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(54) **1'-SUBSTITUTED CARBA-NUCLEOSIDE ANALOGS FOR ANTIVIRAL TREATMENT**

(71) Applicant: **Gilead Sciences, Inc.**, Foster City, CA (US)

(72) Inventors: **Thomas Butler**, Carmel, CA (US); **Aesop Cho**, Mountain View, CA (US); **Choung U. Kim**, San Carlos, CA (US); **Jay P. Parrish**, El Dorado Hills, CA (US); **Oliver L. Saunders**, Clovis, CA (US); **Lijun Zhang**, Los Altos Hills, CA (US)

(73) Assignee: **GILEAD SCIENCES, INC.**, Foster City, CA (US)

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7,285,658	B2	10/2007	Cook et al.
7,368,437	B1	5/2008	Bojack et al.
7,429,571	B2	9/2008	Chand et al.
7,514,410	B2	4/2009	Babu et al.
7,560,434	B2	7/2009	Babu et al.
7,598,230	B2	10/2009	Cook et al.
7,608,597	B2	10/2009	Sommadossi et al.
7,713,941	B2	5/2010	Cook et al.
7,807,653	B2	10/2010	Cook et al.
7,842,672	B2	11/2010	Boojamra et al.
7,973,013	B2*	7/2011	Cho et al. 514/23
7,994,139	B2	8/2011	Babu et al.
8,008,264	B2*	8/2011	Butler et al. 514/23
8,012,941	B2	9/2011	Cho et al.
8,012,942	B2	9/2011	Butler et al.
8,071,568	B2	12/2011	Narjes et al.
8,119,607	B2	2/2012	Francom et al.
8,242,085	B2	8/2012	Babu et al.
8,318,682	B2*	11/2012	Butler et al. 514/23
8,415,308	B2	4/2013	Cho et al.
8,455,451	B2	6/2013	Cho et al.
2003/0050229	A1	3/2003	Sommadossi et al.
2004/0006002	A1	1/2004	Sommadossi et al.

(Continued)

Related U.S. Patent Documents

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(56)

References Cited

U.S. PATENT DOCUMENTS

4,816,570	A	3/1989	Farquhar
4,968,788	A	11/1990	Farquhar
5,663,159	A	9/1997	Starrett, Jr. et al.
5,792,756	A	8/1998	Starrett, Jr. et al.
6,312,662	B1	11/2001	Erion et al.
6,476,030	B1	11/2002	Carling et al.
6,656,915	B1	12/2003	Bantia et al.
6,909,011	B2	6/2005	Skranc et al.
7,105,493	B2	9/2006	Sommadossi et al.
7,176,203	B2	2/2007	Chambers et al.
7,268,119	B2	9/2007	Cook et al.

FOREIGN PATENT DOCUMENTS

CA	2367921	C	9/2000
CN	1498221	A	5/2004

(Continued)

OTHER PUBLICATIONS

Arimilli, MN et al. (1997) "Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs", *Antiviral Chemistry & Chemotherapy*, vol. 8(6), p. 557-564.

Benzaria, S. et al. (1996) "Synthesis in Vitro Antiviral Evaluation, and Stability Studies of Bis(S-acyl-2-thioethyl) Ester Derivatives of 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA) as Potential PMEA Prodrugs with Improved Oral Bioavailability", *Journal of Medicinal Chemistry*, vol. 39, pp. 4958-4965.

Bio, M. et al. (2004), "Practical Synthesis of a Potent Hepatitis C Virus RNA Replication Inhibitor", *Journal of Organic Chemistry*, vol. 69, pp. 6257-6266.

Boback D.R. et al. (2010) "Advances in nucleoside monophosphate prodrugs as anti-HCV agents", *Antiviral Therapy*, vol. 15, pp. 935-950.

(Continued)

Primary Examiner — Jerry D Johnson

(74) *Attorney, Agent, or Firm* — Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C.

(57)

ABSTRACT

Provided are pyrrolo[1,2-f][1,2,4]triazinyl, imidazo[1,5-f][1,2,4]triazinyl, imidazo[1,2-f][1,2,4]triazinyl, and [1,2,4]triazolo[4,3-f][1,2,4]triazinyl nucleosides, nucleoside phosphates and prodrugs thereof, wherein the 1' position of the nucleoside sugar is substituted. The compounds, compositions, and methods provided are useful for the treatment of Flaviviridae virus infections, particularly hepatitis C infections.

33 Claims, No Drawings

(56)

References Cited

U.S. PATENT DOCUMENTS

2004/0023901 A1 2/2004 Cook et al.
 2004/0063658 A1 4/2004 Roberts et al.
 2004/0067901 A1 4/2004 Bhat et al.
 2004/0138170 A1 7/2004 Montgomery et al.
 2005/0187180 A1 8/2005 Loeb et al.
 2005/0215513 A1 9/2005 Boojamra et al.
 2005/0250728 A1 11/2005 Bantia et al.
 2006/0058303 A1 3/2006 Chambers et al.
 2008/0107628 A1 5/2008 Boojamra et al.
 2008/0161324 A1 7/2008 Johansen et al.
 2008/0280842 A1 11/2008 MacCoss et al.
 2009/0004138 A1 1/2009 Francom et al.
 2009/0221524 A1 9/2009 Kotra et al.
 2009/0317361 A1 12/2009 Cho et al.
 2010/0015094 A1 1/2010 Babu et al.
 2010/0016251 A1 1/2010 Sofia et al.
 2010/0021425 A1 1/2010 Butler et al.
 2010/0035835 A1 2/2010 Narjes et al.
 2010/0035836 A1 2/2010 Francom et al.
 2010/0203015 A1 8/2010 Butler et al.
 2010/0234584 A1 9/2010 Chang
 2010/0291031 A2 11/2010 Francom et al.
 2010/0298257 A1 11/2010 Ross et al.
 2011/0070194 A1 3/2011 Cho et al.
 2011/0230654 A1 9/2011 Butler et al.
 2011/0257122 A1 10/2011 Sofia et al.
 2011/0293563 A1 12/2011 Butler et al.
 2012/0009147 A1 1/2012 Cho et al.
 2012/0020921 A1 1/2012 Cho et al.
 2012/0027752 A1 2/2012 Mackman et al.
 2012/0107274 A1 5/2012 Clarke et al.
 2013/0281686 A1 10/2013 Cho et al.

FOREIGN PATENT DOCUMENTS

CN 1852915 A 10/2006
 CN 101043893 A 9/2007
 CN 101611046 A 12/2009
 EA 201071170 A1 8/2011
 EA 201171417 A1 5/2012
 EA 201200525 A1 9/2012
 EP 2 396 340 B1 12/2013
 JP 41017629 B 1/1964
 JP 2004-520367 A 7/2004
 JP 2008-502685 A 1/2008
 JP 2008-518934 A 6/2008
 WO 91/19721 A1 12/1991
 WO 00/56734 A1 9/2000
 WO 01/32153 A2 5/2001
 WO 01/60315 A2 8/2001
 WO 01/90121 A2 11/2001
 WO 02/18404 A2 3/2002
 WO 02/32920 A2 4/2002
 WO 02/057287 A2 7/2002
 WO 02/057425 A2 7/2002
 WO 03/093272 A1 11/2003
 WO 03/093273 A1 11/2003
 WO WO 03/100009 A2 12/2003
 WO 2004/046331 A2 6/2004
 WO 2005/009418 A2 2/2005
 WO 2005/123087 A2 12/2005
 WO 2006/031725 A2 3/2006
 WO 2006/050161 A2 5/2006
 WO 2006/065335 A2 6/2006
 WO 2006/121820 A1 11/2006
 WO 2007/027248 A2 3/2007
 WO 2007/056170 A2 5/2007
 WO 2007/064883 A2 6/2007
 WO 2007/064931 A2 6/2007
 WO WO 2007/097991 A2 8/2007
 WO WO 2007/135134 A1 11/2007
 WO 2008/005542 A2 1/2008
 WO 2008/041079 A2 4/2008
 WO 2008/079206 A1 7/2008
 WO 2008/082601 A2 7/2008

WO 2008/085508 A2 7/2008
 WO 2008/089105 A2 7/2008
 WO 2008/116064 A2 9/2008
 WO WO 2008/121634 A2 10/2008
 WO 2008/141079 A1 11/2008
 WO WO 2009/009951 A1 1/2009
 WO 2009/131926 A1 10/2009
 WO 2009/132123 A1 10/2009
 WO 2009/132135 A1 10/2009
 WO 2010/002877 A2 1/2010
 WO 2010/036407 A2 4/2010
 WO WO 2010/093608 A1 8/2010
 WO WO 2010/111381 A2 9/2010
 WO WO 2010/135569 A1 11/2010
 WO WO 2011/035231 A1 3/2011
 WO WO 2011/035250 A1 3/2011
 WO WO 2011/123672 A1 10/2011
 WO WO 2011/150288 A1 12/2011
 WO WO 2012/012465 A1 1/2012
 WO WO 2012/012776 A1 1/2012
 WO WO 2012/039787 A1 3/2012
 WO WO 2012/039791 A1 3/2012
 WO WO 2012/051570 A1 4/2012

OTHER PUBLICATIONS

Bojack G. et al. (2001), "Design and Synthesis of Inhibitors of Adenosine and AMP Deaminases", *Organic Letters*, vol. 3(6), pp. 839-842.
 Boyer, N. et al. (2000), "Pathogenesis, diagnosis and management of hepatitis C", *Journal of Hepatology*, vol. 32, pp. 98-112.
 Calisher, C. et al. (1989) "Antigenic Relationships between Flaviviruses as Determined by Cross-neutralization Tests with Polyclonal Antisera", *Journal of General Virology*, vol. 70, pp. 37-43.
 De Clercq, E. (2001) "Antiviral drugs: current state of the art", *Journal of Clinical Virology*, vol. 22, pp. 73-89.
 De Clercq, E. (2001) "Molecular Targets for Antiviral Agents" *The Journal of Pharmacology and Experimental Therapeutics*, vol. 297(1), pp. 1-10.
 De Francesco, R. et al. (2003) "Approaching a new era for hepatitis C virus therapy: inhibitors of the NS3-4A serine protease and the NS5B RNA-dependent RNA polymerase", *Antiviral Research*, vol. 58, pp. 1-16.
 De Lombaert, S. et al. (1994) "N-Phosphonomethyl Dipeptides and Their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors", *Journal of Medicinal Chemistry*, vol. 37, pp. 498-511.
 Di Bisceglie, A. et al. (1999) "The Unmet Challenges of Hepatitis C", *Scientific American, Inc.* Oct. pp. 80-85.
 Dolzhenko, A.V. et al. (2008) "Pyrazolo[1,5-a][1,3,5]Triazines(5-AZA-9-Deazapurines): Synthesis and Biological Activity", *Heterocycles*, vol. 75, No. 7.
 Dudfield, P. et al. (1999) "Synthesis of C-ribosyl imidazo[2,1-f][1,2,4]triazines as inhibitors of adenosine and AMP deaminases," *J. Chem. Soc., Perkin Trans 1* 2929-2936.
 Dudfield, P.J. et al. (1999) "Synthesis of C-ribosyl 1,2,4-triazolo[3,4-f][1,2,4]triazines as inhibitors of adenosine and AMP deaminases", *J. Chem. Soc., Perkin Trans 1*, pp. 2937-2942.
 Dymock, B. et al. (2000) "Novel approaches to the treatment of hepatitis C virus infection", *Antiviral Chemistry & Chemotherapy*, vol. 11, pp. 79-96.
 Farquhar, D. et al. (1983), "Biologically Reversible Phosphate-Protective Groups", *Journal of Pharmaceutical Sciences*, vol. 72(3), pp. 324-325.
 Gleeson, P.M. et al. "(2003) Prediction of the potency of inhibitors of adenosine deaminase by QM/MM calculations," *Chem. Comm.* pp. 2180-2181.
 Gordon, C.P. et al. (2005) "Control of Hepatitis C: A Medicinal Chemistry Perspective", *Journal of Medicinal Chemistry*, vol. 48(1), pp. 1-20.
 Haraguchi, K. et al. (1995) "Stereoselective Synthesis of 1'-C-Branched Uracil Nucleosides From Uridine," *Nucleosides & Nucleotides* 14(3-5):417-420.

(56)

References Cited

OTHER PUBLICATIONS

- Hayashi, M. et al. (1992) "C-Nucleosides, a Synthesis of 2-Substituted 7-((β -D-Ribofuranosyl)-Pyrrolo[2,1-f]-1,2,4-Triazines. A New Type of "Purine Like" C-Nucleoside," *Heterocycles* 34(3):569-574.
- Hecker, S.J. et al. (2007) "Liver Targeted Prodrugs of 2'-C-Methyladenosine for Therapy of Hepatitis C Virus Infection", *Journal of Medicinal Chemistry*, vol. 50, pp. 3891-3896.
- International Search Report and Written Opinion for PCT/US2009/041432 mailed on Aug. 11, 2009.
- International Search Report for PCT/US2009/041447, mailed on Aug. 7, 2009.
- International Search Report for PCT/US2010/049471, mailed Nov. 18, 2010.
- International Search Report for PCT/US2010/049508, filed Sep. 20, 2010, mail date Nov. 5, 2010.
- Itoh, Y. et al. (1995) "Divergent and Stereocontrolled Approach to the Synthesis of Uracil Nucleosides Branched at the Anomeric Position," *J. Org. Chem.*, 60:656-662.
- Khamnei, S. et al. (1996) "Neighboring Group Catalysis in the Design of Nucleotide Prodrugs", *Journal of Medicinal Chemistry*, vol. 39, pp. 4109-4115.
- Knutsen, L. et al. (1984) "Synthesis of Imidazo-fused Bridgehead-nitrogen C-Nucleosides via Dehydrative Coupling Reactions of 2,5-Anhydro-3,4,6-tri-O-benzoyl-D-allonic Acid," *J. Chem. Soc. Perkin Trans I* pp. 229-238.
- Knutsen, L. et al. (1985) "Synthesis of Imidazo-fused Bridgehead-nitrogen C-Nucleosides: Coupling-Elimination Reactions of 2,5-Anhydro-3,4,6-tri-O-benzoyl-D-allonic Acid," *J. Chem. Soc. Perkin Trans I* pp. 621-630.
- Kobe, B. et al. (1992) "Use of distance geometry approach for the in vitro antiviral activity evaluation of N-bridgehead C-nucleosides", *European Journal of Medicinal Chemistry*, vol. 27, pp. 259-266.
- McGuigan, C. et al. (1993) "Intracellular Delivery of Bioactive AZT Nucleotides by Aryl Phosphate Derivatives of AZT", *Journal of Medicinal Chemistry*, vol. 36, pp. 1048-1052.
- Mitchell, A.G. et al. (1992) "Bioreversible Protection for the Phospho Group: Bioactivation of the Di(4-acyloxybenzyl) and Mono (4-acyloxybenzyl) Phosphoesters of Methylphosphonate and Phosphonoacetate", *J. Chem. Soc. Perkin Trans. 1*, pp. 2345-2353.
- Mitchell, W. L. et al. (1984) "Synthesis of C-Nucleoside Isosteres of 9-(2-Hydroxyethoxymethyl)guanine (Acyclovir) [1]", *Journal of Heterocyclic Chemistry*, vol. 21, pp. 697-699.
- Moennig, V. et al. (1992) "The Pestiviruses", *Advances in Virus Research*, vol. 41, pp. 53-98.
- Moradpour, D. et al. (2007) "Replication of hepatitis C virus", *Nature Reviews Microbiology*, June, vol. 5, pp. 453-463.
- Nishimura, N. (2001) "Synthesis of pyrrolo[2,1-f][1,2,4]triazine C-nucleosides. Isosteres of sangivamycin, tubercidin, and toyocamycin," *Carbohydrate Research* 331:77-82.
- Otter, B. et al. (1996) "Conformational Properties of Purine-Like C-Nucleosides", *Nucleosides & Nucleotides*, vol. 15 (1-3), pp. 793-807.
- Patil, S. et al. (1994) "4-Aza-7,9-Dideazaadenosine, a New Cytotoxic Synthetic C-Nucleoside Analogue of Adenosine," *Tetrahedron Letters* 35(30):5339-5342.
- Patil, S.A. et al. (1994) "Synthesis of Pyrrolo[2,1-f][1,2,4]triazine Congeners of Nucleic Acid Purines via the N-Amination of 2-Substituted Pyrroles[1]", *Journal of Heterocyclic Chemistry*, vol. 31, pp. 781-786.
- Puech, F. et al. (1993) "Intracellular delivery of nucleoside monophosphates through a reductase-mediated activation process", *Antiviral Research*, vol. 22, pp. 155-174.
- Ramasamy, K. et al. (1986) "Synthesis and Antitumor Activity of Certain 3- β -D-Ribofuranosyl-1,2,4-triazolo[3,4-f]-1,2,4-triazines Related to Formycin Prepared via Ring Closure of a 1,2,4-Triazine Precursor", *Journal of Medicinal Chemistry*, vol. 29, pp. 2231-2235.
- Reddy, K.R. et al. (2005) "Stereoselective synthesis of nucleoside monophosphate HepDirect™ Prodrugs", *Tetrahedron Letters* vol. 46, pp. 4321-4324.
- Schul, W. et al. (2007), "A Dengue Fever Viremia Model in Mice Shows Reduction in Viral Replication and Suppression of the Inflammatory Response after Treatment with Antiviral Drugs", *Journal of Infectious Diseases*, vol. 195, pp. 665-674.
- Scott, L. J. et al. (2002) "Interferon- α -2b Plus Ribavirin", *Drugs*, vol. 62(3), pp. 507-556.
- Written Opinion for PCT/US2010/049471, mailed Nov. 18, 2010.
- Written Opinion for PCT/US2010/049508, filed Sep. 20, 2010, mail date Nov. 5, 2010.
- Yoshimura, Y. et al. (1996) "Synthesis and Biological Evaluation of 1'-C-Cyano-Pyrimidine Nucleosides," *Nucleosides & Nucleotides* 15(1-3):305-324.
- Silverman, R.B., "The Organic Chemistry of Drug Design and Drug Action," 2nd Edition, Elsevier Academic Press, pp. 29-34 (2004).
- Office Action issued in Chinese Patent Application No. 200980114224.2, issued on Nov. 30, 2012 (8 pages).
- Office Action issued in Australian Patent Application No. 2009240642, issued on Aug. 2, 2012 (3 pages).
- Notice of Allowance mailed Jan. 6, 2011 for U.S. Appl. No. 12/428,176.
- Notice of Allowance mailed Apr. 12, 2011 for U.S. Appl. No. 12/428,176.
- Office Action mailed Sep. 23, 2011 for U.S. Appl. No. 13/196,117.
- Notice of Allowance mailed Mar. 27, 2012 for U.S. Appl. No. 13/196,117.
- Notice of Allowance mailed Jul. 16, 2012 for U.S. Appl. No. 13/196,117.
- Office Action mailed Dec. 23, 2010 for U.S. Appl. No. 12/428,234.
- Notice of Allowance mailed Apr. 7, 2011 for U.S. Appl. No. 12/428,234.
- Office Action mailed Dec. 23, 2010 for U.S. Appl. No. 12/702,957.
- Notice of Allowance mailed Apr. 26, 2011 for U.S. Appl. No. 12/702,957.
- Notice of Allowance mailed Feb. 17, 2011 for U.S. Appl. No. 12/885,917.
- Office Action mailed Mar. 27, 2012 for U.S. Appl. No. 13/050,820.
- Office Action mailed Oct. 16, 2012 for U.S. Appl. No. 13/050,820.
- Notice of Allowance mailed Jan. 31, 2013 for U.S. Appl. No. 13/050,820.
- Office Action (Restriction Requirement) mailed Sep. 14, 2012 for U.S. Appl. No. 12/886,248.
- Office Action mailed Nov. 6, 2012 for U.S. Appl. No. 12/886,248.
- Office Action mailed Mar. 4, 2013 for U.S. Appl. No. 12/886,248.
- Notice of Allowance mailed Aug. 10, 2012 for U.S. Appl. No. 13/117,060.
- Notice of Allowance mailed Nov. 28, 2012 for U.S. Appl. No. 13/117,060.
- Office Action (Restriction Requirement) mailed Jul. 3, 2012 for U.S. Appl. No. 13/189,373.
- Office Action mailed Sep. 14, 2012 for U.S. Appl. No. 13/189,373.
- Written Opinion for PCT International Application No. PCT/US2009/041447, mailed Aug. 7, 2009 (6 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2009/041447, mailed Oct. 26, 2010 (7 pages).
- Written Opinion for PCT International Application No. PCT/US2009/041432, mailed Aug. 11, 2009 (6 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2009/041432, mailed Oct. 26, 2010 (7 pages).
- International Search Report for PCT International Application No. PCT/US2010/023586, mailed Aug. 4, 2010 (4 pages).
- Written Opinion for PCT International Application No. PCT/US2010/023586, mailed Aug. 4, 2010 (5 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2010/023586, mailed Aug. 16, 2011 (6 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2010/049471, mailed Mar. 27, 2012 (7 pages).

(56)

References Cited

OTHER PUBLICATIONS

- International Search Report for PCT International Application No. PCT/US2011/028897, mailed Aug. 1, 2011 (6 pages).
- Written Opinion for PCT International Application No. PCT/US2011/028897, mailed Aug. 1, 2011 (6 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2011/028897, mailed Mar. 26, 2013 (7 pages).
- International Search Report for PCT International Application No. PCT/US2011/029441, mailed Aug. 1, 2011 (6 pages).
- Written Opinion for PCT International Application No. PCT/US2011/029441, mailed Aug. 1, 2011 (6 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2011/029441, mailed Mar. 26, 2013 (7 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2010/049508, mailed Mar. 27, 2012 (6 pages).
- International Search Report for PCT International Application No. PCT/US2011/038253, mailed Jul. 29, 2011 (4 pages).
- Written Opinion for PCT International Application No. PCT/US2011/038253, mailed Jul. 29, 2011 (5 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2011/038253, mailed Dec. 4, 2012 (6 pages).
- International Search Report for PCT International Application No. PCT/US2011/044581, mailed Nov. 7, 2011 (4 pages).
- Written Opinion for PCT International Application No. PCT/US2011/044581, mailed Nov. 7, 2011 (6 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2011/044581, mailed Jan. 22, 2013 (7 pages).
- International Search Report for PCT International Application No. PCT/US2011/045102, mailed Nov. 9, 2011 (4 pages).
- Written Opinion for PCT International Application No. PCT/US2011/045102, mailed Nov. 9, 2011 (4 pages).
- International Preliminary Report on Patentability for PCT International Application No. PCT/US2011/045102, mailed Jan. 22, 2013 (5 pages).
- Office Action for CN Patent Application No. 200980114224.2, dated Aug. 19, 2013 (with English translation).
- First Examination Report for CO Patent Application No. 10-121513-5, dated Dec. 10, 2012.
- First Examination Report for EA Patent Application No. 201071170, dated Apr. 25, 2012 (with English translation).
- Second Examination Report for EA Patent Application No. 201071170, dated Oct. 25, 2012 (with English translation).
- First Examination Report for ID Patent Application No. W00 2010 03923, dated Apr. 5, 2013.
- First Examination Report for IL Patent Application No. 208515, dated Jan. 6, 2013 (English translation).
- Supplement to First Examination Report for IL Patent Application No. 208515, dated Jan. 15, 2013 (English translation).
- First Examination Report for JP Patent Application No. 2011-506435, dated Aug. 22, 2013 (with English translation).
- First Examination Report for MX Patent Application No. MX/a/2010/011661, dated Oct. 26, 2011.
- First Examination Report for NZ Patent Application No. 588400, dated Apr. 11, 2011.
- Second Examination Report and Notice of Acceptance for NZ Patent Application No. 588400 dated Jul. 27, 2012.
- First Examination Report for TW Patent Application No. 098113324, dated Oct. 30, 2012 (English translation).
- First Examination Report for VN Patent Application No. 1-2010-02653, dated Apr. 26, 2012 (with English translation).
- First Examination Report for AU Patent Application No. 2009240642, dated Aug. 2, 2012.
- First Examination Report for AU Patent Application No. 2009240630, dated Jun. 14, 2012.
- Second Examination Report for CN Patent Application No. 200980120218.8, dated Jun. 21, 2013 (with English translation).
- First Examination Report for CN Patent Application No. 200980120218.8, dated Nov. 13, 2012 (with English translation).
- First Examination Report for CO Patent Application No. 10-131479, dated Oct. 23, 2012.
- Second Examination Report for CO Patent Application No. 10-131479, dated Jun. 20, 2013.
- First Examination Report for EA Patent Application No. 201071128, dated Apr. 25, 2012 (with English translation).
- Second Examination Report for EA Patent Application No. 201071128, dated Oct. 24, 2012 (with English translation).
- Third Examination Report for EA Patent Application No. 201071128, dated Apr. 29, 2013 (with English translation).
- First Examination Report for ID Patent Application No. W00 2010 03957, dated Apr. 25, 2013 (with English translation).
- First Examination Report for IL Patent Application No. 208701, dated Jan. 13, 2013 (English translation).
- First Examination Report for JP Patent Application No. 2011-506429, dated Aug. 22, 2013 (with English translation).
- First Examination Report for NZ Patent Application No. 588670, dated Apr. 8, 2011.
- First Examination Report for UA Patent Application No. 2010 13030, dated Mar. 2, 2013 (with English translation).
- First Examination Report for VN Patent Application No. 1-2010-02939, dated Apr. 19, 2012 (with English translation).
- Second Examination Report for VN Patent Application No. 1-2010-02939, dated Jul. 26, 2012 (with English translation).
- First Office Action for CL Patent Application No. 1906-2011, dated Aug. 9, 2011 (no English translation available).
- First Office Action for CN Patent Application No. 201080011960.0, dated Jun. 8, 2013 (with English translation).
- First Office Action for EA Patent Application No. 201190110/28, dated Apr. 26, 2012 (with English translation).
- Second Office Action for EA Patent Application No. 201190110/28, dated Jan. 28, 2013 (with English translation).
- Communication under 161/162 for EP Patent Application No. 10704068.5, dated Sep. 6, 2011.
- First Office Action for EP Patent Application No. 10704068.5, dated Jun. 18, 2012.
- First Office Action for IL Patent Application No. 214396, dated Jul. 8, 2013 (English translation).
- Communication under 161/162 for EP Patent Application No. 10763083.2, dated May 11, 2012.
- Notification Prior to Examination for IL Patent Application No. 218599, dated Nov. 13, 2012 (English translation).
- Communication under 161/162 for EP Patent Application No. 11715792.5, dated Apr. 26, 2013.
- Communication under 161/162 for EP Patent Application No. 11743400.1, dated Feb. 26, 2013.
- Communication under 161/162 for EP Patent Application No. 11743709.5, dated Mar. 1, 2013.
- First Office Action for VN Patent Application No. 1-2012-03895, dated Feb. 8, 2013 (with English translation).
- Alessandrini, L. et al., "Synthesis of Differently Protected 1-C-methyl-ribofuranoses Intermediates for the Preparation of Biologically Active 1'-C-methyl-ribonucleosides," *Journal of Carbohydrate Chemistry*, 27(5):332-344, 2008.
- Ali, H.M. et al., "Quantitative structure-activity relationships (QSAR) of two series of O-aryl or N-acyl O-ethyl phosphoramidate and phosphorodiamidate fungicides incorporating amino acid ethyl esters," *Bulletin of Environmental Contamination and Toxicology*, 65(4):415-420, 2000.
- Asbun, W. et al., "Synthesis of 5-substituted Pyrimidines. II," *Journal of Organic Chemistry*, 31:140-142, 1968.
- Ballini, R. et al., "Enantioselective Synthesis of the Lactone Moiety of the Mevinic Acids using D-Xylose as a Chiral Precursor," *Journal of the Chemical Society, Perkin Transactions 1*, 1991:490-491, 1991.
- Bandini, M. et al., "Indium tribromide: a highly effective catalyst for the addition of trimethylsilyl cyanide to α -hetero-substituted ketone," *Tetrahedron Letters*, 42:3041-3043, 2001.

(56)

References Cited

OTHER PUBLICATIONS

- Barker, R. et al., "2,3,5-Tri-O-benzyl-D-ribose and -L-arabinosyl Bromides," *Journal of Organic Chemistry*, 26(11):4605-4609, 1961.
- Belokon, Y. et al., "Optimized catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes and ketones," *Tetrahedron*, 57:771-779, 2001.
- Benksim, A. et al., "A Novel Stereospecific Synthesis of Glycosyl Cyanides from 1,2-O-sulfinyl Derivatives," *Organic Letters*, 6(22):3913-3915, 2004.
- Brown, N., "Progress towards improving antiviral therapy for hepatitis C virus polymerase inhibitors. Part O: Nucleoside analogues," *Expert Opinion*, 18:709-725, 2009.
- Butora et al., "Synthesis and HCV inhibitory properties of 9-deaza- and 7,9-dideaza-7-oxa-2'-C-methyladenosine," *Bioorganic & Medicinal Chemistry*, 15(15):5219-5229, 2007.
- Cabirol, F. et al., "robust and Efficient, yet Uncatalyzed, Synthesis of Triarylsilyl-protected Cyanohydrins from Ketones," *Journal of Organic Chemistry*, 73:2446-2449, 2008.
- Calès, P. et al., "Treatment of liver fibrosis: clinical aspects," *Gastroentérologie Clinique et Biologique*, 33(10-11):958-966, 2009.
- Camps, P., "Studies on Structurally Simple $\alpha\beta$ -butenolides-II," *Tetrahedron*, 38(15):2395-2402, 1982.
- Carroll, S., "Robust Antiviral Efficacy upon Administration of a Nucleoside Analog to Hepatitis C Virus-Infected Chimpanzees," *Antimicrobial Agents and Chemotherapy*, 53(3):926-934, 2009.
- Chapman, J. et al., "RSV604, a Novel Inhibitor of Respiratory Syncytial Virus Replication," *Antimicrobial Agents and Chemotherapy*, 51(9):3346-53, 2007.
- Cihlar, T. et al., "Design and Profiling of GS-9148, a Novel Nucleotide Analog Active against Nucleoside-resistant Variants of Human Immunodeficiency Virus Type 1, and Its Orally Bioavailable Phosphonoamidate Prodrug, GS-9131," *Antimicrobial Agents and Chemotherapy*, 52(2):655-65, 2008.
- Clark, J. et al., "Design, Synthesis, and Antiviral Activity of 2'-Deoxy-2'-fluoro-2'-C-methylcytidine, a Potent Inhibitor of Hepatitis C Virus Replication," *Journal of Medicinal Chemistry*, 48(17):5504-5508, 2005.
- Colacino, E. et al., "Synthesis and Biological Evaluation of Some 5-Nitro- and 5-Amino Derivatives of 2'-Deoxycytidine, 2',3'-Dideoxyuridine, and 2',3'-Dideoxycytidine," *Nucleoside, Nucleotides & Nucleic Acids*, 22(11):2013-2026, 2003.
- Dai, Q. et al., "Synthesis of 2'-C- β -Fluoromethyluridine," *Organic Letters*, 5(6):807-810, 2003.
- De Las Heras, "Synthesis of Ribosyl and Arabinosyl Cyanides by Reaction of 1-O-Acyl Sugars with Trimethylsilyl Cyanide," *Journal of the Chemical Society, Perkin Transactions 1*, 1982:903-907, 1982.
- Domingo, E. et al., "The quasispecies (extremely heterogeneous) nature of viral RNA genome populations: biological relevance—a review," *Gene*, 40:1-8, 1985.
- Dondoni, A. et al., "Thiazole-Based Synthesis of Formyl C-Glycosides," *Journal of Organic Chemistry*, 59:6404-6414, 1994.
- El Safadi, Y. et al., "5-Modified-2'-dU and 2'-dC as Mutagenic Anti HIV-1 Proliferation Agents: Synthesis and Activity," *Journal of Medicinal Chemistry*, 53(4):1534-1545, 2010.
- Fukumoto, T. et al., "Viral Dynamics of Hepatitis C Early After Orthotopic Liver Transplantation: Evidence for Rapid Turnover of Serum Virions," *Hepatology*, 24:1351-1354, 1996.
- Gardelli, C. et al., "Phosphoramidate Prodrugs of 2'-C-Methylcytidine for Therapy of Hepatitis C Virus Infection," *Journal of Medicinal Chemistry*, 52(17):5394-5407, 2009.
- Greene, T.W., *Protective Groups in Organic Chemistry* (John Wiley & Sons, New York, 1991).
- Gudmundsson, K. et al., "Synthesis of imidazo[1,2-a]pyridine C-Nucleosides with an Unexpected Site of Ribosylation," *Journal of Organic Chemistry*, 62:3453-3459, 1997.
- Gudmundsson, K. et al., "The Condensation of 2,6-dichloroimidazo[1,2-a]pyridine C-nucleoside with an Unexpected Site of Ribosylation," *Tetrahedron Letters*, 37(14):2365-2368, 1996.
- Gunic, E. et al., "Cyclic monophosphate prodrugs of base-modified 2'-C-methyl ribonucleosides as potent inhibitors of hepatitis C virus RNA replication," *Bioorganic & Medicinal Chemistry Letters*, 17:2452-2455, 2007.
- Hamann, M. et al., "Synthesis and antiviral evaluation of 7,9-dideaza-8-thiapurine C-nucleoside derivatives," *Collection Symposium Series*, 10:347-349, 2008.
- Hamann, M. et al., "Synthesis and antiviral evaluation of thieno[3,4-d]pyrimidine C-nucleoside analogues of 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydro-adenosine and -inosine," *Bioorganic & Medicinal Chemistry*, 17:2321-2326, 2009.
- Han, H.K. et al., "Synthesis of 1-Chloroacetyl-1-dehydroxy-2,3,5-tri-O-benzoyl- β -D-ribofuranose. A Potentially Versatile Intermediate for the Synthesis of C-Nucleosides," *Synthetic Communications*, 22(19):2815-2822, 1992.
- Harki, D. et al., "Synthesis and Antiviral Activity of 5-Substituted Cytidine Analogues: Identification of a Potent Inhibitor of Viral RNA-Dependent RNA Polymerases," *Journal of Medicinal Chemistry*, 49(21):6166-6169, 2006.
- Hoffman, M. et al., "When, in the Context of Drug Design, Can a Fluorine Atom Successfully Substitute a Hydroxyl Group?," *International Journal of Quantum Chemistry*, 89:419-427, 2002.
- Jasko, M. et al., "5'-Phosphonates of Ribonucleosides and 2'-Deoxyribonucleosides: Synthesis and Antiviral Activity," *Nucleosides & Nucleotides*, 12(8):879-893, 1993.
- Kabat, M. et al., "Nucleosides, CXLVIII, Synthesis of 6-(β -D-Ribofuranosyl)picolinamide: A Novel C-Nucleoside from D-Ribonolactone," *Chemical & Pharmaceutical Bulletin*, 36(2):634-640, 1988.
- Klumpp, K. et al., "The Novel Nucleoside Analog R1479 (4'-Azidocytidine) is a Potent Inhibitor of NS5B-dependent RNA Synthesis and Hepatitis C virus Replication in Cell Culture," *Journal of Biological Chemistry*, 281(7):3793-3799, 2006.
- Lefebvre, I. et al., "Mononucleoside Phosphotriester Derivatives with S-Acyl-2-thioethyl Bioreversible Phosphate-Protecting Groups: Intracellular Delivery of 3'-Azido-2',3'-dideoxythymidine 5'-Monophosphate," *Journal of Medicinal Chemistry*, 38(20):3941-3950, 1995.
- Lefebvre, I. et al., "Synthesis, Decomposition Pathways and 'In Vitro' Evaluation of Bioreversible Phosphotriesters of Azt," *Nucleosides, Nucleotides & Nucleic Acids*, 14(3-5):763-766, 1995.
- Lindell, S. D. et al., "Synthesis and Biochemical Testing of 3-(Carboxyphenylethyl)imidazo[2,1-f][1,2,4]triazines as Inhibitors of AMP Deaminase," *ACS Medicinal Chemistry Letters*, 1(6):286-289, 2010.
- Lovelette, C.A., "1,2,4-Triazines. Synthesis of selected members of the s-triazolo[3,4-f][1,2,4]triazine and tetrazolo[1,5-f][1,2,4]triazine ring systems," *Journal of Heterocyclic Chemistry*, 16:555-560, 1979.
- Martell, M. et al., "Hepatitis C Virus (HCV) Circulates as a Population of Different but Closely Related Genomes: Quasispecies Nature of HCV Genome Distribution," *Journal of Virology*, 66:3225-3229, 1992.
- Mason, S. et al., "Polyadenylation-dependent screening assay for respiratory syncytial virus RNA transcriptase activity and identification of an inhibitor," *Nucleic Acids Research*, 32:4758-4767, 2004.
- Matulic-Adamic, J. et al., "Synthesis of 3-(β -D-Ribofuranosyl)-2-Fluoropyridine and 3-(β -D-Ribofuranosyl)-Pyridin-2-one," *Tetrahedron Letters*, 38(2):203-206, 1997.
- Matulic-Adamic, J. et al., "Synthesis of 5-(β -D-Ribofuranosyl)-Pyridin-2-one: a 'Deletion-Modified' Analogue of Uridine," *Tetrahedron Letters*, 38(10):1669-1672, 1997.
- Meppen, M. et al., "Cyclic phosphoramidates as prodrugs of 2'-C-methylcytidine," *European Journal of Medicinal Chemistry*, 44(9):3765-3770, 2009.
- Meppen, M. et al., "Medi-404—A Prodrug Approach for the Treatment of HCV Infection," *Abstracts of papers, 236th ACS National Meeting*, Philadelphia, PA, United States, Aug. 17-21, 2008.

(56)

References Cited

OTHER PUBLICATIONS

- Migliaccio, G. et al., "Characterization of Resistance to Non-obligate Chain-terminating Ribonucleoside Analogs That Inhibit Hepatitis C Virus Replication in vitro," *The Journal of Biological Chemistry*, 278(49):49164-49170, 2003.
- Moscow, J. et al., "Reduced Folate Carrier Gene (RFC1) Expression and Anti-Folate Resistance in Transfected and Non-Selected Cell Lines," *International Journal of Cancer*, 72:184-190, 1997.
- Neumann, A. et al., "Hepatitis C Viral Dynamics in Vivo and the Antiviral Efficacy of Interferon- α Therapy," *Science*, 282:103-107, 1998.
- Ogura, H. et al., "Reaction of Ethynyl Compounds with Lactones," *Journal of Organic Chemistry*, 37(1):72-75, 1972.
- Pankiewicz, K. et al., "C-Nucleoside Analogues of Nicotinamide Mononucleotide (NMN)," *Nucleosides and Nucleotides*, 7(5 & 6):589-593, 1988.
- Pankiewicz, K. et al., "Efficient Synthesis of 5-(β -D-Ribofuranosyl)nicotinamide and its α -Isomer," *Journal of Organic Chemistry*, 53:3473-3479, 1988.
- Patil, S et al., "C-Glycosylation of Substituted Heterocycles under Friedel-Crafts Conditions (II): Robosylation of Multi-Functionalized Thiophenes and Furans for the Synthesis of Purine-Like C-Nucleosides," *Nucleosides & Nucleotides*, 9(7):937-956, 1990.
- Patil, S.A. et al., "Synthesis of some new thieno[3,4-d]pyrimidines and their C-nucleosides," *Journal of Heterocyclic Chemistry*, 30(2):509-515, 1993.
- Perrone, P. et al., "Application of the Phosphoramidate ProTide Approach to 4'-Azidouridine Confers Sub-micromolar Potency versus Hepatitis C Virus on an Inactive Nucleoside," *Journal of Medicinal Chemistry*, 50(8):1840-1849, 2007.
- Piccirilli, J. et al., "A Direct Route to 3-(D-Ribofuranosyl)pyridine Nucleosides," *Helvetica Chimica Acta*, 74:397-406, 1991.
- Pierra, C. et al., "Synthesis and Pharmacokinetics of Valopicitabine (NM283), and Efficient Prodrug of the Potent Anti-HCV Agent 2'-C-Methylcytidine," *Journal of Medicinal Chemistry*, 49(22):6614-6620, 2006.
- Poduch, E. et al., "Design of Inhibitors of Orotidine Monophosphate Decarboxylase Using Bioisosteric Replacement and Determination of Inhibition Kinetics," *Journal of Medicinal Chemistry*, 49(16):4937-4945, 2006.
- Rao, S. et al., "C-Glycosylation of Substituted Heterocycles under Friedel-Crafts Conditions (I): A Two-Step Synthesis of the Thieno[3,4-d]Pyrimidine C-Nucleoside Analog of Inosine," *Tetrahedron Letters*, 29(29):3537-3540, 1988.
- Schultz, C., "Prodrugs of Biologically Active Phosphate Esters," *Bioorganic & Medicinal Chemistry*, 11:885-898, 2003.
- Srivastav, N. et al., "Antiviral Activity of Various 1-(2'-Deoxy- β -D-Ixofuranosyl), 1-(2'-Fluoro- β -D-xylofuranosyl), 1-(3'-Fluor- β -D-arabinofuranosyl), and 2'-Fluoro-2',3'-didehydro-2',3'-dideoxyribose Pyrimidine Nucleoside Analogues against Duck Hepatitis B Virus (DHBV) and Human Hepatitis B Virus (HBV) Replication," *Journal of Medicinal Chemistry*, 53(19):7156-7166, 2010.
- Tapia, N. et al., "Combination of a Mutagenic Agent with a Reverse Transcriptase Inhibitor Results in Systematic Inhibition of HIV-1 Infection," *Virology*, 338:1-8, 2005.
- Vaghefi, M. et al., "Synthesis and Antiviral Activity of Certain Nucleoside 5'-Phosphonoformate Derivatives," *Journal of Medicinal Chemistry*, 29:1389-1393, 1986.
- Wu, Q. et al., "Synthetic Methodologies for C-Nucleosides," *Synthesis*, 10:1533-1553, 2004.
- Yamanaka, G. et al., "Metabolic Studies on BMS-200475, a New Antiviral Compound Active against Hepatitis B Virus," *Antimicrobial Agents and Chemotherapy*, 43(1):190, 1999.
- Zhang, P. et al., "A Practical Synthesis of (2R)-3,5-di-O-benzoyl-2-fluoro-2-C-methyl-D-ribo- γ -lactone," *Tetrahedron: Asymmetry*, 20:305-312, 2009.
- Office Action (English translation) for Mexican Patent Application No. MX/a/2013/003179, dated Feb. 25, 2014.
- Office Action (with English translation) for Mexican Patent Application No. MX/a/2013/000656, dated Apr. 22, 2014.
- Office Action (with English translation) for Mexican Patent Application No. MX/a/2013/000744, dated Apr. 22, 2014.
- Official Action (ARIPO Form No. 18) with Substantive Search and Examination Report for AP Application No. AP/P/2010/005414, dated Mar. 14, 2014.
- Resolution No. 72986 for Columbian Patent Application No. 10-121513-5 with English translation, received Dec. 23, 2013 (12 pages).
- Third Examination Report for Eurasian Patent Application No. 201071170 with English translation, dated Oct. 10, 2013.
- Statement of Opposition, Mar. 31, 2011, for Ecuador Patent Application No. SP-10-10609, with English translation.
- ARIPO Form 21 and Substantive Examination Report for African Regional Intellectual Property Organization Application No. AP/P/2010/005439, dated Mar. 18, 2014.
- Rejection Decision for Chinese Patent Application No. 200980120218.8 with English translation, dated Feb. 7, 2014.
- Resolution No. 56673 for Columbian Patent Application No. 10-131479 with English translation, dated Sep. 27, 2013.
- Search Report for African Regional Intellectual Property Organization Patent Application No. AP/P/2011/005818, dated Sep. 19, 2013.
- Form 21 for African Regional Intellectual Property Organization Patent Application No. AP/P/2011/005818, dated Sep. 19, 2013.
- Second Office Action for Chilean Patent Application No. 1906-2011 dated Oct. 16, 2013 with English translation.
- Notification of the Second Office Action and Search Report for Chinese Patent Application No. 201080011690.0 with English translation, dated Jan. 8, 2014.
- Third Office Action for Eurasian Patent Application No. 201190110/28, dated Oct. 18, 2013.
- Extended European Search Report for European Patent Application No. 13194605.5, dated Mar. 13, 2014.
- Notification of Defects for Israel Patent Application No. 214396 with English translation, dated Nov. 11, 2013.
- Notice of Reasons for Rejection for Japanese Patent Application No. 2011-549324 with English translation, dated Mar. 26, 2014.
- Office Action for Mexican Patent Application No. MX/a/2011/008409 with English translation, dated Mar. 25, 2014.
- Further Examination Report for New Zealand Patent Application No. 594370, dated Oct. 8, 2013.
- Office Action for Peruvian Patent Application No. 1464 with English translation, dated Sep. 12, 2013.
- Office Action for UA Patent Application No. a 2011 10568 with English translation, received Apr. 7, 2014.
- Patent Examination Report No. 1 for Australian Patent Application No. 2011306066, dated Nov. 21, 2013.
- Opposition for Chilean Patent Application No. 727-2013 with English translation, dated Oct. 15, 2013.
- Notification of the First Office Action and Search Report for Chinese Patent Application No. 20100041902.X with English translation, dated Nov. 12, 2013.
- Office Action No. 425 for Columbian Patent Application No. 12 050 579 with English translation, dated Jan. 21, 2014.
- Opposition for Ecuador Patent Application No. SP-2012-11817, dated May 27, 2013 (English translation not available).
- Communication Pursuant to Article 94(3) EPC for European Patent Application No. 11715792.5, dated Feb. 14, 2014.
- First Examination Report for New Zealand Patent Application No. 608070, dated Nov. 7, 2013.
- Official Action for El Salvador National Phase Entry of PCT International Application No. PCT/US2010/049471 with English translation, dated Nov. 6, 2013.
- Notification of the First Office Action with Search Report for Chinese Patent Application No. 201080041946.2 with English translation, dated Dec. 18, 2013.
- Notification Prior to Examination for Israel Patent Application No. 218752 with English translation, dated Jan. 20, 2014.
- Official Action for Eurasian Patent Application No. 201390133, dated Mar. 27, 2014.

(56)

References Cited

OTHER PUBLICATIONS

Opposition for Ecuador Patent Application No. SP-13-12451, notification date of Apr. 23, 2014 (English translation not yet available). Notification of the First Office Action for Chinese Patent Application No. 201180035776.1 with English translation, dated Feb. 27, 2014.

Office Action for Columbian Patent Application No. 13 004212 with English translation, dated Dec. 4, 2013.

Office Action for Columbian Patent Application No. 11-109.501, dated Nov. 27, 2012 (10 pages).

Office Action for Eurasian Patent Application No. 201390152 with English translation, dated Apr. 14, 2014 (9 pages).

Silverman et al., The Organic Chemistry of Drug Design and Drug Action, 19-23, 1992.

* cited by examiner

**1'-SUBSTITUTED CARBA-NUCLEOSIDE
ANALOGS FOR ANTIVIRAL TREATMENT**

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

CROSS-REFERENCE TO RELATED
APPLICATIONS

This application is a continuation application of U.S. patent application Ser. No. 13/196,117, filed Aug. 2, 2011, which is a continuation of U.S. patent application Ser. No. 12/428,176, filed Apr. 22, 2009, which claims the benefit of U.S. Provisional Application No. 61/047,263, filed Apr. 23, 2008 and U.S. Provisional Application No. 61/139,449, filed Dec. 19, 2008. The contents of the aforementioned applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity, more particularly nucleosides active against Flaviviridae infections and most particularly to inhibitors of hepatitis C virus RNA-dependent RNA polymerase.

BACKGROUND OF THE INVENTION

Viruses comprising the Flaviviridae family comprise at least three distinguishable genera including pestiviruses, flaviviruses, and hepaciviruses (Calisher, et al., J. Gen. Virol., 1993, 70, 37-43). While pestiviruses cause many economically important animal diseases such as bovine viral diarrhea virus (BVDV), classical swine fever virus (CSFV, hog cholera) and border disease of sheep (BDV), their importance in human disease is less well characterized (Moennig, V., et al., Adv. Vir. Res. 1992, 48, 53-98). Flaviviruses are responsible for important human diseases such as dengue fever and yellow fever while hepaciviruses cause hepatitis C virus infections in humans. Other important viral infections caused by the Flaviviridae family include West Nile virus (WNV) Japanese encephalitis virus (JEV), tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis, St Louis encephalitis, Omsk hemorrhagic fever virus and Zika virus. Combined, infections from the Flaviviridae virus family cause significant mortality, morbidity and economic losses throughout the world. Therefore, there is a need to develop effective treatments for Flaviviridae virus infections.

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide (Boyer, N. et al. J. Hepatol. 32:98-112, 2000) so a significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A. M. and Bacon, B. R., Scientific American, October: 80-85, (1999); Gordon, C. P., et al., J. Med. Chem. 2005, 48, 1-20; Maradpour, D.; et al., Nat. Rev. Micro. 2007,

5(6), 453-463). A number of HCV treatments are reviewed by Bymock et al. in Antiviral Chemistry & Chemotherapy, 11:2; 79-95 (2000).

RNA-dependent RNA polymerase (RdRp) is one of the best studied targets for the development of novel HCV therapeutic agents. The NS5B polymerase is a target for inhibitors in early human clinical trials (Sommadossi, J., WO 01/90121 A2, US 2004/0006002 A1). These enzymes have been extensively characterized at the biochemical and structural level, with screening assays for identifying selective inhibitors (De Clercq, E. (2001) J. Pharmacol. Exp. Ther. 297:1-10; De Clercq, E. (2001) J. Clin. Virol. 22:73-89). Biochemical targets such as NS5B are important in developing HCV therapies since HCV does not replicate in the laboratory and there are difficulties in developing cell-based assays and preclinical animal systems.

Currently, there are primarily two antiviral compounds, ribavirin, a nucleoside analog, and interferon-alpha (α) (IFN), which are used for the treatment of chronic HCV infections in humans. Ribavirin alone is not effective in reducing viral RNA levels, has significant toxicity, and is known to induce anemia. The combination of IFN and ribavirin has been reported to be effective in the management of chronic hepatitis C (Scott, L. J., et al. Drugs 2002, 62, 507-556) but less than half the patients given this treatment show a persistent benefit. Other patent applications disclosing the use of nucleoside analogs to treat hepatitis C virus include WO 01/32153, WO 01/60315, WO 02/057425, WO 02/057287, WO 02/032920, WO 02/18404, WO 04/046331, WO2008/089105 and WO2008/141079 but additional treatments for HCV infections have not yet become available for patients. Therefore, drugs having improved antiviral and pharmacokinetic properties with enhanced activity against development of HCV resistance, improved oral bioavailability, greater efficacy, fewer undesirable side effects and extended effective half-life in vivo (De Francesco, R. et al. (2003) Antiviral Research 58:1-16) are urgently needed.

Certain ribosides of the nucleobases pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine have been disclosed in Carbohydrate Research 2001, 331(1), 77-82; Nucleosides & Nucleotides (1996), 15(1-3), 793-807; Tetrahedron Letters (1994), 35(30), 5339-42; Heterocycles (1992), 34(3), 569-74; J. Chem. Soc. Perkin Trans. 1 1985, 3, 621-30; J. Chem. Soc. Perkin Trans. 1 1984, 2, 229-38; WO 2000056734; Organic Letters (2001), 3(6), 839-842; J. Chem. Soc. Perkin Trans. 1 1999, 20, 2929-2936; and J. Med. Chem. 1986, 29(11), 2231-5. However, these compounds have not been disclosed as useful for the treatment of HCV. Babu, Y. S., WO2008/089105 and WO2008/141079, discloses ribosides of pyrrolo[1,2-f][1,2,4]triazine nucleobases with antiviral, anti-HCV, and anti-RdRp activity.

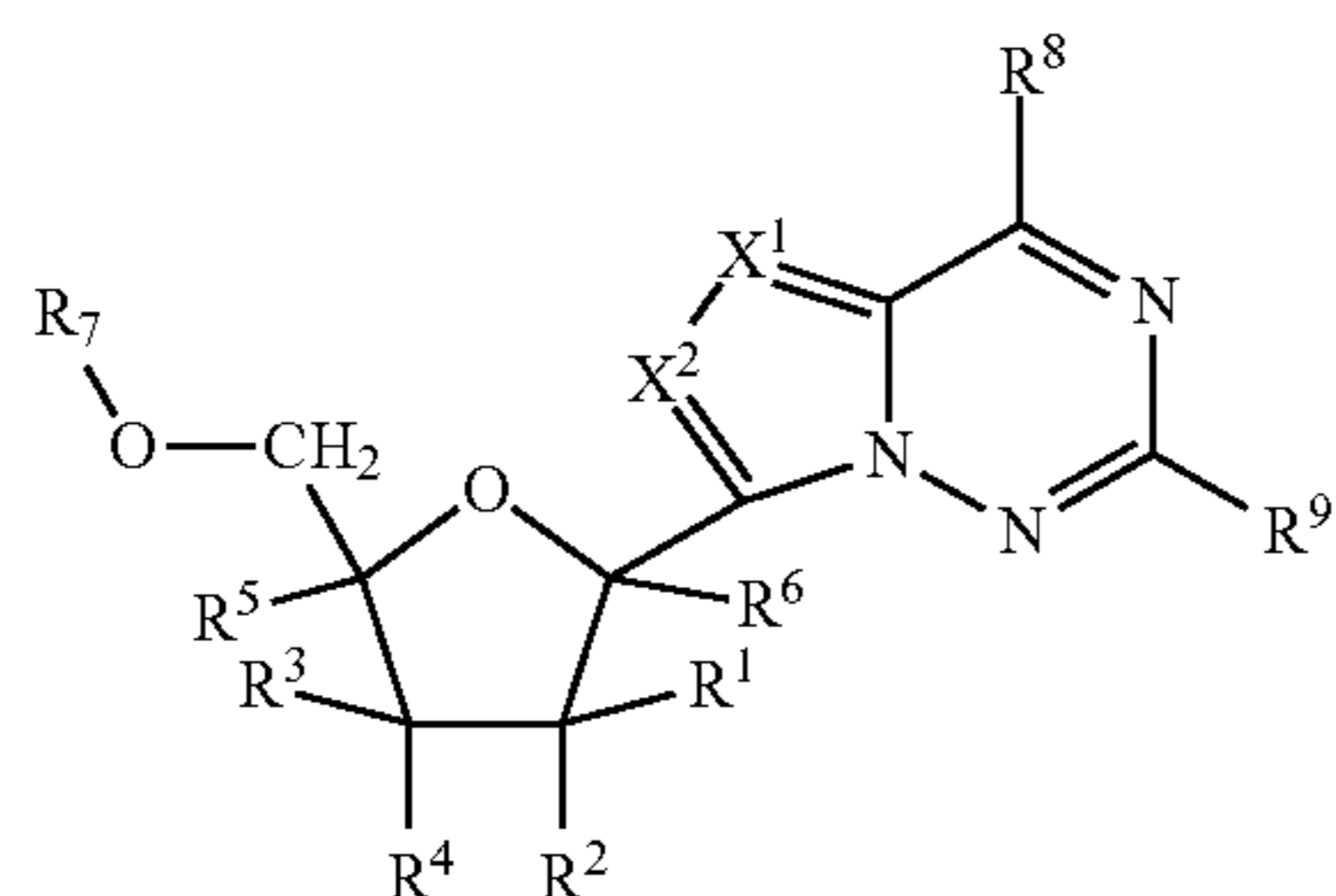
SUMMARY OF THE INVENTION

The instant invention provides compounds that inhibit viruses of the Flaviviridae family. The invention also comprises compounds that inhibit viral nucleic acid polymerases, particularly HCV RNA-dependent RNA poly-

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merase (RdRp), rather than cellular nucleic acid polymerases. Therefore, the compounds of the instant invention are useful for treating Flaviviridae infections in humans and other animals.

In one aspect, this invention provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, thereof;

wherein:

each R^1 , R^2 , R^3 , R^4 , or R^5 is independently H, OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl;

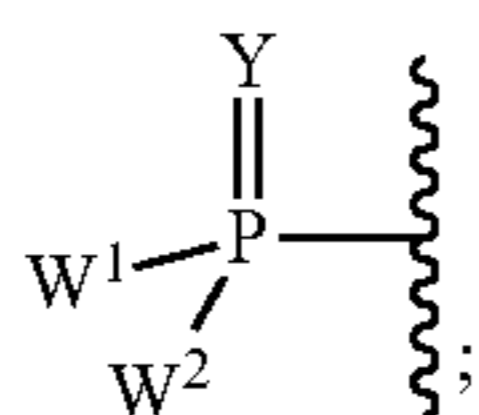
or any two R^1 , R^2 , R^3 , R^4 , or R^5 on adjacent carbon atoms when taken together are $-O(CO)O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

R^6 is OR^a , $N(R^a)_2$, N_3 , CN , NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl(C_1-C_8)alkyl or R^6 and either R^1 or R^2 when taken together are $-O(CO)O-$;

each n is independently 0, 1, or 2;

each R^a is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, aryl(C_1-C_8)alkyl, (C_4-C_8) carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, or

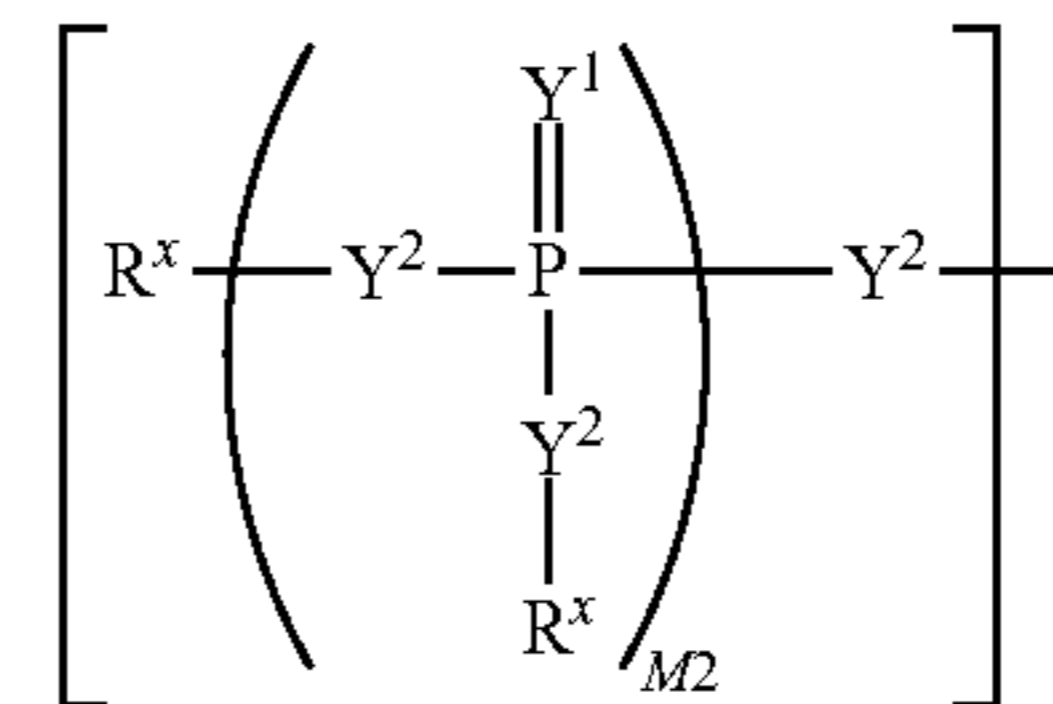


each Y or Y^1 is, independently, O, S, NR, $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, or $N-NR_2$;

W^1 and W^2 , when taken together, are $-Y^3(CR^y)_2$, Y^3- ; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of the Formula Ia:

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Formula Ia



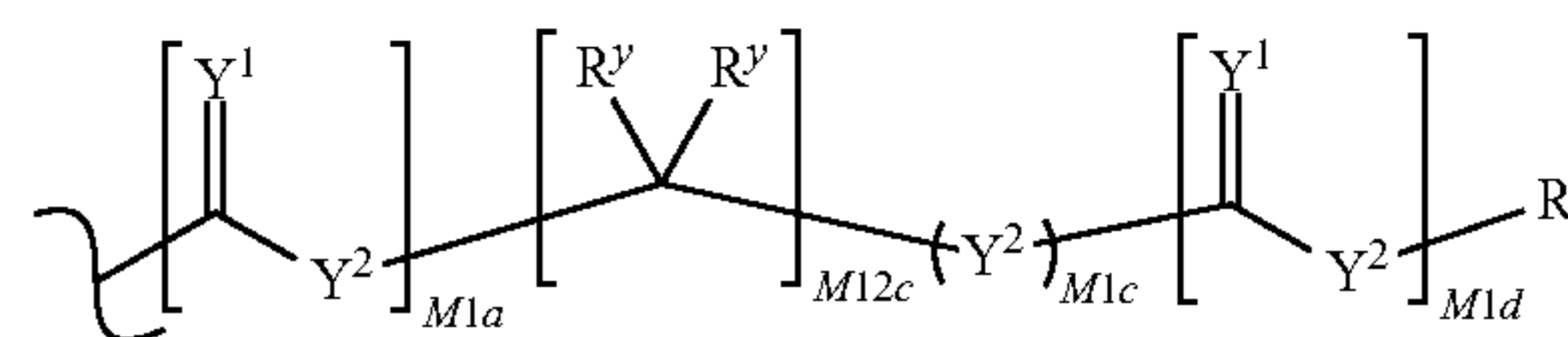
wherein:

each Y^2 is independently a bond, O, CR_2 , NR, $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, $N-NR_2$, S, S-S, $S(O)$, or $S(O)_2$;

each Y^3 is independently O, S, or NR;

M_2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M_{1a} , M_{1c} , and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $+N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$, $-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$, $-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$, $-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, C_6-C_{20} aryl, C_6-C_{20} substituted aryl, C_2-C_{20} heterocyclyl, C_2-C_{20} substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$, or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle wherein W^5 is independently substituted with 0 to 3 R^y groups;

each X^1 or X^2 is independently $C-R^{10}$ or N;

each R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl(C_1-C_8)alkyl, OR^{11} or SR^{11} ;

each R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO , NO_2 , CHO , CN , $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, OR^{11} , R^{11} , OR^{11} or SR^{11} ;

each R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl(C_1-C_8)alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-O-$, $-S-$ or $-NR^a-$;

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wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each R¹, R², R³, R⁴, R⁵, R⁶, R¹¹ or R¹² is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with —O—, —S— or —NR^a—.

In another aspect, the present invention includes compounds of Formula I and pharmaceutically acceptable salts thereof and all racemates, enantiomers, diastereomers, tautomers, polymorphs, pseudopolymorphs and amorphous forms thereof.

In another aspect, the present invention provides novel compounds of Formula I with activity against infectious Flaviviridae viruses. Without wishing to be bound by theory, the compounds of the invention may inhibit viral RNA-dependent RNA polymerase and thus inhibit the replication of the virus. They are useful for treating human patients infected with a human virus such as hepatitis C.

In another aspect, the invention provides a pharmaceutical composition comprising an effective amount of a Formula I compound, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

In another embodiment, the present application provides for combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of Formula I; or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of inhibiting HCV polymerase, comprising contacting a cell infected with HCV with an effective amount of a compound of Formula I; or a pharmaceutically acceptable salts, solvate, and/or ester thereof; and at least one additional therapeutic agent.

In another embodiment, the present application provides for a method of treating and/or preventing a disease caused by a viral infection wherein the viral infection is caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Junjin virus, Murray Valley encephalitis virus, St Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus; by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method of treating HCV in a patient, comprising administering to said patient a therapeutically effective

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amount of a compound of Formula I; or a pharmaceutically acceptable salt, solvate, and/or ester thereof; and at least one additional therapeutic agent.

Another aspect of the invention provides a method for the treatment or prevention of the symptoms or effects of an HCV infection in an infected animal which comprises administering to, i.e. treating, said animal with a pharmaceutical combination composition or formulation comprising an effective amount of a Formula I compound, and a second compound having anti-HCV properties.

In another aspect, the invention also provides a method of inhibiting HCV, comprising administering to a mammal infected with HCV an amount of a Formula I compound, effective to inhibit the replication of HCV in infected cells in said mammal.

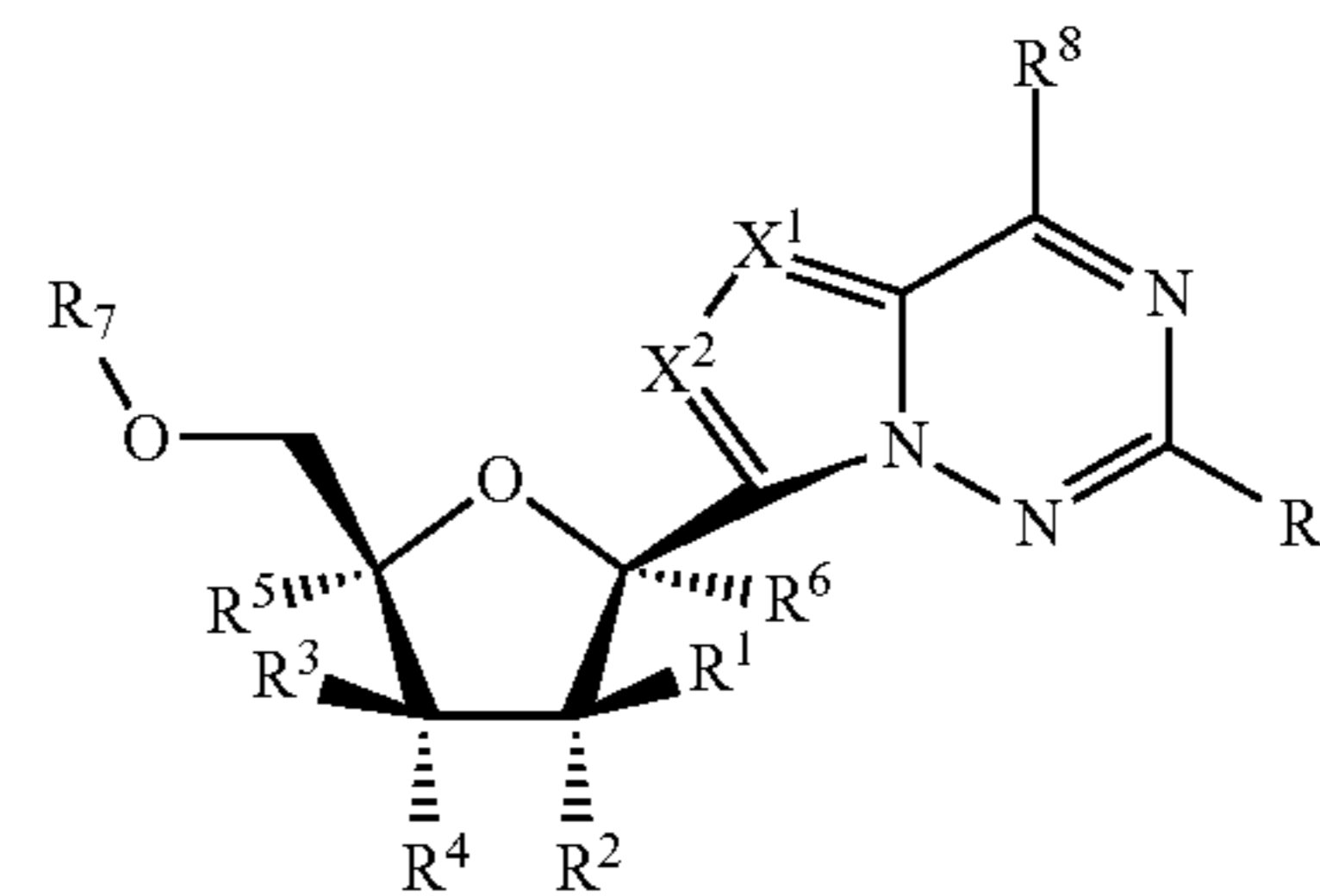
In another aspect, the invention also provides processes and novel intermediates disclosed herein which are useful for preparing Formula I compounds of the invention.

In other aspects, novel methods for synthesis, analysis, separation, isolation, purification, characterization, and testing of the compounds of this invention are provided.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying description, structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention.

In another aspect, compounds of Formula I are represented by Formula II:



Formula II

or a pharmaceutically acceptable salt, thereof; wherein:

each R¹, R², R³, R⁴, or R⁵ is independently H, OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl;

or any two R¹, R², R³, R⁴, or R⁵ on adjacent carbon atoms when taken together are —O(CO)O— or when taken together with the ring carbon atoms to which they are attached form a double bond;

R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted

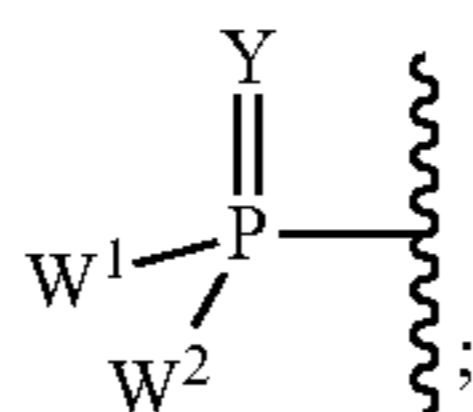
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alkynyl, or aryl(C₁-C₈)alkyl or R⁶ and either R¹ or R² when taken together are —O(CO)O—;

each n is independently 0, 1, or 2;

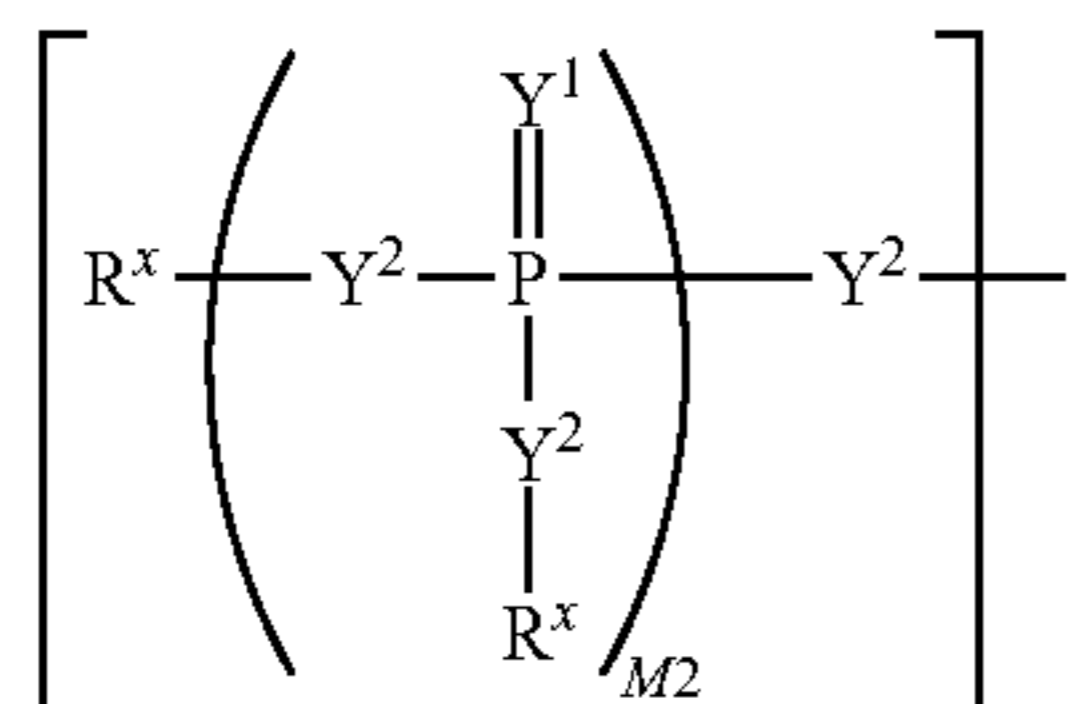
each R^a is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl(C₁-C₈)alkyl, (C₄-C₈)carbocyclolalkyl, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), or —SO₂NR¹¹R¹²;

R⁷ is H, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², or



each Y or Y¹ is, independently, O, S, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), or N—NR₂;

W¹ and W², when taken together, are —Y³(C(R^y)₂)₃Y³—; or one of W¹ or W² together with either R³ or R⁴ is —Y³— and the other of W¹ or W² is Formula Ia; or W¹ and W² are each, independently, a group of the Formula Ia:



Formula Ia

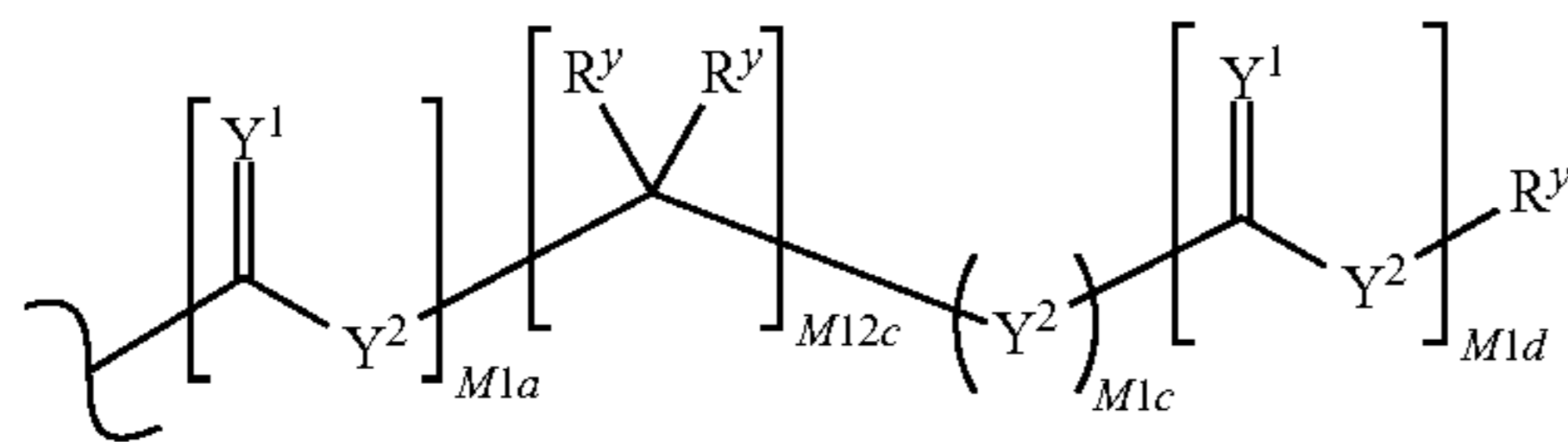
wherein:

each Y² is independently a bond, O, CR₂, NR, ⁺N(O)(R), N(OR), ⁺N(O)(OR), N—NR₂, S, S—S, S(O), or S(O)₂;

each Y³ is independently O, S, or NR;

M₂ is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M_{1a}, M_{1c}, and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, —C(=Y¹)R, —C(=Y¹)OR, —C(=Y¹)N(R)₂, —N(R)₂, ⁺N(R)₃, —SR, —S(O)R, —S(O)₂R, —S(O)₂(OR), —S(O)₂(OR), —OC(=Y¹)R, —OC(=Y¹)OR, —OC(=Y¹)(N(R)₂), —SC(=Y¹)R, —SC(=Y¹)OR, —SC(=Y¹)(N(R)₂), —N(R)C(=Y¹)R, —N(R)C(=Y¹)OR, —N(R)C(=Y¹)N(R)₂, —SO₂NR₂, —CN, —N₃, —NO₂, —OR, or W³; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, C₆-C₂₀aryl, C₆-C₂₀substituted aryl, C₂-C₂₀heterocyclyl, C₂-C₂₀substituted heterocyclyl, arylalkyl or substituted arylalkyl;

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W³ is W⁴ or W⁵; W⁴ is R, —C(Y¹)R^y, —C(Y¹)W⁵, —SO₂R^y, or —SO₂W⁵; and W⁵ is a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

X² is C—R¹⁰ and each X¹ is independently C—R¹⁰ or N;

each R⁸ is independently halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹), —CH=NHR¹¹, —CH=N(OR¹¹), —CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)OR¹¹, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclolalkyl, optionally substituted aryl, optionally substituted heteroaryl, —C(=O)(C₁-C₈)alkyl, —S(O)₁(C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, OR¹¹ or SR¹¹;

each R⁹ or R¹⁰ is independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹), —CH=NHR¹¹, —CH=N(OR¹¹), —CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

each R¹¹ or R¹² is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclolalkyl, optionally substituted aryl, optionally substituted heteroaryl, —C(=O)(C₁-C₈)alkyl, —S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl; or R¹¹ and R¹² taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with —O—, —S— or —NR^a—;

wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each R¹, R², R³, R⁴, R⁵, R⁶, R¹¹ or R¹² is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with —O—, —S— or —NR^a.

In one embodiment of the invention of Formula II, R¹ is (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R¹ is (C₁-C₈)alkyl. In another aspect of this embodiment, R¹ is methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In a preferred aspect of this embodiment, R¹ is methyl. In another preferred aspect of this embodiment, R¹ is H.

In one embodiment of Formula II, R² is H, OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, or (C₂-C₈)substituted alkynyl. In another aspect of this embodiment, R² is H, OR^a, N(R^a)₂, N₃, CN, SR^a or halogen. In another aspect of this embodiment, R² is H, OH, NH₂, N₃, CN, or halogen. In another aspect of this embodiment, R² is OR^a or halogen and R¹ is H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R² is OR^a or F and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In a preferred aspect of this embodiment, R² is OH and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R² is OR^a and R¹ is H. In another preferred aspect of this embodiment, R² is OH and R¹ is H. In another preferred aspect of this embodiment, R² is F and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R² is OR^a and R¹ is methyl. In a particularly preferred aspect of this embodiment, R² is OH and R¹ is methyl.

In one embodiment of Formula II, R³ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In one aspect of this embodiment, R³ is H or F. In a preferred aspect of this embodiment, R³ is H. In another preferred aspect of this embodiment, R³ is H, R² is OR^a or halogen and R¹ is H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R³

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and R⁵ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl (C₁-C₈)alkyl. In another aspect of this embodiment, R² and R⁴ are each OR^a and R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl. In another aspect of this embodiment, R² and R⁴ are both OH and R⁶ is OR^a, N₃, CN, S(O)_nR^a, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, or (C₂-C₈)substituted alkynyl.

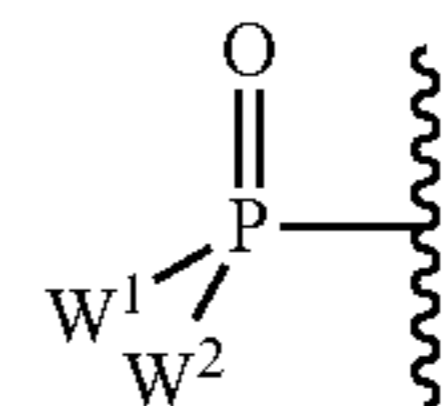
In another embodiment of Formula II, each R¹ and R² is H, one of R³ or R⁴ is OR^a and the other of R³ or R⁴ is (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl. In another aspect of this embodiment, each R¹ and R² is H, one of R³ or R⁴ is OH and the other of R³ or R⁴ is (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl or aryl(C₁-C₈)alkyl.

In another embodiment of Formula II, R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl. In another aspect of this embodiment, R⁵ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R⁵ is H, N₃, CN, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In another aspect of this embodiment, R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another aspect of this embodiment, R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl and R² and R⁴ are each OR^a. In another aspect of this embodiment, R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R² and R⁴ are each OR^a; and R³ and R⁵ are each H. In another aspect of this embodiment, R⁵ is H, N₃, CN, methyl, ethenyl or ethynyl; R⁴ is OR^a and R³ is H. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R⁵ is H or N₃; R⁴ is OR^a; R³ is H; and R² is OR^a. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ and R⁵ are H; and R² and R⁴ are each OH. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ and R⁵ are H; and R² and R⁴, taken together, are —O(CO)O—. In another aspect of this embodiment, R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R³ is H; R² and R⁴ are independently OR^a and R⁵ is N₃. In another aspect of this of this embodiment, R⁶ is N₃, halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl. In another aspect of this of this embodiment, R⁶ is N₃, halogen, CN,

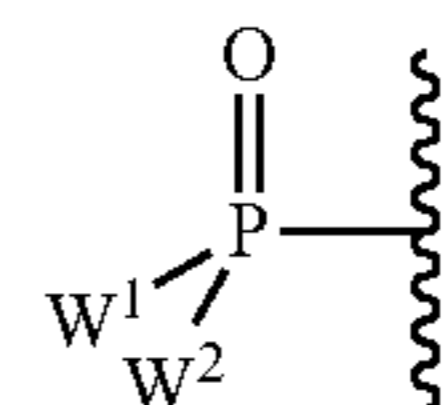
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methyl, hydroxymethyl, ethenyl or ethynyl; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; and R² and R⁴ are each OR^a. In another aspect of this of this embodiment, R⁶ is N₃, halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R² and R⁴ are each OR^a; and R³ and R⁵ are each H.

In one embodiment of Formula II, R⁷ is H, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)SR¹¹ or



In a preferred aspect of this embodiment, R⁷ is H. In another preferred aspect of this embodiment, R⁷ is —C(=O)R¹¹. In another preferred aspect of this embodiment, R⁷ is —C(=O)R¹¹ wherein R¹¹ is (C₁-C₈)alkyl. In another preferred aspect of this embodiment, R⁷ is



In one embodiment of Formula II, X¹ is N or C—R¹⁰. In another aspect of this embodiment, X¹ is N. In another aspect of this embodiment, X¹ is C—R¹⁰. In another aspect of this embodiment, X² is C—H. In another aspect of this embodiment, X¹ is N and X² is C—H. In another aspect of this embodiment, X¹ is C—R¹⁰ and X² is CH. In another aspect of this embodiment, X¹ is C—H and X² is CH. In another aspect of this embodiment, X¹ is CR¹⁰ and R⁶ is OR^a, N₃, halogen, —C(=O)R¹¹, —C(=O)OR¹¹, —C(O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is CR¹⁰, X² is CH; and R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is CR¹⁰, X² is CH; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R³ is H; R² and R⁴ are each OR^a; and R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is CR¹⁰, X² is CH; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; each R³ and R⁵ is H; R² and R⁴ are each OR^a; and R⁶ is methyl, hydroxymethyl, N₃, halogen or CN. In another aspect of this embodiment, X¹ is N and R⁶ is OR^a, N₃, halogen, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), SO₂NR¹¹R¹², CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is N; X² is CH; and R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is N; X² is CH; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R³ is H; R² and R⁴ are each OR^a; and R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is N; X² is CH; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R³ is H; R² and R⁴ are each OR^a; and R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is N; X² is CH; R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; R³ is H; R² and R⁴ are each OR^a; and R⁶ is OR^a, N₃, halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, X¹ is N; X² is CH; R¹ is H,

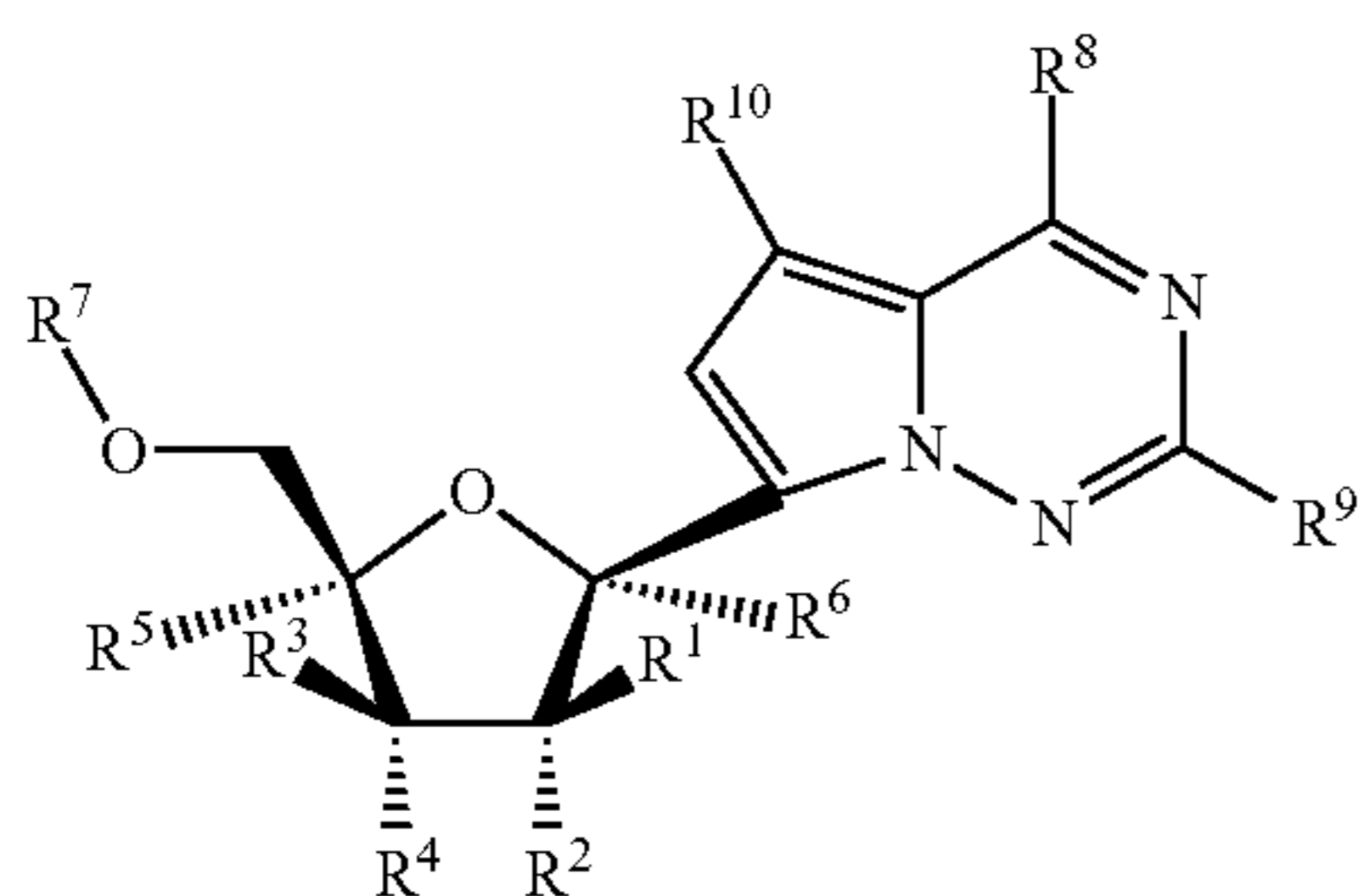
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methyl, CH₂OH, CH₂F, ethenyl, or ethynyl; each R³ and R⁵ is H; R² and R⁴ are each OR^a; and R⁶ is methyl, hydroxymethyl, N₃, halogen or CN.

In another embodiment of Formula II, each R⁸ is independently halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹), —CH=NHR¹¹, —CH=N(OR¹¹), —CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)OR¹¹, —(C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, —C(=O)(C₁-C₈)alkyl, —S(O)_n(C₁-C₈)alkyl, aryl(C₁-C₈)alkyl, OR¹¹ or SR¹¹. In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹. In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹ and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹ and R⁹ is H, halogen, or NR¹¹R¹². In another aspect of this embodiment, each R⁸ is, independently, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², OR¹¹ or SR¹¹ and R⁹ is H, halogen, or NR¹¹R¹² and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁸ is NH₂ and R⁹ is H or halogen. In another preferred aspect of this embodiment, R⁸ is NH₂ and R⁹ is H or halogen and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁸ and R⁹ are each NH₂. In another preferred aspect of this embodiment, R⁸ and R⁹ are each NH₂ and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl. In another preferred aspect of this embodiment, R⁸ is OH and R⁹ is NH₂. In another preferred aspect of this embodiment, R⁸ is OH and R⁹ is NH₂ and R¹ is H, methyl, CH₂OH, CH₂F, ethenyl, or ethynyl.

In another embodiment of Formula II, each R¹⁰ is, independently, H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹), —CH=NHR¹¹, —CH=N(OR¹¹), —CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹. In another aspect of this embodiment, each R¹⁰ is H, halogen, CN or optionally substituted heteroaryl.

In another aspect, compounds of Formula I are represented by Formula III:



Formula III

or a pharmaceutically acceptable salt, thereof; wherein:

R¹ is H or CH₃;

each R², R³, R⁴, or R⁵ is independently H, OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl;

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or any two R², R³, R⁴, or R⁵ on adjacent carbon atoms when taken together are —O(CO)O— or when taken together with the ring carbon atoms to which they are attached form a double bond;

R⁶ is OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, (C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, (C₂-C₈)substituted alkynyl, or aryl(C₁-C₈)alkyl or R⁶ and R² when taken together are —O(CO)O—;

wherein each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each R², R³, R⁴, R⁵, R⁶, R¹¹ or R¹² is, independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with —O—, —S— or —NR^a—; and

all remaining variables are defined as for Formula I.

In one embodiment of Formula III, R¹ is H.

In one embodiment of Formula III, R¹ is CH₃.

In one embodiment of Formula III, R² is H, OR^a, N(R^a)₂, N₃, CN, NO₂, S(O)_nR^a, halogen, (C₁-C₈)alkyl, (C₁-C₈)substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈)substituted alkenyl, (C₂-C₈)alkynyl, or (C₂-C₈)substituted alkynyl. In another aspect of this embodiment, R² is H, OR^a, N(R^a)₂, N₃, CN, SR^a or halogen. In another aspect of this embodiment, R² is H, OH, NH₂, N₃, CN, or halogen. In another aspect of this embodiment, R² is OR^a or halogen and R¹ is methyl. In another aspect of this embodiment, R² is OR^a or halogen and R¹ is H. In another aspect of this embodiment, R² is OR^a or F and R¹ is methyl. In another aspect of this embodiment, R² is OR^a or F and R¹ is H. In a preferred aspect of this embodiment, R² is OH and R¹ is methyl. In another preferred aspect of this embodiment, R² is OR^a and R¹ is H. In another preferred aspect of this embodiment, R² is OH and R¹ is H. In another preferred aspect of this embodiment, R² is F. In another preferred aspect of this embodiment, R² is OR^a and R¹ is methyl.

In one embodiment of Formula III, R³ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In one aspect of this embodiment, R³ is H or F. In a preferred aspect of this embodiment, R³ is H. In another preferred aspect of this embodiment, R³ is H, R² is OR^a or halogen and R¹ is methyl. In another preferred aspect of this embodiment, R³ is H, R² is OR^a or halogen and R¹ is H. In another aspect of this embodiment, R³ is H, R² is OR^a or F and R¹ is methyl. In another aspect of this embodiment, R³ is H, R² is OR^a and R¹ is methyl. In another aspect of this embodiment, R³ is H, R² is OH and R¹ is methyl. In another aspect of this embodiment, R³ is H, R² is OR^a and R¹ is H. In another aspect of this embodiment, R³ is H, R² is OH and R¹ is H. In another aspect of this embodiment, each R¹, R³ and R⁵ is H and R² is OH.

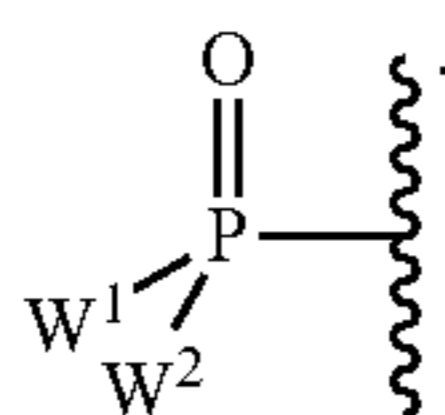
In one embodiment of Formula III, R⁴ is H, OR^a, N(R^a)₂, N₃, CN, SR^a, halogen, (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl. In a preferred aspect of this embodiment, R⁴ is OR^a. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen and R¹ is methyl. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen and R¹ is H. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen, R³ is H and R¹ is methyl. In another preferred aspect of this embodiment, R⁴ is OR^a, R² is OR^a or halogen, R³ is H and R¹ is H. In another preferred embodiment R⁴ is OR^a, R² is OR^a or F

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embodiment, each R^1 and R^2 is H, one of R^3 or R^4 is OR^a and the other of R^3 or R^4 is (C_1-C_8) alkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl or aryl (C_1-C_8) alkyl.

In another embodiment of Formula III, R^6 is OR^a , $N(R^a)_2$, N_3 , CN, NO_2 , $S(O)_nR^a$, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, halogen, (C_1-C_8) alkyl, (C_4-C_8) carbocyclalkyl, (C_1-C_8) substituted alkyl, (C_2-C_8) alkenyl, (C_2-C_8) substituted alkenyl, (C_2-C_8) alkynyl, (C_2-C_8) substituted alkynyl, or aryl (C_1-C_8) alkyl. In another aspect of this embodiment, R^5 is H, N_3 , CN, (C_1-C_8) alkyl, (C_2-C_8) alkenyl or (C_2-C_8) alkynyl. In another aspect of this embodiment, R^1 is H. In another aspect of this embodiment, R^1 is methyl. In another aspect of this embodiment, R^1 is H and R^2 and R^4 are each OR^a . In another aspect of this embodiment, R^1 is methyl and R^2 and R^4 are each OR^a . In another aspect of this embodiment, R^1 is H; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this embodiment, R^1 is methyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this embodiment, R^5 is H, N_3 , CN, methyl, ethenyl or ethynyl; R^4 is OR^a and R^3 is H. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^5 is H or N_3 ; R^4 is OR^a ; R^3 is H; and R^2 is OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H and R^2 and R^4 are, independently, OR^a . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 are each OH. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 and R^5 are H; and R^2 and R^4 , taken together, are $-O(CO)O-$. In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl; R^3 is H; R^2 and R^4 are independently OR^a and R^5 is N_3 . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H; and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is methyl; and R^2 and R^4 are each OR^a . In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is H; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H. In another aspect of this of this embodiment, R^6 is N_3 , halogen, CN, methyl, hydroxymethyl, ethenyl or ethynyl; R^1 is methyl; R^2 and R^4 are each OR^a ; and R^3 and R^5 are each H.

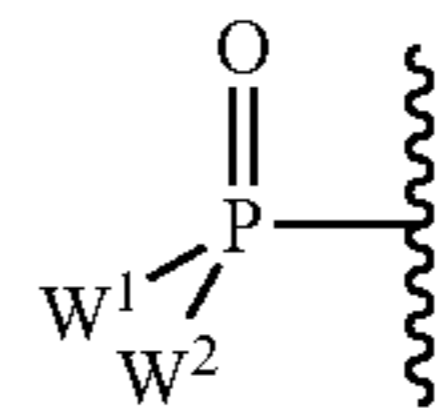
In one embodiment of Formula III, R^7 is H, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)SR^{11}$ or



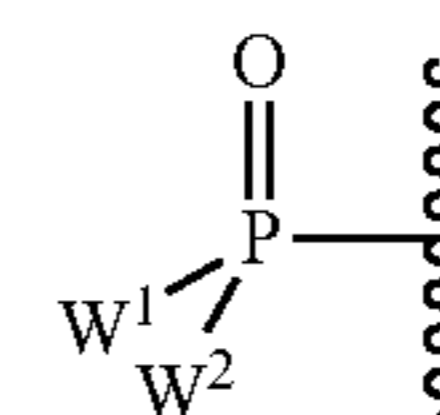
In a preferred aspect of this embodiment, R^7 is H. In another preferred aspect of this embodiment, R^7 is H and R^1 is H. In another preferred aspect of this embodiment, R^7 is

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$-C(=O)R^{11}$. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ and R^1 is H. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl. In another preferred aspect of this embodiment, R^7 is $-C(=O)R^{11}$ wherein R^{11} is (C_1-C_8) alkyl and R^1 is H. In another preferred aspect of this embodiment, R^7 is



In another preferred aspect of this embodiment, R^7 is



and R^1 is H.

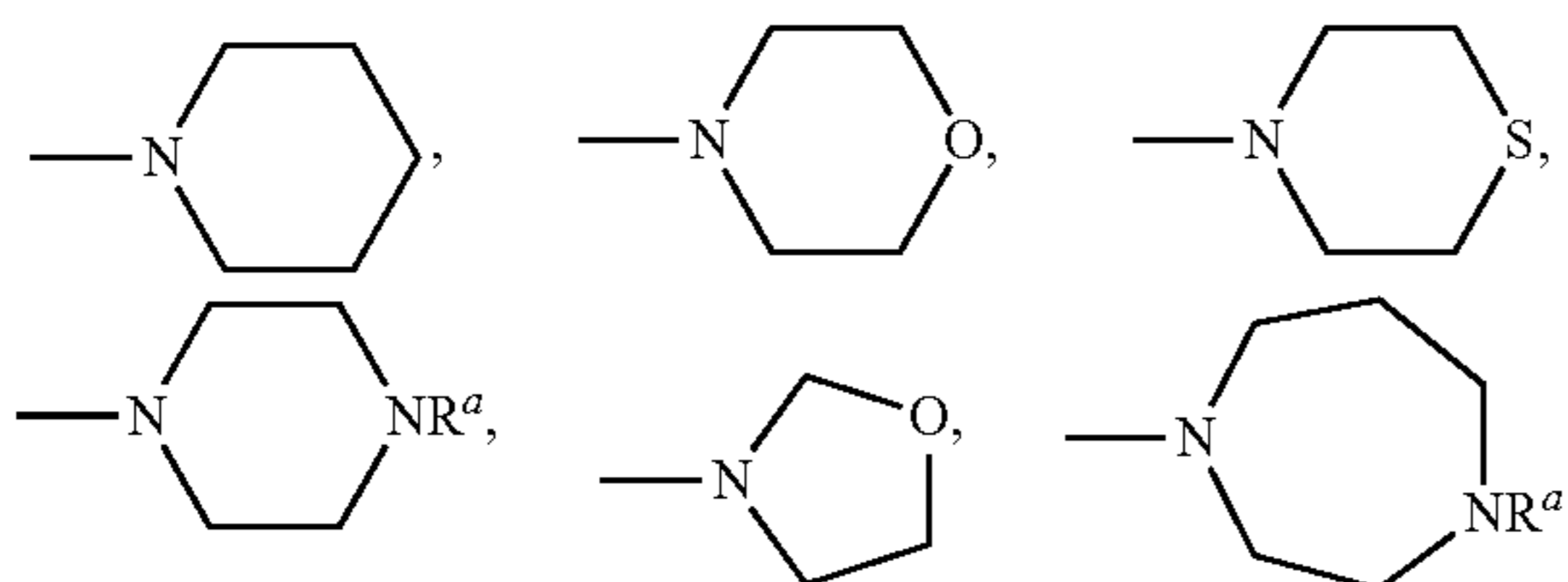
In another embodiment of Formula III, each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl, aryl (C_1-C_8) alkyl, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} . In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^1 is H. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is H. In another aspect of this embodiment, each R^8 is, independently, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, OR^{11} or SR^{11} and R^9 is H, halogen, or $NR^{11}R^{12}$ and R^1 is methyl. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is H. In another preferred aspect of this embodiment, R^8 is NH_2 and R^9 is H or halogen and R^1 is methyl. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 . In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is H. In another preferred aspect of this embodiment, R^8 and R^9 are each NH_2 and R^1 is methyl. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 . In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is H. In another preferred aspect of this embodiment, R^8 is OH and R^9 is NH_2 and R^1 is methyl.

In another embodiment of Formula III, each R^{10} is, independently, H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 , NO, NO_2 , CHO, CN, $-CH(=NR^{11})$, $-CH=NHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$,

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R^{11} , OR^{11} or SR^{11} . In another aspect of this embodiment, R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, each R^{10} is H, halogen, CN or optionally substituted heteroaryl and R^6 is OR^a , N_3 , halogen, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $-C(=O)SR^{11}$, $-S(O)R^{11}$, $-S(O)_2R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, $-SO_2NR^{11}R^{12}$, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, R^{10} is H and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, R^3 is H; R^2 and R^4 are each OR^a ; and R^6 is OR^a , N_3 , halogen, CN, methyl, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl. In another aspect of this embodiment, each R^3 and R^5 is H; R^2 and R^4 are each OR^a ; and R^6 is methyl, hydroxymethyl, N_3 , halogen or CN.

In one embodiment of Formulas I-III, R^{11} or R^{12} is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_4-C_8) carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)$ alkyl, $-S(O)_n(C_1-C_8)$ alkyl or aryl (C_1-C_8) alkyl. In another embodiment, R^{11} and R^{12} taken together with a nitrogen to which they are both attached, form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-O-$, $-S-$ or $-NR^a-$. Therefore, by way of example and not limitation, the moiety $-NR^{11}R^{12}$ can be represented by the heterocycles:



and the like.

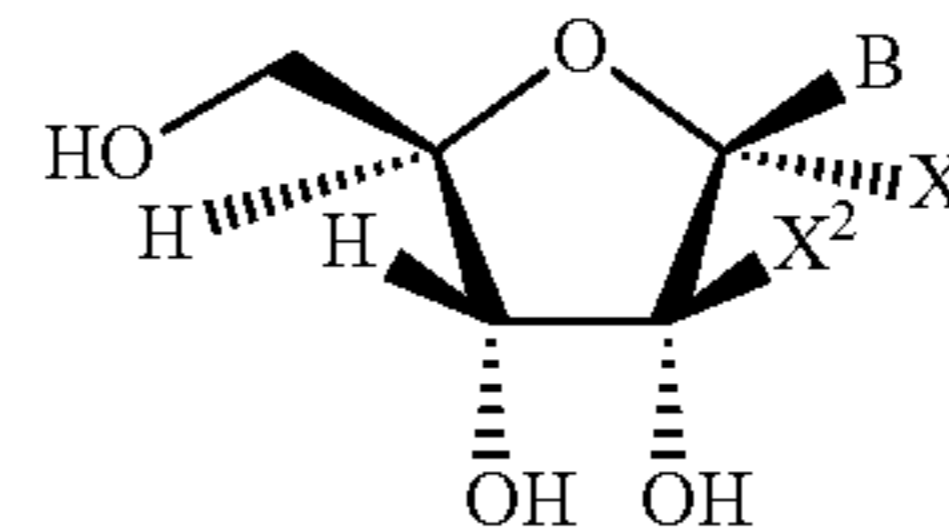
In another embodiment of Formulas I-III, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is, independently, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl, wherein said (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl or aryl (C_1-C_8) alkyl are, independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a . Therefore, by way of example and not limitation, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} could represent moieties such as $-CH(NH_2)CH_3$, $-CH(OH)CH_2CH_3$, $-CH(NH_2)CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CH(N_3)CH_3$, $-(CH_2)_6NH_2$ and the like.

In another embodiment of Formula I-III, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} is (C_1-C_8) alkyl wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8) alkyl may be optionally replaced with $-O-$, $-S-$ or $-NR^a-$. Therefore, by way of example and not limitation, R^2 , R^3 , R^4 , R^5 , R^6 , R^{11} or R^{12} could represent moieties such as $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2OCH(CH_3)_2$, $-CH_2SCH_3$, $-(CH_2)_6OCH_3$, $-(CH_2)_6N(CH_3)_2$ and the like.

20

In still another embodiment, the compounds of Formula I, Formula II, or Formula III are named below in tabular format (Table 6) as compounds of general Formula IV:

Formula IV



wherein X1 and X2, represent substituents attached to the tetrahydrofuran ring as defined in Tables 1-2, below; B is a purine defined in Table 4, below; and X3 represents a ring element of the purine base B as described in Table 3, below.

