7′-Substituted Benzothiazolothio- and Pyridinothiazolothio-Purines as Potent Heat Shock Protein 90 Inhibitors

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We report on the discovery of benzo- and pyridino- thiazolothiopurines as potent heat shock protein 90 inhibitors. The benzothiazole moiety is exceptionally sensitive to substitutions on the aromatic ring with a 7′-substituent essential for activity. Some of these compounds exhibit low nanomolar inhibition activity in a Her-2 degradation assay (28−150 nM), good aqueous solubility, and oral bioavailability profiles in mice. In vivo efficacy experiments demonstrate that compounds of this class inhibit tumor growth in an N87 human colon cancer xenograft model via oral administration as shown with compound **37** (8-(7-chloro-benzothiazol-2-ylsulfanyl)-9-(2-cyclopropylamino-ethyl)-*9H*- purin-6-ylamine).

Introduction

Heat shock protein 90 (Hsp90) is an attractive molecular target because of its importance in regulating biological mechanisms such as cell signaling, proliferation, and survival. These mechanistic features provide a rationale for exploring the therapeutic utility of Hsp90 inhibition for treating a multitude of diseases including cancer,[1] inflammation,[2] neurodegeneration,[3] and cardiac ischemia.[4] Hsp90 performs a key function by maintaining the proper folding conformation of various "client proteins", and inhibition of Hsp90 results in misfolded client proteins which are then rapidly degraded by the proteasome. The Hsp90 clients are comprised of signaling proteins such as kinases, nuclear receptors, and growth factor receptors. Among the more notable clients are clinically validated cancer targets such as estrogen and androgen receptors, HER-2, AKT, Raf-1, and the fusion oncoprotein Bcr-Abl. Since Hsp90 inhibitors simultaneously deplete tumor cells of different oncogenes, it is believed that tumors will be less likely to acquire resistance to Hsp90-targeting drugs. Also, with the recent discovery of an activated form of Hsp90 in cancer cells, it should be possible to design inhibitors which are highly selective for tumor tissues, thereby increasing their safety profile.[5]

1 (geldanamycin,[6] Chart 1), isolated from the microorganism *Streptomyces hygroscopicus*, was identified as the first potent Hsp90 inhibitor.[7,8] Numerous semisynthetic ansamycins were prepared and have demonstrated more or less similar biological activities, with **2** (17-allylamino geldanamycin,[9] Chart 1) being among the most promising druglike molecules. **2** is now the subject of intensive clinical studies for its use as a potential anticancer agent.[10,11] Later, **3** (radicicol,[12] Chart 1), another natural product-derived Hsp90 inhibitor, was identified which showed potent anticancer activity. Only recently have investigators reported on novel nonnatural product-based small molecule Hsp90 inhibitors, including **4** (PU3[13−15]), **5** (11v[16]), and **6** (CCT018159[17]), shown in Chart 1. These compounds bind to the ATP site of Hsp90, as shown by X-ray crystallographic data,[18] and show activity against tumor cells. To realize the full potential of small molecule Hsp90 inhibitors, we[19] and others[14] focused on further optimizing the purine pharmacophore for increased solubility, potency, and oral bioavailability. The efforts reported so far have centered on compounds in which the adenine is linked to a polysubstituted phenyl group via a sulfide or methylene bridge. We now report that replacement of the phenyl group with an appropriately substituted benzothiazole or pyridinothiazole group provides a new and potent series of compounds. The benzothiazole and pyridinothiazole ring residues are believed to reside in the phosphate-binding region of the ATP site and replace the previously reported benzyl ring moiety.[14,15,17,20] The most active representatives, **24**, **27**, **29**, and **36** (IC_{50} = 28−35 nM) show potencies approaching that of **2** (IC_{50} = 15 nM) in a HER-2 degradation assay. Moreover, compound **37** shows statistically significant inhibition of tumor growth in a mouse xenograft model of human cancer via oral administration.

Chemistry

The Hsp90 inhibitor analogues **7**−**30** were prepared using the three-step general procedure outlined in Scheme 1. Alkylation of adenine with the appropriate alkyl halide in the presence of Cs_2CO_3 in DMF gave predominantly the N-9-substituted isomer **40**−**48**.[21,22] Bromination[23] of the purines followed by coupling with substituted benzothiazole-2-thiols (**64**−**68**, **73**, **77**−**78**) in the presence of *t*-BuOK in DMF at elevated temperature provided the final products (**7**−**30**).[24]

The acetoxypropyl intermediate **46** could be prepared either by alkylation of adenine with $AcO-(CH_2)_3-Cl$ (Scheme 1) or by constructing the adenine ring as described by Howson et al.[25] (Scheme 2). Thus, 5-amino-4,6-dichloropyrimidine was treated with 3-aminopropanol to give the diamino-substituted pyrimidine **58**. Cyclization of **58** with triethylorthoformate in acetic anhydride gave 6-chloropurine **59** which was further reacted with ammonia in MeOH to give, without purification, the 9-substituted adenine **60**. Acylation of **60** with acetic anhydride in the presence of DMAP and pyridine afforded the protected alcohol **46** whose NMR spectrum was identical to that of compound **46** obtained via Scheme 1. This unequivocally

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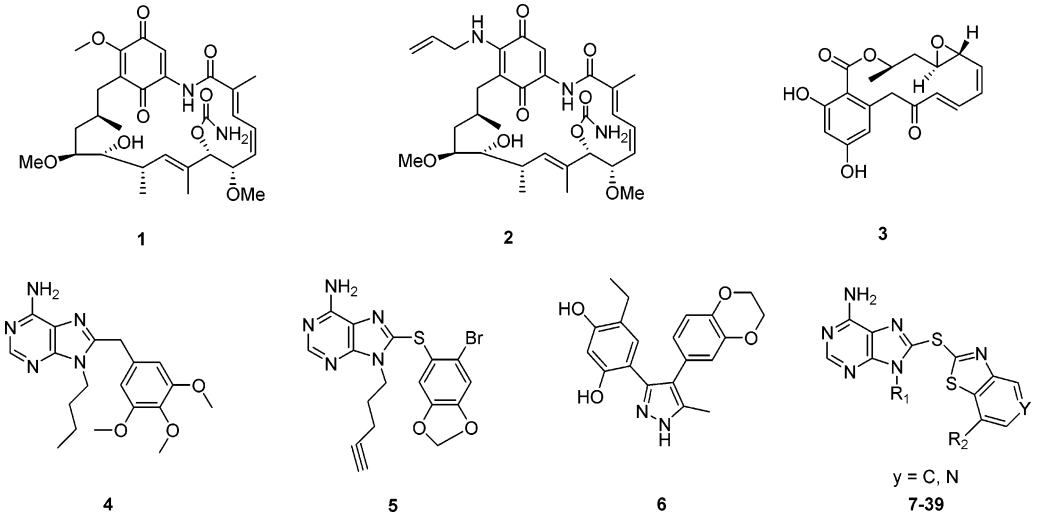
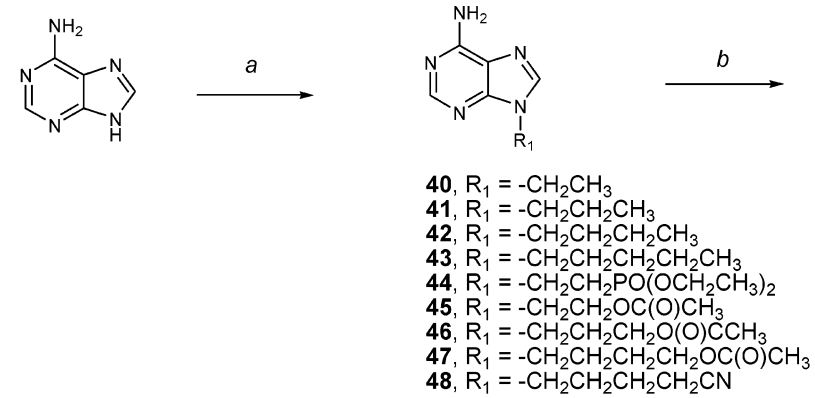
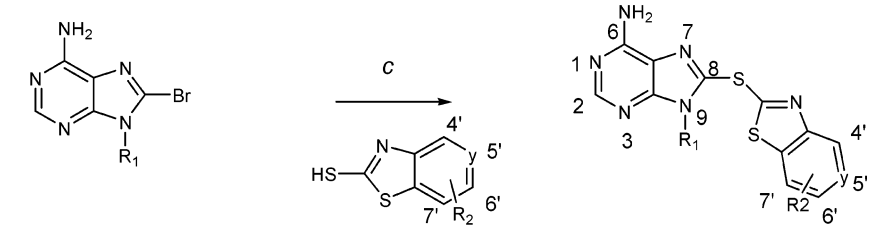
Chart 1. Hsp90 Inhibitors



Scheme 1[a]





49, $R_1 = -CH_2CH_3$
50, $R_1 = -CH_2CH_2CH_3$
51, $R_1 = -CH_2CH_2CH_2CH_3$
52, $R_1 = -CH_2CH_2CH_2CH_2CH_3$
53, $R_1 = -CH_2CH_2PO(OCH_2CH_3)_2$
54, $R_1 = -CH_2CH_2OC(O)CH_3$
55, $R_1 = -CH_2CH_2CH_2OC(O)CH_3$
56, $R_1 = -CH_2CH_2CH_2CH_2OC(O)CH_3$
57, $R_1 = -CH_2CH_2CH_2CH_2CN$

