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Revisiting the SAR of the Antischistosomal Aryl Hydantoin (Ro 13-3978)

Chunkai Wang,[†] Qingjie Zhao,[†] Mireille Vargas,[‡,§] Jeremy O. Jones,[∥] Karen L. White,[⊥] David M. Shackleford,[⊥] Gong Chen,[⊥] Jessica Saunders,[⊥] Alice C. F. Ng,[⊥] Francis C. K. Chiu,[⊥] Yuxiang Dong,[†] Susan A. Charman,[⊥] Jennifer Keiser,[‡,§] and Jonathan L. Vennerstrom*[,†]

[†]College of Pharmacy, University of Nebraska Medical Center, 986125 Nebraska Medical Center, Omaha, Nebraska 68198, United States

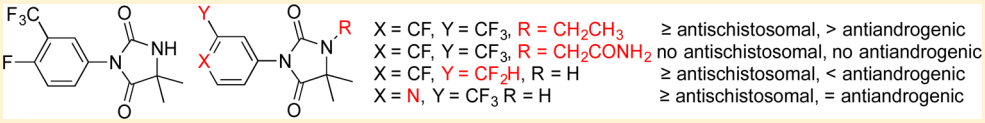
[‡]Department of Medical Parasitology and Infection Biology, Swiss Tropical Institute, Socinstrasse 57, CH-4002 Basel, Switzerland

[§]University of Basel, CH-4003 Basel, Switzerland

[∥]Department of Cancer Biology, Beckman Research Institute, City of Hope National Medical Center, Duarte, California 91010, United States

[⊥]Centre for Drug Candidate Optimisation, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville Campus), 381 Royal Parade, Parkville, Victoria 3052, Australia

Supporting Information



ABSTRACT: The aryl hydantoin **1** (Ro 13-3978) was identified in the early 1980s as a promising antischistosomal lead compound. However, this series of aryl hydantoins produced antiandrogenic side effects in the host, a not unexpected outcome given their close structural similarity to the antiandrogenic drug nilutamide. Building on the known SAR of this compound series, we now describe a number of analogs of **1** designed to maximize structural diversity guided by incorporation of substructures and functional groups known to diminish ligand–androgen receptor interactions. These analogs had calculated polar surface area (PSA), measured $LogD_{7.4}$, aqueous kinetic solubility, and estimated plasma protein binding values in ranges predictive of good ADME profiles. The principal SAR insight was that the hydantoin core of **1** is required for high antischistosomal activity. We identified several compounds with high antischistosomal efficacy that were less antiandrogenic than **1**. These data provide direction for the ongoing optimization of antischistosomal hydantoins.

Schistosomiasis is a tropical parasitic disease caused by infections with flukes of the genus *Schistosoma*.[1] Of these, *Schistosoma mansoni*, *S. hematobium*, and *S. japonicum* cause the largest public health burden.[2,3] Praziquantel (PZ) is the only drug available for treatment of this disease.[4−6] The high drug pressure from the widespread administration of PZ could lead to problematic drug resistance.[7,8] Even so, the discovery of a new drug for schistosomiasis continues to elude us, although several antischistosomal lead compounds and repurposed drugs have been identified in recent years.[9−14]

The introduction of PZ in 1982 likely led to decisions to abandon the development of a number of promising antischistosomal agents that were discovered during the same time period. One of these was **1** (Ro 13-3978) (Figure 1), the lead compound from a series of aryl hydantoins that were investigated in some detail at Hoffmann La-Roche.[15−18] As reported by Link and Stohler,[18] **1** has high oral efficacy against all three major schistosome species—*S. mansoni*, *S. hematobium*, and *S. japonicum*—in a range of animal models. Confirming these data, we found that **1** had single oral dose ED_{50} values of 15 and 140 mg/kg against adult and juvenile *S. mansoni* in a mouse model.[19] In this same schistosome mouse model, PZ is considerably less effective against adult *S. mansoni*, with reported ED_{50} values ranging from 172 to 202 mg/kg,[18,20] and it has no significant activity against juvenile stages of the parasite. Despite the high in vivo antischistosomal efficacy of **1**, we found that this aryl hydantoin at concentrations up to 170 μM had almost no effect on adult *S. mansoni* in vitro.[19] Data generated so far indicate that active metabolites do not account

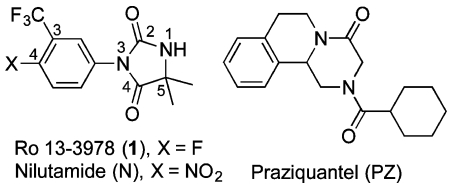


Figure 1.

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for the striking difference between the in vitro and in vivo antischistosomal activity of **1**.[19]

However, this series of aryl hydantoins produced antiandrogenic side effects in the host,[15] a not unexpected outcome given their close structural similarity to the antiandrogenic drug nilutamide (N). We recently demonstrated that N, but not the three structurally diverse androgen receptor (AR) antagonists flutamide, bicalutamide, and cyproterone acetate, has weak, but measurable, antischistosomal activity in *S. mansoni*-infected mice.[21] As phylogenetic evidence indicates that schistosome species do not appear to have AR's,[22] these data led us to hypothesize that, for aryl hydantoins and related heterocycles, the structural requirements for antischistosomal efficacy and AR binding interactions are divergent. In this respect, **1** had no measurable interaction with the AR in a ligand competition assay, but it did block DHT-induced cell proliferation in an androgen-dependent cell line.[23] Despite its antiandrogenic liability, Link and Stohler[18] observed no apparent toxicity following administration of a single 1250 mg/kg dose of **1** to mice.

Highlights from the SAR of this aryl hydantoin compound series conducted by Hoffmann La-Roche[18] are (1) a combination of halogens (F, Cl) and/or CF_3 groups at positions 3 and 4 of the phenyl ring was optimal; (2) electron-donating groups such as methoxy and dimethylamino at these same positions diminished activity; (3) 4-imino derivatives were active; and (4) some N^1-substituted analogs were active. Building on this foundation, we now describe a number of analogs of **1** (**2**–**36**, Tables 1–4) designed to maximize structural diversity guided by incorporation of substructures and functional groups known to diminish ligand–AR interactions. For example, several target compounds maintain the 5,5-dimethylhydantoin core of **1** and incorporate phenethyl (**6**), sulfonamide (**7**, **8**), aromatic halogens (**10**), and C═N bonds (**15**–**20**), functional groups and structural elements demonstrated to abolish or diminish AR ligand affinity.[24−28] The final set of target compounds maintains the 4-fluoro-3-trifluoromethylphenyl substructure of **1** in heterocycle variants of the 5,5-dimethylhydantoin substructure: succinimide **29**, oxazolidinedione **30**, oxolactam **31**, urea **32**, hydantoin transpositional isomer **33**, and the ring-expanded dihydropyrimidinediones **34** and **35**. Hydantoins analogous to **33** had relatively weak AR binding affinity.[24] We now report physicochemical profiling, in vitro ADME, antiandrogenic assessment, plasma exposure, and in vivo antischistosomal activities of these compounds.

CHEMISTRY

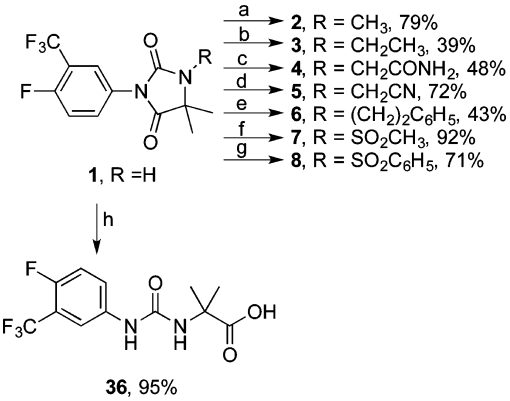
N^1-Alkyl and aralkyl hydantoins **2**–**6** and sulfonamides **7** and **8** were obtained by *N*-alkylation and sulfonylation of **1** according to the methods of Van Dort and Jung[28] and Jung et al.[24] (Scheme 1). Urea carboxylic acid **36** was obtained in high yield by hydrolysis of 1 with aqueous NaOH followed by acidification with dilute HCl.

Target compounds **11**–**13**, **16**, **17**, **19**, and **20** were obtained in variable yields by high-temperature reactions of the corresponding aryl iodides (**37**–**41**, **43**, and **44**) and hyantoin **42** with cuprous oxide[29,30] in dimethylacetamide (DMA) (Scheme 2).

Reactions between aryl iodide **45** and spiro hydantoin **46** or succinimide **47** under these same conditions afforded **27** and **29**, respectively (Scheme 3). Similarly, **14** was obtained by copper-catalyzed coupling of aryl bromide **49** and **42**, whereas **21** was obtained by alkylation of benzyl bromide **50** with **42** (Scheme 4). Compound **32** was obtained in a palladium-catalyzed *N*-arylation reaction[31] between aryl iodide **45** and imidazolidin-2-one **48**[32] (Scheme 3).

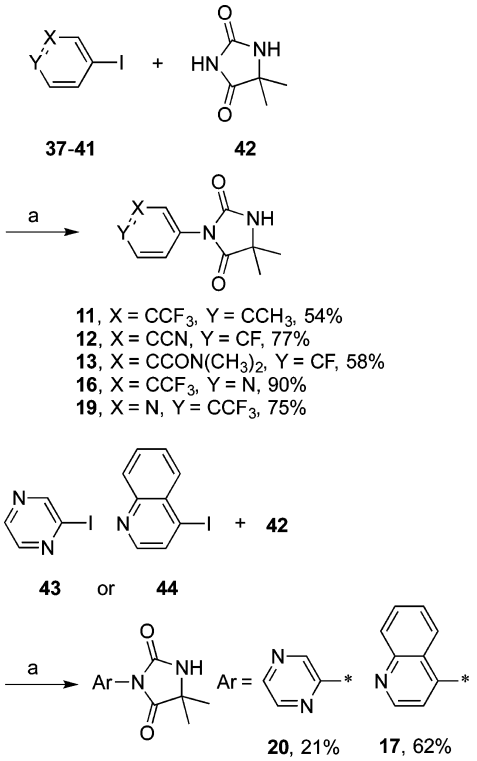
N-Arylation via copper(II) acetate promoted cross-coupling[33−35] of boronic acids **51** and **52** with **42** afforded **18** and **15**; the same cross-coupling reaction between boronic acid **53** and 1,3-oxazolidine-2,4-dione **54** or bicyclic hydantoin **55** afforded **30** and **28**, respectively (Scheme 5).

Scheme 1[a]



[a]Reagents and conditions: (a) NaH, DMF, rt, 0.5 h, then MeI, rt, 2 h; (b) NaH, THF, 0 °C to rt, 0.5 h, then EtI, rt, 3 d; (c) NaH, THF, 0 °C to rt, 0.5 h, then 2-bromoacetamide, rt, 3 d; (d) NaH, DMF, rt, 0.5 h, then 2-bromoacetonitrile, rt, 2 h; (e) NaH, DMF, rt, 0.5 h, then 2-bromoethylbenzene, rt, 2 h; (f) NaH, THF, 0 °C to rt, 0.5 h, then $MeSO_2Cl$, rt, 3 d; (g) NaH, DMF, rt, 0.5 h, then benzenesulfonyl chloride, rt, 2 h; (h) 2 M NaOH, rt, 4 h, then 2 M HCl.

Scheme 2[a]



[a]Reagents and conditions: (a) Cu_2O, DMA, 140–160 °C; 12–72 h.

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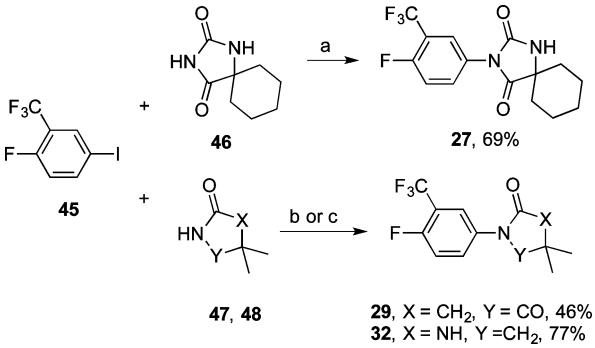
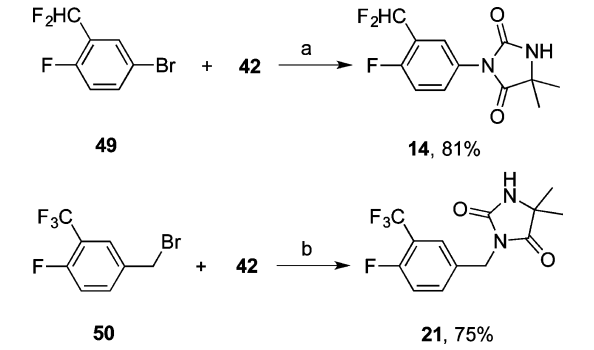
Scheme 3[a]



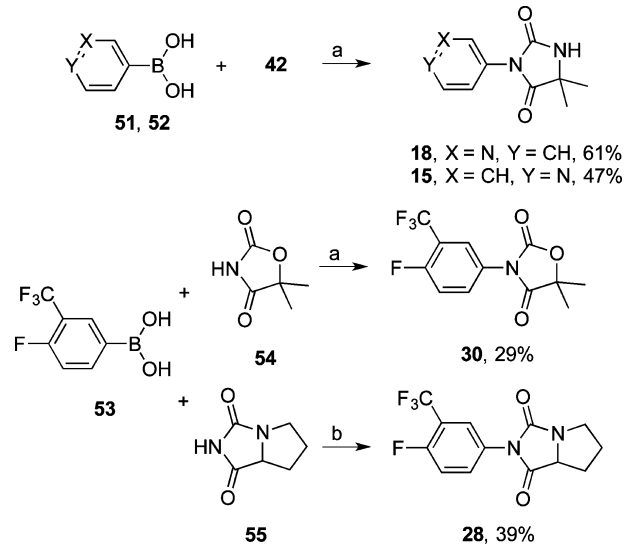
[a]Reagents and conditions: (a) Cu_2O, DMA, 160 °C; 24 h; (b) Cu_2O, DMF, 160 °C; 48 h (**29**); (c) $Pd_2(dba)_3$, Xanthphos, Cs_2CO_3, toluene, 90 °C; 12 h (**32**).