The point of attachment of the core structure ribose is indicated in each of the structures of X1, X2, and B. The point of attachment of the core structure purine is indicated in each of the structures X3. Each structure in Tables 1-4 is represented by an alphanumeric "code". Each structure of a compound of Formula IV can thus be designated in tabular form by combining the "code" representing each structural moiety using the following syntax: X1.X2.X3.B. Thus, for example, X1a.X2c.X3a.B1 represents the following structure:

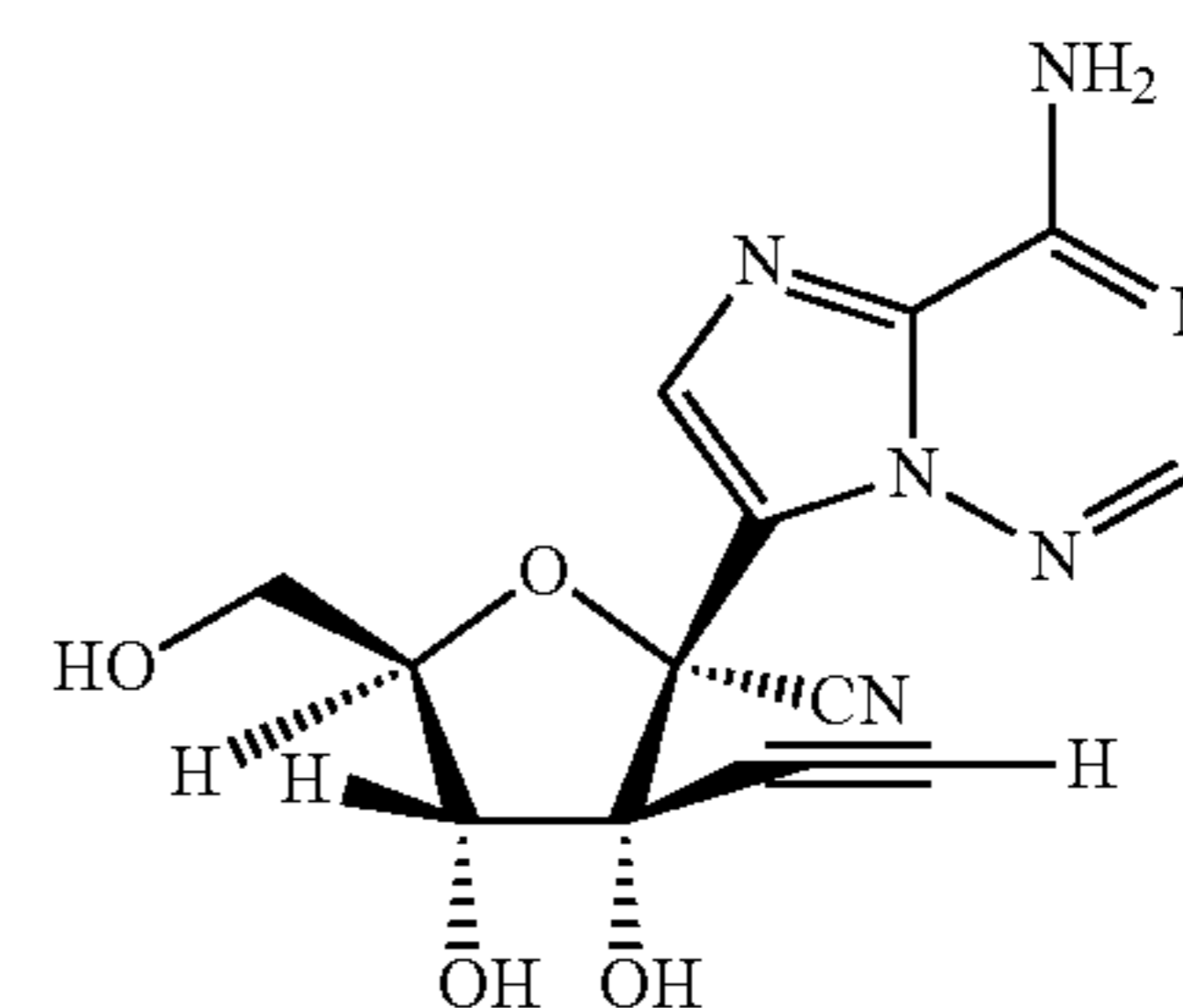


TABLE 1

X1 Structures

Code	Structure
X1a	CN
X1b	CH ₃
X1c	N ₃
X1d	CH ₂ OH

TABLE 2

X2 Structures

Code	Structure
X2a	H
X2b	CH ₃
X2c	

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TABLE 3

X3 Structures	
Code	Structure
X3a	—N=
X3b	—CH=
X3c	—CF=

TABLE 4

B Structures	
Code	Structure
B1	
B2	
B3	
B4	

TABLE 6

List of Compounds of Formula IV

X1a.X2b.X3a.B1, X1a.X2b.X3a.B2, X1a.X2b.X3a.B3, X1a.X2b.X3a.B4,
 X1a.X2b.X3b.B1, X1a.X2b.X3b.B2, X1a.X2b.X3b.B3, X1a.X2b.X3b.B4,
 X1a.X2b.X3c.B1, X1a.X2b.X3c.B2, X1a.X2b.X3c.B3, X1a.X2b.X3c.B4,
 X1a.X2c.X3a.B1, X1a.X2c.X3a.B2, X1a.X2c.X3a.B3, X1a.X2c.X3a.B4,
 X1a.X2c.X3b.B1, X1a.X2c.X3b.B2, X1a.X2c.X3b.B3, X1a.X2c.X3b.B4,
 X1a.X2c.X3c.B1, X1a.X2c.X3c.B2, X1a.X2c.X3c.B3, X1a.X2c.X3c.B4,
 X1b.X2a.X3a.B1, X1b.X2a.X3a.B2, X1b.X2a.X3a.B3, X1b.X2a.X3a.B4,
 X1b.X2a.X3b.B1, X1b.X2a.X3b.B2, X1b.X2a.X3b.B3, X1b.X2a.X3b.B4,
 X1b.X2a.X3c.B1, X1b.X2a.X3c.B2, X1b.X2a.X3c.B3, X1b.X2a.X3c.B4,
 X1b.X2b.X3a.B1, X1b.X2b.X3a.B2, X1b.X2b.X3a.B3, X1b.X2b.X3a.B4,
 X1b.X2b.X3b.B1, X1b.X2b.X3b.B2, X1b.X2b.X3b.B3, X1b.X2b.X3b.B4,
 X1b.X2b.X3c.B1, X1b.X2b.X3c.B2, X1b.X2b.X3c.B3, X1b.X2b.X3c.B4,
 X1b.X2c.X3a.B1, X1b.X2c.X3a.B2, X1b.X2c.X3a.B3, X1b.X2c.X3a.B4,
 X1b.X2c.X3b.B1, X1b.X2c.X3b.B2, X1b.X2c.X3b.B3, X1b.X2c.X3b.B4,
 X1b.X2c.X3c.B1, X1b.X2c.X3c.B2, X1b.X2c.X3c.B3, X1b.X2c.X3c.B4,
 X1c.X2a.X3a.B1, X1c.X2a.X3a.B2, X1c.X2a.X3a.B3, X1c.X2a.X3a.B4,
 X1c.X2a.X3b.B1, X1c.X2a.X3b.B2, X1c.X2a.X3b.B3, X1c.X2a.X3b.B4,

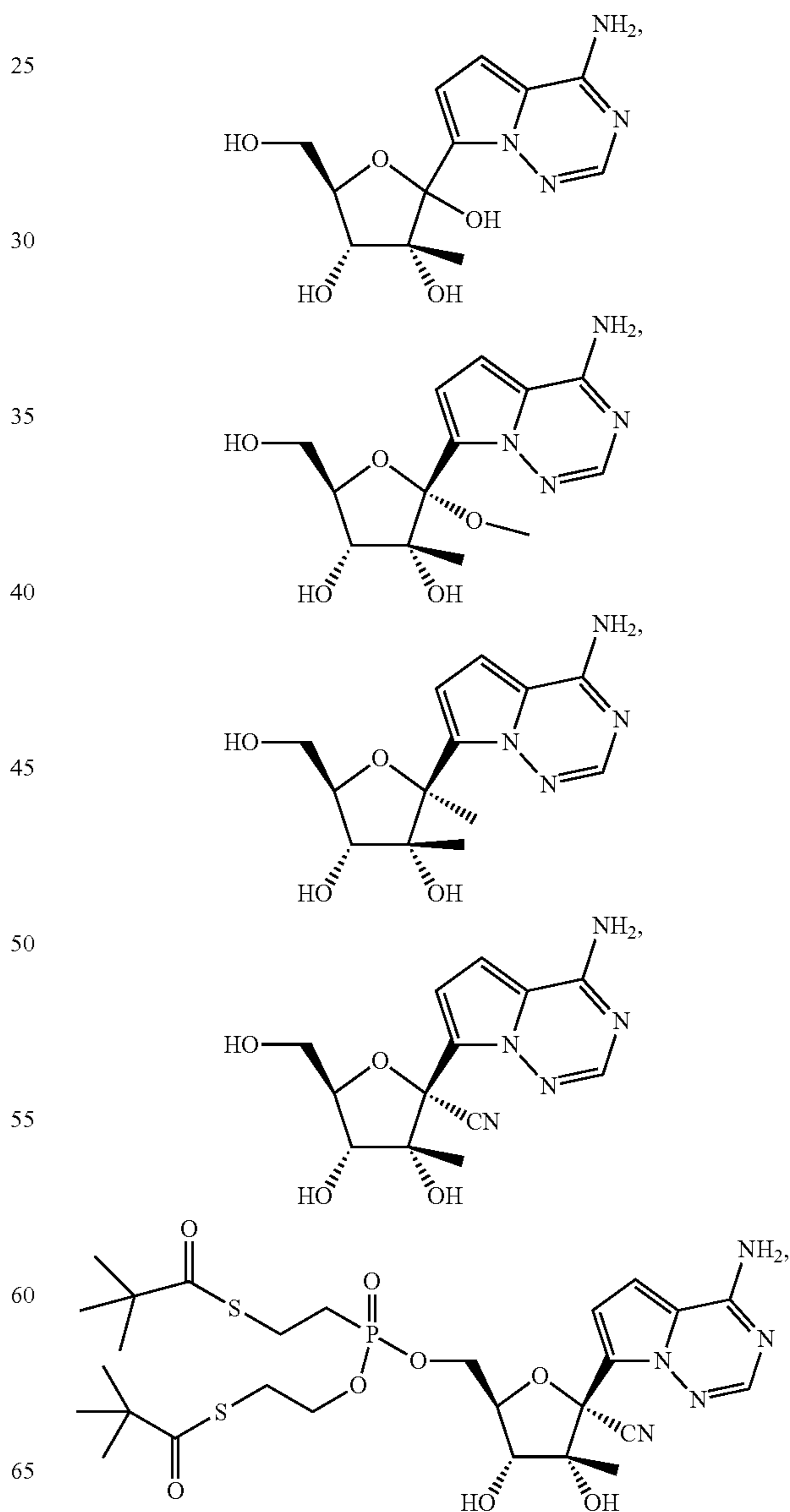
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TABLE 6-continued

List of Compounds of Formula IV

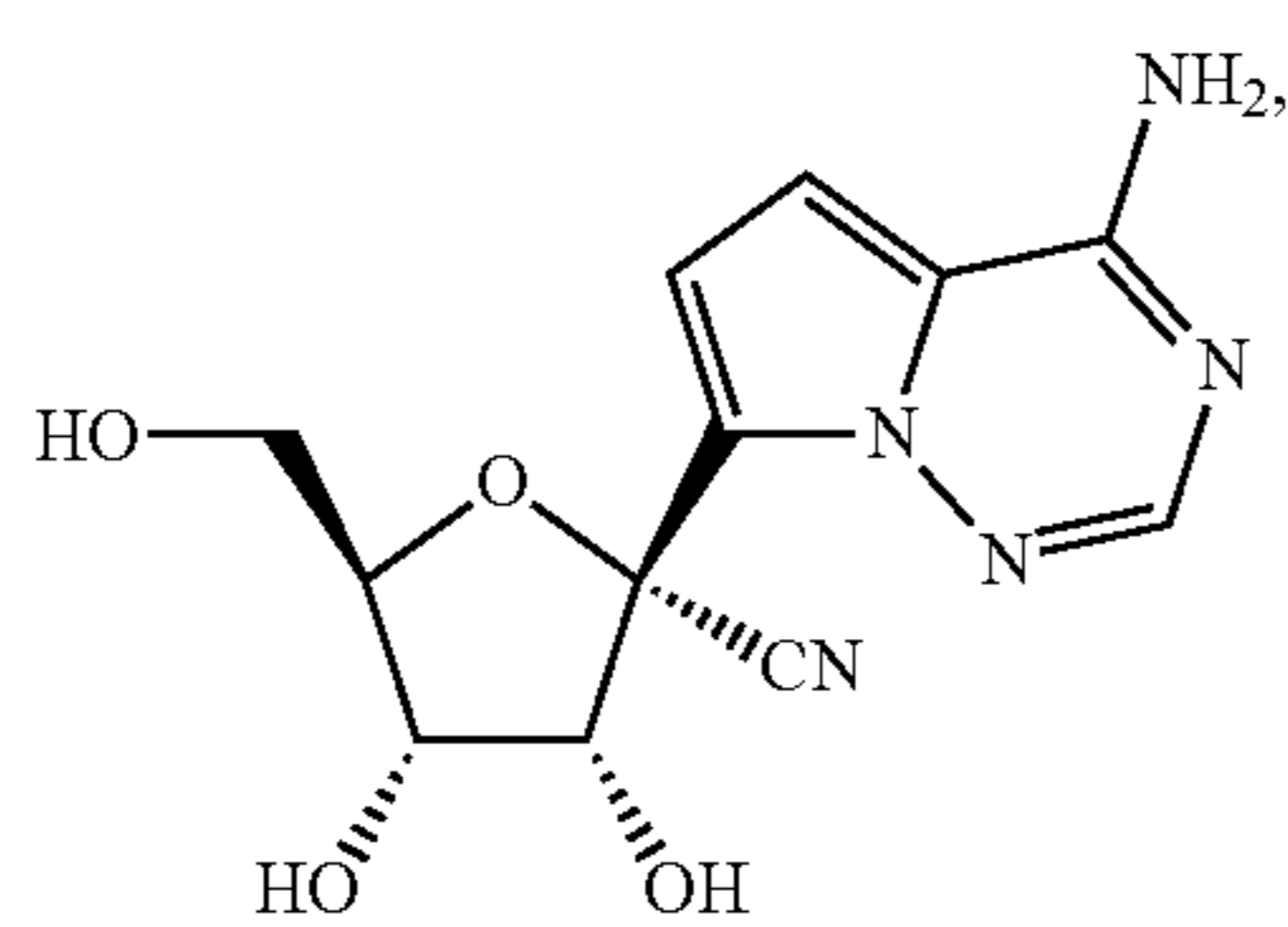
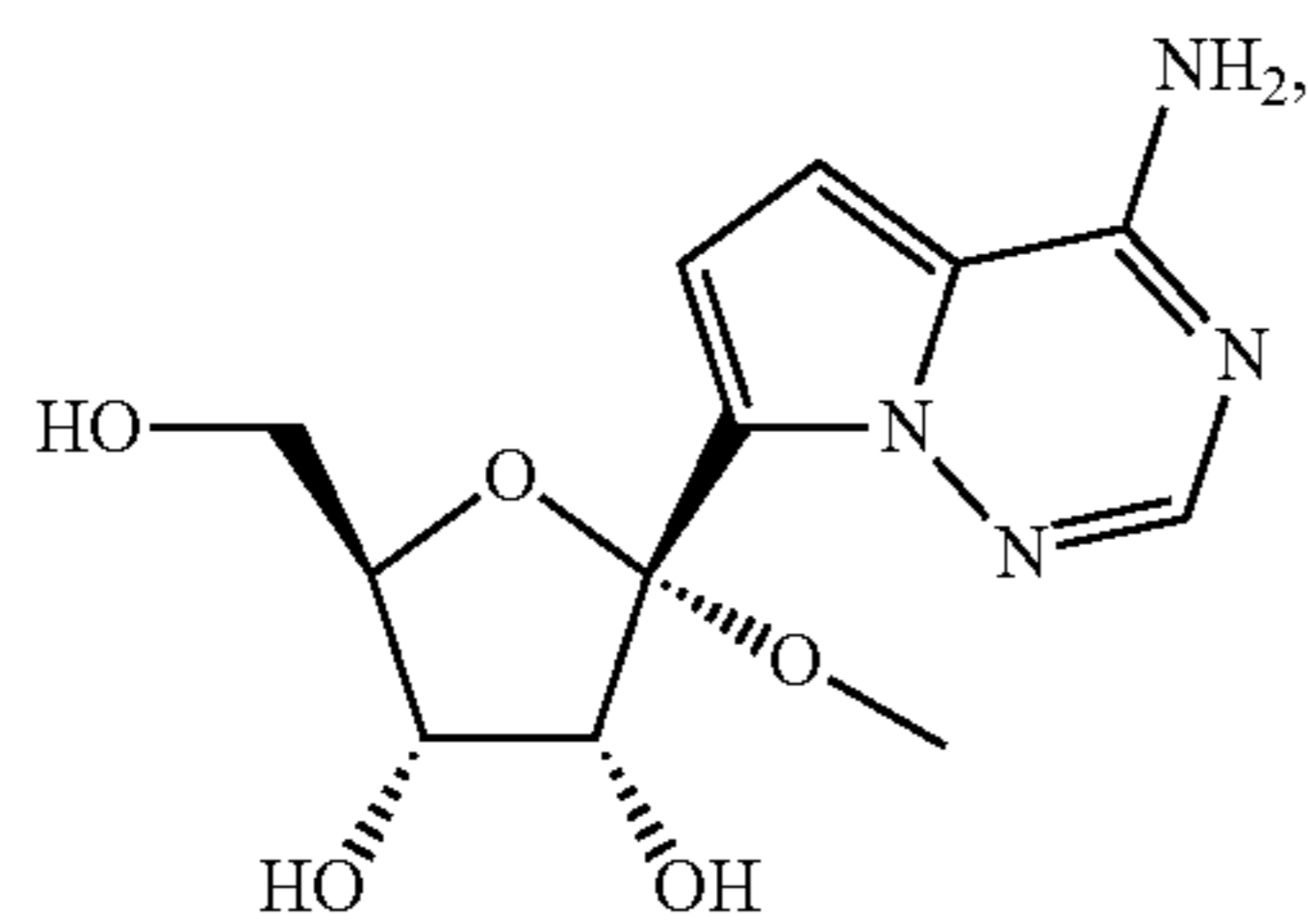
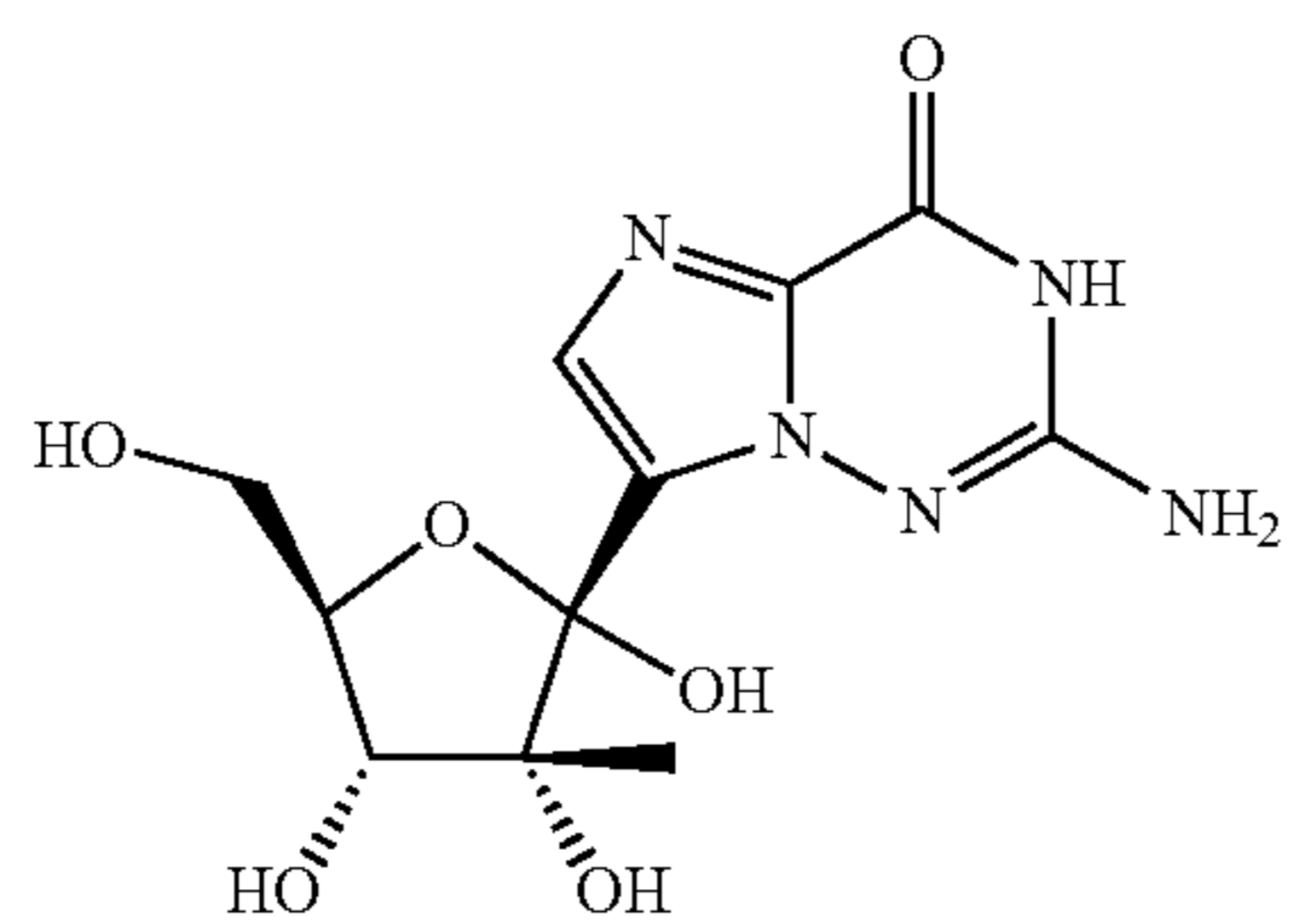
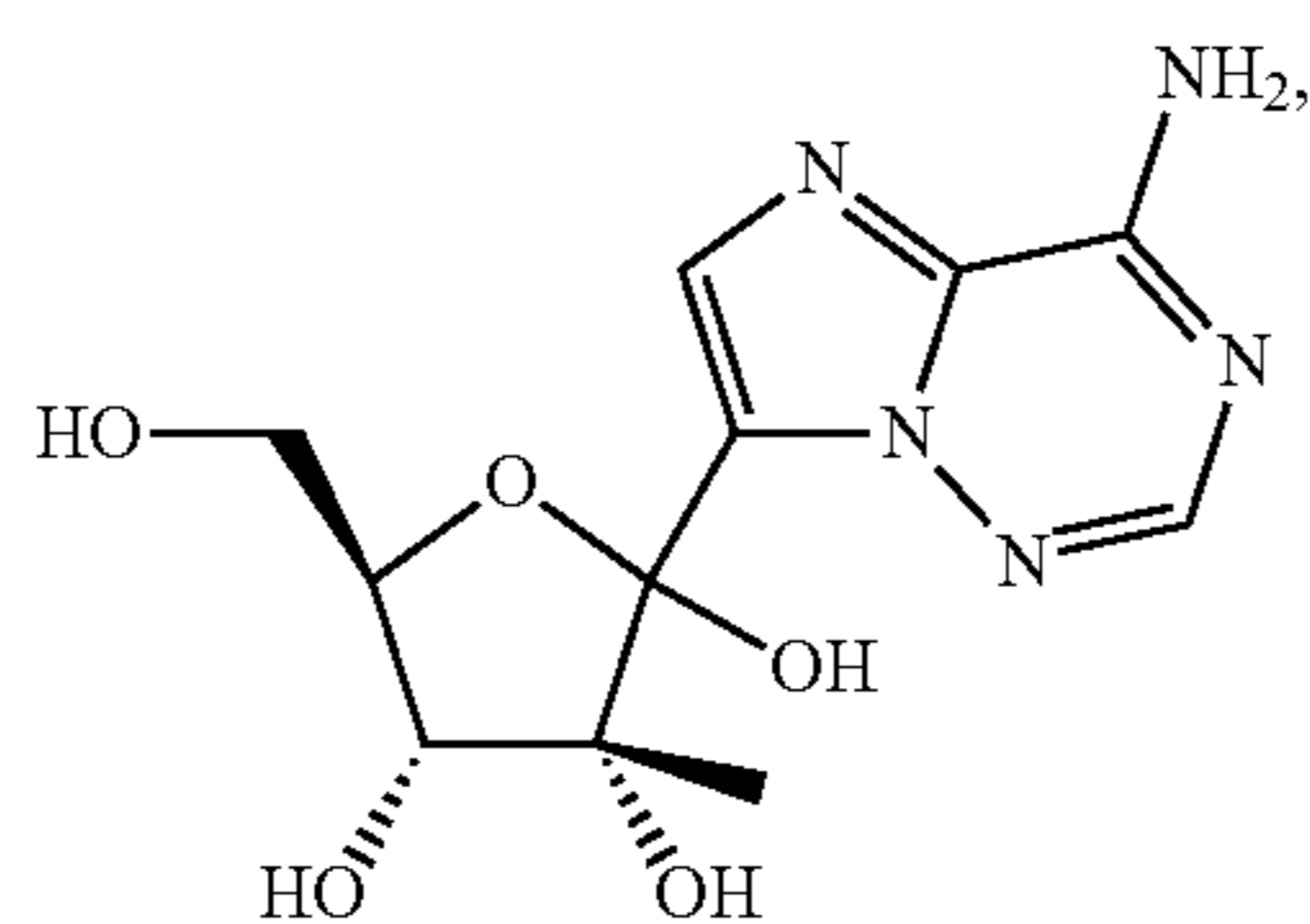
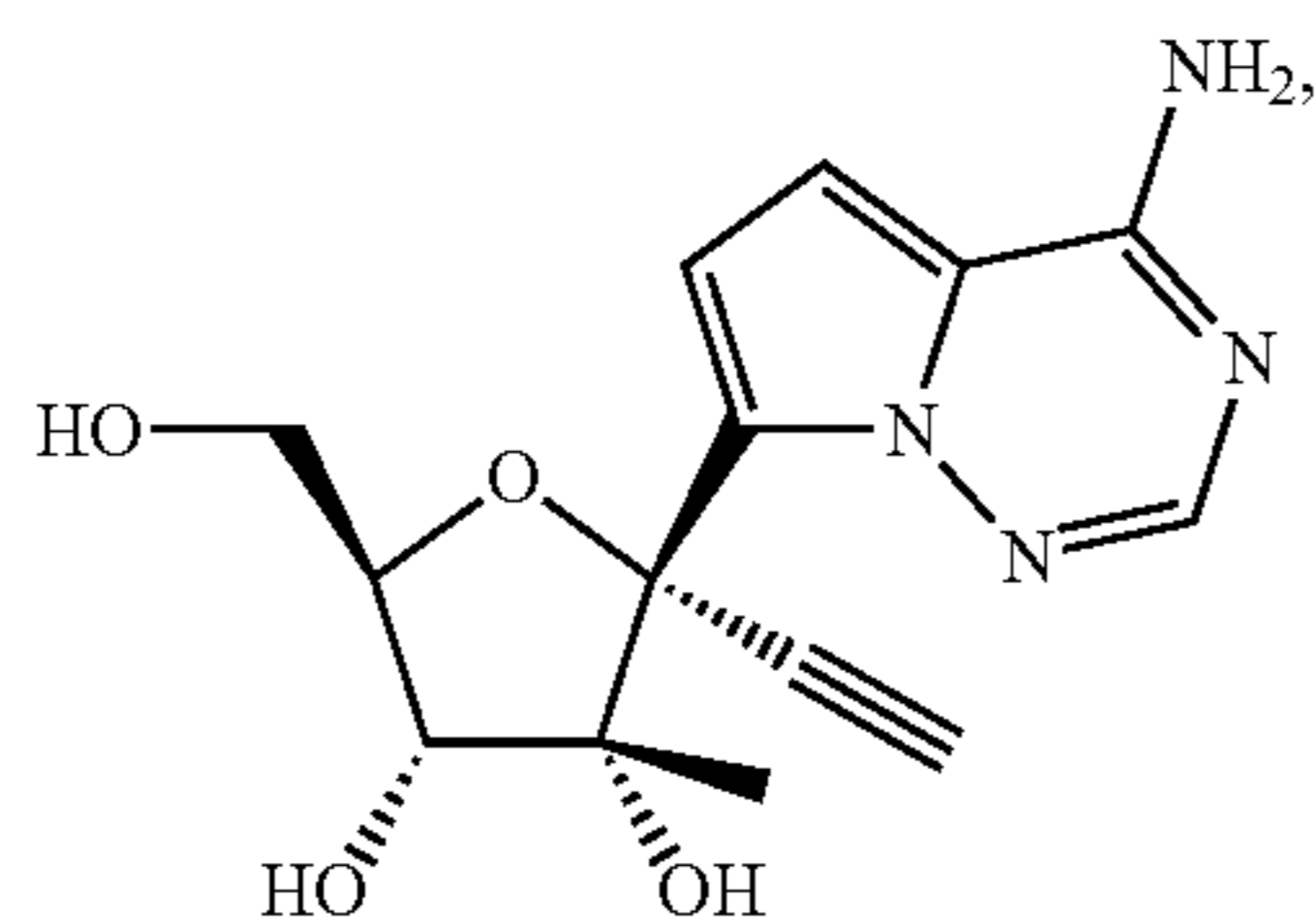
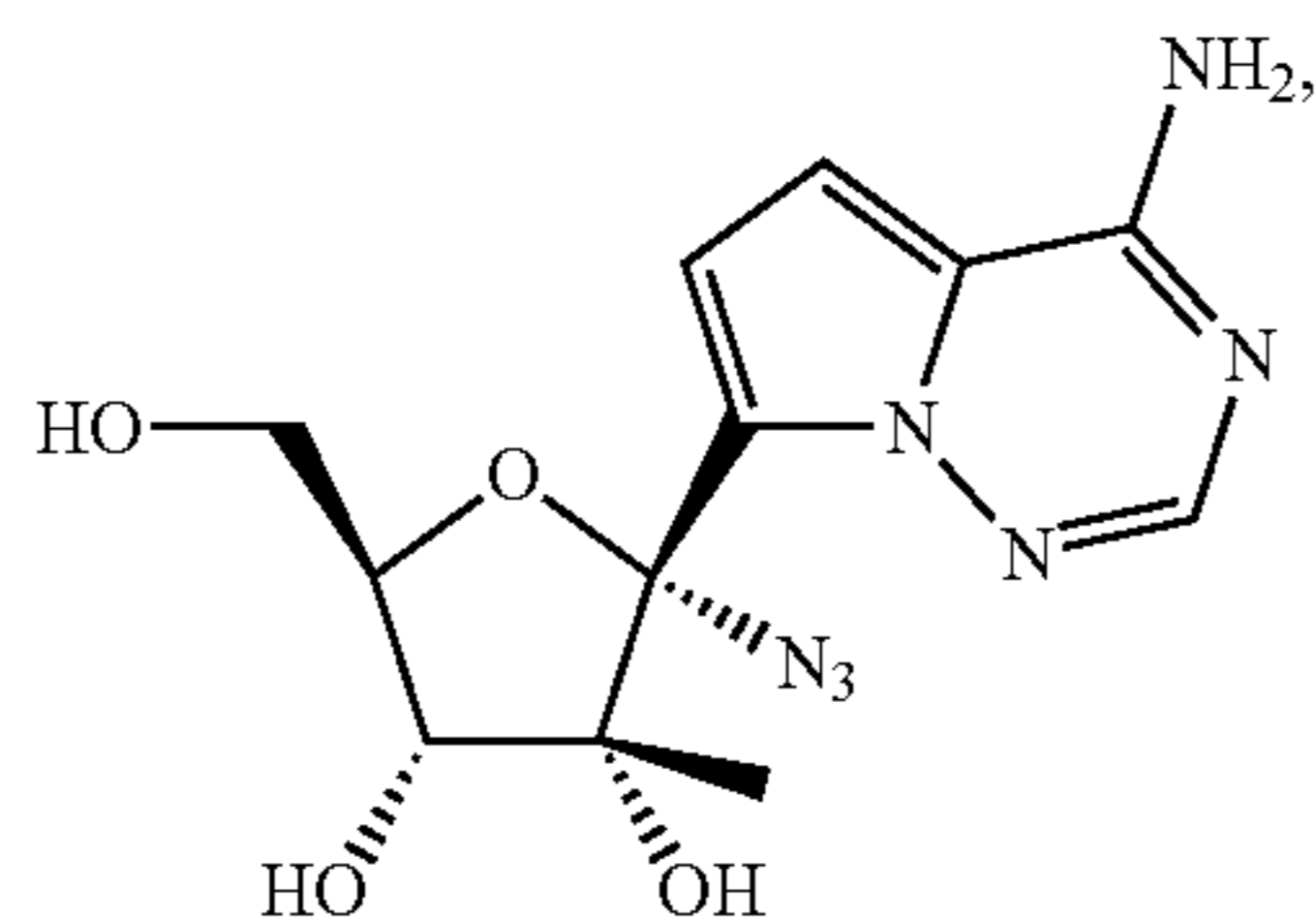
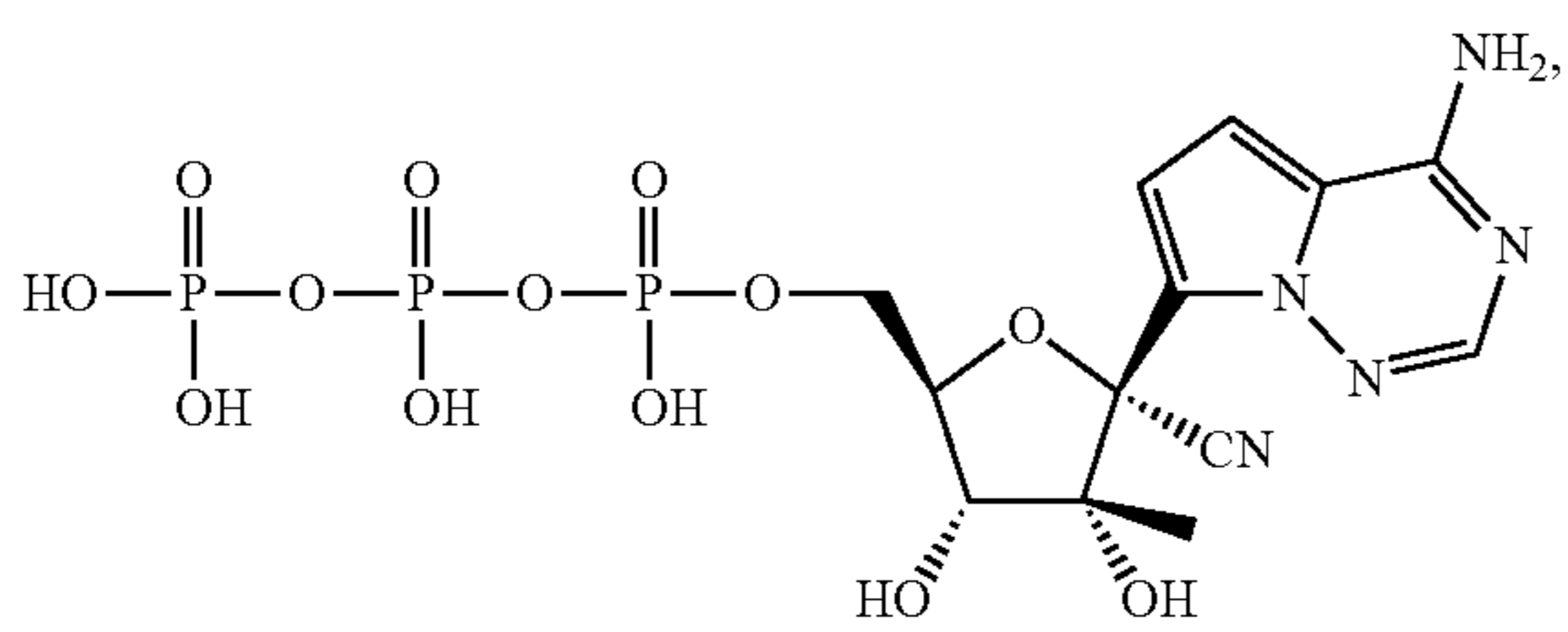
5 X1c.X2a.X3c.B1, X1c.X2a.X3c.B2, X1c.X2a.X3c.B3, X1c.X2a.X3c.B4,
 X1c.X2b.X3a.B1, X1c.X2b.X3a.B2, X1c.X2b.X3a.B3, X1c.X2b.X3a.B4,
 X1c.X2b.X3b.B1, X1c.X2b.X3b.B2, X1c.X2b.X3b.B3, X1c.X2b.X3b.B4,
 10 X1c.X2b.X3c.B1, X1c.X2b.X3c.B2, X1c.X2b.X3c.B3, X1c.X2b.X3c.B4,
 X1c.X2c.X3a.B1, X1c.X2c.X3a.B2, X1c.X2c.X3a.B3, X1c.X2c.X3a.B4,
 X1c.X2c.X3b.B1, X1c.X2c.X3b.B2, X1c.X2c.X3b.B3, X1c.X2c.X3b.B4,
 X1c.X2c.X3c.B1, X1c.X2c.X3c.B2, X1c.X2c.X3c.B3, X1c.X2c.X3c.B4,
 15 X1d.X2a.X3a.B1, X1d.X2a.X3a.B2, X1d.X2a.X3a.B3, X1d.X2a.X3a.B4,
 X1d.X2a.X3b.B1, X1d.X2a.X3b.B2, X1d.X2a.X3b.B3, X1d.X2a.X3b.B4,
 X1d.X2a.X3c.B1, X1d.X2a.X3c.B2, X1d.X2a.X3c.B3, X1d.X2a.X3c.B4.

20 In another embodiment, Formulas I-III is a compound selected from the group consisting of



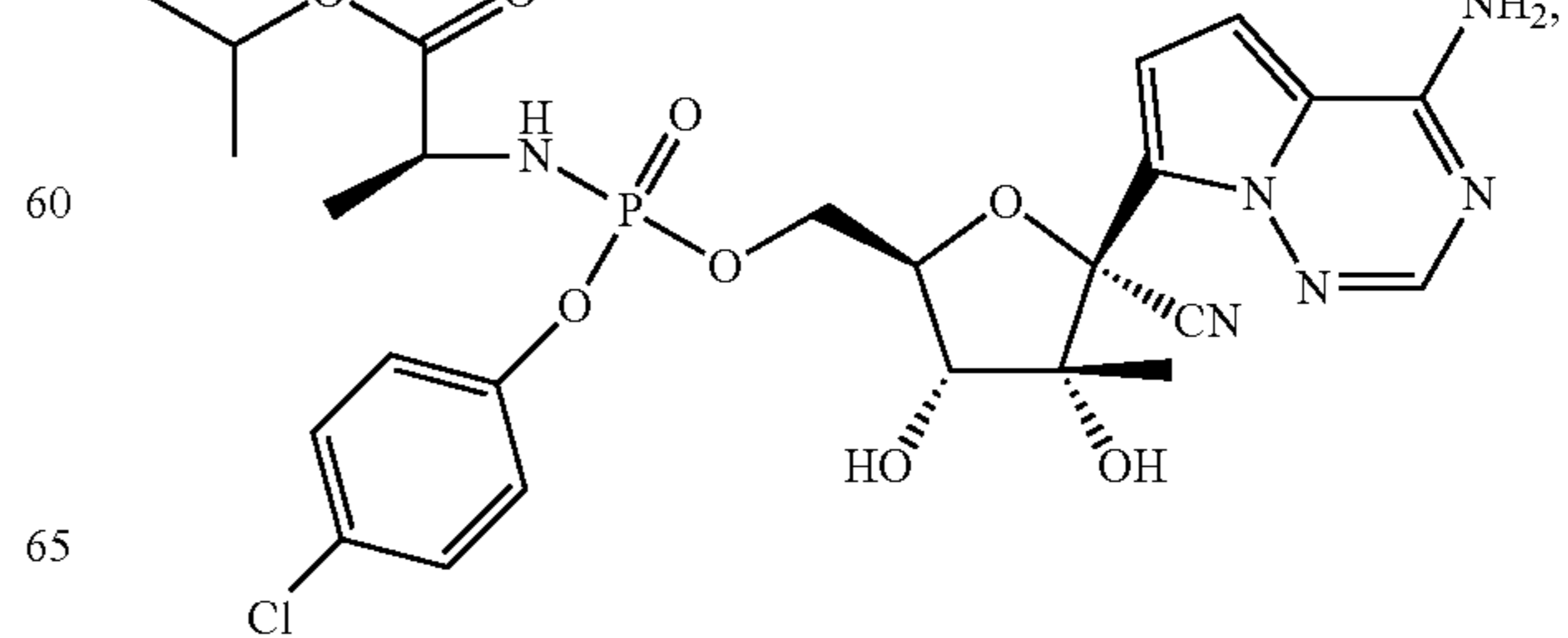
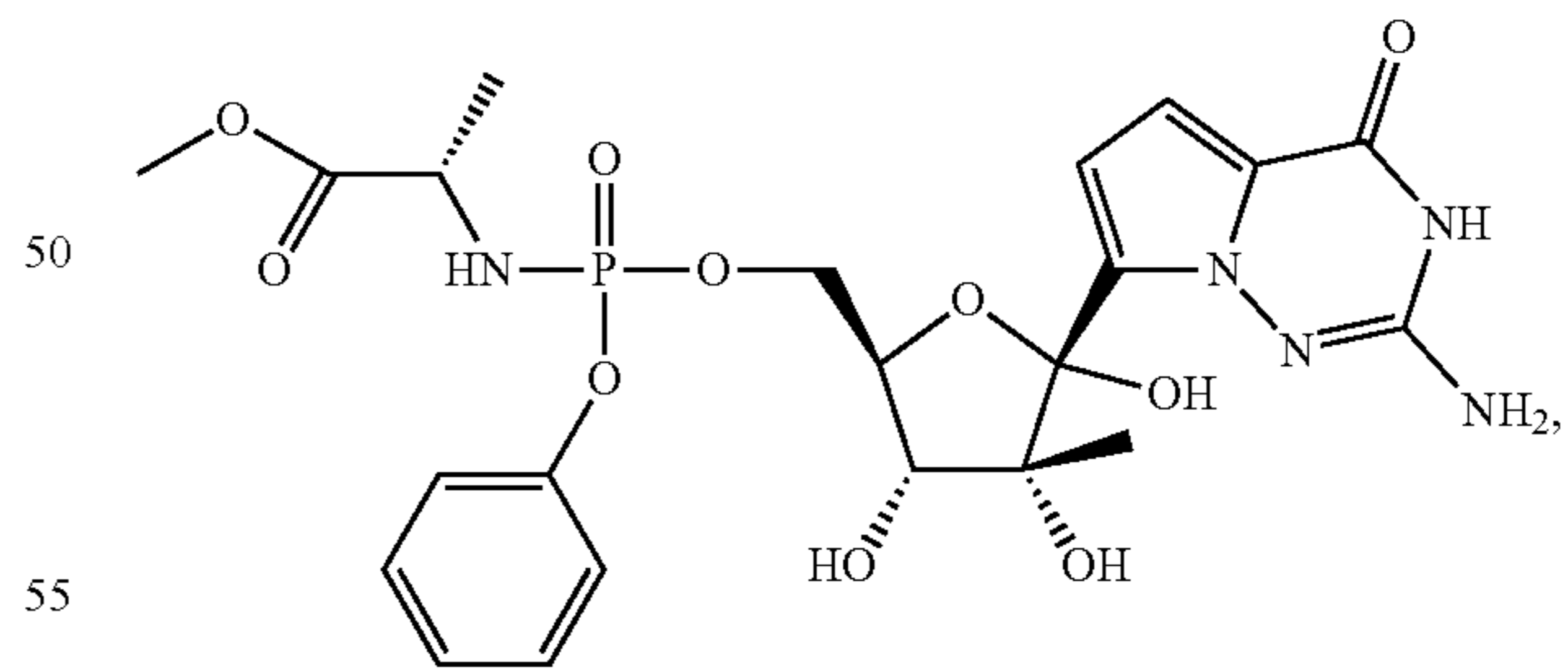
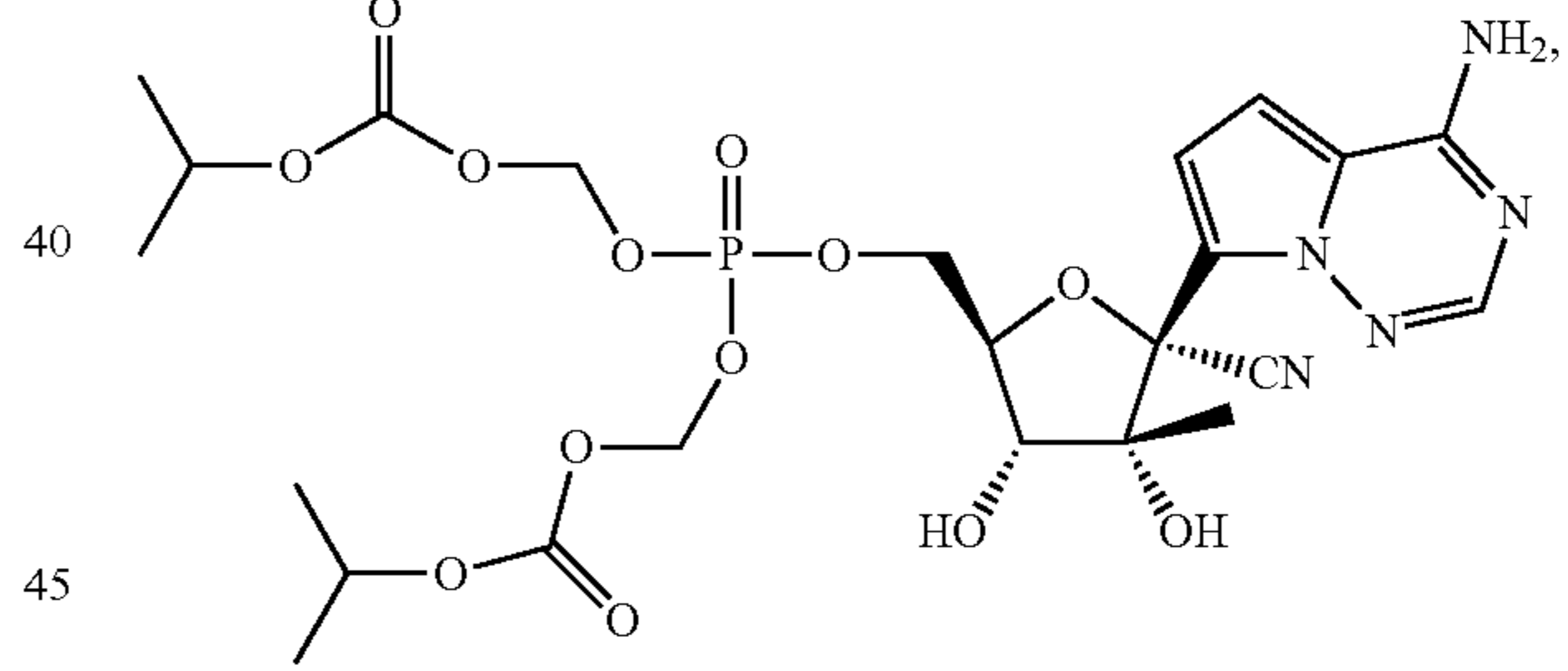
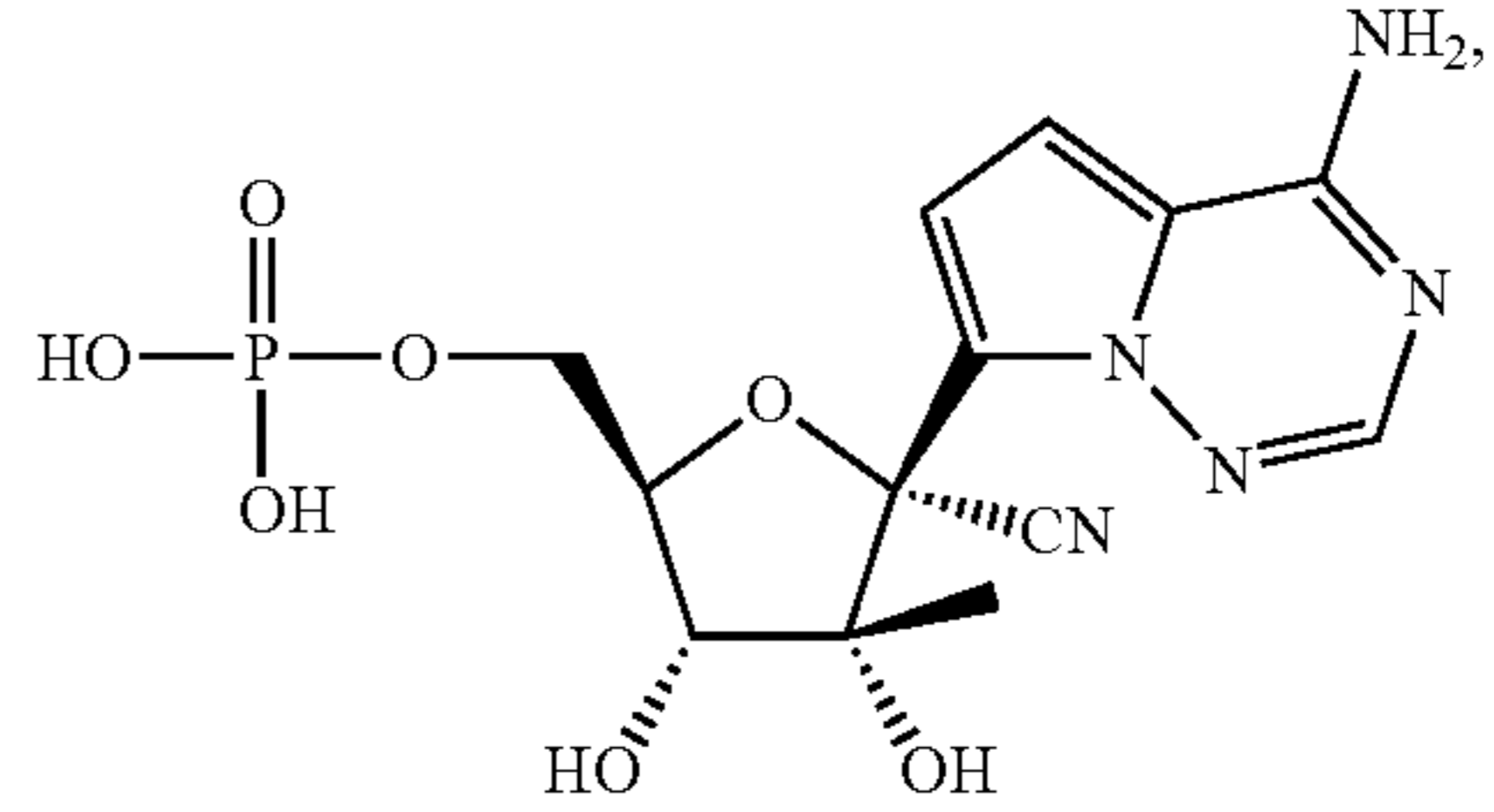
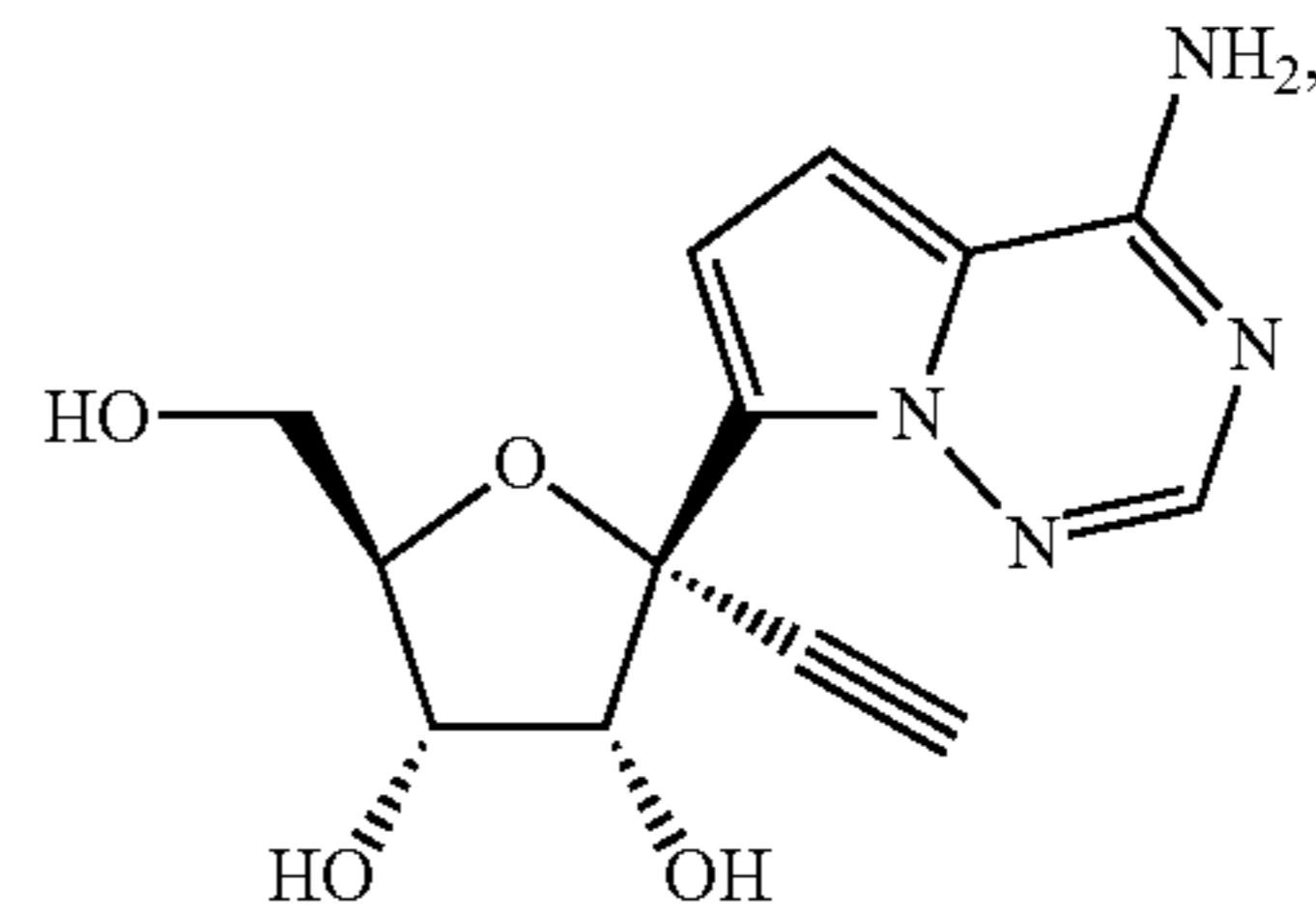
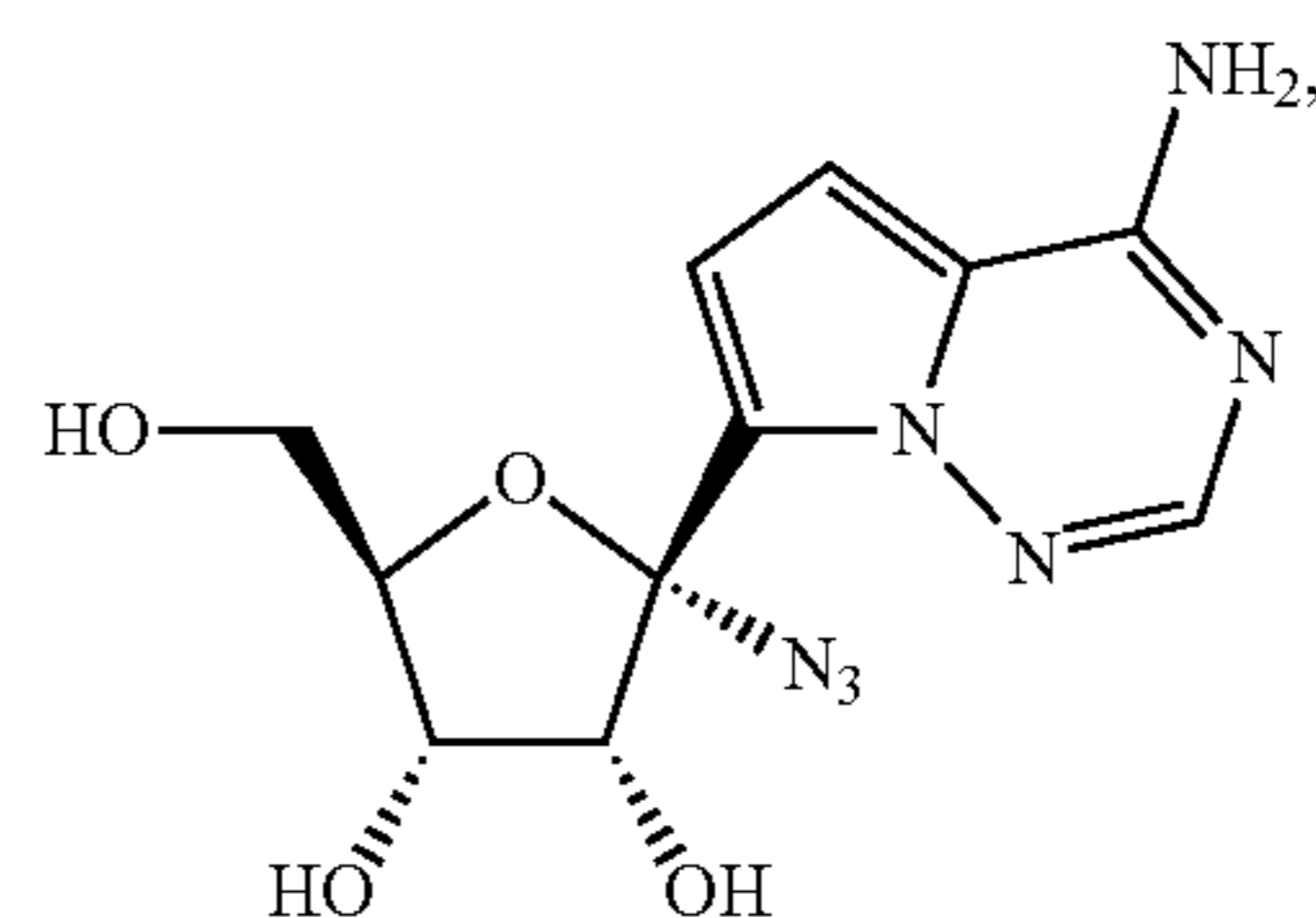
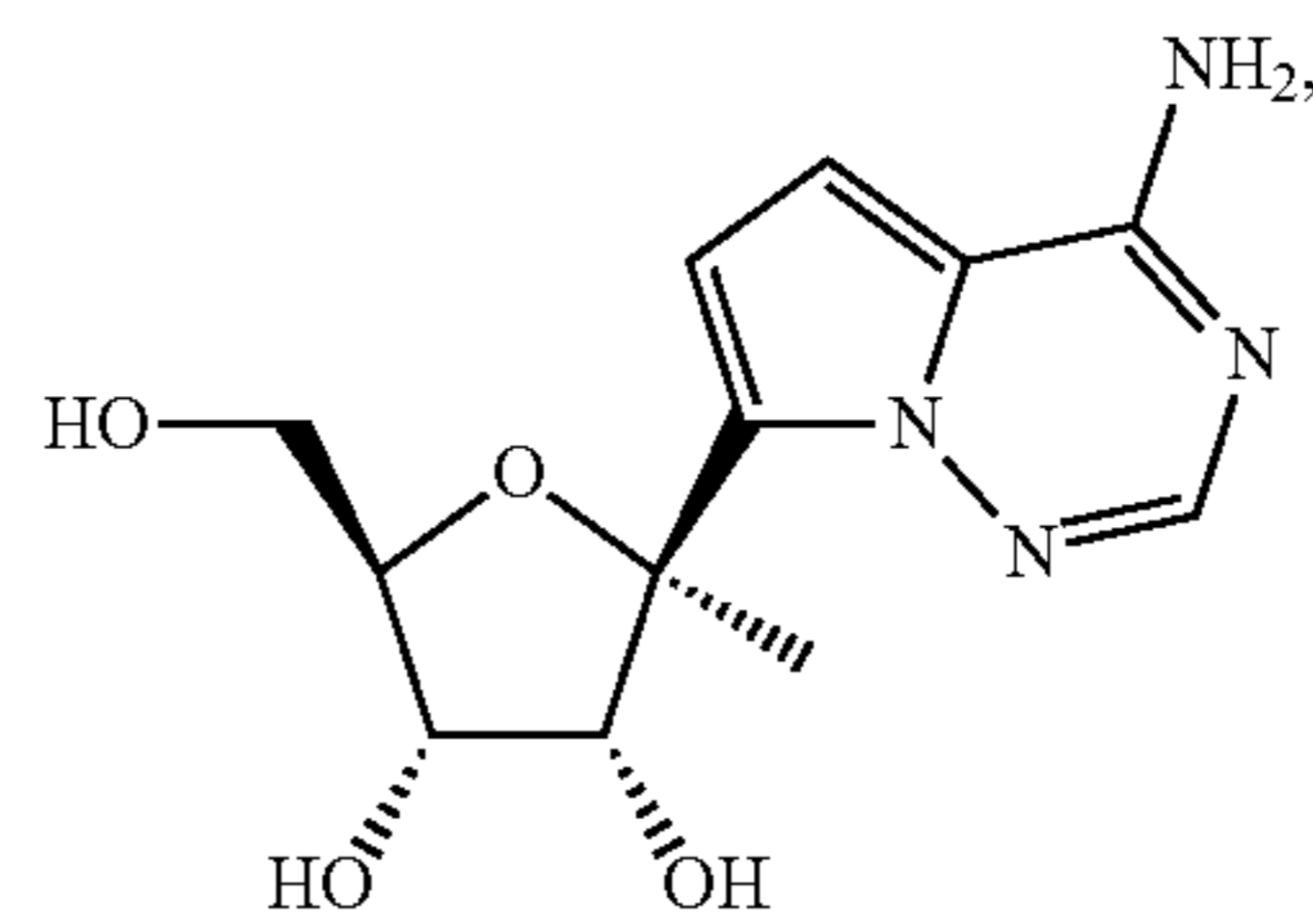
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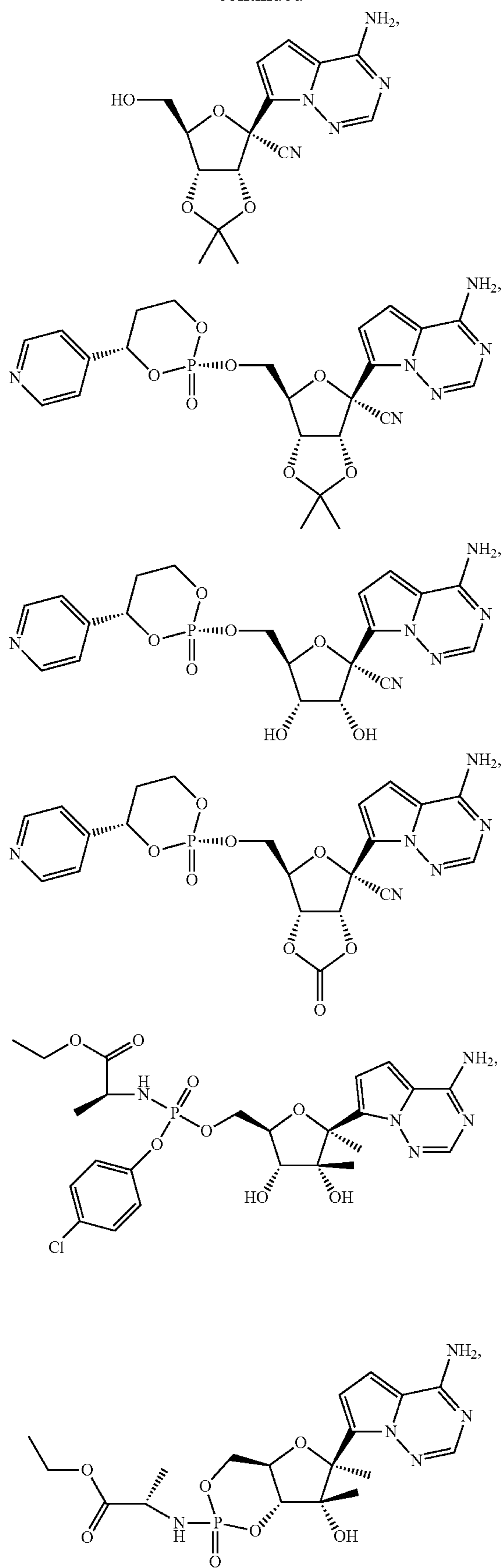
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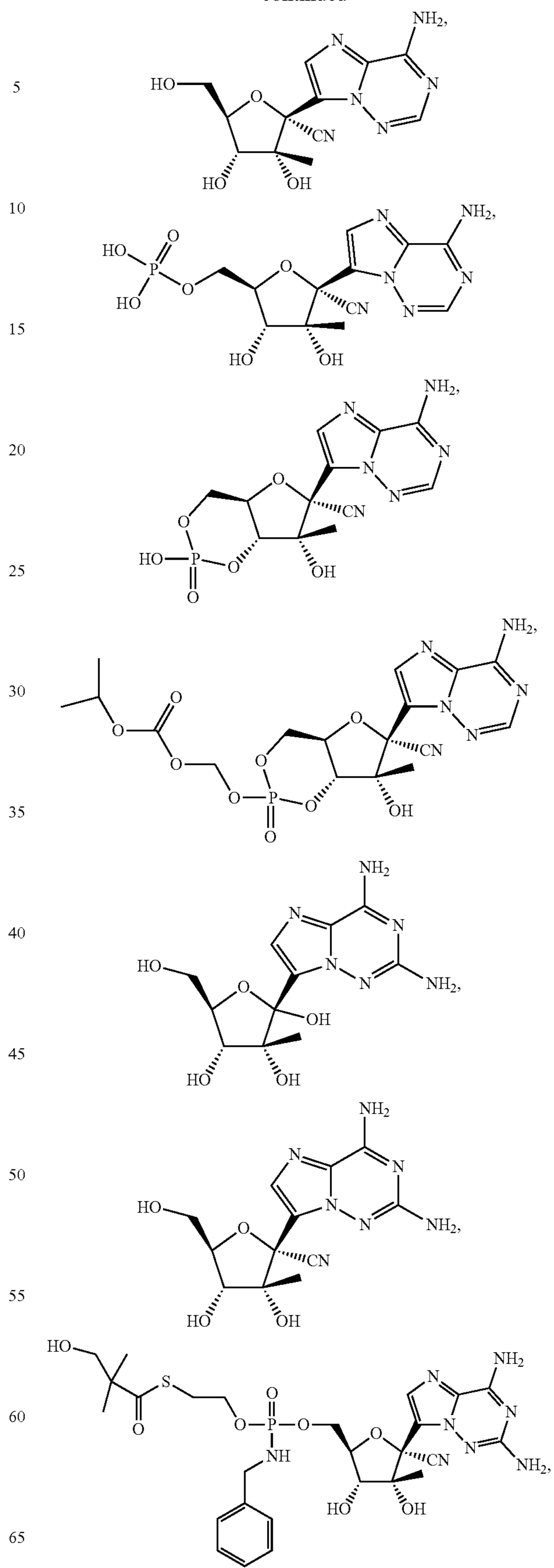
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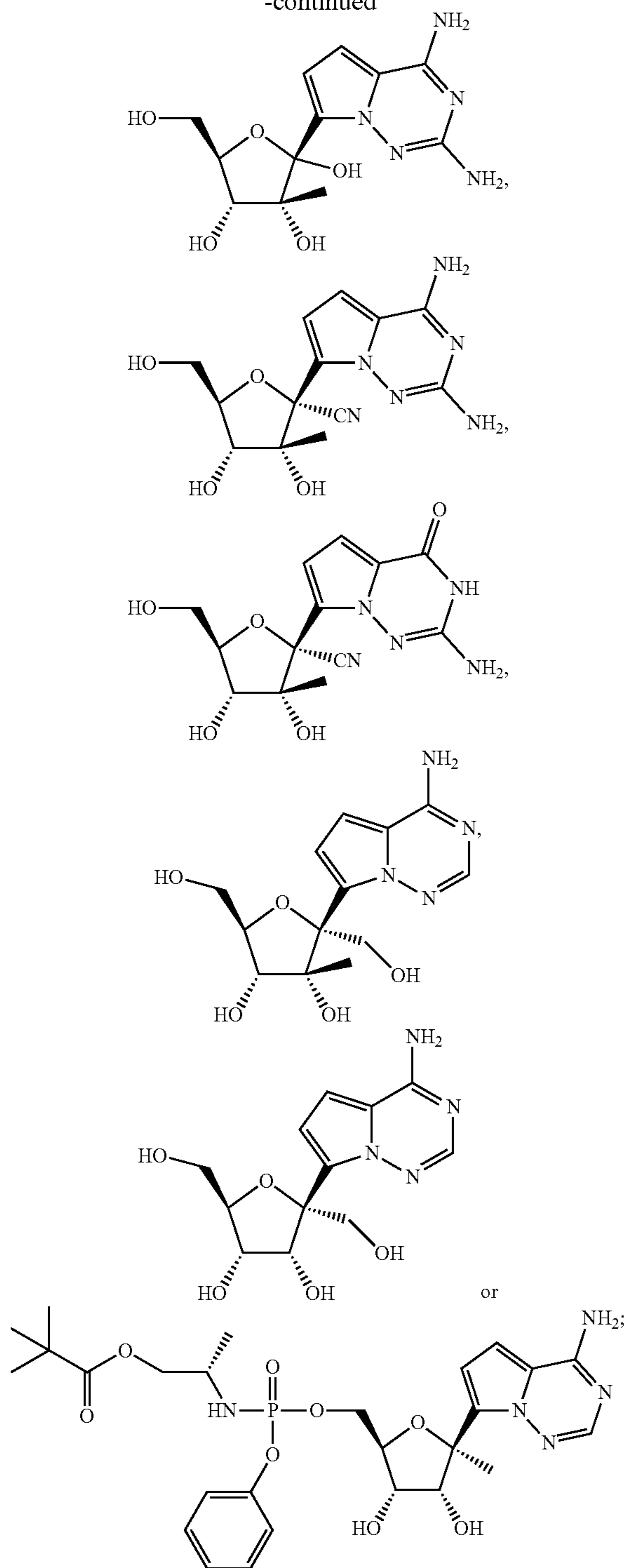
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or a pharmaceutically acceptable salt thereof.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

As used herein, "a compound of the invention" or "a compound of Formula I" means a compound of Formula I or

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a pharmaceutically acceptable salt, thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of Formula (number)" means a compound of that formula and pharmaceutically acceptable salts, thereof.

5 "Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkyl), 1 to 8 carbon atoms (i.e., C₁-C₈ alkyl), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, —CH₃), ethyl (Et, —CH₂CH₃), 1-propyl (n-Pr, n-propyl, —CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, —CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, —CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, —CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, —CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, —C(CH₃)₃), 1-pentyl (n-pentyl, —CH₂CH₂CH₂CH₂CH₃), 2-pentyl (—CH(CH₃)CH₂CH₂CH₃), 3-pentyl (—CH(CH₂CH₃)₂), 2-methyl-2-butyl (—C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (—CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (—CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (—CH₂CH(CH₃)CH₂CH₃), 1-hexyl (—CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (—CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (—CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (—C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (—CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (—CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (—C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (—CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (—C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (—CH(CH₃)C(CH₃)₃), and octyl ((—CH₂)₇CH₃).

30 "Alkoxy" means a group having the formula —O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (i.e., C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (—O—CH₃ or -OMe), ethoxy (—OCH₂CH₃ or -OEt), t-butoxy (—O—C(CH₃)₃ or -OtBu) and the like.

40 "Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (i.e., C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (i.e., C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (i.e., C₁-C₆ haloalkyl). Examples of suitable haloalkyl groups include, but are not limited to, —CF₃, —CHF₂, —CFH₂, —CH₂CF₃, and the like.

50 "Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp² double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (i.e., C₂-C₈ alkenyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (—CH=CH₂), allyl (—CH₂CH=CH₂), cyclopentenyl (—C₅H₇), and 5-hexenyl (—CH₂CH₂CH₂CH₂CH=CH₂).

60 "Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (i.e., C₂-C₈ alkynyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (—CH≡CH), propargyl (—CH₂C≡CH), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent

radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene ($-\text{CH}_2-$), 1,1-ethyl ($-\text{CH}(\text{CH}_3)-$), 1,2-ethyl ($-\text{CH}_2\text{CH}_2-$), 1,1-propyl ($-\text{CH}(\text{CH}_2\text{CH}_3)-$), 1,2-propyl ($-\text{CH}_2\text{CH}(\text{CH}_3)-$), 1,3-propyl ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1,4-butyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), and the like.

“Alkenylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, an alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene ($-\text{CH}=\text{CH}-$).

“Alkynylene” refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene ($-\text{C}\equiv\text{C}-$), propargyl ($-\text{CH}_2\text{C}\equiv\text{C}-$), and 4-pentynyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-$).

“Amino” refers generally to a nitrogen radical which can be considered a derivative of ammonia, having the formula $-\text{N}(\text{X})_2$, where each “X” is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, etc. The hybridization of the nitrogen is approximately sp^3 . Nonlimiting types of amino include $-\text{NH}_2$, $-\text{N}(\text{alkyl})_2$, $-\text{NH}(\text{alkyl})$, $-\text{N}(\text{carbocyclyl})_2$, $-\text{NH}(\text{carbocyclyl})$, $-\text{N}(\text{heterocyclyl})_2$, $-\text{NH}(\text{heterocyclyl})$, $-\text{N}(\text{aryl})_2$, $-\text{NH}(\text{aryl})$, $-\text{N}(\text{alkyl})(\text{aryl})$, $-\text{N}(\text{alkyl})(\text{heterocyclyl})$, $-\text{N}(\text{carbocyclyl})(\text{heterocyclyl})$, $-\text{N}(\text{aryl})(\text{heteroaryl})$, $-\text{N}(\text{alkyl})(\text{heteroaryl})$, etc. The term “alkylamino” refers to an amino group substituted with at least one alkyl group. Nonlimiting examples of amino groups include NH_2 , $-\text{NH}(\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{NH}(\text{phenyl})$, $-\text{N}(\text{phenyl})_2$, $-\text{NH}(\text{benzyl})$, $-\text{N}(\text{benzyl})_2$, etc. Substituted alkylamino refers generally to alkylamino groups, as defined above, in which at least one substituted alkyl, as defined herein, is attached to the amino nitrogen atom. Non-limiting examples of substituted alkylamino includes $-\text{NH}(\text{alkylene-C}(\text{O})-\text{OH})$, $-\text{NH}(\text{alkylene-C}(\text{O})-\text{O-alkyl})$, $-\text{N}(\text{alkylene-C}(\text{O})-\text{OH})_2$, $-\text{N}(\text{alkylene-C}(\text{O})-\text{O-alkyl})_2$, etc.

“Aryl” means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 10 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

“Arylalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 7 to 20 carbon atoms, e.g., the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

“Arylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 8 to 20 carbon atoms, e.g., the alkenyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

“Arylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 8 to 20 carbon atoms, e.g., the alkynyl moiety is 2 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

The term “substituted” in reference to alkyl, alkylene, aryl, arylalkyl, alkoxy, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, “substituted alkyl”, “substituted alkylene”, “substituted aryl”, “substituted arylalkyl”, “substituted heterocyclyl”, and “substituted carbocyclyl” means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, $-\text{X}$, $-\text{R}^b$, $-\text{O}^-$, $=\text{O}$, $-\text{OR}^b$, $-\text{SR}^b$, $-\text{S}^-$, $-\text{NR}^b_2$, $-\text{N}^+\text{R}^b_3$, $=\text{NR}^b$, $-\text{CX}_3$, $-\text{CN}$, $-\text{OCN}$, $-\text{SCN}$, $-\text{N}=\text{C}=\text{O}$, $-\text{NCS}$, $-\text{NO}$, $-\text{NO}_2$, $=\text{N}_2$, $-\text{N}_3$, $-\text{NHC}(=\text{O})\text{R}^b$, $-\text{OC}(=\text{O})\text{R}^b$, $-\text{NHC}(=\text{O})\text{NR}^b_2$, $-\text{S}(=\text{O})_2-$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{S}(=\text{O})_2\text{R}^b$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{S}(\text{O})_2\text{NR}^b_2$, $-\text{S}(=\text{O})\text{R}^b$, $-\text{OP}(=\text{O})(\text{OR}^b)_2$, $-\text{P}(=\text{O})(\text{OR}^b)_2$, $-\text{P}(=\text{O})(\text{O}^-)_2$, $-\text{P}(=\text{O})(\text{OH})_2$, $-\text{P}(\text{O})(\text{OR}^b)(\text{O}^-)$, $-\text{C}(=\text{O})\text{R}^b$, $-\text{C}(=\text{O})\text{X}$, $-\text{C}(\text{S})\text{R}^b$, $-\text{C}(\text{O})\text{OR}^b$, $-\text{C}(\text{O})\text{O}^-$, $-\text{C}(\text{S})\text{OR}^b$, $-\text{C}(\text{O})\text{SR}^b$, $-\text{C}(\text{S})\text{SR}^b$, $-\text{C}(\text{O})\text{NR}^b_2$, $-\text{C}(\text{S})\text{NR}^b_2$, $-\text{C}(=\text{NR}^b)\text{NR}^b_2$, where each X is independently a halogen: F, Cl, Br, or I; and each R^b is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. Unless otherwise indicated, when the term “substituted” is used in conjunction with groups such as arylalkyl, which have two or more moieties capable of substitution, the substituents can be attached to the aryl moiety, the alkyl moiety, or both.

The term “prodrug” as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

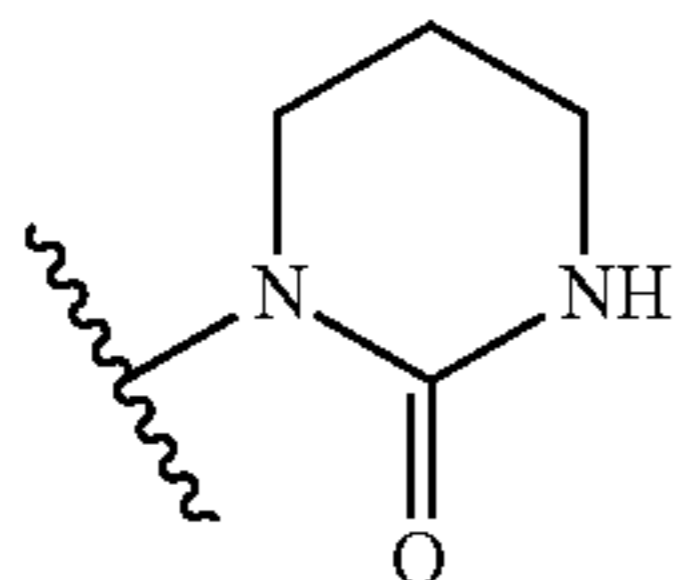
One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I-III should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I-III which have such stability are contemplated as falling within the scope of the present invention.

“Heteroalkyl” refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl

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groups are, respectively, an alkoxy group (e.g., $-\text{OCH}_3$, etc.), an amine (e.g., $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, etc.), or a thioalkyl group (e.g., $-\text{SCH}_3$). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., $-\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_3$, etc.), an alkyl amine (e.g., $-\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, etc.), or a thioalkyl ether (e.g., $-\text{CH}_2-\text{S}-\text{CH}_3$). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., $-\text{CH}_2\text{CH}_2-\text{OH}$), an aminoalkyl group (e.g., $-\text{CH}_2\text{NH}_2$), or an alkyl thiol group (e.g., $-\text{CH}_2\text{CH}_2-\text{SH}$). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A $\text{C}_1\text{-C}_6$ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

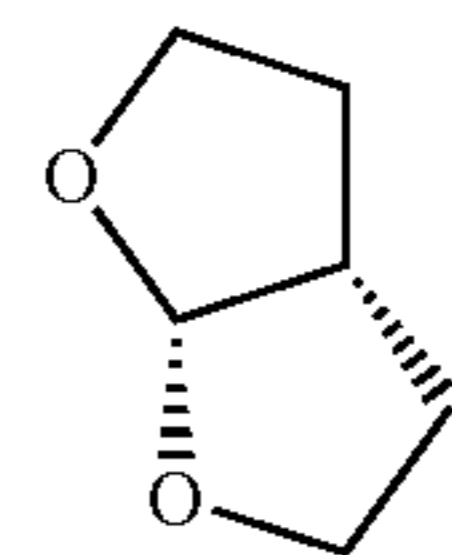
"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (e.g. 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (e.g. O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings, partially unsaturated rings, and aromatic rings (i.e., heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



Examples of heterocycles include by way of example and not limitation pyridyl, dihydropyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolynyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl,

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benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolynyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidene, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (i.e., a heterocyclyl-alkylene- moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl- CH_2- , 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkyl group comprises 3 to 20 carbon atoms, e.g., the alkyl portion of the arylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidinylmethyl, pyrazinylmethyl, etc.

"Heterocyclylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also a sp^2 carbon atom, is replaced with a heterocyclyl radical (i.e., a

heterocyclyl-alkenylene-moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkenyl group comprises 4 to 20 carbon atoms, e.g., the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

“Heterocyclylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (i.e., a heterocyclyl-alkynylene-moiety). The heterocyclyl portion of the heterocyclyl alkynyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocyclyl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclyl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclyl alkynyl group comprises 4 to 20 carbon atoms, e.g., the alkynyl portion of the heterocyclyl alkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 2 to 14 carbon atoms.

“Heteroaryl” refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those aromatic rings listed in the definition of “heterocyclyl”, including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

“Carbocycle” or “carbocyclyl” refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 7 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo[4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo[5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl, tetrahydronaphthalene, and decaline.

“Carbocyclalkyl” refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom is replaced with a carbocyclyl radical as described herein. Typical, but non-limiting, examples of carbocyclalkyl groups include cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

“Arylheteroalkyl” refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached

either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

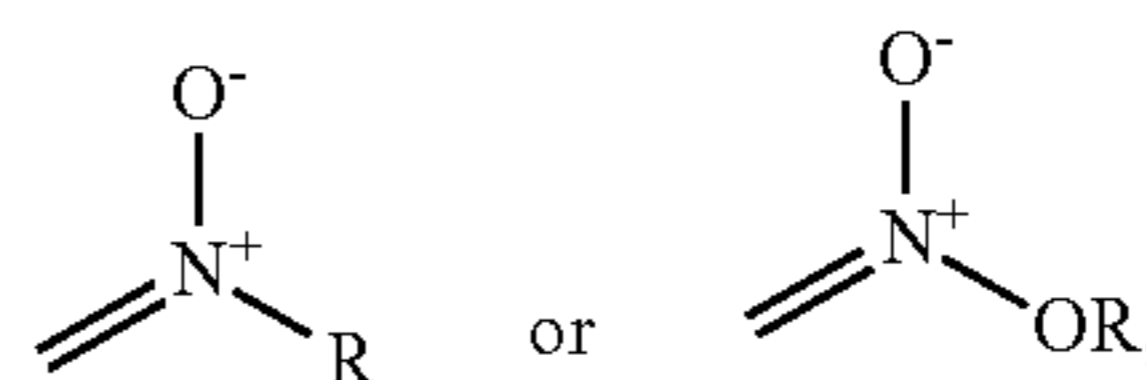
“Heteroarylalkyl” refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include $-\text{CH}_2$ -pyridinyl, $-\text{CH}_2$ -pyrrolyl, $-\text{CH}_2$ -oxazolyl, $-\text{CH}_2$ -indolyl, $-\text{CH}_2$ -isoindolyl, $-\text{CH}_2$ -purinyl, $-\text{CH}_2$ -furanyl, $-\text{CH}_2$ -thienyl, $-\text{CH}_2$ -benzofuranyl, $-\text{CH}_2$ -benzothiophenyl, $-\text{CH}_2$ -carbazolyl, $-\text{CH}_2$ -imidazolyl, $-\text{CH}_2$ -thiazolyl, $-\text{CH}_2$ -isoxazolyl, $-\text{CH}_2$ -pyrazolyl, $-\text{CH}_2$ -isothiazolyl, $-\text{CH}_2$ -quinolyl, $-\text{CH}_2$ -isoquinolyl, $-\text{CH}_2$ -pyridazyl, $-\text{CH}_2$ -pyrimidyl, $-\text{CH}_2$ -pyrazyl, $-\text{CH}(\text{CH}_3)$ -pyridinyl, $-\text{CH}(\text{CH}_3)$ -pyrrolyl, $-\text{CH}(\text{CH}_3)$ -oxazolyl, $-\text{CH}(\text{CH}_3)$ -indolyl, $-\text{CH}(\text{CH}_3)$ -isoindolyl, $-\text{CH}(\text{CH}_3)$ -purinyl, $-\text{CH}(\text{CH}_3)$ -furanyl, $-\text{CH}(\text{CH}_3)$ -thienyl, $-\text{CH}(\text{CH}_3)$ -benzofuranyl, $-\text{CH}(\text{CH}_3)$ -benzothiophenyl, $-\text{CH}(\text{CH}_3)$ -carbazolyl, $-\text{CH}(\text{CH}_3)$ -imidazolyl, $-\text{CH}(\text{CH}_3)$ -thiazolyl, $-\text{CH}(\text{CH}_3)$ -isoxazolyl, $-\text{CH}(\text{CH}_3)$ -pyrazolyl, $-\text{CH}(\text{CH}_3)$ -isothiazolyl, $-\text{CH}(\text{CH}_3)$ -quinolyl, $-\text{CH}(\text{CH}_3)$ -isoquinolyl, $-\text{CH}(\text{CH}_3)$ -pyridazyl, $-\text{CH}(\text{CH}_3)$ -pyrimidyl, $-\text{CH}(\text{CH}_3)$ -pyrazyl, etc.

The term “optionally substituted” in reference to a particular moiety of the compound of Formula I-III (e.g., an optionally substituted aryl group) refers to a moiety wherein all substituents are hydrogen or wherein one or more of the hydrogens of the moiety may be replaced by substituents such as those listed under the definition of “substituted”.

The term “optionally replaced” in reference to a particular moiety of the compound of Formula I-III (e.g., the carbon atoms of said $(\text{C}_1\text{-C}_8)$ alkyl may be optionally replaced by $-\text{O}-$, $-\text{S}-$, or $-\text{NR}^a-$) means that one or more of the methylene groups of the $(\text{C}_1\text{-C}_8)$ alkyl may be replaced by 0, 1, 2, or more of the groups specified (e.g., $-\text{O}-$, $-\text{S}-$, or $-\text{NR}^a-$).

The term “non-terminal carbon atom(s)” in reference to an alkyl, alkenyl, alkynyl, alkylene, alkenylene, or alkylenylene moiety refers to the carbon atoms in the moiety that intervene between the first carbon atom of the moiety and the last carbon atom in the moiety. Therefore, by way of example and not limitation, in the alkyl moiety $-\text{CH}_2(\text{C}^*)\text{H}_2(\text{C}^*)\text{H}_2\text{CH}_3$ or alkylene moiety $-\text{CH}_2(\text{C}^*)\text{H}_2(\text{C}^*)\text{H}_2\text{CH}_2-$ the C^* atoms would be considered to be the non-terminal carbon atoms.

Certain Y and Y^1 alternatives are nitrogen oxides such as $^+\text{N}(\text{O})(\text{R})$ or $^+\text{N}(\text{O})(\text{OR})$. These nitrogen oxides, as shown here attached to a carbon atom, can also be represented by charge separated groups such as

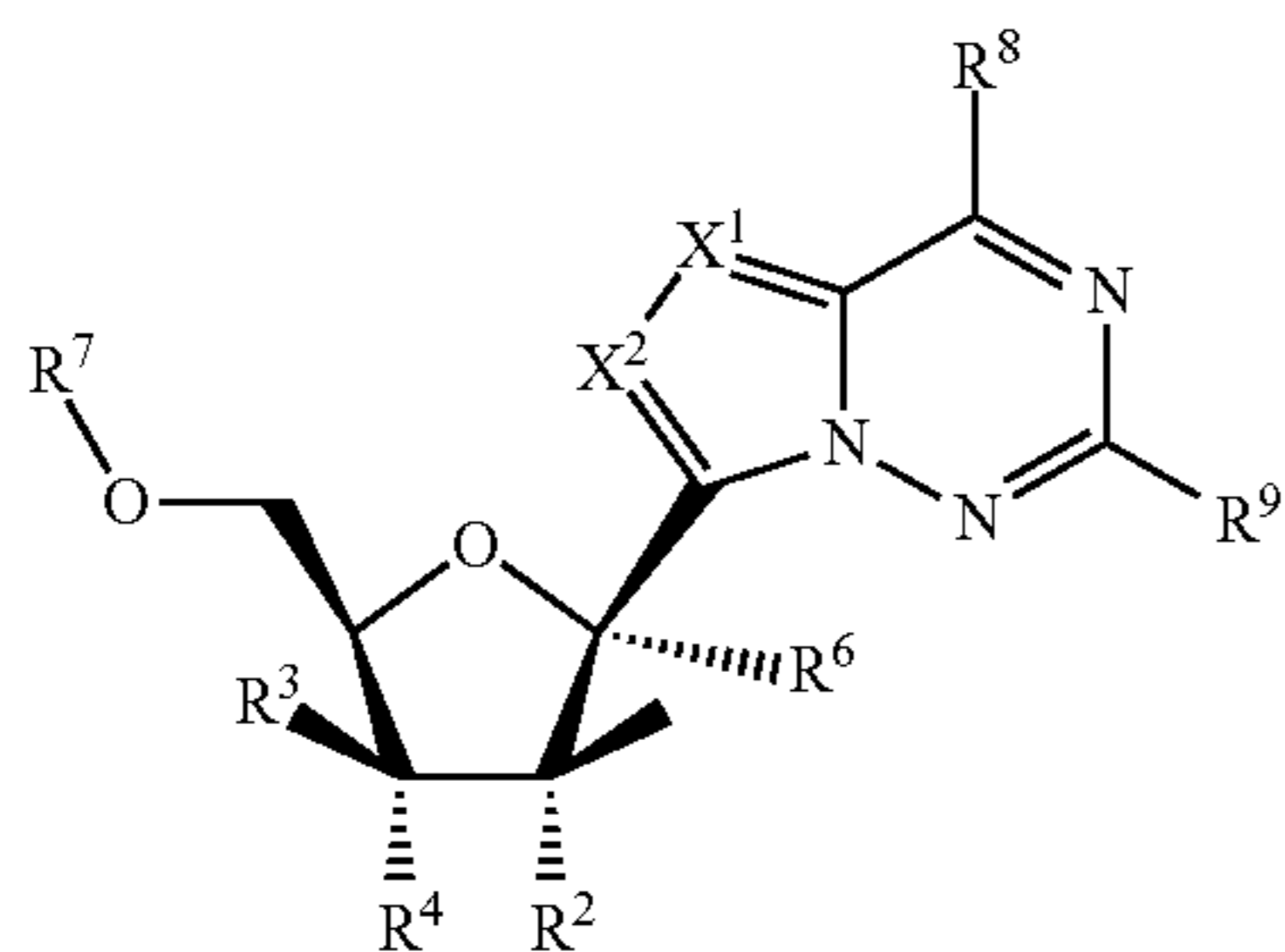


respectively, and are intended to be equivalent to the aforementioned representations for the purposes of describing this invention.

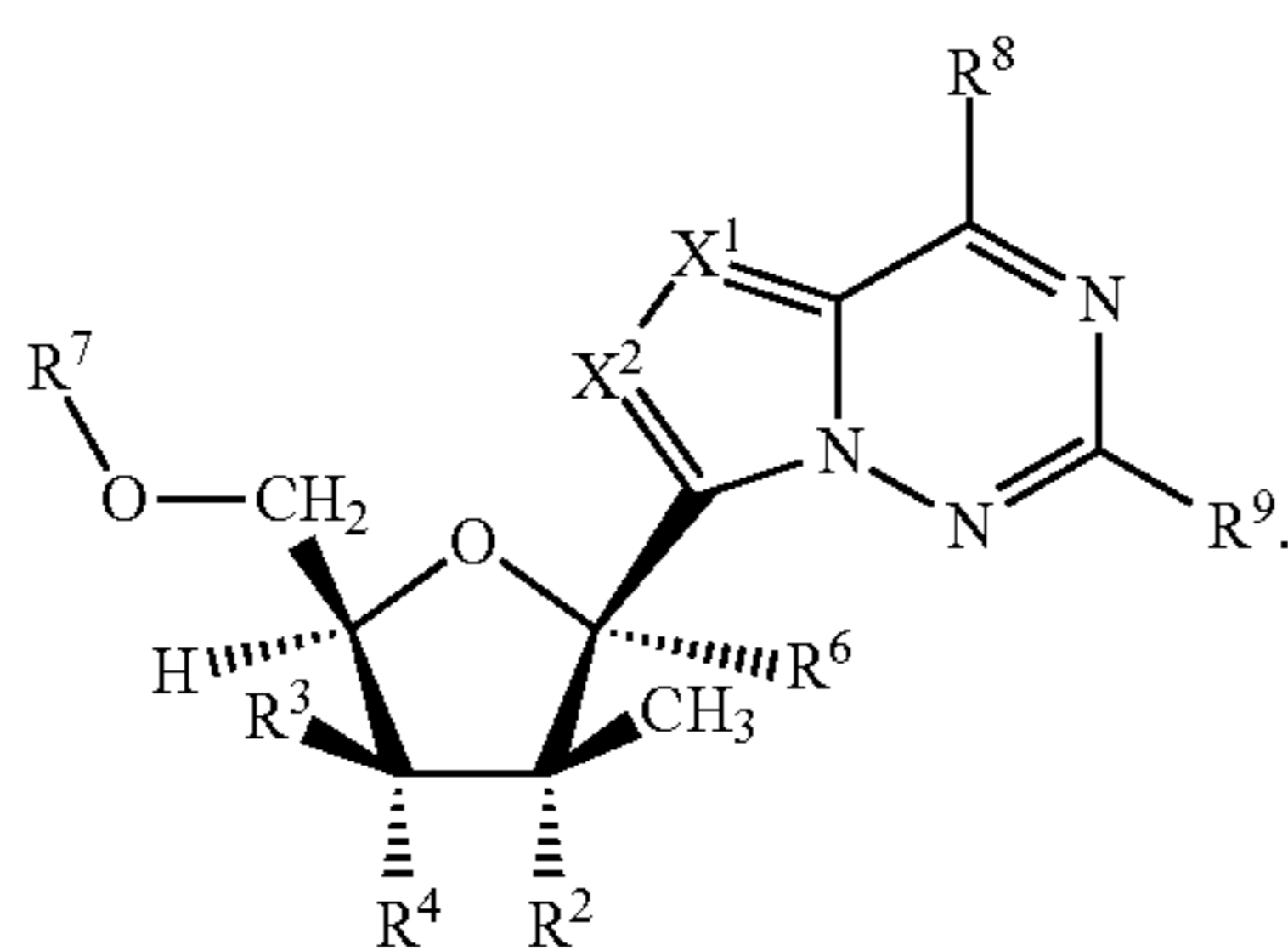
“Linker” or “link” means a chemical moiety comprising a covalent bond or a chain of atoms. Linkers include repeating units of alkyloxy (e.g. polyethyleneoxy, PEG, polymethyleneoxy) and alkylamino (e.g. polyethylenamine, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The terms such as “oxygen-linked”, “nitrogen-linked”, “carbon-linked”, “sulfur-linked”, or “phosphorous-linked” mean that if a bond between two moieties can be formed by using more than one type of atom in a moiety, then the bond formed between the moieties is through the atom specified. For example, a nitrogen-linked amino acid would be bonded through a nitrogen atom of the amino acid rather than through an oxygen or carbon atom of the amino acid.

Unless otherwise specified, the carbon atoms of the compounds of Formula I-III are intended to have a valence of four. In some chemical structure representations where carbon atoms do not have a sufficient number of variables attached to produce a valence of four, the remaining carbon substituents needed to provide a valence of four should be assumed to be hydrogen. For example,



has the same meaning as



“Protecting group” refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as an intermediate in the synthesis of the parental drug substance. Chemical protecting groups and strategies for protection/deprotection are well known in the art. See: “Protective Groups in Organic Chemistry”, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991). Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other

physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties in vitro and in vivo, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug in vivo. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency in vivo than the parental drug. Protecting groups are removed either in vitro, in the instance of chemical intermediates, or in vivo, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

“Prodrug moiety” means a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, “Design and Application of Prodrugs” in Textbook of Drug Design and Development (1991), P. Krosgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy.

A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{30}$ and acyloxymethyl carbonates $\text{CH}_2\text{C}(=\text{O})\text{OR}^{30}$ where R^{30} is C_1 - C_6 alkyl, C_1 - C_6 substituted alkyl, C_6 - C_{20} aryl or C_6 - C_{20} substituted aryl. The acyloxyalkyl ester was used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al (1983) J. Pharm. Sci. 72: 324; also U.S. Pat. Nos. 4,816,570, 4,968, 788, 5663159 and 5792756. In certain compounds of the invention, a prodrug moiety is part of a phosphate group. The acyloxyalkyl ester may be used to deliver phosphoric acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxy-carbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{C}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{C}(=\text{O})\text{OC}(\text{CH}_3)_3$.

The phosphate group may be a phosphate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to those comprising a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (DeLambert et al (1994) J. Med. Chem. 37: 498). Phenyl esters

containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the ortho- or para-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g. esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C—O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al (1992) *J. Chem. Soc. Perkin Trans.* I2345; Brook et al WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier et al WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al, U.S. Pat. No. 6,312,662).

It is to be noted that all enantiomers, diastereomers, and racemic mixtures, tautomers, polymorphs, pseudopolymorphs of compounds within the scope of Formula I, Formula II, or Formula III and pharmaceutically acceptable salts thereof are embraced by the present invention. All mixtures of such enantiomers and diastereomers are within the scope of the present invention.

A compound of Formula I-III and its pharmaceutically acceptable salts may exist as different polymorphs or pseudopolymorphs. As used herein, crystalline polymorphism means the ability of a crystalline compound to exist in different crystal structures. The crystalline polymorphism may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). As used herein, crystalline pseudopolymorphism means the ability of a hydrate or solvate of a compound to exist in different crystal structures. The pseudopolymorphs of the instant invention may exist due to differences in crystal packing (packing pseudopolymorphism) or due to differences in packing between different conformers of the same molecule (conformational pseudopolymorphism). The instant invention comprises all polymorphs and pseudopolymorphs of the compounds of Formula I-III and their pharmaceutically acceptable salts.

A compound of Formula I-III and its pharmaceutically acceptable salts may also exist as an amorphous solid. As used herein, an amorphous solid is a solid in which there is no long-range order of the positions of the atoms in the solid. This definition applies as well when the crystal size is two nanometers or less. Additives, including solvents, may be used to create the amorphous forms of the instant invention. The instant invention comprises all amorphous forms of the compounds of Formula I-III and their pharmaceutically acceptable salts.

Selected substituents comprising the compounds of Formula I-III are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number of com-

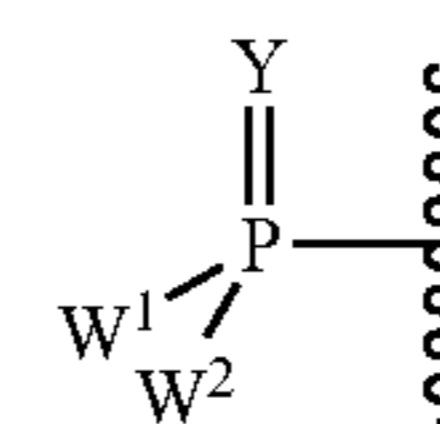
pounds may be present in any given embodiment. For example, R^x comprises a R^y substituent. R^y can be R. R can be W^3 . W^3 can be W^4 and W^4 can be R or comprise substituents comprising R^y . One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by way of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3 and R^y are recursive substituents in certain embodiments. Typically, each recursive substituent can independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given embodiment. More typically, each recursive substituent can independently occur 12 or fewer times in a given embodiment. Even more typically, each recursive substituent can independently occur 3 or fewer times in a given embodiment. For example, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times in a given embodiment. Even more typically, W^3 will occur 0 to 6 times and R^y will occur 0 to 4 times in a given embodiment.

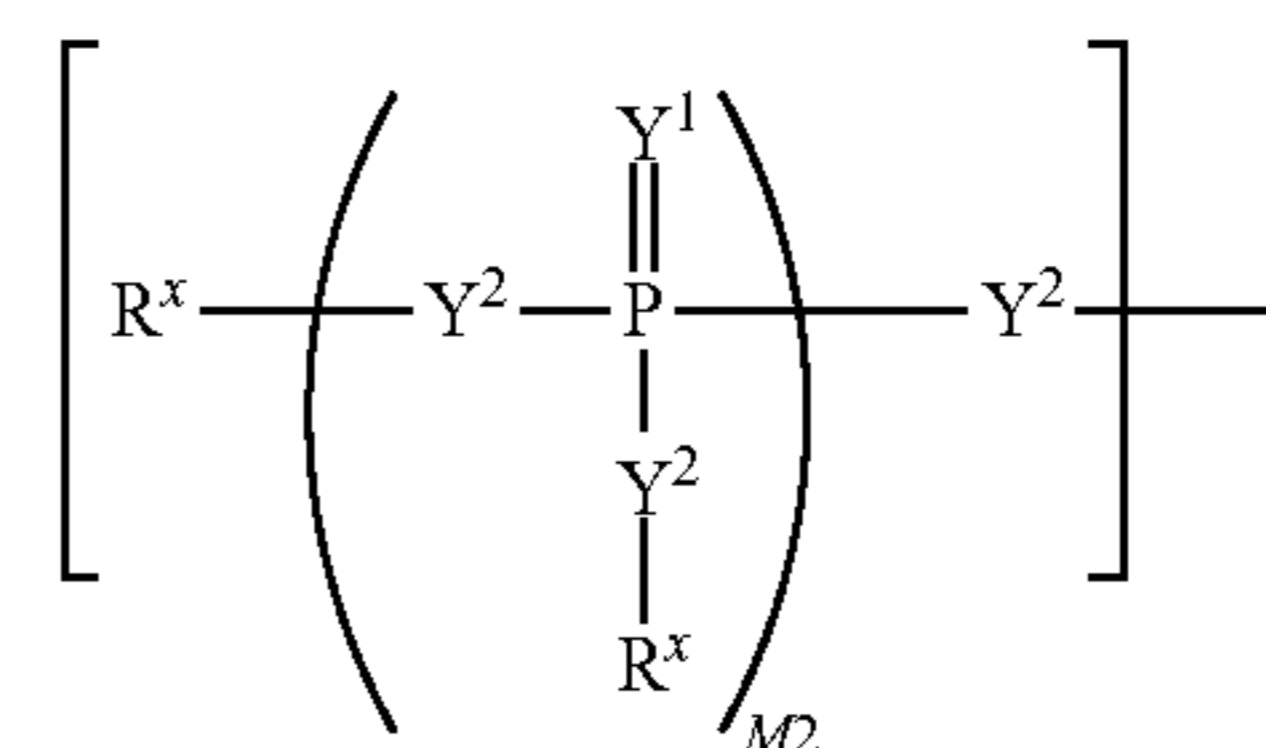
Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an embodiment of the invention, the total number will be determined as set forth above.

The modifier "about" used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with measurement of the particular quantity).

The compounds of the Formula I-III may comprise a phosphate group as R^7 , which may be a prodrug moiety



wherein each Y or Y^1 is, independently, O, S, NR, $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, or $N-NR_2$; W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$; or one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia; or W^1 and W^2 are each, independently, a group of Formula Ia:

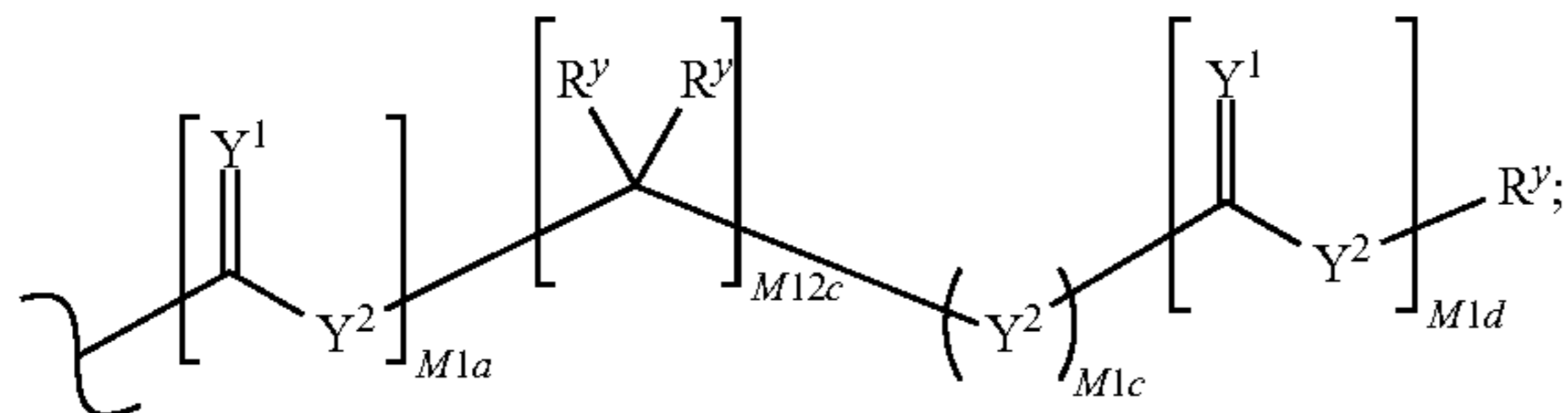


wherein:
 each Y^2 is independently a bond, O, CR_2 , NR, $+N(O)(R)$, $N(OR)$, $+N(O)(OR)$, $N-NR_2$, S, S—S, S(O), or S(O)₂;
 each Y^3 is independently O, S, or NR;
 M_2 is 0, 1 or 2;
 each R^y is independently H, F, Cl, Br, I, OH, R, $-C(Y^1)R$, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-N(R)_3$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$,

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—OC(=Y¹)R, —OC(=Y¹)OR, —OC(=Y¹)(N(R)₂),
 —SC(=Y¹)R, —SC(=Y¹)OR, —SC(=Y¹)(N(R)₂),
 —N(R)C(=Y¹)R, —N(R)C(=Y¹)OR, or —N(R)C(=Y¹)
 N(R)₂, —SO₂—NR₂, —CN, —N₃, —NO₂, —OR, a pro-
 5 protecting group or W³; or when taken together, two R^y on the
 same carbon atom form a carbocyclic ring of 3 to 7 carbon
 atoms;

each R^x is independently R^y, a protecting group, or the
 formula:



wherein:

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R is H, halogen, (C₁-C₈) alkyl, (C₁-C₈) substituted
 alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈)
 25 alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀
 substituted aryl, C₂-C₂₀ heterocycle, C₂-C₂₀ substituted het-
 erocyclyl, arylalkyl, substituted arylalkyl or a protecting
 group;

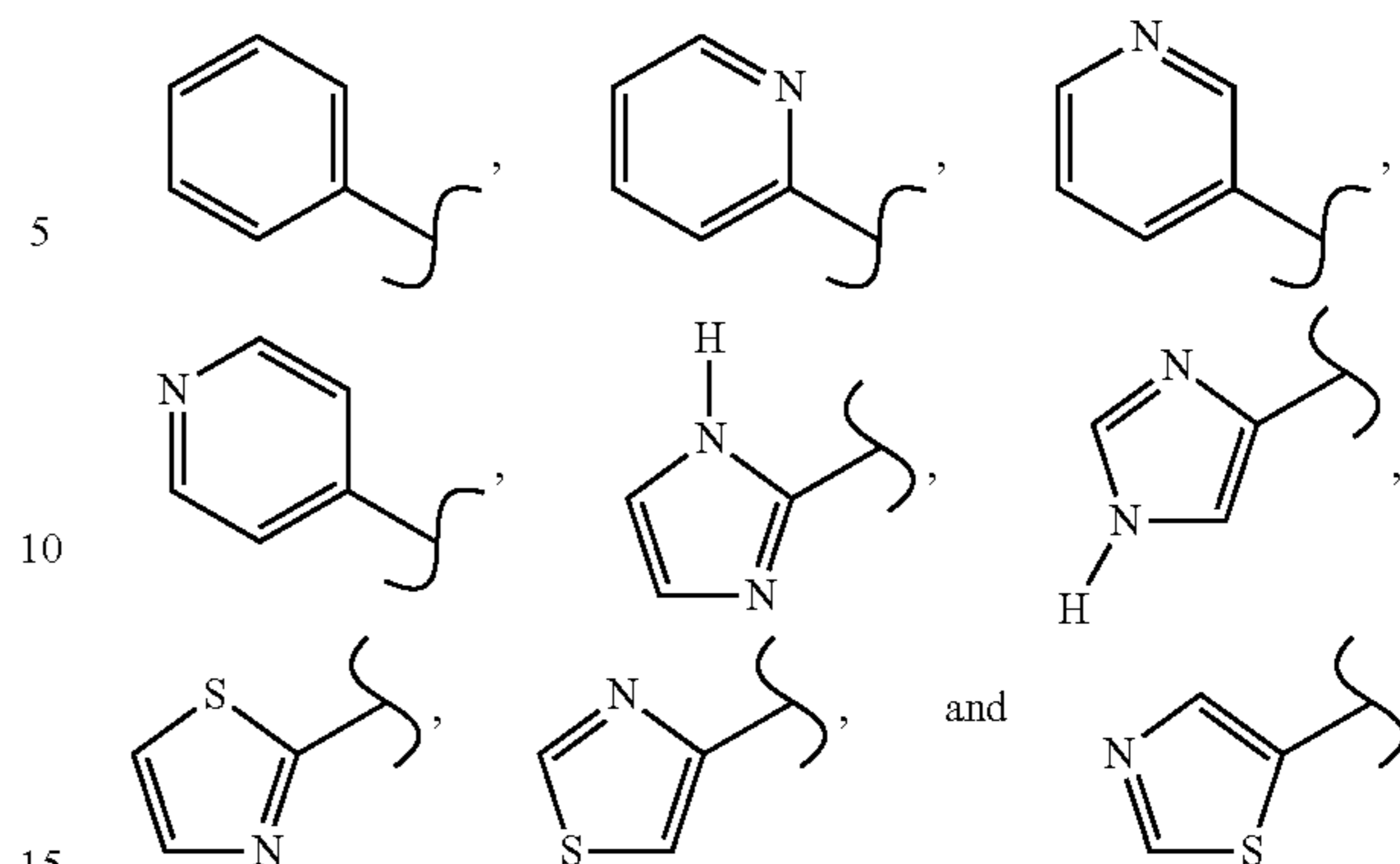
W³ is W⁴ or W⁵; W⁴ is R, —C(Y¹)R^y, —C(Y¹)W⁵,
 —SO₂R^y, or —SO₂W⁵; and W⁵ is a carbocycle or a hetero-
 cycle wherein W⁵ is independently substituted with 0 to 3 R^y
 groups.

W⁵ carbocycles and W⁵ heterocycles may be indepen-
 35 dently substituted with 0 to 3 R^y groups. W⁵ may be a
 saturated, unsaturated or aromatic ring comprising a mono-
 or bicyclic carbocycle or heterocycle. W⁵ may have 3 to 10
 ring atoms, e.g., 3 to 7 ring atoms. The W⁵ rings are saturated
 when containing 3 ring atoms, saturated or mono-unsatur-
 40 ated when containing 4 ring atoms, saturated, or mono- or
 di-unsaturated when containing 5 ring atoms, and saturated,
 mono- or di-unsaturated, or aromatic when containing 6 ring
 atoms.

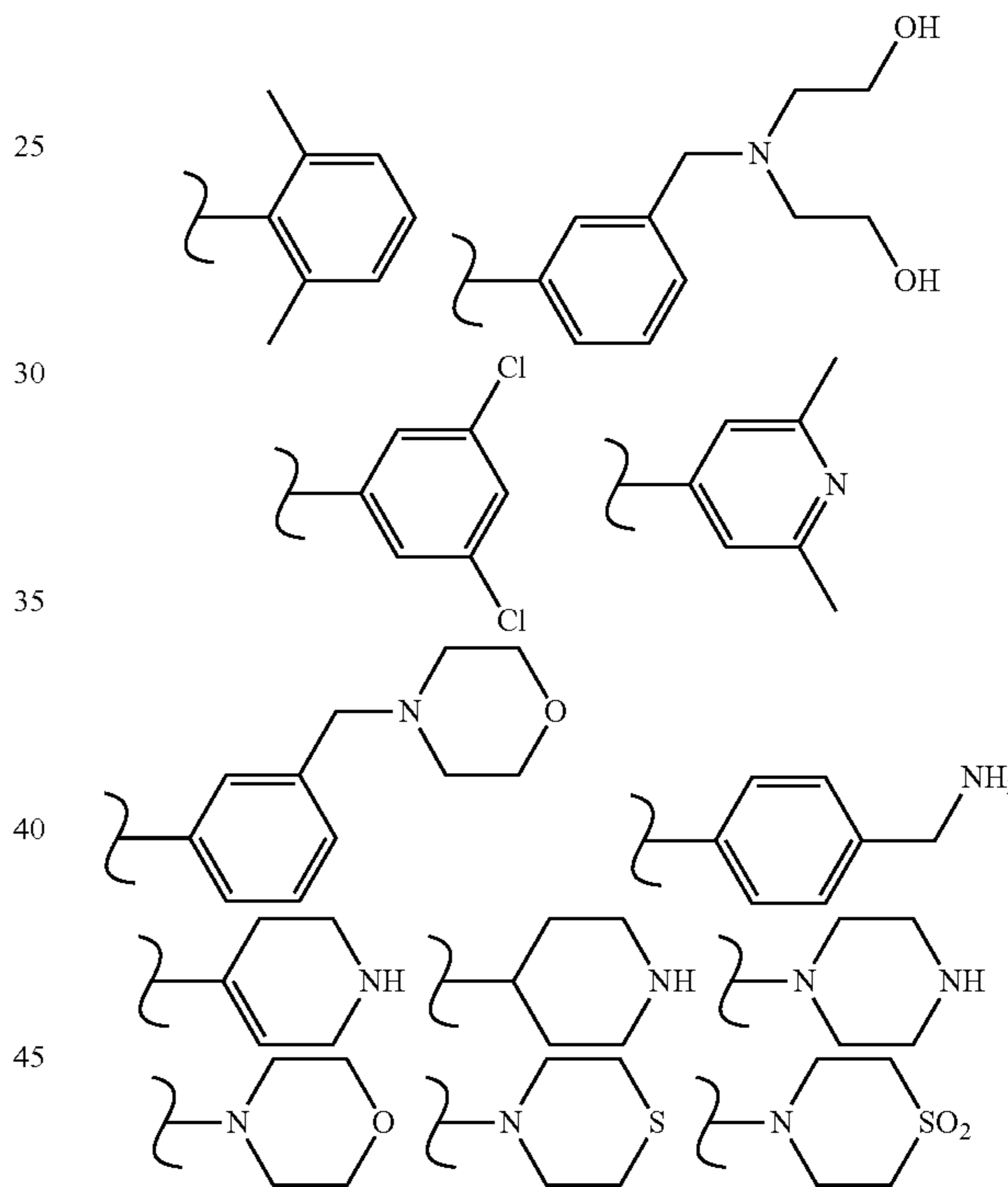
A W⁵ heterocycle may be a monocycle having 3 to 7 ring
 members (2 to 6 carbon atoms and 1 to 3 heteroatoms
 selected from N, O, P, and S) or a bicycle having 7 to 10 ring
 members (4 to 9 carbon atoms and 1 to 3 heteroatoms
 selected from N, O, P, and S). W⁵ heterocyclic monocycles
 may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2
 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms
 (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from
 N and S). W⁵ heterocyclic bicycles have 7 to 10 ring atoms
 (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from
 N, O, and S) arranged as a bicyclo[4,5], [5,5], [5,6], or [6,6]
 system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to
 2 hetero atoms selected from N and S) arranged as a bicyclo[5,6]
 or [6,6] system. The W⁵ heterocycle may be
 50 bonded to Y² through a carbon, nitrogen, sulfur or other
 atom by a stable covalent bond.

W⁵ heterocycles include for example, pyridyl, dihydro-
 pyridyl isomers, piperidine, pyridazinyl, pyrimidinyl,
 pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isox-
 azolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl,
 and pyrrolyl. W⁵ also includes, but is not limited to,
 examples such as:

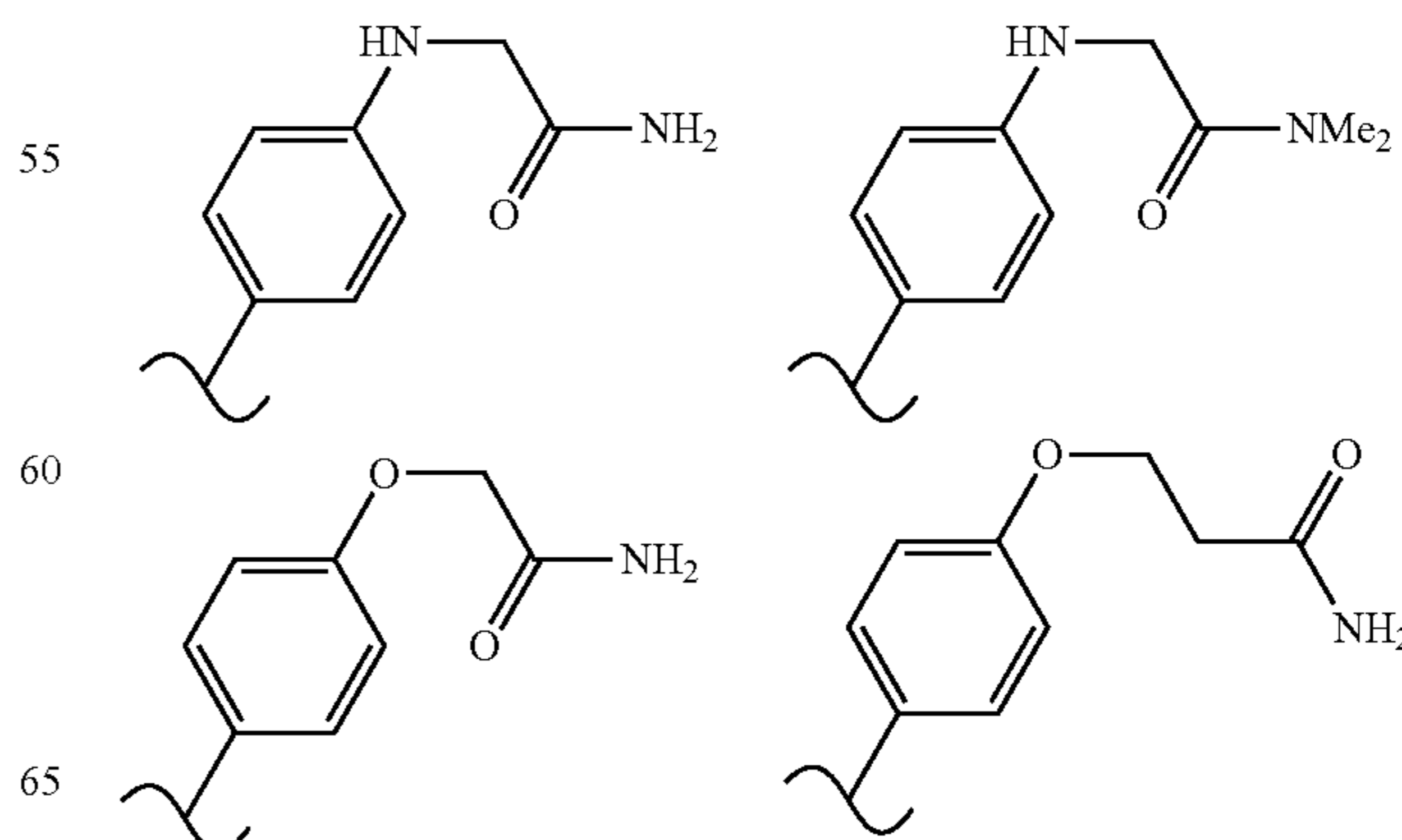
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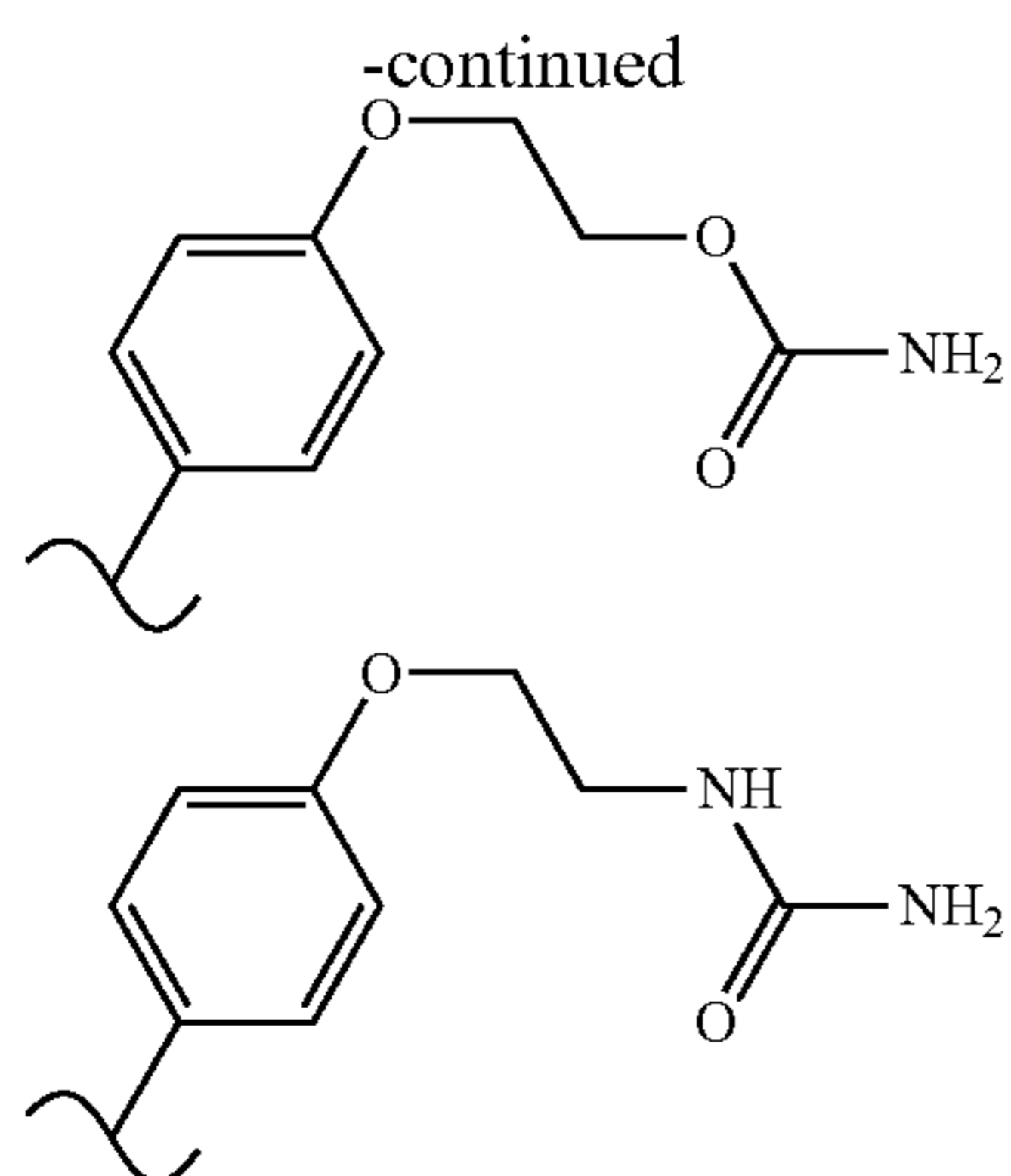
W⁵ carbocycles and heterocycles may be independently
 20 substituted with 0 to 3 R groups, as defined above. For
 example, substituted W⁵ carbocycles include:



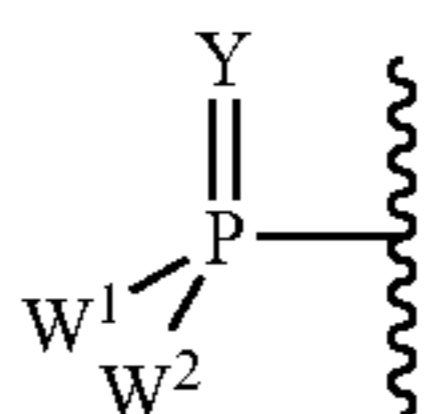
Examples of substituted phenyl carbocycles include:



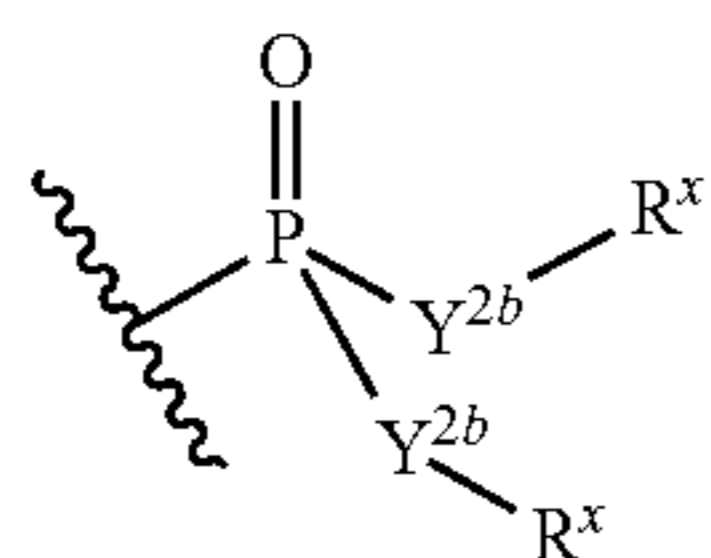
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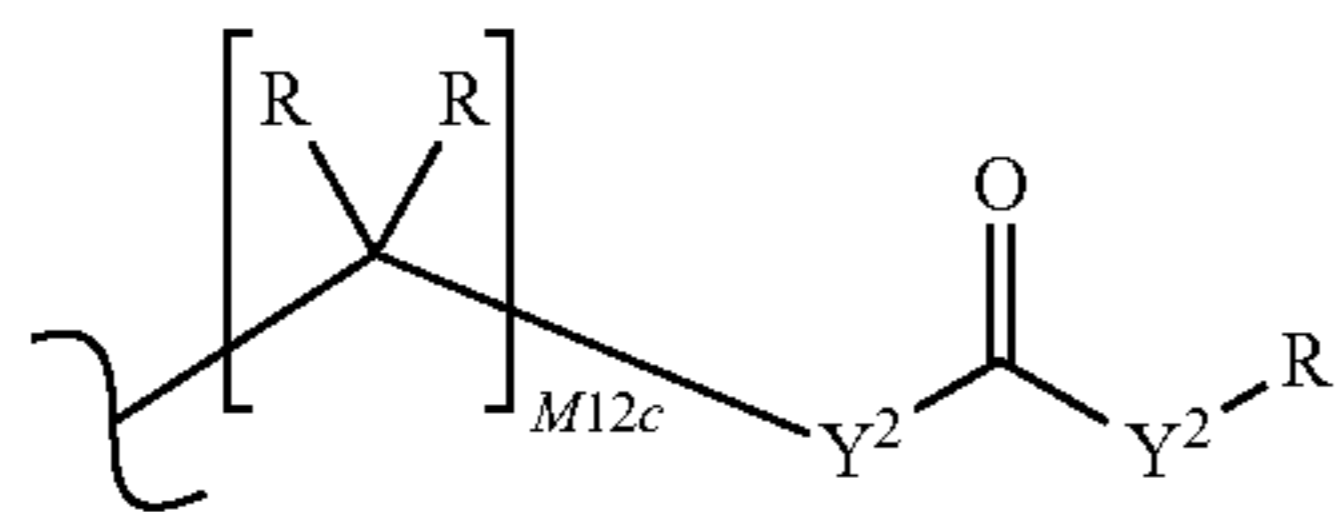
Embodiments of



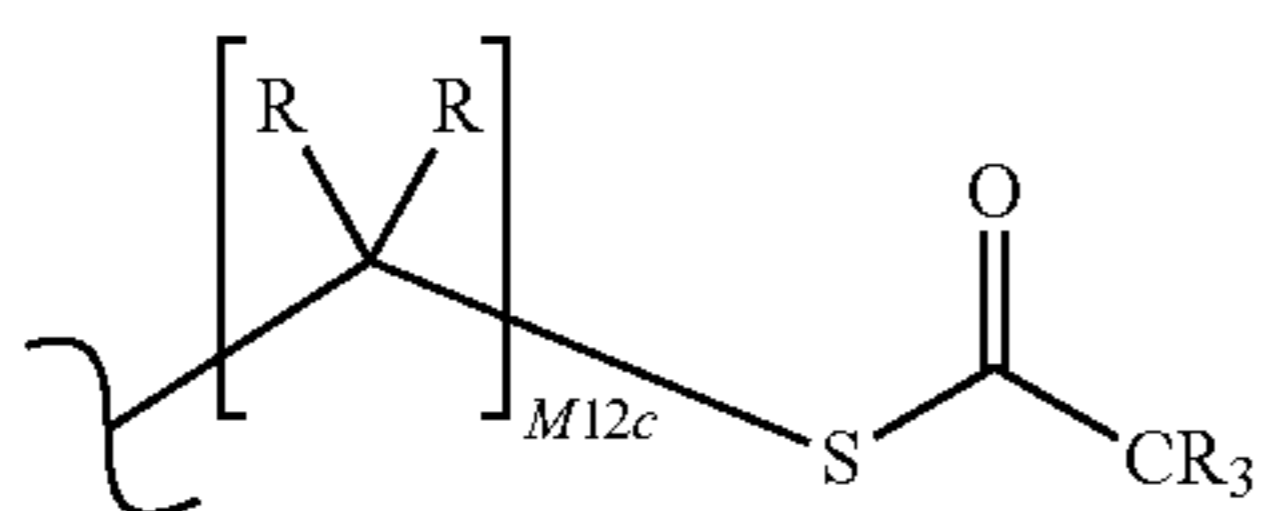
of Formula I-III compounds include substructures such as:



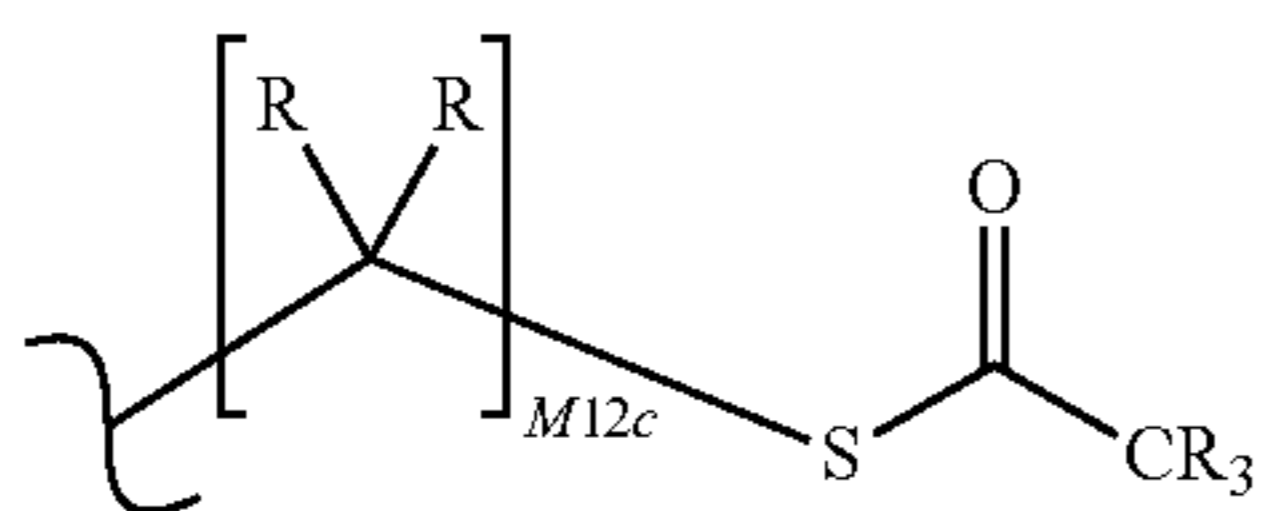
wherein each Y^{2b} is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



wherein M12c is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S. In another preferred aspect of this embodiment, one $Y^{2b}-R^x$ is NH(R) and the other $Y^{2b}-R^x$ is O- R^x wherein R^x is:

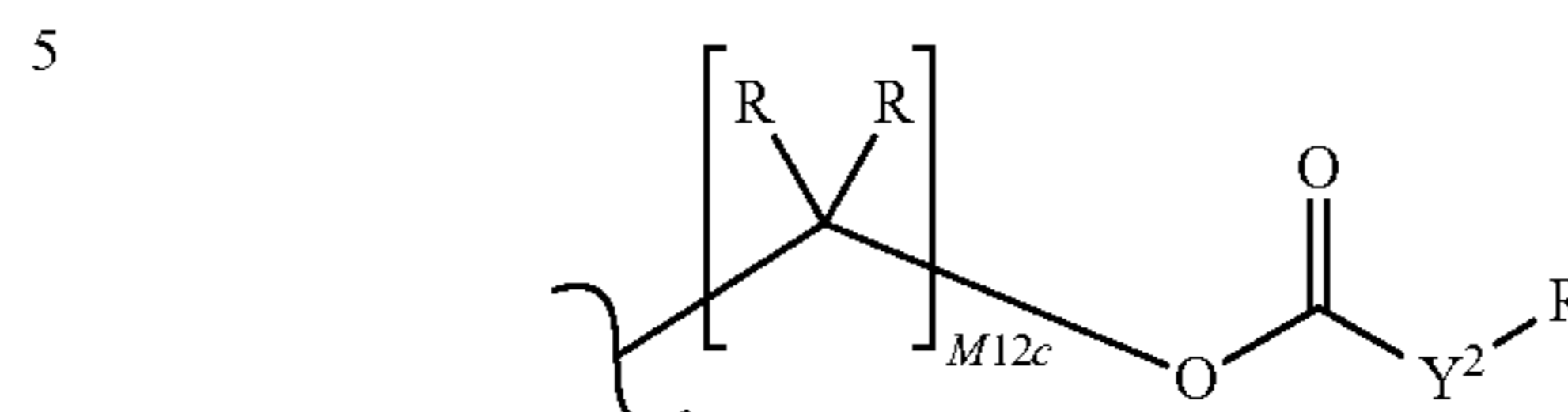


wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



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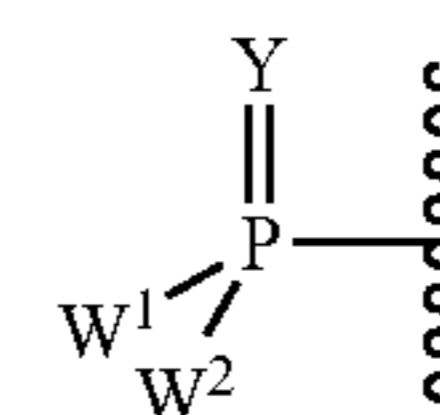
wherein M12c is 2. In another preferred aspect of this embodiment, each Y^{2b} is O and each R^x is independently:



wherein M12c is 1 and Y^2 is a bond, O, or CR_2 .

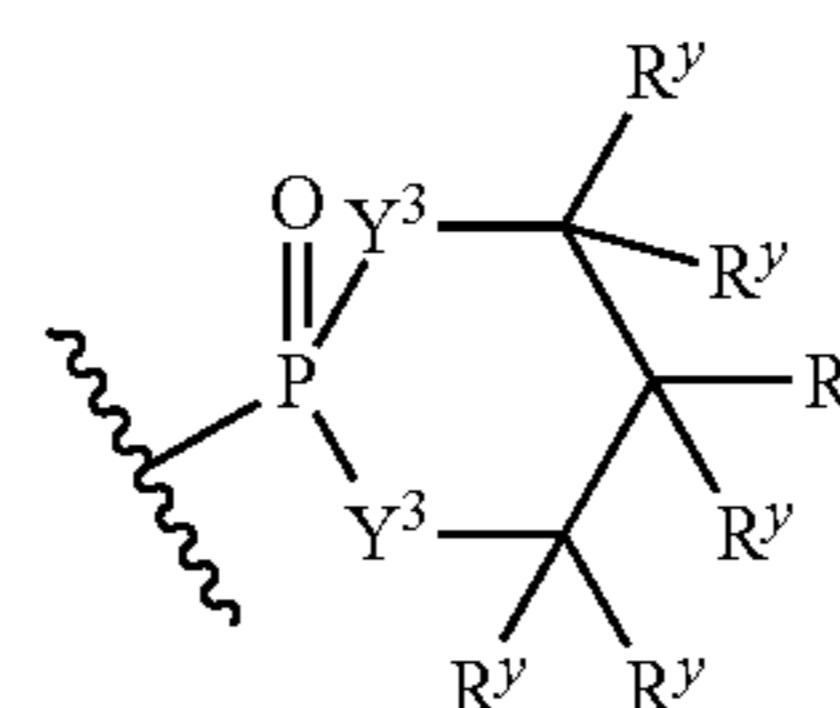
Other embodiments of

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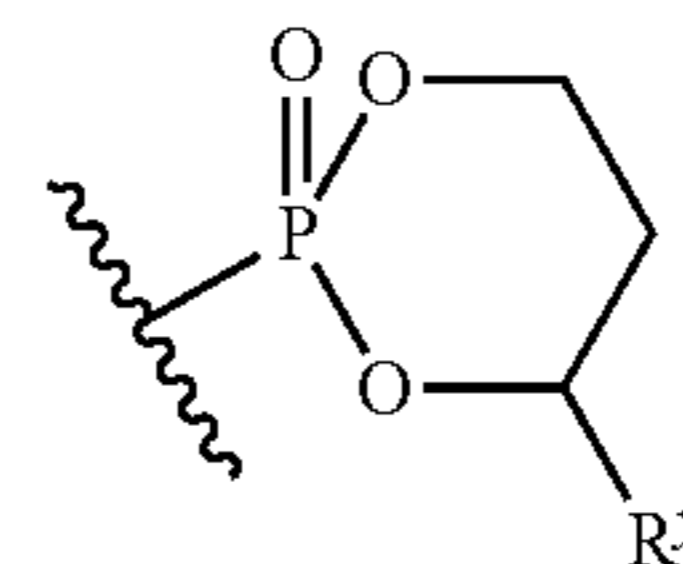
Formula I-III compounds include substructures such as:



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wherein each Y^3 is, independently, O or N(R). In a preferred aspect of this embodiment, each Y^3 is O. In another preferred aspect of this embodiment, the substructure is:

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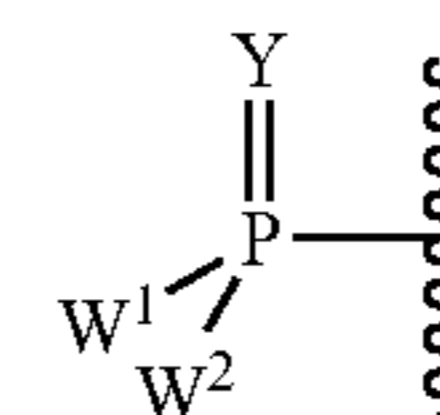


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wherein R^y is W^5 as defined herein.

