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ARTICLE

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Coumarin−Purine Ribofuranoside Conjugates as New Agents against Hepatitis C Virus

Jih Ru Hwu,[*,†,‡] Shu-Yu Lin,[†] Shwu-Chen Tsay,[†] Erik De Clercq,[§] Pieter Leyssen,[§] and Johan Neyts[§]

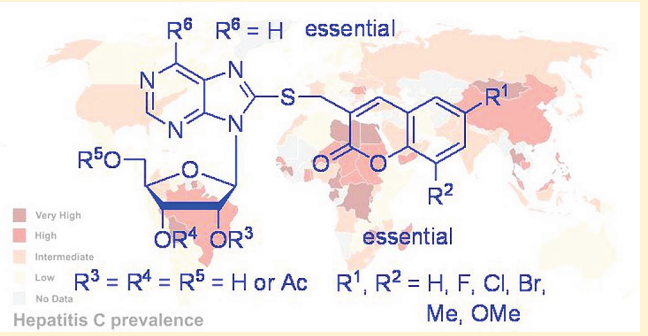
[†]Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30013, R.O.C.

[‡]Department of Chemistry, National Central University, Jhongli City, Taiwan 32001, R.O.C.

[§]Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

Supporting Information

ABSTRACT: About 3% of world's population is infected by the hepatitis C virus (HCV), for which prophylactic vaccine is not available yet. Nowadays, pegylated interferon-α and ribavirin are commonly used to treat HCV; unfortunately these drugs often produce significant side effects. Upon the desperate need of anti-HCV drugs, a plan to establish a new compound library was set that included leads with high antiviral activity, good hydrophilicity, yet low toxicity. Accordingly, 26 new conjugated compounds were synthesized through the chemical coupling of various 9-(β-D-ribofuranosyl)purine-8-thiones with 3-(chloromethyl)coumarins bearing various substituents. A $-SCH_2-$ unit was used to link the coumarin and the purine moieties. The three hydroxyl groups at the 2′-, 3′-, and 5′-positions were selectively protected with an acyl or acetal group in these coumarin−purine ribofuranosides. Their anti-HCV and cytostatic determination assays were performed, and the structure−activity relationship was established. Three conjugates in the family of 8-(coumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)purine possessed an appealing ability to inhibit HCV replication with EC_{50} between 5.5 and 6.6 μM and EC_{90} of ∼20 μM. These data in the new compound library provide clues for the future in the development of anti-HCV leads for viral eradication.



INTRODUCTION

More than 100 000 patients die annually, which is attributable to hepatitis C directly or with the intervention of cofactors such as hepatitis B virus, HIV, or alcohol abuse.[1] The hepatitis C virus (HCV) was first discovered in the United States in 1989.[2] Soon it was revealed to be the cause of many hepatic diseases of previously unknown origin.[3] Unfortunately, more than 50% of people at the highest risk for HCV nowadays are infected and yet unaware of their disease.[1] The spread of its infection and loss of the treatment opportunities become a recipe for disaster.

Many efforts have been devoted to the discovery of drugs against HCV.[4,5] Results from the development of nucleoside analogues offer encouragement, which may improve therapies to treat HCV infection. Recent reports include adenosine 5′-phosphonates by Girardet et al.,[6] phosphoramidates of 4′-substituted purine nucleoside by McGuigan et al.,[7] 9-(2-β-C-methyl-β-D-ribofuranosyl)-6-substituted purine derivatives by Ding et al.,[8] 5′-O-masked 2′-deoxyadenosine analogues by Maruyama et al.,[9] purine ribonucleosides bearing a pyrrol-3-yl or 2-furyl group by Hocek et al.,[10] arylethynyltriazole ribonucleosides by Peng et al.,[11] and 7-deazaneplanocin A analogues by Chu et al.[12]

Adenosine phosphonate analogues constitute a class of promising anti-HCV leads, yet their activity is relatively weak.[6] Use of the phosphoramidate pronucleotide approach successfully overcomes the problem that 4′-azidoadenosine does not inhibit HCV replication in cell culture.[7] A different prodrug approach is the incorporation of two S-(acylthio)ethyl groups into 9-(2′-β-C-methyl-β-D-ribofuranosyl)-6-substituted purines. It improves the potency of the parent compounds by increasing the intracellular levels of 5′-monophosphate metabolites. These nucleotide prodrugs show much enhanced inhibitory activities on HCV RNA replication.[8] Moreover, 2′-deoxyadenosine analogues with a 5′-O-masked hydroxyl group is found to exhibit higher potency than the unmasked analogues.[9] On the other hand, modification of the adenosine moiety by attachment of a five-membered heterocycle in the C-6 position leads to a ribonucleoside with appealing 90% inhibitory concentration for virus replication in the submicromolar range. Unfortunately it is accompanied by a side effect on cellular rRNA and thus lacks for specificity.[10] Ribavirin is the first synthetic nucleoside with an unnatural triazole moiety and exhibits a broad spectrum of antiviral activity against RNA and DNA viruses.[13] Its derivatives in the family of arylethynyltriazole ribonucleosides can also inhibit HCV replication efficiently.[11] Use of unnatural sugar moiety is another approach to develop new leads in the family of nucleosides. For example, the ribofuranose moiety in ribosides is modified to

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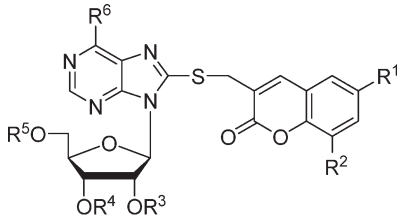
give the corresponding 7-deazaneplanocins, which exhibit significant anti-HCV activity.[12]

In addition to ribonucleosides, some recent inventions provide synthetic methods to give 3,4-disubstituted,[14] 4-thio, 4,5-dithio,[15] and 7,8-fused[16] coumarins, which show activity against HCV. Furthermore, synthetic coumestans bearing different substituents in their A and D rings display interference at the step of NS5B-RNA binary complex formation and is confirmed by cross-linking experiments.[17] Recently, coumarins conjugated with various benzimidazoles[18] and heterobicycles,[19] respectively, have been synthesized. These conjugates exhibit appealing anti-HCV activity and become promising anti-HCV leads. Present-day coumarins and their derivatives still have plenty of room for their improvement as anti-HCV drugs.

To advance the development of new anti-HCV drugs, we synthesized 26 new conjugated compounds through the concept of molecular hybridization for drug design.[20] In this new compound library, we came up with their structure−activity relationship (SAR) and planned to produce several new conjugated compounds with improved efficiency for viral eradication and less toxicity to the host. We attached a coumarin onto a purine ribofuranoside by covalent bonds for generating innovative leads of anti-HCV. We herein report our synthetic strategies on successfully obtaining the targets **1**, which were constituted by three heterocyclic components. The essential functional groups and moieties therein are revealed.



1

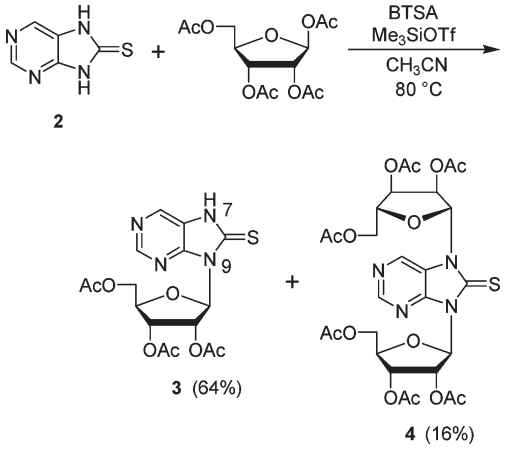
RESULTS

To establish the scaffold of targets **1**, we were facing the following three challenges during their syntheses. First, the pivotal purine nucleus possessed three nucleophilic centers as shown by the structure **2**. They included two NH and one thione groups. A coumarin or a ribofuranose moiety would then have to be incorporated at the right site in the right step. Second, the reaction conditions applied during the synthesis of the targets **1** should be mild enough so that the frail allylic S−C bond and *N*-glycosidic C−N bond therein would remain intact. Third, the reagents to be used in the synthetic steps should not add to the α,β-unsaturated ester group through a Michael addition or induce a ring-opening of the δ-lactone moiety in **1**. Given these unique concerns, we developed sequential synthetic routes shown in Schemes 1−4.

Synthesis of Purine-8-thione−Ribofuranose Conjugates. Some purine ribofuranosides possess anti-HCV activity.[4,6−12] Therefore, we intended to prepare mono- and bisribofuranoside derivatives shown in Scheme 1 for biological assays. Silylation of purine-8-thione (**2**) with bis(trimethylsilyl)acetamide (BTSA) followed by addition of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose at 80 °C provided the desired mono *N*-9 nucleoside **3** and the byproduct bis(ribofuranosyl)purine-8-thione **4** (Scheme 1).

For the monoglycosylation[21] product, we isolated the *N*-9 (instead of the *N*-7) isomer only. Successful preparation of **3** was attributed to the application of the Vorbrüggen procedure[22] by

Scheme 1. Coupling of Purine-8-thione (2) with a Polyacetyl β-D-Ribofuranose To Give Nucleosides 3 and 4



use of the Lewis acid Me_3SiOTf as the catalyst and appropriate conditions that favored the formation of thermodynamically more stable *N*-9 regioisomers. Somewhat surprisingly, these two compounds (i.e., **3** and **4**) did not show significant anti-HCV activity.

Syntheses of Conjugated Coumarin−Thiopurine Nucleosides 6, 7, and 9. Often the coumarin moiety brings biological activities into chemical entities. Hence, we treated **3** with 3-(chloromethyl)coumarins **5** bearing various substitutents, including F, Cl, Br, Me, and OMe, at room temperature to give *O*-polyacyl-*N*-ribofuranosides **6** in 77−93% yields (see Scheme 2). The acyl groups at the 2′ and 3′ positions therein were removable by ammonia in methanol for 45 min at 0 °C to give diols **7**. Performance of these reactions at a longer time or under harsher conditions did not lead to the desired conjugates **9**, in which all of the hydroxyl groups were deprotected. Instead, we found that the S−CH_2 bond in **7** was cleaved.

To pursue a way to obtain the desired conjugates **9**, we first removed all of the acyl groups in **3** successfully by methanolic ammonia to give triol **8** in 92% yield. Coupling of this triol with coumarins **5** with 35% ammonium hydroxide in aqueous acetonitrile led to the targets **9**. The yields ranged from 51−81% and their purity was >98.0%, as determined by HPLC.

Identification of Structures and Analysis of Conformations. We confirmed the structures of conjugates **9** on the basis of their spectroscopic characteristics. For example, the mass spectrum of **9a** in the positive ion mode by the FABMS technique exhibited 443.1016 for the species $[M + H]^+$, which indicates the molecular formula to be $C_{20}H_{18}N_4O_6S$ with a theoretical value of 442.0947. Its IR spectrum showed one strong absorption band at 1713 cm^{-1}, which was attributed to the carbonyl stretching vibration of the coumarin moiety.[23] Its ^{13}C NMR spectrum had resonance at 31.84 and 156.90 ppm for the SCH_2 carbon and the −N=C(−N)(−S) carbon, respectively. On the other hand, the two characteristic singlets occurred at 8.83 and 9.07 ppm for the protons in the purine nucleus and a doublet with J = 6.4 Hz occurred at 5.78 ppm for the glycosidic proton[22] in its ^1H NMR spectrum.

