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Discovery of 4-Aryl-7-Hydroxyindoline-Based $P2Y_1$ Antagonists as Novel Antiplatelet Agents

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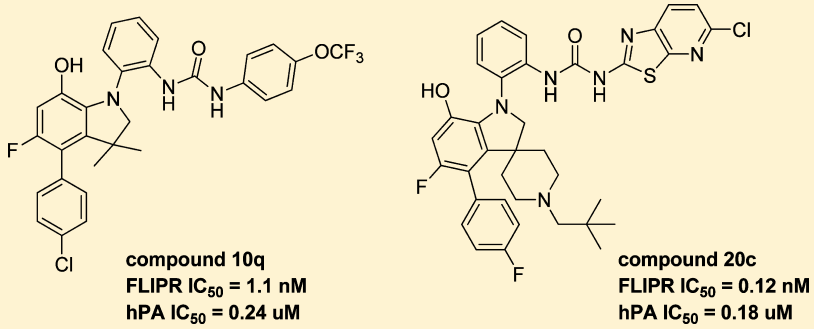

ABSTRACT: Adenosine diphosphate (ADP)-mediated platelet aggregation is signaled through two distinct G protein-coupled receptors (GPCR) on the platelet surface: $P2Y_{12}$ and $P2Y_1$. Blocking $P2Y_{12}$ receptor is a clinically well-validated strategy for antithrombotic therapy. $P2Y_1$ antagonists have been shown to have the potential to provide equivalent antithrombotic efficacy as $P2Y_{12}$ inhibitors with reduced bleeding in preclinical animal models. We have previously reported the discovery of a potent and orally bioavailable $P2Y_1$ antagonist, **1**. This paper describes further optimization of **1** by introducing 4-aryl groups at the hydroxylindoline in two series. In the neutral series, **10q** was identified with excellent potency and desirable pharmacokinetic (PK) profile. It also demonstrated similar antithrombotic efficacy with less bleeding compared with the known $P2Y_{12}$ antagonist prasugrel in rabbit efficacy/bleeding models. In the basic series, **20c** (BMS-884775) was discovered with an improved PK and liability profile over **1**. These results support $P2Y_1$ antagonism as a promising new antiplatelet target.

INTRODUCTION

Adenosine diphosphate (ADP)-mediated platelet aggregation plays a key role in thrombus formation. ADP activation of platelets is signaled through two distinct G-protein coupled receptors (GPCR) on the surface of platelets: $P2Y_{12}$, which is coupled to G-protein i (Gi), and $P2Y_1$, which couples to G-protein q (Gq). ADP is the endogenous activator of the two receptors. Binding of ADP to the $P2Y_1$ receptor results in transitory increases in intracellular free Ca^{2+} and acts as the trigger by stimulating platelets to form small, reversible aggregates.[1] Binding of ADP to the $P2Y_{12}$ receptors results in reduction of cAMP (cyclic adenosine monophosphate) levels and acts as an amplifier of the reaction, driving the reversible aggregates to an irreversible state.[2] Blocking ADP-driven platelet aggregation via $P2Y_{12}$ receptors is a clinically well-validated strategy for antithrombotic therapy. Several successful marketed drugs such as clopidogrel, prasugrel, and ticagrelor are all $P2Y_{12}$ antagonists used to treat peripheral artery disease and acute coronary syndrome (Figure 1).[3] However, there is no clinical validation for $P2Y_1$ antagonists as antithrombotic agents, though preclinically there is ample evidence that blocking the $P2Y_1$ receptor can inhibit platelet aggregation and, consequently, thrombus formation. $P2Y_1$ knockout mice were found to be viable with no apparent developmental abnormalities. They showed no spontaneous bleeding tendency but were resistant to ADP- or collagen-induced acute thromboembolism.[4] The first direct demonstration that inhibition of $P2Y_1$ activity could lead to an antithrombotic effect in vivo was reported by Léon et al.[5] in a model of thromboplastin-induced thromboembolism using a selective $P2Y_1$ antagonist, MRS-2179. Subsequently, MRS-2500[6] and a number of adenine nucleotide-based $P2Y_1$ antagonists had been reported to inhibit ADP activated platelet aggregation in vitro and in vivo. Our in house study with MRS-2500 and the $P2Y_{12}$ antagonist clopidogrel in a rabbit efficacy/bleeding model demonstrated that there are differential effects of $P2Y_1$ antagonism versus $P2Y_{12}$ antagonism on bleeding, with the $P2Y_1$ antagonist MRS-2500 showing the same efficacy but less bleeding compared with the $P2Y_{12}$ antagonist clopidogrel.[7] On the basis of the genetic and pharmacological data, $P2Y_1$ antagonism may offer a new opportunity for the development of novel antiplatelet agents with an improved therapeutic index over $P2Y_{12}$ antagonism.

