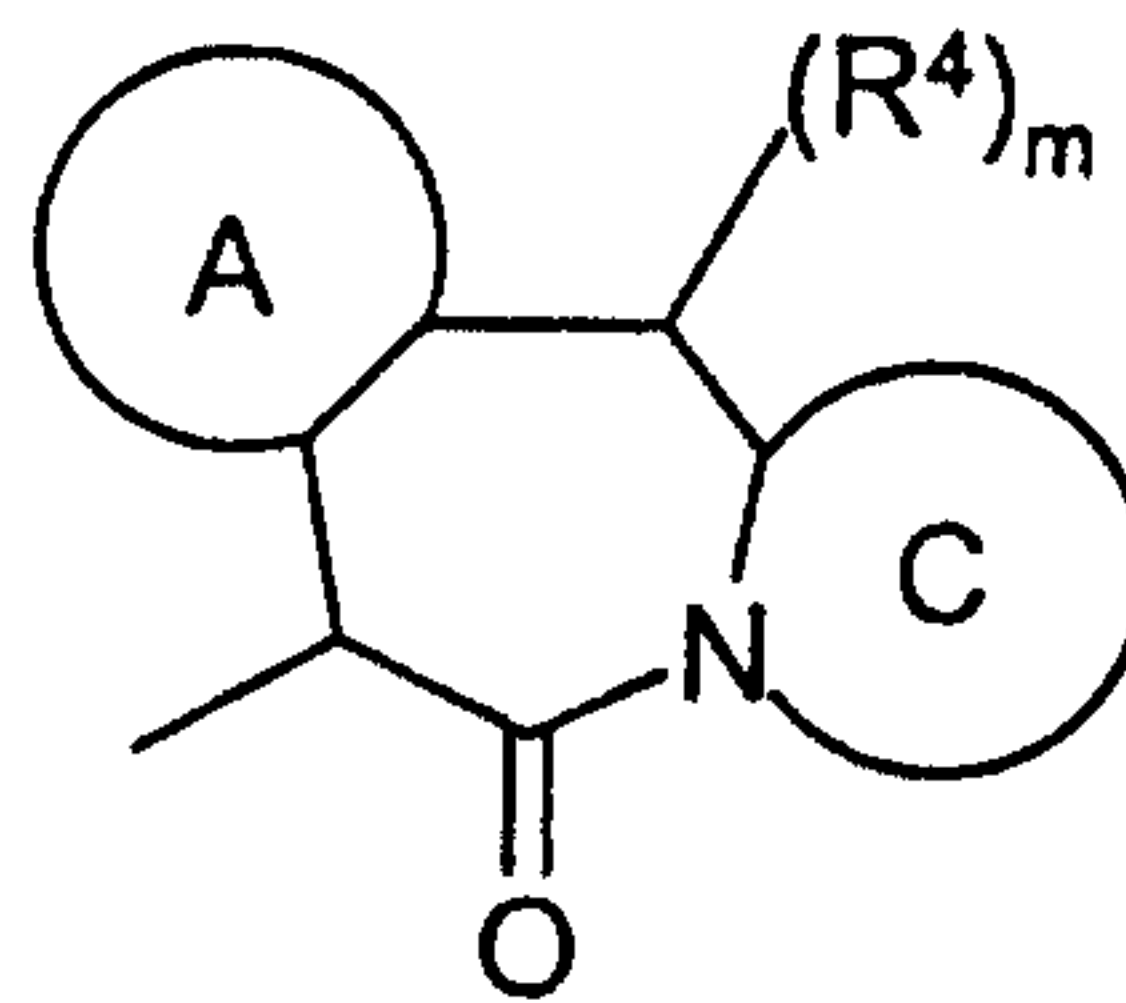
25 p is an integer from 0 to 4; r is an integer from 0 to 3; and salts thereof.

26. The compound of Claim 25 wherein R^5 and R^6 are independently selected from the group consisting of alkoxy, substituted alkoxy, alkyl, substituted alkyl, amino, substituted amino, carboxyl, carboxyalkyl, cyano, halo, nitro, thioalkoxy and substituted thioalkoxy.

