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Synthesis of carbocyclic nucleoside analogs with five-membered heterocyclic nucleobases

Jong hyun Cho[a], **Steven J. Coats**[b], and **Raymond F. Schinazi**[a,*]

[a]Center for AIDS Research, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, and Veterans Affairs Medical Center, Atlanta, GA 30322, USA

[b]RFS Pharma, 1860 Montreal Road Tucker, GA 30084, USA

Abstract

New carbocyclic nucleoside analogs with five-membered heterocyclic nucleobases were synthesized and evaluated as potential anti-HIV and anti-HCV agents. Among the synthesized carbocyclic nucleoside analogs, the pyrazole amide **15f** exhibited modest selective anti-HIV-1 activity (EC_{50} = 24 μM).

Keywords

carbocyclic ribonucleoside; antiviral; five-membered nucleobases

Studies of nucleoside analogs with unmodified naturally occurring nucleo-purine and -pyrimidine bases have been more successful in the development of biologically interesting nucleoside analogs.[1] However, a few nucleosides with five-membered heterocyclic nucleobases, such as the 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (aminoimidazole carboxamide ribonucleotide, AICAR, I) or the inosine 5’-monophosphate (IMP, II), display useful biological activity (Figure 1). Both AICAR and IMP are important intermediates in the *de novo* generation of adenine and guanine nucleotides.[2] AICAR is well known as an adenosine 5’-monophosphate (AMP)-dependent protein kinase (AMPK) activator.[3] It can activate AMPK in times of reduced energy availability (high cellular AMP:ATP ratios) and serves to inhibit anabolic processes.[4,5] In addition, AICAR may play a role in tumor suppression[6] and induction of cellular apoptosis.[3,7]

*Corresponding author. Tel.: +1-404-727-1414; fax: +1-404-727-1330; rschina@emory.edu.

Supplementary Data

Supplementary data (details experimental procedure and characterization data of selected compounds and copies of ^{1}H NMR and ^{13}C NMR spectra are given in supplementary material) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet….

Additionally, AICAR is converted to IMP in two steps by AICAR transformylase and IMP cyclohydrolase in purine nucleotide biosynthesis.[8] IMP is the precursor for both adenosine and guanosine nucleotides. Inosine monophosphate dehydrogenase (IMPDH)[9] catalyzes the oxidation of IMP to xanthosine 5'-monophosphate (XMP) in guanine nucleotide biosynthesis, which is subsequently converted to guanosine monophosphate (GMP) by GMP synthetase.[10] Recently, IMPDH has received a great deal of attention as a promising target for the development of anticancer, antiviral, immunosuppressive, and antimicrobial chemotherapy.[9]

Among the previously reported nucleoside or nucleotide analogs with five-membered heterocyclic nucleobases as activators of AMPK or inhibitors of IMPDH, Bredinin, **1a**[11], first isolated from the mold *Eupenicillium brefeldianum*, is an imidazole containing nucleoside analog IMPDH inhibitor that is used clinically as an immunosuppressive agent (Figure 1). EICAR (5-ethyleneimidazole-4-carboxamide, **1b**)[12] is a 5-alkyne substituted imidazole derivative that shows potent antitumor and antiviral activity. Ribavirin, **2a**[13], is the most clinically important five-membered heterocyclic nucleoside analog. It possesses a 1,2,4-triazole nucleobase on a ribo-sugar and exhibits broad-spectrum antiviral activity (including HIV, hepatitis (A, B and C) virus, influenza, respiratory syncytial virus (RSV), measles and mumps). Taribavirin (viramidine, 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamidine, TCNR, **2b**)[14] is a prodrug of ribavirin with improved liver-targeting pharmacokinetics. It has a shorter half-life, but displays significant antiviral activity against HSV, rhino and parainfluenza viruses. Tiazofurin (1,2-(β-D-ribofuranosyl) thiazole-4-carboxamide, **3**, a synthetic *C*-nucleoside derivative, displayed potent anticancer activity.[15] An early discovery compound, 1,2,3-triazole carbocyclic nucleoside **4**[16], exhibited antiviral activity *versus* vaccinia virus. With these five-membered heterocyclic nucleobase containing nucleoside analogs as a backdrop, we designed novel carbocyclic nucleoside analogs as potential antiviral agents.

Recently, the azide/alkyne cycloaddition reaction[17] has become one of the most synthetically useful tools in the formation of the 1,2,3-triazole heterocyclic ring system. A variety of reaction conditions for this particular click reaction[18] have been reported by multiple groups.[19] For our work, we envisioned the use of the known cyclopentenol **5**[16] to prepare the cyclopentenyl azide **7** for subsequent synthesis of carbocyclic analogs containing five-membered heterocyclic bases (Scheme 1).

The hydroxyl group of compound **5** was reacted with methanesulfonyl chloride (MsCl) to provide the sulfonyl analog **6**, followed by treatment of sodium azide to give its corresponding azide derivative **7** in 89 % yield (2 steps).

