AMP Deaminase Inhibitors. 3. SAR of 3-(Carboxyarylalkyl)coformycin Aglycon Analogues

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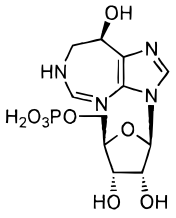
N3-Substituted coformycin aglycon analogues with improved AMP deaminase (AMPDA) inhibitory potency are described. Replacement of the 5-carboxypentyl substituent in the lead AMPDA inhibitor 3-(5-carboxypentyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (**2**) described in the previous article with various carboxyarylalkyl groups resulted in compounds with 10−100-fold improved AMPDA inhibitory potencies. The optimal N3 substituent had *m*-carboxyphenyl with a two-carbon alkyl tether. For example, 3-[2-(3-carboxy-5-ethylphenyl)-ethyl]-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (**43g**) inhibited human AMPDA with a K_i = 0.06 μM. The compounds within the series also exhibited >1000-fold specificity for AMPDA relative to adenosine deaminase.

Introduction

AMP deaminase (AMPDA) represents a potential target for novel antiischemic drug therapy based on its putative role in adenosine production.[1] In the initial communication of our effort to discover AMPDA inhibitors, we described the design of potent, specific, and cell-penetrable AMPDA inhibitors using a transition-state (TS) mimicry strategy.[2,3] As described in the preceding article, the initial set of compounds in this series supported this design concept. This work demonstrated that replacement of the phosphorylated sugar of the potent TS inhibitor coformycin monophosphate (**1**) with a simple carboxyalkyl group resulted in retention of significant AMPDA inhibitory potency. Structure−activity studies showed that AMPDA inhibition was dependent on the terminal carboxylic acid and length of the alkyl group. The lead compound in the series was compound **2** wherein the N3 substituent was 5-carboxypentyl.



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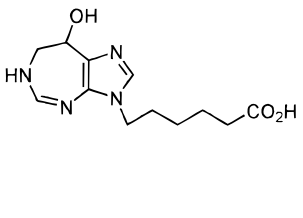
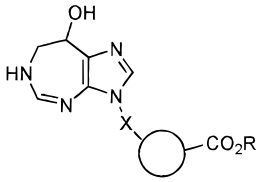


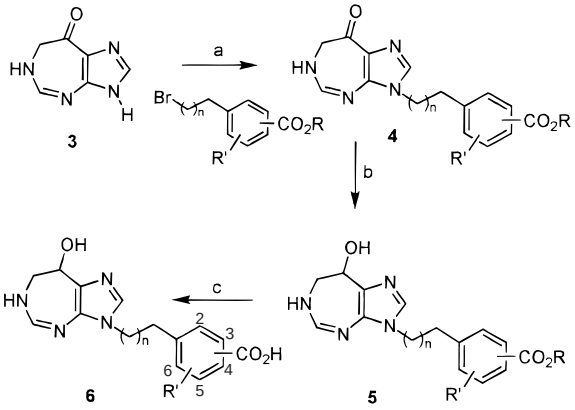
2

To improve the potency of **2**, we focused on replacing the flexible N3 side chain with a more structurally rigid surrogate. One possibility was the incorporation of an aryl group between the alkyl moiety and the carboxylate (Chart 1). Herein we report the optimization of the tether length (X) and the position of the carboxylic acid and how this investigation resulted in generating potent and selective AMPDA inhibitors.

Chart 1



Scheme 1[a]



[a] Reagents: (a) NaH, DMF; NaI; (b) $NaBH_4$, MeOH, CH_2Cl_2; (c) 1 N NaOH, dioxane.

Chemistry

The AMPDA inhibitor analogues (Tables 1 and 2) were prepared using the general three-step procedure outlined in Scheme 1. Alkylation of the heterocycle 6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one **(3)**[4] with an appropriate electrophile in the presence of NaH gave the desired N3 regioisomer as the major product.[5] Reduction of the alkylation products with $NaBH_4$ furnished the corresponding racemic alcohols **5**. Saponification of the esters with aqueous NaOH in dioxane provided the desired carboxylic acids **6**.

Electrophile Preparation. Many of the electrophiles were constructed using palladium-catalyzed coupling reactions. The electrophiles **11** and **12** were prepared from a common intermediate **9**, which was

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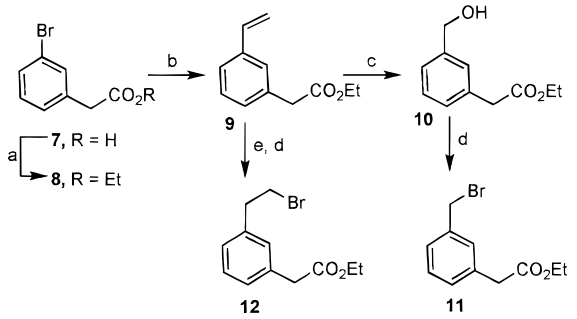
Scheme 2[a]



[a] Reagents: (a) H_2SO_4, EtOH; (b) vinyltributyltin, $Pd(PPh_3)_4$, DMF; (c) i. $NaIO_4$, OsO_4, NMO, *t*-BuOH, THF; $NaHCO_3$, ii. $NaBH_4$, MeOH; (d) CBr_4, PPh_3, CH_2Cl_2; (e) 9-BBN, THF; 30% H_2O_2, 3 N NaOH.

readily prepared from **8** (Scheme 2).[6a] Oxidative cleavage of **9** with $NaIO_4$ in the presence of osmium tetroxide followed by $NaBH_4$ reduction and bromination gave the benzyl bromide derivative **11**. Similarly, hydroboration/oxidation of **9** followed by bromination provided the phenethyl derivative **12**.

Compounds with a three-carbon tether, **16a**−**i** and **17**, were prepared using the sequence depicted in Scheme 3. Intermediates **15a**−**i** were prepared from the corresponding phenols **13a**−**e** and aryl iodides **14f**−**i** using a palladium coupling reaction.[6b] Propargyl alcohols **15a**−**i** were hydrogenated and converted to bromides **16a**−**i**. Propargyl bromide derivative **17** was made from the corresponding alcohol **15g**.

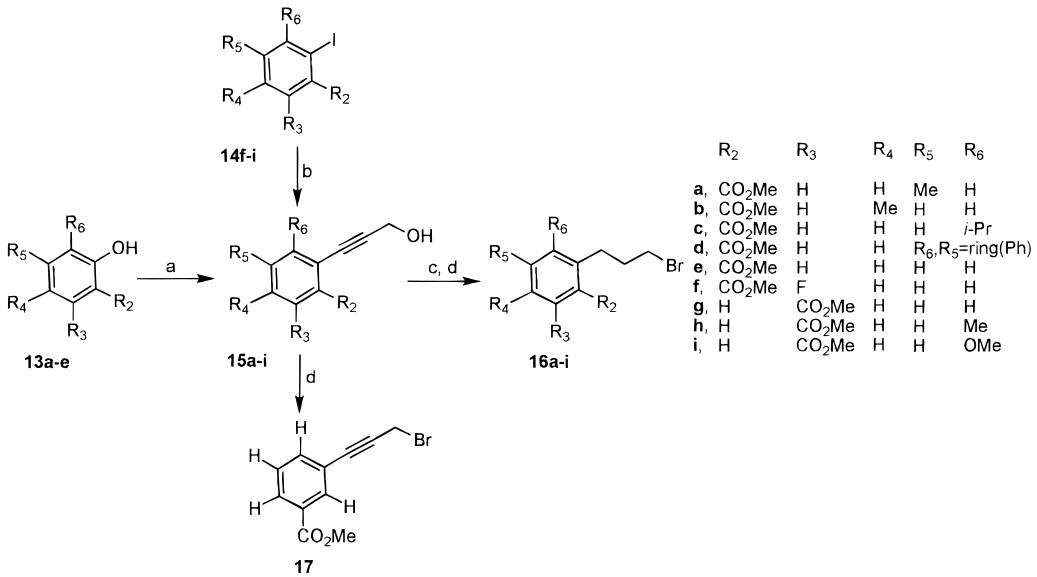
Electrophiles containing a heteroatom in the linker were prepared by the route described in Scheme 4. Mitsunobu reaction or base alkylation of phenols/thiophenols **18a**−**c,f** provided the corresponding alkylation products **19a**−**d**. Compound **18f** was prepared by carboxylation of thiol[7] **18d** followed by esterification.

Heteroaromatic rings were introduced in the side chain using two different approaches. Reaction of TBDMS-protected 2-(3-thienyl)ethanol **20b** with *n*-BuLi followed by methyl chloroformate gave the two regioisomers **21a** and **22**. Deprotection of isomer **21a** followed by bromination gave the electrophile **23** (Scheme 5). Similarly, the 5-substituted regioisomer benzyl 5-(2-bromoethyl)-2-thiophenecarboxylate was made from 2-(2-thienyl)ethanol. Finally, a method similar to that described in Scheme 3 was used for the preparation of three-carbon-tethered heteroaromatic ring electrophiles. The electrophiles methyl 3-(3-bromopropyl)-1-thiophenecarboxylate and methyl 5-(3-bromopropyl)-1-furancarboxylate were prepared from the corresponding starting materials methyl 3-bromo-1-thiophenecarboxylate and methyl 5-bromo-1-furancarboxylate, respectively.

The electrophiles **27a**−**g**, **34a**,**b**, and **39a**−**c** were used to prepare analogues with a *m*-carboxyphenethyl as the N3 substituent. Two different routes were used for their preparation. In some cases, oxidative cleavage of allylphenyl derivatives (Schemes 6 and 7) was used, while in other cases, oxidation of the styryl derivatives was a key step (Scheme 8). Schemes 6 and 7 outline the synthesis of the substituted allylphenyl compounds via palladium-catalyzed coupling reaction and Claisen rearrangement, respectively. Treatment of the allyl derivative, e.g. **25a**, with O_3 followed by in situ reduction of the ozonide with $NaBH_4$ gave the alcohol derivative **26a**, which upon bromination yielded the electrophile **27a**. In the case of compound **25e**, the oxidation was performed using $NaIO_4$ in the presence of RuO_2. The TBDMS-protected derivative **27b** was obtained by a similar sequence from **24b**, which was prepared by halogenation of **24a** with NBS followed by hydroxide displacement and TBDMS protection. The electrophile **27g** was synthesized from the intermediate **26e**.