We ensured the regioselectivity and that the glycosidic bonds of conjugates **9** connected the purine moiety at the *N*-9 position on the basis of the X-ray structure of their starting material **3**. The

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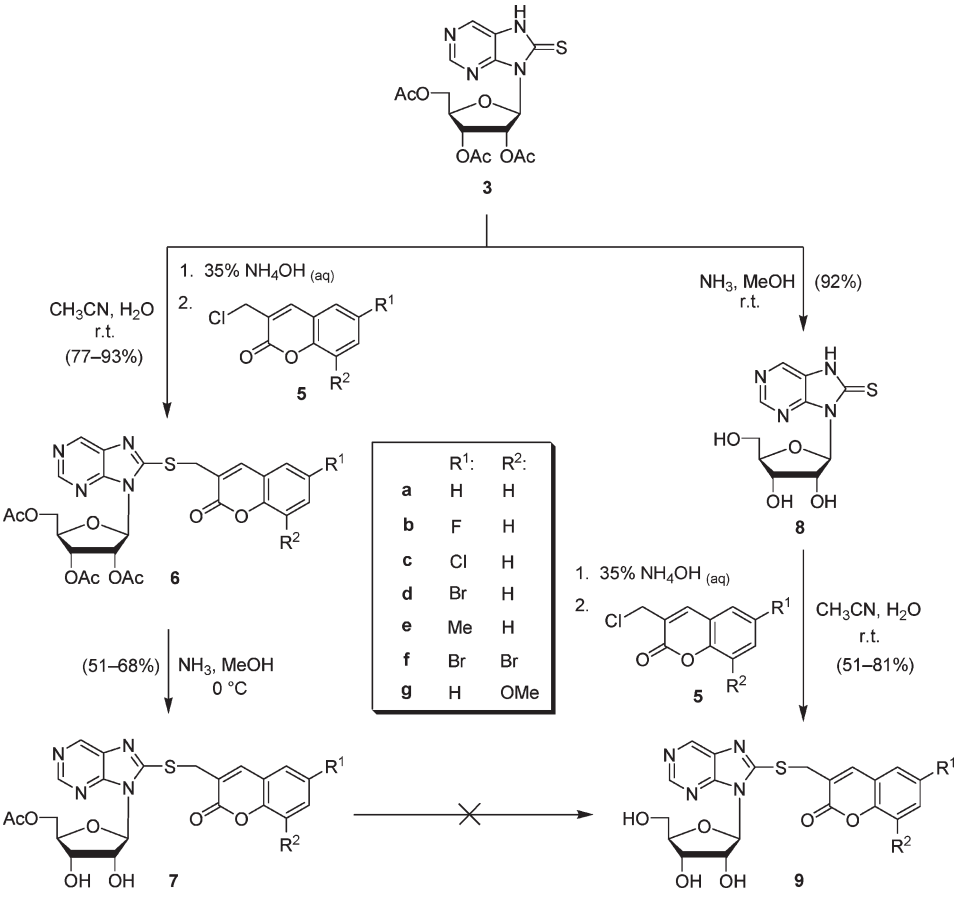
Scheme 2. Syntheses of Conjugated Coumarin−Thiopurine Nucleosides with the Three Hydroxyl Groups Therein Fully, Partially, or Nonprotected



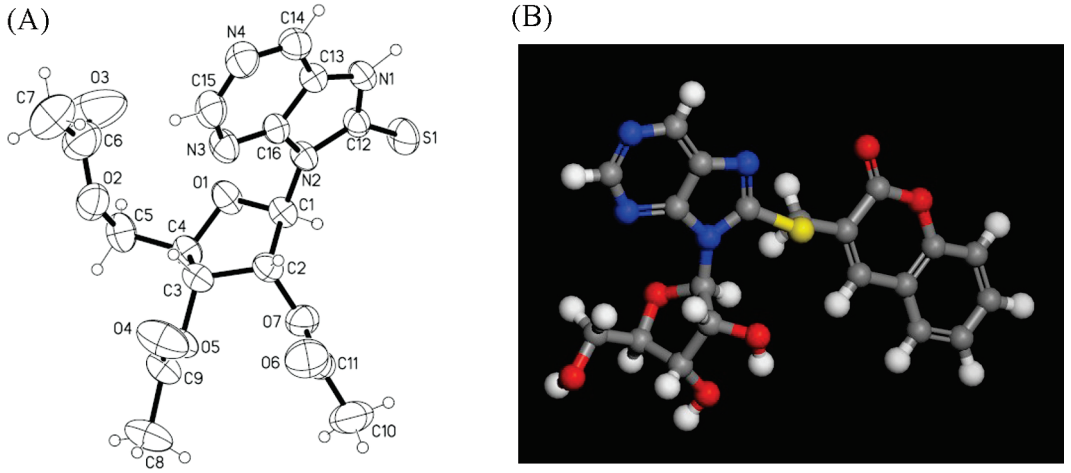


Figure 1. Molecular frameworks: (A) ORTEP diagram of **3** obtained by X-ray diffraction analysis; (B) molecular modeling structure of **9a** obtained through energy minimization by CVFF calculations.

molecular framework of **3**[24] was unequivocally confirmed by single crystal X-ray diffraction analysis (see Figure 1A). Its orthorhombic crystals possessed the space group $P2_12_12_1$ with $a = 9.4553(2)$ Å, $b = 10.9763(3)$ Å, $c = 18.5134(6)$ Å, and $\alpha = \beta = \gamma = 90°$. These results indicate that the glycosylation took place at the *N*-9 nitrogen atom with dihedral angle of 71.9° for O−C(1′)−N(9)−C(4).

As shown in Figure 1A, the crystals of **3** existed in the syn conformation with the thione moiety sticking outward from the ribofuranose unit. Through studies by circular dichroism, Ikehara

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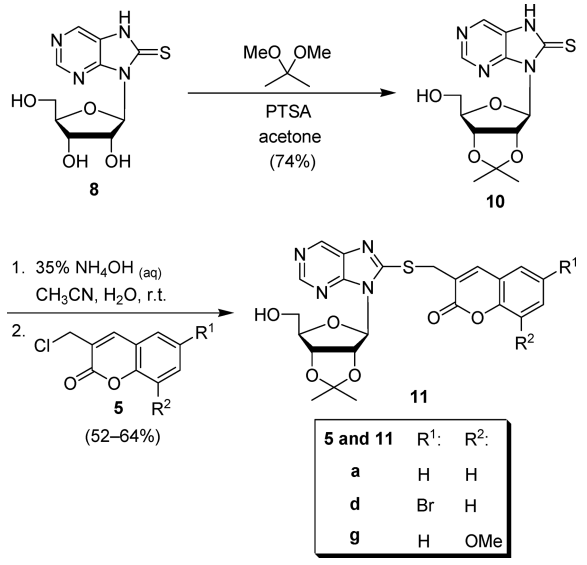
et al.[25] conclude that purine nucleosides with a bulky substituent at the C(8) position would exist in the syn conformation. Therefore, we believe that the noncrystal compound **9a** also held the syn conformation as shown in Figure 1B. Being obtained by our CVFF calculations for energy minimization, this thermodynamically most stable conformation would avoid unfavorable steric and electrostatic interactions between the C(8)-coumarin moiety and the ribofuranose unit.[26]

Selective Protection of the Hydroxyl Groups in Ribofuranosides. To obtain fruitful information for establishing the SAR, we planned to synthesize conjugates of coumarin−purine ribofuranosides **1** with hydroxyl groups protected at different positions. The synthetic strategies shown in Scheme 2 illustrate our efforts on obtaining conjugated compounds with the hydroxyl groups in ribofuranose being fully protected (i.e., **6**), protected at the 5′-position only (i.e., **7**), and fully nonprotected (i.e., **9**). We further performed the synthesis of coumarin−purine ribofuranosides **11**, in which the hydroxyl groups were protected at both the 2′- and the 3′-positions (see Scheme 3). Accordingly, treatment of purine-8-thione ribofuranoside **8** with 2,2-dimethoxypropane in the presence of PTSA and acetone gave the corresponding 2′,3′-acetals **10**. The thione moiety therein reacted with 3-(chloromethyl)coumarins **5** to produce the desired targets **11a,d,g** with a free hydroxyl group at the 5′-position in 52−64% yields with purity of >98.5%. Their structures were fully confirmed by spectroscopic methods. The characteristic peak for the *gem*-dimethyl groups exhibited two singlets at 1.63 and ∼1.33 ppm in their ^{1}H NMR spectra.

Synthesis of Conjugated Coumarin−Adenosines 15. Addition of an amino group at the C(6) position provides a simple way to modify the purine moiety. Conversion of the commercially available adenosine (**12**) to the corresponding thione nucleoside **14**[27] can be accomplished by two steps through the bromide intermediate **13**[28] (see Scheme 4). Under the same conditions as described before, we coupled **14** with coumarins **5**

Scheme 3. Synthesis of Acetalized Coumarin−Purine Ribofuranosides



Scheme 4. Synthesis of Conjugated Compounds of Coumarin−Adenosine Ribofuranosides

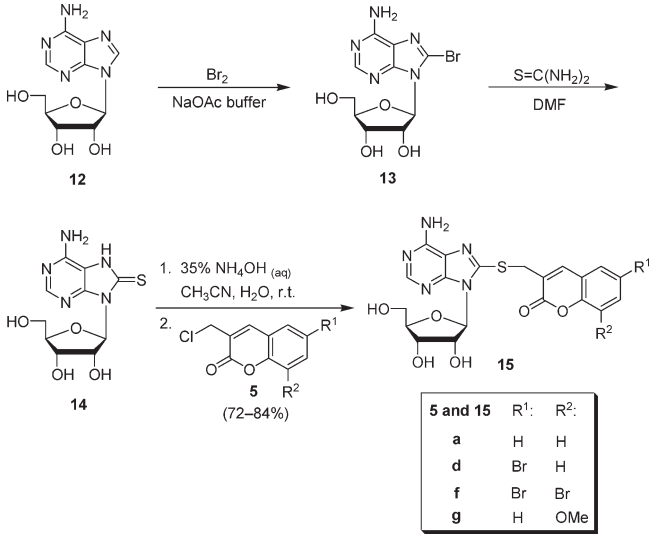
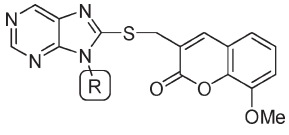


Table 1. Solubility in Water of Conjugates 6g, 7g, 9g, 11g, and 16



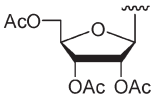
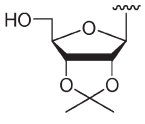
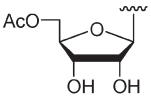
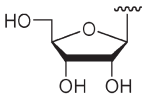
R=	H				
compound	**16**	**6g**	**11g**	**7g**	**9g**
solubility (μg/mL)	31.6	78.3	87.7	216.4	224.1
enhancement factor	1	2.5	2.8	6.8	7.1

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Table 2. Inhibitory Effects of Conjugated Compounds on HCV Subgenomic Replicon Replication in Huh 5-2 Cells

compd[a]	CC_{50}[b] (μM)	EC_{50}[c] (μM)	SI[d]
3[24]	>122	>122	1.0
4	>75	66	>1.1
6a	39	6.6	5.9
6b	7.6	6.1	1.2
6c	7.5	3.2	2.4
6d	6.7	4.9	1.4
6e	16	7.7	2.1
6f	6.0	4.9	1.2
6g	7.5	2.3	3.3
7a	8.7	>8.9	0.98
7b	8.6	3.8	2.3
7d	31	8.3	3.8
7e	16	4.6	3.5
7f	7.0	6.8	1.0
7g	11	5.8	1.9
8[e]	>176	>176	1.0
9a	50	5.5	9.1
9b	36	7.4	4.9
9c	37	4.3	8.5
9e	46	9.2	5.1
9f	36	5.9	6.1
9g	47	9.5	5.0
11a	8.8	2.8	3.2
11d	7.5	2.1	3.6
11g	8.4	1.6	5.2
15a	49	28	1.7
15d	41	27	1.5
15f	36	26	1.4
15g	>103	43	2.4
16[19]	94	20	4.8

[a] Interferon α-2b was used as a (positive) reference compound at 10 000 units/well and reduced the signal in the viral RNA (luciferase) assay to background levels without any cytotoxic activity. The values were obtained as the average of triplicate determinations. [b] Minimum cytotoxic concentration required to cause a microscopically detectable alteration of normal cell morphology. [c] Minimum inhibitory concentration required to reduce virus-induced cytopathogenicity by 50%. [d] Selectivity index (ratio of CC_{50} to EC_{50}). [e] Reported to be toxic to HEp-2 and L1210 cells in culture.[24]

to give the desired coumarin−adenosine conjugates **15a,d,f,g** in good yields for biological assays.

Solubility and Evaluation of the Anti-HCV Activity. Solubility of chemical entities in water plays an important role in their development as a lead for new drugs[29] and is related to the structure−activity relationship. Consequently, we applied the Bookser's method[30] by using HPLC with a UV detector to obtain the water solubility of conjugates **6g**, **7g**, **9g**, **11g**, and **16**.[19] Their data and comparison are listed in Table 1.

