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Discovery of Novel 2-Aminobenzamide Inhibitors of Heat Shock Protein 90 as Potent, Selective and Orally Active Antitumor Agents

Kenneth H. Huang,* James M. Veal, R. Patrick Fadden, John W. Rice, Jeron Eaves, Jon-Paul Strachan, Amy F. Barabasz, Briana E. Foley, Thomas E. Barta, Wei Ma, Melanie A. Silinski, Mei Hu, Jeffrey M. Partridge, Anisa Scott, Laura G. DuBois, Tiffany Freed, Paul M. Steed, Andy J. Ommen, Emilie D. Smith, Philip F. Hughes, Angela R. Woodward, Gunnar J. Hanson, W. Stephen McCall, Christopher J. Markworth, Lindsay Hinkley, Matthew Jenks, Lifeng Geng, Meredith Lewis, James Otto, Bert Pronk, Katleen Verleysen, and Steven E. Hall

Serenex Inc., 323 Foster Street, Durham, North Carolina 27701

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A novel class of heat shock protein 90 (Hsp90) inhibitors was developed from an unbiased screen to identify protein targets for a diverse compound library. These indol-4-one and indazol-4-one derived 2-aminobenzamides showed strong binding affinity to Hsp90, and optimized analogues exhibited nanomolar antiproliferative activity across multiple cancer cell lines. Heat shock protein 70 (Hsp70) induction and specific client protein degradation in cells on treatment with the inhibitors supported Hsp90 inhibition as the mechanism of action. Computational chemistry and X-ray crystallographic analysis of selected member compounds clearly defined the protein−inhibitor interaction and assisted the design of analogues. 4-[6,6-Dimethyl-4-*oxo*-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*trans*-4-hydroxycyclohexyl)amino]benzamide (SNX-2112, **9**) was identified as highly selective and potent (IC_{50} Her2 = 11 nM, HT-29 = 3 nM); its prodrug amino-acetic acid 4-[2-carbamoyl-5-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-phenylamino]-cyclohexyl ester methanesulfonate (SNX-5422, **10**) was orally bioavailable and efficacious in a broad range of xenograft tumor models (e.g. 67% growth delay in a HT-29 model) and is now in multiple phase I clinical trials.

Introduction

Hsp90[a] has received significant recent attention as a therapeutic target for cancer treatment.[1] Hsp90 acts as a molecular chaperone that aids the folding,[2] maturation, transport, and maintenance of conformational stability of its client proteins.[3] Many of these client proteins are involved in critical cellular functions that promote cell growth, proliferation, and survival and are also themselves being pursued as anticancer targets, for example, Her2, c-Met, and Cdk-4 as well as a wide range of mutated proteins.[4] Additionally, Hsp90 is overexpressed in malignant cells and thus these cells may be more dependent on the Hsp90 chaperoning function.[5] An attraction in targeting Hsp90 is the ability to block multiple, possibly redundant, oncogenic signaling pathways with a target-specific agent.[3] The ability to affect multiple targets may also diminish the potential for resistance to Hsp90 inhibitors.[6]

Hsp90 contains three relevant domains:[7] (1) the C-terminal domain which contains an ATP site capable of binding the antibiotic novobiocin,[8] (2) the charged middle linker region,[9] and (3) the N-terminal domain, which also contains an adenine binding pocket and is responsible for the protein's ATPase activity.[10] Inhibition of this ATPase activity disrupts an ongoing "folding" cycle, involving multiple cochaperone proteins, and in turn leads to destabilization, ubiquitination, and ultimately proteasomal degradation of client proteins.[6]

Multiple research efforts have followed the initial discovery that the natural product (Figure 1) geldanamycin (GA, **1**) was a potent inhibitor of Hsp90,[11] and these efforts have led to the discovery of several compounds now undergoing clinical testing. Owing to unacceptable toxicity, GA was not pursued for clinical development, but GA derivatives 17-allylamino-17-demethoxygeldanamycin[12] (17-AAG, **2**) and 17-dimethylamino-ethylamino-17-demethoxygeldanamycin[13,15] (17-DMAG, **3**) have been investigated as less toxic analogues of GA. In particular, 17-AAG was the first Hsp90 inhibitor to undergo clinical trials and has displayed good tolerability and indications of therapeutic efficacy in humans despite issues related to poor solubility and limited bioavailability.[14] IPI-504 (**4**), a 17-AAG analogue containing a reduced hydroquinone moiety, has improved water solubility properties, thereby facilitating formulation for parenteral administration.[15] A second

*To whom correspondence should be addressed. Phone: 919-313-9657. Fax: 919-883-5095. E-mail: khuang@pamlicopharma.com. Current address: Pamlico Pharmaceutical Inc., P.O. Box 110284, 7020 Kit Creek Road, Suite 180, Research Triangle Park, NC 27709.

[a] Abbreviations: Hsp90 and Hsp70, heat shock protein 90 and 70; Her2, human epidermal growth factor receptor 2; HT-29, human colon adenocarcinoma grade II cell line; GA, geldanamycin; 17-AAG, 17-allylamino-17-demethoxygeldanamycin; 17-DMAG, 17-dimethylamino-ethylamino-17-demethoxygeldanamycin; SAR, structure−activity relationship; HOAc, acetic acid; DMF, dimethylformamide; EtOH, ethanol; DMSO, dimethyl sulfoxide; dppf or DPPF, 1,1′-bis(diphenylphosphino)ferrocene; DMAP, 4-dimethylamino-pyridine; THF, tetrahydrofuran; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; TFA, trifluoroacetic acid; MsOH, methanesulfonic acid; PBS, phosphate-buffered saline; LCMS or LC-MS, liquid chromatography−mass spectrometry; HPLC, high pressure liquid chromatography; HRMS, high-resolution mass spectroscopy; TLC, thin layer chromatography.

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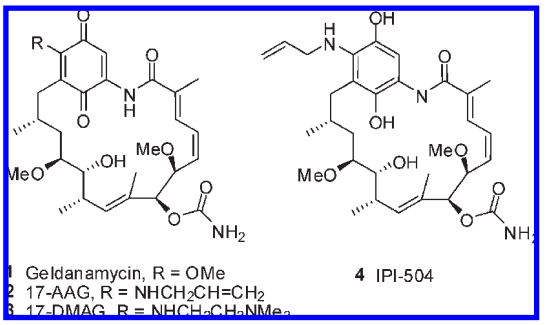


Figure 1. Natural product geldanamycin and its derivatives.

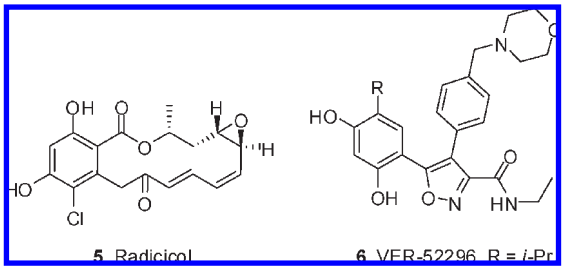


Figure 2. Natural product radicicol and resorcinol derivatives.

natural product radicicol[16] (**5**, Figure 2) was additionally identified as a potent Hsp90 inhibitor in vitro but was largely inactive in tumor xenograft models.[17] However, this scaffold has led to rationally designed resorcinol based pyrazole and isoxazole inhibitors with improved solubility and in vivo potencies. The most advanced clinical compound in this class is VER-52296 (or NVP-AUY922, **6**).[18] A rational choice for an Hsp90 inhibitor that targets ATPase activity is purine based compounds. The first synthetic class of such scaffolds was the PU series, represented by PU24-FCl (**7**, Figure 3), which showed good in vitro potencies but low in vivo efficacy.[19] Further exploration led to another purine based scaffold, and one analogue, the orally bioavailable CNF-2024 (or BIIB021, **8**), is also now in clinical testing.[20]

While the Hsp90 inhibitors evaluated to date have exhibited promising activity, there remains a need for the identification of small molecule inhibitors with enhanced potency and improved pharmacokinetics. Here we report our synthetic and medicinal chemistry efforts in this area that have yielded a new class of Hsp90 inhibitors unrelated to any previously known scaffold (Figure 4). Our exploration has produced a highly potent inhibitor, **9** (SNX-2112), and an orally bioavailable and efficacious prodrug analogue, **10** (SNX-5422), which is now in multiple phase I clinical trials.[21]

Modeling and Medicinal Chemistry Strategies. Through screening of a focused compound library against sets of ATP binding proteins, we identified 4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide **11**[22] (Scheme 1, Figure 5) as a moderate inhibitor of Hsp90 (K_d = 3.7 μM). Although **11** was inactive in multiple cellular assays (IC_{50} > 50 μM), this scaffold was prioritized over multiple other internally identified hits for a number of carefully considered reasons. More specifically, it showed high selectivity for binding to Hsp90, possessed low molecular weight and heteroatom count, and was a chemically novel scaffold. Furthermore, our structural and retrosynthetic analysis indicated it was feasible to make a broad range

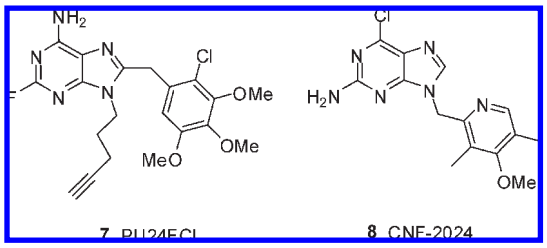


Figure 3. Purine based derivatives.

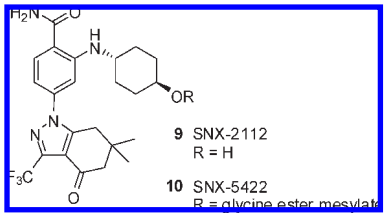
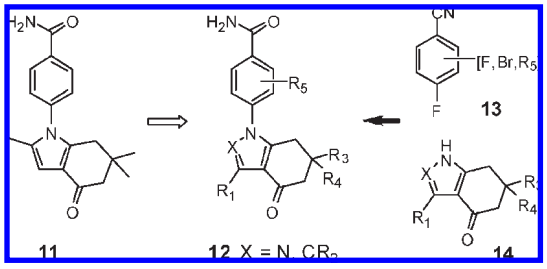


Figure 4. Novel class of 2-aminobenzamide derivatives.

Scheme 1. Hsp90 Screening hit **11**; SAR and Synthetic Strategies



of modifications to nearly all atoms around this scaffold through robust synthetic chemistry, which would enable rapid preparation of numerous diverse analogues for thorough structure−activity relationship (SAR) exploration and structural optimization (Scheme 1).

Computational models for binding of **11** were developed to assist in the design of optimization strategies. The benzamide moiety was considered likely to be a structural isostere for adenine, and so it was modeled to bind consistent with the observed X-ray data for the binding of ADP to N-terminal domain of Hsp90.[23] Specifically, hydrogen bonding, direct and water mediated, to Asp 93 and Thr 184 was anticipated (Figure 5A). For the indolone ring system, two alternative docking orientations were initially viewed as plausible. In one orientation (not shown), the ketone was mapped onto the quinone of GA and reasonable alignment of the respective carbonyl groups from the two molecules was possible. An alternate orientation relied on an induced binding pocket resulting from movement of Leu 107, as was observed in X-ray structures for PU3 and related analogues. In this case, the carbonyl group of the indolone was modeled to hydrogen bond to Tyr 139 with the *gem*-dimethyl being buried into a hydrophobic region formed by Leu 107, Phe 138, and Trp 162 (Figure 5A).

Although both models were considered in detail, this latter model was given preference due to the quality of the potential hydrogen bonding and hydrophobic interactions and the appeal of the *gem*-dimethyl group acting as a

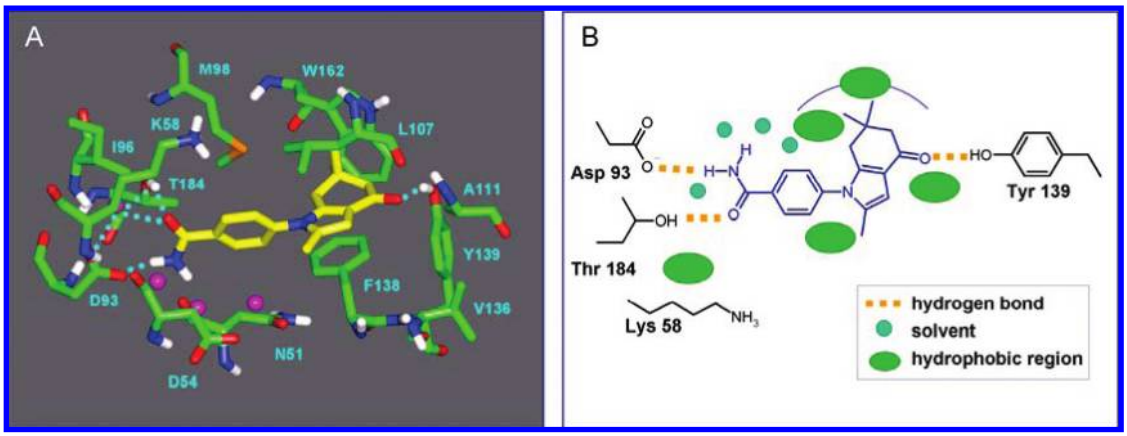
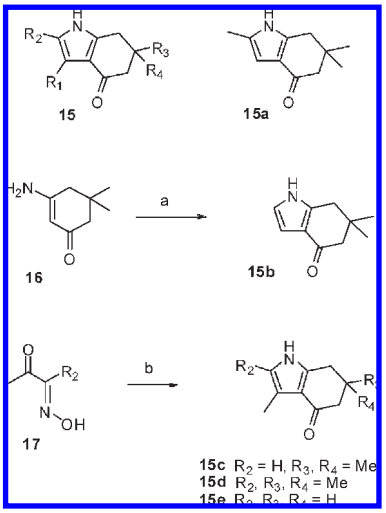


Figure 5. Binding models for hit compound **11**. (A) Docking of **11** into the N-terminal domain of Hsp90 (protein structure from PDB code 3D0B).[22] Putative hydrogen bonds are shown by cyan dots. (B) 2D schematic of the binding site.

Scheme 2. Preparation of Indol-4-ones[a]

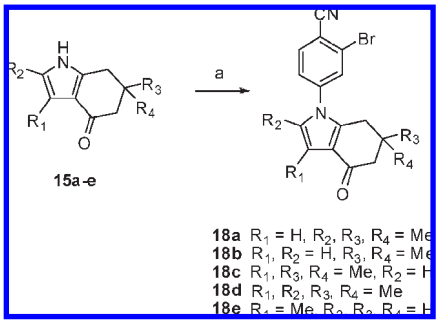


[a] Reagents and conditions: (a) glyoxal, Zn, HOAc, water, 75 °C; (b) Zn, HOAc, water, 75 °C, 5,5-dimethyl-cyclohexane-1,3-dione for **15c**, **15d**; or cyclohexane-1,3-dione for **15e**.

leucine side chain isostere, thereby mimicking the displaced Leu 107. The observations from this model were that substitution appeared quite reasonable ortho to the benzamide with the expectation that these substitutions would orient to the carbonyl side of the amide group (Figure 5B) because the amino side was buried in the back of the Hsp90 binding cleft. There was clear accessible space in this region with the potential to additionally target both hydrophobic and hydrogen bonding regions of Hsp90. Finally, substitution of the pyrrole region appeared to be feasible. Subsequently, X-ray data were obtained for members of this chemical scaffold[22] that overall validated the binding model for **11** and in particular confirmed the orientation for the indolone ring.

Our overall synthetic and medicinal chemistry strategies fully incorporated such binding analysis (Scheme 1). Analogues of the scaffold (**12**) in general could be assembled from top (**13**) and bottom (**14**) building blocks as shown, with each bearing either preinstalled substitutions at designated positions or synthetic handles such as fluoride and bromide that could be conveniently displaced later. The cyano group was designed as both the activator for the sequential substitution

Scheme 3. Syntheses of Indolone Benzonitriles[a]



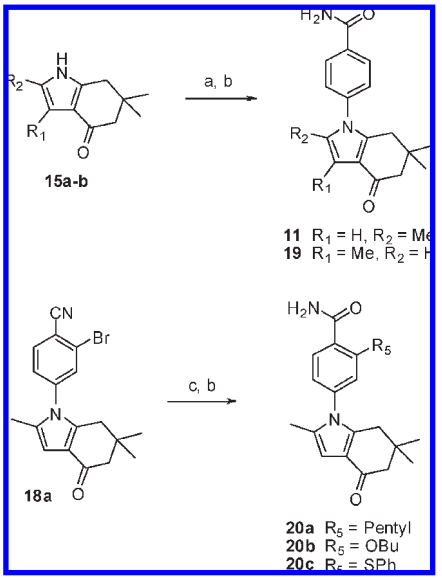
[a] Reagents and conditions: (a) 2-bromo-4-fluoro-benzonitrile, NaH, DMF, rt.

reactions around the benzene ring and a convenient synthetic precursor for the carboxamide.