Another embodiment of

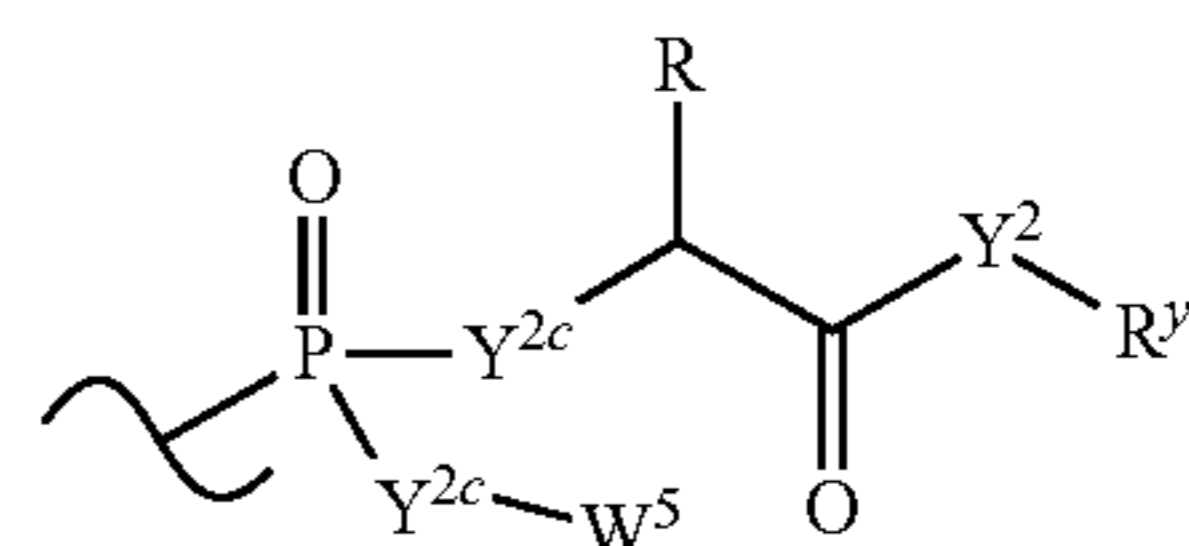
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of Formula I-III includes the substructures:

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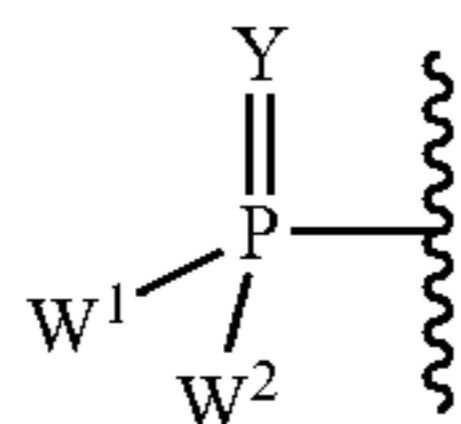


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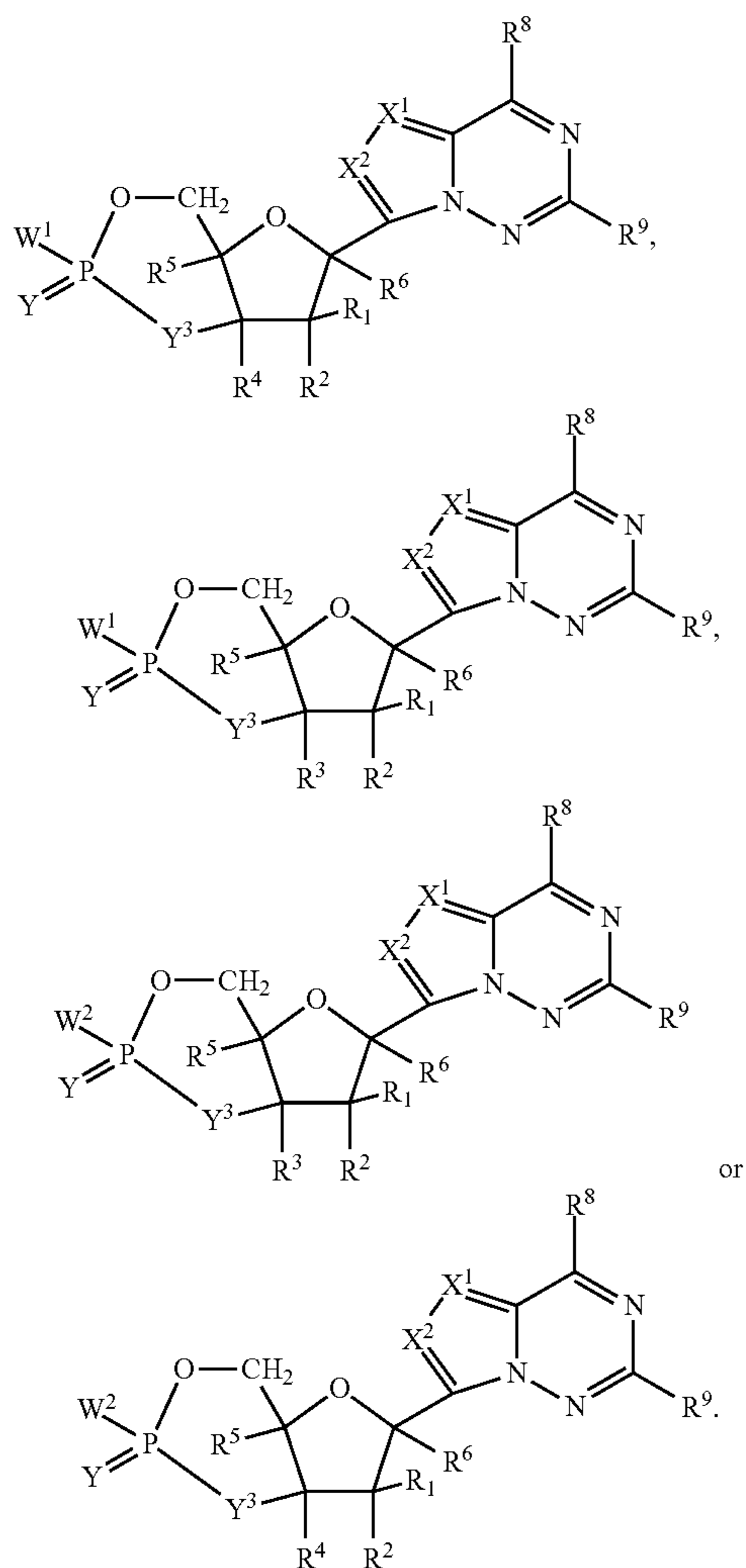
wherein each Y^{2c} is, independently, O, N(R^y) or S.

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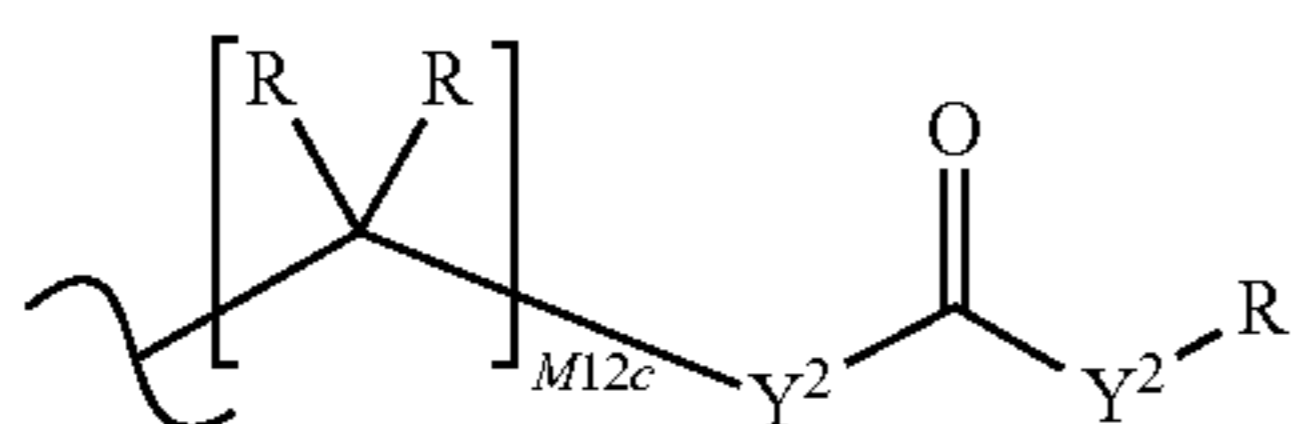
Another embodiment of



of Formula I-III compounds includes the substructures wherein one of W^1 or W^2 together with either R^3 or R^4 is $-Y^3-$ and the other of W^1 or W^2 is Formula Ia. Such an embodiment is represented by a compound of Formula Ib selected from:



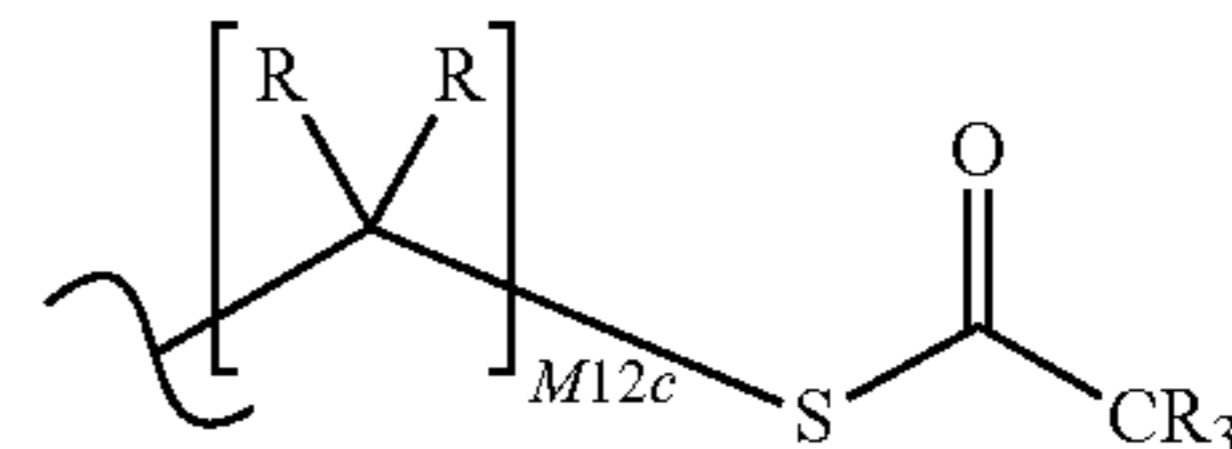
In a preferred aspect of the embodiment of Formula Ib, each Y and Y^3 is O. In another preferred aspect of the embodiment of Formula Ib, W^1 or W^2 is $Y^{2b}-R^x$; each Y, Y^3 and Y^{2b} is O and R^x is:



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wherein $M12c$ is 1, 2 or 3 and each Y^2 is independently a bond, O, CR_2 , or S. In another preferred aspect of the embodiment of Formula Ib, W^1 or W^2 is $Y^{2b}-R^x$; each Y, Y^3 and Y^{2b} is O and R^x is:

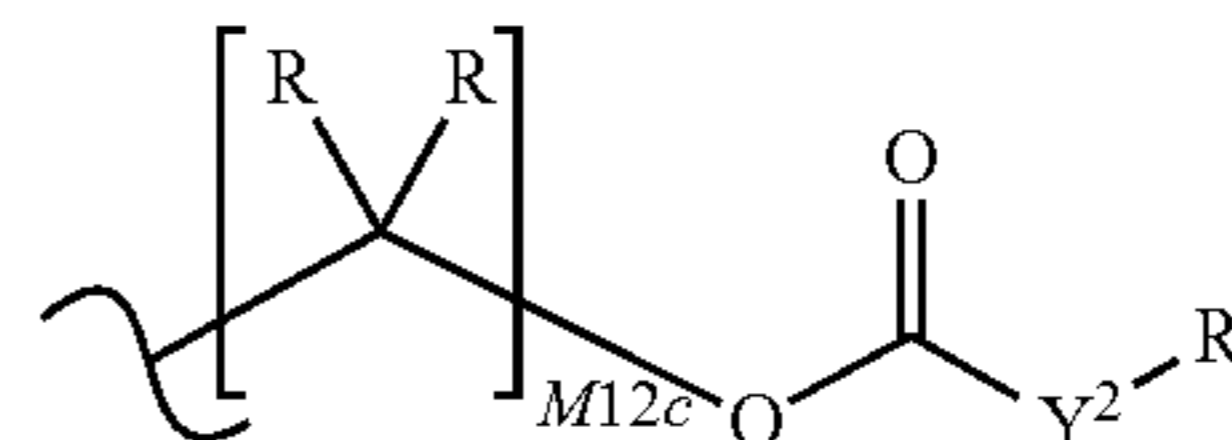
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wherein $M12c$ is 2. In another preferred aspect of the embodiment of Formula Ib, W^1 or W^2 is $Y^{2b}-R^x$; R^x ; each Y, Y^3 and Y^{2b} is O and R^x is:

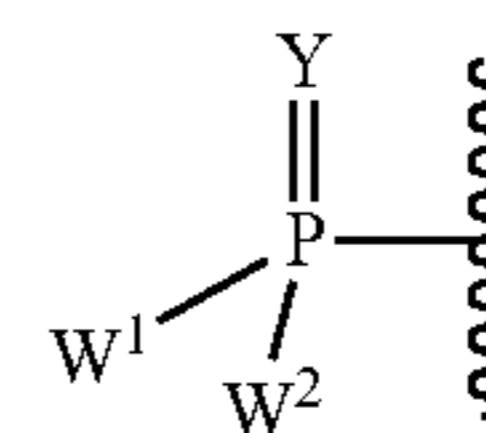
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wherein $M12c$ is 1 and Y^2 is a bond, O, or CR_2 . Another embodiment of

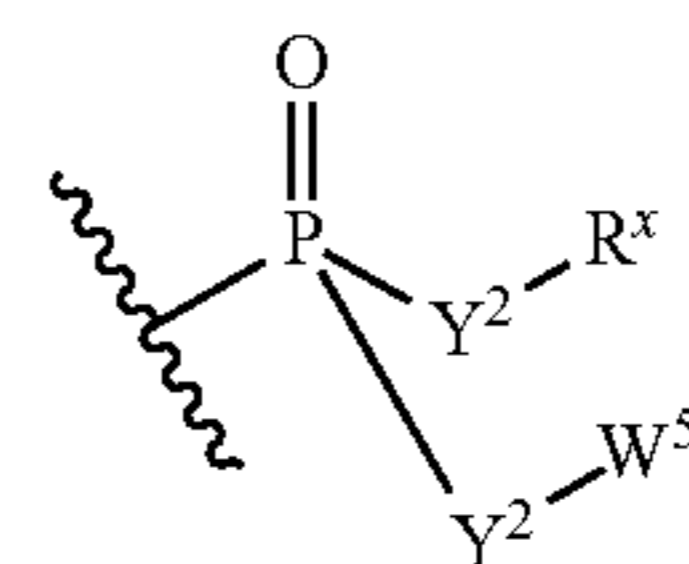
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of Formula I-III compounds includes a substructure:

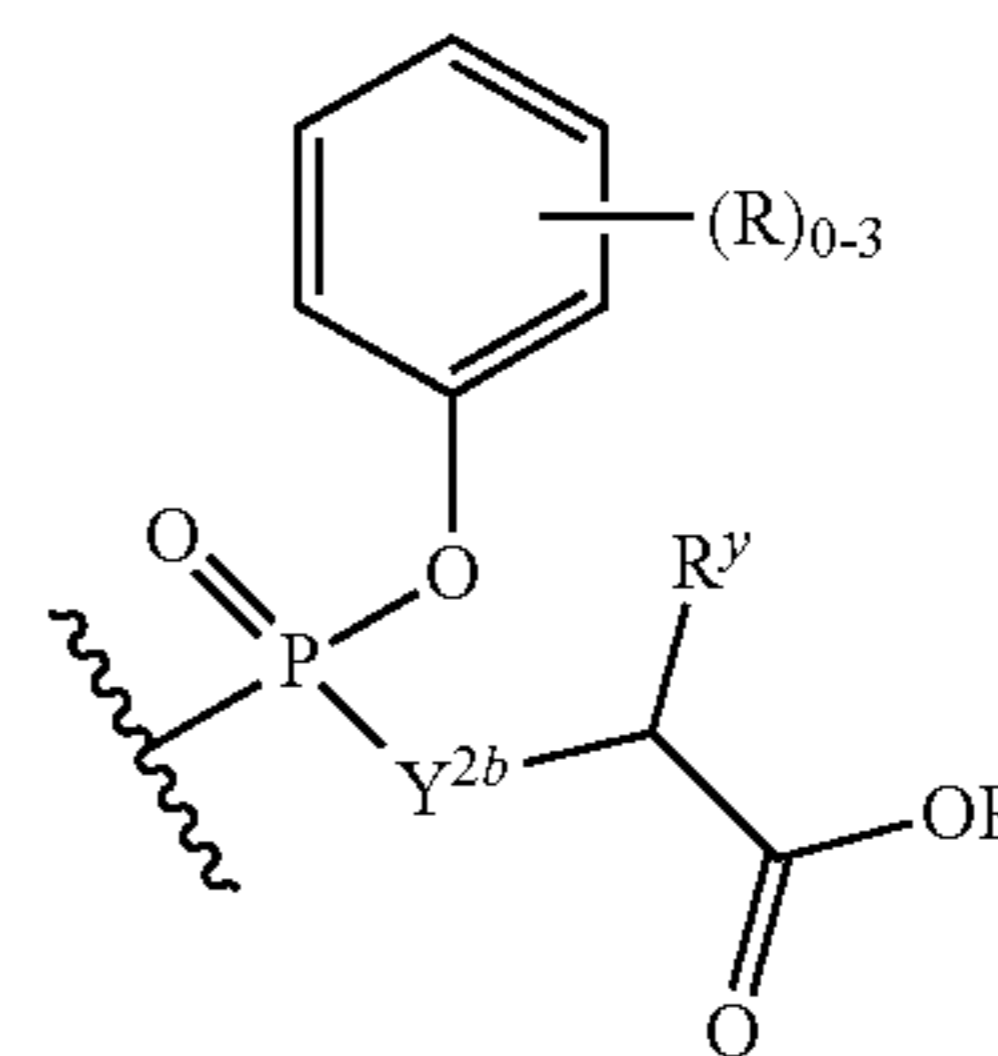
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wherein W^5 is a carbocycle such as phenyl or substituted phenyl. In another aspect of this embodiment, the substructure is:

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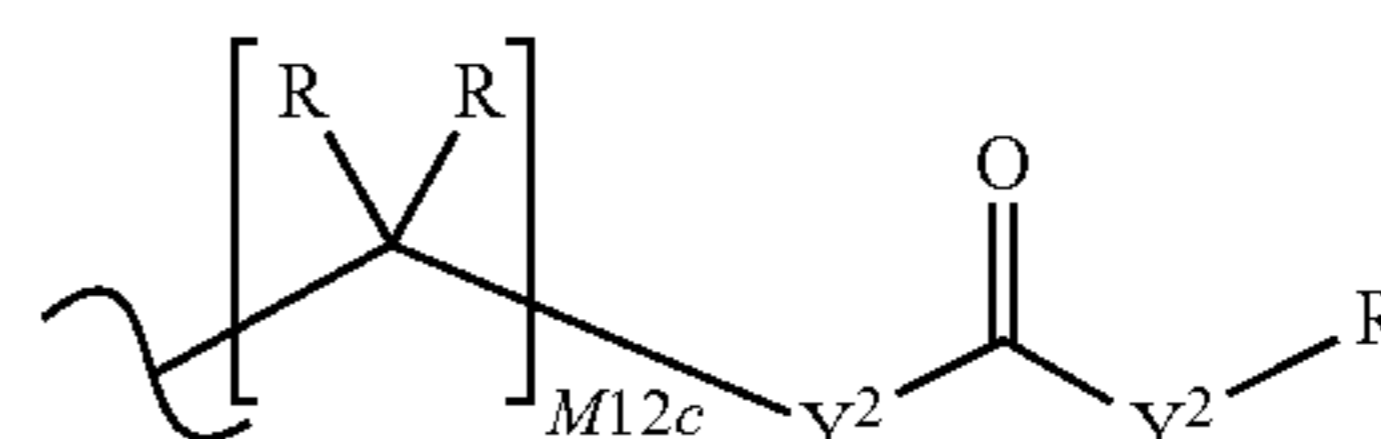


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wherein Y^{2b} is O or $N(R)$ and the phenyl carbocycle is substituted with 0 to 3 R groups. In another aspect of this embodiment of the substructure, R^x is:

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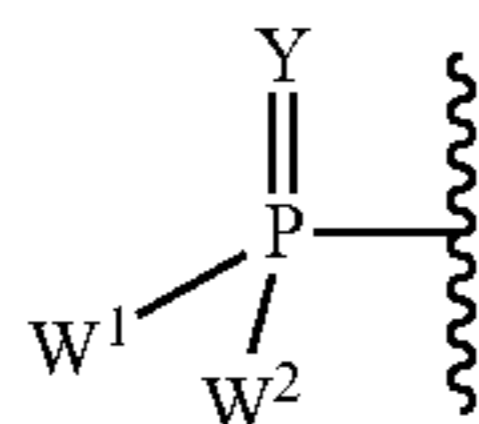


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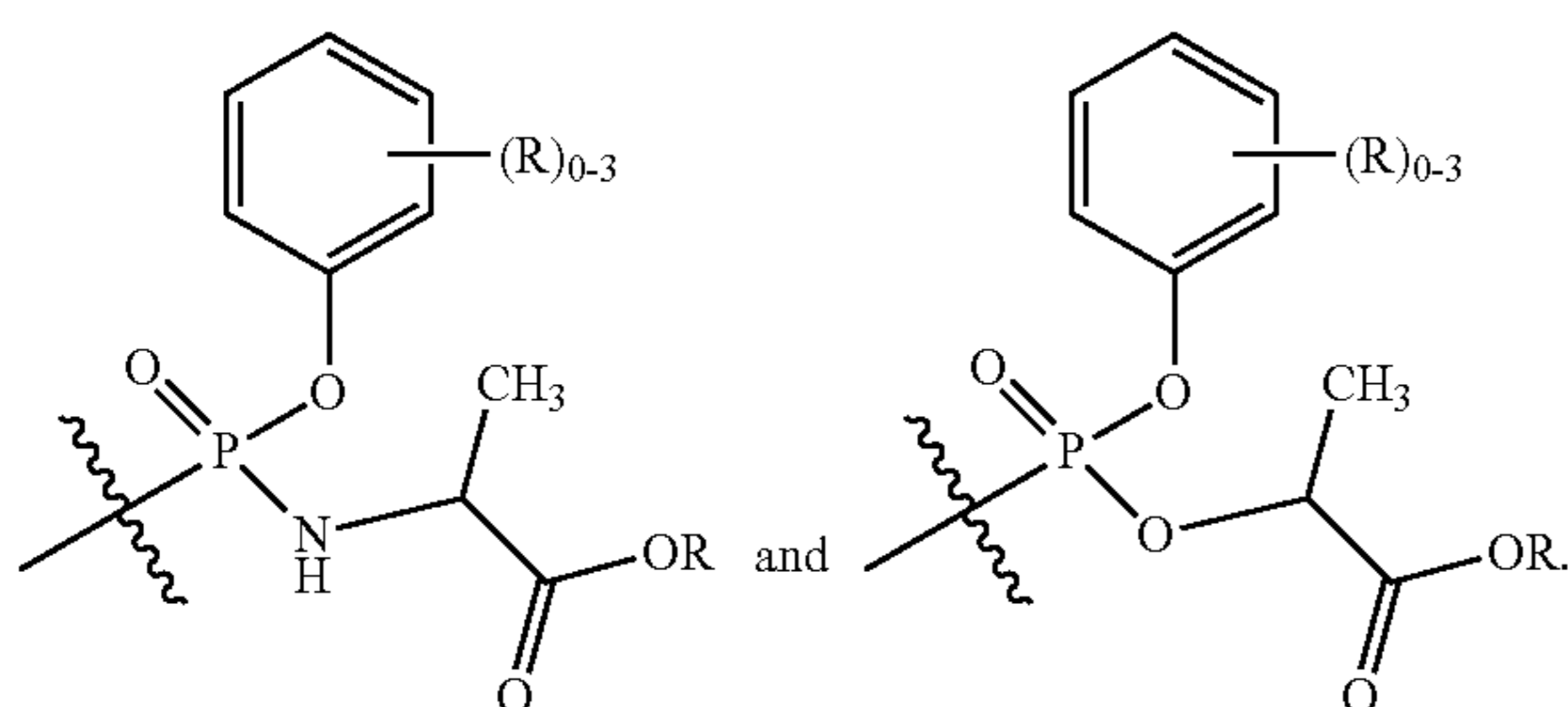
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wherein M12c is 1, 2 or 3 and each Y² is independently a bond, O, CR₂, or S.

Another embodiment of

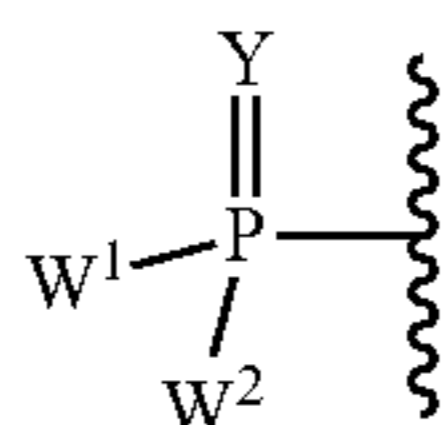


of Formula I-III includes substructures:

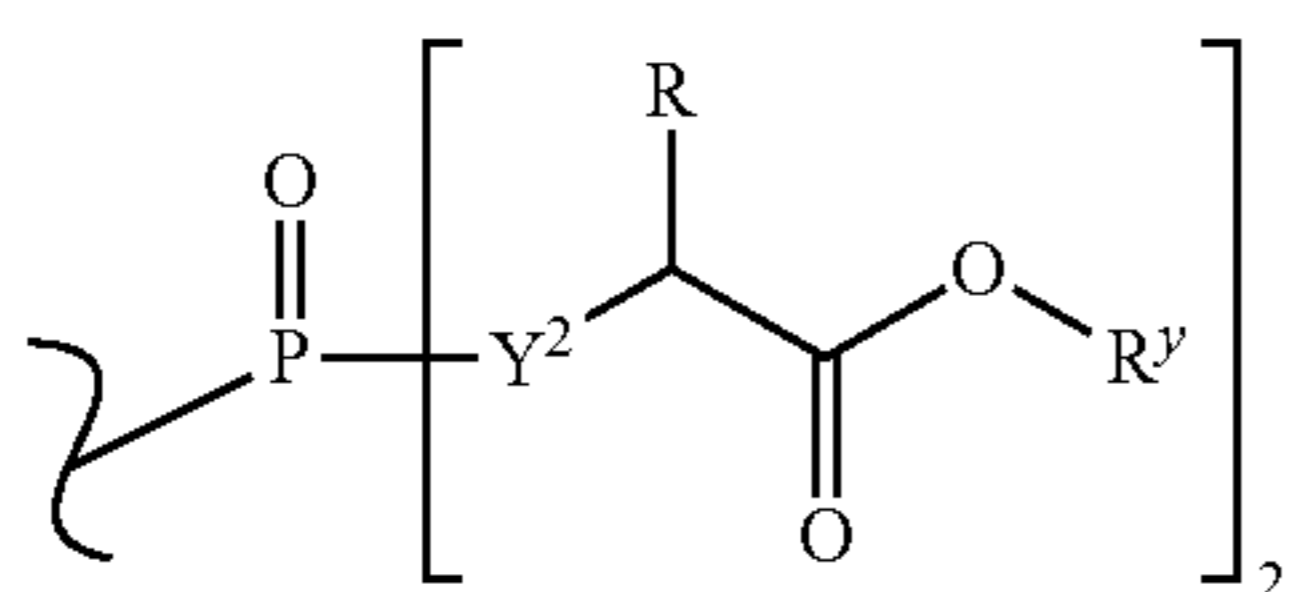


The chiral carbon of the amino acid and lactate moieties may be either the R or S configuration or the racemic mixture.

Another embodiment of



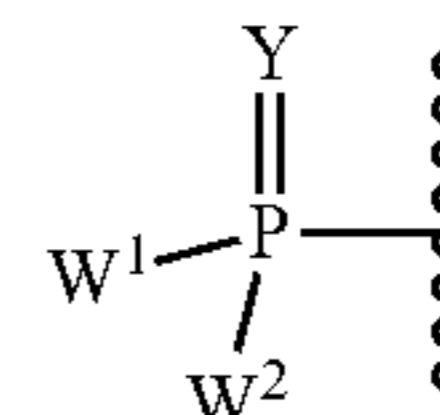
Formula I-III is substructure



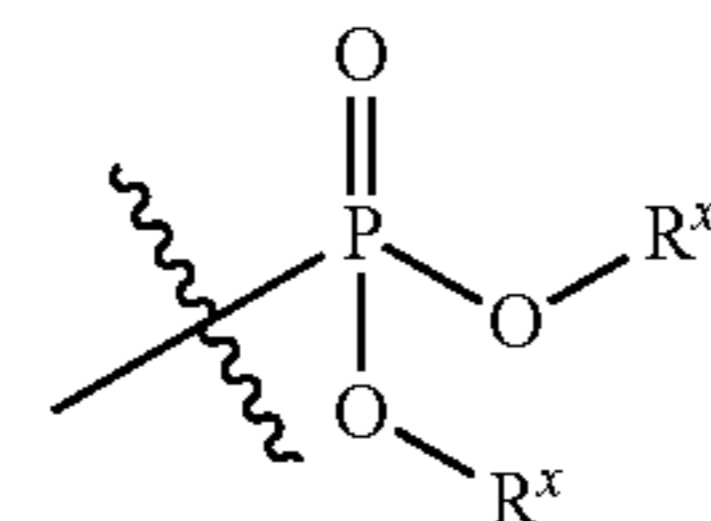
wherein each Y² is, independently, —O— or —NH—. In another preferred aspect of this embodiment, R^y is (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₃) alkynyl or (C₂-C₈) substituted alkynyl. In another preferred aspect of this embodiment, R^y is (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl or (C₂-C₈) substituted alkynyl; and R is CH₃. In another preferred aspect of this embodiment, R^y is (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl or (C₂-C₈) substituted alkynyl; R is CH₃; and each Y² is NH—. In a preferred aspect of this embodiment, W¹ and W² are, independently, nitrogen-linked, naturally occurring amino acids or naturally occurring amino acid esters. In another preferred aspect of this embodiment, W¹ and W² are, independently, naturally-occurring 2-hydroxy carboxylic acids or naturally-occurring 2-hydroxy carboxylic acid esters wherein the acid or ester is linked to P through the 2-hydroxy group.

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Another embodiment of

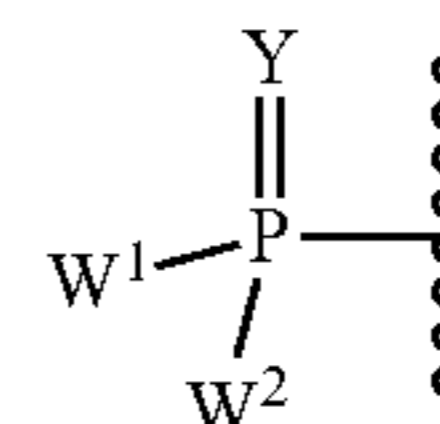


of Formula I, Formula II, or Formula III is substructure:

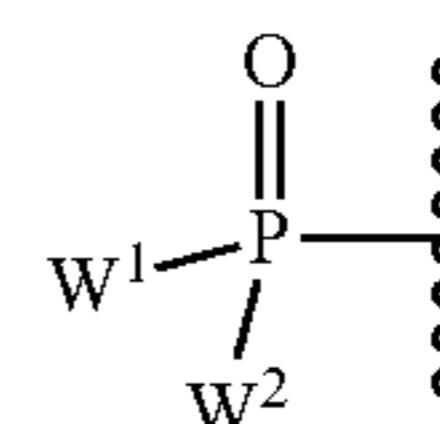


In one preferred aspect of this embodiment, each R^x is, independently, (C₁-C₈) alkyl. In another preferred aspect of this embodiment, each R^x is, independently, C₆-C₂₀ aryl or C₆-C₂₀ substituted aryl.

Another embodiment of



of Formulas I-III is substructure



wherein W¹ and W² are independently selected from one of the formulas in Tables 20.1-20.37 and Table 30.1 below. The variables used in Tables 20.1-20.37 (e.g., W²³, R²¹, etc.) pertain only to Tables 20.1-20.37, unless otherwise indicated.

The variables used in Tables 20.1 to 20.37 have the following definitions:

each R²¹ is independently H or (C₁-C₈)alkyl;

each R²² is independently H, R²¹, R²³ or R²⁴ wherein each R²⁴ is independently substituted with 0 to 3 R²³;

each R²³ is independently R^{23a}, R^{23b}, R^{23c} or R^{23d}, provided that when R²³ is bound to a heteroatom, then R²³ is R^{23c} or R^{23d};

each R^{23a} is independently F, Cl, Br, I, —CN, N₃ or —NO₂;

each R^{23b} is independently Y²¹;

each R^{23c} is independently —R^{2x}, —N(R^{2x})(R^{2x}), —SR^{2x}, —S(O)R^{2x}, —S(O)₂R^{2x}, —S(O)(OR^{2x}), —S(O)₂(OR^{2x}), —OC(=Y²¹)R^{2x}, —OC(=Y²¹)OR^{2x}, —OC(=Y²¹)(N(R^{2x})(R^{2x})), —SC(=Y²¹)R^{2x}, —SC(=Y²¹)OR^{2x}, —SC(=Y²¹)(N(R^{2x})(R^{2x})), —N(R^{2x})C(=Y²¹)R^{2x}, —N(R^{2x})C(=Y²¹)OR^{2x}, or —N(R^{2x})C(=Y²¹)(N(R^{2x})(R^{2x}));

each R^{23d} is independently —C(=Y²¹)R^{2x}, —C(=Y²¹)OR^{2x} or —C(=Y²¹)(N(R^{2x})(R^{2x}));

each R^{2x} is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl, heteroaryl; or two R^{2x} taken together with a nitrogen to which they are both attached

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form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with —O—, —S— or NR²¹—; and wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl may be optionally replaced with —O—, —S— or NR²¹—;

each R²⁴ is independently (C₁-C₈)alkyl, (C₂-C₈)alkenyl, or (C₂-C₈)alkynyl;

each R²⁵ is independently R²⁴ wherein each R²⁴ is substituted with 0 to 3 R²³ groups;

each R^{25a} is independently (C₁-C₈)alkylene, (C₂-C₈)alkenylene, or (C₂-C₈)alkynylene any one of which said (C₁-C₈)alkylene, (C₂-C₈)alkenylene, or (C₂-C₈)alkynylene is substituted with 0-3 R²³ groups;

each W²³ is independently W²⁴ or W²⁵;

each W²⁴ is independently R²⁵, —C(=Y²¹)R²⁵, —C(=Y²¹)W²⁵, —SO₂R²⁵, or —SO₂W²⁵;

each W²⁵ is independently carbocycle or heterocycle wherein W²⁵ is independently substituted with 0 to 3 R²² groups; and

each Y²¹ is independently O or S.

TABLE 20.1

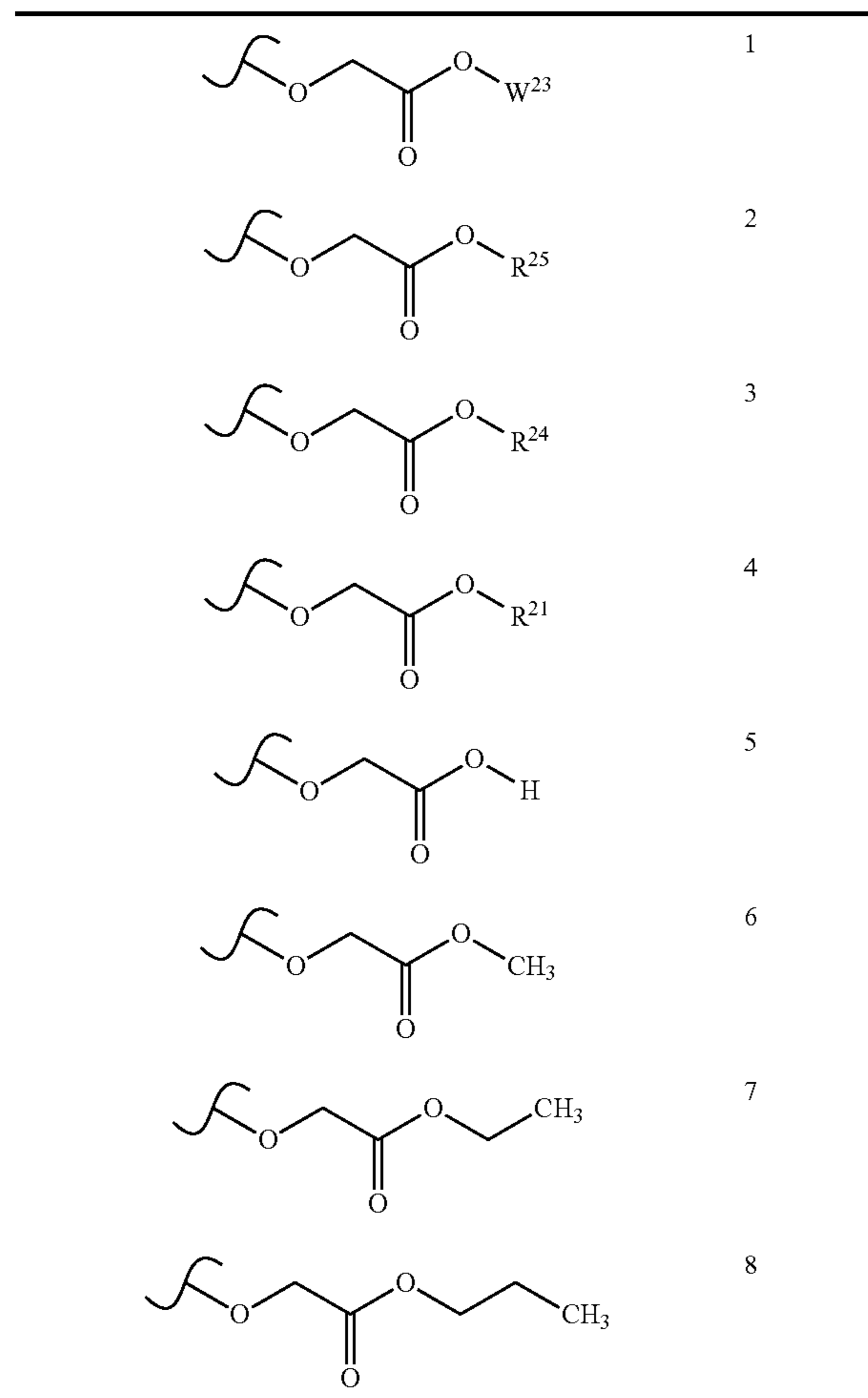
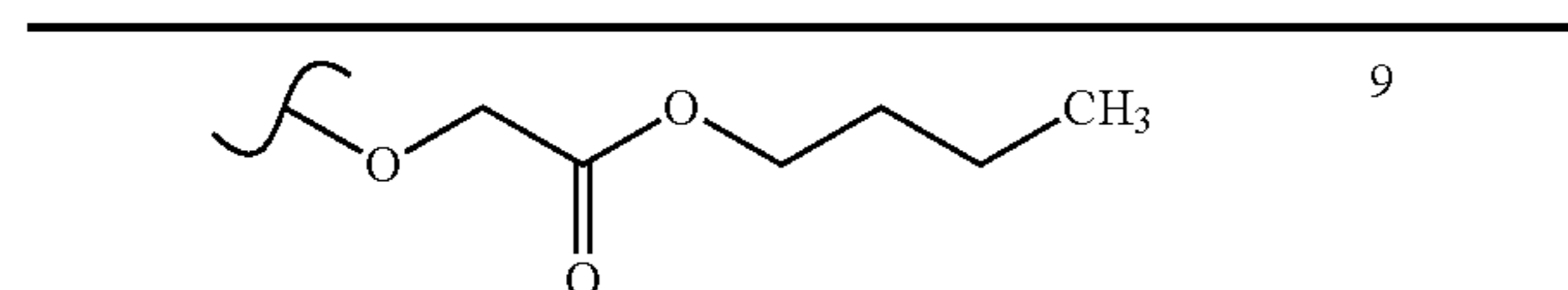


TABLE 20.2



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TABLE 20.2-continued

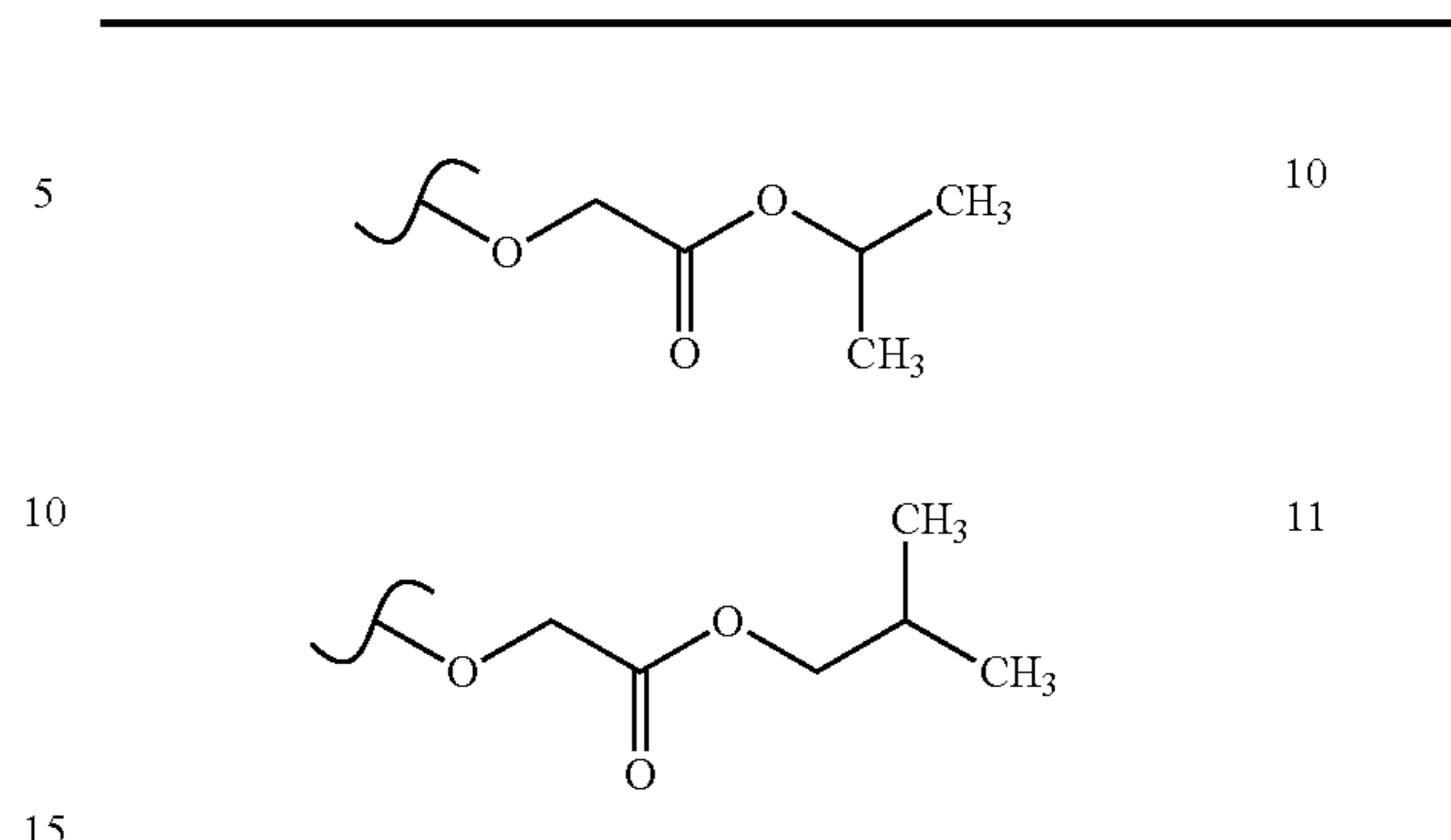
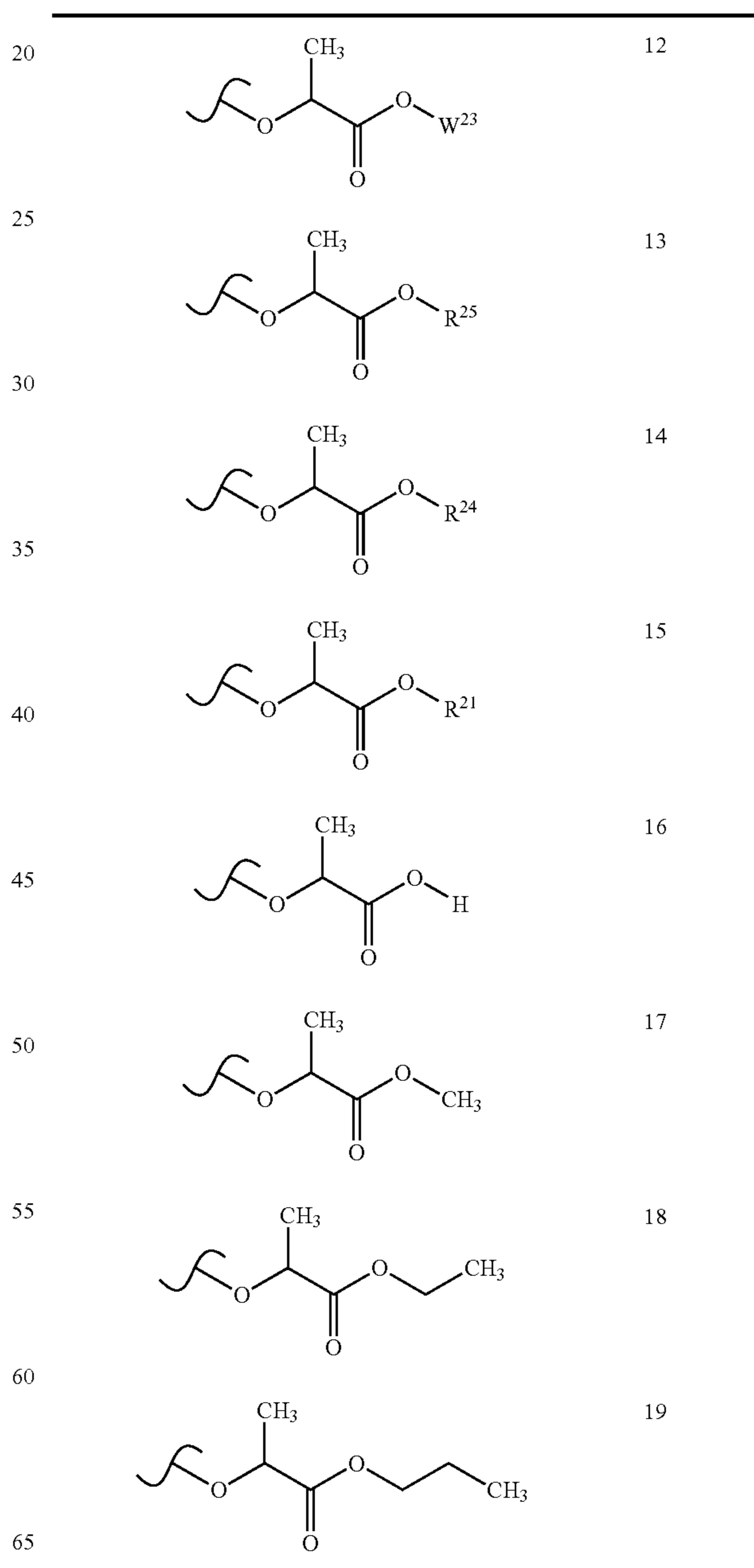


TABLE 20.3



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TABLE 20.4

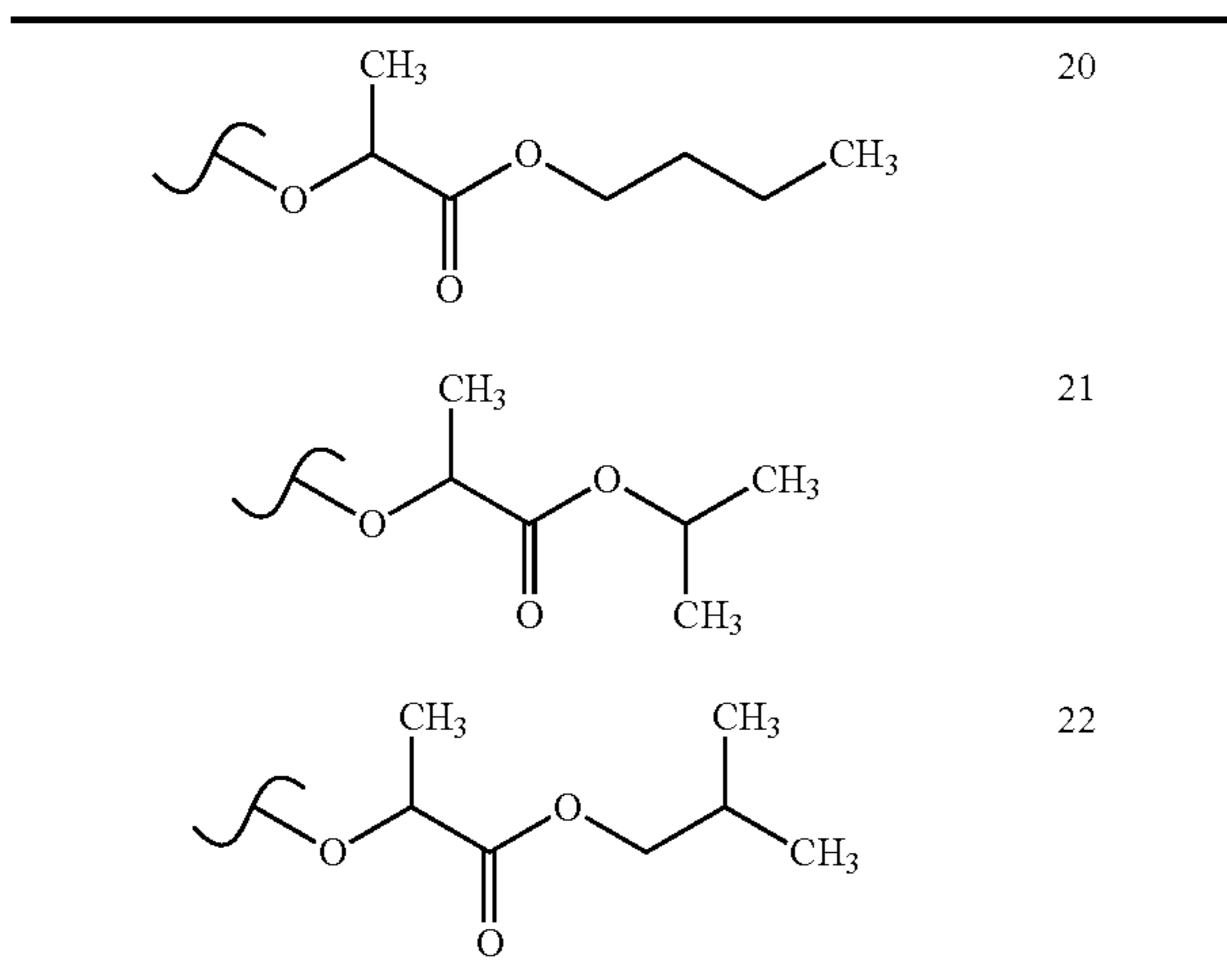
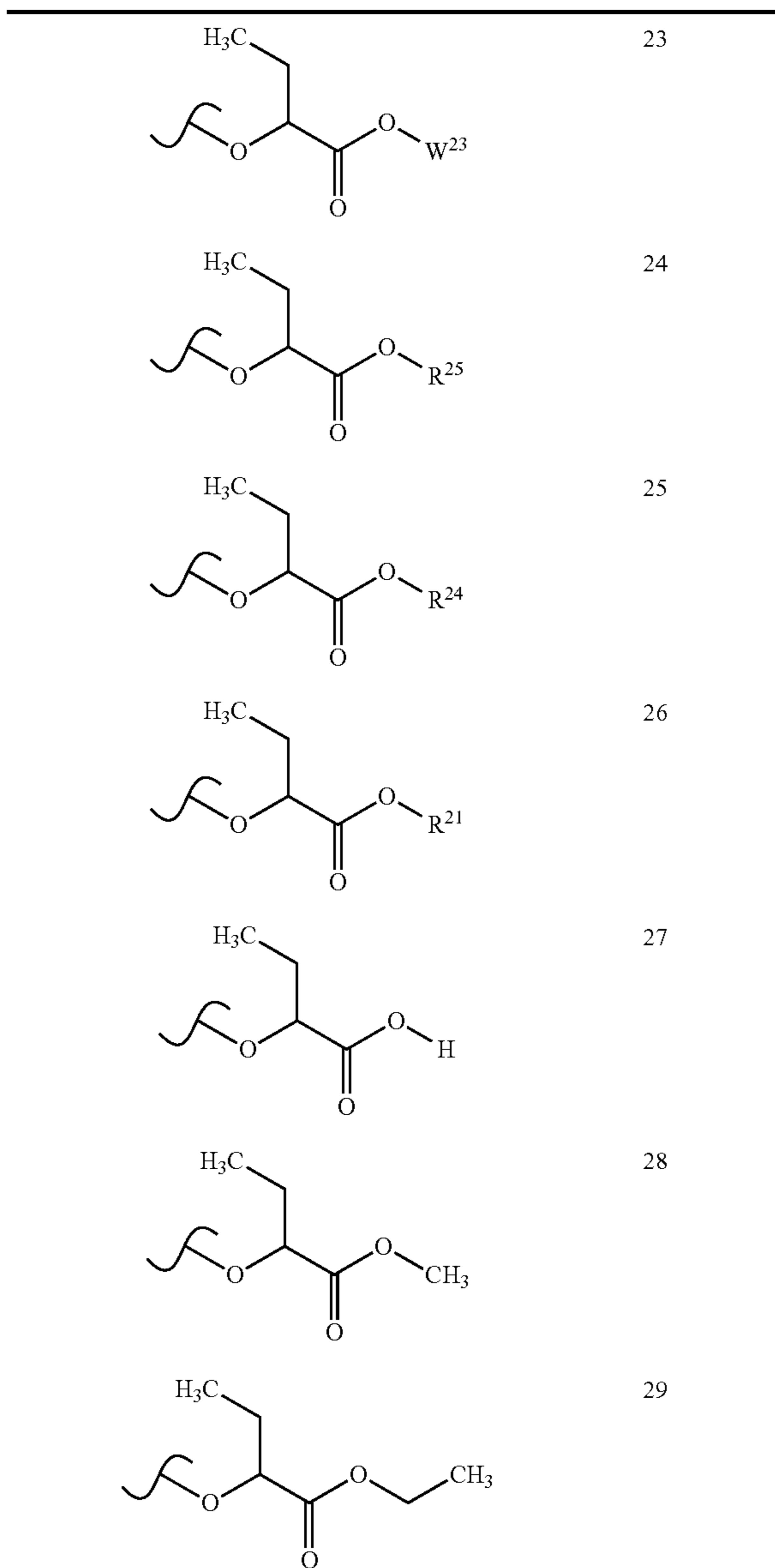


TABLE 20.5



50

TABLE 20.5-continued

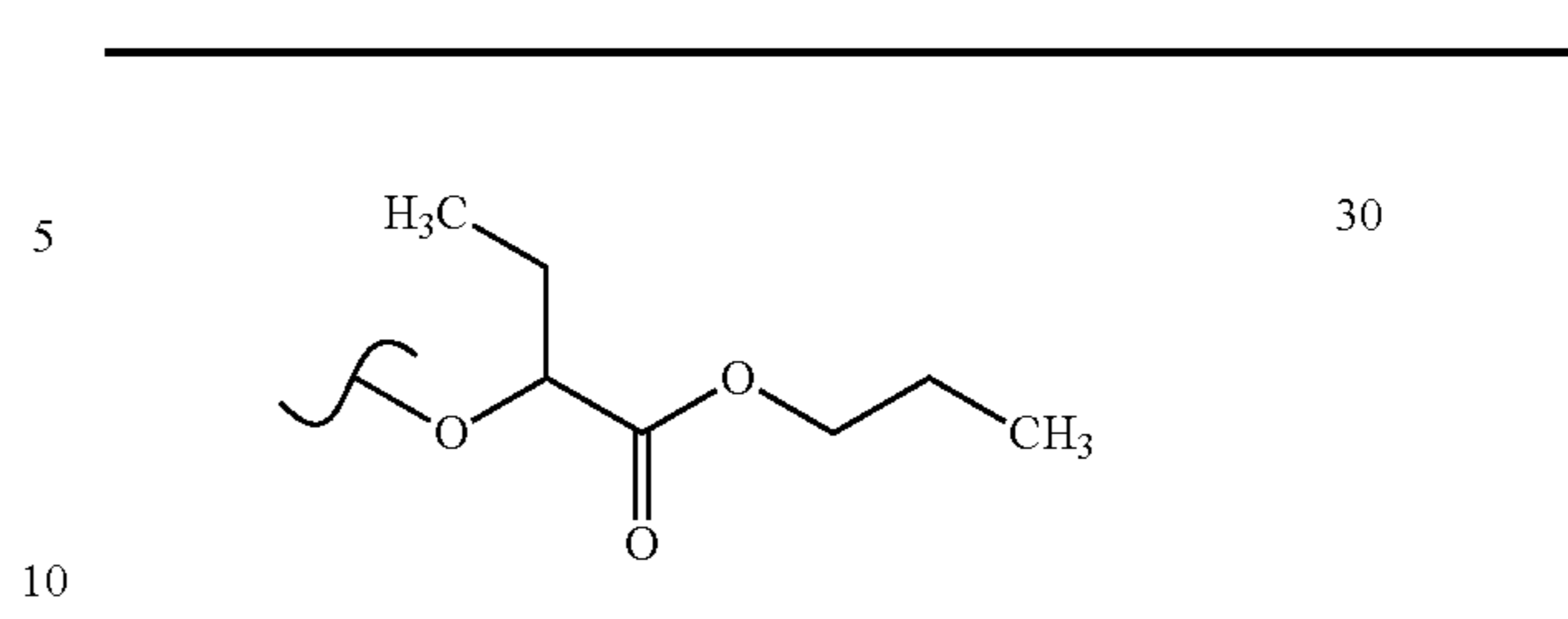


TABLE 20.6

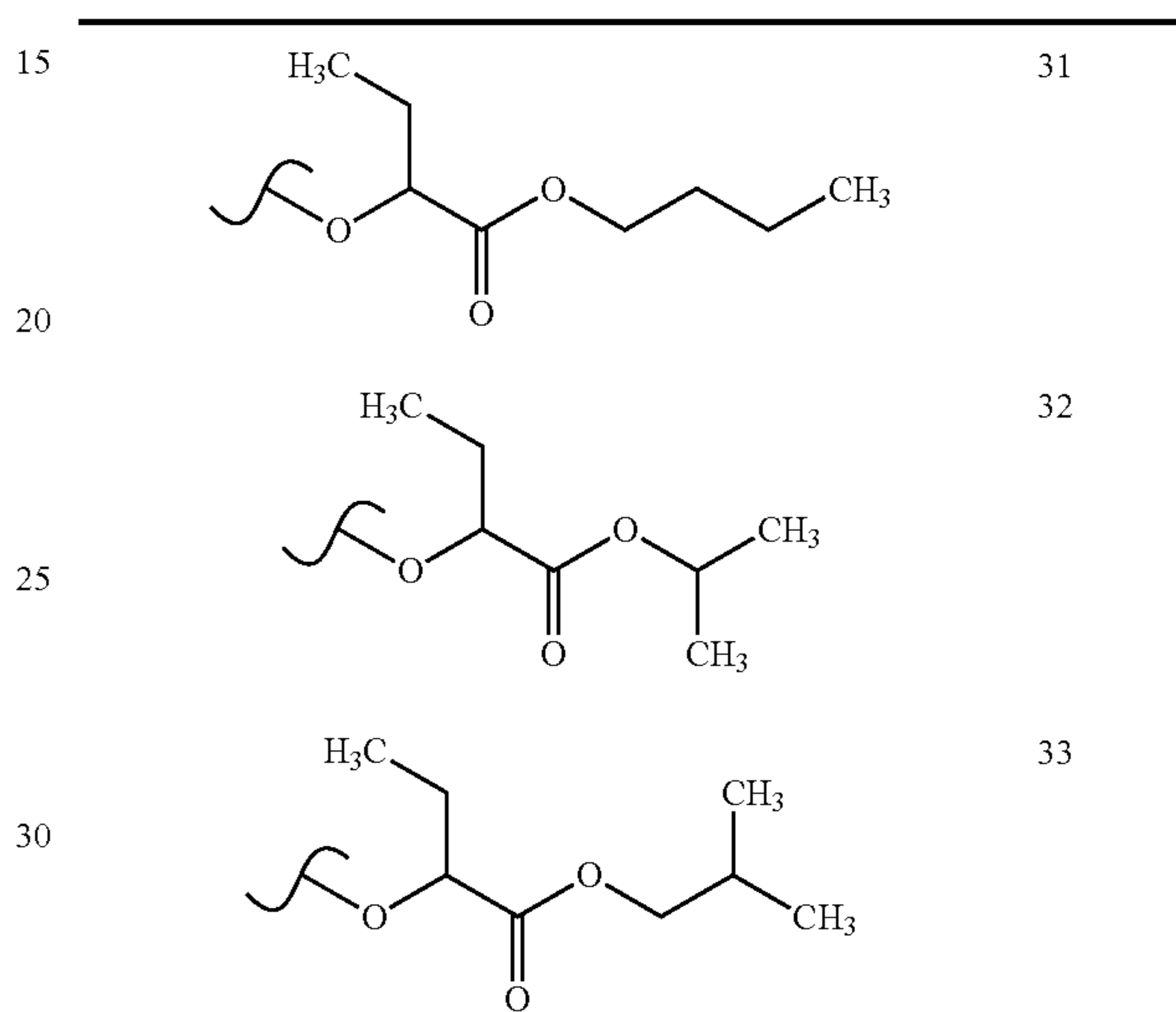
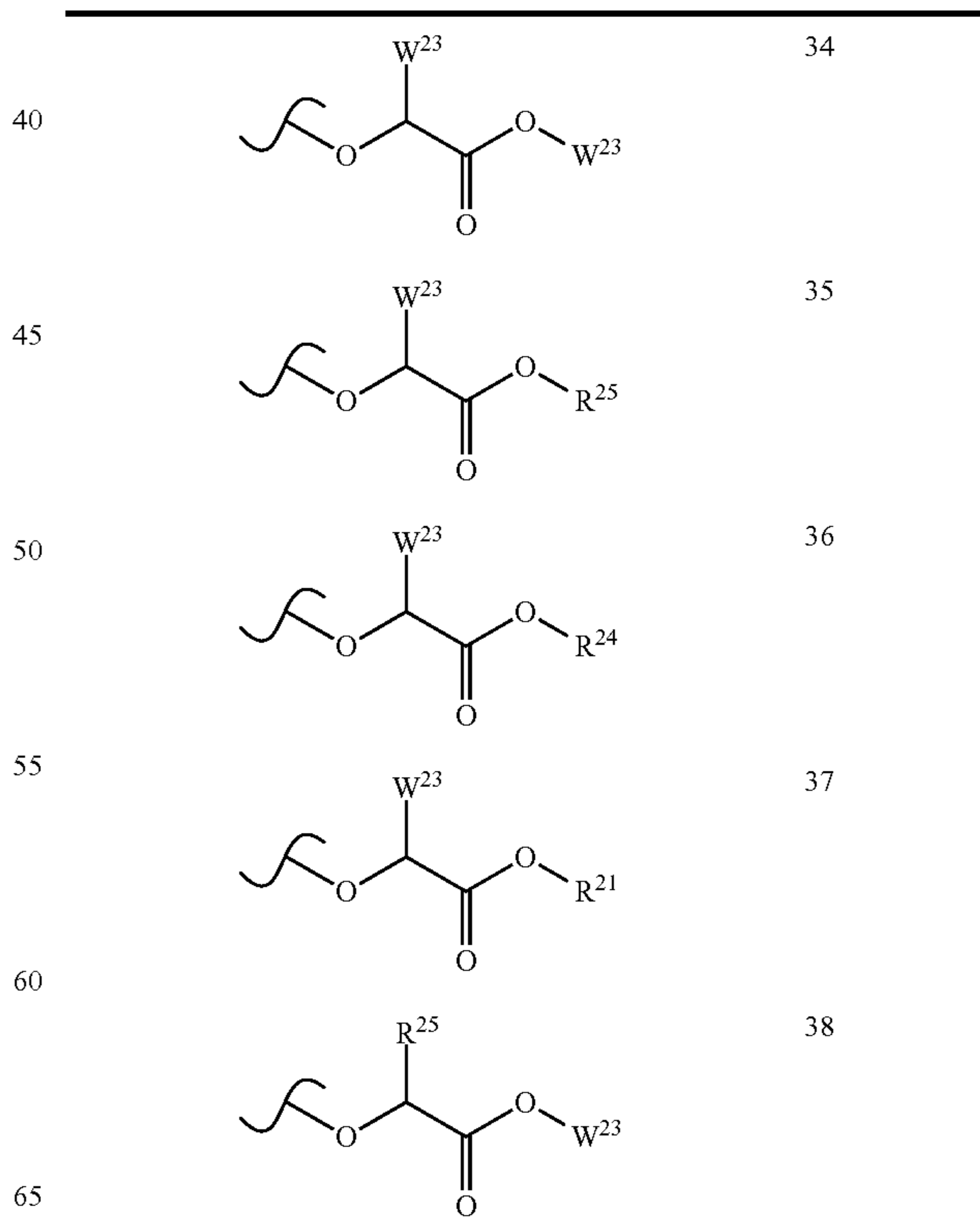


TABLE 20.7



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TABLE 20.7-continued

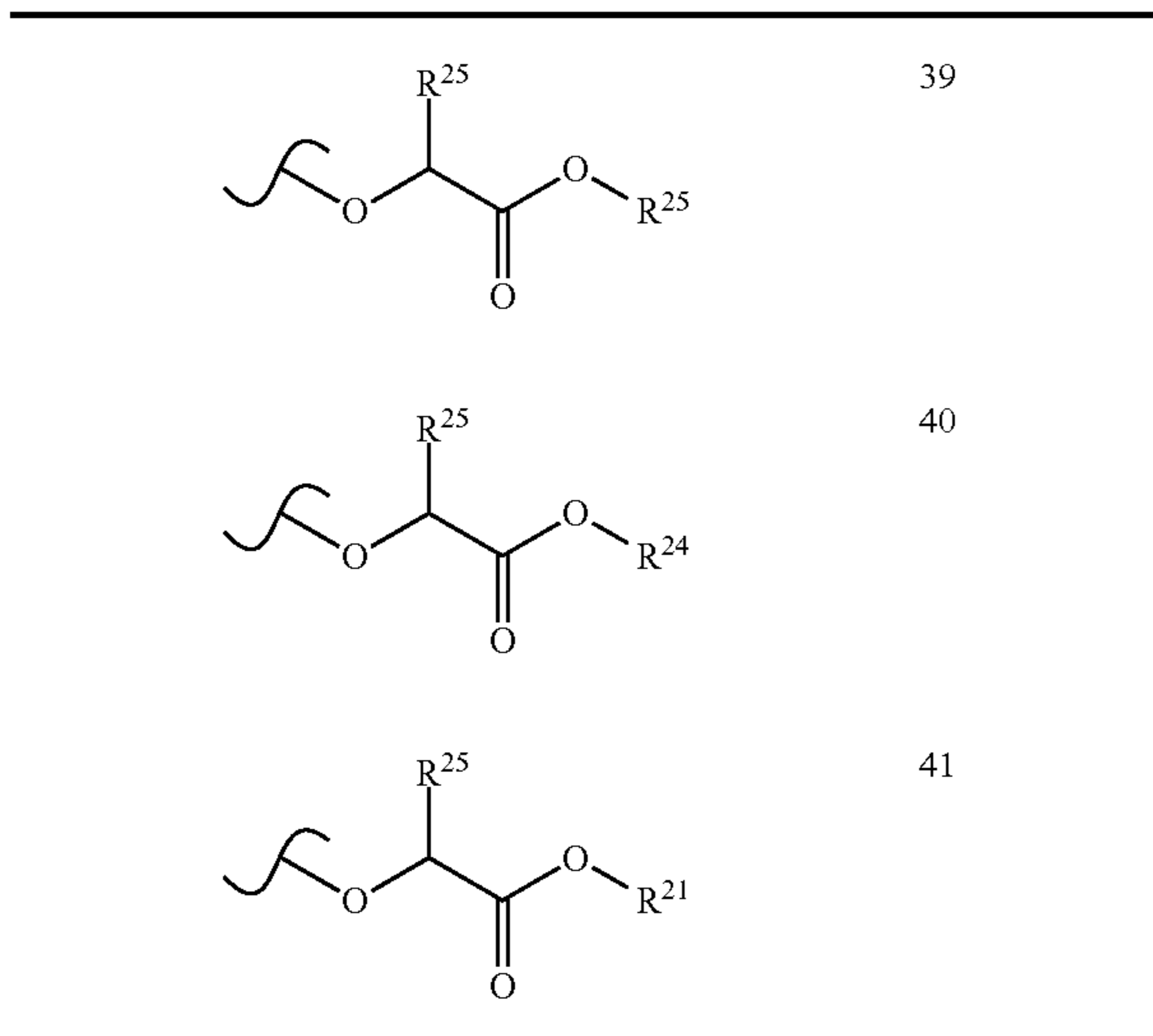
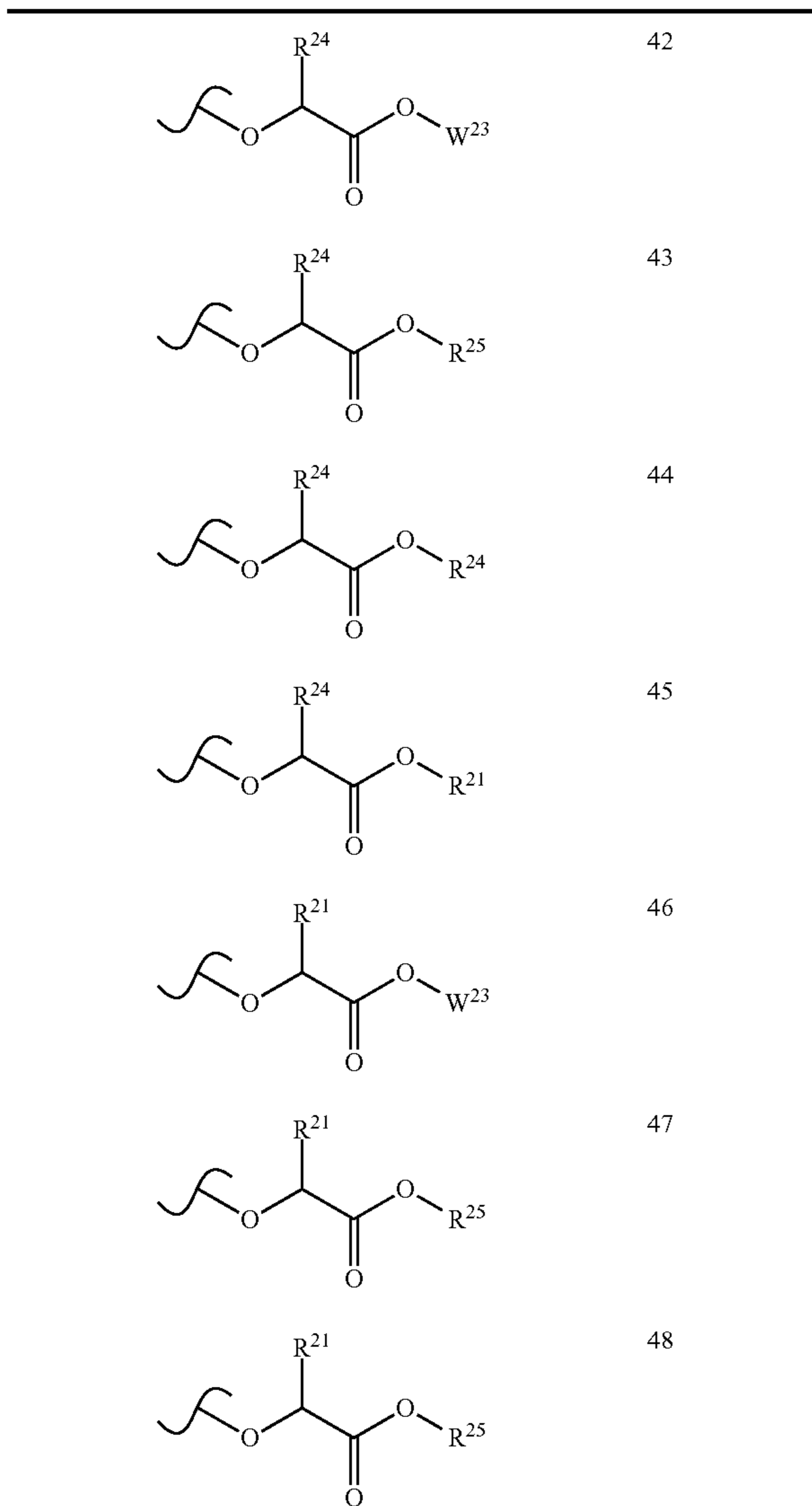


TABLE 20.8



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TABLE 20.8-continued

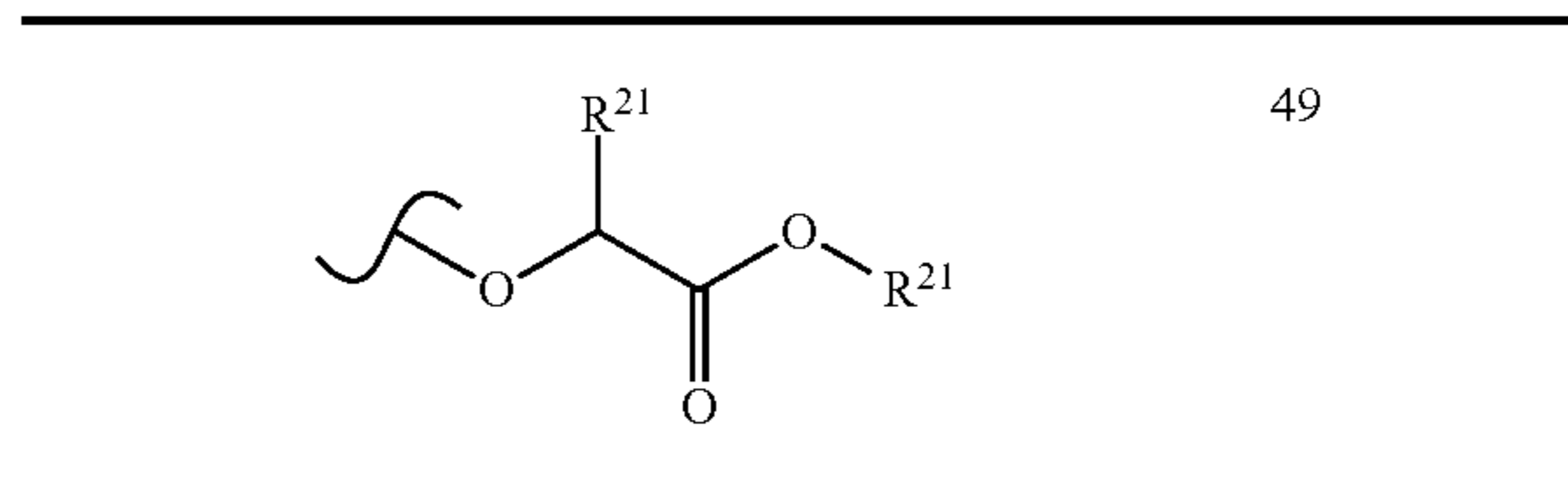


TABLE 20.9

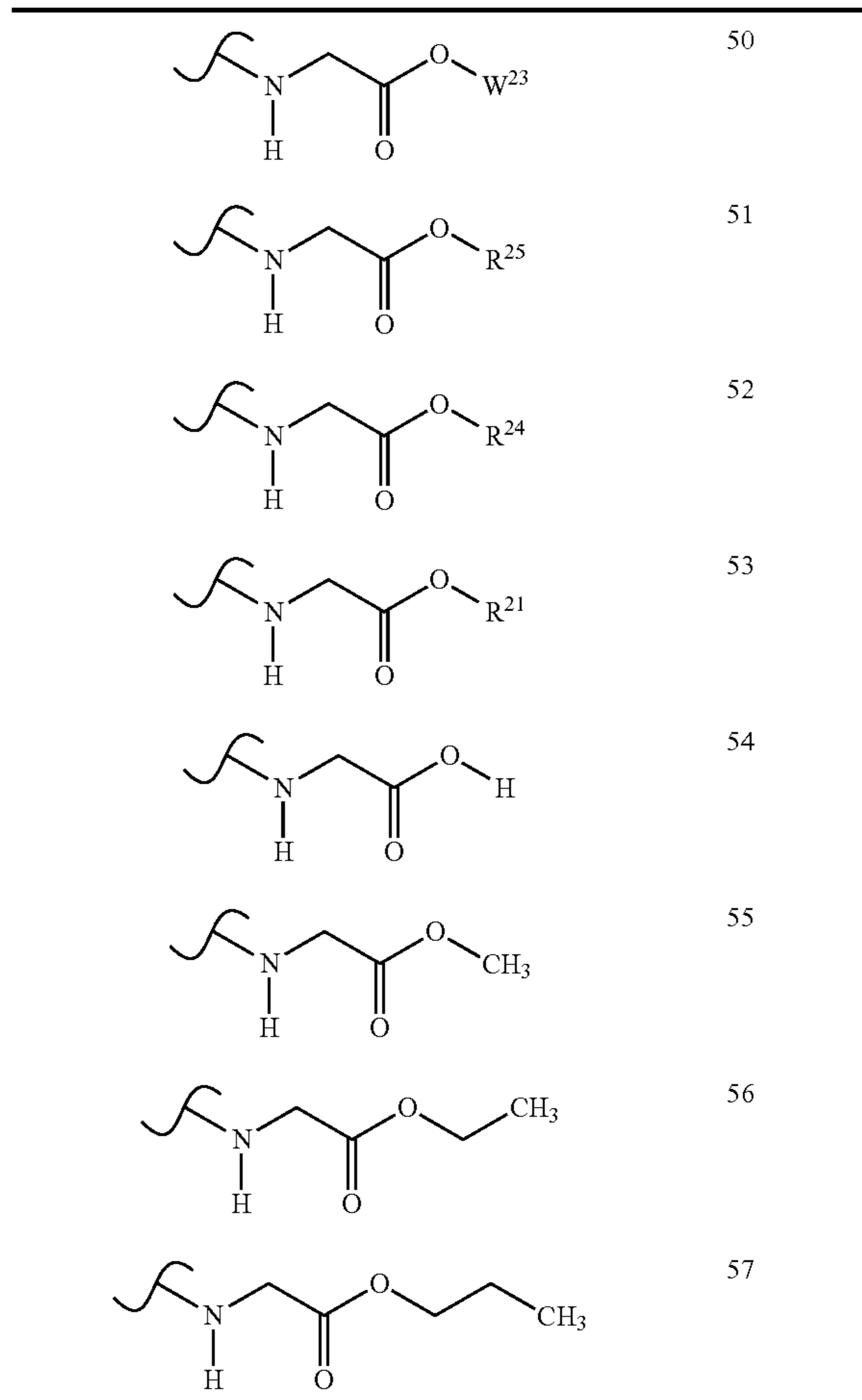
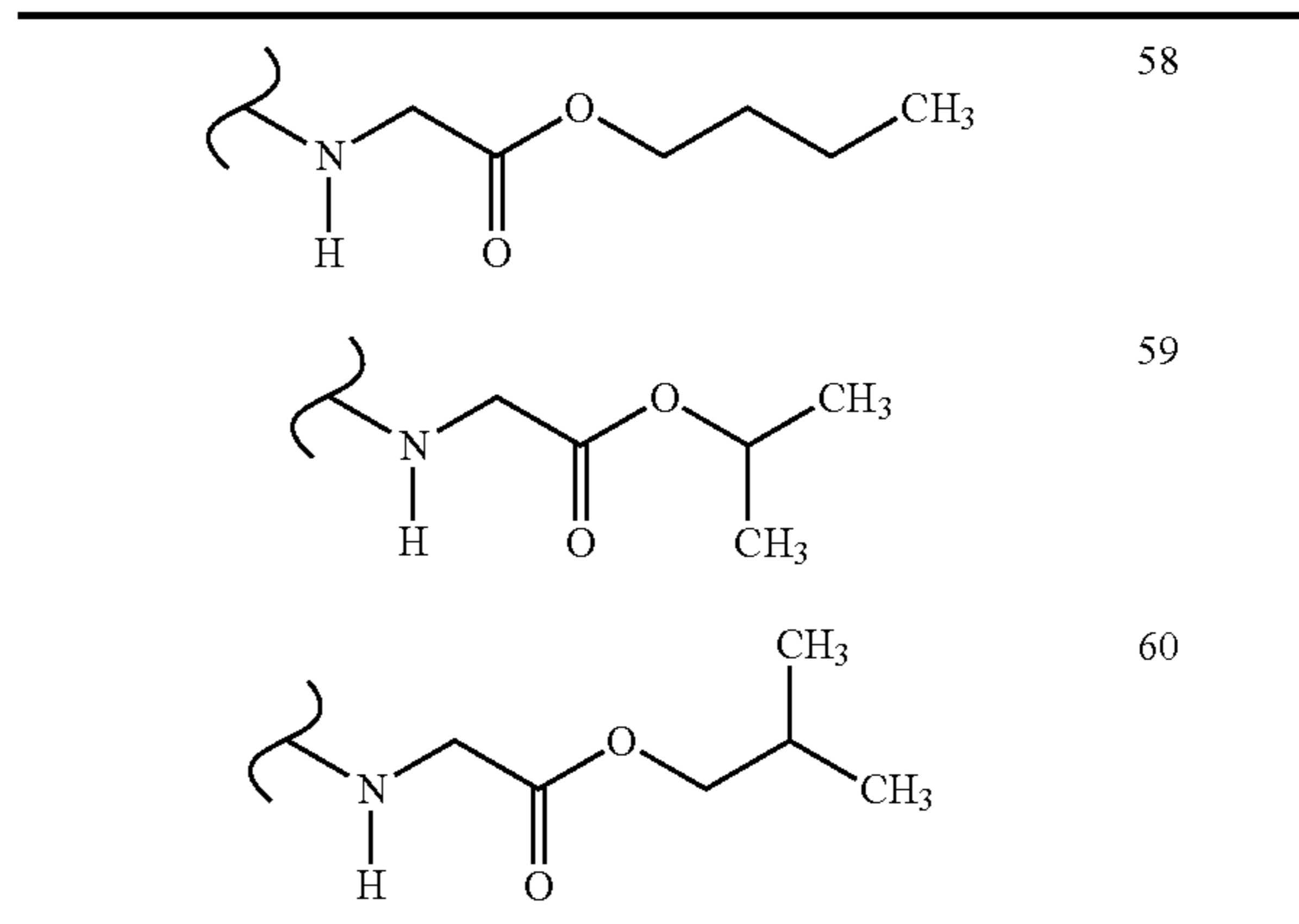


TABLE 20.10



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TABLE 20.11

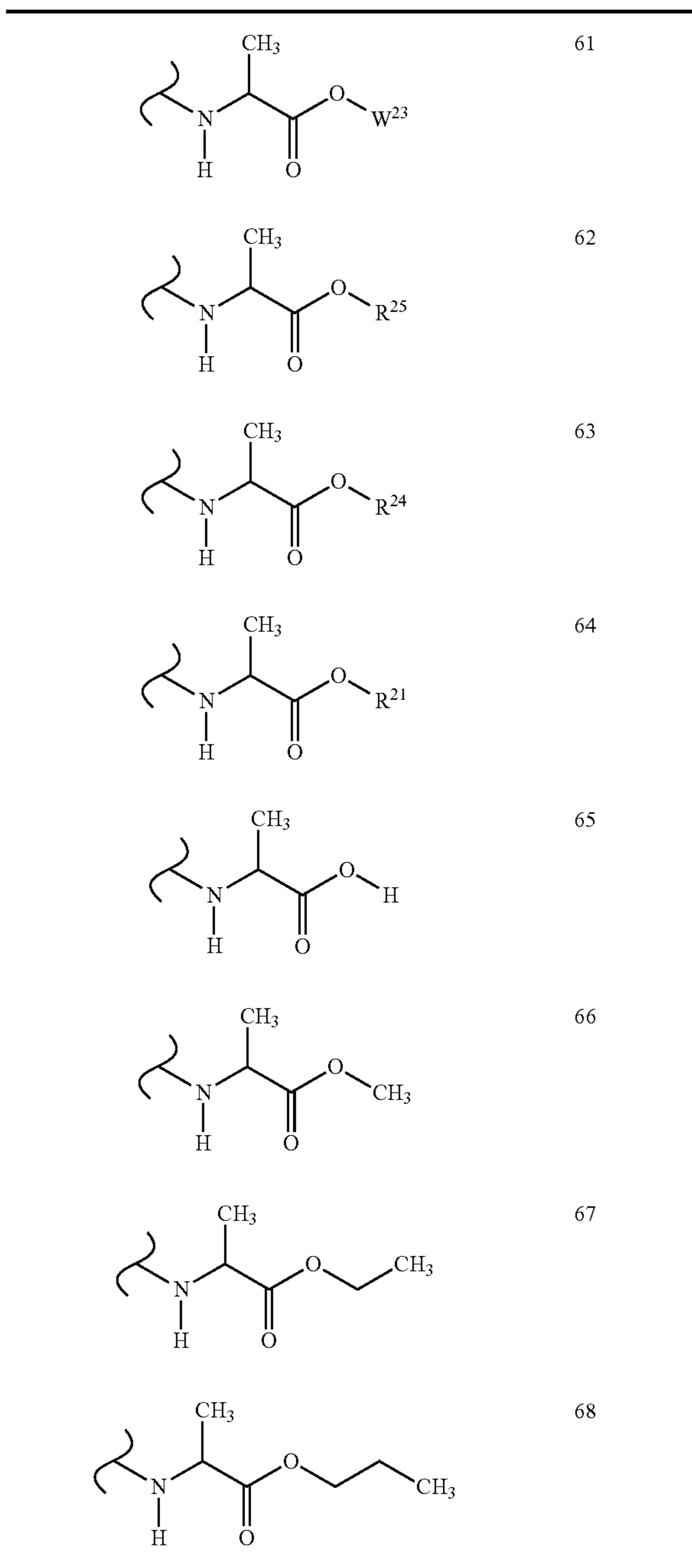
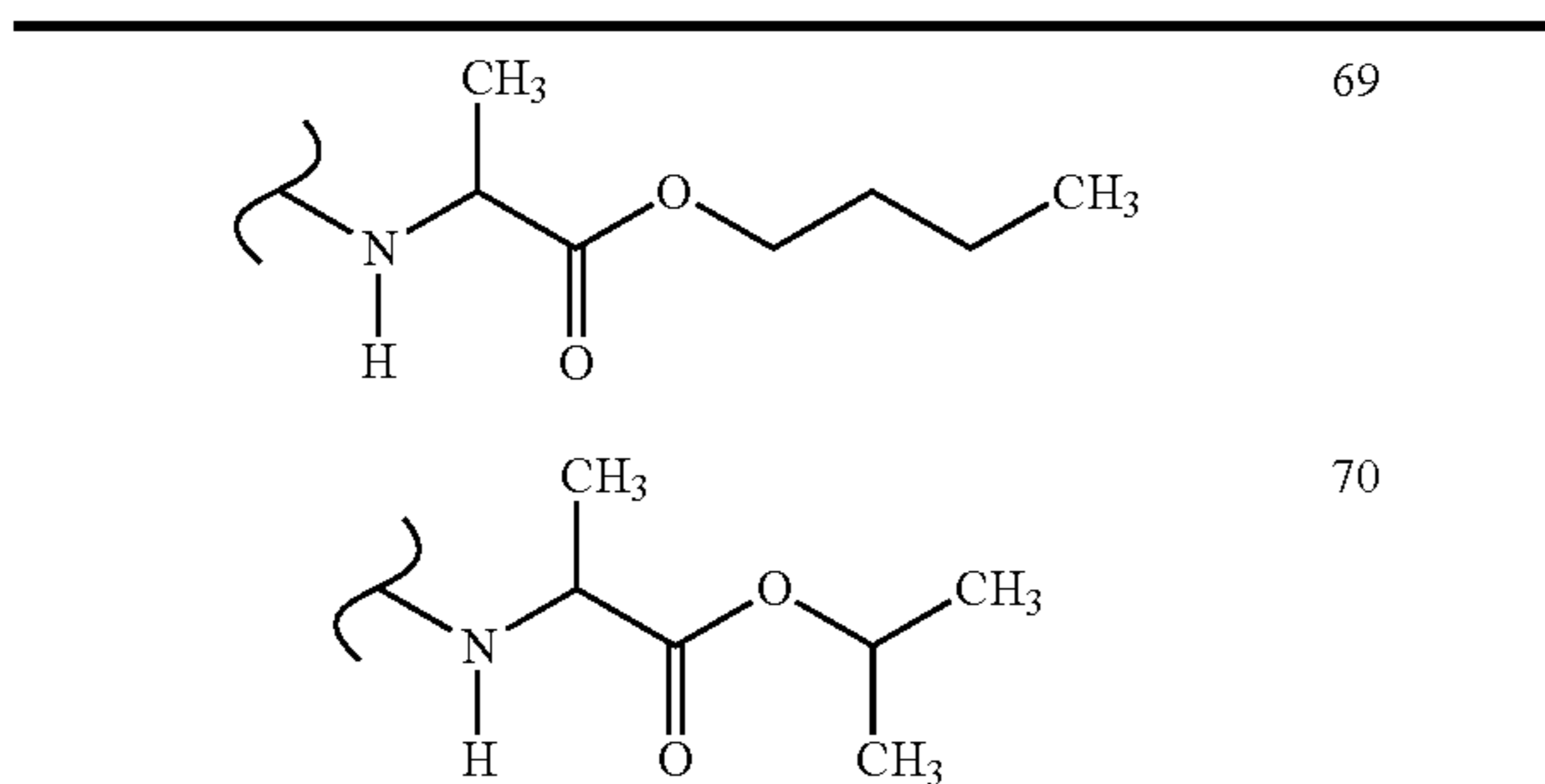


TABLE 20.12



54

TABLE 20.12-continued

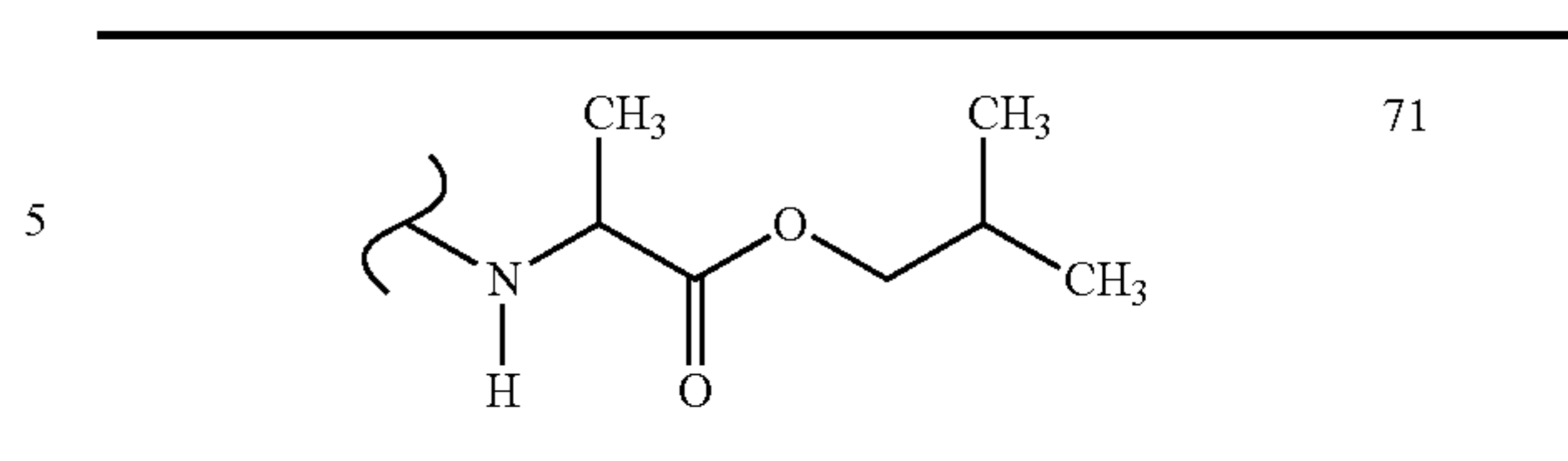


TABLE 20.13

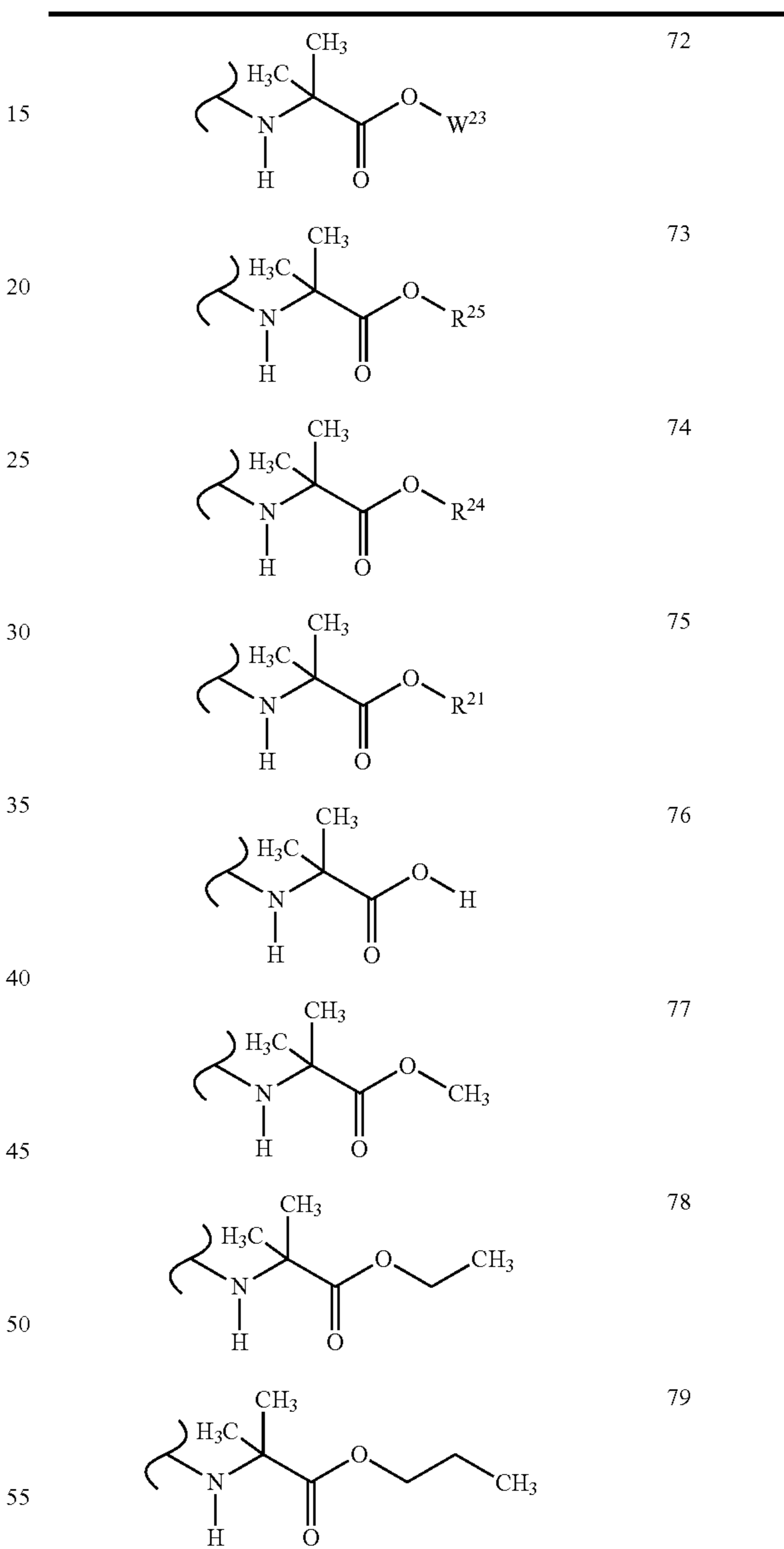
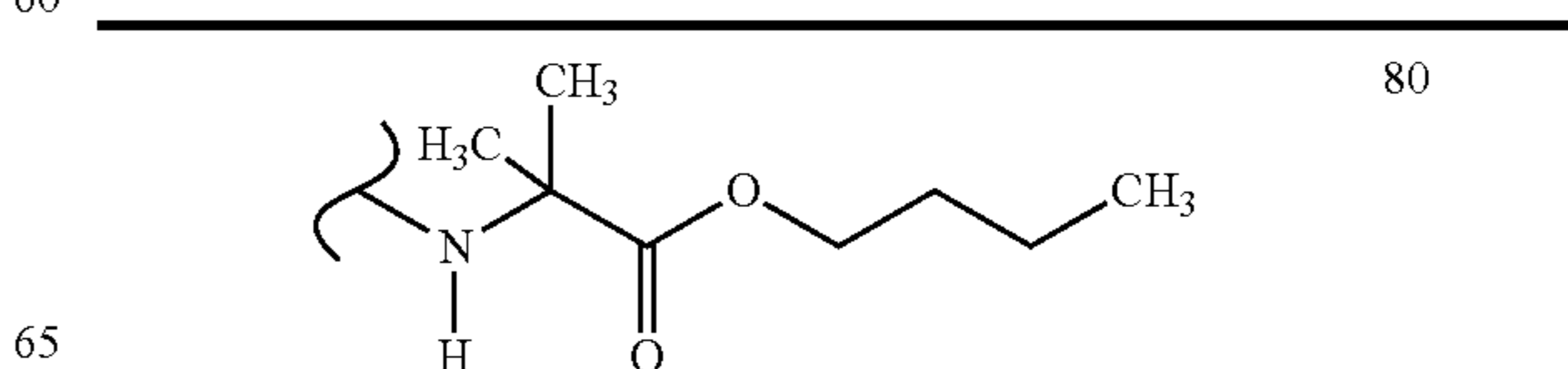


TABLE 20.14



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TABLE 20.14-continued

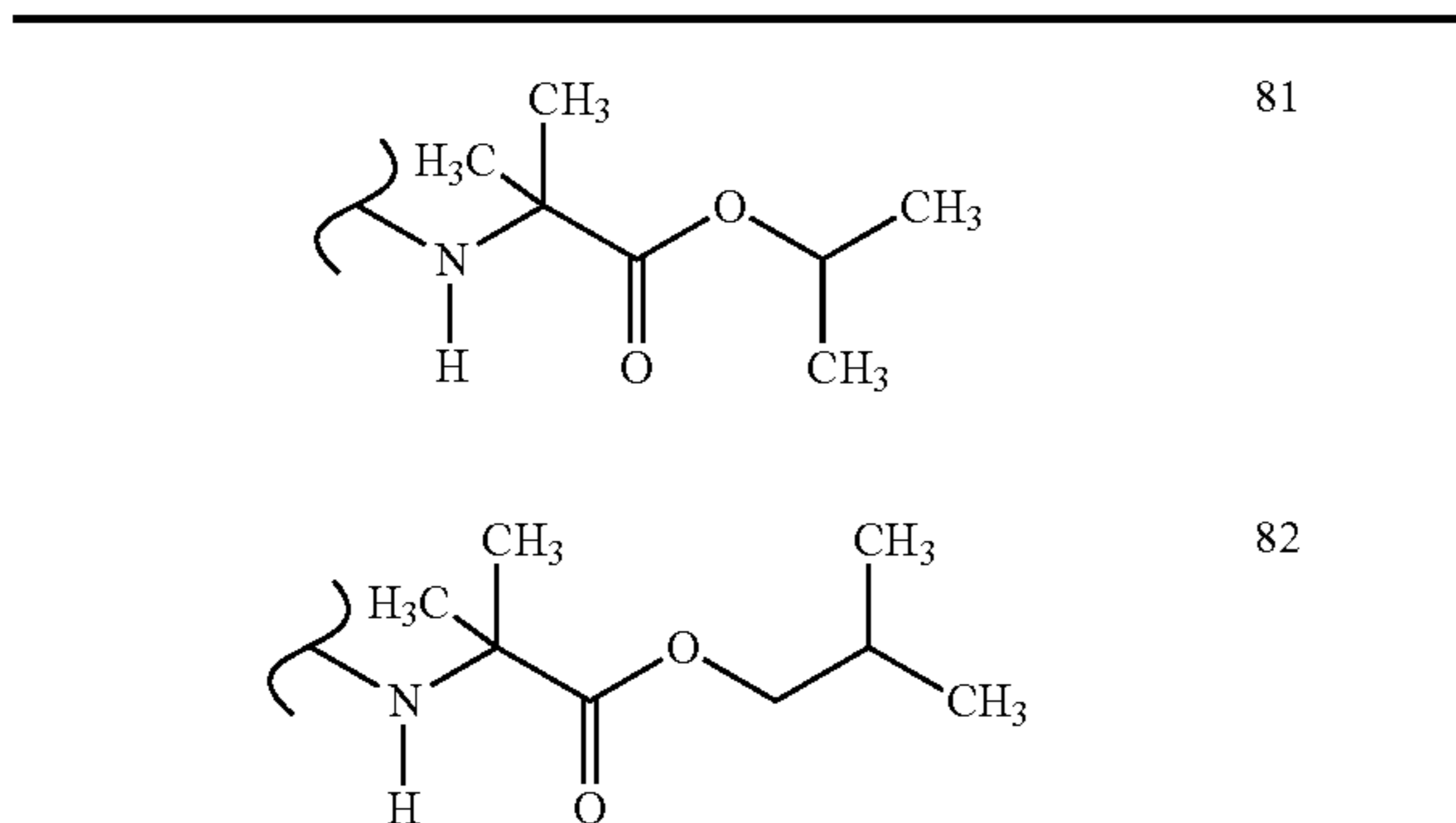
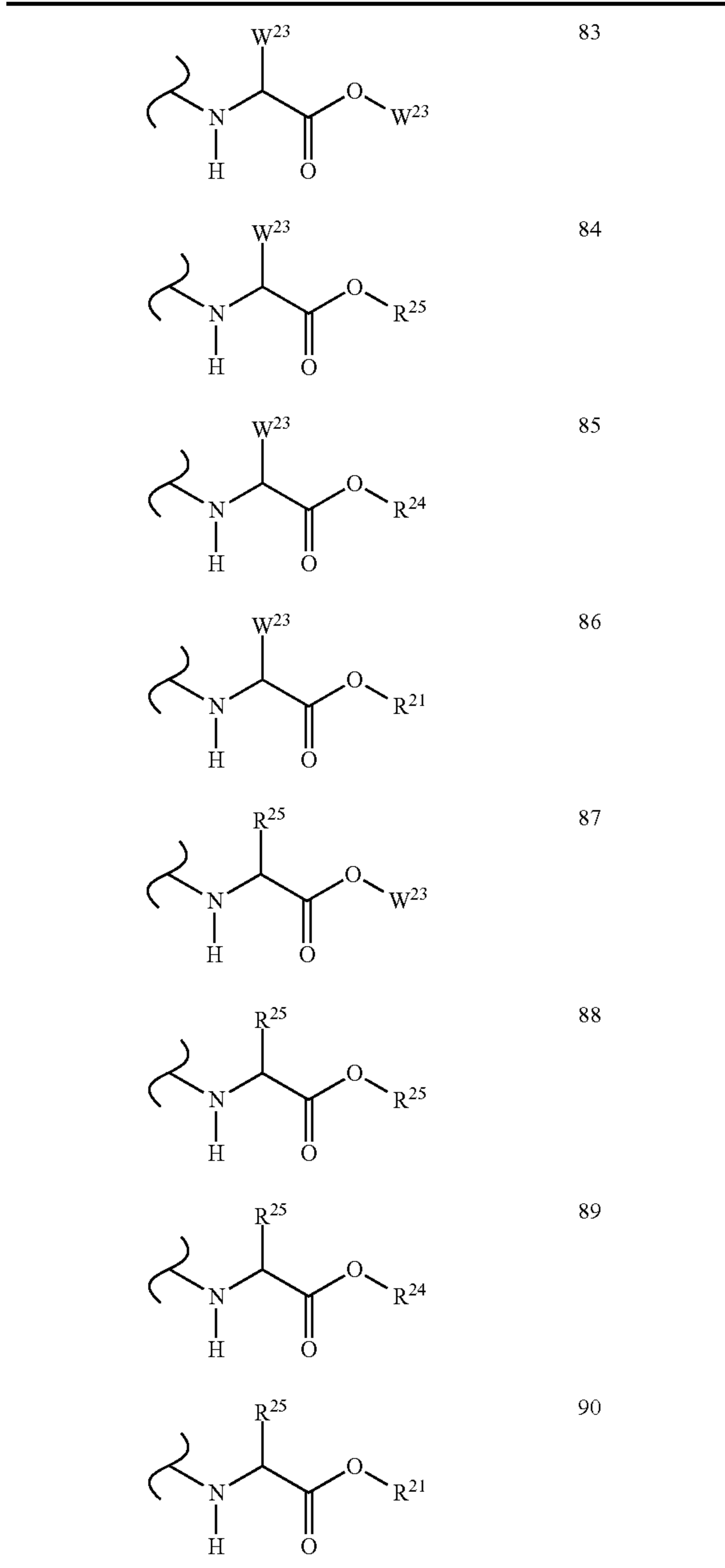


TABLE 20.15



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TABLE 20.16

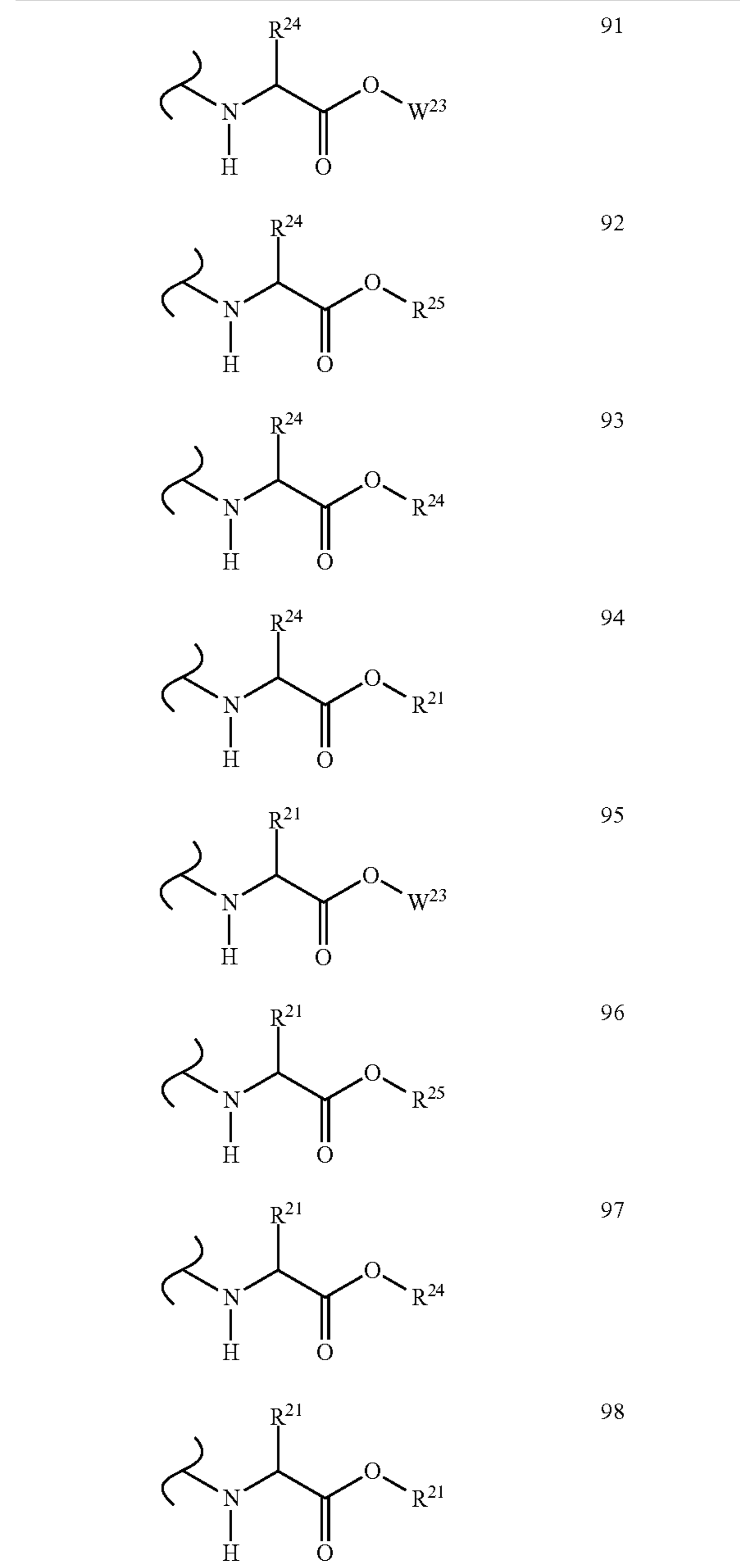
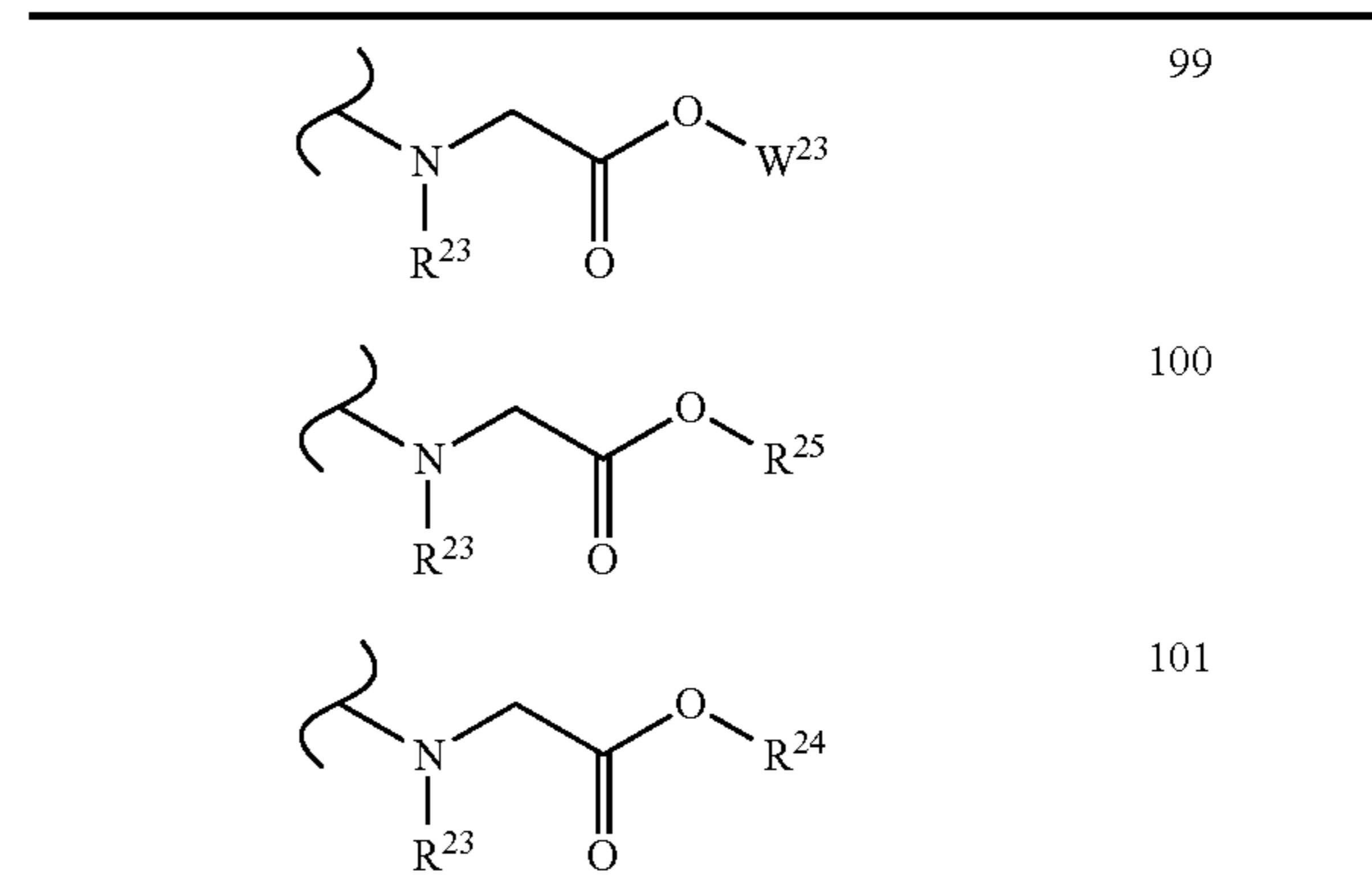


TABLE 20.17



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TABLE 20.17-continued

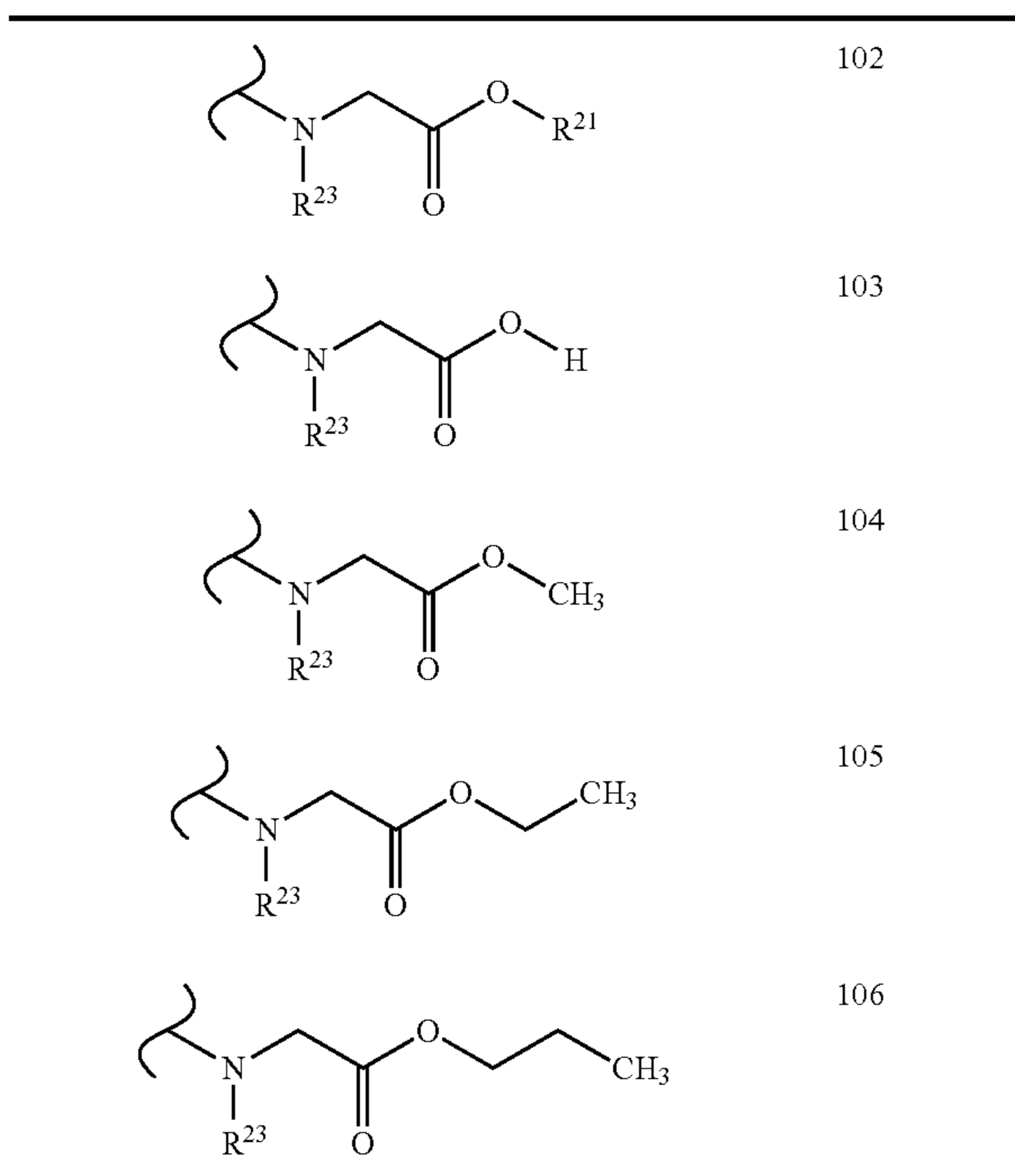


TABLE 20.18

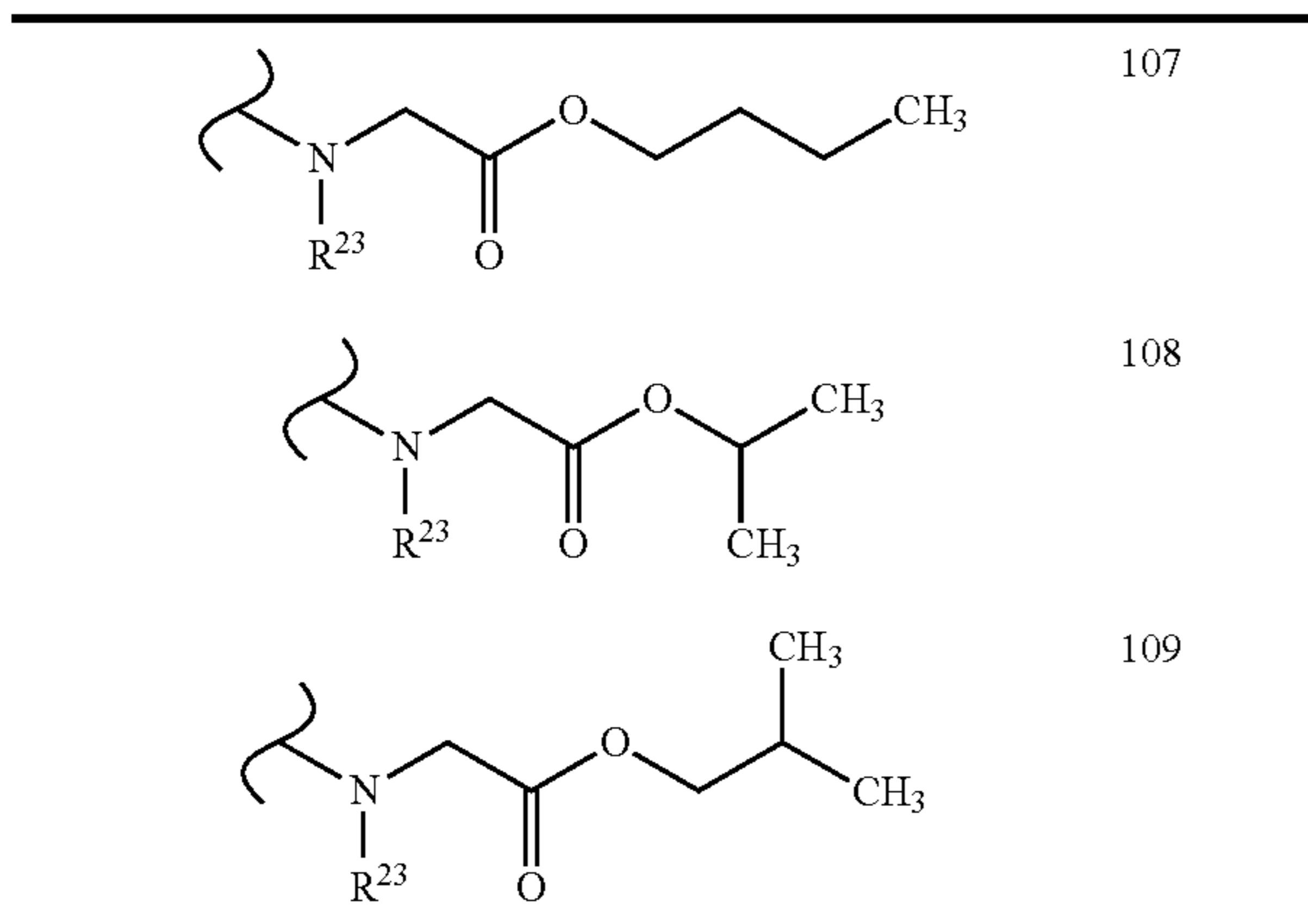
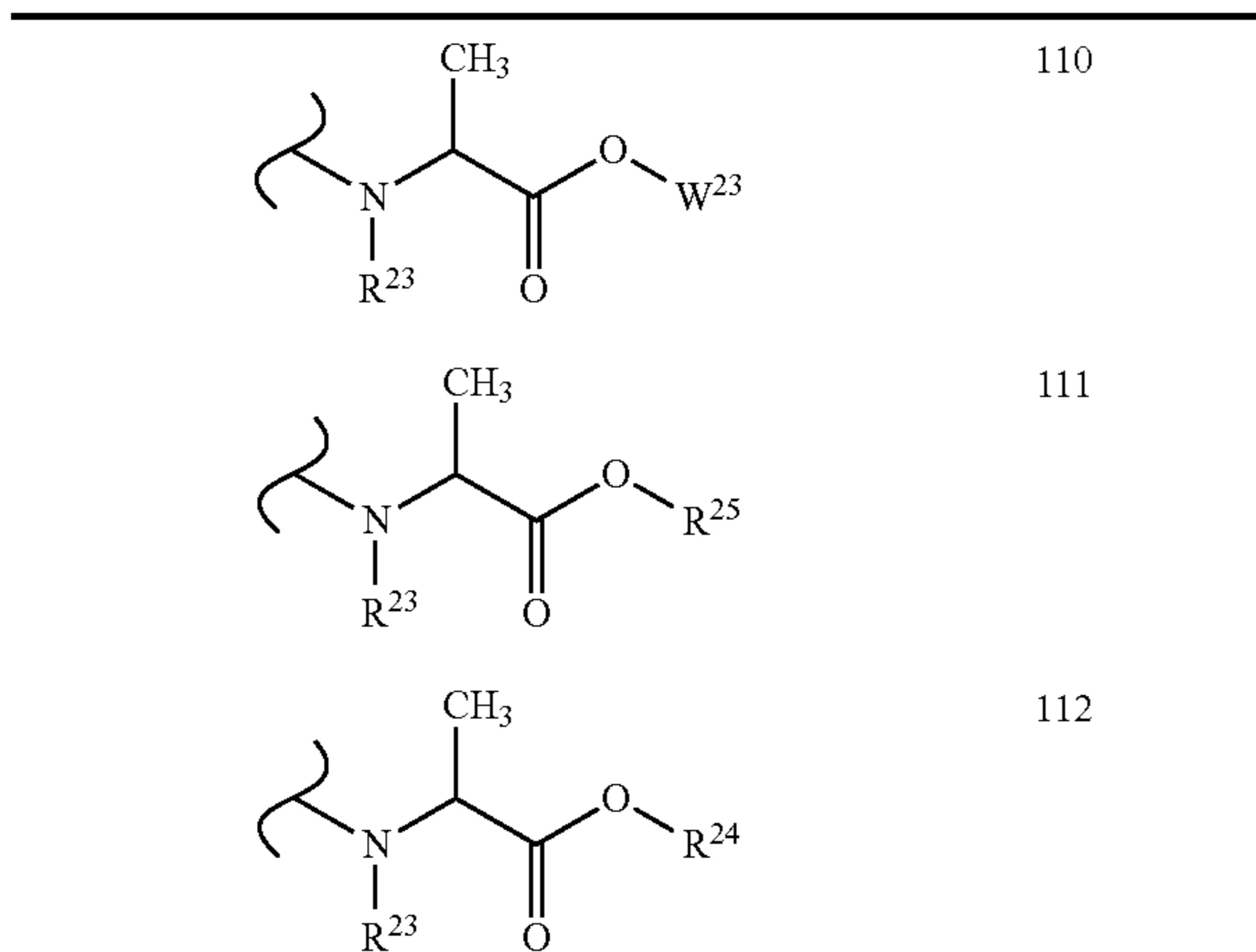