Scheme 4[a]



[a]Reagents and conditions: (a) Cu_2O, DMA, 160 °C, 24 h; (b) K_2CO_3, DMA, 85 °C; 24 h.

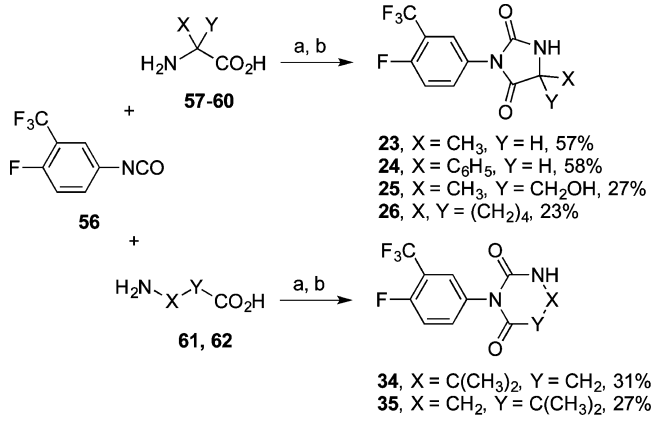
Scheme 5[a]



[a]Reagents and conditions: (a) $Cu(OAc)_2$, MeOH, O_2, 70 °C; 12 h; (b) $Cu(OAc)_2$, pyridine, CH_2Cl_2, rt, 7 d.

Compounds **23**–**26** were obtained in a two-step sequence[18,27,36] by reactions between aryl isocyanate **56** and α-amino acids **57**–**60** in aqueous NaOH to form the corresponding urea carboxylic acids that then cyclized to the hydantoins when exposed to 2–4 M HCl at 110 °C (Scheme 6). Compounds **34** and **35** were obtained by parallel two-step reactions between **56** and β-amino acids **61** and **62**. In some

Scheme 6[a]

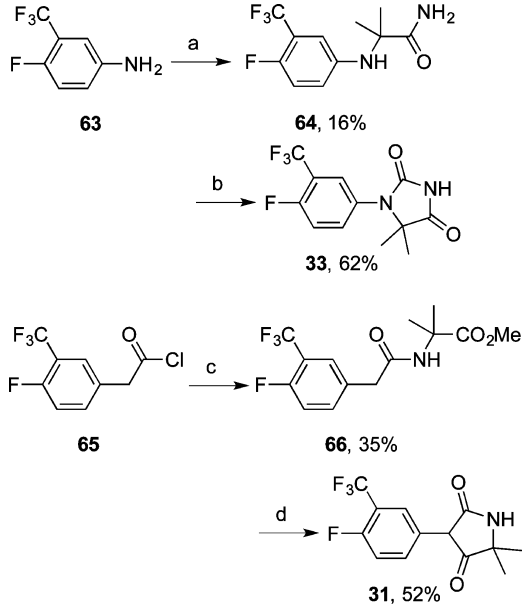


[a]Reagents and conditions: (a) 1–2 M NaOH, 0 °C to rt, 3–12 h; (b) 2–4 M HCl, 110 °C, 2–12 h.

instances, the acyclic urea carboxylic acid reaction intermediates precipitated from the initial reactions after acidification, but these were not usually purified, and were converted directly to the desired hydantoin reaction products. For almost all of these reactions, small amounts of the insoluble symmetrical *N,N*-diarylurea derived from isocyanate **56** were formed.

Oxolactam **31** was obtained by cyclization of the anion of benzyl amide ester **66** in a Dieckmann-type condensation;[37] **66** was obtained from the corresponding acid chloride **65** (Scheme 7). The key intermediate in the synthesis of **33** was *gem*-dimethyl α-amino amide **64**, which was obtained in a one-pot

Scheme 7[a]



[a]Reagents and conditions: (a) 1 M $TiCl_4$ in CH_2Cl_2, formamide, acetone, CH_2Cl_2, 0 °C, 0.5 h, then Zn, 50% H_2O_2 in formamide, 0 °C, 3 h; (b) 2,6-diisopropylphenyl isocyanate, toluene, 250 °C, 5 bar, 10 min, MW; (c) methyl 2-amino-2-methylpropanoate HCl, Et_3N, THF, rt, 12 h; (d) NaH, THF, rt, 12 h, then aq AcOH.

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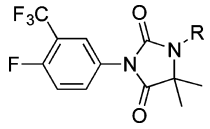
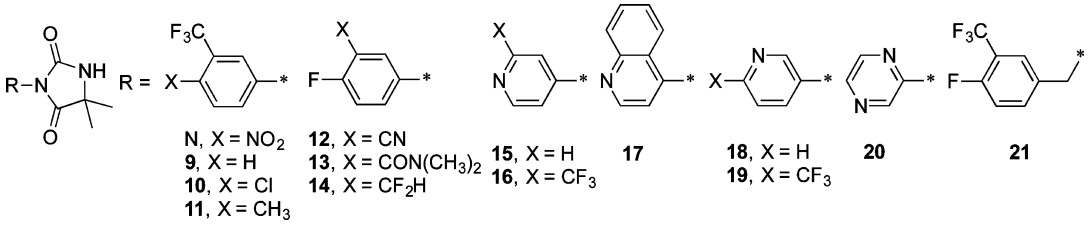
Table 1. Physicochemical, in Vitro ADME, Antiandrogenic, and Antischistosomal Data for N^1-Substituted 4-Fluoro-3-trifluoromethylphenyl Hydantoins



Compd	R	LogD$_{7.4}$[a]	PSA (Å^2)[b]	cPPB (%)[c]	Sol$_{2.0}$/Sol$_{6.5}$ (μg/mL)[d]	h/m CL$_{int}$ (μL/min/mg protein)[e]	LAPC4 IC$_{50}$ (μM)[f]	*S. mansoni* WBR (%) 1 × 100 mg/kg po[g]
1	H	2.7	49.4	52.1	>100/>100	8/<7	4.4	95[h]
2	CH_3	3.2	40.6	40.9	50−100/50−100	16/65	1.3	93*
3	CH_2CH_3	3.5	40.6	49.3	50−100/25−50	30/32	0.14	98*
4	CH_2CONH_2	2.2	83.7	20.3	50−100/50−100	<7/<7	agonist	25
5	CH_2CN	3.4	64.4	48.2	25−50/25−50	ND[j]	0.29	91*
6	$(CH_2)_2C_6H_5$	4.6	40.6	96.2	12.5−25/25−50	>870/740	2.4	54
7	SO_2CH_3	3.8	74.8	66.0	1.6−3.1/1.6−3.1	<7/<7	6.3	19
8	$SO_2C_6H_5$	4.6	74.8	96.1	<1.6/<1.6	210/160	4.3	44
PZ		3.0	40.6	ND	>100/>100	52/790	ND	18[i]

[a]LogD values were estimated by correlation of their chromatographic retention properties using gradient HPLC.[46] [b]Calculated using ChemAxon JChem for Excel. [c]Protein binding values were estimated by correlation of their chromatographic retention properties on a human albumin column.[47] [d]Compounds in DMSO were spiked into either pH 6.5 phosphate buffer or 0.01 M HCl (approximately pH 2.0) and analyzed by nephelometry to determine a concentration range. [e]In vitro intrinsic clearance measured in human and mouse liver microsomes. [f]Cells were then exposed to 10 nM DHT for 24 h in the presence of varying concentrations of test compounds. [g]Groups of five *S. mansoni*-infected NMRI mice were treated on day 49 postinfection with compounds dissolved or suspended in 7% v/v Tween 80, 3% v/v ethanol. At 28 d post-treatment, animals were sacrificed and dissected to assess total worm burden reduction (WBR). *$p < 0.05$ from the Kruskal−Wallis test comparing the medians of the responses between the treatment and control groups. [h]Data from Keiser et al.[19] [i]Data from Keiser et al.[21] [j]ND = not determined.

Table 2. Physicochemical, in Vitro ADME, Antiandrogenic, and Antischistosomal Data for N^3-Substituted Aryl Hydantoins



Compd	LogD$_{7.4}$	PSA (Å^2)	cPPB (%)	Sol$_{2.0}$/Sol$_{6.5}$ (μg/mL)	h/m CL$_{int}$ (μL/min/mg protein)	LAPC4 IC$_{50}$ (μM)	*S. mansoni* WBR (%) 1 × 100 mg/kg po
N	3.0	92.6	70.3	50−100/50−100	<7/<7	0.60/0.45	31[a]
9	2.5	49.4	49.3	>100/>100	<7/<7	6.0	80*
10	3.0	49.4	79.6	>100/>100	<7/<7	1.3	75*[b]
11	2.8	49.4	64.8	>100/>100	<7/16	>10	4.8
12	1.7	73.2	14.6	>100/>100	<7/<7	3.7	10
13	0.9	69.7	5.9	>100/>100	<7/<7	9.1	30
14	2.2	49.4	20.4	>100/>100	<7/<7	≥10	94*
15	0.5	62.3	6.7	50−100/>100	<7/11	3.8	1.8
16	1.9	62.3	22.7	>100/>100	<7/<7	4.5	100*
17	1.2	62.3	16.9	>100/>100	<7/<7	1.3	17
18	0.2	62.3	6.6	>100/>100	<7/<7	9.6	38
19	1.8	62.3	18.3	>100/>100	<7/<7	>10	0
20	0.3	75.2	5.8	>100/>100	<7/<7	>10	42
21	2.9	49.4	82.1	50−100/>100	17/11	4.2	56*

[a]Data from Keiser et al.[21] [b]1/4 mice died.

free radical multicomponent reaction[38] from aniline **63**. Exposure of **64** to 2,6-diisopropylphenyl isocyanate at high temperature[39] effected carbonylative ring closure to hydantoin **33**. Compounds **1**, **9**, **10**, and **22** were synthesized following procedures described by Link et al.[18]

PHYSICOCHEMICAL AND IN VITRO ADME

It is instructive to first consider the physicochemical and in vitro ADME properties of these analogs of **1** (Tables 1−4). The calculated polar surface area (PSA) values of between 32 and 84 Å^2 indicate that the polarity of these compounds is unlikely to be a rate-limiting factor for membrane permeability and oral bioavailability.[40] The measured LogD$_{7.4}$ values for all but two of the compounds ranged from 0 to 4, suggesting that high lipophilicity and the resulting poor aqueous solubility are unlikely to be limiting factors for oral absorption; this was largely borne out by the fairly high aqueous kinetic solubilities of many of these compounds. Compounds with low solubilities

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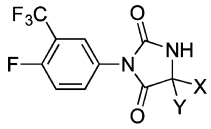
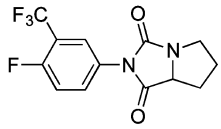
Table 3. Physicochemical, in Vitro ADME, Antiandrogenic, and Antischistosomal Data for 5-Substituted 4-Fluoro-3-trifluoromethylphenyl Hydantoins



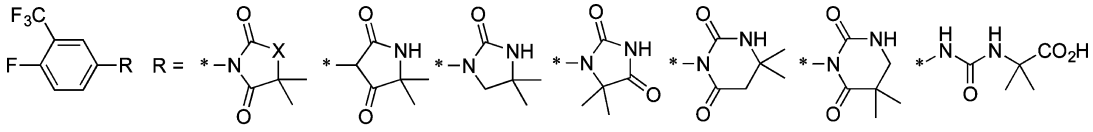
22-27



28

Compd	X, Y	LogD$_{7.4}$	PSA (Å^2)	cPPB (%)	Sol$_{2.0}$/Sol$_{6.5}$ (μg/mL)	h/m CL$_{int}$ (μL/min/mg protein)	LAPC4 IC$_{50}$ (μM)	*S. mansoni* WBR (%) 1 × 100 mg/kg po
22	H, H	2.0	49.4	43.6	>100/>100	<7/13	0.26	0
23	CH_3, H	2.4	49.4	38.6	>100/>100	17/34	>10	66*
24	C_6H_5, H	3.5	49.4	90.0	6.3−12.5/6.3−12.5	22/181	5.3	41
25	CH_3, CH_2OH	1.9	69.6	34.3	25−50/25−50	<7/<7	4.8	0
26	$(CH_2)_4$	3.2	49.4	70.4	50−100/50−100	33/93	0.99	61
27	$(CH_2)_5$	3.5	49.4	74.9	3.1−6.3/3.1−6.3	25/122	4.2	42
28		3.0	40.6	46.0	25−50/25−50	30/144	3.5	0

Table 4. Physicochemical, in Vitro ADME, Antiandrogenic, and Antischistosomal Data for 4-Fluoro-3-trifluoromethylphenyl Hydantoin Heterocycle Variants



29, X = CH_2 **30**, X = O

31

32

33

34

35

36

Compd	LogD$_{7.4}$	PSA (Å^2)	cPPB (%)	Sol$_{2.0}$/Sol$_{6.5}$ (μg/mL)	h/m CL$_{int}$ (μL/min/mg protein)	LAPC4 IC$_{50}$ (μM)	*S. mansoni* WBR (%) 1 × 100 mg/kg po
29	3.4	37.4	42.5	12.5−25/12.5−25	11/10	0.91	42
30	3.7	49.6	58.1	3.1−6.3/3.1−6.3	12/12[a]	2.1	11
31	0.5	46.2	93.3	25−50/>100	<7/<7	>10	0
32	3.2	32.3	78.3	12.5−25/12.5−25	<7/30	8.1	59
33	2.5	49.4	67.1	25−50/25−50	<7/<7	2.8	0
34	2.4	49.4	15.0	25−50/25−50	<7/<7	>10	51[b]
35	2.5	49.4	21.5	12.5−25/12.5−25	9/15	6.9	19
36	1.1	81.3	94.3	25−50/>100	<7/<7	3.1	67

[a]non-NADPH-mediated degradation observed. [b]2/4 mice died.

were sulfonamides **7** and **8**, 5-phenylhydantoin **24**, 5,5-spirocyclopentylhydantoin **27**, and 1,3-oxazolidine-2,4-dione **30**.