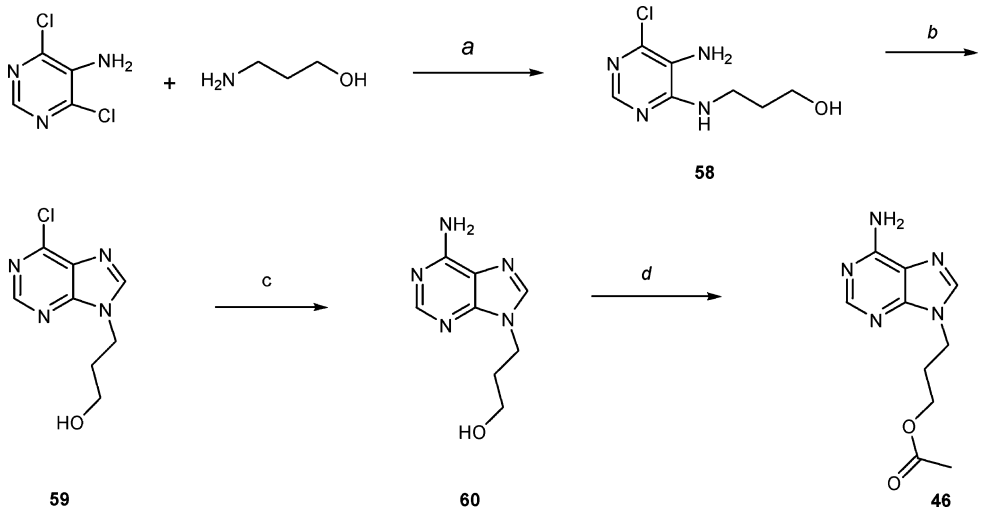
[a] Reagents and conditions: (a) R_1X, Cs_2CO_3, DMF, room temperature −70 °C; (b) Br_2, buffer; (c) *t*-BuOK, DMF, 80−150 °C.

established that the alkylation of the purine in this step occurred predominantly at the 9-position.

Further modification of the 9-alkyl side chain is shown in Scheme 3. The 9-alkyl esters **21**−**23** were hydrolyzed by treatment with NH_3 in MeOH to form the 9-alkylhydroxypurines **31**−**33**. Compounds **31** and **32** were treated with MsCl in DMF, and the resulting crude mesylates **79** and **80** were reacted with appropriate amines to give compounds **34**−**39**.

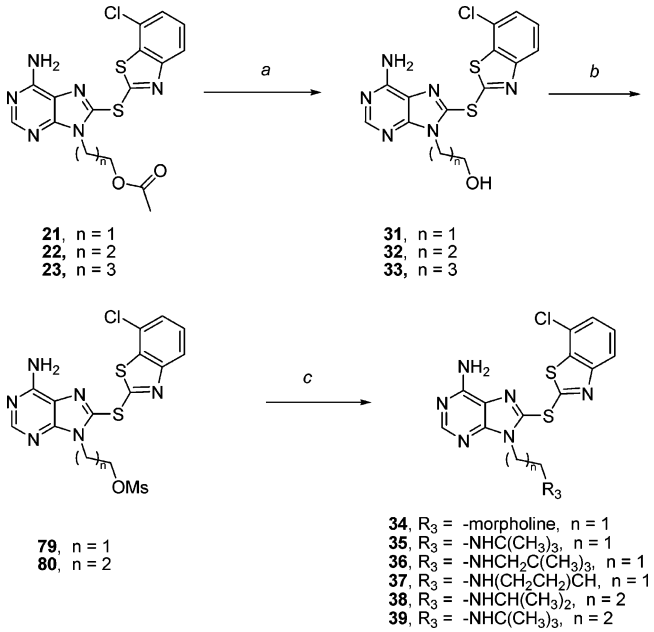
Preparation of Substituted Benzothiazole-2-thiols and Thiazolopyridine-2-thiols. Benzothiazole-2-thiols were obtained by three different synthetic approaches as depicted in Schemes 4−6. These synthetic routes are robust in our hands and amenable for gram-scale preparations. The key reaction in all three routes involved the condensation of 2-haloanilines with the potassium salt of ethyl xanthic acid to give benzothiazole-2-thiols. Reduction of 2-bromo-3-nitrotoluene (Scheme 4) with Fe in EtOH to provided the 2-bromoaniline **61**, which was heated with $EtOCS_2K$ to give the benzothiazole **64**. Alternatively, 2-amino-3-nitrophenol (Scheme 5) was alkylated with MeI or EtI to result in ethers **62a** and **63a**. The amino group was replaced by a Br atom via the Sandmeyer reaction, and the nitro group was reduced with Fe in EtOH to give **62c** and **63c**.

Scheme 2[a]



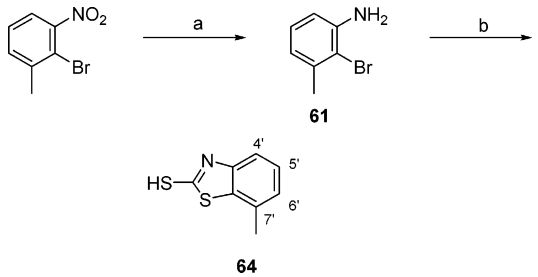
[a] Reagents and conditions: (a) EtOH, reflux 1 h; (b) $HC(OEt)_3$, $(CH_3CO)_2O$, reflux 3 h; (c) NH_3·MeOH, 120 °C; (d) pyridine, DMAP, $(CH_3CO)_2O$, CH_2Cl_2.

Scheme 3[a]



[a] Reagents and conditions: (a) NH_3·MeOH, room temperature, overnight; (b) MsCl, Et_3N, DMF, 0 °C to room temperature; (c) amine, room temperature, overnight.

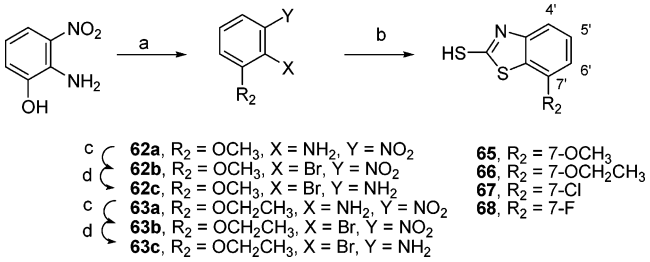
Scheme 4[a]



[a] Reagents and conditions: (a) Fe, EtOH, H^+; (b) CH_3CH_2OCSSK, DMF, 160 °C, 4 h.

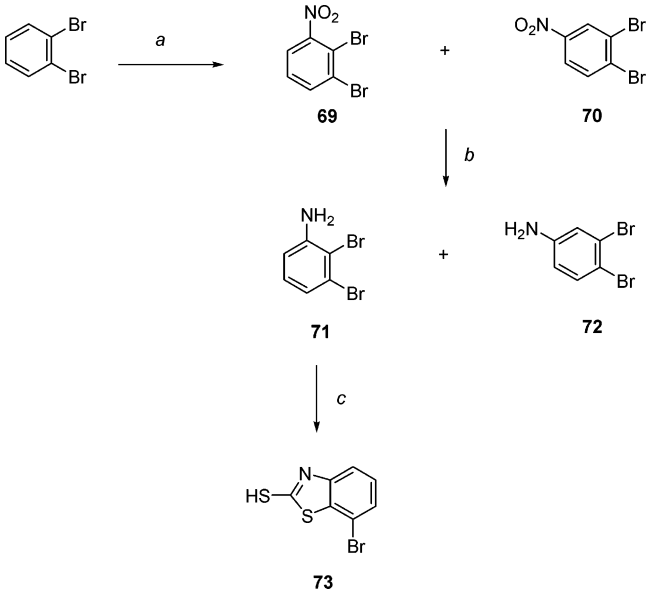
Cyclization with $EtOCS_2K$ provided the benzothiazoles **65** and **66**. In a third route (Scheme 6), nitration of 1,2-dibromobenzene with HNO_3 in H_2SO_4 gave a mixture of two regioisomers, **69** and **70**, followed by reduction with Fe in EtOH to a mixture of

Scheme 5[a]



[a] Reagents and conditions: (a) RI, K_2CO_3, DMF; (b) CH_3CH_2OCSSK, DMF, 160 °C, 4 h; (c) $NaNO_2$, H^+, CuBr; (d) Fe, EtOH, H^+.

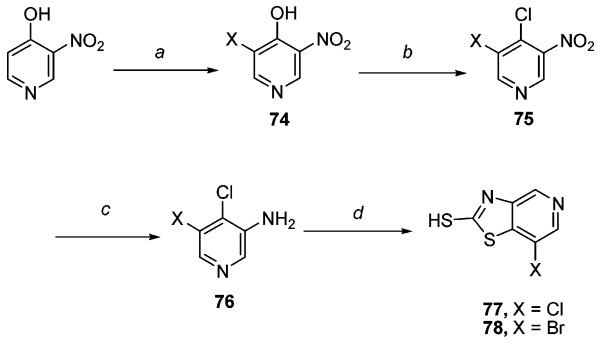
Scheme 6[a]



[a] Reagents and conditions: (a) HNO_3/H_2SO_4; (b) Fe, EtOH, HCl; (c) CH_3CH_2OCSSK, DMF, 160 °C, 4 h.

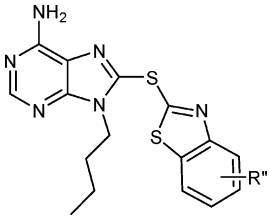
the anilines **71** and **72**, which was treated with $EtOCS_2K$ in DMF at 160 °C for 4 h. Only the desired 2-bromoaniline **71** could undergo cyclization to give, after crystallization, the benzothiazole-2-thiole **73** in 91% yield, while the 3-bromoaniline remained unreacted in solution. The 7-chloro- and 7-fluorobenzothiazole-2-thiole, **67** and **68**, were made directly from commercially available 2,3-dichlorophenylamine and 2,3-di-

Scheme 7[a]



[a] Reagents and conditions: (a) Br_2 or Cl_2 gas, 50% acetic acid; (b) $POCl_3$, DMF, 120 °C, 0.5 h; (c) $SnCl_2 \cdot H_2O$, HCl, room temperature, 2 h; (d) CH_3CH_2OCSSK, DMF, 160°C, 4 h.