TABLE 20.19



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TABLE 20.19-continued

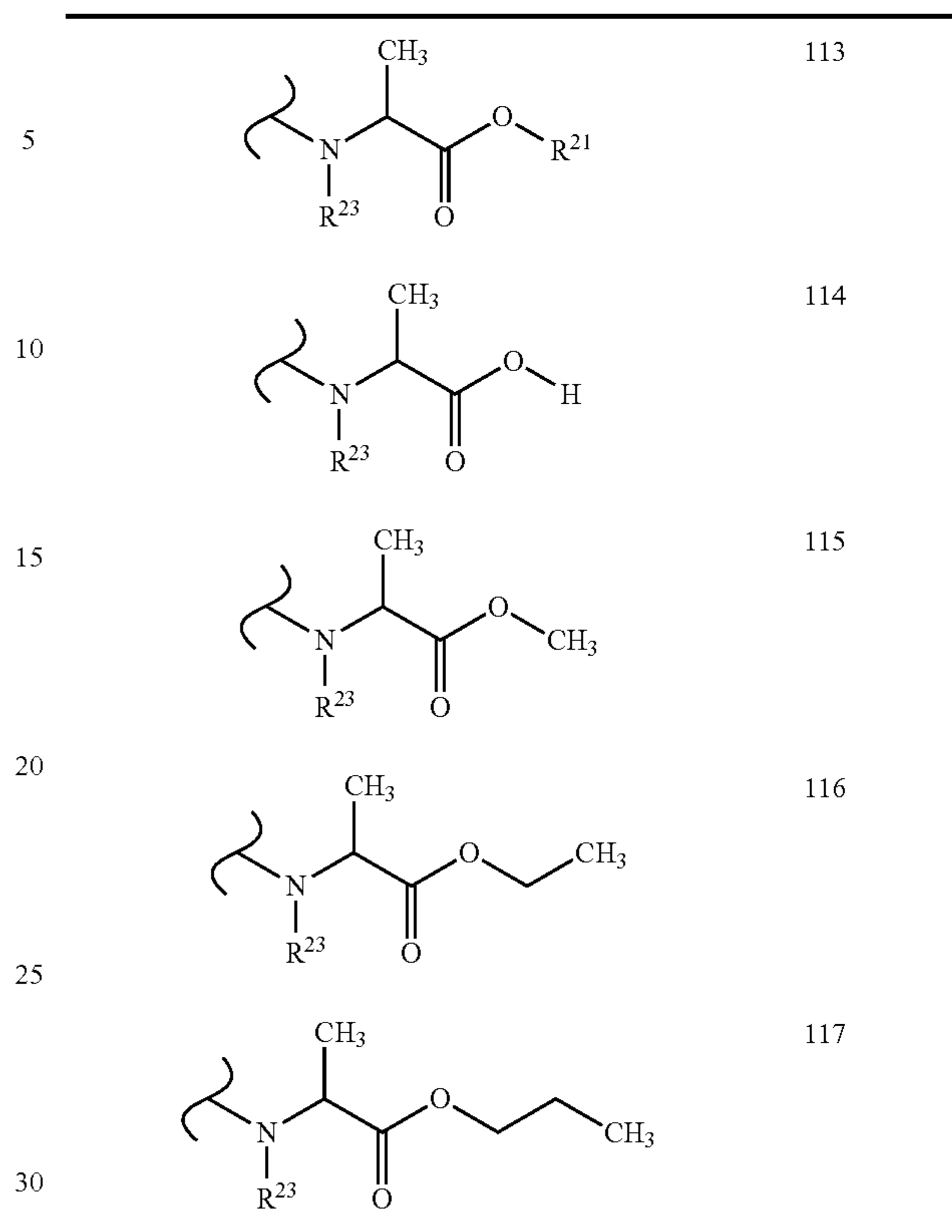


TABLE 20.20

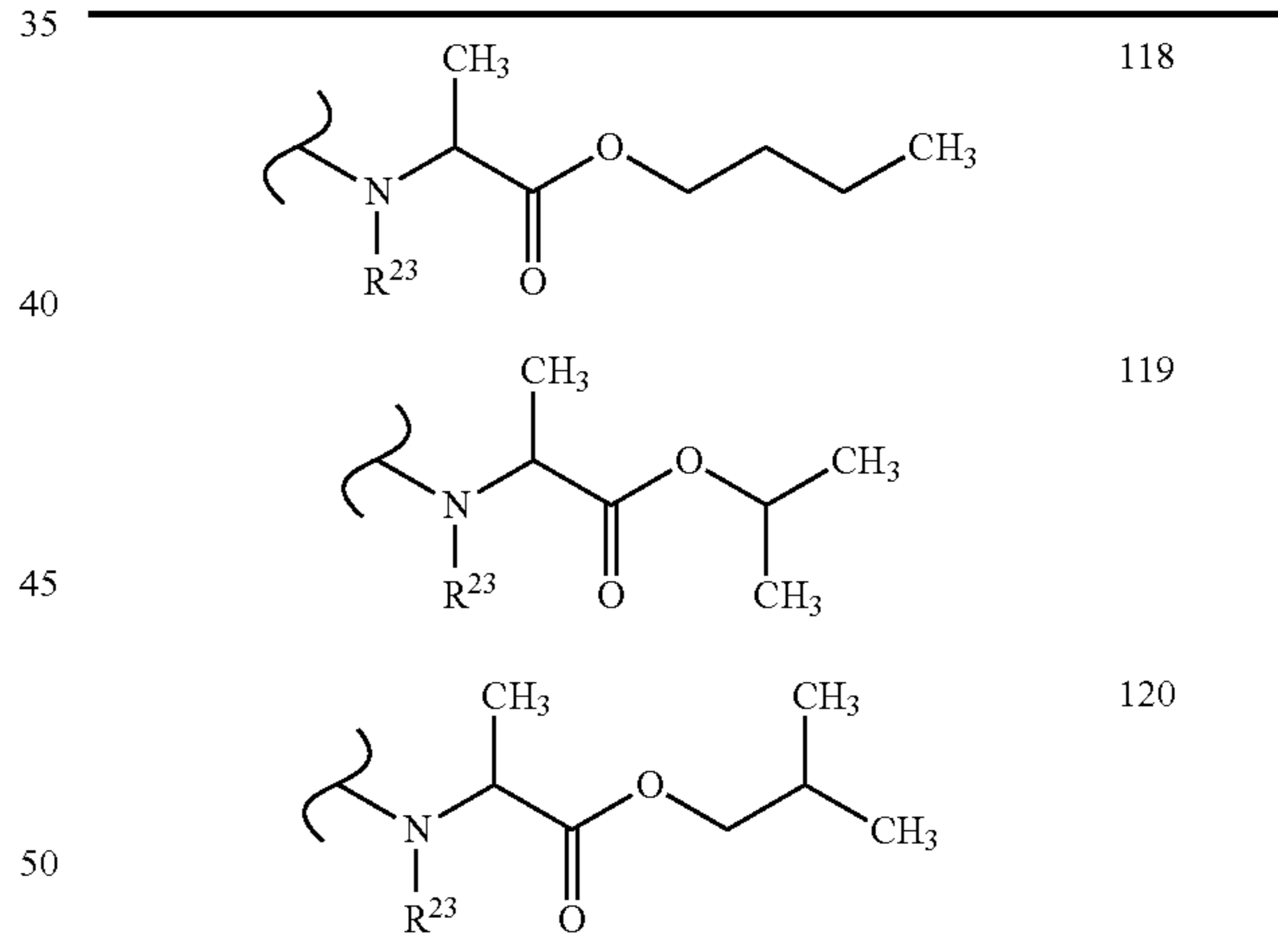
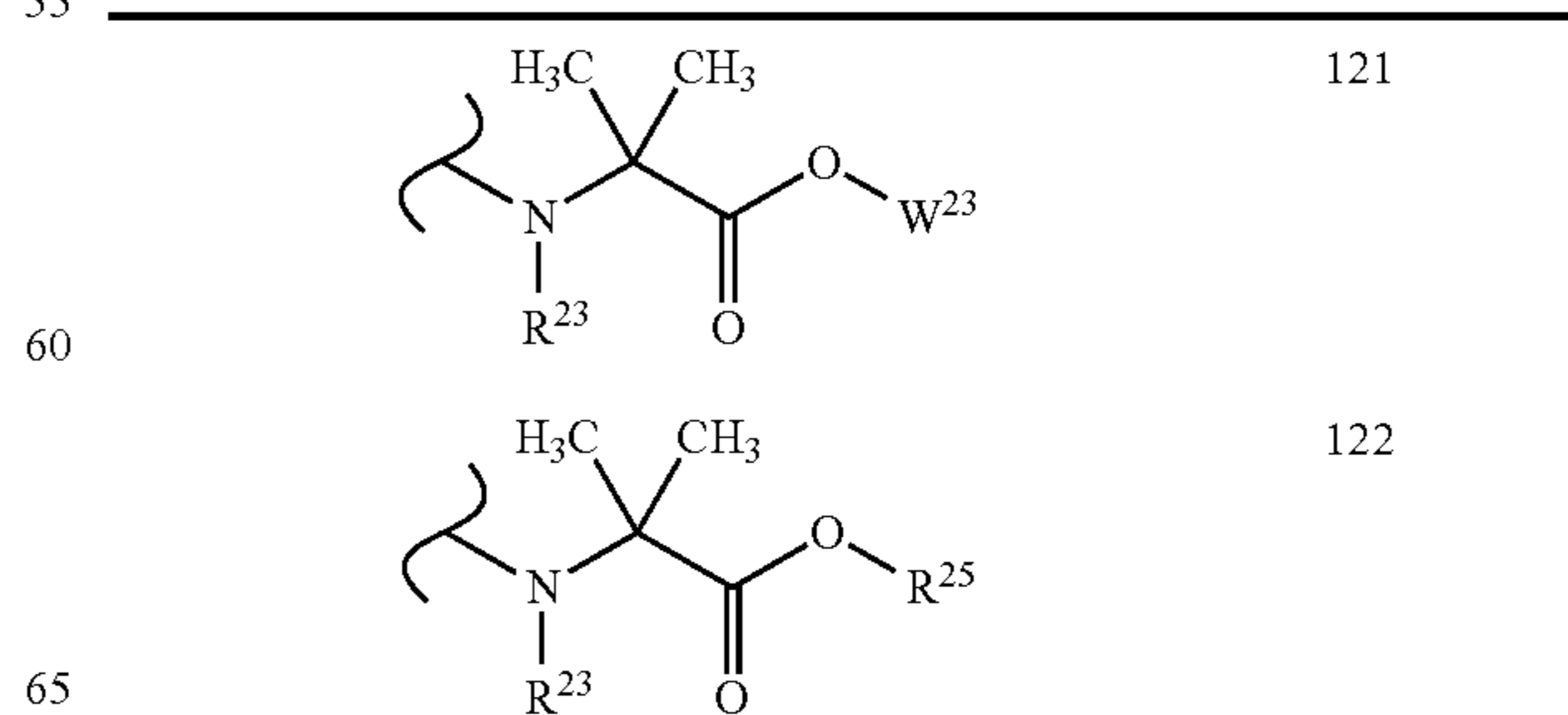


TABLE 20.21



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TABLE 20.21-continued

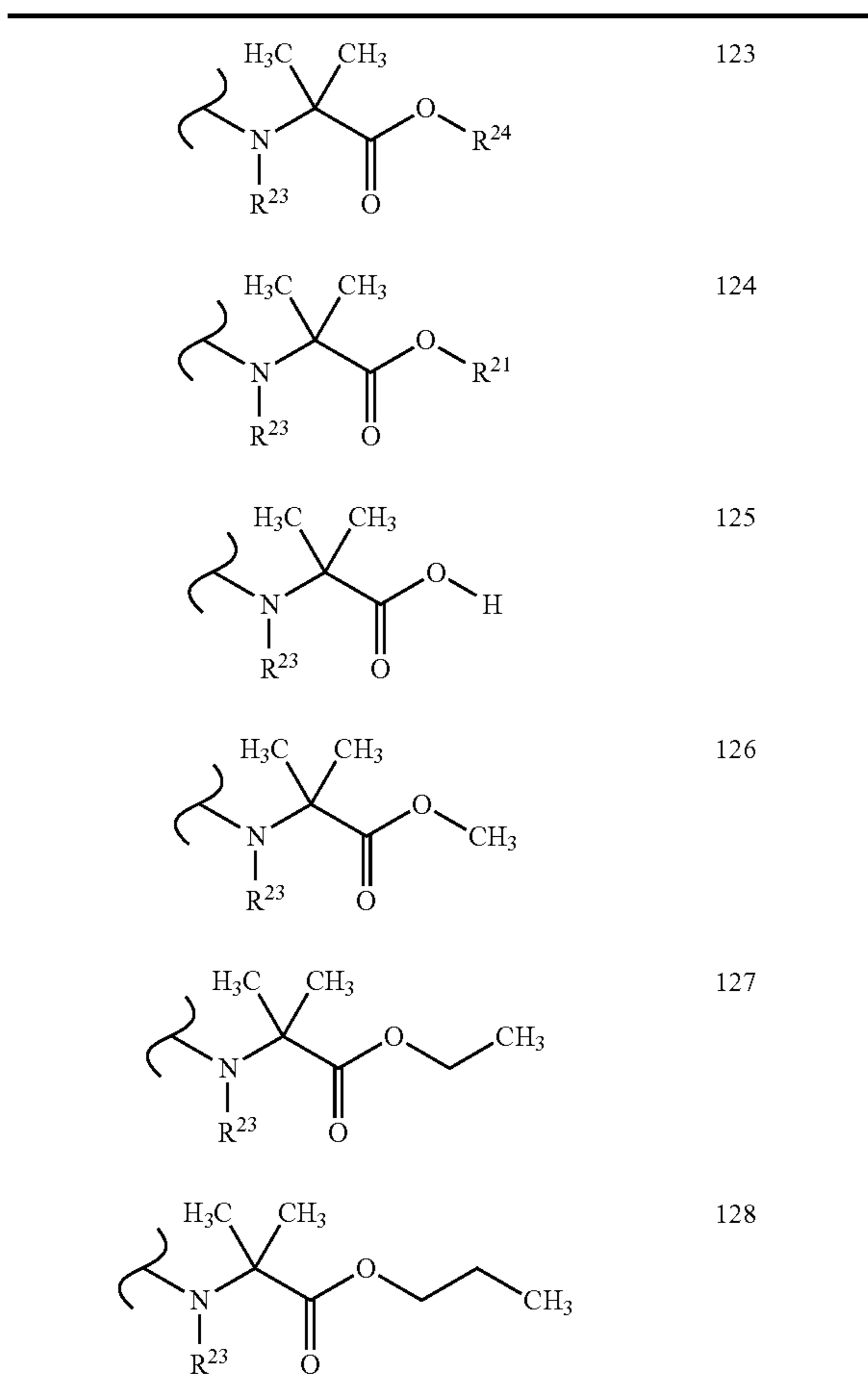


TABLE 20.22

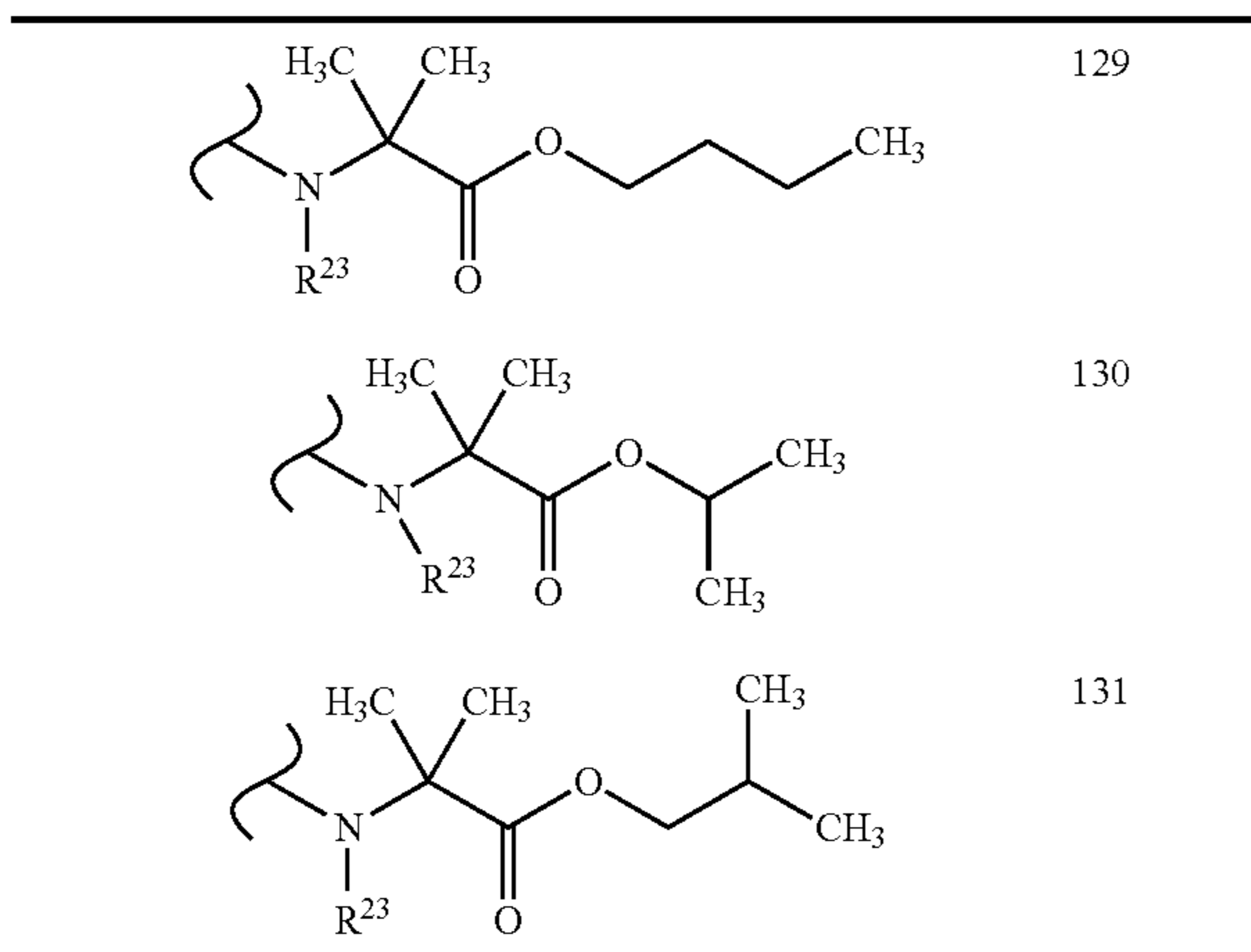
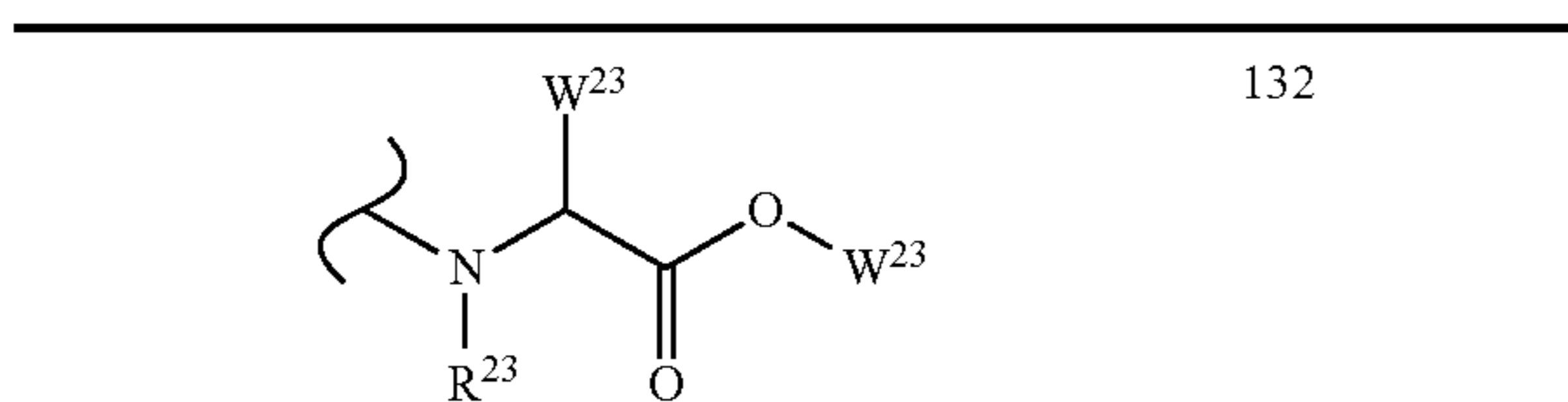


TABLE 20.23



60

TABLE 20.23-continued

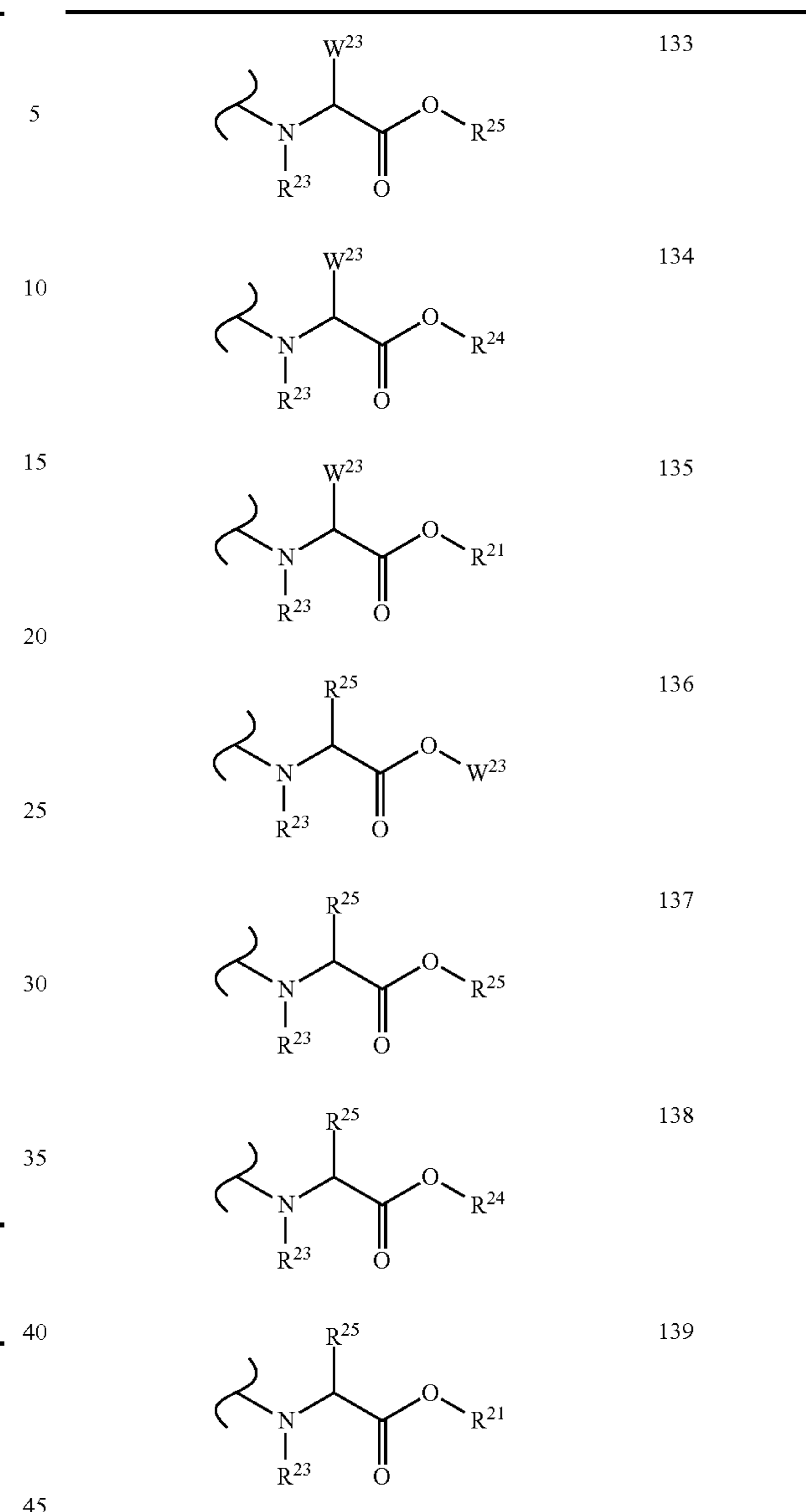
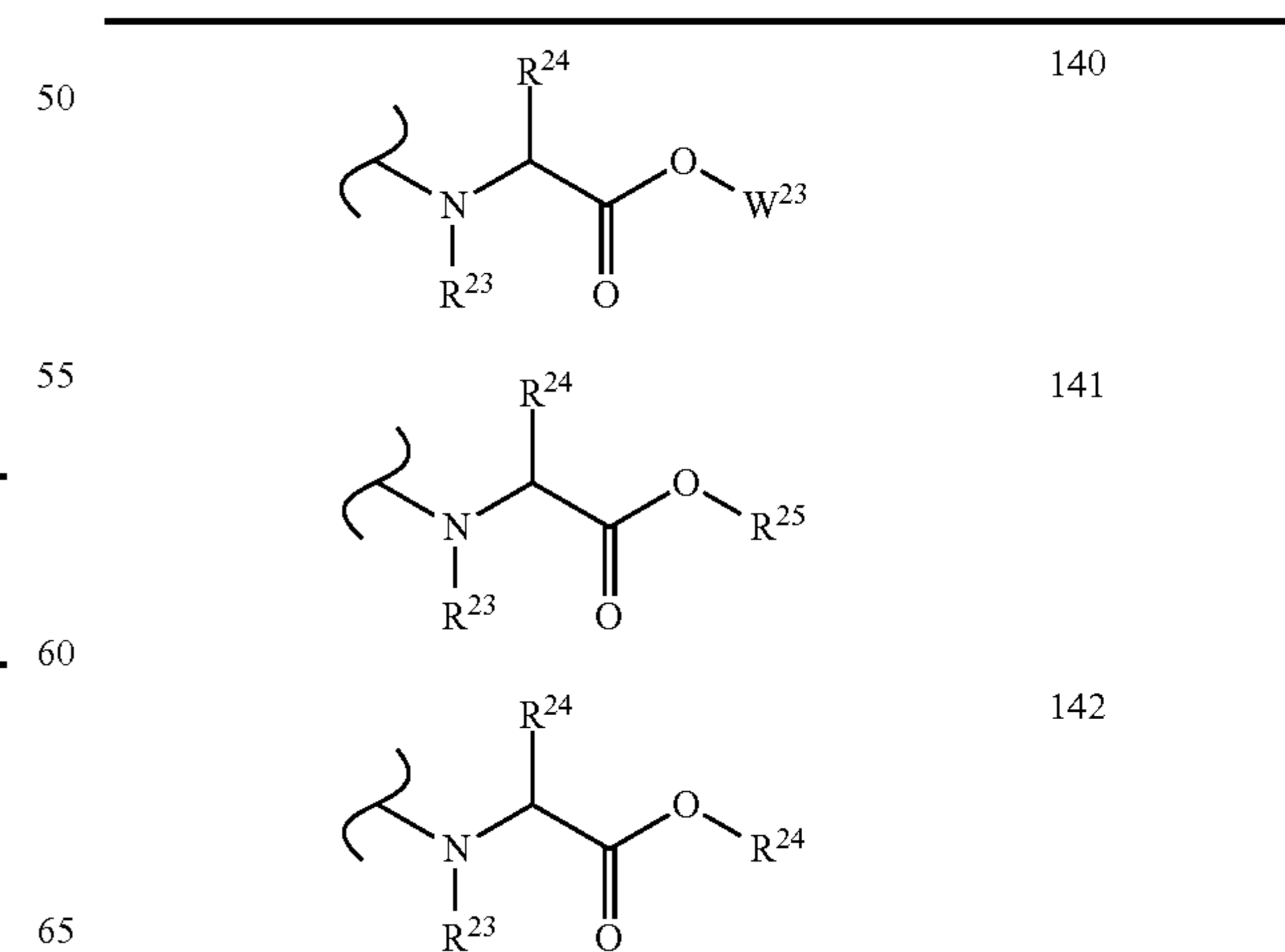


TABLE 20.24



61

TABLE 20.24-continued

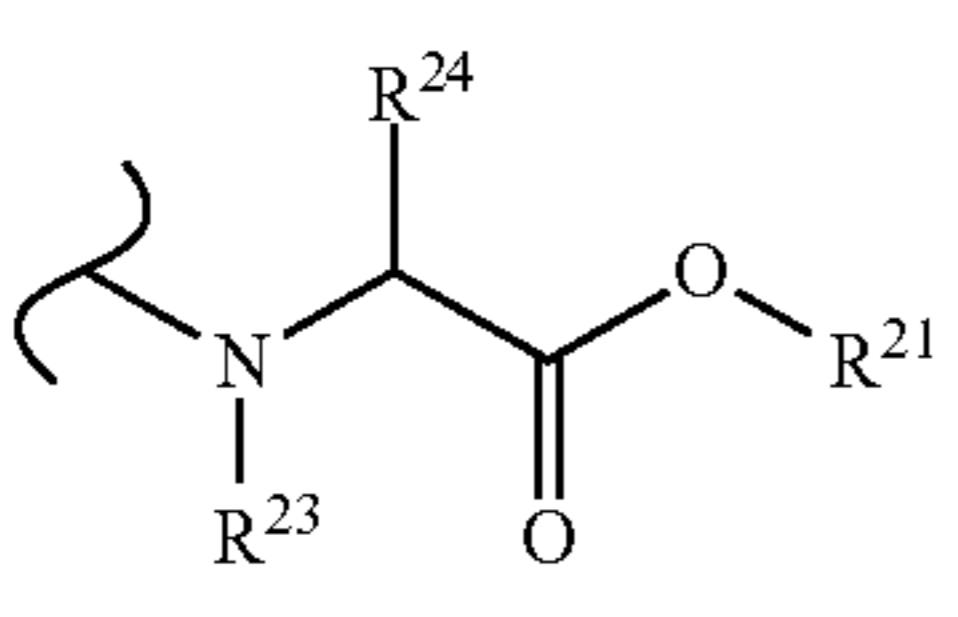
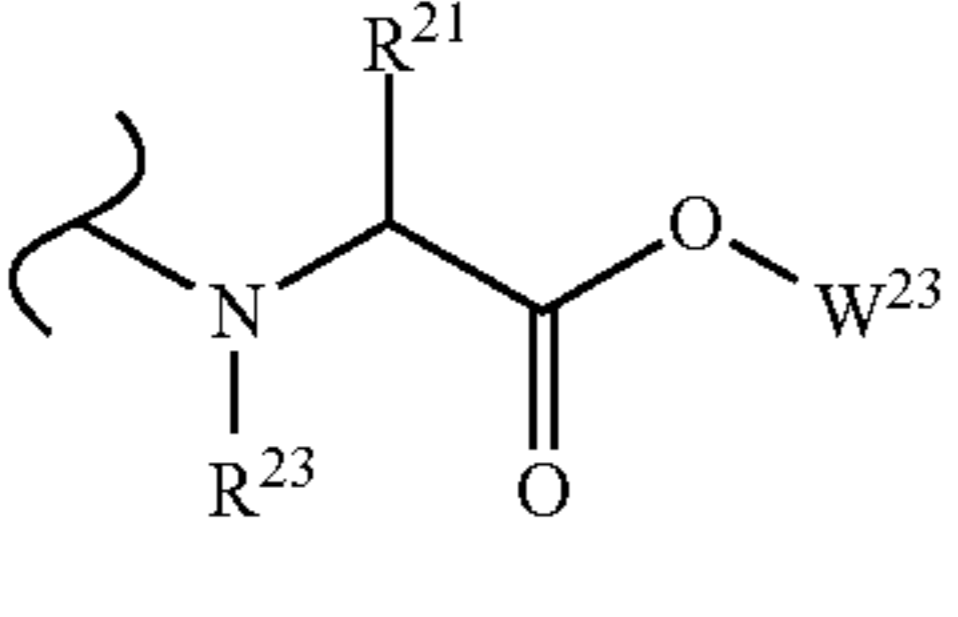
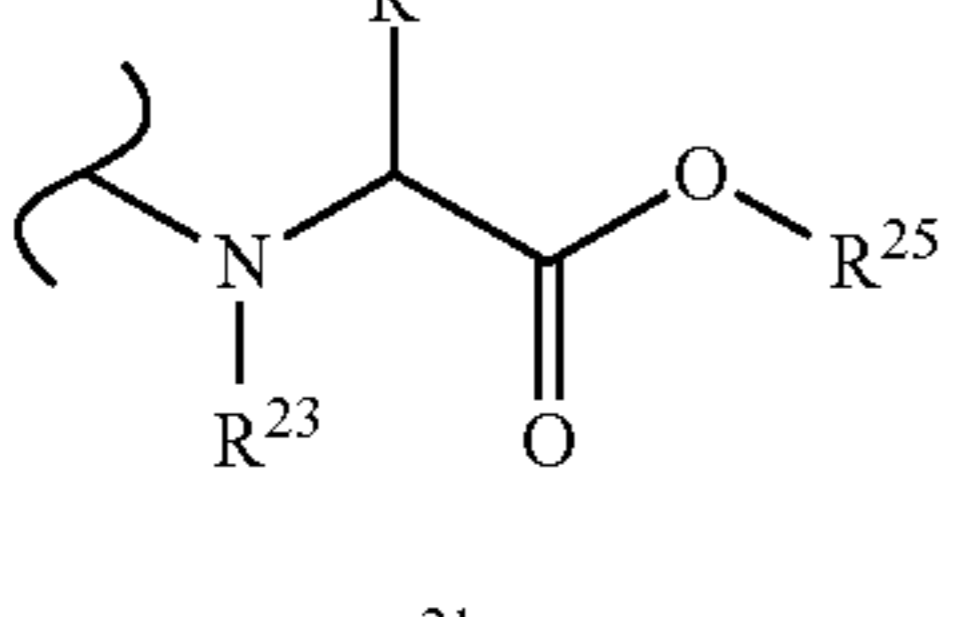
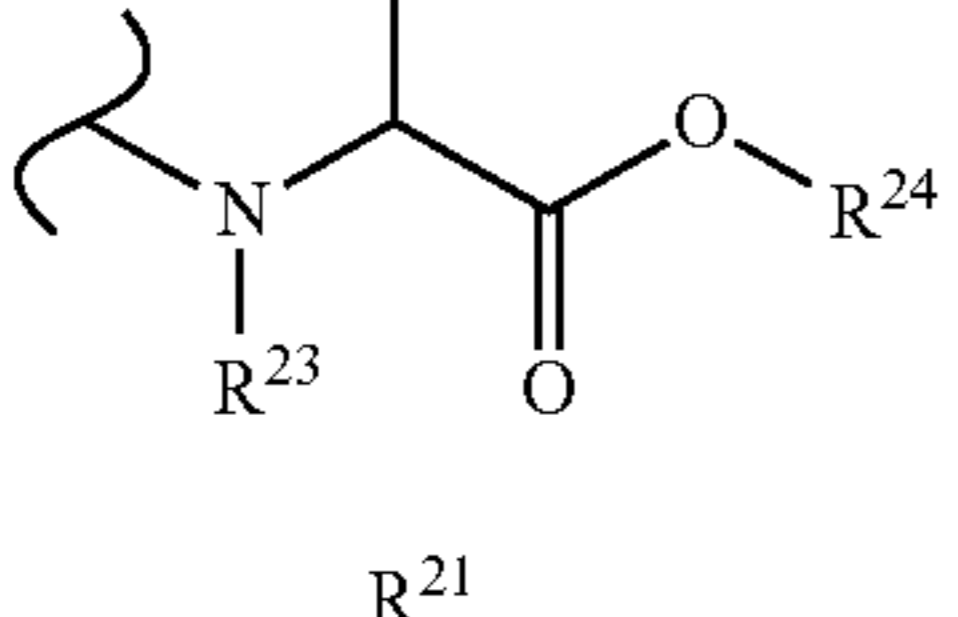
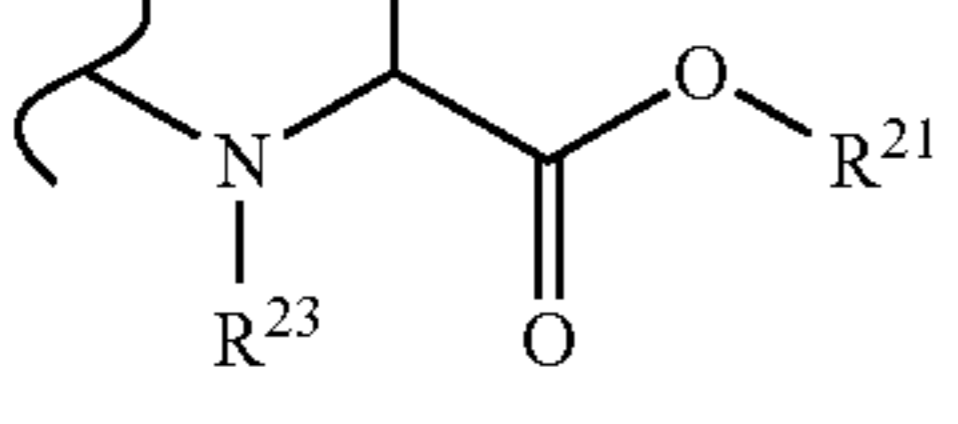
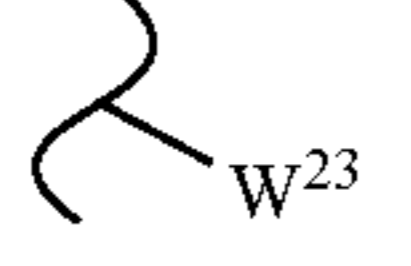
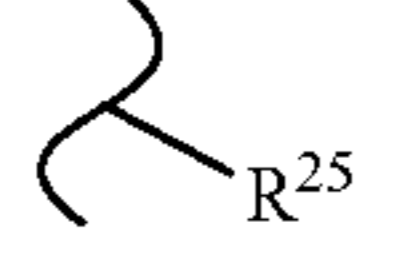
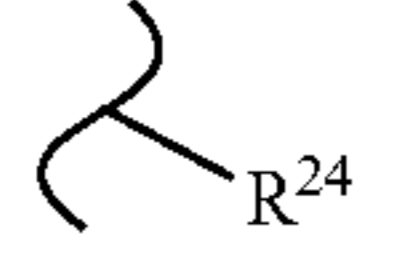
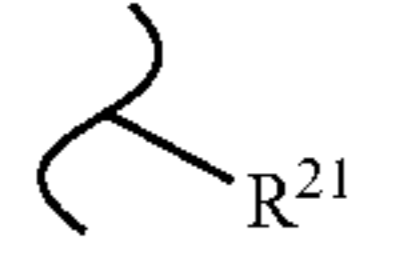
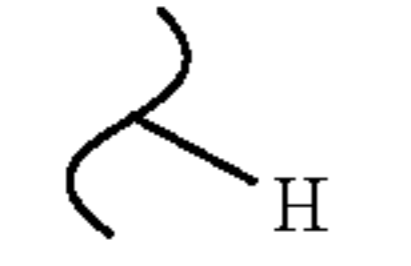
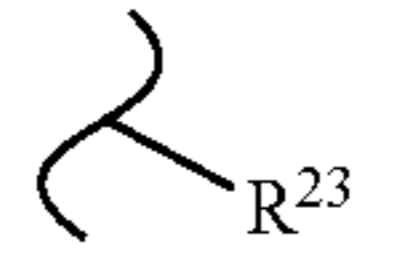
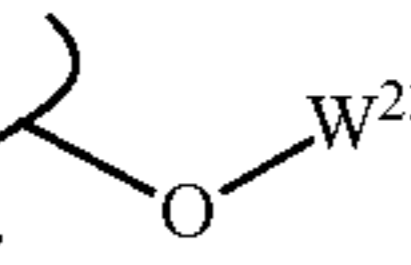
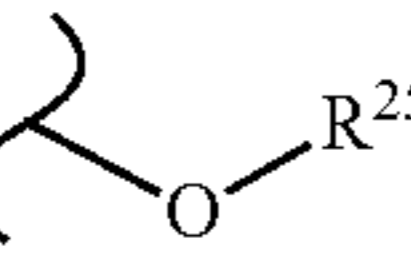
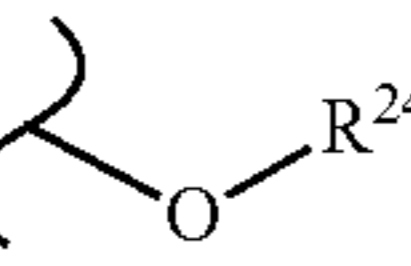
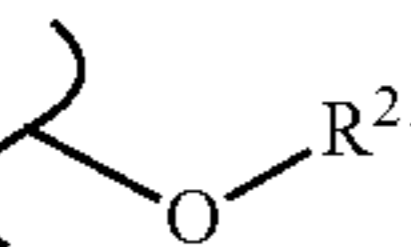
	143
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TABLE 20.25

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TABLE 20.25-continued

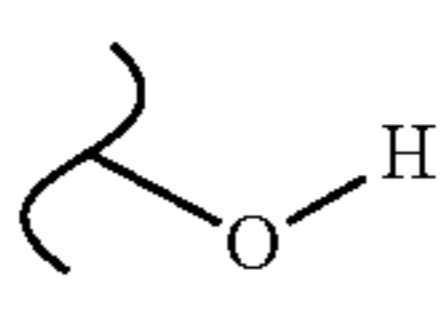
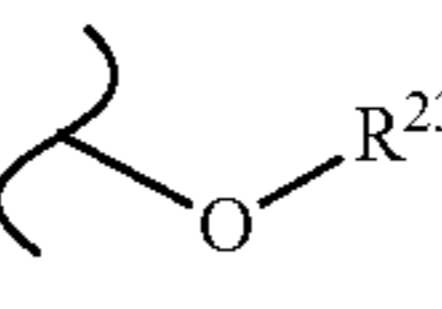
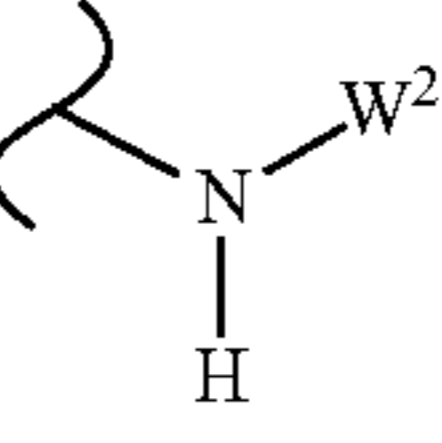
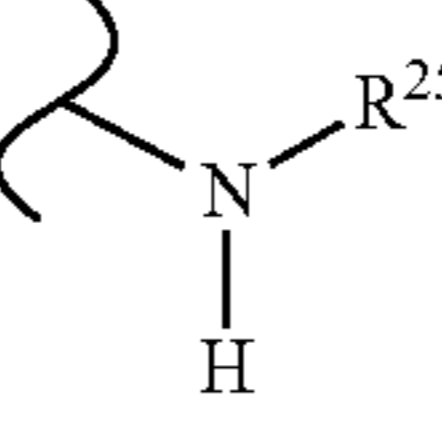
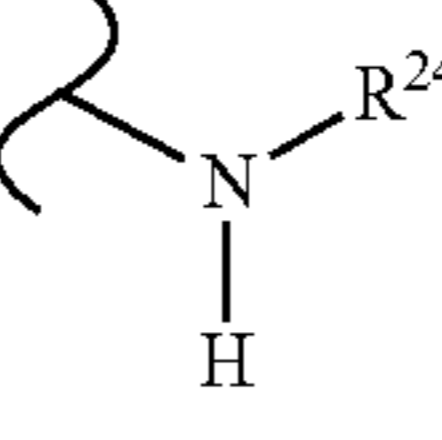
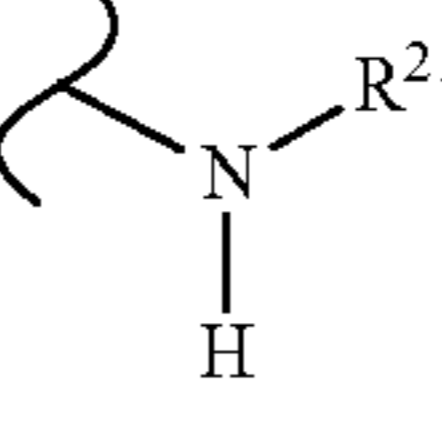
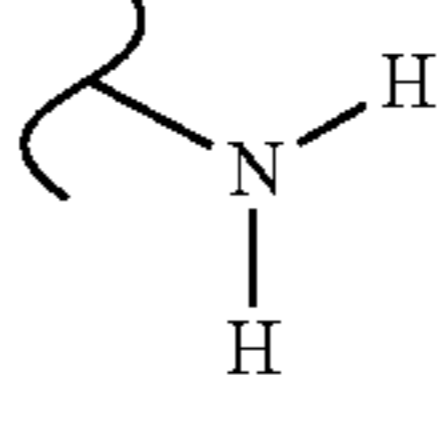
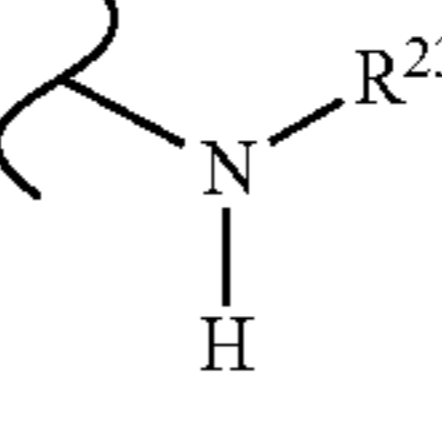
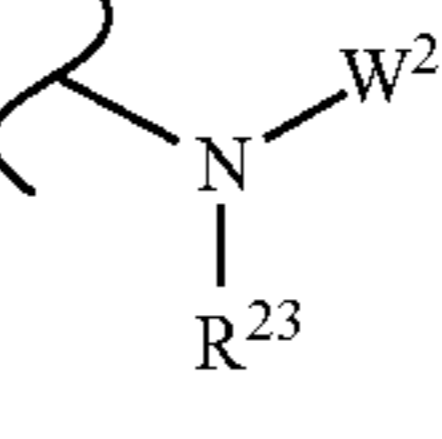
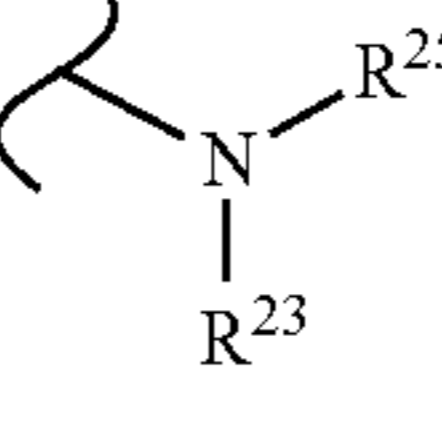
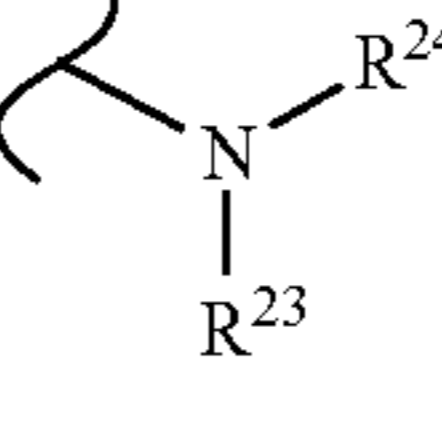
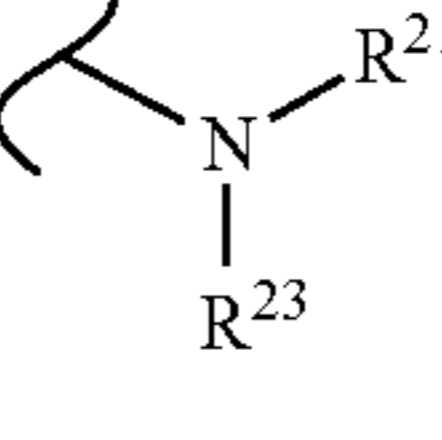
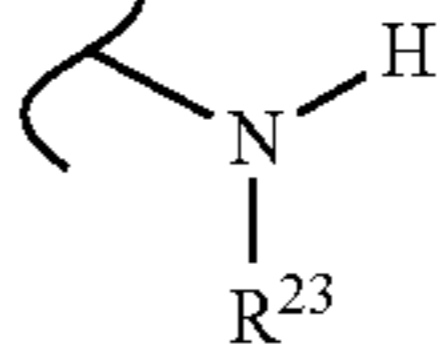
	158
	159

TABLE 20.26

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TABLE 20.26-continued

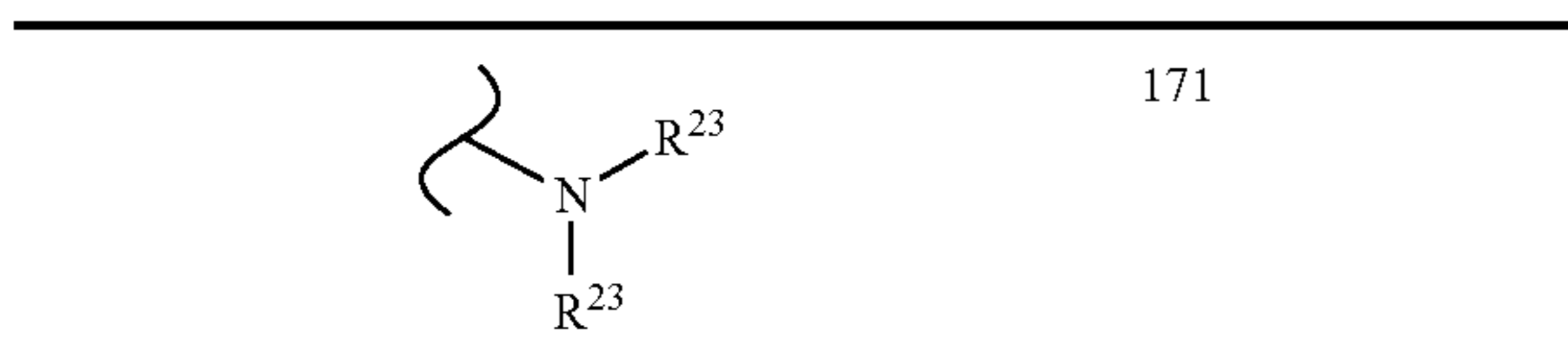


TABLE 20.27

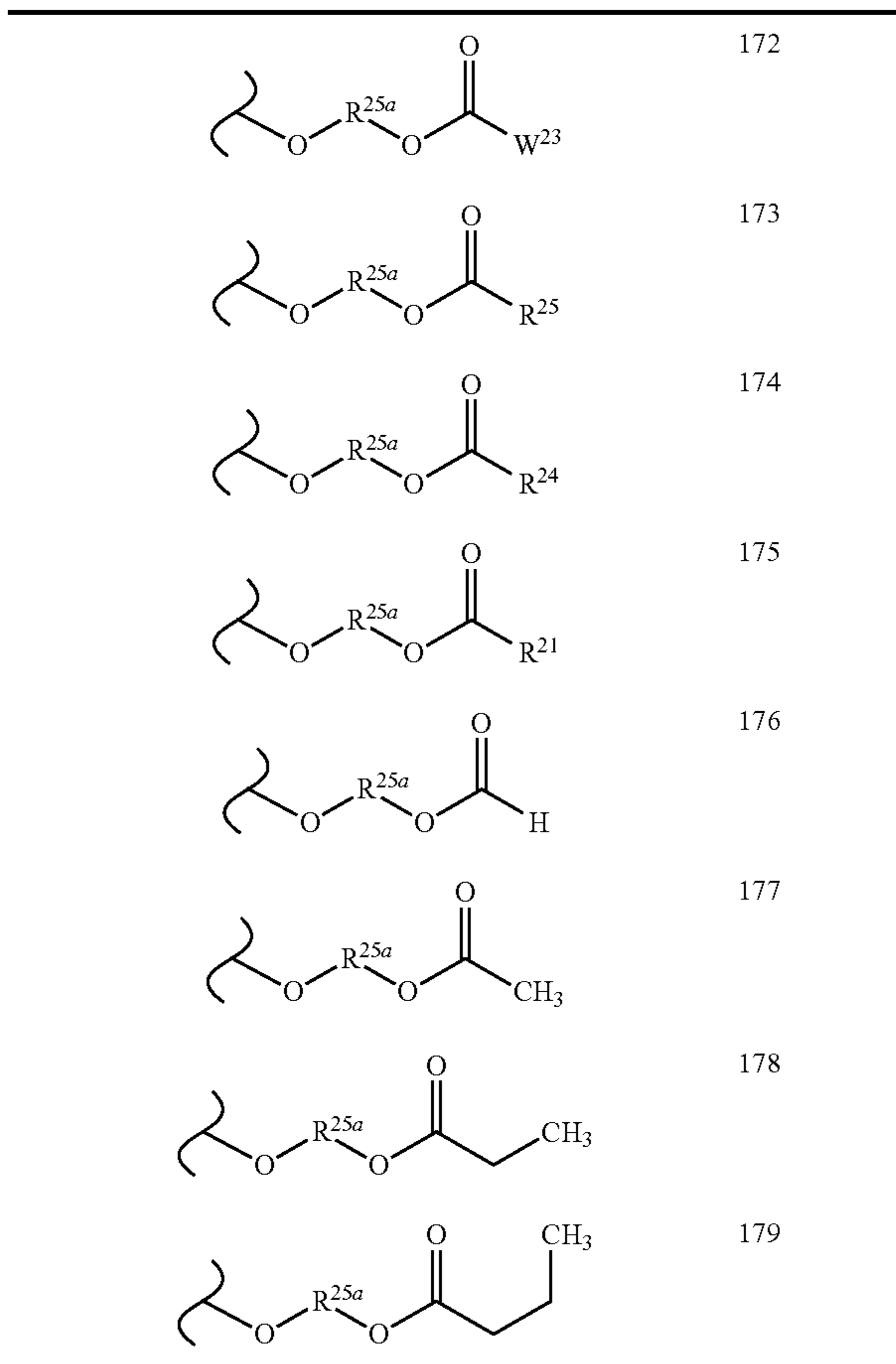
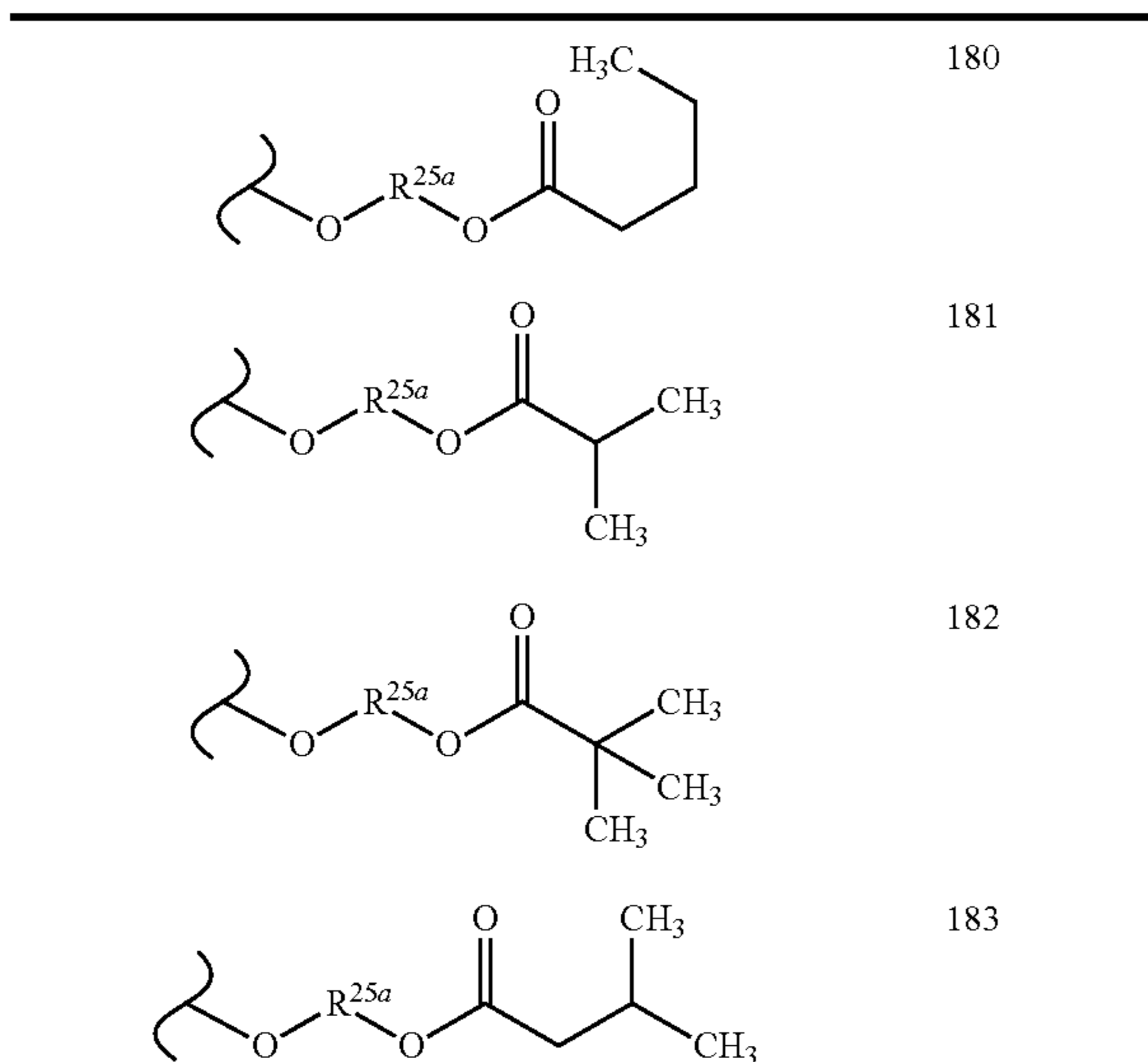


TABLE 20.28



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TABLE 20.28-continued

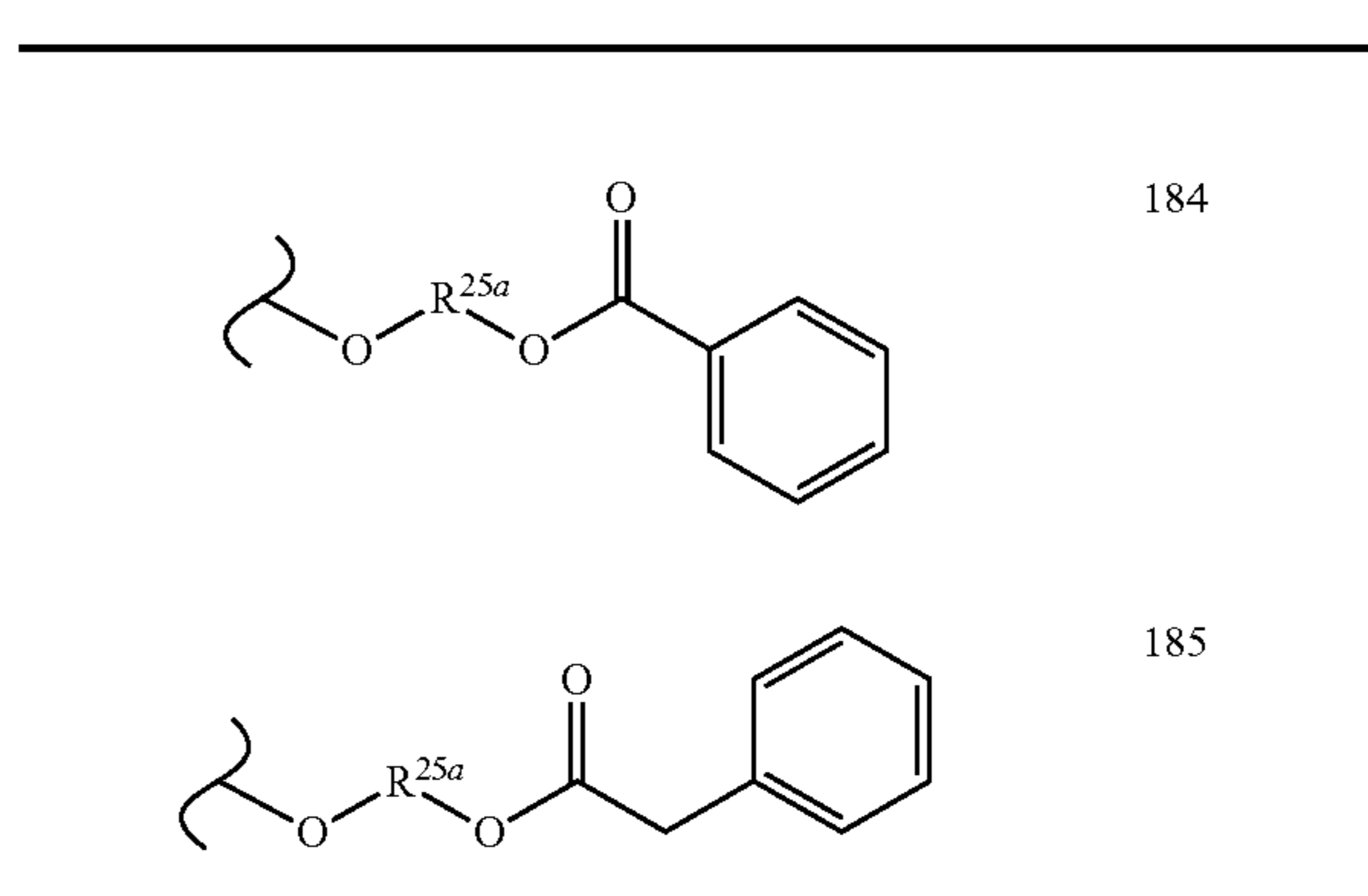


TABLE 20.29

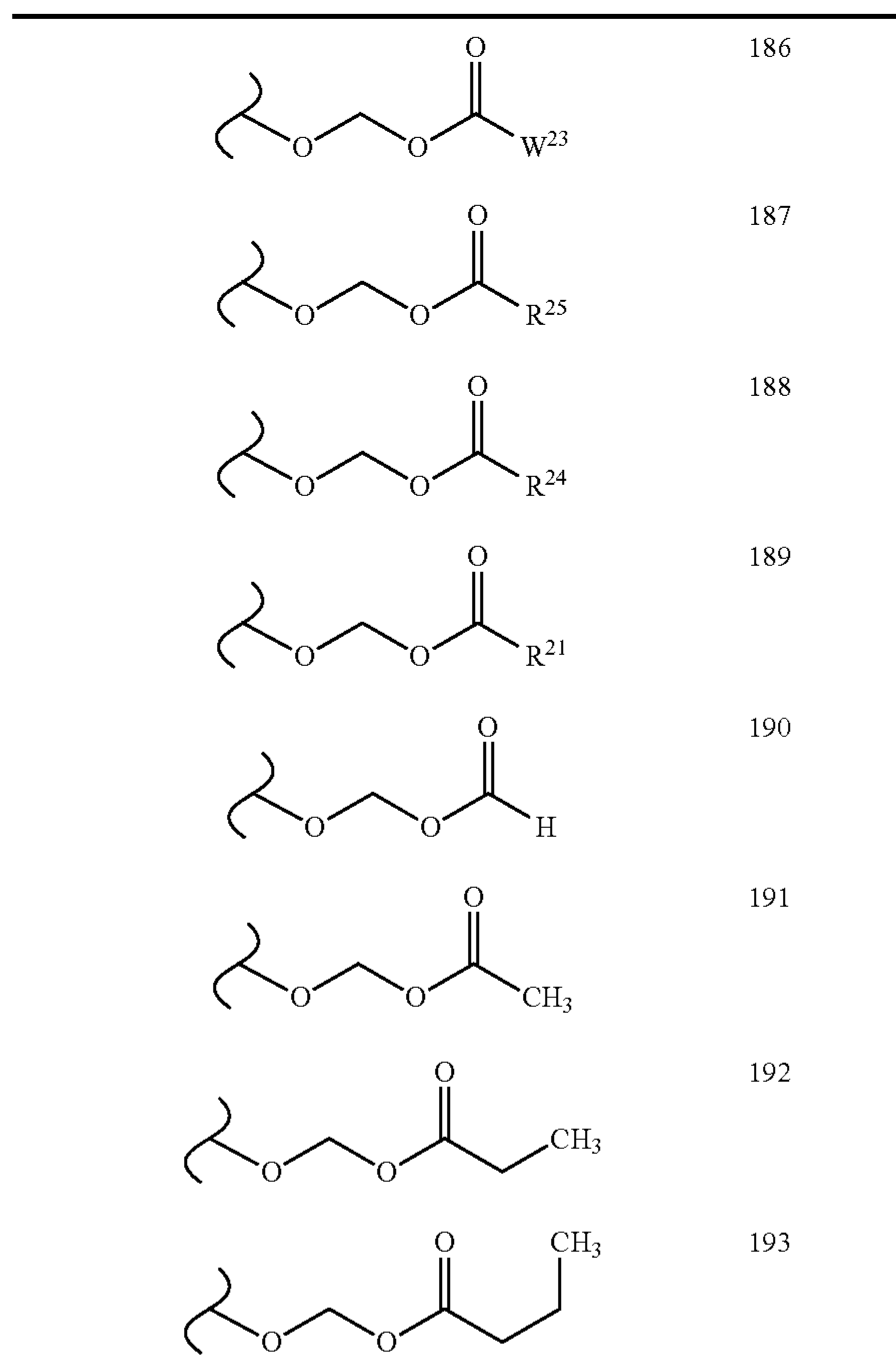
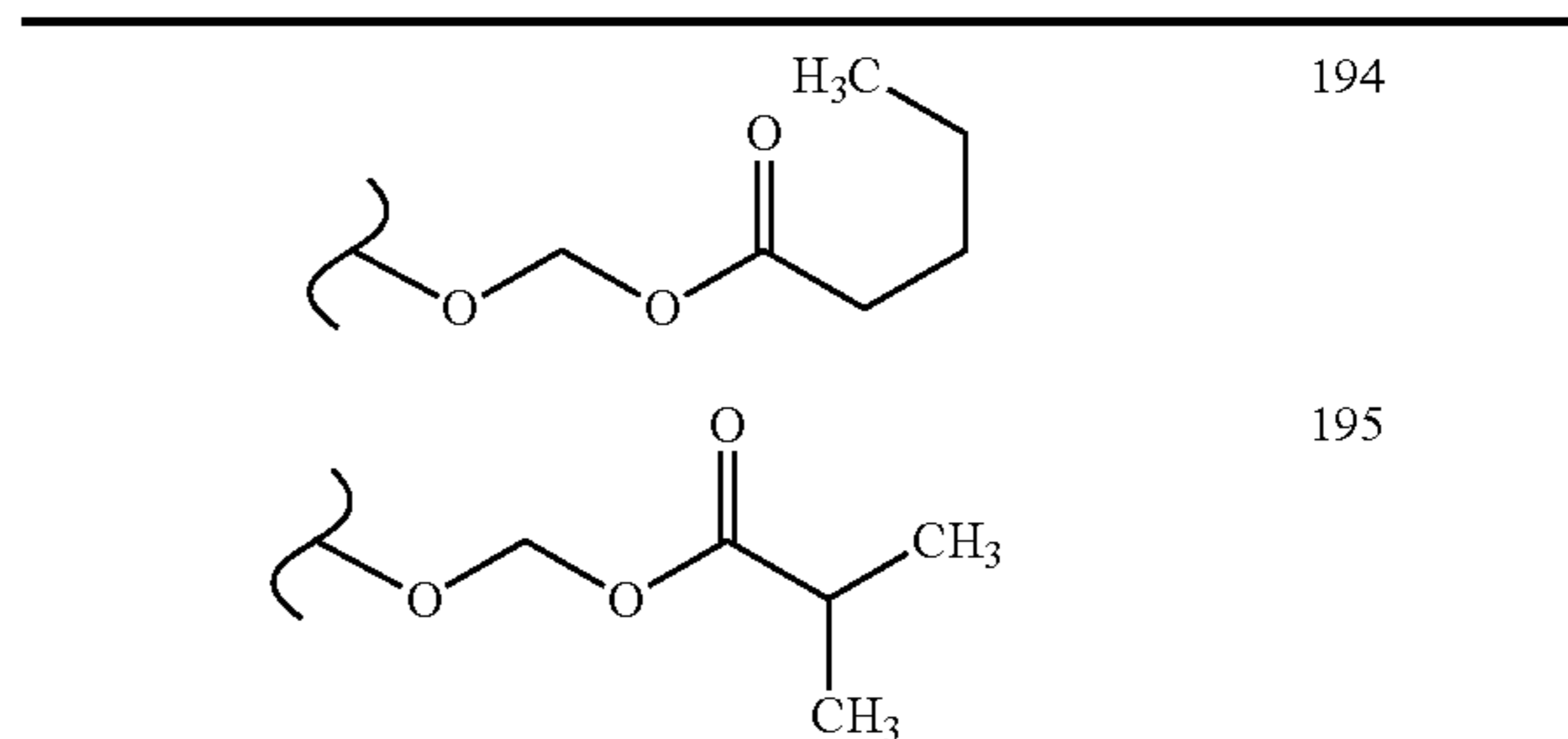


TABLE 20.30



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TABLE 20.30-continued

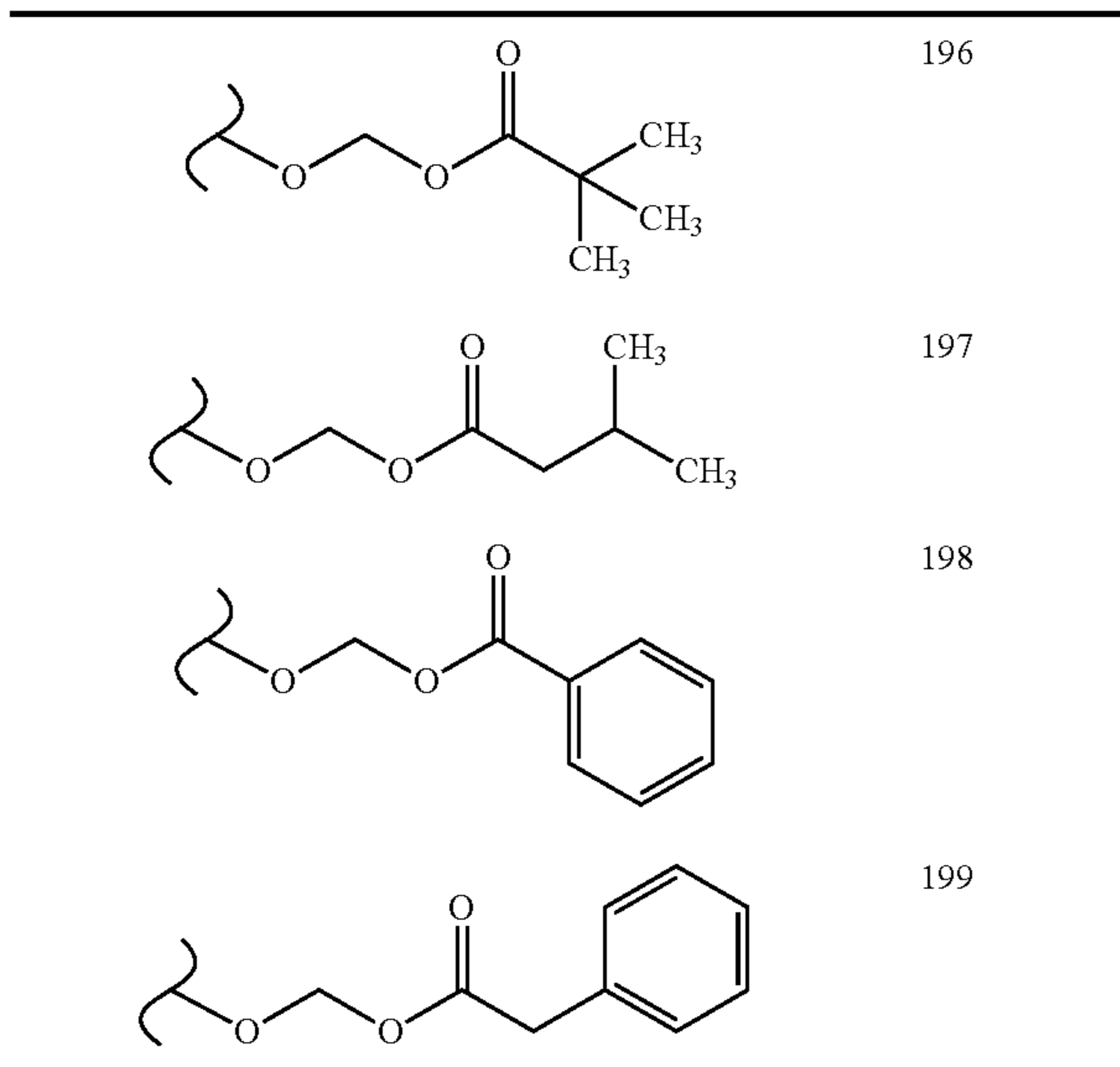


TABLE 20.31

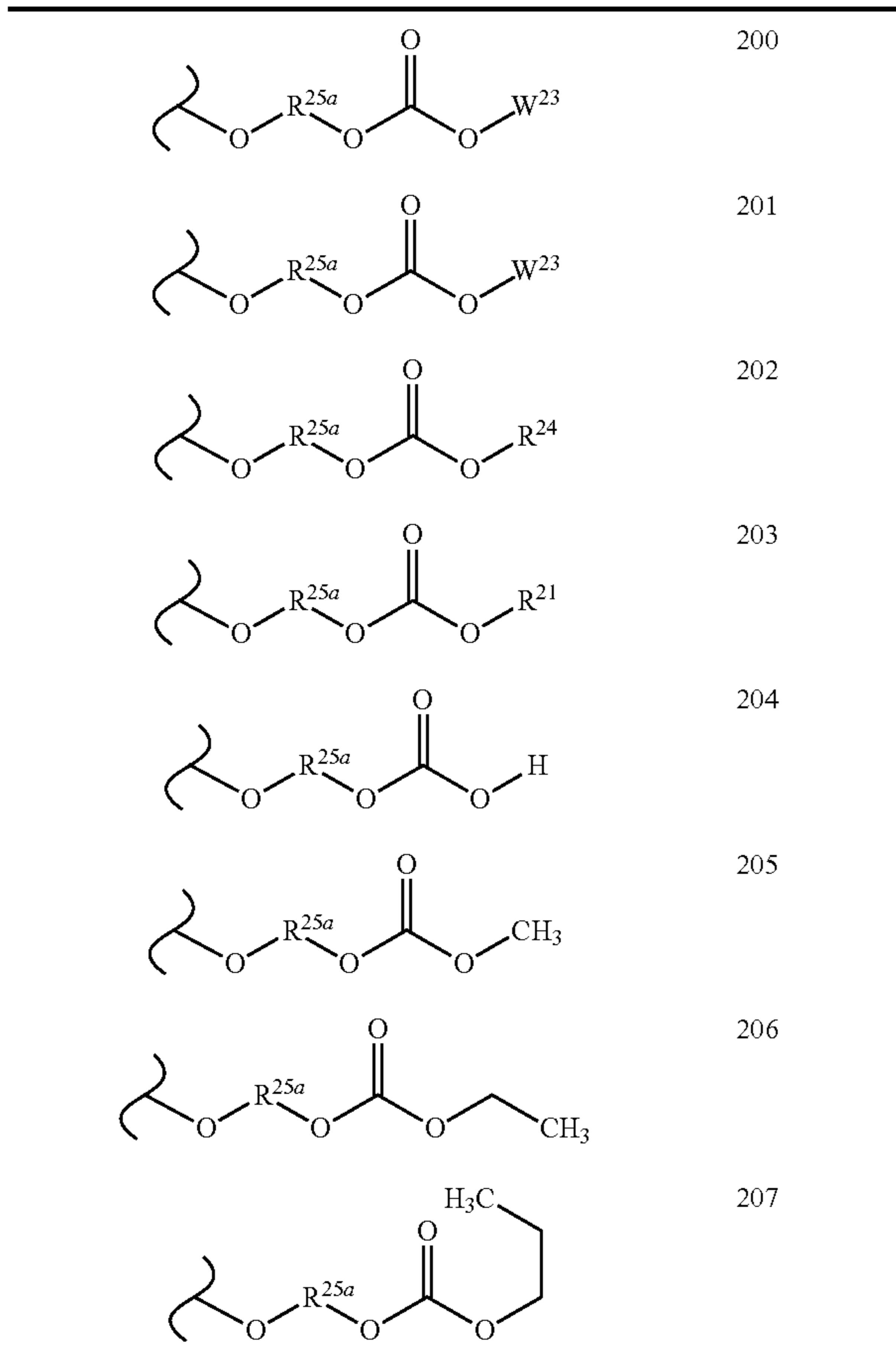
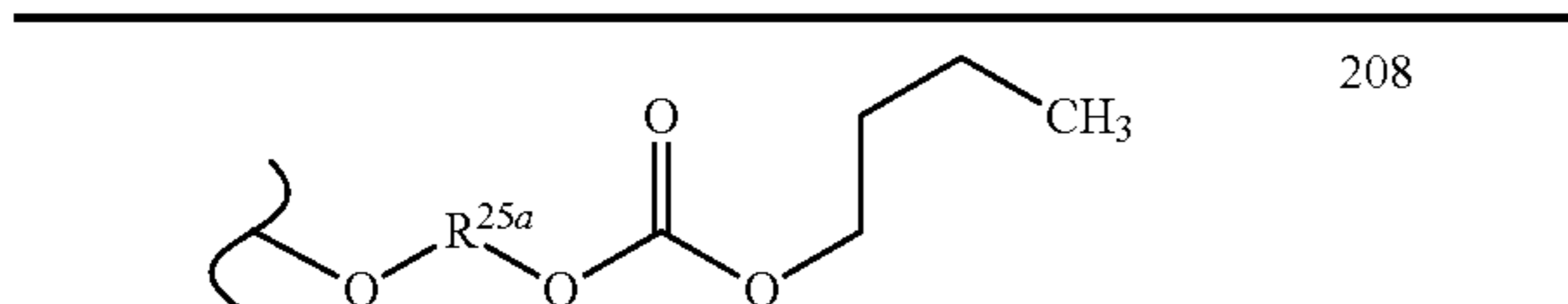


TABLE 20.32



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TABLE 20.32-continued

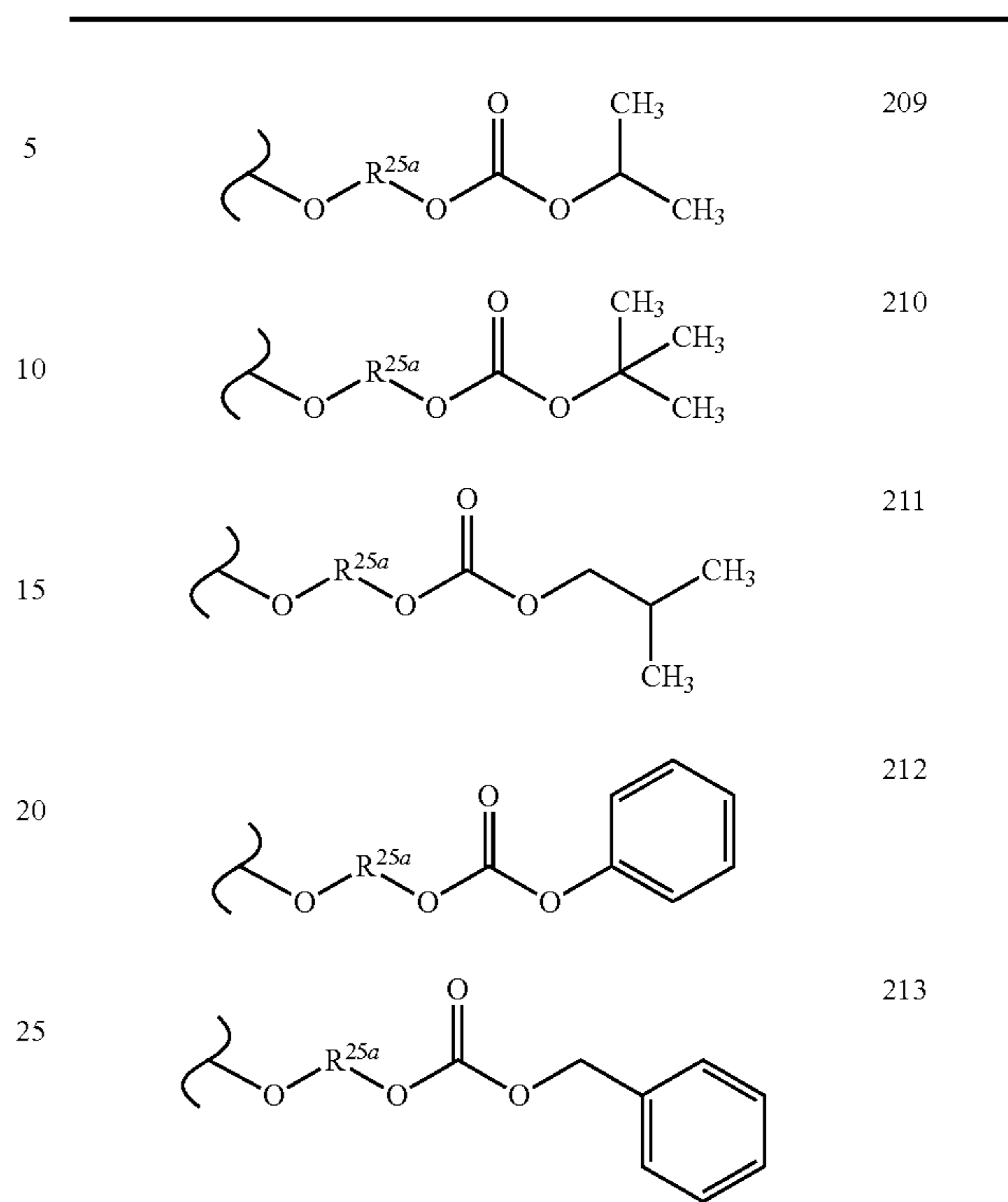
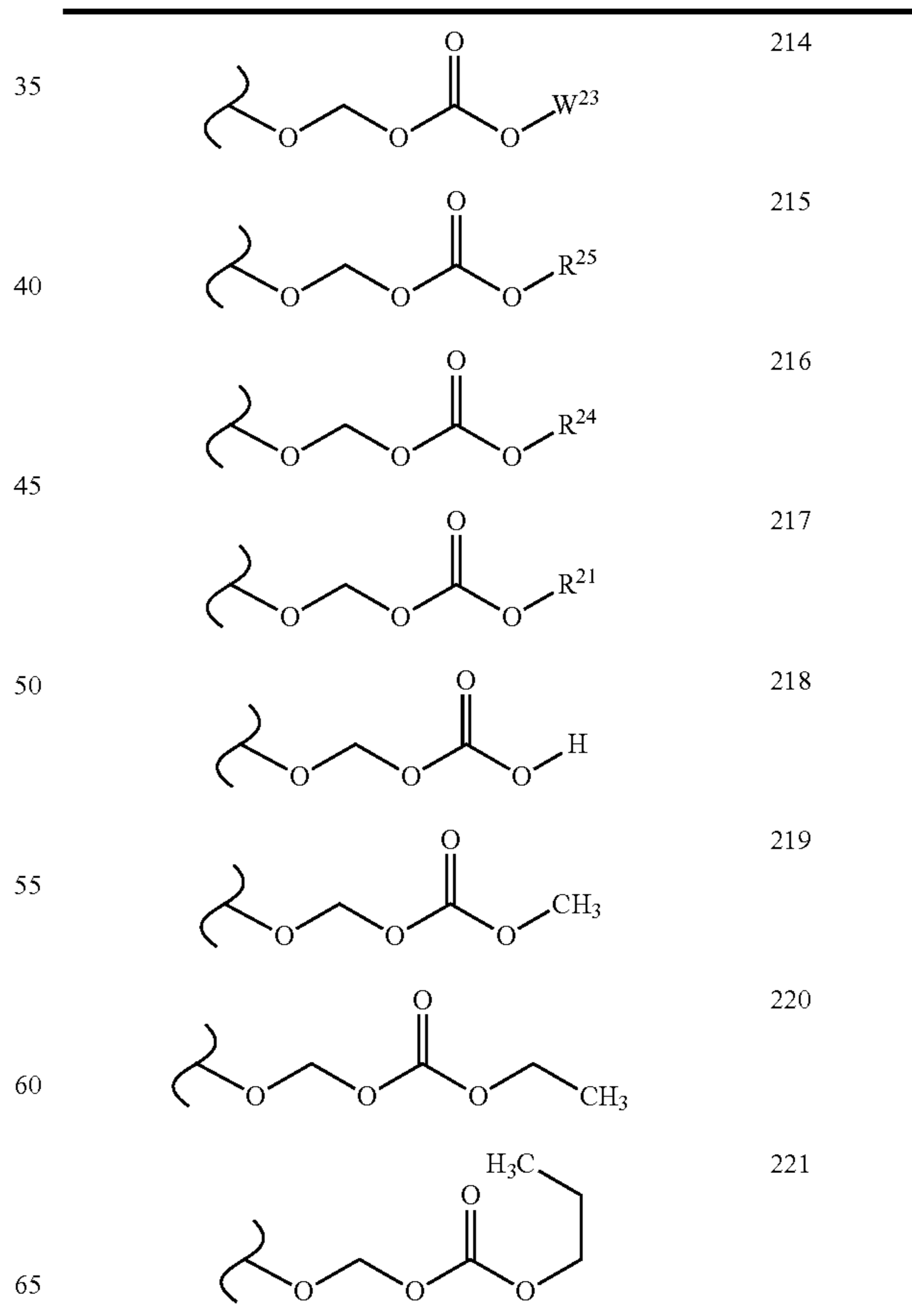


TABLE 20.33



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TABLE 20.34

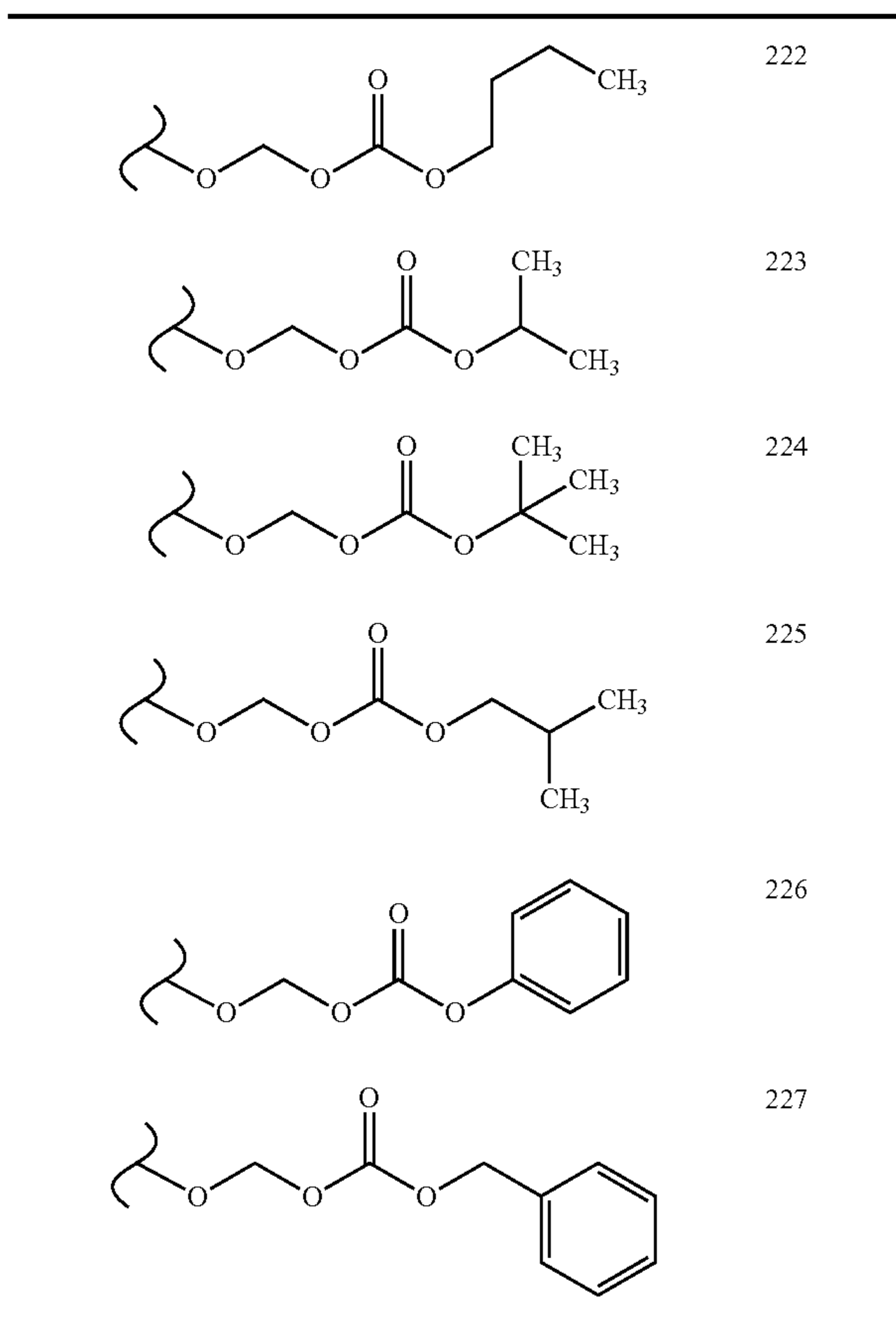
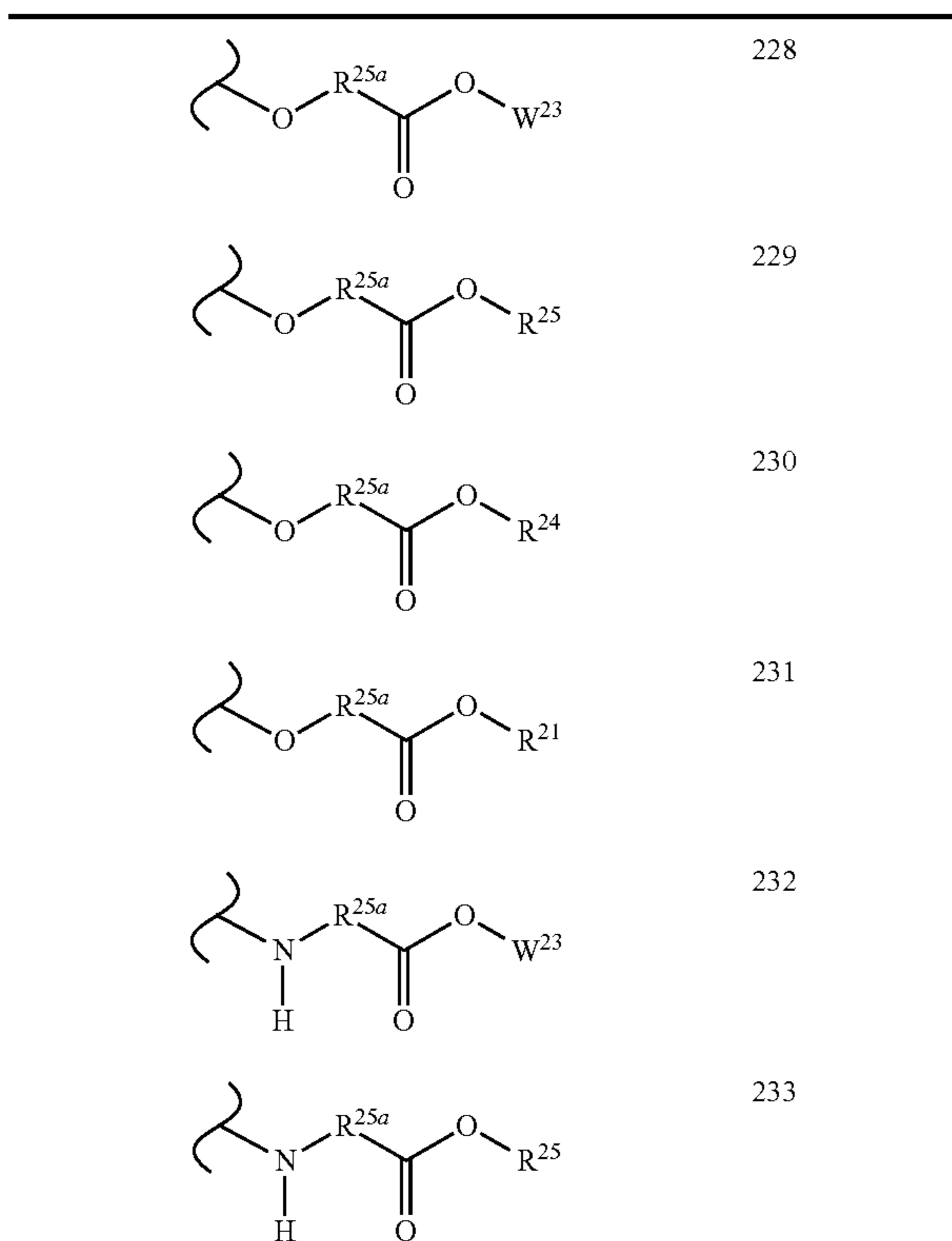


TABLE 20.35



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TABLE 20.35-continued

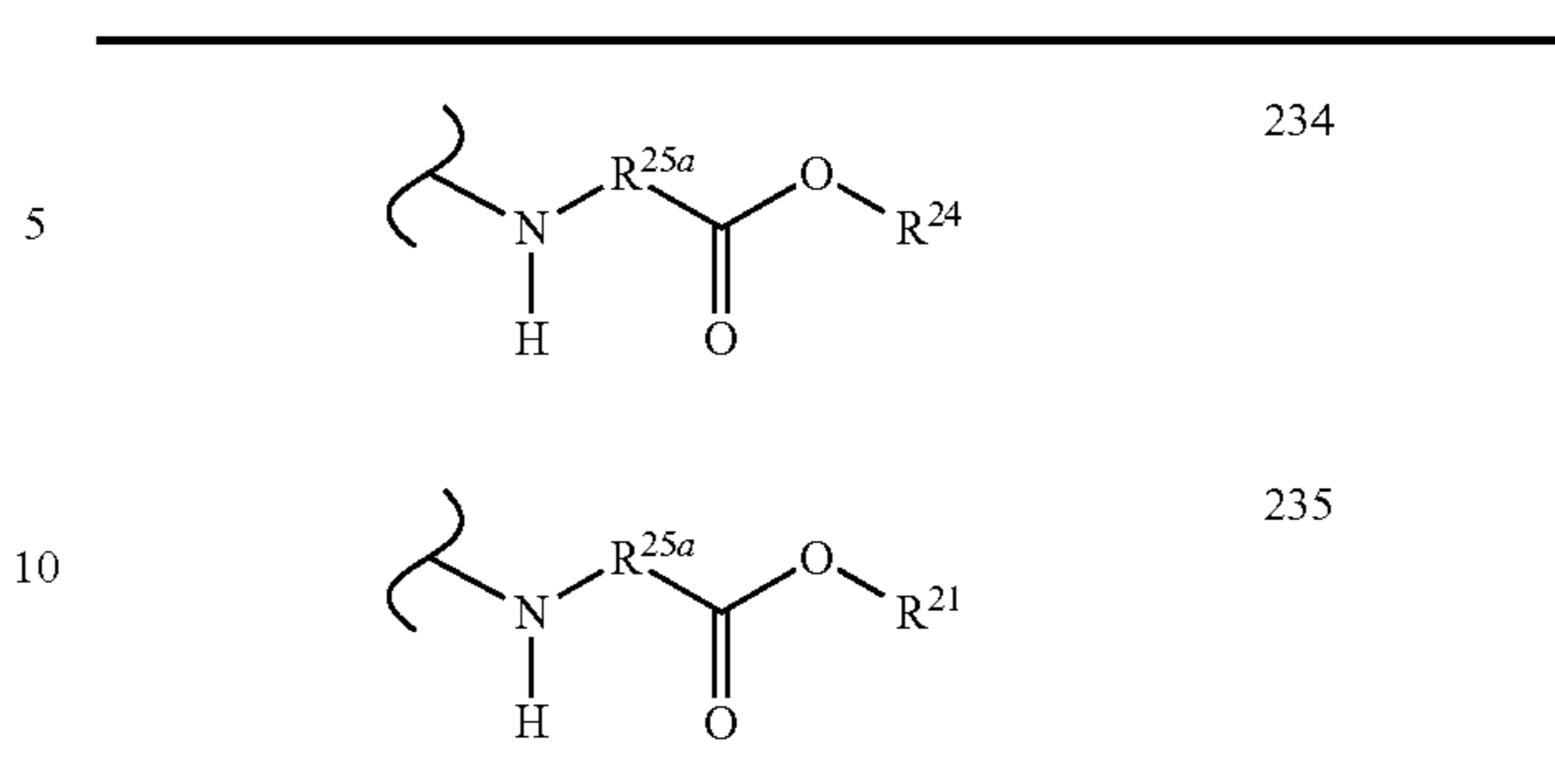


TABLE 20.36

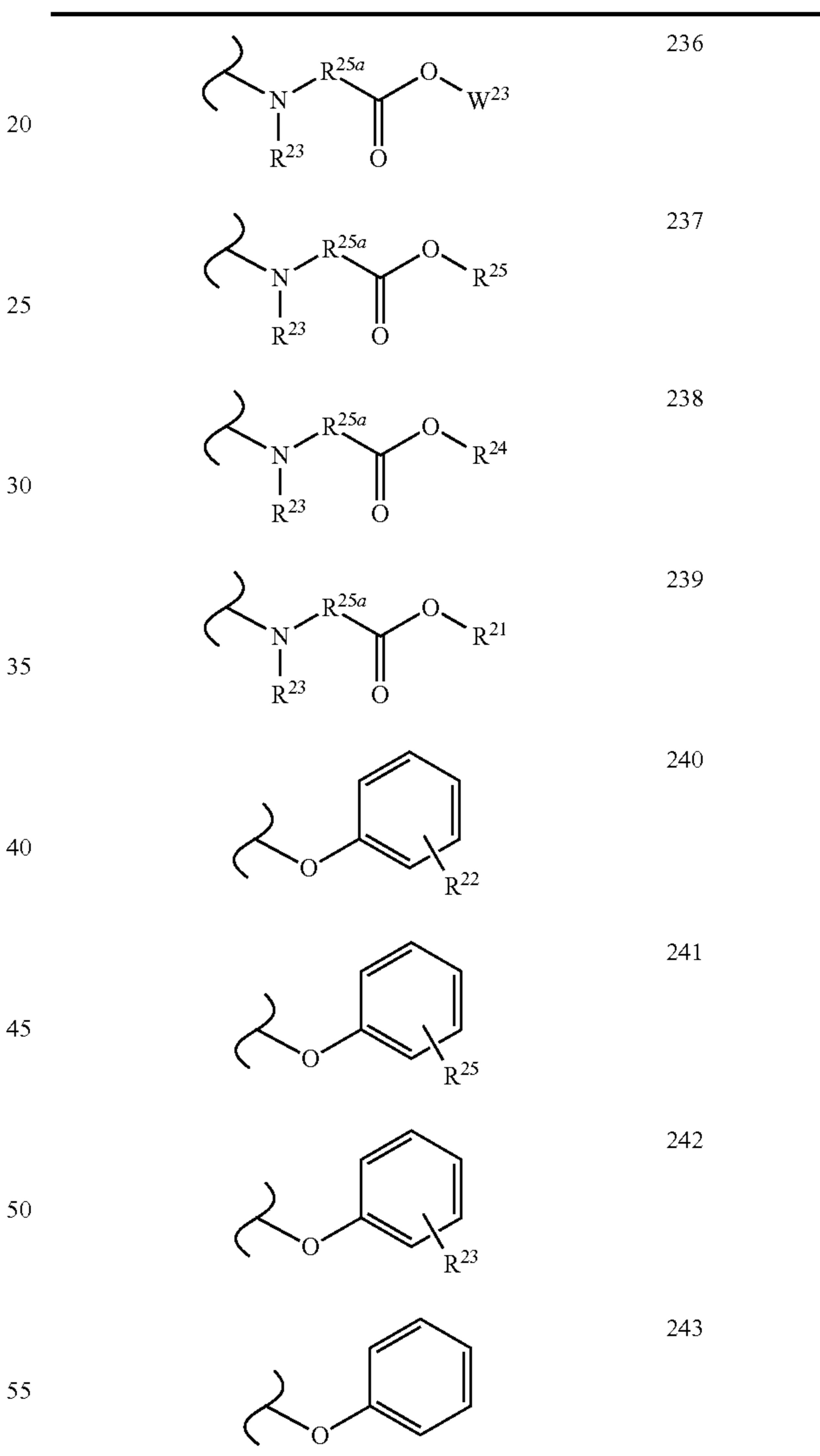
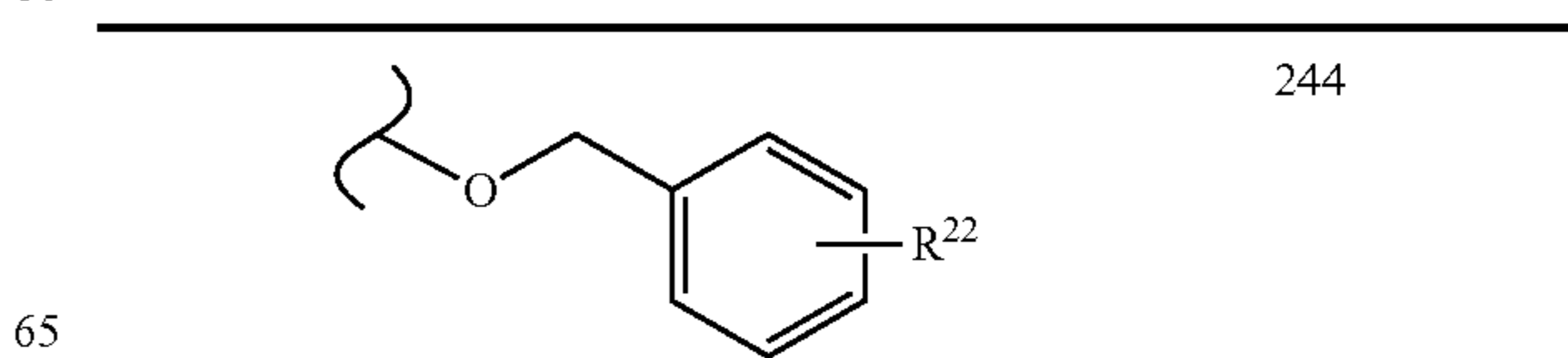


TABLE 20.37



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TABLE 20.37-continued

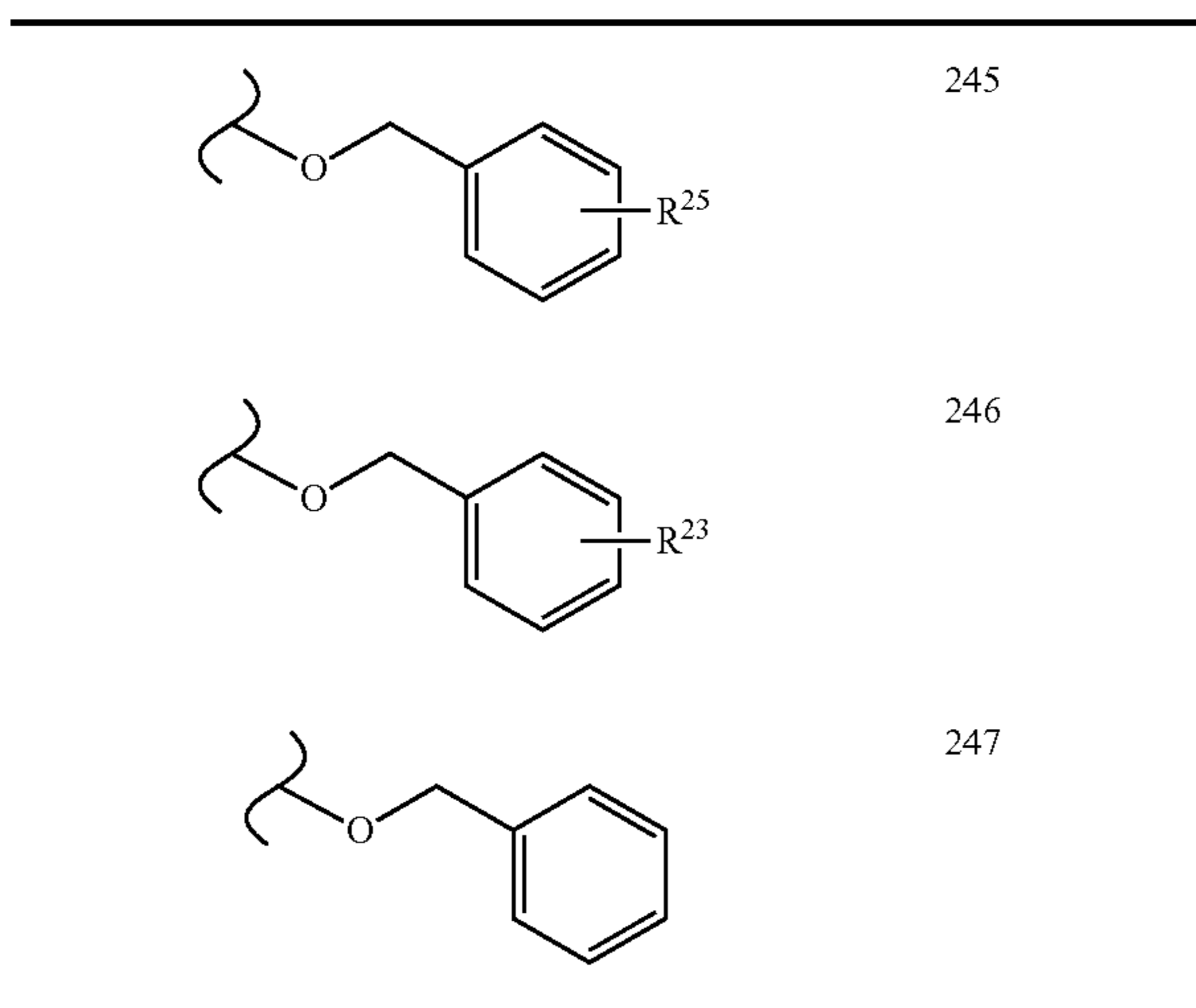
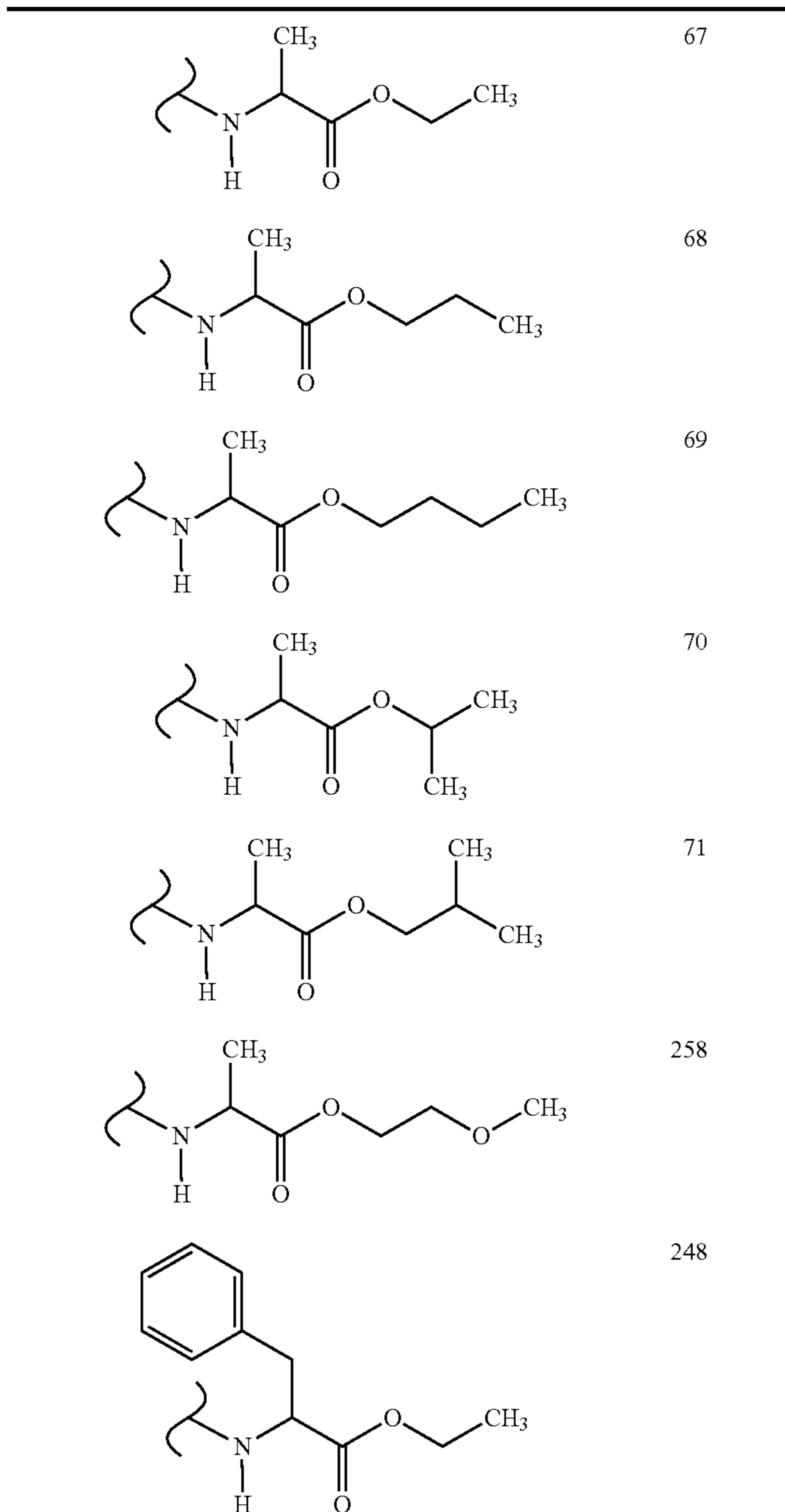
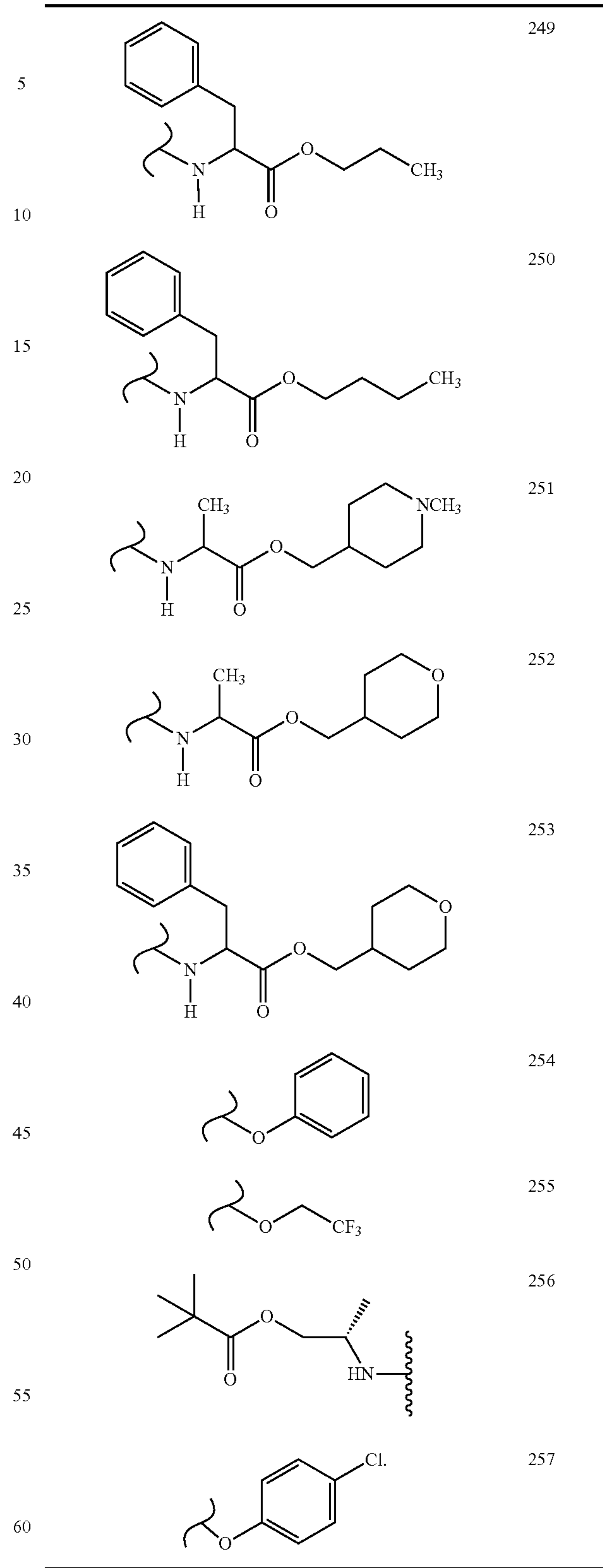


TABLE 30.1



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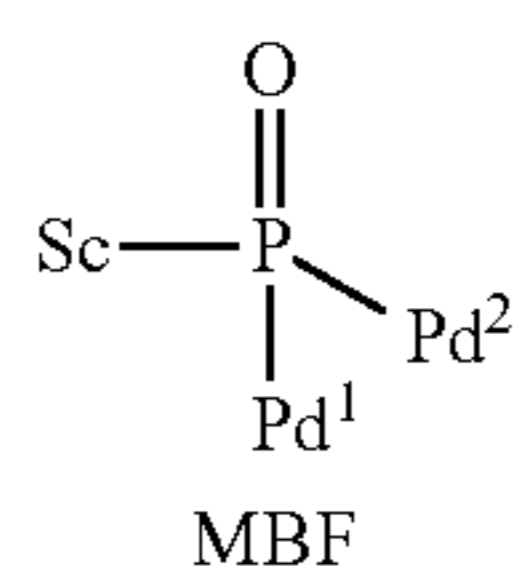
TABLE 30.1-continued



Phosphate Embodiments of Compounds of Formula I-IV

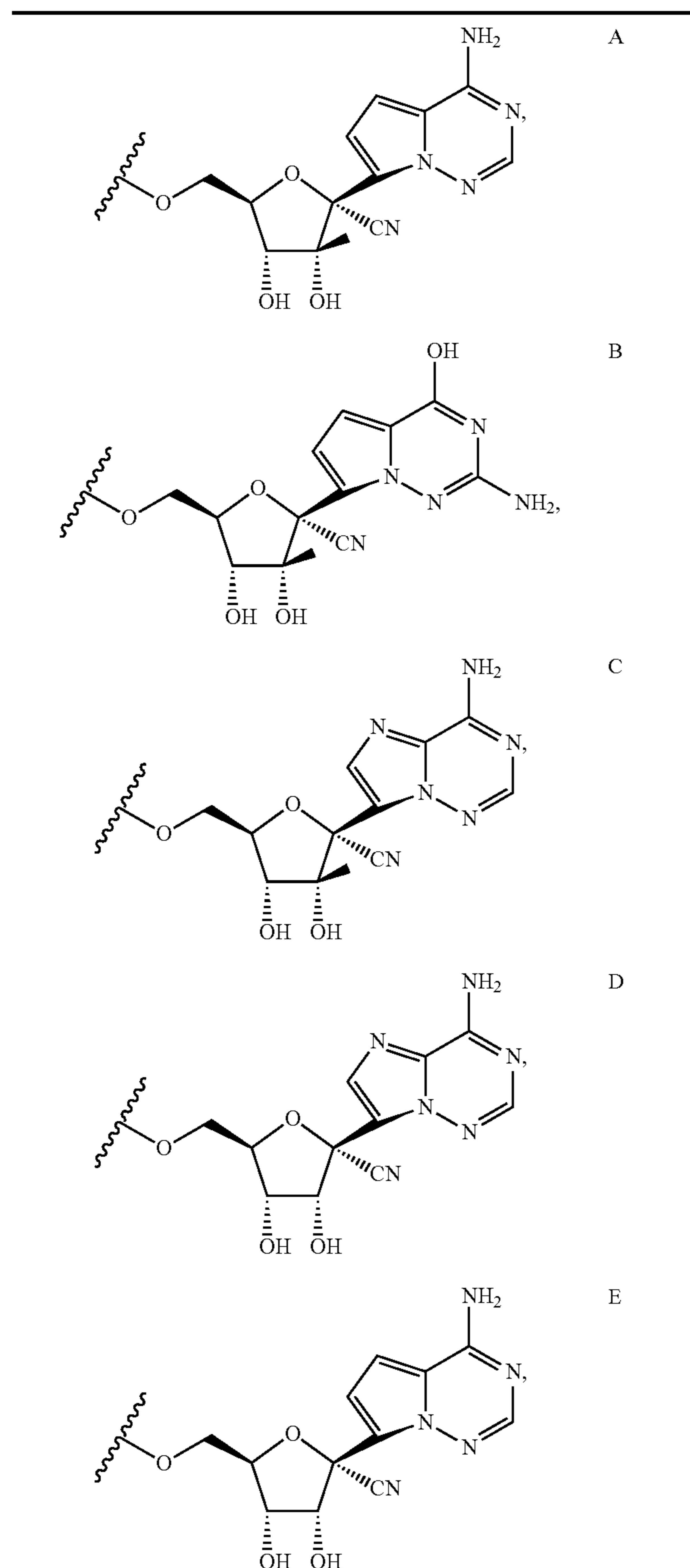
65 By way of example and not limitation, the phosphate embodiments of Formula I-IV may be represented by the general formula "MBF":

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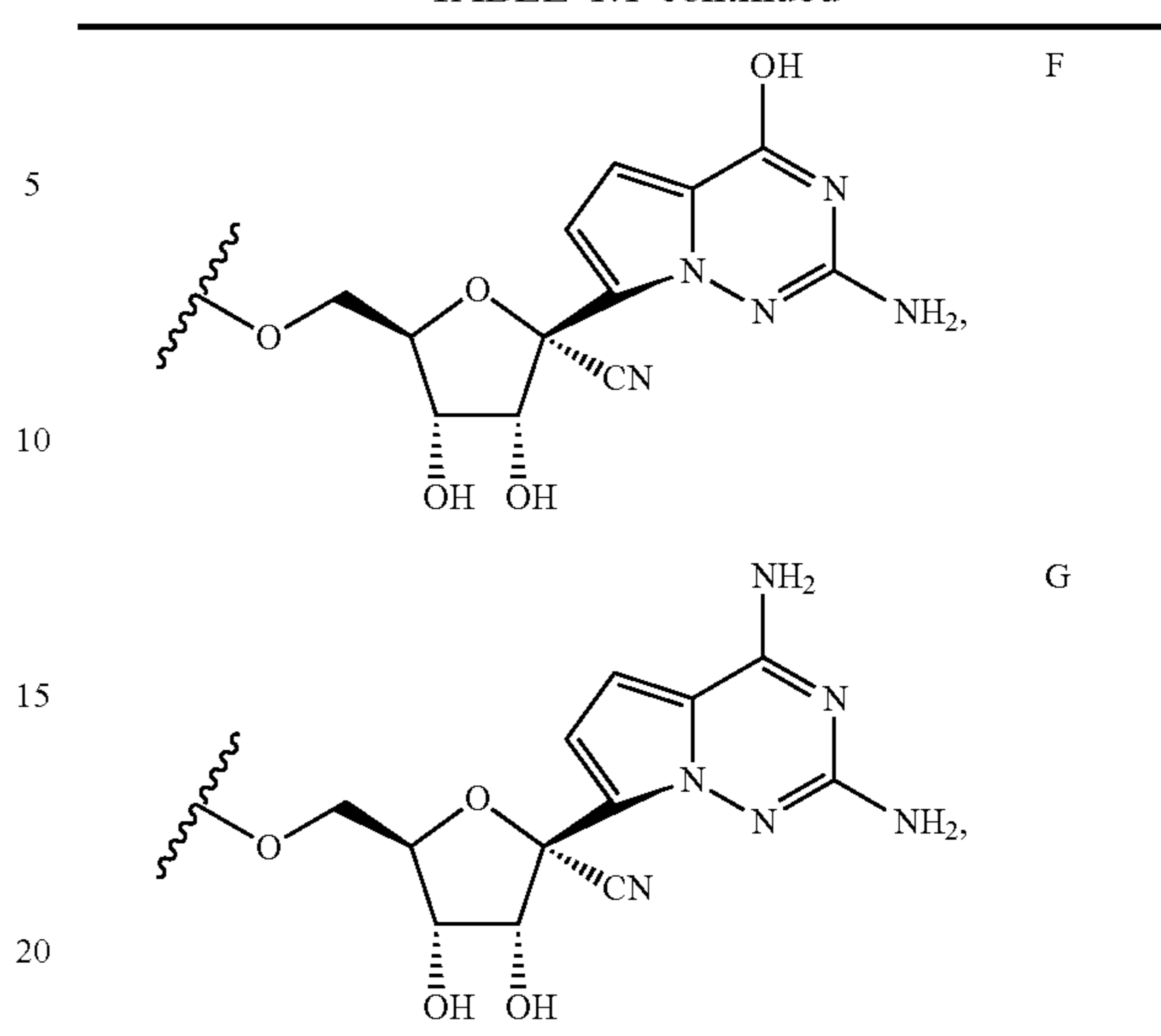
Each embodiment of MBF is depicted as a substituted nucleus (Sc). Sc is described in formulae A-G of Table 1.1 below, wherein Sc is a generic formula for a compound of Formula I, Formula II, or Formula III and the point of attachment to —P(O)Pd¹Pd² is indicated with a wavy line.