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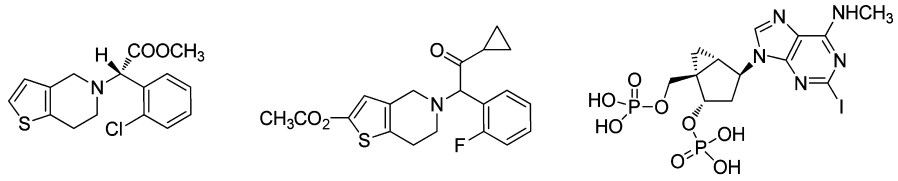

Figure 1. Selected $P2Y_{12}$ and adenine nucleotide-based $P2Y_1$ antagonists.

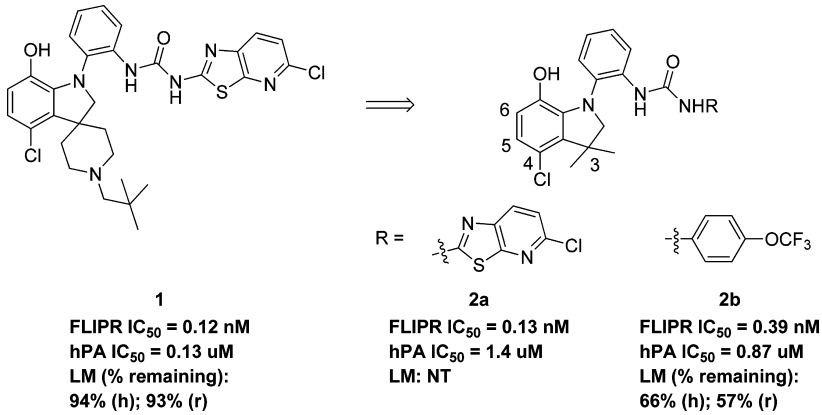

Figure 2. Generation of neutral $P2Y_1$ antagonists from lead compound **1**.

