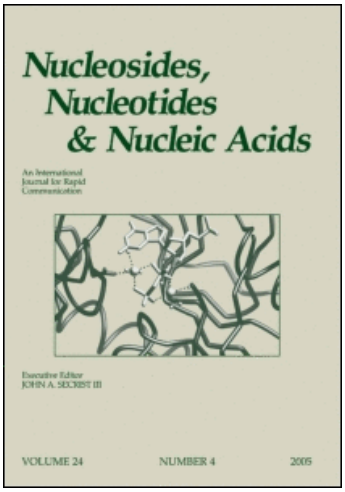

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Carboxyamidation of Purine Nucleosides: New Secondary 8-Carboxamidopurine Nucleosides

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CARBOXYAMIDATION OF PURINE NUCLEOSIDES: NEW SECONDARY 8-CARBOXAMIDOPURINE NUCLEOSIDES

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Abstract. Palladium catalyzed carboxyamidation at the 8-position of 8-bromoadenosine and 8-bromoguanosine nucleosides is a versatile reaction, which allows primary, secondary, heterocyclic, aromatic amine and amino acids to be incorporated into purine nucleosides.

Introduction. The success of nucleosides as anti-viral and anti-neoplastic agents is a source of motivation for preparing new synthetic modifications. The importance of the amide functionality to the biological activity[1] in ribavirin[2] and the recent interest in purine nucleoside antivirals prompted the research described herein. The target of this research was the stream-lined synthesis of a wide array of 8-carboxamidoadenosines and 8-carboxamidoguanosines. More specifically, it was desired to prepare secondary 8-carboxamides of the purine nucleosides with a wide array of amines, including amino acids.

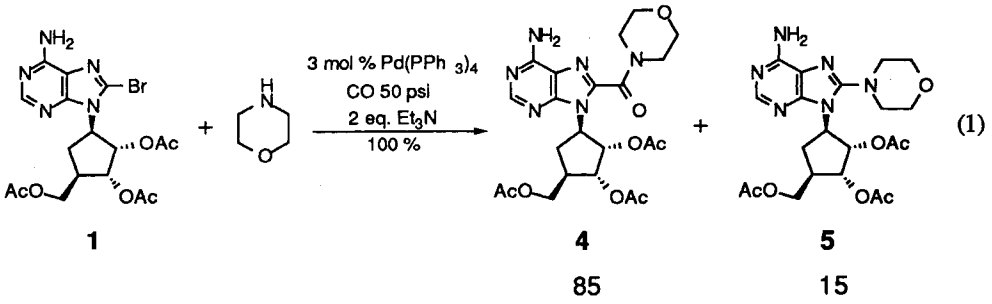
Facile synthetic methods for the modification of purine nucleosides were also desired for the modification of oligonucleotide therapeutics.[3] Recently oligonucleotides have been shown to be potential drugs. Initially, the antisense strategy appeared to be the major paradigm for oligonucleotide therapeutics.[4] More recently, RNA molecules can be evolved that bind with high affinity and specificity[5] to a wide array of medicinally important targets.[6] The affinity of SELEX derived oligonucleotide ligands may be fine tuned by modification of the bases or ribose.[7] Preferably, base modifications would not directly interfere with H-bonding and enrich the structural motifs possible. Ideally, new functionality would be incorporated into both pyrimidine[8] and purine nucleosides in a single step starting from a wide array of commercially available reagents such as amines.

Previously, primary 8-carboxamidoadenosine had been prepared by either, homolytic aceylation,[9] or cyano substitution of 8-bromo derivatives and subsequent