The only compounds with estimated plasma protein binding values ≥90% were aryl sulfonamide **8**, N^1-phenethyl **6**, 5-phenyl **24**, oxolactam imide **31**, and urea carboxylic acid **36**. Notably, these compounds featured either additional aryl substructures (**6**, **8**, **24**) or weak acid functional groups (**31** and **36**). In this respect, we note that **1**, with its pK_a value of 12.1,[17] is largely un-ionized at physiological pH. The metabolic stabilities of the N^1-alkyl and N^1-sulfonamide hydantoin derivatives (Table 1) varied from highly stable (**7**), to intermediate (**2**, **3**), to unstable (**6**, **8**). For N^1-alkyl hydantoins **2** and **3** we observed *N*-dealkylation metabolic reactions to form **1**. Notably, **6** and **8**, with their additional aryl groups, were the most lipophilic members of the series and also had the lowest metabolic stabilities. However, as seen for carboxamide **4**, addition of polar functional groups in the N^1-alkyl substructure can increase metabolic stability. The N^3-aryl hydantoins (Table 2) and hydantoin heterocycle variants (Table 4) had high metabolic stabilities. Hydantoins substituted at the 5 position (Table 3) with combinations of methyl, hydrogen, and hydroxymethyl (**1**, **22**, **23**, **25**) had high metabolic stabilities. However, incorporation of aryl (**24**) or spirocycloalkyl (**26**, **27**) substructures, or linking the 5 and N^1 positions by way of a pyrrolidine heterocycle (**28**), decreased the metabolic stabilities.

ANTIANDROGENIC AND ANTISCHISTOSOMAL ACTIVITIES

We now consider the in vitro antiandrogenic and in vivo antischistosomal properties of these analogs of **1**. The former was assessed by inhibition of dihydrotestosterone (DHT)-induced androgen luciferase reporter activity in the LAPC4 cell line, a cell line with a wild-type androgen receptor (AR), and the latter by measuring worm burden reduction (WBR) in *S. mansoni*-infected mice. As we had previously observed for **1**, none of the compounds at concentrations up to 100 μM had activity against schistosomula or adult *S. mansoni* in vitro. Similarly, none of the compounds was cytotoxic at concentrations up to 30 μM against the rat skeletal myoblast L6 cell line. Contrary to our expectation based on the previous SAR for this compound class, we did not observe decreased antiandrogenic potencies for N^1-substituted sulfonamides **7** and **8** or N^1-phenethyl **6** (Table 1). N^1-Substitution with small alkyl (**2**, **3**) groups increased antiandrogenic potencies, most

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strongly for the latter. Incorporation of nitrile (**5**) and carboxamide (**4**) functional groups into the N^1-alkyl substructure had very different effects; the former was a potent antiandrogen whereas the latter had no antiandrogenic properties and was instead a weak AR agonist. It is known[41] that hydantoins with N^1-cyanomethyl substructures are potent antiandrogens; thus, **5** served as a "negative control compound" for this SAR study. Similar to that of **1**, N^1-substituted hydantoins **2**, **3**, and **5** had high antischistosomal activities; of the remaining compounds in this series, **6** had weak antischistosomal activity.

The antiandrogenic and antischistosomal properties of the N^3-substituted aryl hydantoins exhibit several interesting trends (Table 2). Replacing the 4-F in **1** with a NO_2 (N) or Cl (**10**) increased antiandrogenic potency, whereas a H (**9**) or Me (**11**) at this same position decreased antiandrogenic potency. Of these, hydantoins **9** and **10** had high antischistosomal activities, similar to previously reported data.[18] Replacing the 3-trifluoro in **1** with a nitrile (**12**) had no effect on antiandrogenic potency and abolished antischistosomal activity. However, replacing the 3-trifluoro in **1** with a tertiary carboxamide (**13**) or difluoromethyl (**14**) decreased antiandrogenic potency, and the latter had high antischistosomal activity. Hydantoin **21**, the benzyl derivative of **1**, had similar antiandrogenic potency but substantially reduced antischistosomal activity compared to the latter. As we had anticipated based on the known SAR for antiandrogenic hydantoins, we observed decreased antiandrogenic potencies for some of the derivatives with aromatic C═N bonds; these included pyridines **18** and **19** and pyrazine **20**. However, the only one of the C═N containing hydantoins to have high activity against *S. mansoni* in vivo was **16**, the 4-pyridyl derivative with a trifluoromethyl group, which at 100 mg/kg resulted in cure of all of the infected mice.

As the data in Table 3 illustrate, our initial foray into the SAR of the 5-position of **1** did not bear much fruit. The principle insight gained was to note that removing one, but not both, of the methyl groups (**23**) decreases antiandrogenic activity and retains significant antischistosomal activity. 5,5-Spirocycloalkyl derivatives **26** and **27** had measurable but insignificant worm burden reduction (WBR) values and were no less antiandrogenic than **1**. Bicyclic hydantoin **28** reveals that connecting the 5- and N^1-positions with a pyrrolidine substructure completely abolished antischistosomal activity and offered no improvement in antiandrogenic activity. Finally, the data in Table 4 shows that the hydantoin core of **1** is required for high antischistosomal efficacy. Of these, only cyclic urea **32** and urea carboxylic acid **36** had moderate antischistosomal activities. The latter is the hydrolysis product of **1** and is formed in small quantities when **1** is administered at high doses (*vide infra*, Figure 2a). Interestingly, as reported by Link and Stohler,[18] the methyl ester of **36**, with a single-dose ED_{50} of 62 mg/kg, has significant antischistosomal activity.

MOUSE EXPOSURE

With this compound series, we have the unusual situation where lead compounds have no in vitro activity but generally exhibit in vivo activity. Therefore, to see if there was a correlation between antischistosomal efficacy and plasma exposure and to begin to assess the effect of aryl hydantoin structure on pharmacokinetics, the most active aryl hydantoins (**1**–**3**, **14**, and **16**) and three less active hydantoins (**13**, **23**, **26**) were administered to noninfected mice at single oral doses of 100 mg/kg. From a practical standpoint, it was necessary to assume that exposure profiles generated in noninfected mice provided a reasonable estimation of exposure in *S. mansoni*-infected mice.

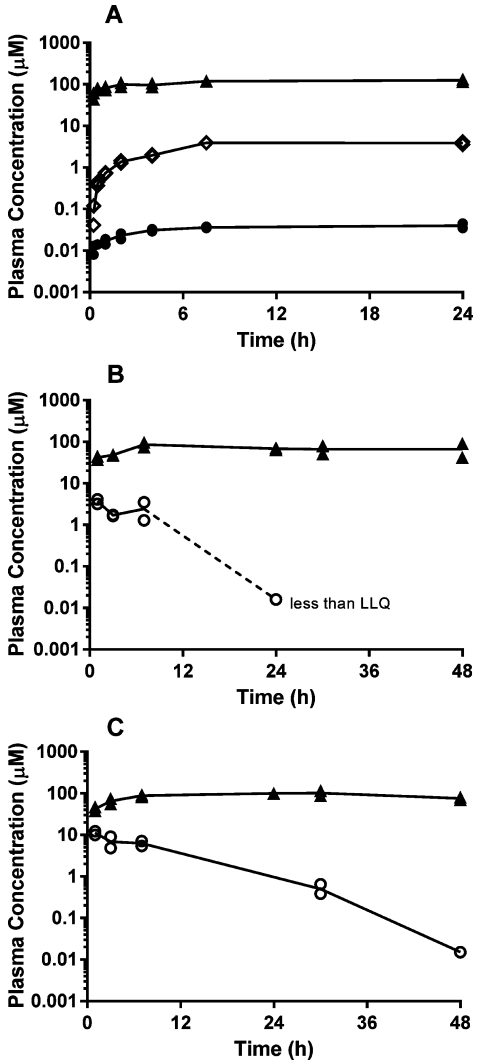

Figure 2. Plasma concentration versus time profiles of (A) **1** (filled triangles) and the metabolites **36** (filled circles) and **25** (open diamonds); (B) **2** (open circles) and the metabolite **1** (filled triangles); and (C) **3** (open circles) and the metabolite **1** (filled triangles) following oral administration of 100 mg/kg to male Swiss outbred mice. Symbols represent individual data points, and the lines represent the mean profiles.

After oral administration of **1**, plasma concentrations increased until 2 h postdose, after which concentrations remained relatively constant up to 24 h, most likely due to saturated clearance processes at the very high concentrations (Figure 2A, Table 5). We also observed low but measurable concentrations of urea carboxylic acid **36**, the hydantoin hydrolysis product, and **25**, the hydroxymethyl metabolite. Based on values for AUC_{0-24h}, the exposures of **36** and **25** were <1% and approximately 3%, respectively, relative to **1**. Following oral administration of **2** or **3** (Figure 2B and 2C), concentrations of the parent compounds rapidly declined with subsequent formation of **1** at maximum concentrations comparable to that seen following dosing with **1** (Figure 2A).

Hydantoins **13**, **14**, **16**, **23**, and **26** were all rapidly absorbed; however, they differed substantially in their plasma exposure profiles. The highest and most prolonged exposures were

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Table 5. Exposure Parameters for Selected Aryl Hydantoins in Male Swiss Outbred Mice Following Oral Administration of 100 mg/kg[a]

Compd	C_{max} (μM)	T_{max} (h)	$AUC_{0\text{-}last}$ (μM·h)
1	124	c.n.d.	2740
2	c.n.d.	1	c.n.d.
3	11.1	1	103
13	488	1	1360
14	112	3	3190
16	155	7	6480
23	26.6	1	163
26	15.0	1	106

[a]c.n.d. = could not determine.

observed for **14** and **16**, where plasma concentrations were comparable to those for **1** (Figure 3A and Table 5). Both the maximum concentrations and the duration of exposures of **23** and **26** were substantially lower, likely due in part to their higher intrinsic clearance, as determined in mouse microsomes (Figure 3B and Table 5). While **13** reached a higher maximum plasma concentration than either **14** or **16**, concentrations declined at a much faster rate, resulting in a considerably reduced duration of exposure (Figure 3B and Table 5). As **13** had a low intrinsic clearance in mouse microsomes, its more rapid rate of elimination is likely due to its lower log D value (0.9), resulting in a lower volume of distribution and, possibly, significant renal excretion.

SUMMARY

Hydantoin **1** and its analogs **2**–**36** had calculated polar surface area (PSA), measured $LogD_{7.4}$, aqueous kinetic solubility, and estimated plasma protein binding values in ranges predictive of good ADME profiles. For N^1-alkyl and N^1-sulfonamide derivatives of **1**, incorporation of polar functional groups increased metabolic stability, whereas incorporation of phenyl substructures decreased metabolic stability. However, none of these possessed both decreased antiandrogenic potency and increased antischistosomal activity. N^3-Aryl hydantoins, hydantoin heterocycle variants, and hydantoins substituted at the 5 position with combinations of methyl, hydrogen, and hydroxymethyl had high metabolic stabilities. The SAR of the N^3-substituted aryl hydantoins was complex, but three of these had high antischistosomal efficacy and were less antiandrogenic than **1**. The SAR of the 5-substituted aryl hydantoins reveals that replacing one of the methyl groups with a hydrogen atom decreases antiandrogenic activity and retains significant antischistosomal activity. Investigation of heterocycle variants showed that the hydantoin core of **1** is required for high antischistosomal activity. In this respect, recent investigations of a series of structurally distinct 4-thiohydantoins reveal that they have activity against *S. mansoni* in vitro;[42] the best of these effected a 71% worm burden reduction (WBR) in *S. mansoni*-infected mice when it was administered as five daily 100 mg/kg oral doses.[43]

Exposure data for selected compounds reveals the following. First, N^1-alkyl hydantoins **2** and **3** had high antischistosomal activities, due most likely to their extensive conversion to **1** by metabolic *N*-dealkylation reactions. Second, N^3-aryl hydantoins **14** and **16**, two of the most active compounds, had, like **1**, high plasma exposures; conversely, N^3-aryl hydantoin **13**, 5-methyl hydantoin **23**, and 5,5-dispirocyclopentyl hydantoin **26**, three less effective compounds, had relatively low plasma exposures. These data are suggestive that antischistosomal efficacy and plasma exposure may correlate. This study provides several insights for the ongoing identification of more effective antischistosomal hydantoins.

EXPERIMENTAL SECTION

General. All reagents were purchased from Sigma-Aldrich, Fisher, or Acros Organics and used without further purification, unless otherwise stated. Melting points were determined with a Stanford Research Systems melting point apparatus and are uncorrected. 1D ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvents. All chemical shifts are reported in parts per million (ppm) and are relative to internal $(CH_3)_4Si$ (0 ppm) for ^{1}H and $CDCl_3$ (77.2 ppm) or DMSO-d_6 (39.5 ppm) for ^{13}C NMR. EI GC-MS data were obtained using an Agilent quadrapole mass spectrometer with 30 m DB-XLB type columns and a He flow rate of 1 mL/min. Silica gel (sg) particle size 32–63 μm was used for all flash column chromatography. Reported reaction temperatures are those of the oil bath. A Biotage microwave reactor was used for selected reactions. Combustion analysis confirmed that all target compounds have a purity of at least 95%.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-1,5,5-trimethylimidazolidine-2,4-dione (**2**).* To a solution of **1** (700 mg, 2.4 mmol) in DMF was added NaH (87 mg, 3.6 mmol) under Ar. The mixture was stirred at rt for 30 min, and then iodomethane (514 mg, 3.6 mmol) was added dropwise. After stirring for 2 h, the mixture was evaporated in vacuo to give a residue which was extracted with brine (30 mL) and EtOAc (3 × 30 mL). The combined organic phase was washed with brine (2 × 30 mL) and dried over $MgSO_4$. After removal of the solvents, the residue was purified by chromatography (sg, hexane:EtOAc, 4:1) to afford **2** as a white solid (580 mg, 79%). mp 110–112 °C; ^{1}H NMR

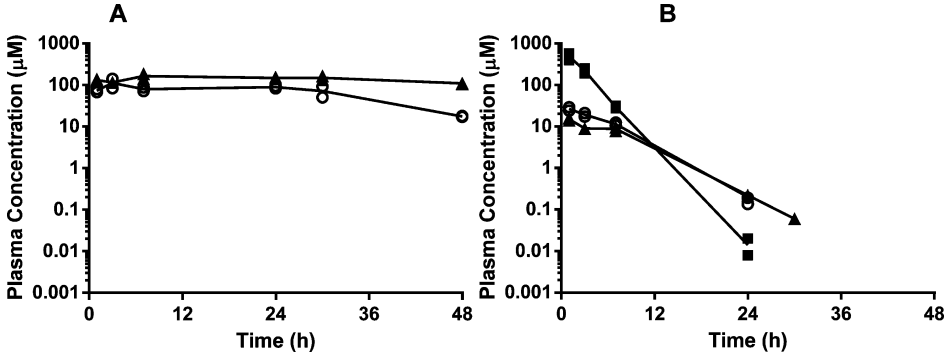

Figure 3. Plasma concentration versus time profiles of (A) **16** (filled triangles) and **14** (open circles) and (B) **13** (filled squares), **23** (open circles), and **26** (filled triangles), following oral administration of 100 mg/kg to male Swiss outbred mice. Symbols represent individual data points, and the lines represent the mean profiles.

