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# Discovery of a Series of Phosphonic Acid-Containing Thiazoles and Orally Bioavailable Diamide Prodrugs That Lower Glucose in Diabetic Animals Through Inhibition of Fructose-1,6-Bisphosphatase

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Oral delivery of previously disclosed purine and benzimidazole fructose-1,6-bisphosphatase (FBPase) inhibitors via prodrugs failed, which was likely due to their high molecular weight ( > 600). Therefore, a smaller scaffold was desired, and a series of phosphonic acid-containing thiazoles, which exhibited high potency against human liver FBPase ($IC_{50}$ of 10−30 nM) and high selectivity relative to other 5′-adenosinemonophosphate (AMP)-binding enzymes, were discovered using a structure-guided drug design approach. The initial lead compound (**30j**) produced profound glucose lowering in rodent models of type 2 diabetes mellitus (T2DM) after parenteral administration. Various phosphonate prodrugs were explored without success, until a novel phosphonic diamide prodrug approach was implemented, which delivered compound **30j** with good oral bioavailability (OBAV) (22−47%). Extensive lead optimization of both the thiazole FBPase inhibitors and their prodrugs culminated in the discovery of compound **35n** (MB06322) as the first oral FBPase inhibitor advancing to human clinical trials as a potential treatment for T2DM.

## Introduction

Fructose-1,6-bisphosphatase (FBPase[a]) catalyzes a rate-controlling step in the gluconeogenesis (GNG) pathway, thereby representing a potential target for controlling the excessive glucose production by the liver in patients with type 2 diabetes mellitus (T2DM).[1] While recognized as a potential target for almost four decades, FBPase has proven to be an extraordinarily challenging target in which to find potent, selective, and orally efficacious drug candidates.[2] Using a structure-based drug design approach, we ultimately were able to find a highly promising series of phosphonic acids that bind to the allosteric AMP binding site of FBPase and act as an AMP mimetic capable of inducing a protein conformational change that results in FBPase inhibition, Figure 1.[3−5] Our initial compound series contained a purine (e.g., compound **1**) and a benzimidazole phosphonic acid (e.g., compound **2**), which demonstrated potent inhibition of human FBPase and elicited significant glucose lowering in both fasted normal rats and rodent diabetic animal models of T2DM after parenteral administration.[6,7] However, not surprisingly, these compound series exhibited very poor oral bioavailability (OBAV) due to the highly negative charged phosphonic acid. To improve OBAV, lipophilic phosphonic acid prodrugs were prepared to mask the negative charge, however, despite extensive efforts exploring both known and novel prodrugs, we were unable to achieve OBAV > 10% in rodents or dogs. For example, benzimidazole **2** is a potent FBPase inhibitor with rapid in vivo glucose lowering activity after intravenous administration, but various prodrugs including the diamide **3** were explored without successfully achieving acceptable OBAV ( > 10%).

The factors limiting OBAV were attributed to oral absorption because both series appeared to be metabolically stable. Most likely the high molecular weight (MW) of prodrugs for both series ( > 600) was a key limitation,[8] and as such we eventually were forced to abandon those series and focus on designing a new scaffold with a significantly lower MW while retaining high FBPase potency and selectivity. Herein we report the design, synthesis, and evaluation of thiazole phosphonic acids as novel FBPase inhibitors. Replacement of the 5,6-fused purine and benzimidazole ring systems with a smaller 5-membered thiazole of lower MW led to significantly improved FBPase inhibitory potency. More importantly, the thiazole FBPase inhibitors proved to be excellent candidates for oral delivery via prodrugs, which led to the discovery of an oral FBPase inhibitor, compound **35n** (MB06322 or CS-917)[3] as the first oral FBPase inhibitor to advance to human clinical trials as a potential treatment for T2DM.

**Inhibitor Design.** High MW was deemed as a potential structural limitation of the purine and benzimidazole FBPase

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[a] Abbreviations: FBPase, fructose-1,6-bisphosphatase; AMP, 5′-adenosinemonophosphate; T2DM, type 2 diabetes mellitus; OBAV, oral bioavailability; GNG, gluconeogenesis; MS, molecular sieves; G-LOW, glucose lowering.



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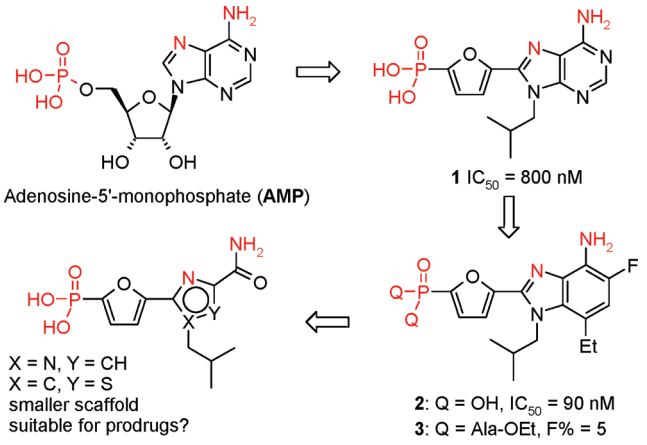



**Figure 1.** Design and evolution of novel AMP mimics.

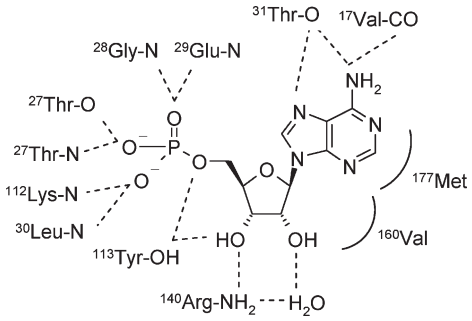
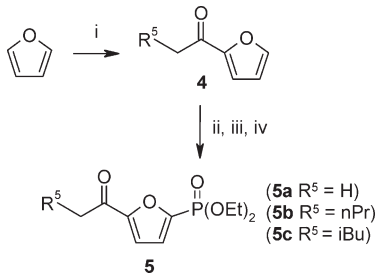



**Figure 2.** AMP interactions with human FBPase.[9]

inhibitor series, which contributed to the inability of using prodrug approaches to deliver these two series of FBPase inhibitors orally. Therefore, we focused our redesign efforts on reducing the number of atoms. The strategy to trim the purine and benzimidazole scaffolds was guided by both existing SAR[6,7] and the X-ray crystal structures of FBPase−inhibitor complexes (e.g., AMP−FBPase complex, Figure 2).[9] Because the six-membered ring portion of the purine/benzimidazole forms few direct interactions with the binding site, efforts focused on five-membered heterocycles that could be substituted in a manner that retained the two hydrogen bond interactions with $^{31}$Thr and $^{17}$Val gained by the amino substituent on the six-membered ring. Following extensive evaluation of compounds containing various five-membered heterocycles and substituents by molecular modeling and in vitro testing,[5] the thiazole scaffold was selected for further investigation.

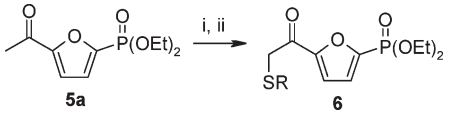
**Synthesis of Thiazole Analogues.** Thiazoles are most often prepared from α-bromoketones and thioamides or thioureas via cyclization reactions. Thus, various ketones containing a diethyl phosphonate group were prepared as shown in Schemes 1−7. The ketones required for thiazole analogues with a 2,5-furanyl linker were readily prepared from either furan or 2-acylfurans, as shown in Scheme 1. Friedel−Crafts acylation of furan with a carboxylic acid ($R^5$-$CH_2CO_2H$) and trifluoroacetic anhydride (TFAA) in the presence of a catalytic amount of $BF_3$−$OEt_2$ gave furan derivatives **4**. Protection of **4** as a cyclic ketal followed by lithiation and addition of diethyl chlorophosphate, and final ketal removal using EtOH−HCl, gave ketones **5** (e.g., **5b** and **5c** were prepared via this route, and **5a** was prepared from 2-acetylfuran in a similar manner).

**Scheme 1**[a]



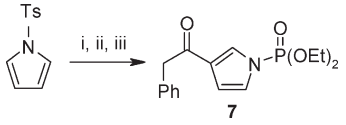

[a] Reagents and conditions: (i) $R^5$-$CH_2CO_2H$, TFAA, $BF_3$·OEt; (ii) $(CH_2OH)_2$, *p*-TsOH, toluene; (iii) LDA, THF, 0 °C, then $ClPO(OEt)_2$; (iv) EtOH, HCl.

**Scheme 2**[a]



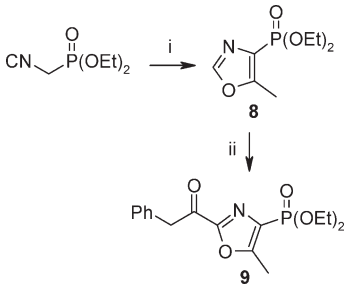

[a] Conditions: (i) $CuBr_2$, EtOAc-$CHCl_3$; (ii) RSNa, EtOH.

**Scheme 3**[a]




[a] Conditions: (i) $PhCH_2COCl$, $AlCl_3$, $(CH_2Cl)_2$; (ii) NaOH, dioxane, 80 °C; (iii) $P(OEt)_3$, $BrCCl_3$.

**Scheme 4**[a]

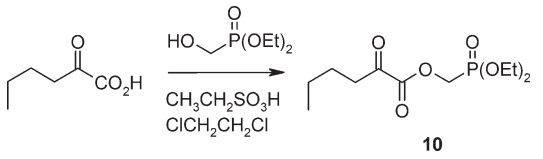



[a] Reagents and conditions: (i) *t*-BuOK, $CH_2Cl_2$, −78 °C, AcCl, −78 °C; (ii) *n*-BuLi, THF, −78 °C, $ZnCl_2$, −78 to 0 °C, CuI, 0 °C, $PhCH_2COCl$.

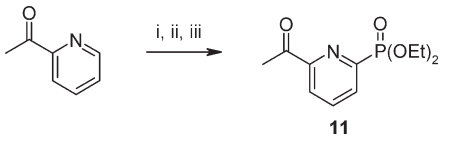
Compound **5a** was used to prepare other sulfide-containing ketones following a previously reported procedure (Scheme 2).[10] Thus, α-bromination of compound **5a** with copper(II) bromide followed by reaction with various sodium salts of mercaptans (RSNa) in ethanol gave ketones **6**.

The ketones required for analogues with a 1,3-pyrrolyl linker were prepared in three steps, as shown in Scheme 3. Friedel−Crafts acylation of *N*-toluenesulfonylpyrrole with phenylacetyl chloride in the presence of aluminum trichloride gave exclusively the 3-phenylacetyl derivative in excellent yield. Removal of the *N*-toluenesulfonyl protecting group using sodium hydroxide and subsequent reaction with triethyl

**Scheme 5**

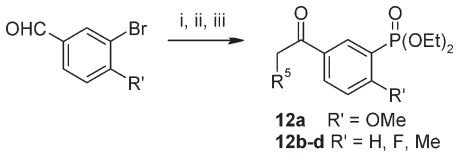



**Scheme 6**[a]




[a] Conditions: (i) $(CH_2OH)_2$, *p*-TsOH, PhMe; (ii) LDA, THF, 0 °C, then $ClPO(OEt)_2$; (iii) EtOH, HCl.

**Scheme 7**[a]




[a] Conditions: (i) $HP(O)(OEt)_2$, $Pd(PPh_3)_4$, TEA, toluene, 100 °C; (ii) $R^5CH_2MgBr$, THF; (iii) PCC, 4 Å MS, $CH_2Cl_2$.

phosphite in $BrCCl_3$ gave keto-pyrrole **7** in 69% yield over the three steps.

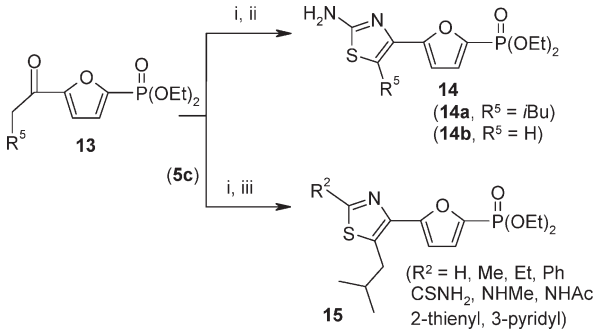
Thiazole analogues containing a 2,4-oxazolyl linker were synthesized from the corresponding keto-oxazoles; these in turn were prepared using a two-step sequence involving preparation of oxazole-phosphonate esters using a minor modification of Schöllkopf's procedure,[11] and their subsequent acylation using a minor modification of Anderson's method;[12] the synthesis of oxazole **9** is exemplified in Scheme 4. Treatment of diethyl (isocyanomethyl)-phosphonate with potassium *tert*-butoxide in dichloromethane followed by addition of acetyl chloride gave oxazole **8** in 37% yield. Lithiation of oxazole **8** using *n*-BuLi followed by transmetalation with zinc(II) chloride produced the 2-ZnCl species of oxazole **8**, which was reacted with phenylacetyl chloride in the presence of cuprous iodide to give the oxazole **9** in 33% yield.