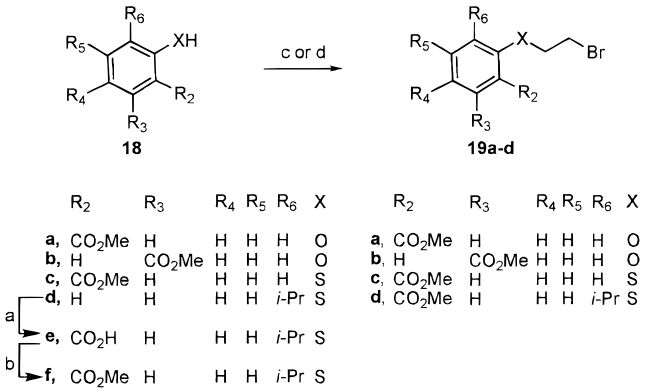
The electrophiles **34a**,**b** were prepared in a five-step sequence (Scheme 7). Alkylation of the methyl 4-hydroxybenzoate **(28)** with allyl bromide followed by Claisen rearrangement in the presence of the Lewis acid BCl_3 in chlorobenzene gave the allyl derivative **29**. Treatment of **29** with O_3 and subsequent reduction of the ozonide with $NaBH_4$ and protection of the resultant hydroxyl group with TBDMSCl provided the intermedi-

Scheme 3[a]



[a] Reagents: (a) i. H_2SO_4, MeOH, ii. Tf_2O, Et_3N, THF, iii. propargyl alcohol, $Pd(PPh_3)_2Cl_2$, Et_2NH, DMF; (b) i. H_2SO_4, MeOH, ii. propargyl alcohol, $Pd(PPh_3)_2Cl_2$, Et_2NH, CuI, DMF; (c) 10% Pd/C, H_2, EtOAc; (d) CBr_4, PPh_3, CH_2Cl_2.

Scheme 4[a]

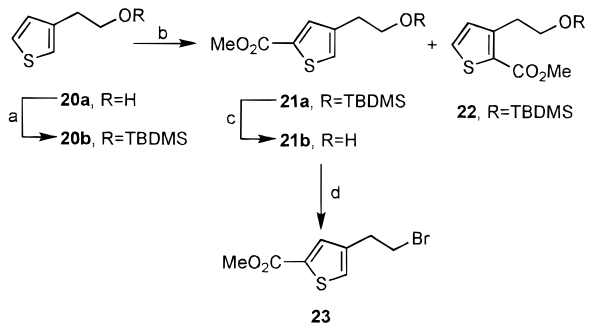


	R_2	R_3	R_4	R_5	R_6	X
a,	CO_2Me	H	H	H	H	O
b,	H	CO_2Me	H	H	H	O
c,	CO_2Me	H	H	H	H	S
d,	H	H	H	H	*i*-Pr	S
e,	CO_2H	H	H	H	*i*-Pr	S
f,	CO_2Me	H	H	H	*i*-Pr	S

	R_2	R_3	R_4	R_5	R_6	X
a,	CO_2Me	H	H	H	H	O
b,	H	CO_2Me	H	H	H	O
c,	CO_2Me	H	H	H	H	S
d,	CO_2Me	H	H	H	*i*-Pr	S

[a] Reagents: (a) *n*-BuLi, cyclohexane, TMEDA, CO_2; (b) MeOH, H_2SO_4; (c) $Br(CH_2)_2Br$, K_2CO_3, DMSO; (d) $Br(CH_2)_2OH$, PPh_3, DEAD, THF.

Scheme 5[a]



[a] Reagents: (a) TBDMSCl, imidazole, DMF; (b) *n*-BuLi, THF, $ClCO_2CH_3$; (c) TBAF, THF; (d) CBr_4, PPh_3, CH_2Cl_2.

ate **30**. The palladium-catalyzed coupling of the triflate of **30** with vinyltributylstannane and allyltributylstannane followed by hydrogenation provided the respective ethyl and propyl derivatives of **32a**,**b**. Desilylation with CSA in methanol followed by bromination gave the compounds **34a**,**b**.

The synthesis of the compounds **39a**−**c** from the intermediate *m*-carboxyalkylstyryl derivatives **37a**−**c** followed the route indicated in Scheme 8. Carbomethoxylation[6c] of compounds **35a**,**b** with CO in the presence of Pd(0) in MeOH followed by Wittig olefination with triphenylphosphinemethyl bromide and *n*-BuLi provided the styryl derivatives **37a**,**b**, whereas **37c** was prepared from **36** by palladium-catalyzed vinylation. These vinyl intermediate derivatives **37a**−**c** were converted to their corresponding bromides **39a**−**c** by hydroboration/oxidation followed by bromination.

Some modifications on the side chain aromatic ring were also introduced at a later stage of the synthesis as shown in Scheme 9. Suzuki cross-coupling of the compound **40a** with substituted phenylboronic acids in the presence of a base provided the biphenyl derivatives **41a**−**d**.[6d] Desilylation of **40b** delivered compound **41e**.

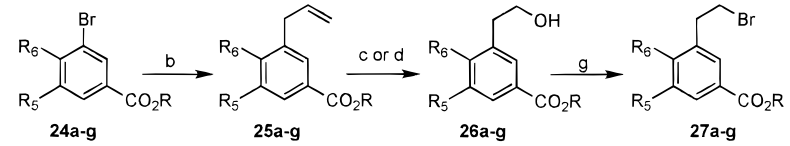
Results

The compounds described above (Tables 1 and 2) were evaluated as inhibitors of porcine heart AMPDA and calf intestinal ADA, and the results are reported in Tables 3−6.[8] The inhibitor initial screening concentrations in general were chosen so that the upper limits of the K_i values determined for AMPDA and ADA inhibition were 125 and 7.5 μM, respectively. In select examples, to evaluate the full extent of the selectivity of the enzyme inhibition, ADA inhibition was evaluated at higher concentrations.

Compounds listed in Table 3 explored the dependence of the AMPDA inhibition activity on the distance between N3 and the carboxylic acid group, which in the initial AMPDA inhibitor series was determined to be 5−6 atoms.[3] As indicated in Table 3 a two-atom tether length and a carboxylic acid group in a *meta* position exhibited a 9-fold improvement over the lead compound **2** (e.g. **42s**, AMPDA K_i = 0.5 μM). In contrast, a carboxylic acid group at the *ortho* or *para* position on the phenyl ring with varied alkyl tether lengths resulted in decreased or no significant enhancement in activity. Similarly, a carboxylic acid group in the *meta* position with a tether length of three atoms showed no improvement over **2**.

To further optimize the series we explored the effect of various phenyl ring substituents on the AMPDA inhibitory potency of **42s**. The results shown in Table 4 indicated that analogues with small substituents such as methyl at the C6 (e.g. **43a**, AMPDA K_i = 0.1 μM) or analogues with an ethyl at the C5 (e.g. **43g**, AMPDA K_i = 0.06 μM) exhibited a 5- and 9-fold increase in potency, respectively, with maintained selectivity. To delineate the effects of size, shape, and polarity of the phenyl substituents on affinity to the enzyme, we examined various substituents at the C5 and C6. Substituents such as bromine (**43h**) and phenyl (**43i**) at the C5 were well-tolerated. Polar substituents such as methoxy, hydroxymethyl, or halogen, such as F, at the C6 of the

Scheme 6[a]



	R_5	R_6	R
a,	H	Me	Et
b,	H	CH_2OZ	Et
c,	H	OMe	Me
d,	H	F	Me
e,	Br	H	Et
f,	H	H	Me
g,	Et	H	Et

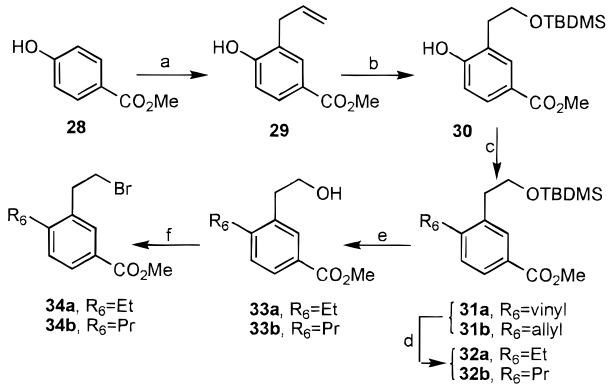
[a] Reagents: (a) i. NBS, benzoyl peroxide, CCl_4, ii. $CaCO_3$, H_2O, dioxane, iii. TBDMSCl, imidazole, DMF; (b) allyltributyltin, $Pd(PPh_3)_4$, DMF; (c) O_3, MeOH; $NaBH_4$; (d) $NaIO_4$, RuO_2, CCl_4, CH_3CN; $NaBH_4$, MeOH (when R_5 = Br); (e) vinyltributyltin, $Pd(PPh_3)_4$, DMF; (f) 10% Pd/C, H_2, EtOAc; (g) CBr_4, PPh_3, CH_2Cl_2.