Table 1. Structure−Activity Relationships of the Benzothiazole Moiety



compd no.	R″	HER-2 IC_{50} (nM)	MTS EC_{50} (nM)
7	H	5000	10000
8	5′-Cl	20000	20000
9	4′-Cl	15000	20000
10	6′-Cl	7000	20000
11	7′-Cl	180	250
12	7′-Br	330	2000
13	7′-F	200	1000
14	7′-Me	300	1300
15	7′-Cl, 6′-Cl	25000	20000
16	7′-OCH_3	190	230
17	7′-OCH_2CH_3	100000	16000

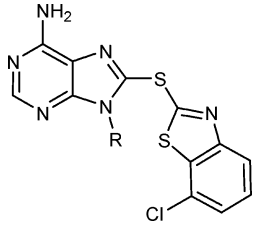
fluorophenylamine with $EtOCS_2K$ at heat condition. The 6-Cl-, 5-Cl-, 4-Cl-, and 7-H-benzothiazole isomers were purchased from Acros.

To prepare the thiazolopyridine-2-thiols **77** and **78** (Scheme 7), the 5-Cl or 5-Br was introduced by halogenation[26] of 3-nitropyridin-4-ol. Subsequently, the 4-OH group was converted to chlorine by treating with $POCl_3$,[27] and the nitro group was reduced to an amino group[24] with $SnCl_2$. Finally, cyclization with the potassium salt of ethyl xanthic acid gave the target compounds **77** and **78**.

Results and Discussion

The structure−activity relationship data of the substituted benzothiazolothiopurine analogues as measured by their ability to degrade the client protein Her-2, is indicated in Table 1. In this assay, **2** and **3** degrade Her-2 with IC_{50} values of 15 and 23 nM, respectively. The parent compound **7**, which carries no substituent on the benzothiazole ring, induces Her-2 degradation in MCF-7 cells with an $IC_{50} = 5000$ nM. Introduction of a chlorine atom in positions 4′, 5′, or 6′ (**8**−**10**) decreases the potency. In sharp contrast, introduction of Cl at the 7′-position (**11**) leads to a nearly 30-fold potency gain ($IC_{50} = 180$ nM). Replacing the Cl^- substituent at the 7′-position with various moieties dramatically affected the potency of Her-2 degradation. For example, activity of the 7′-halide, 7′-OCH_3, and 7′-CH_3 substituted benzothiazolothiopurine analogues (**11**, **12**, **13**, **14**, **16**) range from 180 to 330 nM, with the 7′-chloro exhibiting the best activity. Replacement of the 7′-OCH_3 group with longer alkyl ethers, such as 7′-OCH_2CH_3, reduced the activity by 500-fold. Disubstitution (6′,7′-dichloro) (**15**) resulted in 140-fold less activity compared with that of the monosubstituted analogue (**11**). The entirety of these results suggests that the ATP-binding site of Hsp90 is very sensitive to subtle changes at the 7′-position.

Table 2. Structure−Activity Relationships of the 9-*N*-Alkyl Position



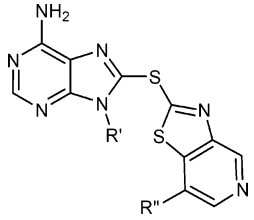
compd no.	R	HER-2 IC_{50} (nM)	MTS EC_{50} (nM)
18	$-CH_2CH_3$	200	800
19	$-CH_2CH_2CH_3$	250	850
11	$-CH_2CH_2CH_2CH_3$	180	250
20	$-CH_2CH_2CH_2CH_2CH_3$	700	6000
21	$-CH_2CH_2OC(O)CH_3$	150	300
22	$-CH_2CH_2CH_2OC(O)CH_3$	90	200
23	$-CH_2CH_2CH_2CH_2OC(O)CH_3$	130	240
24	$-CH_2CH_2PO(OCH_2CH_3)_2$	30	30
25	$-CH_2CH_2CH_2CH_2CN$	110	300
31	$-CH_2CH_2OH$	300	700
32	$-CH_2CH_2CH_2OH$	150	250
33	$-CH_2CH_2CH_2CH_2OH$	150	200
34	$-CH_2CH_2-$morpholine	250	300
35	$-CH_2CH_2NHC(CH_3)_3$	140	300
36	$-CH_2CH_2NHCH_2C(CH_3)_3$	35	30
37	$-CH_2CH_2NH-$cyclopropane	110	300
38	$-CH_2CH_2CH_2NHCH(CH_3)_2$	170	500
39	$-CH_2CH_2CH_2NHC(CH_3)_3$	150	200

Having optimized the benzothiazole substituent (7′-Cl, $IC_{50} = 180$ nM), we turned our attention to the purine N (9) side chain (Table 2). Analogues having short alkyl chains (ethyl, propyl, and butyl—**18**, **19**, and **11**, respectively) have similar activities. Increasing the length of the alkyl group beyond four carbons decreased the activity (**20**). Further substituting the alkyl moiety with various functional groups including alcohols (**31**−**33**), esters (**21**−**23**), and some amines (**34**−**39**) generally did not improve the activity. One exception is the combination of a neopentylamine with a two-carbon linker (**36**), which resulted in significant improvement in HER-2 degradation activity (35 nM) over that of other amine substituents. Moreover, the ethyl phosphonate **24** also showed similar improvement in HER-2 degradation activity (30 nM). Compounds **24** and **36** were the most potent analogues prepared in this series and suggested that two-carbon linkers provided the optimal scaffold.

Although, the benzothiazole compounds exhibited acceptable potencies in the HER-2 degradation assay, as a class, they would benefit from increased solubility in aqueous media. In an attempt to increase overall oral bioavailability for these compounds, we introduced an additional ionizable moiety by replacing the benzothiazole with a pyridinothiazole ring. The Her-2 degradation activity of the most active members of this series is shown in Table 3. In accordance with the SAR data shown for the benzothiazole series, the best analogues contained a two-carbon linker substituted with the diethyl phosphate moiety (compounds **27** and **29**).

To correlate the activity observed on the client protein Her-2 to cell growth inhibition and binding to Hsp90, compounds were tested for cell growth inhibition in an MTS (3-(4,5-dimethylthi-

Table 3. Structure−Activity Relationships of the Pyridothiazole Moiety



compd no.	R′	R″	HER-2 IC_{50} (nM)	MTS EC_{50} (nM)
26	$-CH_2CH_2CH_2CH_3$	Br	400	4000
27	$-CH_2CH_2PO(OCH_2CH_3)_2$	Br	28	100
28	$-CH_2CH_2CH_2CH_3$	Cl	280	1000
29	$-CH_2CH_2PO(OCH_2CH_3)_2$	Cl	30	250
30	$-CH_2CH_2CH_2OC(O)CH_3$	Cl	170	1000

Table 4. Cell Lysate Hsp90 Binding Value for Key Compounds

compd no.	lysate binding EC_{50} (nM)[a]
2	20
3	25
16	200
22	160
23	140
24	60
25	100
29	40
34	150
37	130

[a] For assay condition, see ref 28.

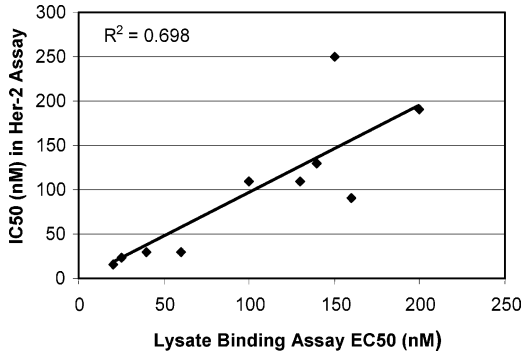


Figure 1. Correlation of lysate binding to Her-2 degradation in MCF7 tumor cells.

azol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium) assay which measures cell viability[28] (Tables 1−3) and a cell lysate competition binding assay[28] (Table 4). As observed with **2** and **3**, all of the compounds exhibit a binding affinity of about 1 μM to recombinant Hsp90 (rHsp90).[5] However, when a subset of compounds was tested in cell lysates derived from MCF7 cells, these compounds showed high-affinity binding to Hsp90 (Table 4). Indeed, the most potent analogues (**24** and **29**) approached the affinity of **2** and **3**, with EC_{50} values of 40 and 60 nM, respectively, versus 20 and 25 nM for **2** and **3**. The cell lysate binding activity correlated well ($R^2 = 0.689$) with the values observed for Her-2 degradation as depicted in Figure 1 confirming that these analogues act through Hsp90.

Similarly, the Her-2 degradation activity translated to cell growth inhibition in MCF7 tumor cells with values ranging from 30 to 500 nM (Tables 1−3). The controls **2** and **3** showed EC_{50} values of 30 and 100 nM, respectively. Overall, the correlation of Her-2 degradation to growth inhibition was high ($R^2 = 0.623$), particularly for the most potent compounds ($EC_{50} < 200$ nM).

Table 5. Solubility Data

compd no.	gastric (PH 2.0) μg/mL	intestinal (PH 6.5) μg/mL	serum (PH 7.4) μg/mL
16	35	2	18
22	220	16	9
23	46	3	*a*
24	98.5	*a*	*a*
25	58.7	4.4	31.3
29	124	38.3	14
34	*a*	*a*	*a*
36	*a*	6	4.9
37	245	21	59
39	*a*	137.7	198.7

[a] Below the level of detection.