The ester-linked keto-phosphonate **10** was prepared via direct Fisher esterification of 2-ketohexanoic acid with diethyl hydroxymethylphosphonate in the presence of ethanesulfonic acid to give **10** in 30% yield (Scheme 5).

The 2,6-pyridyl linked keto-phosphonate **11** was prepared using the three-step procedure described in Scheme 1 for the synthesis of **5a**. Protection of 2-acetylpyridine as the cyclic ketal was accomplished by heating a toluene solution of 2-acetylpyridine and ethylene glycol with a catalytic amount of *p*-TsOH; subsequent lithiation with LDA and reaction with diethyl chlorophosphate, followed by a final cyclic ketal deprotection, gave ketone **11** (Scheme 6).

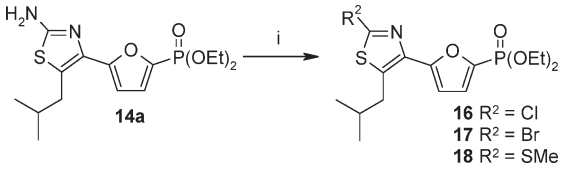
Phenylphosphonates **12** were prepared from their corresponding aryl bromides in three steps as shown in Scheme 7. Phosphonylation of 4-substituted 3-bromobenzaldehydes with diethyl phosphite in the presence of $Pd(PPh_3)_4$ and triethylamine (TEA) gave the corresponding 3-diethylphosphonobenzaldehydes. The $R^5$ groups (defined in Table 5) were

**Scheme 8**[a]



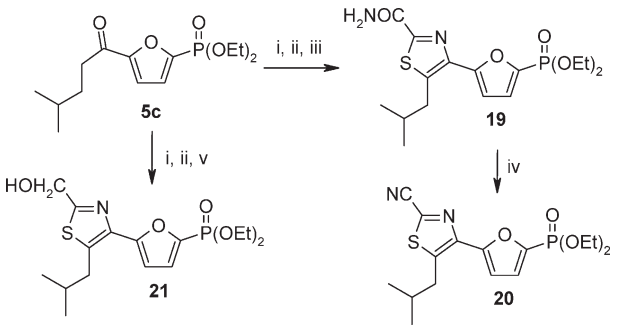

[a] Conditions: (i) $CuBr_2$, EtOAc-$CHCl_3$; (ii) thiourea, EtOH; (iii) $R^2CSNH_2$, EtOH.

**Scheme 9**[a]




[a] Conditions: (i) isoamyl nitrite, acetonitrile, $CuCl_2$ (for **16**) or $CuBr_2$ (for **17**) or TMSSMe (for **18**).

**Scheme 10**[a]



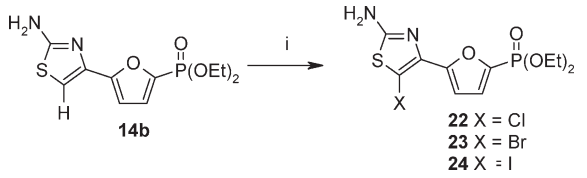

[a] Reagents and conditions: (i) $CuBr_2$, EtOAc-$CHCl_3$; (ii) $EtO_2C$-$CSNH_2$, EtOH; (iii) $NH_3$, EtOH; (iv) TFAA, TEA, THF; (v) $LiBH_4$, EtOH.

introduced via Grignard addition to the aldehyde, followed by oxidation of the resulting alcohol using pyridinium chlorochromate (PCC) in the presence of 4 Å molecular sieves (MS), affording ketones **12a**−**d**.

Phosphonate-containing ketones described in Schemes 1−7 were readily converted to 2-aminothiazoles via the α-bromoketone, derived from bromination using copper(II) bromide. Cyclization reactions with thiourea gave aminothiazoles **14**, whereas cyclization with thioamides gave C2-substituted thiazole analogues **15** (Scheme 8).

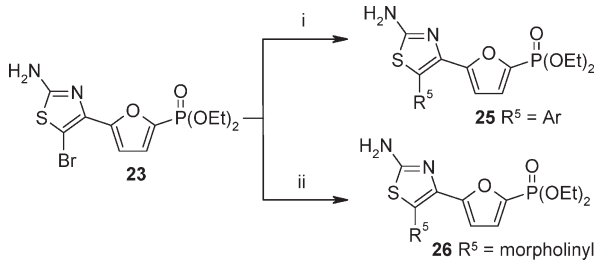
Other C2-thiazole analogues (**16**−**18**) were readily prepared from compound **14a** through Sandmeyer reactions[13,14] (Scheme 9). Direct conversion of the 2-amino group to a 2-chloro group was accomplished by treatment of thiazole **14a** with isoamyl nitrite in the presence of copper(II) chloride, producing thiazole **16**. Alternatively, reactions of thiazole **14a** with isoamyl nitrite and copper(II) bromide or (methylthio)trimethylsilane (TMSSMe) gave thiazoles **17** and **18**, respectively.

**Scheme 11**[a]



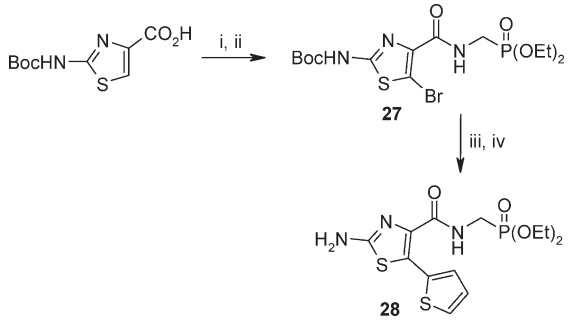

[a] Reagents and conditions: (i) DMF, NCS (for **22**) or NBS (for **23**) or NIS (for **24**).

**Scheme 12**[a]




[a] Reagents and conditions: (i) $Pd(PPh_3)_4$, $ArB(OH)_2$, $K_2CO_3$, DMF-$H_2O$, 80 °C; (ii) $Pd(PPh_3)_4$, morpholine, EtOH, $CH_2Cl_2$.

**Scheme 13**[a]



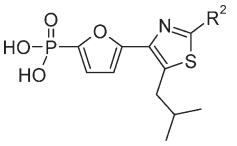

[a] Reagents and conditions: (i) $H_2NCH_2PO(OEt)_2$, EDCI, HOBt, DMF; (ii) $Br_2$, $CH_2Cl_2$; (iii) $Pd(PPh_3)_4$, 2-thienyl-$SnBu_3$, DMF; (iv) TFA, $CH_2Cl_2$.

Three other C2-analogues were prepared from ketone **5c** as shown in Scheme 10. Bromination of ketone **5c** with copper(II) bromide followed by cyclization with ethyl thiooxamate gave a thiazole with an ethoxycarbonyl group at the C2-position, which was treated with ammonia to give carboxamide **19** in 63% yield; alternatively, the C2-ester group was reduced with lithium borohydride to give hydroxymethylthiazole **21** in 87% yield. Dehydration of thiazole **19** using TFAA produced 2-cyanothiazole **20** in 67% yield.

As illustrated in Schemes 1−8, $R^5$ groups were introduced as part of the ketone moiety prior to thiazole ring formation. Alternatively, $R^5$ groups could be introduced after the thiazole was formed. For example, C5-halogenation of thiazole **14b** was readily achieved with NCS, NBS, and NIS, leading to C5-chloro (**22**), C5-bromo (**23**), and C5-iodo (**24**) thiazoles (Scheme 11), respectively.

The C5-bromo group of thiazole **23** served as an excellent handle to introduce other C5-groups via various coupling reactions (Scheme 12). For instance, Suzuki coupling of thiazole **23** with boronic acids gave C5-aryl thiazoles **25**, while Buchwald coupling[15] with morpholine produced 5-morpholinyl thiazole **26**.

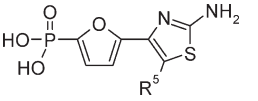
**Table 1.** SAR of C2-Thiazole Analogues of **30a**[a]




| | $R^2$ | HL $IC_{50}$, μM | G-LOW, % |
|---|---|---|---|
| **30a** | Me | 0.1 | 55 |
| **30b** | Et | 0.4 | ND[b] |
| **30c** | vinyl | 1.2 | ND |
| **30d** | $CH_2OH$ | 0.22 | 8 |
| **30e** | H | 0.5 | ND |
| **30f** | Cl | 0.18 | ND |
| **30g** | Br | 0.08 | 3 |
| **30h** | SMe | 0.89 | ND |
| **30i** | CN | 2 | ND |
| **30j** | $NH_2$ | 0.025 | 65 |
| **30k** | NHMe | 1 | ND |
| **30l** | NHAc | 10 | ND |
| **30m** | $CONH_2$ | 2.75 | ND |
| **30n** | $CSNH_2$ | 0.5 | ND |
| **30o** | Ph | 13.5 | ND |
| **30p** | 2-thienyl | 8 | ND |
| **30q** | 3-pyridyl | 5 | ND |

[a] HL, human liver FBPase; $IC_{50}$ is an average of 3 runs; G-LOW, glucose lowering ($C_{max}$) in fasted normal rats after iv administration at doses of 10 mg/kg. [b] ND, not determined.

**Table 2.** SAR of C5-Thiazole Analogues with Various Alkyl Groups[a]



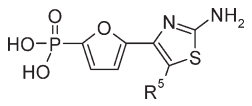

| | $R^5$ | HL $IC_{50}$, μM | G-LOW, % |
|---|---|---|---|
| **30j** | *i*-Bu | 0.025 | 65 |
| **31a** | H | 0.45 | ND[b] |
| **31b** | Me | 0.12 | 7 |
| **31c** | $HOCH_2$ | 0.5 | ND |
| **31d** | *n*-Pr | 0.03 | 64 |
| **31e** | *i*-Pr | 0.028 | 80 |
| **31f** | $CF_3CH_2$ | 0.057 | 46 |
| **31g** | neopentyl | 0.012 | 80 |
| **31h** | cyclobutyl | 0.019 | 24 |
| **31i** | cyclopentyl | 0.021 | 68 |
| **31j** | cyclohexyl | 0.01 | 78 |
| **31k** | cyclopropyl-$CH_2$ | 0.02 | 75 |
| **31l** | cyclopentyl-$CH_2$ | 0.018 | 55 |
| **31m** | cyclohexyl-$CH_2$ | 0.059 | ND |
| **31n** | $PhCH_2$ | 0.15 | −5% |
| **31o** | morpholinyl-$CH_2$ | 0.56 | ND |

[a] HL, human liver FBPase; $IC_{50}$ is an average of 3 runs; G-LOW, glucose lowering ($C_{max}$) in fasted normal rats after i.v. administration at a dose of 10 mg/kg; [b] ND, not determined.

The amide-linked thiazole **28** was prepared in four steps as shown in Scheme 13. Coupling of 2-(*tert*-butyloxycarbonylamino)-4-thiazolecarboxylic acid with diethyl aminomethylphosphonate using EDCI followed by bromination with bromine gave thiazole **27**. Stille coupling of thiazole **27** with 2-(tributylstannyl)thiophene followed by removal of the Boc group gave thiazole **28**.

Final thiazole phosphonic acids (Tables 1−5) were readily obtained via TMSBr-mediated removal of the phosphonate diethyl esters from thiazoles **29** (Scheme 14).

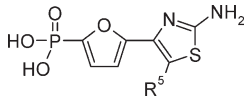
**Table 3.** SAR of C5-Thiazole Analogues with Halo and Heteroatom-Containing Groups[a]



| | $R^5$ | HL $IC_{50}$, $\mu$M | G-LOW, % |
|---|---|---|---|
| **30j** | *i*-Bu | 0.025 | 65 |
| **32a** | Cl | 0.07 | 17 |
| **32b** | Br | 0.05 | 20 |
| **32c** | I | 0.1 | −2 |
| **32d** | 1-morpholinyl | 0.016 | 75 |
| **32e** | EtS | 0.033 | ND[b] |
| **32f** | *n*-PrS | 0.016 | 82 |
| **32g** | *i*-PrS | 0.024 | 48 |
| **32h** | *t*-BuS | 0.024 | ND |
| **32i** | PhS | 0.3 | ND |
| **32j** | $CONMe_2$ | 1.7 | ND |
| **32k** | $CO_2Et$ | 0.014 | 76 |
| **32l** | $CO_2Bn$ | 0.015 | 42 |
| **32m** | *n*-PrSO | 0.858 | ND |

[a] HL, human liver FBPase; $IC_{50}$ is an average of 3 runs; G-LOW, glucose lowering in fasted normal rats after iv administration. [b] ND, not determined.