The 1,3-dipolar cycloaddition reaction of compound **7** with D,L-methyl 2-(*tert*-butoxycarbonylamino) pent-4-ynoate in the presence of CuI and triethylamine gave carbocyclic 1,2,3-triazole derivative **8** in 98% yield.[20] The triazole ester **8** was transformed to its corresponding amide with saturated methanolic ammonia, followed by removal of the *tert*-butyldiphenylsilyl (TBDPS), isopropylidene, and *tert*-butoxycarbonyl (Boc) deprotection groups by methanolic hydrogen chloride to afford the carbocyclic 1,2,3-triazole- propanamide analog **9** in 86% yield over 2 steps (Scheme 1).

The Mitsunobu reaction[21] of compound **5** with *N*Boc-L-histamine methyl ester provided carbocyclic imidazole analog **10** in 76% yield, which was subsequently treated with methanolic ammonia then methanolic hydrogen chloride to gave the carbocyclic imidazole propanamide **11** in 90% yield as a D/L-mixture at the histidine chiral center. The regioselectivity of **10** was determined on the basis of Nuclear Overhauser Effect (1D-NOE). The 1D-NOE showed a significant interaction between H^a and H^b that is only possible with **10** (π-isomer), as the H^a and H^c NOE with τ-isomer **12** would not be observed (Figure 2).

Furthermore, the chiral cyclopentenyl alcohol **5** and sulfonyl derivative **6** were utilized for the synthesis of additional new five-membered heterocyclic nucleoside analogs. The displacement reaction of **5** (or **6**) with commercially available five-membered heterocyclic analogs such as pyrroles, imidazoles, and pyrazoles esters with either a Mitsunobu reaction (*method A for 5*) or nucleophilic conditions of sodium hydride in dimethylformamide (*method B for 6*) afforded their corresponding derivatives **14a**–**h** (Table 1). The reaction of **5** separately with 4,5-dimethylester imidazole carboxylate **13a**, 4-methylester imidazole carboxylate **13b**, 3,5-diethylester pyrazole carboxylate **13e**, 4-ethylester pyrazole carboxylate **13f**, ethyl 3-pyrazolecarboxylate **13g** and ethyl 3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate **13h** in the presence of triphenylphosphine and diisopropyl azodicarboxylate in tetrahydrofuran provided their corresponding methyl ester imidazole nucleoside **14a** (80%), **14b** (76%) and ethyl ester pyrazole nucleosides **14e** (88%), **14f** (92%), **14g** (85%) and **14h** (62%), respectively. Unexpectedly, the Mitsunobu reactions of **5** with ethyl ester pyrrole carboxylates (**13c** and **13d**) afforded only a trace amount of their corresponding pyrrole nucleoside derivatives **14c** and **14d**. Therefore, compound **6** was employed as an alternative approach for the efficient synthesis of pyrrole nucleoside derivatives. The displacement reactions of **6** with 3,5-diethyl ester pyrrole carboxylate **13c** and 5-methyl ester pyrrole carboxylate **13d** were performed under *method B* conditions to obtain the pyrrole nucleoside derivative **14c** (69%) and **14d** (72%), respectively (entry 3 and 4). The imidazole esters **14a**–**b** and pyrazole esters **14e**–**h** were transformed to their corresponding amides with saturated methanolic ammonia, followed by deprotection of TBDPS and isopropylidene groups by using methanolic hydrogen chloride solution to afford the desired compound **15a**–**b** and **15e**–**h**[22] in good yields. However, subsequent removal of TBDPS and isopropylidene groups of **14c**–**d** with methanolic hydrogen chloride, and treatment of deprotected esters with methanolic ammonia solution gave amide **15c** in 40% yield and amide **15d** in 25% yield (2 steps) as the reaction of the pyrrole esters (**14c**–**d**) with the methanolic ammonia provided the amides in low yield. Additionally, the ester intermediates **14a**–**h** were converted to their corresponding cyclic (pyridazine) or acyclic (hydraizde) derivatives **16a**–**h**. The treatment of **14a**–**h** with hydrazine in methanol, followed by deprotection of TBDPS and isopropylidene with methanolic hydrogen chloride to provide pyridazine analog **16a** (87%), as well as hydrazide derivatives (**16b**–**h**)[23] in high yields as summarized in Table 1. The newly synthesized carbocyclic five-membered heterocyclic nucleosides (**9**, **11**, **15a**–**h**, and **16ah**) were evaluated for their antiviral activity *versus* both HIV-1_{LAI} and HCV (genotype 1b). For HCV activity, compounds were evaluated for their ability to inhibit HCV RNA replication using an Huh7 cell based subgenomic replicon assay.[24] Cytotoxicity in Huh7 cells was determined simultaneously with anti-HCV activity by extraction and amplification of both HCV RNA and Huh7

ribosomal RNA (rRNA). In addition, all compounds were evaluated against HIV-1 in human peripheral blood mononuclear (PBM) cells and cytotoxicity was determined in PBM, CEM and Vero cells.[25]

Unfortunately, most of the nucleoside analogs did not show antiviral activity *versus* HIV-1 or HCV. Only the pyrazole amide **15f** showed mild antiviral activity *versus* HIV-1 (median effective concentration or EC_{50} = 24 μM). None of these nucleoside analogs displayed cytotoxicity in PBM, CEM or Vero cells up to 100 μM.