Table 1. Physical Data and Methods of Preparation of AMPDA Inhibitors (Acids)

compd	mp (°C)	starting material; methods	formula[a]	anal.
42a	nd[b]	**14e;** D, L, N, W, X, Y	$C_{16}H_{17}N_4O_3Na·0.25H_2O$	C,H,N
42b	122−125	**13a;** A, C, L, N, W, X, Y	$C_{17}H_{20}N_4O_3·1.1H_2O·0.1AcOH$	C,H,N
42c	204	**13b;** A, C, L, N, W, X, Y	$C_{17}H_{20}N_4O_3·1.5H_2O$	C,H,N
42d	205	**14f;** A, D, L, N, W, X, Y	$C_{16}H_{17}N_4O_3F·1.4H_2O$	C,H,N
42e	210[c]	**13c;** A, C, L, N, W, X, Y	$C_{19}H_{24}N_4O_3·0.6H_2O$	C,H,N
42f	nd[b]	**13d;** A, C, L, N, W, X, Y	$C_{20}H_{20}N_4O_3·1.1H_2O·0.4AcOH$	C,H,N
42g	nd[b]	**18a;** A, F, W, X, Y	$C_{15}H_{15}N_4O_4Na·3.5H_2O$	C,H,N
42h	200	**18c;** A, F, W, X, Y	$C_{15}H_{16}N_4O_3S·0.1AcOH$	C,H,N
42i	nd[b]	**18d;** E, A, F, W, X, Y	$C_{18}H_{22}N_4O_3S·2.0H_2O$	C,H,N
42j	nd[b]	commercially available	$C_{14}H_{13}N_4O_3Na·2.5H_2O$	C,H,N
42k	nd[b]	commercially available	$C_{15}H_{15}N_4O_3Na·2.5H_2O$	C,H,N
42l	nd[b]	**7;** A, J, P, N, W, X, Y	$C_{15}H_{15}N_4O_3Na·2.0H_2O$	C,H,N
42m	206−208[c]	**7;** A, J, B, N, W, X, Y	$C_{15}H_{16}N_4O_3·0.8H_2O$	C,H,N
42n	210[c]	**18b;** A, G, W, X, Y	$C_{15}H_{15}N_4O_4Na·1.0H_2O$	C,H,N
42o	204−206[c]	**14g;** D, L, N, W, X, Y	$C_{16}H_{17}N_4O_3Na·0.25H_2O$	C,H,N
42p	nd[b]	**14h;** A, D, L, N, W, X, Y	$C_{17}H_{19}N_4O_3Na·2.0H_2O$	C,H,N
42q	nd[b]	**14i;** D, L, N, W, X, Y	$C_{17}H_{20}N_4O_4·0.25H_2O$	C,H,N
42r	224−226[c]	**14g;** D, N, W, X, Y	$C_{16}H_{13}N_4O_3Na·1.0H_2O$	C,H,N
42s	210[c]	**24f;** J, M, N, W, X, Y	$C_{15}H_{16}N_4O_3·1.1H_2O$	C,H,N
43a	142−145	**24a;** J, M, N, W, X, Y	$C_{16}H_{18}N_4O_3·2.0H_2O·0.1AcOH$	C,H,N
43b	184−186	**24c;** J, M, N, W, X, Y	$C_{16}H_{18}N_4O_4·0.5H_2O·0.2AcOH$	C,H,N
43c	235[c]	**24d;** J, M, N, W, X, Y	$C_{15}H_{15}N_4O_3F·2.1H_2O·0.1AcOH$	C,H,N
43d	253−256[c]	**24a;** I, J, M, N, W, X, Y	$C_{16}H_{18}N_4O_4·1.5H_2O·0.5AcOH$	C,H,N
43e	215[c]	**28;** Q, M, R, S, L, T, N, W, X, Y	$C_{17}H_{20}N_4O_3·2.7H_2O$[d]	C,H,N
43f	250[c]	**28;** Q, M, R, S, L, T, N, W, X, Y	$C_{18}H_{22}N_4O_3·3.4H_2O·0.2AcOH$	C,H,N
43g	205[c]	**24e;** J, K, J, L, N, W, X, Y	$C_{17}H_{20}N_4O_3·2.0H_2O$	C,H,N
43h	224−226[c]	**24e;** J, K, N, W, X, Y	$C_{15}H_{15}N_4O_3Br·2.0H_2O$	C,H,N
43i	251−253[c]	**24e;** J, K, N, W, X, U, Y	$C_{21}H_{20}N_4O_3·3.5H_2O$	C,H,N
43j	209−211[c]	**24e;** J, K, N, W, X, U, Y	$C_{21}H_{19}N_4O_3F·3.0H_2O$[e]	C,H,N
43k	222−226[c]	**24e;** J, K, N, W, X, U, Y	$C_{21}H_{19}N_4O_3Cl$	LRMS
43l	228−232[c]	**24e;** J, K, N, W, X, U, Y	$C_{21}H_{19}N_4O_3Cl$	LRMS
43m	183	**35b;** O, H, P, N, W, X, Y	$C_{16}H_{18}N_4O_3·1.9H_2O·0.5AcOH$	C,H,N
43n	223−225[c]	**35a;** O, H, P, N, W, X, Y	$C_{15}H_{15}N_4O_3F·2H_2O·0.1AcOH$	C,H,N
43o	196−197	**36;** J, P, N, W, X, Y	$C_{15}H_{15}N_4O_3Cl·2.5H_2O$	C,H,N
44a	nd[b]	same as **44b**	$C_{13}H_{14}N_4O_3S·1.3H_2O$	C,H,N
44b	228−232[c]	**20a;** R, H, V, N, W, X, Y	$C_{13}H_{14}N_4O_3S·1.0H_2O·0.01AcOH$	C,H,N
44c	210	same as **42p**	$C_{14}H_{16}N_4O_3S·1.2H_2O$	C,H,N
44d	190	same as **42q**	$C_{14}H_{16}N_4O_4·0.7H_2O$	C,H,N
44e	240[c]	commercially available	$C_{12}H_{12}N_4O_4Na·1.0H_2O·0.1AcOH$	C,H,N

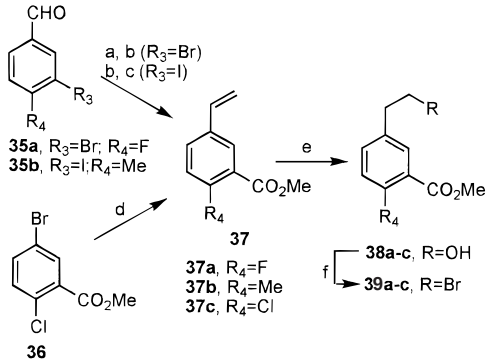
[a] Analyses for C, H, N were within ±0.4% of the theoretical values, unless otherwise stated. [b] Not determind, very deliquescent compound. [c] Decomposed. [d] Calcd: C, 54.16; H, 6.79; N, 14.86. Found: C, 53.91; H, 6.28; N, 14.57. [e] Calcd: C, 56.24; H, 5.62; N, 12.49. Found: C, 56.67; H, 5.20; N, 12.18.

Scheme 7[a]



[a] Reagents: (a) i. allyl bromide, K_2CO_3, acetone, ii. BCl_3, PhCl; (b) i. O_3, MeOH; $NaBH_4$, ii. TBDMSCl, imidazole, DMF; (c) i. Tf_2O, Et_3N, THF, ii. allyltributyltin or vinyltributyltin, $Pd(PPh_3)_2Cl_2$, PPh_3, LiCl, DMF; (d) 10% Pd/C, H_2, EtOAc; (e) CSA, MeOH, CH_2Cl_2; (f) CBr_4, PPh_3, CH_2Cl_2.

Scheme 8[a]



[a] Reagents: (a) $Pd(PPh_3)_4$, MeOH, CO, Et_3N; (b) $P^+Ph_3CH_3Br^-$, *n*-BuLi, THF; (c) *n*-BuLi, THF, $ClCO_2CH_3$; (d) vinyltributyltin, $Pd(PPh_3)_4$, DMF; (e) 9-BBN, THF; 30% H_2O_2, 3 N NaOH; (f) CBr_4, PPh_3, CH_2Cl_2.

phenyl ring showed some decrease in potency as compared to analogues with hydrophobic substituents. Compounds with a halogen at the C4, **43n** and **43o**, were more potent than the corresponding hydrogen or the methyl analogues **42s** and **43m**, respectively (Table 4).

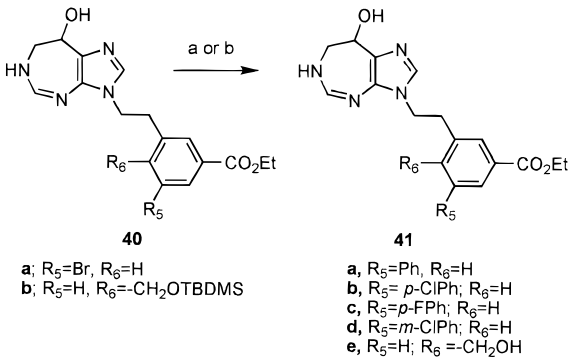
Replacement of the phenyl ring in the side chain with a heteroaromatic ring such as furan or thiophene (e.g. **44b**, AMPDA K_i = 2.2 μM; Table 5) resulted in a decrease in affinity as compared to the phenyl spacer analogues with the same tether (e.g. **42s**, AMPDA K_i = 0.5 μM). The carboxylic esters were also tested as AMPDA inhibitors (Table 6). None of these esters (**45a**−**y)** were as potent as their corresponding parent acids, but in some cases they showed strong ADA binding affinity, especially when there was a three-carbon tether