**Table 4.** SAR of C5-Thiazole Analogues with Aryl Groups[a]



| | $R^5$ | HL $IC_{50}$, $\mu$M | G-LOW, % |
|---|---|---|---|
| **30j** | *i*-Bu | 0.025 | 65 |
| **33a** | Ph | 0.014 | 76 |
| **33b** | 2-MeO-Ph | 0.043 | 66 |
| **33c** | 3-MeO-Ph | 0.021 | 0 |
| **33d** | 4-MeO-Ph | 0.022 | 63 |
| **33e** | 4-MeS-Ph | 0.021 | 72 |
| **33f** | 4-*t*-Bu-Ph | 0.088 | 6 |
| **33g** | 4-$MeO_2C$-Ph | 0.014 | 78 |
| **33h** | 4-F-Ph | 0.016 | 60 |
| **33i** | 4-Cl-Ph | 0.013 | 40 |
| **33j** | 4-Ac-Ph | 0.032 | 43 |
| **33k** | 4-$MeSO_2$-Ph | 0.041 | 78 |
| **33l** | 4-Ph-Ph | 0.034 | 36 |
| **33m** | 2-nathphyl | 0.012 | 20 |
| **33n** | 2-furanyl | 0.04 | 21 |
| **33o** | 2-thienyl | 0.044 | 24 |

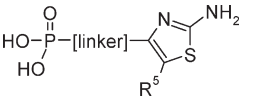
[a] HL, human liver FBPase; $IC_{50}$ is an average of 3 runs; G-LOW, glucose lowering in fasted normal rats after iv administration at a dose of 10 mg/kg.

Direct oxidation of analogue **32f**[10] using mCPBA gave the C5-sulfoxide analogue **32m** in 50% yield, Scheme 15.

To deliver thiazole phosphonate FBPase inhibitors orally, various prodrugs were prepared to mask the double negative charge. The classic acyloxyalkyl ester prodrugs (**35a**−**35e**) were obtained via direct alkylation reactions, while other prodrug esters (**35f**—**35i**) were prepared via the phosphonic dichloride coupling method as depicted in Scheme 16.

Saponification of the diphenyl ester **35g** gave the monophenyl ester of thiazole **30j** as **35j**. The monoester **35j** was also used to prepare mixed amide prodrugs **35k** and **35l** (Scheme 17). Conversion of **35j** to its corresponding monophosphonic chloride followed by reaction with either ammonia or L-alanine ethyl ester gave prodrugs **35k** and **35l**, respectively.

**Table 5.** SAR of Linker Thiazole Analogues[a]

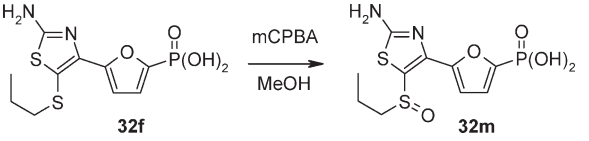


| | linker[b] | $R^5$ | HL $IC_{50}$, $\mu$M | G-LOW, % |
|---|---|---|---|---|
| **31a** | 2,5-furanyl | H | 0.45 | ND[c] |
| **31d** | 2,5-furanyl | *n*-Pr | 0.03 | 64 |
| **33a** | 2,5-furanyl | Ph | 0.014 | 76 |
| **34a** | 2,5-thienyl | *n*-Pr | > 10 | ND |
| **34b** | 1,3-pyrrolyl | Ph | > 10 | ND |
| **34c** | 4,2-oxazolyl-(5-Me) | Ph | 10 | ND |
| **34d** | $-CH_2OCO-$ | *n*-Pr | 0.05 | 63 |
| **34e** | $-CH_2NHCO-$ | 2-thienyl | 0.95 | ND |
| **34f** | 2,6-pyridyl | H | 2 | ND |
| **34g** | 1,3-phenyl | H | 1.3 | ND |
| **34h** | 1,3-phenyl | *n*-Pr | 0.25 | 0 |
| **34i** | 1,3-phenyl-(6-Me) | *n*-Pr | 0.135 | 0 |
| **34j** | 1,3-phenyl-(6-OMe) | *i*-Pr | 0.21 | 9 |
| **34k** | 1,3-phenyl-(6-F) | Ph | 0.08 | 0 |

[a] HL, human liver FBPase; $IC_{50}$ is an average of 3 runs; G-LOW, glucose lowering in fasted normal rats after iv administration at a dose of 10 mg/kg. [b] The first term is connected to the phosphorus atom, e.g. 1,3-pyrrolyl: $-PO(OH)_2$ is connected to the $N^1$ of pyrrole. [c] ND, not determined.

**Scheme 14**

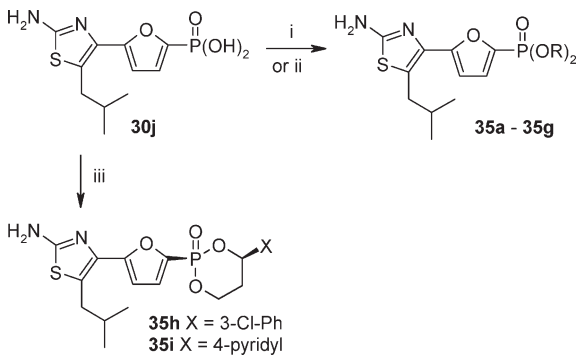

**Scheme 15**




**Evaluations of Thiazole Phosphonic Acids.** Initially, we expected that a thiazole ring with the amino substituent could best be replaced with an amide group at the C2-position. The first thiazole analogue prepared was compound **30a** because thioacetamide was available in our laboratory. Interestingly, the C2-methyl thiazole **30a** potently inhibited human liver FBPase ($IC_{50}$ = 100 nM). Moreover, after intravenous (iv) administration to fasted normal rats at a dose of 10 mg/kg, thiazole **30a** lowered blood glucose ($C_{max}$) by 55% compared to vehicle-treated animals,[6] indicating that thiazole **30a** was also able to inhibit GNG in vivo. The initial encouraging activity exhibited by thiazole **30a** prompted us to explore the SAR of the C2 position further; results are summarized in Table 1.

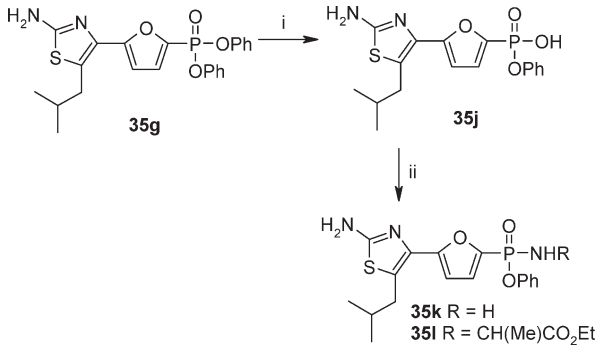
Larger C2-groups such as ethyl and vinyl groups resulted in loss of potency (thiazoles **30b** and **30c**) compared to **30a**, as did adding a hydrogen bond donor HO group (thiazole **30d**). Eliminating the C2-Me group also led to a 5-fold weaker compound in thiazole **30e**, indicating that a suitable C2-group is important for potency. Halo groups (Cl and Br) are tolerated at C2 leading to analogues (**30f** and **30g**) with potency comparable to **30a**, while analogues with C2-SMe and cyano groups (**30h** and **30i**) are significantly weaker ( > 8-fold).

**Scheme 16**[a]




[a] Reagents and conditions: (i) R-I, Hunig's base, DMF (for **35a**−**35e**, Table 6); (ii) $SO_2Cl_2$, then ROH, Hunig's base, DMF (**35f**−**35g**, Table 7); (iii) $SO_2Cl_2$, then $HO(CH_2)_2CH(OH)X$, TEA, THF.

**Scheme 17**[a]




[a] Reagents and conditions: (i) NaOH, EtOH; (ii) $SO_2Cl_2$, then $NH_3$ (for **35k**) or L-alanine ethyl ester (for **35l**), TEA, $CH_2Cl_2$.

Replacement of C2-methyl group with an amino group gave analogue **30j**, which is 4-fold more potent than **30a** and elicits potent glucose lowering in fasted normal rats (65%). *N*-Methylation and acetylation of the 2-amino group of **30j** are detrimental for potency (thiazole **30k** and **30l**). The initially desired C2-amide **30m** has only weak activity ($IC_{50}$ = 2.75 $\mu$M), possibly due to desolvation energy costs associated with the amide carbonyl group. The thioamide analogue **30n** is more potent than the corresponding amide **30m**, which supports this hypothesis. Finally, both aryl and heteroaryl groups were tested at the C2-position but all led to analogues (**30o**−**30q**) with much weaker activity. Therefore, the C2-SAR indicates the binding pocket around the C2-position prefers a small hydrogen bond donating group. Having identified that an amino group is optimal at the C2-position, 2-aminothiazoles with various alkyl groups at the C5-position were explored next and results are summarized in Table 2.

Removal of the C5-isobutyl group gave thiazole **31a**, which is 18-fold weaker than **30j**. Other groups such as methyl and hydroxymethyl at the C5-position (analogues **31b**−**31c**) are also weaker than thiazole **30j**. On the other hand, larger C5-alkyl analogues (**31d**−**31f**) exhibited potency comparable to **30j**, and the bulky C5-neopentyl analogue **31g** produced a 2-fold improvement in potency over thiazole **30j**. C5-cyclic alkyl thiazoles (**31h**−**31j**) are also potent FBPase inhibitors, with thiazole **31j** being the most potent inhibitor ($IC_{50}$ = 10 nM). Insertion of a methylene group between the cyclic alkyl groups and the thiazole core is tolerated, leading to compounds (**31k**−**31m**) with good potency ($IC_{50}$ 18−59 nM), while C5-benzyl and C5-morpholinylmethyl analogues (**31n** and **31o**) are much weaker than thiazole **30j**. Thus, the SAR of C5-alkyl thiazoles indicates that a proper size alkyl group is preferred at the 5-position, and through this effort several thiazole analogues (**31d**, **31e**, **31g**, **31i**, **31j**, and **31k**) with robust glucose lowering activity were discovered.

Exploring the SAR further, halo and heteroatom-containing groups were explored at the 5-position, and results are summarized in Table 3.

Halogens are somewhat tolerated at the 5-position (**32a**−**32c**), with the 5-bromo thiazole being the most potent ($IC_{50}$ = 50 nM). The 5-morpholinyl analogue **32d** is a potent FBPase inhibitor with an $IC_{50}$ of 16 nM; however, it is not very stable chemically at room temperature. The instability of **32d** is possibly due to the highly electron-rich thiazole ring that is likely to be prone for oxidation. Alkylthio groups are well tolerated at the 5-position (**32e**−**32h**), leading to potent FBPase inhibitors ($IC_{50}$ 16−33 nM), while the phenylthio analogue **32i** is 12-fold weaker than thiazole **30j**. The C5-amide analogue **32j** is 68-fold weaker than **30j**, while C5-ester analogues **32k** and **32l** are 2-fold more potent than **30j**. Conversion of the sulfide analogue **32f** to its corresponding sulfoxide **32m** resulted in >34-fold loss in potency. The diethyl ester of 5-bromothiazole **32b** provided an excellent handle to study aryl groups at the 5-position and results are summarized in Table 4.

The 5-phenylthiazole analogue **33a** is 2-fold more potent than **30j**, while various substituted phenyl groups are also tolerated, leading to potent FBPase inhibitors (thiazoles **33b**−**33l**, $IC_{50}$ = 13−88 nM). The 5-(2-naphthyl)thiazole **33m** ($IC_{50}$ = 12 nM) is 2-fold more potent than **30j**, while two C5-heteroaryl analogues (**33n** and **33o**) are slightly weaker than thiazole **30j**. Consistent with modeling studies, the SAR summarized in Tables 2−4 indicates that the C5 groups are well tolerated, with alkyl, ester, and aryl substituents leading to potent FBPase inhibitors ($IC_{50}$ 10−25 nM).

Although the furan linker was the best in the earlier purine and benzimidazole series of FBPase inhibitors, various linking groups were prepared prior to embarking on prodrug efforts. The results are summarized in Table 5.

