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Structure−Activity Relationship for Thiohydantoin Androgen Receptor Antagonists for Castration-Resistant Prostate Cancer (CRPC)

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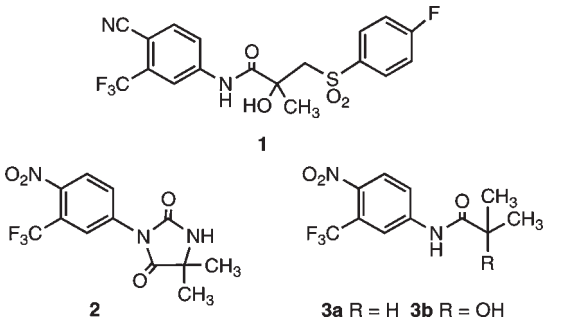
A structure−activity relationship study was carried out on a series of thiohydantoins and their analogues **14** which led to the discovery of **92** (MDV3100) as the clinical candidate for the treatment of hormone refractory prostate cancer.

Introduction

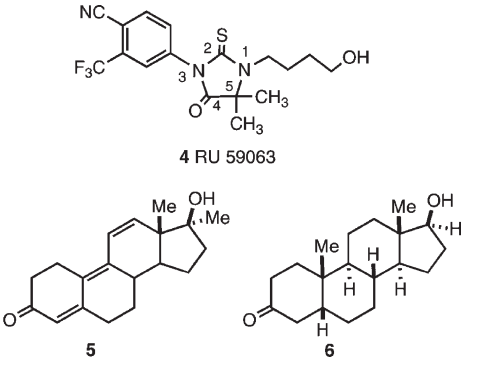
Although prostate cancer can be initially treated with either castration or androgen receptor (AR[a]) antagonists such as bicalutamide **1**, nilutamide **2**, and flutamide **3a** (which is oxidized to the active metabolite hydroxyflutamide **3b**), after a period of approximately 2−4 years, the cancer becomes resistant to such treatment (Scheme 1).[1] Indeed in this castration resistant stage (formerly called hormone refractory or "androgen-independent"), former AR antagonists such as bicalutamide become partial agonists and their use in cancer treatment must be discontinued. Sawyers and co-workers showed that a 3- to 5-fold up-regulation of the androgen receptor was the likely cause of the resistance to anti-androgens.[2] They further demonstrated that castration resistant prostate cancer was still dependent on the ligand binding domain of AR for growth.[2] Therefore, we began a research program aimed at the identification of novel chemical structures that would be potent androgen receptor antagonists, especially in its up-regulated state in castration resistant disease, without any significant agonist effect. We report here the results of our structure−activity relationship (SAR) study that led to the choice of **92** as the lead candidate for the treatment of castration-resistant prostate cancer (CRPC). This compound, named MDV3100, has completed phase 1−2 clinical trials and has now entered a phase 3 randomized trial for drug registration.[3,4]

We examined the literature on the binding of various compounds to the AR[5] and the available crystal structures of the AR[6] (there were only structures of the AR with compounds in an agonist binding mode)[7] and binding calculations.[8] We decided to begin with the structure of one of the strongest known binders to the AR, namely, the nonsteroidal AR agonist RU59063 **4**, the affinity of which for the AR is nearly equal to that of the well-known steroidal agonist R1881

Scheme 1



Scheme 2



5, both of which are slightly higher than that of the natural ligand dihydrotestosterone **6** (DHT) (Scheme 2).[9] Our plan was to vary systematically the structural units of this strong-binding agonist to see if we could obtain a reasonably strong-binding antagonist. We prepared several series of compounds in which each of the functional groups of this molecule was varied, and we measured the binding affinity and both the agonism and antagonism of each.

Synthesis

The syntheses of the compounds varied somewhat but usually involved three general routes. The first (Scheme 3)

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[a] Abbreviations: AR, androgen receptor; CRPC, castration-resistant prostate cancer; DHT, dihydrotestosterone; DMSO, dimethyl sulfoxide; FBS, fetal bovine serum; HR, hormone refractory; PK, pharmacokinetic; PSA, prostate specific antigen; SAR, structure−activity relationship; SCID, severe combined immunodeficient.

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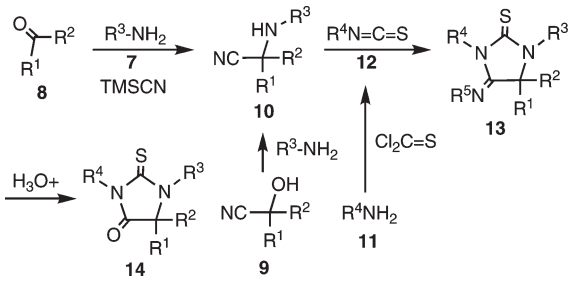
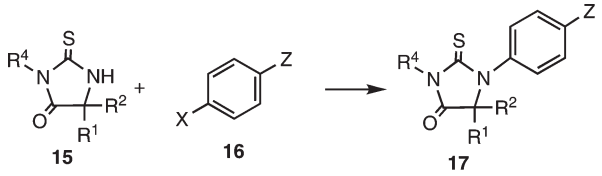
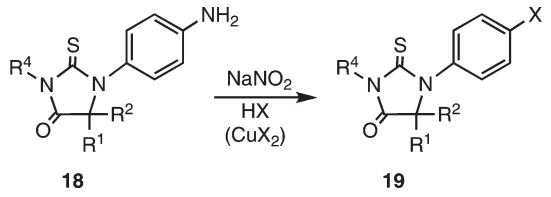
Scheme 3



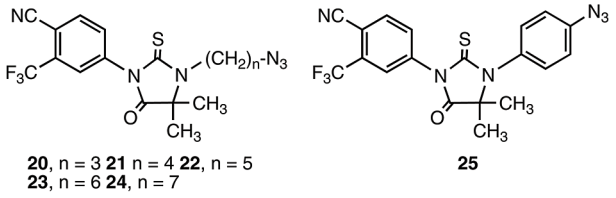
Scheme 4

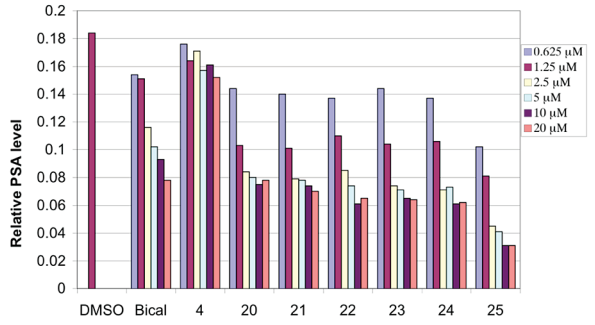


Scheme 5



Scheme 6





was a triply convergent process involving first a Strecker reaction of a substituted amine or aniline **7** with a ketone **8** and trimethylsilyl cyanide (or the preformed cyanohydrin **9**) to generate the cyanoamine **10**. The third component, the isothiocyanate **12**, prepared usually in quantitative yield from the amine **11**, was added to **10** to give the thiohydantoin-4-imine **13** (in which the group on the imine nitrogen could be either hydrogen of a thiocarbamoyl group derived from a second equivalent of the isothiocyanate). Hydrolysis of **13** afforded the desired thiohydantoins **14**. A second general method of synthesis (Scheme 4) utilized an N1-unsubstituted thiohydantoin **15** (prepared from the ketone **8** with ammonium cyanide and hydrolysis) which was added to any of several 4-halo aromatic systems **16**, e.g., X = F, Z = CN, NO_2, etc., to give the 4-substituted phenylthiohydantoins **17**. Finally several additional analogues **19** could be prepared by diazotization of 4-aminophenylthiohydantoins **18** and substitution with various groups, e.g., halogens, cyano, etc. (Scheme 5).

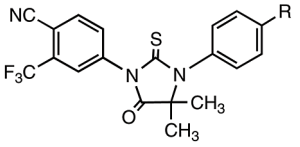
Testing Methods

Several systems were utilized to test the activity of the analogues. We used a prostate specific antigen (PSA) expression readout for normal LNCaP (hormone sensitive) cells and in LNCaP/AR cells, which were engineered (using viral infection with a cDNA encoding for the AR) to express 3- to 5-fold higher levels of the AR to mimic the clinical setting of CRPC.[4] Tests in LNCaP cells were carried out in the presence of fetal bovine serum (FBS), whereas tests in LNCaP/AR cells were carried out in charcoal stripped serum to mimic the androgen depleted, castration resistant state. We also developed a luciferase reporter system utilizing ARR_2PB-Luc, a piece of plasmid DNA that encodes firefly luciferin with AR binding sites in the natural promoter for probasin of rat prostate, which provides an easy quantitative assay for AR activity as a transcription factor.

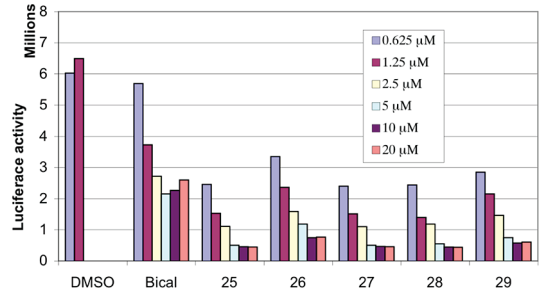
Structure−Activity Relationship

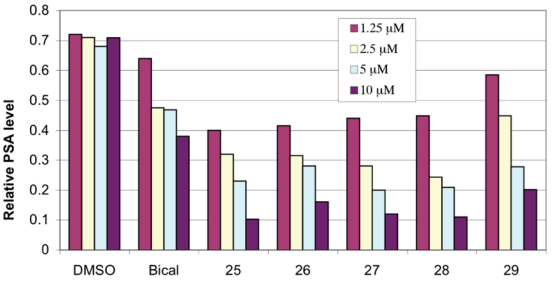
The first set of analogues prepared were analogues with azidoalkyl and azidoaryl groups at N1, **20**−**24** and **25**,[10] with the hope that the small polar azide group might mimic the hydroxyl in **4** and give good binding. The activity vs normal LNCaP (hormone sensitive) cells was measured as relative prostate specific antigen (PSA) level vs vehicle (DMSO) and using bicalutamide as a standard for antagonist activity in this

Scheme 7

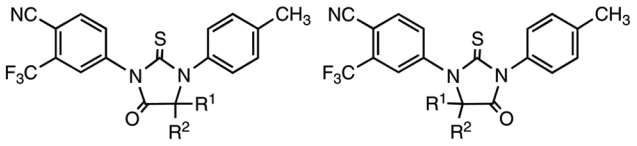


25 R = N_3 **26** R = H **27** R = Me
28 R = OH **29** R = NH_2

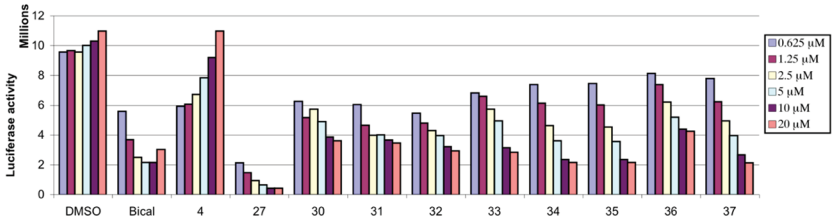




Scheme 8

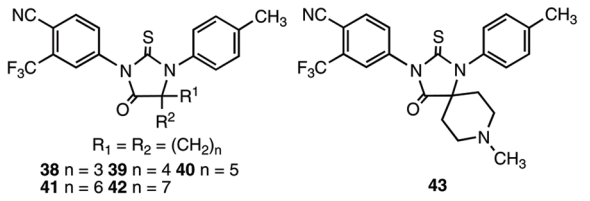


30 R = R' = H
31 R = H R' = Me
32 R = H R' = Et
33 R = H R' = Pr
34 R = R' = Et
35 R = Me R' = Et
36 R = Me R' = Et
37 R = R' = Et

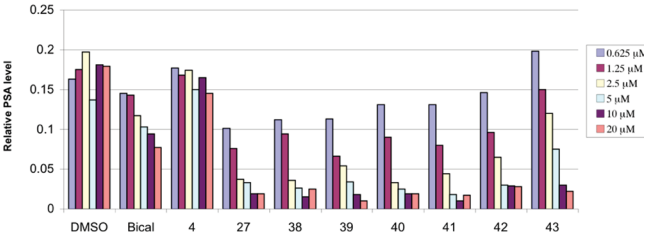


androgen-dependent assay (Scheme 6). It can be seen that all six compounds had activity better than bicalutamide itself but that **25** (the 4-azidophenyl compound) was the best of this group. We next varied the group at the 4-position of the *N*1-phenyl ring, and again all of the analogues, **25**−**29**,[11] were active (Scheme 7), both by the luciferase reporter assay and by relative PSA level. We then kept a methyl group as the substituent at the 4-position of the phenyl ring and varied the alkyl groups in the thiohydantoin ring from hydrogen to methyl, ethyl, and propyl. The activity was measured as relative luciferase activity vs bicalutamide and **27** as standards (Scheme 8). All of these derivatives were much less active than the dimethyl compound **27**, without significant differences between the hydrido analogues **30**−**33** and the dialkyl analogues **34** and **35**.[11] Analogues with the alternative arrangement of the dialkyl substituents and the carbonyl (equivalent to switching the nitrogen substituents), **36** and **37**,[11] also had reduced activity relative to **27**. However, there was little difference in activity among the analogues. We next prepared a set of analogues (Scheme 9) featuring cycloalkyl substituents on the thiohydantoin ring, all of which were made from the corresponding ketones. Their activity was measured by the relative PSA expression levels vs bicalutamide and **27** as standards. All of these derivatives showed good activity with the cyclobutyl and cyclopentyl analogues **38** and **39**,[11] being comparable to the dimethyl analogue **27**. The six-, seven-, and eight-membered rings, **40**−**42**,[11] were slightly less active. The spiro *N*-methylpiperidine analogue **43**[11] was distinctly less active, which may be due to the fact that the nitrogen would likely be charged at cellular pH. We also tested several other aromatic rings and substitution patterns on the *N*1-aryl substituent (Scheme 10) using **27** as the standard. A compound with a methyl group at the 2-position (ortho to the thiohydantoin nitrogen), **44**,[11] was active while one with a charged carboxylic acid group at the 2-position, **45**,[11] was inactive. The compound with chloromethyl groups at C5, **46**,[11] had decreased activity, while the analogue with a fluoromethyl group, **47**,[11] had good activity. Other functional groups were placed at the 4-position of the *N*1-phenyl substituent, and their activity was assayed using a relative PSA readout vs standards (Scheme 11). Nearly all of the substituents showed good activity when compared to the best molecules in their series; e.g., the 4-phenyl and 4-hydroxy analogues **48** and **49**[11] were very similar in activity to **38**. Similarly the 4-cyano and 4-nitro analogues, **50** and **51**,[11] were nearly as active as the

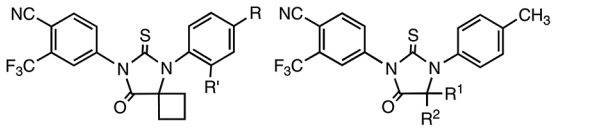
Scheme 9



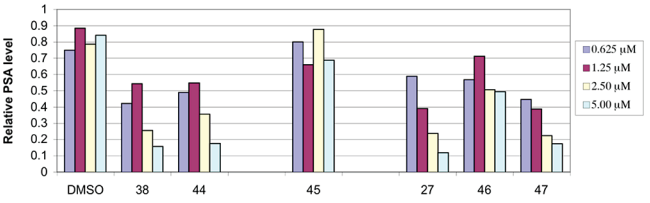
$R_1 = R_2 = (CH_2)_n$
38 n = 3 **39** n = 4 **40** n = 5
41 n = 6 **42** n = 7
43