Table 2. Physical Data and Methods of Preparation of AMPDA and ADA Inhibitors (Esters)

compd	mp (°C)	starting material; methods	formula[a]	anal.
45a	185−186	commercially available	$C_{15}H_{16}N_4O_3 \cdot 0.25H_2O$	C,H,N
45b	170−171	commercially available	$C_{16}H_{18}N_4O_3 \cdot 0.25H_2O$	C,H,N
45c	119−120	**7;** A, J, B, N, W, X	$C_{17}H_{20}N_4O_3 \cdot 0.5H_2O$	C,H,N
45d	188−189[b]	commercially available	$C_{16}H_{18}N_4O_3$	C,H,N
45e	143−144	**24f;** J, M, N, W, X	$C_{16}H_{18}N_4O_3 \cdot 0.25H_2O$	C,H,N
45f	199−201	**24a;** J, M, N, W, X	$C_{17}H_{20}N_4O_3$	C,H,N
45g	80−85	**24a;** J, M, N, W, X	$C_{23}H_{24}N_4O_3$	C,H,N
45h	164−165	**28;** Q, M, R, S, L, T, N, W, X	$C_{19}H_{24}N_4O_3 \cdot 0.7H_2O$	C,H,N
45i	190−195	**24c;** J, M, N, W, X	$C_{17}H_{20}N_4O_4 \cdot 0.2H_2O$	C,H,N
45j	141−143	**24e;** J, K, J, L, N, W, X	$C_{19}H_{24}N_4O_3 \cdot 0.3H_2O$	C,H,N
45k	160−162	**24e;** J, K, N, W, X, U	$C_{23}H_{24}N_4O_3 \cdot 0.5H_2O$	C,H,N
45l	132−133	**24e;** J, K, N, W, X	$C_{17}H_{19}N_4O_3 \cdot 0.5H_2O$	C,H,N
45m	155−156	**3b;** O, H, P, N, W, X	$C_{18}H_{22}N_4O_3 \cdot 0.25H_2O$	C,H,N
45n	144−145	**14e;** D, L, N, W, X	$C_{17}H_{20}N_4O_3 \cdot 0.25H_2O$	C,H,N
45o	165−170	**13a;** A, C, L, N, W, X	$C_{18}H_{22}N_4O_3$	C,H,N
45p	144−145	**13b;** A, C, L, N, W, X	$C_{18}H_{22}N_4O_3 \cdot 0.15H_2O$	C,H,N
45q	131−132	**14f;** A, D, L, N, W, X	$C_{17}H_{19}N_4O_3 \cdot 0.25H_2O$	C,H,N
45r	168−170	**13c;** A, C, L, N, W, X	$C_{20}H_{26}N_4O_3 \cdot 1.2H_2O$	C,H,N
45s	140−145	**14g;** D, L, N, W, X	$C_{17}H_{20}N_4O_3$	C,H,N
45t	165−168	**14h;** A, D, L, N, W, X	$C_{18}H_{22}N_4O_3 \cdot 0.5H_2O$	C,H,N
45u	205−206	**14h;** A, D, L, N, W, X (amide)	$C_{18}H_{23}N_5O_2 \cdot 1.05H_2O$	C,H,N
45v	164−165	**14i;** D, L, N, W, X	$C_{18}H_{22}N_4O_4$	C,H,N
45w	98−100	**13e;** A, C, L, N, W, X	$C_{21}H_{22}N_4O_3 \cdot 1.0H_2O$	C,H,N
45x	180−181	**18a;** A, F, W, X	$C_{16}H_{18}N_4O_4 \cdot 0.5H_2O$	C,H,N
45y	179−180	**18c;** A, F, W, X	$C_{16}H_{18}N_4O_3S$	C,H,N

[a] Analyses for C, H, N were within ±0.4% of the theoretical values, unless otherwise stated. [b] Decomposed.

Scheme 9[a]



[a] Reagents: (a) $R_5B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, ethanol, diglyme (**40a**); (b) TBAF, THF (**40b**).

(e.g. **45o**,**t**). Small substituents such as methyl on the phenyl ring enhanced ADA affinity up to 4-fold (e.g. **45p**, AMPDA $K_i = 1.6\ \mu$M and ADA $K_i = 0.04\ \mu$M). Similar results were also observed with an amide **45u**.[9]

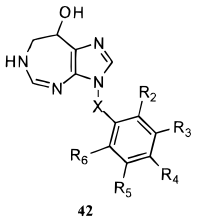
Discussion

N3-Substituted coformycin aglycon analogues containing a terminal carboxylic acid were previously postulated to inhibit AMPDA through a combination of transition-state binding interactions with the heterocycle binding site and an electrostatic interaction between the carboxylic acid group and the phosphate binding site.[2] The preceding paper[3] showed that analogues with a five- or six-carbon spacer between N3 and the carboxylate resulted in AMPDA inhibition with high specificity. This work investigated the effect of introducing structural rigidity into the flexible side chain of the lead compound **2**, through the incorporation of a phenyl ring between the N3 and the carboxylate.

Two variables required optimization, namely the length of the alkyl tether between the diazepine base and the phenyl ring and the position of the carboxylic acid on the phenyl ring. By stepwise variation of these two parameters we identified 10−100-fold more potent inhibitors. For example, compound **42s** with a two-carbon atom tether ($X = -(CH_2)_2-$) and a *m*-carboxylic acid on the phenyl ring was a 9-fold more potent inhibitor of AMPDA than the lead inhibitor **2.** In contrast, compounds in which the carboxylic acid was in the *ortho* and *para* positions (5−6 atoms from the heterocycle to the carboxylic acid group, Table 3) showed weak AMPDA affinity. Compound **42m** showed that replacement of the carboxylic acid group in **42s** with acetic acid resulted in a 20-fold decrease in potency. Similarly, the *m*-carboxylic acid group with a three-carbon atom tether (**42o**) showed decreased potency. These results suggested that the relative position of the carboxylic acid group was crucial to potency.[10]

We next examined the effect of substitutions on the phenyl ring in order to further improve the potency of **42s** through optimization of hydrophobic and hydrophilic interactions. Hydrophobic substituents at the C5 and C6 produced the most potent compounds. Small hydrophobic substituents such as methyl or ethyl at the C5 or C6 of the phenyl ring provided compounds 50−100-fold more potent than compound **2** (e.g. **43a,g**). In contrast, a methyl substituent at the C4, i.e. **43m**, did not have any effect on potency, suggesting that hydrophobic space is confined to the region near the C5 and C6 of the phenyl ring in the active site. Analogues with a bromine or phenyl substituent at the C5 were also well-tolerated, indicating that the hydrophobic space in this region is relatively large. The *n*-propyl substituent at the C6 of the phenyl ring was also well-accepted. Interestingly, halide substituents in the C4 (**43n,o**) provided a 2−3-fold improvement over the hydrogen analogue (**42s**) or its methyl analogue (**43m**). This might suggest that these electron-withdrawing substituents enhance potency by decreasing the pK_a of the carboxylic acid thus increasing the electrostatic interactions with the phosphate binding site.

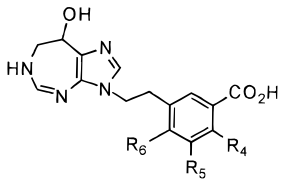
Table 3. AMPDA and ADA Inhibition Constants



42

							K_i (μM)	
compd	X	R_2	R_3	R_4	R_5	R_6	AMPDA	ADA
42a	$-(CH_2)_3-$	CO_2Na	H	H	H	H	12.5	6.1
42b	$-(CH_2)_3-$	CO_2H	H	H	Me	H	24	5.2
42c	$-(CH_2)_3-$	CO_2H	H	Me	H	H	11.8	>7.5
42d	$-(CH_2)_3-$	CO_2H	F	H	H	H	9	>7.5
42e	$-(CH_2)_3-$	CO_2H	H	H	H	*i*-Pr	83.1	>7.5
42f	$-(CH_2)_3-$	CO_2H	H	H	R_5, R_6 = ring (Ph)		6.3	1.8
42g	$-(CH_2)_2-O-$	CO_2Na	H	H	H	H	31.3	270.3
42h	$-(CH_2)_2-S-$	CO_2Na	H	H	H	H	4.5	>500
42i	$-(CH_2)_2-S-$	CO_2H	H	H	H	*i*-Pr	>125	>7.5
42j	$-CH_2-$	H	H	CO_2Na	H	H	>125	>7.5
42k	$-CH_2-$	H	H	CH_2CO_2Na	H	H	92.2	>500
42l	$-CH_2-$	H	CH_2CO_2H	H	H	H	11.2	>7.5
42m	$-(CH_2)_2-$	H	CH_2CO_2Na	H	H	H	44.1	>500
42n	$-(CH_2)_2-O-$	H	CO_2Na	H	H	H	31.8	>7.5
42o	$-(CH_2)_3-$	H	CO_2Na	H	H	H	23.5	2.4
42p	$-(CH_2)_3-$	H	CO_2Na	H	H	Me	5.2	1.2
42q	$-(CH_2)_3-$	H	CO_2H	H	H	OMe	4.2	5.6
42r	$-CH_2-CC-$	H	CO_2Na	H	H	H	>125	2.3
42s	$-(CH_2)_2-$	H	CO_2H	H	H	H	0.51	>7.5

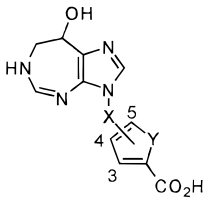
Table 4. *m*-Carboxyphenethyl SAR



43

				K_i (μM)	
compd	R_4	R_5	R_6	AMPDA	ADA
42s	H	H	H	0.51	>7.5
43a	H	H	Me	0.10	>100
43b	H	H	OMe	0.48	>7.5
43c	H	H	CH_2OH	0.35	>7.5
43e	H	H	Et	0.08	>7.5
43f	H	H	Pr	0.19	>7.5
43g	H	Et	H	0.06	>7.5
43h	H	Br	H	0.08	>7.5
43i	H	Ph	H	0.07	>7.5
43j	H	*p*-FPh	H	0.19	>7.5
43k	H	*p*-ClPh	H	0.29	>7.5
43l	H	*m*-ClPh	H	0.18	>7.5
43m	Me	H	H	0.57	>7.5
43n	F	H	H	0.16	>7.5
43o	Cl	H	H	0.22	>7.5

Table 5. Heteroaromatic Spacer SAR



44

				K_i (μM)	
compd	Y	X	substn at carbon	AMPDA	ADA
44a	S	$-(CH_2)_2-$	5	9.5	>7.5
44b	S	$-(CH_2)_2-$	4	2.2	>7.5
44c	S	$-(CH_2)_3-$	3	4.8	1.4
44d	O	$-(CH_2)_3-$	5	13.3	>7.5
44e	O	$-CH_2-$	5	72.0	>3.4

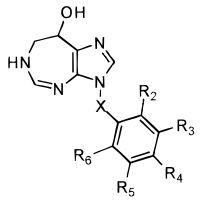
Analogous to the earlier study,[3] carboxylic esters are much weaker inhibitors of AMPDA when compared to their corresponding acids. Interestingly, *o*- and *m*-alkyl esters, especially those with a three-carbon tether on the phenyl ring, showed high ADA affinity.[9]

These results support the postulate that incorporation of an aryl group between N3 and the carboxylate provides additional inhibitory potency by restricting the rotational freedom of the alkyl side chain of compound **2**. Alternately, the enhanced affinity may result from favorable interactions between the π electron cloud of the aromatic ring and the binding site.