hydrolysis,[10] or lithium-halogen exchange of 8-bromo derivatives, acylation with chloroformates followed by amidation of the ester.[11] One example of a 8-carboxamidopurine nucleoside has been prepared directly as a side product of an iron catalyzed alkylation of 8-bromoguanosine.[12] One example of a tertiary amide, 8-*N,N'*-diisopropyl-carboxamidoadenosine was detected as a side product of the lithiation and amidation reactions.[11] In general only reliable synthetic methods for primary amides at the 8-position of adenosine and guanosine were known. Elaboration of previously reported methods to allow for the preparation of 8-carboxamidoadenosine nucleosides from 8-carboxyadenosine would require amidation with amines. At the outset we were concerned to attempt forming the desired secondary amides by condensation of amines with 8-carboxypurine nucleosides because they are well known to undergo spontaneous decarboxylation.[13] We reasoned that mild palladium catalyzed carboxyamidation reactions might be superior for the synthesis of 8-carboxamidoadenosines and guanosines because formation of the intermediate 8-carboxypurine nucleosides could be avoided. In addition, the deglycosylation of 8-carboxamidoadenosine has been reported to be rapid, which suggested that yields would be higher for these modified nucleosides if the number of synthetic manipulations could be minimized.

There are numerous literature reports on palladium catalyzed modification of purine nucleosides.[14] However, previous to the results reported here, palladium catalyzed carboxyamidation was only known for the reaction of aryl or vinyl halides, amines and carbon monoxide.[15] A plethora of amine containing compounds are commercially available potentially allowing for the facile synthesis of 8-carboxamidopurine nucleosides from the 8-bromo derivatives. However, precedent existed for the facile substitution of 8-bromopurine nucleosides with amines to give the corresponding 8-aminopurine nucleosides,[16] making the success of palladium catalyzed carboxyamidation uncertain. Experience with pyrimidines[17] aided the development of palladium catalyzed carboxyamidation methods for the modification of purines.[18] Herein we describe methods useful for the assembly of 8-carboxamidopurine nucleosides with a diverse array of functional groups.

Results and Discussion. Our investigation began with the reaction of **1**, morpholine and carbon monoxide in the presence of a catalytic amount of $Pd(PPh_3)_4$ (eq 1). These initial reaction conditions produced the desired product **4** in high yield (85%) in addition to the substitution product **5** (15%). NMR analysis of the crude reaction mixture revealed no other products. The effect on yield and the ratio of **4**:**5** was studied as a function of solvent, reaction temperature, palladium catalyst, and moderate changes in carbon monoxide pressure (40 - 100 psi.). In all experiments the ratio of **4**:**5** remained the same. In the absence of carbon monoxide and palladium a quantitative yield of **5** was



1 4 5

85 15

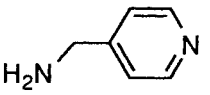
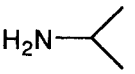
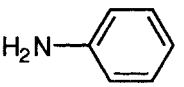
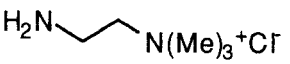
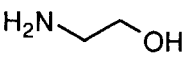
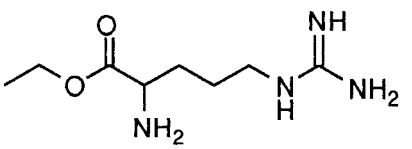
(1)

obtained, reinforcing our fears that a broad array of functionalized amines would give an equally broad number of 8-amino products.

The reaction conditions established during the course of study were 1 equivalent of nucleoside (0.5 mmol), 2 equivalent of amine (1.0 mmol), 2 equivalent of Et_3N (1.0 mmol), 50 psi. of carbon monoxide, and 3 mol % of $Pd(PPh_3)_4$ in DMA or DMF at 80 °C for 24 hours. To investigate the influence of the amine on the success of the carboxyamidation reaction of adenosine a diverse group of amines (Table 1) were treated under the optimized conditions. Excellent yields were obtained for most amines. Surprisingly, of the amines studied only morpholine, *n*-butylamine and 2-aminoethanol gave substitution reactions competitive to carboxyamidation. The reaction of **1** and 2-aminoethanol (entry 9) yielded **12** as the major product (62%) together with the corresponding ester (14%) and direct substitution product (14%). The reaction of *n*-butylamine with **1** produced the amide product (84 %) and (16 %) of the substitution product. In both cases the two products were easily separated by column chromatography. Aniline, a poor nucleophile, also produced a moderate yield of the coupling product with a longer coupling time (3 days, entry 7). The low yield for the reaction of aniline is unclear, but was not the result of instability of the product. The palladium-catalyzed carboxyamidation works surprisingly well with hindered amines, such as *i*-propylamine and *t*-butylamine (entries 5 and 6) providing high yields of carboxyamidation products which would be difficult to obtain using previous synthetic methods such as the reaction of 8-lithio-purines with carbamides. There is no evidence for the formation of the corresponding direct substitution products with these hindered amines.