Table 6. Pharmacokinetic Measurements of Key Compounds

	mouse PK PO	
compd no.	C_{max} at 100 mg/kg ng/mL	AUC at 100 mg/kg PO (ng/mL·min)
22	603	62592
29	*a*	*a*
37	4513	438410

[a] Below the level of detection.

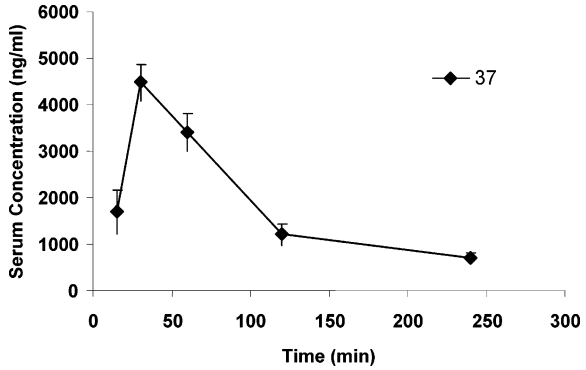


Figure 2. Pharmacokinetic study of **37** delivered at 100 mg/kg via oral gavage.

In preparation for in vivo evaluation of a subset of these analogues, we examined key pharmaceutical characteristics such as solubility and its relationship to oral bioavailablity. Comparison of the ethyl-diethyl phosphate analogue **29** from the pyridinothiazole series with its benzothiazole analogue **24** in a panel of solubility parameters including solubility in simulated gastric fluid, simulated intestinal fluid, and serum showed that the pyridinothiazole derivative was significantly more soluble in all three solutions (Table 5). Whereas the most potent derivatives **24** and **36** were poorly soluble in the majority of the solutions, compounds **22**, **25**, **29**, and **37** showed biologically relevant concentrations in all three solutions, and compounds **22**, **29**, and **37** were subsequently selected for further examination in vivo.

Pharmacokinetic measurements obtained in mice after oral administration at 100 mg/kg are shown in Table 6. Compound **37** was rapidly absorbed reaching a C_{max} of 4513 ng/mL 30 min after dosing with half-life estimated at 90 min (Figure 2). Concentrations for compound **22** were significantly lower than those for **37**. Surprisingly, despite its increased solubility over its benzothiazole analogue **24**, concentrations for **29** were not increased and remained below the level of detection, perhaps as a result of poor permeability properties.

The pharmacologically relevant concentrations observed for **37** in mouse serum identified it as a promising candidate for evaluation in a tumor xenograft growth inhibition study. Mice were treated with N87 cells and when the tumors reached an

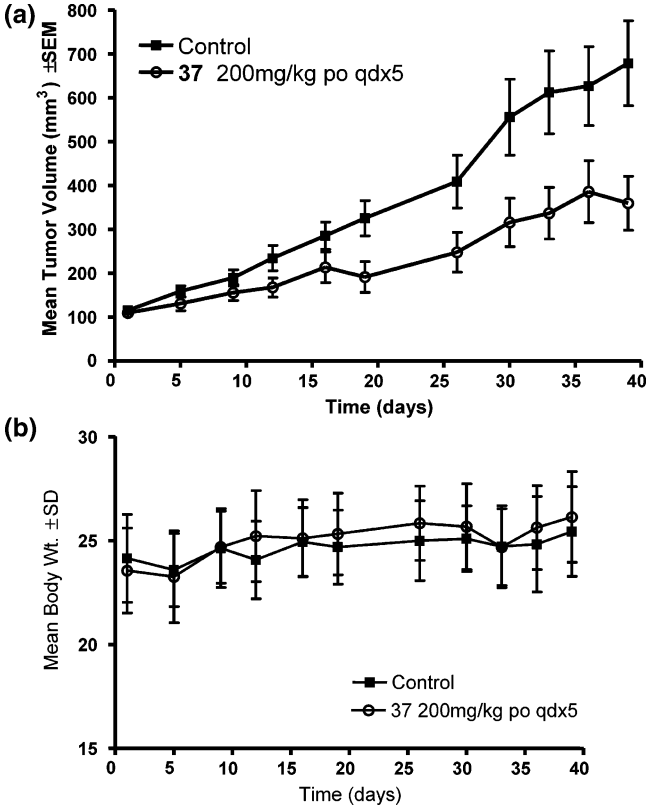


Figure 3. (a) Tumor growth inhibition study of **37** in the N87 xenograft model. (b) Daily body weights of mice dosed with **37** in the N87 xenograft model.

average of 100 mm^3 in size, mice were randomized into groups of 10. Compound **37** was administered orally at 200 mg/kg, 5 days/week. At the end of the study, 56% tumor growth inhibition was observed for **37** as compared with that of the control group (Figure 3a). The observed tumor growth inhibition was statistically significant ($p < 0.05$) as analyzed by standard *t*-test. The body weights of both control and compound-treated animals increased during the treatment regimen (Figure 3b).

Conclusion

Hsp90 inhibitors have increasingly become targets of interest for treating cancer, as evidenced by numerous recent reports. We and others have shown that the ATP-binding site of Hsp90 is amenable to compound optimization and drug development. The benzothiazole and pyridinothiazole series presented in this study indicate that the ATP-binding site is large enough to accommodate bicyclic ring systems. However, the ring substitution requirements are very specific, with the 7′-halogens outperforming all other substitution patterns. The bicyclic ring moieties provide the increase in potency necessary for effective inhibition of tumor cell growth while also providing improvements in pharmaceutical properties required for in vivo activity via the oral route of administration. Future research and discovery efforts will be directed at further evaluating our compound library for additional biological properties of this class of compounds. We will also attempt to increase the potency of these analogues in vivo as 200 mg/kg is still a fairly high dose. Since Hsp90 performs a key role not only in regulating proteins associated with malignant transformation, but also in central nerve system (CNS) disorder and inflammation, it is likely that Hsp90 inhibitors of the class presented here will have additional utility beyond oncology.

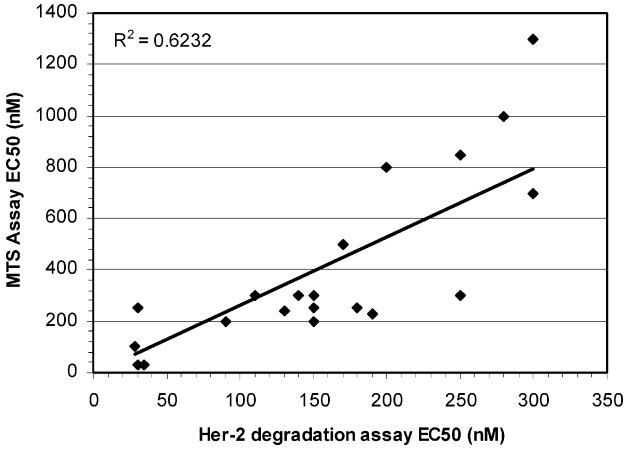


Figure 4. Correlation of MTS assay EC_{50} to Her-2 degradation in MCF7 tumor cells.

Experimental Section

Biology. The biological properties of the above compounds were characterized using a FACS-based assay for quantifying Her-2 degradation in MCF-7 cells, a cell lysate Hsp90 binding assay, and an MTS assay for quantifying cell viability (Figure 4). **2** was used as a reference as described previously.[28]

To quantify Her-2 degradation, compounds were incubated for 16 h with MCF-7 cells, a breast cancer cell line expressing moderate levels of Her-2 on its surface. Inhibition of Hsp90 induces the degradation of Her-2, which was monitored with a combination of fluorescent antibody and fluorescence-activated cell sorter technology (FACS).

The cell lysate Hsp90 binding assay was performed by incubating Hsp90 derived from MCF7 breast cancer cell lysates with biotinylated geldanamycin linked to streptavidin magnetic beads. Hsp90 inhibitors competitively displaced bound Hsp90, and the eluted Hsp90 was detected by quantitative western blots.

Cell viability was determined by a colorimetric assay using the MTS reagent which is converted to a formazan product (a 490 nm color emitting compound) by dehydrogenase enzymes of metabolically active cells.

Pharmacology. Six to eight week old nu/nu athymic female mice were obtained from Harlan Sprague Dawley, (Indianapolis, IN). The mice were maintained in sterilized filter-topped cages or ventilated caging in a room with a 12-h light/12-h dark photoperiod at a temperature of 21−23 °C and a relative humidity of 50 ± 5%. Irradiated pelleted food (Harlan Teklad no. 7912) and autoclaved deionized water were provided ad libitum. Animals were identified by the use of individually numbered ear tags. Experiments were carried out under institutional guidelines for the proper and humane use of animals in research established by the Institute for Laboratory Animal Research (ILAR). Tumor fragments (approximately 2 mm^3) or 5×10^6 tumor cells were inoculated subcutaneously in the right or left flank of the animal. Mice with established tumors (50−200 mm^3) were selected for study ($n = 7-10$/treatment group). Tumor dimensions were measured using calipers, and tumor volumes were calculated using the equation for an ellipsoid sphere $(lw^2)/2 = mm^3$, where *l* and *w* refer to the larger and smaller dimensions collected at each measurement. The test compounds were formulated at a concentration of 10 mg/mL in 5% phospholipon 90G, 8.6% sucrose, adjusted to pH 2 with 1 N HCl. The formulated test compound and the vehicle alone were administered orally (po) at 20 mL/kg. Animals were dosed 5 days per week (Monday through Friday) for 4−6 consecutive weeks. Animals were weighed, and the tumors were measured twice per week. Mice were followed until tumor volumes in the control group reached approximately 1000 mm^3 and were sacrificed by CO_2 euthanasia. The mean tumor volumes of each group were calculated. The change in mean treated tumor volume was divided by the change in mean control tumor volume, subtracted from 1 and multiplied by 100 to give the percent tumor

growth inhibition for each group. Statistical analysis was performed using the standard *t*-test and using GraphPad Prism Software. (A single outlier in the treated group was excluded from analysis so that the data fit a normality test.)