We evaluated the antiviral activities of conjugated compounds in the HCV subgenomic replicon system in Huh 5-2 cells.[31] The antiviral assays and cytostatic determination assays were performed on the basis of the procedures reported by us previously.[32] In Table 2, we list their 50% inhibitory concentrations for virus replication (EC_{50}), host cell growth (CC_{50}), and the selectivity index (SI = CC_{50}/EC_{50}). Among the synthesized 26 new conjugated compounds, **6a**, **9a**, and **9f** were found to inhibit HCV subgenomic replicon replication with potency and exhibited low toxicity. Their EC_{50} values were 6.6, 5.5, and 5.9 μM, individually. Furthermore, we obtained the 90% inhibitory concentrations for virus replication (EC_{90}) for nine conjugated compounds, **6a**, **7d**, **9a**, **9b**, **9c**, **9e**, **9f**, **9g**, and **11d**. Their EC_{90} values were measured as 22, 16, 18, 18, 16, 19, 14, 20, and 2.9 μM, individually. This value could not be obtained for the conjugated compound **11g**; at the most, we obtained its EC_{70} value as 6.1 μM.

In the near future, we will evaluate the antiviral activities on a broad sense by applying these new conjugates in the compound library against various essential, emerging, and neglected RNA viruses. The antiviral assays include hepatitis viruses in Huh 6 or Huh 9-13 cells, HIV-1_{IIIB} and HIV-2_{ROD} in MT-4 cells, vesicular stomatitis virus in E_6SM cells, respiratory syncytial virus in HeLa cells, dengue virus in Vero Fast cells, human rhinovirus and poliovirus in HeLa H1 cells, Chikungunya virus in Vero A cells, and parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 virus, and Punta Toro virus in Vero cell cultures. The results will be reported in due course.

DISCUSSION

Essential Moieties and Functional Groups: Structure−Activity Relationship. The conjugated compounds in the new library primarily contain three components with structural modification: coumarin, purine, and ribofuranose. A $-SCH_2-$ unit was used to link the coumarin and the purine moieties. Through analysis of their biological activities shown in Table 2 and the solubility shown in Table 1, we deduce the following SAR by scrutinizing their EC_{50}, CC_{50}, and SI values.

(1) Attachment of a coumarin moiety to the purine ribofuranoside is the key to gain appealing anti-HCV activity. Incorporation of this moiety greatly increased the HCV inhibition (cf. **3** versus **6a**−**g** and **8** versus **9a**−**g**).

(2) It is allowed to introduce various substitutents with electron-withdrawing or donating ability, including F, Cl, Br, Me, and OMe, onto the coumarin moiety while the resultant conjugates were kept with the same order of the anti-HCV activity (cf. **9a**−**g** with EC_{50} = 4.3−9.5 μM).

(3) The two-component conjugate **16** contained only the coumarin and purine moieties, as shown in Table 2. Addition of the third polyacyl ribofuranose moiety onto it increased both the HCV inhibition and cytotoxicity. A better choice was to add the parent ribofuranose moiety to give the conjugates **9**. As a result, it increased the HCV inhibition.

(4) In comparison with the protected forms at the 2′-, 3′-, and 5′-positions of the purine ribofuranosides, the presence of free −OH groups at all of these positions allowed reduction of their cytotoxicity and increment of the SI values (cf. **9a**−**g** versus **6a**−**g**, **7a**−**g**, and **11a,g**, respectively).

(5) As the order shown in Table 1 for hydrophilicity, the most hydrophilic compound was conjugate **9g**. The least hydrophilic compound was **6g**. Given these concerns, **9a** was considered as an ideal lead.

(6) Modification of the purine moiety of the conjugates **1** by addition of an amino group at the C(6)-position gave the coumarin−adenosine conjugates **15**. In comparison with the corresponding coumarin−purine conjugates **9**, it

resulted in the abatement of both HCV inhibition and the SI values (cf. **15a,f,g** versus **9a,f,g**, respectively).

CONCLUSIONS

A new compound library was established by chemical syntheses; it contained 26 conjugates of coumarin−purine ribofuranosides with a $-SCH_2-$ linker. For establishment of the structure−activity relationship on their anti-HCV activity, the coumarin moiety was allowed to possess various substituents, including F, Cl, Br, Me, and OMe. The purine moiety may contain an amino group. The hydroxyl groups in ribofuranosides may be protected with an acyl or acetal group.

Seven among the 26 new compounds were found to inhibit HCV subgenomic replicon replication in the Huh 5-2 cell line. The most appealing results were associated with conjugates **6a**, **9a**, and **9f**, which inhibited HCV replication at EC_{50} values of 6.6, 5.5, and 5.9 μM, individually. Moreover, guidelines were deduced from the analysis of their structures and anti-HCV activity. It is an essential for the coumarin moiety present in the conjugated compounds to exhibit antiviral activity. This moiety bearing various substituents can be attached to purine ribofuranosides at the C(8) position through a $-SCH_2-$ linker. The presence of a ribofuranose moiety led to increment of the HCV inhibition, wherein the −OH groups kept unmasked at all of the 2′-, 3′-, and 5′-positions led to reduction of their cytotoxicity. These guidelines will be of value for medicinal scientists to design and synthesize new conjugated compounds in the future.

EXPERIMENTAL SECTION

General. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless indicated otherwise. Dichloromethane, acetone, and methanol were purchased from Mallinckrodt Chemical Co. Acetonitrile was purchased from Fischer Scientific Co. Ethyl acetate (EtOAc) and hexanes from Mallinckrodt Chemical Co. were dried and distilled from CaH_2. Trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) was purchased from Fluka Chemika. *N*,*O*-Bistrimethylsilylacetamide (BTSA) was purchased from Merck Chemical Co. Aqueous ammonium hydroxide was purchased from J. T. Baker Chemical Co. *p*-Toluenesulfonic acid monohydrate (PTSA) and 2,2-dimethoxypropane were purchased from Sigma-Aldrich Chemical Co. 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose was purchased from Alfa Aesar Chemical Co. Purine-8-thione[33] (**2**) and 3-(chloromethyl)-coumarins[34] **5** were prepared according to the reported methods.

Melting points were obtained with a Fargo MP-2D melting point apparatus. Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254) purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Silicycle ultra pure silica gel (particle size 40−63 μm, 230−400 mesh). High performance liquid chromatography (HPLC) was performed on two Waters 515 HPLC pumps equipped with a Waters 2489 UV/visible detector and a Thermo 5 μm Hypersil ODS (250 mm × 4.6 mm i.d.). Purity of all compounds was >98.0%, as checked by HPLC.

Infrared (IR) spectra were measured on a Perkin-Elmer model Spectrum One B spectrophotometer. Absorption intensities are recorded with the following abbreviations: s, strong; m, medium; w, weak. High-resolution mass spectra were obtained by means of a JEOL JMS-700 mass spectrometer. Proton NMR spectra were obtained on a Varian Mercury-400 (400 MHz) spectrometer or Bruker AC-400 (400 MHz) spectrometer with use of chloroform-*d*, dimethylsulfoxide-d_6, and methanol-d_4 as solvents. Proton NMR chemical shifts are referenced to the $CHCl_3$ singlet (δ 7.24 ppm), the center of DMSO-d_6 quintet (δ 2.49 ppm), and the center of methanol-d_4 quintet (δ 3.30 ppm). Carbon-13 NMR spectra were performed on a Varian Mercury-400 (100 MHz) spectrometer or Bruker AC-400 (400 MHz) spectrometer by use of chloroform-*d* and dimethylsulfoxide-d_6 as solvents. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm) and DMSO-d_6 septet (δ 39.5 ppm). Multiplicities are recorded with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (hertz).

9-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranos-1′-yl)purine-8-thione (3) and 7,9-Bis(2′,3′,5′-tri-*O*-acetyl- β-D-ribofuranos-1′-yl)-purine-8-thione (4). To a solution of purine-8-thione (2, 417.9 mg, 2.746 mmol, 1.0 equiv) in dry acetonitrile (30 mL) was added BTSA (1.01 mL, 4.12 mmol, 1.5 equiv) under nitrogen atmosphere. After the solution was stirred at 60 °C for 30 min, 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (961.4 mg, 3.021 mmol, 1.0 equiv) and Me_3SiOTf (0.744 mL, 4.12 mmol, 1.5 equiv) were added in sequence. The reaction mixture was heated to 80 °C and stirred for 18 h. Excess solvent was removed under reduced pressure, and the residue was treated with 20% aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford a residue. The residue was purified by use of column chromatography (20% hexanes in EtOAc as the eluant) to give **3** (717.3 mg, 1.748 mmol) in 64% and **4** (288.9 mg, 0.4321 mmol) in 16% as white solid foam for both.

3: mp (recrystallized from methanol/ether) 185.4−186.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.42 (bs, 1 H, NH), 8.82 (s, 1 H, H-2), 8.48 (s, 1 H, H-6), 6.67 (d, *J* = 4.0 Hz, 1 H, H-1′), 6.26 (dd, *J* = 6.0, 4.0 Hz, 1 H, H-2′), 5.88 (dd, *J* = 6.0, 6.0 Hz, 1 H, H-3′), 4.55−4.51 (m, 1 H, H-4′), 4.41−4.37 (m, 1 H, H-5′), 4.34−4.30 (m, 1 H, H-5′), 2.14 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.38 (C═S), 170.89 (C═O), 169.91 (C═O), 169.79 (C═O), 151.99, 150.44, 135.50, 123.42, 87.01, 79.42, 71.61, 70.20, 62.89, 20.75 (CH_3), 20.50 (CH_3), 20.48 (CH_3); IR (neat) 3026 (w), 2941 (w), 2839 (w), 1747 (m), 1465 (s), 1234 (s), 1047 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 411 (MH^+, 56), 329 (21), 260 (12), 259 (80), 139 (63), 77 (18). HRMS (FAB) calcd for $(C_{16}H_{19}N_4O_7S + H)^+$: 411.0974; found 411.0978. For its X-ray crystallographic data, CCDC issued a deposition number 776792. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4: mp (recrystallized from methanol/ether) 69.0−70.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (s, 2 H, H-2 + H-6), 6.83 (d, *J* = 6.8 Hz, 1 H, H-1″), 6.74 (d, *J* = 4.2 Hz, 1 H, H-1′), 6.20 (dd, *J* = 6.0, 4.2 Hz, 1 H, H-2′), 5.83 (dd, *J* = 6.0, 6.0 Hz, 1 H, H-3′), 5.52 (dd, *J* = 6.8, 6.7 Hz, 1 H, H-2″), 5.40 (dd, *J* = 6.7, 4.2 Hz, 1 H, H-3″), 4.51−4.48 (m, 2 H, H-4′ + H-4″), 4.39−4.29 (m, 4 H, 2 × H-5′ + 2 × H-5″), 2.25 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.22 (C═S), 170.49 (C═O), 170.09 (C═O), 169.57 (C═O), 169.50 (C═O), 169.39 (C═O), 169.34 (C═O), 152.63, 149.98, 136.81, 122.64, 87.52, 87.50, 80.22, 79.62, 71.28, 71.09, 70.19, 69.26, 62.92, 62.65, 20.77 (CH_3), 20.65 (CH_3) 20.45 (CH_3), 20.36 (CH_3), 20.33 (CH_3), 20.29 (CH_3); IR (neat) 3022 (w), 2940 (w), 1749 (s), 1606 (w), 1474 (s), 1238 (s), 1047 (s) cm^{-1}; MS (FAB$^+$) *m*/*z* 669 (MH^+, 43), 411 (23), 259 (100), 154 (63), 97 (53). HRMS (FAB) calcd for $(C_{27}H_{32}N_4O_{14}S + H)^+$: 669.1714; found 669.1716.

Standard Procedure 1 for the Preparation of Conjugated Compounds 6 and 11. To a solution containing a thione (**3** or **10**, 1.0 equiv) in water and acetonitrile was added aqueous ammonium hydroxide (0.15 mL). After the solution was stirred at room temperature for 30 min, 3-(chloromethyl)coumarin **5** (1.5 equiv) was added. The solution was then stirred at room temperature for 40 min to 3.0 h, and acetonitrile was removed under reduced pressure. To the residue was

added saturated aqueous NH_4Cl (10 mL), which was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure. The residue was purified by use of column chromatography packed with silica gel to give the desired products with purity of >98.0%, as determined by HPLC.