Synthetic Chemistry. Chemical exploration of this scaffold started with the syntheses of derivatives (**15**) of the indol-4-one moiety. We utilized different routes to construct these building blocks and alter the substitution pattern around the carbon skeleton (Scheme 2). The known 2-methyl indol-4-one (**15a**) was prepared as previously reported from dimedone and chloroacetone.[24] Another known compound, 2,3-dihydrido indolone (**15b**),[25] was prepared through an improved one step treatment of 3-amino-5,5-dimethyl-cyclohex-2-enone (**16**) with glyoxal and zinc powder in a warm mixture of acetic acid (HOAc) and water. 3-Methyl indolone derivatives **15c**,[26] **15d**,[27] and **15e**[28] were reported before; each was prepared here effectively in one step via a modified Knorr procedure[29] from a corresponding available 2-oxime methyl ketone **17** and cyclohexane-1,3-dione in the presence of Zn powder and HOAc. The coupling reaction of 2-bromo-4-fluoro-benzonitrile with substituted indolone derivatives **15a**−**e** mediated by NaH in dimethylformamide (DMF) gave the versatile 2-bromo-benzonitrile intermediates, **18a**−**e** (Scheme 3), which were subsequently transformed into various analogues.[30]

The screening hit **11** and its 3-methyl regioisomer **19** were prepared through a similar coupling reaction between 4-fluoro-benzonitrile and indolone **15a**−**b**, respectively, followed by H_2O_2 catalyzed conversion of the resulting crude indolone benzonitriles into benzamides at room temperature in a mixture of EtOH and dimethyl sulfoxide (DMSO) (4:1 ratio) containing aqueous NaOH[31] (Scheme 4). We found

Scheme 4. Preparation of Benzamide Analogues[a]



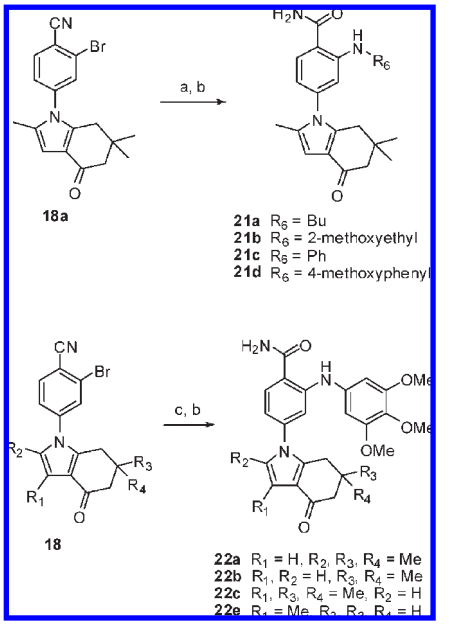
[a] Reagents and conditions: (a) 4-fluoro-benzonitrile, NaH, DMF, rt; (b) EtOH, NaOH, DMSO, H_2O_2, rt; (c) pentylzinc bromide, $PdCl_2$(dppf), THF, 85 °C microwave for **20a**, or NaH, butanol, 100 °C microwave for **20b**, or NaH, thiophenol, 100 °C microwave for **20c**.

the addition of DMSO to our reaction systems consistently improved the yield and accelerated the rate of this hydration process, and many amide products would precipitate from the reaction mixtures within 5−10 min. Derivatives from **11** carrying side chains linked to the phenyl ring through either a CH_2, O, or S ortho to the amide were prepared from **18a** through nucleophilic replacements of the 2-bromide and hydration of the cyano group. Thus, 2-pentyl analogue **20a** was prepared from pentylzinc bromide and catalytic $PdCl_2$(dppf),[32] 2-butoxy analogue **20b** from butanol and NaH, and 2-phenylsulfanyl analogue **20c** from thiophenol and NaH.

Treatment of 2-bromobenzonitriles **18** with amino nucleophiles under Buchwald−Hartwig conditions[33] involving catalytic $Pd(OAc)_2$, 1,1′-bis(diphenylphosphino)ferrocene (DPPF), and NaO*t*Bu in toluene at 110 °C under microwave irradiation introduced amino side chains to the scaffolds, which were converted into a plethora of 2-aminobezamide analogues[30] (Scheme 5). Thus, **18a** was converted into its corresponding butylamine **21a**, 2-methoxyethylamine **21b**, phenylamine **21c**, and 4-methoxyphenylamine **21d** derivatives. Similarly, 2-(3,4,5-trimethoxy-phenylamino)-benzamide analogues **22a**−**c**, **22e** each was prepared from corresponding **18**, with methyl group(s) at varying positions about of tetrahydro-indol-4-one moiety.

The tetrahydro-indol-4-one moieties of the scaffold could be replaced by tetrahydro-indazol-4-ones, which were prepared through a number of different routes. Method A started by substituting the fluorine of 2-bromo-4-fluoro-benzonitrile with hydrazine in tetrahydrofuran (THF) to give a known compound **23**[34] (Scheme 6), followed by reaction of **23** with readily available 2-acetyl-5,5-dimethyl-cyclohexane-1,3-dione in a mixture of EtOH and HOAc at 110 °C in a microwave reactor to afford **24a**, a key 2-bromo-benzoniltrile intermediate. 2-Aminobenzamide analogues were prepared from **24a** through Buchwald−Hartwig coupling reactions with amines followed by hydration of the resulting benzonitriles. Compound **25a**, as an example,

Scheme 5. Synthesis of 2-Aminobenzamide Analogues[a]



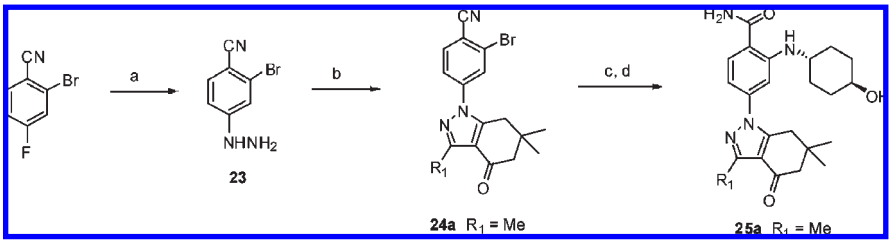
[a] Reagents and conditions: (a) $Pd(OAc)_2$, DPPF, NaO*t*Bu, toluene, amine, or aniline, 110 °C microwave; (b) EtOH, NaOH, DMSO, H_2O_2, rt; (c) $Pd(OAc)_2$, DPPF, NaO*t*Bu, toluene, 3,4,5-trimethoxy-phenylamine, 110 °C microwave.

carries a 2-(*trans*-4-hydroxy-cyclohexylamino) side chain. This method gave efficient entry into facile diversification of the 2-amino side chains. Additional analogues prepared through this method are reported in the Results and Discussion and Experimental Sections.

An alternative synthesis for the indazolone analogues is illustrated as method B (Scheme 7). The C-2 side chain, such as *trans*-4-hydroxy-cyclohexylamino, was introduced first to give **26** by treatment of 2,4-difluorobenzonitrile with *trans*-4-amino-cyclohexanol. Replacement of the second fluorine with hydrazine under heat gave **27**. Known triketones **28a**,[35] **28b**,[36] and novel **28c** were conveniently prepared from the corresponding acid chloride or anhydride and dimedone in warm with catalytic 4-dimethylamino-pyridine (DMAP). Indazol-4-one formations from **28a**−**c** and **27** in hot mixtures of ethanol and acetic acid, followed by hydration of the resulting benzonitriles afforded analogues **29a**−**c**.[30] This method efficiently introduced various substitutions at the C-3 position of the indazolones.

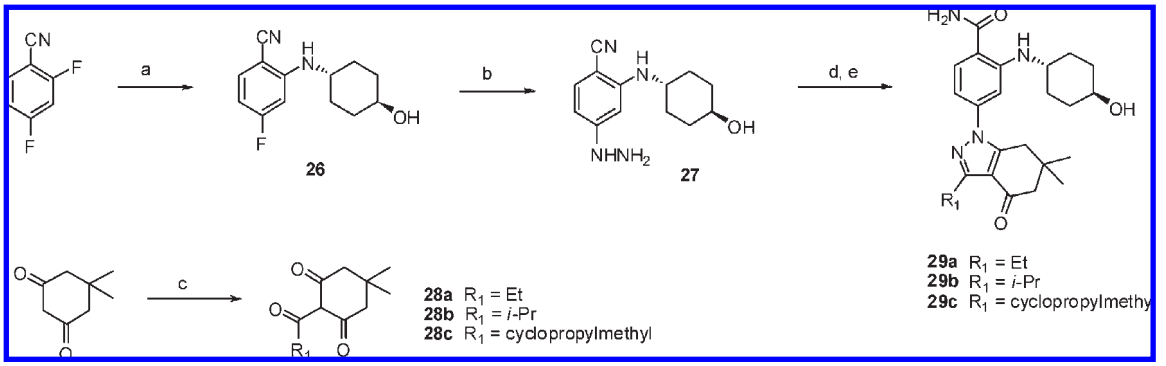
A third route, or method C, was developed to prepare the 3-difluoromethyl and 3-trifluoromethyl substituted indazolone 2-aminobenzamide analogues (Scheme 8). Because of their poor stability, the fluorinated methyl triketones of formula **28** could not be obtained in meaningful yields, therefore the previous two methods were not applicable. Instead, a known tosyl hydrazone intermediate **30** was made from dimedone and tosyl hydrazide as reported.[37] It was subsequently converted into desired indazolone **31a** or **31b** through treatment with trifluoro- or difluoroacetic anhydride in a warm mixture of tetrahydrofuran (THF) and triethylamine, then NaOH in methanol and water.[30] Through similar conditions described above, coupling of **31a** and **31b** with 2-bromo-4-fluoro-benzonitrile regioselectively afforded **32a**, **32b**, respectively, which were converted into the desired 2-(*trans*-4-hydroxy-cyclohexylamino)-benzamide analogues **9** and **33** under Buchwald−Hartwig conditions and nitrile

Scheme 6. Method A for Preparation of Indazolone 2-Aminobenzamide Analogues[a]



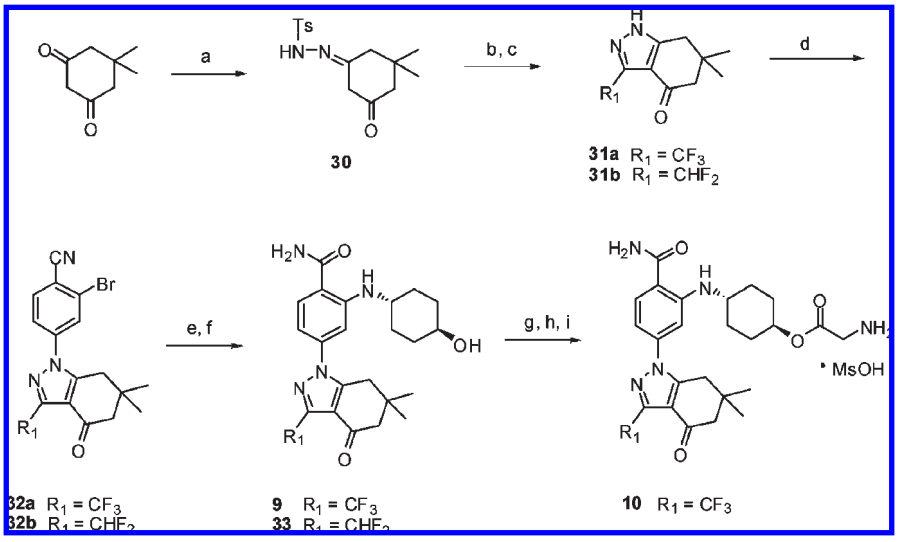
[a] Reagents and conditions: (a) NH_2NH_2, THF, rt; (b) 2-acetyl-5,5-dimethyl-cyclohexane-1,3-dione, EtOH, HOAc, 110 °C microwave; (c) $Pd(OAc)_2$, DPPF, NaO*t*Bu, toluene, *trans*-4-amino-cyclohexanol, 110 °C microwave; (d) EtOH, NaOH, DMSO, H_2O_2, rt.

Scheme 7. Method B for Preparation of Indazolone 2-Aminobenzamide Analogues[a]



[a] Reagents and conditions: (a) *trans*-4-amino-cyclohexanol, THF, triethylamine, 110 °C microwave; (b) NH_2NH_2, THF, heat; (c) R_1COCl or $(R_1CO)_2O$, pyridine, cat. DMAP, 70 °C; (d) **28**, EtOH, HOAc, 110 °C microwave; (e) EtOH, NaOH, DMSO, H_2O_2, rt.

Scheme 8. Method C for Preparation of Indazolone 2-Aminobenzamide Analogues[a]

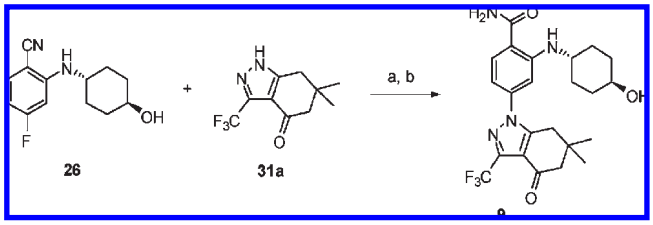


[a] Reagents and conditions: (a) $TsNHNH_2$, cat. *p*-TsOH, toluene, reflux; (b) $(R_1CO)_2O$, THF, triethylamine, 55 °C; (c) NaOH, MeOH, water, rt; (d) 2-Bromo-4-fluoro-benzonitrile, NaH, DMSO, rt; (e) $Pd(OAc)_2$, DPPF, NaO*t*Bu, toluene, *trans*-4-aminocyclohexanol, 110 °C microwave; (f) EtOH, NaOH, DMSO, H_2O_2, rt; (g) *N*-(*tert*-butoxycarbonyl)glycine, EDC, cat. DMAP, CH_2Cl_2, rt; (h) TFA, CH_2Cl_2; (i) methanesulfonic acid, CH_2Cl_2.

hydration. Glycine ester mesylate salt **10** was prepared from **9** through 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), DMAP mediated coupling with *N*-(*tert*-butoxycarbonyl)glycine, deprotection of the Boc group using trifluoroacetic acid (TFA), and salt formation with methanesulfonic acid (MsOH). This method was also highly effective for the preparation of nonfluorinated indazolones of formula **31** from **30** but gave poor regioselectivity (~1:1) for the C−N bond formation in the subsequent coupling reactions with 2-bromo-4-fluoro-benzonitrile.

Yet a fourth route, method D, was developed to prepare the fluorinated 3-methylindazolone 2-aminobenzamide analogues, especially for large scale production of the derivatives (Scheme 9). The 4-fluoride of the 4-fluoro-2-aminobenzonitrile such as **26** was replaced by a fluoro 3-methyl indazol-4-one, such as **31a** in high yield with desired regioselectivity. The nitrile hydration in the end, in this example, afforded compound **9**. Again, the first coupling step was not suitable for nonfluorinated methyl indazolones due to poor regioselectivity.

Scheme 9. Method D for Preparation of Indazolone 2-Aminobenzamide Analogues[a]



[a] Reagents and conditions: (a) NaH, DMF, 100 °C microwave; (b) EtOH, NaOH, DMSO, H_2O_2, rt.

Results and Discussion

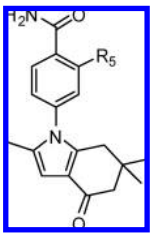
We had envisioned the primary benzamide and indol-4-one carbonyl groups as key structural features of this scaffold that confer tight binding into the ATPase pocket of Hsp90, as described above. This hypothesis was quickly validated by our preliminary SAR explorations. Partial or total loss of binding affinity to Hsp90 occurred when the primary benzamide was replaced with amides with *N*-substitutions, a carboxylic acid or its esters, imidamide, hydroxy imidamide, or its precursor benzonitrile. Similar results were observed when the carbonyl of the indol-4-one was converted into an oxime or other moieties.[30] Our follow-on strategy retained these structural functionalities and focused optimization on the remaining features around the scaffold.

One of our early strategies was to examine the impact of side chains attached to the amido benzene ring of the scaffold on Hsp90 binding affinity and cellular client protein degradation. We had expected such attachments might enhance potencies because they would occupy the same space of enzyme pocket utilized by side chains of PU series of inhibitors as well as rings of 17-AAG (**2**) and radicicol (**5**). Our results indicated there were indeed significant effects on binding affinities, and they were highly dependent on the positions of substitutions and the nature of the linker atoms. In general, the C-3 (meta) substitutions on the benzene frequently led to lower Hsp90 affinity, erratic SAR, or occasional binding to off-target proteins that we did not fully characterize (data not shown). The often reduced and erratic Hsp90 affinity is believed to be due to steric interference with the Leu 107 residue of Hsp90, which is displaced, on ligand binding, to a location proximal to the C-3 position. An additional point of note is that the magnitude of the displacement of Leu 107 is larger relative to the PU24FCl (**7**) and CNF-2024 (**8**) classes of inhibitors due to the bulky gem-dimethyl group attached to the indol-4-one moiety.