Summary

The data presented here demonstrate that introduction of an appropriately positioned phenyl ring into the side chain of compound **2** can significantly enhance AMPDA inhibitory potency (**42s**). Inhibition was dependent on the chain length of the linker tethering the diazepine base to the phenyl ring as well as the relative position of the carboxylic acid functionality on the phenyl ring. Analogues with a two-carbon tether and a carboxylic acid group at the *meta* position exhibited inhibitory potencies ranging from 0.5−0.06 μM. Compounds with small hydrophobic substituents at the C5 and C6 of the phenyl ring exhibited the highest potency, suggesting the presence of a nearby hydrophobic pocket in the active site.

Table 6. Carboxylate Ester SAR



45

							K_i (μM)	
compd	X	R_2	R_3	R_4	R_5	R_6	AMPDA	ADA
45a	$-CH_2-$	H	H	CO_2Me	H	H	170	8.7
45b	$-CH_2-$	H	H	CH_2CO_2Me	H	H	92.6	6.7
45c	$-CH_2-$	H	CH_2CO_2Et	H	H	H	15.9	5.6
45d	$-(CH_2)_2-$	H	H	CO_2Me	H	H	160	81
45e	$-(CH_2)_2-$	H	CO_2Me	H	H	H	16	>7.5
45f	$-(CH_2)_2-$	H	CO_2Et	H	H	Me	11	>7.5
45g	$-(CH_2)_2-$	H	CO_2Bn	H	H	Me	8.1	2.6
45h	$-(CH_2)_2-$	H	CO_2Me	H	H	Pr	14	3.8
45i	$-(CH_2)_2-$	H	CO_2Me	H	H	OMe	21	>7.5
45j	$-(CH_2)_2-$	H	CO_2Et	H	Et	H	6.6	8.9
45k	$-(CH_2)_2-$	H	CO_2Et	H	Ph	H	18	>7.5
45l	$-(CH_2)_2-$	H	CO_2Et	H	Br	H	2.7	>7.5
45m	$-(CH_2)_2-$	H	CO_2Et	Me	H	H	12	>7.5
45n	$-(CH_2)_3-$	CO_2Me	H	H	H	H	32.7	0.16
45o	$-(CH_2)_3-$	CO_2Me	H	H	Me	H	38	0.06
45p	$-(CH_2)_3-$	CO_2Me	H	Me	H	H	1.6	0.04
45q	$-(CH_2)_3-$	CO_2Me	F	H	H	H	1.5	0.32
45r	$-(CH_2)_3-$	CO_2Me	H	H	H	*i*-Pr	14	>7.5
45s	$-(CH_2)_3-$	H	CO_2Me	H	H	H	24.3	0.16
45t	$-(CH_2)_3-$	H	CO_2Me	H	H	Me	22	0.08
45u	$-(CH_2)_3-$	H	CO_2NHMe	H	H	Me	19.8	0.05
45v	$-(CH_2)_3-$	H	CO_2Me	H	H	OMe	52.8	0.13
45w	$-(CH_2)_3-$	CO_2Me	H	H	R_5, R_6 = ring (Ph)		8.3	0.18
45x	$-(CH_2)_2-O-$	CO_2Me	H	H	H	H	60.6	2.3
45y	$-(CH_2)_2-S-$	CO_2Me	H	H	H	H	37.9	11.9

Experimental Section

General Methods. Glassware for moisture-sensitive reactions was flame-dried and cooled to room temperature in a desiccator and all reactions were carried out under an atmosphere of nitrogen. Anhydrous solvents were purchased from Aldrich and stored over 4 Å molecular sieves. THF was freshly distilled from Na/benzophenone ketyl under nitrogen. Flash chromatography was performed on 230−400 mesh EM Science silica gel 60. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian Gemini-200 operating at 200 MHz and recorded in units δ with tetramethylsilane (δ 0.00) as a reference line internal standard. C, H, N microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

Enzyme Assays. The AMPDA and ADA K_i determinations were performed as previously described.[2]

The following general procedures are illustrative.

General Procedure A. Esterification of Aromatic and Aliphatic Acids: Ethyl (3-Bromophenyl)acetate (8). To a solution of 3-bromophenylacetic acid **(7)** (10.17 g, 47.3 mmol) in 150 mL of EtOH was added concentrated H_2SO_4 (5.3 mL, 95.4 mmol). The reaction mixture was refluxed for 96 h. Solvent was removed by distillation and the residue was diluted with 200 mL of water and extracted with ether (2 × 200 mL). The combined organic layers were washed with water, saturated $NaHCO_3$ (3 × 100 mL) and dried ($MgSO_4$). Removal of solvent provided 11.3 g (98%) of ethyl (3-bromophenyl)acetate **(6)** as a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.1 Hz), 3.57 (s, 2H), 4.16 (q, 2H, J = 7.1 Hz), 7.2 (m, 2H, J = 1.8 Hz), 7.4 (m, 2H).

General Procedure B. OsO_4 Oxidation of Olefin: Ethyl (3-Hydroxymethylphenyl)acetate (10). To a solution of ethyl (3-vinylphenyl)acetate **(9)** (3.9 g, 20.5 mmol) in 120 mL of *t*-BuOH, 40 mL of THF and 12 mL of H_2O was added *N*-methylmorpholine *N*-oxide (2.88 g, 24.6 mmol) followed by OsO_4 (12.5 mL, 1.0 mmol; 2.5 wt % in *t*-BuOH). After stirring at room temperature for 7 h, $NaHCO_3$ (20.6 g, 246 mmol), $NaIO_4$ (13.9 g, 65.1 mmol) and 280 mL of H_2O were added. The heterogeneous mixture was stirred for 45 min before it was poured onto a saturated solution of Na_2SO_3. The mixture was extracted with ether and dried ($MgSO_4$). Evaporation of the solvent provided 4.16 g (104%, slightly impure) of ethyl (3-formylphenyl)acetate as an amber-colored oil: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.0 Hz), 3.7 (s, 2H), 4.19 (q, 2H, J = 7.12 Hz), 7.4−7.6 (m, 2H), 7.7−7.9 (m, 2H), 10.0 (s, 1H). The residue was used as is for the next step.

To the ethyl (3-formylphenyl)acetate (3.92 g, 20.4 mmol) in 40 mL of MeOH was added $NaBH_4$ (0.76 g, 20.1 mmol) at 0 °C and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with acetone (0.5 mL) and the solvent was removed under reduced pressure. The residue was diluted with water (25 mL) and extracted with CH_2Cl_2 (350 mL). The combined organic layers were washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (40% EtOAc in hexane) to yield 3.49 g (88%) of ethyl (3-hydroxymethylphenyl)acetate **(10)** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.0 Hz), 3.62 (s, 2H), 4.17 (q, 2H, J = 7.12 Hz), 4.68 (d, 2H, J = 5.9 Hz), 7.2−7.4 (m, 4H).

General Procedure C. Propargylation of Phenols: Methyl 2-(3-Hydroxyprop-1-ynyl)-4-methylbenzoate (15a). To a solution of methyl 2-hydroxy-4-methylbenzoate **(13a)** (3.2 g, 19.1 mmol) and TEA (10.0 mL, 71.7 mmol) in 20 mL of THF cooled to −78 °C was added slowly trifluoromethanesulfonic anhydride (4 mL, 23.8 mmol) and the mixture was allowed to come to room temperature. Upon completion of the reaction by TLC, solvent was evaporated under reduced pressure and the crude residue was used as is for the next step.

The crude triflate was dissolved in 50 mL of DMF and

$(PPh_3)_2Pd(Cl)_2$ (1.3 g, 1.9 mmol), propargyl alcohol (2.3 mL, 40.0 mmol) and Et_3N (5.6 mL, 40.0 mmol) were added. The resultant mixture was heated at 60 °C. Upon completion of the reaction by TLC, the solvent was evaporated under reduced pressure. The residue was diluted with ether (80 mL), washed with 0.1 N HCl (2 × 10 mL) and water (2 × 15 mL), and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (25% EtOAc in hexane) to give 2.2 g (56%) of methyl 2-(3-hydroxyprop-1-ynyl)-4-methylbenzoate **(15a)**: ^{1}H NMR ($CDCl_3$) δ 2.1 (t, 3H, J = 5.1 Hz, exchangeable with D_2O), 2.36 (s, 3H), 3.9 (s, 3H), 4.56 (d, 2H, J = 6.1 Hz), 7.17 (br d, 1H, J = 8.1 Hz), 7.37 (br s, 1H), 7.85 (br d, 1H, J = 8.1 Hz).

General Procedure D. Propargylation of Aromatic Halides: Methyl 2-Fluoro-6-(3-hydroxyprop-1-ynyl)benzoate (15f). To a solution of methyl 6-fluoro-2-iodobenzoate **(14f)** (8.8 g, 31.4 mmol) in 125 mL of Et_2NH under N_2 were added $Pd(PPh_3)_2Cl_2$ (1.1 g, 1.6 mmol), CuI (0.2 g, 1.1 mmol) and propargylic alcohol (3.5 mL, 60.1 mmol). The resulting mixture was stirred for 6 h at which time the reaction was complete by TLC. Solvent was removed under reduced pressure and the residue diluted with ether (200 mL). The ethereal solution was washed with water (2 × 30 mL) and 0.1 N HCl (2 × 20 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue purified by chromatography (50% EtOAc in hexane) to give 5.8 g (91%) of methyl 2-fluoro-6-(3-hydroxyprop-1-ynyl)benzoate **(15f)** as a brown oil: ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.5 (s, 2H), 7.1 (m, 1H), 7.3 (m, 2H).