Isopropyl alanine phenoxy phosphoramidate prodrugs were prepared for nucleoside analogs **15b**, **15f**, **15g** and **15h** and evaluated for antiviral activity and cytotoxicity to determine if the phosphorylation of these nucleoside analogs was the limiting factor for their antiviral activity (Figure 3).

These monophosphate prodrugs did not improve the antiviral activity *versus* HIV-1 or HCV, but also did not increase cytotoxicity *versus* PBM, CEM or Vero cells. Further studies of potential antiviral activity against other RNA viruses is progressing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and notes

1. Simons, C. Nucleoside Mimetics: Their Chemistry and Biological properties. Cardiff University:UK: Gordon and Breach Science Publishers; 2000.
2. (a) Shive W, Ackermann WW, Gordon M, Getzendaner ME, Eakin RE. J. Am. Chem. Soc. 1947; 69:725–726. [PubMed: 20289473] (b) Flaks JG, Erwin MJ, Buchanan JM. J. Biol. Chem. 1957; 288:201–213. [PubMed: 13475309] (c) Lowy BA, Cook JL, London IM. J. Biol. Chem. 1961; 236:1442–1445. [PubMed: 13763872]
3. (a) Hardi DG, Mackintosh RW. BioEssays. 1992; 14:699–704. [PubMed: 1365882] (b) Kemp BE, Mitchelhill DS, Michell BJ, Chen Z-P, Witters LA. Trends. Biochem. Sci. 1999; 24:22–25. [PubMed: 10087918] (c) Caring D. Trends. Biochem. Sci. 2004; 29:18–24. [PubMed: 14729328] (d) Motoshima H, Goldstein BJ, Igata M, Araki E. J. Physiol. 2006; 574:63–71. [PubMed: 16613876]
4. (a) Sullivan JE, Brocklehurst KJ, Marley AE, Carey F, Carling D, Beri RK. FEBS Lett. 1994; 353:33–36. [PubMed: 7926017] (b) Fryer SA, Parbu-patel A, Carling D. J. Biol. Chem. 2002; 277:25226–25232. [PubMed: 11994296]
5. (a) Merrill GF, Kurth EJ, Hardie DG, Winder WW. Am. J. Physiol. 1997:E1107–E1112. [PubMed: 9435525] (b) Hong SP, Leiper FC, Woods A, Carlson M. Proc. Natl. Acad. Sci. U. S. A. 2003; 100:8839–8834. [PubMed: 12847291] (c) Hardi DG, Scott JW, Pan DA, Hudson ER. FEBS Lett. 2003; 546:113–120. [PubMed: 12829246]
6. Sun Y, Connors KE, Yang D-Q. Mol. Cell. Biochem. 2007; 306:239–245. [PubMed: 17786544]