Scheme 10

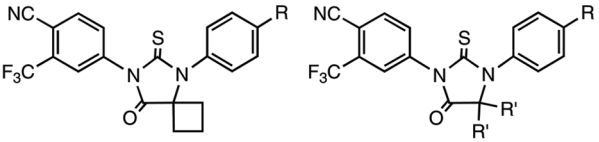


38 R = CH_3 R' = H
44 R = H R' = CH_3
45 R = H R' = CO_2H
27 $R^1 = R^2 = CH_3$
46 $R^1 = R^2 = CH_2Cl$
47 $R^1 = CH_3$ $R^2 = CH_2F$



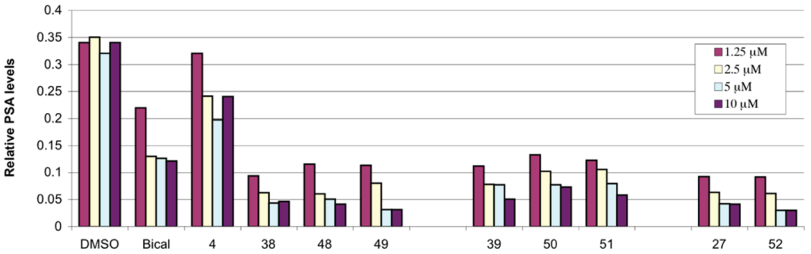
methyl analogue **39**, while the 4-trifluoromethyl analogue **52**[11] was slightly more active than the methyl analogue **27**. Thus, the 4-position of the 1-phenyl ring can bear many different substituents without losing activity. We also prepared and tested various imine and thione analogues of the active series using a relative PSA readout vs **27** and **38** as standards (Scheme 12). In all cases the thiohydantoins with the thiocarbonyl at C2 and the carbonyl at C4 were the most active although the imines, **53** and **54**,[11] were nearly as active as the parent compounds **27** and **38** while the dithiohydantoin and

Scheme 11

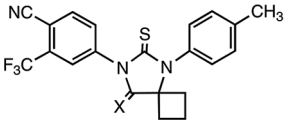


27 R = CH_3
48 R = Ph
49 R = OH

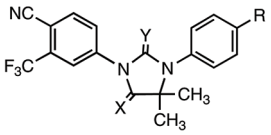
39 R' = R" = $(CH_2)_4$ R = CH_3
50 R' = R" = $(CH_2)_4$ R = CN
51 R' = R" = $(CH_2)_4$ R = NO_2
27 R' = R" = CH_3 R = CH_3
52 R' = R" = CH_3 R = CF_3



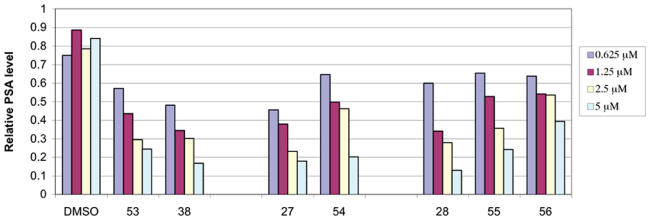
Scheme 12



38 X = O
53 X = NH



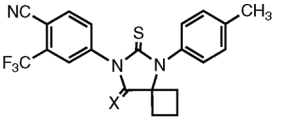
27 X = O Y = S R = CH_3
54 X = NH Y = S R = CH_3
28 X = O Y = S R = OH
55 X = Y = S R = OH
56 X = Y = O R = OH



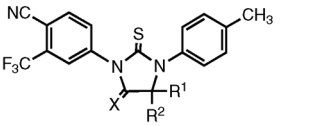
the hydantoin analogues, **55** and **56**,[11] were not as active as the parent thiohydantoin **28**.

Other imine derivatives, e.g., **57** and **60**,[11] were also somewhat active as shown in Scheme 13, using both relative PSA levels and the luciferase assay vs **27** and **38** as standards. The *N*-thiocarbamoyl analogues **58**−**62**[11] were prepared by using an excess of the isothiocyanate, e.g., **12**, in the coupling reaction with the corresponding aniline. They were all active, but they are hydrolyzed to the corresponding thiohydantoins under cellular conditions. The condensation of the cyanoamine **10** with the isothiocyanate **12** gave a small amount of a new chemical entity, namely, the thiazolidine-2,5-dimines, in which the 5-imino anion bears a thiocarbamoyl group. These compounds are presumably formed by attack of the sulfur atom, rather than the nitrogen atom, of the thioamide anion on the nitrile of the cyanoamine with subsequent trapping of that imine anion with another equivalent of the isothiocyanate. Two of these new analogues, **63** and **64**,[11] were tested for activity using both the relative PSA levels and the luciferase reporter assay (Scheme 14). Both of these new compounds showed excellent activity comparable to their parent thiohydantoin analogues **27** and **38**. As far as we can tell, this is the first time any compounds with such a structure have been shown to have antiandrogen activity. Therefore, these compounds

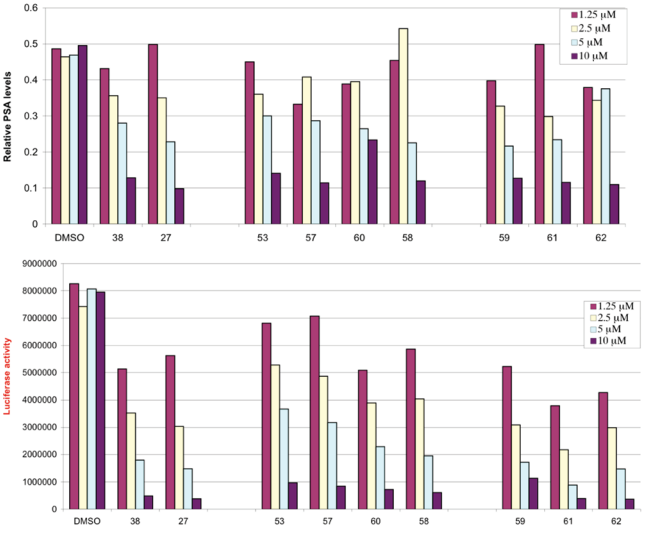
Scheme 13



38 X = O
53 X = NH
57 X = NMe
58 X = NC(=S)NHPh
59 X = $NC(=S)NHC_6H_3$-4-CN-3-CF_3

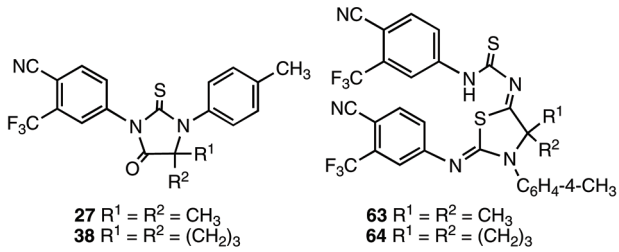


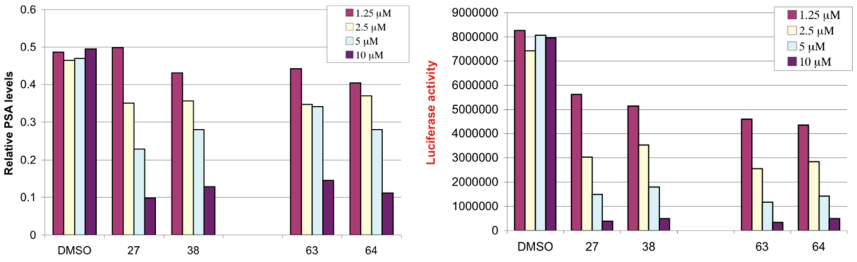
60 R^1 = R^2 = CH_3 X = NEt
61 R^1 = CH_3 R^2 = CH_2F
X = $NC(=S)NHC_6H_3$-4-CN-3-CF_3
62 R^1 = R^2 = CH_3
X = $NC(=S)NHC_6H_3$-4-CN-3-CF_3



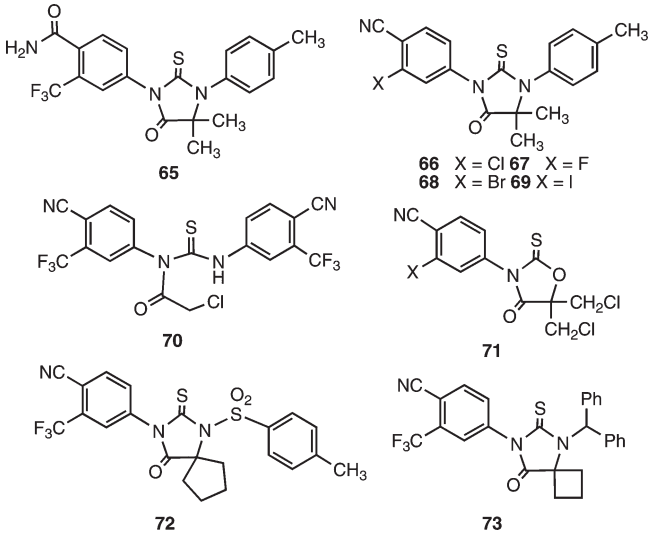
represent a new structural class of antiandrogens. Since the activity of these two new compounds are extremely similar to their thiohydantoin counterparts in both the PSA and luciferase assay systems, it is interesting to speculate whether they are being converted, under the cellular testing conditions, into the thiohydantoins. That would require cleavage of the iminothiourea to the imine, opening of the ring via reformation of the nitrile with ejection of the thiolate anion, and then recyclization of the thioamide anion on to the nitrile via the nitrogen atom. Finally in our early set of compounds, we found several that were essentially devoid of activity (Scheme 15). Various derivatives of the nitrile, e.g., the amide **65**,[11] were inactive as were various analogues in which the ortho

Scheme 14





Scheme 15



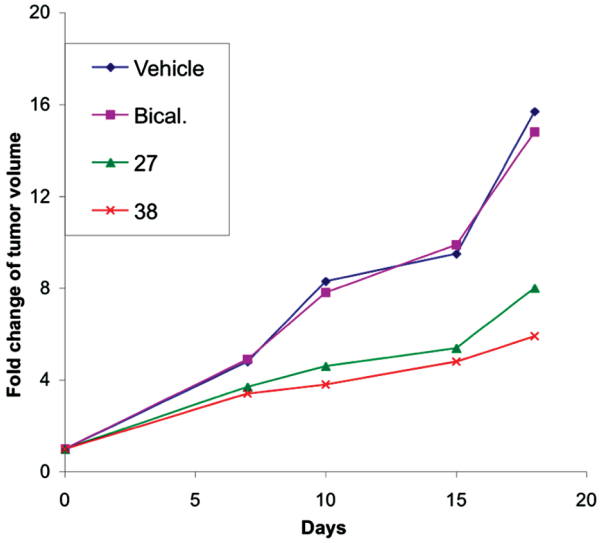


Figure 1. Fold change in tumor volume of xenografts with bical, **27**, and **38** (10 mg/kg).

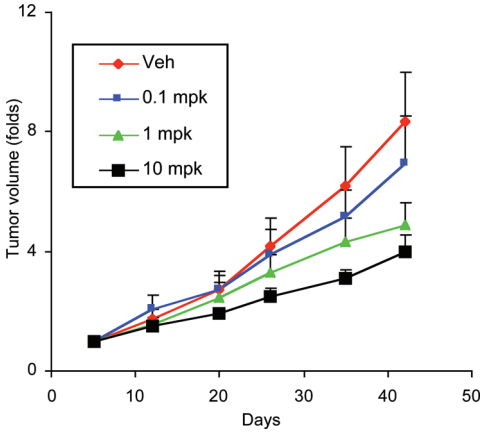


Figure 2. Dose response in change in tumor volume of xenografts with **38**.

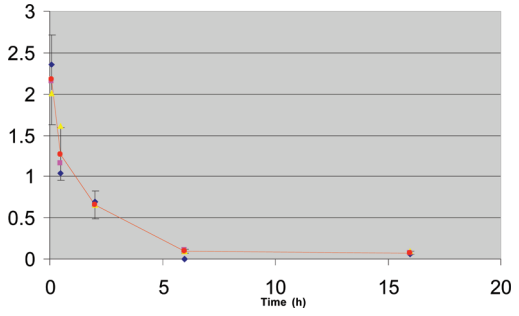
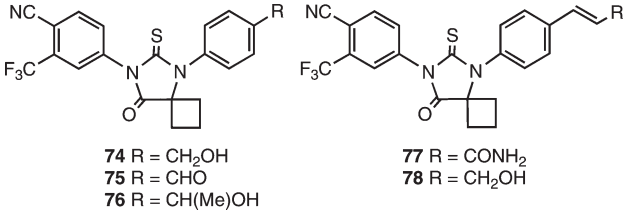


Figure 3. Serum concentration of **38** after iv injection; $n = 3$ mice.

Scheme 16



trifluoromethyl group was replaced by halogens, **66**–**69**.[11] Acyclic analogues, e.g., the chloromethylamide **70**,[11] were

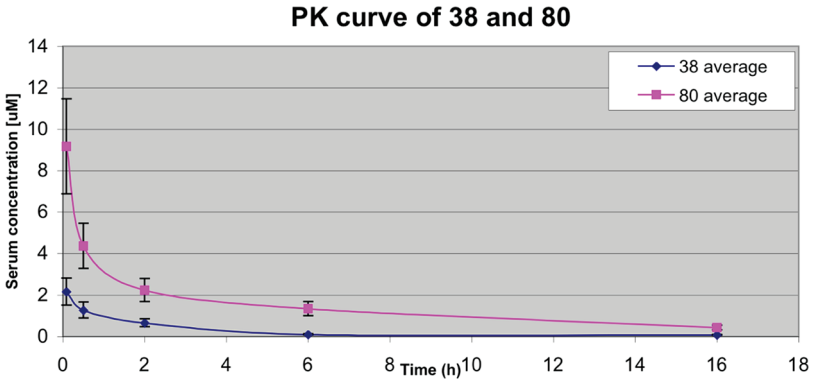
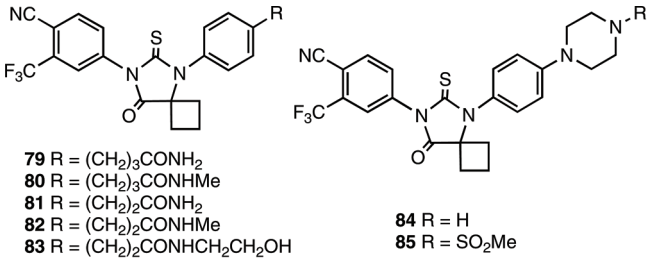
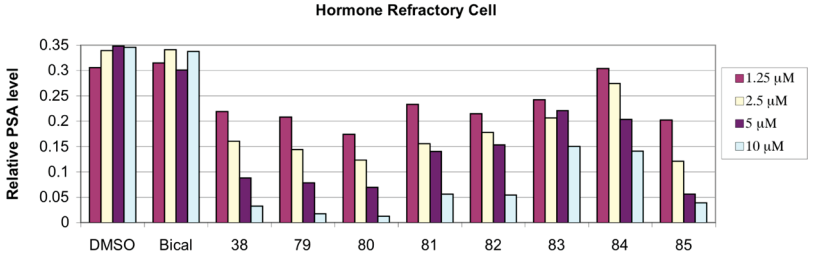


Figure 4. PK curves of **38** and **80**.

Scheme 17

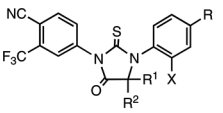




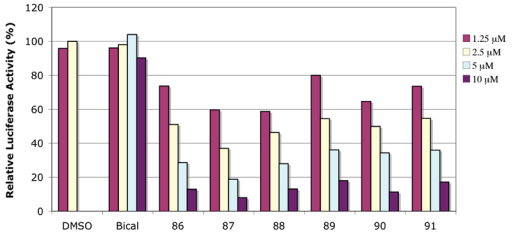
inactive as was the 4-oxooxazolidine-2-thione **71**.[11] Compounds with a spacer group between the ring nitrogen and the aryl group, e.g., the arylsulfonylamide **72** and the benzhydryl analogue **73**,[11] were inactive.