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27. The compound of Claim 8 wherein *W* is a substituted ϵ -caprolactam of the formula:



28. The compound of Claim 27 wherein ring *A* is selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic.

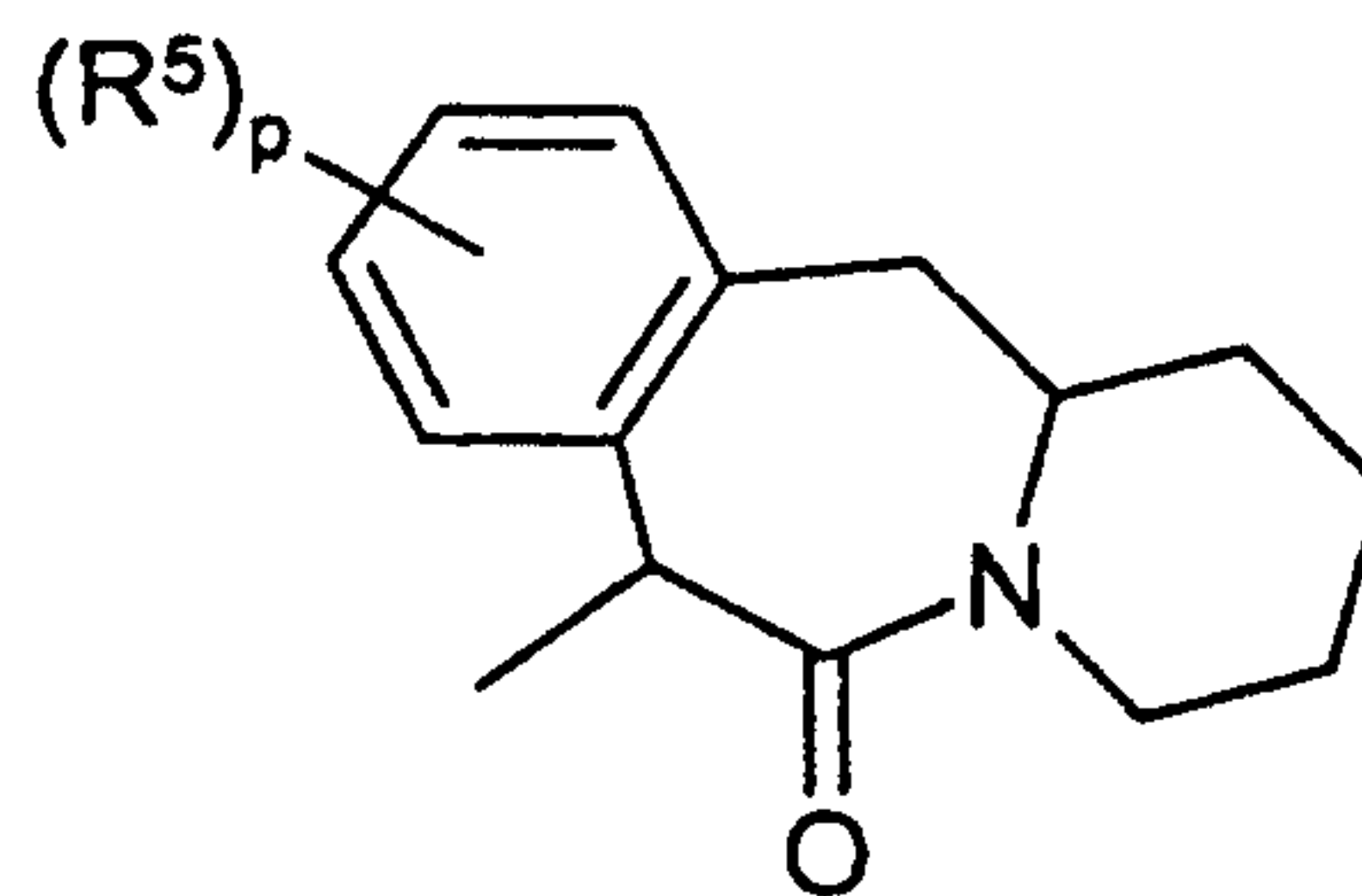
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29. The compound of Claim 22 wherein ring *A* is selected from the group consisting of aryl and cycloalkyl.

30. The compound of Claim 29 wherein ring *A* is aryl.

10

31. The compound of Claim 30 wherein *W* is a substituted ϵ -caprolactam of the formula:



15

wherein

20

each R^5 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;