7. Rattan R, Giri S, Singh AK, Singh I. J. Biol. Chem. 2005; 280:39582–39593. [PubMed: 16176927] and references therein.
8. Ni L, Guan K, Zalkin H, Dixon JE. Gene. 1991; 106:197–205. [PubMed: 1937050]
9. (a) Pankiewicz KW, Patterson SE, Black PL, Jayaram HN, Risal D, Golgstein BM, Stuyver LJ, Schinzai RF. Curr. Med. Chem. 2004; 11:887–900. [PubMed: 15083807] (b) Nair V, Shu Q. Med. Res. Rev. 2008; 28:219–232. [PubMed: 17480004] (c) Hedstrom L. Chem. Rev. 2009; 109:2903–2928. [PubMed: 19480389]
10. (a) Jackson RC, Weber G, Morris HP. Nature. 1975; 256:331–333. [PubMed: 167289] (b) Nair V, Shu Q. Antiviral Chem. Chemother. 2007; 18:245–258.
11. (a) Inou T, Kusaba R, Takahashi I, Sugimoto H, Kuzuhara K, Yamada Y, Yamauchi J, Otsubo O. Transplantation Proc. 1981; 13:135–138.(b) Mizuno K, Tsujino M, Takada M, Hayashi M, Atsmi K, Asano K, Matsuda T. J. Antibiot. 1974; 27:775–782. [PubMed: 4616933]
12. (a) Minakawa N, Takeda T, Sasaki T, Matsuda A, Ueda T. J. Med. Chem. 1991; 34:778–786. [PubMed: 1995901] (b) Balzarini J, Lee C-K, Herdewijn P, De Clercq E. J. Biol. Chem. 1991; 266:21509–21514. [PubMed: 1939181]
13. (a) Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK. Science. 1972; 177:705–706. [PubMed: 4340949] (b) Witkowski JT, Robins RK, Sidwell RW, Simon LN. J. Med. Chem. 1972; 15:1150–1154. [PubMed: 4347550]
14. (a) Willis RC, Robins RK, Seegmiller JE. Mol. Pharmacol. 1980; 18:287–297. [PubMed: 6106888] (b) Witkowski JT, Robins RK, Sidwell RW, Simon LN. J. Med. Chem. 1973; 16:935–937. [PubMed: 4355593]
15. (a) Fuertes M, Garcia Lopez T, Garcia Monoz G, Stud M. J. Org. Chem. 1976; 41:4074.(b) Ramasamy KS, Lau JYN. Nucleosides Nucleotides Nucleic Acids. 2001; 20:1329–1331. [PubMed: 11563015]
16. (a) Cho JH, Amblard F, Coats SJ, Schinazi RF. J. Org. Chem. 2013; 78:723–727. [PubMed: 23231055] (b) Cho JH, Bernard DL, Sidwell RW, Kern ER, Chu CK. J. Med. Chem. 2006; 49:1140–1148. [PubMed: 16451078]
17. (a) Meldal M, Tornφe CW. Chem. Rev. 2008; 108:2952. [PubMed: 18698735] (b) Amblard F, Cho JH, Schinazi RF. Chem. Rev. 2009; 109:4207–4220. [PubMed: 19737023]
18. Wang Q, Chan TR, Hilgraf R, Fokin VV, Sharpless KB, Finn MG. J. Am, Chem. Soc. 2003; 125:3192–3193. [PubMed: 12630856] and references therein.
19. (a) Angell YL, Burgess K. Chem. Soc. Rev. 2007; 36:1674. [PubMed: 17721589] (b) Jewett JC, Bertozzi CR. Chem. Soc. Rev. 2009; 38:3449–3462. [PubMed: 20449062] (c) Iha RK, Wooley KL, Nyström AM, Burke DJ, Kade MJ, Hawker CJ. Chem. Rev. 2009; 109:5620–5658. [PubMed: 19905010] (d) Mamidyala SK, Finn MG. Chem. Soc. Rev. 2010; 39:1252–1261. [PubMed: 20309485] (e) Kappe CO, Van der Eycken EV. Chem. Soc. Rev. 2010; 39:1280–1290. [PubMed: 20309486] (f) Hein JE, Fokin VV. Chem. Soc. Rev. 2010; 39:1302–1315. [PubMed: 20309487] (g) Appukkuttan P, Mehta VP, Van der Eycken EV. Chem. Soc. Rev. 2010; 39:1467–1477. [PubMed: 20419202] (h) Thirumurugan P, Matosiuk D, Jozwiak K. Chem. Rev. 2013; 113:4905–1479. [PubMed: 23531040]
20. Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.43 (m, 6H), 7.23 (d, *J* = 3.6 Hz, 1H), 5.09 (s, 1H), 5.57 (s, 1H), 5.54 (d, *J* = 8.8 Hz, 1H), 5.17 (t, *J* = 5.6 Hz, 1H), 4.68 (d, *J* = 4.8 Hz, 1H), 4.63 (m, 1H), 4.44 (m, 2H), 3.74 (s, 3H), 3.24 (d, *J* = 4.8 Hz, 2H), 1.44 (s, 9H), 1.39 (s, 1H), 1.30 (s, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 151.8, 135.5, 133.1, 129.9, 127.8, 121.6, 120.8, 112.6, 84.8, 83.4, 69.9, 61.2, 52.9, 52.4, 28.3, 27.3, 26.8, 25.9, 19.2; MS-ESI$^+$ *m*/*z* 677 $(M+H)^+$; HRMS-ESI$^+$: *m*/*z* calcd. for $C_{36}H_{49}N_4O_7Si$ $(M+H)^+$ 677.3369, found 677.3365.
21. (a) Mitsunobu O. Synthesis. 1981:1–28.(b) Swamy KCK, Kumar NNB, Balaraman E, Kumar KVPP. Chem. Rev. 2009; 109:2551–2651. [PubMed: 19382806]
22. Compound **15f**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 7.91 (s, 1H), 5.69 (q, *J* = 2.0 Hz, 1H), 5.14 (d, *J* = 2.0 Hz, 1H), 4.41 (d, *J* = 5.2 Hz, 1H), 4.14 (q, *J* = 1.6 Hz, 2H), 4.08 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 151.5, 141.3, 133.6, 125.4, 125.1, 116.8, 79.1, 74.3, 73.6, 60.4; MS-ESI$^+$ *m*/*z* 240 $(M+H)^+$; HRMS-ESI$^+$: *m*/*z* calcd. for $C_{10}H_{14}N_3O_4$ $(M+H)^+$ 240.0980, found 240.0979.