In sharp contrast, the C-2 (ortho) substitutions on the benzene ring showed consistent SAR and tractable enhancement of Hsp90 binding affinity (Table 1) for those substitutions with an NH linker. Compounds containing an oxygen linker, for example, compound **20b**, did not exhibit measurable Hsp90 binding; this observation was consistent with the binding model as electronic repulsion would be expected between the oxygen linker and amide carbonyl oxygen. Analogues containing methylene (**20a**) or sulfide (**20c**) linkers improved only slightly the affinity for Hsp90 compared to the parent hit (**11**), and neither had any measurable cellular potency. Conversely, amine linkers provided a significant advance in optimization. Both alkyl and aryl groups linked through NH at C-2 of the core scaffold improved binding to Hsp90. Additionally, although linear alkyl chains often conferred little or no cellular activity (**21a**, **21b**), incorporation of cyclic aryl groups led to inhibitors able to induce Her2 protein degradation in cellular assays (**21c**, **21d**, **22a**). Oxygen containing rings (**21d**, **22a**) appeared to confer more potent cellular effects than the one without oxygen (**21c**). This last trend was interesting because 17-AAG (**2**) also has an oxygen located in the same space of the Hsp90 binding pocket. Other types of C-2 substitutions without a NH linker were also broadly explored and were generally disfavored (data not shown). The data generated were generally consistent with the binding model in which the NH linker formed a stabilizing intramolecular interaction with the amide carbonyl group, and the alkyl and aryl substitutions were involved in favorable hydrophobic interactions with Hsp90 residues, especially Met 98. Additionally, Lys 58 was modeled to interact with the oxygen containing substitutions, thereby affording an additional hydrogen bond. Compound **22a** was the most potent analogue we could achieve in this series by optimizing only the 2-amino group. Although potent Hsp90 binding affinity was observed, modification of other parts of the scaffold became necessary for improved cellular potencies.

Next we investigated the SAR of the indol-4-one moiety in affecting biological activities by using 2-(3,4,5-trimethoxyphenylamino)benzamide of **22a** as a common and sensitive template (Table 2). Deletion of either the 2-methyl (**22b**) or the gem 6,6-dimethyl (**22e**) of indol-4-ones led to moderate reduction of Hsp90 affinity but significant loss of the cellular effect on Her2 degradation. Moving the C-2 indolone methyl group of **22a** to the C-3 position (**22c**) greatly improved the cellular activity, leading to a compound showing nanomolar potency. Compound **19**, the C-3 methyl regioisomer of **11** and the core scaffold component of **22c**, was still active in cells (Her2 IC_{50} = 8 μM, not shown in tables). While replacement of the *gem*-dimethyl with a single ethyl was allowed, it created

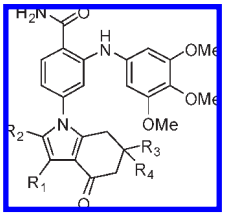
Table 1. 2-Amino Substitutions Enhance both Hsp90 Affinity and Client Effects



compd	R_5	Her-2 degradation[a] IC_{50} (μM)	Hsp90 affinity[b] K_d (μM)
17-AAG		0.003 ± 0.003	0.087
11	H	> 100	3.73
20b	BuO	> 10	> 50
20a	Pentyl	> 10	1.96
20c	PhS	> 10	1.06
21a	BuNH	> 10	0.39
21b	2-(MeO)EtNH	> 10	0.39
21c	PhNH	6.4 ± 1.1	0.37
21d	4-(MeO)PhNH	1.59 ± 0.20	0.69
22a	3,4,5-$(MeO)_3$PhNH	0.49 ± 0.03	0.22

[a] Values were determined from a Her2 imaging assay in AU565 cells.[38] [b] Values were derived from an 8-pt nonenzymatic ATPase assay.[21]

Table 2. Critical Roles of Indolone Methyl Groups



compd	R_1	R_2	R_3, R_4	Her-2 degradation[a] IC_{50} (μM)	Hsp90 affinity[b] K_d (μM)
17-AAG				0.003 ± 0.003	0.087
22a	H	Me	Me	0.49 ± 0.03	0.22
22b	H	H	Me	1.83 ± 0.12	0.59
22e	Me	H	H	1.61 ± 0.18	0.94
22c	Me	H	Me	0.046 ± 0.011	0.39

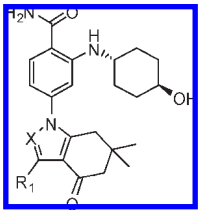
[a] Values were determined from a Her2 imaging assay in AU565 cells. [b] Values were derived from an 8-pt nonenzymatic ATPase assay.

an unwanted chiral center, and larger groups were disfavored at that position (both data not shown). Similarly, 2,3-dimethyl indolone analogues were also less potent, as in one example to be shown later. These results clearly defined the importance of the C-3 methyl and the *gem*-6,6-dimethyl groups of the indolone moiety for potent Hsp90 inhibition and represented the second critical SAR trend we discovered with this chemical scaffold.

At this point in the discovery effort, compound **22c** represented the most advanced analogue and demonstrated both strong Hsp90 binding and potent cellular activity consistent with Hsp90 inhibition as the mechanism of action. However, **22c** was viewed as less than favorable with regards to solubility and CLogP. In fact, this compound was neither orally bioavailable nor effective in mouse xenograft tumor models following ip dosing. Additionally, both the pyrrole moiety and especially the electron rich trimethoxyaniline ring were viewed as potential metabolic liabilities, with the aniline having the potential to be metabolized to reactive quinone species. To address these issues, additional modifications were pursued. Replacement of the trimethoxyaniline ring with a *trans*-4-hydroxycyclohexylamino group afforded compound **34** (Table 3), which was highly potent as an Hsp90 inhibitor. Additionally, this compound was shown to have measurable oral bioavailability (ca. 10% in rat) and good in vivo efficacy in mouse xenograft tumor models following ip dosing (data not shown). Relative to **22c**, the *trans*-4-hydroxycyclohexylamino substitution of **34** was attractive because it was nonaromatic, while still maintaining achirality, and was capable of forming similar favorable interactions with the Hsp90 binding site, namely hydrophobic packing with Met 98 and hydrogen bonding to Lys 58. A binding model for compound **34** overlaid onto 17-DMAG (**3**, Figure 6) illustrates the ability of the compound class to mimic, in an orally available small molecule scaffold, multiple key pharmacophore elements of the natural product ansamycins.

We next replaced the seemingly dispensable 2-hydridocarbon (CH) of the indolone of **34** with nitrogen and explored substitutions at the C-3 position of the resulting indazol-4-ones (Table 3). This new scaffold was designed to lower the electron density and increase the stability of the bottom moieties through the use of a pyrazole replacement for the pyrrole of the original hit. Additionally, the

Table 3. Versatile Indazolones and the Unique Aminocyclohexanol



compd	R_1	X	Her-2 degradation[a] IC_{50} (nM)	Hsp90 affinity[b] K_d (nM)
17-AAG			3 ± 3	87
34	Me	CH	7 ± 3	27
25a	Me	N	30 ± 11	16
9	CF_3	N	10 ± 0.8	16
29a	Et	N	9 ± 2	20
33b	CHF_2	N	16 ± 1	98
29c	*c*-PrMe	N	46 ± 14	41
29b	*i*-Pr	N	203 ± 59	177
35	Me	CMe	64 ± 9	86

[a] Values were determined from a Her2 imaging assay in AU565 cells. [b] Values were derived from an 8-pt nonenzymatic ATPase assay.

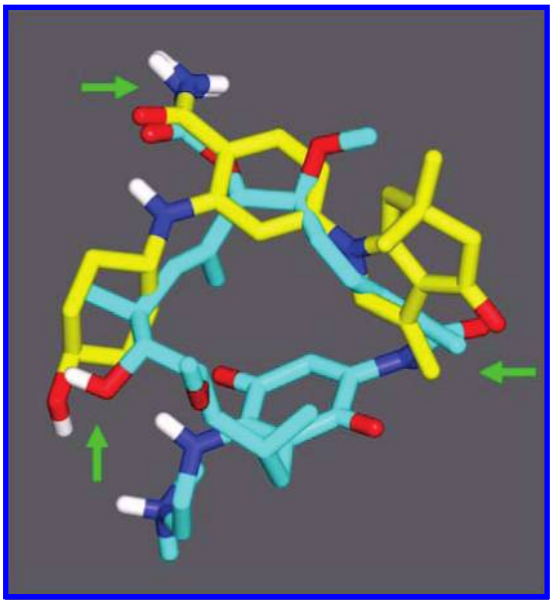
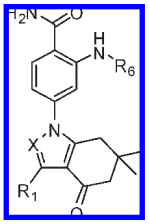


Figure 6. Overlay of binding model for **34** onto 17-DMAG (**3**, from PDB code 1OSF). Green arrows show common pharmacophore elements.

pyrazole provided increased compound polarity and perhaps solubility and the opportunity to gain more structural diversity via synthetic accessibility to the C-3 position of the bottom moieties. These combined modifications significantly lowered the ClogP values of the resulting indazolone analogues listed in the table to within a well acceptable range of 2.34−3.39. Close examination indicated that 3-methyl indazolone **25a** was less potent than its indolone equivalent **34**, but the trifluoromethyl version **9** was equally potent as **34**. Compound **9** would ultimately undergo extensive evaluation (described below); its amorphous form displayed good oral bioavailability (40%, mouse) and in vivo antitumor efficacy in mouse xenograft models following oral dosing.

Table 4. Broad Scope of the 2-Amino Substitutions



compd	R_1	X	R_6	Her-2 degradation[a] IC_{50} (nM)	Hsp90 affinity[b] K_d (nM)
17-AAG				3 ± 3	87
36	Me	N	4-tetrahydropyranyl	50 ± 13	43
37	Me	N	cyclopent-3-enyl	111 ± 19	15
38	CHF_2	N	4-tetrahydrothiopyranyl	35 ± 6	11
39	Me	N	cyclobutyl	229 ± 116	114
40	Me	N	cyclopropylmethyl	184 ± 34	51
41	Me	CH	1-phenylethyl	418 ± 59	1020
42	Me	N	furan-2-ylmethyl	> 1000	216
43	Me	N	2-(methylthio)ethyl	226 ± 44	63
44	Me	N	2-(methylsulfonyl)ethyl	147 ± 32	14
45	Me	N	1-methoxy-propan-2-yl	115 ± 14	67
46	CF_3	N	3-(2-oxopyrrolidin-1-yl)propyl	264 ± 103	94
47	CF_3	N	1,3-dimethoxypropan-2-yl	181 ± 49	78
48	Me	CH	4-piperidinyl	> 7000	843
49	Me	CH	2-morpholinoethyl	> 4000	294
50	CF_3	N	4-*cis*-hydroxycyclohexyl	248 ± 23	530
10	CF_3	N	4-*trans*-(2-aminoacetoxy)cyclohexyl	37 ± 9	41

[a] Values were determined from a Her2 imaging assay in AU565 cells. [b] Values were derived from an 8-pt nonenzymatic ATPase assay.

Table 5. Antiproliferative Activities for Selected Compounds

proliferation assays[a]	17-AAG	**34**	**9**	**10**
A375 (melanoma)	1287 ± 212	9 ± 2	23 ± 5	51 ± 6
LNCAP (prostate)	82 ± 52	4 ± 1	3 ± 1	31 ± 1
MCF-7 (breast)	0.3 ± 0.3	10 ± 5	53 ± 46	16 ± 6
HT-29 (colon)	0.1 ± 0.01	7 ± 2	3 ± 0.7	32 ± 4
SW620 (colon)	328 ± 20	6 ± 1	3 ± 0.5	19 ± 6
SK-MEL-5 (melanoma)	134 ± 14	7 ± 1	6 ± 1	25 ± 6
PC-3 (prostate)	9 ± 4	14 ± 5	17 ± 3	114 ± 14
MDA-MB-231 (breast)	194 ± 74	10 ± 3	6 ± 1	38 ± 9
NCI-H460 (NSCLC)	255 ± 61	248 ± 72	18 ± 4	215 ± 95
HCT-15 (colon)	1487 ± 212	61 ± 5	52 ± 12	190 ± 18
K562 (erythroleukemia)	126 ± 113	3 ± 2	6 ± 1	23 ± 4

[a] Values are IC_{50} in nM and are the means of four experiments with standard deviation shown.[38]

Table 6. Client Impacts for Selected Compounds

client assays[a]	17-AAG	**34**	**9**	**10**
Hsp70 induction (A375 cells)	4 ± 3	14 ± 6	2 ± 0.9	13 ± 3
p-S6 degradation (A375 cells)	32 ± 19	7 ± 3	1 ± 0.6	61 ± 22
Her2 degradation (AU565 cells)	3 ± 3	7 ± 3	11 ± 5	5 ± 1
p-ERK degradation (AU565 cells)	8 ± 7	16 ± 3	41 ± 12	11 ± 3

[a] Values are IC_{50} in nM and are the means of four experiments with standard deviation shown.[38]

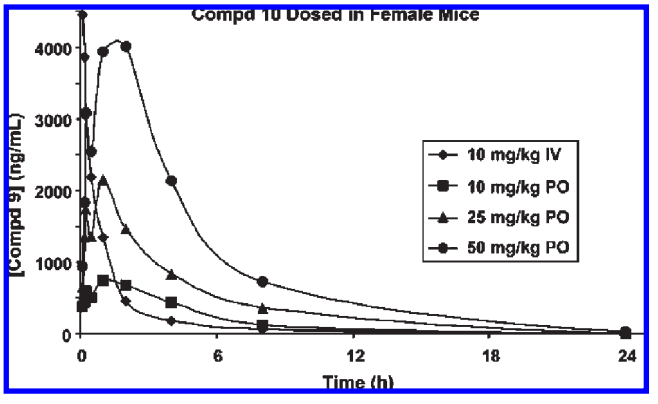


Figure 7. Exposure of compound **9** following iv and oral dosing of compound **10** in female mice. Data are from an average of four animals. Levels of prodrug were below the lower limit of quantitation (LLOQ) at all time points.

A series of other analogues were prepared to further evaluate the SAR (Table 3) of the C-2 and C-3 positions. Ethyl **29a** showed good potency, whereas difluoromethyl analogue **33b**, cyclopropylmethyl **29c**, and isopropyl indazolone **29b** displayed reduced activity. The activity of the 2,3-dimethyl indolone **35** was comparable but not superior to **34** or **22c**. In general, larger or functional groups introduced at available C-2 or C-3 or both positions of the indolone or indazolone led to loss of potencies.

Concurrently, we explored optimization of 2-amino substitutions in conjunction with the favored bottom moieties bearing small C-3 groups and data for representative compounds are summarized (Table 4). The overall SAR trends were consistent with our earlier findings. The favored side chains were aminocyclic structures that contained oxygen (**36**) or a weak hydrogen bond acceptor such as the less stable alkene (**37**) or sulfur (**38**). The less favored side chains were either rings without such H-bond acceptors (**39**) or rings having an extra linear spacer (**40**, **41**, **42**). Open chain structures designed to improve flexibility and solubility, were also less active (**43**, **44**, **45**, **46**, **47**). Particularly disfavored side chains were those containing strongly basic amines (**48**, **49**). The comparator compound, epimeric

Table 7. Pharmacokinetic Data for Compound **10** in Female Mice[a]

dose (mg/kg)	route	T_{max} (h)	C_{max} (ng/mL)	AUCInf (h·ng/mL)	$T_{1/2}$ (h)	Vz_F_obs (mL/kg)	CL_F_obs (mL/h/kg)
10	iv	0.083	4455	4869	2.6	7846	2054
10	po	1	747	3968	2.5	8928	2520
25	po	1	2148	11004	2.9	9594	2272
50	po	2	4015	25153	3.3	9547	1988

[a] Parameters were calculated using WinNonlin software.

4-*cis*-hydroxycyclohexylamino (**50**), was 25- to 30-fold less potent compared to the trans analogue **9**. Compound **10**, the glycine ester prodrug of compound **9** that was made for further evaluation for reasons described below, still maintained nanomolar level of potencies.