8-(Coumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6a). Standard procedure 1 was followed by use of **3** (96.8 mg, 0.236 mmol, 1.0 equiv), water (5.0 mL), acetonitrile (3.0 mL), and 3-(chloromethyl)coumarin (**5a**, 68.9 mg, 0.354 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (25% hexanes in EtOAc as the eluant) to give **6a** (121.1 mg, 0.1972 mmol) in 90% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 75.2−76.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (s, 1 H, H-6), 8.85 (s, 1 H, H-2), 8.07 (s, 1 H, CH═C−COO), 7.52−7.47 (m, 2 H, 2 × ArH), 7.26−7.32 (m, 2 H, 2 × ArH), 6.21 (dd, *J* = 6.0, 5.2 Hz, 1 H, H-2″), 5.99 (d, *J* = 5.2 Hz, 1 H, H-1″), 5.77 (dd, *J* = 6.0, 5.6 Hz, 1 H, H-3″), 4.55 (s, 2 H, SCH_2), 4.46 (dd, *J* = 11.9, 3.2 Hz, 1 H, H-5″), 4.37−4.34 (m, 1 H, H-4″), 4.29 (dd, *J* = 11.9, 5.6 Hz, 1 H, H-5″), 2.14 (s, 3 H, CH_3), 2.02 (s, 6 H, 2 × CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.37 (C═O), 169.41 (C═O), 169.23 (C═O), 161.02, 156.36, 153.63, 153.30, 151.09, 144.88, 141,80, 134.60, 131.73, 128.03, 124.60, 123.90, 119.00, 116.56, 86.85, 80.15, 71.67, 70.30, 62.74, 31.55 (SCH_2), 20.56 (CH_3), 20.41 (CH_3), 20.23 (CH_3); IR (neat) 3064 (w), 2915(w), 2850 (w), 1746 (m), 1717 (s), 1462 (m), 1228 (s), 1049 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 569 (MH^+, 80), 311 (100), 259 (96), 159 (92), 139 (99), 97 (80). HRMS (FAB) calcd for $(C_{26}H_{24}N_4O_9S + H)^+$: 569.1342, found 569.1348.

8-(6′-Fluorocoumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6b). Standard procedure 1 was followed by use of **3** (20.4 mg, 49.7 μmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 3-chloromethyl-6-fluorocoumarin (**5b**, 15.8 mg, 74.3 μmol, 1.5 equiv). After the solution was stirred at room temperature for 1.0 h and then worked up, the residue was purified by use of column chromatography (25% hexanes in EtOAc as the eluant) to give **6b** (27.1 mg, 46.2 μmol) in 93% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 80.2−81.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.93 (s, 1 H, H-6), 8.82 (s, 1 H, H-2), 8.00 (s, 1 H, CH═C−COO), 7.29−7.26 (m, 1 H, ArH), 7.21−7.14 (m, 2 H, 2 × ArH), 6.20 (dd, *J* = 6.0, 4.8 Hz, 1 H, H-2″), 5.97 (d, *J* = 4.8 Hz, 1 H, H-1″), 5.79 (dd, *J* = 6.0, 6.0 Hz, 1 H, H-3″), 4.52 (s, 2 H, SCH_2), 4.46 (dd, *J* = 11.8, 3.2 Hz, 1 H, H-5″), 4.36−4.32 (m, 1 H, H-4″), 4.27 (dd, *J* = 11.8, 5.4 Hz, 1 H, H-5″), 2.12 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.48 (C═O), 169.52 (C═O), 169.38 (C═O), 160.73, 158.77 (d), 155.89, 153.16, 151.30, 149.68, 145.19, 140.79 (d), 134.52, 125.13, 119.69 (d), 119.14 (d), 118.10 (d), 113.33 (d), 86.81, 80.04, 71.73, 70.18, 62.73, 31.28 (SCH_2), 20.63 (CH_3), 20.48 (CH_3), 20.33 (CH_3); IR (neat) 3068 (w), 2923 (w), 1747 (m), 1723 (s), 1584 (m), 1463 (m), 1230 (s), 1049 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 587 (MH^+, 100), 329 (84), 289 (15), 259 (96), 139 (87), 97 (39). HRMS (FAB) calcd for $(C_{26}H_{23}FN_4O_9S + H)^+$: 587.1248, found 587.1252.

8-(6′-Chlorocoumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6c). Standard procedure 1 was followed by use of **3** (30.6 mg, 74.6 μmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 6-chloro-3-(chloromethyl)coumarin (**5c**, 25.6 mg, 112 μmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (25% hexanes in EtOAc as the eluant) to give **6c** (38.8 mg, 64.3 μmol) in 86% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 82.6−84.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.95 (s, 1 H, H-6), 8.81 (s, 1 H, H-2), 7.98 (s, 1 H, CH═C−COO), 7.44−7.39 (m, 2 H, 2 × ArH), 7.23 (d, *J* = 8.4 Hz, 1 H, ArH), 6.21 (dd, *J* = 6.0, 4.8 Hz, 1 H, H-2″), 5.97 (d, *J* = 4.8 Hz, 1 H, H-1″), 5.79 (dd, *J* = 6.0, 5.6 Hz, 1 H, H-3″), 4.51 (s, 2 H, SCH_2), 4.46 (dd, *J* = 12.0, 3.2 Hz, 1 H, H-5″), 4.36−4.32 (m, 1 H, H-4″), 4.27 (dd, *J* = 12.0, 6.4 Hz, 1 H, H-5″), 2.13 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.45 (C═O), 169.49 (C═O), 169.35 (C═O), 160.50, 155.63, 153.08, 151.87, 151.46, 145.44, 140.46, 134.52, 131.59, 129.88, 127.24, 125.20, 120.00, 117.95, 86.80, 80.02, 71.73, 70.18, 62.72, 31.23 (SCH_2), 20.63 (CH_3), 20.47 (CH_3), 20.32 (CH_3); IR (neat) 3061 (w), 2937 (w), 1745 (s), 1723 (s), 1462 (m), 1371 (m), 1230 (s) cm^{-1}; MS (FAB$^+$) *m*/*z* 603 (MH^+, 69), 345 (51), 289 (11), 259 (99), 154 (77), 139 (100). HRMS (FAB) calcd for $(C_{26}H_{23}ClN_4O_9S + H)^+$: 603.0953, found 603.0945.

8-(6′-Bromocoumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6d). Standard procedure 1 was followed by use of **3** (21.2 mg, 51.7 μmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 6-bromo-3-(chloromethyl)coumarin (**5d**, 21.2 mg, 77.5 μmol, 1.5 equiv). After the solution was stirred at room temperature for 1.0 h and then worked up, the residue was purified by use of column chromatography (25% hexanes in EtOAc as the eluant) to give **6d** (29.3 mg, 45.3 μmol) in 87% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 83.1−84.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.94 (s, 1 H, H-6), 8.82 (s, 1 H, H-2), 7.98 (s, 1 H, CH═C−COO), 7.60 (d, *J* = 2.2 Hz, 1 H, ArH), 7.55 (dd, *J* = 8.8, 2.2 Hz, 1 H, ArH), 7.17 (d, *J* = 8.8 Hz, 1 H, ArH), 6.20 (dd, *J* = 6.0, 4.6 Hz, 1 H, H-2″), 5.97 (d, *J* = 4.6 Hz, 1 H, H-1″), 5.79 (dd, *J* = 6.0, 5.6 Hz, 1 H, H-3″), 4.51 (s, 2 H, SCH_2), 4.46 (dd, *J* = 11.8, 3.4 Hz, 1 H, H-5″), 4.35−4.32 (m, 1 H, H-4″), 4.27 (dd, *J* = 11.8, 5.4 Hz, 1 H, H-5″), 2.12 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.52 (C═O), 169.56 (C═O), 169.41 (C═O), 160.50, 155.80, 153.19, 152.41, 151.44, 145.38, 140.41, 134.56, 134.48, 130.35, 125.24, 120.56, 118.30, 117.24, 86.87, 80.10, 71.78, 70.25, 62.78, 31.30 (SCH_2), 20.67 (CH_3), 20.51 (CH_3), 20.36 (CH_3); IR (neat) 3061 (w), 2939 (w), 1745 (s), 1725 (s), 1462 (m), 1370 (m), 1230 (s) cm^{-1}; MS (FAB$^+$) *m*/*z* 647 (MH^+, 22), 391 (46), 259 (77), 154 (89), 139 (100), 107 (40). HRMS (FAB) calcd for $(C_{26}H_{23}BrN_4O_9S + H)^+$: 647.0447, found 647.0444.

8-(6′-Methylcoumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6e). Standard procedure 1 was followed by use of **3** (152.9 mg, 0.3726 mmol, 1.0 equiv), water (5.0 mL), acetonitrile (3.0 mL), and 3-chloromethyl-6-methylcoumarin (**5e**, 116.6 mg, 0.5589 mmol, 1.5 equiv). After the solution was stirred at room temperature for 40 min and then worked up, the residue was purified by use of column chromatography (25% hexanes in EtOAc as the eluant) to give **6e** (201.4 mg, 0.3457 mmol) in 93% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 81.8−83.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.95 (s, 1 H, H-6), 8.82 (s, 1 H, H-2), 8.00 (s, 1 H, CH═C−COO), 7.30−7.19 (m, 3 H, 3 × ArH), 6.25 (dd, *J* = 5.8, 5.0 Hz, 1 H, H-2″), 5.97 (d, *J* = 5.0 Hz, 1 H, H-1″), 5.81 (dd, *J* = 5.8, 5.2 Hz, 1 H, H-3″), 4.53 (s, 2 H, SCH_2), 4.46 (dd, *J* = 11.8, 3.4 Hz, 1 H, H-5″), 4.35−4.32 (m, 1 H, H-4″), 4.28 (dd, *J* = 11.8, 5.4 Hz, 1 H, H-5″), 2.36 (s, 3 H, $ArCH_3$), 2.13 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.50 (C═O), 169.53 (C═O), 169.34 (C═O), 161.34, 156.11, 153.14, 151.72, 151.38, 145.33, 141.91, 134.63, 134.38, 132.79, 127.84, 123.68, 118.71, 116.26, 86.76, 80.04, 71.66, 70.24, 62.78, 31.51 (SCH_2), 20.67 (CH_3), 20.65 (CH_3), 20.50 (CH_3), 20.32 (CH_3); IR (neat) 3001 (w), 2930 (w), 2851 (w), 1748 (m), 1717 (s), 1463 (s), 1231 (s), 1050 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 583 (MH^+, 72), 325 (100), 258 (81), 154 (48), 139 (85). HRMS (FAB) calcd for $(C_{27}H_{26}N_4O_9S + H)^+$: 583.1499, found 583.1505.

8-(6′,8′-Dibromocoumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6f). Standard procedure 1 was followed by use of **3** (35.6 mg, 86.7 μmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 3-chloromethyl-6,8-dibromocoumarin (**5f**, 45.9 mg, 130 μmol, 1.5 equiv). After the solution was stirred at

room temperature for 3.0 h and then worked up, the residue was purified by use of column chromatography (25% hexanes in EtOAc as the eluant) to give **6f** (48.6 mg, 66.9 μmol) in 77% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 89.4−90.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.95 (s, 1 H, H-6), 8.84 (s, 1 H, H-2), 7.93 (s, 1 H, CH═C−COO), 7.82 (d, *J* = 2.2 Hz, 1 H, ArH), 7.54 (d, *J* = 2.2 Hz, 1 H, ArH), 6.16 (dd, *J* = 6.0, 4.8 Hz, 1 H, H-2″), 5.96 (d, *J* = 4.8 Hz, 1 H, H-1″), 5.79 (dd, *J* = 6.0, 6.0 Hz, 1 H, H-3″), 4.52 (s, 2 H, SCH_2), 4.48 (dd, *J* = 12.0, 3.2 Hz, 1 H, H-5″), 4.37−4.33 (m, 1 H, H-4″), 4.28 (dd, *J* = 12.0, 5.6 Hz, 1 H, H-5″), 2.13 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.49 (C═O), 169.54 (C═O), 169.47 (C═O), 159.56, 155.68, 153.17, 151.30, 149.36, 145.16, 139.94, 137.13, 134.46, 129.56, 125.95, 121.28, 117.11, 111.02, 87.00, 80.02, 71.66, 70.15, 62.71, 31.13 (SCH_2), 20.66 (CH_3), 20.48 (CH_3), 20.33 (CH_3); IR (neat) 3068 (w), 2925 (w), 1741 (m), 1733 (s), 1462 (m), 1366 (m), 1225 (s), 1047 (s) cm^{-1}; MS (FAB$^+$) *m*/*z* 725 (MH^+, 31), 543 (12), 469 (68), 307 (25), 259 (100), 154 (98), 139 (98). HRMS (FAB) calcd for $(C_{26}H_{22}Br_2N_4O_9S + H)^+$: 724.9552, found 724.9542.