Replacement of the furan with other five-membered heterocycles is detrimental to FBPase inhibition, leading to inactive compounds (**34a**−**34c**). This reflects the ability of the furan oxygen to receive a strong electrostatic interaction from $^{30}$Leu based on the X-ray structure of human FBPase−compound **30j** complex (Figure 3).[5] Interestingly, replacement of the furan with ester- and amide linked thiazoles (**34d** and **34e**) led to compounds that retained FBPase inhibition, with the ester linker analogue **34d** showing potency comparable to the furan-linked thiazole **31d**. Two six-membered linker analogues (**34f** and **34g**) were also explored, but both lost potency (>4-fold for **34f** and ca. 3-fold for **34g**) compared to their corresponding furan-linked analogue **31a**. The C5-thiazole SAR presented in Tables 2−4 indicates that an alkyl group is required for high potency and because both **34f** and **34g** do not have an equivalent C5-alkyl group, we selected the more potent 1,3-phenyl-linked analogue **34g** for further optimization. Introduction of a propyl group gave analogue **34h**, which is 5-fold more potent than **34g** but still >8-fold weaker than its corresponding furan analogue **31d**. Additional substitutions of the 1,3-phenyl linker and changing the *n*-propyl group (analogues **34i**−**34k**) led to

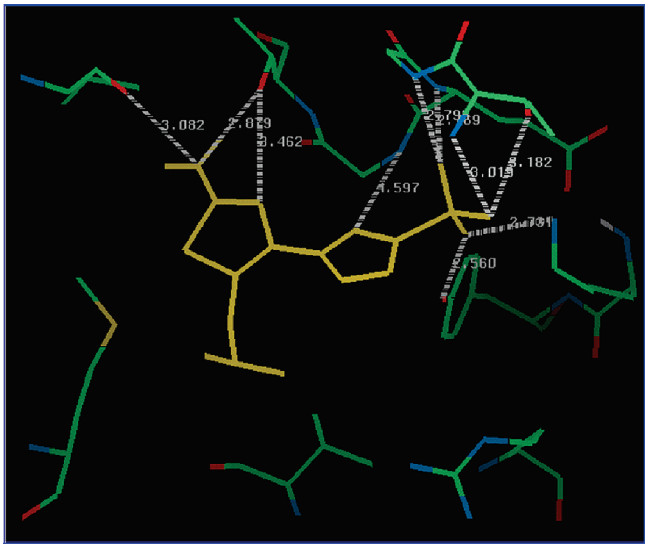



**Figure 3.** X-ray structural analysis of **30j** (in yellow) bound to FBPase.

**Table 6.** Pharmacoketic Profiles of Thiazole **30j** and Benzimidazole **2**[a]

| compound | $T_{1/2}$, h | Cl, L/h/kg | $V_d$, L/kg | protein binding, % | OBAV, % |
|---|---|---|---|---|---|
| **2** | 0.75 | 0.26 | 0.25 | 99, rat; 99.9, human | 2 |
| **30j** | 0.65 | 0.24 | 0.18 | 90, rat; 93, human | 4 |

[a] Fed male Sprague−Dawley rats were used; protein binding determined using heparinized rat and human plasma.

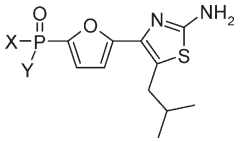
further potency improvement over the initial lead **34g**, with analogue **34k** being the most potent FBPase inhibitor of this series ($IC_{50}$ = 80 nM). However, analogue **34k** is still ca. 6-fold weaker than its corresponding furan-linked analogue **33a** and surprisingly did not lower glucose in the normal fasted rat. The linker SAR indicated that the furan was still optimal for the thiazole scaffold, thus thiazole **30j** was selected for further evaluation. A full pharmacokinetic (PK) study of thiazole **30j** was carried out, and the results are summarized in Table 6.

Thiazole **30j** showed similar PK profile compared to benzimidazole **2**, except plasma protein binding (Table 6); the thiazole scaffold is significantly less protein bound compared to the benzimidazole scaffold, which should translate into more free drugs for the thiazole scaffold.

With the inhibitor optimization completed, attention turned to preparation of phosphonate prodrugs in order to achieve adequate OBAV.[16] A wide variety of prodrugs was prepared to attempt the orally delivery of thiazole **30j**; the OBAV SAR of these prodrugs in rats are summarized in Table 7.

The classic (pivaloyloxy)methyl phosphonate diester (bisPOM) prodrug (**35a**) of thiazole **30j** gave 11% OBAV in our urinary screening assay,[10] which represents a 5-fold improvement over the phosphonic acid **30j**. However, in the fasted normal rat assay, oral administration of prodrug **35a** did not lower glucose, while iv dosing did lower glucose by 53%. The glucose lowering after iv administration is likely due to the rapid conversion of the bisPOM prodrug **35a** to the parent **30j** by esterases in plasma such that iv administration of **35a** is essentially equal to iv dosing of the parent **30j**. Four carbonate prodrugs (**35b**−**35e**) were also studied, with the ethyl carbonate **35d** showing the highest OBAV among the carbonate prodrugs. Prodrug **35d** was tested for oral efficacy at the screening dose of 10 mg/kg; however,

**Table 7.** OBAV SAR of Thiazole **30j** Prodrugs[a]




| | X | Y | MW | OBAV, % | G-LOW, % |
|---|---|---|---|---|---|
| **30j** | | | | 2 | ND[b] |
| **35a** | *t*-$BuCO_2CH_2O$− | X | 530.6 | 11 | 0[c] |
| **35b** | $EtOCO_2CH(Me)O$− | X | 534.5 | ND | 12 |
| **35c** | $PhOCO_2CH_2O$− | X | 602.6 | 7 | ND |
| **35d** | $EtOCO_2CH_2O$− | X | 506.5 | 17 | 40[d] |
| **35e** | *i*-$PrOCO_2CH_2O$− | X | 534.5 | 13 | ND |
| **35f** | 4-AcO-$PhCH_2O$− | X | 598.6 | 8 | ND |
| **35g** | PhO− | X | 454.5 | 0.2 | ND |
| **35h** | 3-Cl-Ph-cyclic ester[e] | | 452.9 | 8 | 53[d] |
| **35i** | 4-pyridyl cyclic ester[e] | | 419.4 | 8 | ND |
| **35j** | PhO− | OH | 378.4 | 1 | ND |
| **35k** | PhO− | $NH_2$ | 377.4 | 7 | ND |
| **35l** | L-alanine-OEt | PhO− | 477.5 | 12 | 46[d] |
| **35m** | glycine-OEt | X | 472.5 | 26 | 51 |
| **35n** | L-alanine-OEt | X | 500.6 | 22 | 59 |
| **35o** | $EtO_2CC(Me)_2NH$ | X | 528.6 | 47 | 45 |

[a] OBAV, determined by measuring urinary excretion of **30j** following oral administration of the prodrug vs iv administration of **30j**; G-LOW, glucose lowering in normal fasted rats after oral administration of a 10 mg/kg dose. [b] ND, not determined. [c] When **35a** was dosed iv, blood glucose was lowered by 53%. [d] Compound dosed at 30 mg/kg orally. [e] Structure is shown in Scheme 17.

similar to the bisPOM prodrug **35a**, it did not produce significant glucose lowering. However, at a higher dose of 30 mg/kg, prodrug **35d** lowered glucose by 40%. Four other esters (**35f**−**35i**), a monophenyl ester (**35j**), and a monophenyl amide (**35k**) were tested as prodrugs, but all gave < 8% OBAV. The 1-(3-chlorophenyl)-1,3-propanyl cyclic ester (HepDirect)[17] prodrug **35h** was also tested at the higher dose of 30 mg/kg, and it lowered blood glucose by 53%. An aryl amidate (McGuigan) prodrug[18] was prepared as compound **35l**, which gave OBAV of 12% but only lowered glucose orally at the higher dose of 30 mg/kg. Overall, although some progress was made toward achieving OBAV of > 15%, no significant oral efficacy was obtained at the screening dose of 10 mg/kg. Therefore, the search was expanded to include novel prodrug types; these efforts culminated in the discovery of phosphonic diamides, a new prodrug class that enabled oral delivery of these thiazole phosphonic acids.[10] Optimization of the phosphonic diamide prodrugs produced three prodrugs (**35m**−**35o**) that showed good OBAV (22−47%). Moreover, all three phosphonic diamide prodrugs elicited significant glucose lowering in fasted rats after oral administration of a 10 mg/kg dose. Extensive confirmatory studies led to the selection of diamide **35n** for further evaluation.

**Efficacy Study in Rodent Models of T2DM.** Compound **35n** inhibits glucose production in both human and rat primary hepatocytes in a concentration-dependent manner.[3] The inhibitory potency of compound **35n** was independent of substrates used for the hepatocyte assay (i.e., lactate or glycerol), which is consistent with the expected mechanism of action, i.e., blocking of GNG via FBPase inhibition. Moreover, compound **35n** demonstrated oral glucose-lowering effects in several rodent models of T2DM (e.g., STZ, ZDF, and GK rats, and db/db mice), establishing it as the first FBPase inhibitor with reported oral activity in animal models.[19−21]

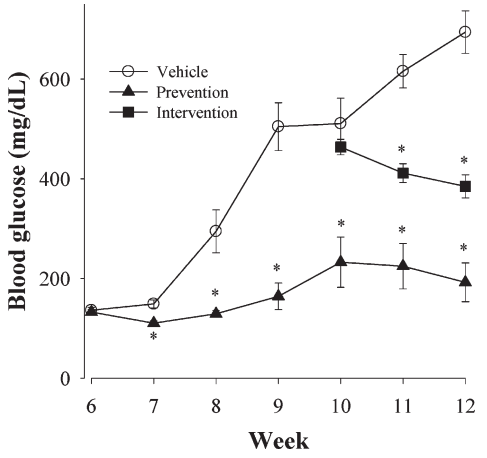



**Figure 4.** Effects of **35n** prevention and intervention therapy in male ZDF rats. Compound **35n** was administered as a food admixture (0.4%, w/w) to 6-week-old (prevention) or 10-week-old (intervention) rats. $n = 8$/group. *$p < 0.05$ compared to controls (ANOVA).

A study was also carried out in six-week old male ZDF rats in both prevention and intervention modes to demonstrate further the potential of compound **35n** as a potential treatment for T2DM.[19] Compound **35n** was studied using three cohorts of rats: one group of control animals treated with vehicle, a second group in which drug treatment was initiated at six weeks of age (prevention mode), and a third group in which drug treatment was initiated at 10 weeks of age (intervention mode). Compound **35n** was administered as a food admixture in these studies (0.4%). In the prevention mode, drug treatment delayed the development of T2DM as indicated by the slow progression of hyperglycemia compared to vehicle-treated animals (Figure 4). In the intervention mode, treatment with **35n** resulted in a marked correction of established hyperglycemia relative to the control group. This study suggests that compound **35n** might be useful to treat both the early and late stages of T2DM.

## Conclusion

Earlier prodrug efforts to achieve oral delivery of the previously reported purine and benzimidazole FBPase inhibitors were unsuccessful, and high molecular weight ( > 600) was suspected as a contributing factor. To discover a new scaffold more amenable to oral delivery, a structure-guided drug design approach was used to trim the 5,6-fused heterocyclic systems of purine and benzimidazole to the five-membered heterocycle thiazole. The thiazole series of FBPase inhibitors proved to not only have improved potency against human liver FBPase (many thiazoles with $IC_{50}$ of 10−30 nM were discovered) but also to be suitable for oral delivery via prodrugs, with the lead compounds achieving oral bioavailability in the range of 25−50%. Compound **30j** demonstrated potent inhibition of glucose production in both rat and human hepatocytes[3] and elicited robust glucose lowering in rodent models of T2DM after parental administration.[19−21] Oral delivery of **30j** was achieved via its phosphonic diamide prodrug, a novel phosphonate prodrug approach designed and used to effectively deliver phosphonate-containing FBPase inhibitors. Extensive lead optimization of both the thiazole FBPase inhibitor series and their prodrugs culminated in the discovery of compound **35n**, the first oral FBPase inhibitor to advance to human clinical trials in patients with T2DM.[22]

## Experimental Section

**General Synthetic Methods.** Compounds **30e**, **30j**, **31c**, **32f**, **32k**, **35a**, **35e**, **35m**, **35n**, and **35o** were prepared according to reported procedures.[3,5] All moisture sensitive reactions were performed under a nitrogen atmosphere using flame-dried glassware and anhydrous solvents purchased from Aldrich. TLC was performed on Analtech Uniplate silica gel GHLF (250 $\mu$m, 10 cm × 20 cm) plates. 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 uncorrected. $^1$H spectra were recorded on Varian Gemini or Mercury spectrometers operating respectively at 200 or 300 MHz. Mass spectra data were determined on a Perkin-Elmer Sciex API2000 LC-MS system. All compounds tested for biological activity have ≥95% purity. Purity was determined via either analytical HPLC (performed on a 4.6 mm × 250 mm YMC ODS-AQ 5 $\mu$m column eluting with a 0.1% aqueous AcOH/MeOH gradient detected at 280 nm) or elemental (C, H, N) microanalyses (performed by NuMega Resonance Laboratories, Inc., San Diego, CA, or by Robertson Microlit Laboratories).

**2-(4-Methylpentanoyl)furan (4).** A solution of furan (225 mL, 3.09 mol) and 4-methylpentanoic acid (276 g, 2.37 mol) in anhydrous toluene (2.25 L) was treated with trifluoroacetic anhydride (400 mL, 2.83 mol) under a nitrogen atmosphere followed by boron trifluoride etherate (29 mL, 0.24 mol). After heating the solution to 50−55 °C for 2 h, the reaction was cooled to 8−10 °C (ice bath) and neutralized with a sodium carbonate solution (21 wt %, 1.8 L, 3.5 mol). The layers were separated, and the organic layer was filtered through a Celite pad. The filtrate was dried ($MgSO_4$) and concentrated in vacuo. The resulting dark oil was purified by vacuum distillation (bp 66−68 °C, 11 mmHg) to give 2-(4-methylpentanoyl)furan as a colorless liquid (310 g, 78%). $^1$H NMR ($CDCl_3$): $\delta$ 7.59 (m, 1H), 7.19 (m, 1H), 6.55 (m, 1H), 2.81 (t, 2H, $J = 6.8$ Hz), 1.61 (m, 3H), 0.98 (d, 6H, $J = 6.8$ Hz).