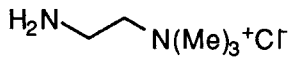
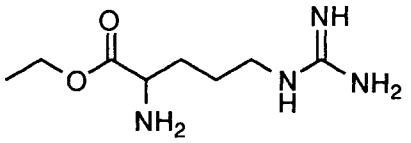
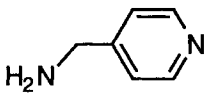
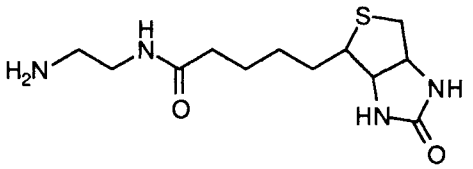
It was of interest to attach amino acid functionality to the nucleoside. Arginine ethyl ester was chosen because it seemed most likely to be problematic because of its unique guanidyl functionality, which might interfere with the carboxyamidation by complexation to the palladium. In addition, it was of interest to prepare purine nucleosides with appended amino acids that contained positively charged groups. Inclusion of positively charged modified bases into oligonucleotides could reduce the overall net negative charge of

TABLE 1. Carboxyamidation yields for **1.**

Entry	Amine	Product #	Isolated Yield (%)
3		6	93
4	H_2N-*n*-Bu	7	84
5		8	95
6	H_2N-*t*-Bu	9	98
7		10	41
8		11	91
9		12	62
10		13	71

1 = 2',3',5'-triacetyl-8-bromoadenosine. All products were the result of reaction at the amine functionality and deprotected prior to characterization and determination of yield.

TABLE 2. Carboxyamidation for **2**.

Entry	Amine	Product #	Isolated Yield (%)
11	H_2N-*t*-Bu	14	85
12		15	98
13		16	88
14		17	81
15		18	56

2 = 2',3',5'-triacetyl-8-bromoguanosine. All products were the result of reaction at the amine functionality and deprotected prior to characterization and determination of yield.

oligonucleotides, depending on the pH of the solution, and could be important for the design of therapeutic agents. Employing the reaction conditions discussed above gave high product yields from the reaction of **1** with arginine (entry 10) suggesting that simpler amino acids should also undergo clean reaction. Attachment of the arginine by the amine as opposed to the guanidyl group is indicated by the down-field shift (4.67 ppm) of the ^1H resonance on the α-carbon. Another cationic group, which would have no pH dependence on its charge, is a quaternary ammonium group (Table 2, entry 8). One example, *N,N',N''*-trimethylethylenediamine chloride (entry 8) gave an excellent yield of the cationic adenosine nucleoside **11**.

Palladium catalyzed reactions of guanosine have been less studied than those of adenosine. The tendency for guanosine derivatives to deglycosylate is well known and would be predicted to be worse when electron withdrawing groups are attached to the ring. Cautiously, it was decided to test carboxyamidation of **2** (Table 2) on those amines which might be most likely to be a problem because of their functionality. Gratifyingly, four of the five amines chosen produced good yields (entries 11 to 14). NMR analysis of the reaction mixtures showed excellent conversion to the desired product, suggesting that the lower yield of **18** is due to loss of the product during the chromatographic purification process. It should be noted that most of the carboxyamidation reactions with adenosine and guanosine appeared to give near quantitative yields as determined by ^{1}H NMR. In addition, the guanosine nucleosides **11** - **15** appeared quite stable under the conditions studied.