While carrying out this SAR study using in vitro assays, we also decided to test the in vivo activity of lead compounds in animals to gauge their pharmacologic properties and ability to impair growth of castration-resistant prostate cancer xenograft models that are also resistant to bicalutamide. Therefore the ability of compounds **27** and **38** to decrease the growth of LAPC4/AR cells or LNCaP/AR cells grown as xenografts in castrate SCID mice was assayed. In a pilot experiment using the LAPC4/AR xenograft model (Figure 1),[12] both compounds were more effective than bicalutamide with **38** being slightly superior, with an IC_{50} value of 124 nM for inhibition of PSA secretion. This thiohydantoin **38** also showed a good dose response in the castration-resistant xenograft assay (Figure 2). However, **38** had a short half-life with a very rapid clearance as shown in Figure 3. This was likely due to both a rapid metabolism (hydroxylation of the aromatic methyl group) and its relatively high clogP value of 4.20 (compared to 2.91 for bicalutamide). Therefore, we decided to prepare additional analogues of **38** that would be more polar. In particular we decided to change the substituents on the aryl ring attached to N1, especially at the 4-position, to see if more polar and more stable analogues could be prepared. Therefore, several simple analogues of **38** were prepared (Scheme 16), all of which showed good activity in the PSA secretion assay. The two benzylic alcohol analogues **74** and **76** as well as the aldehyde **75** exhibited IC_{50} values of 200−300 nM but were considerably more polar than **38**. The extended amide and alcohol analogues **77** and **78** were even more active with IC_{50} values of 100−150 nM. A series of analogues with extended chains and heterocyclic units were prepared, and their activity using PSA levels in the hormone refractory cell line LNCaP/AR was evaluated in vitro (Scheme 17). All the derivatives, with the exception of the (hydroxyethyl)amide and piperazine analogues **83** and **84**, showed good activity, especially compared to bicalutamide which is inactive in this hormone-refractory assay. The most active compound was the *N*-methylbutyramide analogue **80**, which was determined to have an IC_{50} of 92 nM with a clogP of 3.44. But as the data show, several other analogues were also quite active with the *N*-methylamides being generally more active than the amides themselves. The corresponding esters and acids were also prepared as well as the analogous phenylacetamide derivatives (two-carbon chain), but the activity of all of these was weaker (data not shown). Although **80** showed excellent activity, its PK was also poor (Figure 4), although it was somewhat more available than the earlier analogue **38**. Although hydrolysis of the *N*-methylamide to the acid was seen, we postulated that one reason for the low serum concentration of both **38** and **80** was metabolism via oxidation of the electron-rich aromatic ring. To try to eliminate this problem, we decided to prepare

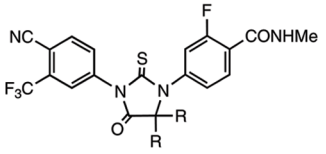
Scheme 18



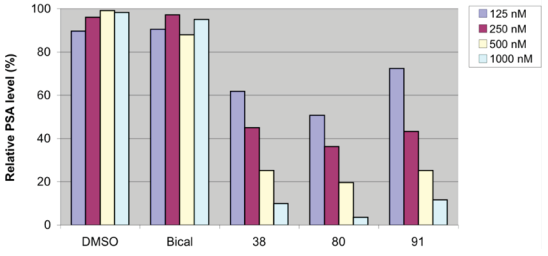
86 $R_1 = R_2 = (CH_2)_3$ R = SO_2Me X = H
87 $R_1 = R_2 = CH_3$ R = CO_2Me X = H
88 $R_1 = R_2 = CH_3$ R = CONHMe X = H
89 $R_1 = R_2 = (CH_2)_3$ R = CONHMe X = H
90 $R_1 = R_2 = (CH_2)_3$ R = OH X = F



Scheme 19



91 $R = (CH_2)_3$
92 $R = CH_3$ MDV3100
93 $R = (CH_2)_4$



analogues that had the electron-withdrawing group attached directly to the aromatic ring (Scheme 18), which yielded several very active compounds based on evaluation in the hormone refractory LNCaP/AR assay. Thus, the sulfone **86**, the ester **87**, and the two amides **88** and **89** showed good activity as did the fluorophenol **90**. However, we found that the 3-fluoroamide analogue **91** (also called RD162)[4,13] had not only excellent activity (Scheme 19) but also a superb pharmacokinetic (PK) profile. Its IC_{50} was 122 nM, and it had a clogP of 3.20. However, the measure of its excellent PK profile was its steady state concentration as shown in Table 1. Compound **91** has almost the exact same exposure after a 10 mg/kg dose as bicalutamide, e.g., 9.9 mM vs 10 mM. And the IC_{50} of **91** is nearly 8 times lower than that of bicalutamide, 122 nM vs 1 mM.

The concentration of **91** after iv and oral administration is shown in Figure 5. With this excellent PK profile, we decided to choose **91** as our lead drug candidate. Its activity on LNCaP/AR (HR) tumor size at 10 and 50 mg/kg once a day

Table 1

compd	IC_{50} (nM)	clogP	C_{ss} 10 mpk (mM)
bicalutamide (**1**)	1000	2.91	10.0
38	124	4.20	NA
80	92	3.44	0.39
91	122	3.20	9.9

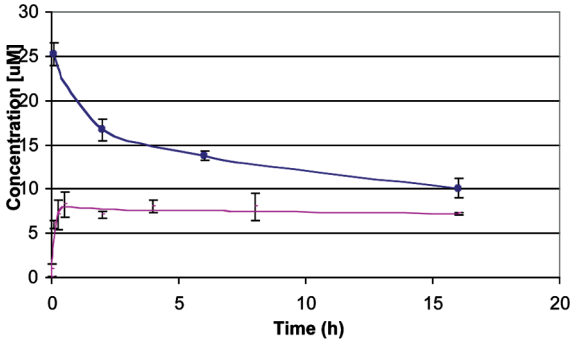


Figure 5. Concentration of **91** after iv (blue) or oral (pink) administration.

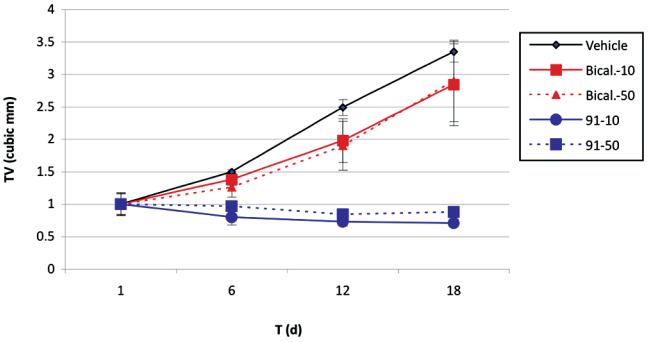


Figure 6. Effect of bicalutamide and **91** on LNCaP/AR (HR) tumor size at 10 and 50 mg/kg once a day.

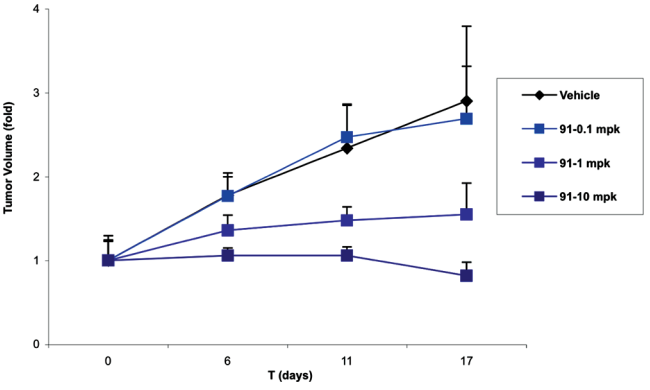


Figure 7. Dose response in tumor volume change of xenografts with **91** at 0.1, 1, and 10 mg/kg once a day.

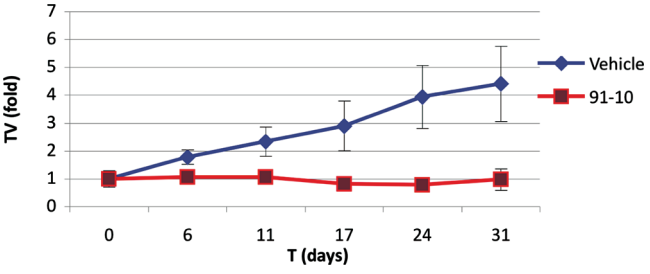
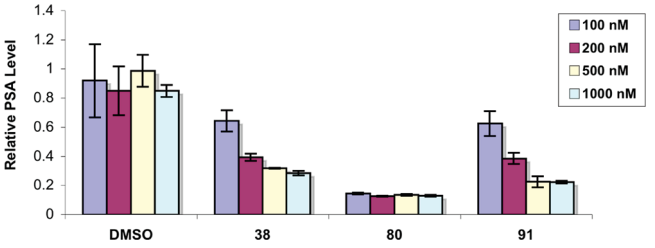


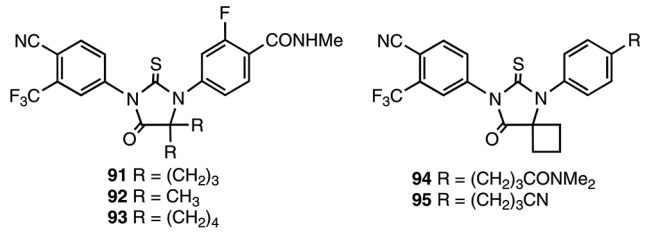
Figure 8. Effect of change in tumor volume of xenografts with **91** at 10 mg/kg once a day.

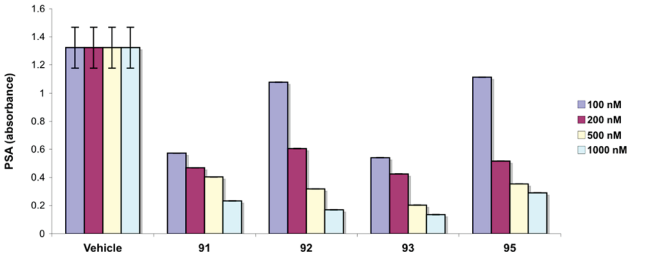
vs bicalutamide at the same dose (Figure 6) shows it to be very active. It is cytostatic at these doses. The dose response of **91** in LNCaP xenografts[14] (Figure 7) shows that at least 1 (mg/kg)/day is required and that 10 (mg/kg)/day is optimal. We also assayed the activity of **91** on LNCaP xenografts over an

Scheme 20. Effect of **38**, **80**, and **91** on Hormone Sensitive LNCaP Cells



Scheme 21





extended period (Figure 8) which showed that it retains activity at 10 (mg/kg)/day for 31 days. Since **91** was initially screened in hormone-refractory models, we also looked at its effect in hormone sensitive cells[15] (Scheme 20) and found good activity vs LNCaP cells, albeit not as good as **80**. But this relative liability is counterbalanced by its excellent PK properties. Thus, it is possible that **91** might be able to be used for treatment of both types of prostate cancer, hormone sensitive and castration-resistant, but one must wait for data from clinical trials.

Several additional analogues of both **80** and **91** were prepared and tested (Scheme 21). We made both the dimethylamide and the nitrile analogues of **80** (**94** and **95**,[13] respectively) in order to try to identify a strong-binding analogue with better PK and, in particular, a longer half-life. Both of these compounds had quite good activity compared to earlier compounds. Two additional analogues of **91** were prepared and tested for their activity on castration resistant prostate cancer, namely, the analogues with the cyclobutyl unit replaced by dimethyl unit, **92**, and cyclopentyl unit, **93**.[13] Both of these new analogues were very active in hormone-refractory LNCaP/AR with essentially the same activity as **91**. A dose−response study (Figure 9) showed **92** to be a little more active than **91**. Since the dimethyl analogue **92** offers the great advantage of an inexpensive starting material, acetone or its cyanohydrin, for its production, it was chosen as the drug candidate and subjected to metabolic stability, toxicology, and further animal studies. This compound **92** (also called RD162′) was licensed by Medivation, Inc. It has now entered phase 3 clinical trials for the treatment of castration-resistant prostate cancer.[4] Further details on this compound will be reported in due course.

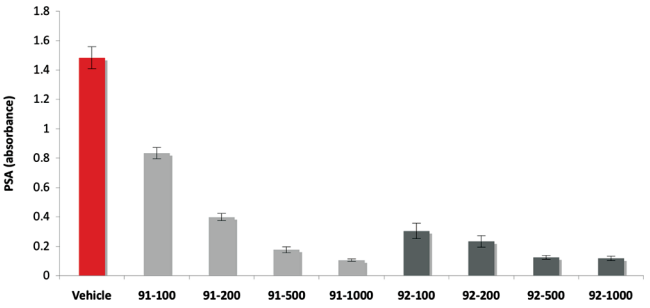


Figure 9. Dose response study of **91** and **92** (nM) on castration resistant LNCaP AR cells.

Conclusion

We have described the structure−activity relationship study that led to the choice of **92** as a clinical candidate for the treatment of castration-resistant prostate cancer. Many analogous diarylthiohydantoins in this series showed good androgen receptor antagonism with essentially no agonism, but the pharmacokinetic properties of **91** and its close analogues **92** and **93** led to the choice of **92** as the clinical candidate.

Experimental Section

General. All reactions were carried out under an argon atmosphere unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether were distilled from benzoquinone ketyl radical under an argon atmosphere. Dichloromethane, toluene, benzene, pyridine, triethylamine, and diisopropylethylamine (DIPEA) were distilled from calcium hydride under an argon atmosphere. Dimethyl sulfoxide (DMSO) was distilled over calcium hydride and stored over 4 Å molecular sieves. All other solvents or reagents were purified according to literature procedures. ^{1}H NMR and ^{13}C NMR spectra were obtained on ARX-400, ARX-500, or Avance-500 spectrometers. The chemical shifts are reported in parts per million (ppm, δ). The coupling constants are reported in hertz (Hz), and the resonance patterns are reported with notations as the following: br (broad), s (singlet), d (double), t (triplet), q (quartet), and m (multiplet). Infrared spectra were recorded on Nicolet 501 or Nicolet AVATAR 370 instrument using liquid films (neat) or in $CDCl_3$ solution on NaCl plates, and only the significant absorption bands are recorded (in cm^{-1}). Thin-layer chromatography (TLC) was carried out using precoated silica gel sheets (Merck 60 F_{254}). Visual detection was performed with ultraviolet light, *p*-anisaldehyde stain, potassium permanganate stain, or iodine. Flash chromatography was performed using SilicaFlash P60 (60 A, 40−63 μm) silica gel from SiliCycle, Inc., with compressed air. HPLC was performed on a Waters HPLC using either a C18 reverse phase column or a normal silica gel column as appropriate. The purity of all final compounds was established to be at least 95% pure by a combination of TLC R_f values in several solvent systems and HPLC. Additionally the absence of any extraneous peaks in the proton NMR spectrum confirmed the high level of purity.

Synthesis of 20−24. 4-Isothiocyanato-2-trifluoromethylbenzonitrile, 12a. 4-Amino-2-trifluoromethylbenzonitrile (2.23 g, 12 mmol) was added portionwise over 15 min into a well-stirred heterogeneous mixture of thiophosgene (1 mL, 13 mmol) in water (22 mL) at 21 °C. Stirring was continued for an additional 1 h. The reaction medium was extracted with chloroform (3 × 15 mL). The combined organic phase was dried over $MgSO_4$ and evaporated to dryness under reduced pressure to yield desired product as brownish solid and was used as such for the next step (2.72 g, 11.9 mmol, 99%).