Pharmacokinetics. Pharmacokinetic evaluations were conducted in groups of three female Balb/C mice (Harlan Sprague−Dawley, Indianapolis, IN). Compounds were formulated at a concentration of 10 mg/mL in 5% phospholipon 90G, 8.6% sucrose, adjusted to pH 2 with 1 N HCl, and administered at a 100 mg/kg dose. Five blood samples were collected from each mouse over 4 h via the retro-orbital sinus. Concentrations of compound in serum were determined using a standardized HPLC−UV method with a 100 ng/mL limit of detection. The area under the serum concentration versus time curve from zero to the time of last measurable concentration (AUC) was estimated using the linear trapezoidal rule. The average observed maximum serum concentration values (C_{max}) were reported.

Chemistry. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere. The organic solvents were purchased from Fisher Scientific. Thin-layer chromatography (TLC) was performed with Whatman K6F silica gel 60A plates. ^{1}H NMR spectra were determined on a Bruker 400 MHz instrument. Mass spectra were recorded on an Agilent ESI-TOF mass spectrometer. HPLC was performed on Agilent 1100 instruments. The HPLC method used for these compounds is as follows: column, Agilent Zorbax 300 SB C18, 4.6 mm × 150 mm, 5 μm; column temperature, ambient; flow rate, 1.0 mL/min; gradient, 5% acetonitrile (0.05% TFA) in water (0.1% TFA) to 100% acetonitrile (0.05% TFA) in 7 min, hold at 100% for 2 min.

General Procedure for 9-Substituted Adenine Coupled with Substituted Benzothiazole-2-thiol (7−30). To substituted benzothiazole-2-thiol (**64**−**68**, **73**, **77**−**78**) (1.1 mmol) in DMF (5 mL) at room temperature was added potassium *tert*-butoxide (1.1 mmol). After 15 min, a solution of 9-substituted 8-bromo adenine (**49**−**57**) (0.37 mmol) in DMF (1 mL) was added, and the mixture was warmed to 130 °C and stirred for 6 h. The reaction mixture was cooled to room temperature, diluted with water, extracted with EtOAc (200 mL), washed (50 mL of brine), dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (5% MeOH/CH_2Cl_2) to give **7**−**30**.

8-(Benzothiazol-2-ylsulfanyl)-9-butyl-*9H*-purine-6-ylamine (7): white powder, 78% yield; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3H), 1.32 (m, 2H), 1.79 (m, 2H), 4.33 (t, J = 7.4 Hz, 2H), 6.62 (s, 2H, NH_2), 7.33 (t, J = 8.2 Hz, 1H), 7.44 (t, J = 7.3 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 8.40 (s, 1H); analysis ($C_{16}H_{16}ClN_6S_2$) C, H, N; HPLC >98% (t_R = 6.80 min).

9-Butyl-8-(5-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (8): white powder, 75% yield; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.33 (m, 2H), 1.83 (m, 2H), 4.33 (t, J = 7.4 Hz, 2H), 6.01 (s, 2H, NH_2), 7.34 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.92 (s, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{16}H_{15}ClN_6S_2$ [M + H]$^+$ 391.0561, found 391.0565; HPLC >96% (t_R = 6.62 min).

9-Butyl-8-(4-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (9): white powder, 72% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 3H), 1.35 (m, 2H), 1.83 (m, 2H), 4.35 (t, J = 7.44 Hz, 2H), 5.98 (s, 2H, NH_2), 7.29 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{16}H_{15}ClN_6S_2$ [M + H]$^+$ 391.0561, found 391.0563; HPLC >99% (t_R = 9.43 min) (5−100−15 method).

9-Butyl-8-(6-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (10): white powder, 77% yield; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.27 (m, 2H), 1.84 (m, 2H), 4.33 (t, J = 7.4 Hz, 2H), 5.82 (s, 2H, NH_2), 7.42 (d, J = 8.7 Hz, 1H), 7.74 (s, 1H), 7.85 (d, J = 8.7 Hz, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{16}H_{15}ClN_6S_2$ [M + H]$^+$ 391.0561, found 391.0561; HPLC >99% (t_R = 6.60 min).

9-Butyl-8-(7-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (11): white powder, 76% yield; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.37 (m, 2H), 1.83 (m, 2H), 4.33 (t, J = 7.3 Hz, 2H), 6.03 (s, 2H, NH_2), 7.36 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{16}H_{15}ClN_6S_2$ [M + H]$^+$ 391.0561, found 391.0564; HPLC >99% (t_R = 9.73 min, method 5−100−15).

8-(7-Bromobenzothiazol-2-ylsulfanyl)-9-butyl-*9H*-purine-6-ylamine (12): white powder, 80% yield; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.38 (m, 2H), 1.83 (m, 2H), 4.34 (t, J = 7.4 Hz, 2H), 5.83 (s, 2H, NH_2), 7.36 (t, J = 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 8.44 (s, 1H).; HRMS, calcd for $C_{16}H_{15}BrN_6S_2$ [M + H]$^+$ 435.0056, found 435.005; HPLC >98% (t_R = 6.51 min).

9-Butyl-8-(7-fluorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (13): white powder, 73% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.35 (m, 2H), 1.82 (m, 2H), 4.33 (t, J = 7.4 Hz, 2H), 5.71 (s, 2H, NH_2), 7.1 (t, J = 8.3 Hz, 1H), 7.44 (m, 1H), 7.75 (d, J = 8.3 Hz, 1H), 8.44 (s, 1H); HRMS, calcd for $C_{16}H_{15}FN_6S_2$ [M + H]$^+$ 375.0856, found 375.0856; HPLC >99% (t_R = 6.14 min).

9-Butyl-8-(7-methylbenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (14): white powder, 79% yield; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3H), 1.34 (m, 2H), 1.80 (m, 2H), 2.47 (s, 3H), 4.33 (t, J = 7.4 Hz, 2H), 6.10 (s, 2H, NH_2), 7.16 (d, J = 7.3 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H), 8.42 (s, 1H); analysis ($C_{17}H_{18}N_6S_2$) C, H, N; HPLC >99% (t_R = 6.27 min).

9-Butyl-8-(6,7-dichlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (15): white powder, 81% yield; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.38 (m, 2H), 1.83 (m, 2H), 4.33 (t, J = 7.4 Hz, 2H), 6.14 (s, 2H, NH_2), 7.51 (d, J = 8.7 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 8.39 (s, 1H); HRMS, calcd for $C_{16}H_{14}Cl_2N_6S_2$ [M + H]$^+$ 425.0171, found 425.0163; HPLC >98% (t_R = 6.92 min).

9-Butyl-8-(7-methoxybenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (16): white powder, 80% yield; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.4 Hz, 3H), 1.35 (m, 2H), 1.82 (m, 2H), 3.96 (s, 3H), 4.33 (t, J = 7.4 Hz, 2H), 5.68 (s, 2H, NH_2), 6.83 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.44 (s, 1H); analysis ($C_{17}H_{18}N_6OS_2$) C, H, N; HPLC >99% (t_R = 6.14 min).

9-Butyl-8-(7-ethoxybenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (17): white powder, 78% yield; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3H), 1.35 (m, 2H), 1.45 (t, J = 7.4 Hz, 3H), 1.82 (m, 2H), 4.21 (t, J = 7.4 Hz, 2H), 4.33 (t, J = 7.4 Hz, 2H), 5.76 (s, 2H, NH_2), 6.80 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 8.44 (s, 1H); HRMS, calcd for $C_{18}H_{20}N_6OS_2$ [M + H]$^+$ 401.1213, found 401.1214; HPLC >96% (t_R = 6.46 min).

9-Ethyl-8-(7-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (18): white powder, 77% yield; ^{1}H NMR ($CDCl_3$) δ 1.46 (t, J = 7.4 Hz, 3H), 4.43 (t, J = 7.4 Hz, 2H), 5.88 (s, 2H, NH_2), 7.35 (d, 8.1 Hz, 1H), 7.43 (t, J = 8.1 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H); HRMS, calcd for $C_{14}H_{11}ClN_6S_2$ [M + H]$^+$ 363.0248, found 363.0247; HPLC >95% (t_R = 5.80 min).

9-Propyl-8-(7-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (19): white powder, 82% yield; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.91 (m, 2H), 4.32 (t, J = 7.4 Hz, 2H), 5.83 (s, 2H, NH_2), 7.35 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.44 (s, 1H); HRMS, calcd for $C_{15}H_{13}ClN_6S_2$ [M + H]$^+$ 377.0404, found 377.0401; HPLC >97% (t_R = 6.01 min).

9-Pentyl-8-(7-chlorobenzothiazol-2-ylsulfanyl)-*9H*-purine-6-ylamine (20): white powder, 87% yield; ^{1}H NMR ($CDCl_3$) δ 0.81 (t, J = 7.4 Hz, 3H), 0.94 (m, 2H), 1.31 (m, 2H), 1.86 (m, 2H), 4.35 (t, J = 7.4 Hz, 2H), 5.97 (s, 2H, NH_2), 7.35 (d, J = 8.1 Hz, 1H), 7.43(t, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 8.44 (s, 1H); HRMS, calcd for $C_{17}H_{17}ClN_6S_2$ [M + H]$^+$ 405.0717, found 405.0716; HPLC >96% (t_R = 7.0 min).