23. Compound **16f**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1H), 7.79 (s, 1H), 5.62 (q, *J* = 1.6 Hz, 1H), 5.08 (d, *J* = 2.4 Hz, 1H), 4.34 (d, *J* = 5.2 Hz, 1H), 4.06 (q, *J* = 2.0, 2H), 4.00 (t, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.7, 151.3, 140.9, 133.1, 125.5, 115.4, 79.0, 74.2, 73.6, 60.4; MS-ESI$^+$ *m*/*z* 255 $(M+H)^+$; HRMS-ESI$^+$: *m*/*z* calcd. for $C_{10}H_{15}N_4O_4$ $(M+H)^+$ 255.1089, found 255.1088.

24. Stuyver LJ, Whitaker T, McBrayer TR, Hernandez-Santiago BI, Lostia S, Tharnish PM, Ramesh M, Chu CK, Jordan R, Shi J, Rachakonda S, Watanabe KA, Otto MJ, Schinazi RF. Antimicrob. Agents Chemother. 2003; 47:244–254. [PubMed: 12499198]

25. (a) Schinazi RF, Sommadossi JP, Saalmann V, Cannon DL, Xie M-W, Hart GC, Smith GA, Hahn EF. Antimicrob. Agents Chemother. 1990; 34:1061–1067. [PubMed: 2393266] (b) Stuyver LJ, Lostia S, Adams M, Mathew JS, Pai BS, Grier S, Tharnish PM, Choi Y, Chong Y, Choo H, Chu CK, Otto MJ, Schinazi RF. Antimicrob. Agents Chemother. 2002; 46:3854–3860. [PubMed: 12435688]

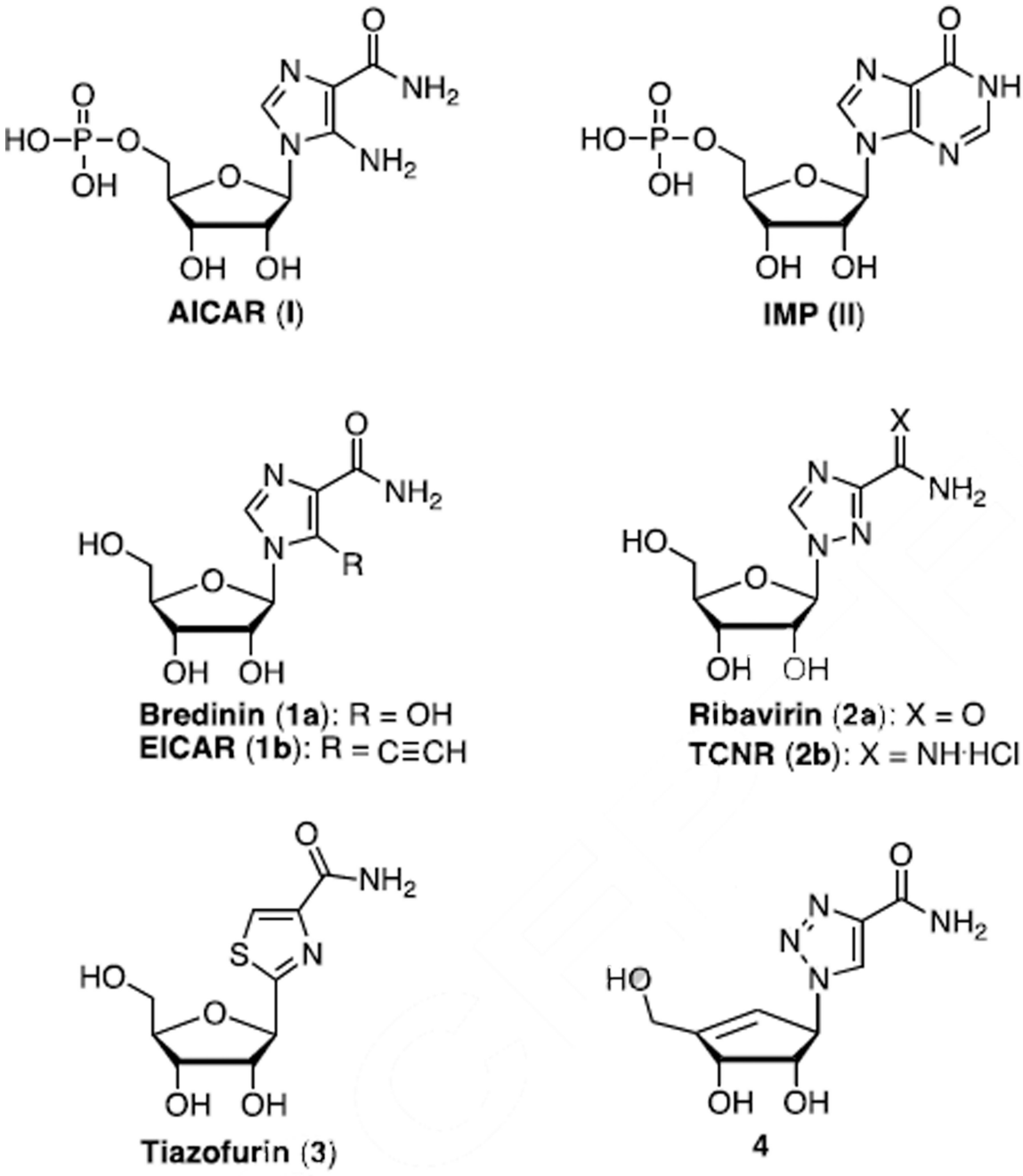


Figure 1.
Structures of AICAR, IMP and related biologically active five-membered heterocyclic nucleobase nucleoside analogs.