Overall, compounds **34** and **9** remained among the most potent compounds. Their detailed cellular activity profiles, along with those of prodrug **10** and 17-AAG (**2**), are presented in Tables 5 and 6. All compounds summarized showed potent antiproliferative activity against a broad range of cancer cell types (Table 5). Additionally, 17-AAG treatment resulted in calculated IC_{50} values spanning a much greater range (0.1−1487 nM) than **9** (3 nM to 53 nM). One explanation for this observation is that the different cell lines tested have differing abilities to reduce 17-AAG to its more potent dihydroquinone form via DT-diaphorase (NQO1).[39] Compounds **9**, **10**, and **34** all exhibited potent effects on Her2 stability and caused expected up-regulation of Hsp70 (Table 6). Additionally, treatment with the inhibitors down regulated both the MAPK and AKT signaling pathways as measured by the loss of p-S6 and p-ERK in treated cells. These pathways are implicated in uncontrolled cellular division and antiapoptotic signaling and have been targeted for drug development. The results shown here highlight the advantage of Hsp90 inhibition as a single mechanism that is capable of modulating a number of known pathways involved in cancer progression.

Lead compounds of this new class appeared highly selective for Hsp90. Routine screening through an internal affinity chromatography assay,[21,40] designed to provide broad profiling of purine binding proteins from either recombinant proteomes or porcine tissues, showed strong Hsp90 binding and an absence of off-target interactions. Furthermore, compound **9**, when screened through a panel of 75 enzymes and receptors at 1 μM, did not display any inhibitory activity greater than 20%, nor did it exhibit significant inhibition against a panel of 9 cytochrome P450 isozymes (both provided by Cerep, Inc., Seattle, WA). This compound was also found sufficiently stable to metabolism by human liver microsome (1 μM; 88% remaining after 1 h in the S9 fractions).

Although amorphous **9** was orally bioavailable ($F \sim 0.4$) and had moderate solubility of 170 μM, its crystalline forms were not, and aqueous solubility of these forms at physiological pH (in phosphate-buffered saline or PBS, 7.4) was reduced 25-fold to 6 μM. To improve bioavailability for oral dosing and also provide additional solubility to allow the flexibility of parenteral administration, a simple amino ester prodrug strategy was explored. One example was a β-analine analogue[21] that showed improved oral bioavailability and was highly water-soluble (~10 mg/mL, pH 2−6); however, it was found to be too stable to esterase hydrolysis both in vitro (60% conversion to **9**, 1 h in mouse plasma) and in vivo. The glycine ester **10** was crystalline, stable, and reasonably soluble (~1 mg/mL, pH 4−6). Conversion of ester **10** to parent **9** was rapid and complete in vivo following oral and intravenous dosing and resulted in excellent exposure of the parent compound (Figure 7). Compound was cleared from normal tissues to below the lower limit of quantitation (LLOQ) by 24 h and exhibited good scaling with oral dose (Table 7).

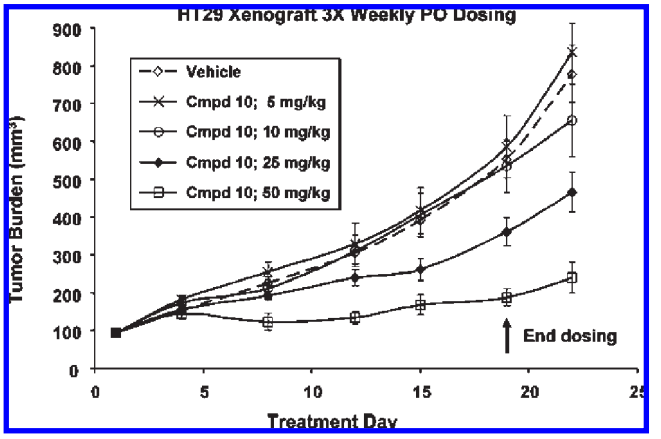


Figure 8. Example of in vivo activity of compound **10** following oral dosing in an HT-29 colon tumor xenograft model. Compound was dosed on a MWF schedule for 3 weeks.

On the basis of the observed favorable pharmacokinetics, compound **10** was evaluated in a range of xenograft models. Shown in Figure 8 is the in vivo antitumor activity of **10** in an HT-29 human colon tumor xenograft model. The compound was orally administered to mice bearing subcutaneous tumors 3 times a week for 3 weeks (qod × 3/2 × 3) at 5, 10, 25, and 50 mg/kg. The 50 mg/kg dose was the most efficacious, demonstrating a 67% growth delay over vehicle control. Median time to end point (TTE) for the 50 mg/kg group was 43.2 days compared to 25.9 days for vehicle control. Two of 10 animals survived to the end of the study (61 days). The 25 mg/kg dose showed tumor growth delay but at a much lower percentage (14%). Median TTE was not statistically significant over vehicle control. On the basis of body weight measurements and clinical observations, compound **10** was well tolerated at all dose levels tested. No treatment related deaths were observed.

Conclusion

A novel class of indol-4-one and indazol-4-one derived 2-aminobenzamides that potently inhibit Hsp90 has been discovered. The overall synthetic schemes developed allowed for facile preparation of the intermediates as well as diverse analogues and were easily scalable. Computational chemistry and X-ray crystallographic analysis of selected member compounds clearly defined the protein−inhibitor interaction and assisted the design of further analogues. Optimized compounds of the new scaffolds exhibited low nanomolar antiproliferation potencies across multiple cancer cell lines with Hsp90 inhibition as a mechanism of action as demonstrated through Hsp70 induction and specific client protein degradation. Compound **10** displayed a superior profile of oral bioavailability and efficacy and was selected as a clinical

candidate; presently, it is being evaluated in multiple phase I clinical trials.

Experimental Section

Determination of Compound Affinity for Hsp90. Test compound affinity for Hsp90 was determined as previously described.[21] Briefly, Hsp90 from porcine spleen extract was isolated by affinity capture on a purine-affinity media. The Hsp90 loaded media was then challenged with test compound at a given concentration, ranging from 0.8 to 500 μM, and the amount of Hsp90 liberated at each concentration was determined by Bradford protein assay. The resulting IC_{50} values were corrected for the ATP ligand concentration and presented as apparent K_d values.

Determination of Cellular Activities of Compounds.[38] All assays were done in 96-well plates. All cell lines were purchased from ATCC. Proliferation rates were measured by seeding cells into 96-well plates, followed by compound addition 24 h later. After addition of compound, cells were allowed to grow for either an additional 72 or 144 h depending on rate of growth. At harvest, media was removed and DNA content for individual wells was determined using CyQuant DNA dye (Invitrogen). Levels of Hsp90 client proteins and phosphoregulated proteins in A375 and AU565 cells were measured by high content analysis (HCA) using an ArrayScan 4.5 (Pittsburgh, PA) instrument after 24 h of treatment with compound, followed by methanol fixation. After fixation in 4% PBS-buffered formalin and permeablization with 0.1% TX-100, cells were probed with anti-Her2 (Millipore), antiphospho-S6 (pS6), anti-pERK (Cell Signaling), and anti-Hsp70 (Assay Design) primary antibodies, followed by TRITC or FITC conjugated secondary antibodies. Nuclei where also stained with Hoechst DNA binding dye. For each well, 250−500 individual nuclei were identified along with the average staining intensity for the client and phosphoproteins for each cell. Average client staining intensities were then calculated for each well.

Pharmacokinetic Studies. In-life work for the pharmacokinetic study was performed at Washington Biotechnology (Columbia, MD). Compound **10** was injected intravenously to one group of 40 female Swiss−Webster mice at 10 mg/kg. Three other groups of 40 animals were dosed orally at 10, 25, and 50 mg/kg. Blood samples were collected from four mice at each time point: 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8, 24, and 48 h after dosing. Whole blood was collected into chilled tubes containing EDTA and NaF, and the blood was converted to plasma in a refrigerated centrifuge. The samples were stored frozen until LC-MS/MS analysis. The concentrations of compounds **9** and **10** in mouse plasma were determined by LC-MS/MS following protein precipitation with acetonitrile. The calibration curve ranges were 3.3−6000 ng/mL and 4.3−7800 ng/mL for **10** and **9**, respectively. The LC-MS/MS system consisted of a Shimadzu Prominence HPLC (Shimadzu, Columbia, MD) coupled to a hybrid triple quadrupole/linear ion trap mass spectrometer with a Turbospray source (QTRAP, Applied Biosystems, Foster City, CA). The samples were injected onto a Synergy Hydro-RP column, 2.0 mm × 30 mm, 4 μm (Phenomenex, Torrance, CA), and the analytes and internal standard were eluted at a flow rate of 0.45 mL/min using a water−methanol gradient in the presence of 0.08 to 0.1% formic acid and 4 mM ammonium formate. The ESI mass spectrometer was operated in positive ion mode using multiple reaction monitoring.

HT-29 Xenograft. In-life work was performed at Piedmont Research Center (Morrisville, NC). Female nude mice (*nu*/*nu*, Harlan) were 11 to 12 weeks old and had a body weight range of 18.7−30.5 g on Day 1 of the study. Compliance was observed with the recommendations of the *Guide for Care and Use of Laboratory Animals* for veterinary care. Xenografts were initiated from HT-29 human colon carcinoma tumors maintained by serial transplantation in athymic nude mice. Each test mouse received a 1 mm^3 HT-29 tumor fragment implanted subcutaneously in the right flank, and the growth of tumors was monitored as the average size approached 80−120 mm^3. Fourteen days later, designated as Day 1 of the study, individual tumor volumes ranged from 63 to 126 mm^3 and the animals were placed into eight groups, each consisting of 10 mice with group mean tumor volumes of 93.2−93.9 mm^3. Micronized **10** was preformulated in 1% microcrystalline cellulose/0.5% Tween80 in water. The solutions were stored at 4 °C during the study and homogenized just prior to dosing. Group 1 vehicle control mice received D5W (5% dextrose) vehicle by oral gavage beginning on Day 1, every other day for three doses, followed by two days without treatment, for three cycles ((qod × 3)/2 × 3 weeks, total of nine doses). Groups 2 to 5 animals received **10** at 5, 10, 25, or 50 mg/kg on the same schedule as vehicle control group ((qod × 3)/2 × 3). Each treatment was administered in a volume of 0.2 mL per 20 g of body weight (10 mL/kg) and was scaled to the body weight of the animal. Tumors were measured twice weekly using calipers.

Chemistry. General. Melting points were recorded using a Stuart SMP3 and are uncorrected. Identity and purity confirmations were performed by LC/UV/MS using a Finnigan Surveyor MSQ system (Thermo Fisher Scientific, Waltham, MA). The diode array detector wavelength was 254 nm, and the MS was operated in positive electrospray ionization mode. The samples were maintained at rt in the autosampler, and an aliquot (5 μL) was injected onto a Thermo BetaBasic-8 column, 50 mm × 4.6 mm, 5 μm (Thermo Fisher Scientific, Waltham, MA) maintained at 35 °C. The samples were eluted at a flow rate of 1 mL/min with a mobile phase system composed of solvent A (water containing 0.1% formic acid) and B (acetonitrile containing 0.08% formic acid) with a linear gradient from 10% B to 90% B in 4 min and then isocratic for 1 min with 90% B. The column was equilibrated back to the initial conditions for 1 min before the next run. High-resolution mass spectroscopic (HRMS) data were provided by Analytical Instrument Group, Inc. (Raleigh, NC). ^{1}H NMR spectra were recorded on a Varian Unity spectrometer at 400 or 300 MHz. Elemental analyses were provided by Prevalere Life Sciences, Inc. (Whitesboro, NY). Purities of all compounds reported here were greater than 95%, by either the LC/UV method described, or elemental analyses, or the two methods combined.

2,6,6-Trimethyl-1,5,6,7-tetrahydroindol-4-one (15a). This compound was prepared as reported previously[24] from 5,5-dimethyl-1,3-cyclohexanedione (20.0 g, 142.7 mmol) and chloroacetone (11.36 mL, 142.7 mmol) over two steps (5 g, 20%) as a tan solid. LCMS m/z = 178.2 $[M + H]^+$, t_R = 2.94 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.01 (bs, 1H, NH), 5.87 (s, 1H), 2.55 (s, 2H), 2.11 (s, 5H), 0.99 (s, 6H); mp = 189.6−191.1 °C. HRMS calcd for $C_{11}H_{15}NO$ 178.1232 $[M + H]^+$, found 178.1231.

6,6-Dimethyl-1,5,6,7-tetrahydroindol-4-one (15b). 3-Amino-5,5-dimethyl-cyclohex-2-enone (**16**, 1.0 g, 7.2 mmol) and glyoxal (40% in H_2O, 1.04 mL, 7.2 mmol) were dissolved in AcOH and H_2O (7:1, 5 mL) solution and warmed to 65 °C. When the reaction temperature had reached 65 °C, Zn powder (923 mg, 14.4 mmol) was added portionwise. Once the addition was complete, the reaction was heated to 90 °C and allowed to stir overnight. After 18 h, the reaction was cooled. The reaction was diluted with H_2O and extracted with EtOAc (3 × 30 mL). The organics were combined and washed with H_2O (2 × 20 mL), once with saturated $NaHCO_3$ solution (20 mL) and once with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. The yellow oil was loaded onto a Biotage column (25 mm) and eluted with solvent gradient (5−65% EtOAc in hexanes). The pure fractions were combined and concentrated to give **15b** (352 mg, 30%) as yellowish solid. LCMS m/z = 164 $[M + H]^+$, t_R = 3.64 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.59 (bs, 1H), 6.69 (s, 1H),

6.19 (s, 1H), 2.77 (m, 2H), 2.18 (m, 2H), 0.97 (s, 6H); mp = 171.2−172.1 °C. HRMS calcd for $C_{10}H_{13}NO$ 164.1076 $[M + H]^+$, found 164.1075.

3,6,6-Trimethyl-1,5,6,7-tetrahydro-indol-4-one (15c). To a solution of *anti*-pyruvic aldehyde-1-oxime (10 g) and 5,5-dimethyl-1,3-cyclohexanedione (16.1 g) in AcOH and H_2O (7:3, 200 mL) was added zinc powder (14.95 g) slowly using a water bath to keep the reaction mixture at rt. The mixture was then refluxed overnight, concentrated to dryness, and partitioned between brine (300 mL) and dichloromethane (300 mL). The pH was adjusted to ca. 6 with saturated aqueous $NaHCO_3$, and then the mixture was extracted with dichloromethane (3 × 200 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography eluting with 5% ethyl acetate in dichloromethane. The combined organic fractions were concentrated, triturated in ether−hexanes (2:1) for 1 h, filtered, and washed with hexanes to give **15c** (9 g, 45%) as a solid. LCMS m/z = 178.2 $[M + H]^+$, t_R = 2.58 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (bs, 1H), 6.41 (s, 1H), 2.55 (s, 2H), 2.14 (s, 2H), 2.11 (s, 3H), 0.98 (s, 6H); mp = 161.3−162.9 °C.HRMS calcd for $C_{11}H_{15}NO$ 178.1232 $[M + H]^+$, found 178.1231.

2,3,6,6-Tetramethyl-1,5,6,7-tetrahydro-indol-4-one (15d). This was prepared by the same procedure as for **15c**. Treatment of 2,3-butanedione monoxime (10 g, 99 mmol) with dimedone (13.9 g, 99 mmol) in acetic acid (96 mL) and water (41 mL) with zinc powder (12.7 g, 198 mmol) afforded **15d** (5.6 g, 30%) as a yellow solid. LCMS m/z = 192.2 $[M + H]^+$, t_R = 2.81 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.79 (bs, 1H), 2.55 (s, 2H), 2.10 (s, 2H), 2.02 (s, 3H), 2.00 (s, 3H), 0.98 (s, 6H); mp = 227.0−228.8 °C. HRMS calcd for $C_{12}H_{17}NO$ 192.1389 $[M + H]^+$, found 192.1388.

3-Methyl-1,5,6,7-tetrahydro-indol-4-one (15e). This was prepared by the same procedure as for **15c**. Treatment of *anti*-pyruvic aldehyde-1-oxime (4 g, 46 mmol) and 1,3-cyclohexanedione (5.14 g, 46 mmol) in AcOH and H_2O (7:3, 85 mL) with zinc powder (5.9 g, 92 mmol) afforded **15e** (1.9 g, 26%) as a solid. LCMS m/z = 150.1 $[M + H]^+$, t_R = 2.04 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.92 (bs, 1H), 6.41 (s, 1H), 2.67 (t, J = 6.16 Hz, 2H), 2.23 (t, J = 6.96 Hz, 2H), 2.11 (s, 3H), 1.99−1.88 (m, 2H); mp = 195.1−197.2 °C. HRMS calcd for $C_9H_{11}NO$ 150.0919 $[M + H]^+$, found 150.0919.