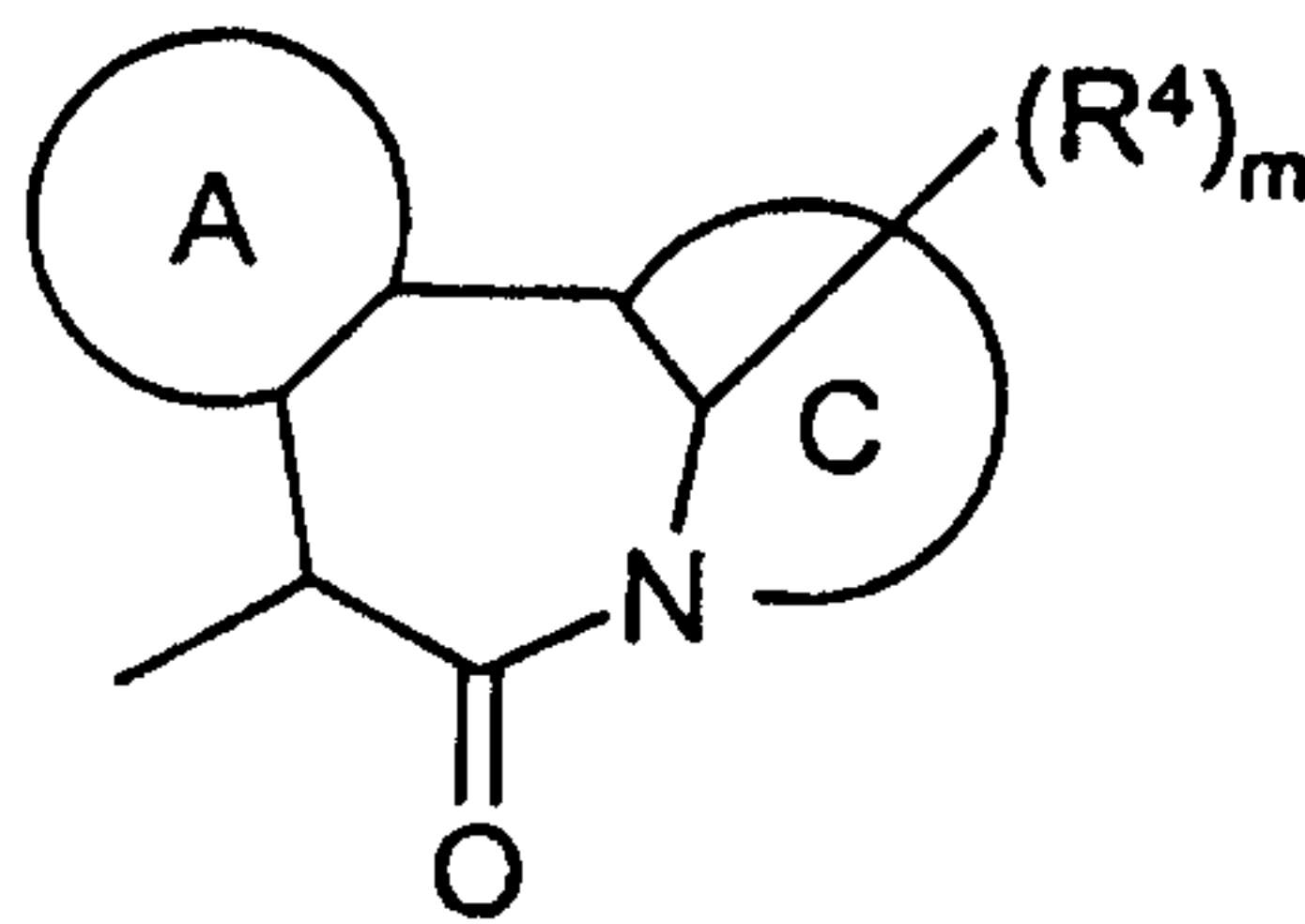
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p is an integer from 0 to 4; and salts thereof.

32. The compound of Claim 31 wherein R^5 is selected from the group consisting of alkoxy, substituted alkoxy, alkyl, substituted alkyl, amino, substituted amino, carboxyl, carboxyalkyl, cyano, halo, nitro, thioalkoxy and substituted thioalkoxy.

33. The compound of Claim 8 wherein W is a substituted ϵ -caprolactam of the formula:



10

34. The compound of Claim 33 wherein ring A is selected from the group consisting of aryl, cycloalkyl, cycloalkenyl, heteroaryl and heterocyclic.