TABLE 1.1

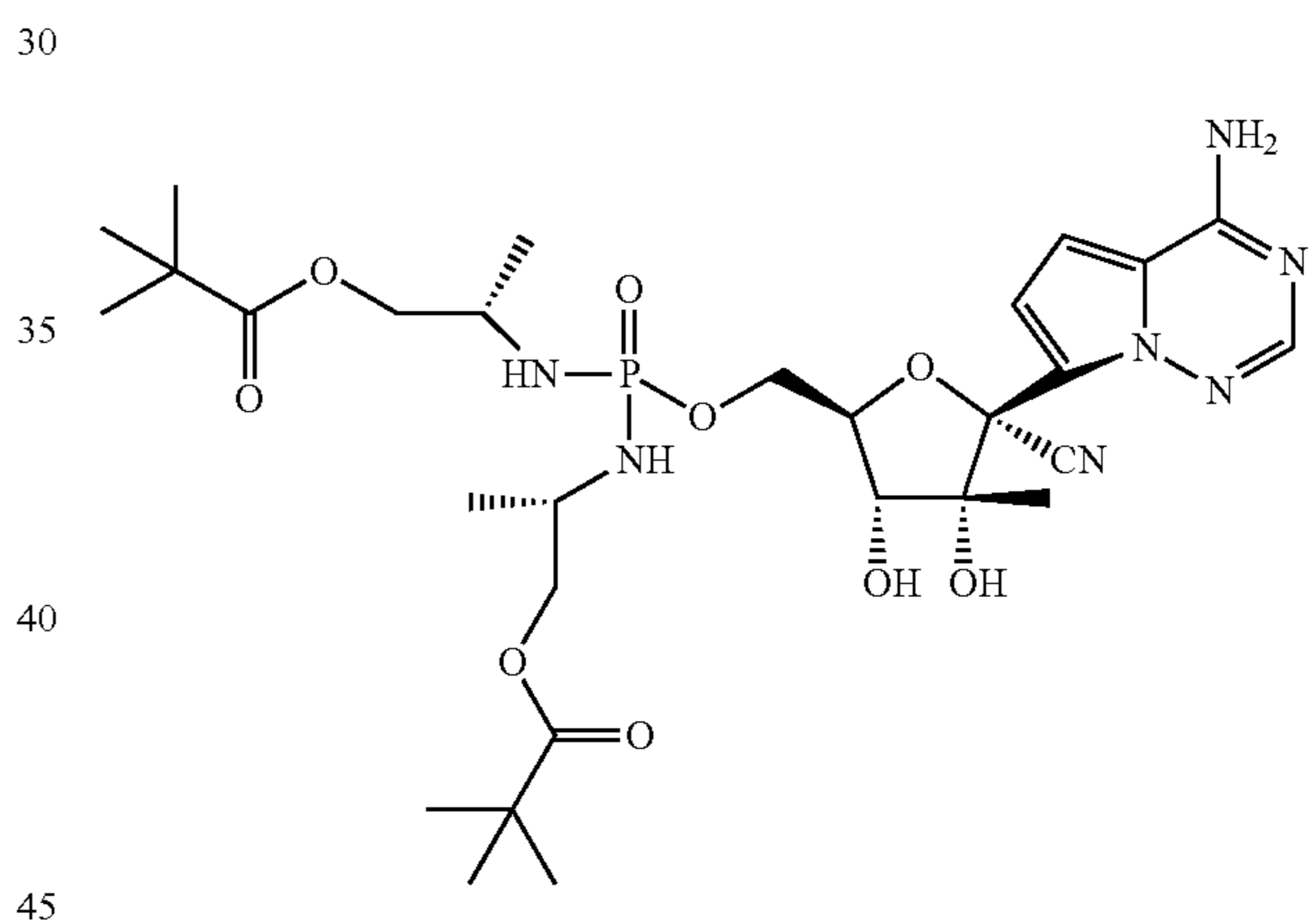


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TABLE 1.1-continued



Combinations of “Sc” and Pd¹ and Pd², independently selected from Table 30.1, can be expressed in the form of Sc.Pd¹.Pd², where Sc is represented by the respective letter A-G from Table 1.1 and Pd¹ and Pd² are represented by the respective number from Table 30.1. Thus, A.256.256 represents the following compound:



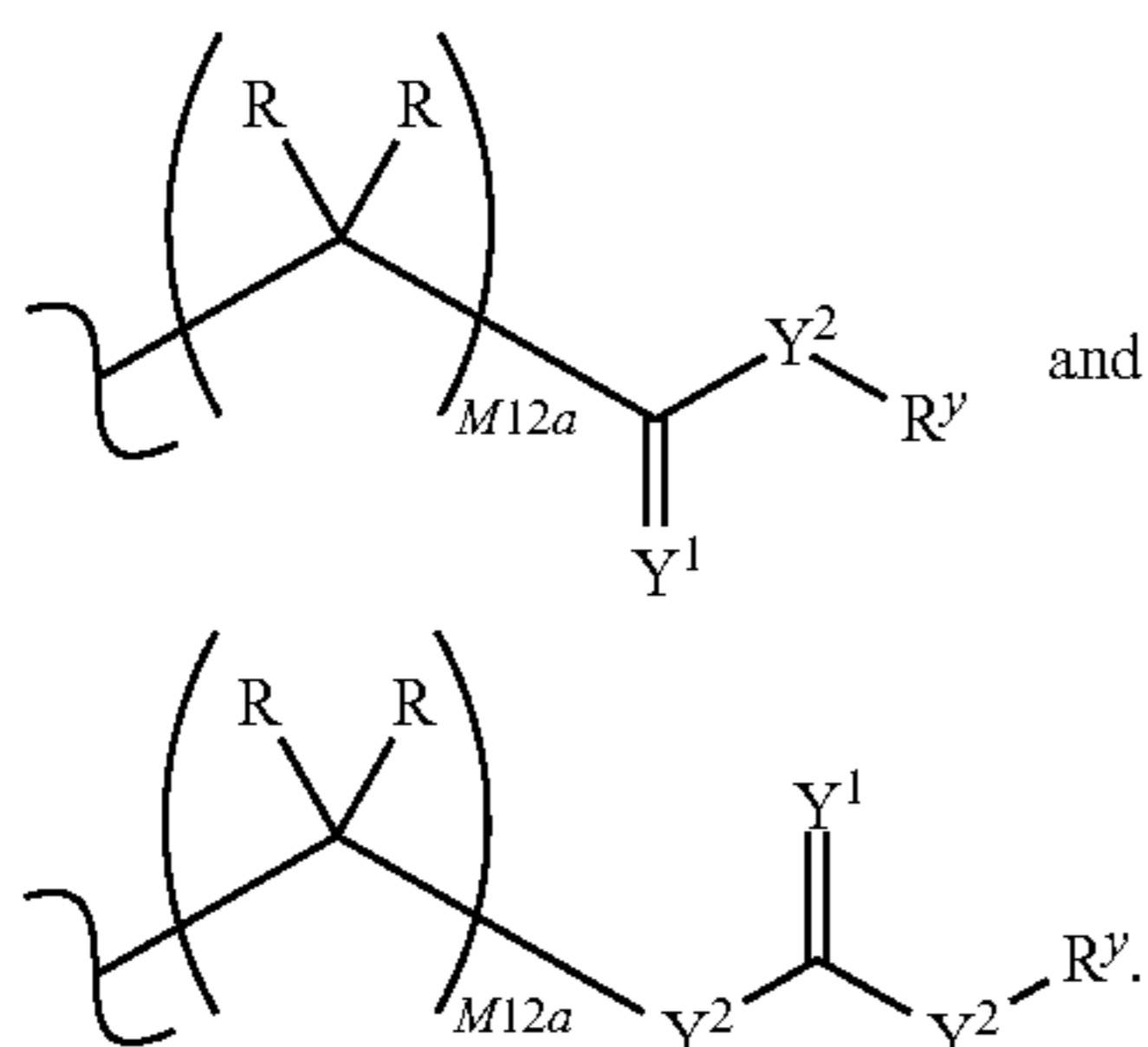
Thereby, Table 7 lists many specific examples of phosphate prodrugs of Formula I-IV.

Table 7: List of Compounds of MBF

50 A.254.67, A.254.68, A.254.69, A.254.70, A.254.71, A.254.258, A.254.248, A.254.249, A.254.250, A.254.251, A.254.252, A.254.253, B.254.67, B.254.68, B.254.69, B.254.70, B.254.71, B.254.258, B.254.248, B.254.249, B.254.250, B.254.251, B.254.252, B.254.253, C.254.67, C.254.68, C.254.69, C.254.70, C.254.71, C.254.258, C.254.248, C.254.249, C.254.250, C.254.251, C.254.252, C.254.253, D.254.67, D.254.68, D.254.69, D.254.70, D.254.71, D.254.258, D.254.248, D.254.249, D.254.250, D.254.251, D.254.252, D.254.253, E.254.67, E.254.68, E.254.69, E.254.70, E.254.71, E.254.258, E.254.248, E.254.249, E.254.250, E.254.251, E.254.252, E.254.253, F.254.67, F.254.68, F.254.69, F.254.70, F.254.71, F.254.258, F.254.248, F.254.249, F.254.250, F.254.251, F.254.252, F.254.253, G.254.67, G.254.68, G.254.69, G.254.70, G.254.71, G.254.258, G.254.248, G.254.249, G.254.250, G.254.251, G.254.252, G.254.253, A.255.67, A.255.68, A.255.69, A.255.70, A.255.71, A.255.258, A.255.248,

A.255.249, A.255.250, A.255.251, A.255.252, A.255.253, B.255.67, B.255.68, B.255.69, B.255.70, B.255.71, B.255.258, B.255.248, B.255.249, B.255.250, B.255.251, B.255.252, B.255.253, C.255.67, C.255.68, C.255.69, C.255.70, C.255.71, C.255.258, C.255.248, C.255.249, C.255.250, C.255.251, C.255.252, C.255.253, D.255.67, D.255.68, D.255.69, D.255.70, D.255.71, D.255.258, D.255.248, D.255.249, D.255.250, D.255.251, D.255.252, D.255.253, E.255.67, E.255.68, E.255.69, E.255.70, E.255.71, E.255.258, E.255.248, E.255.249, E.255.250, E.255.251, E.255.252, E.255.253, F.255.67, F.255.68, F.255.69, F.255.70, F.255.71, F.255.258, F.255.248, F.255.249, F.255.250, F.255.251, F.255.252, F.255.253, G.255.67, G.255.68, G.255.69, G.255.70, G.255.71, G.255.258, G.255.248, G.255.249, G.255.250, G.255.251, G.255.252, G.255.253, A.67.67, A.68.68, A.69.69, A.70.70, A.71.71, A.258.258, A.248.248, A.249.249, A.250.250, A.251.251, A.252.252, A.253.253, B.67.67, B.68.68, B.69.69, B.70.70, B.71.71, B.258.258, B.248.248, B.249.249, B.250.250, B.251.251, B.252.252, B.253.253, C.67.67, C.68.68, C.69.69, C.70.70, C.71.71, C.258.258, C.248.248, C.249.249, C.250.250, C.251.251, C.252.252, C.253.253, D.67.67, D.68.68, D.69.69, D.70.70, D.71.71, D.258.258, D.248.248, D.249.249, D.250.250, D.251.251, D.252.252, D.253.253, E.67.67, E.68.68, E.69.69, E.70.70, E.71.71, E.258.258, E.248.248, E.249.249, E.250.250, E.251.251, E.252.252, E.253.253, F.67.67, F.68.68, F.69.69, F.70.70, F.71.71, F.258.258, F.248.248, F.249.249, F.250.250, F.251.251, F.252.252, F.253.253, G.67.67, G.68.68, G.69.69, G.70.70, G.71.71, G.258.258, G.248.248, G.249.249, G.250.250, G.251.251, G.252.252, G.253.253, A.256.257, B.256.257, C.256.257, D.256.257, E.256.257, F.256.257, G.256.257, A.256.254, B.256.254, C.256.254, D.256.254, E.256.254, F.256.254, G.256.254, A.256.250, B.256.250, C.256.250, D.256.250, E.256.250, F.256.250, G.256.250, A.256.69, B.256.69, C.256.69, D.256.69, E.256.69, F.256.69, G.256.69, A.256.71, B.256.71, C.256.71, D.256.71, E.256.71, F.256.71, G.256.71, A.256.255, B.256.255, C.256.255, D.256.255, E.256.255, F.256.255, G.256.255.

Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides, thioamides, and urea groups:



Any reference to the compounds of the invention described herein also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal or an alkaline earth (for example, Na^+ , Li^+ , K^+ , Ca^{+2} and Mg^{+2}), ammonium and NR_4^+ (wherein R is defined herein). Physiologically acceptable salts of a nitrogen atom or an amino group include (a) acid addition salts formed with inorganic acids, for example, hydrochloric acid, hyd-

robromic acid, sulfuric acid, sulfamic acids, phosphoric acid, nitric acid and the like; (b) salts formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, isethionic acid, lactobionic acid, tannic acid, palmitic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, polygalacturonic acid, malonic acid, sulfosalicylic acid, glycolic acid, 2-hydroxy-3-naphthoate, pamoate, salicylic acid, stearic acid, phthalic acid, mandelic acid, lactic acid, ethanesulfonic acid, lysine, arginine, glutamic acid, glycine, serine, threonine, alanine, isoleucine, leucine and the like; and (c) salts formed from elemental anions for example, chlorine, bromine, and iodine. Physiologically acceptable salts of a compound of a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NR_4^+ .

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

The compounds of the invention, exemplified by Formula I-III may have chiral centers, e.g. chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.


The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

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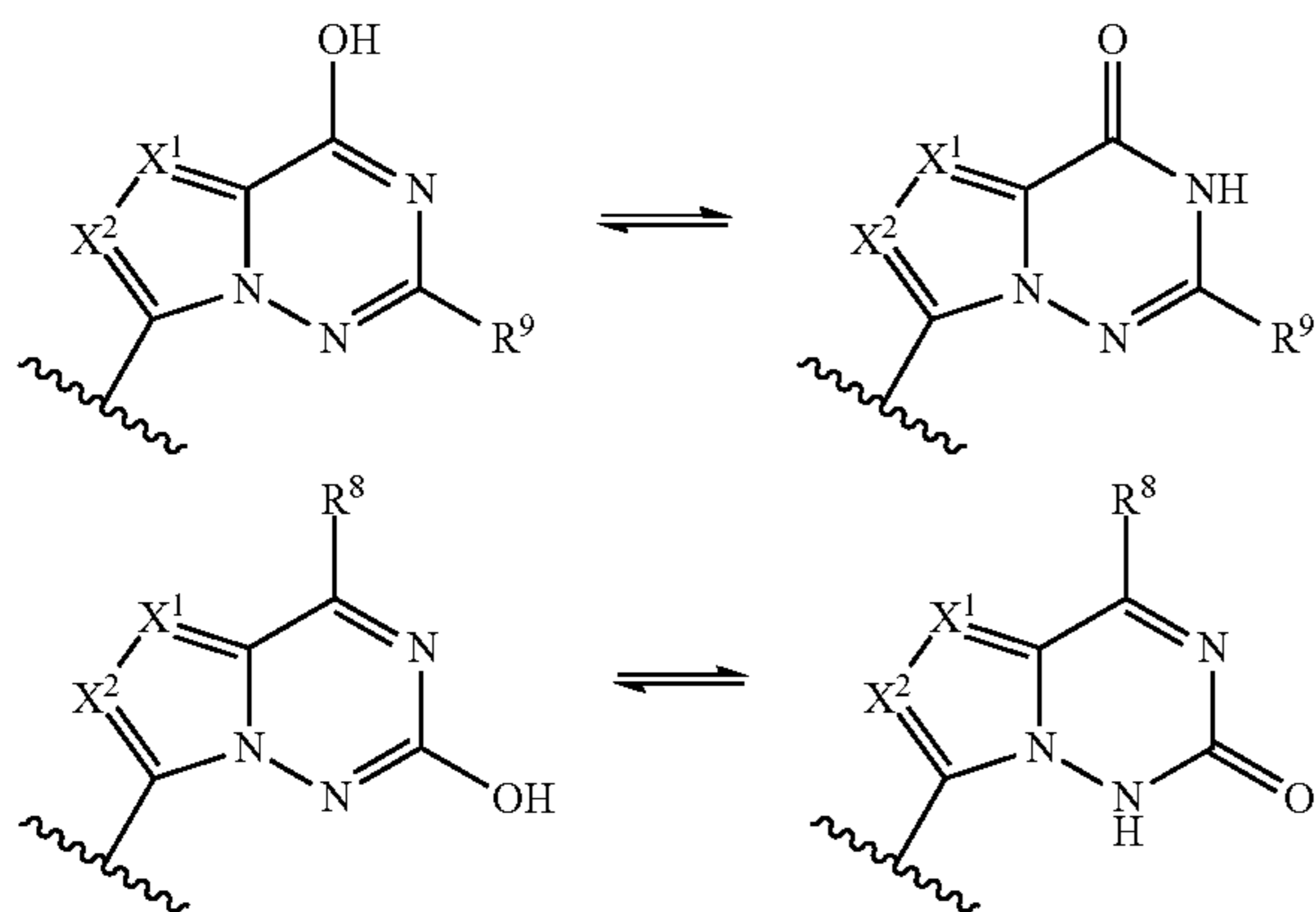
"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l, D and L, or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with S, (-), or l meaning that the compound is levorotatory while a compound prefixed with R, (+), or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R" or "R¹", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines, , indicate the site of covalent bond attachments to the adjoining substructures, groups, moieties, or atoms.

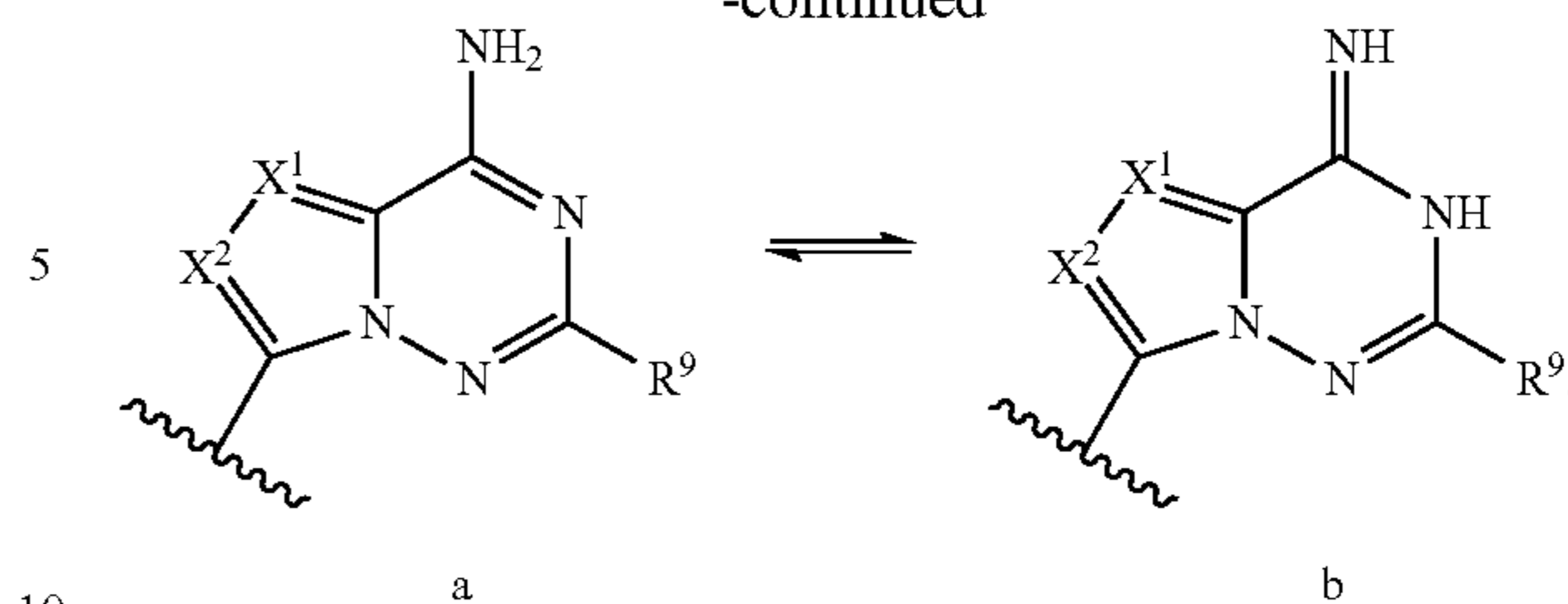
The compounds of the invention can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

One skilled in the art will recognize that the pyrrolo[1,2-f][1,2,4]triazine, imidazo[1,5-f][1,2,4]triazine, imidazo[1,2-f][1,2,4]triazine, and [1,2,4]triazolo[4,3-f][1,2,4]triazine nucleosides can exist in tautomeric forms. For example, but not by way of limitation, structures (a) and (b) can have equivalent tautomeric forms as shown below:



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-continued



All possible tautomeric forms of the heterocycles in all of the embodiments disclosed herein are within the scope of the invention.

15 Methods of Inhibition of HCV Polymerase

Another aspect of the invention relates to methods of inhibiting the activity of HCV polymerase comprising the step of treating a sample suspected of containing HCV with a composition of the invention.

20 Compositions of the invention may act as inhibitors of HCV polymerase, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of HCV polymerase having a geometry unique to HCV polymerase. Compositions binding HCV polymerase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of HCV polymerase. Accordingly, the invention relates to methods of detecting HCV polymerase in a sample suspected of containing HCV polymerase comprising the steps of: treating a sample suspected of containing HCV polymerase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl, carboxyl, sulfhydryl or amino.

35 Within the context of the invention, samples suspected of containing HCV polymerase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which produces HCV polymerase, frequently a pathogenic organism such as HCV. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

40 The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

45 If desired, the activity of HCV polymerase after application of the composition can be observed by any method including direct and indirect methods of detecting HCV polymerase activity. Quantitative, qualitative, and semi-quantitative methods of determining HCV polymerase activ-

ity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Organisms that contain HCV polymerase include the HCV virus. The compounds of this invention are useful in the treatment or prophylaxis of HCV infections in animals or in man.

However, in screening compounds capable of inhibiting human immunodeficiency viruses, it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for HCV Polymerase Inhibitors.

Compositions of the invention are screened for inhibitory activity against HCV polymerase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of HCV polymerase in vitro and compositions showing inhibitory activity are then screened for activity in vivo. Compositions having in vitro K_i (inhibitory constants) of less than about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for in vivo use.

Useful in vitro screens have been described in detail and will not be elaborated here. However, the examples describe suitable in vitro assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextran, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as

capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For infections of the eye or other external tissues e.g. mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three

being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally-occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., hepta-decaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral

preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally-occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10%, and particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in

a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns, such as 0.5, 1, 30, 35 etc., which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HCV infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the

compound is being used prophylactically (lower doses) or against an active viral infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day; typically, from about 0.01 to about 10 mg/kg body weight per day; more typically, from about 0.01 to about 5 mg/kg body weight per day; most typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

25 Combination Therapy

Compositions of the invention are also used in combination with other active ingredients. Preferably, the other active therapeutic ingredients or agents are interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

Combinations of the compounds of Formula I-III are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating an infection (e.g., HCV), the compositions of the invention are combined with other active therapeutic agents (such as those described herein).

Suitable active therapeutic agents or ingredients which can be combined with the compounds of Formula I-III can include interferons, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, indergen, rebif, locteron, AVI-005, PEG-indergen, pegylated IFN-beta, oral interferon alpha, feron, reafteron, intermax alpha, r-IFN-beta, indergen+actimmune, IFN-omega with DUROS, and albuferon; ribavirin analogs, e.g., rebetol, copegus, VX-497, and viremagine (taribavirin); NS5a inhibitors, e.g., A-831, A-689 and BMS-790052; NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125; NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065; alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B; hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451; non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives; and other drugs for treating HCV, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a com-

pound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen+actimmune, IFN-omega with DUROS, albuferon, rebetol, copegus, VX-497, viramidine (taribavirin), A-831, A-689, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, XTL-2125, SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, MitoQ, and LB-84451, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17, KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811 and a pharmaceutically acceptable carrier or excipient.

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Combinations of the compounds of Formula I-III and additional active therapeutic agents may be selected to treat patients infected with HCV and other conditions such as HIV infections. Accordingly, the compounds of Formula I-III may be combined with one or more compounds useful in treating HIV, for example HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin

analog, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) HIV protease inhibitors, e.g., amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, lopinavir+ritonavir, nelfinavir, saquinavir, tipranavir, brexanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), AG1859, DG35, L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, e.g., capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirine), efavirenz, BILR 355 BS, VRX 840773, UK-453,061, RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, e.g., zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (\pm -FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, fosalvudine tidoxil, apricitabine (AVX754), amdoxovir, KP-1461, abacavir+lamivudine, abacavir+lamivudine+zidovudine, zidovudine+lamivudine, 4) a HIV nucleotide inhibitor of reverse transcriptase, e.g., tenofovir, tenofovir disoproxil fumarate+emtricitabine, tenofovir disoproxil fumarate+emtricitabine+efavirenz, and adefovir, 5) a HIV integrase inhibitor, e.g., curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), BMS-707035, MK-2048, BA-011, BMS-538158, GSK364735C, 6) a gp41 inhibitor, e.g., enfuvirtide, sifuvirtide, FB006M, TRI-1144, SPC3, DES6, Locus gp41, CovX, and REP 9, 7) a CXCR4 inhibitor, e.g., AMD-070, 8) an entry inhibitor, e.g., SP01A, TNX-355, 9) a gp120 inhibitor, e.g., BMS-488043 and BlockAide/CR, 10) a G6PD and NADH-oxidase inhibitor, e.g., immunitin, 10) a CCR5 inhibitor, e.g., aplaviroc, vicriviroc, INCB9471, PRO-140, INCB15050, PF-232798, CCR5 mAb004, and maraviroc, 11) an interferon, e.g., pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, IFN alpha-2b XL, rIFN-alpha 2a, consensus IFN alpha, infergen, rebif, locteron, AVI-005, PEG-infergen, pegylated IFN-beta, oral interferon alpha, feron, reaferon, intermax alpha, r-IFN-beta, infergen+actimmune, IFN-omega with DUROS, and albuferon, 12) ribavirin analogs, e.g., rebetol, copegus, VX-497, and viramidine (taribavirin) 13) NS5a inhibitors, e.g., A-831, A-689 and BMS-790052, 14) NS5b polymerase inhibitors, e.g., NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, MK-0608, NM-107, R7128, VCH-759, PF-868554, GSK625433, and XTL-2125, 15) NS3 protease inhibitors, e.g., SCH-503034 (SCH-7), VX-950 (Telaprevir), ITMN-191, and BILN-2065, 16) alpha-glucosidase 1 inhibitors, e.g., MX-3253 (celgosivir) and UT-231B, 17) hepatoprotectants, e.g., IDN-6556, ME 3738, MitoQ, and LB-84451, 18) non-nucleoside inhibitors of HCV, e.g., benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, and phenylalanine derivatives, 19) other drugs for treating HCV, e.g., zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), DEBIO-025, VGX-410C, EMZ-702, AVI 4065, bavituximab, oglufanide, PYN-17,

KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, and NIM811, 19) pharmacokinetic enhancers, e.g., BAS-100 and SPI452, 20) RNAse H inhibitors, e.g., ODN-93 and ODN-112, 21) other anti-HIV agents, e.g., VGV-1, PA-457 (bevirimat), ampligen, HRG214, cytolin, polymun, VGX-410, KD247, AMZ 0026, CYT 99007, A-221 HIV, BAY 50-4798, MDX010 (iplimumab), PBS119, ALG889, and PA-1050040.

It is also possible to combine any compound of the invention with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a

pharmaceutically acceptable salt, solvate, and/or ester thereof, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of inhibiting HCV polymerase in a cell, comprising: contacting a cell infected with HCV with an effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent, whereby HCV polymerase is inhibited.

In still yet another embodiment, the present application provides for methods of treating HCV in a patient, comprising: administering to the patient a therapeutically effective amount of a compound of Formula I-III, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and at least one additional active therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for treating an HCV infection in a patient.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the in vivo metabolic products of the compounds described herein, to the extent such products are novel and unobvious over the prior art. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes novel and unobvious compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. ^{14}C or ^3H) compound of the invention, administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are

easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no HCV polymerase inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37° C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed in vivo. The prodrugs of the invention typically will be stable in the digestive system but may be substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

EXAMPLES

Certain abbreviations and acronyms are used in describing the experimental details. Although most of these would be understood by one skilled in the art, Table 1 contains a list of many of these abbreviations and acronyms.

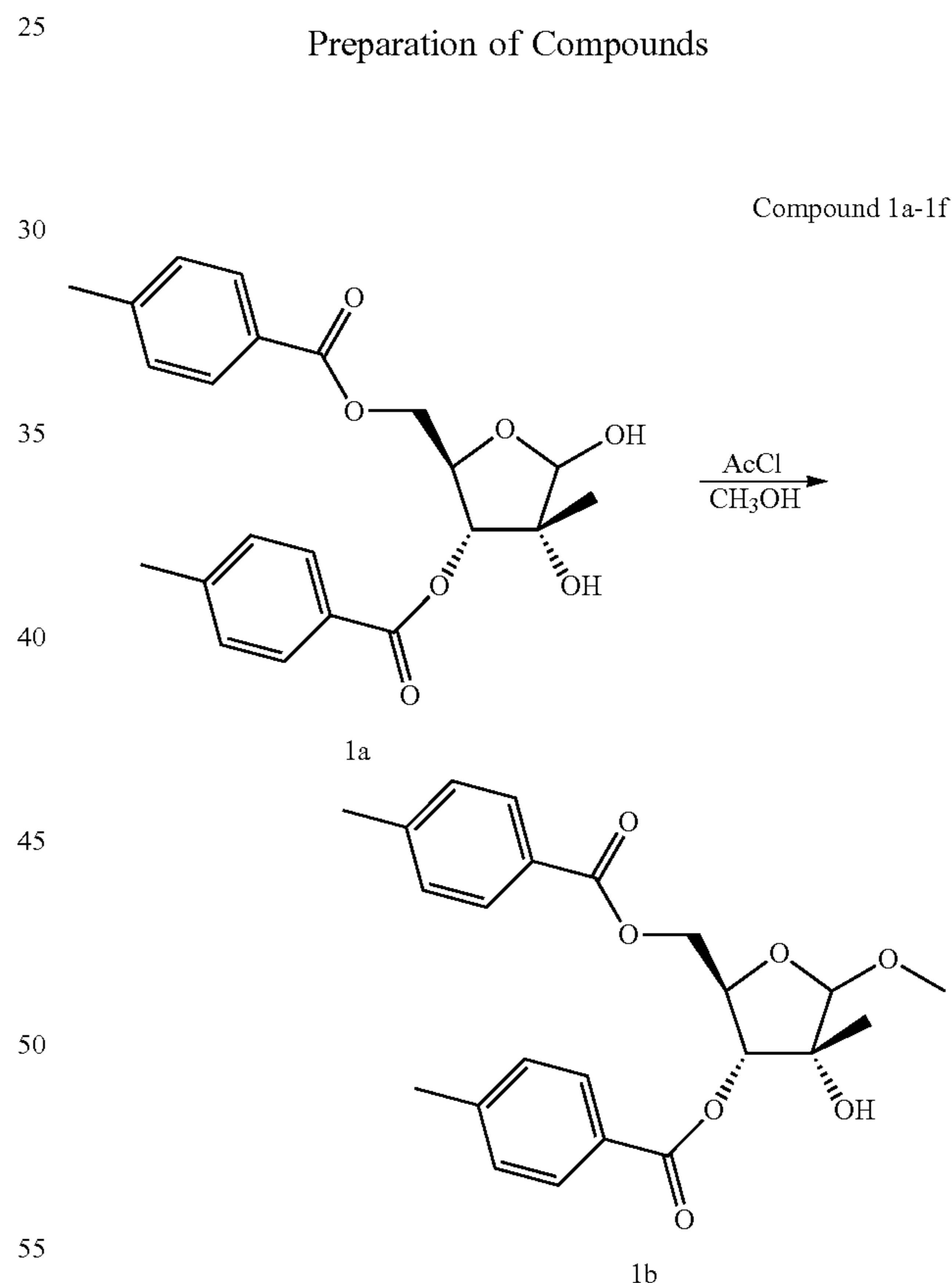
TABLE 1

List of abbreviations and acronyms.	
Abbreviation	Meaning
Ac ₂ O	acetic anhydride
AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
BnBr	benzylbromide
BSA	bis(trimethylsilyl)acetamide
BzCl	benzoyl chloride
CDI	carbonyl diimidazole
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]nonene-5
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DBU	1,5-diazabicyclo[5.4.0]undecene-5
DCA	dichloroacetamide
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxy ethane
DMTCl	dimethoxytrityl chloride
DMSO	dimethylsulfoxide
DMTr	4,4'-dimethoxytrityl
DMF	dimethylformamide
EtOAc	ethyl acetate
ESI	electrospray ionization
HMDS	hexamethyldisilazane
HPLC	High pressure liquid chromatography
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
MCPBA	meta-chloroperbenzoic acid
MeCN	acetonitrile
MeOH	methanol
MMTC	mono methoxytrityl chloride
m/z or m/e	mass to charge ratio
MH ⁺	mass plus 1
MH ⁻	mass minus 1
MsOH	methanesulfonic acid
MS or ms	mass spectrum
NBS	N-bromo succinimide
rt or r.t.	room temperature

TABLE 1-continued

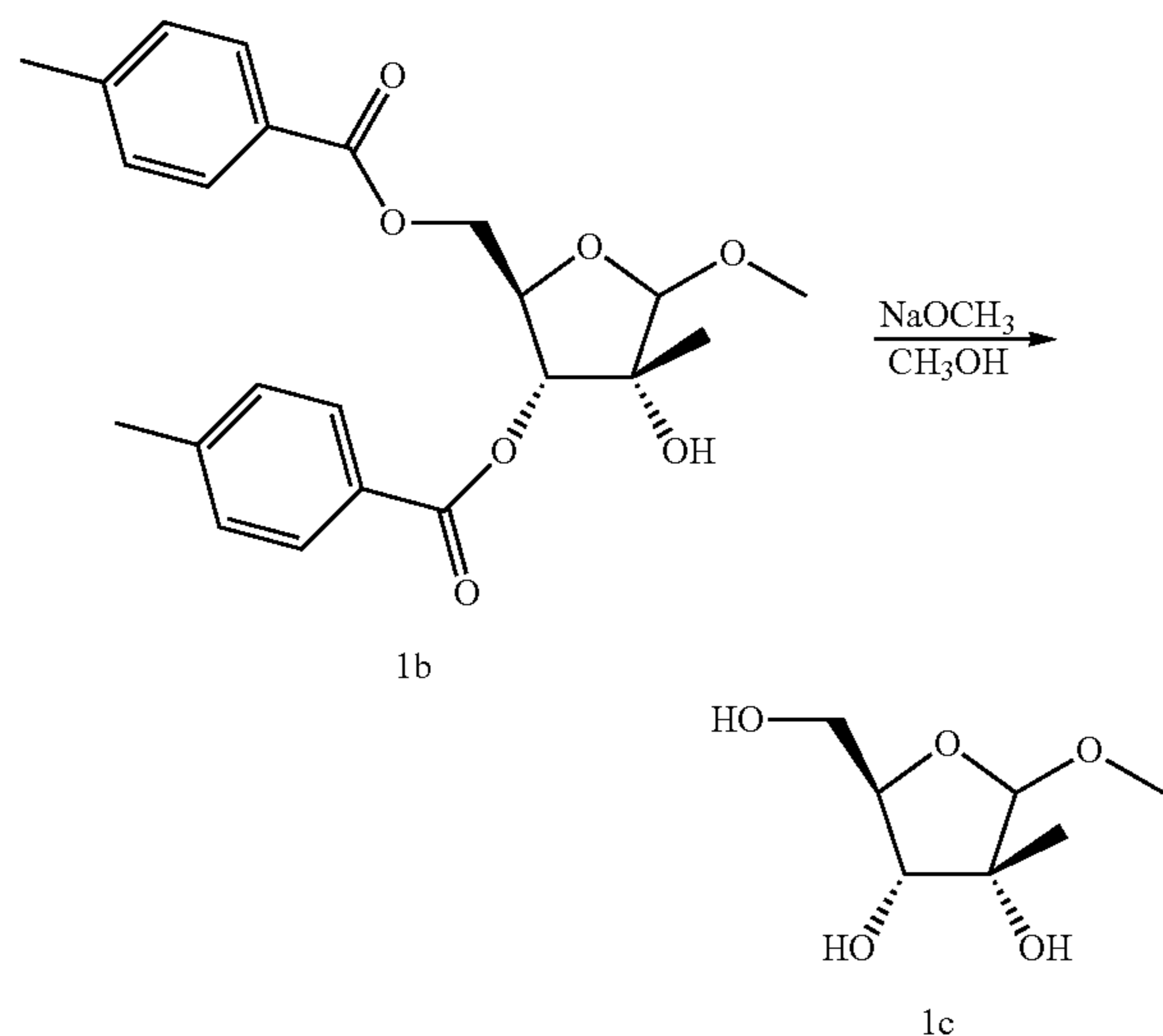
List of abbreviations and acronyms.	
Abbreviation	Meaning
TBAF	tetrabutylammonium fluoride
TMSCl	chlorotrimethylsilane
TMSBr	bromotrimethylsilane
TMSI	iodotrimethylsilane
TEA	triethylamine
TBA	tributylamine
TBAP	tributylammonium pyrophosphate
TBSCl	t-butyltrimethylsilyl chloride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
TLC or tlc	thin layer chromatography
Tr	triphenylmethyl
Tol	4-methylbenzoyl
δ	parts per million down field from tetramethylsilane

Preparation of Compounds

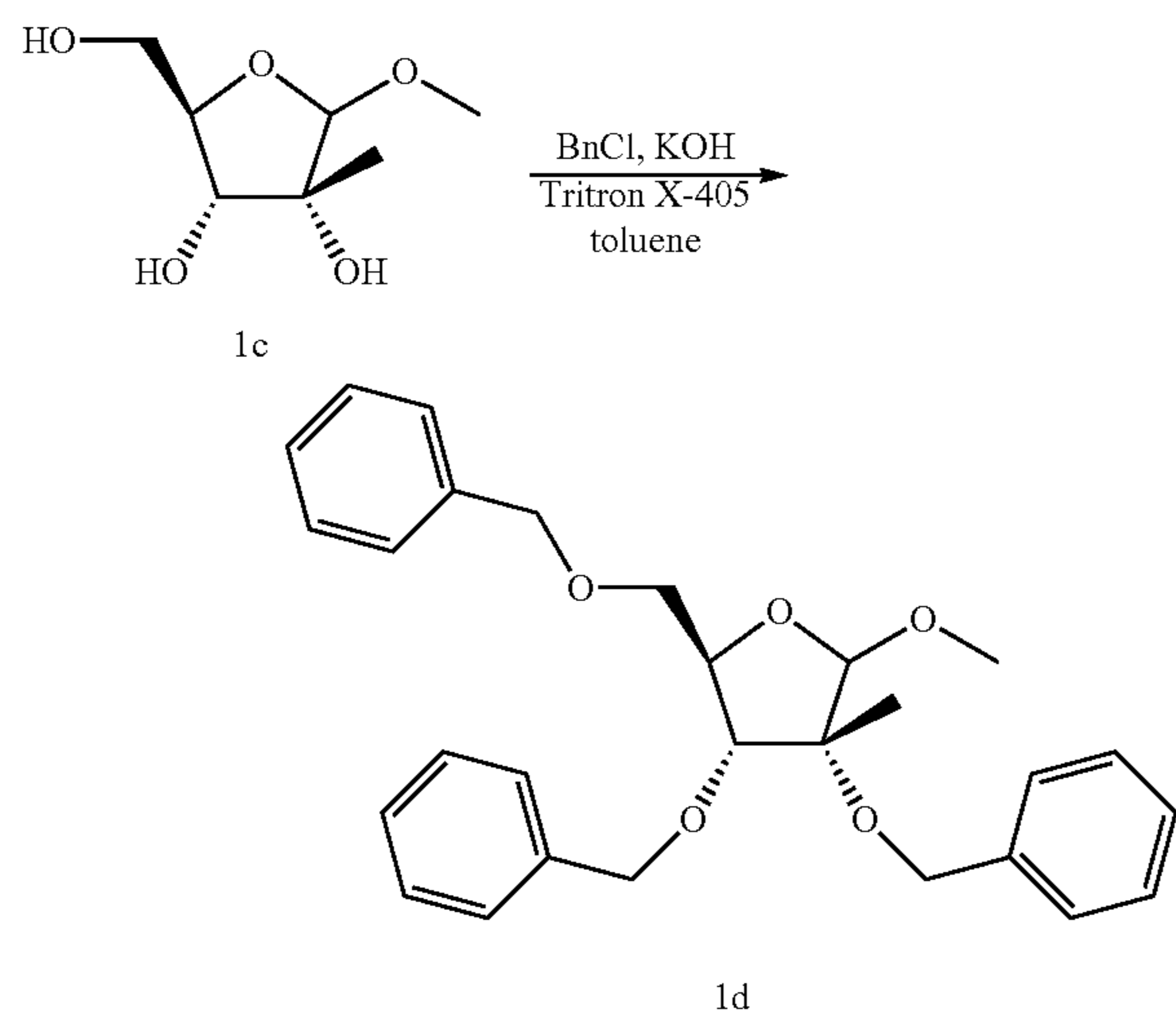


To a solution of 1a (22.0 g, 54.9 mmol, prepared according to the procedures described in J. O. C., 2004, 6257) in methanol (300 mL) was dropwise added acetyl chloride (22 mL) at 0° C. using a dropping funnel over a period of 30 min. and then stirred at room temperature for 16 h. The mixture was concentrated, re-dissolved in ethyl acetate (400 mL), washed with ice-cold 2 N NaOH, and concentrated to dryness, affording the crude methyl ether 1b as an oil. MS=437.2 (M+Na⁺).

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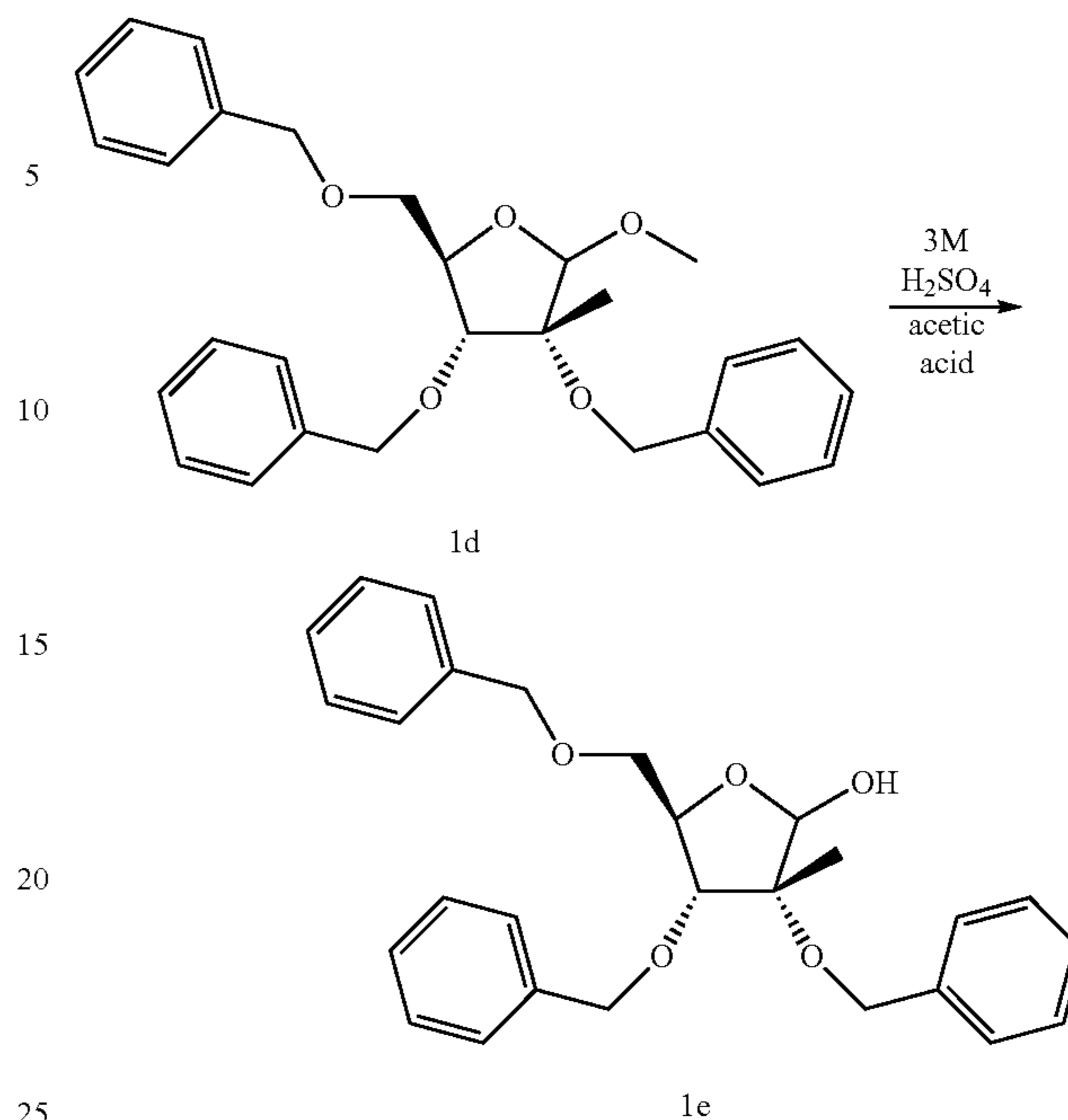


To a solution of 1b (obtained from the previous step) in methanol (300 mL) was added 0.5 M sodium methoxide solution in methanol (20 mL, 10 mmol), and stirred for 16 h at room temperature. The reaction was quenched with 4.0 N HCl solution in dioxane (2.5 mL, 10 mmol). The mixture was then concentrated, affording the crude 1c. MS=201.0 (M+Na⁺).

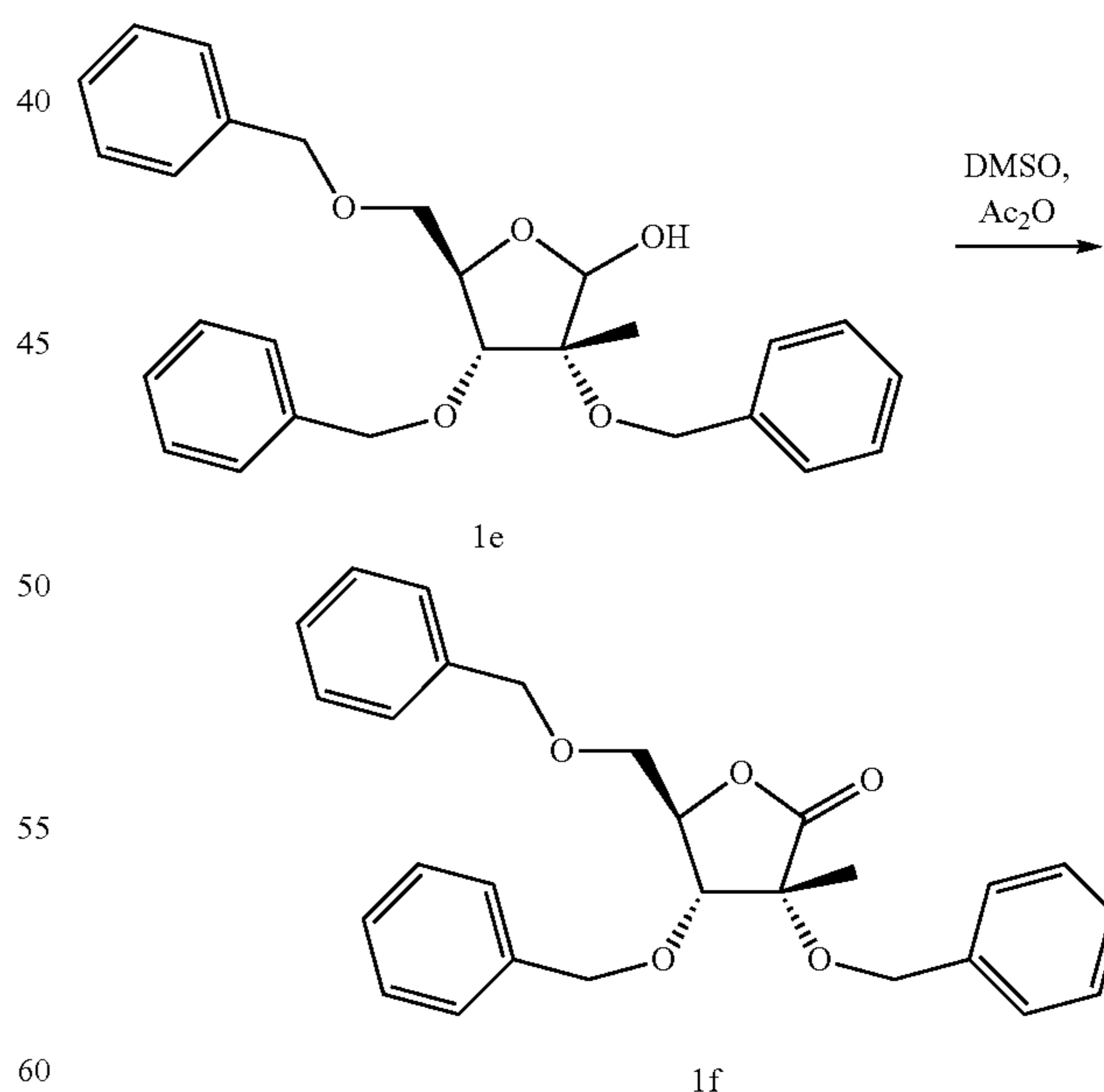


A mixture of 1c (obtained from the previous step), Triton X-405 (70% in water, 6.0 g), 50% KOH (in water, 85 g) in toluene (500 mL) was heated to reflux with a Dean-Stark trap attached. After 1 h collecting ~25 mL of water, benzyl chloride (33 g, 260 mmol) was added and continued to reflux with stirring for 16 h. The mixture was then cooled and partitioned between ethyl acetate (400 mL) and water (300 mL). The organic layer was washed with water (300 mL), and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc/hexanes), affording the methyl ether 1d as an oil (22.0 g, 89% in three steps). ¹H NMR (300 MHz, CDCl₃): δ 7.3 (m, 15H), 4.5-4.9 (m, 7H), 4.37 (m, 1H), 3.87 (d, 1H), 3.56 (m, 2H), 3.52 (s, 3H), 1.40 (s, 3H).

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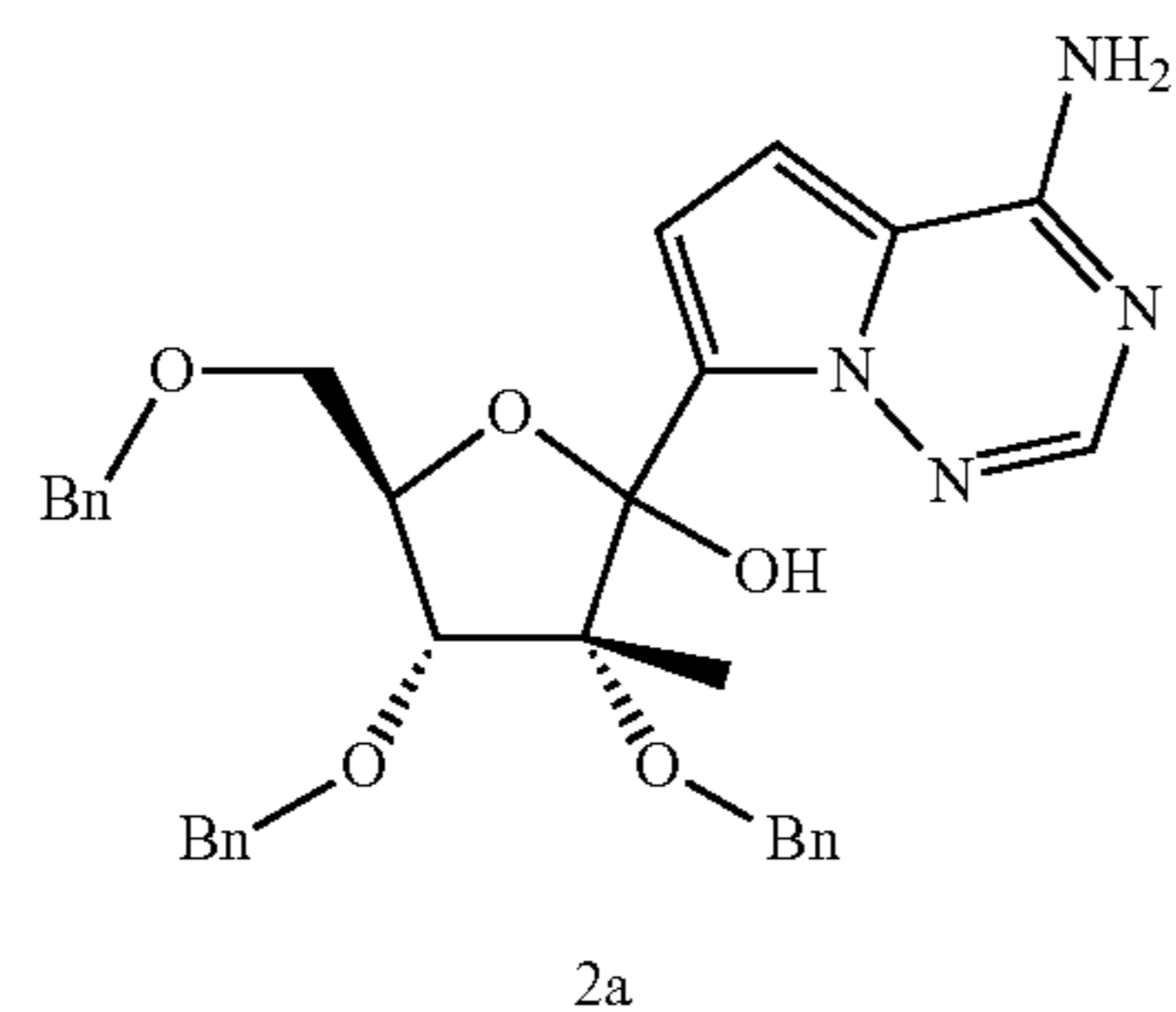
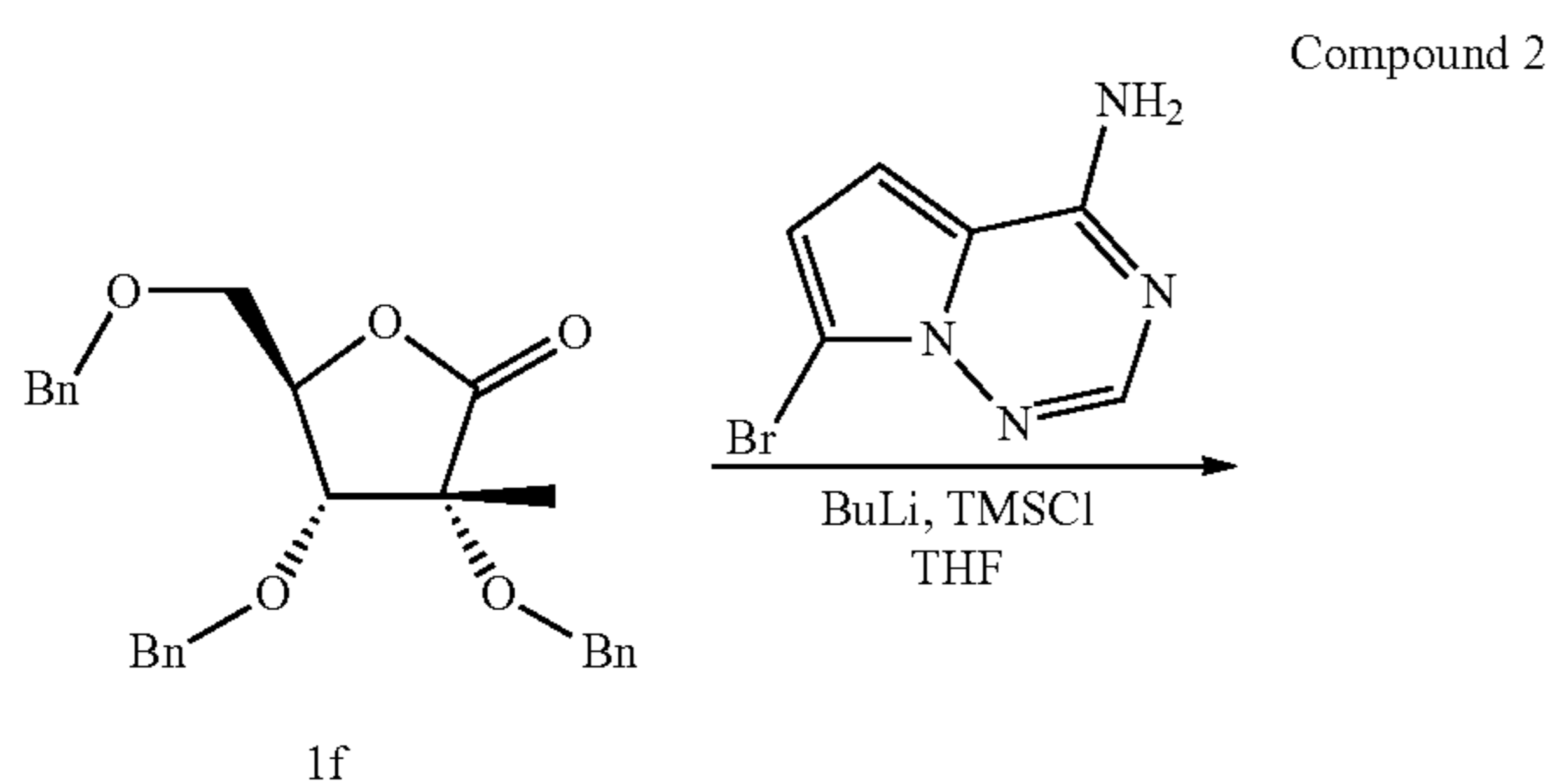
To a solution of 1d (22.0 g, 49.0 mmol) in acetic acid (110 mL) was added ~3 M sulfuric acid (prepared by mixing 4.8 g of concentrated sulfuric acid with 24 mL of water) and stirred at 70° C. for 8 h. The mixture was concentrated to a volume of ~20 mL, and partitioned between ethyl acetate and ice-cold 2N NaOH. The ethyl acetate layer was concentrated, and purified by silica gel column chromatography (~35% EtOAc/hexanes), affording 1e as an oil (17.0 g, 80%). MS=457.2 (M+Na⁺).



To a solution of 1e (45 g, 104 mmol) in DMSO (135 mL) was dropwise added acetic anhydride (90 mL, 815 mmol) at room temperature under argon. The mixture was stirred for 16 h at room temperature, and then poured into ice-water (1 L) while stirring. After ice was completely melted (~30

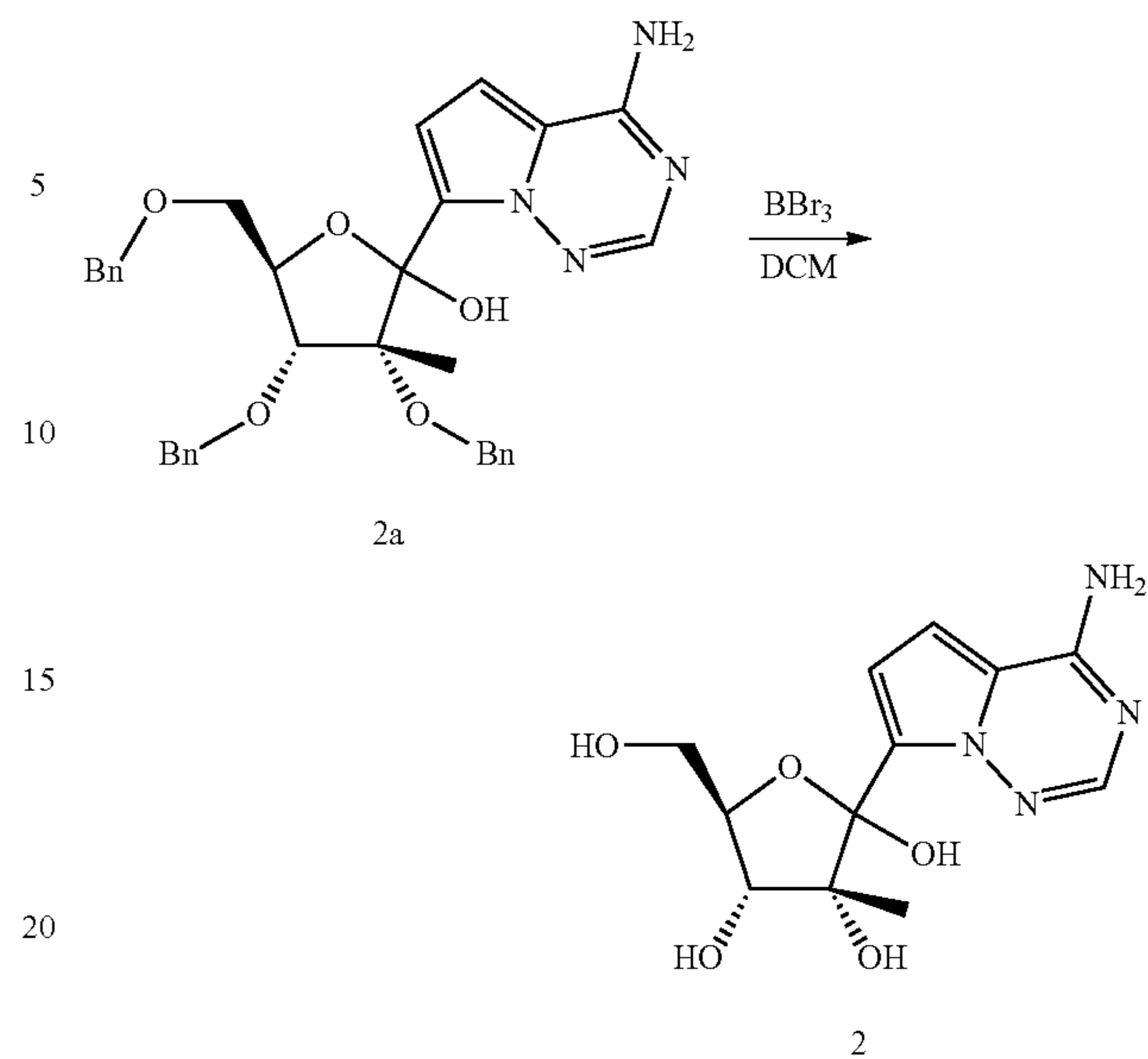
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min), ethyl acetate (~500 mL) was added. The organic layer was separated. This extraction process was repeated three times (3×500 mL). The organic extracts were combined and concentrated. The residue was purified by silica gel column chromatography (~20% EtOAc/hexanes), affording 1f as an oil (39 g, 88%). ¹H NMR (300 MHz, DMSO-d₆): δ 7.3 (m, 15H), 4.4-4.8 (m, 7H), 4.08 (d, J=7.5 Hz, 1H), 3.75 (dd, J=2.4, 11.4 Hz, 1H), 3.64 (dd, J=5.4, 11.4 Hz, 1H), 1.51 (s, 3H).

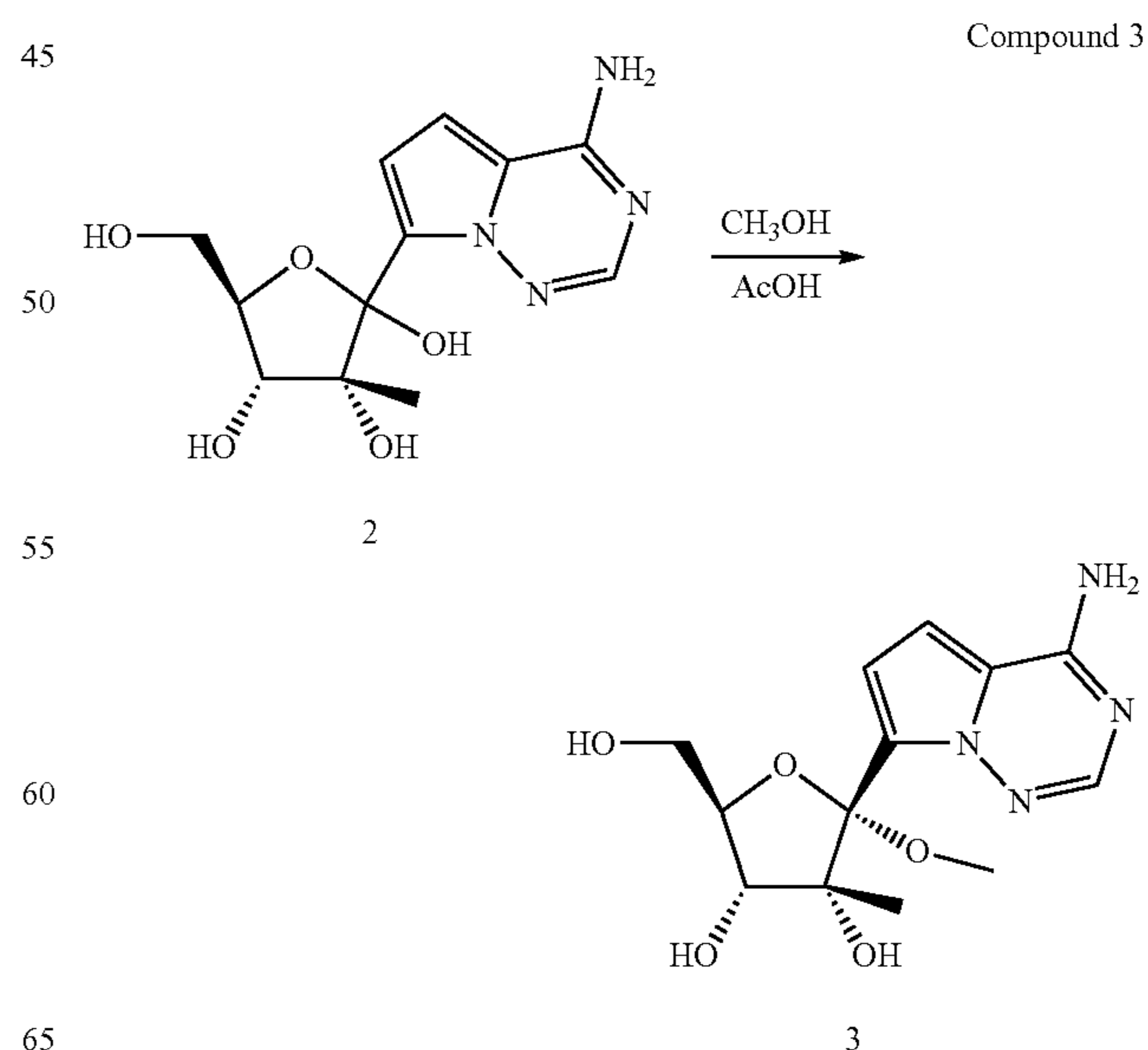


To a dry, argon purged round bottom flask (100 mL) were added 7-bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (234 mg, 1.10 mmol) (prepared according to WO2007056170) and anhydrous THF (1.5 mL). TMSCl (276 μL, 2.2 mmol) was then added and the reaction mixture stirred for 2 h. The flask was placed into a dry ice/acetone bath (~-78° C.) and BuLi (2.5 mL, 4.0 mmol, 1.6M in hexanes) was added dropwise. After 1 h, a solution of 1f (432.5 mg, 1.0 mmol) in THF was cooled to 0° C. and then added to the reaction flask dropwise. After 1 h of stirring at -78° C., the flask was warmed to 0° C. and sat. NH₄Cl (5 mL) was added to quench the reaction. The organics were extracted using EtOAc (3×10 L) and the combined organic layers were dried using MgSO₄. The solvent was removed under reduced pressure and the crude material was purified using flash chromatography (hexanes/EtOAc). 560 mg (99%) of 2a was isolated as a mixture of two anomers. LC/MS=567.2 (M+H⁺). ¹H NMR (300 MHz, CDCl₃): δ 7.85 (m, 1H), 7.27 (m, 15H), 7.01 (m, 1H), 6.51 (m, 1H), 4.66 (m, 8H), 4.40 (m, 2H), 3.79 (m, 3H), 1.62 (s, 2'-CH₃ from the one anomer), 1.18 (s, 2'-CH₃ from the other anomer).

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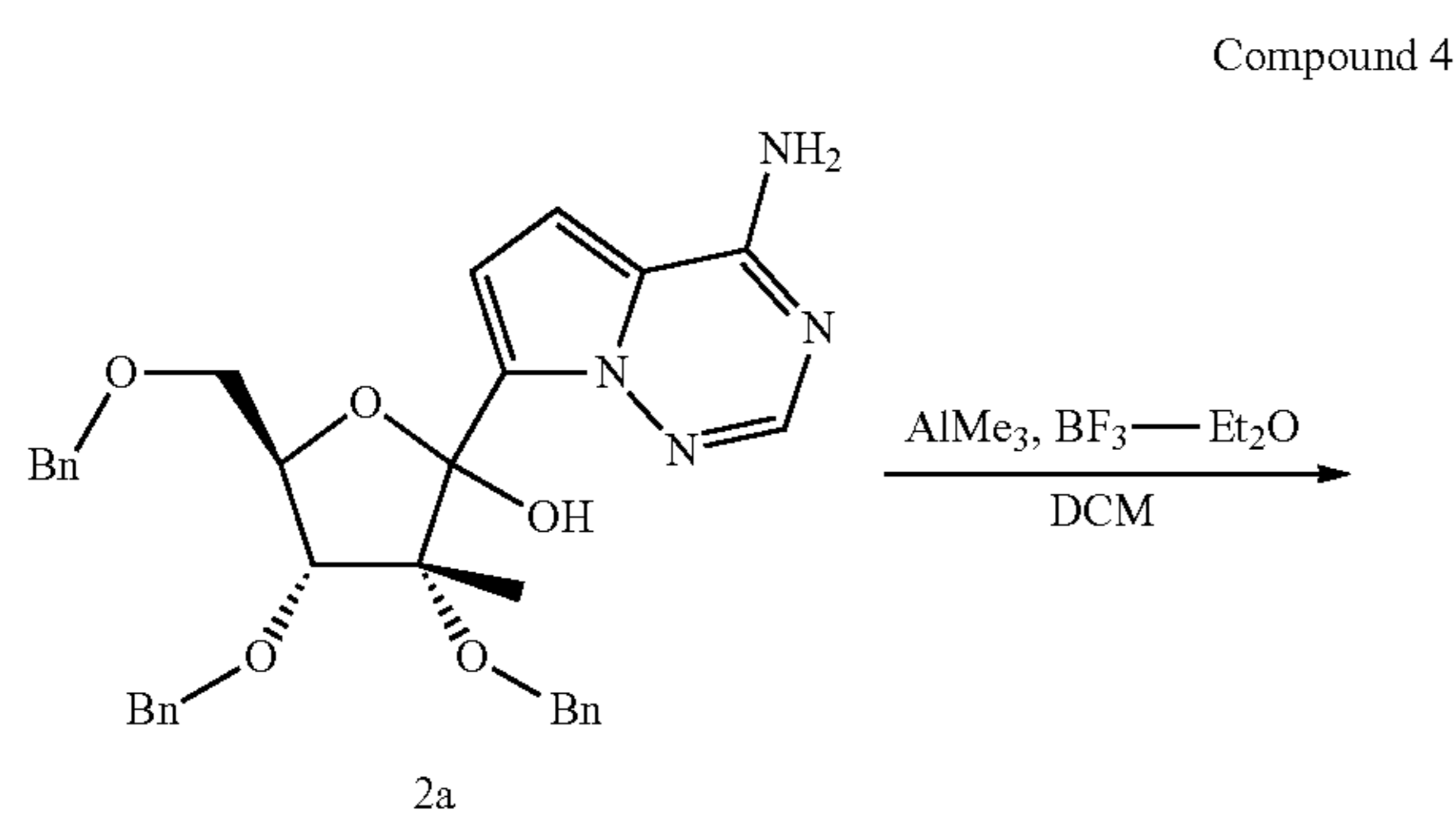


To a dry, argon purged round bottom flask (50 mL) were added compound 2a (185 mg, 0.33 mmol) and anhydrous dichloromethane (10 mL). The flask was placed into a dry ice/acetone bath (~-78° C.) and the solution stirred for 10 min. BBr₃ (0.25 mL, 0.25 mmol, 1.0 M in DCM) was then added and the reaction continued to stir at -78° C. until complete disappearance of the starting material. After 1 h, a solution of pyridine (2 mL) in MeOH (10 mL) was added and the flask was warmed to room temperature. The solvent was removed under reduced pressure and the crude material was re-dissolved in MeOH. After this process was repeated two more times, the crude material was then dissolved in water and purified using a Gilson Preparatory HPLC system (acetonitrile/H₂O). 49 mg (50%) of Compound 2 was isolated as an isomeric mixture. LC/MS=297.1 (M+H⁺). ¹H NMR (300 MHz, D₂O): δ 7.68 (m, 1H), 6.80 (m, 2H), 4.04 (m, 2H), 3.78 (m, 2H), 3.65 (m, 1H), 1.30 (s, 2'-CH₃), 0.80 (s, 2'-CH₃).

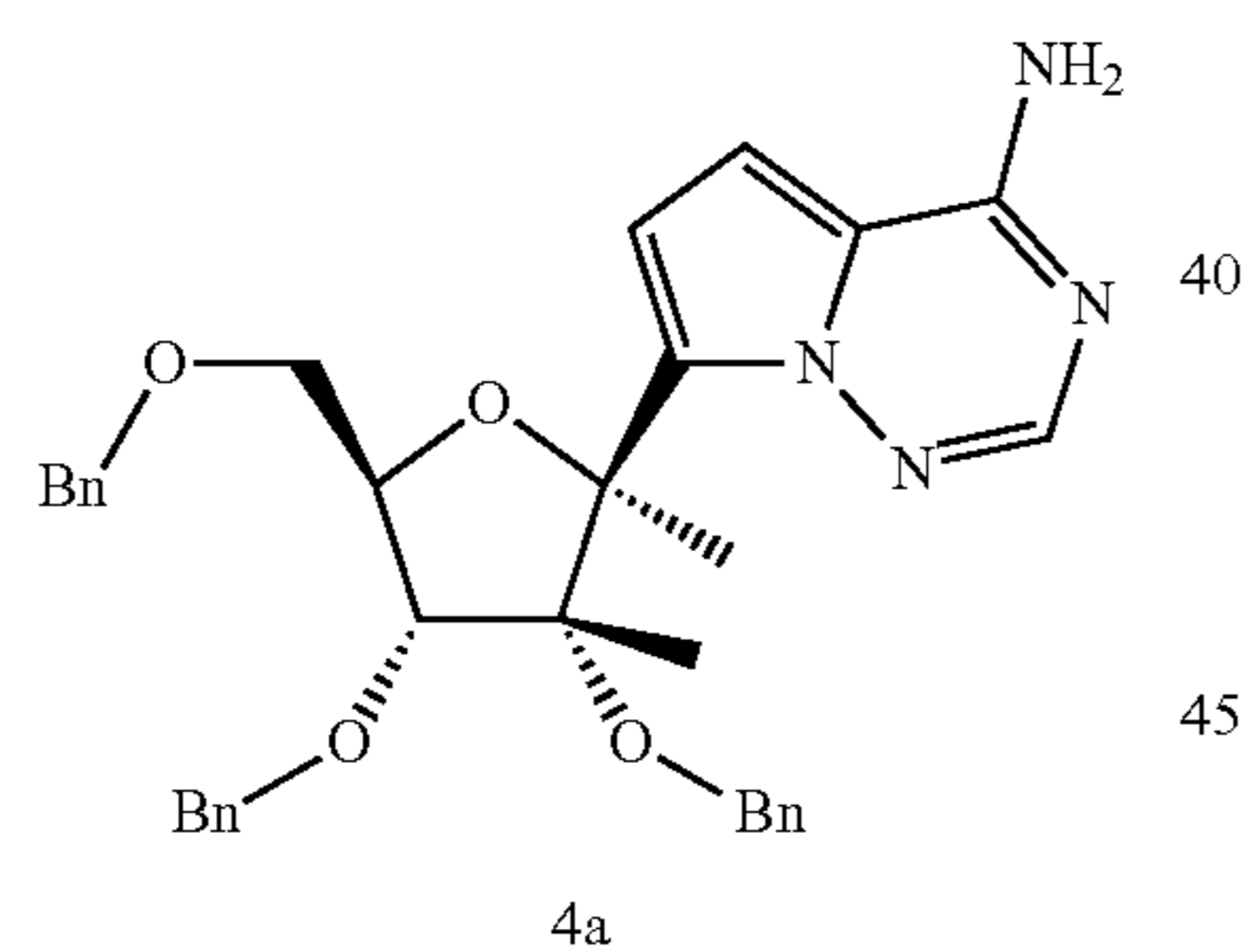


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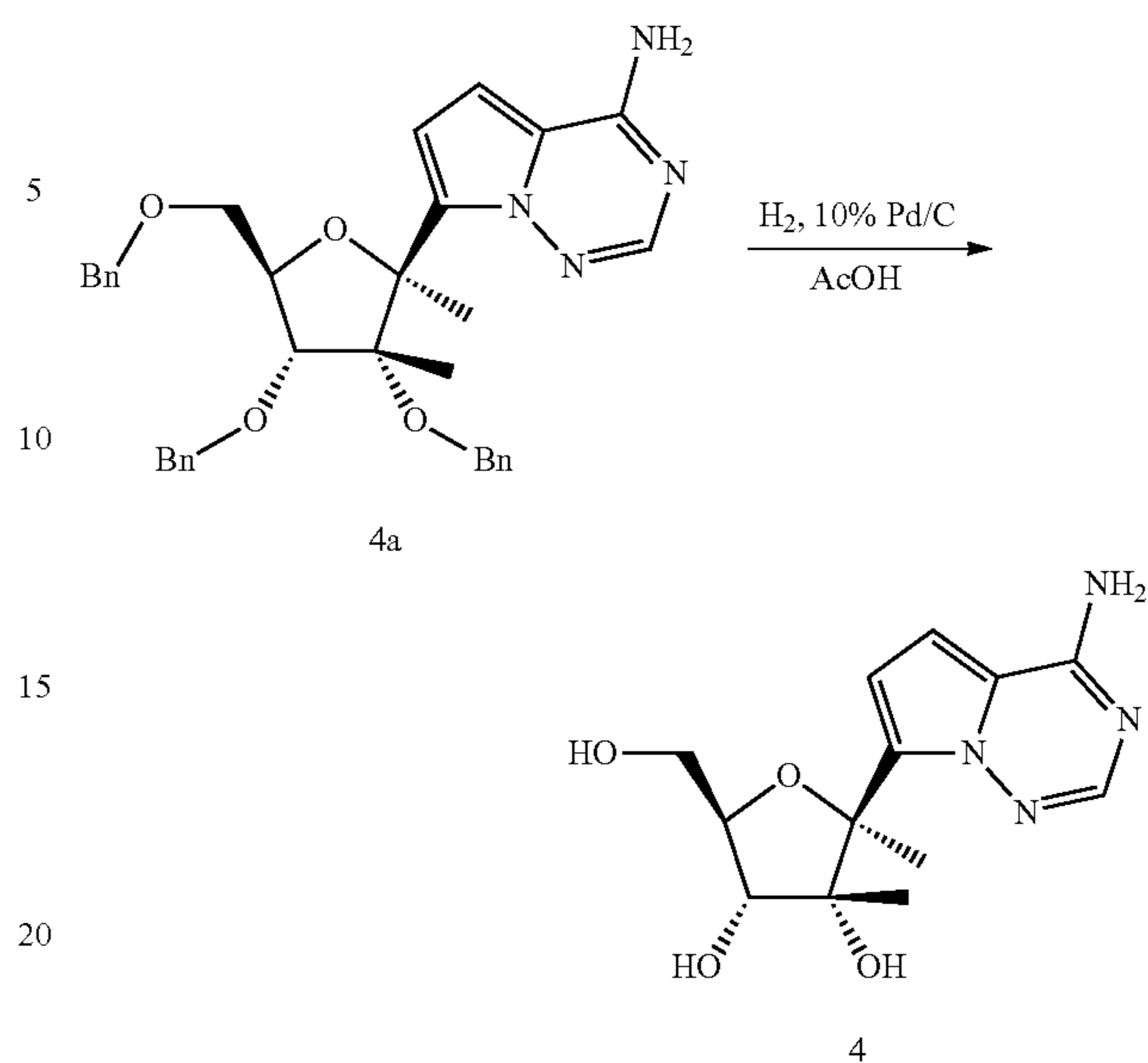
To a dry, argon purged round bottom flask (100 mL) were added Compound 2 (12 mg, 0.04 mmol) (2) and anhydrous MeOH (5 mL). Acetic acid (5 mL) was then added and the reaction stirred overnight at room temperature. Saturated NaHCO₃ was added to neutralize the reaction mixture and the crude material was purified using a Gilson Preparatory HPLC system (acetonitrile-H₂O). 2 mg (16%) of the desired material Compound 3 was isolated. LC/MS=311.2 (M+H⁺). ¹H NMR (300 MHz, D₂O): δ 7.71 (s, 1H), 6.78 (s, 2H), 3.98 (m, 1H), 3.83 (dd, 1H), 3.74 (dd, 1H), 3.62 (d, 1H), 2.94 (s, 3H), 0.76 (s, 3H). The other alpha-isomer was also isolated; ¹H NMR (300 MHz, D₂O): δ 7.65 (s, 1H), 6.78 (d, 1H), 6.75 (d, 1H), 4.03 (m, 2H), 3.77 (dd, 1H), 3.59 (d, 1H), 2.95 (s, 3H), 1.31 (s, 3H).



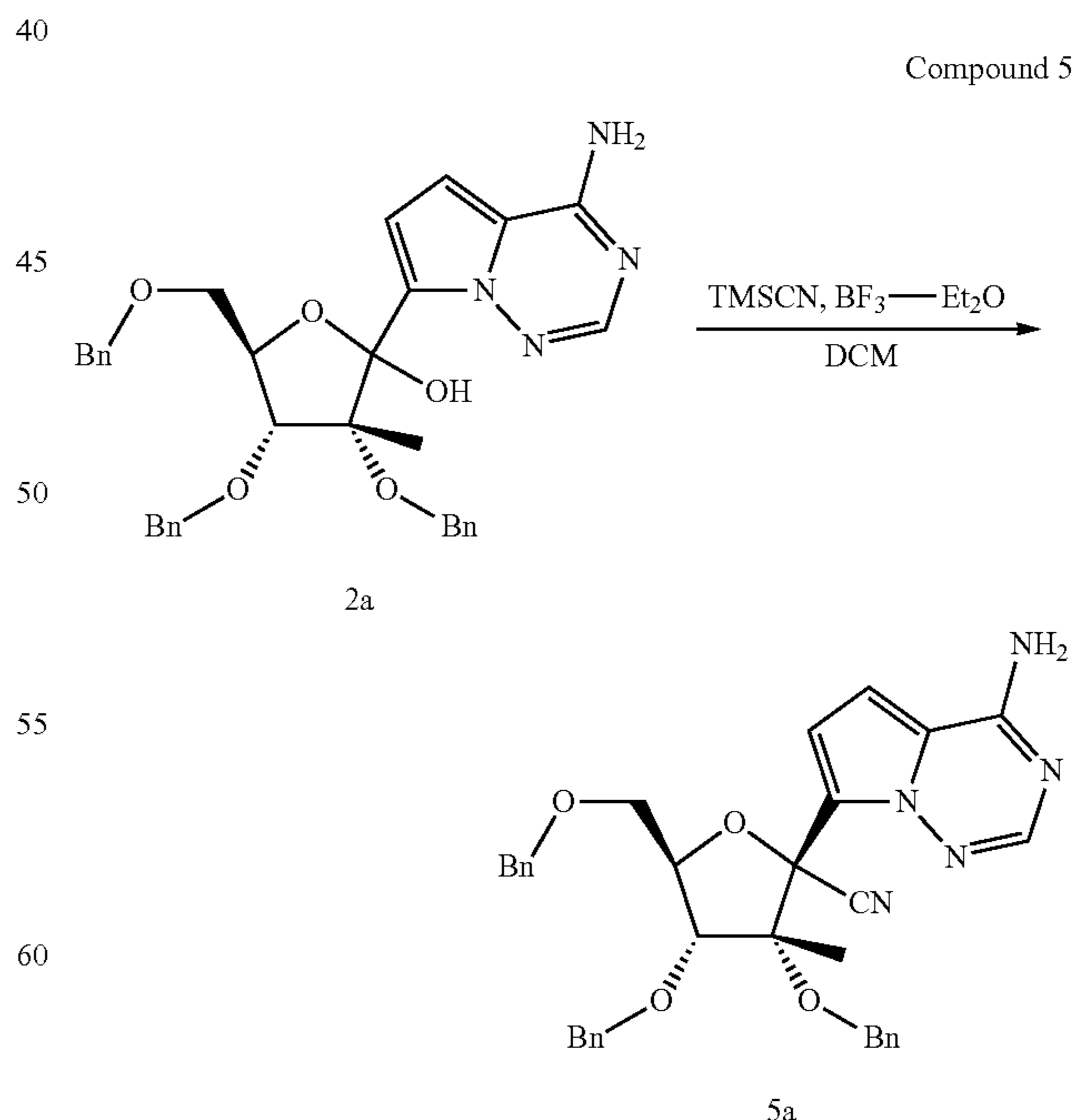
To a dry, argon purged round bottom flask (50 mL) were added compound 2a (220 mg, 0.39 mmol) and anhydrous dichloromethane (10 mL). The flask was placed into a dry ice/acetone bath (~-78° C.) and the solution stirred for 10 min. BF₃-Et₂O (0.10 mL) was added dropwise and the reaction stirred for 10 min. AlMe₃ (0.58 mL, 1.16 mmol, 2.0 M in toluene) was then added. After a few minutes, the dry ice/acetone bath was removed and the reaction mixture warmed to room temperature over 4 h. A solution of pyridine (2 mL) in MeOH (10 mL) was added and the solvent was removed under reduced pressure. The crude material was purified using flash chromatography (hexanes/EtOAc). 164 mg (74%) of the desired material 4a was isolated. LC/MS=565.2 (M+H⁺). ¹H NMR (300 MHz, CD₃OD): δ 7.71 (s, 1H), 7.32 (m, 15H), 7.02 (m, 1H), 6.78 (m, 1H), 4.62 (m, 8H), 4.21 (m, 1H), 4.04 (m, 1H), 3.84 (m, 1H), 1.95 (s, 3H), 1.10 (s, 3H).



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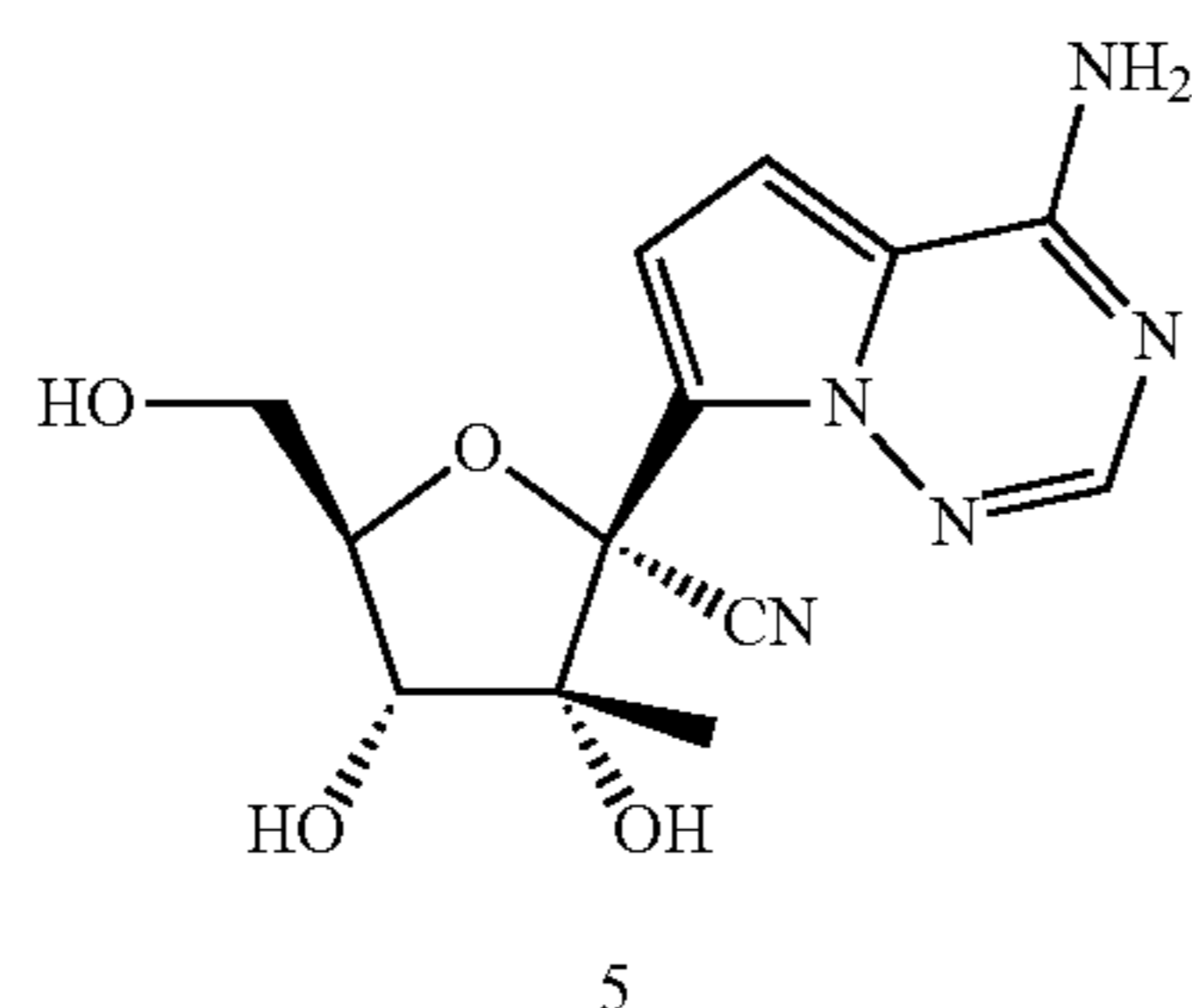
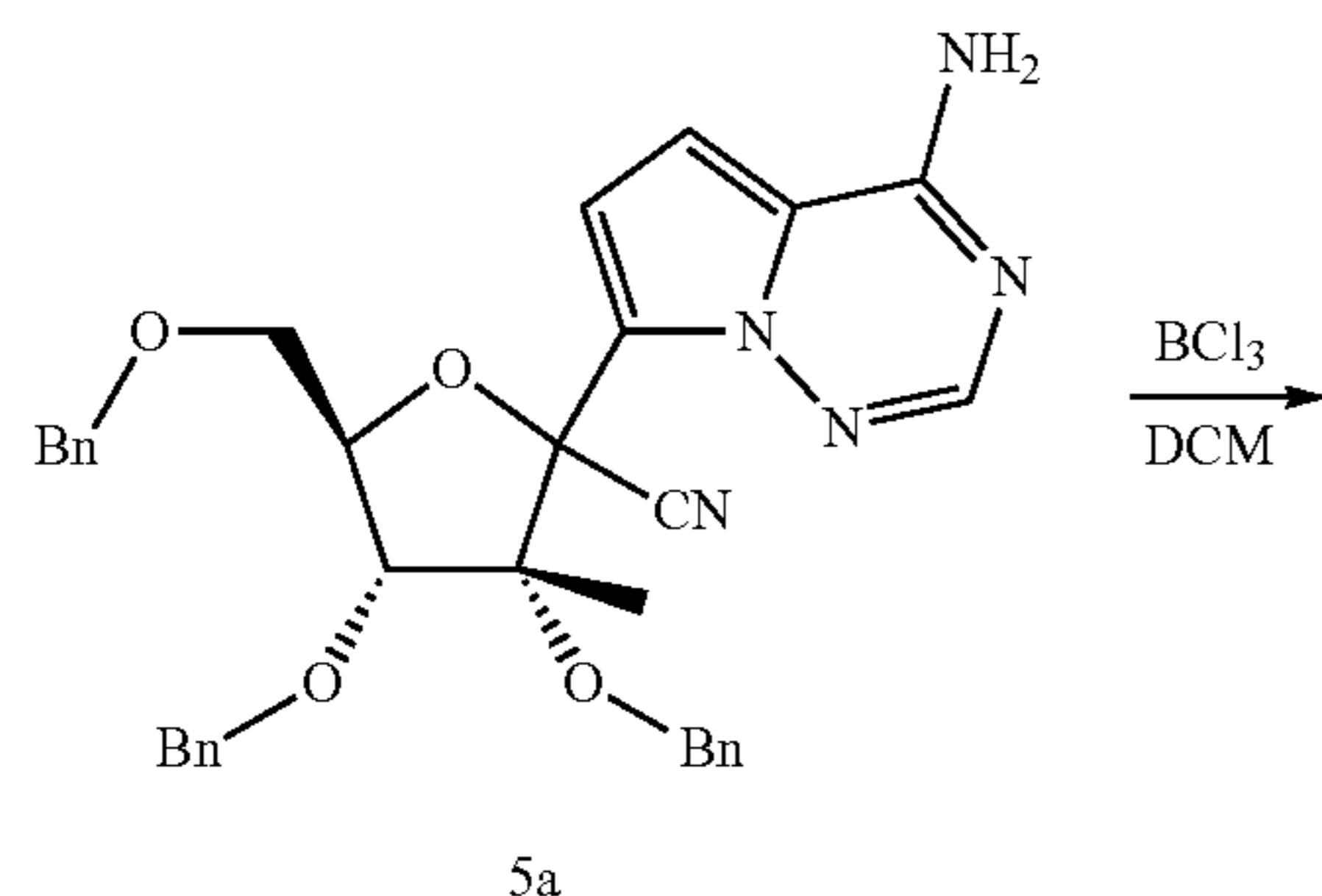
To a dry, argon purged round bottom flask (50 mL) were added compound 4a (164 mg, 0.29 mmol) and glacial acetic acid (10 mL). Pd/C (100 mg, 10% by wt.) was then added and the flask was equipped with a balloon containing hydrogen gas. The flask was purged two times to ensure all of the argon had been replaced with hydrogen. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then neutralized using NaHCO₃ and filtered to remove the catalyst. The crude material was purified using a Gilson Preparatory HPLC system (acetonitrile/H₂O). 6 mg (7%) of the desired material Compound 4 was isolated. LC/MS=295.1 (M+H⁺). ¹H NMR (300 MHz, D₂O): δ 7.66 (s, 1H), 6.72 (m, 1H), 6.64 (m, 1H), 3.93 (m, 1H), 3.76 (m, 3H), 1.63 (s, 3H), 0.76 (s, 3H).



To a solution of compound 2a (1 g, 1.77 mmol) in CH₂Cl₂ (20 mL) at 0° C. was added TMSCN (1.4 mL, 10.5 mmol)

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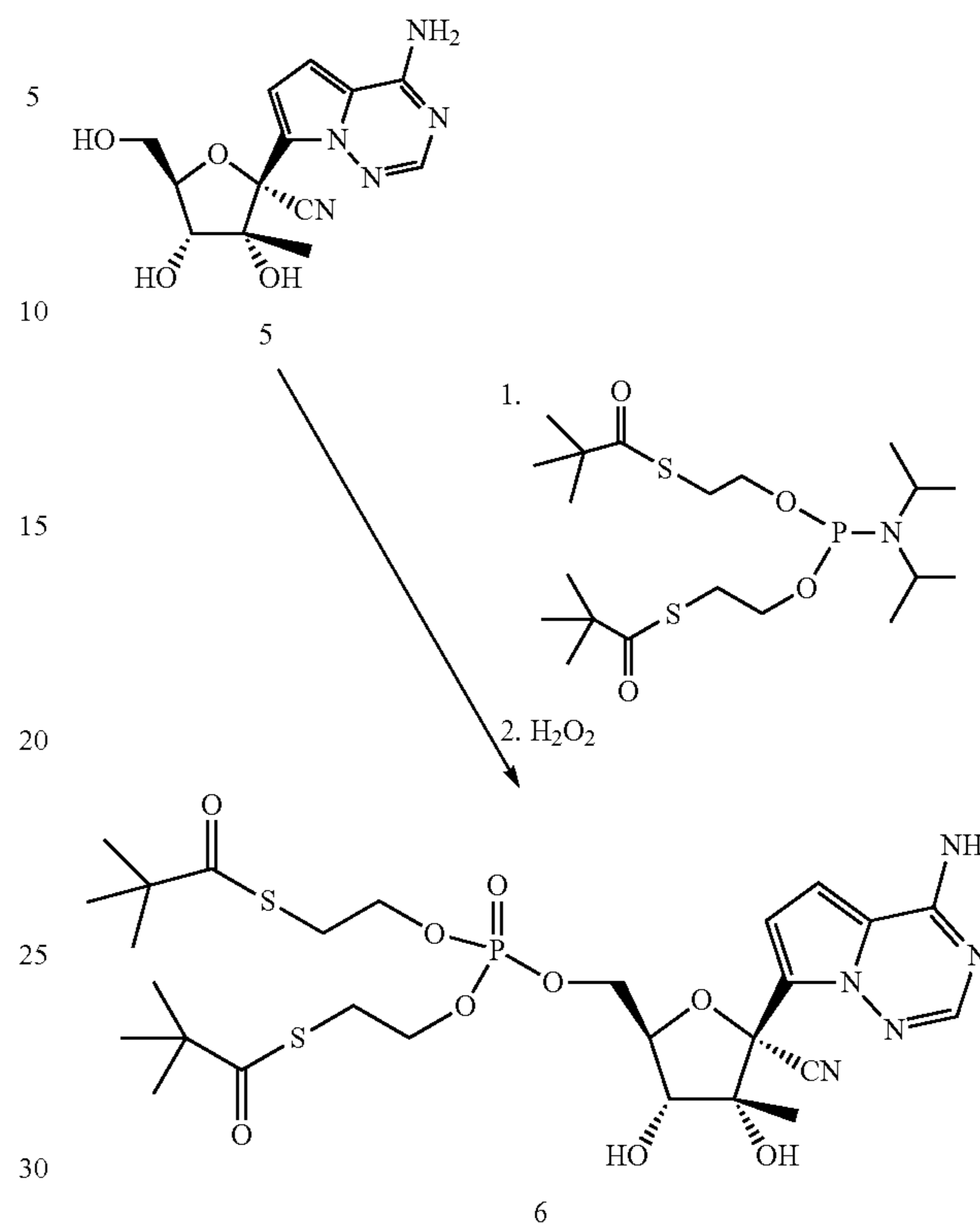
and $\text{BF}_3\text{-Et}_2\text{O}$ (1 mL, 8.1 mmol). The reaction mixture was stirred at 0°C . for 0.5 h, then at room temperature for additional 0.5 h. The reaction was quenched with NaHCO_3 at 0°C ., and diluted with $\text{CH}_3\text{CO}_2\text{Et}$. The organic phase was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by chromatography on silica gel, eluted with $\text{CH}_3\text{CO}_2\text{Et}$ -hexanes (1:1 to 2:1), to give the desired compound 5a (620 mg, 61%) as an isomeric mixture. MS=576.1 ($\text{M}+\text{H}^+$).



To a solution of compound 5a (150 mg, 0.26 mmol) in CH_2Cl_2 (4 mL) at -78°C . was added BCl_3 (2 mL, 1M in CH_2Cl_2). The reaction mixture was stirred at -78°C . for 1 h. The reaction was quenched at -78°C . by dropwise addition of TEA (2 mL) and MeOH (5 mL). The mixture was allowed to warm up to room temperature, evaporated, and co-evaporated with MeOH several times. The residue was treated with NaHCO_3 (1 g in 10 mL H_2O), concentrated and purified by HPLC to give the desired product Compound 5 (48 mg, 60%). ^1H NMR (300 MHz, D_2O): δ 7.74 (s, 1H), 6.76 (d, $J=5$ Hz, 1H), 6.73 (d, $J=5$ Hz, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.8 (m, 2H), 0.84 (s, 3H). MS=305.9 ($\text{M}+\text{H}^+$). The other alpha-anomer was also obtained (9 mg, 11%): ^1H NMR (300 MHz, D_2O): δ 7.70 (s, 1H), 6.8 (d, $J=5$ Hz, 1H), 6.7 (d, $J=5$ Hz, 1H), 4.25 (d, $J=9$ Hz, 1H), 4.07 (m, 1H), 3.85 (m, 1H), 3.7 (m, 1H), 1.6 (s, 3H). MS=306.1 ($\text{M}+\text{H}^+$).

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Compound 6



To a solution of compound 5 (30 mg, 0.098 mmol) and 1H-tetrazole (30 mg, 0.43 mmol) in anhydrous CH_3CN (1 mL) at 0°C . was added 2,2-dimethyl-thiopropionic acid S-(2-{diisopropylamino-[2-(2,2-dimethyl-propionyl sulfanyl)-ethoxy]-phosphanyloxy}-ethyl)ester (90 mg, 0.2 mmol) (described in J. Med. Chem., 1995, 3941). The reaction mixture was stirred at 0°C . for 1 h, then H_2O_2 (30%, 80 μL) was added and stirred for 0.5 h at 0°C . The reaction was quenched with sodium thiosulfate (1 M, 1 mL) and NaHCO_3 , diluted with $\text{CH}_3\text{CO}_2\text{Et}$. The organic phase was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by HPLC to give the desired Compound 6 (28 mg, 42%). ^1H NMR (300 MHz, CDCl_3): δ 8.04 (s, 1H), 6.85 (d, $J=4.5$ Hz, 1H), 6.73 (d, $J=4.5$ Hz, 1H), 6.0 (brs, 2H), 4.6 (m, 1H), 4.4 (m, 2H), 4.1 (m, 4H), 4.0 (d, $J=4$ Hz, 1H), 3.15 (m, 4H), 1.24 (s, 18H), 0.99 (s, 3H). ^{31}P NMR (300 MHz, CDCl_3): δ -1.825. MS=673.9 ($\text{M}+\text{H}^+$), 672.1 ($\text{M}-\text{H}^-$)

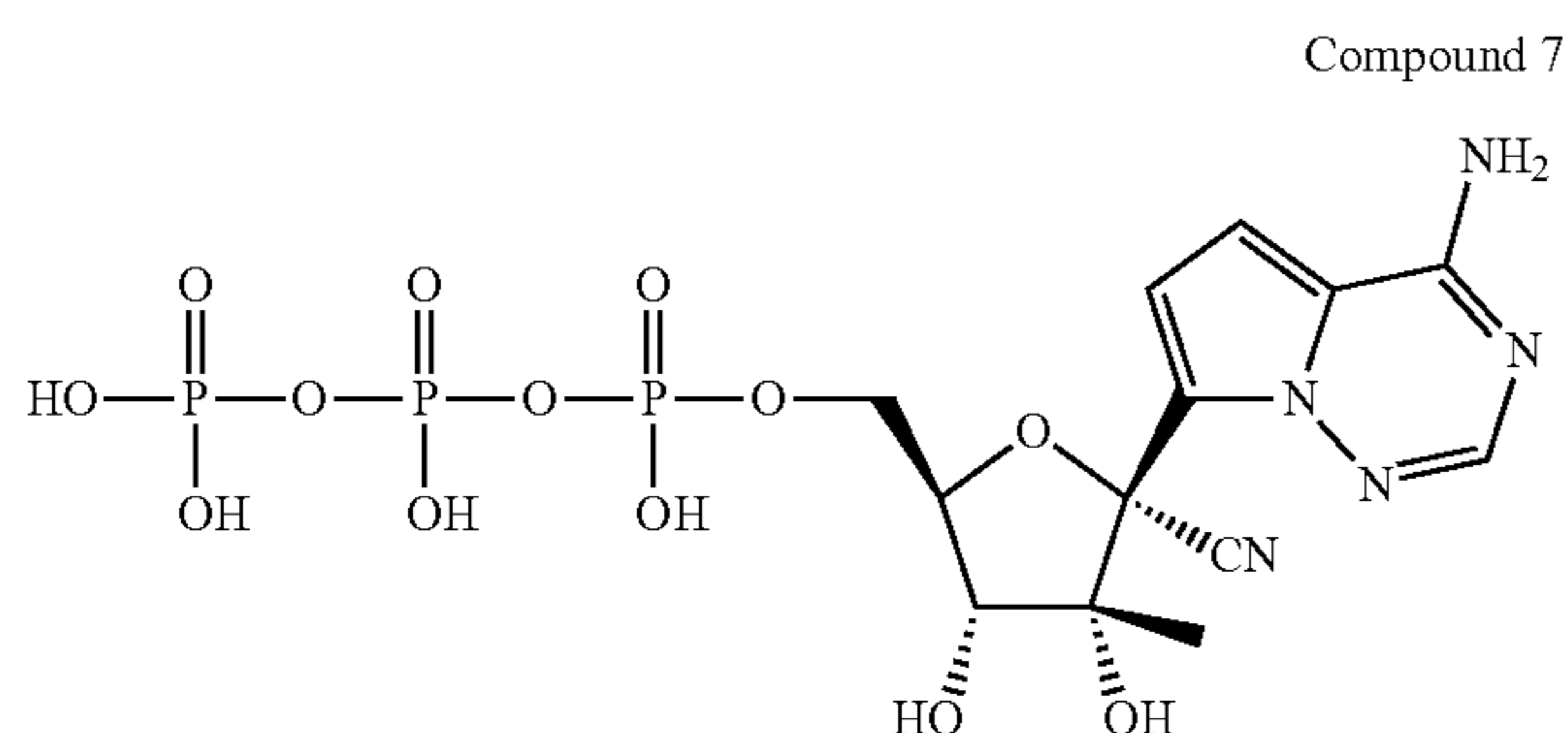
General Procedure for Preparation of a Nucleoside Triphosphate:

To a pear-shaped flask (5-15 mL) is charged with a nucleoside (~20 mg). Trimethyl phosphate (0.5-1.0 mL) is added. The solution is cooled with ice-water bath. POCl_3 (40-45 mg) is added and stirred at 0°C . until the reaction is complete (1 to 4 h; the reaction progress is monitored by ion-exchange

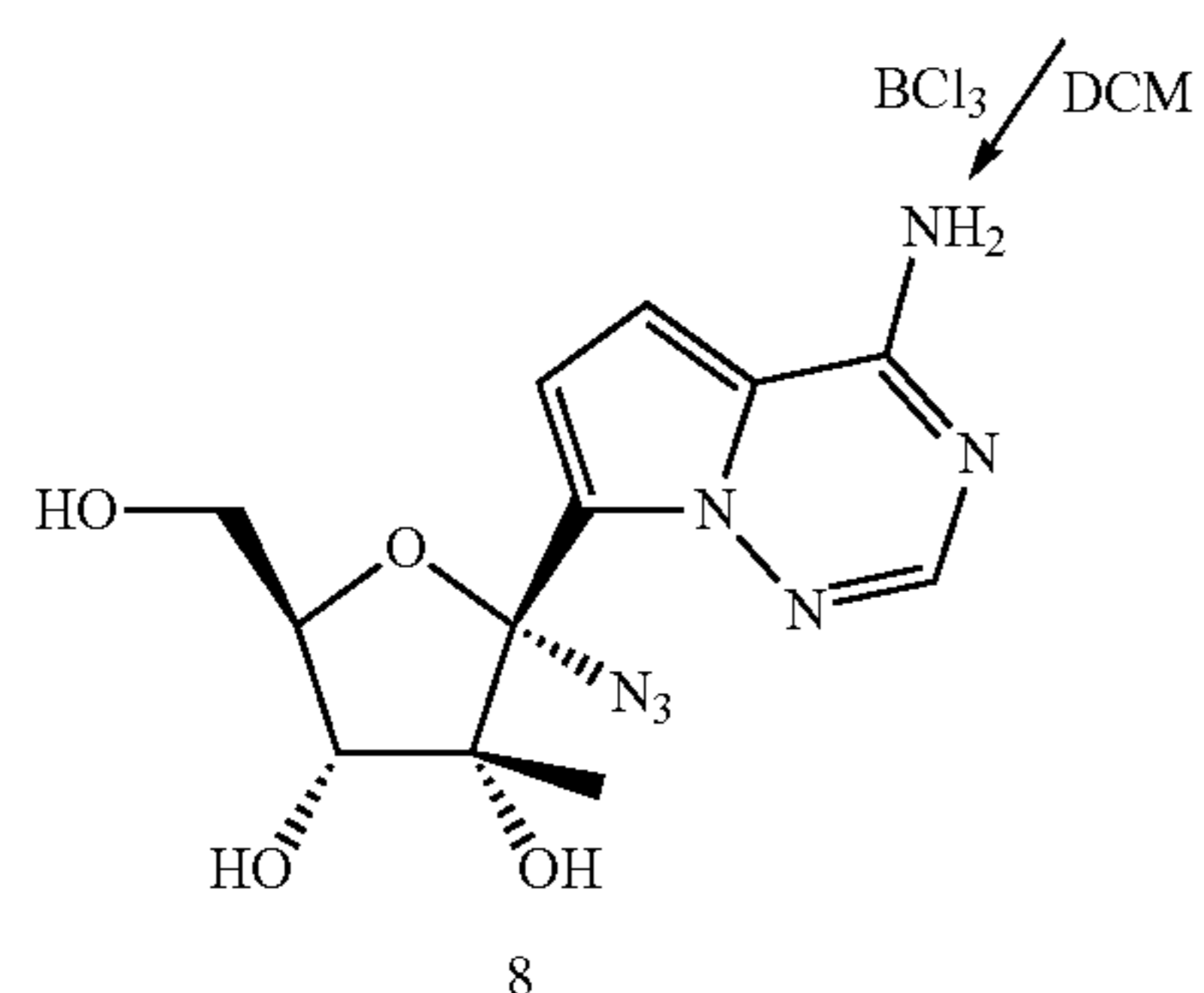
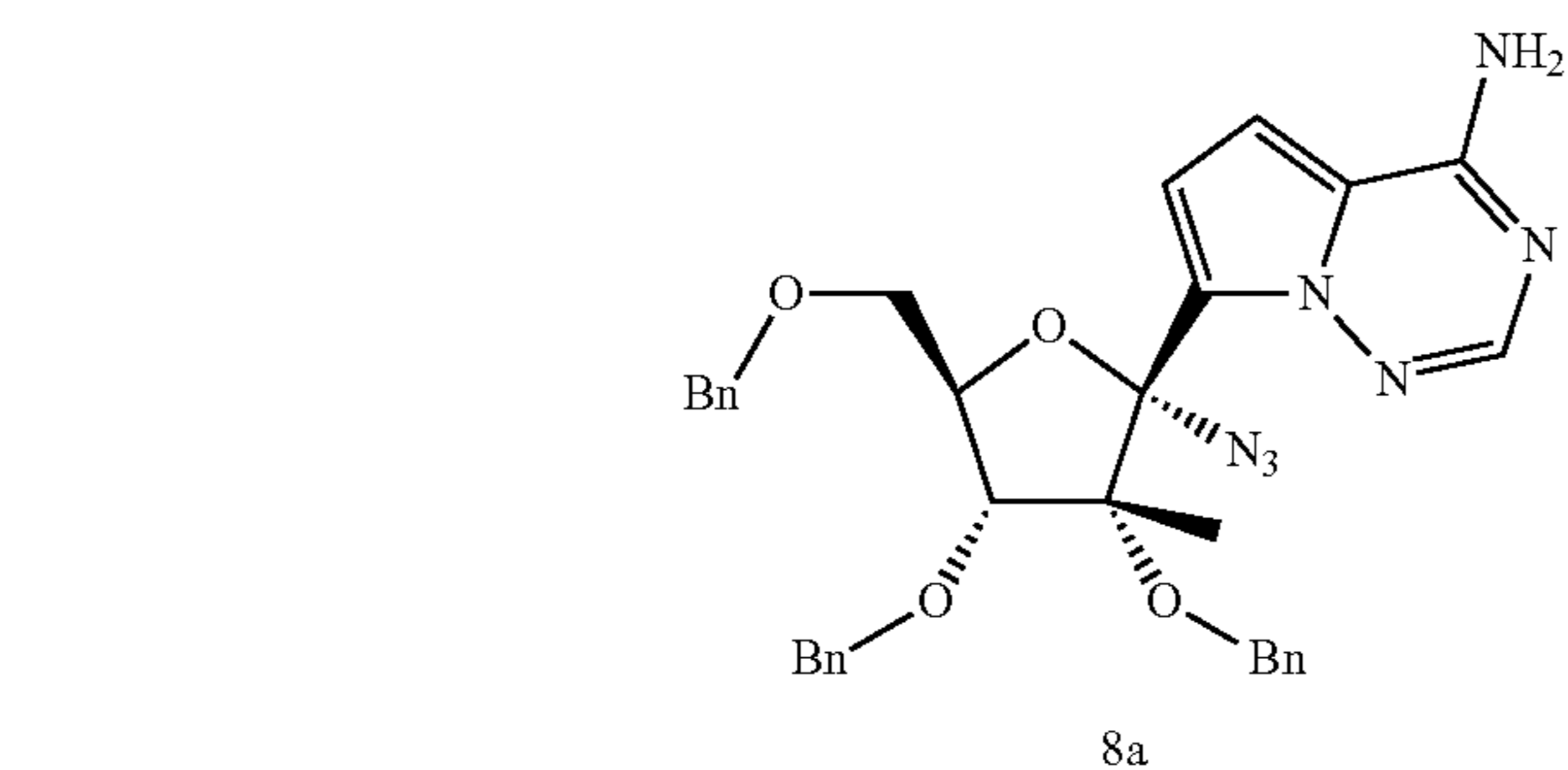
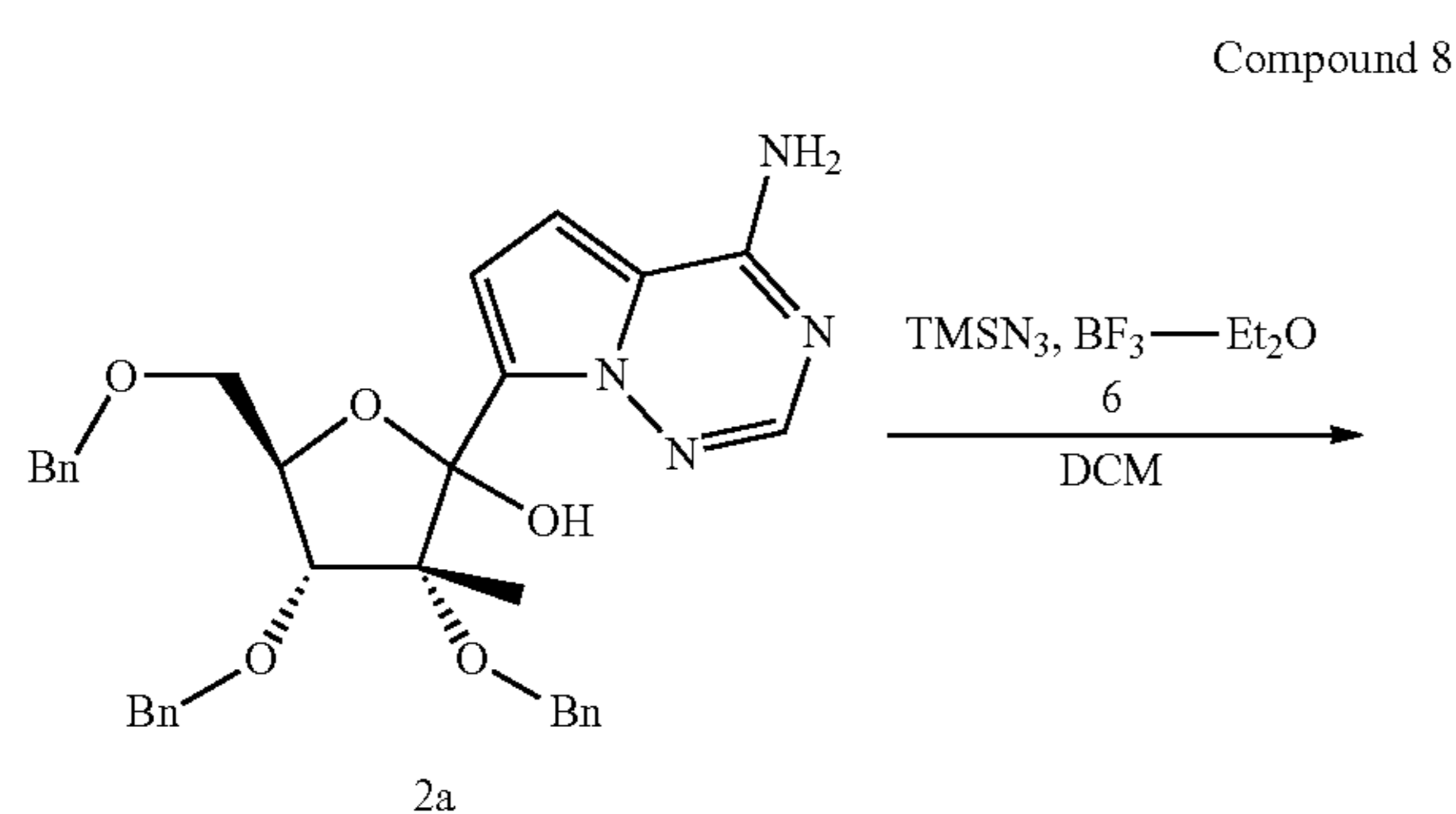
HPLC; analytical samples are prepared by taking ~3 μL of the reaction mixture and diluting it with 1.0 M $\text{Et}_3\text{NH}_2\text{CO}_3$ (30-50 μL). A solution of pyrophosphate- Bu_3N (250 mg) and Bu_3N (90-105 mg) in acetonitrile or DMF (1-1.5 mL) is then added. The mixture is stirred at 0°C . for 0.3 to 2.5 h, and then the reaction is quenched with 1.0 M $\text{Et}_3\text{NH}_2\text{CO}_3$ (~5 mL). The resulting mixture is stirred for additional 0.5-1 h while warming up to room temperature. The mixture is

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concentrated to dryness, re-dissolved in water (4 mL), and purified by ion exchange HPLC. The fractions containing the desired product is concentrated to dryness, dissolved in water (~5 mL), concentrated to dryness, and again dissolved in water (~5 mL). NaHCO₃ (30-50 mg) is added and concentrated to dryness. The residue is dissolved in water and concentrated to dryness again. This process is repeated 2-5 times. The residue is then subjected to C-18 HPLC purification, affording the desired product as a sodium salt.