Conclusion. Carboxyamidation at the 8-position of purine nucleosides is a versatile reaction that allows a wide variety of amine functional groups to be integrated into the nucleoside in good yield regardless of added functionality or charge. In contrast to previous synthetic methods for the synthesis of primary 8-carboxamidopurine nucleosides, amines containing primary, secondary, heterocyclic, aromatic amine, amino acid and one example of an amine bearing a quaternary ammonium salt were attached successfully. Hindered amines gave excellent yields of the desired amides, which would be difficult to obtain by previous conventional synthetic methods. In addition, hindered amines gave none of the direct substitution products. Under the mild conditions studied, some amines gave varying amounts of direct substitution of bromide at the 8-position. We are currently investigating the biological activity of these purine nucleosides as well as their incorporation into oligonucleotides by use of SELEX protocols.

Experimental. The ^{1}H and ^{13}C NMR spectra were obtained in CD_3OD, D_2O, $CDCl_3$, or DMSO-d_6 on a Bruker ARX300 spectrometer using the residual proton resonances as a reference. Fast atom bombardment mass spectra (FAB MS) were obtained with a VG 70 SE & ZAB2-EQ/FAB(+). The reagents 8-bromoadenosine, 8-bromoguanosine hydrate, morpholine, *n*-butylamine, *i*-propylamine, *t*-butylamine, aniline, 4-aminomethyl pyridine, 2-(aminoethyl)trimethylammonium chloride, arginine, ethanolamine, triethylamine, DMF and DMA were purchased from Aldrich Chemical Company and were used as supplied. The reagent N-(2-aminoethyl)biotinamide hydrobromide was purchased from Molecular Probes, Inc. and used as supplied.

General synthetic procedure. To a glass bomb with Teflon valves was added nucleoside (0.5 mmol), amine (1.0 mmol), $Pd(PPh_3)_4$ (0.015 mmol), triethylamine (1.0 mmol) and DMF (or DMA). The glass bomb was evacuated and charged with CO (50 psi) before heating to the desired temperature for 24 hours. The DMF was removed by vacuum

and the residue was purified by flash chromatography with silica gel using a mixture of methanol (5 - 30 %) and methylene chloride.

4. ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.10 (s, 3 H), 2.14 (s, 3 H), 3.77 (m, 2 H), 3.86 (m, 6 H), 4.36 (m, 2 H), 4.49 (m, 1 H), 5.84 (t, *J* = 6.3 Hz, 1 H), 5.92 (s, 2 H), 6.12 (dd, *J* = 6.3, 4.0 Hz, 1 H), 6.44 (d, *J* = 4.0 Hz, 1 H), 8.40 (s, 1 H); ^{13}C NMR (DMSO/D_2O) δ 20.5, 20.6, 20.7, 42.8, 47.9, 63.1, 66.6, 66.9, 70.4, 73.3, 79.9, 88.1, 118.3, 142.9, 150.1, 152.2, 155.1, 158.7, 169.6, 169.7, 170.6; MS (FAB) m/z $(M + 1)^+$ 507.1838 (Calc. 507.1840 for $C_{21}H_{26}N_6O_9 + H^+$).

6. ^{1}H NMR (D_2O) δ 3.72 (dd, *J* = 12.5, 2.3 Hz, 1 H), 3.88 (dd, *J* = 12.5, 2.0 Hz, 1 H), 4.16 (m, 1 H), 4.37 (m, 1 H), 4.65 (s, 2 H), 4.98 (m, 1 H), 7.14 (d, *J* = 7.2 Hz, 1 H), 7.43 (d, *J* = 5.7 Hz, 2 H), 8.18 (s, 1 H), 8.47 (d, *J* = 5.7 Hz, 2 H); ^{13}C NMR (D_2O/CD_3OH, 10/1) δ 43.0, 64.1, 73.0, 74.7, 88.5, 91.3, 120.1, 124.0, 143.2, 150.2, 150.6, 151.5, 154.6, 158.8, 161.0; MS (FAB) m/z $(M + 1)^+$ 402.1522 (Calc. 402.1526 for $C_{17}H_{19}N_7O_5 + H^+$).