1,4-Diazidobutane, 20a. To a mixture of 1,4-dibromobutane (21.6 g, 100 mmol) in DMF (100 mL) was added an aqueous solution of sodium azide (13.65 g, 210 mmol in 50 mL of water).

The mixture was stirred and heated to 80 °C for 20 h, and then the medium was washed with brine (200 mL) and extracted with hexane (3 × 300 mL). The combined organic layer was dried over $MgSO_4$ and concentrated to yield 1,4-diazidobutane as a liquid (13.72 g, 9.8 mmol, 98%).

4-Azidobutylamine, 20b. To a mixture of 1,4-diazidobutane **20a** (4.20 g, 30 mmol), aqueous 1 M HCl (60 mL), diethyl ether (20 mL), and ethyl acetate (20 mL) cooled to 0 °C was added triphenylphosphine portionwise during 1 h. The mixture was warmed to 21 °C and stirred for an additional 20 h, and then the organic layer was separated from the aqueous layer. The aqueous phase was washed with ethyl ether (2 × 50 mL) to remove triphenylphosphine oxide residual. The aqueous phase was basified to a pH 13 by aqueous NaOH and then was extracted with dichloromethane (3 × 100 mL). The combined dichloromethane layer was dried over $MgSO_4$ and concentrated to yield 4-azidobutylamine (2.74 g, 24 mmol, 80%) as a liquid.

2-(4-Azidobutylamino)-2-methylpropionitrile, 20c. A mixture of 4-azidobutylamine **20b** (0.57 g, 5 mmol), acetone cyanohydrin (0.425 g, 5 mmol), and Na_2SO_4 (0.2 g) was stirred at 21 °C for 12 h. The mixture was diluted with hexane and filtered off. The filtrate was concentrated to yield 2-(4-azidobutylamino)-2-methylpropionitrile (0.896 g, 4.95 mmol, 99%) as a liquid.

4-[3-(4-Azidobutyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 20d. A mixture of isothiocyanate **12a** (0.684 g, 3 mmol), **20c** (0.543 g, 3 mmol), and triethylamine (0.04 g, 0.4 mmol) in THF (6 mL) was refluxed for 1 h. The medium was concentrated and chromatographed (dichloromethane/acetone, 6:1) to obtain **20d** (0.834 g, 2.04 mmol, 68%) as an off-white solid.

4-[3-(4-Azidobutyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 20. A mixture of **20d** (0.818 g, 2.0 mmol), aqueous 1 M HCl (5 mL), and methanol (20 mL) was heated to reflux for 1 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (25 mL) and extracted with dichloromethane (50 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 9:1) to yield **20** (0.803 g, 1.96 mmol, 98%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 6H), 1.63−1.71 (m, 2H), 1.88−1.96 (m, 2H), 3.37 (t, J = 6.6 Hz, 2H), 3.71 (t, J = 8.1 Hz, 2H), 7.77 (dd, J = 8.2, 1.8 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 25.5, 26.4, 43.7, 50.9, 65.1, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.9 Hz), 132.1, 133.4 (q, J = 33.0 Hz), 135.1, 137.1, 175.2, 178.4.

The same procedure was applied for the synthesis of **21**−**24**.

4-[3-(3-Azidopropyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 6H), 2.01−2.08 (m, 2H), 3.38 (t, J = 6.4 Hz, 2H), 3.71 (t, J = 7.8 Hz, 2H), 7.74 (dd, J = 8.2, 1.8 Hz, 1H), 7.87 (d, J = 1.8 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 27.4, 41.6, 49.0, 65.2, 109.6, 114.9, 120.0 (q, J = 272.4 Hz), 127.0 (q, J = 4.9 Hz), 132.3, 132.9 (q, J = 33.0 Hz), 135.2, 137.3, 175.1, 178.5.

4-[3-(5-Azidopentyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44−1.50 (m, 2H), 1.56 (s, 6H), 1.61−1.67 (m, 2H), 1.80−1.86 (m, 2H), 3.27 (t, J = 6.7 Hz, 2H), 3.67 (t, J = 8.2 Hz, 2H), 7.77 (dd, J = 8.2, 1.8 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 24.2, 27.6, 28.3, 44.0, 51.2, 65.1, 109.8, 114.9, 121.9 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 132.2, 133.2 (q, J = 33.0 Hz), 135.1, 137.2, 175.2, 178.3.

4-[3-(6-Azidohexyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31−1.41 (m, 4H), 1.51 (s, 6H), 1.52−1.59 (m, 2H), 1.74−1.81 (m, 2H), 3.20 (t, J = 6.7 Hz, 2H), 3.62 (t, J = 8.2 Hz, 2H), 7.75 (dd, J = 8.2, 1.8 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 26.1, 26.5, 27.8, 28.6, 44.1, 51.2, 65.1, 109.5, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 132.2, 133.2 (q, J = 33.0 Hz), 135.1, 137.3, 175.2, 178.1.

4-[3-(7-Azidoheptyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 24. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30−1.42 (m, 6H), 1.53 (s, 6H), 1.54−1.59 (m, 2H), 1.74−1.81 (m, 2H), 3.21 (t, J = 6.7 Hz, 2H), 3.64 (t, J = 8.2 Hz, 2H), 7.76 (dd, J = 8.2, 1.8 Hz, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 26.5, 26.6, 26.8, 27.9, 28.6, 44.2, 51.3, 65.1, 109.6, 114.9, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 132.2, 133.2 (q, J = 33.0 Hz), 135.1, 137.3, 175.3, 178.1.

Synthesis of 26. 2-Methyl-2-phenylaminopropanenitrile, 26a. A mixture of aniline (0.931 g, 10 mmol) and acetone cyanohydrin (2 mL) was heated to reflux and stirred for 20 h. After being cooled to 21 °C, the reaction mixture was poured into ethyl acetate (40 mL) and washed with cold water (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to dryness to yield **26a** (1.51 g, 9.4 mmol, 94%) as a brown slurry liquid.

4-[3-Phenyl-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 26. A mixture of isothiocyanate **12a** (0.274 g, 1.2 mmol) and **26a** (0.160 g, 1 mmol) in DMF (0.2 mL) was stirred for 48 h. To this mixture were added methanol (10 mL) and 2 N HCl (3 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **26** (0.276 g, 0.71 mmol, 71%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 7.28−7.31 (m, 2H), 7.50−7.58 (m, 3H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.96−7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7, 66.4, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 129.8, 129.9, 132.2, 133.4 (q, J = 33.2 Hz), 135.1, 135.2, 137.2, 175.0, 179.9.

Synthesis of 27. 2-Methyl-2-(4-methylphenyl)aminopropanenitrile, 27a. A mixture of *p*-toluidine (1.07 g, 10 mmol) and acetone cyanohydrin (10 mL) was heated to 80 °C and stirred for 4 h. The medium was concentrated and dried under vacuum to yield **27a** (1.72 g, 9.9 mmol, 99%) as a brown solid.

4-[3-(4-Methylphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 27. A mixture of isothiocyanate **12a** (0.547 g, 2.4 mmol) and **27a** (0.348 g, 2 mmol) in DMF (0.6 mL) was stirred for 36 h. To this mixture were added methanol (20 mL) and 2 N HCl (5 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (30 mL) and extracted with ethyl acetate (40 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **27** (0.596 g, 1.48 mmol, 74%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 2.44 (s, 3H), 7.17−7.20 (m, 2H), 7.33−7.36 (m, 2H), 7.86 (dd, J = 8.3, 1.8 Hz, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 23.6, 66.4, 110.0, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.2, 130.6, 132.2, 132.3, 133.4 (q, J = 33.2 Hz), 135.2, 137.2, 140.1, 175.1, 179.9.

Synthesis of 28. 2-(4-Hydroxyphenylamino)-2-methylpropanenitrile, 28a. A mixture of 4-aminophenol (1.09 g, 10 mmol), acetone cyanohydrin (10 mL), and $MgSO_4$ (2 g) was heated to 80 °C and stirred for 4 h. After concentration of the reaction medium under vacuum, compound **28a** was crystallized from water (20 mL). The solid was filtered and dried to yield **28a** (1.69 g, 9.6 mmol, 96%).

4-[3-(4-Hydroxyphenyl)-5-imino-4,4-dimethyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 28b. Triethylamine (0.101 g, 1 mmol) was added to a solution of isothiocyanate **12a** (0.456 g, 2 mmol) and **28a** (0.352 g, 2 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C for 48 h and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 85:15) to afford **28b** (0.274 g, 0.68 mmol, 34%).

4-[3-(4-Hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 28. A mixture of **28b** (0.202 g, 0.5 mmol) in aqueous 2 N HCl (2 mL) and methanol

(5 mL) was heated to reflux for 2 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 9:1) to yield **28** (0.198 g, 0.49 mmol, 98%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (s, 6H), 6.26 (s, OH), 6.90−6.93 (m, 2H), 7.11−7.14 (m, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 66.5, 109.9, 114.9, 115.7, 116.8, 121.9 (q, J = 272.7 Hz), 127.2 (q, J = 4.7 Hz), 130.6, 132.3, 133.5 (q, J = 33.2 Hz), 135.3, 137.2, 157.0, 175.3, 180.2.

Synthesis of 29. 4-Aminophenyl)carbamic Acid *tert*-Butyl Ester, 29a. An aqueous solution of potassium carbonate (1.52 g, 11 mmol in 5 mL of water) was added to a solution of 1,4-diaminobenzene (3.24 g, 30 mmol) in a mixture of THF (30 mL) and DMF (10 mL). To this mixture was added di-*tert*-butyl pyrocarbonate, Boc_2O (2.18 g, 10 mmol), dropwise over 0.5 h. The reaction mixture was stirred for an additional 4 h at 21 °C. The mixture was then poured into cold water (40 mL) and extracted with chloroform (3 × 50 mL). The combined organic phase was dried over $MgSO_4$ and concentrated to yield a brown residue which was subjected to flash chromatography (dichloromethane/acetone, 4:1) to afford **29a** as a yellow solid (1.98 g, 9.5 mmol, 95%) (yield based on Boc_2O).

{4-[(1-Cyano-1-methylethyl)amino]phenyl}carbamic Acid *tert*-Butyl Ester, 29b. A mixture of **29a** (0.83 g, 4 mmol) and acetone cyanohydrin (4 mL) and $MgSO_4$ (2 g) was heated to 80 °C and stirred over 2.5 h. After the mixture was cooled to 21 °C, compound **29b** was crystallized from water (30 mL). The solid was filtered and dried to yield **29b** (1.08 g, 3.9 mmol, 98%).

{4-[3-(4-Cyano-3-trifluoromethylphenyl)-4-imino-5,5-dimethyl-2-thioxoimidazolidin-1-yl]phenyl}carbamic Acid *tert*-Butyl Ester, 29c. Triethylamine (0.202 g, 2 mmol) was added to a solution of isothiocyanate **12a** (0.456 g, 2 mmol) and **29b** (0.57 g, 2 mmol) in dry THF (5 mL). The reaction mixture was stirred at 21 °C for 15 h and then concentrated to yield a dark residue which was subjected to flash chromatography (ethyl ether/acetone, 97:3) to afford **29c** (0.15 g, 0.3 mmol, 15%).

4-[3-(4-Aminophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 29. A mixture of **29c** (0.15 g, 0.3 mmol) in aqueous 3 N HCl (1 mL) and methanol (4 mL) was heated to reflux for 2 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (5 mL) and extracted with dichloromethane (8 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 9:1) to yield **29** (0.118 g, 0.29 mmol, 97%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 6.73−6.75 (m, 2H), 7.00−7.03 (m, 2H), 8.02 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 66.2, 109.1, 114.3, 114.9, 120.4, 122.0 (q, J = 272.5 Hz), 127.0 (q, J = 4.9 Hz), 130.4, 132.5 (q, J = 33.0 Hz), 133.4, 135.6, 138.5, 149.2, 175.3, 180.4.

Synthesis of 25. 4-[3-(4-Azidophenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 25. An aqueous solution of sulfuric acid (25 wt %, 1 mL) was added to a solution of **29** (0.10 g, 0.25 mmol) in acetone (1 mL) cooled to −5 °C. An aqueous solution of $NaNO_2$ (0.024 g, 0.35 mmol, in 0.5 mL of water) was added slowly to the above mixture over 0.1 h. The reaction mixture was allowed to stir at −5 °C for an additional 1 h, and then an aqueous solution of NaN_3 (0.02 g, 0.3 mmol in 0.3 mL of water) was added dropwise. Upon completion of the addition, the reaction medium was warmed to 21 °C and stirred for an additional 3 h. The product was extracted with dichloromethane (3 × 5 mL). The combined organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **25** (0.08 g, 0.18 mmol, 72%) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 6H), 7.17−7.20 (m, 2H), 7.27−7.30 (m, 2H), 7.84 (dd, J_1 = 8.3, 1.8 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 66.4, 110.1, 114.8, 120.4, 122.1 (q, J = 272.5 Hz), 127.0 (q, J = 4.7 Hz), 131.1, 131.5, 132.3, 133.3 (q, J = 33.0 Hz), 135.3, 137.1, 141.7, 174.8, 180.1. MS for $C_{19}H_{13}F_3N_6OS$, calculated 430.4, found 430.1.

Synthesis of 30−37. *N*-(4-Cyano-3-trifluoromethylphenyl)-*N*′-(4-methylphenyl)thiourea, 30a. Addition of a solution of 4-methylaniline in DMF to a solution of the isothiocyanate **12a** in DMF solution at 21 °C for 1 h afforded the desired unsymmetrical thiourea **30a** in 99% yield.

4-[3-(4-Methylphenyl)-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 30. Treatment of a solution of the thiourea **30a** in THF at 0 °C with a solution of chloroacetyl chloride in THF for 1 h gave a 95% yield of a 1:1 mixture of the two thiohydantoins, the 4-oxo and the 5-oxo regioisomers **30** and **30b**. These were easily separated by column chromatography, using silica gel (dichloromethane), to give pure **30**.

4-[3-(4-Methylphenyl)-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 31. To a suspension of NaH in THF cooled to 0 °C was added the unsubstituted thiohydantoin **30**, and the mixture was stirred for 30 min. A solution of methyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the pure 4-methylthiohydantoin **31**.

4-[3-(4-Methylphenyl)-4-ethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 32. To a suspension of NaH in THF cooled to 0 °C was added the unsubstituted thiohydantoin **30**, and the mixture was stirred for 30 min. A solution of ethyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the pure 4-ethylthiohydantoin **32**.

4-[3-(4-Methylphenyl)-5-oxo-4-propyl-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 33. To a suspension of NaH in THF cooled to 0 °C was added the unsubstituted thiohydantoin **30**, and the mixture was stirred for 30 min. A solution of propyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the pure 4-propylthiohydantoin **33**.

4-[3-(4-Methylphenyl)-4,4-diethyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 34. To a suspension of NaH in THF cooled to 0 °C was added the 4-ethylthiohydantoin **32**, and the mixture was stirred for 30 min. A solution of ethyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the pure 4,4-diethylthiohydantoin **34**.

4-[3-(4-Methylphenyl)-4-ethyl-4-methyl-5-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 35. To a suspension of NaH in THF cooled to 0 °C was added the 4-methylthiohydantoin **31**, and the mixture was stirred for 30 min. A solution of ethyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the pure 4,4-diethylthiohydantoin **35**.

4-[3-(4-Methylphenyl)-5-ethyl-5-methyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 36. To a suspension of NaH in THF cooled to 0 °C was added the unsubstituted 4-oxothiohydantoin **30b**, and the mixture was stirred for 30 min. A solution of methyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the 5-methyl-4-oxothiohydantoin **36a**. To a suspension of NaH in THF cooled to 0 °C was added the monomethyl 4-oxothiohydantoin **36a**, and the mixture was stirred for 30 min. A solution

of ethyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the 5-ethyl-5-methyl-4-oxothiohydantoin **36**.