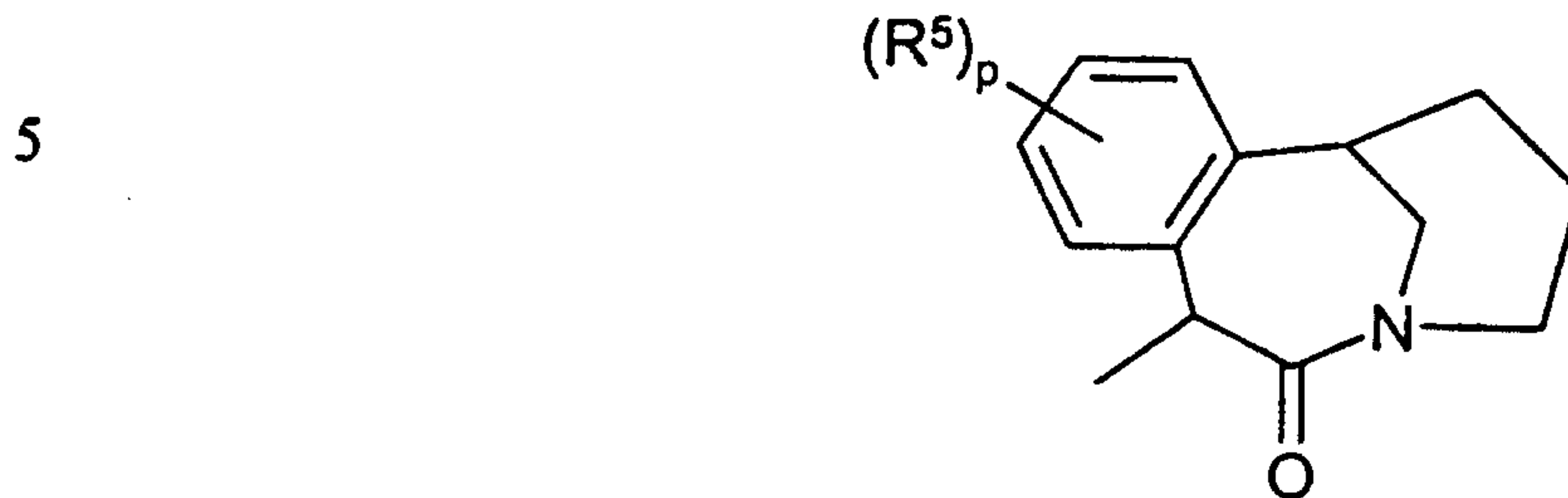
35. The compound of Claim 34 wherein ring A is selected from the group consisting of aryl and cycloalkyl.

36. The compound of Claim 35 wherein ring A is aryl.

20

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37. The compound of Claim 36 wherein *W* is a substituted ϵ -caprolactam of the formula:



wherein

10 each R^5 is independently selected from the group consisting of acyl, acylamino, acyloxy, alkenyl, substituted alkenyl, alkoxy, substituted alkoxy, alkyl, substituted alkyl, alkynyl, substituted alkynyl, amino, substituted amino, aminoacyl, aryl, aryloxy, carboxyl, carboxyalkyl, cyano, cycloalkyl, substituted cycloalkyl, halo, heteroaryl, heterocyclic, nitro, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO₂-alkyl, -SO₂-substituted alkyl, -SO₂-aryl, and -SO₂-heteroaryl;
 15 *p* is an integer from 0 to 4; and salts thereof.

38. The compound of Claim 37 wherein R^5 is selected from the group
 20 consisting of alkoxy, substituted alkoxy, alkyl, substituted alkyl, amino, substituted amino, carboxyl, carboxyalkyl, cyano, halo, nitro, thioalkoxy and substituted thioalkoxy.

39. A compound selected from the group consisting of:
 25 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 30 5-amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 5-(*N*-Boc-amino)-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
 35

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- 5-amino-7-(methoxycarbonylmethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-(*N*-Boc-amino)-7-(3,3-dimethyl-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-(3,3-dimethyl-2-butanonyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-cyclopropymethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-amino-7-methyl-1,2,3,4,5,7-hexahydro-6H-dicyclohexyl[b,d]azepin-6-one
- 30 5-(*N*-Boc-L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-alaninyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-(*N*-Boc-L-valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-(*N*-Boc-L-*tert*-leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-*tert*-leucinyl)amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-(*N*-Boc-L-alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

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- 5-(L-alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-(*N*-Boc-L-alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-alaninyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-(*N*-Boc-L-alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-alaninyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-(*N*-Boc-L-alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-alaninyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 20 5-(*N*-Boc-L-alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-alaninyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 25 5-(*N*-Boc-L-valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 30 5-(*N*-Boc-L-valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 35 5-(*N*-Boc-L-valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 40 5-(*N*-Boc-L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-(L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 45 5-(L-valinyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

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- 5-(*N*-Boc-L-valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5 5-(L-valinyl)amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-(*N*-Boc-L-valinyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 10 5-(L-valinyl)amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-amino-9,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 15 5-amino-10,13-difluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one
- 5-aminohexahydropyrido[a]benz[d]azepin-6-one
- 20 9-amino-5,6-Dihydro-4H-quinolizino[8,1-ab][3]benzazepin-8(9H)-one
- 20 9-(*N'*-Boc-L-alaninyl)amino-5,6-Dihydro-4H-quinolizino[8,1-ab][3]benzazepin-8(9H)-one
- 25 9-(*N'*-L-alaninyl)amino-5,6-dihydro-4H-quinolizino[8,1-ab][3]benzazepin-8(9H)-one
- 7-amino-1,3,4,7,12,12a-hexahydropyrido[2,1-b][3]benzazepin-6(2H)-one
- 30 1-amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 30 1-(*N'*-Boc-L-alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- 35 1-(*N'*-L-alaninyl)amino-4,5,6,7-tetrahydro-3,7-methano-3H-3-benzazonin-2(1H)-one
- and salts thereof.
- 40