7. ^{1}H NMR (DMSO-d_6) δ 0.91 (t, *J* = 7.2 Hz, 3 H), 1.34 (m, 2 H), 1.52 (m, 2 H), 3.31 (t, *J* = 7.2 Hz, 1 H), 3.53 (m, 1 H), 3.68 (m, 2 H), 3.95 (d, *J* = 2.7 Hz, 1 H), 4.20 (m, 1 H), 4.96 (dd, *J* = 12.0, 6.4 Hz, 1 H), 5.13 (d, *J* = 4.4 Hz, 1 H,), 5.25 (d, *J* = 6.7 Hz, 1 H), 5.59 (dd, *J* = 8.9, 3.4 Hz, 1 H), 6.69 (d, *J* = 6.7 Hz, 1 H), 7.60 (s, 2 H), 8.18 (s, 1 H), 8.73 (t, *J* = 5.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 23.2, 29.1, 40.5, 48.1, 71.8, 80.4, 81.3, 95.8, 98.6, 127.4, 152.2, 159.5, 162.9, 166.4, 168.2; MS (FAB) m/z $(M + 1)^+$ 367.1723 (Calc. 367.1729 for $C_{15}H_{22}N_6O_5 + H^+$).

8. ^{1}H NMR (CD_3OD) δ 1.27 (d, *J* = 6.5 Hz, 6 H), 3.73 (dd, *J* = 12.5, 2.6 Hz, 1 H), 3.89 (dd, *J* = 12.5, 2.2 Hz, 1 H), 4.17 (m, 1 H), 4.21 (q, *J* = 6.0 Hz, 1 H), 4.37 (dd, *J* = 5.3, 2.0 Hz, 1 H), 4.96 (dd, *J* = 7.0, 5.3 Hz, 1 H), 7.07 (d, *J* = 7.0 Hz, 1 H), 8.19 (s, 1 H); ^{13}C NMR (CD_3OD) δ 22.5, 43.1, 64.1, 72.9, 74.7, 88.4, 91.3, 119.9, 144.0, 151.4, 154.4, 158.7, 159.8; MS (FAB) m/z $(M + 1)^+$ 353.1574 (Calc. 353.1573 for $C_{14}H_{20}N_6O_5 + H^+$).

9. ^{1}H NMR (DMSO-d_6/D_2O, 4/1) δ 1.37 (s, 9 H), 3.52 (dd, *J* = 12.3, 3.1 Hz, 1 H), 3.66 (dd, *J* = 12.3, 3.1 Hz, 1 H), 3.94 (m, 1 H), 4.18 (m, 1 H), 4.91 (t, *J* = 5.5 Hz, 1 H), 6.74 (d, *J* = 6.8 Hz, 1 H,), 8.15 (s, 1 H); ^{13}C NMR (DMSO/D_2O) δ 28.7, 52.0, 62.7, 71.3, 72.4, 86.7, 89.5, 118.1, 143.2, 150.4, 153.9, 157.2, 158.6; MS (FAB) m/z $(M + 1)^+$ 367.1723 (Calc. 367.1717 for $C_{15}H_{22}N_6O_5 + H^+$).

10. ^{1}H NMR (DMSO-d_6/D_2O, 4/1) δ 3.74 (dd, J = 12.5, 2.3 Hz, 1 H), 3.91 (dd, J = 12.5, 2.3 Hz, 1 H), 4.19 (m, 1 H), 4.39 (dd, J = 5.4, 2.0 Hz, 1 H), 4.99 (dd, J = 7.1, 5.5 Hz, 1 H), 7.18 (m, 2 H,), 7.39 (t, J = 5.6 Hz, 2 H), 7.74 (d, J = 5.6 Hz, 2 H), 8.21 (s, 1 H); ^{13}C NMR (DMSO-d_6/D_2O, 4:1) δ 62.2, 70.9, 71.9, 86.4, 89.1, 118.0, 120.0, 124.5, 128.9, 138.0, 142.7, 150.1, 153.7, 157.0, 157.3 ; MS (FAB) m/z (M + 1)$^+$ 387.1419 (Calc. 387.1417 for $C_{17}H_{18}N_6O_5$ + H^+).