Acetic Acid 2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-ethyl Ester (21): white powder, 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 4.48 (t, J = 5.0 Hz, 2H), 4.64 (t, J = 5.0 Hz, 2H), 5.87 (s, 2H, NH_2), 7.37 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{16}H_{13}ClN_6O_2S_2$ [M + H]$^+$ 421.0303, found 421.0304; HPLC >98% (t_R = 5.58 min).

Acetic Acid 2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-propyl Ester (22): white powder, 83% yield; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3H), 2.26 (m, 2H), 4.08 (t, J = 5.9 Hz, 2H), 4.47 (t, J = 7.0 Hz, 2H), 6.06 (s, 2H, NH_2), 7.36 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.42 (s, 1H); HRMS, calcd for $C_{17}H_{15}ClN_6O_2S_2$ $[M + H]^+$ 435.0459, found 435.0454; HPLC >98% (t_R = 5.77 min).

Acetic Acid 4-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-butyl Ester (23): white powder, 82% yield; ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 2H), 1.91(m, 2H), 1.96 (s, 3H), 4.04 (t, J = 6.4 Hz, 2H), 4.39 (t, J = 7.3 Hz, 2H), 6.31 (s, 2H, NH_2), 7.33 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.41 (s, 1H); HRMS, calcd for $C_{18}H_{17}ClN_6O_2S_2$ $[M + H]^+$ 449.0616, found 449.0624; HPLC >95% (t_R = 5.90 min).

{**2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-ethyl**}**-phosphonic Acid Diethyl Ester (24):** white powder, 85% yield; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 6H, $2CH_3$), 2.52 (m, 4H, $2CH_2$), 4.07 (m, 2H, CH_2), 4.65 (m, 2H, CH_2), 5.67 (bs, 2H, NH_2), 7.38 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 8.53 (s, 1H); HRMS, calcd for $C_{18}H_{20}ClN_6O_3PS_2$ $[M + H]^+$ 499.0537, found 499.0536; HPLC >98% (t_R = 5.67 min).

5-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-pentanenitrile (25): white powder, 83% yield; ^{1}H NMR ($CDCl_3$) δ1.71 (m, 2H), 2.05 (m, 2H), 2.42 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 5.2 Hz, 2H), 5.88 (bs, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.45 (s, 1H); HRMS, calcd for $C_{17}H_{14}ClN_7S_2$ $[M + H]^+$ 416.0513, found 416.0508; HPLC >96% (t_R = 5.69 min).

8-(7-Bromothiazolo[5,4-*b*]pyridin-2-ylsulfanyl)-9-butyl-9*H*-purine-6-ylamine (26): white powder, 81% yield; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.34 (m, 2H), 1.85 (m, 2H), 4.36 (t, J = 7.3 Hz, 2H), 5.74 (s, 2H), 8.50 (s, 1H), 8.70(s, 1H), 9.20 (s, 1H); HRMS, calcd for $C_{15}H_{14}BrN_7S_2$ $[M + H]^+$ 436.0008, found 436.0014; HPLC >96% (t_R = 5.79 min).

{**2-[6-Amino-8-(7-bromothiazole[4,5-*c*]pyridin-2-ylsulfanyl)-purin-9-yl]ethyl**}**-phosphonic Acid Diethyl Ester (27):** white powder, 65% yield; ^{1}H NMR ($CDCl_3$) δ 1.28(t, J = 7.1 Hz, 6H, $2CH_3$), 2.52 (m, 2H, CH_2), 4.07 (m, 4H, $2CH_2$), 4.65 (m, 2H, CH_2), 5.71 (bs, 2H, NH_2), 8.46 (s, 1H), 8.58(s, 1H), 9.25 (s, 1H); HRMS, calcd for $C_{17}H_{19}BrN_7O_3PS_2$ $[M + H]^+$ 543.9984, found 543.9984; HPLC >95% (t_R = 5.02 min).

9-Butyl-8-(7-chlorothiazole[4,5-*c*]pyridin-2-ylsulfanyl)-9*H*-purin-6-ylamine (28): white powder, 86% yield; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H), 1.38 (m, 2H), 1.86 (m, 2H), 4.35 (t, J = 7.4 Hz, 2H), 5.74 (s, 2H, NH_2), 8.46 (s 1H), 8.49 (s, 1H), 9.10 (s, 1H); HRMS, calcd for $C_{15}H_{14}ClN_7S_2$ $[M + H]^+$ 392.0513, found 392.0514; HPLC >96% (t_R = 5.90 min).

{**2-[6-Amino-8-(7-chlorothiazolo[4,5-*c*]pyridinl-2-ylsulfanyl)-purin-9-yl]-ethyl**}**-phosphonic Acid Diethyl Ester (29):** white powder, 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 6H, $2CH_3$), 2.52 (m, 2H, CH_2), 4.07 (m, 4H, $2CH_2$), 4.65 (m, 2H, CH_2), 5.76 (bs, 2H, NH_2), 8.46 (s, 1H), 8.52 (s, 1H), 9.08 (s, 1H); HRMS, calcd for $C_{17}H_{19}ClN_7O_3PS_2$ $[M + H]^+$ 500.049, found 500.0488; HPLC >96% (t_R = 4.97 min).

Acetic Acid 3-[6-Amino-8-(7-chlorothiazolo[4,5-*c*]pyridin-2-ylsulfanyl)-purin-9-yl]-propyl Ester (30): white powder, 83% yield; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 3H), 2.26 (m, 2H), 4.09 (t, J = 5.9 Hz, 2H), 4.47 (t, J = 7.0 Hz, 2H), 5.75 (s, 2H, NH_2), 8.45 (s, 1H), 8.50 (s, 1H), 9.09 (s, 1H); HRMS, calcd for $C_{16}H_{14}ClN_7O_2S_2$ $[M + H]^+$ 436.0412, found 436.0406; HPLC >95% (t_R = 5.06 min).

General Procedure for the Syntheses of Compounds 31−33. To **21−23** was added an excess of NH_3 in MeOH at room temperature. The mixture was stirred overnight at room temperature. The excess of ammonia was removed by rotoevaporation. The residue was purified by chromatography (silica gel) (5% MeOH/CH_2Cl_2) to give **31−33**.

2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-ethanol (31): white powder, 74% yield; ^{1}H NMR (DMSO-d_6) δ 3.58 (m, 2H), 4.33 (t, J = 5.9 Hz, 2H), 5.04 (t, J = 5.0 Hz, 1H, OH), 7.55 (m, 2H), 7.64 (s, 2H, NH_2), 7.93 (m, 1H), 8.26 (s, 1H); HRMS, calcd for $C_{14}H_{11}ClN_6OS_2$ $[M + H]^+$ 379.0197, found 379.0204; HPLC >96% (t_R = 5.01 min).

2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-propan-1-ol (32): white powder, 81% yield; ^{1}H NMR ($CDCl_3$) δ 1.93 (m, 2H), 3.47 (m, 2H), 4.24 (m, 1H, OH), 4.52 (t, J = 7.0 Hz, 2H), 5.78 (s, 2H, NH_2), 7.39 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{15}H_{13}ClN_6OS_2$ $[M + H]^+$ 393.0354, found 393.0359; HPLC >99% (t_R = 5.13 min).

2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-butan-1-ol (33): white powder, 76% yield; ^{1}H NMR ($CDCl_3$) δ 1.59 (m, 2H), 1.93 (m, 2H), 3.72 (t, J = 6.1 Hz, 2H), 4.10 (m, 1H, OH), 4.47 (t, J = 7.0 Hz, 2H), 5.91 (s, 2H, NH_2), 7.36 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 8.49 (s, 1H); HRMS, calcd for $C_{16}H_{15}ClN_6OS_2$ $[M + H]^+$ 407.051, found 407.0512; HPLC >98% (t_R = 5.22 min).

General Procedure for the Syntheses of Compounds 34−39. To **79** or **80** (0.22 mmol) was added 1 mL of the appropriate amine. The reaction mixture was stirred overnight at room temperature. The excess amine was removed by rotoevaporation. The residue was purified by flash chromatography (silica gel) (5% MeOH/CH_2Cl_2) to give **34−39**.

8-(7-Chlorobenzothiazo-2-ylsulfanyl)-9-(2-morpholin-4-yl-ethyl)-9*H*-purin-6-ylamine (34): white powder, 83% yield; ^{1}H NMR ($CDCl_3$) δ 2.48(t, J = 4.46 Hz, 4H), 2.76 (t, J = 5.8 Hz, 2H), 3.64 (t, J = 4.4 Hz, 4H), 4.45 (t, J = 5.8 Hz, 2H), 5.85 (bs, 2H, NH_2), 7.35 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 8.42 (s, 1H); HRMS, calcd for $C_{18}H_{18}ClN_7OS_2$ $[M - H]^-$ 446.063, found 446.0629; HPLC >95% (t_R = 4.71 min).

9-(2-*tert*-Butylamino-ethyl)-8-(7-chlorobenzothiazole-2-ylsulfanyl)-9*H*-purin-6-ylamine (35): white powder, 30% yield; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 9H), 3.00 (t, J = 4.8 Hz, 2H), 4.46 (t, J = 4.9 Hz, 2H), 5.77 (s, 2H, NH_2), 7.35 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H); HRMS, calcd for $C_{18}H_{20}ClN_7S_2$ $[M + H]^+$ 434.0983, found 434.0988; HPLC >99% (t_R = 5.04 min).