General Procedure E. Carboxylation of Thiophenols: 3-Isopropylthiosalicylic Acid (18e). To a solution of *n*-BuLi (43 mL, 68.8 mmol) and TMEDA (10 mL, 66.3 mmol) in 70 mL of cyclohexane was added 2-isopropylthiophenol **(18d)** (4.6 mL, 30.4 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. The orange solution was added via cannula to a large excess of powdered dry ice and the resultant red solution was stirred at room temperature for 16 h. The reaction mixture was diluted with 1 N HCl until the aqueous layer was acidic and extracted with ether (3 × 50 mL). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (15% MeOH in CH_2Cl_2) to give 4.0 g (68%) of 3-isopropylthiosalicylic acid **(18e)** as a green solid: mp 75 °C; ^{1}H NMR (CD_3OD) δ 1.23 (d, 6H, J = 6.8 Hz), 3.38 (m, 1H), 7.1 (t, 1H, J = 7.8 Hz), 7.35 (d, 1H, J = 6.4 Hz), 7.88 (d, 1H, J = 9.2 Hz).

General Procedure F. O- or S-Alkylation of Phenols or Thiophenols Using K_2CO_3: Methyl 2-(2-Bromoethoxy)-benzoate (19a). To a solution of methyl salicylate **(18a)** (3.9 mL, 30.1 mmol) in 30 mL of DMSO was added K_2CO_3 (8.8 g, 63.7 mmol) followed by 1,2-dibromoethane (5.2 mL, 60.3 mmol). After 3.5 h at room temperature the mixture was diluted with water (100 mL) and extracted with ether (240 mL). The combined organic layers were washed with water and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (25% EtOAc in hexane) to give 2.0 g (26.5%) of methyl 2-(2-bromoethoxy)benzoate **(19a):** ^{1}H NMR (DMSO-d_6) δ 3.78 (t, 2H, J = 5.2 Hz), 3.80 (s, 3H), 4.4 (t, 2H, J = 5.3 Hz), 7.0−7.2 (m, 2H), 7.4−7.7 (m, 2H).

General Procedure G. O- or S-Alkylation Using Mitsunobu Method: Methyl 3-(2-Bromoethoxy)benzoate (19b). To a mixture of methyl 3-hydroxybenzoate **(18b)** (1.8 g, 11.7 mmol), PPh_3 (6.6 g, 26.1 mmol) and 2-bromoethanol (1.8 mL, 25.9 mmol) in 40 mL of THF was added DEAD (4.0 mL, 26.1 mmol) slowly dropwise at 0 °C. The resultant mixture was stirred at room temperature for 16 h and the solvent was evaporated. The residue was diluted with ether (80 mL), washed with water (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (CH_2Cl_2) to give 1.6 g (53%) of methyl 3-(2-bromoethoxy)benzoate **(19b)** as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 3.83 (t, 2H, J = 5.2 Hz), 3.86 (s, 3H), 4.4 (t, 2H, J = 5.2 Hz), 7.2−7.7 (m, 4H).

General Procedure H. Carboxylation of the Aromatic Rings: Methyl 4-(*tert*-Butyldimethylsilyloxyethyl)-2-thiophenecarboxylate (21a). To a solution of 3-(*tert*-butyldimethylsilyloxyethyl)thiophene **(20b)** (6.8 g, 28.0 mmol) in 50 mL of dry THF was added *n*-BuLi (3.4 mL, 34.0 mmol) slowly at −78 °C under N_2 and the mixture was stirred for 5 h at which time the reaction had reached ambient temperature. The resulting enolate solution was again cooled to −78 °C, methyl chloroformate (2.6 mL, 33.6 mmol) was added, and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was slowly quenched with water and diluted with 200 mL of ether. The ether layer was washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (5% EtOAc in hexane) to give 5.3 g (63%) of the product mixture methyl 4-(*tert*-butyldimethylsilyloxyethyl)-2-thiophenecarboxylate and methyl 3-(*tert*-butyldimethylsilyloxyethyl)-2-thiophenecarboxylate. Although a small R_f difference by TLC was evident, they could not be separated by chromatography. However, from one of the column fractions a small amount of the pure required regioisomer, methyl 4-(*tert*-butyldimethylsilyloxyethyl)-2-thiophenecarboxylate **(21a)** was isolated for the NMR identification: ^{1}H NMR ($CDCl_3$) δ 0.0 (s, 6H), 0.87 (s, 9H), 2.8 (t, 2H, J = 6.58 Hz), 3.8 (t, 2H, J = 6.54 Hz), 3.87 (s, 3H), 7.24 (d, 1H,J = 1.4 Hz), 7.67 (d, 1H, J = 1.5 Hz).

Procedure I. Ethyl 3-Bromo-4-(*tert*-butyldimethylsilyloxymethyl)benzoate (24b). A mixture of ethyl 3-bromo-4-methylbenzoate **(24a)** (12.0 g, 49.37 mmol), *N*-bromosuccinamide (8.2 g, 46.0 mmol) and a catalytic amount of benzoyl peroxide (100 mg) in 150 mL of CCl_4 was refluxed for 8 h. The resulting suspension was filtered to remove the byproducts. The filtrate was diluted with CH_2Cl_2 (600 mL), washed with water, $NaHCO_3$, dried ($MgSO_4$) and evaporated to give 8.2 g of crude product. This crude mixture, of which the major component was the required ethyl 3-bromo-4-bromomethylbenzoate, was used directly in the next reaction without further purification.

To a solution of ethyl 3-bromo-4-(bromomethyl)benzoate in (7.25 g, 22.5 mmol, crude from step 1) in 100 mL of dioxane was added a solution of $CaCO_3$ (10 g, 100 mmol) in 100 mL of H_2O. The resultant milky white suspension was heated at 100 °C for 12 h, and the solvent was removed under vacuum. The residue was diluted with EtOAc (300 mL), washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (10% followed by 40% EtOAc in hexane) to give 4.3 g of ethyl 3-bromo-4-(hydroxymethyl)benzoate as an oil: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 7.1 Hz), 2.2 (t, 1H, J = 5.8 Hz, exchangeable with D_2O), 4.37 (q, 2H, J = 7.1 Hz), 4.8 (d, 2H, J = 5.8 Hz), 7.59 (d, 1H, J = 8.0 Hz), 7.95 (dd, 1H, J_1 = 8.0 Hz, J_2 = 1.7 Hz), 8.2 (d, 1H, J = 1.7 Hz).

A mixture of ethyl 3-bromo-4-(hydroxymethyl)benzoate (8.6 g, 33.2 mmol), *tert*-butyldimethylsilyl chloride (5.0 g, 33.2 mmol), and imidazole (4.5 g, 66.4 mmol) in 200 mL of DMF was stirred at room temperature for 45 min. The reaction mixture was diluted with ether (400 mL), washed with water (3 × 60 mL) and brine and dried ($MgSO_4$). The solvent was evaporated to give 12.0 g (98%) of ethyl 3-bromo-4-(*tert*-butyldimethylsilyloxymethyl)benzoate **(24b)** that was used directly in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 6H), 0.93 (s, 9H), 1.32 (t, 3H, J = 7.0 Hz), 3.4 (d, 2H, J = 6.2 Hz), 4.31 (q, 2H, J = 7.0 Hz), 7.61 (d, 1H, J = 7.9 Hz), 7.87 (d, 1H, J = 7.9 Hz), 8.22 (br s, 1H).

General Procedure J. Allylation or Vinylation of the Aromatic Halides: Methyl 3-Propenylbenzoate (24f). To a solution of methyl 3-bromobenzoate (14.95 g, 69.5 mmol) in 200 mL of dry DMF under nitrogen were added $Pd(PPh_3)_4$ (4.15 g, 3.6 mmol) and allyltributyltin (26 mL, 84.0 mmol). The mixture was degassed with N_2 for 5 min and heated at 80 °C for 36 h. NMR analysis indicated complete reaction. After cooling, it was partitioned between ether and brine. The organic phase was stirred over 10% aqueous NaF solution for 4 h. The ether layer was separated, washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (5% EtOAc in hexane) to give 10.3 g (85%) of methyl 3-propenylbenzoate **(25f)** as an

oil: ^{1}H NMR ($CDCl_3$) δ 3.43 (d, 2H, J = 6.8 Hz), 3.91 (s, 3H), 5.1 (m, 2H), 5.9 (m, 1H), 7.37 (m, 2H), 7.87 (m, 2H).

General Procedure K. $NaIO_4$ Oxidation of the Arylpropenyls: Ethyl 3-Bromo-5-(2-hydroxyethyl)benzoate (26e). To a solution of ethyl 3-bromo-5-(1-propenyl)benzoate **(25e)** (1.0 g, 3.88 mmol) in a mixture of solvents CCl_4 (4 mL), CH_3CN (4 mL), and H_2O (6.0 mL) were added $NaIO_4$ (2.0 g, 9.55 mmol) and RuO_2 (56.2 mg, 0.42 mmol) and the resulting dark mixture was stirred for 15 min. The reaction mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with water, brine and dried ($MgSO_4$). The solvent was removed and the residue was used as is for the next step.

The crude aldehyde was taken into 5 mL of MeOH, $NaBH_4$ (0.15 g, 4.16 mmol) was added at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with acetone (0.5 mL) and the solvent was removed under reduced pressure. The residue was diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (40% EtOAc in hexane) to give 0.33 g of ethyl 3-bromo-5-allylbenzoate and 0.25 g of ethyl 3-bromo-5-(2-hydroxyethyl)benzoate **(26e)** (36%, based on the recovered starting material) as oils: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 7.6 Hz), 1.48 (t, 1H, J = 6.2 Hz, exchangeable with D_2O), 2.89 (t, 2H, J = 6.6 Hz), 3.9 (q, 2H, J = 6.2 Hz, collapsed to t with D_2O), 4.37 (q, 2H, J = 7.0 Hz), 7.58 (br s, 1H), 7.8 (br s, 1H), 8.0 (br s, 1H).