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($CDCl_3$) δ 1.51 (s, 6H), 2.98 (s, 3H), 7.29 (t, J = 9.3 Hz, 1H), 7.66–7.69 (m, 1H), 7.77 (d, J = 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.28, 24.68, 61.22, 117.48 (m), 118.96 (qd, J = 33.6, 13.9 Hz), 122.03 (q, J = 272.5 Hz), 124.80 (m), 128.07 (d, J = 3.6 Hz), 131.23 (d, J = 8.6 Hz), 153.44, 158.48 (q, J = 258.2 Hz), 175.14. Anal. Calcd for $C_{13}H_{12}F_4N_2O_2$: C, 51.32; H, 3.98; N, 9.21; Found: C, 51.20; H, 3.92; N, 9.39.

*1-Ethyl-3-[4-fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethylimidazolidine-2,4-dione (**3**).* To a solution of **1** (700 mg, 2.4 mmol) in THF (7.5 mL) was added NaH (87 mg, 3.6 mmol) in THF (7.5 mL) at 0 °C under Ar. The reaction mixture was then stirred at rt for 3 h before dropwise addition of iodoethane (561 mg, 3.6 mmol). The reaction mixture was stirred at rt for 72 h before quenching with acetic acid (600 mg, 10 mmol) and H_2O (1 mL). Solvent removal in vacuo gave a residue which was crystallized from H_2O. The residue was further purified by chromatography (sg, EtOAc:hexane, 1:4) to afford **3** as a white solid (301 mg, 39%). mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 1.53 (s, 6H), 3.43 (q, J = 7.2 Hz, 2H), 7.29 (t, J = 9.4 Hz, 1H), 7.65–7.74 (m, 1H), 7.78 (dd, J = 6.3, 2.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 15.14, 23.58, 35.08, 61.97, 117.60 (d, J = 22.1 Hz), 119.11 (qd, J = 33.6, 13.6 Hz), 122.21 (q, J = 272.5 Hz), 124.95 (q, J = 4.5 Hz), 128.25 (d, J = 3.6 Hz), 131.34 (d, J = 8.9 Hz), 153.46, 158.60 (d, J = 258.1 Hz), 175.28. Anal. Calcd for $C_{14}H_{14}F_4N_2O_2$: C, 52.83; H, 4.43; N, 8.80. Found: C, 52.80, H, 4.60, N, 8.71.

*2-[3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl]acetamide (**4**).* To a solution of **1** (1.04 g, 3.6 mmol) in THF (15 mL) was added NaH (163 mg, 6.8 mmol) in THF (15 mL) at 0 °C under Ar. The mixture was then stirred at rt for 3 h before dropwise addition of 2-bromoacetamide (937 mg, 6.8 mmol). The reaction mixture was stirred at rt for 72 h before quenching with acetic acid (600 mg, 10 mmol). Solvent removal in vacuo gave a residue which was crystallized from CH_2Cl_2 to afford **4** as a white solid (600 mg, 48%). mp 186–187 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (s, 6H), 3.90 (s, 2H), 7.25 (s, 1H), 7.50 (s, 1H), 7.69 (t, J = 9.7 Hz, 1H), 7.80–7.86 (m, 1H), 7.90 (dd, J = 6.6, 2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 22.04, 41.90, 61.62, 116.72 (qd, J = 32.9, 13.6 Hz), 117.84 (d, J = 21.8 Hz), 122.21 (q, J = 272.4 Hz), 125.36 (q, J = 5.0 Hz), 128.74 (d, J = 3.3 Hz), 133.37 (d, J = 9.3 Hz), 153.50, 157.56 (dq, J = 254.9, 1.9 Hz), 169.63, 175.02. Anal. Calcd for $C_{14}H_{13}F_4N_3O_3$: C, 48.42; H, 3.77; N, 12.10. Found: C, 48.70, H, 4.01, N, 11.89.

*2-[3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyl-2,4-dioxoimidazolidin-1-yl]acetonitrile (**5**).* To a solution of **1** (700 mg, 2.4 mmol) in DMF was added NaH (116 mg, 4.8 mmol) under Ar. The mixture was stirred at rt for 30 min, and then 2-bromoacetonitrile (578 mg, 4.8 mmol) was added dropwise. After stirring for 2 h, the mixture was evaporated in vacuo to give a residue which was extracted with brine (30 mL) and EtOAc (3 × 30 mL). The combined organic phase was washed with brine (2 × 30 mL) and dried over $MgSO_4$. After removal of the solvents, the residue was purified by chromatography (sg, hexane:EtOAc, 2:1) to afford **5** as a white solid (573 mg, 72%). mp 147–149 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 6H), 4.37 (s, 2H), 7.32 (t, J = 9.3 Hz, 1H), 7.66–7.69 (m, 1H), 7.75 (dd, J = 2.4, 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.75, 27.14, 62.11, 114.73, 117.81 (d, J = 22.1 Hz), 119.28 (qd, J = 33.6, 13.9 Hz), 121.90 (q, J = 273.0 Hz), 124.89 (q, J = 1.9 Hz), 127.28(d, J = 4.4 Hz), 131.27 (d, J = 9.6 Hz), 153.13, 158.83(q, J = 257.2 Hz), 173.71. Anal. Calcd for $C_{14}H_{11}F_4N_3O_2$: C, 51.07; H, 3.37; N, 12.76; Found: C, 51.29; H, 3.60; N, 12.52.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyl-1-phenethylimidazolidine-2,4-dione (**6**).* To a solution of **1** (700 mg, 2.4 mmol) in DMF (15 mL) was added NaH (87 mg, 3.6 mmol) under Ar. The mixture was stirred at rt for 30 min, and then 2-bromoethylbenzene (670 mg, 3.6 mmol) was added dropwise. After stirring for 2 h, the mixture was evaporated in vacuo to give a residue which was extracted with brine (30 mL) and EtOAc (3 × 30 mL). The combined organic phase was washed with brine (2 × 30 mL) and dried over $MgSO_4$. After removal of the solvents, the residue was purified by chromatography (sg, hexane:EtOAc, 4:1) to afford **6** as a white solid (410 mg, 43%). mp 98–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6H), 3.05 (t, J = 7.8 Hz, 2H), 3.53 (t, J = 8.3 Hz, 2H), 7.24–7.34 (m, 6H), 7.69–7.72 (m, 1H), 7.78 (dd, J = 2.4, 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.12, 35.34, 42.23, 61.86, 117.46 (d, J = 22.2 Hz), 118.94 (qd, J = 33.1, 13.9 Hz), 122.04 (q, J = 272.0 Hz), 124.72 (m), 126.81, 128.69, 128.81, 131.14 (d, J = 8.5 Hz), 138.23, 153.62, 158.49 (d, J = 258.2 Hz), 174.94. Anal. Calcd for $C_{20}H_{18}F_4N_2O_2$: C, 60.91; H, 4.60; N, 7.10; Found: C, 60.70; H, 4.89; N, 7.26.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyl-1-(methylsulfonyl)imidazolidine-2,4-dione (**7**).* To a solution of **1** (700 mg, 2.4 mmol) in THF (7.5 mL) was added NaH (100 mg, 4.1 mmol) in THF (7.5 mL) at 0 °C under Ar. The reaction mixture was then stirred at rt for 30 min before dropwise addition of methanesulfonyl chloride (410 mg, 3.6 mmol). After further stirring at rt for 72 h, the reaction was quenched with acetic acid (4 mL). Removal of solvents in vacuo gave a residue to which was added H_2O (30 mL). The resulting precipitate was filtered and crystallized from 1:5 EtOAc:hexane to afford **7** as a white solid (812 mg, 92%). mp 207–208 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 6H), 3.44 (s, 3H), 7.35 (t, J = 9.2 Hz, 1H), 7.67 (dt, J = 7.4, 3.5 Hz, 1H), 7.75 (dd, J = 6.1, 2.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 24.19, 43.53, 66.73, 118.19 (d, J = 22.3 Hz), 119.70 (qd, J = 33.9, 13.9 Hz), 121.95 (q, J = 272.6 Hz), 125.36 (qd, J = 6.9, 4.5 Hz), 126.56, 131.70 (d, J = 9.4 Hz), 151.70, 159.31 (d, J = 259.9 Hz), 173.02. Anal. Calcd for $C_{13}H_{12}F_4N_2O_4S$: C, 42.39; H, 3.28; N, 7.61. Found: C, 42.40; H, 3.46; N, 7.49.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyl-1-(phenylsulfonyl)imidazolidine-2,4-dione (**8**).* To a solution of **1** (700 mg, 2.4 mmol) in DMF (15 mL) was added NaH (87 mg, 3.6 mmol) under Ar. The mixture was stirred at rt for 30 min, and then benzenesulfonyl chloride (639 mg, 3.6 mmol) was added dropwise. After stirring for 2 h, the mixture was evaporated in vacuo to give a residue which was extracted with brine (30 mL) and EtOAc (3 × 30 mL). The combined organic phase was washed with brine (2 × 30 mL) and dried over $MgSO_4$. After removal of the solvents, the residue was purified by chromatography (sg, hexane:EtOAc, 4:1) to afford **8** as a white solid (739 mg, 71%). mp 153–155 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 6H), 7.27 (t, J = 9.4 Hz, 1H), 7.57–7.71 (m, 5H), 8.13 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 24.26, 66.75, 117.80 (d, J = 22.2 Hz), 119.29 (qd, J = 34.1, 13.9 Hz), 121.77(q, J = 272.5 Hz), 125.14 (m), 126.46 (d, J = 3.8 Hz), 128.73, 129.16, 131.54 (d, J = 9.1 Hz), 134.59, 138.32, 150.57, 158.99 (d, J = 259.6 Hz), 172.81. Anal. Calcd for $C_{18}H_{14}F_4N_2O_4S$ 0.67 H_2O: C, 48.87; H, 3.49; N, 6.33; Found: C, 48.71; H, 3.09; N, 6.12.

*5,5-Dimethyl-3-[4-methyl-3-(trifluoromethyl)phenyl]-imidazolidine-2,4-dione (**11**).* To a solution of 5,5-dimethylimidazolidine-2,4-dione (**42**) (568 mg, 4.44 mmol) and Cu_2O (240 mg, 1.68 mmol) in DMA (15 mL) was added 4-iodo-1-methyl-2-(trifluoromethyl)benzene (**37**) (1.00 g, 3.5 mmol). After stirring at 160 °C for 12 h, the solvent was evaporated in vacuo to give a crude product which was further purified by sg chromatography using successive elution with hexane, EtOAc, and EtOH to afford **11** as a white solid (536 mg, 54%). mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 6H), 2.51 (s, 3H), 5.52 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.70 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 18.43, 24.65, 57.85, 123.92 (q, J = 5.2 Hz), 124.09 (q, J = 273.6 Hz), 127.54 (q, J = 29.6 Hz), 130.37, 130.41, 132.59, 135.53, 153.85, 176.21. Anal. Calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.55; H, 4.58; N, 9.79; Found: C, 54.45; H, 4.73; N, 9.62.

*5-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-2-fluorobenzonitrile (**12**).* To a solution of **42** (0.674, 5.3 mmol) and Cu_2O (290 mg, 2 mmol) in DMA (4 mL) was added 2-fluoro-5-iodobenzonitrile (**38**) (1.0 g, 4.1 mmol). After it was heated to 160 °C for 48 h, the solvent was evaporated in vacuo. After addition of EtOAc (100 mL), the resulting precipitate was filtered and the filtrate was concentrated and purified by chromatography (sg, EtOAc) followed by recrystallization from 1:20 ethanol:H_2O to afford **12** as a white solid (768 mg, 77%). mp 145–147 °C; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 6H), 6.70 (s, 1H), 7.33 (t, J = 8.8 Hz, 1H), 7.78–7.81 (m, 1H), 7.84 (dd, J = 2.4, 5.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.15, 58.83, 102.08(d, J = 17.3 Hz), 112.99, 117.08 (d, J = 21.1 Hz), 128.52 (d, J = 3.4 Hz), 130.48, 132.28 (d, J = 8.6 Hz), 154.41, 161.74 (d, J = 261.0 Hz),175.47. Anal. Calcd for $C_{12}H_{10}FN_3O_2$: C, 58.30; H, 4.08; N, 17.00; Found: C, 58.08; H, 4.26; N, 17.28.