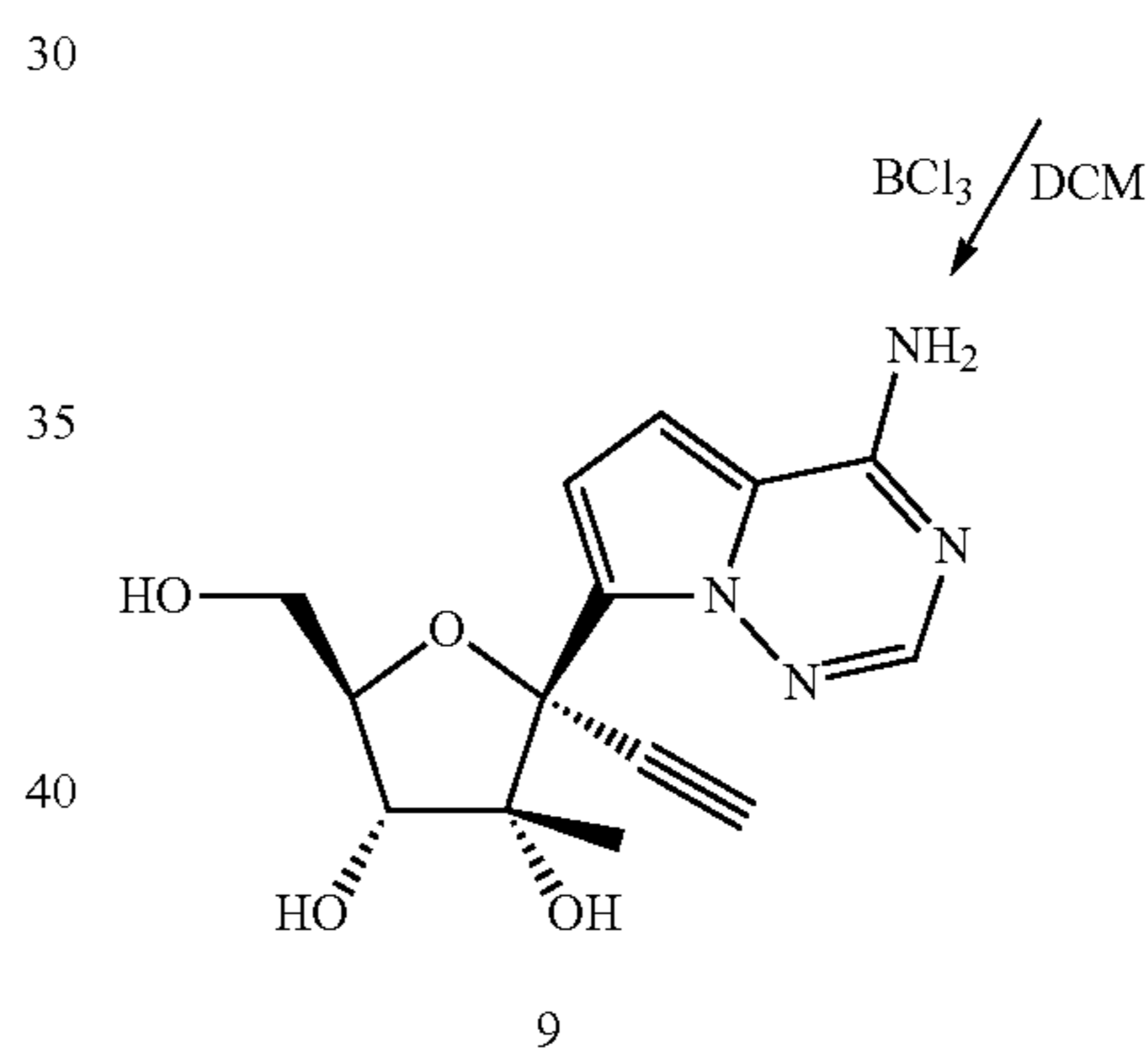
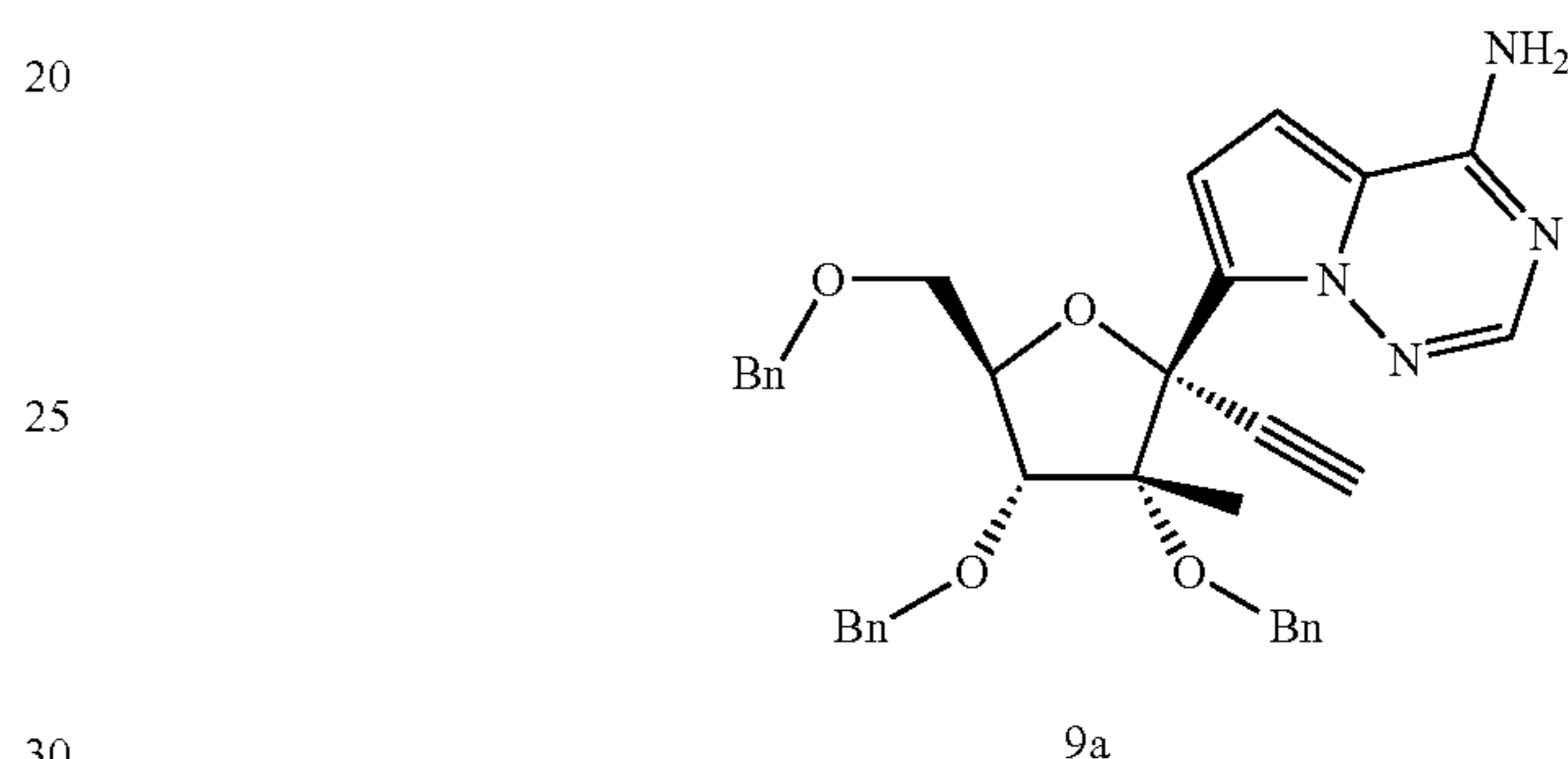
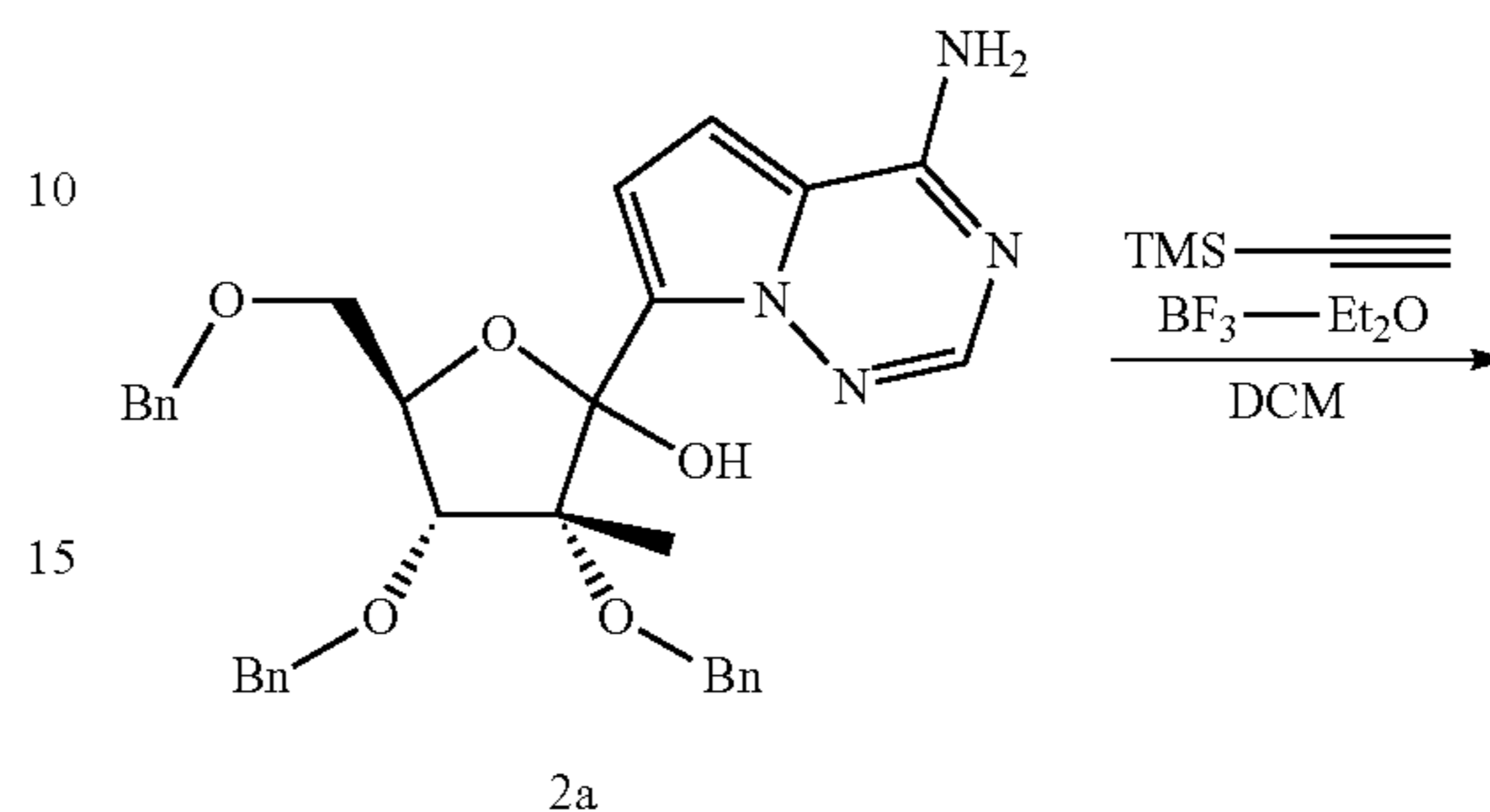
Compound 7 was prepared by the general method using Compound 5 as starting material. ¹H NMR (300 MHz, D₂O): δ 7.76 (s, 1H), 6.95 (d, J=4.5 Hz, 1H), 6.8 (d, J=4.5 Hz, 1H), 4.25 (m, 3H), 4.0 (d, J=6 Hz, 1H), 0.92 (s, 3H). ³¹P NMR (300 MHz, D₂O): δ -5.6, -10.7, -21.4. MS=545.8 (M+H⁺), 544.0 (M-H⁻).



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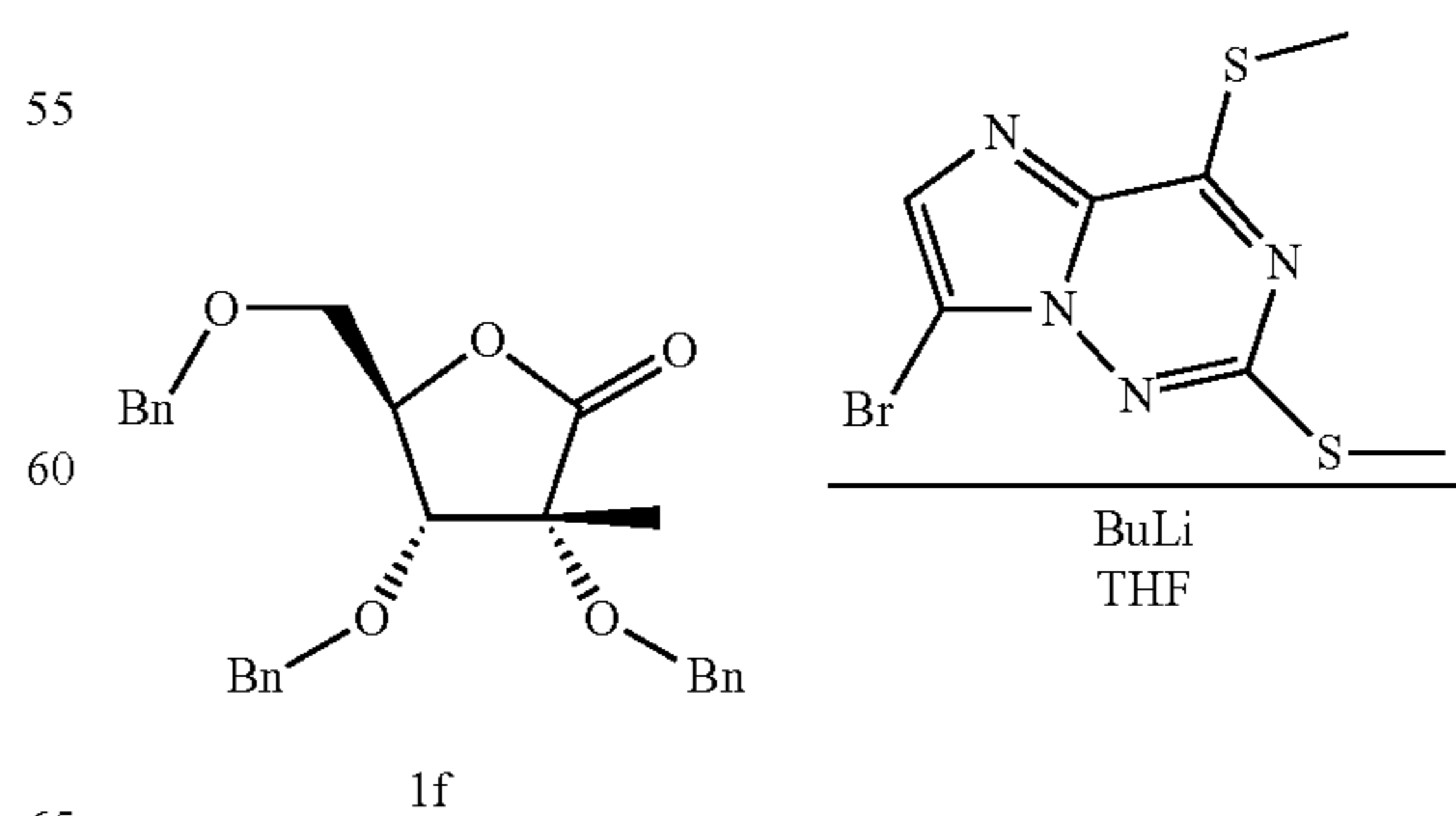
Compound 8 may be obtained from 2a in a manner similar to that described in preparation of Compound 5 except using TMSN₃ instead of TMSCN.

Compound 9



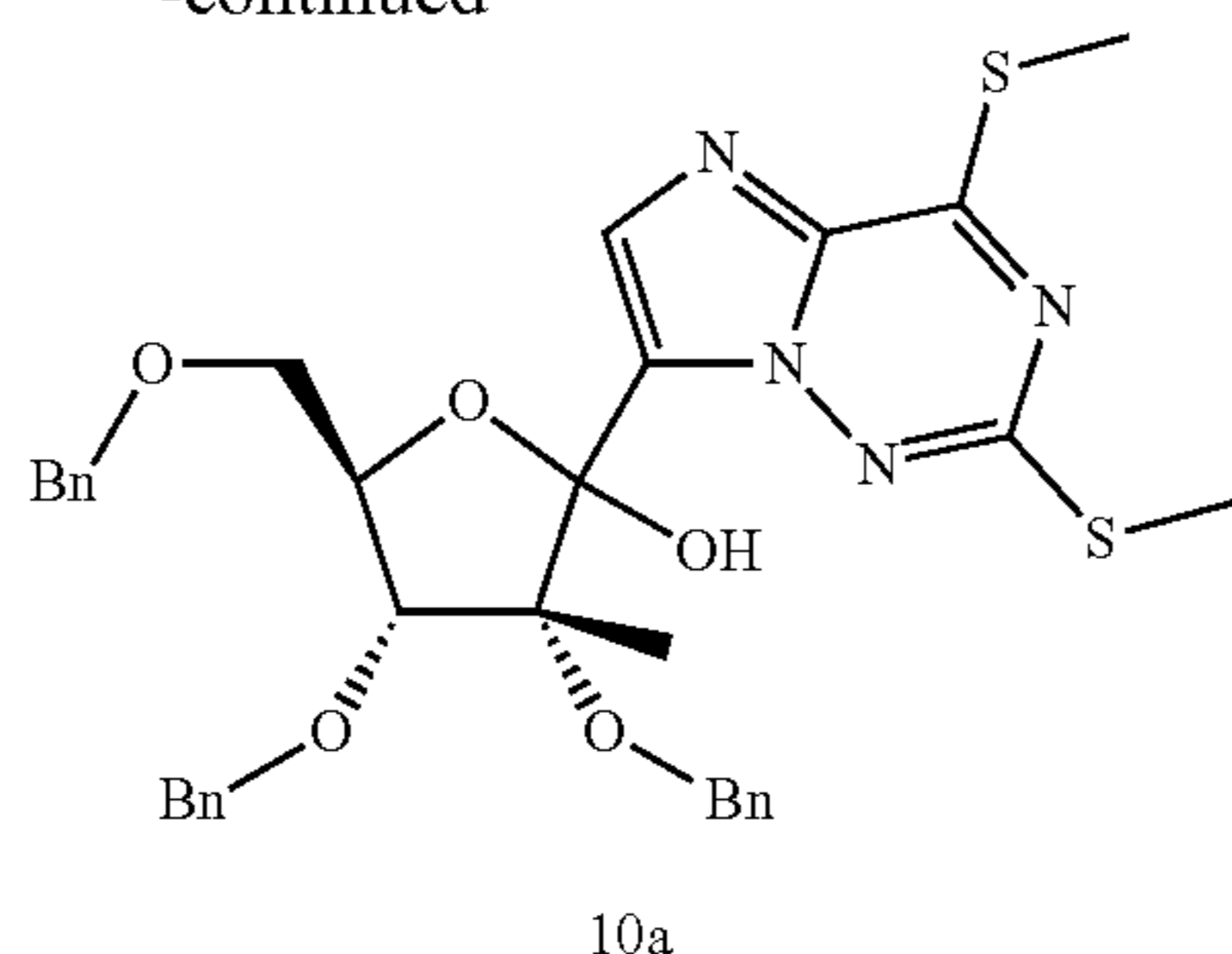
Compound 9 may be obtained from 2a in a manner similar to that described in preparation of Compound 5 except using TMS-acetylene instead of TMSCN.

Compound 10

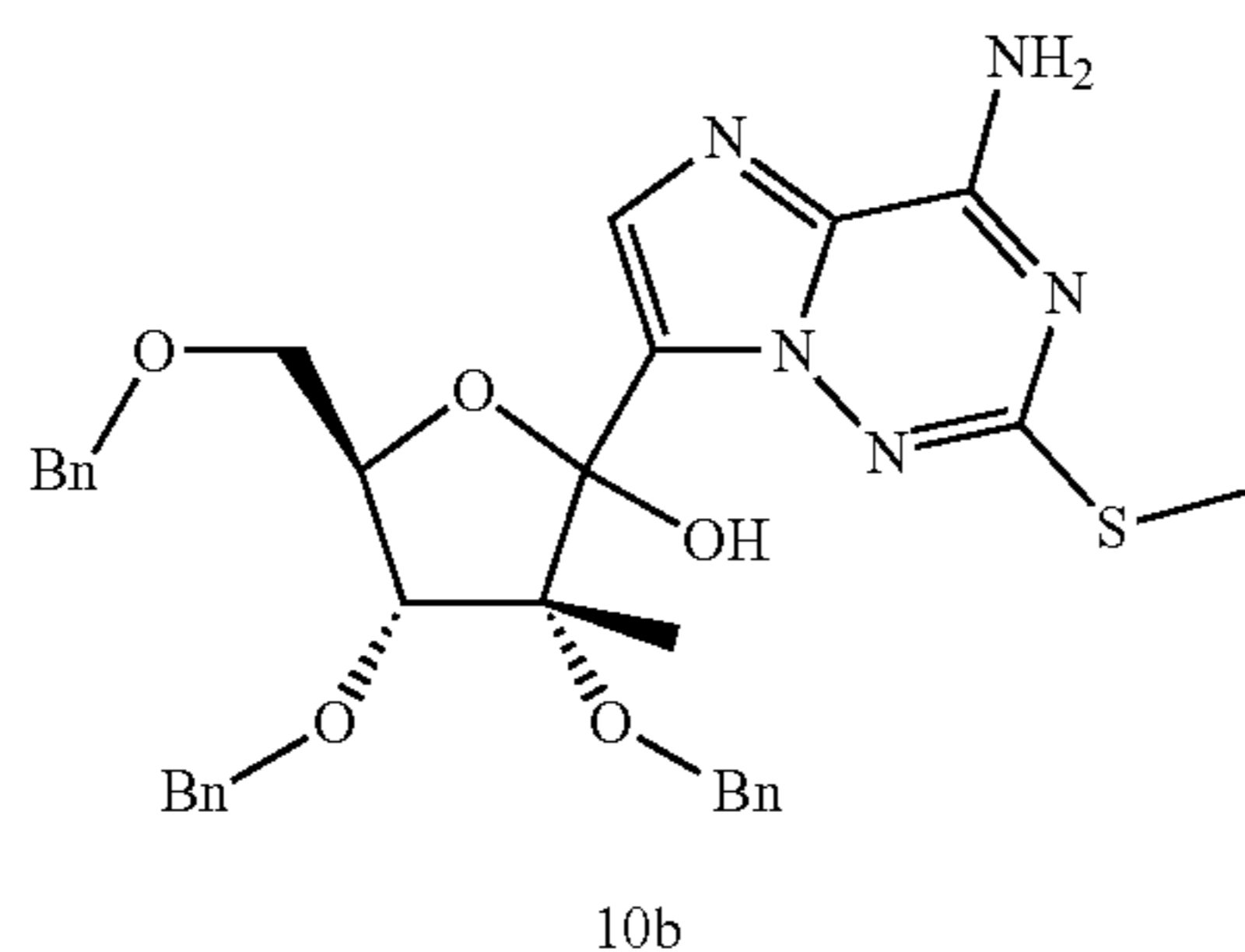
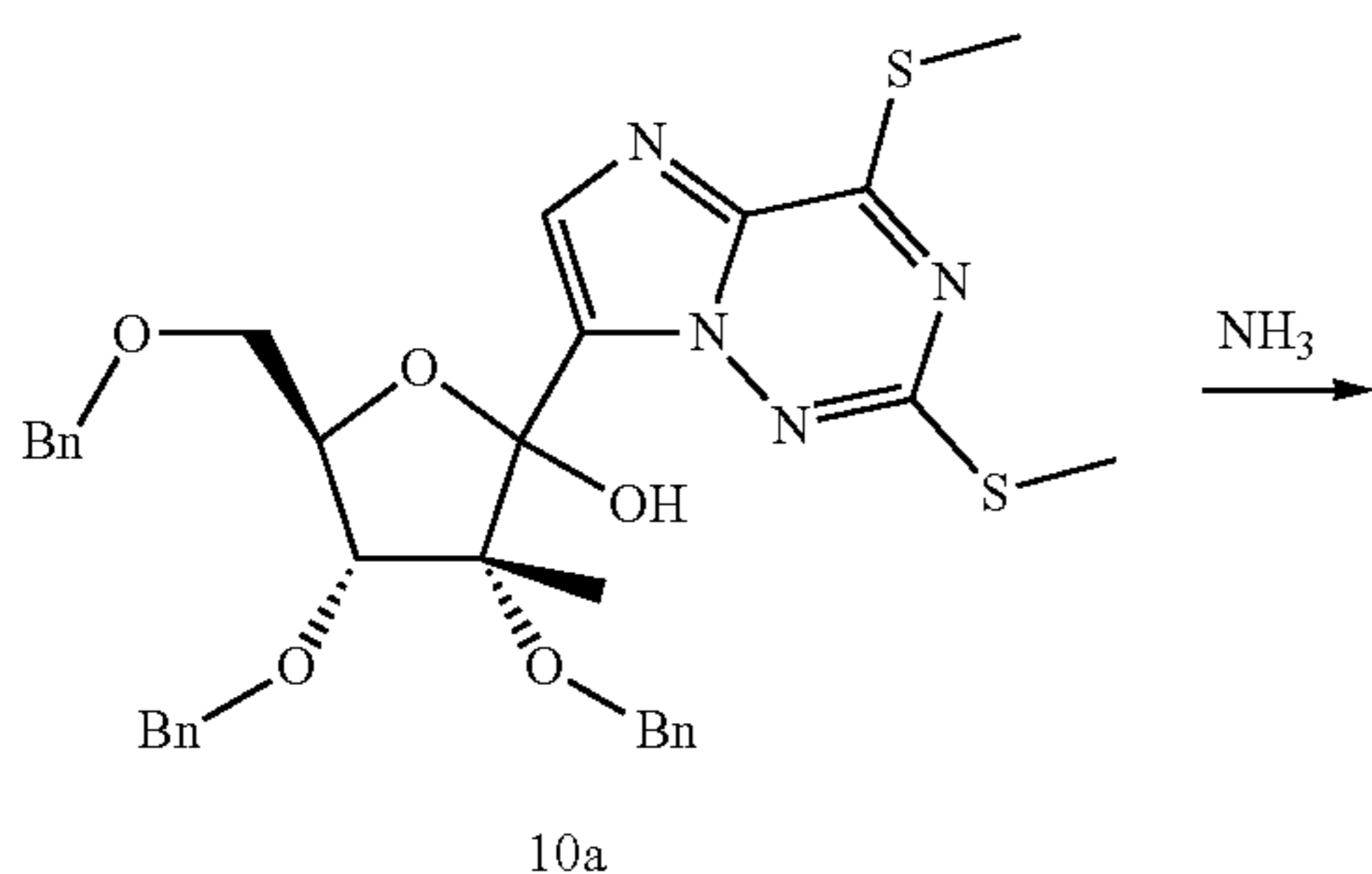


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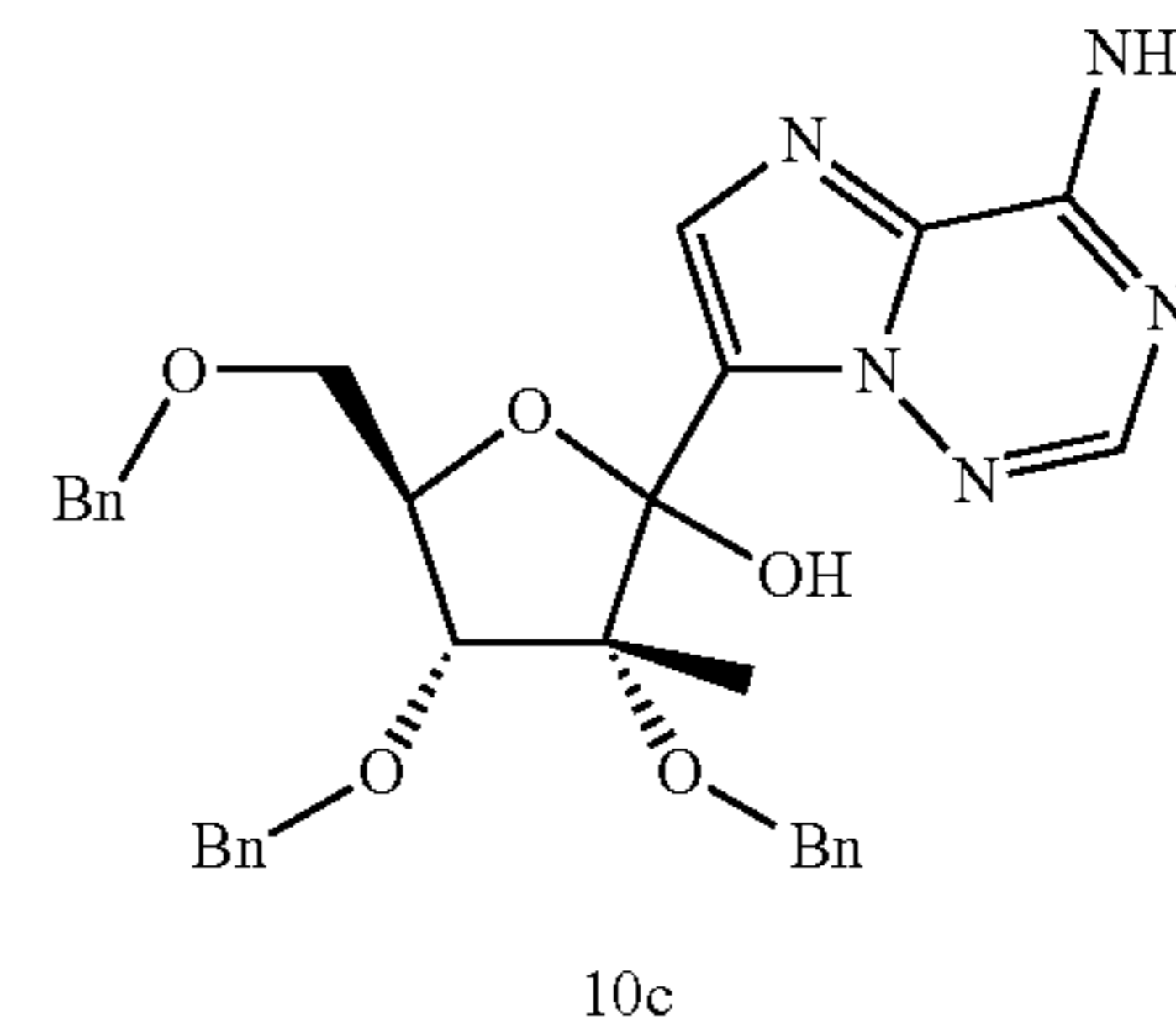
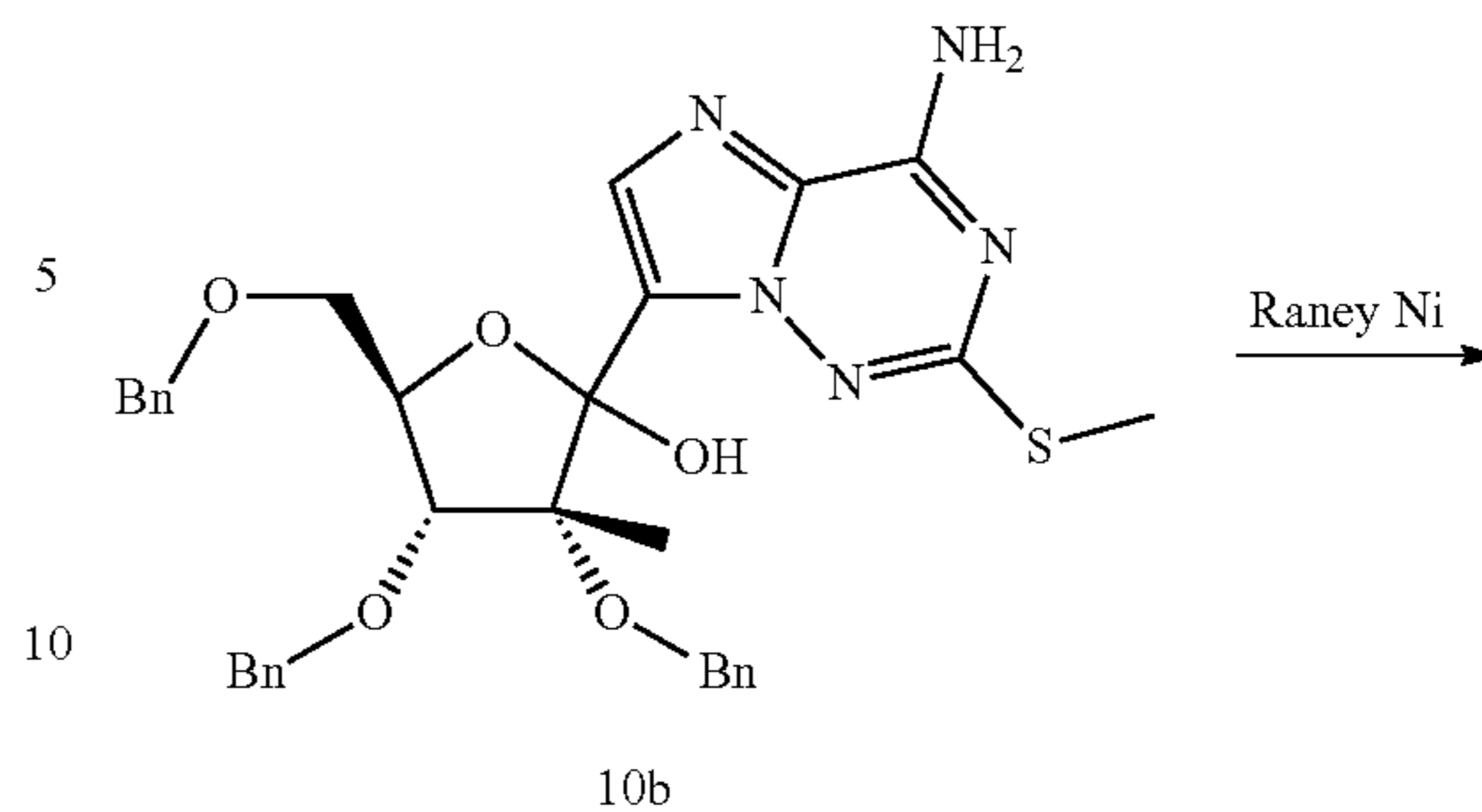


To a suspension of 7-bromo-2,4-bis-methylsulfanyl-imidazo[2,1-f][1,2,4]triazine (prepared according to WO2008116064, 600 mg, 2.06 mmol) in anhydrous THF (6 mL) was dropwise added BuLi (1.6 M in hexanes, 1.75 mL, 2.81 mmol) at -78°C . The suspension became red brown solution after 5 min, and then THF (0.6 mL) was added dropwise to the mixture. The mixture was then allowed to warm up to room temperature. After 30 min, saturated NH_4Cl was added to quench the reaction. The mixture was diluted with ethyl acetate; the organic layer was washed with brine and concentrated in vacuo. The residue was purified by silica gel column chromatography (~40% EtOAc/hexanes), affording 10a as an isomeric mixture (0.77 g, 64%). MS=645.2 ($\text{M}+\text{H}^+$).

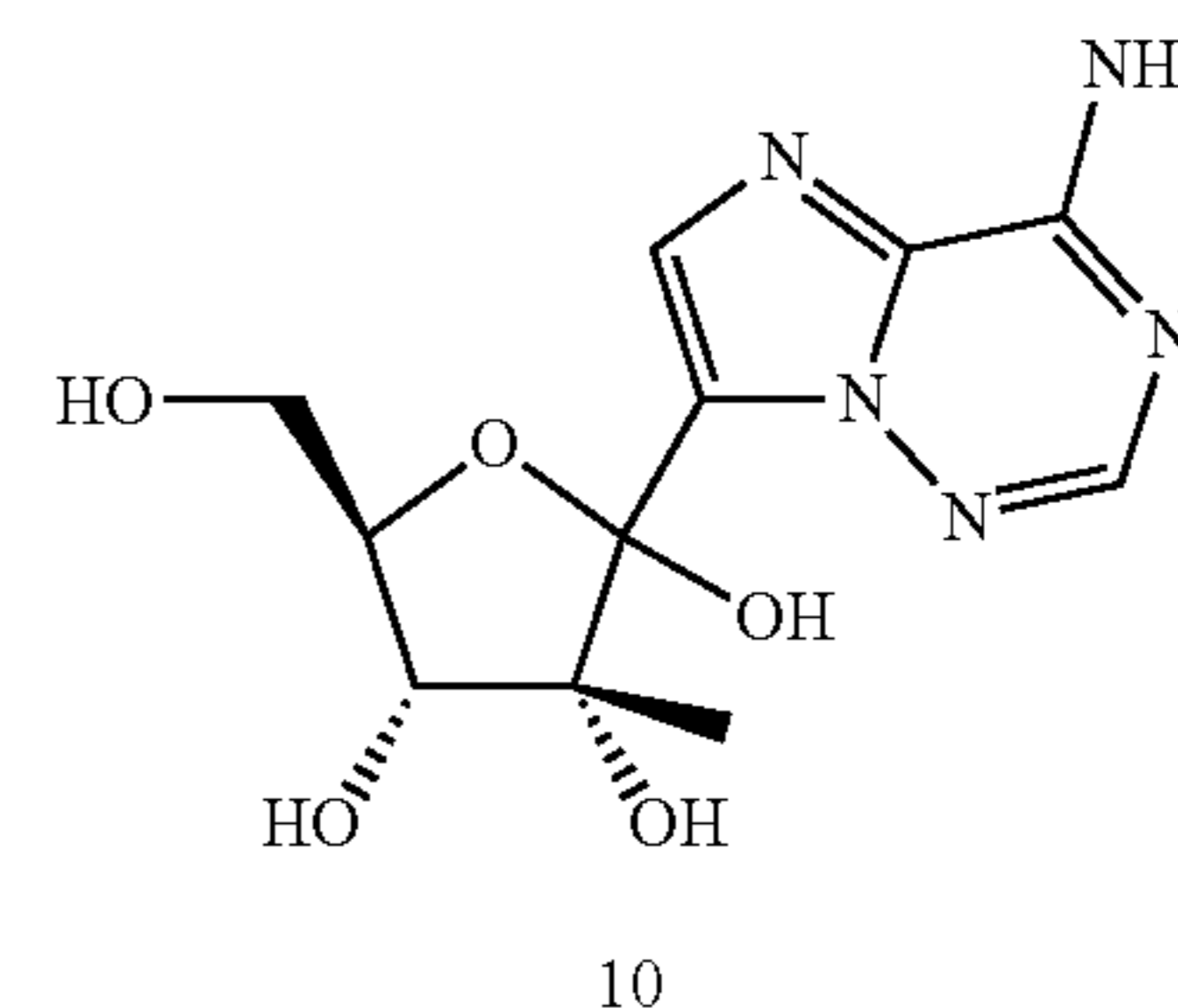
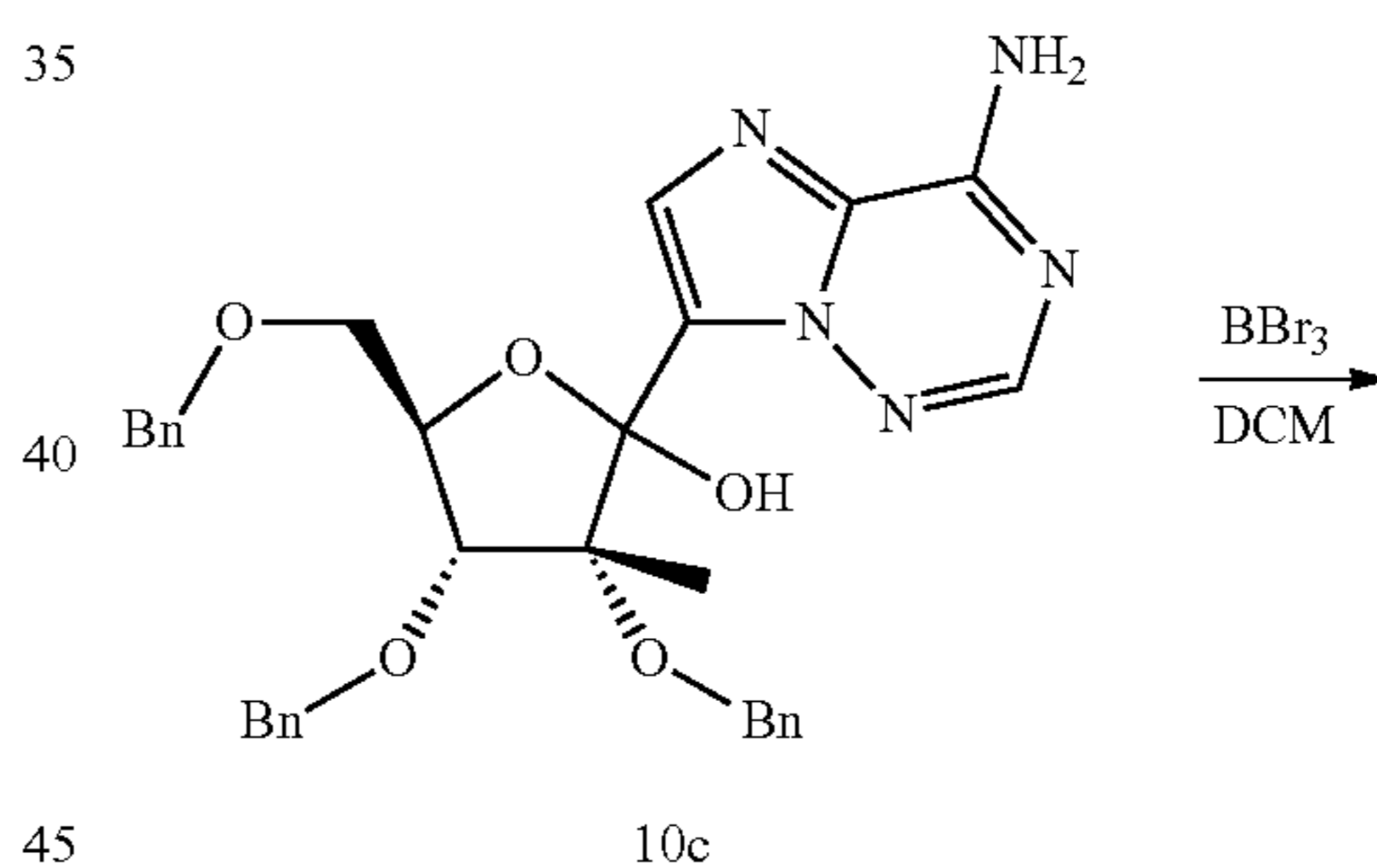


Compound 10a (2.0 g, 3.10 mmol) was transferred to a steel bomb reactor, and cooled at -78°C . Liquid ammonia (~20 mL) was collected at -78°C and added to the bomb reactor. The bomb reactor was tightly sealed and warmed up to room temperature. The mixture was then heated at 50°C for 20 h. Complete conversion occurred. After the gas was vented, the residue was purified by silica gel column chromatography (EtOAc/hexanes), affording the product 10b as a pale yellow solid (1.78 g, 94%). MS=614.3 ($\text{M}+\text{H}^+$).

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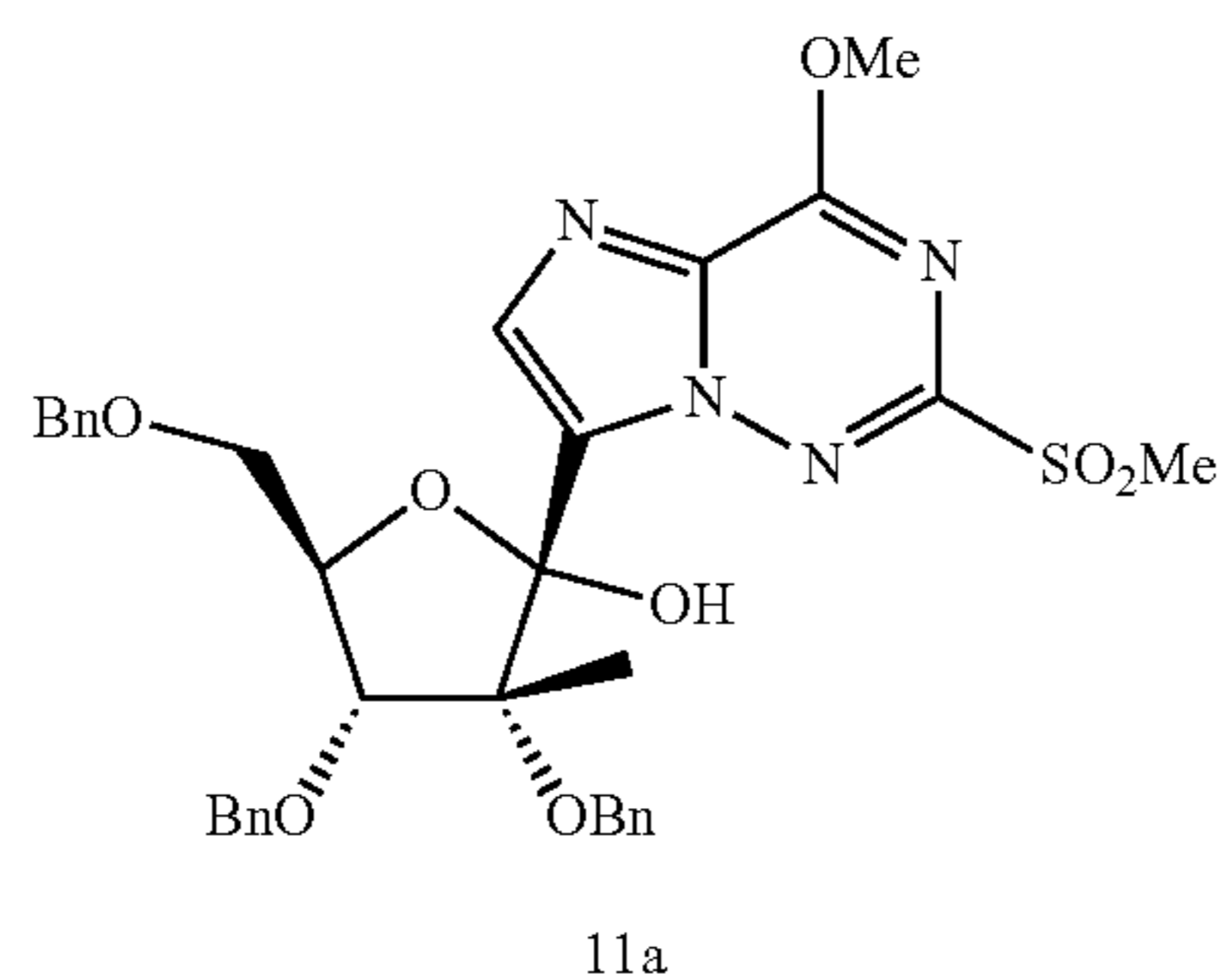
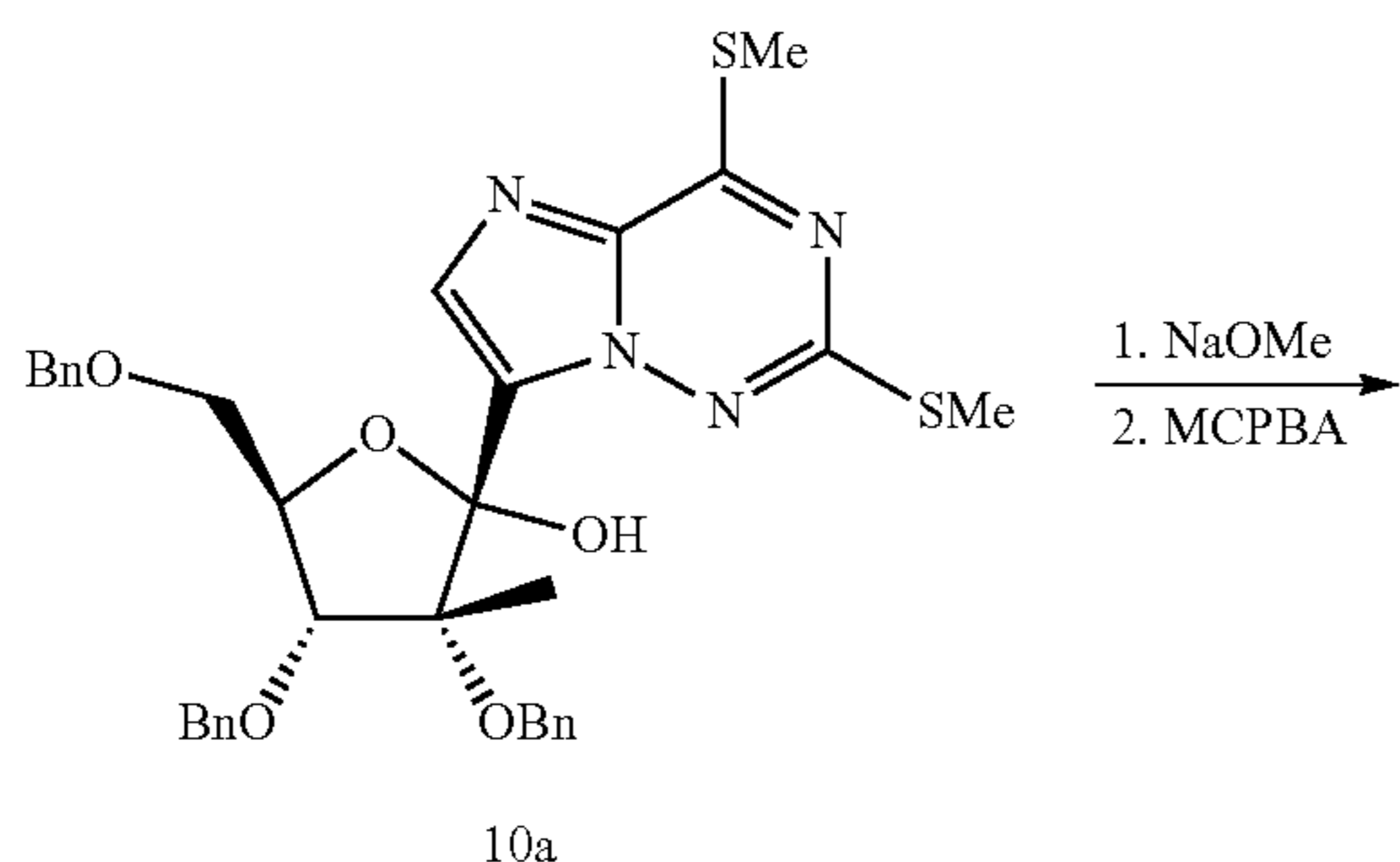
A solution of 10b (100 mg) in ethanol (about 10 ml) is treated with Raney Ni (about 500 mg) that is neutralized by washing with H_2O . The mixture is then heated to about 35 to about 80°C until the reaction is complete. The catalyst is removed by filtration and the solution is concentrated in vacuo. The residue is purified by chromatography to give 10c.



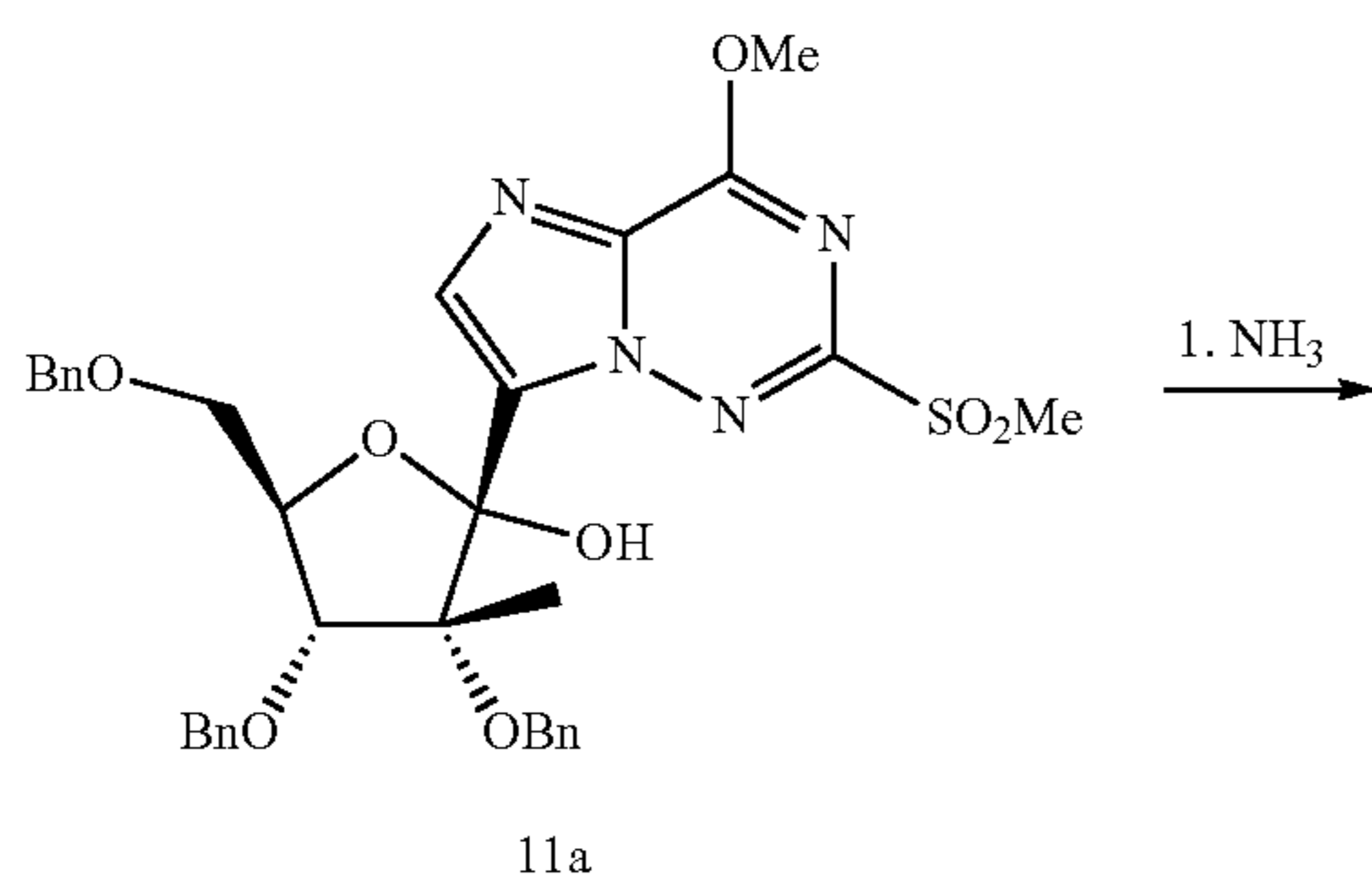
Compound 10c may be treated with BBr_3 in a manner similar to that described in preparation of compound 2 to give Compound 10.

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Compound 11



10a is treated with about one to ten mole equivalents of an alkali metal salt of methanol in a suitable solvent such as dioxane for about one to 48 hours. The mixture may also be heated from about 60 to about 110° C. for about one to 24 hours to complete the reaction. The mixture is neutralized with a strong acid and the intermediate is isolated by extraction and chromatography. The intermediate is dissolved in DCM and treated with about two to about four mole equivalents of MCPBA for about one to about 24 hours. The mixture is treated with saturated NaHCO₃ and the solution is extracted with EtOAc. The organic layer is washed with saturated NaHCO₃ and brine and dried over MgSO₄. The solvent is removed in vacuo and the mixture is purified by chromatography to give 11a.



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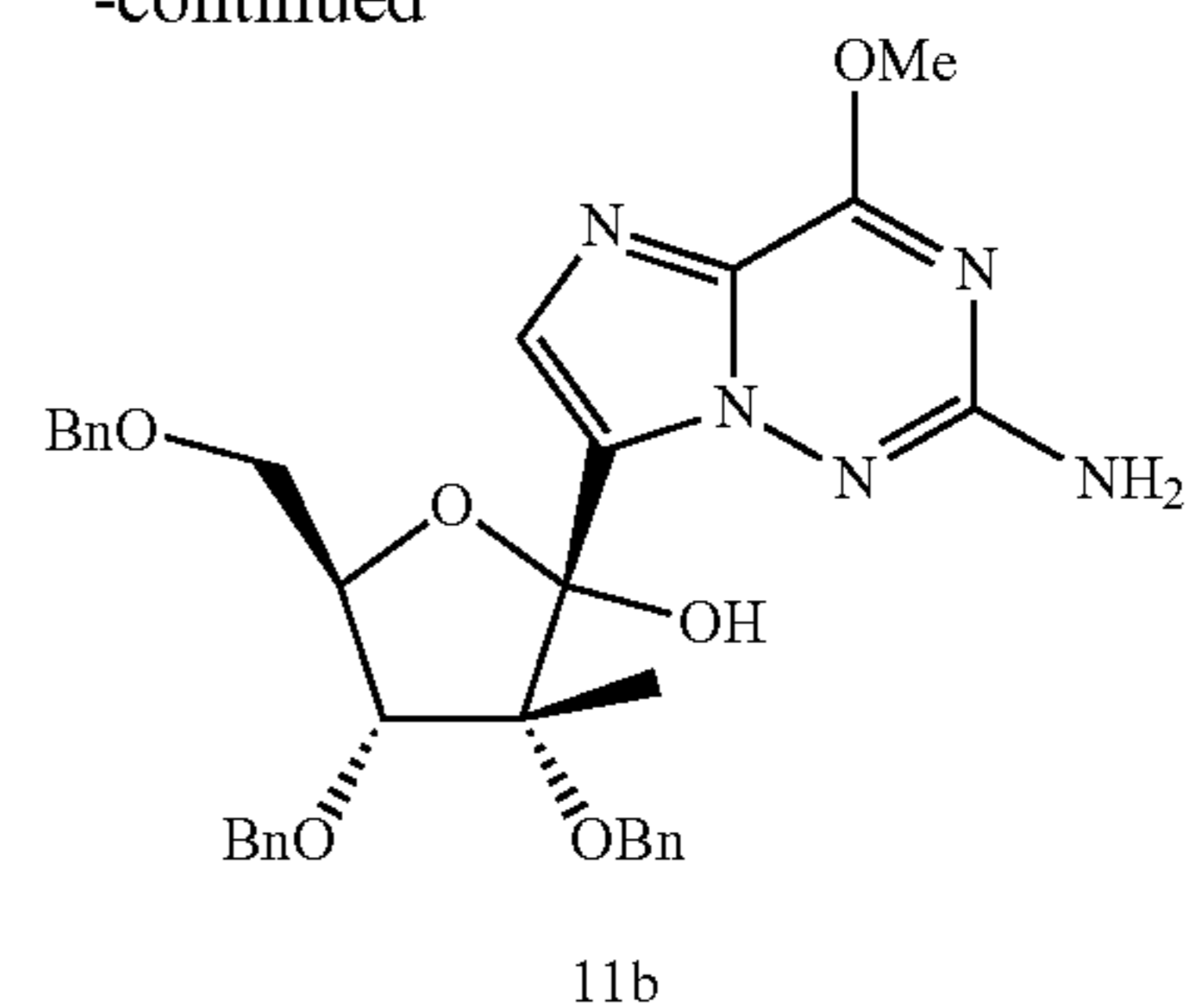
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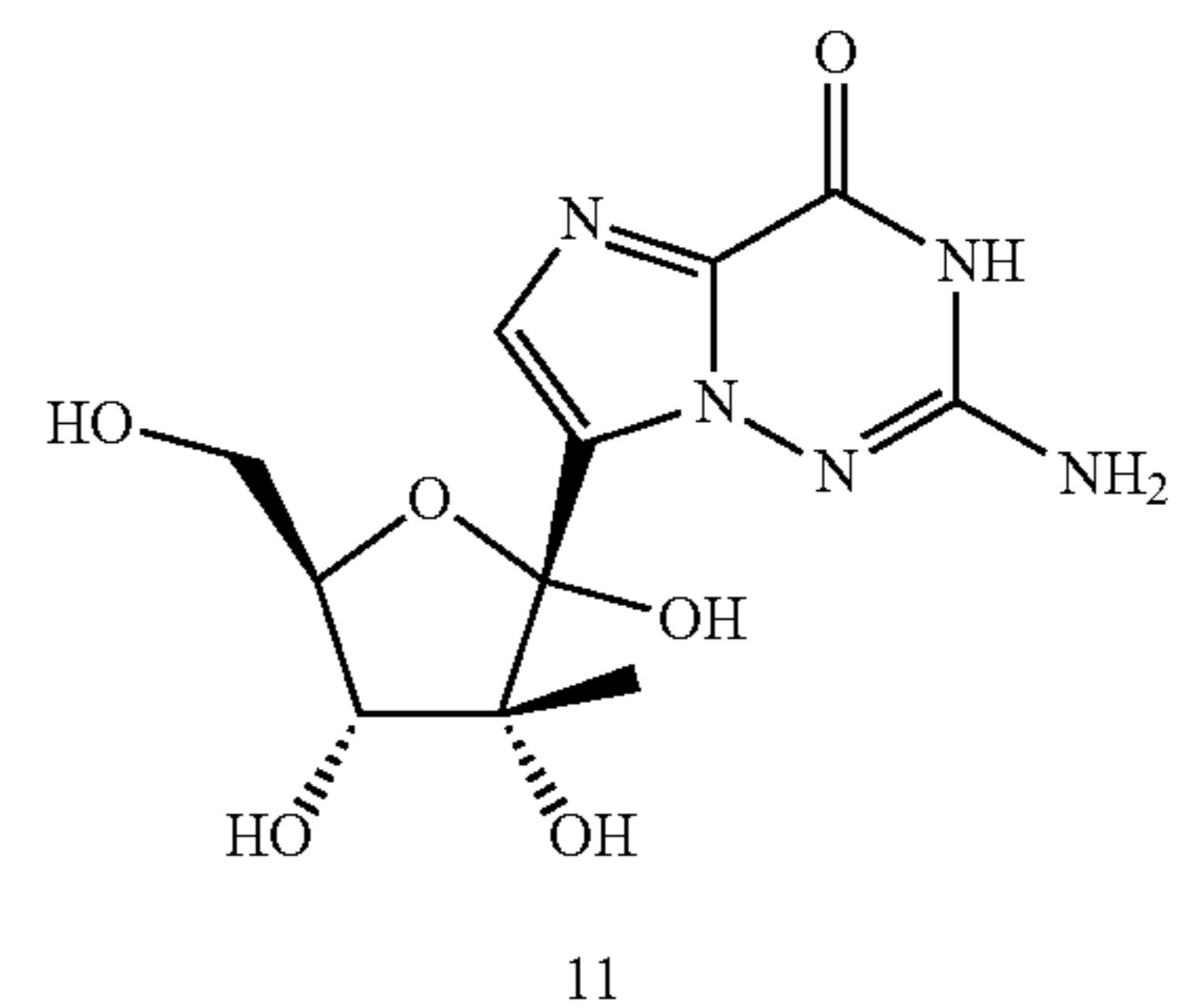
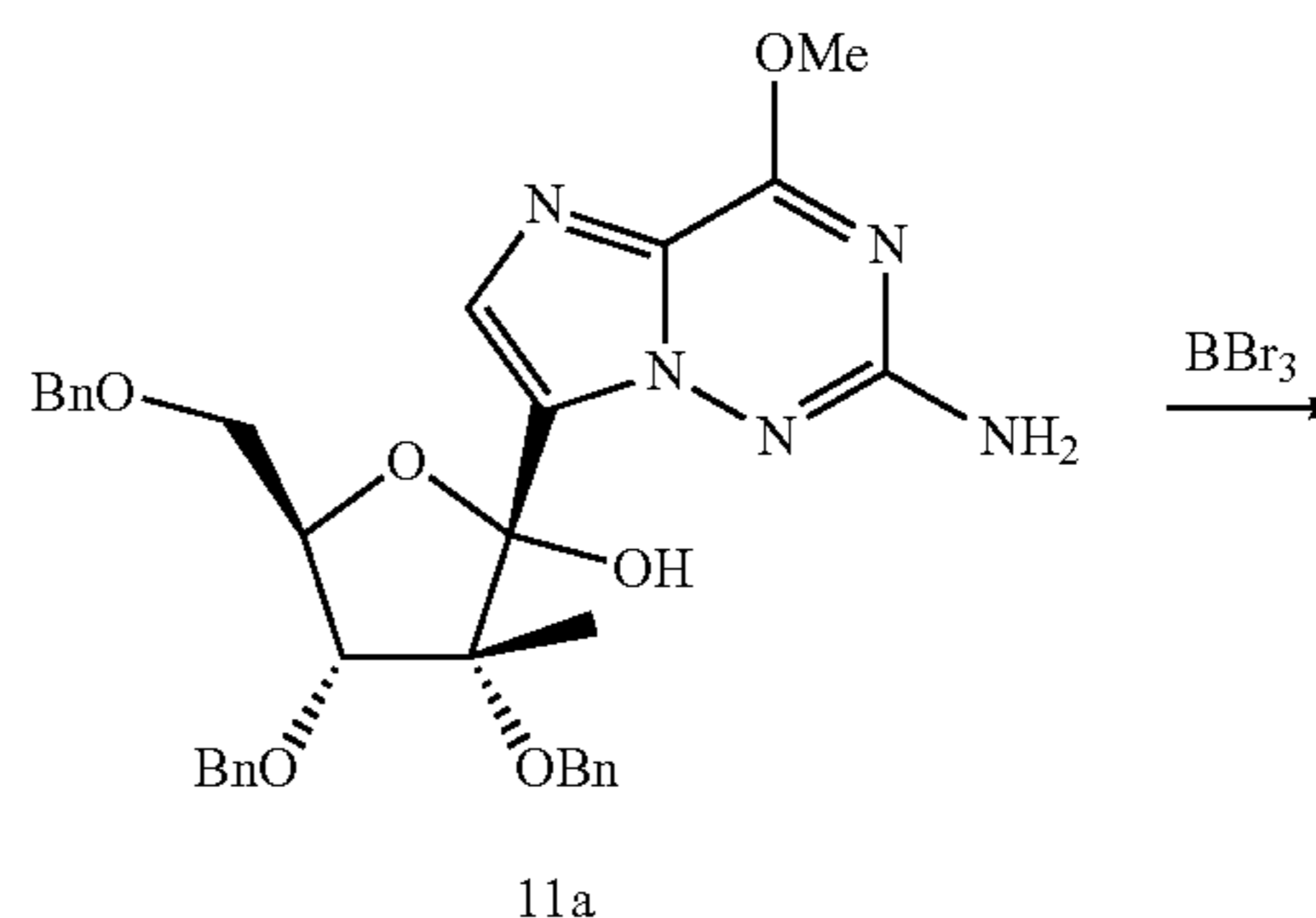
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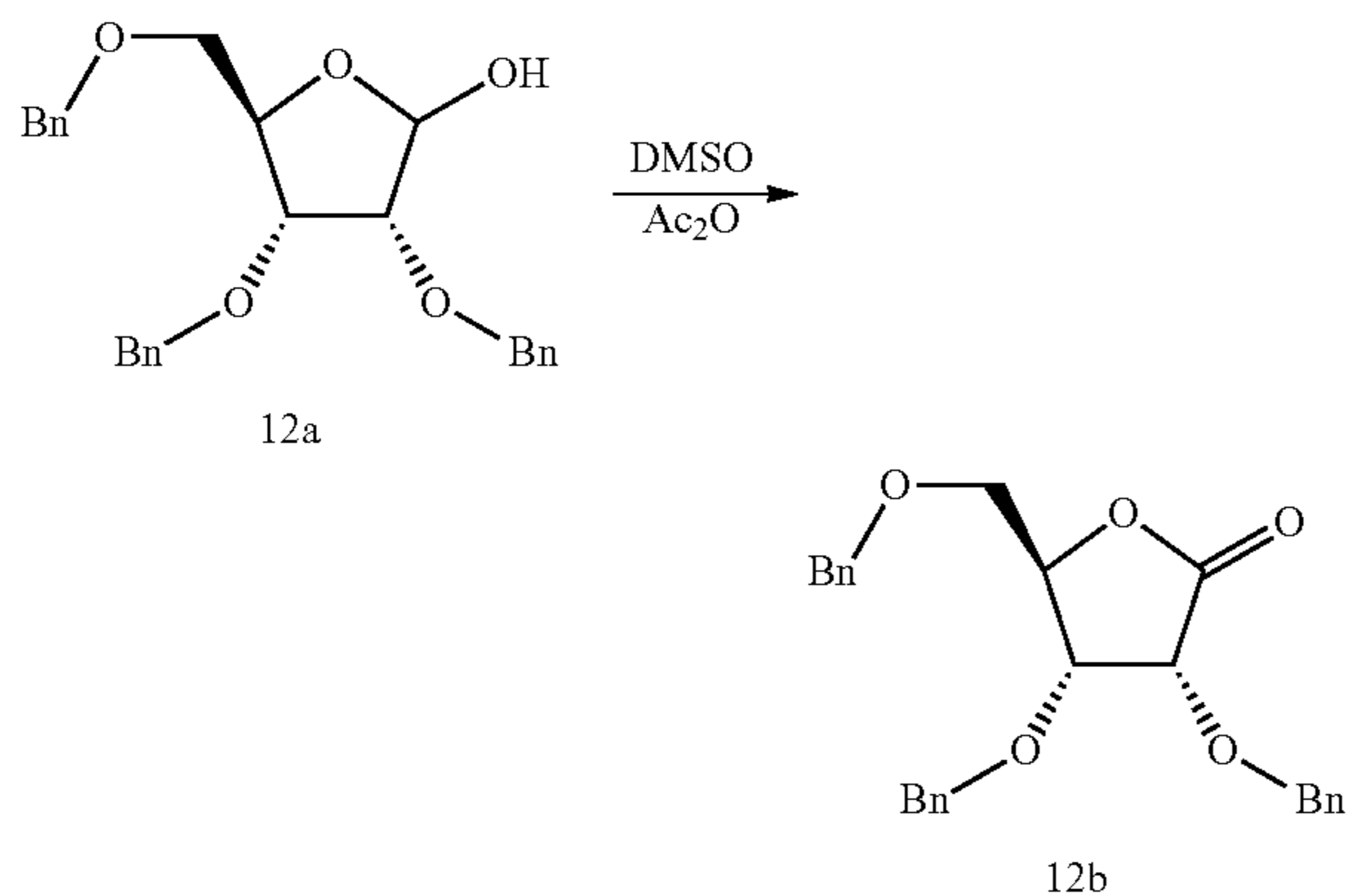
A solution of 11a in a suitable solvent such as methanol or THF is treated with about five to ten mole equivalents of NH₃ in methanol or THF. The reaction is followed by TLC. After about one to 48 hours, the solvent is evaporated and 11b is isolated by chromatography. Alternatively, the mixture of 11a and NH₃ is heated in a sealed glass tube or Parr bomb to about 60 to about 120° C. for about one to about 48 hours and subsequently isolated in the same manner as described.



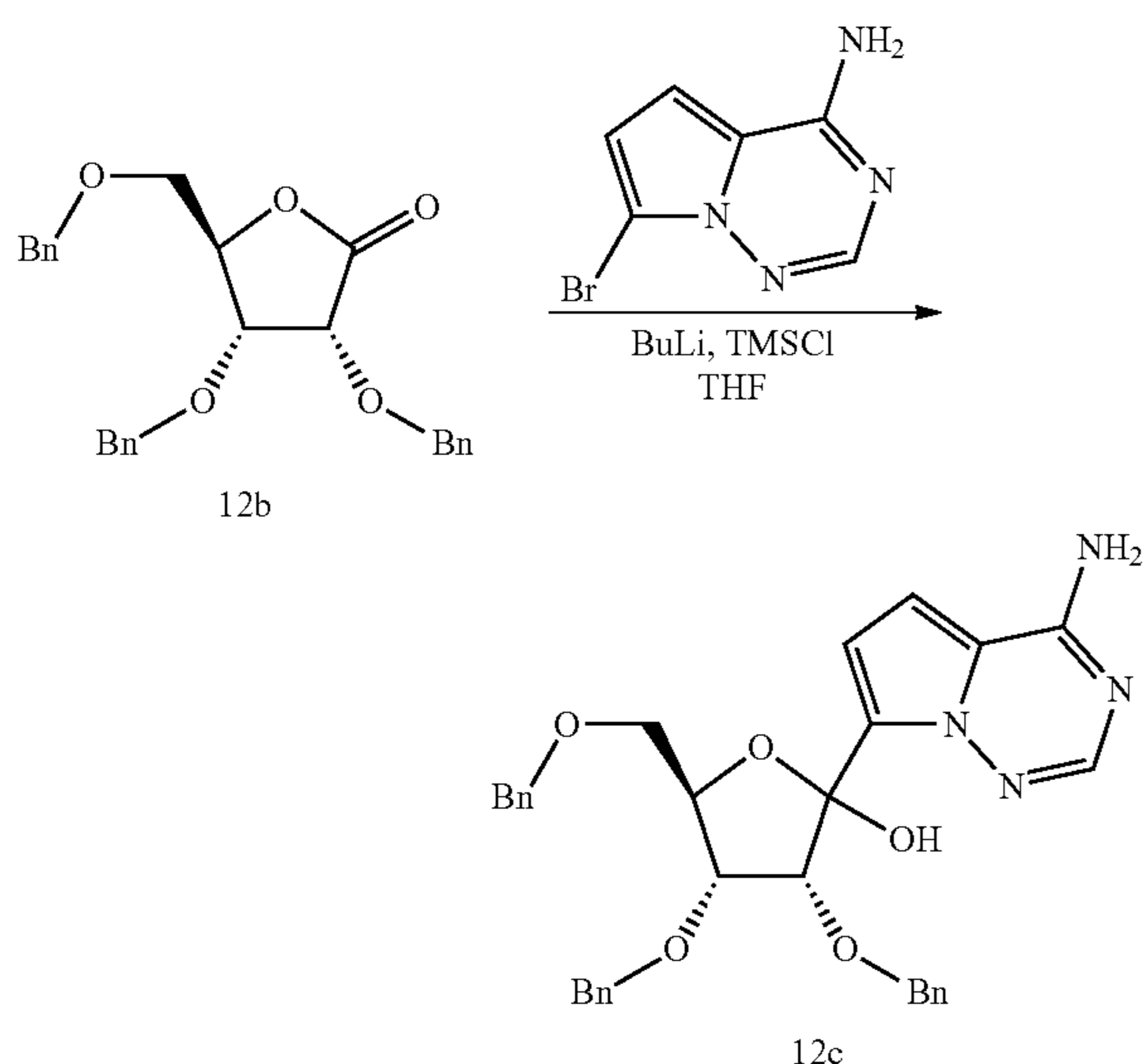
11b in DCM is cooled to about -78° C. and treated with about four to 10 mole equivalents of BBr₃ for about one to about 24 hours. The mixture is treated with about 4:1 MeOH-pyridine and the solution was warmed to room temperature. The solvent is removed in vacuo and the mixture is treated with concentrated NH₄OH followed by removal of solvent (×3). The mixture is purified by reverse phase HPLC to give 11.

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Compound 12



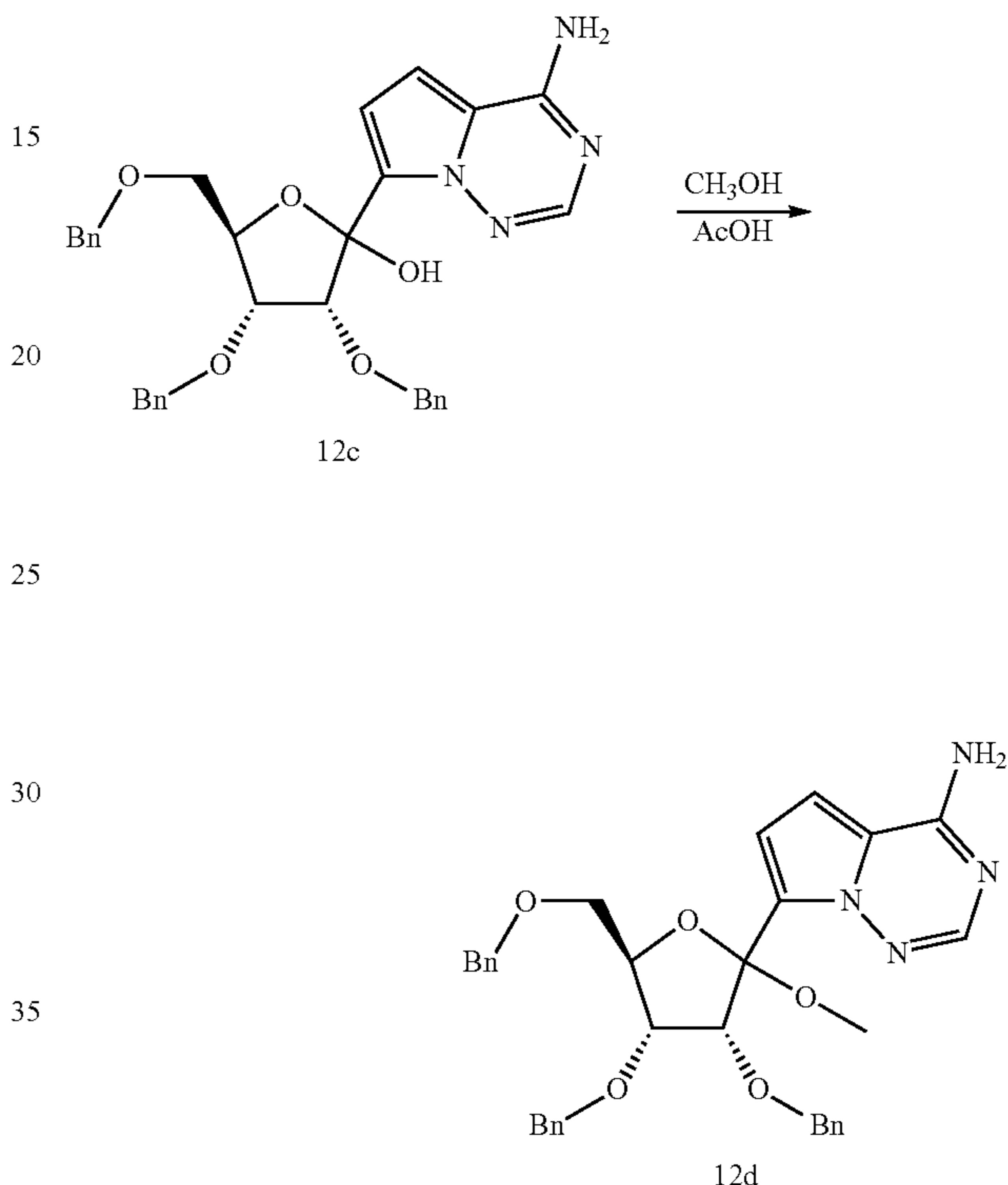
Compound 12a (prepared according to J. Org. Chem., 1961, 26, 4605; 10.0 g, 23.8 mmol) was dissolved in anhydrous DMSO (30 mL) and placed under nitrogen. Acetic anhydride (20 mL) was added, and the mixture was stirred for 48 h at room temperature. When the reaction was complete by LC/MS, it was poured onto 500 mL ice water and stirred for 20 min. The aqueous layer was extracted with ethyl acetate (3×200 mL). The organic extracts were combined and washed with water (3×200 mL). The aqueous layers were discarded and the organic was dried over anhydrous MgSO₄ and evaporated to dryness. The residue was taken up in DCM and loaded onto a silica gel column. The final product 12b was purified by elution with 25% EtOAc/hexanes; 96% yield. ¹H-NMR (CD₃CN): δ 3.63-3.75 (m, 2H), 4.27 (d, 1H), 4.50-4.57 (m, 3H), 4.65 (s, 3H), 4.69-4.80 (m, 2H), 7.25 (d, 2H), 7.39 (m, 13H).



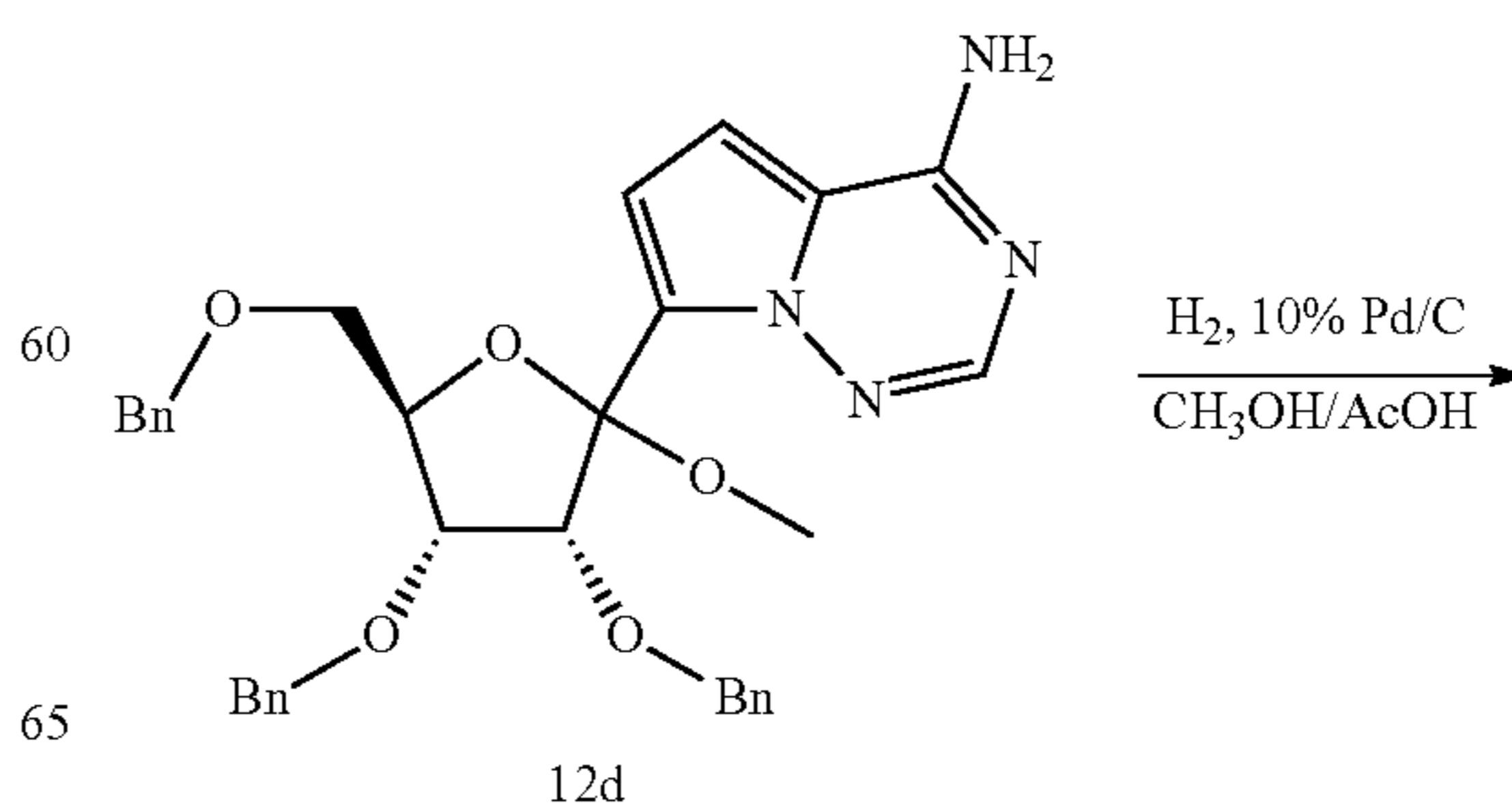
7-Bromo-pyrrolo[2,1-f][1,2,4]triazin-4-ylamine (prepared according to WO2007056170, 0.5 g, 2.4 mmol) was suspended in anhydrous THF (10 mL). Under nitrogen with stirring, TMSCl (0.668 mL, 5.28 mmol) was added and the mixture was stirred for 20 min. at room temperature. The reaction was then cooled to -78° C. and a solution of BuLi (6.0 mL, 1.6 N in hexanes) was added slowly. The reaction was stirred for 10 min. at -78° C. and then the lactone 12b

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was added via syringe. When the reaction was complete by LC/MS, acetic acid was added to quench. Solvents were removed by rotary evaporation and the residue was taken up in a mixture of 50:50 dichloromethane/water (100 mL). The organic layer was collected and washed with 50 mL additional water, dried over anhydrous MgSO₄ and filtered. Evaporation and purification by column chromatography (0-50% EtOAc:hexanes) provided a 1:1 mixture of anomers 12c; 25% yield. LC/MS (m/z: 553, M+H⁺).

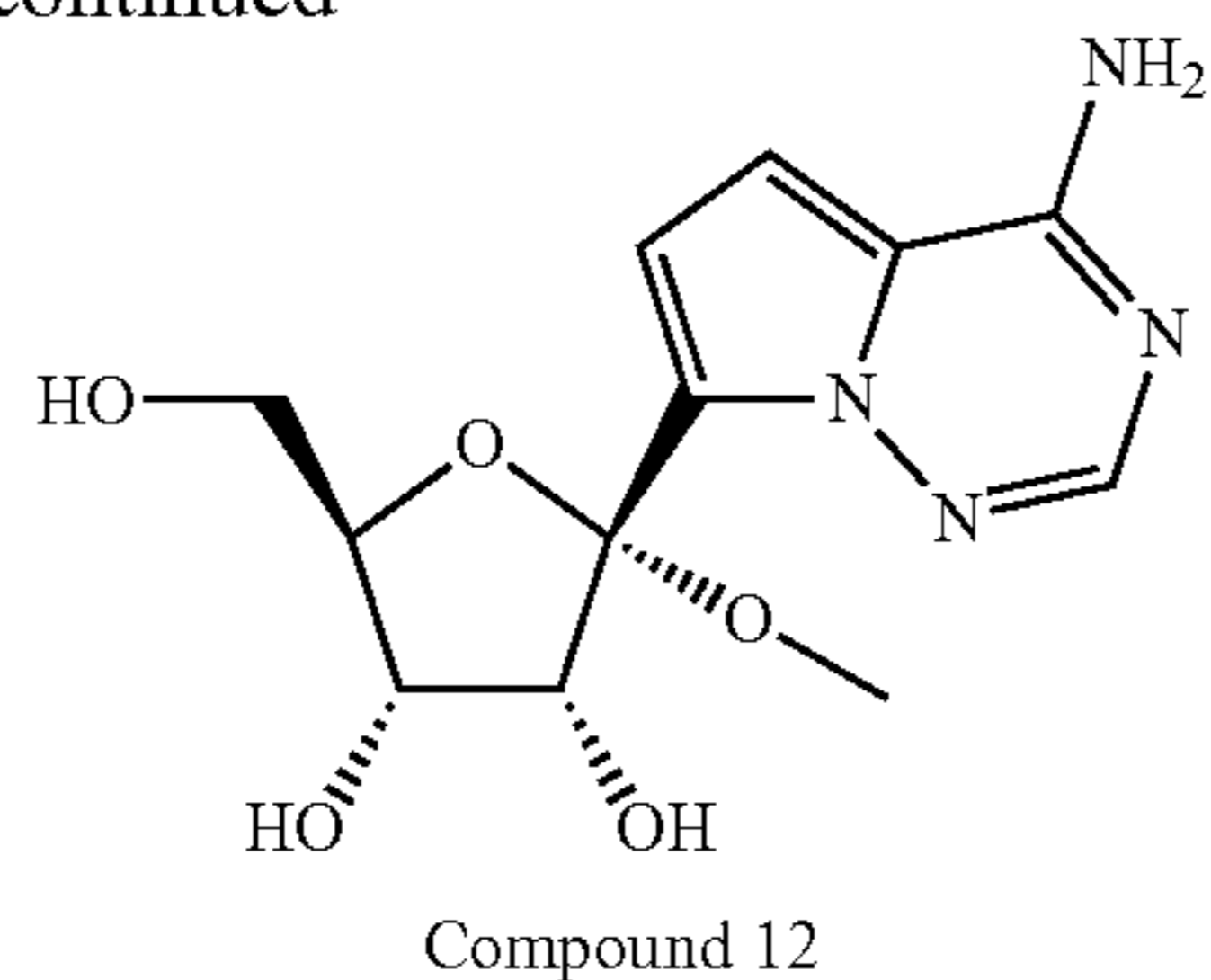


Compound 12c (0.4 g, 0.725 mmol) was stirred in a 1:1 mixture of acetic acid and methanol (10 mL) for 12 h. When the reaction was complete by LC/MS, solvents were removed by high vacuum. The residue was taken up in dichloromethane and loaded onto a silica gel column. A mixture of anomers was eluted using a gradient of 0-75% ethyl acetate and hexanes; 51.4% yield of compound 12d. ¹H-NMR (CD₃CN): δ 2.87 (s, 3H), 3.58-3.79 (dd, 2H), 4.11-4.19 (m, 1H), 4.23-4.33 (m, 1H), 4.39-4.42 (m, 1H), 4.49-4.60 (m, 3H), 4.68-4.73 (m, 2H), 6.22 (bs, 2H), 6.72 (d, 2H), 6.79 (d, 1H), 6.84 (d, 1H), 7.17 (m, 2H), 7.39 (m, 13H), 7.84 (s, 1H).



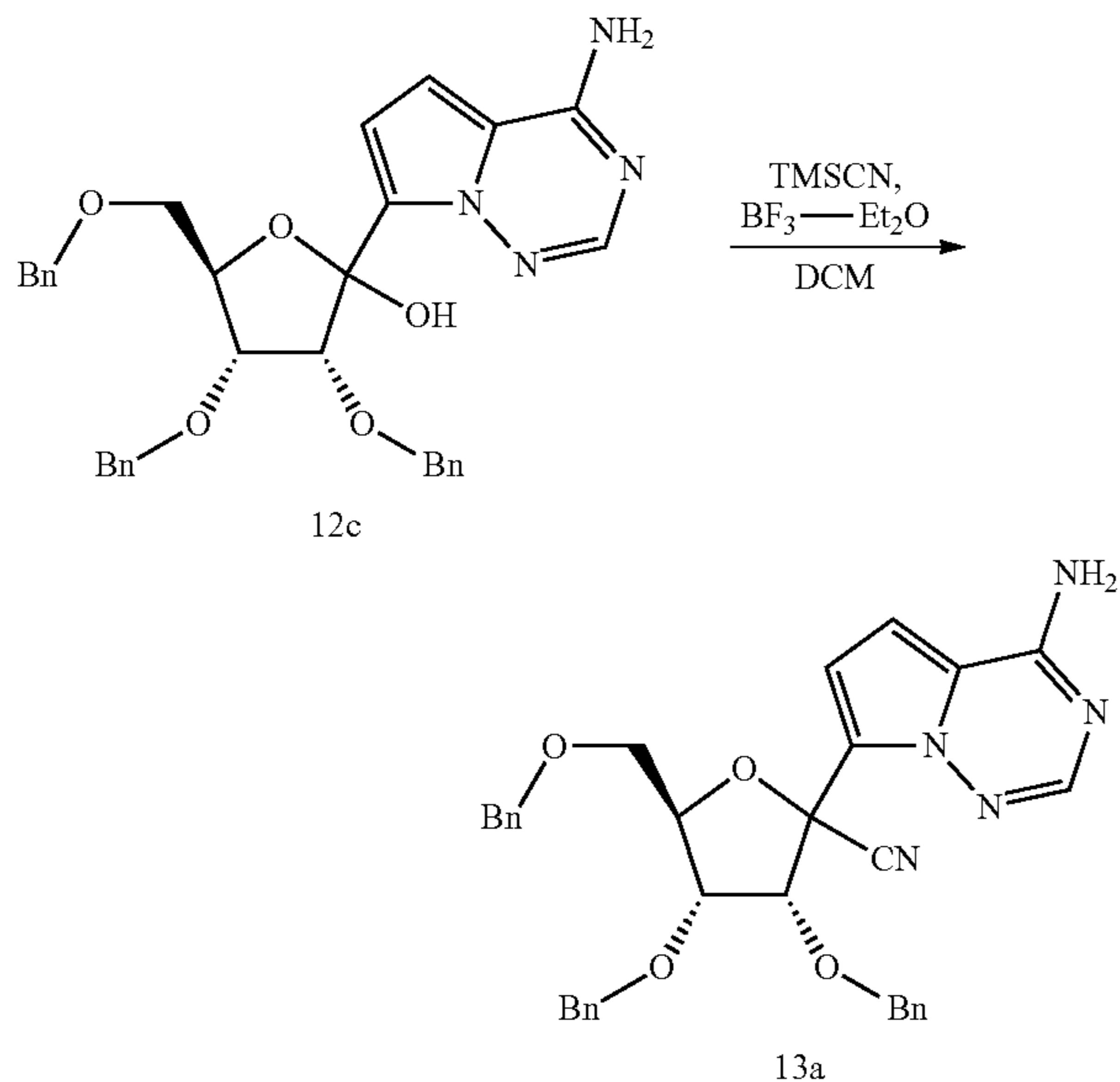
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Compound 12d (0.150 g, 0.265 mmol) was dissolved in a 1:1 mixture of methanol and acetic acid (20 mL). 10% Pd/C (150 mg) was added and the reaction was flushed with nitrogen three times. With stirring, hydrogen gas was introduced. The reaction was stirred under hydrogen for 16 h. When the reaction was complete by LC/MS, the catalyst was filtered off and solvents removed under vacuum. The residue was redissolved in a mixture of water and TEA (to keep pH at ~10), and both anomers were purified by prep HPLC under neutral conditions; a total of 51% yield. ¹H-NMR of compound 12 (D₂O): δ 3.16 (s, 3H), 3.69-3.84 (dd, 2H), 4.07-4.10 (m, 1H), 4.22-4.24 (m, 1H), 6.74 (d, 1H), 6.78 (d, 1H), 7.70 (s, 1H). ¹H-NMR of the other alpha-anomer (D₂O): δ 2.87 (s, 3H), 3.58-3.84 (dd, 2H), 3.99-4.09 (m, 1H), 4.30-4.38 (m, 1H), 4.49 (d, 1H), 6.75 (d, 1H), 6.82 (d, 1H), 7.69 (s, 1H).

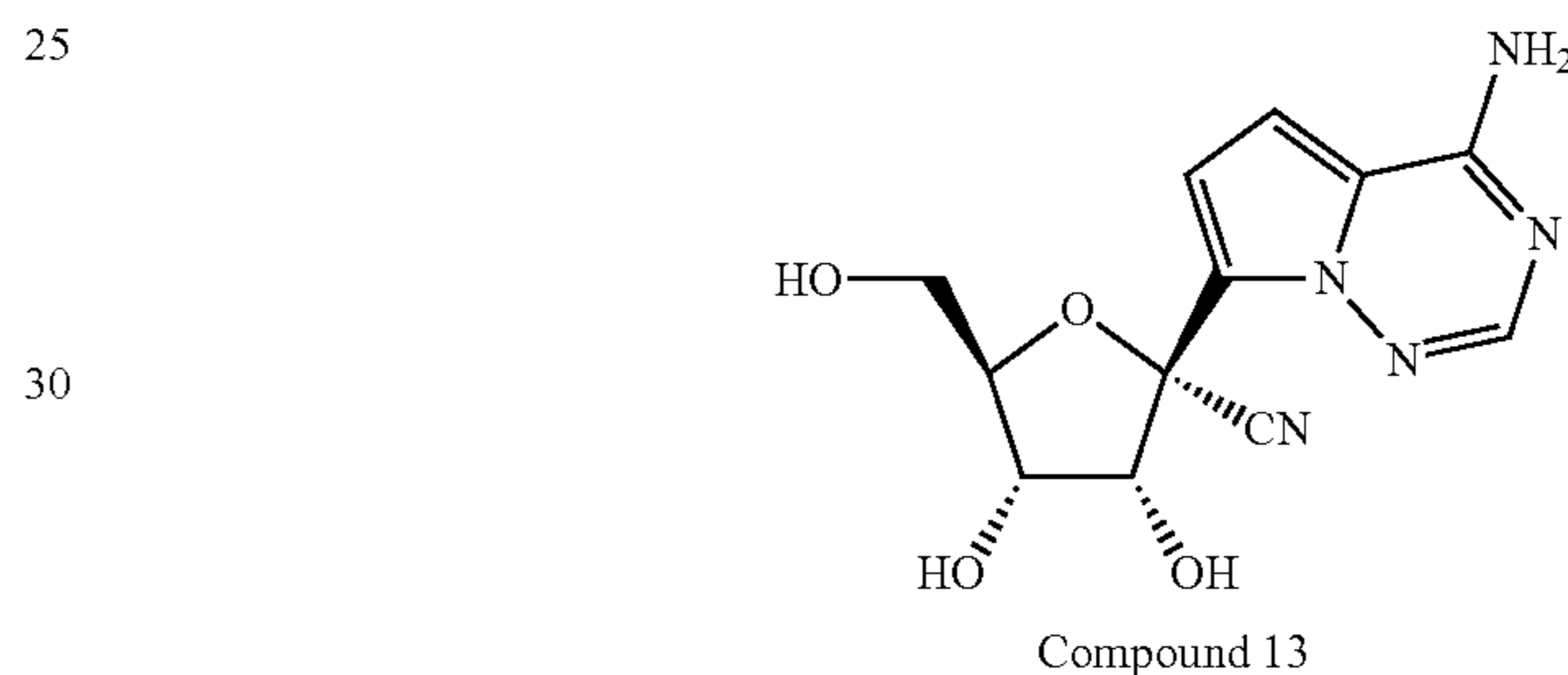
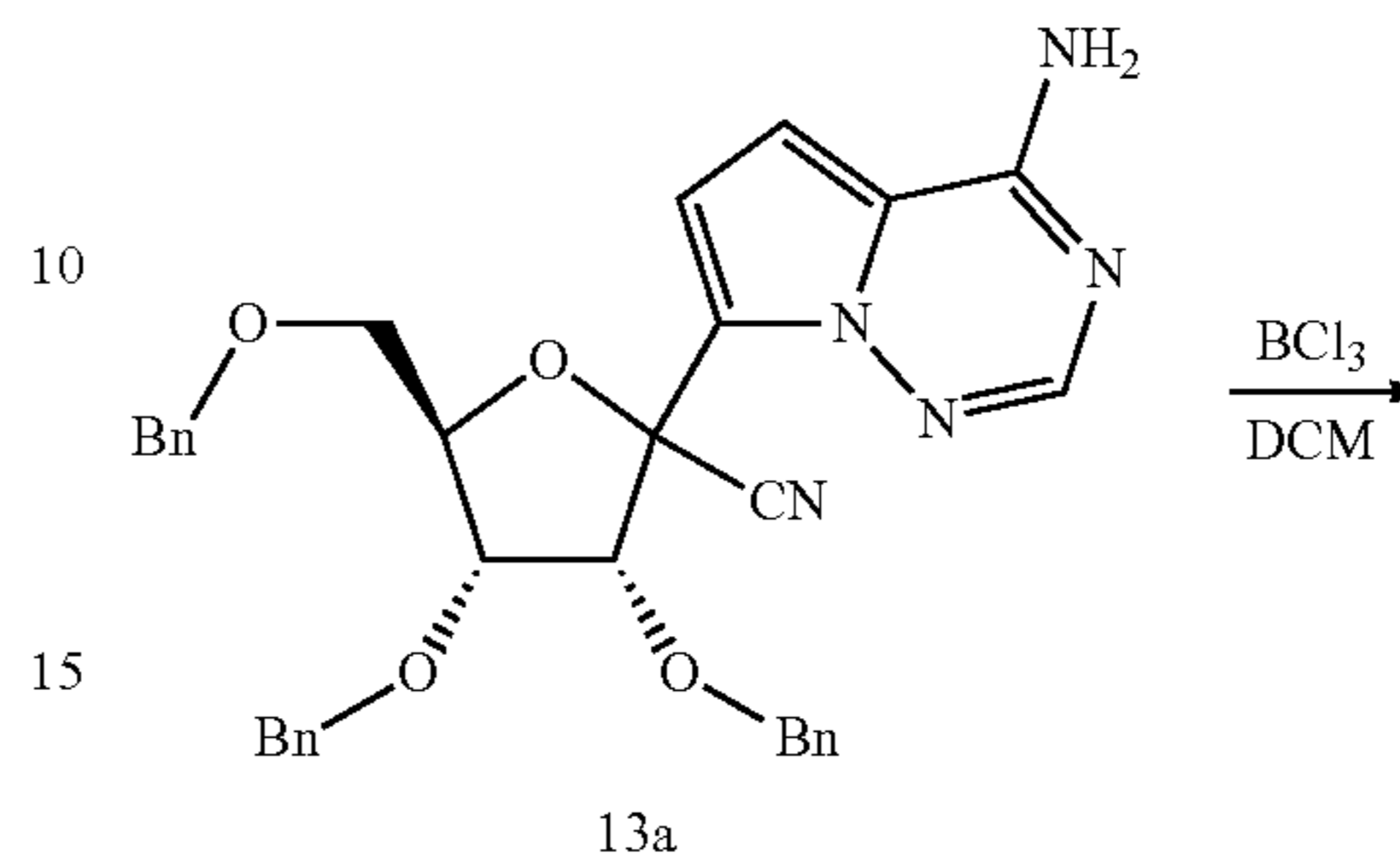
Compound 13



Compound 12c (0.28 g, 0.51 mmol) was dissolved in anhydrous dichloromethane and placed under nitrogen. Trimethylsilyl cyanide (0.35 mL) was added and the mixture was cooled to 0° C. After stirring for 10 min., boron trifluoride etherate (50 ul) was added and the reaction was allowed to warm to room temperature. When the reaction was complete by LC/MS, triethylamine was added to quench and solvents were removed by rotary evaporation. The residue was taken up in dichloromethane and loaded onto a silica gel column. A mixture of anomers was eluted using a gradient of 0-75% ethyl acetate and hexanes; 37% yield of 13a. ¹H-NMR (CD₃CN): δ 3.61-3.90 (m, 2H),

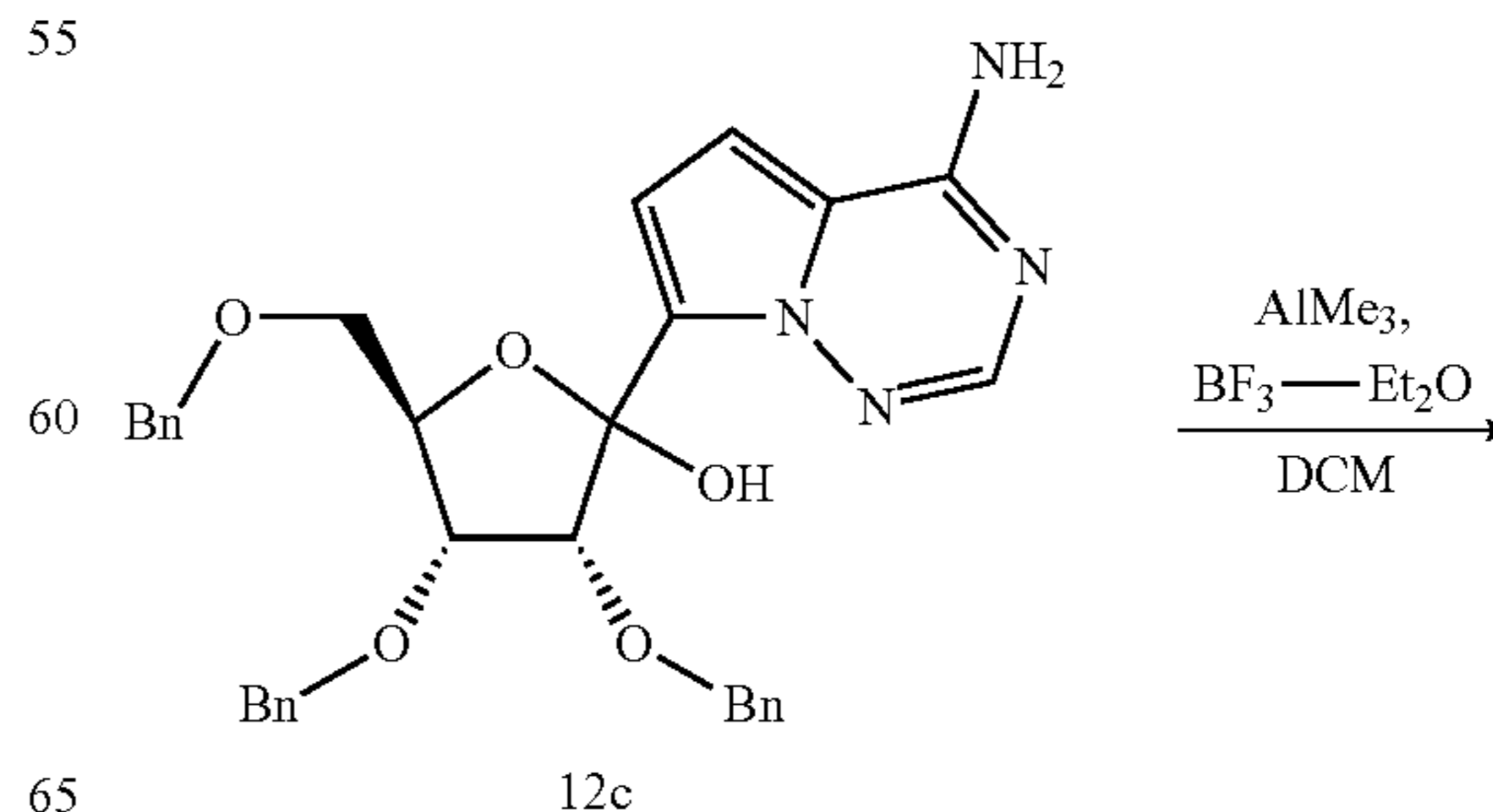
106

4.09-4.19 (m, 2H), 4.30-4.88 (m, 7H), 4.96 (d, 0.5H), 5.10 (d, 0.5H), 6.41 (bs, 2H), 6.73-6.78 (m, 1H), 6.81-6.88 (m, 1H), 7.17 (m, 2H), 7.39 (m, 13H), 7.86 (s, 0.5H), 7.93 (s, 0.5H).



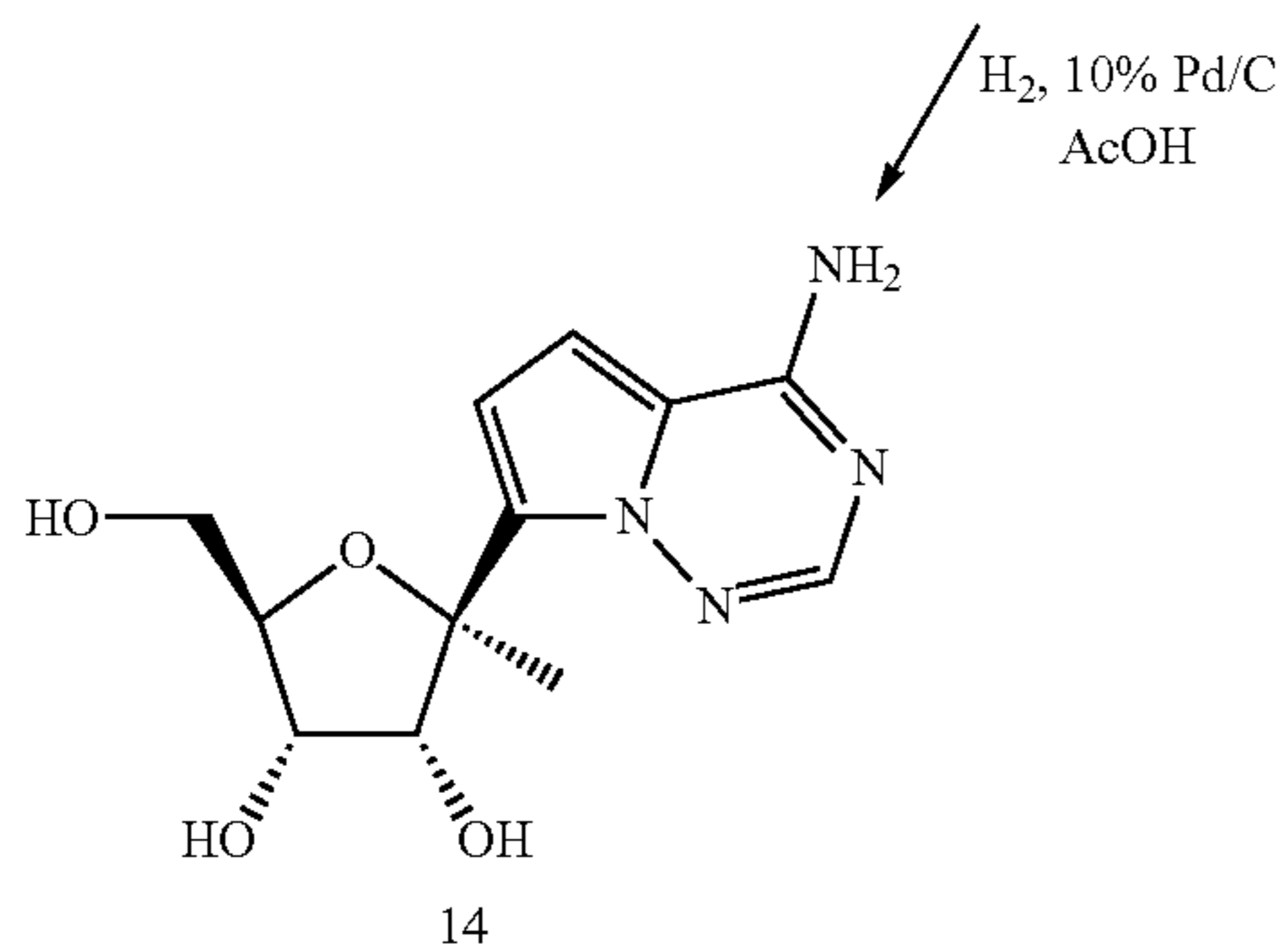
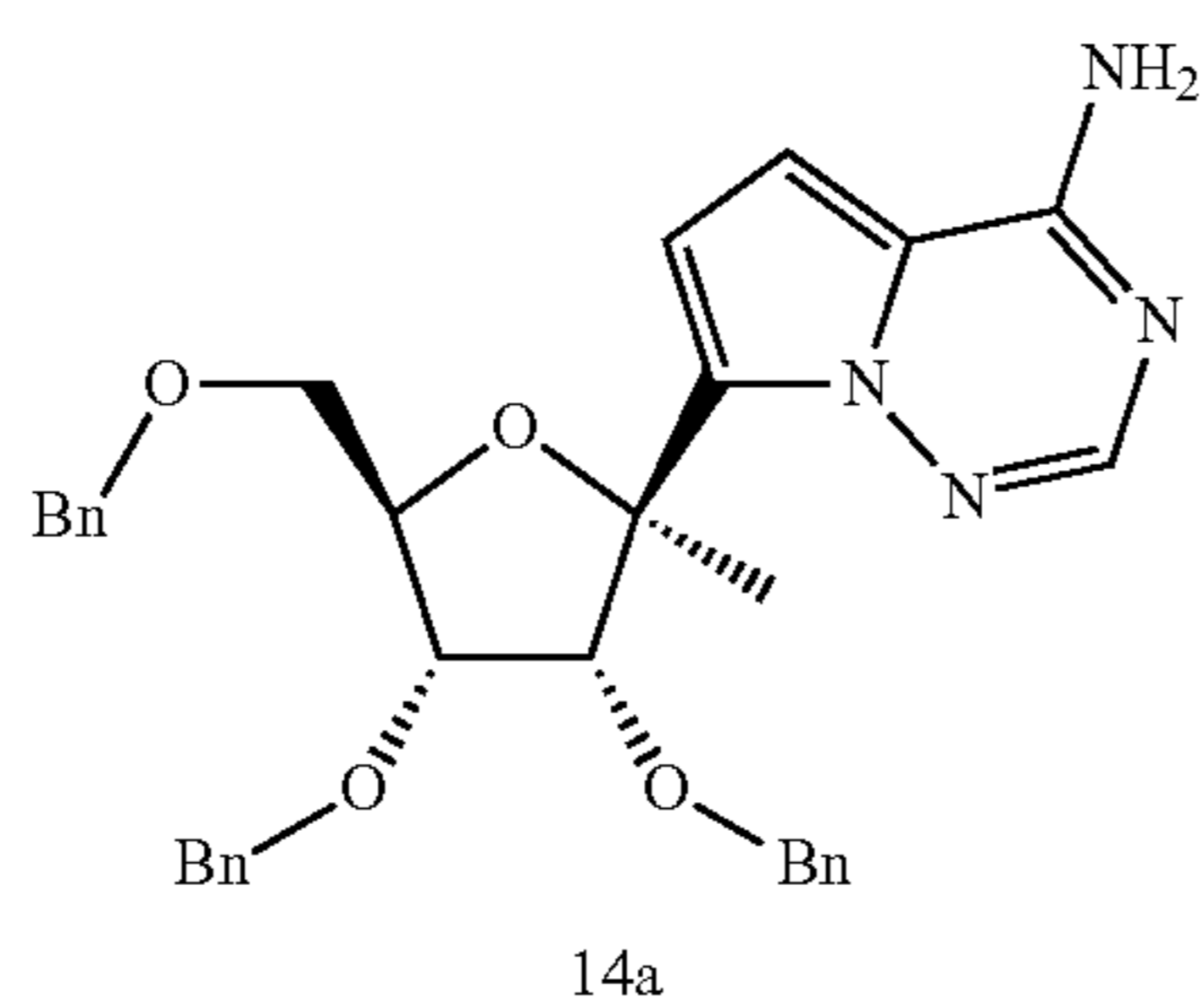
Compound 13a (0.70 mg, 0.124 mmol) was dissolved in anhydrous dichloromethane (2 ml), placed under nitrogen, and cooled to -78° C. A solution of 1 N boron trichloride in dichloromethane (0.506 ml) was added and the reaction stirred for 1 hat -78° C. When the reaction was complete by LC/MS, methanol was added to quench. The reaction was allowed to rise to room temperature and solvents were removed by rotary evaporation. The product anomers were purified by prep-HPLC; a total of 74% yield. ¹H-NMR of Compound 13 (D₂O): δ 3.65-3.75 (dd, 2H), 4.12 (t, 1H), 4.29 (q, 1H), 4.80 (d, 1H), 6.97 (d, 1H), 7.14 (d, 1H), 7.93 (s, 1H). ¹H-NMR of the other alpha-anomer (D₂O): δ 3.72-3.93 (dd, 2H), 4.16-4.19 (m, 1H), 4.60-4.62 (m, 1H), 5.01 (d, 1H), 6.95 (d, 1H), 7.28 (d, 1H), 7.96 (s, 1H).