**Diethyl (5-Acetylfuran-2-yl)phosphonate (5a).** A solution of 2-acetylfuran (102 g, 926 mmol) and ethylene glycol (78 mL, 1399 mmol) in anhydrous benzene (500 mL) was treated with *p*-toluenesulfonic acid (8 g, 42 mmol) and heated to reflux while removing water with a Dean−Stark trap. After 3 h, the reaction was cooled to room temperature, diluted with benzene (150 mL), and washed with aqueous sodium hydroxide (0.5 M, 300 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to give the desired cyclic ketal as a dark oil (134 g, 93%). A solution of the ketal in anhydrous THF (350 mL) was treated with 1,4-diazabicyclo[2,2,2]octane (97.5 g, 869 mmol), cooled to −42 °C, and treated with a solution of *n*-butyl lithium (2.5 M, 347 mL) in hexane via an addition funnel at a speed that maintained the reaction temperature between −43 and −40 °C. After the addition was complete, the solution was stirred at 0−2 °C for 1 h. In a separate flask, a solution of diethyl chlorophosphate (138 mL, 955 mmol) in anhydrous THF (350 mL) was cooled to −45 °C and treated with the above generated lithiated 2-acetylfuran cyclic ketal solution (cooled to −8 °C) via a cannula at a rate that maintained the reaction temperature between −44 and −40 °C. After the addition was complete, the reaction was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was partitioned between ethyl acetate (600 mL) and water (600 mL). The aqueous phase was extracted again with ethyl acetate (500 mL), and the organic extracts were combined, washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a dark oil (214 g). The crude 5-diethylphosphono-2-acetylfuran cyclic ketal was dissolved in methanol (500 mL) and treated with hydrochloric acid (1 N, 200 mL). After heating at 60 °C for 12 h, the methanol was removed in vacuo and the resulting dark oil was partitioned between ethyl acetate (600 mL) and saturated sodium bicarbonate solution (300 mL). The layers were separated, and the aqueous phase was extracted

with EtOAc (400 mL). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a dark oil (167 g). The residue was purified by vacuum distillation 126−145 °C/0.10 Torr to give compound **5a** as a pale-orange oil (112 g, 61%). $^1$H NMR ($CDCl_3$): $\delta$ 7.18 (m, 2H), 4.19 (m, 4H), 2.49 (s, 3H), 1.28 (t, 6H, $J$ = 7.2 Hz).

**Diethyl (5-Pentanoylfuran-2-yl)phosphonate (5b).** Prepared in analogous fashion to compound **5a** from 1-furan-2-yl-pentan-1-one to give **5b** as a brown oil. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.20 (m, 2H), 4.20 (m, 4H), 2.82 (t, 2H, $J$ = 7.4 Hz), 1.76−0.90 (m, 13H).

**Diethyl [5-(4-Methylpentanoyl)furan-2-yl]phosphonate (5c).** Prepared in analogous fashion to compound **5a** from furan **4** to give **5c** (purified via vacuum distillation, 126−145 °C/0.10 Torr) as a pale-orange oil (112 g, 61%). $^1$H NMR ($CDCl_3$): $\delta$ 7.19 (m, 2H), 4.22 (m, 4H), 2.87 (t, 2H, $J$ = 6.6 Hz), 1.61 (m, 3H), 1.39 (m, 6H), 0.97 (d, 6H, $J$ = 6.6 Hz).

**General Procedure for Synthesis of Thiazoles 14 and 15 from Ketones 13. 2-Amino-4-[2-(5-diethylphosphono)furanyl]thiazole (14b).** A solution of (5-acetyl-furan-2-yl)-phosphonic acid diethyl ester (**5a**) (2 g, 8.12 mmol) in anhydrous ethyl acetate (20 mL) and chloroform (20 mL) was treated with copper(II) bromide (5 g, 22.4 mmol) and stirred at room temperature under nitrogen for 24 h. The reaction was quenched with saturated ammonium chloride and extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil. $^1$H NMR ($CDCl_3$): $\delta$ 7.33 (m, 1H), 7.21 (s, 1H), 4.38 (s, 2H), 4.23 (m, 4H), 1.39 (m, 6H).

The crude 2-bromoacetyl-5-diethylphosphonofuran (137 mg, 0.423 mmol) was dissolved in anhydrous ethanol (2 mL) and treated with thiourea (64 mg, 0.846 mmol). After heating at reflux for 2 h, the reaction mixture was cooled, quenched with saturated sodium bicarbonate, and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and filtered, and the filtrate was concentrated under reduced pressure to give a yellow solid. The crude solid was purified by flash chromatography ($SiO_2$, 1 cm × 15 cm, 50, 65, 80, and 100% EtOAc−hexane, gradient elution) to give compound **14b** as a yellow solid (90 mg, 70%). Melting point 144−148 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.13 (m, 1H), 6.78 (s, 1H), 6.61 (m, 1H), 6.38 (bs, 2H), 4.35 (m, 4H), 1.35 (m, 6H). $[MH]^+$ calcd for $C_{11}H_{15}N_2O_4PS$ 303; found:303. Anal. Calcd for $C_{11}H_{15}N_2O_4PS + 0.1H_2O$: C, 43.45; H, 5.04; N, 9.21. Found: C, 43.14; H, 4.88; N, 9.14.

**General Procedure for Syntheses of 2-Halothiazoles (16−18). 2-Chloro-4-[2-(5-diethylphosphono)furanyl]-5-isobutylthiazole (16).** A solution of compound **14a** (400 mg, 1.12 mmol) in acetonitrile (10 mL) was treated with copper(II) chloride (180 mg, 1.34 mmol), cooled to 0 °C, and then added isoamyl nitrite (197 mg, 1.68 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h and then partitioned between EtOAc and water. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography ($SiO_2$, 2 cm × 15 cm, 50% EtOAc−hexane) to give compound **16** as a yellow solid (279 mg, 66%). $^1$H NMR ($CDCl_3$): $\delta$ 7.21 (m, 1H), 6.82 (m, 1H), 4.17 (m, 4H), 2.99 (d, 2H, $J$ = 7.0 Hz), 1.93 (m, 1H), 1.38 (t, 6H, $J$ = 7.2 Hz), 0.99 (d, 6H, $J$ = 7.0 Hz).

**2-Carbamoyl-4-[2-(5-diethylphosphono)furanyl]-5-isobutylthiazole (19).** A suspension of **5c** (500 g, 1.65 mol) and copper(II) bromide (838 g, 3.76 mol) in anhydrous ethanol (5.5 L) was heated to reflux under nitrogen for 1 h. The reaction was then cooled to room temperature, filtered, and the solid washed with ethanol (0.5 L). The combined filtrate and washing was concentrated under reduced pressure to an oil, which was dissolved in ethyl acetate (4 L) and quenched with a saturated sodium bicarbonate solution (2.8 L). The resulting mixture was filtered through a Celite pad (washed with ethyl acetate, 0.5 L), and the layers were separated. The aqueous phase was extracted with ethyl acetate (2.5 L), and the organic phases were combined and washed with a saturated solution of ammonium chloride, which was subsequently re-extracted with dichloromethane (2 × 30 mL). The organic extracts were combined, washed with brine (1.2 L), dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude diethyl [5-(2-bromo-4-methyl-pentanoyl)-furan-2-yl]phosphonate as a greenish−yellow oil (587 g, 93%).

The above bromoketone (7.16 g, 18.79 mmol) was then dissolved in anhydrous ethanol (90 mL), treated with ethyl thiooxamate (5 g, 37.59 mmol), and heated at reflux. After 14 h, the reaction mixture was cooled to room temperature, concentrated under reduced pressure, neutralized with saturated sodium bicarbonate (50 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated under reduced pressure to give a light-orange solid. The crude solid was purified by flash chromatography ($SiO_2$, 5 cm ×15 cm, 50% EtOAc−hexane) to give 2-ethoxycarbonyl-4-[2-(5-diethylphosphono)-furanyl]-5-isobutylthiazole as a yellow solid (4.5 g, 58%).

A solution of 2-ethoxycarbonyl-4-[2-(5-diethylphosphono)-furanyl]-5-isobutylthiazole (250 mg, 0.60 mmol) in ammonia-saturated methanol (5 mL) was stirred at room temperature for 18 h. The reaction solution was evaporated to give compound **19** as white solid (145 mg, 63%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.23−7.26 (m, 1 H), 6.83−6.86 (m, 1 H), 4.11−4.22 (m, 4 H), 3.04 (d, $J$ = 7 Hz, 2 H), 1.93−2.03 (m, 1 H), 1.30−1.37 (m, 6 H), 0.99 (d, $J$ = 7 Hz, 6 H).

**2-Cyano-4-[2-(5-diethylphosphono)furanyl]-5-isobutylthiazole (20).** A suspension of **19** (145 mg, 0.375 mmol) in THF (2 mL) was treated with TEA (228 mg, 2.25 mmol), cooled to 0 °C, and then treated with TFAA (236 mg, 1.13 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated sodium bicarbonate (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography ($SiO_2$, 2 cm × 15 cm, 60% EtOAc−hexane) to give compound **20** (92 mg, 67%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.23−7.26 (m, 1 H), 6.90−6.98 (m, 1 H), 4.08−4.24 (m, 4 H), 3.11 (d, $J$ = 7 Hz, 2 H), 1.93−2.03 (m, 1 H), 1.25−1.39 (m, 6 H), 1.11 (d, $J$ = 7 Hz, 6 H).

**2-Hydroxymethyl-4-[2-(5-diethylphosphono)furanyl]-5-isobutylthiazole (21).** A solution of 2-ethoxycarbonyl-4-[2-(5-diethylphosphono)furanyl]-5-isobutylthiazole (see above procedure for compound **19**, 3.12 g, 7.50 mmol) in ethanol (60 mL) was cooled to 0 °C and treated with a solution of lithium borohydride (2 M, 4.48 mL) in THF. The reaction solution was stirred at room temperature for 1 h and then at 60 °C for 1 h. The cooled reaction solution was evaporated to dryness, and the residue was partitioned between EtOAc and water. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography ($SiO_2$, 3 cm × 15 cm, 60% EtOAc−hexane) to give compound **21** as colorless oil (2.4 g, 87%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.13−7.18 (m, 1 H), 6.69−6.74 (m, 1 H), 4.91 (s, 2 H), 3.97−4.17 (m, 4 H), 2.86 (d, $J$ = 7 Hz, 2 H), 1.78−1.92 (m, 1 H), 1.21−1.32 (m, 6 H), 0.92 (d, $J$ = 7 Hz, 6 H).

**General Procedure for C5-Halogenation of Thiazole 14b. 2-Amino-4-[2-(5-diethylphosphono)furanyl]-5-bromothiazole (23).** A solution of compound **14b** (5.0 g, 17 mmol) in anhydrous chloroform (70 mL) was cooled to 0 °C and treated with *N*-bromosuccinimide (3.63 g, 20 mmol) under nitrogen. The reaction was allowed to warm to room temperature after 15 min and then stirred for 2 h. After quenching with saturated $Na_2S_2O_3$ (20 mL), the resulting mixture was diluted with water (20 mL) and extracted with dichloromethane (2 × 30 mL). The combined organics were dried ($MgSO_4$) and evaporated to give a yellow solid, which was purified by flash chromatography ($SiO_2$, 5 cm × 10 cm, 100% EtOAc) to give compound **23** as a brown solid

(4.4 g, 68%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.72−7.77 (m, 1 H), 7.08−7.13 (m, 1 H), 4.10−4.27 (m, 4 H), 1.32−1.40 (m, 6 H).

**General Procedure for Suzuki Couplings of Thiazole 23. 2-Amino-4-[2-(5-diethylphosphono)furanyl]-5-phenylthiazole (25).** Compound **23** (388 mg, 1 mmol), tetrakis(triphenylphosphine) palladium (116 mg, 0.1 mmol), and phenyl boronic acid (247 mg, 2 mmol) were suspended in DME−MeOH (5:1, 5 mL) and treated with a solution of saturated sodium carbonate (0.8 mL). After heating at 80 °C for 8 h, the reaction mixture was cooled, diluted with dichloromethane (20 mL), dried ($MgSO_4$), and filtered through a Celite pad (washed with dichloromethane, 3 × 5 mL). The filtrate was evaporated to dryness, and the resulting brown solid was crystallized in ethyl acetate and hexane to give **25** as a white solid (77 mg, 20%). White flakes (EtOAc−hexane). Melting point 198−200 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.42−7.35 (m, 5H), 7.03 (m, 1H), 6.64 (bs, 2H), 6.39 (m, 1H), 4.15 (m, 4H), 1.25 (t, 6H, $J$ = 7.2 Hz). $[MH]^+$ calcd for $C_{17}H_{19}N_2O_4PS$, 379; found, 379. Anal. Calcd for $C_{17}H_{19}N_2O_4PS$: C, 53.96; H, 5.06; N, 7.40. Found: C, 54.06; H, 4.88; N, 7.33.