4-[3-(4-Methylphenyl)-5,5-diethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-trifluoromethylbenzonitrile, 37. To a suspension of NaH in THF cooled to 0 °C was added the unsubstituted 4-oxothiohydantoin **30b**, and the mixture was stirred for 30 min. A solution of ethyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the 5-ethyl-4-oxothiohydantoin **37a**. To a suspension of NaH in THF cooled to 0 °C was added the monoethyl 4-oxothiohydantoin **37a**, and the mixture was stirred for 30 min. A solution of ethyl iodide in THF was added and the mixture stirred for 5 h. Normal aqueous workup and extraction afforded the crude product which was purified by column chromatography, using silica gel (dichloromethane), to give in 5% yield the 5,5-diethyl-4-oxothiohydantoin **37**.

Synthesis of 39. 1-(4-Methylphenyl)aminocyclopentanecarbonitrile, 39a. Trimethylsilyl cyanide (0.865 mL, 7 mmol) was added dropwise to a mixture of *p*-toluidine (0.535 g, 5 mmol) and cyclopentanone (0.589 g, 7 mmol). The reaction mixture was stirred at 21 °C for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **39a** (0.981 g, 4.9 mmol, 98%) as a yellowish solid.

4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 39. A mixture of isothiocyanate **12a** (0.296 g, 1.3 mmol) and **39a** (0.2 g, 1 mmol) in DMF (0.2 mL) was stirred for 48 h. To this mixture were added methanol (10 mL) and aqueous 2 N HCl (3 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **39** (0.3 g, 0.7 mmol, 70%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47−1.57 (m, 2H), 1.81−1.92 (m, 2H), 2.20−2.24 (m, 2H), 2.27−2.34 (m, 2H), 2.43 (s, 3H), 7.18−7.22 (m, 2H), 7.33−7.36 (m, 2H), 7.86 (dd, J = 8.2, 1.8 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 25.2, 36.3, 75.1, 110.0, 114.9, 121.9 (q, J = 272.5 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 130.7, 123.2, 133.0, 133.4 (q, J = 33.2 Hz), 135.1, 137.4, 140.0, 176.3, 180.2.

Synthesis of 38. 1-(4-Methylphenyl)aminocyclobutanecarbonitrile, 38a. Trimethylsilyl cyanide (0.93 mL, 7 mmol) was added dropwise to a mixture of *p*-toluidine (0.535 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at 21 °C for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **38a** (0.912 g, 4.9 mmol, 98%) as a yellowish solid.

4-(8-Oxo-6-thioxo-5-(4-methylphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 38. A mixture of isothiocyanate **12a** (0.912 g, 4 mmol) and **38a** (0.558 g, 3 mmol) in DMF (0.5 mL) was stirred at 21 °C for 24 h. To this mixture were added methanol (30 mL) and aqueous 2 N HCl (6 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **38** (0.959 g, 2.31 mmol, 77%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62−1.69 (m, 1H), 2.16−2.22 (m, 1H), 2.46 (s, 3H), 2.55−2.66 (m, 4H), 7.19−7.26 (m, 2H), 7.36−7.42 (m, 2H), 7.86 (dd, J = 8.3, 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 21.3, 31.4, 67.4, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.5, 130.8, 132.2, 132.4, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 140.1, 175.0, 180.0.

Synthesis of 40. 1-(4-Methylphenyl)aminocyclohexanecarbonitrile, 40a. Sodium cyanide (0.147 g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cyclohexanone (0.294 g, 3 mmol) in 90% acetic acid (3 mL). The reaction mixture was stirred at 21 °C for 12 h, and then 20 mL of ethyl acetate was added. The organic layer was washed with water (3 × 10 mL), dried over magnesium sulfate, and concentrated under vacuum to dryness to yield **40a** (0.398 g, 1.86 mmol, 93%) as a brown solid.

4-(4-Imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 40b. Triethylamine (0.05 g, 0.5 mmol) was added to a solution of isothiocyanate **12a** (0.228 g, 1 mmol) and **40a** (0.214 g, 1 mmol) in THF (2 mL). The reaction mixture was stirred at 21 °C for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford **40b** (0.035 g, 0.08 mmol, 8%).

4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 40. A mixture of **40b** (0.035 g, 0.08 mmol) in aqueous 2 N HCl (1 mL) and methanol (3 mL) was heated to reflux for 2 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (5 mL) and extracted with ethyl acetate (6 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **40** (0.034 g, 0.076 mmol, 95%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.02−1.05 (m, 1H), 1.64−1.76 (m, 4H), 2.03−2.12 (m, 5H), 2.44 (s, 3H), 7.12−7.15 (m, 2H), 7.33−7.36 (m, 2H), 7.85 (dd, J = 8.2, 1.8 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 21.3, 24.0, 32.6, 67.4, 109.9, 114.9, 122.0 (q, J = 272.5 Hz), 127.3 (q, J = 4.6 Hz), 130.0, 130.5, 132.0, 132.5, 133.3 (q, J = 33.2 Hz), 135.2, 137.3, 140.1, 174.1, 180.1.

Synthesis of 41. 1-(4-Methylphenyl)aminocycloheptanecarbonitrile, 41a. Sodium cyanide (0.147 g, 3 mmol) was added to a mixture of *p*-toluidine (0.214 g, 2 mmol) and cycloheptanone (0.337 g, 3 mmol) in acetic acid 90% (3 mL). The reaction mixture was stirred at 21 °C for 12 h, and then 20 mL of ethyl acetate was added. The organic layer was washed with water (3 × 10 mL), dried over magnesium sulfate, and concentrated under vacuum to dryness to yield **41a** (0.438 g, 1.92 mmol, 96%) as a brown solid.

4-(4-Imino-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.6]undec-3-yl)-2-trifluoromethylbenzonitrile, 41b. Triethylamine (0.05 g, 0.5 mmol) was added to a solution of isothiocyanate **12a** (0.228 g, 1 mmol) and **41a** (0.228 g, 1 mmol) in THF (2 mL). The reaction mixture was stirred at 21 °C for 2 days and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 95:5) to afford **41b** (0.036 g, 0.08 mmol, 8%).

4-(4-Oxo-2-thioxo-1-(4-methylphenyl)-1,3-diazaspiro[4.6]undec-3-yl)-2-trifluoromethylbenzonitrile, 41. A mixture of **41b** (0.036 g, 0.08 mmol) in aqueous 2 N HCl (1 mL) and methanol (3 mL) was heated to reflux for 2 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (5 mL) and extracted with ethyl acetate (6 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **41** (0.034 g, 0.075 mmol, 94%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24−134 (m, 2H), 1.37−1.43 (m, 2H), 1.53−1.60 (m, 2H), 1.74−1.82 (m, 2H), 2.19−2.25 (m, 4H), 2.44 (s, 3H), 7.16−7.19 (m, 2H), 7.32−7.35 (m, 2H), 7.83 (dd, J = 8.2, 1.8 Hz, 1H), 7.95−7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 22.2, 30.9, 36.3, 71.1, 110.0, 114.9, 121.9 (q, J = 272.5 Hz), 127.2 (q, J = 4.6 Hz), 129.6, 130.5, 132.3, 133.0, 133.2 (q, J = 33.2 Hz), 135.1, 137.4, 140.0, 175.9, 179.7.

Synthesis of 43. 1-Methyl-4-(4-methylphenylamino)piperidine-4-carbonitrile, 43a. Sodium cyanide (0.318 g, 6.5 mmol) was added to a mixture of *p*-toluidine (0.535 g, 5 mmol) and 1-methyl-4-piperidinone (0.678 g, 6 mmol) in acetic acid 90% (5 mL). The reaction mixture was stirred at 21 °C for 6 h, and

then 100 mL of dichloromethane was added. The organic layer was washed with aqueous 2 N NaOH (2 × 50 mL), dried over magnesium sulfate, concentrated, and chromatographed (dichloromethane and then acetone) to obtain **43a** (0.722 g, 3.15 mmol, 63%).

4-(4-Imino-8-methyl-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro-[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 43b. Triethylamine (0.02, 0.2 mmol) was added to a solution of isothiocyanate **12a** (0.228 g, 1 mmol) and **43a** (0.114 g, 0.5 mmol) in THF (2 mL). The reaction mixture was stirred at 21 °C for 20 h and then concentrated to yield a dark residue which was subjected to flash chromatography (dichloromethane/acetone, 90:10, and then acetone) to afford **43b** (0.059 g, 0.13 mmol, 26%).

4-(8-Methyl-4-oxo-2-thioxo-1-(4-methylphenyl)-1,3,8-triazaspiro-[4.5]dec-3-yl)-2-trifluoromethylbenzonitrile, 43. A mixture of **43b** (0.059 g, 0.13 mmol) in aqueous 2 N HCl (1 mL) and methanol (3 mL) was heated to reflux for 2 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (5 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 60:40) to yield **43** (0.055 g, 0.012 mmol, 92%) as a white powder. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.93−1.99 (m, 1H), 2.00−2.04 (m, 1H), 2.18 (s, 3H), 2.24−2.28 (m, 2H), 2.38 (s, 3H), 2.61−2.72 (m, 4H), 7.18−7−20 (m, 2H), 7.32−7.35 (m, 2H), 8.03 (dd, J_1 = 8.2, 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 20.3, 31.4, 45.1, 49.8, 65.1, 109.1, 114.8, 122.4 (q, J = 275.1 Hz), 127.7 (q, J = 4.8 Hz), 130.0, 130.5, 131.9 (q, J = 32.6 Hz), 132.6, 133.5, 135.6, 138.3, 139.4, 174.0, 180.6.

Synthesis of 49. 1-(4-Hydroxyphenyl)aminocyclobutanecarbonitrile, 49a. Trimethylsilyl cyanide (0.93 mL, 7 mmol) was added dropwise to a mixture of 4-hydroxyaniline (0.545 g, 5 mmol) and cyclobutanone (0.42 g, 6 mmol). The reaction mixture was stirred at 21 °C for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane/acetone, 98:2) to yield **49a** (0.903 g, 4.8 mmol, 96%) as a yellowish solid.

4-(8-Oxo-6-thioxo-5-(4-hydroxyphenyl)-5,7-diazaspiro[3.4]oct-7-yl)-2-trifluoromethylbenzonitrile, 49. A mixture of isothiocyanate **12a** (0.57 g, 2.5 mmol) and **49a** (0.376 g, 2 mmol) in DMF (0.5 mL) was stirred at 21 °C for 40 h. To this mixture were added methanol (30 mL) and aqueous 2 N HCl (5 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (40 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 98:2) to yield **49** (0.659 g, 1.58 mmol, 79%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55−1.63 (m, 1H), 2.01−2.09 (m, 1H), 2.50−2.65 (m, 4H), 6.97−7.01 (m, 2H), 7.20−7.24 (m, 2H), 8.02 (dd, J = 8.3, 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 31.3, 67.5, 108.9, 114.8, 116.1, 123.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.9 Hz), 131.3, 131.8 (q, J = 32.7 Hz), 133.3, 135.5, 136.2, 138.5, 158.1, 175.1, 180.7.

Synthesis of 50 and 51. 1-Aminocyclopentanecarbonitrile, 50a. Anhydrous ammonia was bubbled into a mixture of cyclopentanone (0.452 g) and trimethylsilyl cyanide (0.66 mL, 5 mmol). The ammonia was refluxed with a dry ice−acetone condenser. After 1 h of reflux, the ammonia was allowed to evaporate from the medium and then the remaining mixture was concentrated under vacuum to yield **50a** (0.522 g, 4.75 mmol, 95%) as a colorless liquid.

4-(4-Imino-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 50b. Triethylamine (0.101 g, 0.1 mmol) was added to a solution of isothiocyanate **12a** (0.684 g, 3 mmol) and **50a** (0.33 g, 3 mmol) in THF (5 mL). The reaction mixture was stirred at 21 °C for 5 h and then concentrated to yield a brown residue which was subjected to flash chromatography (dichloromethane/acetone, 93:7) to afford **50b** (0.741 g, 2.19 mmol, 73%).

4-(4-Oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl)-2-trifluoromethylbenzonitrile, 50c. A mixture of **50b** (0.741 g, 2.19 mmol) in aqueous 2 N HCl (4 mL) and methanol (20 mL) was heated to reflux for 1 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (20 mL) and extracted with ethyl acetate (40 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **50c** (0.72 g, 2.12 mmol, 97%) as a white powder.

4-[1-(4-Cyanophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile, 50. A mixture of **50c** (0.0678 g, 0.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.061 g, 0.4 mmol), and 4-fluorocyanobenzene (0.048 g, 0.4 mmol) in dimethylformamide (0.5 mL) was placed in a sealed tube under argon and heated to 140 °C for 5 days. The reaction mixture was poured into ethyl acetate (5 mL) and washed with water (2 × 10 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **50** (0.023 g, 0.052 mmol, 26%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.51−1.55 (m, 2H), 1.90−1.93 (m, 2H), 2.12−2.16 (m, 2H), 2.33−2.38 (m, 2H), 7.47−7.50 (m, 2H), 7.81−7.87 (m, 3H), 7.95−7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.5, 75.3, 110.3, 113.9, 114.7, 117.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.8 Hz), 131.2, 132.1, 133.6 (q, J = 34.3 Hz), 133.8, 135.3, 136.9, 140.0, 175.6, 180.1.

4-[1-(4-Nitrophenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]non-3-yl]-2-trifluoromethylbenzonitrile, 51. A mixture of **50c** (0.0678 g, 0.2 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.05 g, 0.33 mmol), and 4-fluoronitrobenzene (0.056 g, 0.4 mmol) in dimethylformamide (0.5 mL) was placed in a sealed tube under argon and heated to 130 °C for 40 h. The reaction mixture was poured into ethyl acetate (5 mL) and washed with water (2 × 10 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **51** (0.038 g, 0.084 mmol, 42%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53−1.56 (m, 2H), 1.90−1.93 (m, 2H), 2.14−2.18 (m, 2H), 2.37−2.40 (m, 2H), 7.54−7.57 (m, 2H), 7.85 (dd, J = 8.2, 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H), 8.39−8.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2, 36.5, 75.3, 110.3, 114.8, 121.8 (q, J = 272.6 Hz), 125.2, 127.0 (q, J = 4.7 Hz), 131.4, 132.1, 133.6 (q, J = 34.3 Hz), 135.3, 136.9, 141.7, 148.1, 175.6, 180.2.

Synthesis of 52. 2-Methyl-2-(4-trifluoromethylphenyl)aminopropanenitrile, 52a. A mixture of 4-trifluoromethylaniline (1.61 g, 10 mmol), acetone cyanohydrin (5 mL), and magnesium sulfate (2 g) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (50 mL) and then washed with water (3 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to dryness to yield **52a** (2.166 g, 9.5 mmol, 95%) as brown solid.

4-(4,4-Dimethyl-5-oxo-2-thioxo-3-(4-trifluoromethylphenyl)-imidazolidin-1-yl)-2-trifluoromethylbenzonitrile, 52. A mixture of isothiocyanate **12a** (0.114 g, 0.5 mmol) and **52a** (0.092 g, 0.4 mmol) in DMF (0.3 mL) was stirred at 21 °C for 48 h. To this mixture were added methanol (10 mL) and aqueous 2 N HCl (3 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **52** (0.117 g, 0.256 mmol, 64%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 7.45−7.49 (m, 2H), 7.80−7.83 (m, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 66.6, 110.3, 114.8, 121.8 (q, J = 272.6 Hz), 123.5 (q, J = 271.1 Hz), 127.0 (q, J = 4.6 Hz), 127.1 (q, J = 4.7 Hz), 130.3, 131.9 (q, J = 32.9 Hz), 132.2, 133.5 (q, J = 33.3 Hz), 135.3, 136.9, 138.4, 174.6, 179.9.