2-Bromo-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (18a). 15a (3.54 g, 20 mmol) and 2-bromo-4-fluorobenzonitrile (4 g, 20 mmol) were dissolved in anhydrous DMF (50 mL). NaH (95%, 960 mg, 40 mmol) was added to the solution, and the reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was cooled to rt and poured to saturated NH_4Cl solution (250 mL), extracted by EtOAc (3 × 150 mL), dried over Na_2SO_4, filtered, concentrated, and purified using a Biotage column eluted with 50% EtOAc in hexanes to give **18a** (4.4 g, 62%). LCMS m/z = 357, 359 $[M + H]^+$, t_R = 3.75 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.12 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.64 (dd, J = 18 and 8.4 Hz, 1H), 6.23 (s, 1H), 2.99 (s, 1H), 2.49 (s, 2H), 2.21 (s, 2H), 2.04 (s, 3H), 0.96 (s, 6H); mp = 160− 164 °C. HRMS calcd for $C_{18}H_{17}N_2OBr$ 357.0603 $[M + H]^+$, found 357.0604.

2-Bromo-4-(6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (18b). Using the same procedure as described for compound **18a**, treatment of **15b** (250 mg, 1.5 mmol) with NaH (61 mg, 1.5 mmol) and 2-bromo-4-fluorobenzonitrile (450 mg, 2.25 mmol) afforded **18b**. LCMS m/z = 343 $[M + H]^+$, t_R = 3.68 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10 (d, J = 6 Hz, 1H), 8.06 (s, 1H), 7.70 (d, J = 5.1 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 6.53 (s, 1H), 2.78 (s, 2H), 2.27 (s, 2H), 0.98 (s, 6H); mp =171.2−172.1 °C. HRMS calcd for $C_{17}H_{15}N_2OBr$ 343.0446 $[M + H]^+$, found 343.0445.

2-Bromo-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (18c). Using the same procedure as described for compound **18a**, treatment of 2-bromo-4-fluorobenzonitrile (13.27 g, 66.4 mmol) with **15c** (9.8 g, 55.3 mmol) afforded **18c** (16.5 g, 84%). LCMS m/z = 357.0 $[M + H]^+$, t_R = 3.95 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.07 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.66 (dd, J = 11.4 and 4.5 Hz, 1H), 6.98 (d, J = 0.9 Hz, 1H), 2.24 (s, 2H), 2.20 (s, 3H), 0.98 (s, 6H); mp = 222.0−225.4 °C. HRMS calcd for $C_{18}H_{17}N_2OBr$ 357.0603 $[M + H]^+$, found 357.0604.

2-Bromo-4-(2,3,6,6-tetramethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (18d). Using the same procedure as described for compound **18a**, treatment of 2-bromo-4-fluorobenzonitrile (0.275 g, 1.37 mmol) with **15d** (0.314 g, 1.64 mmol) yielded **18d** (0.23 g, 46%). LCMS m/z = 371 $[M + H]^+$, t_R = 4.06 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.60 (dd, J = 8.3 and 1.9 Hz, 1H), 2.44 (s, 2H), 2.20 (s, 2H), 2.15 (s, 3H), 1.93 (s, 3H), 0.95 (s, 6H); mp = 204.6−208.8 °C. HRMS calcd for $C_{19}H_{19}N_2OBr$ 371.0759 $[M + H]^+$, found 371.0760.

2-Bromo-4-(3-methyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (18e). Using the same procedure as described for compound **18a**, treatment of 2-bromo-4-fluorobenzonitrile (0.39 g, 1.95 mmol) with **15e** (0.314 g, 1.64 mmol) afforded **18e** (0.41 g, 64%). LCMS m/z = 329 $[M + H]^+$, t_R = 3.64 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.07 (d, J = 6 Hz, 1H), 8.01 (s, 1H), 7.66 (d, J = 6 Hz, 1H), 6.97 (s, 1H), 2.83 (s, 2H), 2.34 (s, 2H), 2.19 (s, 3H), 1.98 (s, 2H); mp = 190.2−198.2 °C. HRMS calcd for $C_{16}H_{13}N_2OBr$ 329.0290 $[M + H]^+$, found 329.0290.

General Procedure for Hydration of Benzonitriles into Benzamides. A crude or purified benzonitrile intermediate (3 mmol) was dissolved in a mixture of EtOH and DMSO (4:1, 10−20 mL), 1 N NaOH aq solution (1−3 mL), and H_2O_2 (30%, 1−2 mL). The reaction mixture was stirred at rt or higher temperature as indicated, for 10 min to 3 h until the disappearance of the benzonitrile by thin layer chromatography (TLC). The mixture was poured into saturated NH_4Cl aq solution (100 mL), extracted with EtOAc (3 × 50 mL), the combined organic layers dried over Na_2SO_4, filtered, and concentrated to give a crude product. This was purified by silica gel chromatography eluted with 10−50% EtOAc in hexanes followed by removal of solvent to give the benzamide.

4-(2,6,6-Trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (11). 15a (600 mg, 3.4 mmol) and 4-fluorobenzonitrile (410 mg, 3.4 mmol) were dissolved in anhydrous DMF (20 mL). NaH (95%, 162 mg, 6.8 mmol) was added to this solution, and the reaction mixture was stirred at 100 °C overnight. The reaction mixture was cooled to rt and poured into saturated NH_4Cl aq solution (250 mL), extracted with EtOAc (3 × 150 mL), dried over Na_2SO_4, filtered, and concentrated to give crude 4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzonitrile (LCMS m/z = 279 $[M + H]^+$; t_R = 3.49 min). Hydration of the benzonitrile afforded **11** (570 mg, 57% two steps). LCMS m/z = 297.2 $[M + H]^+$, t_R = 2.60 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.01 (d, J = 6 Hz, 2H), 7.52 (s, 1H), 7.45 (d, J = 6.3 Hz, 2H), 2.41 (s, 2H), 2.22 (s, 2H), 2.01 (s, 3H), 0.96 (s, 6H); mp = 199.0−203.0 °C. Anal. ($C_{18}H_{20}N_2O_2$) C, H, N.

4-(3,6,6-Trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (19). Using the same procedures as described for compound **11**, treatment of **15c** (177.3 mg, 1 mmol) with 4-fluorobenzonitrile (121.1 mg, 1 mmol) afforded **19** (237.1 mg, 80% two steps) as a white powder. LCMS m/z = 297.2 $[M + H]^+$, t_R = 2.75 min. ^{1}H NMR (400 MHz DMSO-d_6): δ 8.05 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 6.86 (s, 1H), 2.69 (s, 2H), 2.24 (s, 2H), 2.20 (s, 3H), 0.97 (s, 6H); mp = 246.8−248.0 °C. HRMS calcd for $C_{18}H_{20}N_2O_2$ 297.1604 $[M + H]^+$, found 297.1603.

2-(Pentyl)-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydroindol-1-yl)-benzamide (20a). 18a (200 mg, 0.56 mmol), pentylzinc bromide solution (0.5 M in THF, 2.24 mL, 1.12 mmol), and $PdCl_2$(dppf) (20.4 mg, 0.028 mmol) were placed in a microwave vial. The reagents were stirred and the vessel purged with nitrogen. The reaction vessel was sealed and heated to 85 °C for 600 s. Upon cooling, the reaction was quenched with 10% HCl, and washed with EtOAc (3×). The organic layer was washed with saturated $NaHCO_3$ (1×), brine (1×), and dried over $MgSO_4$. Solvent was removed in vacuo. The residue crude benzonitrile was hydrated at 50 °C for 2 h to afford **20a** as a white powder (28 mg, 14%). LCMS m/z = 367.2 $[M + H]^+$, t_R = 3.49 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.88 (bs, 1H), 7.47 (bs, 1H), 7.44 (s, 1H), 7.21−7.19 (m, 2H),

6.20 (d, J = 0.9 Hz, 1H), 2.78 (t, J = 7.5 Hz, 2H), 2.40 (s, 2H), 2.21 (s, 2H), 2.01 (s, 3H), 1.59−1.54 (m, 2H), 1.28−1.22 (m, 4H), 0.96 (s, 6H), 0.83 (t, J = 6.6 Hz, 3H); mp = 176.6−177.8 °C. Anal. ($C_{23}H_{30}N_2O_2$) C, H, N.

2-(Butoxy)-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydroindol-1-yl)-benzamide (20b). 18a (71 mg, 0.2 mmol), butanol (0.5 mL), and NaH (9.6 mg, 0.4 mmol) were placed in a microwave vial. The reagents were stirred, and the vessel purged with nitrogen. The reaction vessel was sealed and heated to 100 °C for 600 s. Upon cooling, the reaction mixture was treated with 1 N KOH (11.2 mg, 0.2 mmol) and H_2O_2 (0.47 mL). After stirring this solution at 50 °C for 2 h, the mixture of nitrile and amide was purified by column chromatography (silica, gradient EtOAc in hexanes) to afford **20b** as a white powder (36.4 mg, 49%). LCMS m/z = 369.2 $[M + H]^+$, t_R = 3.49 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (d, J = 8.1 Hz, 1H), 7.65 (bs, 1H), 7.59 (bs, 1H), 7.12 (d, J = 2.1 Hz, 1H), 6.99 (dd, J = 6.3, 2.1 Hz, 1H), 6.20 (d, J = 0.9 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 2.44 (s, 2H), 2.21 (s, 2H), 2.04 (s, 3H), 1.76−1.69 (m, 2H), 1.46−1.38 (m, 2H), 0.97 (s, 6H), 0.91 (t, J = 8.1 Hz, 3H); mp = 197.0−199.0 °C. HRMS calcd for $C_{22}H_{28}N_2O_3$ 369.2180 $[M + H]^+$, found 369.2177.

2-Phenylsulfanyl-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (20c). Using the same procedure as described for **20b**, treatment of **18a** (100 mg, 0.28 mmol), thiophenol (0.0286 mL, 0.28 mmol) with NaH (14.1 mg, 0.56 mmol) in DMF (1 mL) gave **20c** (23%). LCMS m/z = 405.1 $[M + H]^+$, t_R = 3.23 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.08 (bs, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.63 (bs, 1H), 7.54−7.51 (m, 2H), 7.46−7.43 (m, 3H), 7.22 (dd, J = 6.3, 2.1 Hz, 1H), 6.58 (d, J = 1.8 Hz, 1H), 6.11 (d, J = 0.3 Hz, 1H), 2.48 (s, 2H), 2.16 (s, 2H), 1.87 (s, 3H), 0.88 (s, 6H); mp = 109.0−113.0 °C. HRMS calcd for $C_{24}H_{24}N_2O_2S$ 405.1638 $[M + H]^+$, found 405.1637.

2-(Butylamino)-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (21a). 18a (200 mg, 558 μmol), $Pd(OAc)_2$ (13 mg, 56 μmol), DPPF (31 mg, 56 μmol), and potassium phosphate (355 mg, 1.7 mmol) were dissolved in dioxane (4 mL) followed by *n*-butylamine (144 mg, 1.7 mmol) and the solution bubbled with nitrogen for 1 h. More *n*-butylamine (144 mg, 1.7 mmol) was added and the mixture heated to 100 °C under nitrogen for 16 h. The reaction mixture was treated with water (15 mL), and extracted with toluene (2 × 15 mL). The toluene layers were added to a column and chromatographed (silica gel, 0 to 50% ethyl acetate in hexanes) to give the intermediate nitrile as a crystalline solid (120 mg, 61%). The benzonitrile (80 mg) was hydrated to give **21a** (46 mg, 54%) as a white powder. LCMS m/z = 368.2 $[M + H]^+$, t_R = 3.58 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (t, J = 5.2 Hz, 1H), 7.92 (bs, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.26 (bs, 1H), 6.51 (d, J = 1.8 Hz, 1H), 6.43 (dd, J = 6.4, 1.8 Hz, 1H), 6.17 (s, 1H), 3.09 (m, 2H), 2.45 (s, 2H), 2.21 (s, 2H), 2.04 (s, 3H), 1.48−1.56 (m, 2H), 1.31−1.40 (m, 2H), 0.97 (s, 6H), 0.89 (t, J = 7.3 Hz, 3H); mp = 253−255 °C. HRMS calcd for $C_{22}H_{29}N_3O_2$ 368.2339 $[M + H]^+$, found 368.2339.

2-[(2-Methoxyethyl)amino]-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (21b). 18a (100 mg, 0.28 mmol), 2-methoxyethylamine (84.1 mg, 1.12 mmol), $Pd(OAc)_2$ (9.4 mg, 5 mol %), DPPF (15.5 mg, 10 mol %), and NaO*t*Bu (53.8 mg, 0.56 mmol) were treated using the same procedure as for **21a** followed by hydration at 50 °C for 2 h to afford **21b** as a yellow powder (43.9 mg, 43%). LCMS m/z = 370.2 $[M + H]^+$, t_R = 2.93 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (bs, 1H), 7.92 (bs, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.26 (bs, 1H), 6.56 (s, 1H), 6.45 (d, J = 1.5 Hz, 1H), 6.17 (s, 1H), 3.49 (t, J = 5.1 Hz, 2H), 3.32 (s, 5H), 2.49 (s, 2H), 2.21 (s, 2H), 2.04 (s, 3H), 0.97 (s, 6H); mp = 221−222 °C. HRMS calcd for $C_{21}H_{27}N_3O_3$ 370.2133 $[M + H]^+$, found 370.2132.

2-(Phenylamino)-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydroindol-1-yl)benzamide (21c). 18a (107.2 mg, 0.3 mmol), aniline (111.8 mg, 1.2 mmol), $Pd(OAc)_2$ (10.1 mmol, 5 mol %), DPPF (16.6 mg, 10 mol %), and NaO*t*Bu (57.7 mg, 0.6 mmol) were treated using the same procedure as for **21a** followed by hydration at 50 °C for 2 h to afford **21c** as a yellow powder (55.6 mg, 47%). LCMS m/z = 388.1 $[M + H]^+$, t_R = 3.48 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (bs, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.61 (bs, 1H), 7.34 (s, 1H), 7.30 (d, J = 7.5 Hz, 2H), 7.20 (d, J = 7.2 Hz, 2H), 7.02 (t, J = 2.21 Hz, 1H), 6.90 (s, 1H), 6.72 (d, J = 1.2 Hz, 1H), 6.15 (s, 1H), 2.43 (s, 2H), 2.19 (s, 2H), 1.96 (s, 3H), 0.95 (s, 6H); mp = 224−226 °C. HRMS calcd for $C_{24}H_{25}N_3O_2$ 388.2026 $[M + H]^+$, found 388.2024.

2-(4-Methoxy-phenylamino)-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (21d). 18a (71.5 mg, 0.2 mmol), *p*-anisidine (98.5 mg, 0.8 mmol), $Pd(OAc)_2$ (6.7 mg, 5 mol %), DPPF (11.1 mg, 10 mol %), and NaO*t*Bu (38.4 mg, 0.4 mmol) were treated using the same procedure as for **21a** followed by hydration at 50 °C for 2 h to afford **21d** as a yellow powder (43.9 mg, 43%). LCMS m/z = 418.2 $[M + H]^+$, t_R = 3.40 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (bs, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.58 (bs, 1H), 7.18 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.2 Hz, 1H), 6.59 (s, 1H), 6.13 (s, 1H), 3.71 (s, 3H), 2.40 (s, 2H), 2.18 (s, 2H), 2.00 (s, 3H), 0.94 (s, 6H); mp = 221−222 °C. HRMS calcd for $C_{25}H_{27}N_3O_3$ 418.2133 $[M + H]^+$, found 418.2130.

2-[(3,4,5-Trimethoxyphenyl)amino]-4-(2,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (22a). Using the same methods as described for compound **21d**, the title compound **22a** (1.786 g) was prepared from **18a**. LCMS m/z = 478.2 $[M + H]^+$, t_R = 3.25 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (bs, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.58 (bs, 1H), 6.84 (s, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.51 (s, 2H), 6.14 (s, 1H), 3.72 (s, 6H), 3.59 (s, 3H), 2.98 (s, 1H), 2.42 (s, 2H), 2.18 (s, 2H), 1.96 (s, 3H), 0.93 (s, 6H); mp = 246.0−247.0 °C. Anal. ($C_{27}H_{31}N_3O_5$) C, H, N.

2-[(3,4,5-Trimethoxyphenyl)amino]-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (22c). Using the same methods as described for compound **21d**, the title compound **22c** (28.4 mg, 20%) was prepared from treatment of **18c** (107.1 mg, 0.3 mmol) with 3,4,5-trimethoxyaniline (219.9 mg, 1.2 mmol), Pd $(OAc)_2$ (3.4 mg, 5 mol %), DPPF (16.6 mg, 10 mol %), and NaO*t*Bu (57.7 mg, 0.6 mmol) followed by nitrile hydration, as a yellow powder. LCMS m/z = 478.2 $[M + H]^+$, t_R = 3.38 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 8.10 (bs, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.50 (bs, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.77 (s, 1H), 6.76 (dd, J = 8.4 and 2.4 Hz, 1H), 6.54 (s, 1H), 3.82 (s, 6H), 3.61 (s, 3H), 2.55 (s, 2H), 2.14 (s, 2H), 2.11 (s, 3H), 0.98 (s, 6H); mp = 125.6−128.2 °C. HRMS calcd for $C_{27}H_{31}N_3O_5$ 478.2345 $[M + H]^+$, found 478.2340.