**2-Amino-4-[2-(5-diethylphosphono)furanyl]-5-morpholinyl-thiazole (26).** Compound **23** (168 mg, 0.44 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), morpholine (77 mg, 0.88 mmol), 2-(di-*tert*-butylphosphino)biphenyl (3 mg, 0.01 mmol), and *t*BuOK (1M, 0.97 mL) in DMF (2 mL) were heated at 80 °C for 8 h under nitrogen. The cooled reaction mixture was diluted with phosphate buffer (pH = 7) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by preparative TLC (100% EtOAc) to give **26** as a yellow solid (25 mg, 15%). $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.13−7.18 (m, 1H), 6.89−6.94 (m, 1H), 4.02−4.30 (m, 4H), 3.80−3.88 (m, 4H), 2.81−2.89 (m, 4H), 1.29−1.39 (m, 6H).

**General Procedures for TMSBr-Mediated Removal of Phosphonate Diesters. 2-Methyl-5-isobutyl-4-[2-(5-phosphono)furanyl]-thiazole (30a).** A solution of 2-methyl-5-isobutyl-4-[2-(5-diethylphosphono)furanyl]thiazole (1.31 g, 3.68 mmol) in anhydrous dichloromethane (18 mL) was treated with TMSBr (6.48 g, 36.8 mmol) at room temperature. After stirring for 16 h, the reaction solution was evaporated to dryness and the residue was azeotroped with methanol (3 × 10 mL). The residue was suspended in water (20 mL). The resulting solid was collected via filtration (washed with water, 3 × 10 mL; dichloromethane, 2 × 5 mL) and dried under vacuum to give compound **30a** as an off-white solid (1.02 g, 92%). $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 0.98 (d, 6H, $J$ = 6.8 Hz), 1.80−2.00 (m, 1H), 3.04 (d, 2H, $J$ = 6.8 Hz), 6.78 (m, 1H), 7.08 (m, 1H). Anal. ($C_{12}H_{16}NO_4PS \cdot 0.25CH_2C1_2$) C, H, N.

The following compounds were prepared in a similar manner as compound **30a**:

**2-Ethyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30b).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 0.96 (d, 6H, $J$ = 6.6 Hz), 1.41 (t, 3H, $J$ = 7.1 Hz), 1.84−2.02 (m, 1H), 3.04−3.20 (m, 4H), 6.87 (m, 1H), 7.15 (m, 1H). Anal. ($C_{13}H_{18}NO_4PS \cdot 1HBr$) C, H, N.

**2-Vinyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30c).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 0.9p (d, 6H, $J$ = 6.8 Hz), 1.94 (m, 1H), 3.04 (d, 2H, $J$ = 6.8 Hz), 3.30−3.80 (m, 2H), 5.65 (m, 1H), 6.82 (m, 1H), 7.11 (m, 1H). Anal. ($C_{13}H_{16}NO_4PS \cdot 1HBr \cdot 0.1H_2O$) C, H, N.

**2-Hydroxymethyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30d).** Melting point 160−170 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.89 (d, 6H, $J$ = 6.7 Hz), 1.72−1.80 (m, 1H), 2.93 (d, 2H, $J$ = 7.1 Hz), 4.64 (s, 2H), 6.87 (m, 1H), 6.91 (m, 2H). Anal. ($C_{12}H_{16}NO_5PS \cdot 0.75HBr$) C, H, N.

**5-Isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30e).** Melting point 164−166 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.66 (s, 1H), 6.50 (m, 2H), 2.78 (d, 2H, $J$ = 6.6 Hz), 1.75 (m, 1H), 0.74 (d, 6H, $J$ = 6.6 Hz). Anal. ($C_{11}H_{14}NO_4PS$) C, H, N.

**2-Chloro-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30f).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 0.98 (d, 6H, $J$ = 7.1 Hz), 1.84−2.02 (m, 1H), 3.04 (d, 2H, $J$ = 7.1 Hz), 6.81 (m, 1H), 7.18 (m, 1H). Anal. ($C_{11}H_{13}NO_4PSCl$) C, H, N.

**2-Bromo-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30g).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.00 (d, 6H, $J$ = 7.0 Hz), 1.82−2.02 (m, 1H), 3.04 (d, 2H, $J$ = 7.0 Hz), 6.82 (m, 1H), 7.17 (m, 1H). Anal. ($C_{11}H_{13}NO_4PSBr$) C, H, N.

**2-Methylthio-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30h).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 0.99 (d, 6H, $J$ = 7.0 Hz), 1.84−2.02 (m, 1H), 2.70 (s, 3H), 3.02 (d, 2H, $J$ = 7.0 Hz), 6.80 (m, 1H), 7.08 (m, 1H). Anal. ($C_{12}H_{16}NO_4PS_2$) C, H, N.

**2-Cyano-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30i).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.01 (d, 6H, $J$ = 6.6 Hz), 1.94−2.04 (m, 1H), 3.18 (d, 2H, $J$ = 6.6 Hz), 6.93 (m, 1H), 7.09 (m, 1H). Anal. ($C_{12}H_{13}N_2O_4SP \cdot 0.09HBr$) C, H, N.

**2-Methylamino-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30k).** Melting point 202−205 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.91 (d, 6H), 1.64−1.82 (m, 1H), 2.80 (m, 5H), 6.51 (m, 1H), 6.79 (brs, 1H). Anal. ($C_{12}H_{17}N_2O_4PS \cdot 0.5H_2O$) C, H, N.

**2-Acetamido-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30l).** Melting point 179−181 °C. $^1$H NMR (200 MHz, $D_2O$ + NaOD) $\delta$ 0.76 (d, 6H), 1.64−1.80 (m, 1H), 1.89 (s, 3H), 2.59 (d, 2H), 6.36 (brs, 1H), 6.50 (brs, 1H). Anal. ($C_{13}H_{17}N_2O_5PS \cdot 0.25H_2O$) C, H, N.

**2-Carbamoyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30m).** As a solid. Melting point 185−186 °C. $^1$H NMR (200 MHz, $D_2O$) $\delta$ 0.78 (d, 6H, $J$ = 6.9 Hz), 1.67−1.86 (m, 1H), 3.78 (m, 2H), 6.54 (brs, 2H). Anal. ($C_{12}H_{15}N_2O_5PS$) C, H, N.

**2-Thiocarbamoyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30n).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.03 (d, 6H), 1.94−2.08 (m, 1H), 3.08 (d, 2H), 6.82(m, 1H), 6.95 (m, 1H). Anal. ($C_{12}H_{15}N_2O_4PS_2 \cdot 0.1HBr \cdot 0.3EtOAc$) C, H, N.

**2-Phenyl-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30o).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.03 (d, $J$ = 6.6 Hz, 6H), 1.94−214 (m, 1H), 3.11 (d, $J$ = 7.0 Hz, 2H), 6.93 (m, 1H), 7.12 (m, 1H), 7.47 (m, 3H), 7.96 (m, 2H). Anal. ($C_{17}H_{18}NO_4PS \cdot 1HBr$) C, H, N.

**2-(2-Thienyl)-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30p).** $^1$H NMR (200 MHz, $D_2O$ + NaOD) $\delta$ 0.75 (d, $J$ = 6.6 Hz, 6H), 1.64−1.88 (m, 1H), 2.71 (d, $J$ = 7.2 Hz, 2H), 6.51 (m, 2H), 6.95 (brs, 1H). 7.39 (brs, 1H). Anal. ($C_{15}H_{16}NO_4PS_2 \cdot 0.75H_2O$) C, H, N.

**2-(3-Pyridyl)-5-isobutyl-4-[2-(5-phosphono)furanyl]thiazole (30q).** $^1$H NMR (200 MHz, $D_2O$ + NaOD) $\delta$ 0.72 (brs, 6H), 1.67 (brs, 1H), 2.64 (brs, 2H), 6.52 (m, 2H), 7.25 (brs, 1H), 7.94 (brs, 1H), 8.28 (brs, 1H), 8.65 (brs, 1H). Anal. ($C_{16}H_{17}N_2O_4PS \cdot 3.75HBr$) C, H, N.

**2-Amino-5-methyl-4-[2-(5-phosphono)furanyl]thiazole (31a).** Melting point 200−220 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.44 (s, 3H), 6.65 (m, 1H), 6.95 (m, 1H). Anal. ($C_8H_9N_2O_4PS \cdot 0.65HBr$) C, H, N.

**2-Amino-5-hydroxymethyl-4-[2-(5-phosphono)furanyl]thiazole (31b).** Melting point 167 °C (decomp). $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 4.72 (s, 2H), 5.71 (s, 1H), 6.49 (m, 1H), 6.81 (m, 1H), 7.02 (bs, 2H). Anal. ($C_8H_9N_2O_5PS$) C, H, N.

**2-Amino-5-propyl-4-[2-(5-phosphono)furanyl]thiazole (31c).** Melting point 235−237 °C. $^1$H NMR (200 MHz, $D_2O$) $\delta$ 0.76 (t, 3H, $J$ = 6.6 Hz), 1.38 (m, 2H), 2.72 (t, 2H, $J$ = 6.6 Hz), 6.38 (brs, 1H), 6.55 (brs, 1H). Anal. ($C_{10}H_{13}N_2O_4PS \cdot 0.3H_2O$) C, H, N.

**2-Amino-5-isopropyl-4-[2-(5-phosphono)furanyl]thiazole (31d).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.37 (d, 6H), 3.58−3.78 (m, 1H), 6.84 (m, 1H), 7.10 (m, 1H). Anal. ($C_{10}H_{13}N_2O_4PS \cdot 1HBr$) C, H, N.

**2-Amino-5-(2,2,2-trifluoroethyl)-4-[2-(5-phosphono)furanyl]-thiazole (31e).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 4.01 (q, 2H, $J$ = 7.6 Hz), 6.59 (m, 1H), 6.89 (m, 1H), 7.21 (bs, 2H). Anal. ($C_9H_8N_2F_3O_4PS$) C, H, N.

**2-Amino-5-neopentyl-4-[2-(5-phosphono)furanyl]thiazole (31f).** Melting point 240−241 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.90 (s, 9H), 2.81 (s, 2H), 6.50 (m, 1H), 6.82 (m, 1H), 6.95 (bs, 2H). Anal. ($C_{12}H_{12}N_2O_4PS \cdot 0.2H_2O$) C, H, N.

**2-Amino-5-cyclobutyl-4-[2-(5-phosphono)furanyl]thiazole (31g).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.72−2.42 (m, 6H), 4.01

(m, 1H), 6.48 (m, 1H), 6.85 (m, 1H), 7.05 (bs, 2H). Anal. ($C_{11}H_{13}N_2O_4PS \cdot 0.15HBr \cdot 0.15H_2O$) C, H, N.

**2-Amino-5-cyclopentyl-4-[2-(5-phosphono)furanyl]thiazole (31h).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.32−2.22 (m, 8H), 3.61 (m, 1H), 6.47 (m, 1H), 6.95 (m, 3H). Anal. ($C_{12}H_{15}N_2O_4PS \cdot 0.25HBr \cdot 0.2$acetone) C, H, N.

**2-Amino-5-cyclohexyl-4-[2-(5-phosphono)furanyl]thiazole (31i).** $^1$H NMR (200 MHz, $D_2O$) $\delta$ 1.02−1.79 (m, 10H), 2.94 (m, 1H), 6.32 (m, 1H), 6.52 (m, 1H). Anal. ($C_{13}H_{17}N_2O_4PS \cdot 0.2HBr$) C, H, N.

**2-Amino-5-cyclopropylmethyl-4-[2-(5-phosphono)furanyl]-thiazole (31j).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.21 (m, 2H), 0.43 (m, 2H), 0.97 (m, 1H), 2.81 (d, 2H, $J$ = 6.6 Hz), 6.51 (m, 1H), 6.91 (m, 3H). Anal. ($C_{11}H_{13}N_2O_4PS \cdot 0.2$EtOAc) C, H, N.

**2-Amino-5-cyclopentylmethyl-4-[2-(5-phosphono)furanyl]-thiazole (31k).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.13−2.13 (m, 9H), 2.80 (d, 2H, $J$ = 7.0 Hz), 6.50 (m, 1H), 6.87 (m, 1H), 6.95 (bs, 2H). Anal. ($C_{13}H_{17}N_2O_4PS \cdot 0.2HBr \cdot 0.2H_2O$) C, H, N.

**2-Amino-5-cyclohexylmethyl-4-[2-(5-phosphono)furanyl]-thiazole (31l).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.83−1.73 (m, 11H), 2.78 (d, 2H, $J$ = 7.0 Hz), 6.49 (m, 1H), 6.87 (m, 1H), 6.94 (bs, 2H). Anal. ($C_{14}H_{19}N_2O_4PS \cdot 0.2HBr \cdot 0.5H_2O \cdot 0.1$acetone) C, H, N.