8-(8′-Methoxycoumarin-3′-yl)methylthio-9-(2″,3″,5″-tri-*O*-acetyl-β-D-ribofuranos-1″-yl)purine (6g). Standard procedure 1 was followed by use of **3** (97.4 mg, 0.237 mmol, 1.0 equiv), water (5.0 mL), acetonitrile (3.0 mL), and 3-chloromethyl-8-methoxycoumarin (**5g**, 79.9 mg, 0.356 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (20% hexanes in EtOAc as the eluant) to give **6g** (113.8 mg, 0.1901 mmol) in 80% yield as white solids: mp (recrystallized from dichloromethane/diethyl ether) 79.8−81.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.94 (s, 1 H, H-6), 8.81 (s, 1 H, H-2), 8.03 (s, 1 H, CH═C−COO), 7.17 (dd, *J* = 8.0, 8.0 Hz, 1 H, ArH), 7.03 (d, *J* = 8.0 Hz, 2 H, 2 × ArH), 6.26 (dd, *J* = 5.6, 5.0 Hz, 1 H, H-2″), 5.97 (d, *J* = 5.0 Hz, 1 H, H-1″), 5.80 (dd, *J* = 5.6, 5.6 Hz, 1 H, H-3″), 4.53 (s, 2 H, SCH_2), 4.46 (dd, *J* = 11.6, 3.2 Hz, 1 H, H-5″), 4.36−4.32 (m, 1 H, H-4″), 4.26 (dd, *J* = 11.6, 5.2 Hz, 1 H, H-5″), 3.93 (s, 3 H, $ArOCH_3$), 2.13 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.50(C═O), 169.53 (C═O), 169.35 (C═O), 160.59, 156.28, 153.22, 151.25 147.11, 145.13, 143.29, 142.03, 134.65, 124.52, 124.15, 119.65, 119.47, 113.71, 86.84, 80.10, 71.68, 70.29, 62.78, 56.27 (OCH_3), 31.53 (SCH_2), 20.66 (CH_3), 20.51 (CH_3), 20.33 (CH_3); IR (neat) 3016 (w), 2936 (w), 2851 (w), 1748 (m), 1720 (s), 1463 (m), 1232 (s), 1106 (s) cm^{-1}; MS (FAB$^+$) *m*/*z* 599 (MH^+, 71), 341 (84), 259 (73), 154 (100), 136 (97), 97 (58). HRMS (FAB) calcd for $(C_{27}H_{26}N_4O_{10}S + H)^+$: 599.1448, found 599.1439.

Standard Procedure 2 for the Preparation of the 9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(coumarin-3′-yl)methylthio]-purines 7. To a solution containing **6** (1.0 equiv) in methanol (10 mL) was added saturated methanolic ammonia (15 mL) at 0 °C. After the solution was stirred at 0 °C for 45 min, it was concentrated under reduced pressure. To the residue was added saturated aqueous NH_4Cl (20 mL), which was extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure. The residue was purified by use of column chromatography packed with silica gel to give the desired products with purity of >98.0%, as determined by HPLC.

9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(coumarin-3′-yl)-methylthio]purine (7a). Standard procedure 2 was followed by use of **6a** (89.3 mg, 0.157 mmol). After the solution was stirred for 45 min and then worked up, the residue was purified by use of column chromatography (0−3% methanol in EtOAc as the eluant) to give **7a** (39.5 mg, 81.5 μmol) in 52% yield as white solids: mp (recrystallized from dichloromethane/methanol) 91.2−92.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (s, 1 H, H-6), 8.75 (s, 1 H, H-2), 8.06 (s, 1 H, CH═C−COO), 7.51−7.46 (m, 2 H, 2 × ArH), 7.32−7.25 (m, 2 H, 2 × ArH), 5.92 (d, *J* = 4.0 Hz, 1 H, H-1″), 5.10 (dd, *J* = 9.7, 4.0 Hz, 1 H, H-2″), 4.70 (dd, *J* = 9.7, 5.0 Hz, 1 H, H-3″), 4.52 (s, 2 H, SCH_2), 4.41 (dd, *J* = 12.0, 3.6 Hz, 1 H, H-5″), 4.30−4.22 (m, 2 H, H-4″ + H-5″), 3.71 (br, 1 H, OH), 2.91 (br, 1 H, OH), 1.99 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.93(C═O), 161.21, 156.73, 153.52, 153.25 150.98, 144.97, 141.96, 134.53, 131.85, 128.03, 124.72, 123.93, 118.97, 116.64, 89.34, 82.15, 72.34, 70.67, 65.57, 31.42 (SCH_2), 20.74 (CH_3); IR (neat) 3406 (br, OH), 3054 (w), 2930 (w), 1741 (m), 1716 (s), 1609 (m), 1463 (m), 1238 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 485 (MH^+, 67), 311 (86), 307 (45), 282 (56), 136 (100). HRMS (FAB) calcd for $(C_{22}H_{20}N_4O_7S + H)^+$: 485.1131, found 485.1133.

9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(6′-fluorocoumarin-3′-yl)methylthio]purine (7b). Standard procedure 2 was followed by use of **6b** (104.1 mg, 0.1775 mmol). After the solution was stirred for 45 min and then worked up, the residue was purified by use of column chromatography (0−2% methanol in EtOAc as the eluant) to give **7b** (49.9 mg, 99.3 μmol) in 56% yield as white solids: mp (recrystallized from dichloromethane/methanol) 105.6−107.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1 H, H-6), 8.75 (s, 1 H, H-2), 8.02 (s, 1 H, CH═C−COO), 7.30−7.26 (m, 1 H, ArH), 7.22−7.17 (m, 2 H, 2 × ArH), 5.93 (d, *J* = 4.6 Hz, 1 H, H-1″), 5.10 (dd, *J* = 5.2, 4.6 Hz, 1 H, H-2″), 4.66 (dd, *J* = 5.2, 5.2 Hz, 1 H, H-3″), 4.51 (s, 2 H, SCH_2), 4.43 (dd, *J* = 11.4, 3.0 Hz, 1 H, H-5″), 4.31−4.24 (m, 2 H, H-4″ + H-5″), 1.99 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.95 (C═O), 160.85, 158.85 (d), 156.66, 153.31 150.97, 149.65, 144.88, 140.90, 134.49, 125.26, 119.72 (d), 119.25 (d), 118.21 (d), 113.32 (d), 89.38, 82.25, 72.22, 70.69, 63.65, 31.27 (SCH_2), 20.75 (CH_3); IR (neat) 3418 (br, OH), 3068 (w), 2926(w), 2849 (w), 1716 (s), 1440 (s), 1238 (s), 1044 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 503 (MH^+, 41), 329 (100), 177 (44), 154 (97), 136 (75). HRMS (FAB) calcd for $(C_{22}H_{20}FN_4O_7S + H)^+$: 503.1037; found 503.1031.

9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(6′-bromocoumarin-3′-yl)methylthio]purine (7d). Standard procedure 2 was followed by use of **6d** (94.4 mg, 0.146 mmol). After the solution was stirred for 45 min and then worked up, the residue was purified by use of column chromatography (0−2% methanol in EtOAc as the eluant) to give **7d** (47.3 mg, 84.0 μmol) in 57% yield as white solids: mp (recrystallized from dichloromethane/methanol) 132.1−133.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92 (s, 1 H, H-6), 8.77 (s, 1 H, H-2), 7.99 (s, 1 H, CH═C−COO), 7.60 (d, *J* = 2.0 Hz, 1 H, ArH), 7.56 (dd, *J* = 8.7, 2.0 Hz, 1 H, ArH), 7.19 (d, *J* = 8.7 Hz, 1 H, ArH), 5.91 (d, *J* = 4.6 Hz, 1 H, H-1″), 5.08 (dd, *J* = 5.2, 4.6 Hz, 1 H, H-2″), 4.70 (dd, *J* = 5.2, 5.2 Hz, 1 H, H-3″), 4.50 (s, 2 H, SCH_2), 4.41 (dd, *J* = 12.2, 3.4 Hz, 1 H, H-5″), 4.31−4.22 (m, 2 H, H-4″ + H-5″), 3.66 (br, 1 H, OH), 2.92 (br, 1 H, OH), 1.98 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.91 (C═O), 160.52, 156.59, 153.27, 152.31, 150.97, 144.96, 140.43, 134.53, 134.51, 130.27, 125.29, 120.50, 118.33, 117.29, 89.36, 82.23, 72.29, 70.70, 63.58, 31.21 (SCH_2), 20.74 (CH_3); IR (neat) 3418 (br, OH), 3019 (w), 2925 (w), 2853 (w), 1723 (s), 1463 (m), 1240 (s), 1044 (m) cm^{-1}; MS (FAB$^+$) *m*/*z* 563 (MH^+, 12), 391 (19), 307 (45), 291 (50), 213 (90), 154 (100). HRMS (FAB) calcd for $(C_{22}H_{19}BrN_4O_7S + H)^+$: 563.0236, found 563.0227.

9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(6′-methylcoumarin-3′-yl)methylthio]purine (7e). Standard procedure 2 was followed by use of **6e** (122.8 mg, 0.2108 mmol). After the solution was stirred for 45 min and then worked up, the residue was purified by use of column chromatography (0−4% methanol in EtOAc as the eluant) to give **7e** (71.1 mg, 0.143 mmol) in 68% yield as light yellow solids: mp (recrystallized from dichloromethane/methanol) 131.2−132.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (s, 1 H, H-6), 8.76 (s, 1 H, H-2), 7.99 (s, 1 H, CH═C−COO), 7.31−7.28 (m, 2 H, 2 × ArH), 7.19 (d, *J* = 8.4 Hz, 1 H, ArH), 5.93 (d, *J* = 4.6 Hz, 1 H, H-1″), 5.09 (dd, *J* = 5.4, 4.6 Hz, 1 H, H-2″), 4.70 (dd, *J* = 5.6, 5.4 Hz, 1 H, H-3″), 4.51 (s, 2 H, SCH_2), 4.41 (dd, *J* = 12.0, 3.6 Hz, 1 H, H-5″), 4.31−4.21 (m, 2 H, H-4″ + H-5″), 3.66 (br, 1 H, OH), 2.89 (br, 1 H, OH), 2.36 (s, 3 H, $ArCH_3$), 1.99 (s,

3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.88 (C═O), 161.42, 156.83, 153.29, 151.71, 150.99, 144.99, 141.95, 134.58, 134.48, 132.87, 127.80, 123.79, 118.75, 116.35, 89.39, 82.20, 72.35, 70.76, 63.59, 31.54 (SCH_2), 20.72 (CH_3), 20.70 (CH_3); IR (neat) 3407 (br, OH), 3067 (w), 2924 (w), 2849 (w), 1737 (m), 1714 (s), 1463 (m), 1235 (s) cm^{-1}; MS (FAB^+) m/z 499 (MH^+, 34), 307 (43), 289 (24), 173 (35), 154 (100), 107 (34). HRMS (FAB) calcd for $(C_{23}H_{22}N_4O_7S + H)^+$: 499.1297, found 499.1287.

9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(6′,8′-dibromocoumarin-3′-yl)methylthio]purine (7f). Standard procedure 2 was followed by use of **6f** (84.8 mg, 0.117 mmol). After the solution was stirred for 45 min and then worked up, the residue was purified by use of column chromatography (0−3% methanol in EtOAc as the eluant) to give **7f** (38.8 mg, 60.4 μmol) in 52% yield as light yellow solids: mp (recrystallized from dichloromethane/methanol) 107.9−109.2 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.90 (s, 1 H, H-6), 8.76 (s, 1 H, H-2), 7.96 (s, 1 H, CH═C−COO), 7.82 (d, J = 2.2 Hz, 1 H, ArH), 7.55 (d, J = 2.2 Hz, 1 H, ArH), 5.89 (d, J = 4.4 Hz, 1 H, H-1″), 5.08 (br, 1 H, H-2″), 4.69 (br, 1 H, H-3″), 4.50 (s, 2 H, SCH_2), 4.41 (dd, J = 11.4, 3.0 Hz, 1 H, H-5″), 4.31−4.24 (m, 2 H, H-4″ + H-5″), 3.75 (br, 1 H, OH), 2.94 (br, 1 H, OH), 1.99 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.93 (C═O), 159.65, 156.42, 153.26, 150.97, 149.25, 144.91, 140.08, 137.17, 134.40, 129.51, 126.07, 121.24, 117.19, 111.08, 89.32, 82.25, 72.23, 70.69, 63.58, 30.94 (SCH_2), 20.77 (CH_3); IR (neat) 3418 (br, OH), 3078 (m), 2932 (w), 1734 (s), 1710 (s), 1464 (m), 1365 (m), 1236 (m), 1046 (m) cm^{-1}; MS (FAB^+) m/z 641 (MH^+, 6), 469 (14), 307 (55), 213 (23), 154 (100), 136 (95). HRMS (FAB) calcd for $(C_{22}H_{18}Br_2N_4O_7S + H)^+$: 640.9341, found 640.9354.