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*5-(4,4-Dimethyl-2,5-dioxoimidazolidin-1-yl)-2-fluoro-N,N-dimethylbenzamide (**13**).* To a solution of **42** (640 mg, 5.0 mmol) and Cu_2O (259 mg, 1.8 mmol) in DMA (10 mL) was added 2-fluoro-5-iodo-*N*,*N*-dimethylbenzamide (**39**) (496 mg, 1.7 mmol). The mixture was then heated to 150 °C for 48 h. Solvent removal in vacuo gave a crude product which was further purified by sg chromatography using successive elution with hexane, EtOAc, and ethanol followed by crystallization from a 1:10 EtOAc:hexane mixture to afford **13** as a white solid (296 mg, 58%). mp 166−168 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (s, 6H), 2.87 (s, 3H), 3.01 (s, 3H), 7.41 (t, J = 9.1 Hz, 1H), 7.44 (dd, J = 6.0, 2.5 Hz, 1H), 7.51 (ddd, J = 8.9, 4.8, 2.6 Hz, 1H), 8.59 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 24.68, 34.33, 37.85, 57.85, 116.21 (d, J = 23.3 Hz), 124.76 (d, J = 20.0 Hz), 127.11 (d, J = 4.7 Hz), 128.69 (d, J = 3.0 Hz), 129.62 (d, J = 8.7 Hz), 153.93, 156.32 (d, J = 246.5 Hz), 164.45, 176.27. Anal. Calcd for $C_{14}H_{16}FN_3O_3$: C, 57.33; H, 5.50; N, 14.33. Found: C, 57.51; H, 5.25; N, 14.22.

*3-[3-(Difluoromethyl)-4-fluorophenyl]-5,5-dimethylimidazolidine-2,4-dione (**14**).* To a solution of **42** (2.54 g, 19.8 mmol) and Cu_2O (1.09 g, 7.6 mmol) in DMA (30 mL) was added 4-bromo-2-(difluoromethyl)-1-fluorobenzene (**49**) (3.50 g, 15.5 mmol). After the reaction mixture was heated at 160 °C for 24 h, the solvent was removed in vacuo. The residue was purified by chromatography (sg, EtOAc) and then crystallized successively from hexane (15 mL) and H_2O (20 mL) to afford **14** as a white solid (3.43 g, 81%). mp 158−159 °C; ^{1}H NMR (DMSO-d_6) δ 1.41 (s, 6H), 7.26 (t, J = 54.1 Hz, 1H), 7.51 (t, J = 9.5 Hz, 1H), 7.59−7.68 (m, 1H), 7.72 (dd, J = 6.4, 2.5 Hz, 1H), 8.62 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 24.60, 57.85, 111.52 (td, J = 236.2, 3.5 Hz), 116.72 (d, J = 21.8 Hz), 121.46 (td, J = 23.4, 14.0 Hz), 125.75 (d, J = 3.3 Hz), 128.68 (d, J = 3.3 Hz), 131.64 (d, J = 9.0 Hz), 153.79, 158.38 (dt, J = 251.3, 4.8 Hz), 176.17. Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 52.72, H, 4.19, N, 10.12.

*5,5-Dimethyl-3-(pyridin-4-yl)imidazolidine-2,4-dione (**15**).* To a solution of **42** (5.38 g, 42 mmol) and $Cu(OAc)_2$ (543 mg, 3 mmol) in methanol (150 mL) was added pyridin-4-ylboronic acid (**53**) (3.6 g, 29 mmol) under O_2. The mixture was heated at 70 °C overnight. The solvent was then filtered through silica gel to remove copper, and the resulting cake was washed with methanol (100 mL). Evaporation of the filtrate gave a crude product which was further purified by crystallization from a saturated Na_2CO_3 solution (20 mL) to afford **15** as a white solid (2.8 g, 47%). mp 201−203 °C; ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 6H), 7.57 (d, J = 5.6 Hz, 2H), 8.67 (d, J = 6.1 Hz, 2H), 8.74 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 24.70, 57.75, 119.62, 139.85, 150.26, 153.08, 175.88. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.14; H, 5.64; N, 20.57.

*5,5-Dimethyl-3-[2-(trifluoromethyl)pyridin-4-yl]imidazolidine-2,4-dione (**16**).* To a solution of **42** (776 mg, 6.1 mmol) and Cu_2O (288 mg, 2.0 mmol) in DMA (30 mL) was added 4-iodo-2-(trifluoromethyl)pyridine (**39**) (750 mg, 2.8 mmol). After stirring at 140 °C for 24 h, the solvent was evaporated in vacuo to give a crude product which was further purified by sg chromatography using successive elution with hexane and EtOAc to afford **16** as a white solid (674 mg, 90%). mp 195−197 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (s, 6H), 7.95 (dd, J = 5.4, 1.9 Hz, 1H), 8.14 (d, J = 1.8, 1H), 8.87 (d, J = 5.4 Hz, 1H), 8.89 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.61, 57.82, 116.17, 121.39 (q, J = 274.3 Hz), 122.29, 141.72, 146.94 (q, J = 34.1 Hz), 151.15, 152.68, 175.71. Anal. Calcd for $C_{11}H_{10}F_3N_3O_2$: C, 48.36; H, 3.69; N, 15.38. Found: C, 47.97; H, 4.00; N, 15.64.

*5,5-Dimethyl-3-(quinolin-4-yl)imidazolidine-2,4-dione (**17**).* To a solution of **42** (384 mg, 3 mmol) and Cu_2O (142 mg, 1 mmol) in DMA (5 mL) was added 4-iodoquinoline (**44**) (163 mg, 0.64 mmol). After the reaction mixture was heated at 150 °C for 72 h, the solvent was removed in vacuo. The residue was purified by sg chromatography using successive elution with hexane, EtOAc, and ethanol to afford **17** as a pale yellow solid (101 mg, 62%). mp 194−196 °C; ^{1}H NMR (DMSO-d_6) δ 1.50 (s, 3H), 1.57 (s, 3H), 7.61 (d, J = 4.6 Hz, 1H), 7.65−7.76 (m, 2H), 7.86 (t, J = 7.2 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.83 (s, 1H), 9.05 (d, J = 4.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 24.50, 25.26, 58.77, 121.60, 122.83, 124.72, 127.58, 129.42, 130.15, 137.08, 148.77, 150.73, 153.60, 176.45. Anal. Calcd for $C_{14}H_{13}N_3O_2$ H_2O: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.82; H, 5.08; N, 15.30.

*5,5-Dimethyl-3-(pyridin-3-yl)imidazolidine-2,4-dione (**18**).* To a solution of **42** (1.792 g, 14 mmol) and $Cu(OAc)_2$ (181 mg, 1 mmol) in methanol (50 mL) was added pyridin-3-ylboronic acid (**52**) (1.23 g, 10 mmol) under O_2. The mixture was heated at 70 °C overnight. The solvent was then filtered through silica gel to remove copper, and the resulting cake was washed with methanol (100 mL). Evaporation of the filtrate gave a crude product which was further purified by successive crystallizations from diethyl ether (10 mL) and saturated Na_2CO_3 (10 mL) to afford **18** as a white solid (1.258 g, 61%). mp 160−162 °C; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 6H), 6.85 (s, 1H), 7.43 (dd, J = 4.4, 7.8 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 8.62 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.22, 58.87, 123.57, 128.78, 133.15, 146.79, 148.65, 154.72, 175.79. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48; Found: C, 58.70; H, 5.36; N, 20.19.

*5,5-Dimethyl-3-[6-(trifluoromethyl)pyridin-3-yl]imidazolidine-2,4-dione (**19**).* To a solution of **42** (384 mg, 3.00 mmol) and Cu_2O (143 mg, 1.00 mmol) in DMA (10 mL) was added 5-iodo-2-(trifluoromethyl)pyridine (**41**) (476 mg, 1.74 mmol), and the mixture was heated to 140 °C for 48 h. After solvent removal in vacuo, the crude product was purified by sg chromatography using successive elution with hexane and EtOAc. After removal of the solvents in vacuo, the residue was crystallized from 1:20 EtOAc:hexane. The resulting precipitate was collected by filtration and rinsed by H_2O (5 mL) to give **19** as a white solid (357 mg, 75%). mp 173−174 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 6 H), 8.08 (d, J = 8.3 Hz, 1 H), 8.20 (d, J = 8.3 Hz, 1 H), 8.80 (s, 1 H), 8.88 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 24.80, 58.36, 121.16, 121.61(q, J = 273.9 Hz), 132.27, 135.50, 144.63 (q, J = 34.4 Hz), 147.43, 153.32,176.10. Anal. Calcd for $C_{11}H_{10}F_3N_3O_2$: C, 48.36; H, 3.69; N, 15.38. Found C, 48.48; H, 3.81; N, 15.16.

*5,5-Dimethyl-3-(pyrazin-2-yl)imidazolidine-2,4-dione (**20**).* To a solution of **42** (1.28 g, 10.0 mmol) and Cu_2O (357.5 mg, 2.5 mmol) in DMA (20 mL) was added 2-iodopyrazine (**43**) (1.00 g, 4.9 mmol). The reaction mixture was then heated to 140 °C for 24 h. After solvent removal in vacuo, the crude product was purified by sg chromatography using successive elutions with hexane, EtOAc, and ethanol. After removal of the solvents in vacuo, the residue was crystallized from a mixture of ether (0.5 mL) and hexane (10 mL). The resulting precipitate was collected by filtration to give **20** as a pale yellow solid (210 mg, 21%). mp 149−151 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 6H), 8.66−8.90 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 24.65, 58.38, 142.76, 143.72, 143.91, 144.38, 153.05, 175.80. Anal. Calcd for $C_9H_{10}N_4O_2$; C, 52.42; H, 4.89; N, 27.17. Found: C, 52.34; H, 5.00; N, 27.21.

*3-[4-Fluoro-3-(trifluoromethyl)benzyl]-5,5-dimethylimidazolidine-2,4-dione (**21**).* A mixture of 4-(bromomethyl)-1-fluoro-2-(trifluoromethyl)benzene (**50**) (1.552 g, 6.0 mmol), **42** (647 mg, 5.1 mmol), and K_2CO_3 (2.004 g, 14.5 mmol) in DMA (12.5 mL) was stirred at 85 °C for 24 h. The mixture was extracted with EtOAc (3 × 50 mL) and H_2O (50 mL). The organic phase was combined, dried, and evaporated in vacuo to give a residue which was further purified by chromatography (sg, EtOAc:hexane, 1:3) and crystallized from H_2O to afford **21** as a white solid (1.16 g, 75%). mp 86−87 °C; ^{1}H NMR (DMSO-d_6) δ 1.32 (s, 6H), 4.63 (s, 2H), 7.50 (dd, J = 10.7, 8.6 Hz, 1H), 7.56−7.63 (m, 1H), 7.66 (d, J = 7.0 Hz, 1H), 8.46 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.53, 39.91, 58.03, 116.53 (qd, J = 32.4, 12.6 Hz), 117.55 (d, J = 20.7 Hz), 122.47 (q, J = 272.0 Hz), 126.07 (q, J = 4.7 Hz), 133.99, 134.04 (d, J = 5.3 Hz), 154.91, 158.10 (dq, J = 253.2, 2.3 Hz), 177.22. Anal. Calcd for $C_{13}H_{12}F_4N_2O_2$: C, 51.32; H, 3.98; N, 9.21. Found: C, 51.49; H, 4.12; N, 9.34.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5-methylimidazolidine-2,4-dione (**23**).* **Step 1.** To a solution of 2-aminopropanoic acid (**57**) (2.225 g, 25 mmol) in 1 M NaOH (40 mL) was added 1-fluoro-4-isocyanato-2-(trifluoromethyl)benzene (**56**) (6.15 g, 30 mmol) in CH_3CN (15 mL) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 3 h and then warmed to rt overnight. **Step 2.** The reaction mixture was adjusted to pH 3.0 by 32% HCl and concentrated in vacuo. The resulting precipitate was crystallized from 1:40 EtOAc:hexane to give 2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]-

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ureido]propanoic acid as a white solid (5.157 g, 70%), 1.1 g (3.74 mmol) of which was suspended in 4 M HCl (50 mL) and then heated at 110 °C overnight. After the reaction mixture was cooled to rt, the resulting precipitate was filtered to afford **23** as a white solid (845 mg, 82%). mp 153−154 °C; ^{1}H NMR (DMSO-d_6) δ 1.38 (d, J = 6.9 Hz, 3H), 4.27 (q, J = 6.9 Hz, 1H), 7.65 (t, J = 9.7 Hz, 1H), 7.76−7.83 (m, 1H), 7.87 (dd, J = 6.7, 2.5 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.94, 52.23, 116.73 (qd, J = 32.8, 13.4 Hz), 117.76 (d, J = 21.8 Hz), 122.23 (q, J = 272.1 Hz), 125.47 (q, J = 5.1 Hz), 128.95 (d, J = 3.5 Hz), 133.43 (d, J = 9.3 Hz), 154.84, 157.50 (dq, J = 254.3, 2.1 Hz), 173.81. Anal. Calcd for $C_{11}H_8F_4N_2O_2 \cdot 0.5H_2O$: C, 46.33; H, 3.18; N, 9.82; Found: C, 46.61; H, 3.19; N, 9.81.