Compound 14



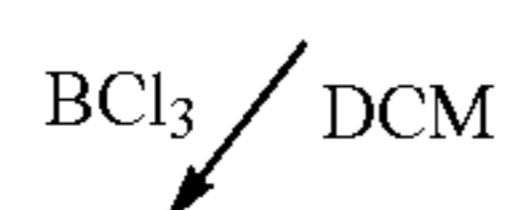
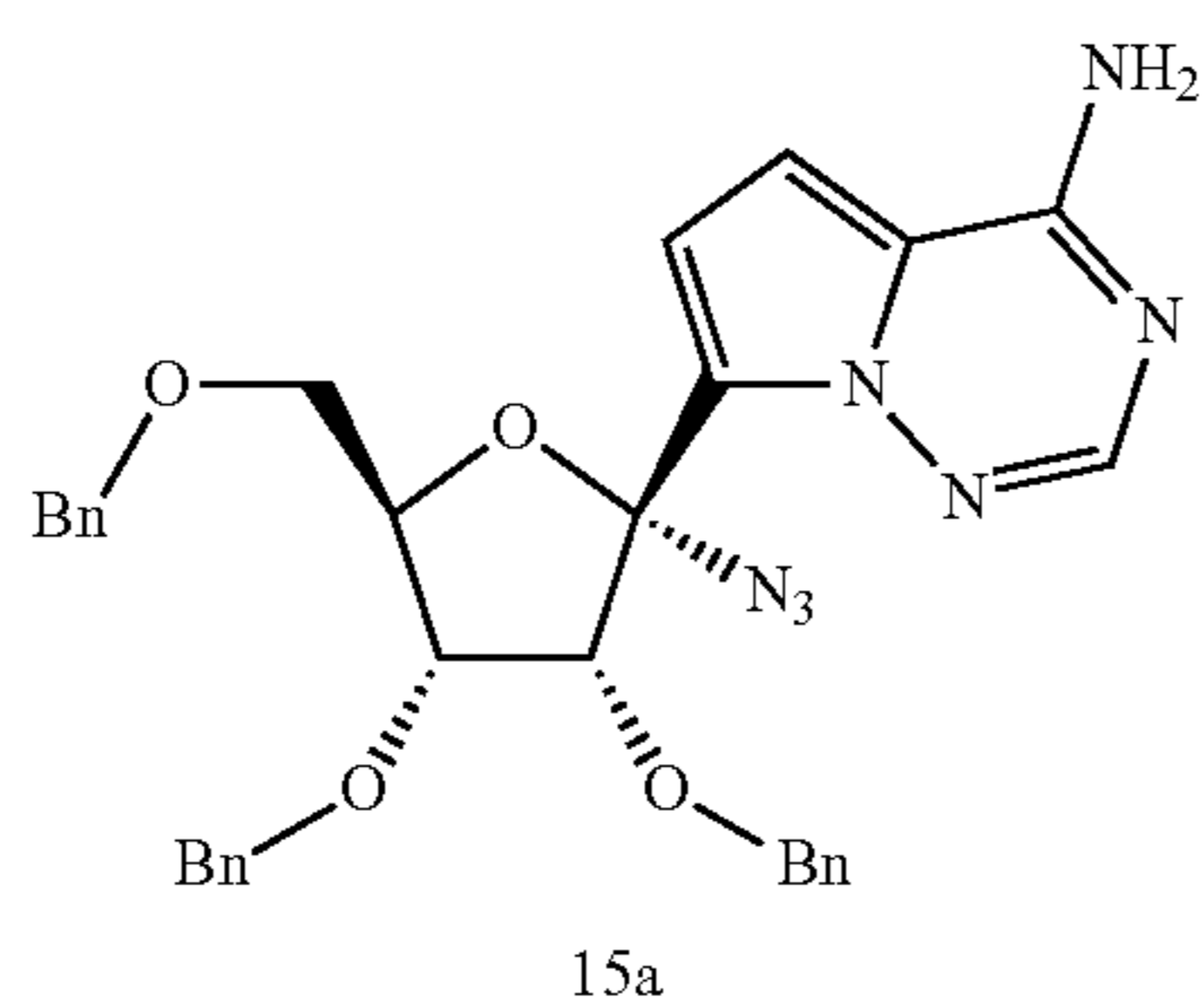
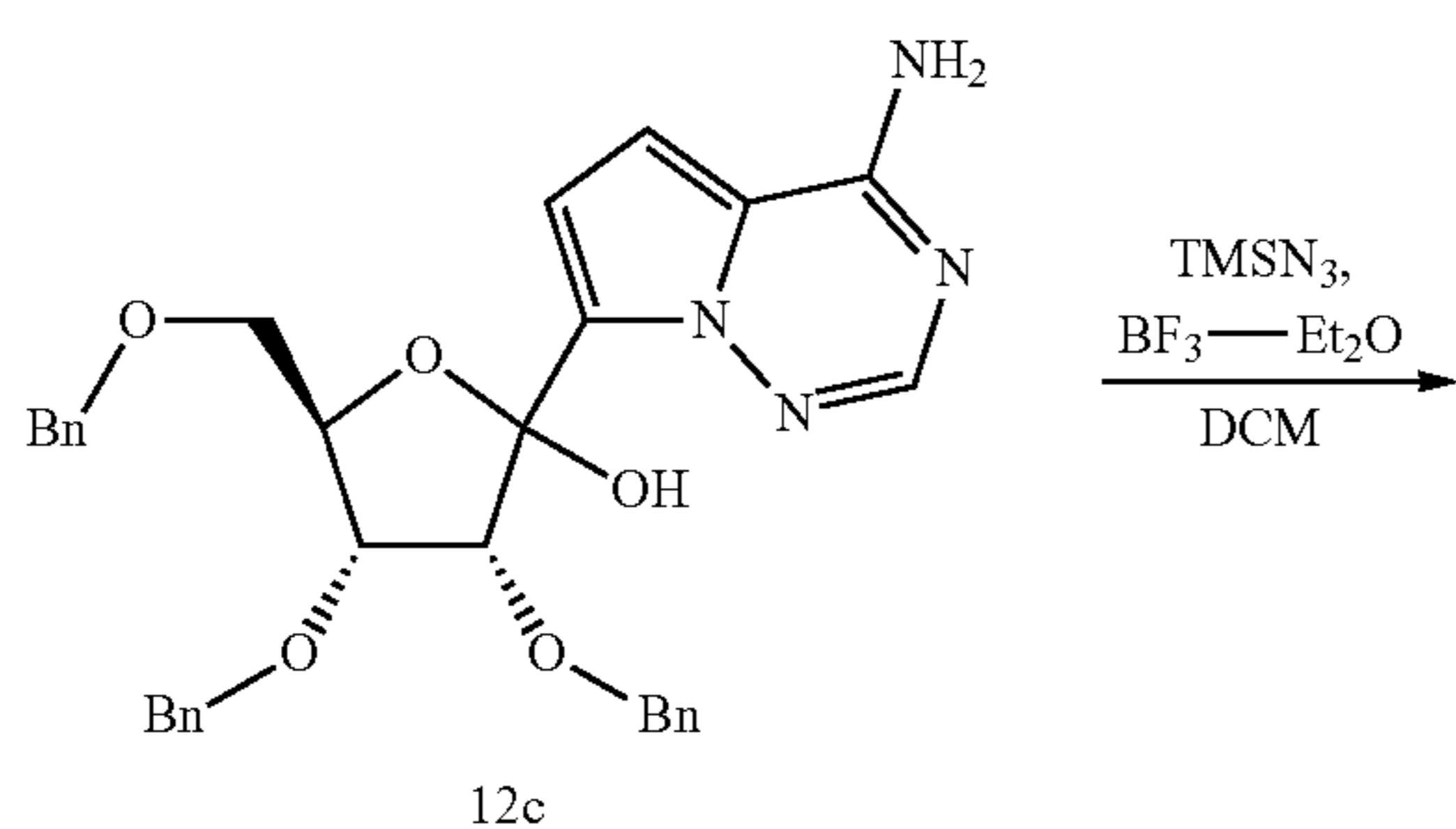
107

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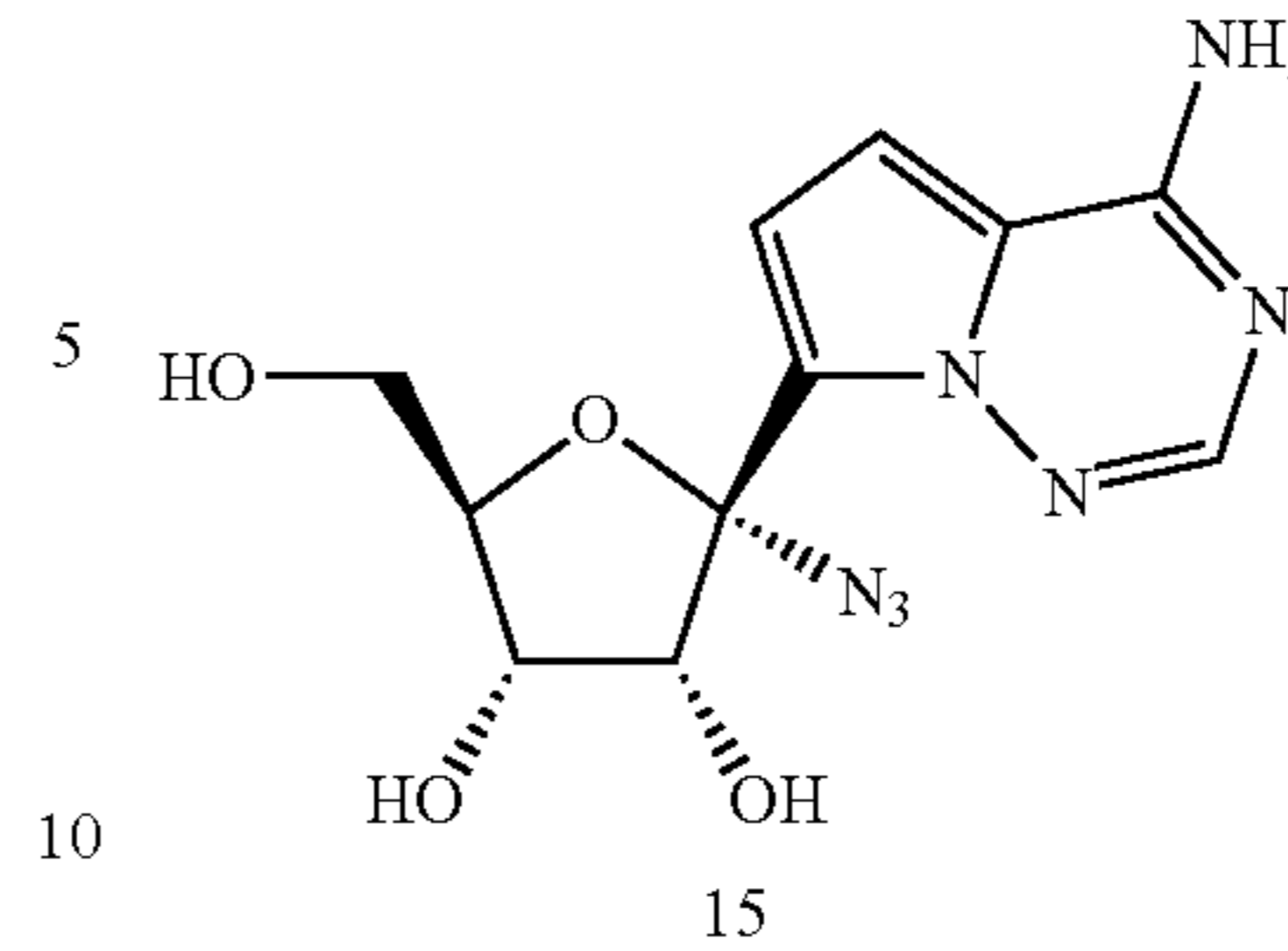


Compound 14 may be obtained from 12c in a manner similar to the method used to synthesize Compound 4.

Compound 15

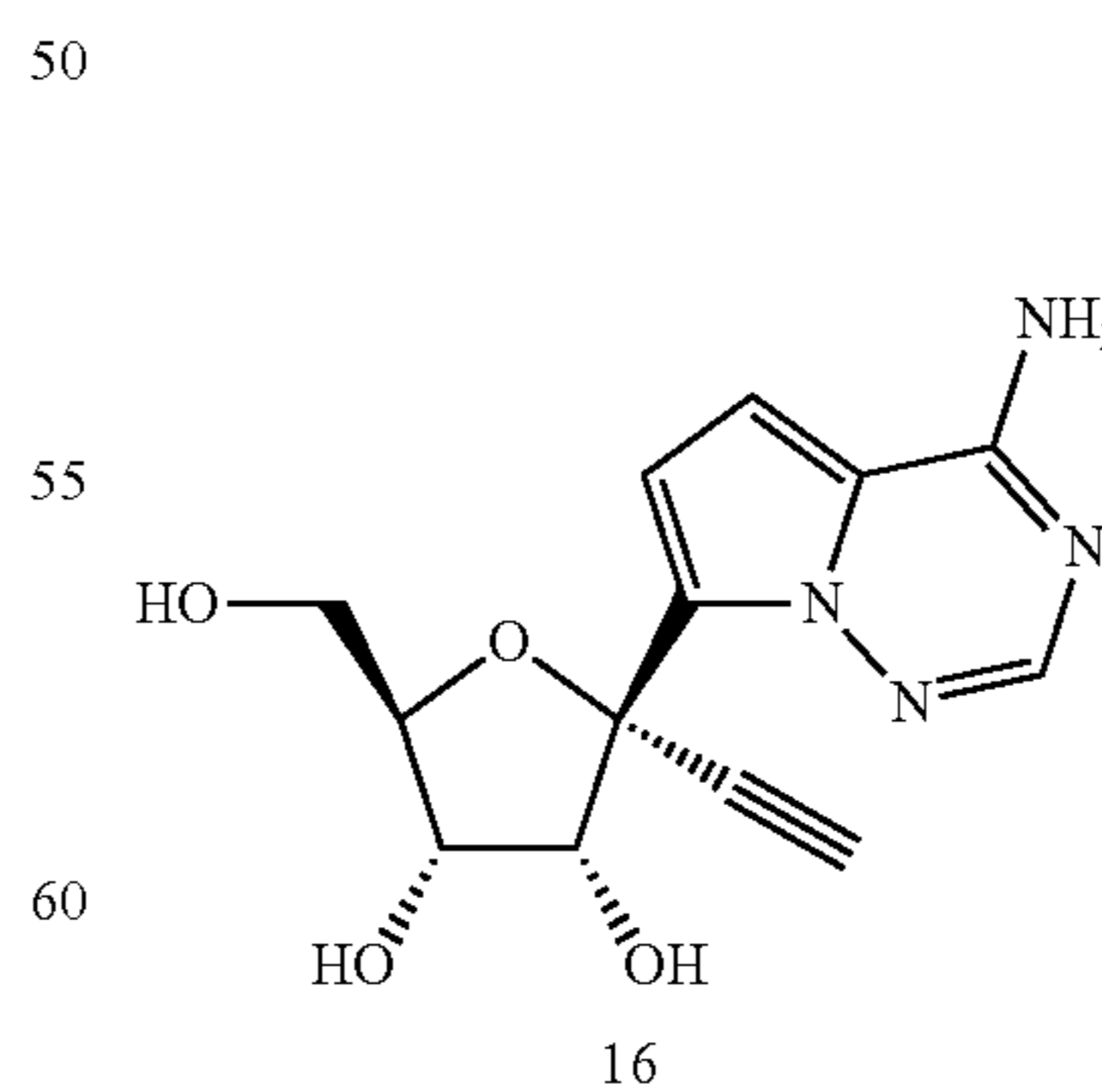
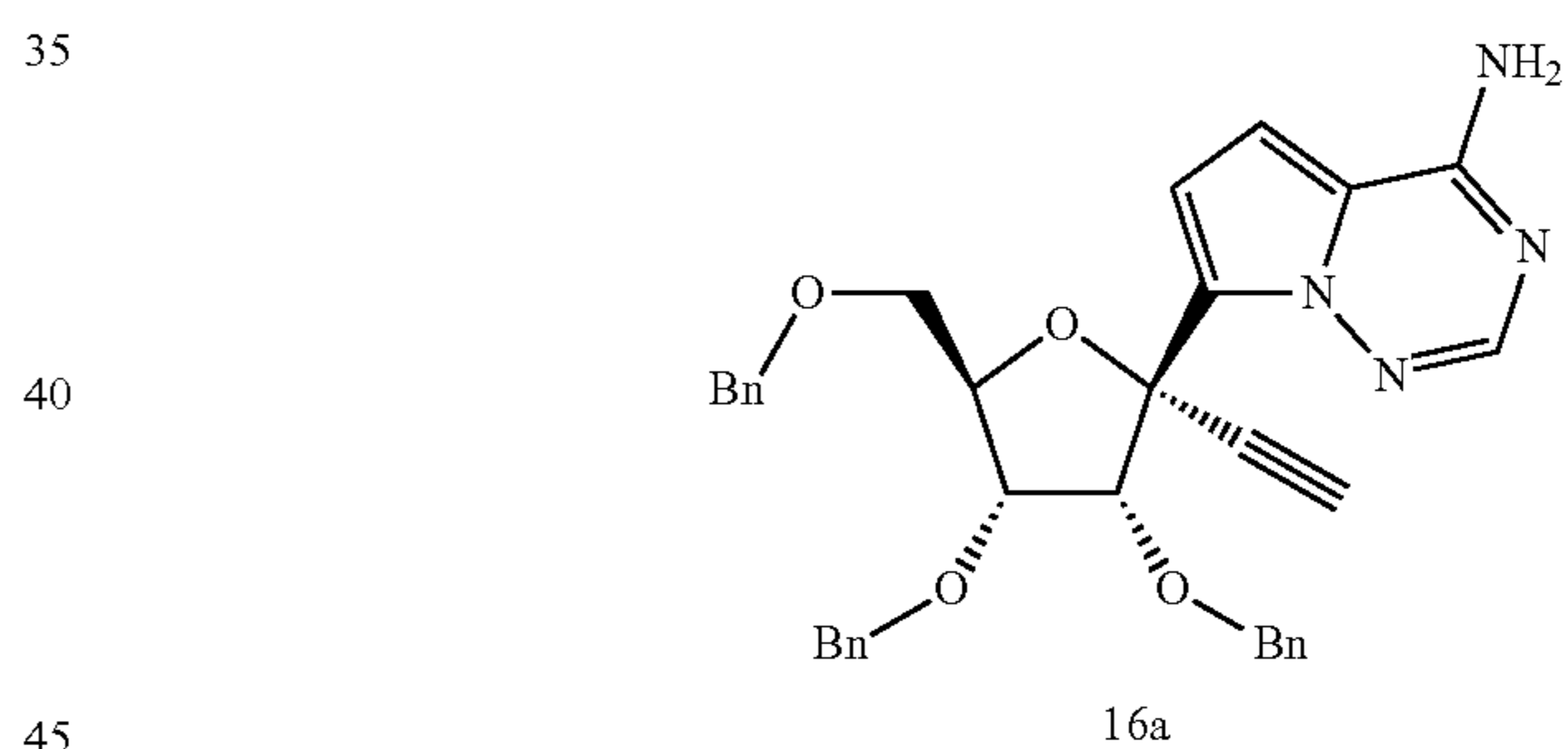
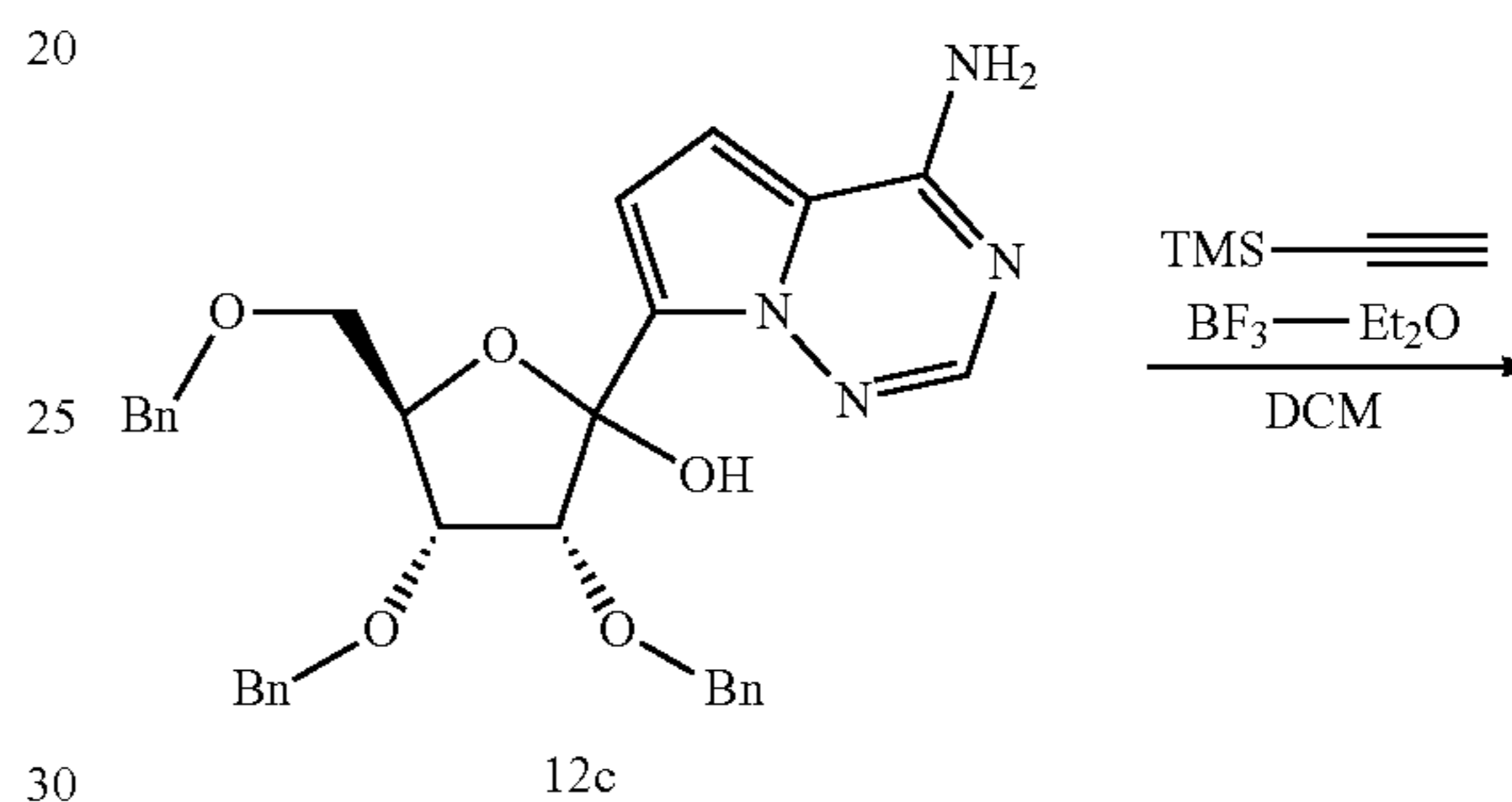
**108**

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Compound 15 may be obtained from 12c in a manner similar to that described in preparation of Compound 13 except using TMSN_3 instead of TMSCN .

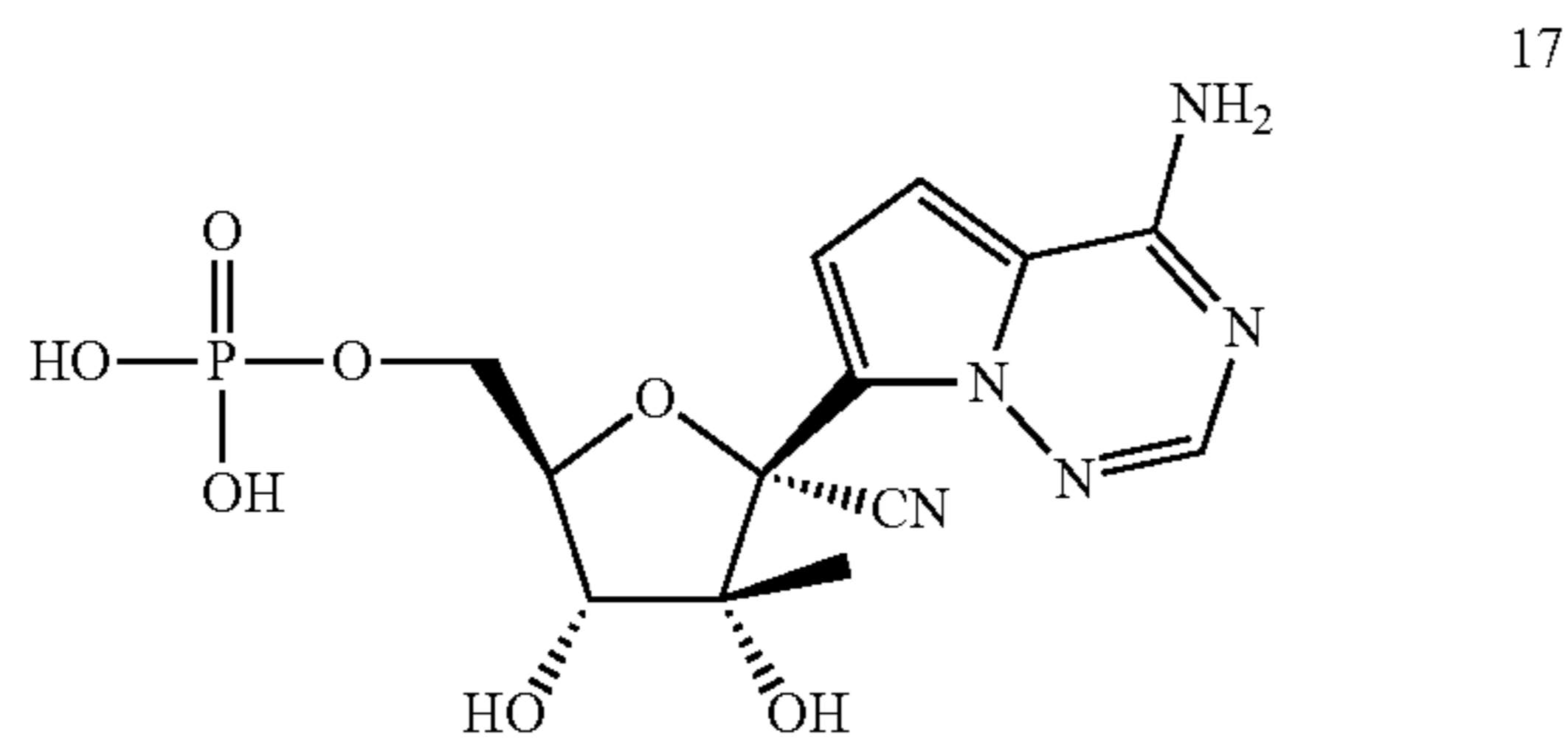
Compound 16



Compound 16 may be obtained from 12c in a manner similar to that described in preparation of Compound 13 except using TMS-acetylene instead of TMSCN .

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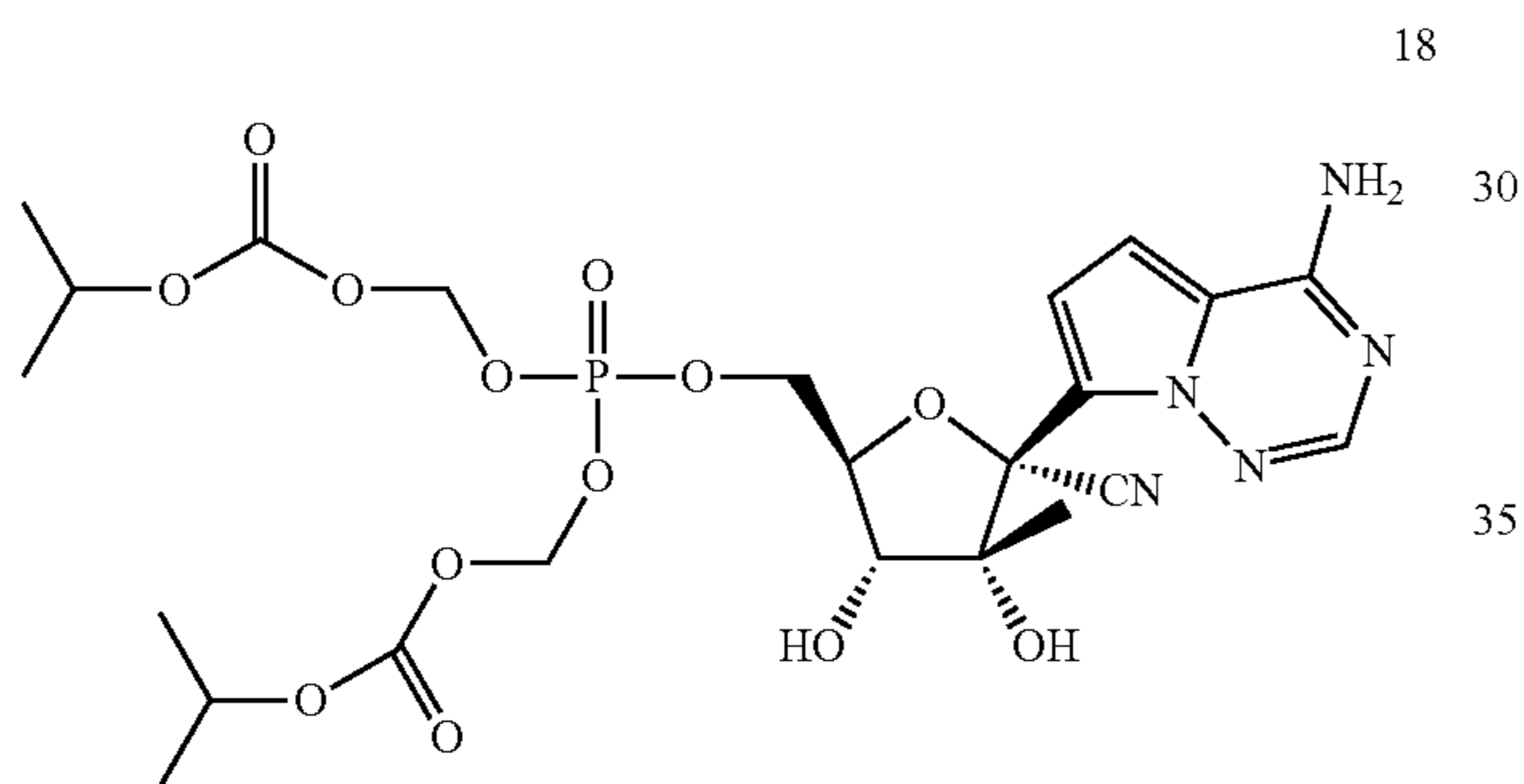
Compound 17



A mixture of about 0.05 mmol of Compound 5 and about 0.5 mL of trimethylphosphate is sealed in a container for about one to about 48 hours. The mixture is cooled to about -10 to about 10° C. and about 0.075 mmol of phosphorous oxychloride is added. After about one to about 24 hours, the reaction is quenched with about 0.5 mL of 1M tetraethylammonium bicarbonate and the desired fraction are isolated by anion exchange chromatography. The appropriate fractions are then desalted by reverse-phase chromatography to give Compound 17.

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Compound 18

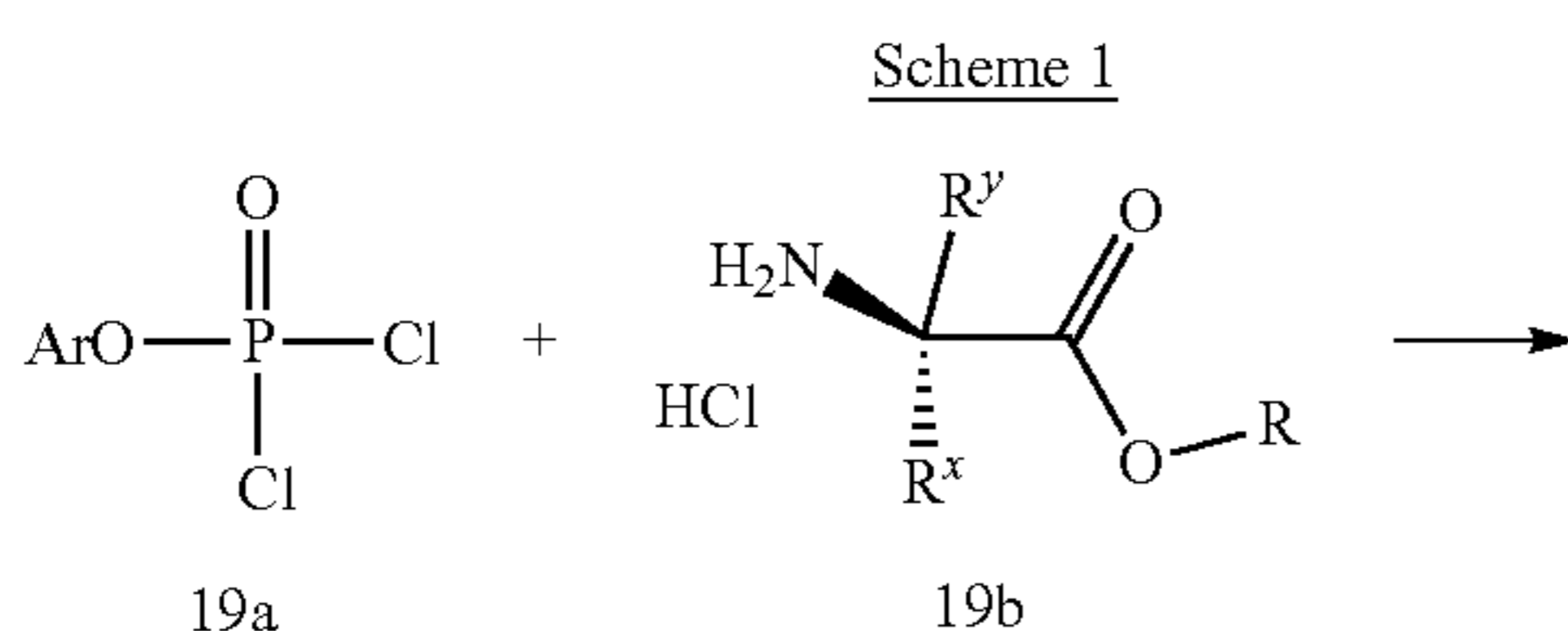


Compound 17 (about 1.19 mmol) is dried over phosphorous pentoxide in a vacuum for about overnight. The dried material is suspended in about 4 mL of anhydrous DMF and about 4.92 mmol DIPEA. About 7.34 mmol of iso-propyl chloromethyl carbonate (Antiviral Chemistry & Chemotherapy 8:557 (1997)) is added and the mixture is heated to about 25 to about 60° C. for about 30 min to about 24 hours. Heating is removed for about one to about 48 hours and the reaction filtered. The filtrate is diluted with water, Compound 18 is partitioned into CH_2Cl_2 , the organic solution is dried and evaporated, and the residue is purified by reverse-phase HPLC to isolate Compound 18.

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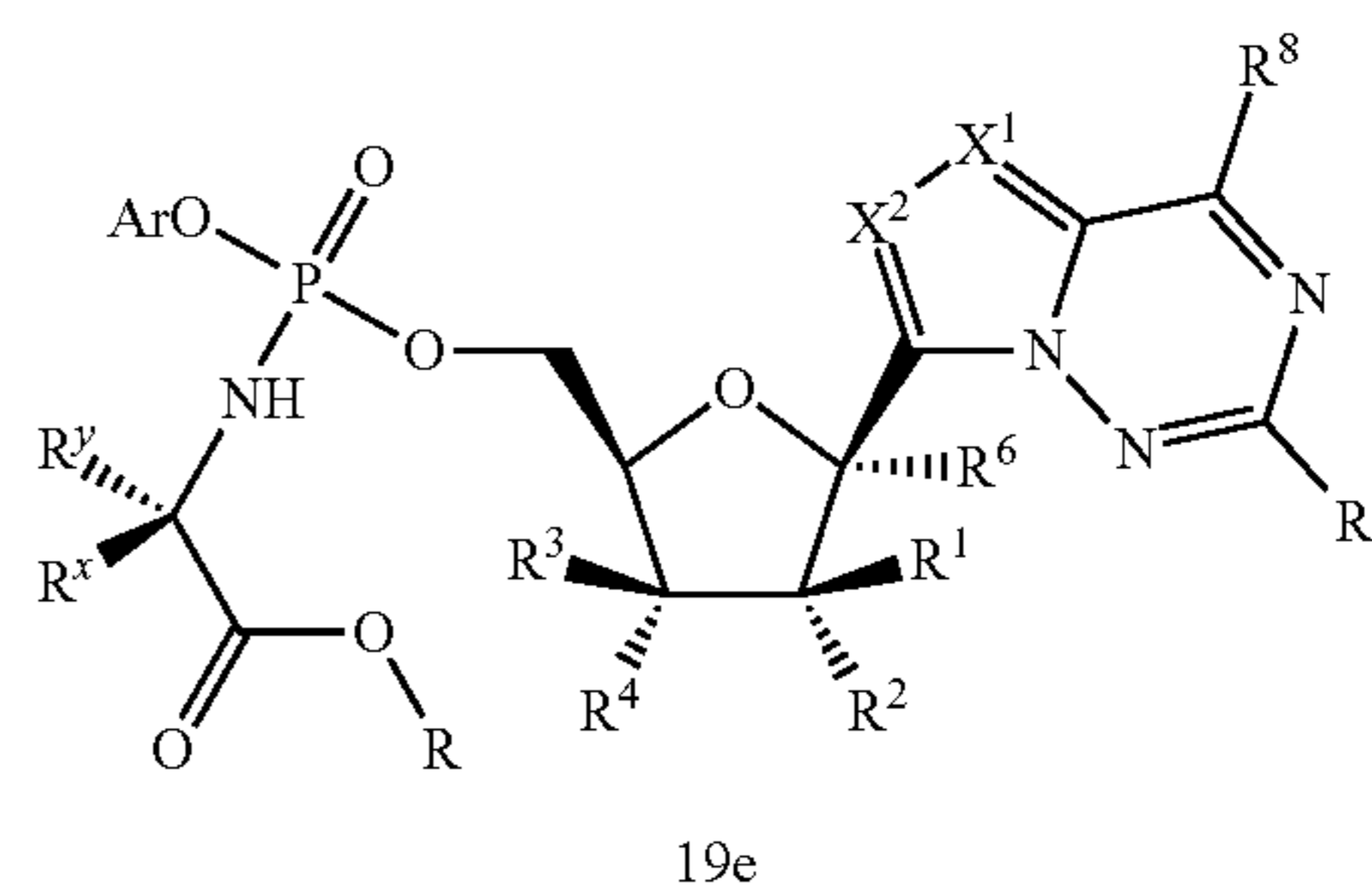
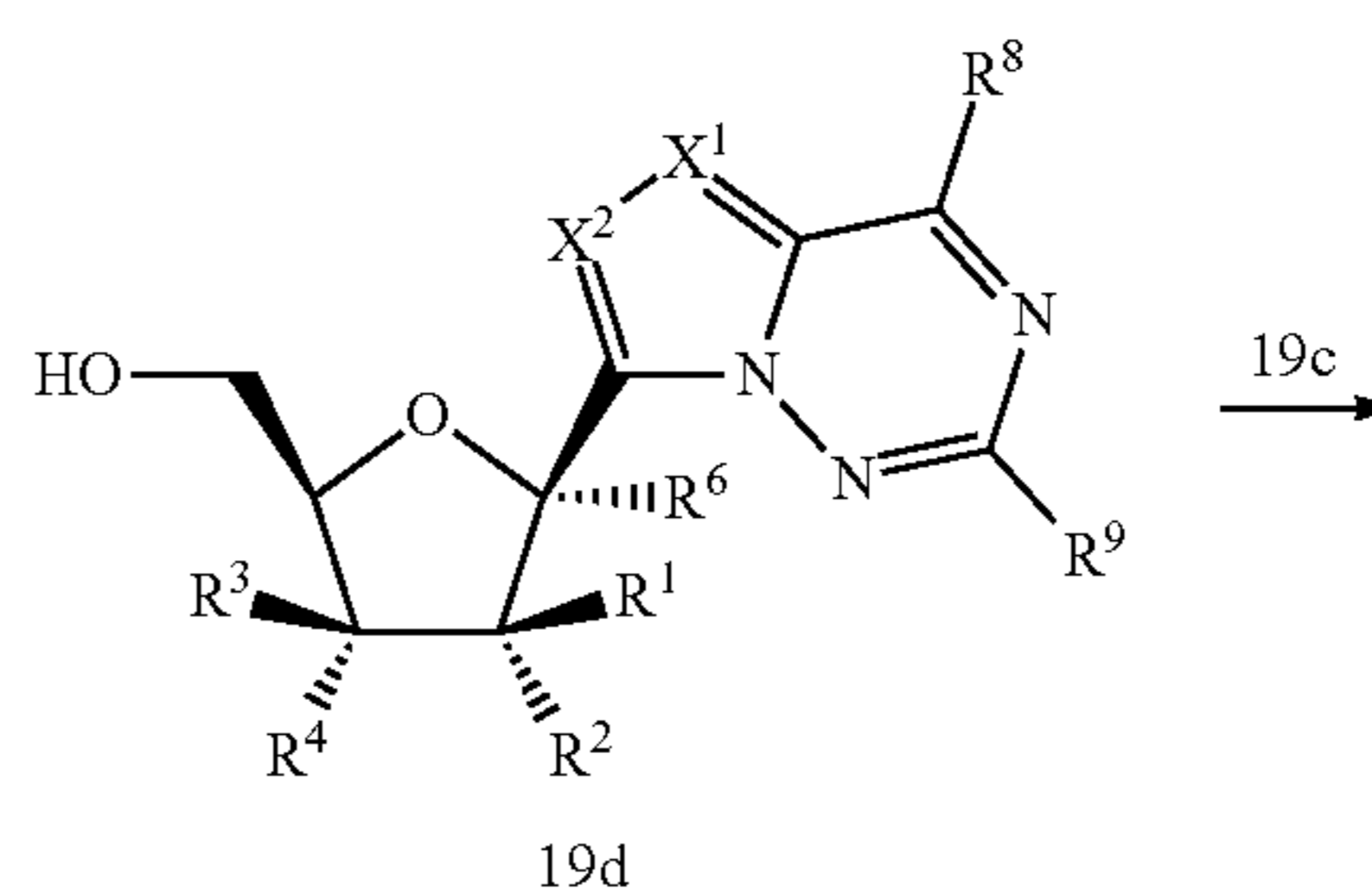
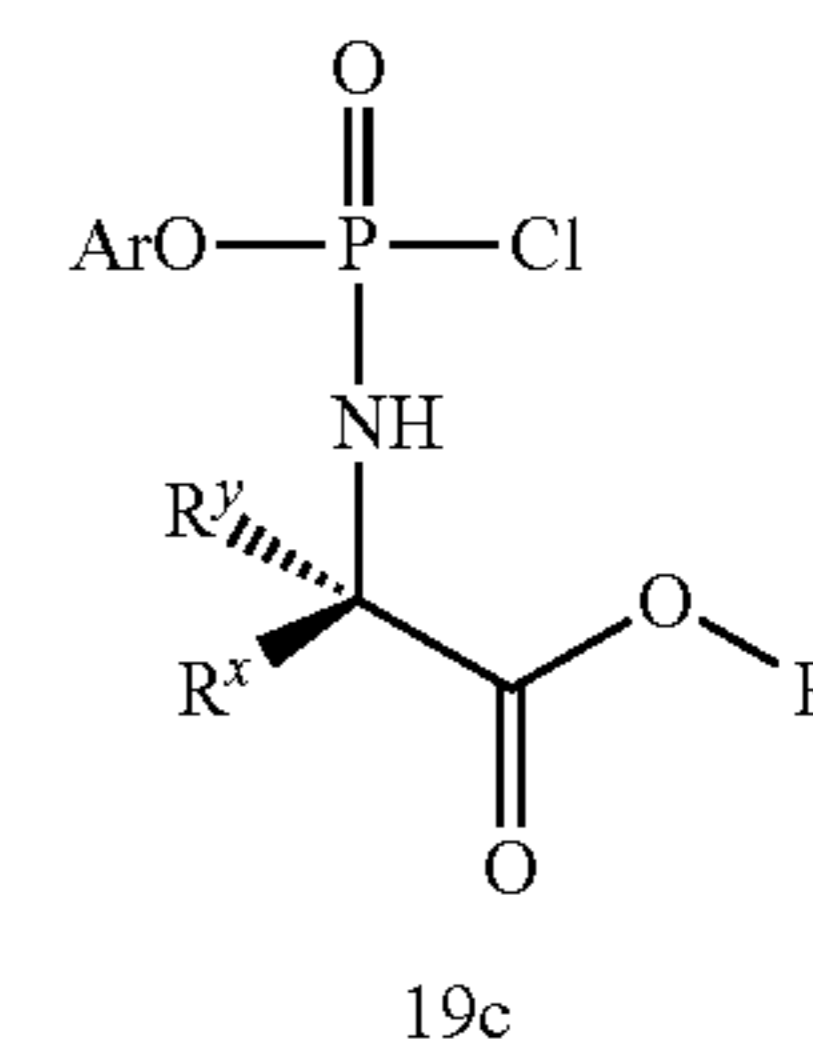
Mono Phosphoramidate Prodrugs

Non-limiting examples of mono-phosphoramidate prodrugs comprising the instant invention may be prepared according to general Scheme 1.



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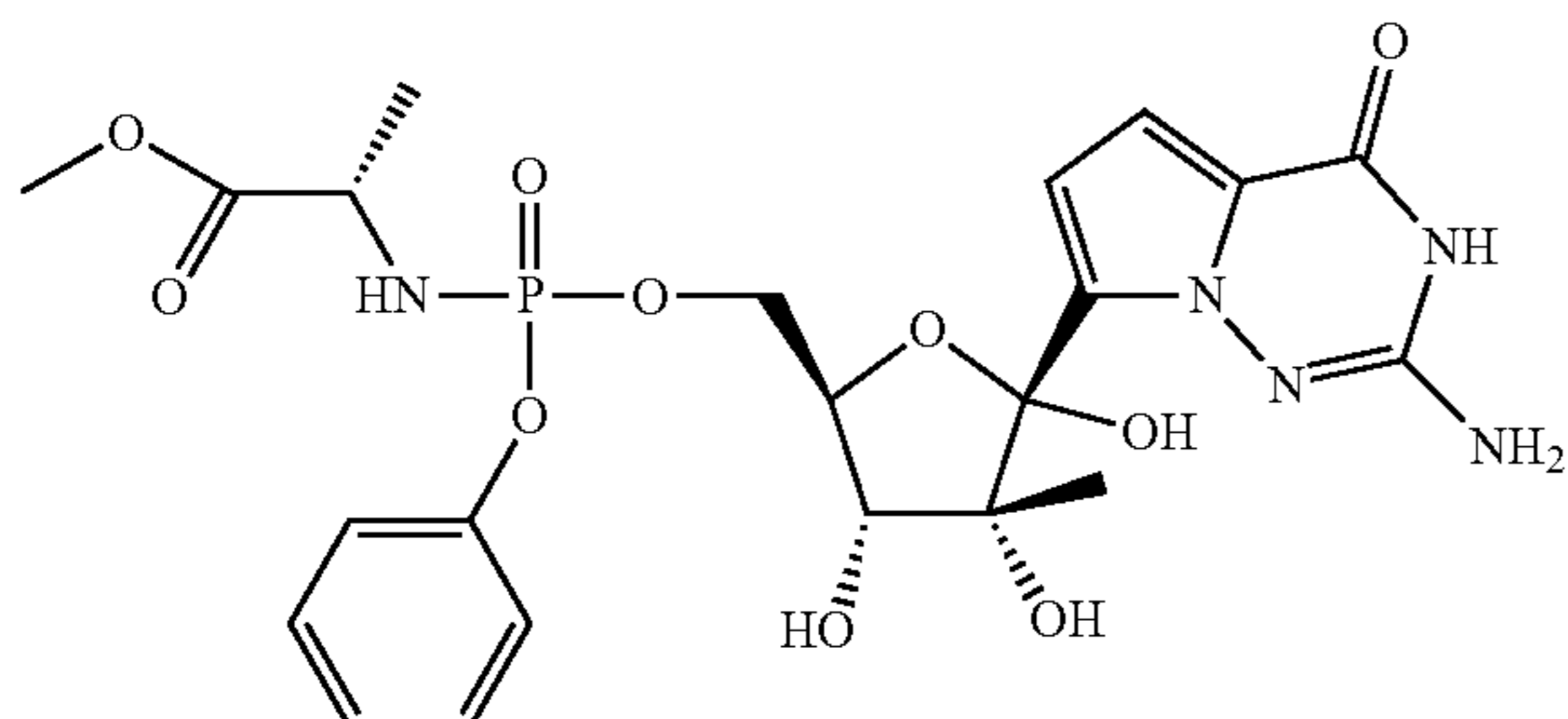


The general procedure comprises the reaction of an amino acid ester salt 19b, e.g., HCl salt, with an aryl dichlorophosphate 19a in the presence of about two to ten equivalents of a suitable base to give the phosphoramidate 19c. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. Tertiary amines are particularly preferred. Preferably, the product of each step is used directly in the subsequent steps without recrystallization or chromatography. Specific, but non-limiting, examples of 19a, 19b, and 19c can be found in WO 2006/121820 that is hereby incorporated by reference in its entirety. A nucleoside base 19d reacts with the phosphoramidate 19c in the presence of a suitable base. Suitable bases include, but are not limited to, imidazoles, pyridines such as lutidine and DMAP, tertiary amines such as triethylamine and DABCO, and substituted amidines such as DBN and DBU. The product 19e may be isolated by recrystallization and/or chromatography.

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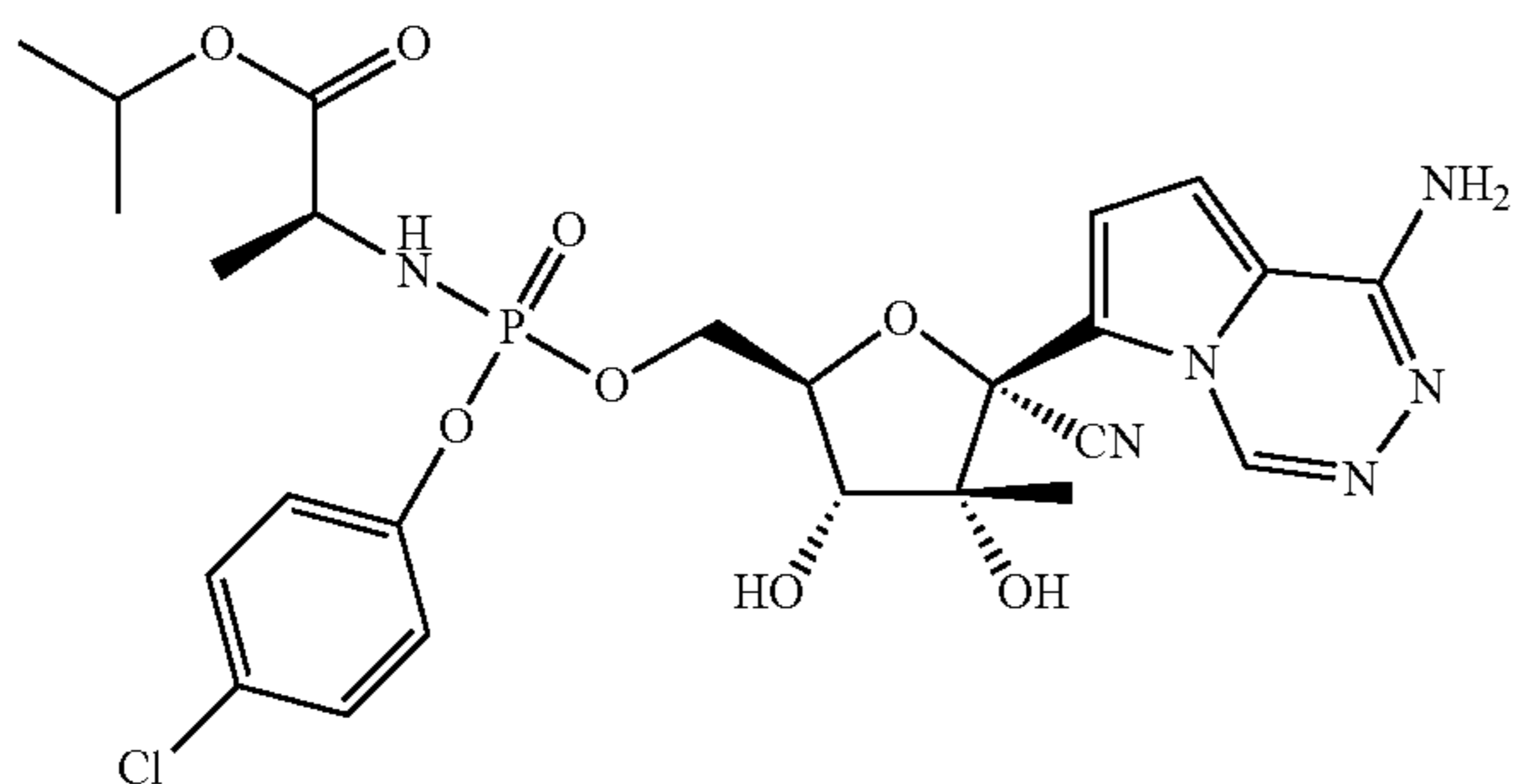
111

Compound 20



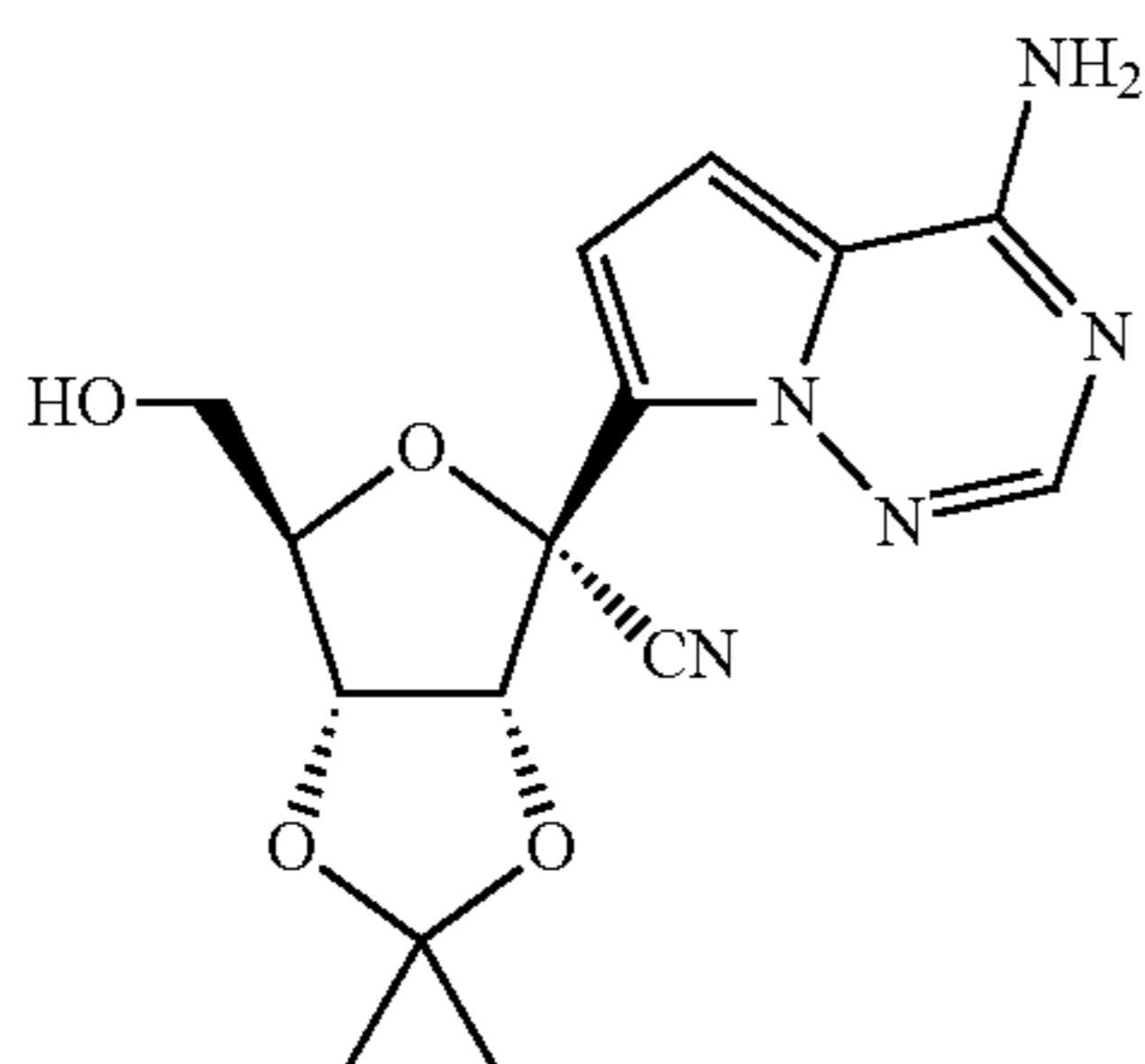
About 3.1 mmol of phenyl methoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* 1993, 36, 1048-1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of Compound 11 and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give Compound 20.

Compound 21



About 3.1 mmol of 4-chlorophenyl 2-propoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, *J. Med. Chem.* 1993, 36, 1048-1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of Compound 5 and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give Compound 21.

Compound 22

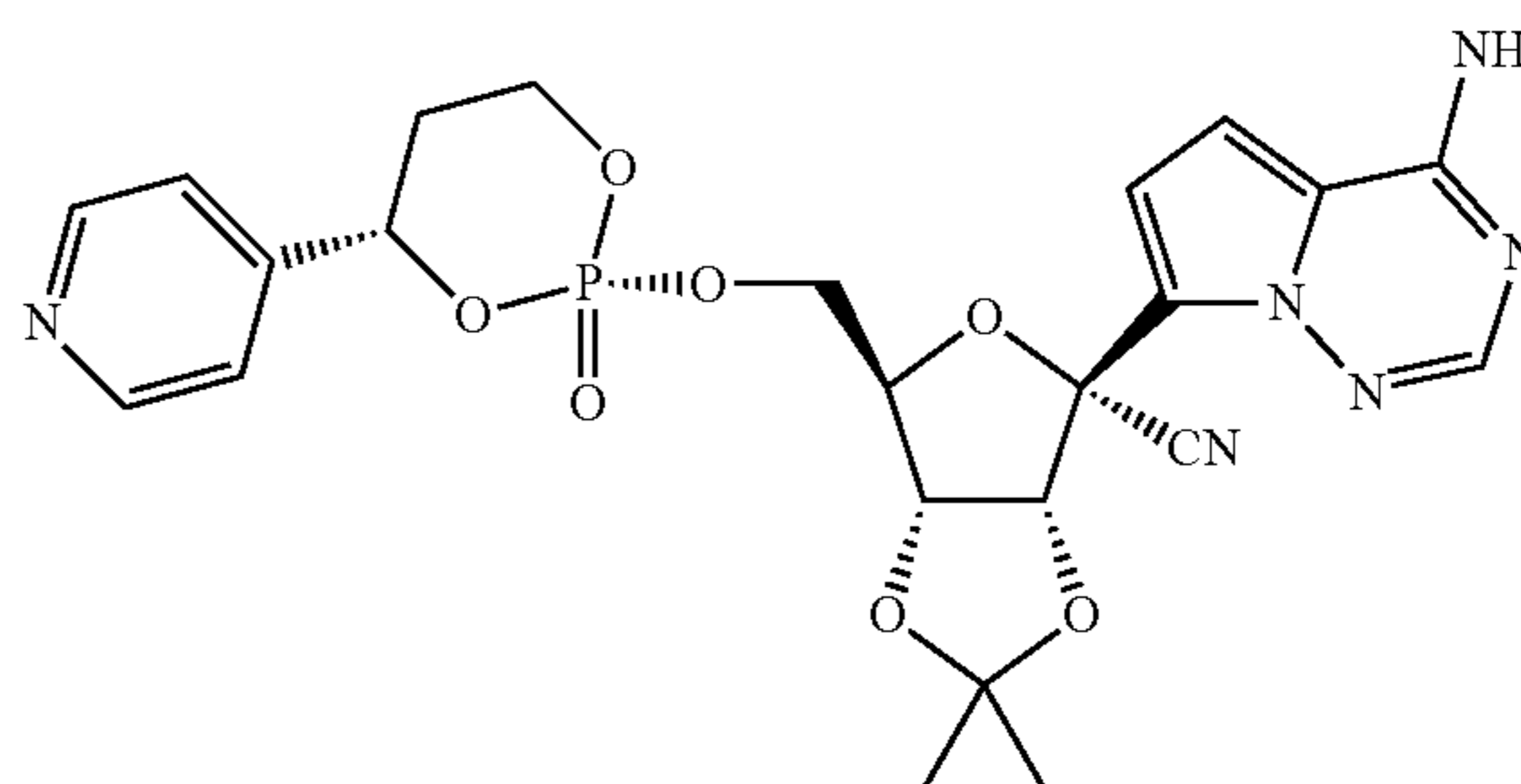


A mixture of about 0.52 mmol of Compound 13 and about 12 mL dry acetone, about 0.7 mL of 2,2,-dimethoxypropane

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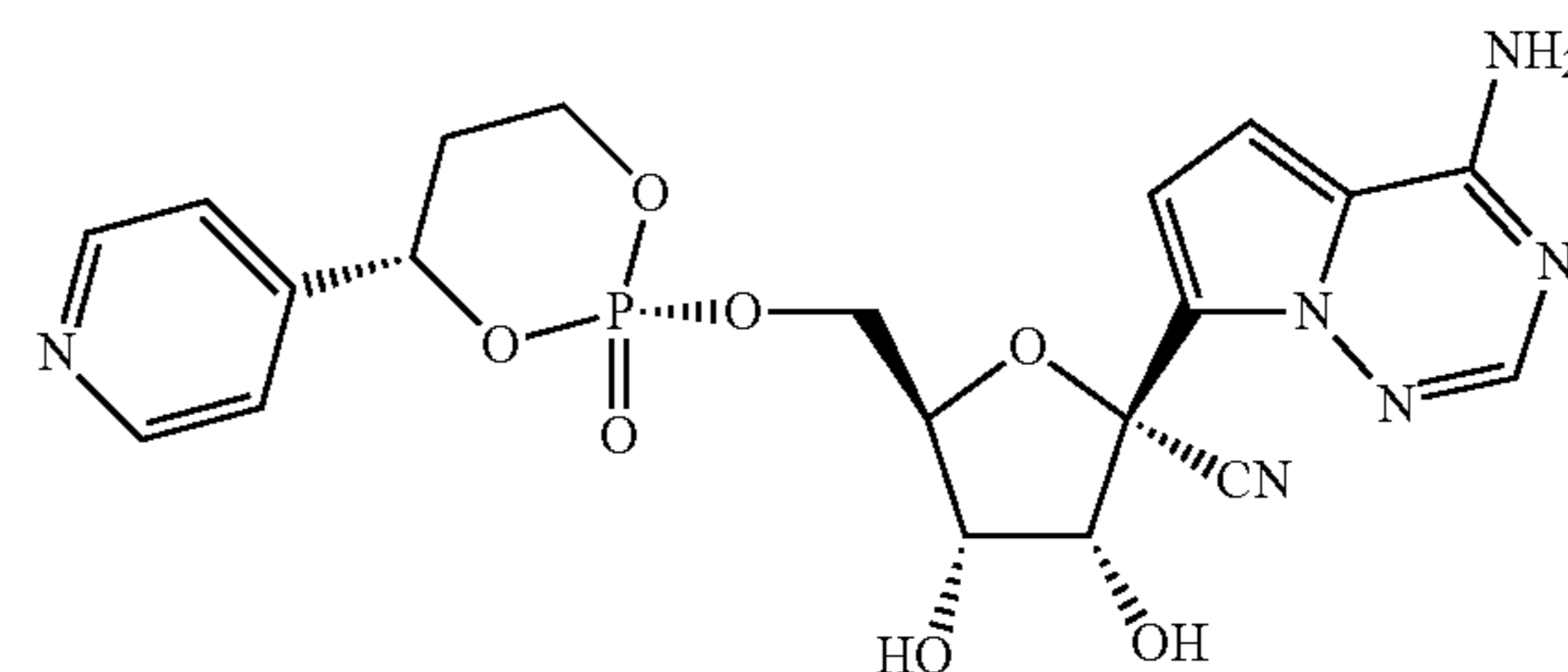
and about 1.28 mmol of di-p-nitrophenylphosphoric acid is stirred for about 24 hours to about seven days. The reaction mixture is neutralized with about 20 mL of 0.1 N NaHCO_3 and the acetone is evaporated. The desired material is partitioned into chloroform, the chloroform solution is dried, and the solvent is evaporated. Compound 22 is purified from the residue by conventional means.

Compound 23



A solution of about 0.53 mmol of Compound 22 in about 5 mL of DMF is treated with about 1 mL of a 1 M solution of t-butylmagnesium chloride in THF. After about 30 min to about 5 hours, a solution of about 0.65 mmol of trans-4-[(5)-pyridin-4-yl]-2-(4-nitrophenoxy)-2-oxo-1,3,2-dioxaphosphorinane (Reddy, *Tetrahedron Letters* 2005, 4321-4324) is added and the reaction is stirred for about one to about 24 hours. The solution is concentrated in a vacuum and the residue is purified by chromatography to give Compound 23.

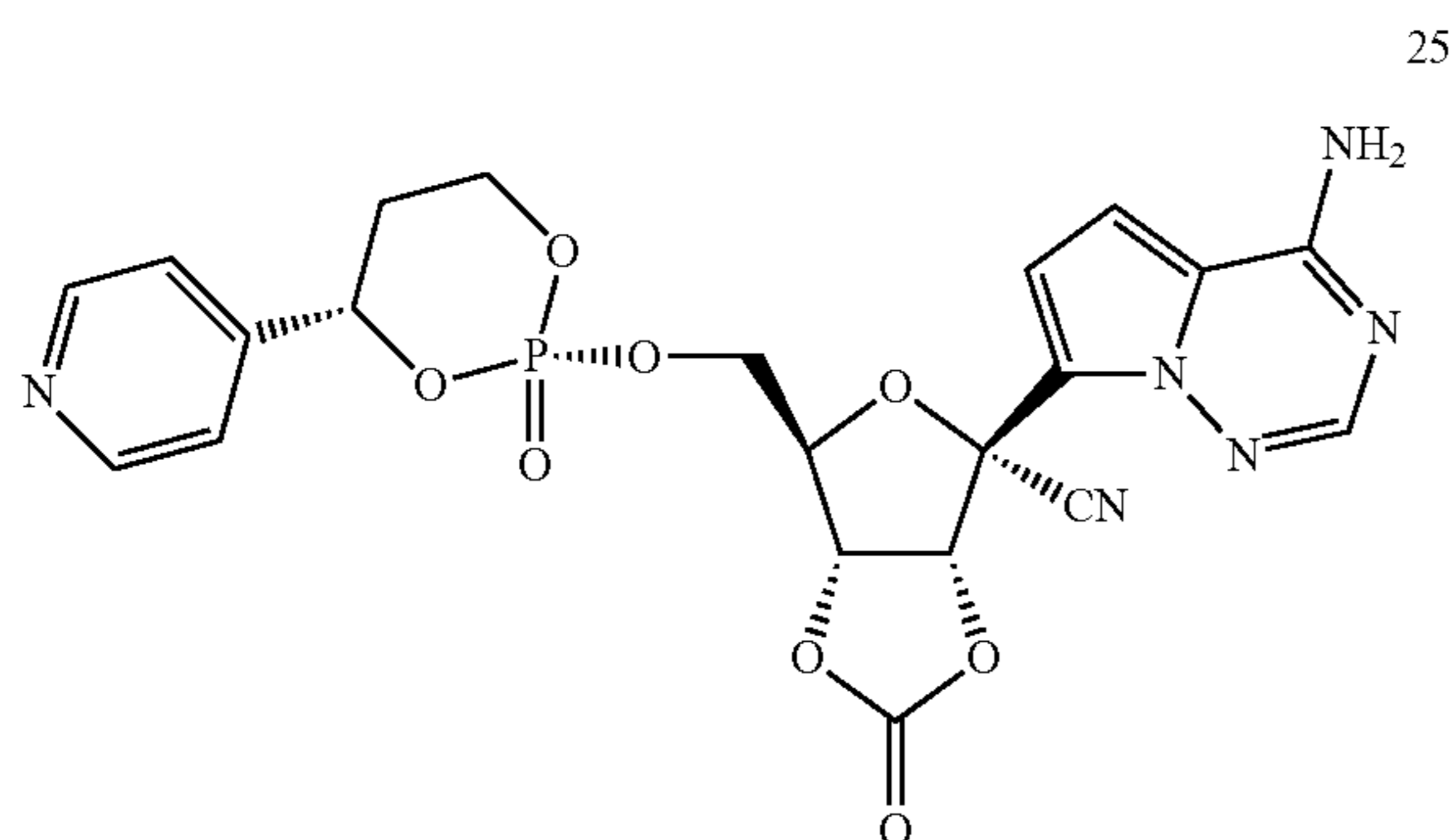
Compound 24



A solution of about 70% aqueous trifluoroacetic acid is cooled to 0° C. and is treated with about 0.32 mmol of Compound 23 for about one to 24 hours. The solution is concentrated and the residue is purified by chromatography to give Compound 24.

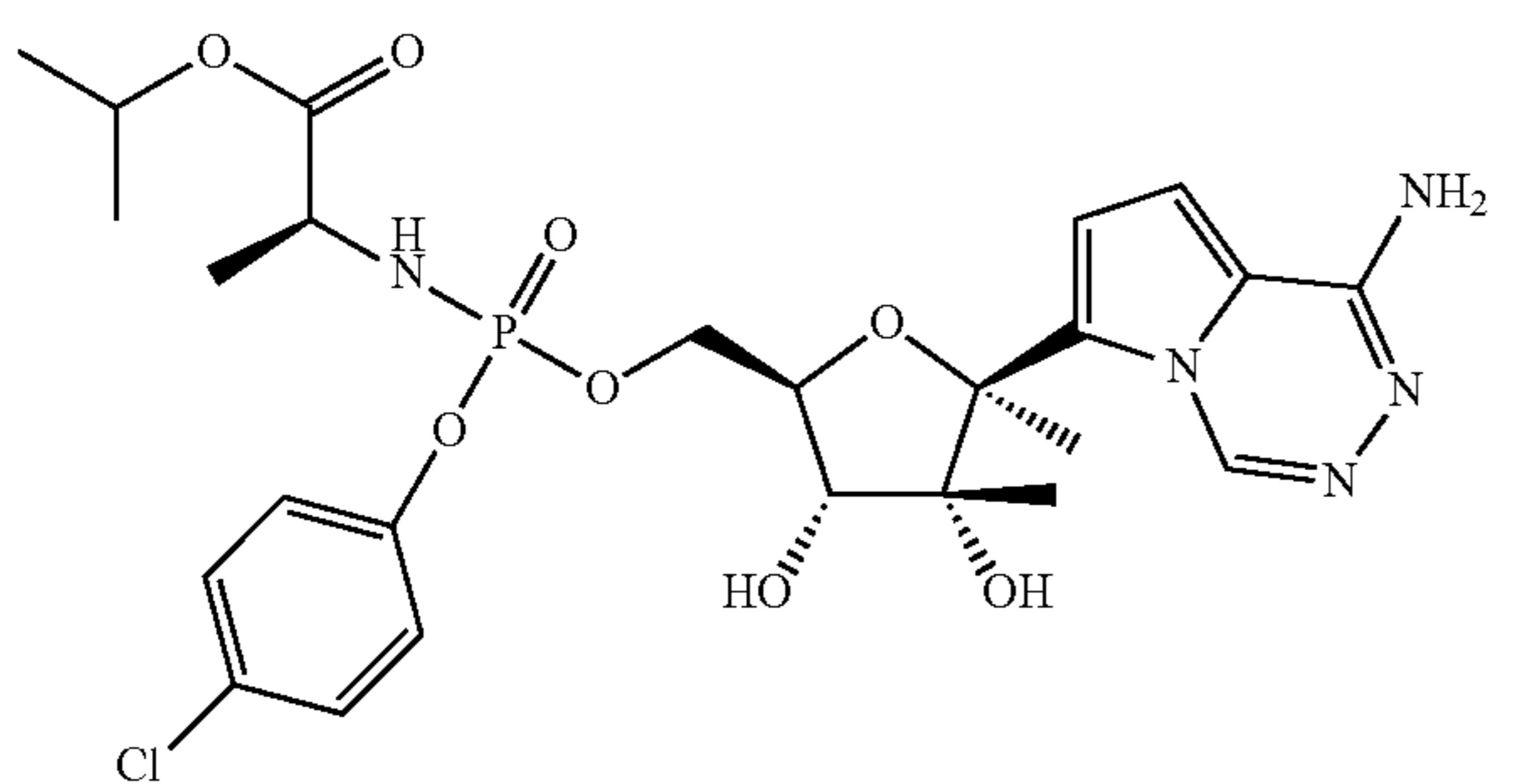
113

Compound 25



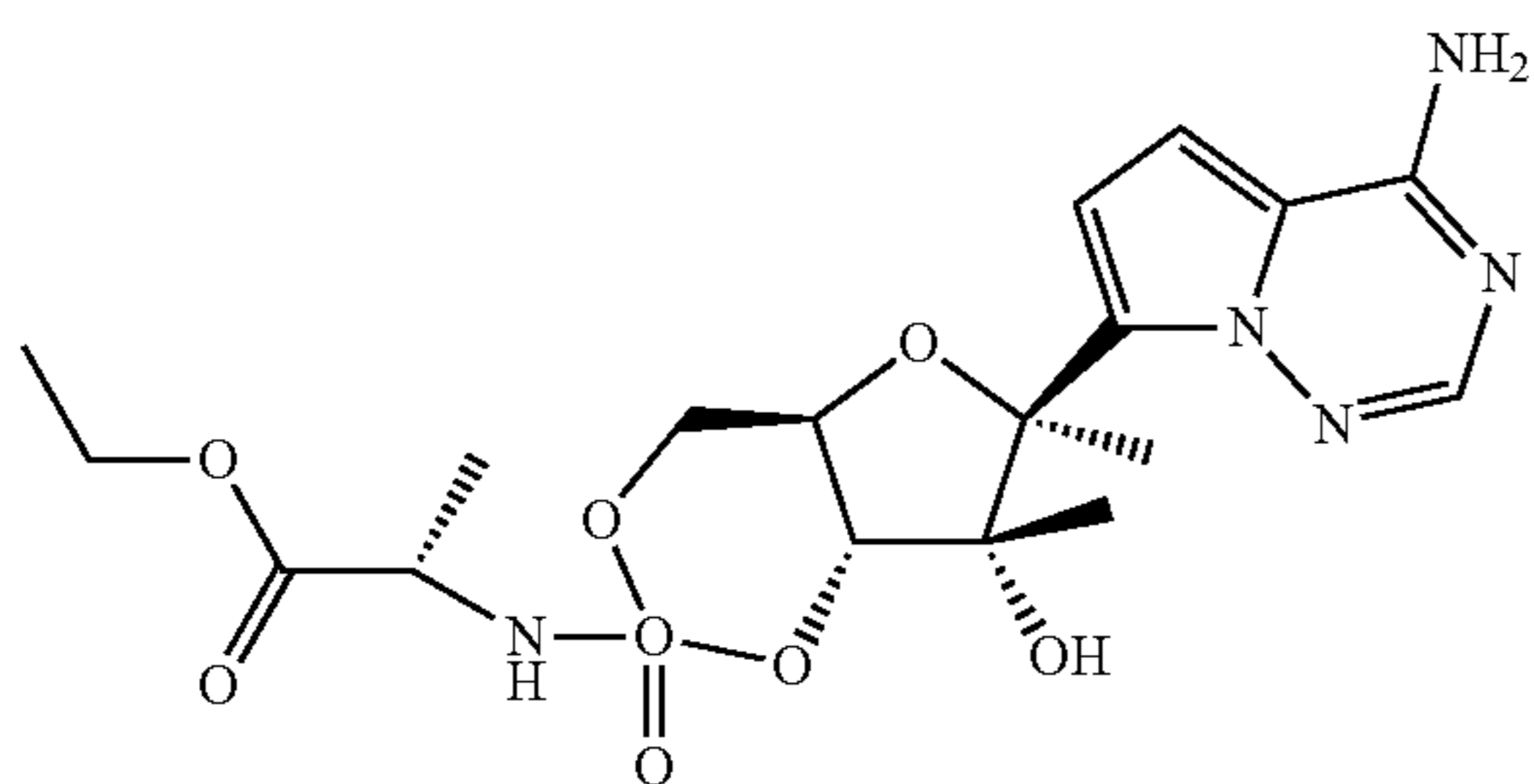
A solution of about 1.56 mmol of Compound 24 in about 15 mL of THF is treated with about 4.32 mmol of CDI. After about one to about 24 hours, the solvent is evaporated and the residue is purified by chromatography to give Compound 25.

Compound 26



About 3.1 mmol of 4-chlorophenyl 2-ethoxyalaninyl phosphorochloridate (prepared according to McGuigan et al, J. Med. Chem. 1993, 36, 1048-1052) in about 3 mL of THF is added to a mixture of about 0.5 mmol of Compound 4 and about 3.8 mmol of N-methylimidazole in about 3 mL THF. The reaction is stirred for about 24 hours and the solvent is removed under reduced pressure. The residue is purified by reverse-phase HPLC to give Compound 26.

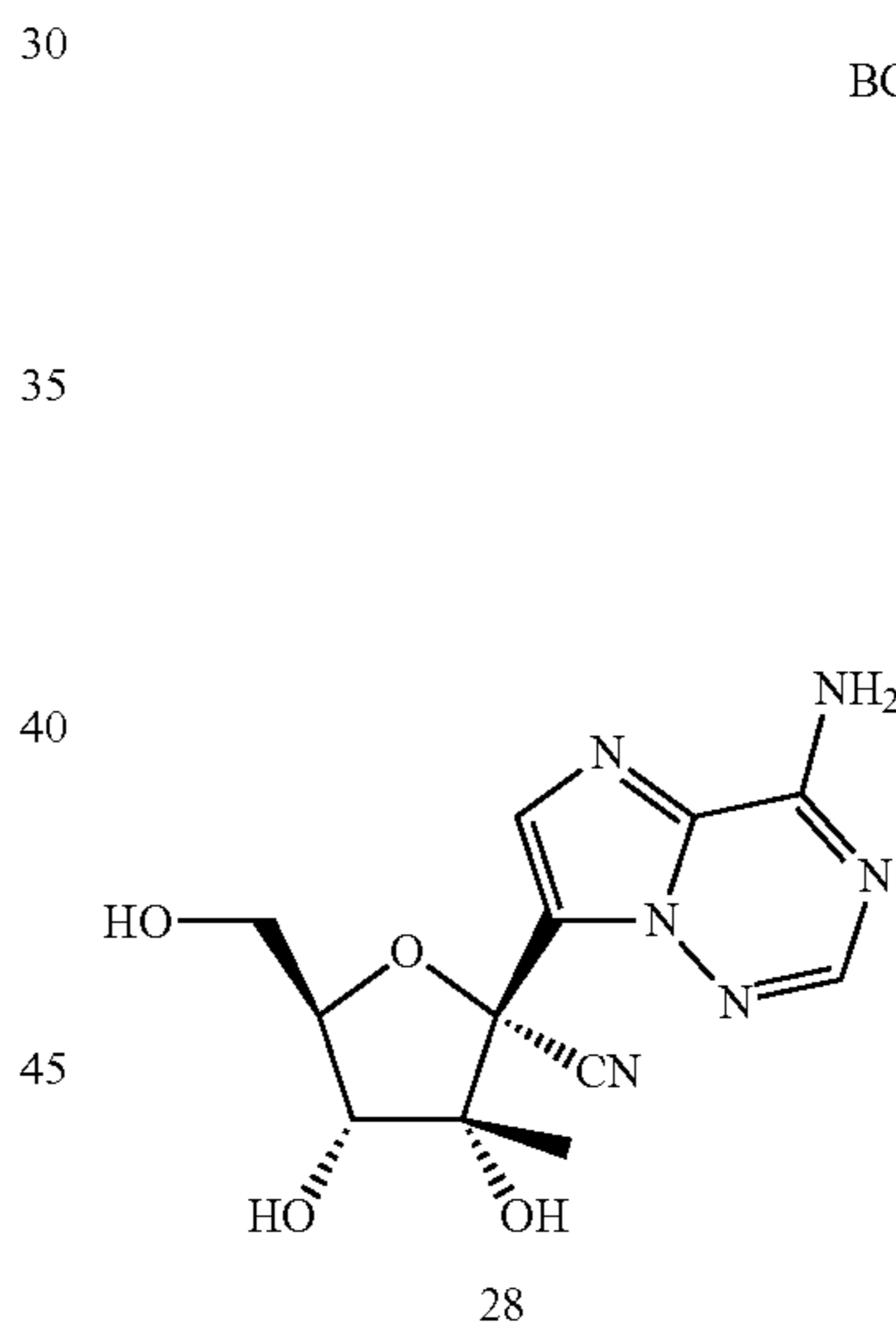
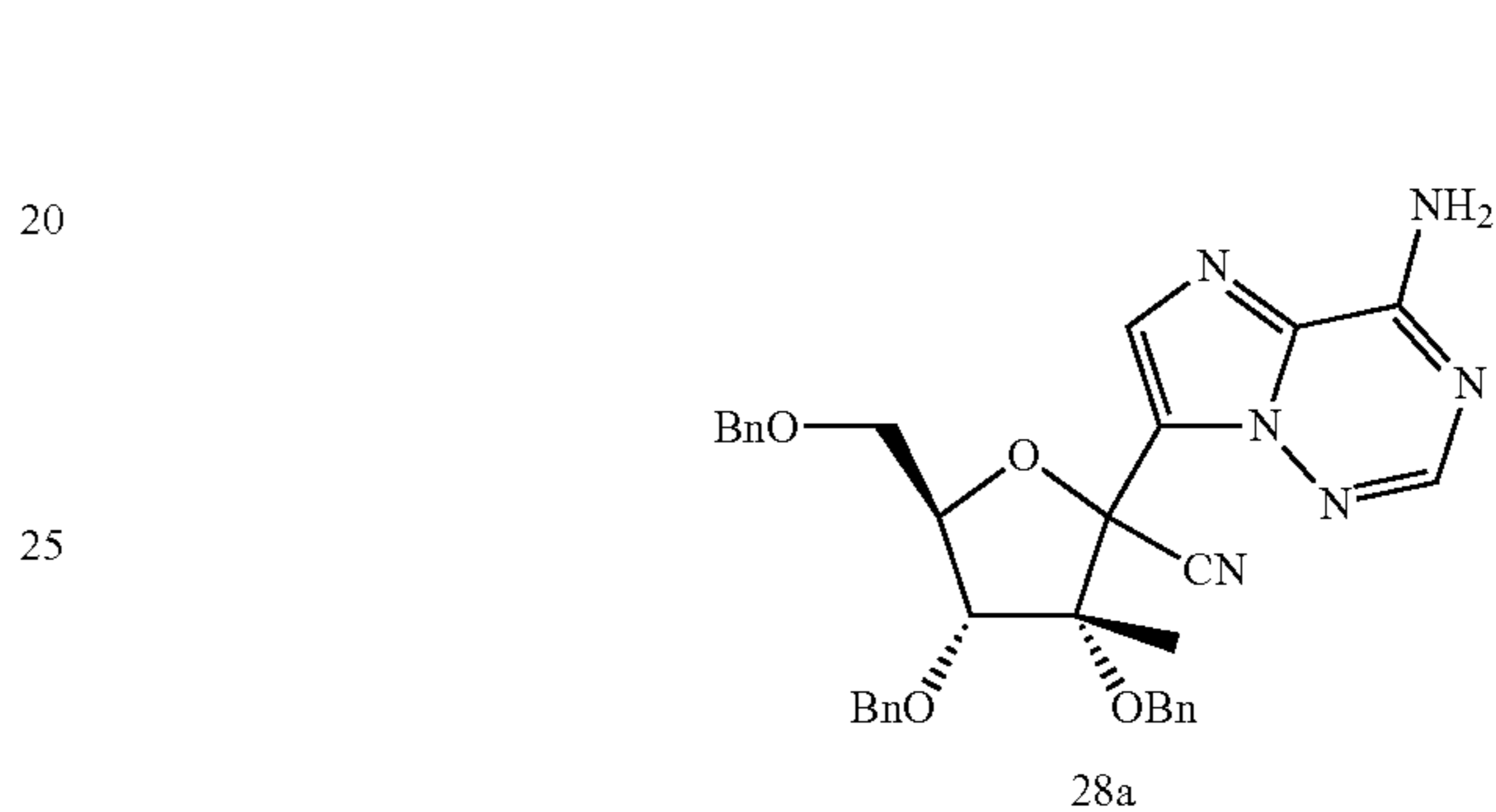
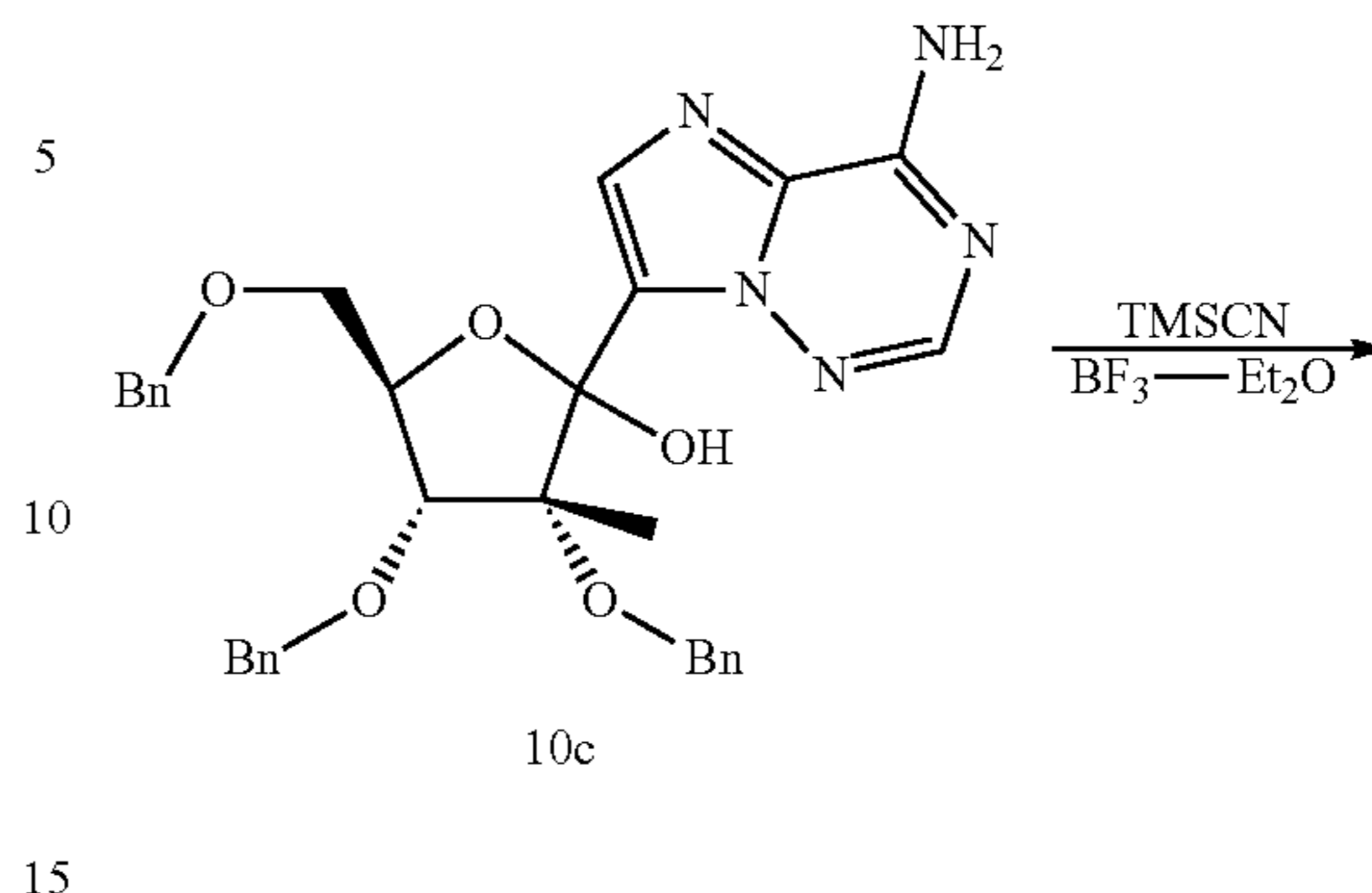
Compound 27



A solution of Compound 26 in DMSO is treated with about 3 mole equivalents of potassium t-butoxide for about 15 min to 24 hours. The reaction is quenched with 1N HCl and Compound 27 is isolated by reverse-phase HPLC.

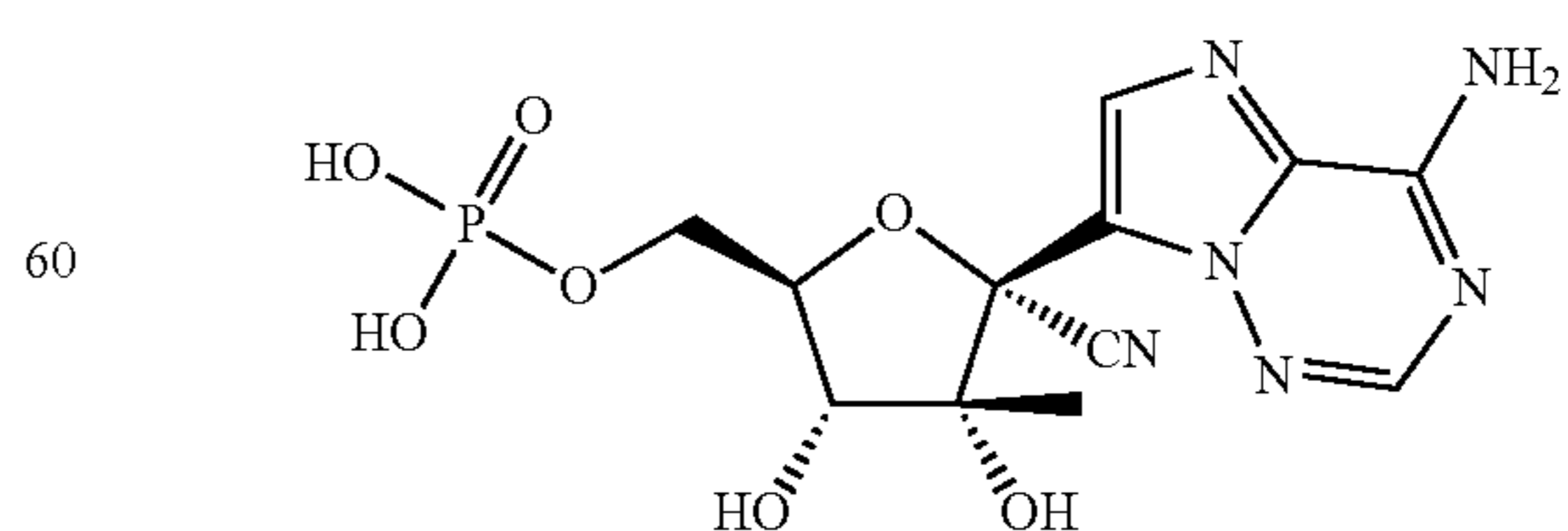
114

Compound 28



Compound 28 is prepared in the same manner as Compound 5 but using Compound 10c as a starting material.

Compound 29

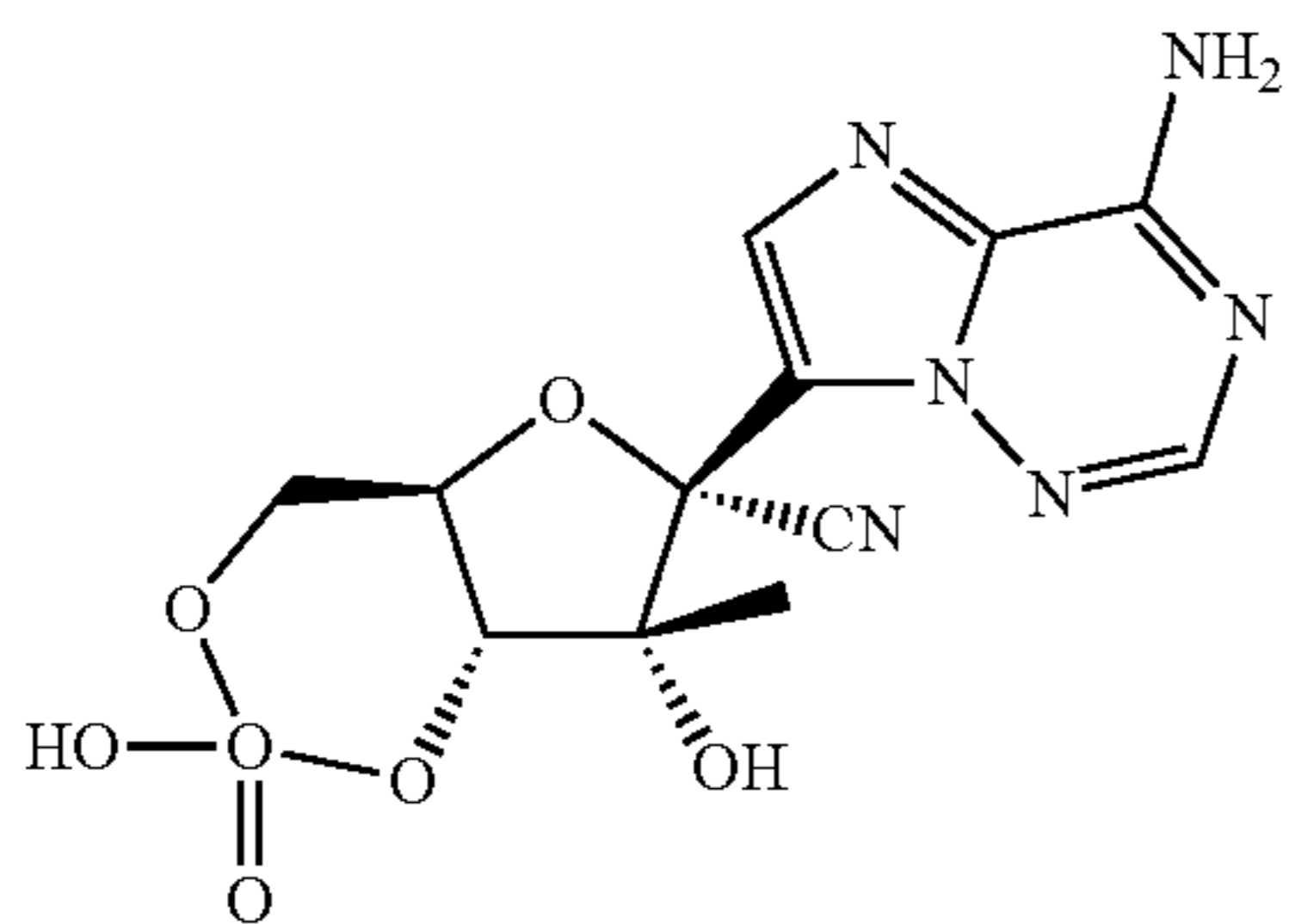


Compound 29 is prepared in the same manner as Compound 17 using Compound 28 as a starting material.

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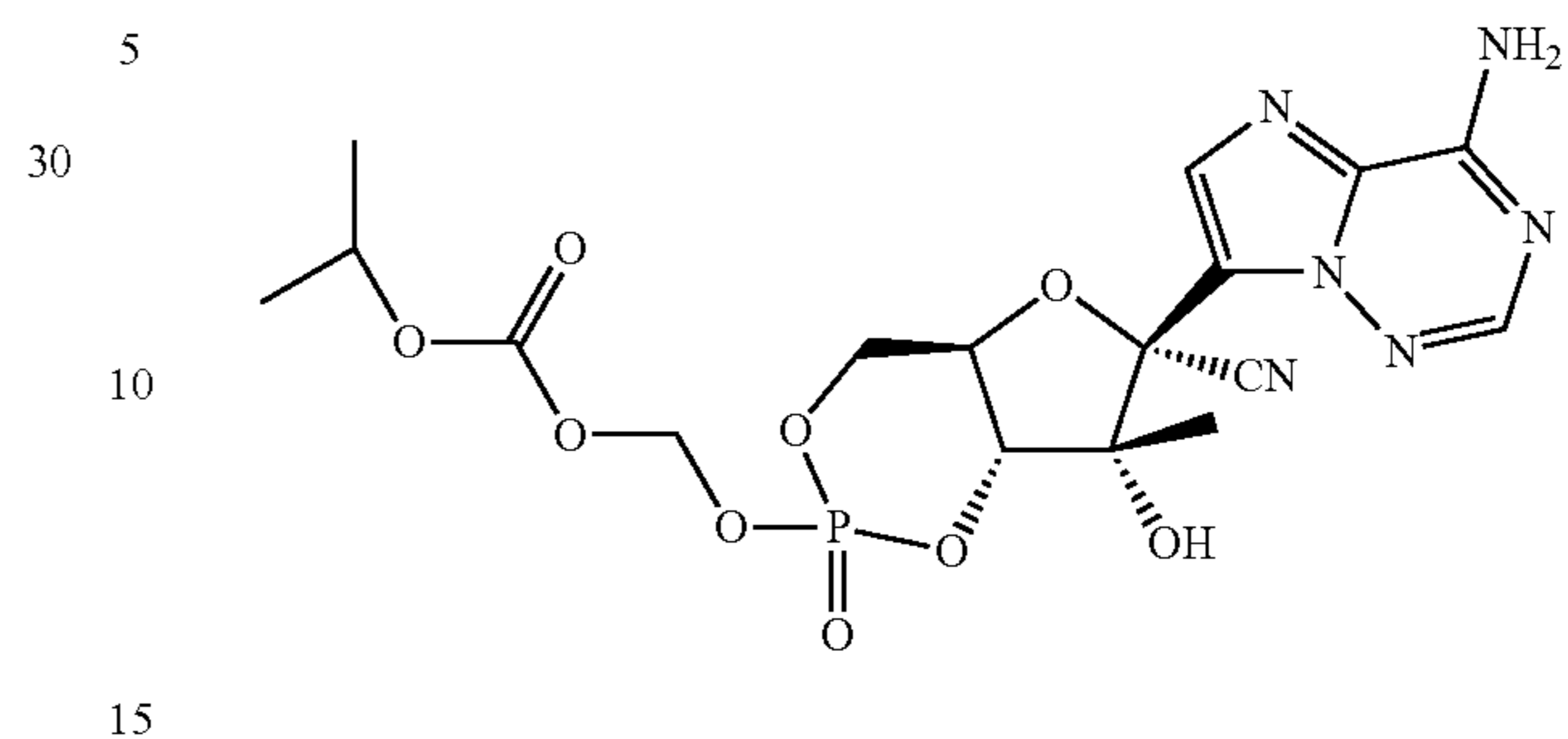
116

Compound 30



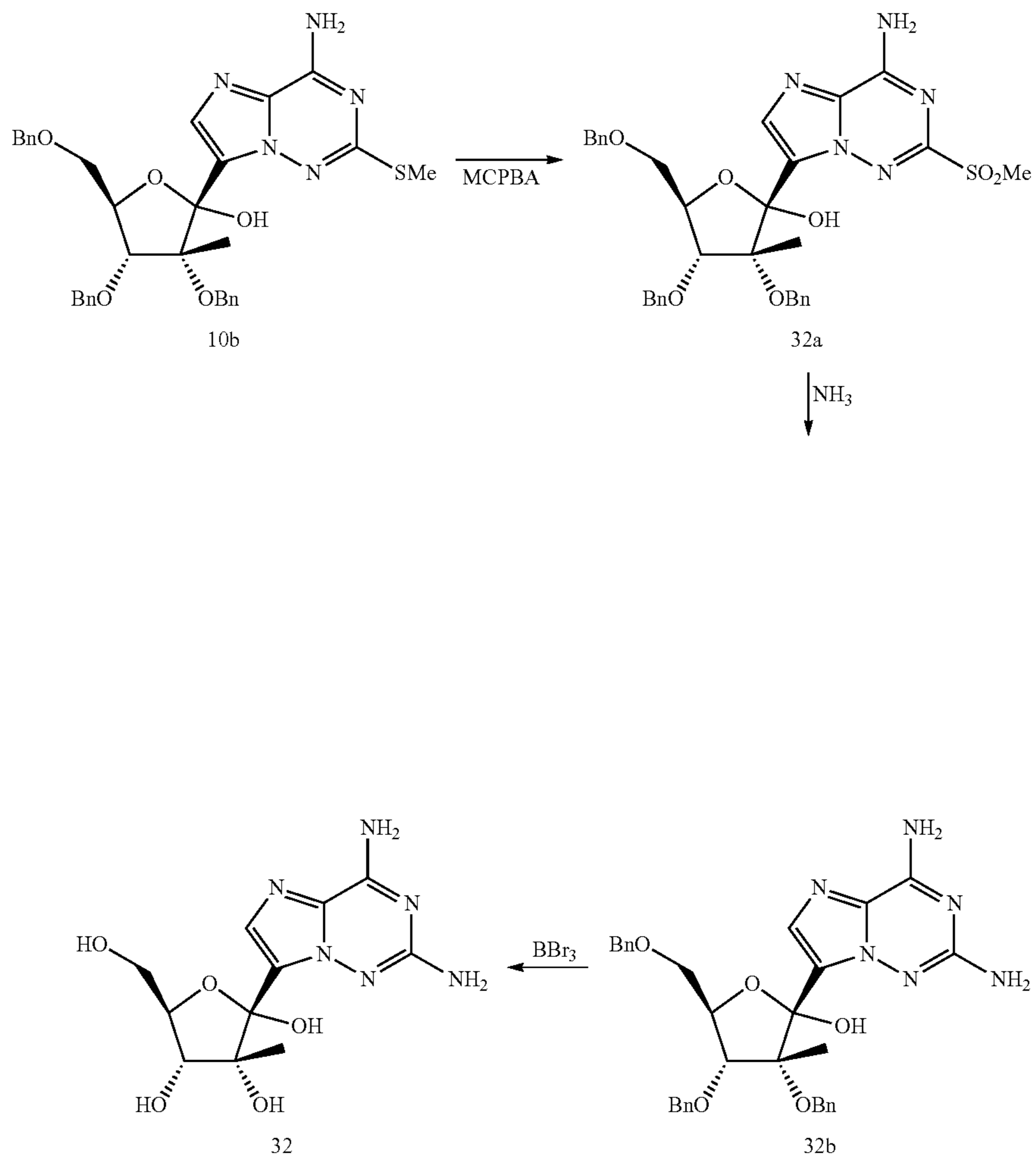
Compound 30 is prepared by treating Compound 29 with about one to about five equivalents of DCC in pyridine and heating the reaction to reflux for about one to about 24 hours. Compound 30 is isolated by conventional ion exchange and reverse-phase HPLC.

Compound 31



A solution of about 0.4 mmol of Compound 30 in about 10 mL of DMF is treated with about 0.8 mmol of DIPEA and about 0.8 mmol of chloromethyl isopropyl carbonate (WO2007/027248). The reaction is heated to about 25 to about 80° C. for about 15 min to about 24 hours. The solvent is removed under vacuum and the residue is purified by HPLC to give Compound 31.

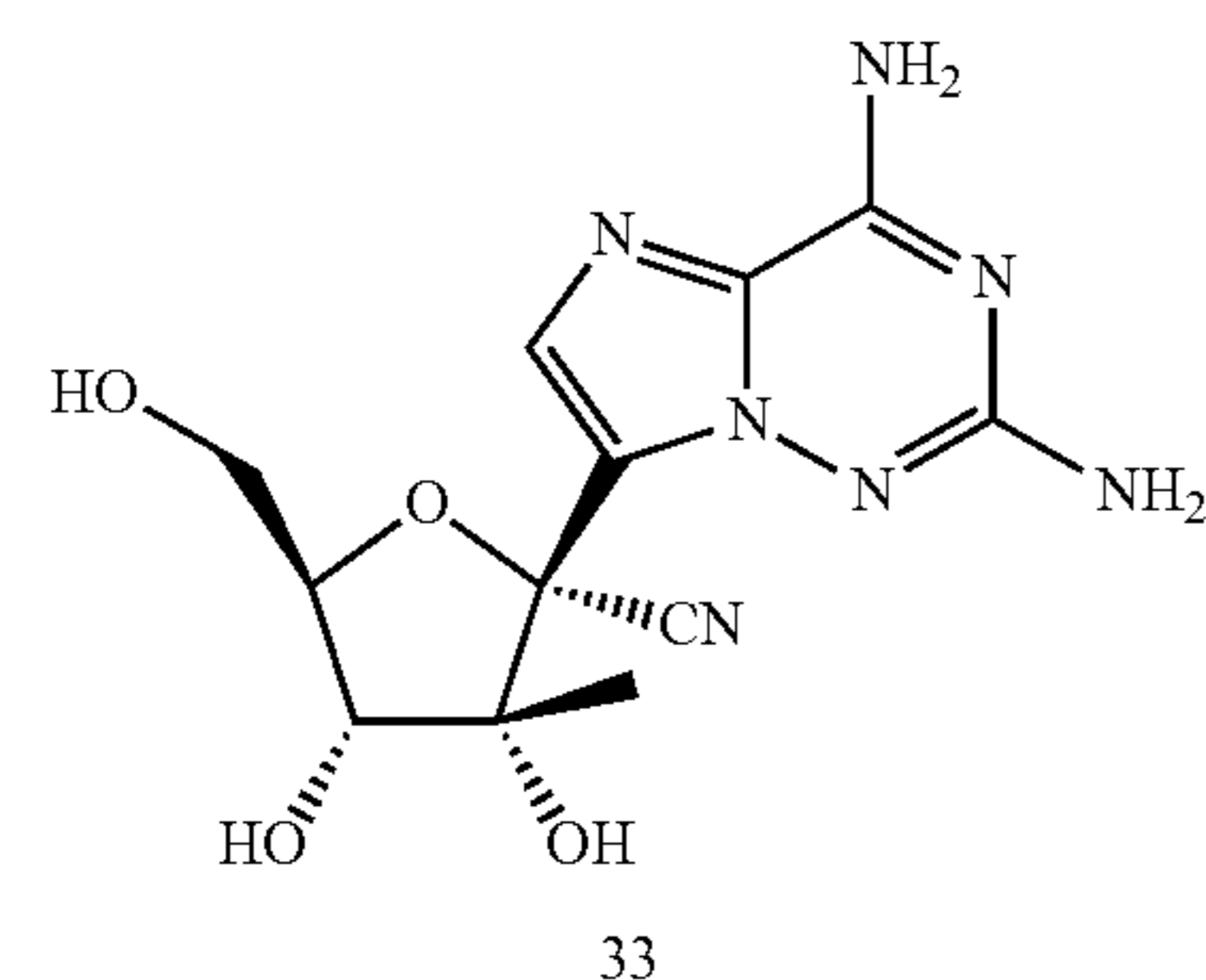
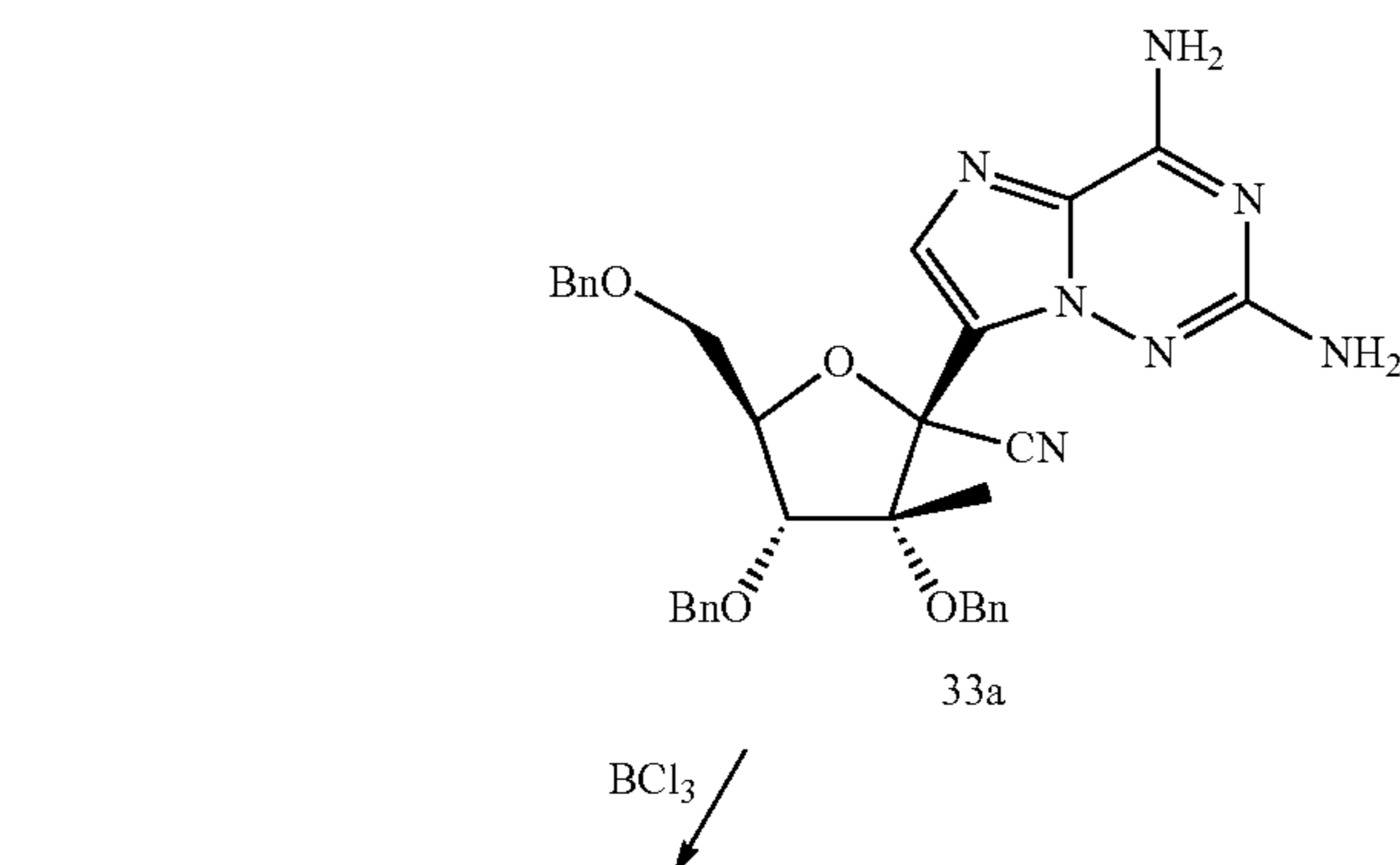
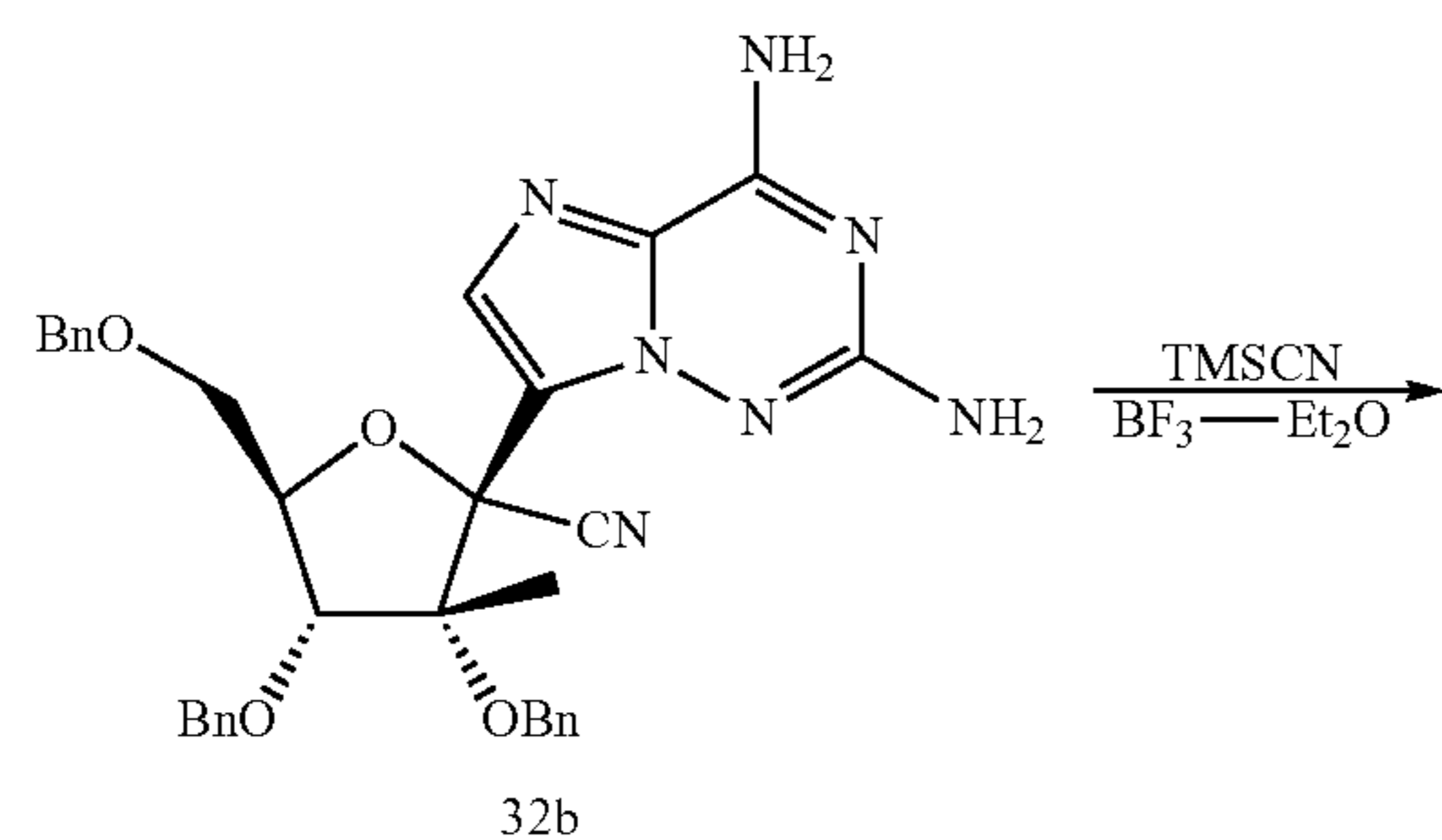
Compound 32



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Compound 10b is dissolved in DCM and treated with about two to about four mole equivalents of MCPBA for about one to about 24 hours. The mixture is treated with saturated NaHCO_3 and the solution is extracted with EtOAc. The organic layer is washed with saturated NaHCO_3 and brine and dried over MgSO_4 . The solvent is removed in vacuo and the mixture is purified by chromatography to give 32a. Compound 32a is transferred to a steel bomb reactor, and is cooled at -78°C . Liquid ammonia is collected at -78°C and is added to the bomb reactor. The bomb reactor is tightly sealed and is warmed up to room temperature. The mixture is heated at about 50°C for about 24 h. The gas is vented and 32b is isolated by chromatography. Compound 32b is converted to Compound 32 in the same manner as for the conversion of Compound 2a to Compound 2.

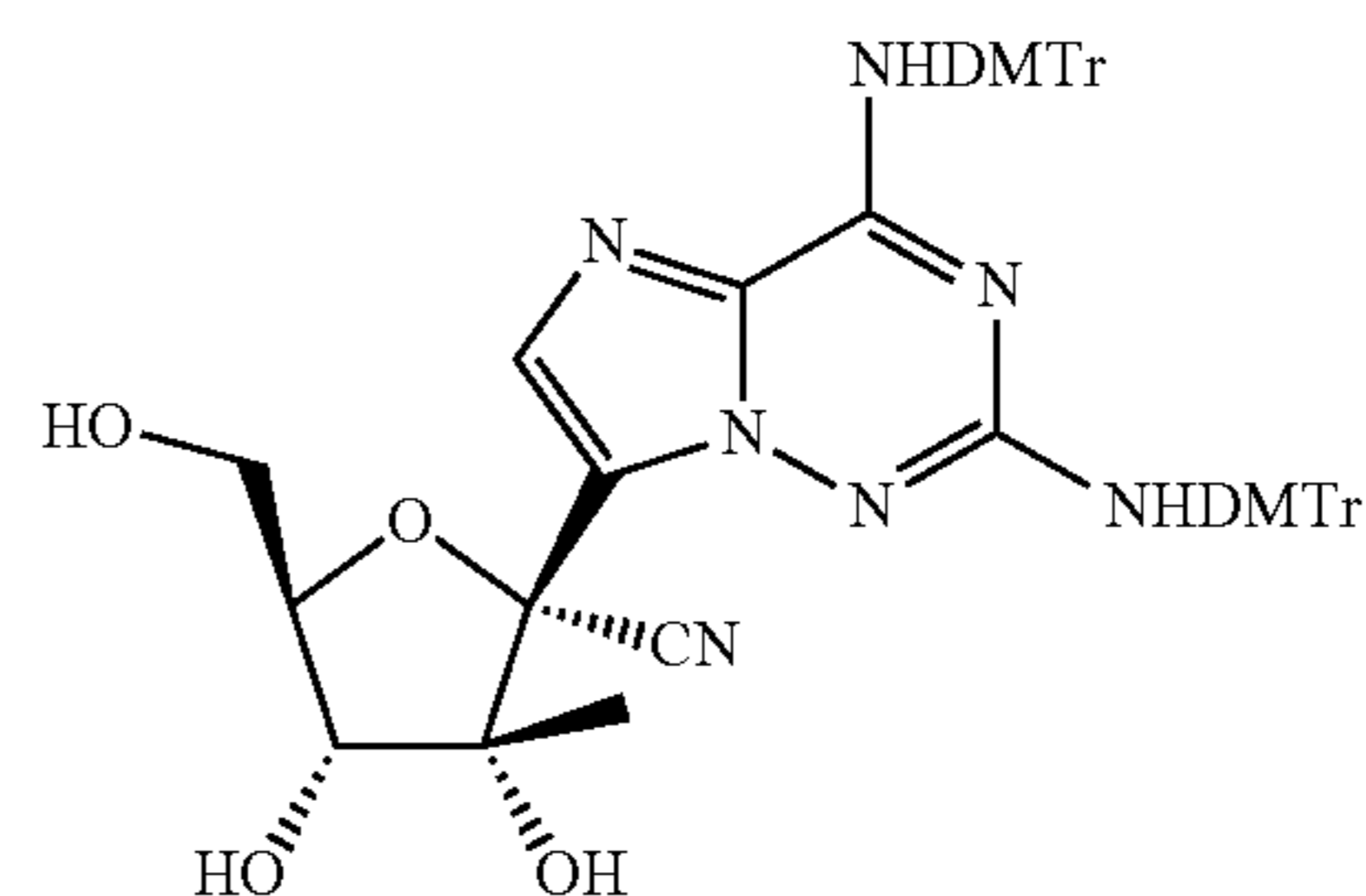
Compound 33



Compound 32b is converted to Compound 33 in the same manner as the conversion of Compound 2a to Compound 5.

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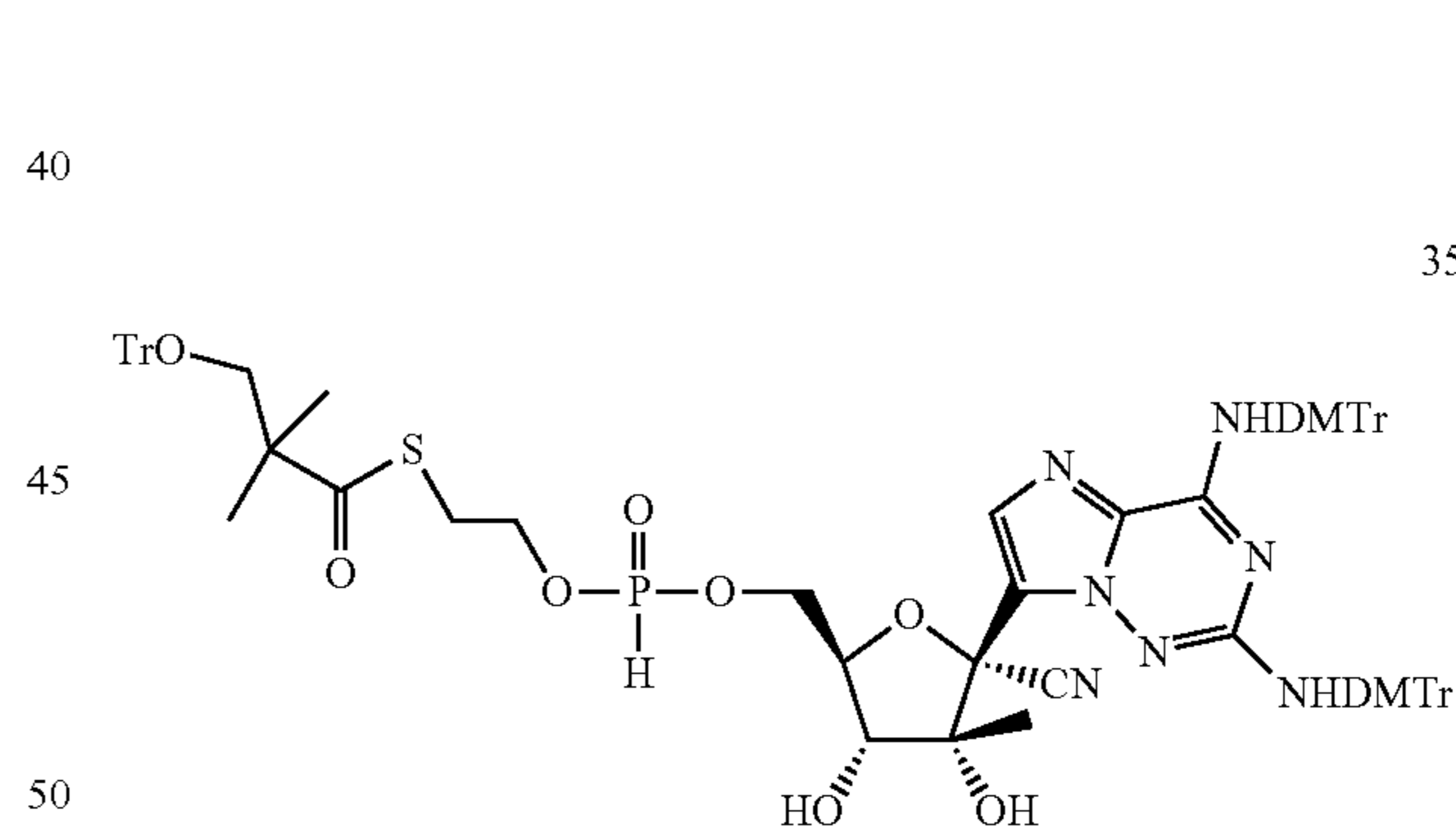
Compound 34



34

Compound 33 (about 0.22 mmol) is dissolved in anhydrous pyridine (about 2 mL) and chlorotrimethylsilane (about 0.17 mL) is added. The mixture is stirred at about 0 to about 25°C for about one to about 24 hours. Additional chlorotrimethylsilane (about 0.1 mL) is added and the reaction is stirred for about one to about 24 hours. 4,4'-Dimethoxytrityl chloride (about 0.66 mmol) and DMAP (about 0.11 to about 0.22 mmol) is sequentially added. The mixture is stirred for about one to about 24 hours. A solution of TBAF (1.0 M, about 0.22 mL) in THF is added and the reaction is stirred for about one to about 24 hours. The mixture is partitioned between ethyl acetate and water. The ethyl acetate layer is dried and concentrated. The residue is purified chromatography to afford Compound 34 which may be a mixture of mono- and di-dimethoxytritylated compounds.