8-(7-Chlorobenzothiazol-2-ylsulfanyl)-9-[2-(2,2-dimethyl-propylamino)-ethyl]-9*H*-purin-6-ylamine (36): white powder, 31% yield; ^{1}H NMR ($CDCl_3$) δ 0.82 (s, 9H), 2.31 (s, 2H), 3.05 (t, J = 4.8 Hz, 2H), 4.47 (t, J = 4.9 Hz, 2H), 5.74 (s, 2H, NH_2), 7.35 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H); analysis ($C_{18}H_{22}ClN_7S_2$) C, H, N; HPLC >99% (t_R = 5.31 min).

8-(7-Chlorobenzothiazol-2-ylsulfanyl)-9-(2-cyclopropylamino-ethyl)-9*H*-purin-6-ylamine (37): white powder, 42% yield; ^{1}H NMR ($CDCl_3$) δ 0.16 (m, 2H), 0.36 (m, 2H), 2.15 (m, 1H), 3.15 (t, J = 4.8 Hz, 2H), 4.46 (t, J = 4.9 Hz, 2H), 5.70 (s, 2H, NH_2), 7.35 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H); HRMS calcd for $C_{17}H_{16}ClN_7S_2$ $[M + H]^+$ 418.067, found 418.0680; HPLC >99% (t_R = 4.95 min).

8-(7-Chlorobenzothiazol-2-ylsulfanyl)-9-(3-isopropylamino-propyl)-9*H*-purin-6-ylamine (38): white powder, 45% yield; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, J = 5.5 Hz, 6H), 2.28 (m, 1H), 2.80 (m, 2H), 3.40 (m, 2H), 4.52 (t, J = 7.3 Hz, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 8.28 (s, 1H); HRMS, calcd for $C_{18}H_{20}ClN_7S_2$ $[M + H]^+$ 434.0983, found 434.0989; HPLC >96% (t_R = 4.81 min).

9-(3-*tert*-Butylamino-propyl)-8-(7-chlorobenzothiazol-2-ylsulfanyl)-9*H*-purin-6-ylamine (39): white powder, 45% yield; ^{1}H NMR ($CDCl_3$) δ1.32 (s, 9H), 2.22 (m, 2H), 3.02 (t, J = 7.3 Hz, 2H), 4.53 (t, J = 7.3 Hz, 2H), 5.67 (bs, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 8.4 Hz, 1H), 7.86 (d, J = 1.1 Hz, 1H), 8.34 (s, 1H); HRMS, calcd for $C_{19}H_{22}ClN_7S_2$ $[M + H]^+$ 448.1139, found 448.1144; HPLC >99% (t_R = 5.00 min).

General Procedure for Alkylation of Adenines (40−48). To a mixture of adenine (10 g, 74 mmol) and cesium carbonate (28.93 g, 88.8 mmol) in DMF (100 mL) was added alkyl halide (88.8 mmol) at room temperature. The reaction mixture was stirred at room temperature or heated to 50 °C for 16 h and quenched with

water (200 mL). The precipitate was filtered and dried under vacuum to give products **40**−**48**.

9-Ethyl-*9H*-purine-6-ylamine (40): white powder, 91% yield; ^{1}H NMR ($CDCl_3$) δ1.25 (t, J = 7.36 Hz, 3H), 4.31 (m, 2H), 5.7 (bs, 2H), 7.84 (s, 1H), 8.40 (s, 1H).

9-Propyl-*9H*-purine-6-ylamine (41): white powder, 93% yield; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 2.0 (m, 2H), 4.13 (t, J = 7.3 Hz, 2H), 5.8 (bs, 2H), 7.81 (s, 1H), 8.38 (s, 1H).

9-Butyl-*9H*-purin-6-ylamine (42): white powder, 95% yield; ^{1}H NMR (DMSO) δ 0.89 (t, J = 7.36 Hz, 3H), 1.20 (m, 2H), 1.77 (m, 2H), 4.13 (t, J = 7.3 Hz, 2H), 7.17 (s, 1H), 8.14 (s, 1H).

9-Pentyl-*9H*-purine-6-ylamine (43): white powder, 91% yield; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.32 (m, 4H), 1.95 (m, 2H), 4.41 (t, J = 7.3 Hz, 2H), 5.68 (bs, 2H), 7.81 (s, 1H), 8.39 (s, 1H).

[2-(6-Aminopurin-9-yl)-ethyl]-phosphonic Acid (44): white powder, 79% yield; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6H, J = 2.1 Hz, $2CH_3$), 2.46 (m, 2H, CH_2), 4.06 (m, 4H, $2CH_2$), 4.53 (m, 2H, CH_2), 5.75 (bs, 2H, NH_2), 7.87 (s, 1H, CH═), 8.38 (s, 1H, CH═).

Acetic Acid 2-(6-Aminopurin-9-yl)-ethyl Ester (45): white powder, 91% yield; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 4.47 (m, 4H), 5.62 (s, 2H, NH_2), 7.85 (s, 1H), 8.39 (s, 1H).

Acetic Acid 2-(6-Aminopurin-9-yl)-propyl Ester (46): white powder, 89% yield; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.28 (m, 2H), 4.12 (t, J = 7.0 Hz, 2H), 4.34 (t, J = 7.0 Hz, 2H), 5.68 (s, 2H, NH_2), 7.83 (s, 1H), 8.39 (s, 1H).

Acetic Acid 4-(6-Aminopurin-9-yl)-butyl Ester (47): white powder, 88% yield; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 2H), 1.95 (m, 2H), 2.07 (s, 3H), 4.14 (t, J = 7.4 Hz, 2H), 4.29 (t, J = 7.3 Hz, 2H), 5.62 (s, 2H, NH_2), 7.85 (s, 1H), 8.39 (s, 1H).

5-(6-Aminopurin-9-yl)-pentanenitrile (48): white powder, 89% yield; ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 1.54 (m, 2H), 2.56 (t, J = 7.1 Hz, 2H), 4.38 (t, J = 5.2 Hz, 2H), 7.84 (s, 1H), 8.37 (s, 1H).

General Procedure for Bromination of 9-Substituted Adenines (49−**57).** 9-Substituted-*9H*-purin-6-ylamine **40**−**48** (52.35 mmol) was suspended in HOAC/NaOAC buffer (6 mL), THF (6 mL), and MeOH (6 mL) before slowly adding Br_2 (104.7 mmol) at room temperature. After the addition of Br_2 was complete, the reaction mixture became clear and stirring was continued at room temperature for 0.5 h. The reaction mixture was concentrated to one-third of its original volume, extracted with EtOAc, washed (water then brine), dried ($MgSO_4$), and concentrated to give crude **49**−**57**. The pure material **49**−**57** was obtained by recrystallization from MeOH.

8-Bromo-9-ethyl-*9H*-purin-6-ylamine (49): brown powder, 80% yield; ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 7.3 Hz, 3H), 4.29 (m, 2H), 5.7 (bs, 2H), 8.37 (s, 1H).

8-Bromo-9-propyl-*9H*-purin-6-ylamine (50): brown powder, 82% yield; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, J = 7.3 Hz, 3H), 2.0 (m, 2H), 4.20 (t, J = 7.3 Hz, 2H), 5.70 (bs, 2H), 8.38 (s, 1H).

8-Bromo-9-Butyl-*9H*-purin-6-ylamine (51): brown powder, 77% yield; ^{1}H NMR (MeOH-d_4) δ 0.98 (t, J = 7.3 Hz, 3H), 1.40 (m, 2H), 1.80 (m, 2H), 4.24 (t, J = 7.3 Hz, 2H), 8.28 (s, 1H).

8-Bromo-9-pentyl-*9H*-purin-6-ylamine (52): brown powder, 78% yield; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.32 (m, 4H), 1.95 (m, 2H), 4.47 (t, J = 7.3 Hz, 2H), 5.68 (bs, 2H), 8.39 (s, 1H).

[2-(6-Amino-8-bromopurin-9-yl)-ethyl]-phosphonic Acid Diethyl Ester (53): brown powder, 75% yield; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6H, J = 2.1 Hz, $2CH_3$), 2.46(m, 2H, CH_2), 4.06 (m, 4H, $2CH_2$), 4.53 (m, 2H, CH_2), 5.84 (bs, 2H, NH_2), 8.33 (s, 1H, CH═).

Acetic Acid 3-(6-Amino-8-bromopurin-9-yl)-ethyl Ester (54): brown powder, 76% yield; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 4.51 (m, 4H), 5.82 (s, 2H, NH_2), 8.34 (s, 1H).

Acetic Acid 3-(6-Amino-8-bromopurin-9-yl)-propyl Ester (55): brown powder, 92% yield; ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.28 (m, 2H), 4.12 (t, J = 7.0 Hz, 2H), 4.34 (t, J = 7.0 Hz, 2H), 6.18(s, 2H, NH_2), 8.31 (s, 1H).

Acetic Acid 3-(6-Amino-8-bromopurin-9-yl)-butyl Ester (56): brown powder, 79% yield; ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 2H), 1.95 (m, 2H), 2.07 (s, 3H), 4.14 (t, J = 7.4 Hz, 2H), 4.29 (t, J = 7.3 Hz, 2H), 5.62 (s, 2H, NH_2), 8.35 (s, 1H).

5-(6-Amino-8-bromopurin-9-yl)-pentanenitrile (57): brown powder, 82% yield; ^{1}H NMR ($CDCl_3$) δ1.71 (m, 2H), 2.05 (m, 2H), 2.42 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 5.2 Hz, 2H), 5.88 (bs, 2H), 8.45 (s, 1H).

Compounds 58−**60** were prepared by a similar method as described in ref 25.

3-(5-Amino-6-chloropyrimidine-4-ylamino)propan-ol (58): white powder, 80% yield; ^{1}H NMR (DMSO-d_6) δ1.78 (m, 2H), 3.41 (m, 2H), 4.07 (m, 2H), 5.10 (bs, 2H), 6.99 (bs, 1H), 7.71 (s, 1H).