*(R)-3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5-phenylimidazolidine-2,4-dione (**24**).* **Step 1.** To a solution of (*R*)-2-amino-2-phenylacetic acid (**58**) (1.057 g, 7.0 mmol) in 1 M NaOH (10 mL) was added **56** (2.05 g, 10 mmol) in CH_3CN (5 mL) at 0 °C dropwise. The mixture was stirred at 0 °C for 3 h, and then 1,4-dioxane (10 mL) was added according to the method of Cooper et al.[44] After stirring at rt for 12 h, the reaction mixture was adjusted to pH 2 by 32% HCl and concentrated in vacuo. **Step 2.** The resulting precipitate was successively crystallized from 1:10 EtOH:H_2O and 1:10 EtOAc:hexane to give (*R*)-2-[3-[4-fluoro-3-(trifluoromethyl)phenyl]ureido]-2-phenylacetic acid as a white solid (1.661 g, 67%), 818 mg of which was then suspended in 4 M HCl (50 mL) and heated at 110 °C overnight. After the reaction mixture was cooled to 0 °C, the resulting precipitate was filtered to give **24** as a white solid (678 mg, 87%). mp 166−168 °C; ^{1}H NMR (DMSO-d_6) δ 5.37 (s, 1H), 7.33−7.54 (m, 5H), 7.67 (dd, J = 10.0, 9.7 Hz, 1H), 7.78−7.88 (m, 1H), 7.92 (dd, J = 6.7, 2.5 Hz, 1H), 9.10 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 60.36, 117.01 (qd, J = 32.8, 13.5 Hz), 118.05 (d, J = 21.8 Hz), 122.40 (q, J = 272.7 Hz), 125.89, 127.55, 128.76, 128.89, 128.97 (d, J = 3.4 Hz), 133.80 (d, J = 9.3 Hz), 135.55, 155.33, 157.85 (d, J = 258.6 Hz), 171.60. Anal. Calcd for $C_{16}H_{10}F_4N_2O_2$: C, 56.81; H, 2.98; N, 8.28. Found: C, 56.66; H, 3.12; N, 8.18.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5-(hydroxymethyl)-5-methylimidazolidine-2,4-dione (**25**).* **Step 1.** To a solution of 2-amino-3-hydroxy-2-methylpropanoic acid (**59**) (537 mg, 4.5 mmol) in dioxane (23 mL) was added **56** (8.10 g, 39.5 mmol) under Ar. After the reaction mixture was stirred at 80 °C for 6 h, it was cooled to rt, diluted with CH_2Cl_2 (25 mL), and extracted with 2 M NaOH (3 × 25 mL). After the combined aqueous layers were separated and filtered to remove the insoluble *N,N*-diarylurea side product, the filtrate was acidified with 2 M HCl (100 mL) and concentrated. **Step 2.** The residue was suspended in 2 M HCl (50 mL) and then heated at 110 °C for 4 h. After the reaction mixture was cooled to rt, the resulting precipitate was collected by filtration to give **25** (370 mg, 27%) as a white solid. mp 166−168 °C; ^{1}H NMR (DMSO-d_6) δ 1.30 (s, 3H), 3.43 (d, J = 10.7 Hz, 1H), 3.67 (d, J = 11.2 Hz, 1H), 7.66 (t, J = 10.3 Hz, 1H), 7.76−7.77 (m, 1H), 7.81 (d, J = 6.3, 1H), 8.52 (s, 1H); ^{13}C NMR (DMSO-d_6) 18.97, 63.52, 65.38, 117.00 (q, J = 32.5 Hz), 118.07 (d, J = 22.0 Hz), 122.40 (q, J = 273.0 Hz), 125.20, 129.15, 133.29 (d, J = 9.2 Hz), 154.78, 157.61 (d, J = 254.2 Hz), 175.04. Anal. Calcd for $C_{12}H_{10}F_4N_2O_3$: C, 47.07; H, 3.29; N, 9.15. Found: C, 46.91, H, 3.46, N, 9.32.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-1,3-diazaspiro[4.4]nonane-2,4-dione (**26**).* **Step 1.** To a solution of 1-aminocyclopentane-1-carboxylic acid (**60**) (1.161 g, 9.0 mmol) in 1 M NaOH (15 mL) was added a solution of **56** (1.83 g, 8.9 mmol) in CH_3CN (10 mL) at 0 °C dropwise. The mixture was stirred at 0 °C for 3 h and then warmed to rt overnight. The reaction mixture was adjusted to pH 1.0 by 32% HCl and concentrated in vacuo. **Step 2.** The resulting precipitate was collected by filtration, and the solid was then suspended in 4 M HCl (50 mL) and heated at 110 °C overnight. After the reaction mixture was cooled to rt, the resulting precipitate was filtered and crystallized from diethyl ether to give **26** as a white solid (660 mg, 23%). mp 151−152 °C; ^{1}H NMR (DMSO-d_6) δ 1.67−1.92 (m, 6H), 2.01−2.16 (m, 2H), 7.65 (dd, J = 10.5, 9.0 Hz, 1H), 7.78−7.84 (m, 1H), 7.90 (dd, J = 6.6, 2.6 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.82, 37.58, 67.49, 116.86 (qd, J = 33.2, 13.4 Hz), 117.89 (d, J = 21.9 Hz), 122.43 (q, J = 272.4 Hz), 125.72, 129.14, 133.61 (d, J = 9.0 Hz), 154.16, 157.65 (d, J = 253.1 Hz), 176.55. Anal. Calcd for $C_{14}H_{12}F_4N_2O_2$: C, 53.17; H, 3.82; N, 8.86. Found: C, 52.89; H, 4.00; N, 8.89.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-1,3-diazaspiro[4.5]decane-2,4-dione (**27**).* To a solution of 1,3-diazaspiro[4.5]decane-2,4-dione (**46**) (840 mg, 5.0 mmol) and Cu_2O (290 mg, 2.0 mmol) in DMA (20 mL) was added 1-fluoro-4-iodo-2-(trifluoromethyl)benzene (**45**) (1170 mg, 4.0 mmol). After it was heated at 160 °C for 24 h, the solvent was evaporated in vacuo. The residue was purified by sg chromatography (EtOAc) to afford **27** as a white solid (917 mg, 69%). mp 213-215 °C; ^{1}H NMR (DMSO-d_6) δ 1.25−1.40 (m, 1H) 1.58 (br s, 3H) 1.64−1.83 (m, 6H) 7.65 (t, J = 9.7 Hz, 1H), 7.77−7.84 (m, 1H) 7.89 (d, J = 6.35 Hz, 1H) 9.05 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.93, 24.56, 33.33, 61.27, 116.88 (qd, J = 33.0, 13.3), 117.9 (d, J = 22.0), 122.4 (q, J = 272.5), 125.87 (d, J = 4.1), 129.03, 133.76 (d, J = 9.2), 154.27, 157.7 (d, J = 254.7), 175.64. Anal. Calcd for $C_{15}H_{14}F_4N_2O_2$: C, 54.55; H, 4.27; N, 8.48. Found: C, 54.38; H, 4.40; N, 8.49.

*2-[4-Fluoro-3-(trifluoromethyl)phenyl]tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3(2H)-dione (**28**).* To a solution of tetrahydro-1H-pyrrolo[1,2-*c*]imidazole-1,3(2H)-dione (**55**) (538 mg, 3.8 mmol), $Cu(OAc)_2$ (1.370 g, 7.6 mmol), and pyridine (900 mg, 11.4 mmol) in CH_2Cl_2 (38 mL) was added [4-fluoro-3-(trifluoromethyl)phenyl]-boronic acid (**53**) (2.359 g, 11.3 mmol). After stirring at rt for 7 days, the solvent was removed in vacuo. The residue was purified by chromatography (sg, EtOAc) and then crystallized from hexane to afford **28** as a white solid (443 mg, 39%). mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.78−1.93 (m, 1H), 2.06−2.30 (m, 2H), 2.32−2.45 (m, 1H), 3.37 (ddd, J = 11.6, 8.5, 4.6 Hz, 1H), 3.80 (dt, J = 11.5, 7.8 Hz, 1H), 4.27 (dd, J = 9.4, 7.5 Hz, 1H), 7.29 (t, J = 9.3 Hz, 1H), 7.60−7.68 (m, 1H), 7.74 (dd, J = 6.2, 2.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 26.38, 26.50, 45.30, 62.94, 116.77 (qd, J = 33.1, 13.5 Hz), 117.87 (d, J = 21.8 Hz), 122.20 (q, J = 272.0 Hz), 125.68, 128.89 (d, J = 3.4 Hz), 133.59 (d, J = 9.4 Hz), 157.66 (d, J = 255.0 Hz), 158.26, 172.45. Anal. Calcd for $C_{13}H_{10}F_4N_2O_2$: C, 51.66; H, 3.34; N, 9.27. Found: C, 51.70; H, 3.40; N, 9.55.

*1-[4-Fluoro-3-(trifluoromethyl)phenyl]-3,3-dimethylpyrrolidine-2,5-dione (**29**).* To a solution of 3,3-dimethylpyrrolidine-2,5-dione (**47**) (1.71 g, 13.5 mmol) and Cu_2O (0.74 g, 5.2 mmol) in DMF (15 mL) was added 1-fluoro-4-iodo-2-(trifluoromethyl)benzene (**45**) (3.0 g, 10.3 mmol), and the mixture was heated to reflux for 48 h. After cooling to rt, the solvent was evaporated in vacuo. After addition of concentrated NH_4OH (20 mL) and H_2O (15 mL), the resulting precipitate was filtered and purified by chromatography (sg, hexane:EtOAc, 5:1) to afford **29** as a white solid (1.39 g, 46%). mp 134−136 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 6H), 2.74 (s, 2H), 7.33 (t, J = 9.3 Hz, 1H), 7.53−7.56 (m, 1H), 7.62 (d, J = 5.9 Hz, 1H);^{13}C NMR ($CDCl_3$) δ 25.60, 40.23, 43.62, 117.67 (d, J = 22.1 Hz), 119.15 (qd, J = 34.6, 13.4 Hz), 121.95(q, J = 272.5 Hz), 125.33 (m), 128.0 (d, J = 3.8 Hz), 131.9(d, J = 8.6 Hz), 158.89 (d, J = 258.6 Hz), 174.20, 181.67. Anal. Calcd for $C_{13}H_{11}F_4NO_2$: C, 53.99; H, 3.83; N, 4.84; Found: C, 54.00; H, 3.82; N, 4.89.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyloxazolidine-2,4-dione (**30**).* To a solution of 5,5-dimethyloxazolidine-2,4-dione (**54**) (903 mg, 7.0 mmol) and $Cu(OAc)_2$ (90 mg, 0.5 mmol) in methanol (25 mL) was added (4-fluoro-3-(trifluoromethyl)phenyl)-boronic acid (**53**) (1.04 g, 5.0 mmol) under O_2. The mixture was heated at 70 °C overnight. After cooling to rt, the solvent was evaporated in vacuo. The residue was purified by chromatography with successive elution with hexane and EtOAc followed by crystallization from 1:10 ethanol:H_2O to afford **30** as a white solid (421 mg, 29%). mp 174−176 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 6H), 7.34 (t, J = 8.8 Hz, 1H), 7.69−7.72 (m, 1H), 7.79 (dd, J = 2.4, 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.74, 83.80, 117.99 (d, J = 22.1 Hz), 119.48 (qd, J = 34.1, 20.2 Hz), 121.81 (q, J = 272.5 Hz), 124.53 (m), 127.12 (d, J = 3.4 Hz), 130.89 (d, J = 9.1 Hz), 152.54, 159.01 (dq, J = 259.6, 1.9 Hz), 174.32. Anal. Calcd for $C_{12}H_9F_4NO_3$: C, 49.49; H, 3.12; N, 4.81; Found: C, 49.21; H, 3.06; N, 4.80.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethylpyrrolidine-2,4-dione (**31**).* **Step 1.** A mixture of 2-[4-fluoro-3-(trifluoromethyl)-

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phenyl]acetic acid (2.22 g, 10 mmol) and $SOCl_2$ (4 mL) was stirred at 80 °C overnight. The reaction mixture was concentrated in vacuo to afford 2-[4-fluoro-3-(trifluoromethyl)phenyl]acetyl chloride (**65**), which was used for the next step without further purification. **Step 2.** To a solution of methyl 2-amino-2-methylpropanoate HCl salt (1.53 g, 10 mmol) and Et_3N (5.0 g, 50 mmol) in THF (47.5 mL) was added **65** in THF (2.5 mL), and the reaction mixture was stirred at rt overnight. After filtration to remove insoluble TEA HCl salt, the filtrate was concentrated in vacuo. The residue was purified by chromatography (sg, EtOAc:hexane, 1:1) to afford methyl 2-[2-[4-fluoro-3-(trifluoromethyl)phenyl]acetamido]-2-methylpropanoate (**66**) as a white solid (1.13 g, 35%). ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 6H), 3.50 (s, 3H), 3.52 (s, 2H), 7.45 (dd, J = 10.9, 8.6 Hz, 1H), 7.52−7.61 (m, 1H), 7.63 (d, J = 7.7 Hz, 1H), 8.54 (s, 1H). **Step 3.** To a solution of **66** (860 mg, 2.68 mmol) in THF (7 mL) was added a suspension of NaH (300 mg, 12.5 mmol) in THF (6.4 mL) dropwise under Ar. The reaction mixture was stirred at rt for 12 before quenching with a mixture of acetic acid (1.2 g, 20 mmol) and H_2O (1 mL). Solvent removal in vacuo gave a crude product which was crystallized from hexane to afford **31** as a white solid (406 mg, 52%). mp 217−219 °C; ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 6H), 7.46 (dd, J = 10.8, 8.9 Hz, 1H), 7.83 (s, 1H), 8.30−8.40 (m, 1H), 8.47 (dd, J = 7.4, 2.2 Hz, 1H), 11.68 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 24.54, 56.49, 98.64, 115.88 (qd, J = 31.8, 12.2 Hz), 116.56 (d, J = 20.1 Hz), 122.87 (q, J = 271.4 Hz), 124.55 (q, J = 4.8 Hz), 129.75 (d, J = 3.7 Hz), 132.87 (d, J = 8.0 Hz), 156.37 (d, J = 250.9 Hz), 170.39, 176.13. Anal. Calcd for $C_{13}H_{11}F_4NO_2$: C, 53.99; H, 3.83; N, 4.84. Found: C, 54.09; H, 3.92; N, 4.60.