Synthesis of 74−76. 1-(4-Hydroxymethylphenylamino)cyclobutanecarbonitrile, 74a. Trimethylsilyl cyanide (0.66 mL, 5 mmol) was added dropwise to a mixture of 4-aminobenzyl alcohol (0.492 g, 4 mmol) and cyclobutanone (0.35 g, 5 mmol) in dichloromethane

(10 mL). The reaction mixture was stirred at 21 °C for 6 h and then concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane) to yield **74a** (0.677 g, 3.36 mmol, 84%) as a brown solid.

4-[8-(4-Hydroxymethylphenyl)-5-oxo-7-thioxo-6-azaspiro[3.4]oct-6-yl]-2-trifluoromethylbenzonitrile, 74. A mixture of isothiocyanate **12a** (0.342 g, 1.5 mmol) and **74a** (0.21 g, 1 mmol) in dry DMF (0.5 mL) was stirred at 21 °C for 24 h. To this mixture were added methanol (20 mL) and HCl aqueous 2 N (5 mL). The second mixture was refluxed for 6 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (40 mL) and extracted with ethyl acetate (60 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 90:10) to yield **74** (0.296 g, 0.69 mmol, 69%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63−1.68 (m, 1H), 2.17−2.26 (m, 1H), 2.52−2.68 (m, 4H), 4.75 (s, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 7.88 (dd, J = 8.3, 1.8 Hz, 1H), 7.95−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 64.4, 67.5, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 128.3, 130.0, 132.2, 133.3, 133.4 (q, J = 33.2 Hz), 134.2, 137.2, 142.9, 174.9, 179.9.

4-[5-(4-Formylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile, 75. To a mixture of **74** (0.303 g, 0.7 mmol) and the Dess−Martin periodinane (0.417 g, 1 mmol) in dichloromethane (5 mL) was added pyridine (1.01 g, 1 mmol). The mixture was stirred for 2 h at 21 °C, and then ethyl ether (10 mL) was added to precipitate the byproduct of the reaction. After filtration and concentration under reduced pressure, the mixture was chromatographed (dichloromethane/acetone, 95:5) to yield **75** (0.24 g, 0.56 mmol, 80%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62−1.73 (m, 1H), 2.24−2.30 (m, 1H), 2.50−2.58 (m, 2H), 2.69−2.75 (m, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.97−7.99 (m, 2H), 8.11 (d, J = 8.1 Hz, 2H), 10.12 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.7, 67.5, 110.2, 114.8, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 129.1, 131.0, 131.2, 132.2, 133.3 (q, J = 33.2 Hz), 135.3, 136.9, 140.5, 174.5, 179.8, 190.8.

4-{5-[4-(1-Hydroxyethyl)phenyl]-8-oxo-6-thioxo-5,7-diazaspiro-[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 76. A mixture of **75** (0.043 g, 0.1 mmol) and THF (1 mL) in a flamed-dried flask was placed under argon and cooled to −78 °C. Methylmagnesium iodide (1.1 mL, 0.1 M) was added. The mixture was stirred at −78 °C for 30 min and warmed slowly to 21 °C. The medium was washed with water (3 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 95:5) to yield **76** (0.037 g, 0.082 mmol, 82%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57 (d, J = 6.5 Hz, 3H), 1.61−1.71 (m, 1H), 2.09 (d, J = 3.2 Hz, OH), 2.16−2.28 (m, 1H), 2.52−2.60 (m, 2H), 2.63−2.69 (m, 2H), 5.00 (qd, J = 6.5, 3.1 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.95−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 25.3, 31.5, 67.4, 69.8, 110.0, 114.9, 121.9 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.1, 129.9, 132.2, 133.4 (q, J = 33.2 Hz), 134.1, 135.2, 137.1, 147.6, 174.9, 179.9.

Synthesis of 77 and 78. (*E*)-3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}-acrylic Acid Ethyl Ester, 77a. A mixture of **75** (0.043 g, 0.1 mmol) and (carbethoxymethylene)triphenylphosphorane (0.039 g, 0.12 mmol) in dichloromethane (2 mL) was stirred at 21 °C for 10 h. The mixture was concentrated and chromatographed (dichloromethane) to yield **77a** (0.048 g, 0.096 mmol, 96%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, J = 7.1 Hz, 3H), 1.66−1.70 (m, 1H), 2.19−2.65 (m, 1H), 2.51−2.69 (m, 2H), 2.66−2.72 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 6.51 (d, J = 16.1 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 16.1 Hz, 1H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 14.3, 31.6, 60.8, 67.5, 110.0, 114.9, 120.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 129.5, 130.5, 132.2, 133.4 (q, J = 33.2 Hz), 135.2, 136.0, 136.5, 137.0, 142.7, 166.5, 174.7, 179.8.

(*E*)-3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}acrylic Acid, 77b. A mixture of **77a** (0.025 g, 0.05 mmol) and a solution of sodium hydroxide (2 mL, 2 M) in methanol (2 mL) was stirred at 21 °C for 5 h. The methanol was evaporated. The residue was adjusted to pH 5 by aqueous 2 N HCl and then extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **77b** (0.02 g, 0.042 mmol, 85%).

(*E*)-3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}-2-propanamide, 77. To a suspension of **77b** (0.02 g, 0.042 mmol) in THF (1 mL) cooled to −5 °C was added thionyl chloride (0.007 mL, 0.1 mmol). The medium was stirred at −5 °C for 1 h. Then ammonia was bubbled into the mixture. The excess of ammonia was condensed by a reflux condenser cooled at −78 °C for 30 min and then was allowed to evaporate. The medium was filtered and the filtrate was concentrated and chromatographed (dichloromethane/acetone, 70:30) to yield **77** (0.014 g, 0.03 mmol, 71%) as an off-white powder. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.49−1.52 (m, 1H), 1.88−1.93 (m, 1H), 2.37−2.46 (m, 2H), 2.57−2.62 (m, 2H), 6.66 (d, J = 15.9 Hz, 1H), 7.16 (bs, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 15.9 Hz, 1H), 7.58 (bs, 1H), 7.78 (d, J = 8.3 Hz, 2H), 8.03 (dd, J = 8.3, 1.8 Hz, 1H), 8.23 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H).

(*E*)-4-{5-[4-(3-Hydroxy-1-propenyl)phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 78. To a mixture of **77a** (0.05 g, 0.1 mmol) in dichloromethane (2 mL) at −78 °C was added a solution of diisobutylaluminum hydride in THF (0.11 mL, 1 M, 0.11 mmol). The mixture was stirred at −78 °C for 3 h. After being warmed to 21 °C, the mixture was washed with an aqueous solution of sodium thiosulfate and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 95:5) to yield **78** (0.040 g, 0.089 mmol, 89%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57−1.68 (m, 1H), 2.17−2.39 (m, 1H), 2.55−2.61 (m, 2H), 2.61−2.67 (m, 2H), 4.39 (d, J = 4.7 Hz, 2H), 6.47 (dt, J_1 = 16.0, 5.3 Hz, 1H), 6.70 (d, J = 16.0 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.5, 63.4, 67.4, 110.0, 114.8, 120.5, 121.8 (q, J = 272.6 Hz), 127.0 (q, J = 4.7 Hz), 127.9, 129.2, 130.1, 131.1, 132.1, 133.4 (q, J = 33.2 Hz), 135.2, 137.1, 138.4, 174.8, 179.9.

Synthesis of 79 and 80. 4-[4-(1-Cyanocyclobutylamino)phenyl]butanoic Acid, 79a. Trimethylsilyl cyanide (0.50 g, 5 mmol) was added dropwise to a mixture of 4-(4-aminophenyl)butyric acid (0.537 g, 3 mmol), cyclobutanone (0.35 g, 5 mmol), and sodium sulfate (1 g) in 1,4-dioxane (10 mL). The mixture was stirred for 15 h. After filtration to remove the sodium sulfate, the mixture was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane/acetone, 50:50) to yield **79a** (0.665 g, 2.58 mmol, 86%) as a yellowish solid.

4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}butanoic Acid Methyl Ester, 79b. A mixture of isothiocyanate **12a** (0.547 g, 2.4 mmol) and **79a** (0.342 g, 1.5 mmol) in DMF (2 mL) was stirred at 21 °C for 15 h. To this mixture were added methanol (10 mL) and aqueous 2 N HCl (5 mL). The second mixture was refluxed for 3 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **79b** (0.594 g, 1.18 mmol, 79%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60−1.70 (m, 1H), 1.98−2.07 (m, 2H), 2.14−2.26 (m, 1H), 2.40 (t, J = 7.4 Hz, 2H), 2.52−2.60 (m, 2H), 2.62−2.68 (m, 2H), 2.74 (t, J = 7.4 Hz, 2H), 3.68 (s, 3H), 7.22 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.86 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.1, 31.4, 33.5, 34.8, 51.7, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1

(q, J = 4.7 Hz), 129.7, 130.1, 132.3, 133.0, 133.3 (q, J = 33.2 Hz), 135.2, 137.2, 143.5, 173.8, 175.0, 179.9.

4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diaza-spiro[3.4]oct-5-yl]phenyl}butanoic Acid, 79c. A mixture of **79b** (0.501 g, 1 mmol) and a solution of sodium hydroxide (10 mL, 2 M) in methanol (10 mL) was stirred at 21 °C for 5 h. The methanol was evaporated. The residue was adjusted to pH 5 by aqueous 2 M HCl, and then the mixture was extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **79c** (0.482 g, 0.99 mmol, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60−1.70 (m, 1H), 1.98−2.07 (m, 2H), 2.14−2.26 (m, 1H), 2.45 (t, J = 7.3 Hz, 2H), 2.51−2.59 (m, 2H), 2.62−2.68 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 25.9, 31.4, 33.4, 34.7, 67.5, 109.9, 114.9, 121.9 (q, J = 272.6 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 130.1, 132.3, 133.0, 133.4 (q, J = 33.1 Hz), 135.2, 137.2, 143.3, 174.9, 178.9, 179.9.

4-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}butanamide, 79. To a suspension of **79c** (0.097 g, 0.2 mmol) in THF (10 mL) cooled to −5 °C was added thionyl chloride (0.019 mL, 0.26 mmol). The mixture was stirred at −5 °C for 1 h. Then ammonia was bubbled into the mixture. The excess ammonia was condensed by a reflux condenser cooled to −78 °C for 30 min and then was allowed to evaporate. The mixture was filtered. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 70:30) to yield **79** (0.093 g, 0.19 mmol, 95%) as an off-white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57−1.70 (m, 1H), 2.00−2.08 (m, 2H), 2.16−2.25 (m, 1H), 2.31 (t, J = 7.3 Hz, 2H), 2.51−2.59 (m, 2H), 2.62−2.68 (m, 2H), 2.77 (t, J = 7.3 Hz, 2H), 5.56 (bs, 1H), 5.65 (bs, 1H), 7.22 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.5, 31.4, 34.8, 35.0, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 130.1, 132.2, 133.0, 133.3 (q, J = 33.2 Hz), 135.2, 137.2, 143.5, 173.8, 174.9, 179.9.

***N*-Methyl-4-{4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}butanamide, 80.** To a suspension of **79c** (0.097 g, 0.2 mmol) in THF (10 mL) cooled to −5 °C was added thionyl chloride (0.019 mL, 0.26 mmol). The mixture was stirred at −5 °C for 1 h. Then methylamine was bubbled into the mixture at −5 °C for 30 min. The mixture was filtered. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 75:25) to yield **80** (0.095 g, 0.19 mmol, 95%) as an off-white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52−1.64 (m, 1H), 1.94−2.01 (m, 2H), 2.10−2.17 (m, 1H), 2.20 (t, J = 7.3 Hz, 2H), 2.46−2.62 (m, 4H), 2.69 (t, J = 7.3 Hz, 2H), 2.73 (d, J = 4.7 Hz, 3H), 6.09 (bs, 1H), 7.16 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 8.3, 1.8 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 26.2, 26.8, 31.4, 35.0, 35.7, 67.5, 109.7, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.7, 130.0, 132.3, 133.3 (q, J = 33.2 Hz), 133.8, 135.2, 137.3, 143.7, 173.3, 174.9, 179.8.

Synthesis of 81−83. 3-[4-(1-Cyanocyclobutylamino)phenyl]-propanoic Acid, 81a. Trimethylsilyl cyanide (0.4 g, 4 mmol) was added dropwise to a mixture of 3-(4-aminophenyl)propionic acid (0.33 g, 2 mmol), cyclobutanone (0.35 g, 5 mmol), and sodium sulfate (1 g) in 1,4-dioxane (5 mL). The mixture was stirred for 15 h. After filtration to remove sodium sulfate, the mixture was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane/acetone, 50:50) to yield **81a** (0.472 g, 1.93 mmol, 97%) as a yellowish solid.

3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}propanoic Acid Methyl Ester, 81b. A mixture of isothiocyanate **12a** (0.661 g, 2.9 mmol) and **81a** (0.472 g, 1.93 mmol) in DMF (2 mL) was stirred at 21 °C for 15 h. To this mixture were added methanol (10 mL) and aqueous 2 N HCl (5 mL, 2 M). The second mixture was refluxed for 3 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane) to yield **81b** (0.582 g, 1.19 mmol, 62%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60−1.70 (m, 1H), 2.14−2.26 (m, 1H), 2.51−2.56 (m, 2H), 2.58−2.67 (m, 2H), 2.71 (t, J = 7.8 Hz, 2H), 3.05 (t, J = 7.8 Hz, 2H), 3.69 (s, 3H), 7.23 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 30.5, 31.4, 35.1, 51.8, 67.5, 109.9, 114.9, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.9, 130.0, 132.3, 133.2, 133.3 (q, J = 33.2 Hz), 135.7, 137.2, 142.5, 173.1, 174.9, 179.9.

3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}propanoic Acid, 81c. A mixture of **81b** (0.487 g, 1 mmol) in methanol (10 mL) and solution of sodium hydroxide (10 mL, 2 M) was stirred at 21 °C for 5 h. The methanol was evaporated. The residue was adjusted to pH 5 by aqueous 2 N HCl and was then extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to dryness to obtain **81c** (0.472 g, 0.99 mmol, 99%).

3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}propanamide, 81. To a suspension of **81c** (0.094 g, 0.2 mmol) in THF (10 mL) cooled at −5 °C was added thionyl chloride (0.019 mL, 0.26 mmol). The medium was stirred at −5 °C for 1 h. Then ammonia was bubbled into the mixture. The excess ammonia was condensed by a reflux condenser cooled to −78 °C for 30 min and then was allowed to evaporate. The mixture was filtered. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 70:30) to yield **81** (0.09 g, 0.19 mmol, 95%) as an off-white powder. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.52−160 (m, 1H), 2.01−2.09 (m, 1H), 2.49−2.58 (m, 4H), 2.61−2.67 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H), 6.20 (bs, 1H), 6.78 (bs, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 8.03 (dd, J = 8.3 Hz, 1.8 Hz, 1H), 8.15 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 30.7, 31.2, 36.4, 67.5, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.5 (q, J = 4.7 Hz), 129.5, 130.0, 131.8 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.2, 171.6, 174.9, 178.0.

3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}-*N*-methylpropanamide, 82. To a suspension of **81c** (0.094 g, 0.2 mmol) in THF (10 mL) cooled to −5 °C was added thionyl chloride (0.019 mL, 0.26 mmol). The mixture was stirred at −5 °C for 1 h. Then methylamine was bubbled into the mixture at −5 °C for 30 min. The medium was filtered. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 75:25) to yield **82** (0.092 g, 0.19 mmol, 95%) as an off-white powder. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51−1.60 (m, 1H), 2.01−2.11 (m, 1H), 2.48−2.58 (m, 4H), 2.61−2.67 (m, 2H), 2.77 (d, J = 4.6 Hz, 3H), 2.98 (t, J = 7.5 Hz, 2H), 7.03 (bs, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 8.01 (dd, J = 8.3, 1.8 Hz, 1H), 8.13 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 25.3, 30.0, 31.2, 37.0, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.7 Hz), 129.5, 130.0, 131.9 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.1, 171.7, 175.0, 178.0.