9-(5″-*O*-Acetyl-β-D-ribofuranos-1″-yl)-8-[(8′-methoxycoumarin-3′-yl)methylthio]purine (7g). Standard procedure 2 was followed by use of **6g** (110.7 mg, 0.1849 mmol). After the solution was stirred for 45 min and then worked up, the residue was purified by use of column chromatography (0−4% methanol in EtOAc as the eluant) to give **7g** (47.5 mg, 94.7 μmol) in 51% yield as white solids: mp (recrystallized from dichloromethane/methanol) 92.3−93.8 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.89 (s, 1 H, H-6), 8.75 (s, 1 H, H-2), 8.02 (s, 1 H, CH═C−COO), 7.17 (dd, J = 8.0, 8.0 Hz, 1 H, ArH), 7.03 (d, J = 8.0 Hz, 1 H, ArH), 5.93 (d, J = 4.4 Hz, 1 H, H-1″), 5.07 (dd, J = 5.4, 4.4 Hz, 1 H, H-2″), 4.69 (dd, J = 5.6, 5.4 Hz, 1 H, H-3″), 4.50 (s, 2 H, SCH_2), 4.41 (dd, J = 12.0, 3.6 Hz, 1 H, H-5″), 4.31−4.22 (m, 2 H, H-4″ + H-5″), 3.92 (s, 3 H, $ArOCH_3$), 1.99 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.93 (C═O), 160.72, 156.68, 153.24, 150.98, 147.05, 144.94, 143.13, 142.12, 134.52, 124.61, 124.18, 119.61, 119.40, 113.67, 89.34, 82.13, 72.29, 70.66, 63.60, 56.25 (OCH_3), 31.54 (SCH_2), 20.76 (CH_3); IR (neat) 3442 (br, OH), 3012 (w), 2924 (w), 1715 (s), 1464 (m), 1274 (m), 1107 (s) cm^{-1}; MS (FAB^+) m/z 515 (MH^+, 39), 341 (63), 289 (20), 189 (45), 154 (100), 136 (88). HRMS (FAB) calcd for $(C_{23}H_{22}N_4O_8S + H)^+$: 515.1237, found 515.1238.

9-(β-D-Ribofuranos-1′-yl)purine-8-thione (8). To a solution of **3**[24] (210.6 mg, 0.5132 mmol, 1.0 equiv) in methanol (10 mL) was added saturated methanolic ammonia (20 mL) under nitrogen atmosphere. After the reaction mixture was stirred at room temperature for 36 h, it was concentrated under reduced pressure to afford a residue. The residue was purified by use of column chromatography (10% methanol in EtOAc as the eluant) to give **8** (134.2 mg, 0.4721 mmol) in 92% yield as white solids: mp (recrystallized from methanol) 222.6−223.7 °C; ^1H NMR (MeOD-d_4, 400 MHz) δ 8.68 (s, 1 H, H-2), 8.46 (s, 1 H, H-6), 6.66 (d, J = 5.6 Hz, 1 H, H-1″), 5.11 (dd, J = 5.6, 5.6 Hz, 1 H, H-2″), 4.48 (dd, J = 5.6, 3.8 Hz, 1 H, H-3″), 4.11−4.08 (m, 1 H, H-4″), 3.86 (dd, J = 12.3, 3.0 Hz, 1 H, H-5″), 3.74 (dd, J = 12.3, 4.4 Hz, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.62 (C═S), 151.06, 150.28, 136.04, 124.39, 88.68, 85.28, 70.51, 70.32, 61.99; IR (KBr) 3326 (br, OH), 3067 (s), 2954 (s), 1626 (m), 1501 (s), 1472 (s), 1266 (s), 1118 (m) cm^{-1}; MS (FAB^+) m/z 285 (MH^+, 20), 235 (39), 219 (25), 165 (35), 136 (100). HRMS (FAB) calcd for $(C_{10}H_{12}N_4O_4S + H)^+$: 285.0658, found 285.0650.

Standard Procedure 3 for the Preparation of Conjugated Compounds 9 and 15. To a solution containing a thione (**8** or **14**, 1.0 equiv) in water (2.5 mL) and acetonitrile (1.5 mL) was added aqueous ammonium hydroxide. After the solution was stirred at room temperature for 30 min, a 3-(chloromethyl)coumarin (**5**, 1.5 equiv) was added and stirring was continued at room temperature for 15 min to 2.0 h. Acetonitrile therein was removed under reduced pressure, and water was further removed under reduced pressure with Kügelrohr GKR-51 containing P_2O_5. The residue was purified by use of column chromatography packed with silica gel to give the desired products with purity of >98.0%, as determined by HPLC.

8-(Coumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)-purine (9a). Standard procedure 3 was followed by use of **8** (43.3 mg, 0.153 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.25 mL), and 3-(chloromethyl)coumarin (**5a**, 44.8 mg, 0.230 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (3−5% methanol in EtOAc as the eluant) to give **9a** (54.9 mg, 0.124 mmol) in 81% yield as white solids: mp (recrystallized from dichloromethane/methanol) 170.7−172.1 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.07 (s, 1 H, H-6), 8.83 (s, 1 H, H-2), 8.26 (s, 1 H, CH═C−COO), 7.68 (d, J = 7.6 Hz, 1 H, ArH), 7.60 (dd, J = 8.2, 7.4 Hz, 1 H, ArH), 7.41 (d, J = 8.2 Hz, 1 H, ArH), 7.34 (dd, J = 7.6, 7.4 Hz, 1 H, ArH), 5.78 (d, J = 6.4 Hz, 1 H, H-1″), 5.47 (d, J = 6.0 Hz, 1 H, OH), 5.29 (d, J = 5.2 Hz, 1 H, OH), 5.11−5.06 (m, 1 H, H-2″), 4.96 (dd, J = 6.4, 5.2 Hz, 1 H, OH), 4.54 (d, J = 14.6 Hz, 1 H, SCH), 4.52 (d, J = 14.6 Hz, 1 H, SCH), 4.22−4.18 (m, 1 H, H-3″), 3.95−3.91 (m, 1 H, H-4″), 3.68−3.63 (m, 1 H, H-5″), 3.54−3.48 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.92 (C═O), 156.90, 153.40, 153.28, 151.29, 145.77, 142.55, 134.76, 132.61, 129.02, 125.39, 123.78, 119.20, 116.60, 89.13, 86.68, 71.38, 70.93, 62.25, 31.84 (SCH_2); IR (KBr) 3335 (br, OH), 3161 (w), 2946 (w), 1713 (s), 1594 (m), 1470 (m), 1073 (m) cm^{-1}; MS (FAB^+) m/z 443 (MH^+, 12), 307 (69), 289 (38), 154 (100), 136 (93), 89 (40). HRMS (FAB) calcd for $(C_{20}H_{18}N_4O_6S + H)^+$: 443.1025, found 443.1016.

8-(6′-Fluorocoumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)purine (9b). Standard procedure 3 was followed by use of **8** (49.7 mg, 0.175 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.25 mL), and 3-chloromethyl-6-fluorocoumarin (**5b**, 55.8 mg, 0.262 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (3−5% methanol in EtOAc as the eluant) to give **9b** (52.4 mg, 0.114 mmol) in 65% yield as white solids: mp (recrystallized from dichloromethane/methanol) 183.2−184.3 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.06 (s, 1 H, H-6), 8.83 (s, 1 H, H-2), 8.22 (s, 1 H, CH═C−COO), 7.66−7.63 (m, 1 H, ArH), 7.48−7.46 (m, 2 H, 2 × ArH), 5.78 (d, J = 6.4 Hz, 1 H, H-1″), 5.47 (d, J = 6.4 Hz, 1 H, OH), 5.28 (d, J = 4.8 Hz, 1 H, OH), 5.10−5.06 (m, 1 H, H-2″), 4.96 (dd, J = 6.4, 5.6 Hz, 1 H, OH), 4.56 (d, J = 13.8 Hz, 1 H, SCH), 4.52 (d, J = 13.8 Hz, 1 H, SCH), 4.22−4.19 (m, 1 H, H-3″), 3.95−3.91 (m, 1 H, H-4″), 3.69−3.63 (m, 1 H, H-5″), 3.54−3.48 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.22, 158.31 (d), 156.37, 152.99, 151.03, 149.46, 145.56, 141.04, 134.43, 124.84, 119.89 (d), 119.33 (d), 118.30 (d), 113.91 (d), 88.75, 86.39, 70.98, 70.61, 61.93, 31.33 (SCH_2); IR (KBr) 3367 (br, OH), 3154 (m), 2924 (w), 1713 (s), 1582 (m), 1441 (m), 1093 (m) cm^{-1}; MS (FAB^+) m/z 461 (MH^+, 31), 329 (97), 177 (71), 154 (100), 107 (58), 91 (94). HRMS (FAB) calcd for $(C_{20}H_{17}FN_4O_6S + H)^+$: 461.0931, found 461.0938.

8-(6′-Chlorocoumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)purine (9c). Standard procedure 3 was followed by use of **8** (38.5 mg, 0.135 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.25 mL), and 6-chloro-3-(chloromethyl)coumarin (**5c**, 46.4 mg, 0.203 mmol, 1.5 equiv). After the solution was stirred at room temperature for

2.0 h and then worked up, the residue was purified by use of column chromatography (0−5% methanol in EtOAc as the eluant) to give **9c** (39.6 mg, 83.0 μmol) in 62% yield as white solids: mp (recrystallized from dichloromethane/methanol) 189.9−191.3 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.07 (s, 1 H, H-6), 8.83 (s, 1 H, H-2), 8.22 (s, 1 H, CH═C−COO), 7.88 (d, J = 1.6 Hz, 1 H, ArH), 7.62 (dd, J = 9.0, 1.6 Hz, 1 H, ArH), 7.60 (d, J = 9.0 Hz, 1 H, ArH), 5.78 (d, J = 6.0 Hz, 1 H, H-1″), 5.47 (d, J = 6.4 Hz, 1 H, OH), 5.28 (d, J = 4.8 Hz, 1 H, OH), 5.10−5.05 (m, 1 H, H-2″), 4.95 (dd, J = 6.0, 5.2 Hz, 1 H, OH), 4.55 (d, J = 14.4 Hz, 1 H, SCH), 4.51 (d, J = 14.4 Hz, 1 H, SCH), 4.21−4.19 (m, 1 H, H-3″), 3.94−3.92 (m, 1 H, H-4″), 3.68−3.63 (m, 1 H, H-5″), 3.54−3.48 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.82, 156.11, 152.84, 151.57, 150.89, 145.44, 140.48, 134.27, 131.46, 128.48, 127.58, 124.84, 120.19, 118.15, 88.58, 86.23, 70.77, 70.43, 61.75, 31.11 (SCH_2); IR (KBr) 3390 (br, OH), 3168 (m), 2936 (w), 1716 (s), 1596 (m), 1472 (m), 1092 (m) cm^{-1}; MS (FAB$^+$) m/z 477 (MH^+, 18), 307 (56), 235 (16), 154 (100), 136 (92), 120 (28). HRMS (FAB) calcd for $(C_{20}H_{17}ClN_4O_6S + H)^+$: 477.0636, found 477.0625.