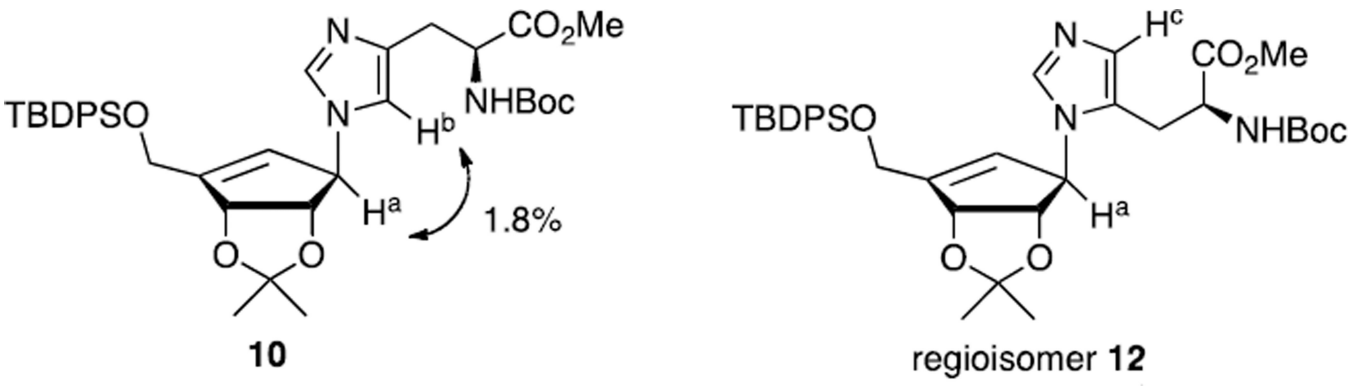


Figure 2.
1D-NOE spectra of compound **10** and its isomer **12**.