4-(6,6-Dimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)-2-[(3,4,5-trimethoxyphenyl)amino]benzamide (22b). Using the same procedure as described for compound **21d**, **18b** (150 mg, 0.44 mmol) was converted to **22b** (0.103 g, 81%). LCMS m/z = 464.2 $[M + H]^+$, t_R = 3.18 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13 (bs, 1H), 7.83 (d, J = 6 Hz, 1H), 7.57 (bs, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 6.77 (d, J = 6.3 Hz, 1H), 6.55 (s, 1H), 6.44 (s, 1H), 3.73 (s, 6H), 3.61 (s, 3H), 2.64 (s, 2H), 2.24 (s, 2H), 0.94 (s, 6H); mp = 145.2−146.7 °C. HRMS calcd for $C_{26}H_{29}N_3O_5$ 464.2182 $[M + H]^+$, found 464.2182.

4-(3-Methyl-4-*oxo*-4,5,6,7-tetrahydroindol-1-yl)-2-(3,4,5-trimethoxyphenylamino)benzamide (22e). Using the same procedure as described for compound **21d**, **18e** (0.227 g, 0.7 mmol) was converted to **22e** (0.199 g, 66%). LCMS m/z = 450 $[M + H]^+$, t_R = 3.15 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 8.10 (bs, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.50 (bs, 1H), 6.98 (s, 1H), 6.77 (s, 1H), 6.76 (dd, J = 8.4, 8.4 Hz, 1H), 6.54 (s, 2H), 3.62 (s, 3H), 2.76 (t, J = 6.0 Hz, 2H), 2.48 (s, 6H), 2.31 (s, 2H), 2.16 (s, 3H), 1.97−1.93 (m, 2H); mp = 134.3−137.0 °C. Anal. ($C_{25}H_{27}N_3O_5$) C, H, N.

3-Bromo-4-cyanophenylhydrazine (23). In a clean, dry 250 mL round-bottom flask, 2-bromo-4-fluorobenzonitrile (25.34 g) was dissolved in THF (50 mL) under N_2. To this solution was slowly added anhydrous hydrazine (50 mL). The solution color changed from yellow to red−orange. The reaction was allowed to stir at rt for 16 h. A yellow−white crystalline solid precipitated

from the solution. The mixture was then diluted with THF (50 mL) to dissolve the solids. The organic layer was then washed with saturated sodium bicarbonate solution until the pH of the organic layer was approximately 8.5. The organic layer was isolated, and the solvent was removed under reduced pressure to give a white solid. This was place in a fritted glass funnel and washed with water (1.5 L), followed by diethyl ether (ca. 200 mL). The ether wash was then combined with the white solid and dried under reduced pressure. Title compound **23** was isolated as a fluffy, white or off-white solid (23.43 g, 87.2%). LCMS m/z = 212.1 $[M + H]^+$, t_R = 2.13 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (s, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 2 Hz, 1H), 6.71 (dd, J = 8.7, 2 Hz, 1H), 4.38 (bs, 2H); mp = 143.4−146.5 °C.

2-Bromo-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (24a). In a clean, dry 20 mL microwave reaction vial, **23** (2.49 g) was combined with 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione (2.14 g). The contents of the vial were dissolved in ethanol and acetic acid (12 mL, 3:1). The vial was sealed and agitated on a vortex. The vial was then placed in the microwave reactor and heated to 150 °C for 15 min. The vial was then cooled and placed in a refrigerator for 1 h. The cooled solution was then diluted with water (8 mL) and poured onto a fritted glass funnel. The orange solid was washed with H_2O (100 mL), followed by ethanol (25 mL). The solid was then dried under reduced pressure. Title compound **24a** was obtained as a light-orange crystalline solid (3.75 g, 89%). LCMS m/z = 358.3 $[M + H]^+$, t_R = 3.75 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 2 Hz, 1H), 7.79 (dd, J = 2, 8.2 Hz, 1H), 2.99 (s, 2H), 2.39 (s, 3H), 2.32 (s, 2H), 1.01 (s, 6H); mp = 196.8−198.2 °C. HRMS calcd for $C_{17}H_{16}N_3OBr$ 358.0555 $[M + H]^+$, found 358.0556.

2-(*trans*-4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indazol-1-yl)-benzamide (25a). A microwave vial was charged with **24a** (2 g, 5.58 mmol), *trans*-4-aminocyclohexanol (1.29 g, 11.1 mmol), $Pd(OAc)_2$ (64 mg, 5 mol %), DPPF (312 mg, 10 mol %), and NaO*t*Bu (1.08 g, 11.1 mmol). The reagents were suspended in toluene (15 mL) and were heated with microwave to 170 °C for 3 h. After allowing the reaction vessel to cool, the suspension was filtered and the filtrate evaporated. The residue was purified by flash chromatography, and the benzonitrile was hydrated to yield **25a** (0.8 g, 67%) as a yellow powder. LCMS m/z = 411.2 $[M + H]^+$, t_R = 2.60 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.35 (d, J = 7.8 Hz, 1H), 7.88 (bs, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.22 (bs, 1H), 6.75 (d, J = 1.8 Hz, 1H), 6.65 (dd, J = 8.6, 1.8 Hz, 1H), 3.46 (m, 1H), 2.92 (s, 2H), 2.38 (s, 3H), 2.32 (s, 2H), 1.97 (m, 2H), 1.82 (m, 2H), 1.27 (m, 4H), 0.99 (s, 6H); mp = 133.8−136.1 °C. HRMS calcd for $C_{23}H_{30}N_4O_3$ 411.2398 $[M + H]^+$, found 411.2398.

4-Fluoro-2-(4-*trans*-hydroxy-cyclohexylamino)-benzonitrile (26). 2,4-Difluorobenzonitrile (50.0 g, 0.359 mol), *trans*-4-aminocyclohexanol (41.4 g, 0.359 mol), and diisopropylethylamine (62.6 mL, 0.359 mol) were dissolved in DMSO (300 mL). The reaction vessel was outfitted with a reflux condenser to avoid loss of diisopropylethylamine. The reaction mixture was then placed in an oil bath that had been preheated to 150 °C and was stirred at this temperature for 20 min. The solution was then cooled, poured into saturated aqueous NH_4Cl (750 mL), and extracted with EtOAc (200 mL × 3). The combined organics were washed with brine (150 mL × 3), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (1:1 EtOAc in hexanes) to afford **26** (20.9 g, 25%) as a white powder. LCMS m/z = 235.1 $[M + H]^+$, t_R = 1.77 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (m, 1H), 6.64 (m, 1H), 6.42 (m, 1H), 5.76 (bs, 1H), 4.54 (m, 1H), 3.28−3.43 (m, 2H), 1.81 (m, 4H), 1.31 (m, 4H); mp = 126.2−128.9 °C. HRMS calcd for $C_{13}H_{15}N_2OF$ 235.1247 $[M + H]^+$, found 235.1246.

4-Hydrazino-2-(4-*trans*-hydroxy-cyclohexylamino)-benzonitrile (27). 26 (537 mg, 2.29 mmol) was dissolved in hydrazine (2 g, 64 mmol) and heated to 60 °C and stirred for 30 min. The mixture was partially concentrated and then partitioned between EtOAc (25 mL) and half saturated $NaHCO_3$ (25 mL). The organic layer was dried by $MgSO_4$ and concentrated to give **27** (400 mg, 70%) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 (bs, 3H), 8.76 (bs, 1H), 7.37 (m, 1H), 6.42 (m, 1H), 6.26 (m, 1H), 5.39 (bs, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 1.93 (m, 4H), 1.38 (m, 4H); mp = 216−127.5 °C. HRMS calcd for $C_{13}H_{18}N_4O$ 247.1559 $[M + H]^+$, found 247.1559.

5,5-Dimethyl-2-propionyl-cyclohexane-1,3-dione (28a). 5,5-Dimethyl-1,3-cyclohexanedione (14 g, 100 mmol) and DMAP (3.7 g, 30 mmol) were dissolved in methylene chloride (100 mL) and treated with Hunig's base (17.5 mL, 100 mmol). A solution of propionyl chloride (9.25 g, 100 mmol) in methylene chloride (25 mL) was added dropwise. The mixture was heated to reflux. After 2 h, TLC showed mostly product with a trace of the intermediate. The mixture was concentrated then partitioned between 1 N HCl (50 mL) and hexanes−EtOAc (2:1, 150 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$, concentrated, and chromatographed using a Biotage column (40 mm) eluted with EtOAc in hexanes (0 to 20%) to give **28a** (17.56 g, 89%). LCMS m/z = 197.2 $[M + H]^+$, t_R = 3.53 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.95 (q, J = 7.2 Hz, 2H), 2.25−2.65 (bs, 4H), 1.01 (t, J = 7.2 Hz, 3H), 0.97 (s, 6H); mp = 37.7−38.5 °C. HRMS calcd for $C_{11}H_{16}O_3$ 197.1180 $[M + H]^+$, found 197.1177.

2-(Isobutyryl)-5,5-dimethylcyclohexane-1,3-dione (28b). 5,5-Dimethyl-1,3-cyclohexanedione (1 g, 7.13 mmol) and DMAP (260 mg, 2.14 mmol) were dissolved in methylene chloride (10 mL) and treated with Hunig's base (920 mg, 7.13 mmol). Isobutyric anhydride (1.13 g, 7.13 mmol) was added dropwise and the mixture stirred. After 4 days, the solution was diluted with dichloroethane (10 mL) and heated to 65 °C for 1 d. The mixture was concentrated and partitioned between 1 N HCl (15 mL) and hexanes (15 mL). The organic layer was added to a column and the aqueous layer was extracted with more hexanes (5 mL), which was also added to a column. The mixture was chromatographed (silica gel, 0 to 20% EtOAc in hexanes) to give **28b** (195 mg, 14%) as an oil. LCMS m/z = 211.2 $[M + H]^+$, t_R = 3.88 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.85 (sept, J = 6.8 Hz, 1H), 2.27−2.66 (bs, 4H), 1.03 (d, J = 6.8 Hz, 6H), 0.98 (s, 6H).

2-(2-Cyclopropylacetyl)-5,5-dimethylcyclohexane-1,3-dione (28c). To 5,5-dimethyl-1,3-cyclohexanedione (6.93 g, 49.4 mmol), cyclopropylacetic acid (3.4 mL, 33 mmol), and DMAP (6.04 g, 49.4 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added dropwise a solution of *N*,*N*-dicyclohexylcarbodiimide (8.15 g, 39.5 mmol) in CH_2Cl_2 (90 mL). The solution was allowed to warm to 25 °C and stirred for 14 h. The crude mixture was filtered through celite and concentrated. It was taken up in EtOAc (200 mL) and washed with 2 M aqueous HCl (2 × 200 mL). The aqueous layer was back-extracted with EtOAc (200 mL). The combined organic portions were washed with saturated aqueous NaCl (200 mL) and dried over Na_2SO_4. Purification by gradient flash chromatography, eluted with EtOAc in hexanes (0% to 25%) provided **28c** (6.2 g, 85%) as a pale yellow oil. LCMS m/z = 223.1 $[M + H]^+$, t_R = 3.86 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.54 (bs, 3H), 8.76 (bs, 1H), 7.37 (m, 1H), 6.42 (m, 1H), 6.26 (m, 1H), 5.39 (bs, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 1.93 (m, 4H), 1.38 (m, 4H). HRMS calcd for $C_{13}H_{18}O_3$ 223.1336 $[M + H]^+$, found 223.1334.

4-(3-Ethyl-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-indazol-1-yl)-2-(4-hydroxy-cyclohexylamino)-benzamide (29a). 28a (107 mg, 1 equiv) and **27** (140 mg, 1 equiv) were combined in AcOH and EtOH (1:5, 20 mL) and microwaved at 120 °C for 10 min. The reaction mixture was concentrated to dryness, and residue crude benzonitrile hydrated to afford **29a** (130 mg, 56%). LCMS m/z = 425.2 $[M + H]^+$, t_R = 2.83 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (d, J = 7.6 Hz, 1H), 7.88 (b, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.21 (b, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.66 (dd, J = 8.5, 2.0 Hz, 1H), 4.57 (d, J = 4.1 Hz, 1H), 3.51−3.42 (m, 1H), 2.92 (s, 2H), 2.8 (q, J = 7.5 Hz, 2H), 2.32 (s, 2H), 2.00−1.96 (m, 2H), 1.83−1.79 (m, 2H), 1.36−1.21 (m, 4H), 1.81 (t, J = 7.5 Hz, 3H), 0.99 (s, 6H); mp =

201.1−202.6 °C. HRMS calcd for $C_{24}H_{32}N_4O_3$ 425.2555 $[M + H]^+$, found 425.2552.

2-[(*trans*-4-Hydroxycyclohexyl)amino]-4-(3-isopropyl-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (29b). **28b** (120 mg, 0.57 mmol), **27** (130 mg, 0.46 mmol), and sodium acetate (59 mg, 0.71 mmol) were combined in methanol (4 mL) and stirred at rt for 16 h. The reaction mixture was concentrated and the residue hydrated to give **29b** (126 mg, 63%) as a pink solid. Half of the material was recrystallized from methanol/water for analysis. LCMS m/z = 439 $[M + H]^+$, t_R = 3.13 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (d, J = 7.7 Hz, 1H), 7.88 (bs, 1H), 7.71 (d, J = 8.7 Hz, 1H), 7.20 (bs, 1H), 6.77 (d, J = 1.8 Hz, 1H), 6.67 (dd, J = 1.8, 8.7 Hz, 1 H), 4.56 (d, J = 4 Hz, 1H), 3.47 (m, 1H), 3.29 (m, 1H) 2.92 (s, 2H), 2.33 (s, 2H), 1.94−2.03 (m, 2H), 1.77−1.86 (m, 2H), 1.14−1.38 (m, 5H), 1.24 (d, J = 6.8 Hz, 6H), 0.99 (s, 6H); mp 191−192 °C. HRMS calcd for $C_{25}H_{34}N_4O_3$ 439.2711 $[M + H]^+$, found 439.2709.

4-[3-(Cyclopropylmethyl)-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*trans*-4-hydroxycyclohexyl)amino]benzamide (29c). 28c (253 mg, 1.14 mmol) and **27** (281 mg, 1.14 mmol) in a mixture of EtOAc, EtOH, and AcOH (4:3:1, 2.2 mL) was stirred at 150 °C for 16 h. The reaction mixture was diluted with EtOAc (20 mL) and stirred at 25 °C for 16 h. The reaction mixture was then washed with saturated $NaHCO_3$ (1 × 50 mL), and the aqueous layer was back-extracted with EtOAc (1 × 20 mL). The reaction was concentrated and purified by column chromatography eluted with 75% EtOAc in hexanes to provide 4-(3-cyclopropylmethyl-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydroindazol-1-yl)-2-(4-hydroxycyclohexylamino)-benzonitrile (220 mg, 45%) as an orange solid. The benzonitrile was hydrated to provide **29c** (215 mg, 94%) as a white solid. LCMS m/z = 451.2 $[M + H]^+$, t_R = 3.10 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (d, J = 7.6 Hz, 1H), 7.71 (bs, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.04 (bs, 1H), 6.61 (d, J = 1.9 Hz, 1H), 6.50 (dd, J = 8.5, 1.9 Hz, 1H), 4.38 (d, J = 4.1 Hz, 1H), 3.34−3.24 (m, 1H), 3.13−3.09 (m, 1H), 2.77 (s, 2H), 2.54 (d, J = 6.9 Hz, 2H), 2.16 (s, 2H), 1.85−1.78 (m, 2H), 1.68−1.60 (m, 2H), 1.20−0.90 (m, 3H), 0.83 (s, 6H), 0.24−0.18 (m, 2H), 0.03−0.01 (m, 2H); mp = 214.5−218.9 °C. Anal. ($C_{26}H_{34}N_4O_3$) C, H, N.

3,3-Dimethyl-5-(*p*-tolylsulfonylhydrazono)-cyclohexanone (30). This compound was prepared as previously reported[37] from 5,5-dimethyl-1,3-cyclohexanedione (7.0 g, 49.9 mmol) and *p*-toluenesulfonylhydrazide (9.3 g, 49.9 mmol) in heated toluene (300 mL) as a light-yellow solid (14.26 g, 93%): LCMS m/z = 309.1 $[M + H]^+$, t_R = 2.68 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.74 (bs, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 2.48 (s, 2H), 2.36 (s, 3H), 2.04 (s, 2H), 1.90 (s, 2H), 0.87 (s, 6H); mp = 201.5−202.7 °C. HRMS calcd for $C_{15}H_{20}N_2O_3S$ 309.1275 $[M + H]^+$, found 309.1272.