**2-Amino-5-benzyl-4-[2-(5-phosphono)furanyl]thiazole (31m).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 4.23 (s, 2H), 6.52 (m, 1H), 6.89 (m, 1H), 6.98 (bs, 2H), 7.26 (m, 5H). Anal. ($C_{14}H_{13}N_2O_4PS \cdot 1H_2O$) C, H, N.

**2-Amino-5-[(4-morpholinyl)methyl]-4-[2-(5-phosphono)furanyl]-thiazole dihydrobromide (31n).** $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 3.37−4.04 (m, 8H), 4.82 (s, 2H), 7.18 (m, 2H). Anal. ($C_{12}H_{18}Br_2N_3O_5PS \cdot 0.25HBr$) C, H, N.

**2-Amino-5-chloro-4-[2-(5-phosphono)furanyl]thiazole (32a).** Melting point > 250 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.81 (m, 1H), 6.99 (m, 1H), 7,55 (bs, 2H). Anal. ($C_7H_6N_2O_4PSCl$) C, H, N.

**2-Amino-5-bromo-4-[2-(5-phosphono)furanyl]thiazole (32b).** Melting point 224 °C (decomp). $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.83 (m, 1H), 6.92 (m, 1H), 7.43 (bs, 2H). Anal. ($C_7H_6N_2O_4PSBr$) C, H, N.

**2-Amino-5-iodo-4-[2-(5-phosphono)furanyl]thiazole (32c).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.65 (m, 1H), 6.91(m, 3H). Anal. ($C_7H_6N_2O_4PSI$) C, H, N.

**2-Amino-5-(*N*-morpholinyl)-4-[2-(5-phosphono)furanyl]thiazole (32d).** Melting point 215−220 °C. $^1$H NMR (200 MHz, $D_2O$) $\delta$ 2.78 (m, 4H), 3.74 (m, 4H), 6.52 (m, 1H), 6.62 (m, 1H). Anal. ($C_{11}H_{14}N_3O_5PS \cdot 0.45CH_2Cl_2$) C, H, N.

**2-Amino-5-ethylthio-4-[2-(5-phosphono)furanyl]thiazole (32e).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.15 (t, 3H, $J$ = 7.4 Hz), 2.73 (q, 2H, $J$ = 7.4 Hz), 6.91 (bs, 2H), 6.95 (m, 1H), 7.39 (m, 1H). Anal. ($C_9H_{11}N_2O_4PS_2 \cdot 0.45HBr$) C, H, N.

**2-Amino-5-isopropylthio-4-[2-(5-phosphono)furanyl]thiazole hydrobromide (32g).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.18 (d, 6H, $J$ = 6.6 Hz), 3.18 (m, 1H), 4.34 (bs, 2H), 6.92 (m, 1H), 7.02 (m, 1H). Anal. ($C_{10}H_{14}N_2O_4PS_2Br$) C, H, N.

**2-Amino-5-*tert*-butylthio-4-[2-(5-phosphono)furanyl]thiazole (32h).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.25 (s, 9H), 6.85 (m, 1H), 7.12 (m, 1H), 7.41 (bs, 2H). Anal. ($C_{11}H_{15}N_2O_4PS_2 \cdot 0.6CH_2Cl_2$) C, H, N.

**2-Amino-5-phenylthio-4-[2-(5-phosphono)furanyl]thiazole (32i).** Melting point 157 °C (decomp). $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.86 (m, 1H), 7.18−7.39 (m, 6H), 7.65 (bs, 2H). Anal. ($C_{13}H_{11}N_2O_4PS_2$) C, H, N.

**2-Amino-5-[(*N*,*N*-dimethyl)carbamoyl]-4-[2-(5-phosphono)-furanyl]thiazole (32j).** $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.06 (s, 6H), 5.81 (bs, 2H), 6.58 (m, 1H), 6.92 (m, 1H). Anal. ($C_{10}H_{14}N_3O_5PS \cdot 1.3HBr \cdot 1H_2O \cdot 0.3$acetone) C, H, N.

**2-Amino-5-benzyloxycarbonyl-4-[2-(5-phosphono)furanyl]-thiazole (32l).** Melting point 248 °C (decomp). $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 5.22 (s, 2H), 6.94 (m, 1H), 7.36 (m, 5H), 7.54 (m, 1H), 8.02 (bs, 2H). Anal. ($C_{10}H_{14}N_3O_5PS \cdot 0.2H_2O$) C, H, N.

**2-Amino-5-(2-methoxyphenyl)-4-[2-(5-phosphono)furanyl]-thiazole (33b).** Melting point 198−202 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 3.65 (s, 3H), 6.01 (m, 1H), 6.74 (m, 1H), 6.90−7.40 (m, 6H). Anal. ($C_{14}H_{13}N_2O_5PS \cdot 0.24HBr$) C, H, N.

**2-Amino-5-(3-methoxyphenyl)-4-[2-(5-phosphono)furanyl]-thiazole (33c).** Melting point 188−195 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 3.71 (s, 3H), 6.31 (m, 1H), 6.80−7.30 (m, 7H). Anal. ($C_{14}H_{13}N_2O_5PS \cdot 0.4HBr$) C, H, N.

**2-Amino-5-(4-methoxyphenyl)-4-[2-(5-phosphono)furanyl]-thiazole (33d).** Melting point 190−210 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 3.78 (s, 3H), 6.21 (m, 1H), 6.79 (m, 1H), 6.84−7.31 (m, 6H). Anal. ($C_{14}H_{13}N_2O_5PS \cdot 1.1H_2O$) C, H, N.

**2-Amino-5-(4-methylthiophenyl)-4-[2-(5-phosphono)furanyl]-thiazole (33e).** Melting point 204−206 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.45 (s, 3H), 6.31 (m, 1H), 6.81 (m, 1H), 7.20−7.32 (m, 6H). Anal. ($C_{14}H_{13}N_2O_4PS_2 \cdot 1H_2O$) C, H, N.

**2-Amino-5-(4-*tert*-butylphenyl)-4-[2-(5-phosphono)furanyl]-thiazole (33f).** Melting point 201−204 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 1.25 (s, 9H), 6.26 (m, 1H), 6.81 (m, 1H), 7.20−7.40 (m, 6H). Anal. ($C_{17}H_{19}N_2O_4PS \cdot 0.3HBr$) C, H, N.

**2-Amino-5-(4-methoxycarbonylphenyl)-4-[2-(5-phosphono)-furanyl]thiazole (33g).** Melting point 190−210 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 3.82 (s, 3H), 6.46 (m, 1H), 6.84 (m, 1H), 7.40−7.98 (m, 6H). Anal. ($C_{15}H_{13}N_2O_6PS \cdot 0.2HBr$) C, H, N.

**2-Amino-5-(4-fluorophenyl)-4-[2-(5-phosphono)furanyl]thiazole (33h).** Melting point 211−213 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.30 (m, 1H), 6.81 (m, 1H) 7.12−7.40 (m, 6H). Anal. ($C_{13}H_{10}N_2O_4PSF \cdot 0.5H_2O$) C, H, N.

**2-Amino-5-(4-chlorophenyl)-4-[2-(5-phosphono)furanyl]thiazole (33i).** Melting point 204−208 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.39 (m, 1H), 6.81 (m, 1H), 7.22−7.40 (m, 6H). Anal. ($C_{11}H_9N_2O_5PS \cdot 0.6H_2O$) C, H, N.

**2-Amino-5-(4-acetylphenyl)-4-[2-(5-phosphono)furanyl]thiazole (33j).** Melting point 193−195 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 2.52 (s, 3H), 6.45 (m, 1H), 6.84 (m, 1H), 7.40−7.98 (m, 6H). Anal. ($C_{15}H_{13}N_2O_5PS$) C, H, N.

**2-Amino-5-(4-methanesulfonyl)-4-[2-(5-phosphono)furanyl]thiazole (33k).** Melting point 220−225 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 3.20 (s, 3H), 6.50 (m, 1H), 6.84 (m, 1H), 7.40- 7.86 (m, 6H). Anal. ($C_{14}H_{13}N_2O_6PS_2 \cdot 0.65H_2O$) C, H, N.

**2-Amino-5-(4-phenylphenyl)-4-[2-(5-phosphono)furanyl]thiazole (33l).** Melting point 201−210 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.40 (m, 1H), 6.82 (m, 1H), 7.22 (m, 1H), 7.40−7.68 (m, 11H). Anal. ($C_{19}H_{15}N_2O_4PS \cdot 0.15HBr$) C, H, N.

**2-Amino-5-(2-naphthyl)-4-[2-(5-phosphono)furanyl]thiazole (33m).** Melting point 205−212 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.36 (m, 1H), 6.81 (m, 1H), 7.29 (bs, 2H), 7.40−7.98 (m, 7H). Anal. ($C_{17}H_{13}N_2O_4PS \cdot 0.6HBr \cdot 0.7$acetone) C, H, N.

**2-Amino-5-(2-furanyl)-4-[2-(5-phosphono)furanyl]thiazole (33n).** Melting point 190−210 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 6.56 (m, 1H), 6.64 (m, 1H), 6.93 (m, 1H), 7.02 (m, 1H), 7.40 (brs, 2H), 7.68 (s, 1H). Anal. ($C_{11}H_9N_2O_5PS \cdot 0.25HBr$) C, H, N.

**2-Amino-5-(2-thienyl)-4-[2-(5-phosphono)furanyl]thiazole (33o).** $^1$H NMR (200 MHz, $D_2O$) $\delta$ 6.20 (m, 1H), 6.40 (m, 1H), 6.93 (m, 1H), 7.04 (m, 1H), 7.30 (d, 1H). Anal. ($C_{11}H_9N_2O_4PS_2 \cdot 0.3$EtOAc $\cdot 0.11HBr$) C, H, N.

**2-Amino-5-phenyl-4-[3-(1-phosphono)pyrrolyl]thiazole (34b).** Melting point > 200 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.0 (s, 1H), 7.4 (m, 5H), 6.79 (s, 1H), 5.60 (s, 1H). LC-MS $m/z$ = 322.3 $[C_{13}H_{12}N_3O_3PS + H]^+$. Anal. ($C_{13}H_{12}N_3O_3PS \cdot 1.3H_2O$) C, H, N.

**2-Amino-5-phenyl-4-[2-(5-methyl-4-phosphono)oxazolyl]-thiazole (34c).** Melting point 190 °C (decomp). $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 2.39 (s, 3H), 7.39 (m, 5H). Anal. ($C_{13}H_{12}N_3O_4PS \cdot 1H_2O$) C, H, N.

**2-Amino-5-propyl-4-phosphonomethoxycarbonylthiazole (34d).** Melting point 134 °C (decomp). $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.88 (t, 3H, $J$ = 7.4 Hz), 1.54 (m, 2H), 2.98 (t, 2H, $J$ = 7.4 Hz), 4.25 (d, 2H, $J$ = 8.8 Hz), 7.02 (bs, 2H). Anal. ($C_8H_{13}N_2O_5PS$) C, H, N.

**2-Amino-5-(2-thienyl)-4-[(*N*-phosphonomethyl)carbamoyl]-thiazole (34e).** Melting point 245 °C (decomp). $^1$H NMR (200 MHz, $D_2O$) $\delta$ 3.18 (d, 2H, $J$ = 13 Hz), 6.90 (m, 1H), 7.09 (m, 1H), 7.31 (m, 1H). Anal. ($C_9H_{10}N_3O_4PS_2 \cdot 1HBr \cdot 0.1EtOAc$) C, H, N.

**2-Amino-4-[2-(6-phosphono)pyridyl]thiazole (34f).** $^1$H NMR (200 MHz, $D_2O$) $\delta$ 7.09−8.40 (m, 4H). Anal. ($C_8H_9N_3O_3PS_2 \cdot 1HBr$) C, H, N.

**2-Amino-4-[1-(3-phosphono)phenyl]thiazole (34g).** Melting point 210−214 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.19−8.04 (m, 7H). Anal. ($C_9H_9N_2O_3PS \cdot 0.8HBr \cdot 0.4CH_2Cl_2$) C, H, N.

**2-Amino-5-propyl-4-[1-(3-phosphono)phenyl]thiazole (34h).** Melting point > 220 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.92 (t, 3H, $J$ = 7.4 Hz), 1.57 (m, 2H, $J$ = 7.4 Hz), 2.69 (t, 2H, $J$ = 7.4 Hz), 6.92 (bs, 2H), 7.42−7.93 (m, 4H). Anal. ($C_{12}H_{15}N_2O_3PS \cdot 0.09H_2O$) C, H, N.

**2-Amino-5-propyl- 4-[1-(4-methyl-3-phosphono)phenyl]thiazole (34i).** Melting point > 220 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 0.89 (t, 3H, $J$ = 7.0 Hz), 1.5 (m, 2H), 2.49 (s, 3H), 2.65 (t, 2H, $J$ = 7.0 Hz), 6.96 (bs, 2H), 7.25−8.00 (m, 3H). Anal. ($C_{13}H_{17}N_2O_3PS \cdot 0.3H_2O$) C, H, N.