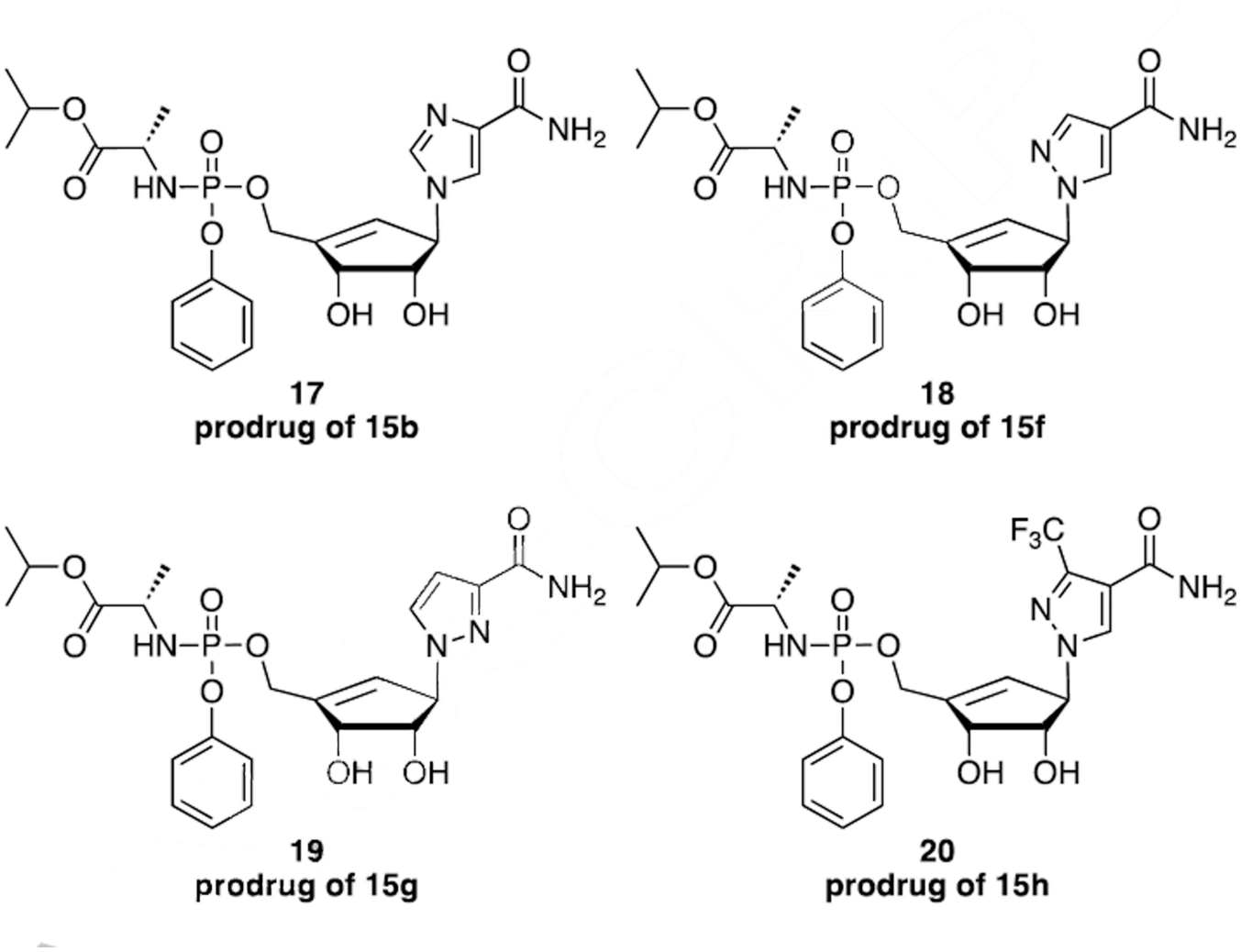
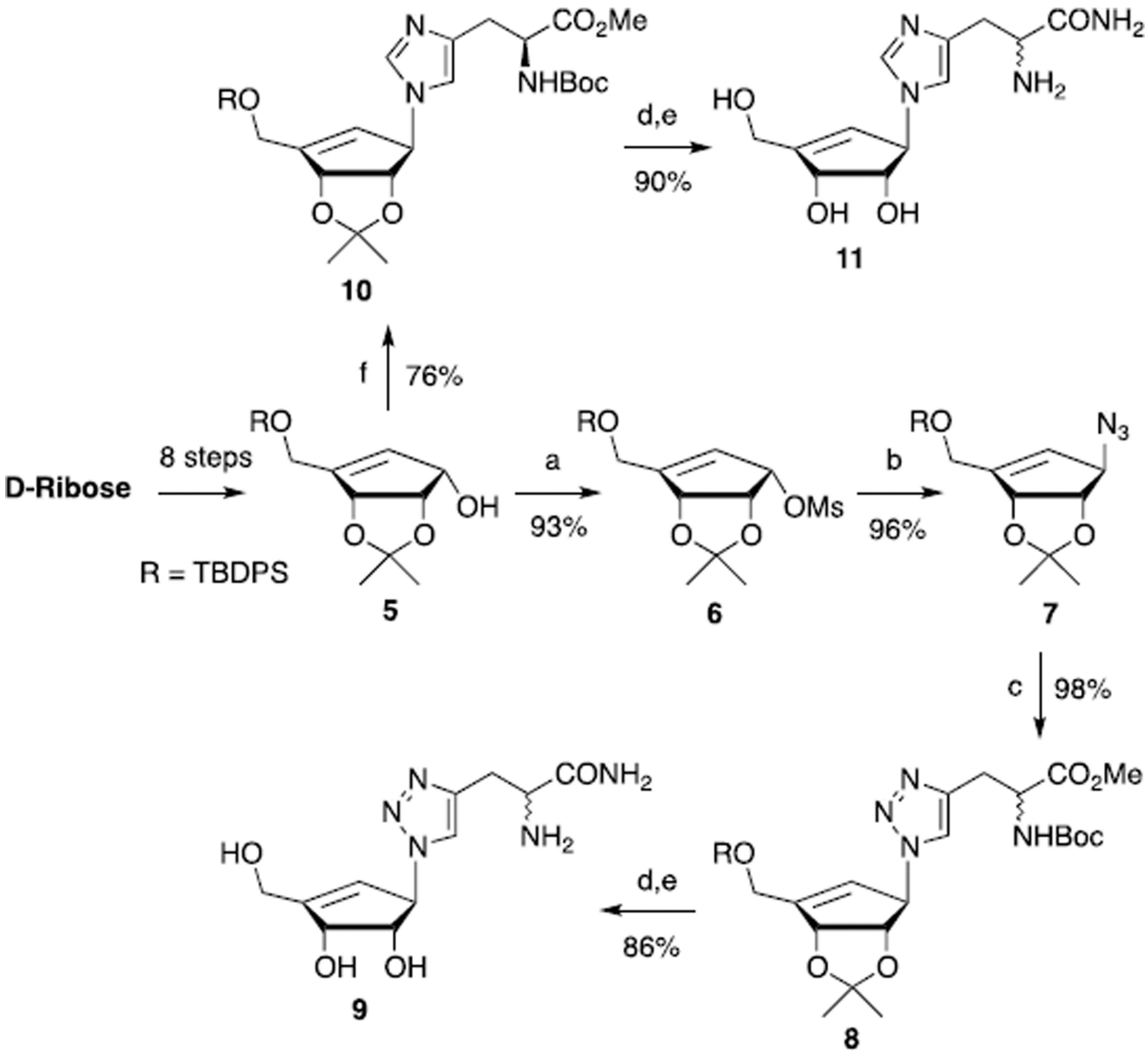


Figure 3.
Phosphoramidate prodrugs of nucleoside analogs **15b**, **15f**, **15g** and **15h**.