6,6-Dimethyl-3-trifluoromethyl-1,5,6,7-tetrahydro-indazol-4-one (31a). To a suspension of **30** (4.0 g, 12.97 mmol) in a mixture of THF (72 mL) and triethylamine (24 mL) was added trifluoroacetic anhydride (1.8 mL, 12.97 mmol). The dark-red reaction mixture was heated at 55 °C. After 15 min, the reaction mixture was homogeneous. After 2 h, the reaction mixture was cooled to rt. Methanol (16 mL) and a 1:1 solution of water and 1 M aqueous sodium hydroxide (16 mL) were added. After stirring for 3 h, the reaction mixture was diluted with 50 mL of saturated aqueous ammonium chloride and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was filtered through a plug of silica gel and eluted with ethyl acetate. The filtrate was concentrated in vacuo, and the residue was treated with ether. The solids were collected by filtration and washed with ether. The filtrate was concentrated in vacuo, and the resulting residue was treated with ether. The solids were collected by filtration, washed with ether, and combined with the initial solids to provide **31a** (1.24 g, 41%) as a reddish-orange solid. LCMS m/z = 233.2 $[M + H]^+$, t_R = 2.92 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.78 (s, 2H); 2.35 (s, 2H), 1.01 (s, 6H); mp = 209−214 °C. HRMS calcd for $C_{10}H_{11}N_2OF_3$ 233.0902 $[M + H]^+$, found 233.0901.

3-Difluoromethyl-6,6-dimethyl-1,5,6,7-tetrahydro-indazol-4-one (31b). The title compound (3.12 g, 50.6%) was prepared using the same procedure as for **31a** from **30** (8.86 g) and difluoroacetic anhydride (5 g) in a mixture of THF (100 mL) and triethylamine (30 mL). LCMS m/z = 215.2 $[M + H]^+$, t_R = 2.51 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.04 (t, 1H, J = 53 Hz), 2.76 (s, 2H); 2.32 (s, 2H), 1.01 (s, 6H); mp = 145.1−146.8 °C. HRMS calcd for $C_{10}H_{12}N_2OF_2$ 215.0996 $[M + H]^+$, found 215.0997.

2-Bromo-4-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (32a). NaH (168 mg, 7.02 mmol) was added to a solution of **31a** (1.63 g, 7.02 mmol) in anhydrous DMSO (35 mL). After 15 min, 2-bromo-4-fluorobenzonitrile (2.25 g, 11.23 mmol) was added as a solid. The reaction mixture was heated at 45 °C. After 23 h, the reaction mixture was cooled to rt and quenched with saturated aqueous NH_4Cl (10 mL). The mixture was diluted with water and extracted with EtOAc (4×). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified on a Biotage column (SiO_2, hexanes−EtOAc) to afford **32a** (1.83 g, 63%) as an off-white powder. LCMS m/z = 412.0 $[M + H]^+$, t_R = 4.06 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 8.4 and 2.1 Hz, 1H), 3.03 (s, 2H), 2.43 (s, 2H), 1.02 (s, 6H); mp = 168.0−172.0 °C. HRMS calcd for $C_{17}H_{13}N_3OBrF_3$ 412.0273 $[M + H]^+$, found 412.0273.

2-Bromo-4-(6,6-dimethyl-4-*oxo*-3-difluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-benzonitrile (32b). Compound **32b** was prepared (2.82 g, 49.2%) as a white solid using the same procedure as for **32a** from **31b** (3.12 g) and 2-bromo-4-fluorobenzonitrile (4.67 g). LCMS m/z = 394 $[M + H]^+$, t_R = 3.88 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (m, 2H), 7.86 (dd, J = 8.4, 1.8 Hz, 1H), 7.22 (t, J = 54 Hz, 1H), 3.03 (s, 2H), 2.48 (s, 2H), 1.02 (s, 6H); mp = 163.5−165.7 °C. HRMS calcd for $C_{17}H_{14}N_3OBrF_2$ 394.0367 $[M + H]^+$, found 394.0368.

4-[6,6-Dimethyl-4-*oxo*-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*trans*-4-hydroxycyclohexyl)amino]benzamide (9). A microwave vial was charged with **32a** (0.080 g, 0.19 mmol), *trans*-4-aminocyclohexanol (0.044 g, 0.38 mmol), $Pd(OAc)_2$ (2.5 mg, 5 mol %), DPPF (11.1 mg, 10 mol %), and NaO*t*Bu (0.038 g, 0.38 mmol). The reagents were suspended in toluene (0.5 mL) and were heated in a microwave to 170 °C for 3 h. After cooling, the suspension was filtered and the filtrate evaporated. The residue was purified by flash chromatography to afford 4-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(4-hydroxy-cyclohexylamino)-benzonitrile. LC/MS m/z = 447 $[M + H]^+$. The benzonitrile (17.1 g, 38.3 mmol) was hydrated to afford **9** (15.0 g, 84%) as a white amorphous owder. LCMS m/z = 465.2 $[M + H]^+$, t_R = 3.11 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36 (d, J = 7.72 Hz, 1H), 7.94 (bs, 1H), 7.76 (d, J = 8.44 Hz, 1H), 7.29 (bs, 1H), 6.86 (s, 1H), 6.69 (dd, J = 8.4, 1.96 Hz, 1H), 3.51−3.41 (m, J = 4.24 Hz, 1H), 2.95 (s, 2H), 2.43 (s, 2H), 1.99−1.95 (m, 2H), 1.82−1.78 (m, 2H), 1.35−1.15 (m, 4H), 1.02 (s, 6H); mp = 265.2−266.3 °C. Anal. ($C_{23}H_{27}N_4O_3F_3$) C, H, N.

4-[3-(Difluoromethyl)-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*trans*-4-hydroxycyclohexyl)amino]benzamide (33). **32b** (0.394 g, 1 mmol), *trans*-4-aminocyclohexanol (0.288 g, 2.5 mmol), $Pd(OAc)_2$ (11.2 mg, 5 mol %), DPPF (55.4 mg, 10 mol %), and NaO*t*Bu (0.192 g, 2 mmol) were suspended in toluene (2 mL). The reaction was microwaved at 120 °C for 20 min, cooled, and concentrated. The residue was diluted with H_2O, extracted with EtOAc (3×). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (CH_2Cl_2) to afford 4-[3-(difluoromethyl)-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*trans*-4-hydroxycyclohexyl)amino]benzonitrile. The benzonitrile was hydrated to afford **33** (0.165 g, 37%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.37 (d, J =

7.5 Hz, 1H), 7.94 (bs, 1H), 7.75 (d, J = 7.1 Hz, 1H), 7.28 (bs, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.68 (dd, J = 7.1 and 1.8 Hz, 1H), 4.57 (d, J = 4.2, 1H), 3.47−3.44 (m, 1H), 2.96 (s, 2H), 2.40 (s, 2H), 1.99−1.97 (m, 2H), 1.82−1.79 (m, 2H), 1.37−1.22 (m, 5H), 1.01 (s, 6H); mp = 155.0−158.0 °C. Anal. ($C_{23}H_{28}N_4O_3F_2$) C, H, N.

Amino-acetic Acid 4-[2-Carbamoyl-5-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-phenylamino]-cyclohexyl Ester Methanesulfonate (10). A mixture of **9** (44.8 g, 96.45 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (37.0 g, 192.9 mmol), 4-dimethylaminopyridine (1.18 g, 9.645 mmol), and *N*-(*tert*-butoxycarbonyl)glycine (33.8 g, 192.9 mmol) in CH_2Cl_2 (1 L) was stirred at rt for overnight. The reaction mixture was poured into H_2O (1 L), the organics were collected, and the aqueous layer was extracted 2 times with CH_2Cl_2 (500 mL). The organics were combined and washed one time each with saturated $NaHCO_3$, 1 N HCl, and brine. The organics were then dried over Na_2SO_4 and concentrated to a pale-yellow oil and then purified on a Biotage column eluted with EtOAc in hexanes (30−80%). Pure fractions were combined and concentrated to give *tert*-butoxycarbonylamino-acetic acid 4-[2-carbamoyl-5-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-phenylamino]-cyclohexyl ester (49.31 g). LCMS m/z = 622 $[M + H]^+$. This compound (49.31 g, 79.32 mmol) was suspended in CH_2Cl_2, cooled to 0 °C, and a mixture of trifluoroacetic acid and CH_2Cl_2 (150 mL, 1:1) was added dropwise over 10 min. The reaction was then stirred at 0 °C for 10 min, and at rt for 90 min. To the resulting suspension was added H_2O (1 L) and K_2CO_3 (77 g, 555 mmol). This was stirred for 10 min and then filtered to give amino-acetic acid 4-[2-carbamoyl-5-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-phenylamino]-cyclohexyl ester (25.6 g). LCMS m/z = 522 $[M + H]^+$. This free amine (25.6 g, 49.1 mmol) was suspended in a mixture of CH_2Cl_2 and MeOH (700 mL, 4:1), and methanesulfonic acid (3.18 mL, 49.1 mmol) was added. After stirred for 90 min, the mixture was filtered under vacuum to afford **10** (27.5 g) as a white powder. LCMS m/z = 522.3 $[M + H]^+$, t_R = 2.38 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (s, 3H), 7.99 (bs, 1H), 7.78 (d, J = 8.44 Hz, 1H), 7.32 (bs, 1H), 6.88 (d, J = 1.92 Hz, 1H), 6.72 (dd, J = 8.4, 1.96 Hz, 1H), 4.86−4.80 (m, 1H), 3.81−3.79 (m, 2H), 2.96 (s, 2H), 2.43 (s, 2H), 2.30 (s, 3H), 2.05−2.02 (m, 2H), 1.95−1.91 (m, 2H), 1.63−1.54 (m, 2H), 1.42−1.33 (m, 2H), 1.01 (s, 6H); mp = 297.7−298.9 °C. Anal. ($C_{26}H_{34}N_5O_7SF_3$) C, H, N.

4-[6,6-Dimethyl-4-*oxo*-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*trans*-4-hydroxycyclohexyl)amino]benzamide (9), Alternative Synthesis. NaH (225 mg, 9.39 mmol) was added to a solution of **31a** (1.98 g, 8.54 mmol) in *N*,*N*-dimethylacetamide (17.1 mL) at rt. After gas evolution ceased, **26** (2.0 g, 8.54 mmol) was added and the flask was fitted with a condenser and heated to 150 °C. After 6 h, the reaction mixture was cooled to rt, poured into saturated aqueous NH_4Cl (200 mL), and extracted with methyl *t*-butyl ether (100 mL × 3). The combined organic layers were washed with brine (100 mL × 2), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (1:1 EtOAc in hexanes) to give 4-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(4-hydroxy-cyclohexylamino)-benzonitrile (2.91 g, 76%). LCMS m/z = 447.5 $[M + H]^+$. The benzonitrile was hydrated to **9** (2.7 g, 90%). LCMS m/z = 465.4 $[M + H]^+$. All analytical data were identical to those of the same compound made by the previous method.

2-(*trans*-4-Hydroxy-cyclohexylamino)-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (34). A microwave vial was charged with **18c** (1.072 g, 3 mmol), *trans*-4-aminocyclohexanol (1.382 g, 12 mmol), $Pd(OAc)_2$ (33.7 mg, 5 mol %), DPPF (166.3 mg), and NaO*t*Bu (576.7 mg, 6 mmol). The reagents were suspended in toluene (20 mL) and were heated with a microwave to 115 °C for 12 min. After allowing the reaction vessel to cool, the suspension was filtered and the filtrate evaporated. The residue was purified by flash chromatography, and hydration of the benzonitrile yielded **34** (575 mg, 47%) as a yellow powder. LCMS m/z = 410.2 $[M + H]^+$, t_R = 2.89. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.10 (d, J = 5.44 Hz, 1H), 7.44 (d, J = 6.64 Hz, 1H), 7.26 (s, 1H), 6.55 (d, J = 17.88 Hz, 2H), 6.44 (d, J = 6.64 Hz, 1H), 3.75 (bs, 1H), 2.66 (s, 2H), 2.15 (d, J = 8.76 Hz, 2H), 2.05 (bs, 4H), 1.59 (s, 3H), 1.49−1.37 (m, 5H), 1.26 (t, J = 5.52 Hz, 2H), 1.08 (s, 6H); mp = 170.7−173.4 °C. Anal. ($C_{24}H_{31}N_3O_3$) C, H, N.

2-[(*trans*-4-Hydroxycyclohexyl)amino]-4-(2,3,6,6-tetramethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (35). 15d (1.91 g, 10 mmol) was dissolved in DMAC (60 mL). NaH (360 mg, 15 mmol) was added, and the reaction mixture was allowed to stir at rt for 30 min. **26** (2.34 g, 10 mmol) was added, and the reaction mixture was stirred at 150 °C for overnight. Upon completion, the crude reaction mixture was poured into saturated NH_4Cl aq solution, extracted with EtOAc (3 × 300 mL), dried over Na_2SO_4, filtered, and concentrated to give 2-[(*trans*-4-hydroxycyclohexyl)amino]-4-(2,3,6,6-tetramethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzonitrile. This was hydrated to give **35** (500 mg, 12% for 2 steps). LCMS m/z = 424.20 $[M + H]^+$, t_R = 2.96 min; mp = 194.9−199.0 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, J = 6.2 Hz, 1H), 8.24 (d, J = 5.7 Hz, 1H), 7.89 (bs, 1H), 7.69(d, J = 5.7 Hz, 1H), 7.23 (bs, 1H), 3.49−3.41 (m, 1H), 2.66 (s, 2H), 2.42 (s, 3H), 2.28 (s, 3H), 2.15 (m, 2H), 2.05 (bs, 4H), 1.49−1.37 (m, 5H), 1.16 (t, J = 5.1 Hz, 2H), 0.95 (s, 6H). Anal. ($C_{25}H_{33}N_3O_3$) C, H, N.

2-(Tetrahydro-pyran-4-ylamino)-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,-tetrahydro-indazol-1-yl)-benzamide (36). Using the same procedure as described for compound **34**, treatment of **24a** (1.26 mmol, 450 mg) with $Pd(OAc)_2$ (0.06 mmol, 14 mg), 4-aminotetrahydropyran (2.52 mmol, 255 mg), DPPF (0.13 mmol, 70 mg), and NaO*t*Bu (2.52 mmol, 242 mg) followed by hydration of the benzonitrile yielded **36** (69%). LCMS m/z = 397.2 $[M + H]^+$, t_R = 2.83 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (d, J = 10.2 Hz, 1H), 7.86 (bs, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.23 (bs, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.67 (dd, J = 6.6, 1.8 Hz, 1H), 3.83 (m, 2H), 3.63 (m, 1H), 3.43 (m, 2H), 2.90 (s, 2H), 2.38 (s, 3H), 2.31 (s, 2H), 1.95 (m, 2H), 1.39 (m, 2H), 0.99 (s, 6H); mp = 171.8−174.6 °C. Anal. ($C_{22}H_{28}N_4O_3$) C, H, N.

2-(Cyclopent-3-enylamino)-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indazol-1-yl)benzamide (37). Using the same procedure as described for compound **34**, treatment of **24a** (2.00 g, 5.6 mmol) with $Pd(OAc)_2$ (64 mg, 5% mmol), 1-amino-3-cyclopentene hydrochloride salt (1.34 g, 11.2 mmol), DPPF (328 mg, 10% mmol), sodium hydroxide (0.5 M, 2.24 mL, 11.2 mmol), and NaO*t*Bu (1.13 g, 11.2 mmol) followed by hydration of the benzonitrile yielded **37** (2.8 g, 63%). LCMS m/z = 379.2 $[M + H]^+$, t_R = 3.38 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.53 (d, J = 6.6 Hz, 1H), 7.91 (bs, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.24 (bs, 1H), 6.74 (d, J = 1.8 Hz, 1H), 6.69 (dd, J = 8.1, 2.1 Hz, 1H), 5.75 (s, 2H), 4.17−4.11 (m, 1H), 2.93 (s, 2H), 2.84−2.76 (m, 2H), 2.52 (s, 2H), 2.38 (s, 3H), 2.31 (s, 2H), 2.17 (dd, J = 15 and 3.3 Hz, 2H), 1.00 (s, 6H); mp = 165.0−168.2 °C. HRMS calcd for $C_{22}H_{26}N_4O_2$ 379.2135 $[M + H]^+$, found 379.2133.