11. ^{1}H NMR (CD_3OD) δ 3.27 (s, 9 H), 3.65 (t, J = 6.4 Hz, 2 H), 3.73 (dd, J = 12.5, 2.5 Hz, 1 H), 3.90 (m, 3 H), 4.17 (m, 1 H), 4.36 (dd, J = 5.4, 1.7 Hz, 1 H), 4.96 (dd, J = 7.1, 5.4 Hz, 1 H,), 7.16 (d, J = 7.1 Hz, 1 H,), 8.19 (s, 1 H); ^{13}C NMR (CD_3OD) δ 35.0, 54.1, 64.1, 65.6, 73.0, 74.6, 88.7, 91.1, 120.1, 142.7, 151.5, 154.7, 158.9, 161.1; MS (FAB) m/z (M - Cl^-)$^+$ 396.1995 (Calc. 396.1995 for $C_{16}H_{26}N_7O_5$ Cl).

12. ^{1}H NMR (DMSO-d_6/D_2O, 4/1) δ 3.35 (m, 2 H), 3.53 (m,3 H), 3.67 (dd, J = 12.5, 3.1 Hz, 1 H), 3.96 (m, 1 H), 4.17 (dd J = 5.2, 2.2 Hz, 1 H), 4.89 (t, J = 5.9 Hz, 1 H),6.86 (d, J = 6.8 Hz, 1 H), 8.15 (s, 1 H); ^{13}C NMR (DMSO-d_6/D_2O, 4/1) δ 42.0, 59.8, 62.7, 71.3, 72.4, 86.7, 89.5, 118.0, 142.4, 150.5, 154.0, 157.3, 159.7; MS (FAB) m/z (M + 1)$^+$ 355.1372 (Calc. 355.1366 for $C_{13}H_{18}N_6O_6$ + H^+).

13. ^{1}H NMR (CD_3OD) δ 1.28 (t, J = 7.1 Hz, 3 H), 1.75 (m, 2 H), 1.96 (m, 1 H), 2.07 (m, 1 H), 3.27 (m, 2 H), 3.73 (dd, J = 12.6, 3.0 Hz, 1 H), 3.88 (dd, J = 12.6, 2.3 Hz, 1 H), 4.18 (m, 1 H,), 4.23 (q, J = 7.1 Hz, 2 H), 4.41 (dd, J = 5.4, 1.9 Hz, 1 H), 4.67 (dd, J = 8.9, 5.5 Hz, 1 H), 5.01 (dd, J = 7.0, 5.5 Hz, 1 H), 7.09 (d, J = 7.0 Hz, 1 H), 8.17 (s, 1 H); ^{13}C NMR (D_2O/ CD_3OD) δ 14.4, 25.6, 28.7, 41.5, 53.8, 63.1, 63.9, 72.0, 74.0, 87.5, 90.3, 119.2, 142.4, 150.4, 154.4, 157.4, 157.7, 160.1, 174.0; MS (FAB) m/z (M + 1)$^+$ 496.2261 (Calc. 496.2268 for $C_{19}H_{29}N_9O_7$ + H^+).

14. ^{1}H NMR (CD_3OD) δ 1.44 (s, 9 H), 3.74 (dd, J = 12.2, 3.0 Hz, 1 H), 3.86 (dd, J = 12.2, 3.9 Hz, 1 H), 4.07 (dd, J = 6.5, 3.3 Hz, 1 H), 4.39 (dd, J = 6.0, 3.4 Hz, 1 H), 4.95 (t, J = 6.0 Hz, 1 H), 6.93 (d, J = 6.0 Hz, 1 H); ^{13}C NMR (DMSO/D_2O) δ 28.9, 52.9, 64.0, 72.4, 73.8, 87.4, 91.1, 117.5, 141.6, 154.1, 155.5, 159.7, 159.9; MS (FAB) m/z (M + 1)$^+$ 383.1676 (Calc. 383.1679 for $C_{15}H_{22}N_6O_6$ + H^+).