RESULTS AND DISCUSSION

Adenine nucleotide-based $P2Y_1$ antagonists such as MRS-2500 (Figure 1) exhibited potent antagonist activity. However, they are unsuitable as oral drug candidates due to their lack of oral bioavailability. As a result, nonnucleotide $P2Y_1$ antagonists have been sought in an attempt to find another chemotype with potency, oral bioavailability, and desirable pharmacokinetic (PK) properties. A number of novel chemotypes have been disclosed as $P2Y_1$ antagonists from high-throughput screening (HTS) or virtual screening efforts.[8] We had previously reported a series of structure−activity relationship (SAR) studies on the optimization of a biaryl urea HTS hit resulting in the discovery of **1**,[9] a potent and orally available $P2Y_1$ antagonist with an IC_{50} of 120 pM in the FLIPR (fluorescent imaging plate reader) assay and 130 nM in the functional assay (hPA: human platelet-rich plasma was used in the presence of 10 μM ADP). Compound **1** exhibited excellent liver microsomal stability, with greater than 90% remaining after 10 min incubation with human or rat liver microsomes. However, **1** showed potent inhibition of human ether-à-go-go-related gene (hERG) in the patch clamp assay (96% inhibition at 1 μM), though it did not cause significant QTc prolongation in a rabbit EP (electrophysiology) study, most likely due to its high protein binding (rabbit, 99.3% bound). To further expand the SAR on this series and to mitigate the potential off-target liabilities such as hERG inhibition, two closely related series, the neutral series where spiropiperidine was removed and the basic series where the spiropiperidine was retained, were pursued simultaneously. The SAR discoveries in the neutral series were readily applied to the basic series. In the neutral series, removal of the basic nitrogen of the spiropiperidine resulted in analogues as exemplified by **2a** and **2b** (Figure 2). Though **2a** and **2b** retained most of the potency of **1**, liver microsomal stability decreased. Subsequently, metabolic identification studies were performed on these compounds and the C3 *gem*-dimethyl groups were identified as the metabolic soft spots. To improve the metabolic stability of this neutral series, functional groups that had higher oxidation states (alcohol, acid, ester) or a CF_3 group generally known to be metabolically stable were introduced at the C3 position.

The general synthesis of analogues in Tables 1, 2, and 4 (**10p** and **10r**) from the neutral series is shown in Scheme 1. Substituted 2-methoxyanilines **3** were converted to their corresponding hydrazines **4** by treatment with sodium nitrate, followed by reduction with tin(II) chloride in the presence of concentrated HCl. Indolines **5** were prepared via Fisher indoline synthesis by reacting the hydrazines **4** with various 2-substituted propionaldehydes, followed by reduction of the intermediate imines with $NaBH_4$ or $NaBH_3CN$. N-Arylation of indolines **5** with 1-bromo-2-nitrobenzene under Buchwald conditions afforded compounds **6**, which were reduced with Zn/NH_4Cl to give anilines **7**. Ureas **8** could be obtained either by treatment of **7** directly with isocyanate or by first converting **7** to *p*-nitrophenylcarbamate, followed by reacting with aminoheterocycles in the presence of 4-dimethylaminopyridine (DMAP) at 80 °C. Demethylation of compounds **8** (when X = Cl and R = H) with $AlCl_3$ under microwave irradiation or with BCl_3/Bu_4NI or with $BBr_3{\cdot}Me_2S$ at 85 °C afforded final compounds **2a**−**e** in Table 1. Reduction of **2e** by $LiBH_4$ provided **2f**. The 4-aryl-substituted analogues **9** were prepared via Suzuki coupling of compounds **8** (X = Br, Ar = 4-OCF_3Ph) with various boronic acids, followed by demethylation with $AlCl_3$ under microwave condition or with BCl_3/ Bu_4NI.

Alternatively, 4-(4-fluorophenyl) analogues with different urea substitutions in Table 3 and 5-fluoro-4-aryl analogues in Tables 4 (**10o** and **10q**) and 5 can be synthesized by a modified sequence from Scheme 1 as shown in Scheme 2. The 4-aryl groups were introduced earlier in the synthesis via Suzuki coupling of bromide **6** with various arylboronic acids to give compounds **11**, which were reduced to compounds **12** by Zn/NH_4Cl. The ureas **9** were prepared by either treatment with isocyanates or first