3-{4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]phenyl}-*N*-(2-hydroxyethyl)propanamide, 83. To a suspension of **81c** (0.094 g, 0.2 mmol) in THF (10 mL) cooled to −5 °C was added thionyl chloride (0.019 mL, 0.26 mmol). The mixture was stirred at −5 °C for 1 h. Then 2-aminoethanol (0.0183 g, 0.03 mmol) was added into the mixture at −5 °C. After being stirred for an additional 30 min, the mixture was filtered. The filtrate was concentrated and chromatographed (dichloromethane/acetone, 50:50) to yield **83** (0.093 g, 0.18 mmol, 90%) as an off-white powder. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.51−161 (m, 1H), 2.01−2.11 (m, 1H), 2.49−2.66 (m, 6H), 2.99 (t, J = 7.5 Hz, 2H), 3.27 (dd, J = 11.2, 5.6 Hz, 2H), 3.51 (dd, J = 11.2, 5.6 Hz, 2H), 3.87 (bs, OH), 7.20 (bs, NH), 7.33 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2

Hz, 2H), 8.02 (dd, J = 8.3, 1.8 Hz, 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 13.4, 31.0, 31.2, 37.1, 42.0, 61.2, 67.6, 109.0, 114.8, 122.5 (q, J = 271.5 Hz), 127.4 (q, J = 4.7 Hz), 129.6, 130.0, 131.9 (q, J = 32.5 Hz), 133.3, 133.8, 135.6, 138.4, 143.0, 171.9, 175.0, 178.1.

Synthesis of 84 and 85. 4-(4-Aminophenyl)piperazine-1-carboxylic Acid *tert*-Butyl Ester, 84a. A mixture of 4-iodoaniline (0.654 g, 3 mmol), piperazine-1-carboxylic acid *tert*-butyl ester (0.67 g, 3.6 mmol), potassium phosphate (1.272 g, 6 mmol), ethylene glycol (0.33 mL), and copper iodide (0.03 g, 0.15 mmol) in 2-propanol (3 mL) was placed in a sealed tube and heated under argon atmosphere to 80 °C for 30 h. After being cooled to 21 °C, the mixture was washed with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 70:30) to yield **84a** (0.36 g, 1.3 mmol, 43%) as a yellow powder.

4-[4-(1-Cyanocyclobutylamino)phenyl]piperazine-1-carboxylic Acid *tert*-Butyl Ester, 84b. Trimethylsilyl cyanide (0.3 g, 3 mmol) was added dropwise to a mixture of **84a** (0.415 g, 1.5 mmol), cyclobutanone (0.21 g, 3 mmol), and sodium sulfate (1 g) in dichloromethane (5 mL). The mixture was stirred for 15 h. After filtration to remove the sodium sulfate, the mixture was concentrated under vacuum to obtain a brown liquid which was subjected to chromatography (dichloromethane/acetone, 75:25) to yield **84b** (0.448 g, 1.26 mmol, 84%) as a yellow solid.

4-[8-Oxo-5-(4-piperazin-1-ylphenyl)-6-thioxo-5,7-diazaspiro-[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile, 84. A mixture of isothiocyanate **12a** (0.228 g, 1 mmol) and **84b** (0.472 g, 0.63 mmol) in DMF (1 mL) was stirred at 21 °C for 20 h. The mixture was concentrated and chromatographed (dichloromethane/acetone, 90:10) to yield the crude thiohydantoin imine **84c** (0.173 g, 0.296 mmol, 47%) as an off-white powder. A mixture of this crude imine **84c** (0.117 g, 0.2 mmol), methanol (5 mL), and aqueous 2 N HCl (2 mL) was refluxed for 2 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 50:50, and then methanol/acetone, 50:50) to yield **84** (0.089 g, 0.184 mmol, 92%) as a white powder. ^{1}H NMR (CD_3OD, 400 MHz) δ 1.51−1.61 (m, 1H), 2.01−2.11 (m, 1H), 2.48−2.59 (m, 4H), 2.95 (t, J = 4.6 Hz, 4H), 3.19 (t, J = 4.7 Hz, 4H), 7.03 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.9 Hz, 2H), 7.86 (dd, J = 8.3, 1.8 Hz, 1H), 8.02 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 1.8 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 13.2, 30.9, 45.1, 48.9, 67.5, 108.9, 114.8, 115.9, 122.3 (q, J = 271.7 Hz), 126.4, 127.3 (q, J = 4.7 Hz), 130.4, 132.2 (q, J = 33.2 Hz), 133.0, 135.4, 138.1, 152.1, 175.4, 180.4.

4-{5-[4-(4-Methanesulfonylpiperazin-1-yl)phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-7-yl}-2-trifluoromethylbenzonitrile, 85. A mixture of **84** (0.049 g, 0.1 mmol), methanesulfonyl chloride (0.012 mL, 0.15 mmol), and triethylamine (0.15 mL) in dichloromethane was stirred at 21 °C for 5 h. The mixture was filtered and the filtrate was concentrated and chromatographed (dichloromethane/acetone, 95:5) to yield **85** (0.042 g, 0.074 mmol, 74%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62−1.70 (m, 1H), 2.14−2.23 (m, 1H), 2.51−2.58 (m, 2H), 2.61−2.67 (m, 2H), 2.84 (s, 3H), 3.39 (s, 8H), 7.05 (d, J = 8.9 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 7.84 (dd, J = 8.3, 1.8 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.4, 34.6, 45.7, 48.4, 67.5, 109.8, 114.9, 117.0, 121.9 (q, J = 272.7 Hz), 126.8, 127.1 (q, J = 4.7 Hz), 130.7, 132.3, 133.4 (q, J = 33.2 Hz), 135.2, 137.3, 151.1, 175.0, 180.2.

Synthesis of 86. 1-(4-Methanesulfonylphenylamino)cyclobutanecarbonitrile, 86a. Trimethylsilyl cyanide (0.4 g, 4 mmol) was added dropwise to a mixture of 4-methanesulfonylphenylamine hydrochloride (0.415 g, 2 mmol), cyclobutanone (0.28 g, 4 mmol), and sodium sulfate (1 g) in DMF (3 mL). The mixture was stirred for 15 h at 120 °C. After filtration to remove the sodium sulfate, the filtrate was washed with brine and extracted with ethyl acetate. The organic layer was concentrated and chromatographed (dichloromethane/acetone, 90:10) to yield **86a** (0.116 g, 0.44 mmol, 22%) as a yellowish solid. 4-Methanesulfonylphenylamine (0.201 g, 1.17 mmol, 59%) was also recovered.

4-[5-(4-Methanesulfonylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro-[3.4]oct-7-yl]-2-trifluoromethylbenzonitrile, 86. A mixture of isothiocyanate **12a** (0.0.141 g, 0.62 mmol) and **86a** (0.11 g, 0.42 mmol) in dry DMF (2 mL) was stirred at 21 °C for 3 days. To this mixture were added methanol (10 mL) and aqueous 2 N HCl (5 mL). The second mixture was refluxed for 3 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 97:3) to yield **86** (0.031 g, 0.065 mmol, 15%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63−1.72 (m, 1H), 2.21−2.28 (m, 1H), 2.46−2.54 (m, 2H), 2.68.2.74 (m, 2H), 3.16 (s, 3H), 7.57 (d, J = 8.3 Hz, 2H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 31.8, 44.4, 67.5, 110.2, 114.8, 122.4 (q, J = 271.5 Hz), 127.0 (q, J = 4.9 Hz), 129.4, 131.4, 132.1, 133.6 (q, J = 33.3 Hz), 135.3, 136.8, 140.3, 141.8, 174.4, 179.9.

Synthesis of 87 and 88. 4-Aminobenzoic Acid Methyl Ester, 87a. Concentrated sulfuric acid was slowly added to a mixture of 4-aminobenzoic acid (4 g, 29.2 mmol) in methanol cooled to 0 °C. After the addition, the mixture was stirred at 21 °C for 5 h. The mixture was washed with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to obtain **87a** (4.22 g, 27.9 mmol, 96%) as an off-white solid.

4-[(Cyanodimethylmethyl)amino]benzoic Acid Methyl Ester, 87b. A mixture of 4-aminobenzoic acid methyl ester (0.32 g, 2.12 mmol), acetone cyanohydrin (3 mL), and sodium sulfate (1 g) was refluxed for 15 h. After filtration to remove the sodium sulfate, the filtrate was washed with brine and extracted with ethyl acetate. The organic layer was concentrated and chromatographed (dichloromethane/acetone, 60:40) to yield **87b** (0.398 g, 1.95 mmol, 92%) as a white solid.

4-[3-(4-Cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]benzoic Acid Methyl Ester, 87. A mixture of isothiocyanate **12a** (0.228 g, 1 mmol) and **87b** (0.14 g, 0.64 mmol) in DMF (2 mL) was heated under microwave irradiation at 60 °C for 12 h. To this mixture were added methanol (6 mL) and aqueous 2 N HCl (2 mL). The second mixture was refluxed for 4 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane; dichloromethane/acetone, 75:25) to yield **87** (0.18 g, 0.4 mmol, 63%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60 (s, 6H), 3.95 (s, 3H), 7.40 (d, J = 8.6 Hz, 2H), 7.84 (dd, J = 8.2, 1.9 Hz, 1H), 7.96 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 52.6, 66.6, 110.3, 114.8, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 129.8, 131.2, 131.4, 132.2, 133.5 (q, J = 32.3 Hz), 135.3, 137.0, 139.2, 165.9, 174.7, 179.7.

4-[3-(4-Cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-*N*-methylbenzamide, 88. A mixture of **87** (0.02 g, 0.0435 mmol) and methylamine (2 mL distilled from its 40% aqueous solution) was kept at −20 °C for 15 h. After evaporation of the methylamine, the mixture was chromatographed (dichloromethane/acetone, 80:20) to yield **88** (0.01 g, 0.0224 mmol, 51%). The ester **87** (0.08 g, 0.0179 mmol, 41%) was also recovered. ^{1}H NMR (acetone-d_6, 400 MHz) δ 1.60 (s, 6H), 2.90 (d, J = 4.6 Hz, 3H), 7.48 (d, J = 8.6 Hz, 2H), 7.80 (bs, 1H), 7.99 (d, J = 8.6 Hz, 2H), 8.06 (dd, J = 8.2, 1.8 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 23.8, 54.0, 66.5, 110.3, 114.8, 121.9 (q, J = 272.7 Hz), 127.1 (q, J = 4.7 Hz), 128.2, 129.9, 133.5 (q, J = 32.3 Hz), 135.7, 135.8, 138.2, 138.3, 139.2, 166.0, 174.9, 179.7.

Synthesis of 89. 4-(1-Cyanocyclobutylamino)benzoic Acid, 89a. Sodium cyanide (0.245 g, 5 mmol) was added to a mixture of 4-aminobenzoic acid (0.274 g, 2 mmol) and cyclobutanone (0.21 g, 3 mmol) in 90% acetic acid (4.5 mL). The reaction mixture was stirred at 21 °C for 15 h. The mixture was washed with aqueous HCl (pH 2) and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to dryness under vacuum to yield **89a** (0.426 g, 1.97 mmol, 99%) as a white solid.

4-[7-(4-Cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]benzoic Acid Methyl Ester, 89b. A mixture of isothiocyanate **12a** (0.51 g, 2.22 mmol) and **89a** (0.343 g, 1.59 mmol) in DMF (2 mL) was heated under microwave irradiation at 60 °C and stirred for 16 h. To this mixture were added methanol (10 mL) and aqueous 2 M HCl (5 mL). The second mixture was refluxed for 12 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 95:5) to yield **89b** (0.09 g, 0.196 mmol, 12%) as a white powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67−1.71 (m, 1H), 2.20−2.26 (m, 1H), 2.49−2.57 (m, 2H), 2.66−2.73 (m, 2H), 3.96 (s, 3H), 7.42 (d, J = 8.4 Hz, 2H), 7.85 (dd, J = 8.3, 1.7 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 1.7 Hz, 1H), 8.26 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 31.6, 52.6, 67.5, 110.1, 114.8, 121.8 (q, J = 272.7 Hz), 127.0 (q, J = 4.7 Hz), 130.2, 131.4, 131.5, 132.2, 133.4 (q, J = 33.2 Hz), 135.2, 137.0, 139.2, 165.9, 174.6, 179.7.

***N*-Methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]benzamide, 89.** A mixture of **89b** (0.046 g, 0.1 mmol) and methylamine (1 mL distilled from its 40% aqueous solution) was kept at −20 °C for 15 h. After evaporation of the methylamine, the mixture was chromatographed (dichloromethane/acetone, 80:20) to yield **89** (0.041 g, 0.085, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63−1.70 (m, 1H), 2.18−2.26 (m, 1H), 2.48−2.56 (m, 2H), 2.65−2.71 (m, 2H), 3.05 (d, J = 4.8 Hz, 3H), 6.32 (bs, 1H), 7.39 (d, J = 8.3 Hz, 2H), 7.84 (dd, J = 8.3, 1.7 Hz, 1H), 7.95−7.98 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.0, 31.6, 67.4, 110.3, 114.8, 121.8 (q, J = 272.7 Hz), 127.0 (q, J = 4.7 Hz), 128.7, 130.3, 132.1, 133.3 (q, J = 33.2 Hz), 135.2, 136.3, 137.0, 137.8, 167.2, 174.6, 179.8.

Synthesis of 91. *N*-Methyl-2-fluoro-4-nitrobenzamide, 91a. Thionyl chloride (2.38 g, 20 mmol) was added slowly to a solution of 2-fluoro-4-nitrobenzoic acid (2.97 g, 16 mmol) in DMF (50 mL) cooled at −5 °C. The mixture was stirred for an additional 1 h at −5 °C. Methylamine (0.62 g, 20 mmol; freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 h. Ethyl acetate (300 mL) was added to the mixture, which was washed with brine (3 × 150 mL). The organic layer was dried over $MgSO_4$ and concentrated to yield **91a** (2.89 g, 14.6 mmol, 91%) as a yellow solid. ^{1}H NMR (acetone-d_6, 400 MHz) δ 3.05 (d, J = 4.3 Hz, 3H), 6.31 (dd, J = 13.5, 2.1 Hz, 1H), 6.40 (dd, J = 8.5, 2.1 Hz, 1H), 7.64 (dd, J = 8.6, 8.6 Hz, 1H).

***N*-Methyl-2-fluoro-4-aminobenzamide, 91b.** A mixture of **91a** (2.89 g, 14.6 mmol) and iron (5.04 g, 90 mmol) in ethyl acetate (40 mL) and acetic acid (40 mL) was refluxed for 1 h. The solid particles were filtered off. The filtrate was washed with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 95:5) to yield **91b** (2.3 g, 13.7 mmol, 94%) as an off-white solid. ^{1}H NMR (acetone-d_6, 400 MHz) δ 2.86 (d, J = 4.3 Hz, 3H), 5.50 (bs, 2H), 6.37 (dd, J_1 = 14.7, 2.1 Hz, 1H), 6.50 (dd, J = 8.5, 2.1 Hz, 1H), 7.06 (bs, 1H), 7.68 (dd, J = 8.8, 8.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 25.8, 99.6 (d, J = 13.8 Hz), 109.2 (d, J = 12.8 Hz), 110.0 (d, J = 1.6 Hz), 132.5 (d, J = 4.8 Hz), 153.5 (d, J = 12.6 Hz), 162.2 (d, J = 242.5 Hz), 164.0 (d, J = 3.1 Hz).