15. ^{1}H NMR (D_2O) δ 3.24 (s, 9 H), 3.64 (t, J = 6.6 Hz, 2 H), 3.91 (m, 4 H), 4.20 (m, 1 H), 4.52 (dd, J = 5.1, 3.7 Hz, 1 H), 5.05 (t, J = 6.2 Hz, 1 H,), 6.85 (d, J = 6.2 Hz, 1 H,); ^{13}C NMR (CD_3OD) δ 34.6, 54.4, 63.0, 65.0, 71.7, 73.1, 86.6, 90.1,

117.6, 140.1, 153.9, 155.1, 160.5, 161.1; MS (FAB) m/z (M - Cl^-)$^+$ 412.1950 (Calc. 412.1945 for $C_{16}H_{26}N_7O_6$ - Cl^-).

16. ^{1}H NMR (CD_3OD) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 1.72 (m, 2 H), 1.89 (m, 1 H), 2.03 (m, 1 H), 3.23 (m, 2 H), 3.74 (dd, *J* = 12.2, 3.8 Hz, 1 H), 3.86 (dd, *J* = 12.2, 2.9 Hz, 1 H), 4.06 (m, 1 H,), 4.21 (q, *J* = 7.1, Hz, 2 H), 4.39 (dd, *J* = 5.7, 3.3 Hz, 1 H), 4.61 (dd, *J* = 9.1, 4.7 Hz, 1 H), 4.98 (t, *J* = 6.2 Hz, 1 H), 6.98 (d, *J* = 6.3 Hz, 1 H); ^{13}C NMR (DMSO/D_2O) δ 14.6, 26.4, 29.7, 41.9, 53.4, 62.8, 64.0, 72.5, 73.7, 87.5, 91.1, 118.1, 140.1, 154.3, 155.9, 158.7, 160.3, 160.7, 172.9; MS (FAB) m/z (M + 1)$^+$ 512.2219 (Calc. 512.2217 for $C_{19}H_{29}N_9O_8$ + H^+).

17. ^{1}H NMR (DMSO-d_6/D_2O, 4/1) δ 3.51 (m, 1 H), 3.64 (dd, *J* = 11.9, 4.4 Hz, 1 H), 3.79 (dd *J* = 9.6, 4.4 Hz, 1 H), 4.17 (dd, *J* = 5.5, 4.4 Hz, 1 H), 4.42 (d, *J* = 6.3 Hz, 2 H), 4.91 (t, *J* = 5.8 Hz, 1 H), 6.62 (s, 2 H), 6.71 (d, *J* = 5.8 Hz, 1 H), 7.29 (d, *J* = 5.7 Hz, 2 H), 8.49 (d, *J* = 6.2 Hz, 2 H), 9.45 (t, *J* = 6.2 Hz, 1 H); ^{13}C NMR (DMSO-d_6/D_2O, 4/1) δ 41.3, 62.2, 70.4, 71.1, 85.4, 89.0, 116.3, 122.3, 138.3, 148.4, 149.6, 152.8, 153.7, 156.7, 159.1; MS (FAB) m/z (M + 1)$^+$ 418.1482 (Calc. 418.1488 for $C_{19}H_{21}N_4O_7$ + H^+).

18. ^{1}H NMR (CD_3OD) δ 1.17 (m, 2 H), 1.26 (t, *J* = 12.0 Hz, 2 H), 1.39 (m, 1 H), 1.50 (m, 3 H), 2.23 (t, *J* = 12.0 Hz, 2 H), 2.63 (d, *J* = 13.5 Hz, 1 H), 2.80 (dd, *J* = 13.5, 8.0 Hz, 1 H), 2.90 (m, 1 H), 3.18 (m, 2 H), 3.48 (m, 4 H), 3.81 (dd, *J* = 14.5, 4.0 Hz, 1 H), 3.91 (dd, *J* = 11.5, 3.6 Hz, 1 H), 4.08 (m, 1 H), 4.19 (m, 1 H), 4.40 (m, 1 H), 4.47 (m, 1 H), 4.96 (t, *J* = 6.2 Hz, 1 H), 6.83 (d, *J* = 6.2 Hz, 1 H); MS (FAB) m/z (M + 1)$^+$ 596.2251 (Calc. 596.2264 for $C_{23}H_{33}N_9O_8S$ + H^+).

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