General Procedure L. Hydrogenation of Vinyl or Allyl: Ethyl 3-Ethyl-5-(2-hydroxyethyl)benzoate (26g). To a solution of ethyl 3-vinyl-5-(2-hydroxyethyl)benzoate (0.36 g, 1.62 mmol) in 30 mL of EtOAc was added 10% Pd/C (0.1 g). The mixture was hydrogenated at 30 psi H_2 pressure for 1 h, at which time NMR analysis indicated completion of the reaction. The catalyst was filtered through Celite, and the filtrate was evaporated to give 0.35 g (100%) of ethyl 3-ethyl-5-(2-hydroxyethyl)benzoate **(26g)** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.7 Hz), 1.4 (t, 3H, J = 7.1 Hz), 2.68 (q, 2H, J = 7.5 Hz), 2.9 (t, 2H, J = 6.4 Hz), 3.9 (m, 2H), 4.37 (q, 2H, J = 7.1 Hz), 7.26 (br s, 1H), 7.73 (br s, 1H), 7.76 (br s, 1H).

General Procedure M. Ozonolysis of the Arylpropenyls: Methyl 3-(2-Hydroxyethyl)benzoate (26f). A solution of methyl 3-(2-propenyl)benzoate **(25f)** (10.0 g, 56.7 mmol) in 150 mL of MeOH was cooled to −78 °C. Ozone was bubbled through the solution until a blue color developed. After 5 min, the excess ozone was removed with a nitrogen purge, and $NaBH_4$ (32.3 g, 85.5 mmol) was added slowly at −78 °C. The solution was allowed to warm to 20 °C and stirred for 14 h. The solvent was removed under vacuum, and the residue partitioned between ether and brine. The organic phase was washed with water, dried and concentrated. The crude product was purified by column chromatography (40% EtOAc in hexane) to give 6.87 g of methyl 3-(2-hydroxyethyl)benzoate **(26f)** (67%): ^{1}H NMR ($CDCl_3$) δ 1.51 (t, 1H, exchangeable with D_2O), 2.92 (t, 2H, J = 6.5 Hz), 3.91 (s, 3H), 3.88 (q, 2H, J = 6.3 Hz, collapsed to t with D_2O), 7.42 (m, 2H), 7.91 (m, 2H).

General Procedure N. Halogenation of Alcohols: Methyl 3-(2-Bromoethyl)benzoate (27f). To a solution of methyl 3-(2-hydroxyethyl)benzoate **(26f)** (6.2 g, 34.4 mmol) in 70 mL of dry CH_2Cl_2 under N_2 was added triphenylphosphine (11.0 g, 41.9 mmol) followed by carbon tetrabromide (13.69 g, 41.3 mmol) slowly at 0 °C. The resulting mixture was stirred for 30 min at which time TLC analysis indicated complete reaction. The solvent was removed and the residue was purified by chromatography (5% EtOAc in hexane) to give 8.0 g (96%) of methyl 3-(2-bromoethyl)benzoate **(27f)** as an oil: ^{1}H NMR ($CDCl_3$) δ 3.22 (t, 2H, J = 7.3 Hz), 3.59 (t, 2H, J = 7.1 Hz), 3.92(s, 1H), 7.41 (m, 2H), 7.92 (m, 2H).

Procedure O: Methyl 2-Fluoro-5-vinylbenzoate (37a). To a solution of 3-bromo-4-fluorobenzaldehyde **(35a)** (14h, 9.0 g, 44.3 mmol) in 20 mL of dry DMF were added triethylamine (10.0 mL, 71.7 mmol), MeOH (15 mL), and tetrakis(triphenylphosphine)palladium (2.5 g, 2.16 mmol), and the mixture was heated at 90 °C at 40 psi CO pressure in bomb for 16 h. After cooling, it was partitioned between ether and brine. The ether layer was separated, washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue purified by chromatography (10% EtOAc in hexane) to give 4.0 g of starting material and 4.0 g (50%) of methyl 2-fluoro-5-formylbenzoate as an oil: ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.3 (dd, 1H, J_1 = 10.6 Hz, J_2 = 8.6 Hz), 8.1 (m, 1H), 8.47 (dd, 1H, J_1 = 7.1 Hz, J_2 = 2.1 Hz), 10.0 (s, 1H).

To a suspension of methyltriphenylphosphonium bromide (5.88 g, 16.46 mmol) in 50 mL of THF under N_2 was added *n*-BuLi (8.2 mL, 13.12 mmol, 1.6 mmol in hexane) slowly at 0 °C. After stirring for 1.5 h at 0 °C, a solution of methyl 2-fluoro-5-formylbenzoate (2.0 g, 10.98 mmol) in 10 mL of THF was added to the yellow syrup. The resultant light yellow mixture was stirred for additional 3 h at room temperature and was diluted with ether (200 mL). The ether layer was washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue purified by chromatography (10% EtOAc in hexane) to give 0.8 g (40%) of methyl 2-fluoro-5-vinylbenzoate **(37a)** (16 h) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 5.3 (d, 1H, J = 10.7 Hz), 5.74 (d, 1H, J = 17.58 Hz), 6.7 (dd, 1H, J_1 = 10.9 Hz, J_2 = 17.6 Hz), 7.1 (dd, 1H, J_1 = 10.8 Hz, J_2 = 8.5 Hz), 7.55 (m, 1H), 7.96 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.0 Hz).

General Procedure P. 9-BBN Oxidation of the Vinylaryls: Methyl 2-Fluoro-5-(2-hydroxyethyl)benzoate (38a). To a solution of 9-BBN dimer (1.62 g, 6.66 mmol) in 10 mL of THF was added a solution of methyl 2-fluoro-5-vinylbenzoate **(37a)** (0.8 g, 4.44 mmol) in 20 mL of THF and the resulting solution was stirred for 16 h. The solution was cooled to −30 °C and slowly treated with 30% H_2O_2 (1.5 mL, 13.5 mmol), followed by 3 N NaOH (2.3 mL, 7.0 mmol). The reaction was allowed to warm to 0−10 °C and stirred for 1 h at which time the heterogeneous solution was diluted with water (50 mL) and extracted with ether (3 × 50 mL). The combined ether layers were washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (30% EtOAc in hexane) to give 0.44 g (50%) of methyl 2-fluoro-5-(2-hydroxyethyl)benzoate **(38a)** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (t, 1H, J = 5.8 Hz, exchangeable with D2O), 2.87 (t, 2H, J = 6.3 Hz), 3.9 (s, 3H), 3.85 (q, 2H, J = 5.86 Hz), 7.1 (dd, 1H, J_1 = 10.5 Hz, J_2 = 8.5 Hz), 7.4 (m, 1H), 7.8 (dd, 1H, J_1 = 6.9 Hz, J_2 = 2.2 Hz).

Procedure Q. Methyl 3-(2-Propenyl)-4-hydroxybenzoate (29). To a solution of methyl 4-hydroxybenzoate **(28)** (15.23 g, 0.10 mol) in 200 mL of acetone under N_2 was added allyl bromide (17.3 mL, 0.20 mol) followed by K_2CO_3 (69.71 g, 0.50 mol) slowly at 0 °C. The resulting suspension was stirred for 16 h, and the solvent removed under vacuum. The residue was diluted with ether (500 mL), washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give 21.96 g of methyl 4-(3-propenyloxy)benzoate as an oil. The crude mixture was used directly in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 3.8 (s, 3H), 4.58 (dd, 2H, J_1 = 5.3 Hz, J_2 = 1.5 Hz), 5.3(m, 2H), 6.0 (m, 1H), 6.9 (d, 2H, J = 8.9 Hz), 7.9 (d, 2H, J = 8.9 Hz).

To a solution of methyl 4-(3-propenyloxy)benzoate (19.53 g, 0.10 mol) in 200 mL of chlorobenzene under N_2 was added BCl_3 (102 mL, 0.1 mol). After 8 h at room temperature the mixture was poured on to ice (200 g) and extracted with ether (3150 mL). The combined ether layers were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure to give a brown residue of methyl 3-(2-propenyl)-4-hydroxybenzoate (**29**). The crude mixture was used directly in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 3.9 (s, 3H), 3.45 (d, 2H, J = 7.1 Hz), 5.15 (m, 2H), 6.0 (m, 1H), 6.85 (d, 1H, J = 8.9 Hz), 7.95 (m, 2H).

General Procedure R. TBDMS Protection of the Alcohols: Methyl 3-(2-*tert*-Butyldimethylsilyloxy)-4-hydroxybenzoate (30). A mixture of methyl 3-(2-hydroxyethyl)-4-hydroxybenzoate (2.4 g, 12.2 mmol), *tert*-butyldimethylsilyl chloride (2.03 g, 13.5 mmol), DMAP (0.15 g, 1.2 mmol) and imidazole (1.01 g, 14.8 mmol) in 25 mL of DMF was stirred at room temperature for 14 h then diluted with ether (60 mL)

and washed with water. The aqueous layer was separated and extracted with ether (3 × 30 mL). The combined ether layers were washed with water and brine and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (5% EtOAc in hexane) to give 2.71 g (71%) of methyl 3-(2-*tert*-butyldimethylsilyloxy)-4-hydroxybenzoate **(30)** as an oil: ^{1}H NMR ($CDCl_3$) δ 0.1 (s, 6H), 0.9 (s, 9H), 2.92 (t, 2H, J = 5.1 Hz), 3.9 (t, 2H, J = 4.9 Hz), 3.87 (s, 3H), 6.92 (d, 1H,J = 8.4 Hz), 7.75 (d, 1H, J = 2.1 Hz), 7.1 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 8.95(s, 1H).