3-(6-Chloro-9*H*-purin-9-yl)propan-1-ol (59): white powder, 85% yield; ^{1}H NMR (DMSO-d_6) δ2.03 (m, 2H), 3.44 (m, 2H), 4.37 (t, J = 7.0 Hz, 2H), 8.70 (s, 1H), 8.78 (s, 1H).

3-(6-Amino-9*H*-purin-9-yl)propan-1-ol (60): white powder, 91% yield; ^{1}H NMR (DMSO-d_6) δ1.94 (m, 2H), 3.41 (m, 2H), 4.21 (t, J = 7.0 Hz, 2H), 4.70 (t, J = 5.1 Hz, 1H, OH), 7.18 (s, 2H, NH_2), 8.11 (s, 1H), 8.13 (s, 1H).

7-Methyl-benzothiazole-2-thiol (64). To a solution of 2-bromo-3-nitrotoluene (2.5 g, 11.57 mmol) in EtOH (18 mL) was added Fe (1.94 g, 34.7 mmol) and concentrated HCl (1 mL) at room temperature. The reaction mixture was heated at reflux for 1.5 h and then cooled to room temperature. The solvent was removed, and the residue was diluted with NH_4Cl (saturated) and extracted with EtOAc (3×). The combined extracts were washed (water then brine), dried ($MgSO_4$), and concentrated to give crude **61** in 90% yield. Compound **61** (1 g, 5.37 mmol) reacted with *O*-ethylxanthic acid, potassium salt (1.03 g, 6.45 mmol) in DMF to form **64** as a white powder in 89% yield. ^{1}H NMR (CD_3OD) δ 2.41 (s, 3H), 7.10 (m, 2H), 7.29 (t, J = 8.1 Hz, 1H).

7-Methoxy-benzothiazole-2-thiol (65). To a solution of 2-amino-3-nitrophenol (10 g, 64.9 mmol) in DMF at room temperature was added K_2CO_3 (9.86 g, 71.4 mmol) and iodomethane (10.13 g, 71.4 mmol). The reaction mixture was stirred overnight, and then the solvent was removed in vacuo. The residue was diluted with NH_4Cl (saturated) and extracted with EtOAc (3×), and the combined extracts were washed (water then brine), dried ($MgSO_4$), and concentrated to give crude **62a**. Pure **62a** was obtained by crystallization from EtOAC and hexanes in 90% yield. The 2-methoxy-6-nitro-phenylamine **62a** was converted to 2-bromo-1-methoxy-3-nitrobenzene **62b** by using ($NaNO_2$, aq H_2SO_4 and CuBr, aq HBr) a known method.[29] Compound **62b** (1.8 g, 7.76 mmol) was treated with iron (1.3 g, 23.27 mmol) in EtOH (20 mL)/HCl (1.5 mL) to give **62c** (1.36 g, 6.73 mmol) followed by reacting with *O*-ethylxanthic acid, potassium salt (1.61 g, 10.1 mmol) in DMF to form **65** as a white powder in 89% yield. ^{1}H NMR (CD_3OD) δ 3.95 (s, 3H), 6.74 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H).

7-Ethoxybenzothiazole-2-thiol (66) was prepared by the same method described for **65** except that iodoethane was used instead of iodomethane. Compound **66** was obtained as a white powder (70% yield). ^{1}H NMR (CD_3OD) δ 1.44 (t, J = 7.4 Hz, 3H), 4.21 (t, J = 7.4 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H).

7-Chlorobenzothiazole-2-thiol (67). To a solution of 2,3-dichloro-phenylamine (2 g, 12.34 mmol) in DMF (10 mL) at room temperature was added *O*-ethylxanthic acid, potassium salt (2.37 g, 14.81 mmol). The reaction mixture was heated to 150 °C and stirred for 4 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The crude material was diluted with NH_4Cl (saturated), and the precipitate collected on a filter, washed with water (50 mL × 2), and dried under vacuum to give **67** (2.2 g, 10.94 mmol) in 89% yield. ^{1}H NMR ($CDCl_3$) δ 7.16 (d, J = 7.8 Hz, 1H), 7.38 (m, 2H), 10.0 (s, 1H).

7-Fluorobenzothiazole-2-thiol (68) was prepared by the same method described for **67** except that 2,3-difluoro-phenylamine was used instead of 2,3-dichloro-phenylamine. Compound **68** was obtained as a white powder (89% yield). ^{1}H NMR ($CDCl_3$) δ 7.0 (t, J = 8.3 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.38 (m, 1H).

7-Bromobenzothiazole-2-thiol (73). To a mixture of HNO_3 (90 mL) and H_2SO_4 (45 mL) at 0 °C was added 1,2-dibromo-benzene

(35 g, 148.3 mmol). The mixture was stirred at 0 °C for 30 min and then poured into 1.4 L of ice water. The precipitated solid was filtered, washed with water, and dried under vacuum (pump) to give a mixture of **69** and **70** in a 1:4 ratio (95% yield). The mixture of **69** and **70** (40 g, 142 mmol) was treated with Fe (23.9 g, 427 mmol) in a solution comprised of 50% EtOH/H_2O (270 mL) and HCl (15 mL). The mixture was heated to 85 °C for 2 h, then cooled to room temperature and concentrated. The crude material was extracted with EtOAc (3×), and the combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated to give a mixture of **71** and **72** in a 1:4 ratio (91% yield). The mixture of **71** and **72** (8.75 g, 34.86 mmol) was added to a solution of *O*-ethylxanthic acid, potassium salt (33.47 g, 52.3 mmol) in DMF (150 mL) and heated to 160 °C for 4 h. Only compound **71** reacted to form compound **73**. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The crude material was suspended in NH_4Cl (saturated) and the precipitate collected on a filter, washed with water (50 mL × 2), and dried under vacuum to give product **73** as a white solid (91% yield). ^{1}H NMR (CD_3OD) δ 7.21 (t, J = 6.3 Hz, 1H), 7.29 (d, J = 6.3 Hz, 1H), 7.34 (d, J = 7.3 Hz, 1H).

7-Chlorothiazole[4,5-*c*]pyridine-2-thiol (77). Chlorine gas (Cl_2) was bubbled through a solution of 3-nitro-pyridin-4-ol (15 g, 107 mmol) in 50% aqueous acetic acid (200 mL) for 20 min at room temperature. The resulting precipitate was filtered and washed with water. Pure **74** was obtained after crystallization from EtOH in 95% yield. To a solution of **74** (14 g, 79.8 mmol) in DMF (30 mL) at room temperature was added $POCl_3$ (7.42 mL, 79.8 mmol). The mixture was heated to 120 °C for 30 min and then cooled to room temperature. The reaction mixture was neutralized with $NaHCO_3$ (saturated) and then extracted with EtOAc (3×). The combined extracts were washed (water then brine), dried ($MgSO_4$), and concentrated to give **75** as a white powder in 94% yield. Compound **75** (14 g, 72.16 mmol) was dissolved in a mixed solution of HCl (160 mL) and ether (80 mL) at room temperature and treated with $SnCl_2$ (162.8 g, 721.6 mmol). The reaction mixture was allowed to stir for 2 h at room temperature. The solution was cooled to 0 °C in an ice-bath, and then the precipitate was collected via filtration. The resulting solid was suspended in distilled water, and the mixture was adjusted to neutral pH by the addition of concentrated NH_4OH at 0 °C. The resulting solution was extracted with EtOAc, washed with water, brine, dried ($MgSO_4$), concentrated, and crystallized from EtOAc/hexane to give **76** with 85% yield. Compound **76** (5 g, 30.5 mmol) was further reacted with *O*-ethylxanthic acid, potassium salt (7.32 g, 45.7 mmol) to form **77** in 87% yield. ^{1}H NMR (DMSO) δ 8.08 (s, 1H), 8.35 (s, 1H).

7-Bromothiazole[4,5-*c*]pyridine-2-thiol (78) was prepared by the same method described for **77** except that bromine was used instead of chlorine gas. Compound **78** was obtained as a white powder (85% yield). ^{1}H NMR (DMSO-d_6) δ 8.48 (s, 1H), 8.54 (s, 1H).

Methanesulfonic Acid 2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-ethyl Ester (79). To a solution of **31** (100 mg, 0.29 mmol) in 5 mL of DMF at 0 °C was slowly added methanesulfonyl chloride (33.7 μL, 0.45 mmol) and triethylamine (48.6 μL, 0.35 mmol). The reaction mixture was stirred for 10 min at 0 °C followed by concentration to ca. 1 mL. The product was obtained as a solid after quenching with water followed by filtration. Compound **79** was obtained as a white powder (85% yield). ^{1}H NMR ($CDCl_3$) δ 2.9 (s, 3H), 4.68 (t, J = 4.9 Hz, 2H), 4.75 (t, J = 4.9 Hz, 2H), 5.88 (s, 2H, NH_2), 7.37 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H).

Methanesulfonic Acid 2-[6-Amino-8-(7-chlorobenzothiazol-2-ylsulfanyl)-purin-9-yl]-propyl Ester (80) was prepared by the same method described for **79** except that **32** was used instead of **31**. Compound **80** was obtained as a white powder (87% yield). ^{1}HNMR ($CDCl_3$) δ 1.93 (m, 2H), 2.91 (s, 3H), 3.47 (m, 2H), 4.52 (t, J = 7.0 Hz, 2H), 5.78 (s, 2H, NH_2), 7.39 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.43 (s, 1H).

Supporting Information Available: HRMS, HPLC, NMR data for the compounds synthesized and the experimental conditions for the solubility assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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