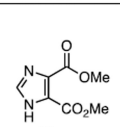
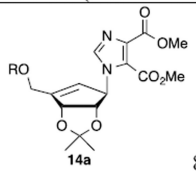
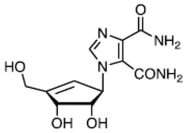
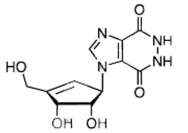
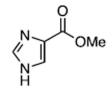
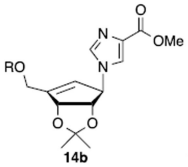
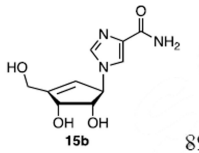
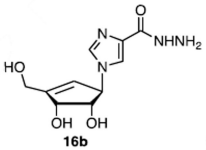
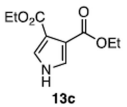
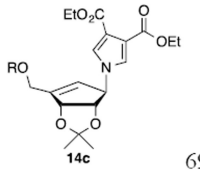
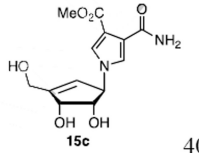
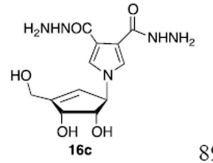
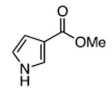
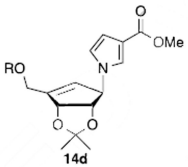
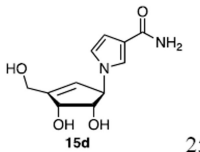
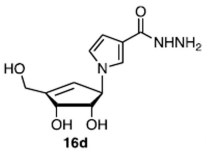
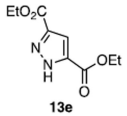
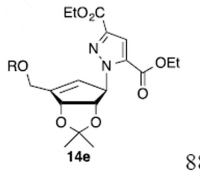
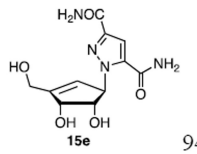
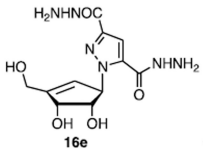
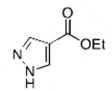
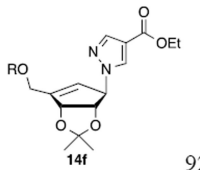
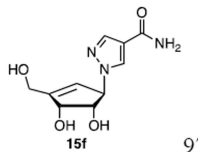
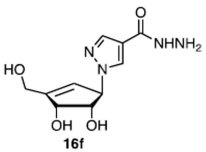
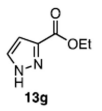
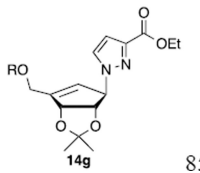
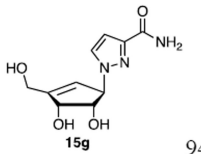
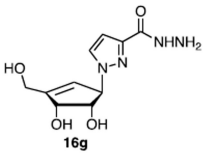


Scheme 1.

Reagents and reaction conditions: a) see reference 16 for synthesis of **5**, MsCl, Et_3N, CH_2Cl_2, 0 °C, 3h; b) NaN_3, DMF, 70 °C, 8h; c) D,L-methyl 2-(*t*-butoxycarbonylamino)pent-4-ynoate, CuI, Et_3N, THF, rt, 12h; d) NH_3/MeOH, rt, 12h; e) HCl/MeOH, rt, 6h; f) *N*-Boc-L-histidine methyl ester, DIAD, PPh_3, THF, rt, 12h.

Table 1

Results of coupling reactions and synthesis of carbocyclic nucleoside analogs

Entry	Heterocyclic base	Starting sugar Method	Product of coupling step, Yield (R = TBDPS)[a]	Product with ammonia, Yield[a]	Product with hydrazide, Yield[a]
1	 13a	**5** A[b]	 14a 80%	 15a 91%	 16a 87%
2	 13b	**5** A[b]	 14b 76%	 15b 89%	 16b 90%
3	 13c	**6** B[c]	 14c 69%	 15c 40%	 16c 89%
4	 13d	**6** B[c]	 14d 72%	 15d 25%	 16d 90%
5	 13e	**5** A[b]	 14e 88%	 15e 94%	 16e 97%
6	 13f	**5** A[b]	 14f 92%	 15f 97%	 16f 95%
7	 13g	**5** A[b]	 14g 85%	 15g 94%	 16g 96%

8	5			
	A[b]		62%	
	A[b]		89%	
	A[b]		94%	

[a]The yield was obtained after silica gel column chromatography.

[b]Mitsunobu reaction was used (method A).

[c]NaH/DMF was used (method B)