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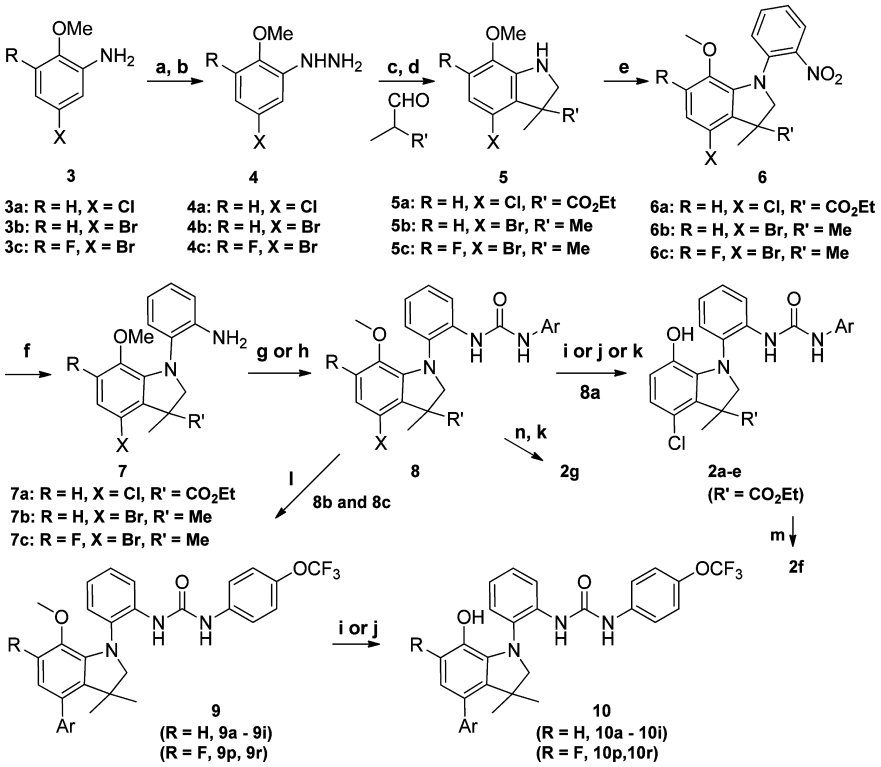
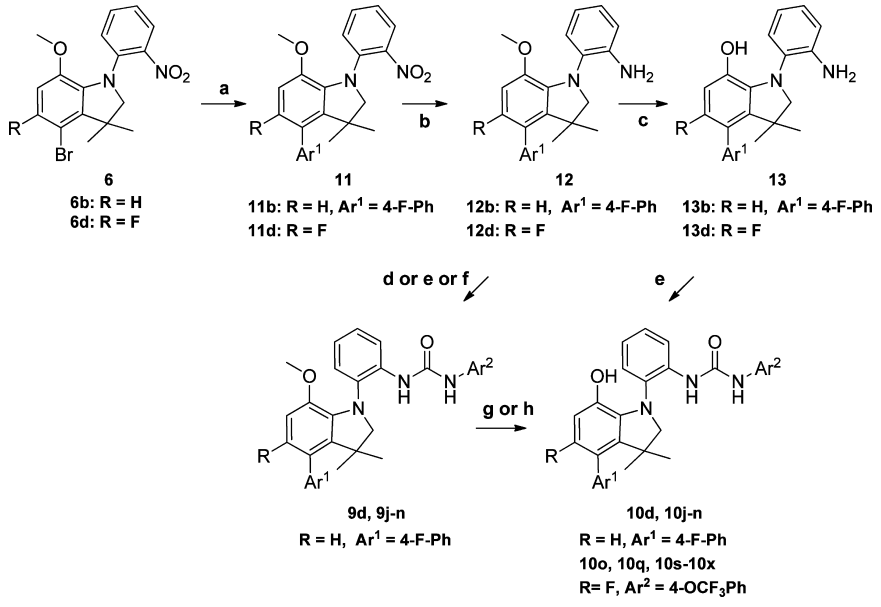
Scheme 1. General Synthesis of Analogues from the Neutral Series[a]