***N*-Methyl-4-(1-cyanocyclobutylamino)-2-fluorobenzamide, 91c.** Sodium cyanide (1.47 g, 30 mmol) was added to a mixture of **91b** (1.68 g, 10 mmol) and cyclobutanone (1.4 g, 20 mmol) in 90% acetic acid (20 mL). The reaction mixture was stirred at 80 °C for 24 h. The mixture was washed with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to dryness under vacuum. The solid was washed with a 50:50 mixture of ethyl ether and hexane (10 mL) to remove cyclobutanone cyanohydrin to afford after filtration **91c** (2.19 g, 8.87 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.87−1.95 (m, 1H), 2.16−2.27 (m, 1H), 2.35−2.41 (m, 2H), 2.76−2.83 (m, 2H), 2.97 (d, J = 4.4 Hz, 3H), 4.68 (bs, 1H), 6.29 (dd, J = 14.3, 1.8 Hz, 1H), 6.48 (dd, J = 8.3, 1.8 Hz, 1H), 6.75 (q, J = 4.4 Hz, 1H), 7.90 (dd, J = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 26.7, 33.9, 49.4, 100.2 (d, J = 29.5 Hz), 110.6, 111.0 (d, J = 11.8 Hz), 120.8, 133.1 (d, J = 4.2 Hz), 148.4 (d, J = 12.0 Hz), 162.0 (d, J = 244.1 Hz), 164.4 (d, J = 3.6 Hz).

***N*-Methyl-4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluorobenzamide, 91.** A mixture of isothiocyanate **12a** (2.16 g, 9.47 mmol) and **91c** (1.303 g, 5.27 mmol) in DMF (20 mL) was heated under microwave irradiation at 80 °C for 16 h. To this mixture was added methanol (50 mL) and aqueous 2 N HCl (20 mL). The second mixture was refluxed for 3 h. After being cooled to 21 °C, the reaction mixture was poured into cold water (100 mL) and extracted with ethyl acetate (150 mL). The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 95:5) to yield **91** (1.43 g, 3.0 mmol, 57%) as a yellow powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65−1.75 (m, 1H), 2.18−2.30 (m, 1H), 2.49−2.57 (m, 2H), 2.67−2.73 (m, 2H), 3.07 (d, J = 4.4 Hz, 3H), 6.75 (q, J = 4.6 Hz, 1H), 7.17 (dd, J = 11.5, 1.9 Hz, 1H), 7.26 (dd, J = 8.3, 1.9 Hz, 1H), 7.83 (dd, J = 8.2, 2.0 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 8.30 (dd, J = 8.3, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 27.0, 31.7, 67.4, 110.3, 114.8, 118.2, 118.5, 121.9 (q, J = 272.7 Hz), 126.6, 127.0 (q, J = 4.8 Hz), 132.1, 133.3 (q, J = 33.2 Hz), 133.8, 135.3, 136.8, 139.1 (d, J = 10.9 Hz), 160.5 (d, J = 249.1 Hz), 162.7 (d, J = 3.3 Hz), 174.3, 179.8; ^{19}F NMR ($CDCl_3$, 100 MHz) δ −111.13, −62.58.

Synthesis of 92. 2-Fluoro-4-nitrobenzoic Acid, 92a. Periodic acid (1.69 g, 7.41 mmol) was dissolved in acetonitrile (25 mL) by vigorous stirring, and then chromium trioxide (0.16 g, 1.60 mmol) was dissolved into the solution. 2-Fluoro-4-nitrotoluene (0.33 g, 2.13 mmol) was added to the above solution with stirring. A white precipitate formed immediately with exothermic reaction. After 1 h of stirring, the supernatant liquid of the reaction mixture was decanted to a flask, and the solvent was removed by evaporation. The residues were extracted with dichloromethane (2 × 30 mL) and water (2 × 30 mL). The organic layer was dried over $MgSO_4$ and concentrated to give **92a** (0.32 mg, 81%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (ddd, 1H, J = 9.9, 2.2, 0.3 Hz), 8.13 (ddd, 1H, J = 8.6, 2.2, 0.9 Hz), 8.25 (ddd, 1H, J = 8.6, 7.0, 0.3 Hz).

***N*-Methyl-2-fluoro-4-(1,1-dimethylcyanomethyl)aminobenzamide, 92b.** A mixture of **91b** (96 mg, 0.57 mmol), acetone cyanohydrin (0.3 mL, 3.14 mmol), and magnesium sulfate (50 mg) was heated to 80 °C and stirred for 12 h. To the medium was added ethyl acetate (25 mL), and then the sample was washed with water (2 × 25 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 95:5) to give **92b** (101 mg, 75%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (s, 6H), 2.98 (dd, 3H, J = 4.8, 1.1 Hz), 6.58 (dd, 1H, J = 14.6, 2.3 Hz), 6.63 (dd, 1H, J = 8.7, 2.3 Hz), 6.66 (br s, 1H), 7.94 (dd, 1H, J = 8.7, 8.7 Hz).

***N*-Methyl-4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-fluorobenzamide, 92.** A mixture of **92b** (30 mg, 0.13 mmol) and **12a** (58 mg, 0.26 mmol) in DMF (1 mL) was heated under microwave irradiation at 100 °C for 11 h. To this mixture was added methanol (20 mL) and aqueous 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column

chromatography (dichloromethane/acetone, 95:5) to give **92** (30 mg, 51%) as colorless crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.61 (s, 6H), 3.07 (d, 3H, J = 4.1 Hz), 6.71 (m, 1 H), 7.15 (dd, 1H, J = 11.7, 2.0 Hz), 7.24 (dd, 1H, J = 8.4, 2.0 Hz), 7.83 (dd, 1H, J = 8.2, 2.1 Hz), 7.95 (d, 1H, J = 2.1 Hz), 7.99 (d, 1H, J = 8.2 Hz), 8.28 (dd, 1H, J = 8.4, 8.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.8, 26.9, 66.5, 110.3, 114.6, 117.7, 117.9, 121.7 (q, J = 272.3 Hz), 126.1, 126.9 (q, J = 4.6 Hz), 132.0, 133.3, 133.6 (q, J = 33.4 Hz), 135.2, 136.7, 138.9 (d, J = 10.8 Hz), 160.3 (d, J = 248.6 Hz), 162.6 (d, J = 3.3 Hz), 174.3, 179.6. ^{19}F NMR ($CDCl_3$, 100 MHz) δ −111.13, −62.58. HRMS: found 465.1023 $[M + H]^+$, calculated for $[C_{21}H_{16}F_4N_4O_2S + H]^+$ 465.1003.

Synthesis of 93. *N*-Methyl-4-(1-cyanocyclopentylamino)-2-fluorobenzamide, 93a. A mixture of **91b** (62 mg, 0.37 mmol), cyclopentanone (0.07 mL, 0.74 mmol), and TMSCN (0.1 mL, 0.74 mmol) was heated to 80 °C and stirred for 13 h. To the medium was added ethyl acetate (2 × 20 mL), and then the sample was washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 95:5) to give **93a** (61 mg, 63%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82−1.95 (m, 4H), 2.10−2.18 (m, 2H), 2.36−2.45 (m, 2H), 2.99 (dd, 3H, J = 4.8, 1.1 Hz), 4.60 (br s, 1H), 6.50 (dd, 1H, J = 14.6, 2.3 Hz), 6.59 (dd, 1H, J = 8.8, 2.3 Hz), 6.65 (br s, 1H), 7.95 (dd, 1H, J = 8.8, 8.8 Hz).

***N*-Methyl-4-[3-(4-cyano-3-trifluoromethylphenyl)-4-oxo-2-thioxo-1,3-diazaspiro[4.4]nonan-1-yl]-2-fluorobenzamide, 93.** A mixture of **93a** (57 mg, 0.22 mmol) and **12a** (0.15 g, 0.65 mmol) in DMF (3 mL) was heated under microwave irradiation at 130 °C for 12 h. To this mixture was added methanol (20 mL) and aqueous 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 95:5) to give **93** (56 mg, 48%) as a pale-yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49−1.59 (m, 2H), 1.85−1.96 (m, 2H), 2.13−2.21 (m, 2H), 2.32−2.41 (m, 2H), 3.07 (d, 3H, J = 4.3 Hz), 6.67−6.77 (m, 1H), 7.17 (dd, 1H, J = 11.7, 1.8 Hz), 7.27 (dd, 1H, J = 8.4, 1.8 Hz), 7.84 (dd, 1 H, J = 8.3, 1.8 Hz), 7.96 (d, 1H, J = 1.8 Hz), 7.98 (d, 1H, J = 8.3 Hz), 8.28 (dd, 1H, J = 8.4, 8.4 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.1, 26.9, 36.3, 75.2, 110.2, 114.6, 118.1, 118.3, 121.7 (q, J = 275.9 Hz), 126.4, 127.0 (q, J = 3.8 Hz), 132.0, 133.3, 133.5 (q, J = 33.4 Hz), 135.1, 136.8, 139.6 (d, J = 10.1 Hz), 160.3 (d, J = 245.4 Hz), 162.5 (d, J = 3.3 Hz), 175.5, 179.9. ^{19}F NMR ($CDCl_3$, 100 MHz) δ −111.23, −62.57. HRMS: found 491.1156 $[M + H]^+$, calculated for $[C_{23}H_{18}F_4N_4O_2S + H]^+$ 491.1159.

Synthesis of 94. 4-[4-(2,2,2-Trifluoroacetylamino)phenyl]butyric Acid, 94a. Trifluoroacetic anhydride (0.85 mL, 6.14 mmol) was added to a solution of 4-(4-aminophenyl)butyric acid (0.5 g, 2.79 mmol) in chloroform (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The mixture was partitioned with chloroform (20 mL) and water (20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 9:1) to give **94a** (0.53 g, 69%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.96 (p, 2H, J = 7.5 Hz), 2.38 (t, 2H, J = 7.5 Hz), 2.68 (t, 2H, J = 7.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.48 (d, 2H, J = 8.5 Hz), 7.81 (br s, 1H).

***N*,*N*-Dimethyl-4-[4-(2,2,2-trifluoroacetylamino)phenyl]butyramide, 94b.** Thionyl chloride (71 mg, 0.60 mmol) was added slowly to a solution of **94a** (0.15 g, 0.55 mmol) in DMF (5 mL) cooled at −5 °C. The mixture was stirred for an additional 1 h at −5 °C. Excess dimethylamine (freshly distilled from its 40% aqueous solution) was added to the reaction medium. The second mixture was stirred for an additional 1 h. Ethyl acetate (50 mL) was added to the mixture, which was washed with brine (2 × 50 mL). The organic layer was dried over $MgSO_4$ and concentrated to yield **94b** (0.17 g, quantitative) as a yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.89 (p, 2H, J = 7.7 Hz), 2.27 (t, 2H, J = 7.7 Hz), 2.60 (t, 2H, J = 7.7 Hz), 2.89 (s, 3H), 2.91 (s, 3H), 7.11 (d, 2H, J = 8.6 Hz), 7.55 (d, 2H, J = 8.6 Hz), 9.70 (br s, 1H).

***N*,*N*-Dimethyl-4-(4-aminophenyl)butyramide, 94c.** A 1 N NaOH solution (3 mL) was added to a solution of **94b** (0.17 g, 0.55 mmol) in MeOH (2 mL) at room temperature. The mixture was stirred for 14 h. The mixture was partitioned with chloroform (25 mL) and water (25 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 9:1) to give **94c** (74 mg, 66%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.91 (p, 2H, J = 7.7 Hz), 2.28 (t, 2H, J = 7.7 Hz), 2.56 (t, 2H, J = 7.7 Hz), 2.92 (s, 6H), 3.56 (br s, 2H), 6.61 (d, 2H, J = 8.3 Hz), 6.97 (d, 2H, J = 8.3 Hz).

***N*,*N*-Dimethyl-4-[4-(1-cyanocyclobutylamino)phenyl]butyramide, 94d.** A mixture of **94c** (74 mg, 0.36 mmol), cyclobutanone (54 mg, 0.78 mmol), and TMSCN (77 mg, 0.78 mmol) was heated to 80 °C and stirred for 15 h. To the medium was added ethyl acetate (2 × 20 mL), and then the sample was washed with water (2 × 20 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 9:1) to give **94d** (58 mg, 57%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93 (p, 2H, J = 7.6 Hz), 2.11−2.28 (m, 2H), 2.30 (t, 2H, J = 7.6 Hz), 2.33−2.42 (m, 2H), 2.60 (t, 2H, J = 7.6 Hz), 2.75−2.83 (m, 2H), 2.93 (s, 3H), 2.94 (s, 3H), 3.94 (br s, 1H), 6.59 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 8.5 Hz).

***N*,*N*-Dimethyl-4-[4-(7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-5-yl)phenyl]butanamide, 94.** A mixture of **94d** (58 mg, 0.20 mmol) and **12a** (74 mg, 0.32 mmol) in DMF (3 mL) was heated under reflux for 2 h. To this mixture was added methanol (20 mL) and aqueous 1 N HCl (5 mL). The second mixture was refluxed for 1.5 h. After being cooled to room temperature, the reaction mixture was poured into cold water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over $MgSO_4$ and concentrated and the residue was purified with SiO_2 column chromatography (dichloromethane/acetone, 95:5) to give **94** (44 mg, 42%) as a pale-yellowish solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.62−1.73 (m, 1H), 2.04 (p, 2H, J = 7.5 Hz), 2.15−2.30 (m, 1H), 2.40 (t, 2H, J = 7.5 Hz), 2.52−2.63 (m, 2 H), 2.62−2.70 (m, 2H), 2.78 (t, 2H, J = 7.5 Hz), 2.96 (s, 3H), 2.99 (s, 3H), 7.22 (d, 2H, J = 8.3 Hz), 7.42 (d, 2H, J = 8.3 Hz), 7.86 (d, 1H, J = 8.2 Hz), 7.97 (d, 1H, J = 8.2 Hz), 7.98 (s, 1H).

Synthesis of 95. 4-[5-(4-(3-Cyanopropyl)phenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]octan-7-yl]-2-(trifluoromethyl)benzonitrile, 95. A solution of DMSO (0.01 mL, 0.12 mmol) in dry dichloromethane (1 mL) was added to a stirred solution of oxalyl chloride (0.01 mL, 0.09 mmol) in dry dichloromethane (2 mL) at −78 °C. After 15 min, a dichloromethane solution of **79** (35 mg, 0.07 mmol) was added to the reaction mixture. Stirring was continued for 20 min at −78 °C, and then triethylamine (0.03 mL, 0.22 mmol) was added. After 30 min at −78 °C, the reaction mixture was warmed to room temperature, and then reaction was quenched with saturated aqueous NH_4Cl solution. The reaction mixture was diluted with dichloromethane and extracted with dichloromethane. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed (dichloromethane/acetone, 95:5) to yield **95** (29 mg, 87%) as a viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.63−1.73 (m, 1H), 2.07 (p, 2H, J = 7.3 Hz), 2.18−2.30 (m, 1H), 2.42 (t, 2H, J = 7.3 Hz), 2.52−2.62 (m, 2H), 2.63−2.73 (m, 2H), 2.90 (t, 2H, J = 7.3 Hz), 7.27 (d, 2H, J = 8.4), 7.43 (d, 2H, J = 8.4 Hz), 7.86 (dd, 1H, J = 8.3, 1.8 Hz), 7.98 (d, 1H, J = 8.3 Hz), 7.98 (d, 1 H, J = 1.8).

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(15) LNCaP in 10% FBS, split on day 1, add drugs on day 5, harvest on day 6 and day 10 for PSA.