Compound 35

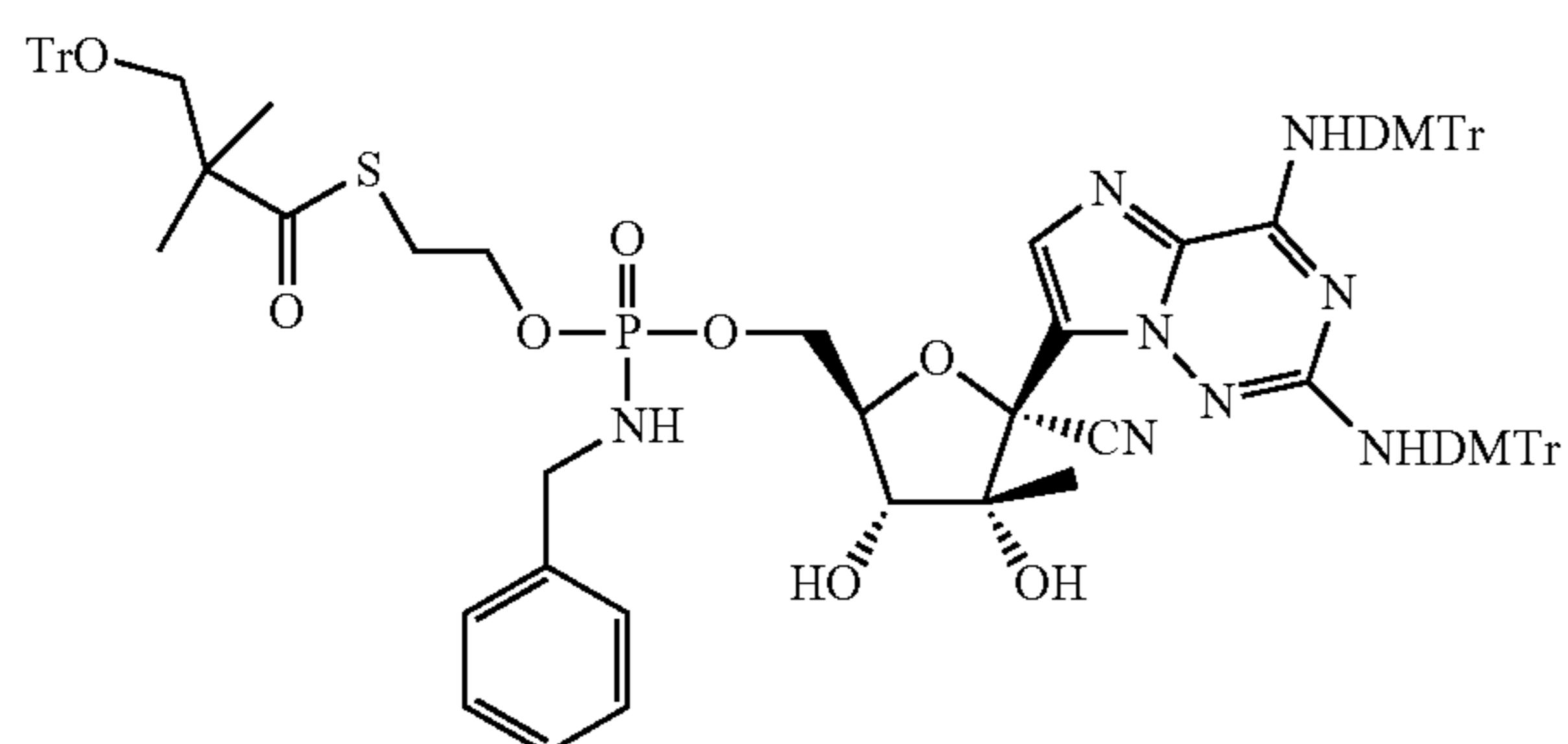


35

A mixture of about 1.25 mmol of Compound 34 and about 1.9 mmol of triethylammonium 2-(2,2-dimethyl-3-(trityloxy)propanoylthio)ethyl phosphonate (WO2008082601) is dissolved in anhydrous pyridine (about 19 mL). Pivaloyl chloride (about 2.5 mmol) is added dropwise at about -30 to about 0°C and the solution is stirred for about 30 min to about 24 hours. The reaction is diluted with methylene chloride and is neutralized with aqueous ammonium chloride (about 0.5M). The methylene chloride phase is evaporated and the residue is dried and is purified by chromatography to give Compound 35 which may be a mixture of mono- and di-dimethoxytritylated compounds.

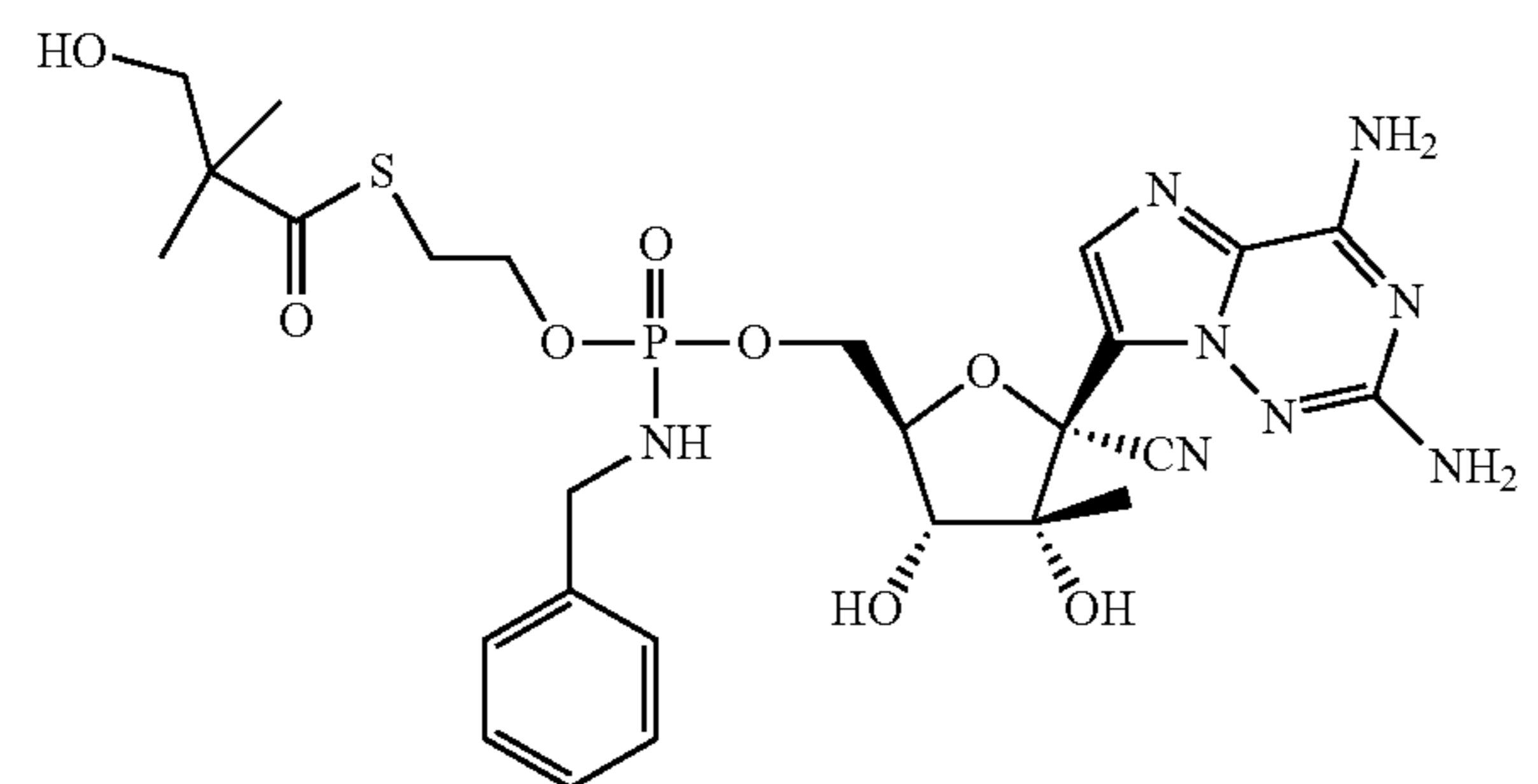
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Compound 36



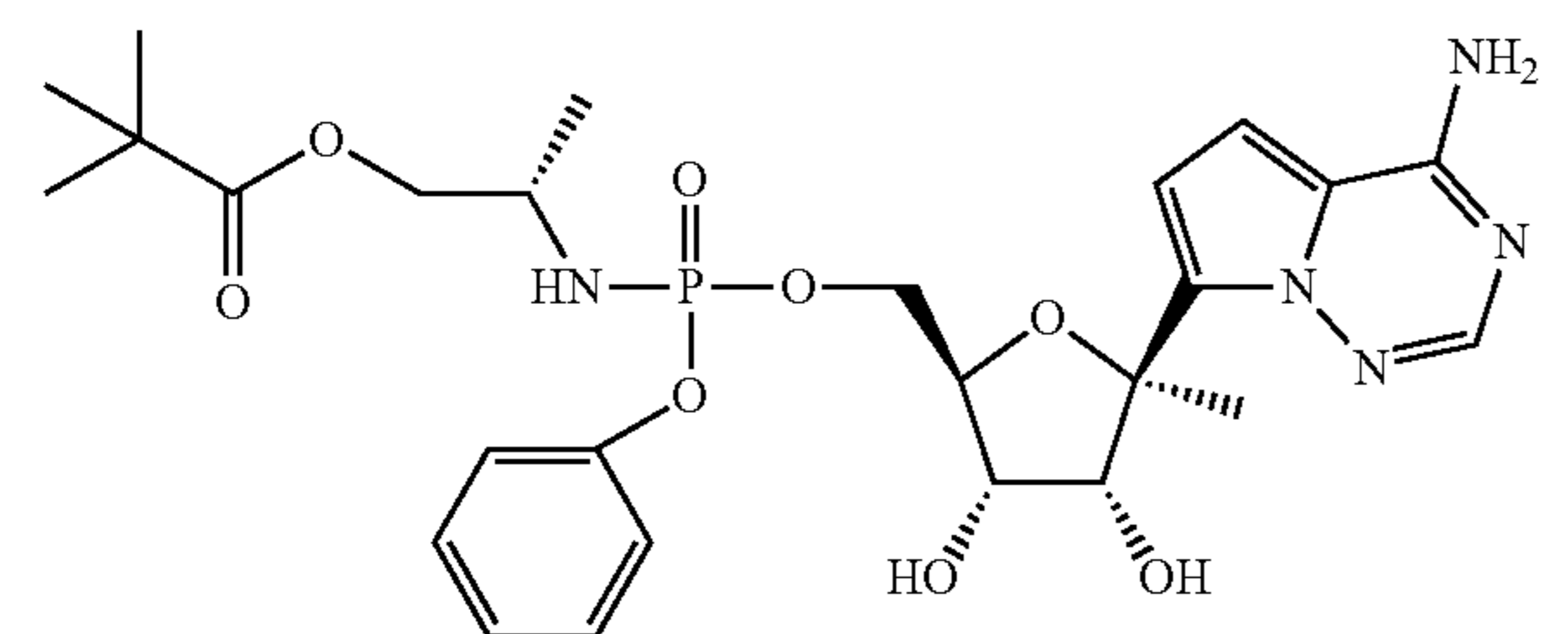
To a solution of about 0.49 mmol of Compound 35 in anhydrous carbon tetrachloride (about 5 mL) is added dropwise benzylamine (about 2.45 mmol). The reaction mixture is stirred for about one to about 24 hours. The solvent is evaporated and the residue is purified by chromatography to give Compound 36 which may be a mixture of mono- and di-dimethoxytritylated compounds.

Compound 37



A solution of about 2 mmol of Compound 36 in methylene chloride (about 10 mL) is treated with an aqueous solution of trifluoroacetic acid (90%, about 10 mL). The reaction mixture is stirred at about 25 to about 60° C. for about one to about 24 hours. The reaction mixture is diluted with ethanol, the volatiles are evaporated and the residue is purified by chromatography to give Compound 37.

Compound 38

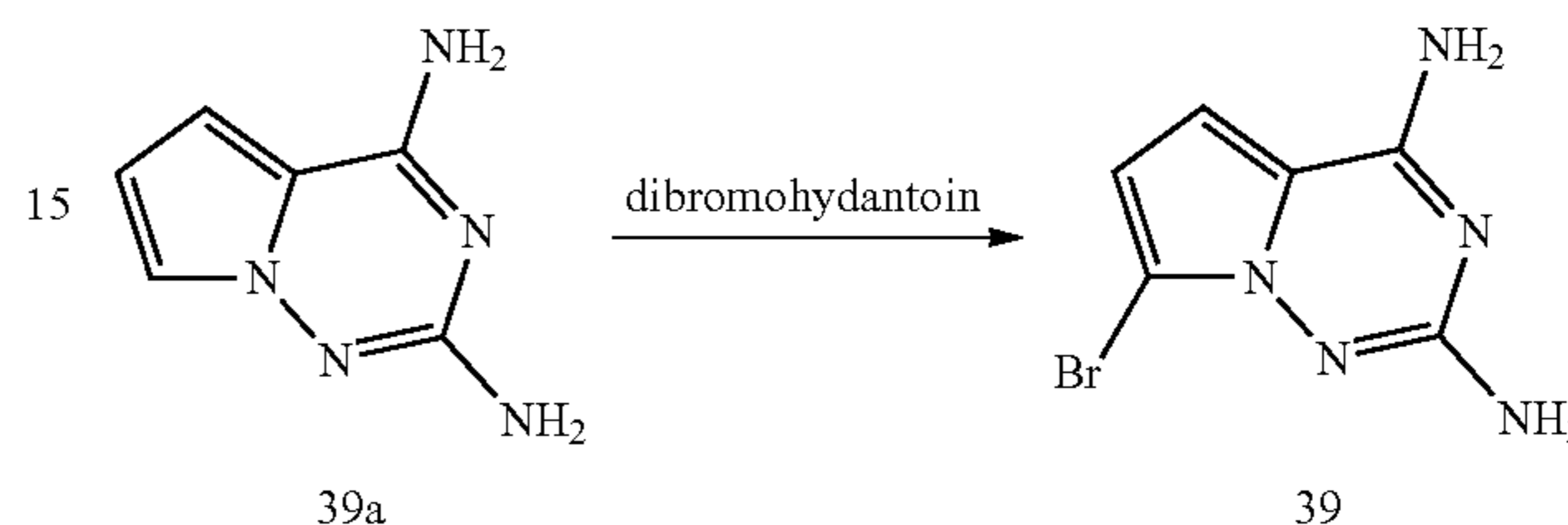


About 90 mM Compound 14 in THF is cooled to about -78° C. and about 2.2 to about 4.4 equivalents of t-butylmagnesium chloride (about 1 M in THF) is added. The mixture is warmed to about 0° C. for about 30 min and is

120

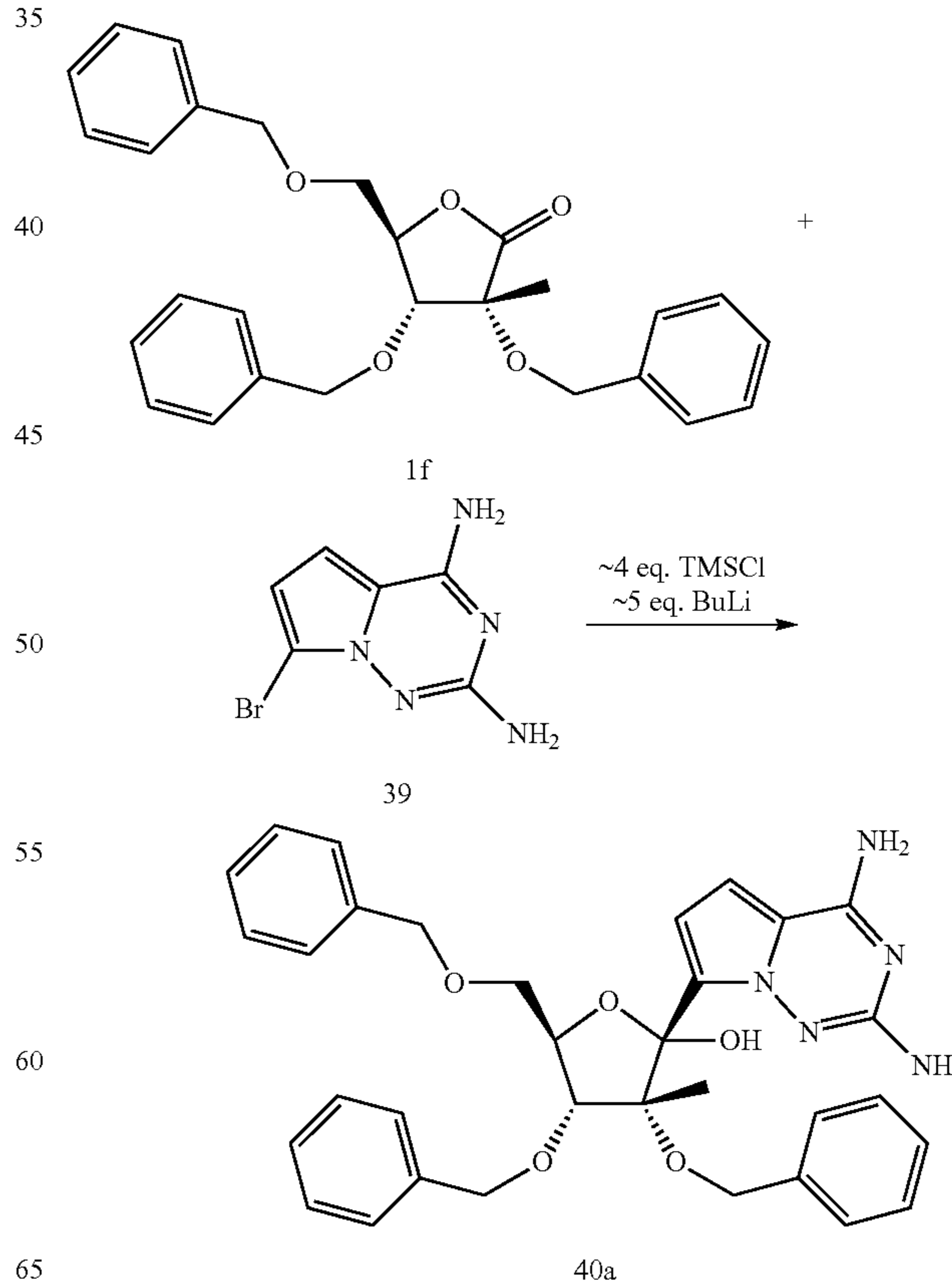
again cooled to about -78° C. A solution of (2S)-2-[[chloro(1-phenoxy)phosphoryl]amino]propyl pivaloate (WO2008085508) (1 M in THF, about 2 equivalents) is added dropwise. The cooling is removed and the reaction is stirred for about one to about 24 hours. The reaction is quenched with water and the mixture is extracted with ethyl acetate. The extracts are dried and evaporated and the residue purified by chromatography to give Compound 38.

Compound 39



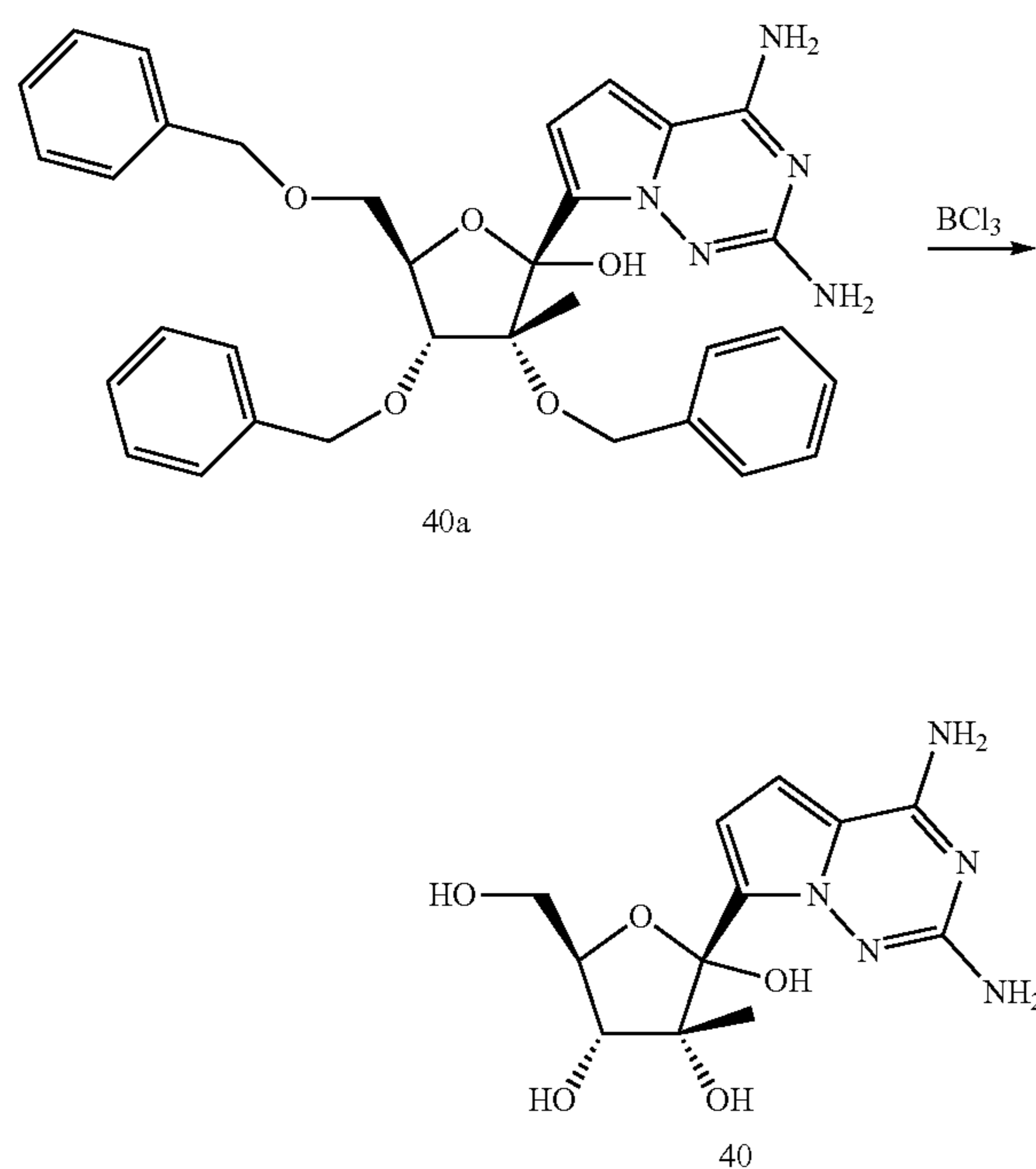
A solution of about one part Compound 39a (Patil, et al.; Journal of Heterocyclic Chemistry 1994, 31(4), 781-6) in anhydrous DMF is cooled to about -20° C. and about 0.5 parts of 1,3-dibromo-5,5-dimethylhydantoin is added in portions. After about one to about 24 hours, a saturated aqueous sodium bisulfate solution is added and the solids are collected by filtration. The solids are partitioned between ethyl acetate and dilute aqueous sodium carbonate. The organic phase is washed with dilute sodium carbonate then dried and concentrated to give Compound 39.

Compound 40



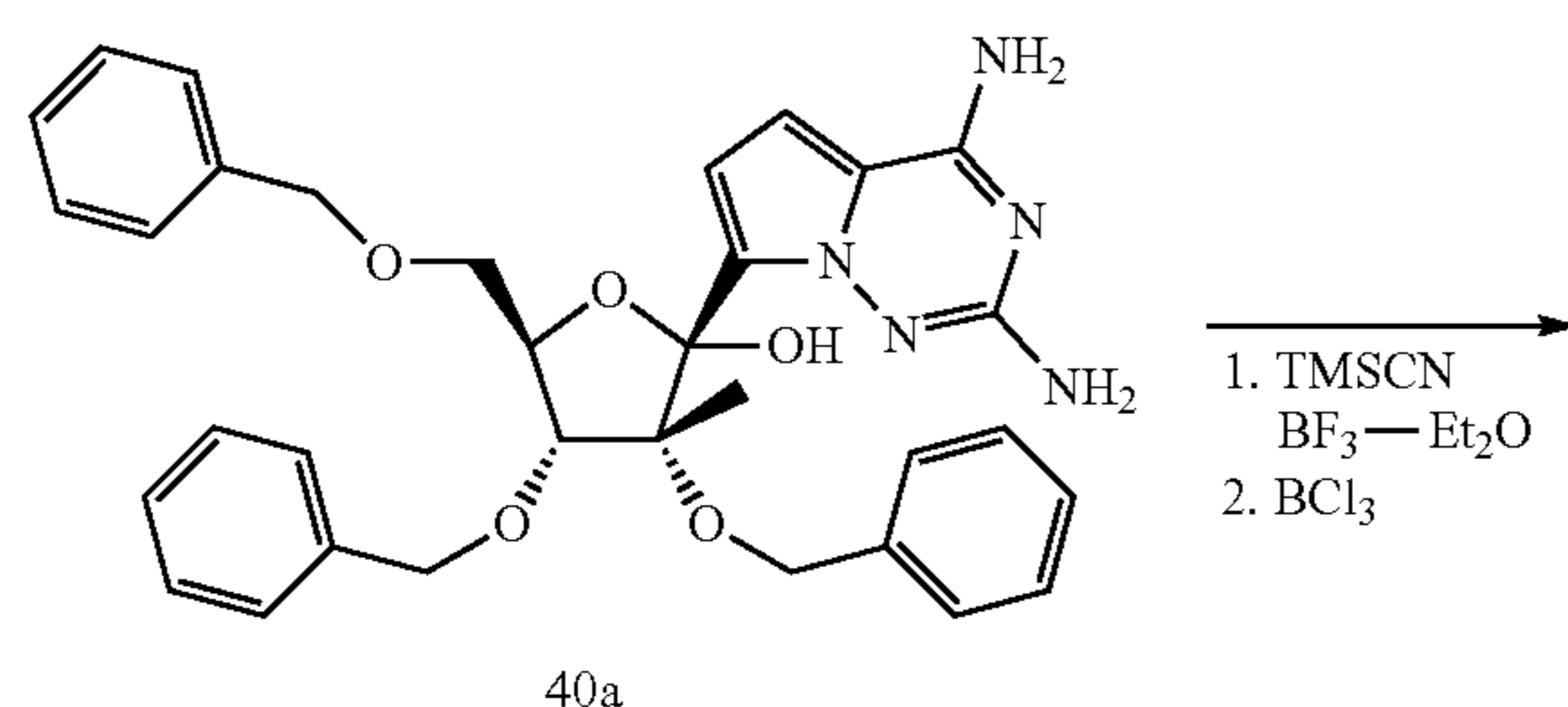
121

A solution of about one part of 39 and about four parts of trimethylsilylchloride in THF is stirred at about 20 to about 60° C. for about 30 min to about six hours. The solution is cooled to about -70 to about -100° C. and a solution of about five parts of butyllithium in hexanes is added. After about 30 min. to about three hours, the reaction is allowed to warm to about 0° C. over about three hours. The reaction is quenched with saturated NaHCO₃ and the mixture is extracted with ether. The ether extracts are washed with brine, dried, and the solvent evaporated to give 40a which may be further purified by chromatography.



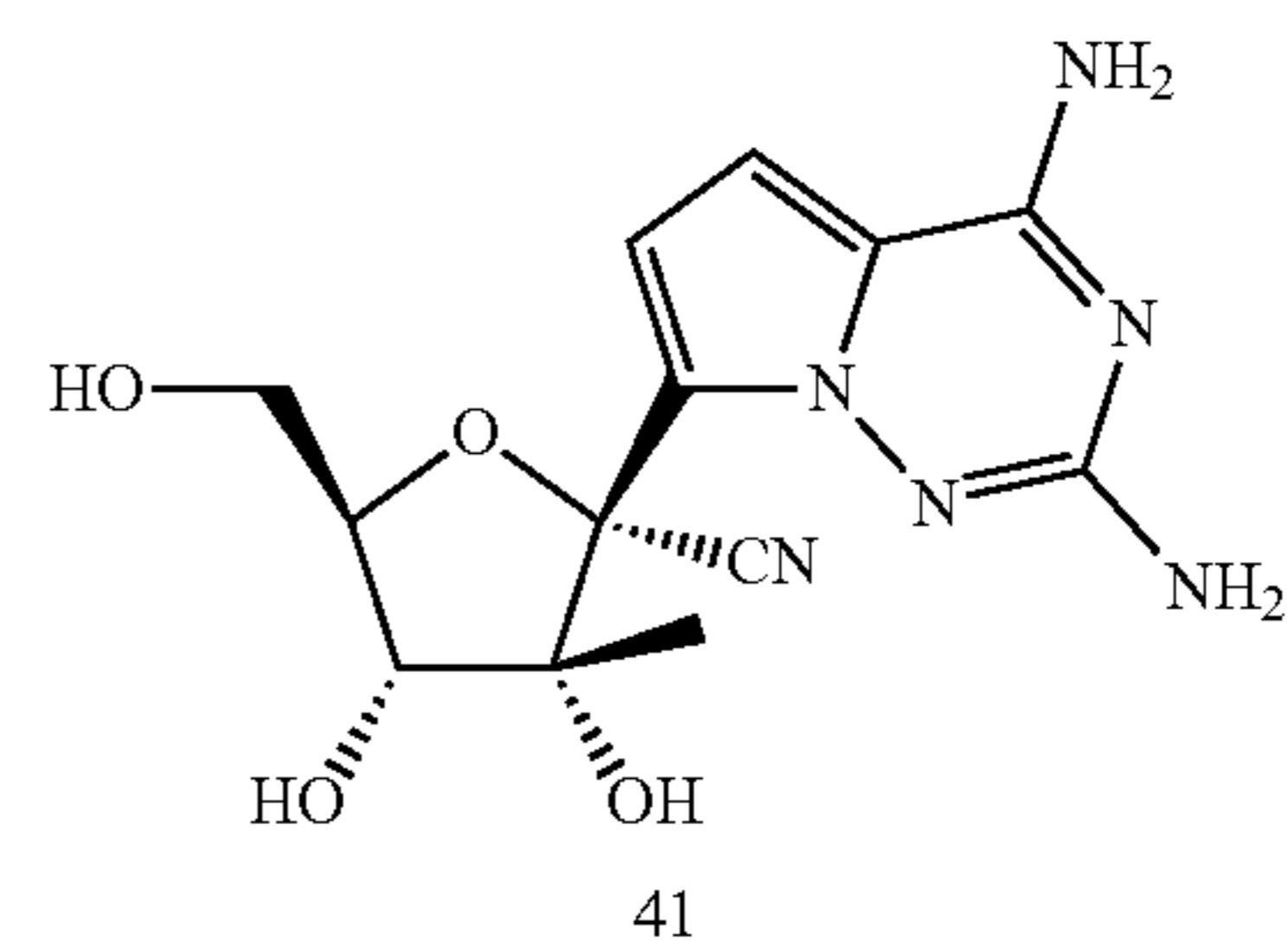
A solution of one part of 40a in dichloromethane is cooled to about -100 to about -70° C. A 1.0 M solution of BCl₃ in dichloromethane (about 10 to 20 parts) is added and the reaction is stirred for about 30 min. to about 3 hours. A mixture of pyridine and methanol (about 1:2) is then added to quench the reaction. The resulting mixture is slowly warmed to room temperature and concentrated. The residue is suspended in about 27% ammonium hydroxide and concentrated. This process is repeated twice. The residue is re-dissolved in methanol and concentrated. This process is repeated once. The residue is purified by RP-HPLC to give 40.

Compound 41



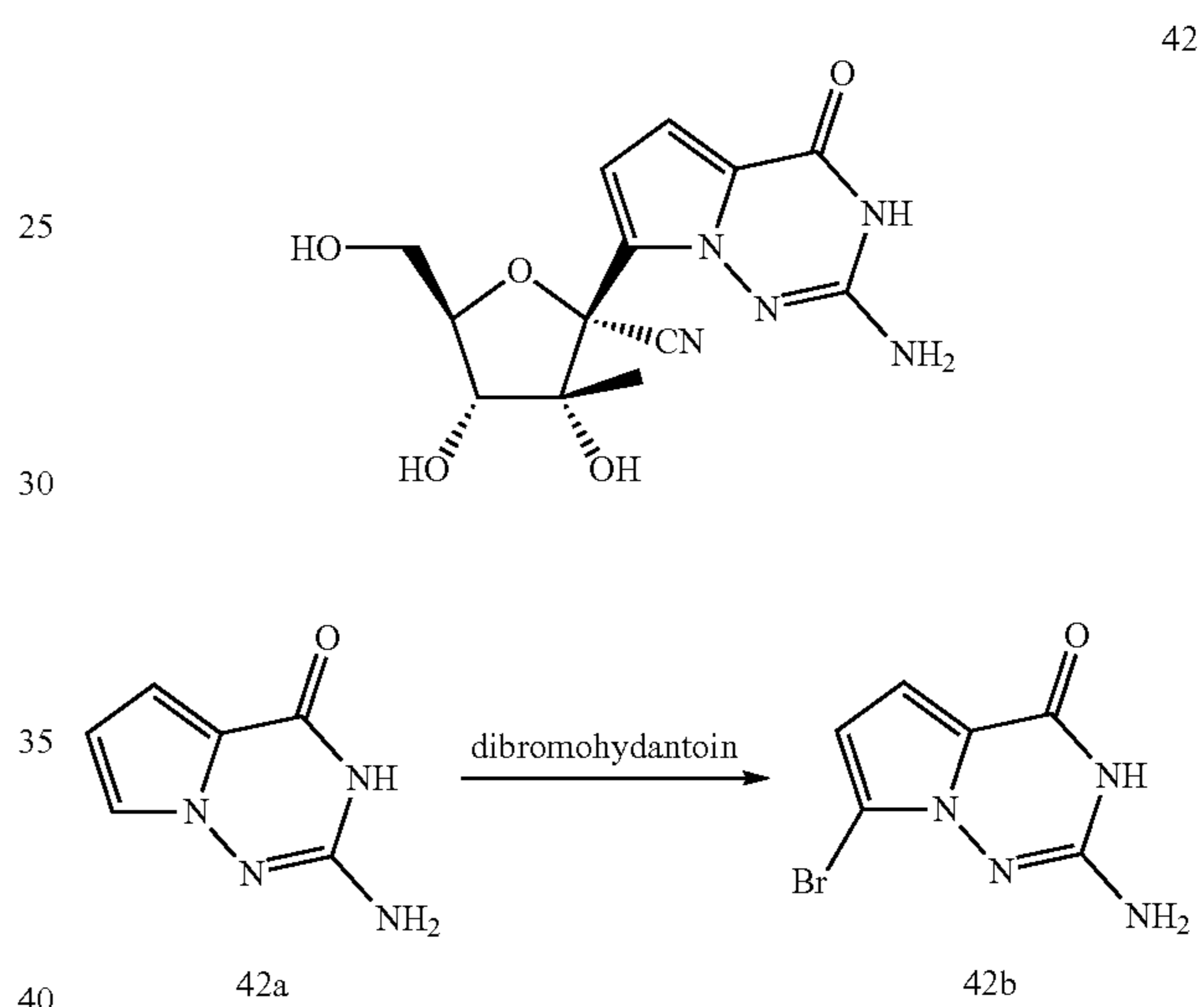
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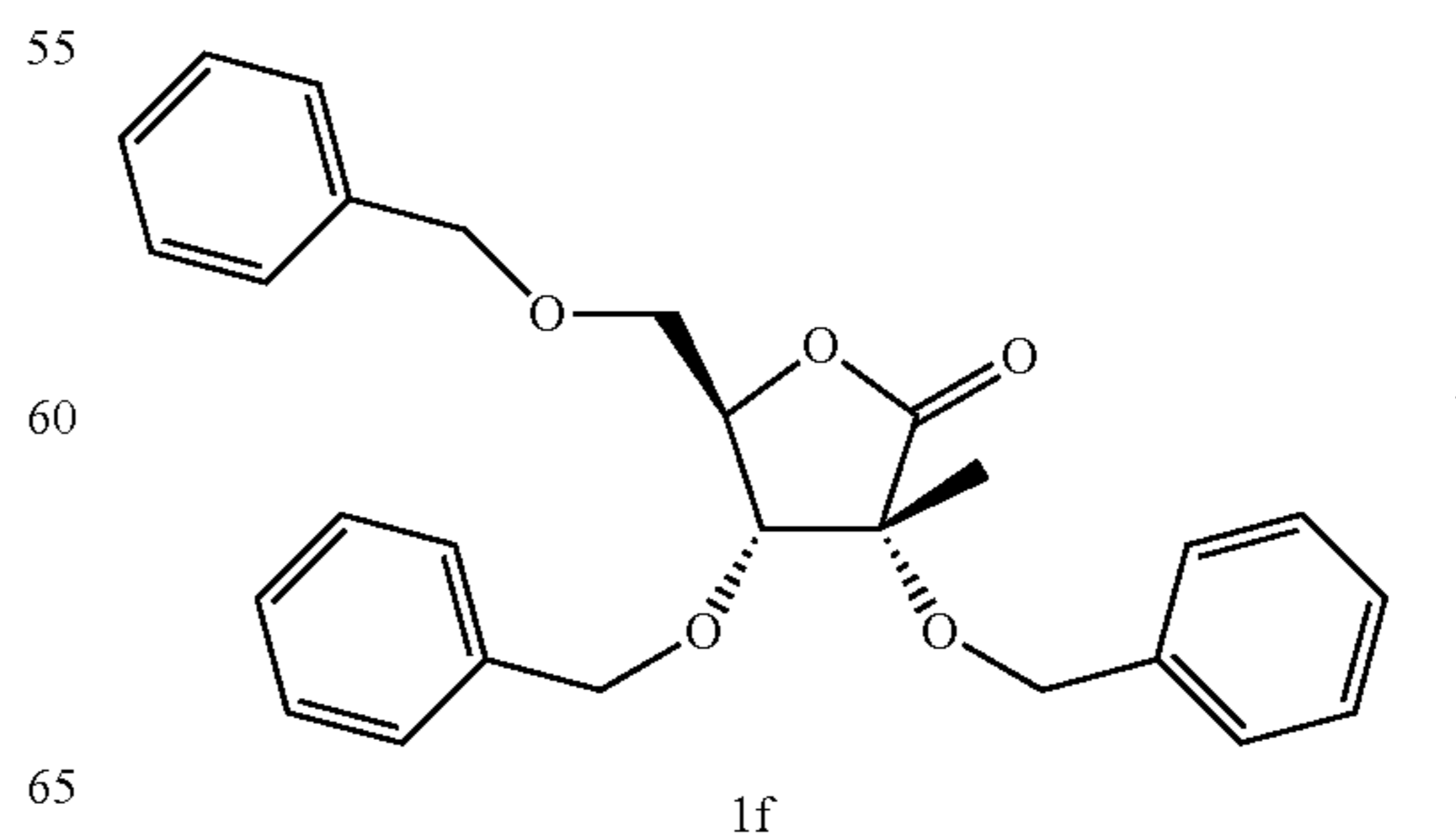


Compound 41 may be prepared from Compound 40a in the same manner as Compound 5 was prepared from Compound 2a.

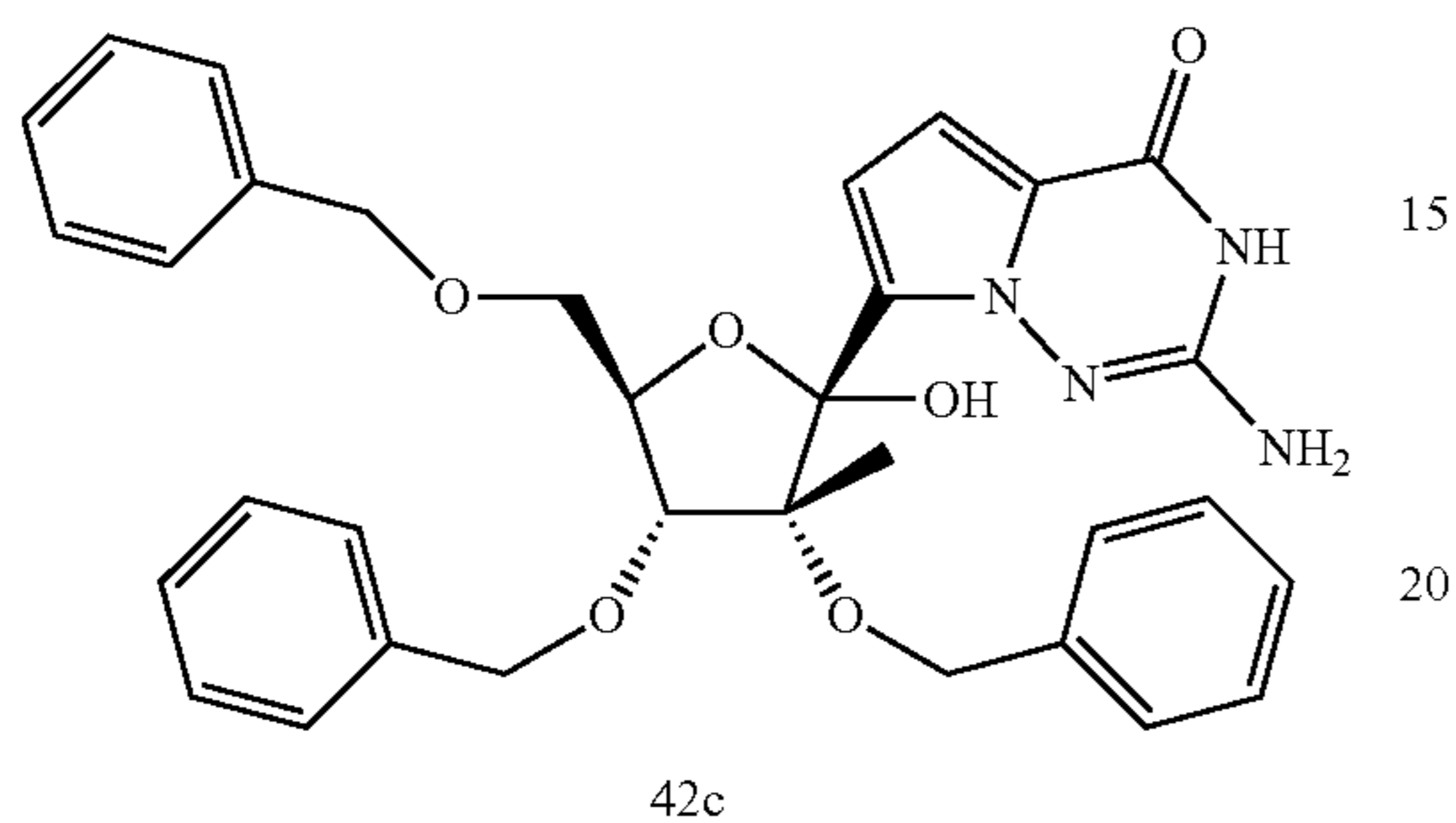
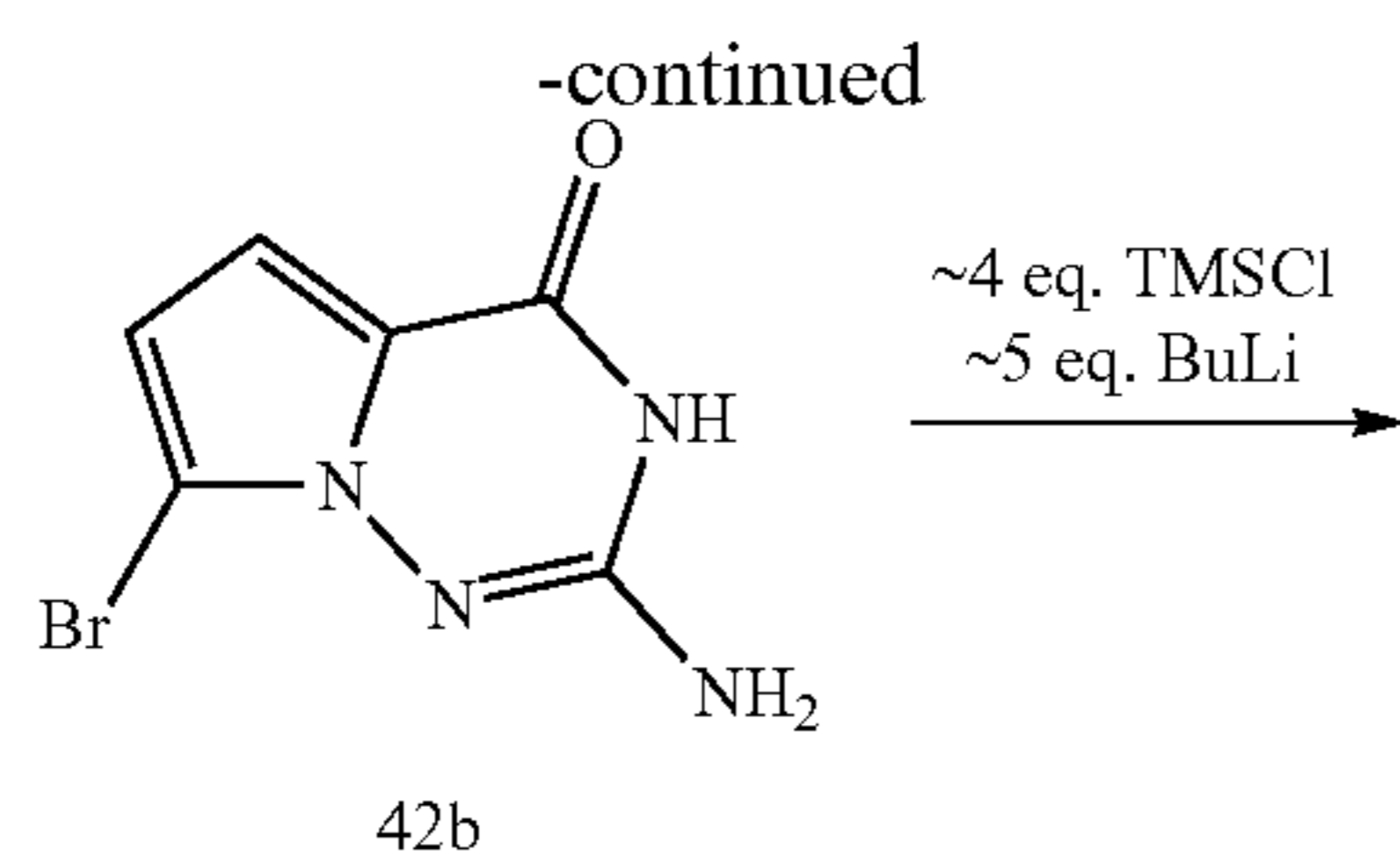
Compound 42



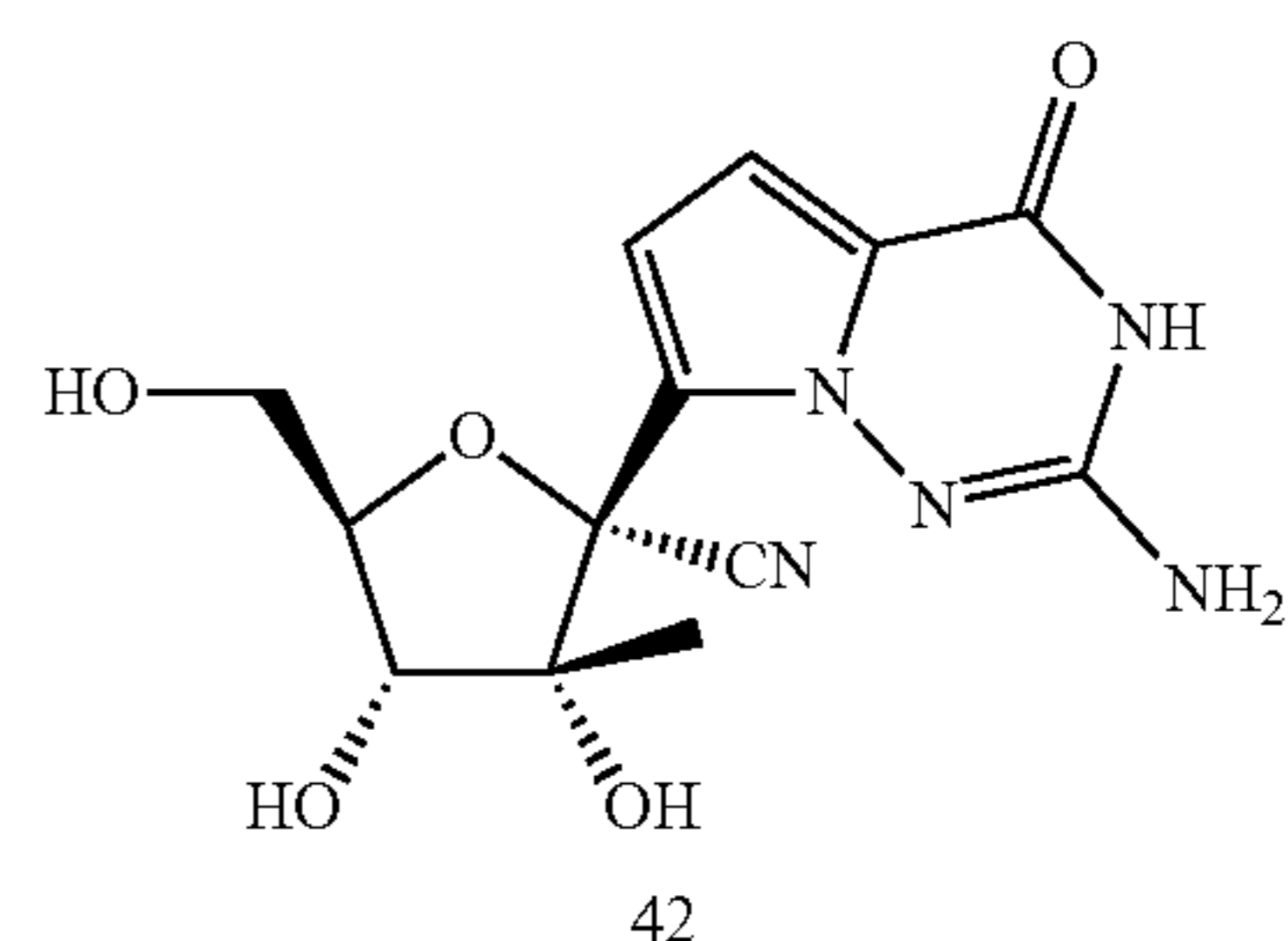
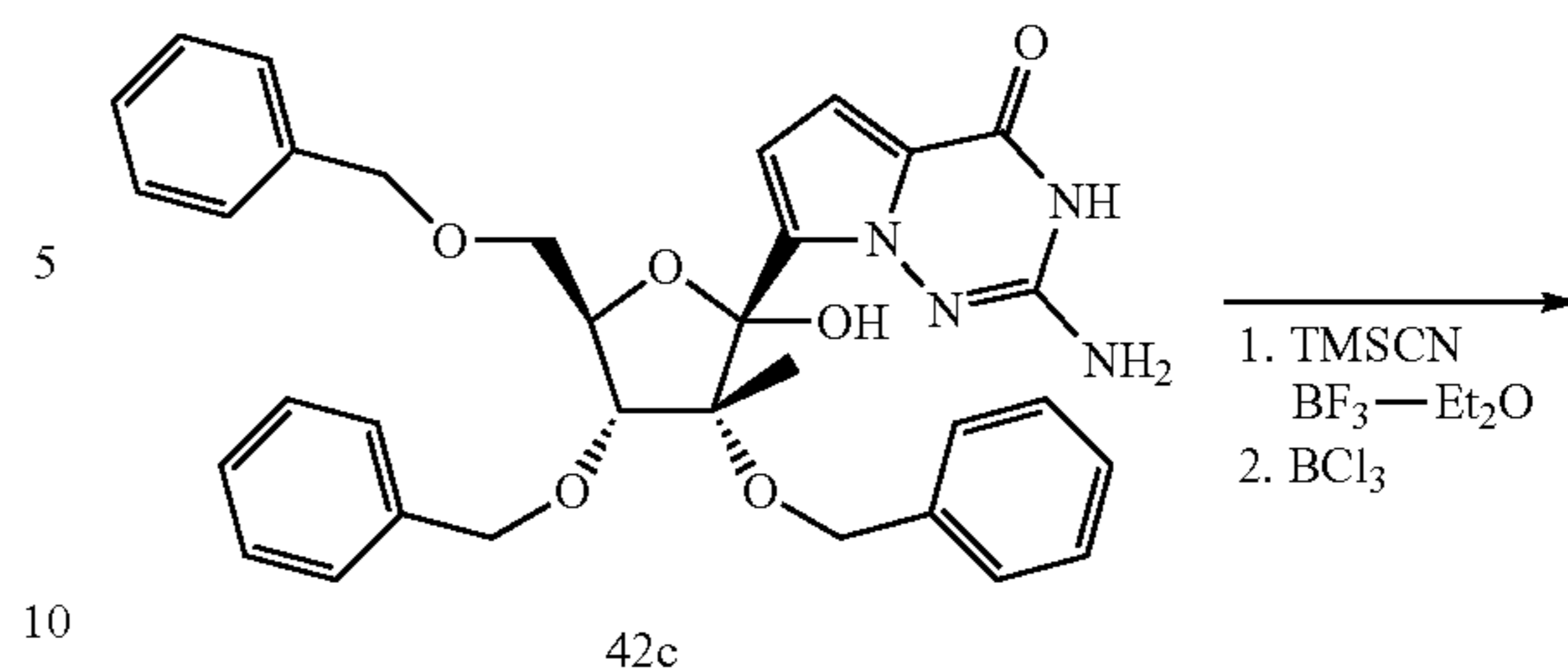
A solution of about one part Compound 42a (Patil, et al.; Journal of Heterocyclic Chemistry 1994, 31(4), 781-6) in anhydrous DMF is cooled to about -20° C. and about 0.5 parts of 1,3-dibromo-5,5-dimethylhydantoin is added in portions. After about one to about 24 hours, a saturated aqueous sodium bisulfite solution is added and the solids are collected by filtration. The solids are partitioned between ethyl acetate and dilute aqueous sodium carbonate. The organic phase is washed with dilute sodium carbonate then dried and concentrated to give Compound 42b.



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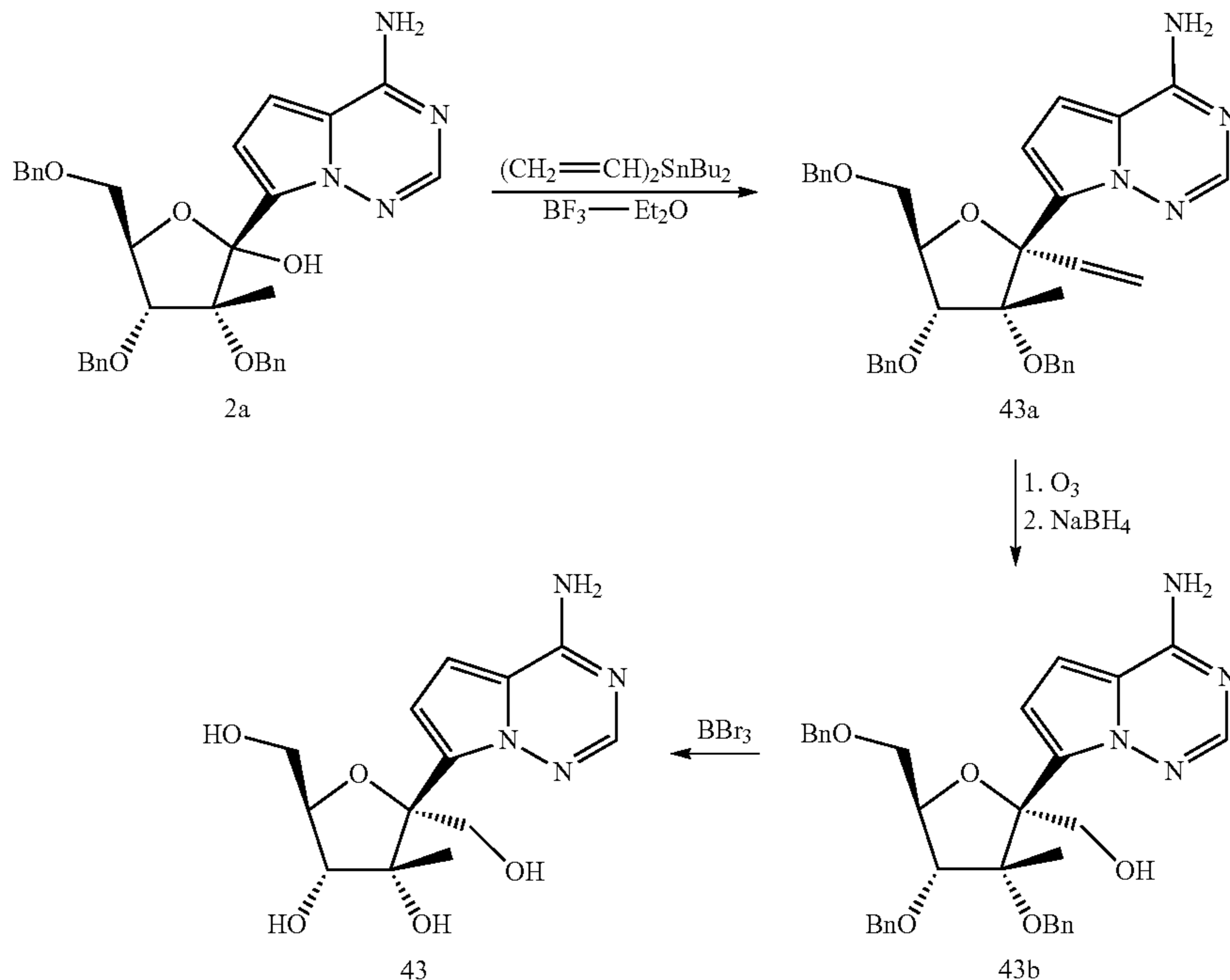
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A solution of about one part of 42b and about four parts of trimethylsilylchloride in THF is stirred at about 20 to about 60° C. for about 30 min to about six hours. The solution is cooled to about -70 to about -100° C. and a

Compound 42 may be prepared from Compound 42a in the same manner as Compound 5 was prepared from Compound 2a.

Compound 43



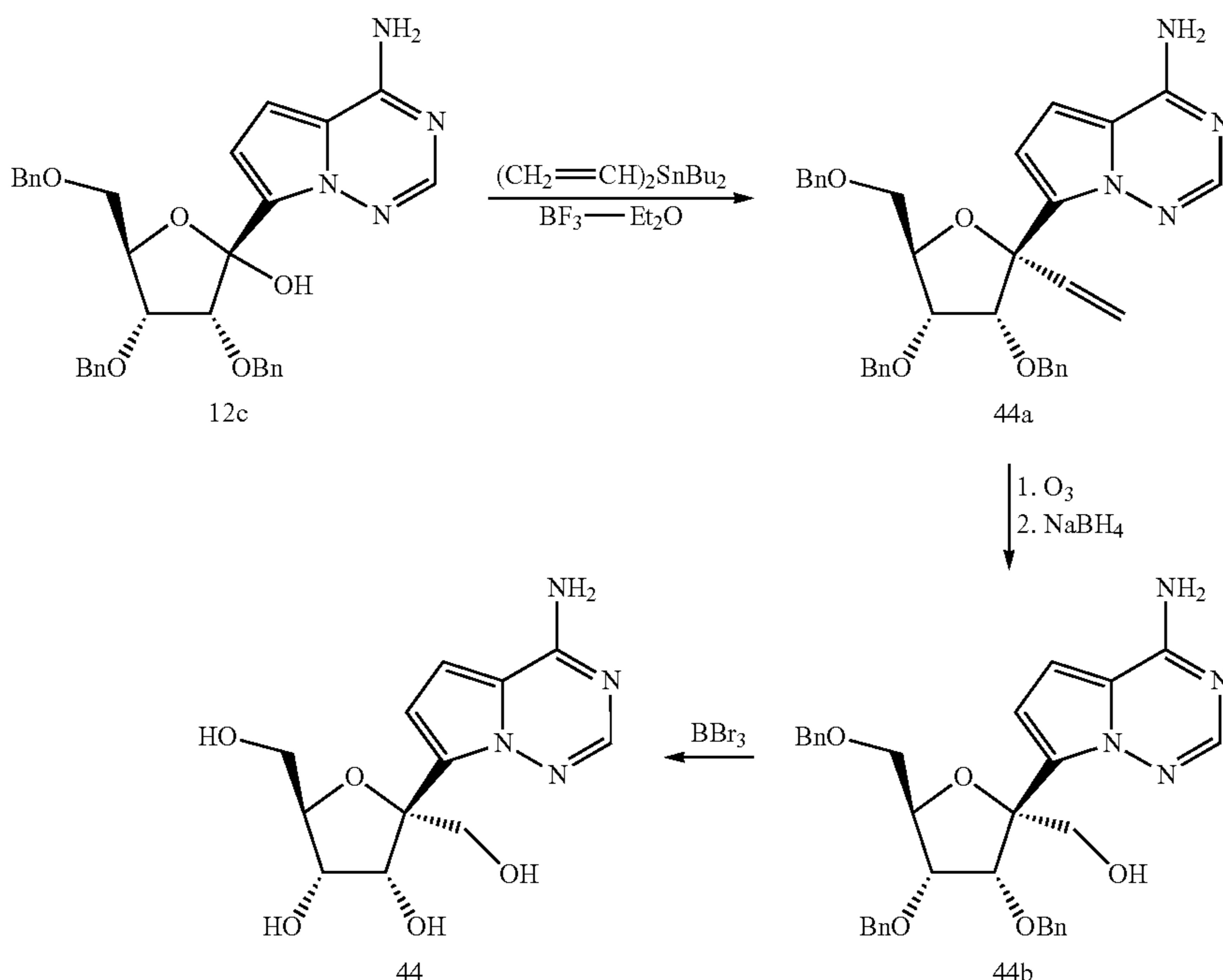
solution of about five parts of butyllithium in hexanes is added. After about 30 min. to about three hours, the reaction is allowed to warm to about 0° C. over about three hours. The reaction is quenched with saturated NaHCO₃ and the mixture is extracted with ether. The ether extracts are washed with brine, dried, and the solvent evaporated to give 42c which may be further purified by chromatography.

A solution of one part of Compound 2a in CH₂Cl₂ is treated with about two parts of BF₃·OEt₂ at about -78° C. under an argon atmosphere and about three parts of (CH₂=CH)₂SnBu₂. The reaction temperature is gradually raised to rt during about one to four hours. Usual extractive workup followed by purification by chromatography will give Compound 43a. Compound 43a is dissolved in methanol and dichloromethane and cooled to about -78°

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C. Ozone is bubbled into the stirred solution for about 1.5 hours at -78°C . The solution is then flushed with nitrogen to remove the ozone. Sodium borohydride (about 8 equivalents) is then added in small portions over about 5 minutes at -78°C . Methanol is added and the reaction is slowly warmed to about 0°C . After about 1.5 hours, the reaction is quenched with saturated bicarbonate solution and extracted with CH_2Cl_2 . The combined organics are washed with brine, dried, filtered and the solvent is removed in vacuo. The residue is purified by chromatography to give Compound 43b. Compound 43b may be debenzylated in the same manner as Compound 2a to give Compound 43 that may be further purified by chromatography.

Compound 44



Compound 44 may be obtained in the same manner as Compound 43, starting with Compound 12c.

Antiviral Activity

Another aspect of the invention relates to methods of inhibiting viral infections, comprising the step of treating a sample or subject suspected of needing such inhibition with a composition of the invention.

Within the context of the invention samples suspected of containing a virus include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an organism which induces a viral infection, frequently a pathogenic organism such as a tumor virus. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

If desired, the anti-virus activity of a compound of the invention after application of the composition can be

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observed by any method including direct and indirect methods of detecting such activity. Quantitative, qualitative, and semiquantitative methods of determining such activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

The antiviral activity of a compound of the invention can be measured using standard screening protocols that are known. For example, the antiviral activity of a compound can be measured using the following general protocols.

Cell-Based Flavivirus Immunodetection Assay

BHK21 or A549 cells are trypsinized, counted and diluted to 2×10^5 cells/mL in Hams F-12 media (A549 cells) or RPMI-1640 media (BHK21 cells) supplemented with 2% fetal bovine serum (FBS) and 1% penicillin/streptomycin. 2×10^4 cells are dispensed in a clear 96-well tissue culture plates per well and placed at 37°C , 5% CO_2 overnight. On the next day, the cells are infected with viruses at multiplicity of infection (MOI) of 0.3 in the presence of varied concentrations of test compounds for 1 hour at 37°C and 5% CO_2 for another 48 hours. The cells are washed once with PBS and fixed with cold methanol for 10 min. After washing twice with PBS, the fixed cells are blocked with PBS containing 1% FBS and 0.05% Tween-20 for 1 hour at room temperature. The primary antibody solution (4G2) is then added at a concentration of 1:20 to 1:100 in PBS containing 1% FBS and 0.05% Tween-20 for 3 hours. The cells are then washed three times with PBS followed by one hour incubation with horseradish peroxidase (HRP)-conjugated anti-mouse IgG (Sigma, 1:2000 dilution). After washing three times with PBS, 50 microliters of 3,3',5,5'-tetramethylbenzidine (TMB) substrate solution (Sigma) is added to each well for two minutes. The reaction is stopped by addition of 0.5 M sulfuric acid. The plates are read at 450 nm

absorbance for viral load quantification. After measurement, the cells are washed three times with PBS followed by incubation with propidium iodide for 5 min. The plate is read in a Tecan Safire™ reader (excitation 537 nm, emission 617 nm) for cell number quantification. Dose response curves are plotted from the mean absorbance versus the log of the concentration of test compounds. The EC₅₀ is calculated by non-linear regression analysis. A positive control such as N-nonyl-deoxyojirimycin may be used.

Cell-Based Flavivirus Cytopathic Effect Assay

For testing against West Nile virus or Japanese encephalitis virus, BHK21 cells are trypsinized and diluted to a concentration of 4×10⁵ cells/mL in RPMI-1640 media supplemented with 2% FBS and 1% penicillin/streptomycin. For testing against dengue virus, Huh7 cells are trypsinized and diluted to a concentration of 4×10⁵ cells/mL in DMEM media supplemented with 5% FBS and 1% penicillin/streptomycin. A 50 microliter of cell suspension (2×10⁴ cells) is dispensed per well in a 96-well optical bottom PIT polymer-based plates (Nunc). Cells are grown overnight in culture medium at 37° C., 5% CO₂, and then infected with West Nile virus (e.g. B956 strain) or Japanese encephalitis virus (e.g. Nakayama strain) at MOI=0.3, or with dengue virus (e.g. DEN-2 NGC strain) at MOI=1, in the presence of different concentrations of test compounds. The plates containing the virus and the compounds are further incubated at 37° C., 5% CO₂ for 72 hours. At the end of incubation, 100 microliters of CellTiter-Glo™ reagent is added into each well. Contents are mixed for 2 minutes on an orbital shaker to induce cell lysis. The plates are incubated at room temperature for 10 minutes to stabilize luminescent signal. Luminescence reading is recorded using a plate reader. A positive control such as N-nonyl-deoxyojirimycin may be used.

Antiviral Activity in a Mouse Model of Dengue Infection.

Compounds are tested *in vivo* in a mouse model of dengue virus infection (Schul et al. *J. Infectious Dis.* 2007; 195: 665-74). Six to ten week old AG129 mice (B&K Universal Ltd, Hill, UK) are housed in individually ventilated cages. Mice are injected intraperitoneally with 0.4 mL TSV01 dengue virus 2 suspension. Blood samples are taken by retro orbital puncture under isoflurane anaesthesia. Blood samples are collected in tubes containing sodium citrate to a final concentration of 0.4%, and immediately centrifuged for 3 minutes at 6000 g to obtain plasma. Plasma (20 microliters) is diluted in 780 microliters RPMI-1640 medium and snap frozen in liquid nitrogen for plaque assay analysis. The remaining plasma is reserved for cytokine and NS1 protein level determination. Mice develop dengue viremia rising over several days, peaking on day 3 post-infection.

For testing of antiviral activity, a compound of the invention is dissolved in vehicle fluid, e.g. 10% ethanol, 30% PEG 300 and 60% D5W (5% dextrose in water; or 6N HCl (1.5 eq):1N NaOH (pH adjusted to 3.5): 100 mM citrate buffer pH 3.5 (0.9% v/v:2.5% v/v: 96.6% v/v). Thirty six 6-10 week old AG129 mice are divided into six groups of six mice each. All mice are infected with dengue virus as described above (day 0). Group 1 is dosed by oral gavage of 200 mL/mouse with 0.2 mg/kg of a compound of the invention twice a day (once early in the morning and once late in the afternoon) for three consecutive days starting on day 0 (first dose just before dengue infection). Groups 2, 3 and 4 are dosed the same way with 1 mg/kg, 5 mg/kg and 25 mg/kg of the compound, respectively. A positive control may be used, such as (2R,3R,4R,5R)-2-(2-amino-6-hydroxy-purin-9-yl)-5-hydroxymethyl-3-methyltetrahydro-furan-3,4-diol, dosed by oral gavage of 200 microliters/

mouse the same way as the previous groups. A further group is treated with only vehicle fluid.

On day 3 post-infection approximately 100 microliter blood samples (anti-coagulated with sodium citrate) are taken from the mice by retro-orbital puncture under isoflurane anaesthesia. Plasma is obtained from each blood sample by centrifugation and snap frozen in liquid nitrogen for plague assay analysis. The collected plasma samples are analyzed by plague assay as described in Schul et al. Cytokines are also analysed as described by Schul. NS1 protein levels are analysed using a Platelia™ kit (BioRad Laboratories). An antiviral effect is indicated by a reduction in cytokine levels and/or NS1 protein levels.

Typically, reductions in viremia of about 5-100 fold, more typically 10-60 fold, most typically 20-30 fold, are obtained with 5-50 mg/kg bid dosages of the compounds of the invention.

HCV IC₅₀ Determination

Assay Protocol: NS5b polymerase assay (40 μL) was assembled by adding 28 μL polymerase mixture (final concentration: 50 mM Tris-HCl at pH 7.5, 10 mM KCL, 5 mM MgCl₂, 1 mM DTT, 10 mM EDTA, 4 ng/μL of RNA template, and 75 nM HCV Δ21 NS5b polymerase) to assay plates followed by 4 μL of compound dilution. The polymerase and compound were pre-incubated at 35° C. for 10 minutes before the addition of 8 μL of nucleotide substrate mixture (33P-α-labeled competing nucleotide at K_M and 0.5 mM of the remaining three nucleotides). The assay plates were covered and incubated at 35° C. for 90 mM. Reactions were then filtered through 96-well DEAE-81 filter plates via vacuum. The filter plates were then washed under vacuum with multiple volumes of 0.125 M NaHPO₄, water, and ethanol to remove unincorporated label. Plates were then counted on TopCount to assess the level of product synthesis over background controls. The IC₅₀ value is determined using Prism fitting program.

Preferably, compounds described herein inhibited NS5b polymerase with an IC₅₀'s below 1000 μM, more preferably below 100 μM, and most preferably below 10 μM. For example, compound 17 has an IC₅₀ below 1 μM.

HCV EC₅₀ Determination

Replicon cells were seeded in 96-well plates at a density of 8×10³ cells per well in 100 μL of culture medium, excluding Geneticin. Compound was serially diluted in 100% DMSO and then added to the cells at a 1:200 dilution, achieving a final concentration of 0.5% DMSO and a total volume of 200 μL. Plates were incubated at 37° C. for 3 days, after which culture medium was removed and cells were lysed in lysis buffer provided by Promega's luciferase assay system. Following the manufacturer's instruction, 100 μL of luciferase substrate was added to the lysed cells and luciferase activity was measured in a TopCount luminometer. Preferably, compounds described herein have EC₅₀'s below 1000 μM, more preferably below 100 μM, and most preferably below 10 μM.

Representative examples of the activity of the compounds Formula I-III are shown in the Table below wherein A represents an EC₅₀ below 1 μM, B represents an EC₅₀ between 1 and 10 μM, and C represents an EC₅₀ between 10 and 100 μM.

Example No.	EC ₅₀ , μM
2	C
3	C
4	C

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Example No.	EC ₅₀ , μM
5	C
6	A
12	B
13	B

The cytotoxicity of a compound of the invention can be determined using the following general protocol.

Cytotoxicity Cell Culture Assay (Determination of CC50):

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate.

Assay Protocol for Determination of CC50:

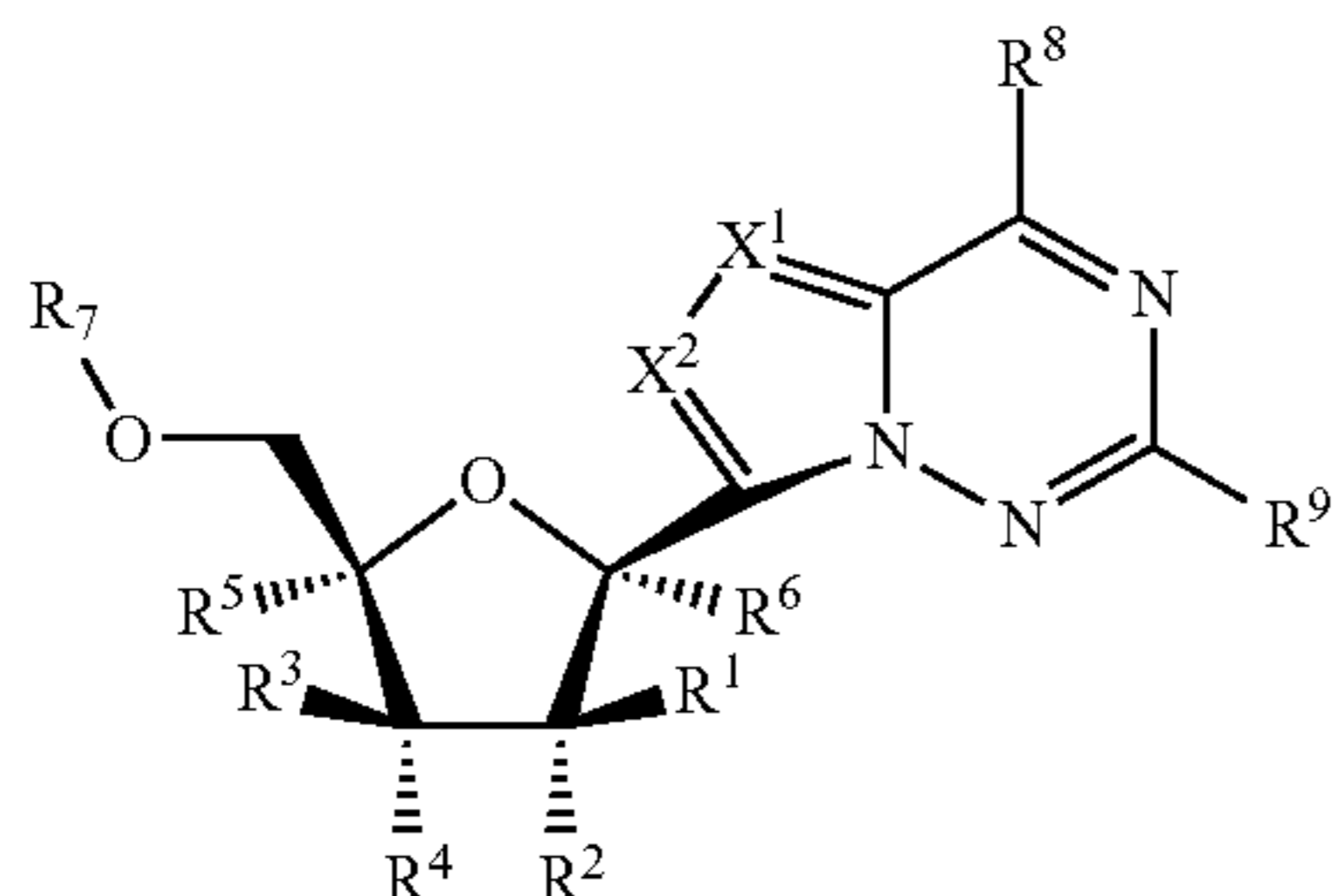
1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.
2. Distribute the cells into a 96-well plate (20,000 cell in 100 μl media per well) and add various concentrations of the tested compound in triplicate (100 μl/well). Include untreated control.
3. Incubate the cells for 5 days at 37° C.
4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2 mg/ml in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55° C. for 5 min. Add 50 μl of N-methylphenazonium methasulfate (5 μg/ml) per 6 ml of XTT solution.
5. Remove 100 μl media from each well on the assay plate and add 100 μl of the XTT substrate solution per well. Incubate at 37° C. for 45 to 60 min in a CO₂ incubator.
6. Add 20 μl of 2% Triton X-100 per well to stop the metabolic conversion of XTT.
7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.
8. Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

All publications, patents, and patent documents cited herein above are incorporated by reference herein, as though individually incorporated by reference.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, one skilled in the art will understand that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is:

1. A compound of Formula II:



Formula II

or a pharmaceutically acceptable salt, thereof;
wherein:

R¹, R³, and R⁵ are H;

R² and R⁴ are, independently, OR^a;

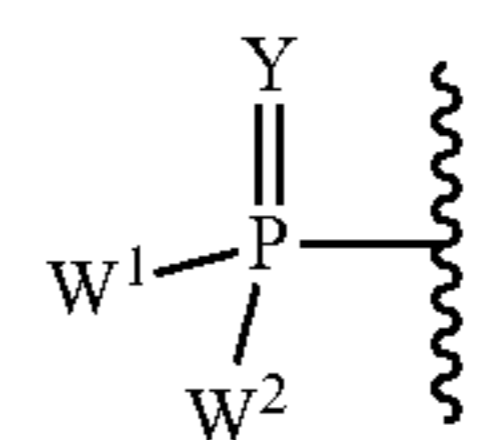
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R⁶ is OR^a, N₃, CN, S(O)_nR^a, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², halogen, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl;

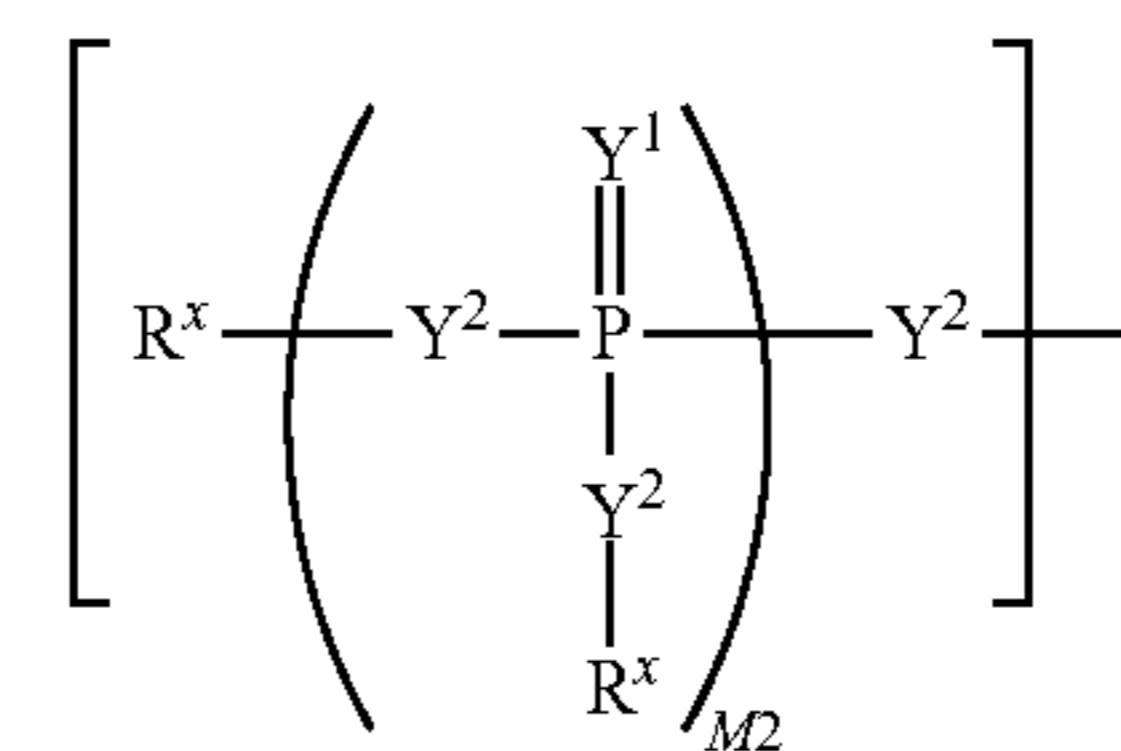
each n is independently 0, 1, or 2;

each R^a is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl(C₁-C₈)alkyl, (C₄-C₈)carbocyclylalkyl, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², C(=O)SR¹¹, S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), or —SO₂NR¹¹R¹²;

R⁷ is H, —C(=O)R¹¹, —C(=O)OR¹¹, —C(=O)NR¹¹R¹², —C(=O)SR¹¹, —S(O)R¹¹, —S(O)₂R¹¹, —S(O)(OR¹¹), —S(O)₂(OR¹¹), —SO₂NR¹¹R¹², or



W¹ and W², when taken together, are —Y³(C(R^y)₂)₃Y³—; or W¹ and W² are each, independently, a group of the Formula Ia:



Formula Ia

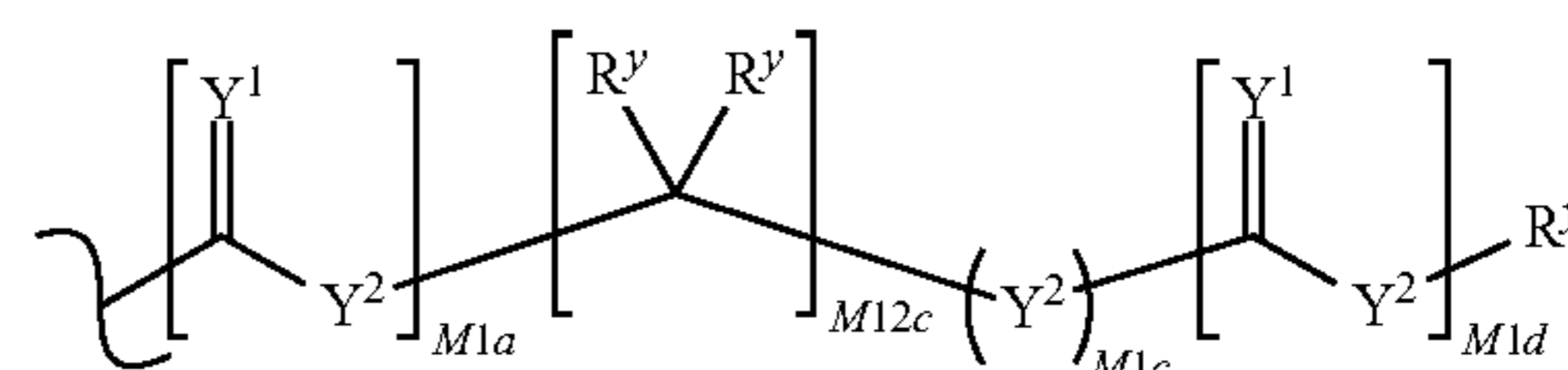
Y and each Y¹ are independently O, S, NR, [⁺N(O)(R)]⁺N(O⁻)(R), N(OR), [⁺N(O)(OR)]⁺N(O⁻)(OR), or N—NR₂;

each Y² is independently a bond, O, CR₂, NR, [⁺N(O)(R)]⁺N(O⁻)(R), N(OR), [⁺N(O)(OR)]⁺N(O⁻)(OR), N—NR₂, S, S—S, S(O), or S(O)₂;

each Y³ is independently O, S, or NR;

M₂ is 0, 1 or 2;

each R^x is independently R^y or the formula:



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wherein:

each M_{1a}, M_{1c}, and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, —C(=Y¹)R, —C(=Y¹)OR, —C(=Y¹)N(R)₂, —N(R)₂, [⁺N(R)₃]⁺N(R)₃, —SR, —S(O)R, —S(O)₂R, —S(O)(OR), —S(O)₂(OR), —OC(=Y¹)R, —OC(=Y¹)OR, —OC(=Y¹)(N(R)₂), —SC(=Y¹)R, —SC(=Y¹)OR, —SC(=Y¹)(N(R)₂), —N(R)C(=Y¹)R, —N(R)C(=Y¹)OR, —N(R)C(=Y¹)N(R)₂, —SO₂NR₂, —CN, —N₃, —NO₂, —OR, or W³; or when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

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each R is independently H, (C₁-C₈) alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkynyl, (C₂-C₈) substituted alkynyl, C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocyclyl, C₂-C₂₀ substituted heterocyclyl, arylalkyl or substituted arylalkyl;

W³ is W⁴ or W⁵; W⁴ is R, —C(Y¹)R^y, —C(Y¹)W⁵, —SO₂R^y, or —SO₂W⁵; and W⁵ is a carbocycle or a heterocycle wherein W⁵ is independently substituted with 0 to 3 R^y groups;

X² is C—R¹⁰ and X¹ is C—R¹⁰ or N;

R⁸ is halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹), —CH=NHR¹¹, —CH=N(OR¹¹), —CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)OR¹¹, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, —C(=O)(C₁-C₈)alkyl, [—S(O)_n(C₁-C₈)alkyl]—S(O)_n(C₁-C₈)alkyl, aryl (C₁-C₈)alkyl, OR¹¹ or SR¹¹;

R⁹ and each R¹⁰ are independently H, halogen, NR¹¹R¹², N(R¹¹)OR¹¹, NR¹¹NR¹¹R¹², N₃, NO, NO₂, CHO, CN, —CH(=NR¹¹), —CH=NHR¹¹, —CH=N(OR¹¹), —CH(OR¹¹)₂, —C(=O)NR¹¹R¹², —C(=S)NR¹¹R¹², —C(=O)OR¹¹, R¹¹, OR¹¹ or SR¹¹;

each R¹¹ and each R¹² are independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl, optionally substituted aryl, optionally substituted heteroaryl, —C(=O)(C₁-C₈)alkyl, —S(O)_n(C₁-C₈)alkyl or aryl(C₁-C₈)alkyl; or R¹¹ and R¹² taken together with a nitrogen to which they are both attached to form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with —O—, —S— or —NR^a—;

wherein substituted methyl, substituted ethenyl and substituted ethynyl of R⁶ and each (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl or aryl(C₁-C₈)alkyl of each of R¹¹ and R¹² are independently, optionally substituted with one or more halo, hydroxy, CN, N₃, N(R^a)₂ or OR^a; and

wherein one or more of the non-terminal carbon atoms of each said (C₁-C₈)alkyl is optionally replaced with —O—, —S— or —NR^a—.

2. The compound according to claim 1, wherein R⁶ is OR^a, N₃, halogen, CN, substituted methyl, ethenyl, substituted ethenyl, ethynyl, or substituted ethynyl.

3. The compound according to claim 1, wherein R² and R⁴ are OH.

4. The compound according to claim 2, wherein R² and R⁴ are OH.

5. The compound according to claim 1, wherein R⁶ is CN.

6. The compound according to claim 4, wherein R⁶ is CN.

7. The compound according to claim 4, wherein R⁹ is NR¹¹R¹².

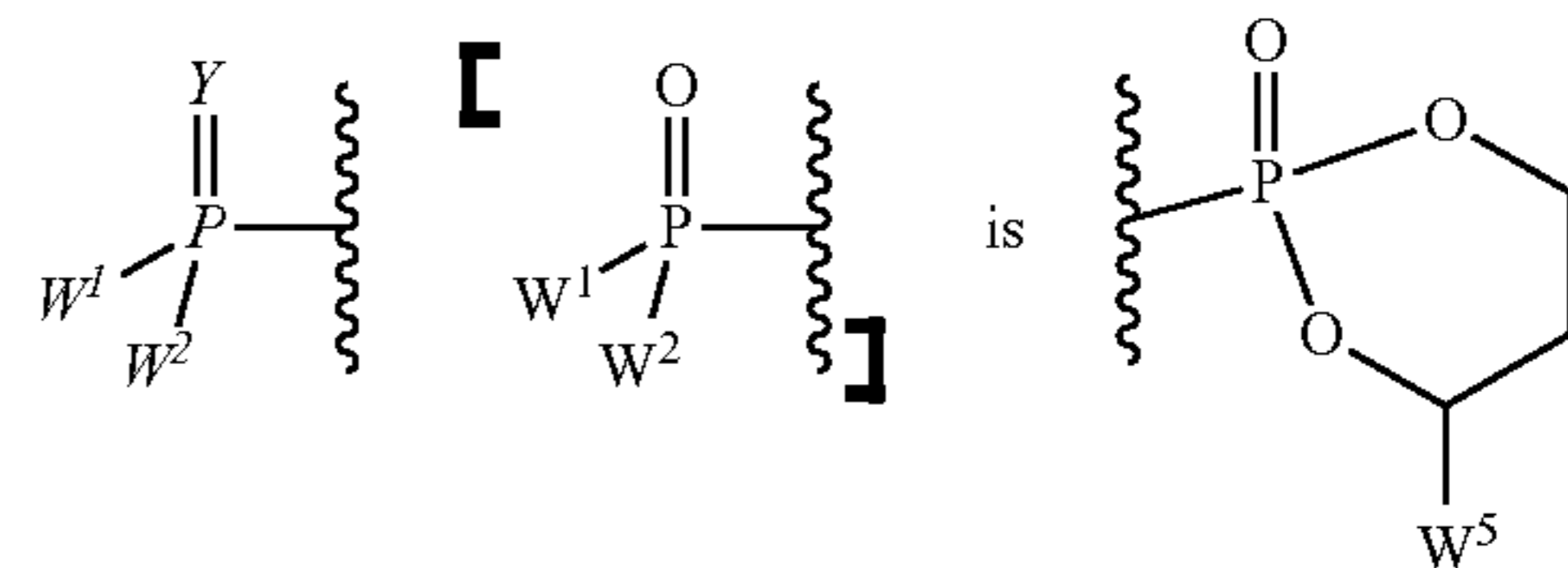
8. The compound according to claim 7, wherein X² is C—H.

9. The compound according to claim 8, wherein X¹ is C—H.

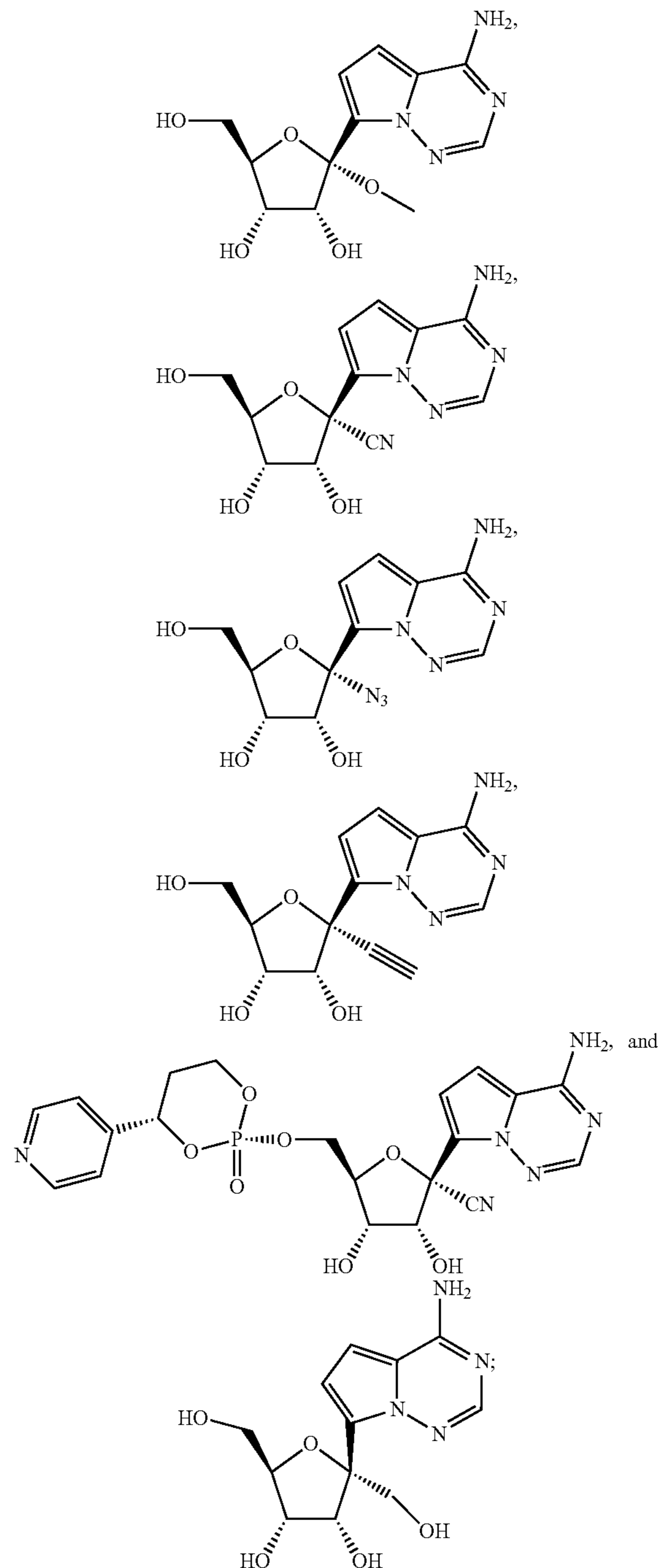
10. The compound according to claim 9, wherein R⁷ is H.

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11. The compound according to claim 9, wherein



12. A compound selected from the group consisting of



or a pharmaceutically acceptable salt thereof.

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13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13 further comprising at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5a inhibitors, NS5b polymerase inhibitors, [alphaglucoisidase] *alpha*-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

15. A method of inhibiting HCV polymerase comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

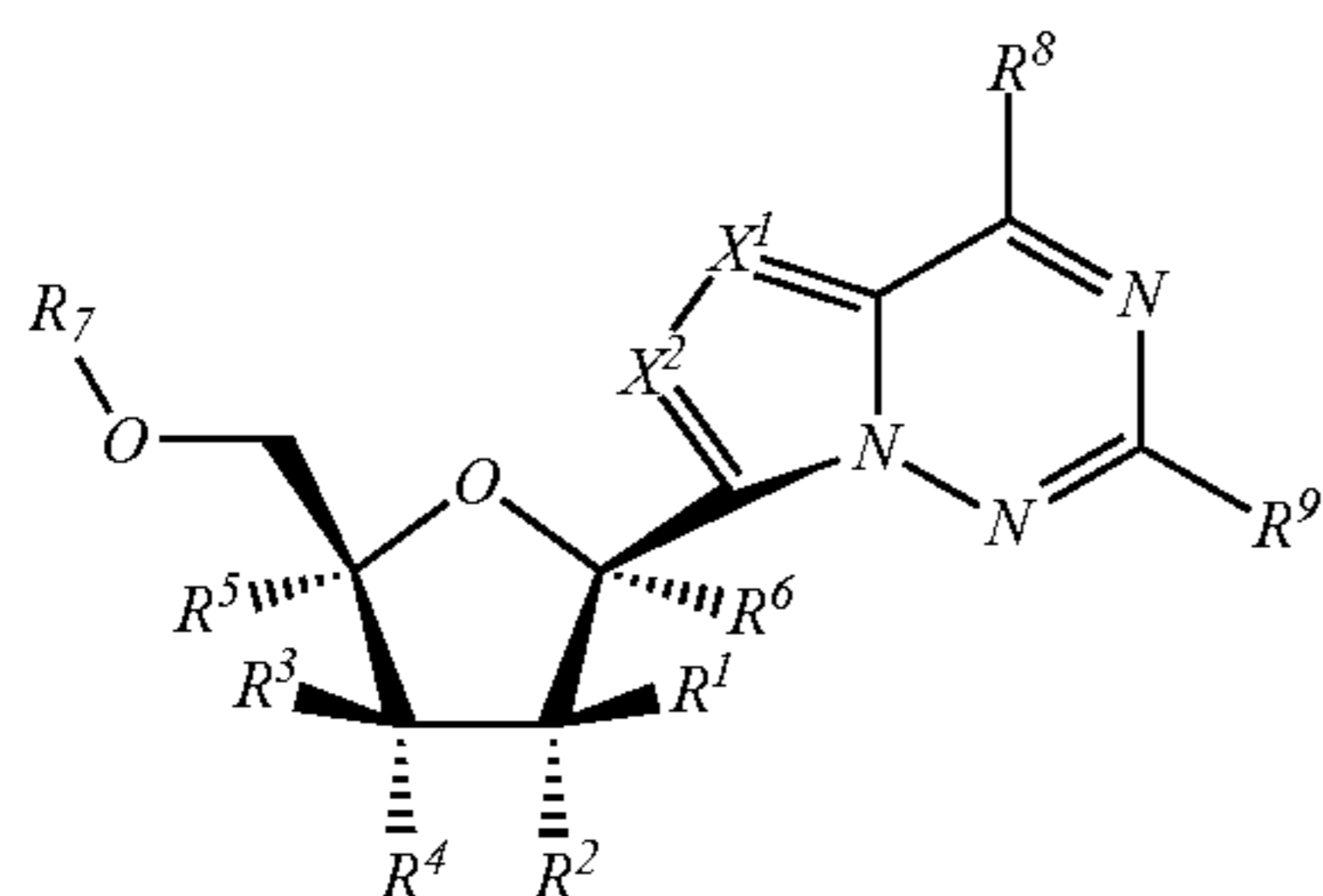
16. A method of treating a viral infection caused by a virus selected from the group consisting of dengue virus, yellow fever virus, West Nile virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kunjin virus, Murray Valley encephalitis virus, St. Louis encephalitis virus, Omsk hemorrhagic fever virus, bovine viral diarrhea virus, Zika virus and Hepatitis C virus comprising administering to a mammal in need thereof a therapeutically effective amount of a compound or pharmaceutical composition of claim 1.

17. The method of claim 16, wherein the viral infection is caused by Hepatitis C virus.

18. The method of claim 17 further comprising administering at least one additional therapeutic agent selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, NS5b polymerase inhibitors, NS5a inhibitors, alpha-glucosidase 1 inhibitors, cyclophilin inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

19. The method of claim 16, wherein the viral infection is caused by Zika virus.

20. A compound of



Formula II

or a pharmaceutically acceptable salt, thereof;
wherein:

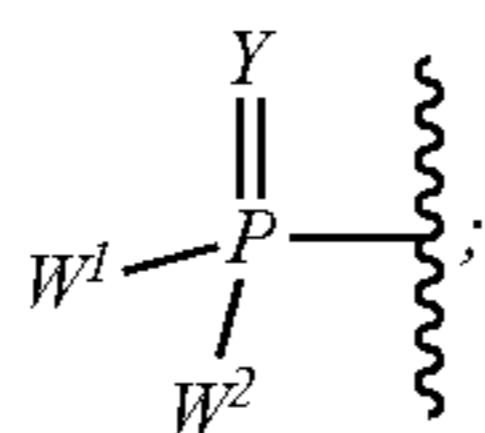
R^1 , R^3 , and R^5 are H;

R^2 and R^4 are OH;

R^6 is CN;

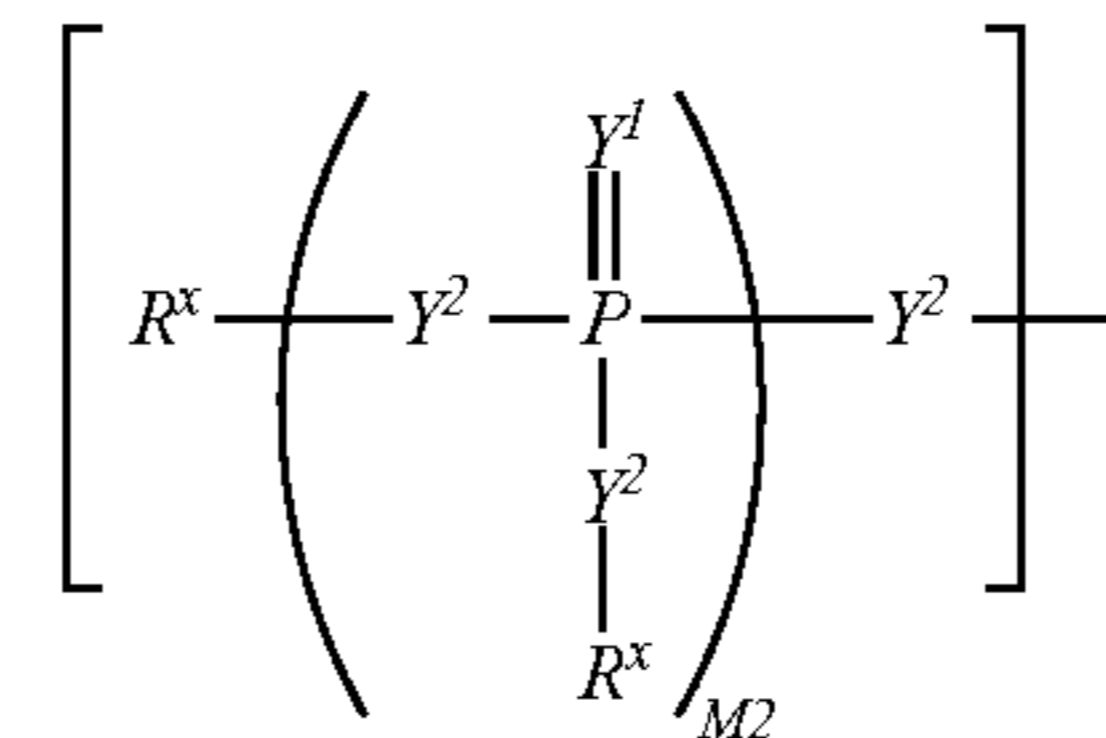
each R^a is independently H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, aryl(C₁-C₈)alkyl, (C₄-C₈)carbocyclalkyl, $-C(=O)R^{11}$, $-C(=O)OR^{11}$, $-C(=O)NR^{11}R^{12}$, $C(=O)SR^{11}$, $S(O)R^{11}$, $-S(O)R^{11}$, $-S(O)(OR^{11})$, $-S(O)_2(OR^{11})$, or $-SO_2NR^{11}R^{12}$;

R^7 is



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W^1 and W^2 , when taken together, are $-Y^3(C(R^y)_2)_3Y^3-$;
or W^1 and W^2 are each, independently, a group of the Formula Ia:



Formula Ia

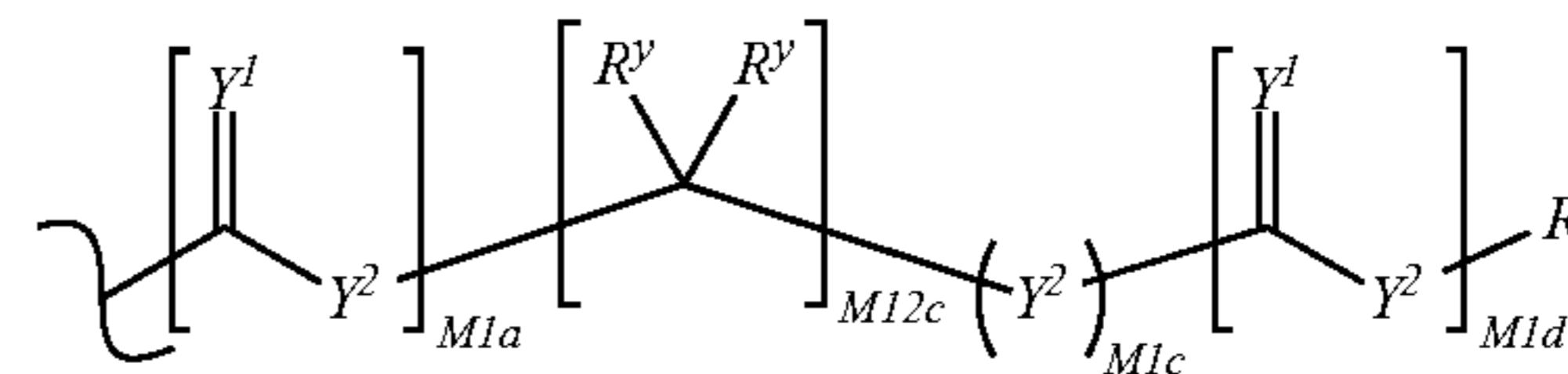
Y and each Y^1 are O, S, NR, $+N(O^-)(R)$, $N(OR)$, $+N(O^-)(OR)$, or $N-NR_2$;

each Y^2 is independently a bond, O, CR₂, NR, $+N(O^-)(R)$, $N(OR)$, $+N(O^-)(OR)$, $N-NR_2$, S, S-S, S(O), or S(O)₂;

each Y^3 is independently O, S, or NR;

M_2 is 0, 1 or 2;

each R^x is independently R^y or the formula:



wherein:

each M_{1a} , M_{1c} , and M_{1d} is independently 0 or 1;

M_{12c} is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each R^y is independently H, F, Cl, Br, I, OH, R, $-C(=Y^1)$

R, $-C(=Y^1)OR$, $-C(=Y^1)N(R)_2$, $-N(R)_2$, $-N(R)_3$,

$-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)(OR)$, $-S(O)_2(OR)$,

$-OC(=Y^1)R$, $-OC(=Y^1)OR$, $-OC(=Y^1)(N(R)_2)$,

$-SC(=Y^1)R$, $-SC(=Y^1)OR$, $-SC(=Y^1)(N(R)_2)$,

$-N(R)C(=Y^1)R$, $-N(R)C(=Y^1)OR$, $-N(R)C(=Y^1)N$

$(R)_2$, $-SO_2NR_2$, $-CN$, $-N_3$, $-NO_2$, $-OR$, or W^3 ; or

when taken together, two R^y on the same carbon atom form a carbocyclic ring of 3 to 7 carbon atoms;

each R is independently H, (C₁-C₈)alkyl, (C₁-C₈) substituted alkyl, (C₂-C₈)alkenyl, (C₂-C₈) substituted alkenyl, (C₂-C₈) alkenyl, (C₂-C₈) substituted alkenyl,

C₆-C₂₀ aryl, C₆-C₂₀ substituted aryl, C₂-C₂₀ heterocycl, C₂-C₂₀ substituted heterocycl, arylalkyl or substituted arylalkyl;

W^3 is W^4 or W^5 ; W^4 is R, $-C(Y^1)R^y$, $-C(Y^1)W^5$, $-SO_2R^y$,

or $-SO_2W^5$; and W^5 is a carbocycle or a heterocycle

wherein W^5 is independently substituted with 0 to 3 R^y

groups;

X^2 is C-H and X^1 is C-H;

R^8 is halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3 ,

NO, NO₂, CHO, CN, $-CH(=NR^{11})$, $-CH=NHR^{11}$,

$-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$,

$-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclalkyl,

optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)alkyl$, $-S(O)_m(C_1-C_8)alkyl$,

aryl(C₁-C₈)alkyl, OR¹¹ or SR¹¹;

R^9 is H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$,

N_3 , NO, NO₂, CHO, CN, $-CH(=NR^{11})$,

$-CH=NHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$,

$-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$,

R^{11} , OR¹¹ or SR¹¹;

each R^{11} and each R^{12} are independently H, (C₁-C₈)alkyl,

(C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₄-C₈)carbocyclal-

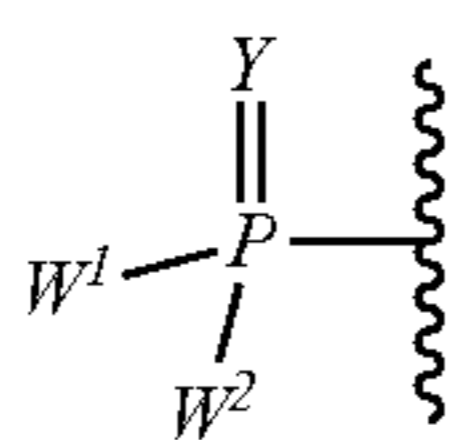
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kyl, optionally substituted aryl, optionally substituted heteroaryl, $-C(=O)(C_1-C_8)\text{alkyl}$, $-S(O)_n(C_1-C_8)\text{alkyl}$ or aryl(C_1-C_8)alkyl; or R^{11} and R^{12} taken together with a nitrogen to which they are both attached to form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with $-O-$, $-S-$ or $-NR^a-$;

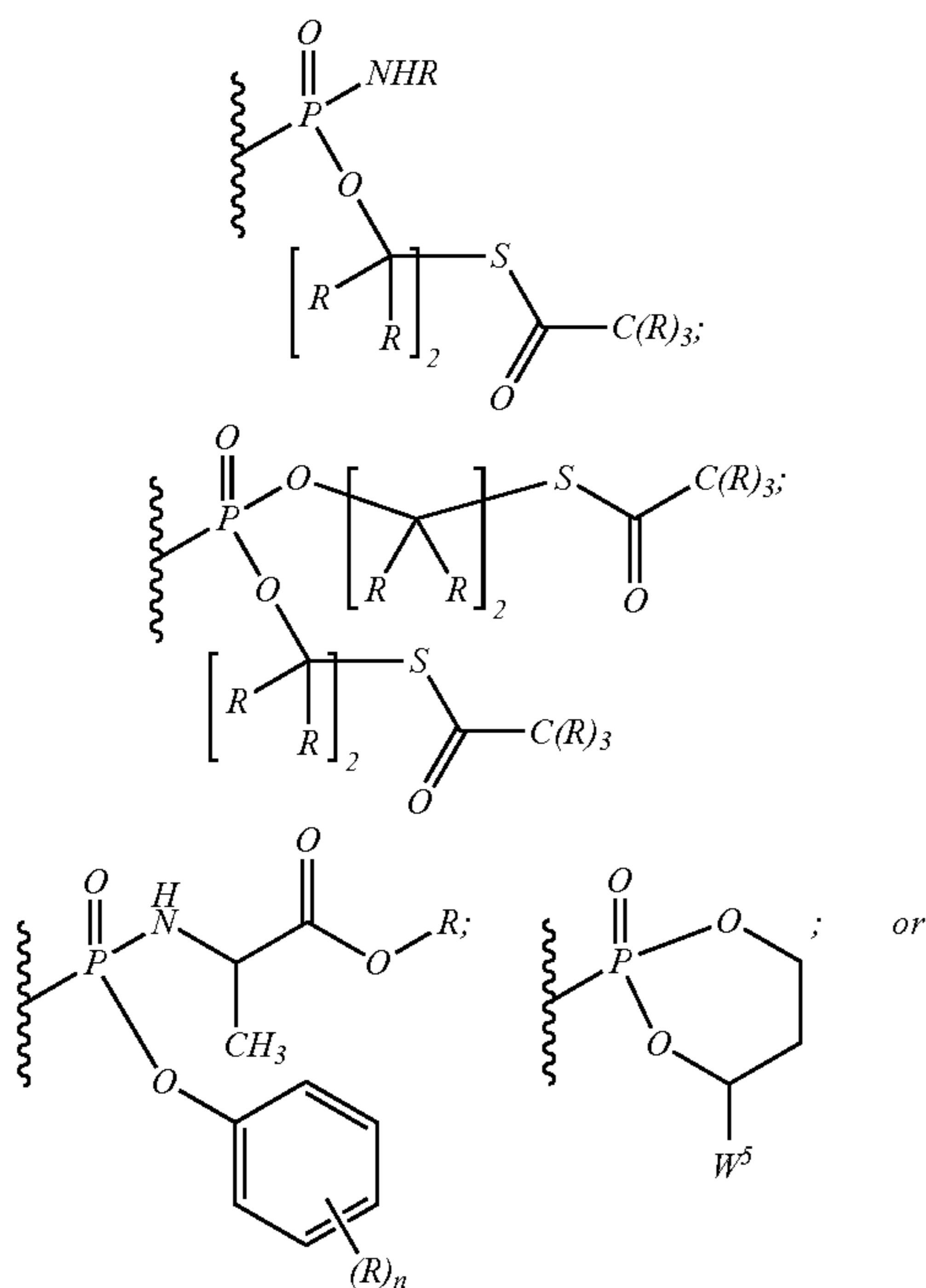
wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl or aryl(C_1-C_8)alkyl of each of R^{11} and R^{12} are independently, optionally substituted with one or more halo, hydroxy, CN, N_3 , $N(R^a)_2$ or OR^a ; and

wherein one or more of the non-terminal carbon atoms of each said (C_1-C_8)alkyl is optionally replaced with $-O-$, $-S-$ or $-NR^a-$.

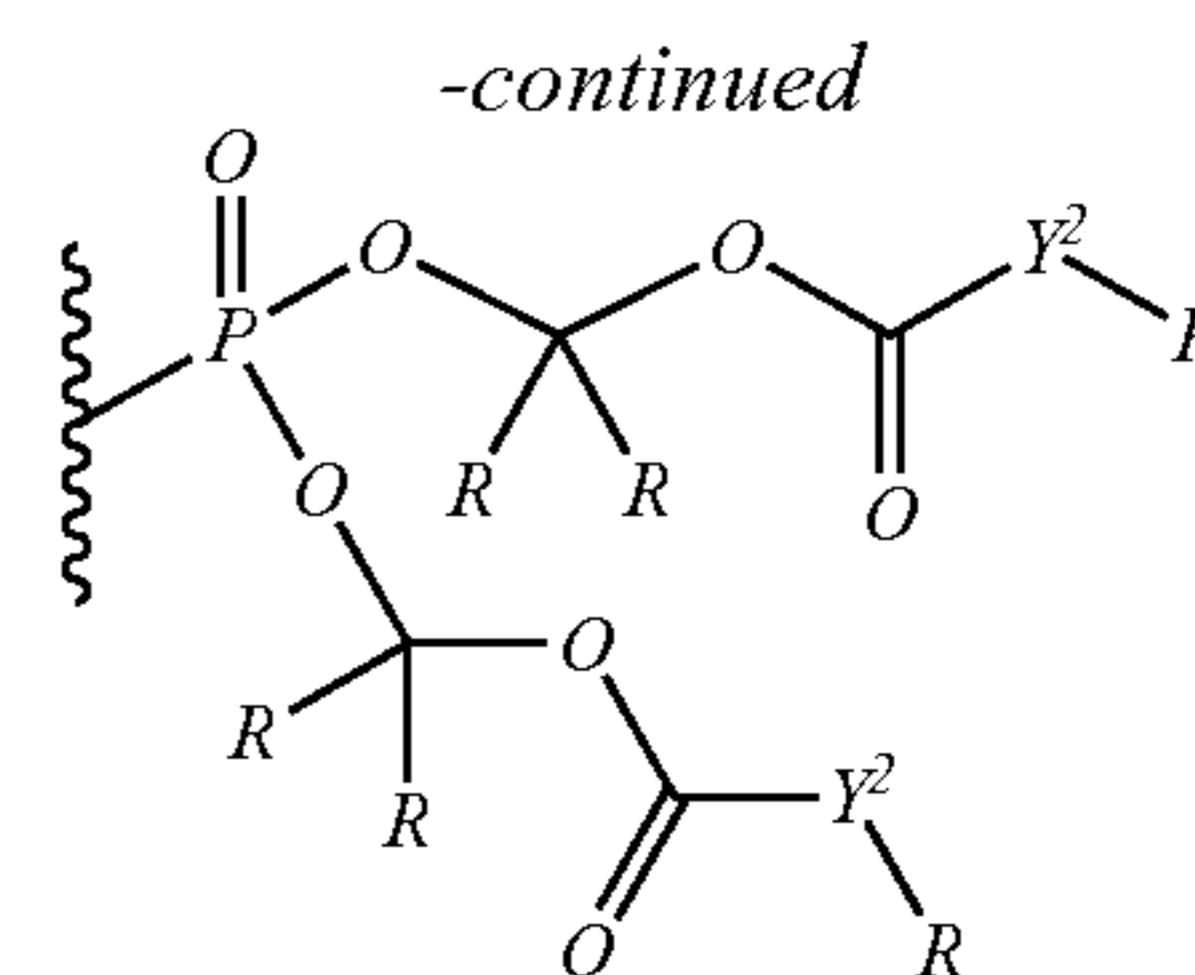
21. The compound of claim 20, wherein



is selected from



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wherein Y^2 is, independently, a bond, O, or CR_2 .

22. The compound of claim 20, wherein W^1 and W^2 are each, independently, a group of the Formula Ia.

23. A pharmaceutical composition comprising the compound of claim 20.

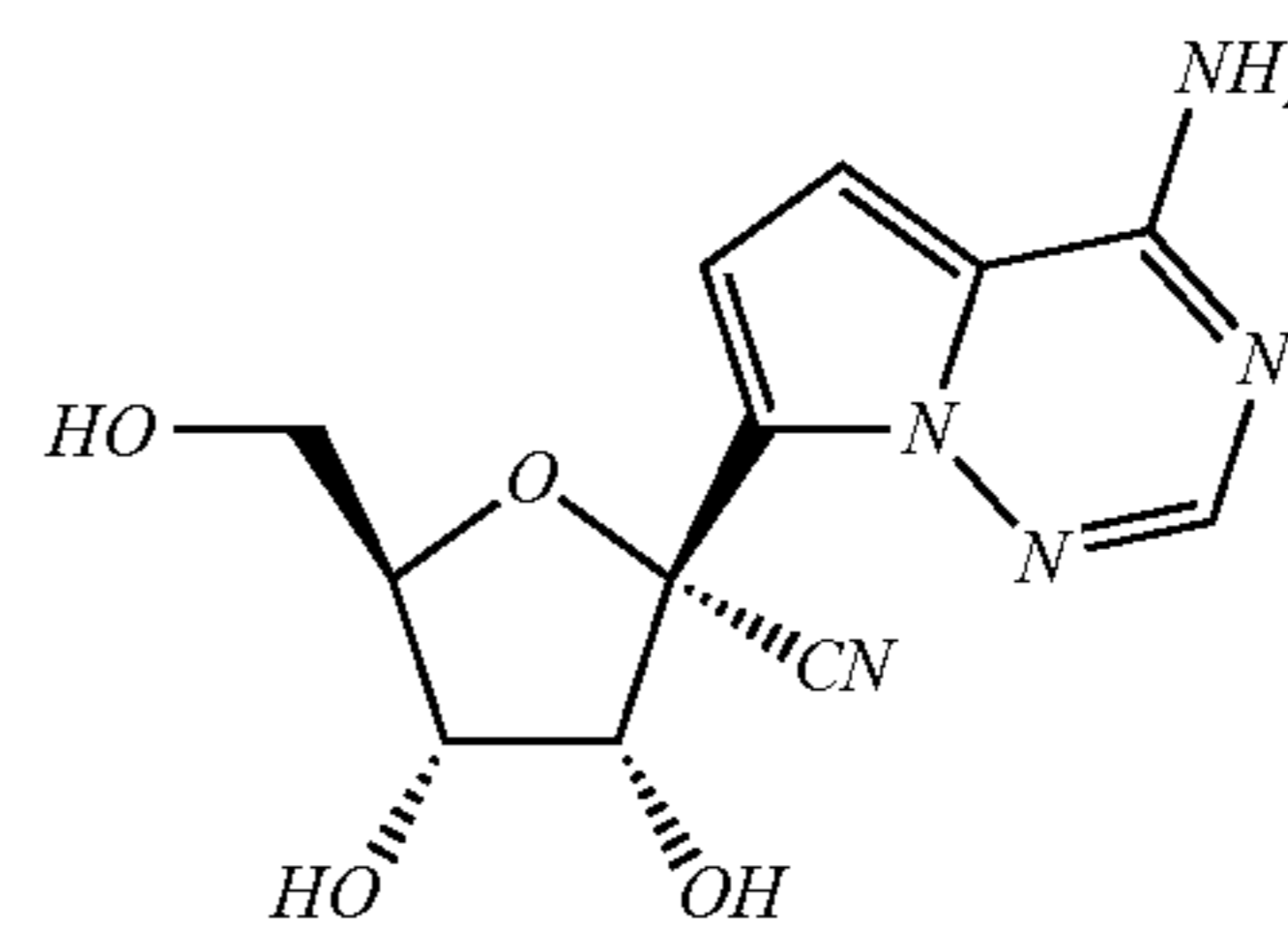
24. A method of treating a Flaviviridae viral infection in a human in need thereof by administering the compound of claim 20.

25. The method of treating a Flaviviridae viral infection of claim 24 wherein the Flaviviridae viral infection is caused by a Zika virus.

26. A method of treating a Flaviviridae viral infection by contacting a cell with the compound of claim 20.

27. The method of treating a Flaviviridae viral infection of claim 26 wherein the Flaviviridae viral infection is caused by a Zika virus.

28. A compound:



29. A pharmaceutical composition comprising the compound of claim 28.

30. A method of treating a Flaviviridae viral infection in a human in need thereof by administering the compound of claim 28.

31. The method of treating a Flaviviridae viral infection of claim 30 wherein the Flaviviridae viral infection is caused by a Zika virus.

32. A method of treating a Flaviviridae viral infection by contacting a cell with the compound of claim 28.

33. The method of treating a Flaviviridae viral infection of claim 32 wherein the Flaviviridae viral infection is caused by a Zika virus.

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