General Procedure S. Allylation or Vinylation of the Phenols: Methyl 3-(2-*tert*-Butyldimethylsilyloxyethyl)-4-vinylbenzoate (31a). A solution of methyl 3-(2-*tert*-butyldimethylsilyloxyethyl)-4-hydroxybenzoate **(30)** (1.26 g, 4.0 mmol) and triethylamine (3.3 mL, 23.7 mmol) in 15 mL of THF was cooled to −78 °C and trifluoromethanesulfonic anhydride (0.74 mL, 4.4 mmol) was added slowly and allowed to come to room temperature. Upon completion of the reaction by TLC, the solvent was evaporated under reduced pressure and the residue was used as is for the next step.

The crude triflate was dissolved in 10 mL of DMF and $(PPh_3)_2Pd(Cl)_2$ (0.4 g, 0.62 mmol), PPh_3 (0.43 g, 1.6 mmol) and LiCl (1.4 g, 32.9 mmol) were added followed by vinyltributyl tin (2.5 mL, 8.06 mmol). The resultant mixture was heated at 90 °C for 14 h. The solvent was evaporated and the residue was diluted with ether (60 mL), washed with water (210 mL) and saturated NaF (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (5% EtOAc in hexane) to give 0.95 g (70%) of methyl 3-(2-*tert*-butyldimethylsilyloxyethyl)-4-vinylbenzoate **(31a)**: ^{1}H NMR ($CDCl_3$) δ −0.05 (s, 6H), 0.8 (s, 9H), 2.9 (t, 2H, J = 6.9 Hz), 3.8 (t, 2H, J = 6.9 Hz), 3.9 (s, 3H), 5.4 (d, 1H, J = 11 Hz), 5.7 (d, 1H, J = 17.4 Hz), 7.1 (dd, 1H, J_1 = 11 Hz, J_2 = 17.4 Hz), 7.53 (d, 1H, J = 8.7 Hz), 7.8−7.9 (m, 2H).

General Procedure T. TBDMS Deprotection Using Camphorsulfonic Acid: Methyl 3-(2-Hydroxyethyl)-4-propylbenzoate (33b). A mixture of methyl 3-(2-*tert*-butyldimethylsilyloxyethyl)-4-propylbenzoate **(31b)** (0.85 g, 2.54 mmol), camphorsulfonic acid (56.7 mg, 0.24 mmol), MeOH (3 mL), and CH_2Cl_2 (3 mL) was stirred at room temperature for 2 h at which time additional camphorsulfonic acid (54.3 mg, 0.23 mmol) was added in an attempt to make the reaction go to completion. After 14 h at room temperature solvent was removed and the residue was diluted with ether (60 mL), washed with water (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed and the residue was purified by chromatography (30% EtOAc in hexane) to give 0.50 g (90%) of methyl 3-(2-hydroxyethyl)-4-propylbenzoate **(33b)**: ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3H, J = 6.8 Hz), 1.47 (t, 1H, J = 5.8 Hz, exchangeable with D2O), 1.64 (sext, 2H, J = 7.7 Hz), 2.67 (t, 2H, J = 7.6 Hz), 2.95 (t, 2H, J = 6.9 Hz), 3.9 (s, 3H), 3.86 (q, 2H, J = 6.8 Hz), 7.24 (d, 1H, J = 8.3 H), 7.7−7.9 (m, 2H).

General Procedure U. Arylation Using Pd Catalyst: 3-(3-*p*-Fluorophenyl-5-carbethoxyphenethyl)coformycin Aglycon (41c). A suspension of 3-(3-bromo-5-carbethoxyphenethyl)coformycin aglycon **(40)** (0.4 g, 0.98 mmol), *p*-fluorophenylboronic acid (0.36 g, 2.9 mmol), $Pd(PPh_3)_4$ (0.11 g, 0.1 mmol), saturated Na_2CO_3 (3.0 mL) and ethanol (1.0 mL) in 20 mL of diglyme was heated at 95 °C for 1.5 h. The solvent was evaporated under reduced pressure and azeotroped with ethanol (2 × 10 mL). The residue was taken into 15 mL of 50% methanol in CH_2Cl_2, SiO_2 (2.0 g) was added, and the solvent was removed. The powder was applied to the top of a column and eluted with 12% methanol in CH_2Cl_2 to give 0.2 g (50%) of 3-(3-*p*-fluorophenyl-5-carbethoxyphenethyl)coformycin aglycon **(41c)**: ^{1}H NMR (DMSO-d_6) δ 1.33 (t, 3H, J = 7.2 Hz), 3.1 (m, 4H), 4.17 (t, 2H, J = 7.0 Hz), 4.33 (q, 2H, J = 7.1 Hz), 4.8 (m, 1H), 4.92 (d, 1H, J = 5.1 Hz), 6.9 (d, 1H, J = 4.3 Hz), 7.17 (s, 1H), 7.2−7.8 (m, 7H), 7.99 (br s, 1H).

Procedure V. TBDMS Deprotection Using TBAF: 3-(2-Hydroxymethyl-5-carbethoxyphenethyl)coformycin Aglycon (41e). To a solution of 3-(2-(*tert*-butyldimethylsilyloxymethyl)-5-carbethoxyphenethyl)coformycin aglycon **(40b)** (0.25 g, 0.52 mmol) in 3 mL of THF was added tetrabutylammonium fluoride (0.75 mL, 0.75 mmol; 1.0 M solution in THF) at 0 °C and was stirred for 3 h. SiO_2 (2.0 g) was added to the reaction mixture and the solvent was removed. The powder was applied to the top of a column and eluted with 12% methanol in CH_2Cl_2 to give 0.14 g (73%) of 3-(2-hydroxymethyl-5-carbethoxyphenethyl)coformycin aglycon **(41e)**: ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, J = 7.1 Hz), 2.9−3.2 (m, 4H), 3.9−4.2 (m, 2H), 4.29 (q, 2H, J = 7.1 Hz), 4.7−5.0 (m, 2H), 7.0−7.9 (series m, 6H).

General Procedure W. Alkylation of the Aglycon: 3-[2-(3-Carbethoxy-6-methylphenyl)ethyl]-6,7-dihydroimidazo-[4,5-*d*][1,3]diazepin-8(3*H*)-one: According to the procedure previously described[3] ketone **3** (2.0 g, 13.4 mmol) was alkylated with **27a** (3.97 g, 14.63). Chromatography on SiO_2 with a CH_2Cl_2/MeOH gradient of 20:1, 18:1 and 15:1 provided 1.77 g (39%) of 3-[2-(3-carboxyethoxy-6-methylphenyl)ethyl]-6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one as a light yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, J = 7.1 Hz), 2.3 (s, 3H), 3.1 (t, 2H, J = 7.2 Hz), 3.74 (d, 2H, J = 4.2 Hz), 4.2 (t, 2H, J = 7.2 Hz), 4.3 (q, 2H, J = 7.0 Hz), 7.3 (m, 1H), 7.46 (d, 1H, J = 4.7 Hz), 7.5 (br s, 1H), 7.7 (m, 2H), 8.4 (m, 1H).

General Procedure X. Reduction: 3-[2-(3-Carbethoxy-6-methylphenyl)ethyl]coformycin Aglycon (45f). According to the procedure previously described[3] 3-[2-(3-carboxyethoxy-6-methylphenyl)ethyl]-6,7-dihydroimidazo[4,5-*d*][1,3]diazepin-8(3*H*)-one (1.77 g, 5.2 mmol) was reduced with $NaBH_4$ (255 mg, 6.8 mmol). Chromatography on SiO_2 with a CH_2Cl_2/MeOH gradient of 20:1, 15:1 and 10:1 provided 1.3 g (73%) of 3-[2-(3-carbethoxy-6-methylphenyl)ethyl]coformycin aglycon **(45f)** as a light green solid: mp 148−150 °C; ^{1}H NMR (DMSO-d_6) δ 1.33 (t, 3H, J = 7.0 Hz), 2.3 (s, 3H), 3.0 (t, 2H, J = 7.1 Hz), 3.2 (m, 2H), 4.1 (m, 2H), 4.3 (q, 2H, J = 7.0 Hz), 4.8 (m, 1H), 4.9 (d, 1H, J = 5.3 Hz), 7.0 (d, 1H, J = 4.4 Hz), 7.2 (s, 1H), 7.3 (d, 1H, J = 8.4 Hz), 7.5 (m, 1H), 7.7 (m, 2H). Anal. ($C_{18}H_{22}N_4O_3$) C, H, N.

General Procedure Y. Hydrolysis: 3-[2-(3-Carboxy-6-methylphenyl)ethyl]coformycin Aglycon (43a). According to the procedure previously described[3] 3-[2-(3-carbethoxy-6-methylphenyl)ethyl]coformycin aglycon **(45f)** (1.0 g, 2.9 mmol) was hydrolyzed with 0.1 N NaOH (35 mL, 3.5 mmol) in 20 mL of dioxane. The product was isolated with DOWEX-18-400 acetate ion-exchange resin to provide 0.8 g (88%) of 3-[2-(3-carboxy-6-methylphenyl)ethyl]coformycin aglycon **(43a)** as a white powder: mp 160−170 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.3 (s, 3H), 3.0 (t, 2H, J = 7.3 Hz), 3.2 (br s, 2H), 4.1 (t, 2H, J = 7.3 Hz), 4.8 (t, 1H, J = 2.6 Hz), 7.03 (d, 1H, J = 4.4 Hz), 7.2 (s, 1H), 7.23 (d, 1H, J = 7.8 Hz), 7.52 (m, 1H), 7.6 (m, 2H). Anal. ($C_{16}H_{18}N_4O_3 \cdot 0.1CH_3CO_2H \cdot 2.0H_2O$) C, H, N.

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Supporting Information Available: Elemental analysis data for the final acids (Table 1) and final esters (Table 2) and ^{1}H NMR data of the key intermediates and electrophiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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