*1-[4-Fluoro-3-(trifluoromethyl)phenyl]-4,4-dimethylimidazolidin-2-one (**32**).* To a solution of 4,4-dimethyl-2-imidazolidinone (**48**) (500 mg, 4.4 mmol), Cs_2CO_3 (2.460 g, 7.5 mmol), Xantphos (108 mg, 0.19 mmol), and $Pd_2(dba)_3$ (84 mg, 0.09 mmol) in toluene (40 mL) was added 1-fluoro-4-iodo-2-(trifluoromethyl)benzene (**45**) (1.270 g, 4.4 mmol). The reaction mixture was stirred at 90 °C for 12 h under Ar. Evaporation gave a crude product which was purified by washing with water (25 mL), chromatography (sg, EtOAc), and recrystallizion from hexane to afford **32** as a white solid (939 mg, 77%). mp 147−148 °C; ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 6H), 3.64 (s, 2H), 7.39 (s, 1H), 7.45 (t, J = 9.8 Hz, 1H), 7.72 (dt, J = 9.2, 3.6 Hz, 1H), 8.05 (dd, J = 6.4, 2.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 28.20, 50.57, 57.07, 114.69 (q, J = 5.2 Hz), 116.22 (qd, J = 32.1, 12.9 Hz), 117.29 (d, J = 21.3 Hz), 122.30 (d, J = 7.7 Hz), 122.66 (q, J = 272.3 Hz), 137.58, 153.26 (d, J = 247.5 Hz), 157.02. Anal. Calcd for $C_{12}H_{12}F_4N_2O$: C, 52.18; H, 4.38; N, 10.14. Found: C, 52.32; H, 4.57; N, 10.26.

*1-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethylimidazolidine-2,4-dione (**33**).* **Step 1.** To a mixture of 4-fluoro-3-(trifluoromethyl)aniline (**63**) (1.791 g, 10 mmol), formamide (50 mL), and acetone (25 mL) was added 1 M $TiCl_4$ in CH_2Cl_2 (12.5 mL) at 0 °C under Ar. After 1 h, Zn powder (1.5 g, 23 mmol) was added followed by dropwise addition of 50% H_2O_2 (1.75 mL) in formamide (23.25 mL) over 3 h. The reaction was quenched with H_2O (25 mL), and the pH adjusted to 8 with concentrated ammonium hydroxide followed by extraction with EtOAc (3 × 50 mL). The combined organic layers were concentrated in vacuo, and the residue was dissolved in $CHCl_3$ (100 mL). The solution was then washed with H_2O (3 × 25 mL). Evaporation gave a crude product which was further purified by successive recrystallizations from a mixture of CH_2Cl_2 (5 mL) and hexane (1 mL) and a mixture of acetic acid (150 mg) and H_2O (1 mL) to afford 2-[[4-fluoro-3-(trifluoromethyl)-phenyl]amino]-2-methylpropanamide (**66**) as a white solid (418 mg, 16%); ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 6H), 6.18 (s, 1H), 6.71 (dt, J = 9.0, 3.6 Hz, 1H), 6.81 (dd, J = 6.0, 3.0 Hz, 1H), 7.05 (s, 1H), 7.22 (t, J = 9.8 Hz, 1H), 7.34 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 25.22, 56.63, 111.09 (q, J = 4.7 Hz), 116.20 (qd, J = 31.5, 13.0 Hz), 117.16 (d, J = 21.2 Hz), 118.79 (d, J = 7.4 Hz), 122.92 (q, J = 272.0 Hz), 143.20 (d, J = 1.9 Hz), 150.44 (dq, J = 241.0, 2.4 Hz), 177.13. **Step 2.** To a solution of **66** (160 mg, 0.6 mmol) in toluene (5 mL) was added 2-isocyanato-1,3-diisopropylbenzene (143 mg, 0.7 mmol). After the mixture was heated to 250 °C at 5 bar for 10 min under microwave irradiation in a sealed tube, the solvent was evaporated in vacuo. The residue was purified by sg chromatography eluting successively with CH_2Cl_2 and 1:3 acetone:hexane to afford **33** as a white solid (108 mg, 62%). mp 193−195 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 6H), 7.63 (t, J = 9.7 Hz, 1H), 7.71−7.78 (m, 1H), 7.84 (dd, J = 6.6, 2.6 Hz, 1H), 11.26 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.09, 64.21, 117.25 (qd, J = 32.8, 13.2 Hz), 118.25 (d, J = 21.5 Hz), 122.18 (q, J = 273.5 Hz), 128.19, 131.44 (d, J = 3.4 Hz), 135.86 (d, J = 9.2 Hz), 154.99, 157.87 (d, J = 254.8 Hz), 177.14. Anal. Calcd for $C_{12}H_{10}F_4N_2O_2$: C, 49.66; H, 3.47; N, 9.65. Found: C, 49.71, H, 3.58, N, 9.80.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-6,6-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**34**).* **Step 1.** To a solution of 3-amino-3-methylbutanoic acid (**61**) (585 mg, 5.0 mmol) in 2 M NaOH (5 mL) was added **56** (1.95 g, 9.5 mmol). After it was stirred at rt for 4 h, the reaction mixture was filtered to remove the insoluble *N,N*-diarylurea side product, and the filtrate was adjusted to pH 1.0 with 2 M HCl and concentrated. **Step 2.** The residue was suspended in 2 M HCl (50 mL) and then heated at 110 °C for 2 h. After the reaction mixture was cooled to rt, the resulting precipitate was filtered and washed with H_2O (20 mL) to give **34** as a white solid (477 mg, 31%). mp 225−226 °C; ^{1}H NMR (DMSO-d_6) δ 1.31 (s, 6H), 2.74 (s, 2H), 7.53−7.64 (m, 2H), 7.71 (dd, J = 6.7, 2.4 Hz, 1H), 8.18 (s, 1H);^{13}C NMR (DMSO-d_6) δ 28.11, 44.32, 48.22, 116.88 (qd, J = 32.6, 13.3 Hz), 117.68 (d, J = 21.5 Hz), 122.54 (q, J = 272.3 Hz), 128.60 (d, J = 4.8 Hz), 132.82 (d, J = 3.5 Hz), 136.61 (d, J = 9.1 Hz), 152.51, 158.16 (d, J = 254.0 Hz), 169.81. Anal. Calcd for $C_{13}H_{12}F_4N_2O_2$ 0.5 H_2O: C, 49.85; H, 4.18; N, 8.94. Found: C, 49.79; H, 4.51; N, 8.81.

*3-[4-Fluoro-3-(trifluoromethyl)phenyl]-5,5-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**35**).* **Step 1.** To a solution of 3-amino-2,2-dimethylpropanoic acid hydrochloride (**62**) (700 mg, 4.6 mmol) in 2 M NaOH (5 mL) was added **56** (1.95 g, 9.5 mmol), and the reaction mixture was stirred at rt for 4 h. After filtration to remove the insoluble *N,N*-diarylurea side product, the filtrate was adjusted to pH 1.0 with 2 M HCl and concentrated to afford 3-[3-[4-fluoro-3-(trifluoromethyl)-phenyl]ureido]-2,2-dimethylpropanoic acid (480 mg, 32%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 1.09 (s, 6H), 3.22 (d, J = 6.2 Hz, 2H), 6.25 (t, J = 6.2 Hz, 1H), 7.36 (t, J = 9.8 Hz, 1H), 7.43−7.53 (m, 1H), 7.95 (dd, J = 6.5, 2.8 Hz, 1H), 8.99 (s, 1H), 12.39 (s, 1H). **Step 2.** 3-[3-[4-Fluoro-3-(trifluoromethyl)phenyl]ureido]-2,2-dimethylpropanoic acid (450 mg, 1.4 mmol) was suspended in 2 M HCl (50 mL) and then heated at 110 °C for 12 h. After the reaction mixture was cooled to rt, the resulting precipitate was filtered and washed with saturated $NaHCO_3$ (30 mL) to give **35** as a white solid (355 mg, 83%). mp 214−215 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 6H), 3.18 (s, 1H), 3.18 (d, J = 2.8 Hz, 1H), 7.52−7.59 (m, 2H), 7.63−7.69 (m, 1H), 8.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 22.35, 37.39, 46.31, 116.60 (qd, J = 32.9, 13.7 Hz), 117.41 (d, J = 21.5 Hz), 122.34 (q, J = 271.9 Hz), 128.34, 133.07 (d, J = 3.5 Hz), 136.42 (d, J = 9.2 Hz), 153.02, 157.88 (d, J = 253.6 Hz), 175.33. Anal. Calcd for $C_{13}H_{12}F_4N_2O_2$: C, 51.32; H, 3.98; N, 9.21. Found: C, 51.19; H, 3.99; N, 9.12.

*2-[3-[4-Fluoro-3-(trifluoromethyl)phenyl]ureido]-2-methylpropanoic acid (**36**).* Hydantoin **1** (1.20 g, 4.1 mmol) was added to 2 M NaOH (40 mL). The reaction mixture was stirred at rt for 4 h, and then quenched with 2 M HCl (50 mL). The precipitate was filtered and rinsed with H_2O (20 mL) and then dried to afford **36** as a white solid (1.20 g, 95%). mp 196.5−197.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.43 (s, 6H), 6.61 (s, 1H), 7.37 (t, J = 9.8 Hz, 1H), 7.47−7.50 (m,1H), 7.96−7.97 (m, 1H), 8.87 (s, 1H), 12.44 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.42, 55.13, 115.12 (d, J = 5.0 Hz), 116.45 (qd, J = 31.6, 12.8 Hz), 117.65 (d, J = 21.5 Hz), 122.85 (q, J = 272.1 Hz), 123.42 (d, J = 7.8 Hz), 137.34, 153.32 (d, J = 246.9 Hz), 154.37, 176.31. Anal. Calcd for $C_{12}H_{12}F_4N_2O_3$: C, 46.76; H, 3.92; N, 9.09. Found: C, 46.50; H, 4.04; N, 9.19.

Polar Surface Area (PSA). PSA values (Å^2) were calculated using ChemAxon Instant JChem (ver 16.4).

Kinetic Solubility. Compounds in DMSO (10 mg/mL) were diluted into either pH 6.5 phosphate buffer or 0.01 M HCl (approximately pH 2.0), with the final DMSO concentration being 1%. Samples were then analyzed via nephelometry to determine a solubility range.[45]

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Partition Coefficient. Partition coefficient values (Log D) of the test compounds were estimated by correlation of their chromatographic retention properties against the characteristics of a series of standard compounds with known partition coefficient values using gradient HPLC (modification of a method reported by Lombardo et al.[46]

Plasma Protein Binding. Plasma protein binding values of the test compounds were estimated by correlation of their chromatographic retention properties on a human albumin column against the characteristics of a series of standard compounds with known protein binding values. The method employed is a gradient HPLC based derivation of the method developed by Valko et al.[47]

In Vitro Metabolic Stability. Metabolic stability assays were performed by incubating test compounds in liver microsomes at 37 °C and 0.4 mg/mL protein concentration. The metabolic reaction was initiated by the addition of an NADPH-regenerating system and quenched at various time points over a 60 min incubation period by the addition of acetonitrile containing diazepam as internal standard. Control samples (containing no NADPH) were included (and quenched at 2, 30, and 60 min) to monitor for potential degradation in the absence of cofactor. Compound concentrations were determined by LC/MS by comparison to calibration standards prepared in prequenched microsomal matrix.

Mouse Exposure Studies. Pharmacokinetic studies in mice were conducted at Monash University, Parkville, Australia, and were performed in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. The study protocol adhered to the principles of reduction, refinement, and replacement and was approved by the Monash Institute of Pharmaceutical Sciences Animal Ethics Committee. The systemic exposure of the aryl hydantoins was studied in nonfasted male Swiss outbred mice weighing 25−33 g (7 mice per compound). Mice had access to food and water ad libitum throughout the pre- and postdose sampling period. Formulations were prepared by dispersing the aryl hydantoins in Tween 80 and then adding ethanol and Milli-Q water (final composition 7% v/v Tween 80, 3% v/v ethanol). Following vortexing and sonication, samples formed either uniform suspensions (**1**−**3**, **14**, **16**, **23**, **26**) or a colorless solution (**13**). Compound formulations were mixed by inverting the tubes prior to drawing each dosing volume. All animals were dosed orally by gavage (10 mL/kg dose volume) within 1 h of formulation preparation. Following administration, blood samples were collected from 0.25 to 48 h postdose (n = 2 mice per time point). A maximum of two samples were obtained from each mouse, with samples being taken either via submandibular bleed (approximately 120 μL; conscious sampling) or terminal cardiac puncture (0.6 mL; while mice were under deep anesthesia using inhaled isoflurane). No urine samples were collected, as mice were housed in bedded cages during the study. Blood was collected directly into polypropylene Eppendorf tubes containing heparin as anticoagulant and stabilization cocktail (containing Complete (a protease inhibitor cocktail), potassium fluoride, and EDTA) to minimize the potential for ex vivo degradation of the aryl hydantoins in blood/plasma samples. Once collected, blood samples were centrifuged immediately, and supernatant plasma was removed and stored at −80 °C until analysis by LCMS. Plasma concentrations were determined by comparison to calibration standards prepared in blank plasma and treated the same as the plasma samples. Plasma concentration−time data were analyzed using noncompartmental methods (PKSolver Version 2.0).

***S. mansoni* in Vivo Studies.** The in vivo study was approved by the local veterinary agency, based on Swiss cantonal and national regulations (permission no. 2070). As described by Keiser,[48] cercariae of *S. mansoni* were obtained from infected *Biomphalaria glabrata*. NMRI mice were infected subcutaneously with approximately 100 *S. mansoni* cercariae. At 49 d after infection, groups of four mice were treated with single 100 mg/kg oral doses of compounds in a 7% (v/v) Tween 80% and 3% (v/v) ethanol vehicle (10 mL/kg). Untreated mice (n = 8) served as controls. At 21 d post-treatment, animals were killed by the CO_2 method and dissected. Worms were removed by picking, then sexed and counted.

Androgen-Dependent Cell-Based Assay. As described by Jones and Diamond,[49] LAPC4 cells were cultured in phenol red free RPMI 1640 media supplemented with antibiotics and 10% FBS. For all transfections, pools of cells were transfected using Lipofectamine Plus (Invitrogen) with PSA-luciferase[50] and pRL-SV40 (Promega) as a normalization control. The following day, the cells were replated, 0.3 nM DHT and test compounds were added, and 24 h later luciferase production was measured (Dual luciferase assay kit; Promega), normalizing the firefly signal to the renilla signal. Mean-effect plots (log[compound] vs log[fractional effect]) were generated to determine the IC_{50} values for each test compound or combinations of test compounds at constant ratios.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.6b01410.