8-(6′-Methylcoumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)purine (9e). Standard procedure 3 was followed by use of **8** (40.6 mg, 0.143 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.25 mL), and 3-chloromethyl-6-methylcoumarin (**5e**, 44.7 mg, 0.214 mmol, 1.5 equiv). After the solution was stirred at room temperature for 30 min and then worked up, the residue was purified by use of column chromatography (0−5% methanol in EtOAc as the eluant) to give **9e** (48.1 mg, 0.105 mmol) in 74% yield as white solids: mp (recrystallized from dichloromethane/methanol) 184.7−186.1 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.07 (s, 1 H, H-6), 8.83 (s, 1 H, H-2), 8.18 (s, 1 H, CH═C−COO), 7.50 (s, 1 H, ArH), 7.40 (d, J = 8.6 Hz, 1 H, ArH), 7.30 (d, J = 8.6 Hz, 1 H, ArH), 5.78 (d, J = 6.4 Hz, 1 H, H-1″), 5.48 (d, J = 6.0 Hz, 1 H, OH), 5.27 (d, J = 4.4 Hz, 1 H, OH), 5.10−5.06 (m, 1 H, H-2″), 4.97 (dd, J = 6.0, 5.6 Hz, 1 H, OH), 4.55 (d, J = 14.2 Hz, 1 H, SCH), 4.51 (d, J = 14.2 Hz, 1 H, SCH), 4.21−4.19 (m, 1 H, H-3″), 3.94−3.92 (m, 1 H, H-4″), 3.68−3.63 (m, 1 H, H-5″), 3.54−3.48 (m, 1 H, H-5″), 2.32 (s, 3H, $ArCH_3$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.36, 156.30, 152.84, 151.10, 150.86, 145.36, 141.73, 134.29, 134.05, 132.80, 128.13, 123.36, 118.49, 115.90, 88.57, 86.23, 70.75, 70.44, 61.76, 31.24 (SCH_2), 20.20 (CH_3); IR (KBr) 3371 (br, OH), 3029 (w), 2924 (m), 1712 (s), 1470 (m), 1232 (m), 1094 (m) cm^{-1}; MS (FAB$^+$) m/z 457 (MH^+, 14), 307 (48), 289 (26), 154 (100), 136 (93). HRMS (FAB) calcd for $(C_{21}H_{20}N_4O_6S + H)^+$: 457.1182, found 457.1174.

8-(6′,8′-Dibromocoumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)purine (9f). Standard procedure 3 was followed by use of **8** (40.2 mg, 0.141 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.25 mL), and 3-chloromethyl-6,8-dibromocoumarin (**5f**, 74.7 mg, 0.212 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (3−5% methanol in EtOAc as the eluant) to give **9f** (62.6 mg, 0.104 mmol) in 74% yield as white solids: mp (recrystallized from dichloromethane/methanol) 180.7−182.2 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.06 (s, 1 H, H-6), 8.83 (s, 1 H, H-2), 8.20 (s, 1 H, CH═C−COO), 8.11 (d, J = 2.2 Hz, 1 H, ArH), 8.03 (d, J = 2.2 Hz, 1 H, ArH), 5.79 (d, J = 6.4 Hz, 1 H, H-1″), 5.45 (d, J = 6.4 Hz, 1 H, OH), 5.27 (d, J = 5.2 Hz, 1 H, OH), 5.09−5.04 (m, 1 H, H-2″), 4.95 (dd, J = 6.4, 5.2 Hz, 1 H, OH), 4.57 (d, J = 14.2 Hz, 1 H, SCH), 4.52 (d, J = 14.2 Hz, 1 H, SCH), 4.22−4.19 (m, 1 H, H-3″), 3.95−3.92 (m, 1 H, H-4″), 3.69−3.63 (m, 1 H, H-5″), 3.55−3.49 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ159.17, 155.99, 152.84, 150.91, 148.88, 145.47, 140.19, 136.27, 134.25, 130.27, 125.54, 121.66, 116.42, 110.12, 88.59, 86.24, 70.81, 70.44, 61.76, 30.94 (SCH_2); IR (KBr) 3351 (br, OH), 3068 (w), 2924 (w), 1729 (s), 1591 (m), 1465 (m), 1245 (m), 1053 (m) cm^{-1}; MS (FAB$^+$) m/z 599 (MH^+, 2), 307 (20), 154 (100), 136 (72), 107 (22). HRMS (FAB) calcd for $(C_{20}H_{16}Br_2N_4O_6S + H)^+$: 598.9236, found 598.9234.

8-(8′-Methoxycoumarin-3′-yl)methylthio-9-(β-D-ribofuranos-1″-yl)purine (9g). Standard procedure 3 was followed by use of **8** (39.8 mg, 0.140 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.25 mL), and 3-chloromethyl-8-methoxycoumarin (**5g**, 47.2 mg, 0.210 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (5% methanol in EtOAc as the eluant) to give **9g** (33.5 mg, 69.4 μmol) in 51% yield as white solids: mp (recrystallized from dichloromethane/methanol) 169.8−171.2 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.06 (s, 1 H, H-6), 8.82 (s, 1 H, H-2), 8.22 (s, 1 H, CH═C−COO), 7.29−7.25 (m, 3 H, 3 × ArH), 5.78 (d, J = 6.4 Hz, 1 H, H-1″), 5.46 (d, J = 6.0 Hz, 1 H, OH), 5.27 (d, J = 5.2 Hz, 1 H, OH), 5.10−5.05 (m, 1 H, H-2″), 4.95 (dd, J = 6.4, 5.6 Hz, 1 H, OH), 4.56 (d, J = 14.0 Hz, 1 H, SCH), 4.51 (d, J = 14.0 Hz, 1 H, SCH), 4.22−4.18 (m, 1 H, H-3″), 3.94−3.92 (m, 1 H, H-4″), 3.91 (s, 3H, OCH_3), 3.68−3.63 (m, 1 H, H-5″), 3.54−3.50 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.99, 156.32, 152.87, 150.92, 146.42, 145.41, 142.26, 142.05, 134.33, 124.80, 123.67, 119.67, 119.35, 114.24, 88.57, 86.26, 70.74, 70.47, 61.78, 56.13 (OCH_3), 31.23 (SCH_2); IR (KBr) 3400 (br, OH), 3351 (br, OH), 3075 (w), 2938 (w), 1710 (s), 1467 (m), 1103 (m) cm^{-1}; MS (FAB$^+$) m/z 473 (MH^+, 8), 307 (25), 154 (100), 136 (75), 107 (22). HRMS (FAB) calcd for $(C_{21}H_{20}N_4O_7S + H)^+$: 473.1131, found 473.1120.

9-(2′,3′-*O*-Isopropylidene-β-D-ribofuranos-1′-yl)purine-8-thione (10). To a solution of **8** (68.5 mg, 0.241 mmol, 1.0 equiv) in 2,2-dimethoxypropane (6.0 mL) and acetone (12 mL) was added PTSA (45.8 mg, 0.241 mmol, 1.0 equiv) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h. Excess solvent was removed under reduced pressure, and the residue was treated with aqueous $NaHCO_3$ solution (10%, 20 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure. The residue was purified by use of column chromatography (5% methanol in EtOAc as the eluant) to give **10** (57.6 mg, 0.178 mmol) in 74% yield as white solids: mp (recrystallized from dichloromethane/methanol) 142.6−144.1 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.78 (s, 1 H, H-2), 8.56 (s, 1 H, H-6), 6.59 (d, J = 2.4 Hz, 1 H, H-1″), 5.53 (dd, J = 6.4, 2.4 Hz, 1 H, H-2″), 5.02 (dd, J = 6.4, 3.6 Hz, 1 H, H-3″), 4.91 (dd, J = 6.0, 6.0 Hz, 1 H, OH), 4.10−4.06 (m, 1 H, H-4″), 3.62−3.51 (m, 1 H, H-5″), 3.50−3.46 (m, 1 H, H-5″), 1.53 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.59 (C═S), 151.38, 149.75, 136.96, 123.79, 113.25, 88.50, 87.13, 82.01, 81.59, 61.59, 27.15 (CH_3), 25.28 (CH_3); IR (neat) 3329 (br, OH), 3180 (m), 2988 (m), 1657 (s), 1455 (s), 1217 (m), 1101 (m) cm^{-1}. MS (FAB$^+$) m/z 325 (MH^+, 2), 307 (39), 289 (21), 154 (100), 136 (90), 107 (33). HRMS (FAB) calcd for $(C_{13}H_{26}N_4O_4S + H)^+$: 325.0971, found 325.0961.

8-(Coumarin-3′-yl)methylthio-9-(2″,3″-*O*-isopropylidene-β-D-ribofuranos-1″-yl)purine (11a). Standard procedure 1 was followed by use of **10** (42.7 mg, 0.132 mmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 3-(chloromethyl)coumarin (**5a**, 38.5 mg, 0.198 mmol, 1.5 equiv). After the solution was stirred at room temperature for 1.0 h and then worked up, the residue was purified by use of column chromatography (100% EtOAc as the eluant) to give **11a** (33.1 mg, 68.6 μmol) in 52% yield as white solids: mp (recrystallized from dichloromethane/hexanes) 109.1−110.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (s, 1 H, H-6), 8.77 (s, 1 H, H-2), 8.06 (s, 1 H, CH═C−COO), 7.50−7.44 (m, 2 H, 2 × ArH), 7.31−7.22 (m, 2 H, 2 × ArH), 5.93 (d, J = 5.2 Hz, 1 H, H-1″), 5.63 (d, J = 10.8 Hz, 1 H, OH), 5.19 (dd, J = 5.6, 5.2 Hz, 1 H, H-2′), 5.03 (d, J = 5.2 Hz, 1 H, H-3″), 4.60 (d, J = 14.0 Hz, 1 H, SCH), 4.47 (d, J = 14.0 Hz, 1 H, SCH), 4.49−4.46 (m, 1 H, H-4″), 3.90−3.93 (m, 1 H, H-5″), 3.78−3.72 (m, 1 H, H-5″), 1.65 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.01 (C═O), 156.23, 153.60, 152.44, 150.62, 145.95, 141.83, 135.36,

131.79, 127.99, 124.62, 123.95, 118.97, 116.63, 114.32, 92.12, 85.59, 82.39, 81.42, 63.21, 31.44 (SCH_2), 27.67 (CH_3), 25.37 (CH_3); IR (neat) 3324 (br, OH), 3068 (w), 2933 (m), 1717 (s), 1463 (m), 1290 (m), 1102 (m) cm^{-1}; MS (FAB^+) m/z 483 (MH^+, 38), 311 (100), 159 (43), 136 (62), 107 (17). HRMS (FAB) calcd for $(C_{23}H_{22}N_4O_6S + H)^+$: 483.1338, found 483.1336.

8-(6′-Bromocoumarin-3′-yl)methylthio-9-(2″,3″-*O*-isopropylidene-β-D-ribofuranos-1″-yl)purine (11d). Standard procedure 1 was followed by use of **10** (40.9 mg, 0.126 mmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 6-bromo-3-(chloromethyl)coumarin (**5d**, 51.7 mg, 0.189 mmol, 1.5 equiv). After the solution was stirred at room temperature for 2.0 h and then worked up, the residue was purified by use of column chromatography (100% EtOAc as the eluant) to give **11d** (43.8 mg, 78.0 μmol) in 62% yield as white solids: mp (recrystallized from dichloromethane/hexanes) 151.4−152.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.99 (s, 1 H, H-6), 8.79 (s, 1 H, H-2), 8.01 (s, 1 H, CH═C−COO), 7.60−7.56 (m, 2 H, ArH), 7.31−7.22 (d, J = 12.0 Hz, 1 H, ArH), 5.91 (d, J = 5.2 Hz, 1 H, H-1″), 5.76 (d, J = 12.0 Hz, 1 H, OH), 5.19 (dd, J = 5.6, 5.2 Hz, 1 H, H-2′), 5.03 (d, J = 5.6 Hz, 1 H, H-3″), 4.58 (d, J = 14.0 Hz, 1 H, SCH), 4.46 (d, J = 14.0 Hz, 1 H, SCH), 4.49−4.44 (m, 1 H, H-4″), 3.94−3.91 (m, 1 H, H-5″), 3.79−3.73 (m, 1 H, H-5″), 1.65 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ160.40 (C═O), 155.95, 152.40, 152.35, 150.68, 146.07, 140.38, 135.31, 134.51, 130.24, 125.25, 120.47, 118.34, 117.22, 114.31, 92.19, 85.55, 82.34, 81.44, 63.22, 31.19 (SCH_2), 27.70 (CH_3), 25.37 (CH_3); IR (neat) 3322 (br, OH), 3064 (w), 2989 (w), 1725 (s), 1716 (s), 1463 (m), 1221 (m), 1102 (m) cm^{-1}; MS (FAB^+) m/z 563 (MH^+, 16), 391 (100), 239 (35), 154 (44), 107 (15). HRMS (FAB) calcd for $(C_{23}H_{21}BrN_4O_6S + H)^+$: 561.0443, found 561.0441.