4-(3-Difluoromethyl-6,6-dimethyl-4-*oxo*-4,5,6,7-tetrahydro-indazol-1-yl)-2-(tetrahydro-thiopyran-4-ylamino)-benzamide (38). Using the same procedure as described for compound **34**, treatment of **32b** (2.54 mmol, 1.00 g) with $Pd(OAc)_2$ (0.13 mmol, 29 mg), 4-aminotetrahydrothiopyran (1.30 mmol, 423 mg), DPPF (0.27 mmol, 150 mg), and NaO*t*Bu (5.37 mmol, 516 mg) followed by hydration of the benzonitrile yielded **38** (77%). LCMS m/z = 449.1 $[M + H]^+$, t_R = 3.58 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (d, J = 8.1 Hz, 1H), 7.99 (bs, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.34 (bs, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.71 (dd, J = 6.3, 2.1 Hz, 1H), 3.53−3.50 (m, 1H), 2.95 (s, 2H), 2.76−2.61 (m, 4H), 2.39 (s, 2H), 2.21−2.19 (m, 2H), 1.97−1.96 (s, 1H), 1.59−1.52 (m, 2H), 1.01 (s, 6H); mp = 209.0−210.3 °C. Anal. ($C_{22}H_{26}N_4O_2SF_2$) C, H, N.

2-(Cyclobutylamino)-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (39). Using the same procedure as described for compound **34**, treatment of **24a** (1.00 mmol, 357 mg) with $Pd(OAc)_2$ (0.13 mmol, 30 mg), aminocyclobutane (3.0 mmol, 0.26 mL), DPPF (0.10 mmol, 56 mg), and NaO*t*Bu (2.0 mmol, 192 mg) followed by hydration of the

benzonitrile yielded **39** (72%). LCMS m/z = 367.2 $[M + H]^+$, t_R = 3.38 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, J = 6 Hz, 1H), 7.86 (bs, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.24 (bs, 1H), 6.70 (dd, J = 2.1 and 0.3 Hz, 1H), 6.60 (d, J = 2.1 Hz, 1H), 3.93 (m, 1H), 2.90 (s, 2H), 2.38 (m, 5H), 2.31 (s, 2H), 1.78 (m, 4H), 0.99 (s, 6H); mp = 197.3−200.4 °C. Anal. ($C_{21}H_{26}N_4O_2$) C, H, N.

2-[(Cyclopropylmethyl)amino]-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (40). Using the same procedure as described for compound **34**, treatment of **24a** (351.6 mg, 0.96 mmol) with cyclopropanemethylamine (139.6 mg, 1.92 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), DPPF (54.4 mg, 0.1 mmol), and NaO*t*Bu (188.6 mg, 1.92 mmol) followed by hydration of the benzonitrile afforded **40** (285 mg, 83% over 2 steps). LCMS m/z = 367.2 $[M + H]^+$, t_R = 3.32 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.41 (t, J = 4.8 Hz, 1H), 7.91 (bs, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.24 (bs, 1H), 6.73 (d, J = 1.8 Hz, 1H), 6.65 (dd, J = 8.4 and 1.8 Hz, 1H), 3.09−2.98 (m, 2 H), 2.92 (s, 2H), 2.38 (s, 3H), 2.31 (s, 2H), 1.10−1.05 (m, 1H), 0.99 (s, 6H), 0.53−0.44 (m, 2H), 0.26−0.21 (m, 2H); mp = 184.0−187.0 °C. Anal. ($C_{21}H_{26}N_4O_2$) C, H, N.

2-{[(1*S*)-1-Phenylethyl]amino}-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (41). Using the same procedure as described for compound **34**, treatment of **18c** (420.8 mg) with (*S*)-methylbenzylamine (299.8 mL.), $Pd(OAc)_2$ (13.2 mg), DPPF (65.3 mg), and NaO*t*Bu (226.4 mg) followed by hydration of the benzonitrile afforded **41** (126 mg, 27%). LCMS m/z = 416.2 $[M + H]^+$, t_R = 3.77 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (d, J = 6.6 Hz, 1H), 8.00−7.93 (m, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.33 (s, 1H), 7.32 (m, 4H), 7.23−7.17 (m, 1H), 6.58 (d, J = 0.9 Hz, 1H), 6.48 (dd, J = 8.3 and 2.0 Hz, 1H), 6.30 (d, J = 2.1 Hz, 1H), 4.67−4.62 (m, 1H), 2.93 (s, 1H), 2.69 (s, 1H), 2.11 (s, 2H), 1.43 (d, J = 6.6 Hz, 3H), 0.85 (s, 3H), 0.82 (s, 3H); mp = 82.9−86.8 °C.

2-[(2-Furylmethyl)amino]-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (42). Using the same procedure as described for compound **34**, treatment of **24a** (396.6 mg, 1 equiv) with furfurylamine (204.8 mL, 2 equiv), $Pd(OAc)_2$ (12.4 mg, 5% equiv), DPPF (61.4 mg, 10% equiv), and NaO*t*Bu (212.8 mg, 2 equiv) followed by hydrolysis of the benzonitrile afforded **42** (105 mg, 25%). LCMS m/z = 393.2 $[M + H]^+$, t_R = 3.43 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.73 (bs, 1H), 7.94 (bs, 1H), 7.75 (bs, 1H), 7.59−7.58 (m, 1H), 7.32 (bs, 1H), 6.84 (bs, 1H), 6.78−6.70 (m, 1H), 6.40−6.38 (m, 1H), 6.32 (bs, 1H), 4.42 (bs, 2H), 2.81 (s, 2H), 2.37 (s, 3H), 2.30 (s, 2H), 0.98 (s, 6H); mp = 172.6−176.4 °C. HRMS calcd for $C_{22}H_{24}N_4O_3$ 393.1929 $[M + H]^+$, found 393.1928.

2-{[2-(Methylthio)ethyl]amino}-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (43). Using the same procedure as described for compound **34**, treatment of **24a** (1.81 g, 5.14 mmol) with $Pd(OAc)_2$ (56 mg, 0.25 mmol), 2-(methylthio)ethylamine (0.95 mL, 10.28 mmol), DPPF (0.28 g, 0.51 mmol), and NaO*t*Bu (0.99 g, 10.28 mmol) followed by hydration of the benzonitrile yielded **43** (1.48 g, 75%). LCMS m/z = 387.2 $[M + H]^+$, t_R = 3.16 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.50 (t, J = 5.7 Hz, 1H), 7.91 (bs, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.26 (bs, 1H), 6.78 (d, J = 2.2 Hz, 1H), 6.69 (dd, J = 8.7 and 2.2 Hz, 1H), 3.36 (m, 2H), 2.92 (s, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.38 (s, 3H), 2.33 (s, 2H), 2.10 (s, 3H), 0.99 (s, 6H); mp = 104.8−106.8 °C. Anal. ($C_{20}H_{26}N_4O_2S$) C, H, N.

2-{[2-(Methylsulfonyl)ethyl]amino}-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (44). To a solution of **43** (3.07 g, 7.94 mmol) in $CHCl_3$ (45 mL) was added MCPBA (2.74 g, 15.88 mmol), and the reaction mixture was stirred at rt for 1 h. The solvent was evaporated under vacuum, and $NaHCO_3$ (saturated, 20 mL) was added to the residue. The aqueous phase was extracted with EtOAc (3×). The combined organic layers were dried over Na_2SO_4, and concentrated. Purification of the residue by column chromatography (SiO_2, EtOAc) afforded **44** (0.26 g, 8%). LCMS m/z = 419.1 $[M + H]^+$, t_R = 2.55 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.50 (t, J = 6.1 Hz, 1H), 7.94 (bs, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.31 (bs, 1H), 6.81 (d, J = 1.8 Hz, 1H), 6.76 (dd, J = 8.4 and 1.8 Hz, 1H), 3.63 (q, J = 6.4 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H), 3.02 (s, 3H), 2.95 (s, 2H), 2.39 (s, 3H), 2.31 (s, 2H), 1.00 (s, 6H); mp = 194.1−195.8 °C. Anal. ($C_{20}H_{26}N_4O_4S$) C, H, N.

2-[(2-Methoxy-1-methylethyl)amino]-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indazol-1-yl)benzamide (45). Using the same procedure as described for compound **34**, treatment of **24a** (1.00 mmol, 357 mg) with $Pd(OAc)_2$ (0.13 mmol, 30 mg), 2-amino-1-methoxypropane (2.0 mmol, 0.21 mL), DPPF (0.10 mmol, 56 mg), and NaO*t*Bu (2.0 mmol, 192 mg) followed by hydration of the benzonitrile yielded **45** (77%). LCMS m/z = 385.2 $[M + H]^+$, t_R = 3.07 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (d, J = 7.8 Hz, 1H), 7.89 (bs, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.22 (bs, 1H), 6.79 (d, J = 2.4 Hz, 1H), 6.66 (dd, J = 6.6 and 1.8 Hz, 1H), 3.77−3.69 (m, 1H), 3.40−3.30 (m, 2H), 3.27 (s, 3H), 2.91 (s, 2H), 2.38 (s, 3H), 2.31 (s, 2H), 1.14 (d, J = 6.3 Hz, 3H), 1.00 (s, 3H), 0.99 (s, 3H); mp = 177.2−179.7 °C. Anal. ($C_{21}H_{28}N_4O_3$) C, H, N.

4-[6,6-Dimethyl-4-*oxo*-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}benzamide (46). Using the same procedure as described for compound **34**, treatment of **32a** (0.41 g, 0.984 mmol) with $Pd(OAc)_2$ (11 mg, 0.049 mmol), 1-(3-aminopropyl)pyrrolidinone (0.28 mL, 1.97 mmol), DPPF (0.055 g, 0.098 mmol), and NaO*t*Bu (0.1892 g, 1.97 mmol) followed by hydration of the benzonitrile yielded **46** (0.158 g, 33%). LCMS m/z = 492.2 $[M + H]^+$, t_R = 3.17 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38 (m, 1H), 7.98 (bs, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.35 (bs, 1H), 6.78 (d, 1H), 6.71 (dd, J = 8.4 and 2.1 Hz, 1H), 3.25 (m, 4H), 3.12 (m, 2H), 2.95 (s, 2H), 2.42 (s, 2H), 2.19 (m, 2H), 1.87 (m, 2H), 1.75 (m, 2H), 1.01 (s, 6H); mp = 92.1−93.8 °C. HRMS calcd for $C_{24}H_{28}N_5O_3F_3$ 492.2224 $[M + H]^+$, found 492.2222.

4-[6,6-Dimethyl-4-*oxo*-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-{[2-methoxy-1-(methoxymethyl)ethyl]amino}benzamide (47). 2,4-Difluorobenzonitrile (1.17 g, 8.39 mmol), 2-amino-1,3-dimethoxypropane (1 g, 8.39 mmol), and diisopropylethylamine (1.46 mL, 8.39 mmol) were dissolved in DMSO (10 mL) and stirred at 150 °C for 30 min. The reaction mixture was then cooled to rt and poured into saturated NH_4Cl. The aqueous phase was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by column chromatography (SiO_2, 10% to 20% EtOAc in hexanes) afforded 4-fluoro-2-(2-methoxy-1-methoxymethyl-ethylamino)-benzonitrile (0.376 g, 19%). LCMS m/z = 239 $[M + H]^+$.

4-Fluoro-2-(2-methoxy-1-methoxymethyl-ethylamino)-benzonitrile (0.376 g, 1.58 mmol), **31a** (0.37 g, 1.58 mmol), and NaH (60% in mineral oil, 0.076 g, 1.9 mmol) were suspended in DMF (2 mL). The reaction mixture was microwaved at 200 °C for 10 min, cooled to rt, and treated with saturated NH_4Cl. The aqueous phase was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by column chromatography (SiO_2, 50% EtOAc in hexanes) afforded 4-(6,6-dimethyl-4-*oxo*-3-trifluoromethyl-4,5,6,7-tetrahydro-indazol-1-yl)-2-(2-methoxy-1-methoxymethyl-ethylamino)-benzonitrile (0.515 g, 72%). LCMS m/z = 451 $[M + H]^+$. The benzonitrile was hydrated at rt for 30 min to afford **47** (0.55 g, 100%). LCMS m/z = 469.2 $[M + H]^+$, t_R = 3.52 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.56 (d, J = 5.4 Hz, 1H), 7.98 (bs, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.30 (bs, 1H), 6.94 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 8.1 and 1.8 Hz, 1H), 3.82 (m, 1H), 3.42 (d, J = 5.4 Hz, 4H), 3.28 (s, 6H), 2.96 (s, 2H), 2.43 (s, 2H), 1.02 (s, 6H); mp = 85.3−88.7 °C. Anal. ($C_{22}H_{27}N_4O_4F_3$) C, H, N.

2-(Piperidin-4-ylamino)-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-indol-1-yl)-benzamide (48). Compound **18c** (2.0 g, 5.6 mmol), $Pd(OAc)_2$ (63 mg, 0.3 mmol), 1-*N*-Boc-4-aminopiperidine (4.4 g, 22.4 mmol), DPPF (310 mg, 0.6 mmol), and NaO*t*Bu (1.08 g, 11.2 mmol) were suspended in toluene (20 mL) in a microwave vial and purged for 15 min with N_2. The reaction vessel was placed in the microwave reactor for 15 min at 115 °C.

The mixture was filtered through celite and concentrated to give 4-[2-cyano-5-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-inden-1-yl)-phenylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (1.7 g, 64%) as a yellow solid. This was dissolved in CH_2Cl_2 (50 mL). Trifluoroacetic acid (5.5 mL) was added, and the reaction mixture was stirred at rt. Once TLC analysis showed complete consumption of starting material, the reaction mixture was concentrated in vacuo to give a dark oil of the crude benzonitrile, which was hydrated to afford **48**. LCMS m/z = 395.2 $[M + H]^+$, t_R = 2.13. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, J = 5.7 Hz, 1H), 7.91 (bs, 1H), 7.70 (d, J = 5.7 Hz, 1H), 7.25 (bs, 1H), 6.84 (s, 1H), 6.71 (s, 1H), 6.52 (d, J = 6.3 Hz, 1H), 4.13 (m, 1H), 3.74 (m, 2H), 3.351 (m, 2H), 2.71 (s, 2H), 2.52 (m, 2H), 2.23 (s, 2H), 2.20 (s, 3H), 1.97 (m, 2H), 0.98 (s, 6H); mp: 99.7−101.9 °C. HRMS calcd for $C_{23}H_{30}N_4O_2$ 395.2448 $[M + H]^+$, found 395.2448.

2-[(2-Morpholin-4-ylethyl)amino]-4-(3,6,6-trimethyl-4-*oxo*-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzamide (49). Using the same procedure as described for compound **34**, treatment of **18c** (178 mg, 0.5 mmol) with $Pd(OAc)_2$ (5.6 mg, 0.03 mmol), 4-(2-aminoethyl)morpholine (260 mg, 2.0 mmol), DPPF (28 mg, 0.05 mmol), and NaO*t*Bu (96 mg, 1.0 mmol) followed by hydration of the benzonitrile yielded **49** (105 mg, 49% over 2 steps). LCMS m/z = 425.2 $[M + H]^+$, t_R = 2.02 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.10 (bs, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.21 (bs, 1H), 6.83 (s, 1H), 6.58 (s, 1H), 6.51 (d, J = 7.8 Hz, 1H), 3.57 (s, 4H), 2.70 (s, 2H), 2.53 (s, 2H), 2.40 (s, 4H), 2.23 (s, 2H), 2.19 (s, 3H), 0.97 (s, 6H); mp = 207.0−210.0 °C. HRMS calcd for $C_{24}H_{32}N_4O_3$ 425.2555 $[M + H]^+$, found 425.2552.

4-[6,6-Dimethyl-4-*oxo*-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-indazol-1-yl]-2-[(*cis*-4-hydroxycyclohexyl)amino]benzamide (50). Using the same procedure as described for compound **34**, treatment of **32a** (1.03 g, 2.5 mmol) with $Pd(OAc)_2$ (28 mg, 0.13 mmol), *cis*-4-aminocyclohexanol (862 mg, 7.5 mmol), DPPF (139 mg, 0.3 mmol), and NaO*t*Bu (481 mg, 5.0 mmol) followed by hydration of the benzonitrile yielded **50** (356 mg, 32% over 2 steps). LCMS m/z = 465.2 $[M + H]^+$, t_R = 3.27 min. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.61 (d, J = 7.8 Hz, 1H), 7.98 (bs, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.32 (bs, 1H), 6.83 (d, J = 1.5 Hz, 1H), 6.68 (dd, J = 8.4 and 1.5 Hz, 1H), 3.62 (bs, 1H), 3.48 (bs, 1H), 2.95 (s, 2H), 2.42 (s, 2H), 1.62−1.48 (m, 8H), 1.01 (s, 6H); mp = 154.0−156.0 °C. Anal. ($C_{23}H_{27}N_4O_3F_3$) C, H, N.

Supporting Information Available: Additional analytical data including elemental analyses and LC-UV spectra for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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