SMILES data (CSV)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 402.559.5362. Fax: 402.559.9543. Email: jvenners@unmc.edu.

ORCID

Jonathan L. Vennerstrom: 0000-0003-0075-2336

Present Address

For Q.Z.: Shanghai Institute of Materia Medica, Chinese Academy of Sciences, No. 501, Haike Rd., Pudong New District, Shanghai 201210, China.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AR, androgen receptor; DMA, dimethylacetamide; N, nilutamide; PZ, praziquantel; WBR, worm burden reduction

■ REFERENCES

(1) Hotez, P. J.; Brindley, P. J.; Bethony, J. M.; King, C. H.; Pearce, E. J.; Jacobson, J. Helminth infections: The great neglected tropical diseases. *J. Clin. Invest.* **2008**, *118*, 1311−1321.

(2) Gryseels, B. Schistosomiasis. *Infect. Dis. Clin. North Am.* **2012**, *26*, 383−397.

(3) Colley, D. G.; Bustinduy, A. L.; Secor, W. E.; King, C. H. Human schistosomiasis. *Lancet* **2014**, *383*, 2253−2264.

(4) Utzinger, J.; N'goran, E. K.; Caffrey, C. R.; Keiser, J. From innovation to application: Social-ecological context, diagnostics, drugs and integrated control of schistosomiasis. *Acta Trop.* **2011**, *120*, S121−S137.

(5) Olliaro, P.; Delgado-Romero, P.; Keiser, J. The little we know about the pharmacokinetics and pharmacodynamics of praziquantel (racemate and R-enantiomer). *J. Antimicrob. Chemother.* **2014**, *69*, 863−870.

(6) Cioli, D.; Pica-Mattoccia, L.; Basso, A.; Guidi, A. Schistosomiasis control: Praziquantel forever? *Mol. Biochem. Parasitol.* **2014**, *195*, 23−29.

(7) Melman, S. D.; Steinauer, M. L.; Cunningham, C.; Kubatko, L. S.; Mwangi, I. N.; Wynn, N. B.; Mutuku, M. W.; Karanja, D. M.; Colley,

DOI: 10.1021/acs.jmedchem.6b01410
J. Med. Chem. 2016, 59, 10705−10718

D. G.; Black, C. L.; Secor, W. E.; Mkoji, G. M.; Loker, E. S. Reduced susceptibility to praziquantel among naturally occurring Kenyan isolates of *Schistosoma mansoni*. *PLoS Neglected Trop. Dis.* **2009**, *3*, e504.
(8) Kasinathan, R. S.; Greenberg, R. M. Pharmacology and potential physiological significance of schistosome multidrug resistance transporters. *Exp. Parasitol.* **2012**, *132*, 2−6.
(9) Caffrey, C. R.; Williams, D. L.; Todd, M. H.; Nelson, D. L.; Utzinger, J. Chemotherapeutic development strategies for schistosomiasis. In *Antiparasitic and Antibacterial Drug Discovery*; Selzer, P. M., Ed.; Wiley−Blackwell: Weinheim, 2009; pp 301−321.
(10) Abdulla, M.-H.; Ruelas, D. S.; Wolff, B.; Snedecor, J.; Lim, K.-C.; Xu, F.; Renslo, A. R.; Williams, J.; McKerrow, J. H.; Caffrey, C. R. Drug discovery for schistosomiasis: Hit and lead compounds identified in a library of known drugs by medium-throughput phenotypic screening. *PLoS Neglected Trop. Dis.* **2009**, *3*, e478.
(11) Keiser, J.; Utzinger, J. Antimalarials in the treatment of schistosomiasis. *Curr. Pharm. Des.* **2012**, *18*, 3531−3538.
(12) Liu, Y.-X.; Wu, W.; Liang, Y.-J.; Jie, Z.-L.; Wang, H.; Wang, W.; Huang, Y.-X. New uses for old drugs: The tale of artemisinin derivatives in the elimination of schistosomiasis japonica in China. *Molecules* **2014**, *19*, 15058−15074.
(13) Panic, G.; Vargas, M.; Keiser, J.; Scandale, I. Activity profile of an FDA-approved compound library against *Schistosoma mansoni*. *PLoS Neglected Trop. Dis.* **2015**, *9*, e0003962.
(14) Thétiot-Laurent, S. A.-L.; Boissier, J.; Robert, A.; Meunier, B. Schistosomiasis Chemotherapy. *Angew. Chem., Int. Ed.* **2013**, *52*, 7936−7956.
(15) Bernauer, K.; Link, H.; Stohler, H. Antiandrogenic and schistosomicidal imidazolidine derivatives. U. S. Patent 4,234,736. 1980.
(16) Forget, E.; Félix, H.; Notteghem, M. J.; Léger, N. Appréciation de l'activité de dérivés schistosomicides en microscopie électronique. *Bull. Soc. Pathol. Ex.* **1982**, *75*, 192−200.
(17) Hansen, J. B.; Hafliger, O. Determination of the dissociation constant of a weak acid using a dissolution rate method. *J. Pharm. Sci.* **1983**, *72*, 429−431.
(18) Link, H.; Stohler, H. R. 3-Arylhydantoine, eine substanzklasse mit schistosomizider wirkung. *Eur. J. Med. Chem. − Chim. Ther.* **1984**, *19*, 261−265.
(19) Keiser, J.; Panic, G.; Vargas, M.; Wang, C.; Dong, Y.; Gautam, N.; Vennerstrom, J. L. Aryl hydantoin Ro 13−3978, a broad spectrum antischistosomal. *J. Antimicrob. Chemother.* **2015**, *70*, 1788−1797.
(20) Keiser, J.; Manneck, T.; Vargas, M. Interactions of mefloquine with praziquantel in the *Schistosoma mansoni* mouse model and in vitro. *J. Antimicrob. Chemother.* **2011**, *66*, 1791−1797.
(21) Keiser, J.; Vargas, M.; Vennerstrom, J. L. Activity of antiandrogens against juvenile and adult *Schistosoma mansoni* in mice. *J. Antimicrob. Chemother.* **2010**, *65*, 1991−1995.
(22) de Mendonça, R. L.; Escrivá, H.; Bouton, D.; Laudet, V.; Pierce, R. J. Hormones and nuclear receptors in schistosome fevelopment. *Parasitol. Today* **2000**, *16*, 233−240.
(23) Wang, C.; Zhao, Z.; Min, J.; Muniyan, X.; Vargas, M.; Wang, X.; Dong, Y.; Guy, R. K.; Lin, M.-F.; Keiser, J.; Vennerstrom, J. L. Antischistosomal versus antiandrogenic properties of aryl hydantoin Ro 13−3978. *Am. J. Trop. Med. Hyg.* **2014**, *90*, 1156−1158.
(24) Jung, M. E.; Ouk, S.; Yoo, D.; Sawyers, C. L.; Chen, C.; Tran, C.; Wongvipat, J. Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J. Med. Chem.* **2010**, *53*, 2779−2796.
(25) Liu, B.; Su, L.; Geng, J.; Liu, J.; Zhao, G. Developments in nonsteroidal antiandrogens targeting the androgen receptor. *ChemMedChem* **2010**, *5*, 1651−1661.
(26) Vinggaard, A. M.; Niemelä, J.; Wedebye, E. B.; Jensen, G. E. Screening of 397 chemicals and development of a quantitative structure-activity relationship model for androgen receptor antagonism. *Chem. Res. Toxicol.* **2008**, *21*, 813−823.
(27) Zhang, X.; Allan, G. F.; Sbriscia, T.; Linton, O.; Lundeen, S. G.; Sui, Z. Synthesis and SAR of novel hydantoin derivatives as selective androgen receptor modulators. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5763−5766.
(28) Van Dort, M. E.; Jung, Y.-W. Synthesis and structure−activity studies of side-chain derivatized arylhydantoins for investigation as androgen receptor radioligands. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1045−1047.
(29) Li, Q.; Wu, W.-Z.; Sun, J.; Lü, W.; Cai, J.-C. Synthesis of nilutamide and its analogue. *Chin. J. Pharm.* **2004**, *358*, 455−456.
(30) Auvin, S.; Lanco, C.; Chao, Q.; Gu, K. Preparation of novel imidazolidine-2,4-dione derivatives for treating breast or prostate cancers. Int. Pat. Appl. WO 2015100613 A1, July 9 2015.
(31) Muci, A. R.; Buchwald, S. L. Practical palladium catalysts for CN and CO bond formation. In *Cross-Coupling Reactions*; Miyaura, N., Ed.; Springer: MA, 2002; Vol. *219*, pp 131−209.
(32) Bergauer, M.; Bertani, B.; Biagetti, M.; Bromidge, S. M.; Falchi, A.; Leslie, C. P.; Merlo, G.; Pizzi, D. A.; Rinaldi, M.; Stasi, L. P.; Tibasco, J.; Vong, A. K. K.; Ward, S. E. Preparation of quinolines and quinazolines as ligands for 5-HT1 receptors and their use in the treatment of CNS disorders, in particular serotonin-related disorders. Int. Pat. Appl. WO 2005014552 A1, February 17, 2005.
(33) Hügel, H. M.; Rix, C. J.; Fleck, K. Comparison of copper(II) acetate promoted N-arylation of 5,5-dimethylhydantoin and other imides with triarylbismuthanes and arylboronic acids. *Synlett* **2006**, *14*, 2290−2292.
(34) Lan, J.; Zhang, G.; Yu, X.; You, J.; Chen, L.; Yan, M.; Xie, R. A simple copper salt catalyzed N-arylation of amines, amides, imides, and sulfonamides with arylboronic acids. *Synlett* **2004**, *35*, 1095−1097.
(35) Chan, D. M.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N-and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.
(36) Hroch, L.; Hrusková, M.; Schmitz, J.; Schnakenburg, G.; Gütschow, M. 3, 5, 5-Trisubstituted hydantoins from activated (benzyloxycarbonylamino) malonic acids. *Synthesis* **2012**, *44*, 1907−1914.
(37) Vystrcil, A.; Cerny, J. Model compounds of physostigmine. *Collect. Czech. Chem. Commun.* **1959**, *24*, 804−808.
(38) Pastori, N.; Greco, C.; Clerici, A.; Punta, C.; Porta, O. Free-radical addition to ketimines generated in situ. New one-pot synthesis of quaternary α-aminoamides promoted by a $H_2O_2/TiCl_4$− Zn/$HCONH_2$ system. *Org. Lett.* **2010**, *12*, 3898−3901.
(39) Biadatti, T.; Dumais, L.; Aubert, J.; Lamy, L. Nouveaux derives de N-phenul acatamide, inhibiteurs de l'enzyme soat-1, compositions pharmaceutiques et cosmetiques les contentant. FR2920774 A1, March 13, 2009.
(40) Palm, K.; Stenberg, P.; Luthman, K.; Artursson, P. Polar molecular surface properties predict the intestinal absorption of drugs in humans. *Pharm. Res.* **1997**, *14*, 568−571.
(41) Battmann, T.; Branche, C.; Bouchoux, F.; Cerede, E.; Philibert, D.; Goubet, F.; Teutsch, G.; Gaillard-Kelly, M. Pharmacological profile of RU 58642, a potent systemic antiandrogen for the treatment of androgen-dependent disorders. *J. Steroid Biochem. Mol. Biol.* **1998**, *64*, 103−111.
(42) Pitta, M. G.; Silva, A. C.; Neves, J. K.; Silva, P. G.; Irmão, J. I.; Malagueño, E.; Santana, J. V.; Lima, M. C.; Galdino, S. L.; Pitta, I. R.; Albuquerque, M. C. New imidazolidinic bioisosters: Potential candidates for antischistosomal drugs. *Mem. Inst. Oswaldo Cruz.* **2006**, *101*, 313−316.
(43) da Silva, A. C.; Neves, J. K.; Irmão, J. I.; Costa, V. M.; Souza, V. M.; de Medeiros, P. L.; da Silva, E. C.; de Lima, M. C. A.; Pitta, I. R.; Albuquerque, M. C.; Galdino, S. L. Study of the activity of 3-benzyl-5-(4-chloro-arylazo)-4-thioxo-imidazolidin-2-one against *Schistosomiasis mansoni* in mice. *Sci. World J.* **2012**, *2012*, 520524.
(44) Cooper, D. G.; Porter, R. A. Preparation of glycine transporter GlyT1 inhibitors for treating neurological and neuropsychiatric disorders. Int. Pat. Appl. WO 2009034062 A1 (19 March 2009).
(45) Bevan, C. D.; Lloyd, R. S. A high-throughput screening method for the determination of aqueous drug solubility using laser nephelometry in microtiter plates. *Anal. Chem.* **2000**, *72*, 1781−1787.

DOI: 10.1021/acs.jmedchem.6b01410
J. Med. Chem. 2016, 59, 10705−10718

(46) Lombardo, F.; Shalaeva, M. Y.; Tupper, K. A.; Gao, F. $ElogD_{oct}$:A tool for lipophilicity determination in drug discovery. 2. Basic and neutral compounds. *J. Med. Chem.* **2001**, *44*, 2490−2497.
(47) Valko, K.; Nunhuck, S.; Bevan, C.; Abraham, M. H.; Reynolds, D. P. Fast gradient HPLC method to determine compounds binding to human serum albumin. Relationships with octanol/water and immobilized artificial membrane lipophilicity. *J. Pharm. Sci.* **2003**, *92*, 2236−2248.
(48) Keiser, J. In vitro and in vivo trematode models for chemotherapeutic studies. *Parasitology* **2010**, *137*, 589−603.
(49) Jones, J. O.; Diamond, M. I. A cellular conformation-based screen for androgen receptor inhibitors. *ACS Chem. Biol.* **2008**, *3*, 412−418.
(50) Bolton, E. C.; So, A. Y.; Chaivorapol, C.; Haqq, C. M.; Li, H.; Yamamoto, K. R. Cell- and gene-specific regulation of primary target genes by the androgen receptor. *Genes Dev.* **2007**, *21*, 2005−2017.

DOI: 10.1021/acs.jmedchem.6b01410
J. Med. Chem. 2016, 59, 10705−10718