8-(8′-Methoxycoumarin-3′-yl)methylthio-9-(2″,3″-*O*-isopropylidene-β-D-ribofuranos-1″-yl)purine (11g). Standard procedure 1 was followed by use of **10** (33.4 mg, 0.103 mmol, 1.0 equiv), water (2.5 mL), acetonitrile (1.5 mL), and 3-chloromethyl-8-methoxycoumarin (**5g**, 34.7 mg, 0.155 mmol, 1.5 equiv). After the solution was stirred at room temperature for 1.0 h and then worked up, the residue was purified by use of column chromatography (0−4% methanol in EtOAc as the eluant) to give **11g** (33.9 mg, 66.1 μmol) in 64% yield as white solids: mp (recrystallized from dichloromethane/hexanes) 109.7−111.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.97 (s, 1 H, H-6), 8.78 (s, 1 H, H-2), 8.03 (s, 1 H, CH═C−COO), 7.17 (dd, J = 7.8, 7.6 Hz, 1 H, ArH), 7.19−7.15 (m, 2 H, 2 × ArH), 5.91 (d, J = 5.2 Hz, 1 H, H-1″), 5.66 (d, J = 10.8 Hz, 1 H, OH), 5.18 (dd, J = 5.2, 5.2 Hz, 1 H, H-2′), 5.02 (d, J = 5.6 Hz, 1 H, H-3″), 4.60 (d, J = 13.8 Hz, 1 H, SCH), 4.48 (d, J = 13.8 Hz, 1 H, SCH), 4.50−4.46 (m, 1 H, H-4″), 3.93−3.90 (m, 4 H, $ArOCH_3$ + H-5″), 3.79−3.73 (m, 1 H, H-5″), 1.65 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.51 (C═O), 156.28, 152.43, 150.68, 147.12, 145.95, 143.26, 141.98, 135.38, 124.51, 124.22, 119.61, 119.37, 114.33, 113.68, 92.15, 85.54, 82.38, 81.44, 63.23, 56.26 (OCH_3) 31.44 (SCH_2), 27.69 (CH_3), 25.37 (CH_3); IR (neat) 3356 (br, OH), 3061 (w), 2937 (m), 1716 (s), 1463 (m), 1274 (m), 1220 (m), 1105 (s) cm^{-1}; MS (FAB^+) m/z 513 (MH^+, 25), 241 (100), 189 (52), 154 (85). HRMS (FAB) calcd for $(C_{24}H_{24}N_4O_7S + H)^+$: 513.1444, found 513.1453.

8-[(Coumarin-3′-yl)methylthio]adenosine (15a). Standard procedure 3 was followed by use of 8-mercaptoadenosine (**14**, 32.1 mg, 0.107 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.15 mL), and 3-(chloromethyl)coumarin (**5a**, 31.3 mg, 0.161 mmol, 1.5 equiv). After the solution was stirred at room temperature for 1.0 h and then worked up, the residue was purified by use of column chromatography (5−10% methanol in EtOAc as the eluant) to give **15a** (41.2 mg, 90.1 μmol) in 84% yield as white solids: mp (recrystallized from dichloromethane/methanol) 179.3−181.0 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.44 (s, 1 H, H-2), 8.04 (s, 1 H, CH═C−COO), 7.68 (d, J = 7.6 Hz, 1 H, ArH), 7.60 (dd, J = 8.4, 7.2 Hz, 1 H, ArH), 7.46 (s, 2 H, NH_2), 7.40 (d, J = 8.4 Hz, 1 H, ArH), 7.34 (dd, J = 7.6, 7.2 Hz, 1 H, ArH), 5.68 (d, J = 7.2 Hz, 1 H, H-1″), 5.59 (dd, J = 8.8, 4.4 Hz, 1 H, OH), 5.40 (d, J = 6.8 Hz, 1 H, OH), 5.20 (d, J = 4.4 Hz, 1 H, OH), 4.96−4.91 (m, 1 H, H-2″), 4.39 (d, J = 13.8 Hz, 1 H, SCH), 4.35 (d, J = 13.8 Hz, 1 H, SCH), 4.13−4.09 (m, 1 H, H-3″), 3.92−3.89 (m, 1 H, H-4″), 3.64−3.59 (m, 1 H, H-5″), 3.51−3.44 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ160.16 (C═O), 154.60, 152.99, 151.43, 150.52, 147.87, 142.29, 131.78, 128.35, 124.71, 123.45, 119.46, 118.95, 116.11, 88.74, 86.66, 71.29, 70.90, 62.13, 31.74 (SCH_2); IR (KBr) 3438 (br, OH), 3223 (w), 2932 (w), 1715 (s), 1602 (s), 1462 (m), 1316 (m), 1226 (m) cm^{-1}; MS (FAB^+) m/z 458 (MH^+, 50), 326 (59), 289 (45), 154 (100), 107 (62). HRMS (FAB) calcd for $(C_{20}H_{19}N_5O_6S + H)^+$: 458.1131, found 458.1139.

8-[(6′-Bromocoumarin-3′-yl)methylthio]adenosine (15d). Standard procedure 3 was followed by use of **14** (25.3 mg, 84.5 μmol, 1.0 equiv), aqueous ammonium hydroxide (0.15 mL), and 6-bromo-3-(chloromethyl)coumarin (**5d**, 34.7 mg, 0.127 mmol, 1.5 equiv). After the solution was stirred at room temperature for 15 min and then worked up, the residue was purified by use of column chromatography (5−10% methanol in EtOAc as the eluant) to give **15d** (32.7 mg, 61.0 μmol) in 72% yield as white solids: mp (recrystallized from dichloromethane/methanol) 217.2−218.7 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.41 (s, 1 H, H-2), 8.04 (s, 1 H, CH═C−COO), 7.94 (d, J = 2.4 Hz, 1 H, ArH), 7.73 (dd, J = 8.8, 2.4 Hz, 1 H, ArH), 7.44 (s, 2 H, NH_2), 7.38 (d, J = 8.8 Hz, 1 H, ArH), 5.67 (d, J = 7.2 Hz, 1 H, H-1″), 5.59 (dd, J = 8.6, 3.4 Hz, 1 H, OH), 5.41 (d, J = 6.4 Hz, 1 H, OH), 5.22 (d, J = 4.4 Hz, 1 H, OH), 4.95−4.91 (m, 1 H, H-2″), 4.37 (d, J = 14.6 Hz, 1 H, SCH), 4.33 (d, J = 14.6 Hz, 1 H, SCH), 4.13−4.09 (m, 1 H, H-3″), 3.92−3.89 (m, 1 H, H-4″), 3.64−3.60 (m, 1 H, H-5″), 3.51−3.45 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ159.75 (C═O), 154.61, 152.09, 151.49, 150.55, 147.89, 141.12, 134.12, 130.30, 124.67, 120.90, 119.49, 118.51, 116.27, 88.75, 86.72, 71.33, 70.94, 62.16, 31.67 (SCH_2); IR (KBr) 3435 (br, OH), 3099 (w), 2850 (w), 1717 (s), 1660 (m), 1470 (m), 1232 (m), 1094 (m) cm^{-1}; MS (FAB^+) m/z 536 (MH^+, 28), 307 (66), 289 (56), 168 (38), 154 (100). HRMS (FAB) calcd for $(C_{20}H_{18}BrN_5O_6S + H)^+$: 536.0239, found 536.0247.

8-[(6′,8′-Dibromocoumarin-3′-yl)methylthio]adenosine (15f). Standard procedure 3 was followed by use of **14** (42.2 mg, 0.141 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.15 mL), and 3-chloromethyl-6,8-dibromocoumarin (**5f**, 74.5 mg, 0.211 mmol, 1.5 equiv). After the solution was stirred at room temperature for 90 min and then worked up, the residue was purified by use of column chromatography (0−9% methanol in EtOAc as the eluant) to give **15f** (72.1 mg, 0.117 mmol) in 83% yield as white solids: mp (recrystallized from dichloromethane/methanol) 168.5−170.1 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.37 (s, 1 H, H-2), 8.10 (d, J = 2.0 Hz, 1 H, ArH), 8.04 (s, 1 H, CH═C−COO), 7.95 (d, J = 2.0 Hz, 1 H, ArH), 7.44 (s, 2 H, NH_2), 5.67 (d, J = 7.2 Hz, 1 H, H-1″), 5.58 (dd, J = 8.6, 3.4 Hz, 1 H, OH), 5.40 (d, J = 6.8 Hz, 1 H, OH), 5.22 (d, J = 4.4 Hz, 1 H, OH), 4.95−4.90 (m, 1 H, H-2″), 4.37 (d, J = 15.0 Hz, 1 H, SCH), 4.34 (d, J = 15.0 Hz, 1 H, SCH), 4.12−4.09 (m, 1 H, H-3″), 3.92−3.89 (m, 1 H, H-4″), 3.63−3.59 (m, 1 H, H-5″), 3.50−3.44 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ159.08 (C═O), 154.61, 151.49, 150.51, 148.96, 147.69, 140.85, 136.11, 129.92, 125.35, 121.82, 119.47, 116.31, 110.20, 88.73, 86.70, 71.32, 70.89, 62.13, 31.56 (SCH_2); IR (KBr) 3337 (br, OH), 3061 (w), 1723 (s), 1633 (m), 1453 (m), 1244 (m), 1127 (m) cm^{-1}; MS (FAB^+) m/z 614 (MH^+, 6), 307 (68), 289 (45), 168 (11), 154 (100), 107 (63). HRMS (FAB) calcd for $(C_{20}H_{17}Br_2N_5O_6S + H)^+$: 613.9345, found 613.9335.

8-[(8′-Methoxycoumarin-3′-yl)methylthio]adenosine (15g). Standard procedure 3 was followed by use of **14** (57.7 mg, 0.193 mmol, 1.0 equiv), aqueous ammonium hydroxide (0.15 mL), and 3-chloromethyl-8-methoxycoumarin (**5g**, 64.5 mg, 0.290 mmol, 1.5 equiv). After the solution was stirred at room temperature for 90 min and then worked up, the residue was purified by use of column chromatography (0−10%

methanol in EtOAc as the eluant) to give **15g** (79.2 mg, 0.162 mmol) in 84% yield as white solids: mp (recrystallized from dichloromethane/methanol) 150.3−151.9 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.39 (s, 1 H, H-2), 8.04 (s, 1 H, CH═C−COO), 7.42 (s, 2 H, NH_2), 7.27−7.20 (m, 3 H, 3 × ArH), 5.69 (d, J = 7.2 Hz, 1 H, H-1″), 5.53 (dd, J = 8.6, 3.8 Hz, 1 H, OH), 5.40 (d, J = 5.6 Hz, 1 H, OH), 5.18 (br, 1 H, OH), 4.93−4.90 (m, 1 H, H-2″), 4.39 (d, J = 13.6 Hz, 1 H, SCH), 4.35 (d, J = 13.6 Hz, 1 H, SCH), 4.13−4.10 (m, 1 H, H-3″), 3.93−3.90 (m, 1 H, H-4″), 3.89 (s, 3H, OCH_3), 3.64−3.59 (m, 1 H, H-5″), 3.51−3.45 (m, 1 H, H-5″); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.89 (C═O), 154.61, 151.45, 150.53, 147.83, 146.40, 142.51, 142.31, 124.68, 123.61, 119.52, 119.50, 119.46, 114.09, 88.74, 86.68, 71.31, 70.91, 62.14, 56.12 (OCH_3), 31.72 (SCH_2); IR (KBr) 3450 (br, OH), 3143 (w), 2872 (w), 1712 (s), 1641 (m), 1482 (m), 1276 (m), 1196 (m) cm^{-1}; MS (FAB$^+$) m/z 488 (MH^+, 13), 356 (23), 189 (45), 154 (100), 136 (94). HRMS (FAB) calcd for $(C_{21}H_{21}N_5O_7S + H)^+$: 488.1240, found 488.1243.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra and HPLC data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*Phone: 886-35-725813. Fax: 886-35-721594. E-mail: jrhwu@mx.nthu.edu.tw.

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■ ABBREVIATIONS USED

BTSA, bistrimethylsilylacetamide; CC_{50}, 50% inhibitory concentrations for host cell growth; CCDC, Cambridge Crystallographic Data Center; CVFF, consistent valence force field; EC_{50}, 50% inhibitory concentrations for virus replication; EC_{90}, 90% inhibitory concentrations for virus replication; EtOAc, ethyl acetate; HCV, hepatitis C virus; Me_3SiOTf, trimethylsilyl trifluoromethanesulfonate; PTSA, *p*-toluenesulfonic acid monohydrate; SI, selectivity index, ratio of CC_{50} to EC_{50}

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