**2-Amino-5-isopropyl- 4-[1-(4-methoxy-3-phosphono)phenyl]-thiazole (34j).** Melting point > 220 °C. $^1$H NMR (200 MHz, $D_2O$) $\delta$ 1.18 (d, 6H, $J$ = 7.0 Hz), 3.18 (m, 1H), 3.81 (s, 3H), 7.02−7.85 (m, 3H). Anal. ($C_{13}H_{17}N_2O_4PS$) C, H, N.

**2-Amino-5-phenyl- 4-[1-(4-fluoro-3-phosphono)phenyl]thiazole (34k).** Melting point > 220 °C. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.01−7.99 (m, 10H). Anal. ($C_{15}H_{12}N_2O_3PSF \cdot 0.09HBr$) C, H, N.

**2-Amino-4-[2-(5-phosphono)furanyl]-5-(propane-1-sulfinyl)-thiazole (32m).** A solution of **32f**[10] (100 mg, 0.3 mmol) in MeOH (10 mL) was treated with *m*CPBA (70 mg, 0.3 mmol), and the reaction mixture was heated to 50 °C. After stirring for 5 h, the cooled reaction solution was evaporated in vauuo and the residue was treated with water (5 mL). The resulting white solid was removed by filtration, and the filtrate was concentrated to give a yellow oil, which was purified by HPLC using a 10−70% acetonitrile gradient containing 0.05% TFA. The pure fractions were combined and lyophilized to give **32m** (50 mg, 50%) as a white solid. Melting point 120 °C (decomp). $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 1.08 (t, 3H, $J$ = 7.0 Hz), 1.79 (m, 2H), 3.15 (m, 2H), 6.89 (m, 1H), 7.08 (m, 1H). Anal. ($C_{10}H_{13}N_2O_5PS_2 \cdot 0.2H_2O \cdot 1TFA$) C, H, N.

**2-Amino-4-{2-[5-bis(1-(1-ethoxycarbonyloxy)ethyl)phosphono]-furanyl}-5-isobutyl-thiazole (35b).** A suspension of **30j** (284 mg, 0.94 mmol) in anhydrous DMPU (5 mL) was treated with TEA (254 mg, 2.5 mmol) and 1-(1-ethoxycarbonyloxy)-iodoethane (500 mg, 2.0 mmol) at room temperature under nitrogen. After 24 h, the reaction solution was evaporated to dryness and the residue was purified by flash chromatography ($SiO_2$, 3 cm × 15 cm, 65−100% EtOAc−hexane, gradient elution) to give **35b** as a yellow solid (160 mg, 32%). Melting point 76−78 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.25 (m, 1H), 6.62 (m, 1H), 6.45 (m, 2H), 5.19 (bs, 2H), 4.08 (m, 4H), 2.81 (d, 2H, $J$ = 7.1 Hz), 1.85 (m, 1H), 1.63 (d, 6H, $J$ = 7.0 Hz), 1.19 (m, 6H), 0.97 (d, 6H, $J$ = 7.1 Hz). Anal. ($C_{21}H_{31}N_2O_{10}PS$) C, H, N.

**2-Amino-4-{2-[5-bis(phenoxycarbonyloxymethyl)phosphono]-furanyl}-5-isobutyl-thiazole (35c).** This compound was prepared in a similar manner as compound **35b** from thiazole **30j**. $^1$H NMR ($CDCl_3$): $\delta$ 7.40−7.11 (m, 12H), 5.89 (d, 4H, $J$ = 14 Hz), 5.10 (bs, 2H), 2.81 (d, 2H, $J$ = 6.8 Hz), 1.81 (m, 1H), 0.93 (m, 6H). Anal. ($C_{27}H_{27}N_2O_{10}PS$) C, H, N.

**2-Amino-4-{2-[5-bis(ethoxycarbonyloxymethyl)phosphono]-furanyl}-5-isobutyl-thiazole (35d).** This compound was prepared in a similar manner as compound **35b** from thiazole **30j**. $^1$H NMR ($CDCl_3$): $\delta$ 7.21 (m, 1H), 6.61 (m, 1H), 5.75 (d, 4H, $J$ = 13.2 Hz), 5.59 (bs, 2H), 4.20 (q, 4H, $J$ = 7.4 Hz), 2.79 (d, 2H, $J$ = 6.6 Hz), 1.89 (m, 1H), 1.275 (t, 6H, $J$ = 7.4 Hz), 0.97 (d, 6H, $J$ = 6.6 Hz). Anal. ($C_{19}H_{27}N_2O_{10}PS$) C, H, N.

**2-Amino-4-[2-(5-bis(*p*-acetoxybenzyl)phosphono)furanyl]-5-isobutylthiazole (35f).** A suspension **30j** (302 mg, 1 mmol) in anhydrous 1,2-dichloroethane (5 mL) was treated with thionyl chloride (816 mg, 6.85 mmol) followed by anhydrous pyridine (49 mg, 0.62 mmol). The resulting mixture was heated to reflux for 2 h, cooled, and evaporated to dryness. The residue was treated with a solution of 4-acetoxybenzyl alcohol (665 mg, 4 mmol) and *N*,*N*-diisopropylethylamine (1 mL, 6 mmol) in anhydrous $CH_2Cl_2$ (5 mL) at room temperature. After stirring at room temperature for 12 h, the reaction was quenched with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The organics were combined, dried ($MgSO_4$), and evaporated, and the resulting residue purified by flash chromatography ($SiO_2$, 1 cm × 15 cm, 65−100% EtOAc−hexane, gradient elution) to give **35f** as a brown foam (60 mg, 10%). $^1$H NMR ($CDCl_3$): $\delta$ 7.34 (d, 2H, $J$ = 8.7 Hz), 7.14 (m, 1H), 7.05 (d, 2H, $J$ = 9.0 Hz), 6.58 (m, 1H), 5.70 (bs, 2H), 5.16−5.01 (m, 4H), 2.72 (d, 2H, $J$ = 6.9 Hz), 2.29 (s, 6H), 1.81 (m, 1H), 0.91 (m, 6H). $[MH]^+$ calcd for $C_{29}H_{31}N_2O_8PS$ 599; found 599. Anal. ($C_{29}H_{31}N_2O_8PS$) C, H, N.

**2-Amino-4-[2-(5-diphenylphosphono)furanyl]-5-isobutylthiazole (35g).** This compound was prepared in a similar manner as compound **35f** from thiazole **30j** (500 mg, 1.65 mmol) to give **35g** as a light-yellow solid (120 mg, 16%). Melting point 128−129 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.38−7.18 (m, 11H), 6.63 (m, 1H), 5.51 (bs, 2H), 2.79 (d, 2H, $J$ = 6.6 Hz), 1.83 (m, 1H), 0.97 (d, 6H, $J$ = 6.6 Hz). Anal. ($C_{23}H_{23}N_2O_4PS$) C, H, N.

**2-Amino-4-[2-(5-(1-(3-bromophenyl)-1,3-propyl)phosphono)-furanyl]-5-isobutyl-thiazole (35h).** A suspension **30j** (420 mg, 1.5 mmol) in anhydrous dichloromethane (10 mL) was treated with thionyl chloride (10 mL, 137 mmol). The resulting mixture was then heated to reflux. After 1.5 h, the reaction solution was cooled and evaporated to dryness and the residue was treated with a solution of 1-(3-chlorophenyl)propane-1,3-diol (252 mg, 1.35 mmol) and anhydrous pyridine (0.35 mL) in anhydrous $CH_2Cl_2$ (10 mL). After stirring at room temperature for 12 h, the reaction was quenched with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The organics were combined, dried ($MgSO_4$), and evaporated, and the resulting residue was purified by flash chromatography ($SiO_2$, 1 cm × 15 cm, 1, 2, and 3% methanol−$CH_2Cl_2$, gradient elution) to give **35h** as a yellow gum (170 mg, 25%). $^1$H NMR ($CDCl_3$): $\delta$ 7.41−7.20 (m, 5H), 6.71 (m, 1H), 5.78 (m, 1H), 5.13 (bs, 2H), 4.90−4.40 (m, 2H), 2.82 (d, 2H, $J$ = 6.7 Hz), 2.60−1.79 (m, 3H), 0.99 (d, 6H, $J$ = 6.7 Hz). Anal. ($C_{20}H_{22}N_2O_4PSCl \cdot 0.25H_2O$) C, H, N.

**2-Amino-4-{2-[5-(1-(4-pyridyl)-1,3-propyl)phosphono]furanyl}-5-isobutylthiazole (35i).** This compound was prepared in a similar manner as compound **35h** from thiazole **30j** (500 mg, 1.65 mmol) to give **35i** as a light-yellow solid (120 mg, 16%). Melting point 101−106 °C. $^1$H NMR ($CDCl_3$): $\delta$ 8.69 (m, 2H), 7.39 (m, 2H), 7.22 (m, 1H), 6.66 (m, 1H), 5.62 (m, 1H), 5.21 (bs, 2H), 4.65 (m, 2H), 2.81 (d, 2H, $J$ = 6.6 Hz), 2.38 (m, 2H), 1.88 (m, 1H), 0.91 (d, 6H, $J$ = 6.6 Hz). Anal. ($C_{19}H_{22}N_3O_4PS \cdot 1.25H_2O$) C, H, N.

**2-Amino-4-[2-(5-monophenylphosphono)furanyl]-5-isobutyl-thiazole (35j).** A solution of **35g** (1.8 g, 3.96 mmol) in acetonitrile (60 mL) and water (15 mL) was treated with lithium hydroxide (1 N, 5.9 mL) at room temperature. After 4 h, the reaction solution was concentrated under vacuum and diluted with water (80 mL). The pH of the resulting solution was adjusted to 4 by addition of 6 N HCl. The resulting white solid was collected through filtration (washed with water, 3 × 10 mL) and dried under vacuum to give **35j** as a white solid (1.4 g, 93%). Melting point 256 °C (decomp). $^1$H NMR (DMSO-$d_6$): $\delta$ 7.31−7.01 (m, 6H), 6.59 (m, 1H), 5.80 (bs, 2H), 2.75 (d, 2H, $J$ = 6.6 Hz), 1.73 (m, 1H), 0.82 (d, 6H, $J$ = 6.6 Hz). Anal. ($C_{17}H_{19}N_2O_4PS$) C, H, N.

**2-Amino-4-[2-(5-(*O*-phenyl)-(*N*-((*S*)-1-ethoxycarbonyl)ethyl)-phosphonamido)-furanyl]-5-isobutylthiazole (35l).** A suspension of **30j** (302 mg, 1 mmol) in anhydrous 1,2-dichloroethane (5 mL) was treated with thionyl chloride (815 mg, 6.85 mmol), followed by anhydrous pyridine (49 mg, 0.62 mmol). After refluxing for 2 h, the reaction mixture was cooled and evaporated to dryness. The resulting residue was dissolved in anhydrous $CH_2Cl_2$ (2 mL),

cooled to 0 °C, and treated with a solution of phenol (1 mmol). After stirring at room temperature for 1 h, the reaction was treated with a solution of L-alanine ethyl ester hydrogen chloride salt and *N*,*N*-diisopropylethylamine (0.5 mL) in anhydrous $CH_2Cl_2$ (2 mL) and stirred an additional 12 h at room temperature. The reaction was then quenched with saturated $NaHCO_3$ (20 mL) and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography ($SiO_2$, 1 cm × 15 cm, 65−100% EtOAc−hexane, gradient elution) to give **35l** as a yellow gum (125 mg, 26%). $^1$H NMR ($CDCl_3$): $\delta$ 7.24−7.03 (m, 6H), 6.55 (m, 1H), 4.93 (bs, 2H), 4.15−4.01 (m, 3H), 3.77 (q, 1H,, $J$ = 10.2 Hz), 2.77 (d, 2H, $J$ = 6.9 Hz), 1.81 (m, 1H), 1.33−0.89 (m, 12H). $[MH]^+$ calcd for $C_{22}H_{28}N_3O_5PS$ 478; found 478. Anal. ($C_{22}H_{28}N_3O_5PS$) C, H, N.

**2-Amino-4-[2-(5-monophenyl-monoamino-phosphono)furanyl]-5-isobutylthiazole (35k).** This compound was prepared in a similar manner as compound **35l** from thiazole **30j**. Melting point 205 °C (decomp). $^1$H NMR (200 MHz, DMSO-$d_6$): $\delta$ 7.39−6.98 (m, 6H), 6.53 (m, 1H), 5.41 (d, 2H, $J$ = 7.6 Hz), 3.31 (bs, 2H), 2.78 (d, 2H, $J$ = 6.6 Hz), 1.73 (m, 1H), 0.92 (d, 6H, $J$ = 6.6 Hz). Anal. ($C_{17}H_{20}N_3O_3PS \cdot 0.3H_2O \cdot 0.3HCl$) C, H, N.

**Biological Methods.** FBPase enzyme assay, oral bioavailability determination, and glucose lowering in Sprague−Dawley rats and Zucker Diabetic rats assays were carried out as previously reported.[3,6,10,19,20]

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**Supporting Information Available:** Experimental procedures for the preparation of compounds **7**−**12**, **27**−**28**, and elemental analysis data for all final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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