[a]Reagents and conditions: (a) $NaNO_2$, HCl; (b) $SnCl_2$, 34−92% for 2 steps; (c) HCl in dioxane, or H_2SO_4 in EtOH; (d) $NaBH_4$ or $NaBH_3CN$ in MeOH, 15−86%; (e) 1-bromo-2-nitrobenzene, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene, 115 °C, 57−96%; (f) Zn, NH_4Cl, EtOAc/MeOH, 58−100%; (g) OCN-*p*-OCF_3Ph, CH_2Cl_2, 41−98%; (h) $ClCO_2$-*p*-NO_2Ph, K_2CO_3, CH_2Cl_2, then NH_2Ar, DMAP, 80 °C, 5 h, 23−50%; (i) $AlCl_3$, CH_2Cl_2, microwave irradiation, 100 °C, 10 min, 13−22%; (j) BCl_3, Bu_4NI, CH_2Cl_2, −78 °C to rt, 15−82%; (k) BBr_3·Me_2S, 85 °C, 6 h, 22−34%; (l) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 100 °C, 55−100%; (m) $LiBH_4$, THF/toluene, 100 °C, 6 h, 23%; (n) NaOH/THF/MeOH, 6 days, 65%.

Scheme 2. Synthesis of 4-(4-Fluorophenyl) and 5-Fluoro-4-aryl Analogues[a]



[a]Reagents and conditions: (a) arylboronic acids, $Pd(PPh_3)_4$, Na_2CO_3, 100 °C, 84−98%; (b) Zn, NH_4Cl, EtOAc/MeOH, 83−96%; (c) BCl_3, Bu_4NI, CH_2Cl_2, −78 °C to rt, 39−90%; (d) OCN-*p*-OCF_3Ph, CH_2Cl_2, 99%; (e) $ClCO_2$-*p*-NO_2Ph, K_2CO_3, CH_2Cl_2, then NH_2Ar, DMAP, microwave 100 °C, 10 min, 56−96%; (f) 2-methyl- (or 2-chloro-) thiazole-4-carboxylic acid, DPPA, NEt_3, tol. 100 °C, 1 h, 90−94%; (g) BCl_3, Bu_4NI, CH_2Cl_2, −78 °C to rt, 26−97%; (h) $AlCl_3$, CH_2Cl_2, microwave irradiation, 100 °C, 10 min, 13−22%.

activation with *p*-nitrophenyl chloroformate followed by reaction with aminoheterocycles in the presence of DMAP at 80 °C.

For the preparation of 2-chloro or 2-methylthiazole urea analogues **10k** and **10l**, Curtis rearrangement of 2-chloro- (or 2-methyl-)

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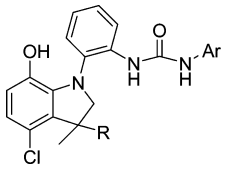
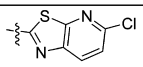
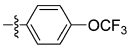
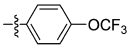
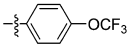
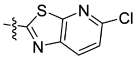
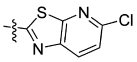
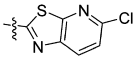
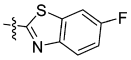
Table 1. Structure–Activity Relationship of C3-Substituted 7-Hydroxylindolines[a]



compd #	Ar	R	FLIPR IC_{50} (nM)[a]	PA IC_{50} (μM)[b]	LM (h, r, m)[c] % remaining
2a		Me	0.14±0.04	1.4±0.24	NT
2b		Me	0.39±0.28	0.87	66, 57, 58
2c		CH_2CF_3	1.96±0.16	2.9	79, 58, 66
2d		CO_2Et	0.09±0.03	3.1	NT
2e		CO_2Et	0.05±0.01	0.61	47, 14, 54
2f		CH_2OH	NT	72%@40 μM	NT[d]
2g		CO_2H	NT	90%@40 μM	NT
2h		CONHMe	NT	46%@40 μM	16, 5, 16

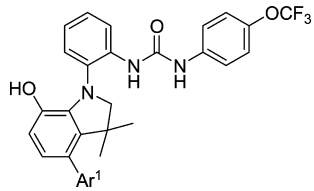
[a]FLIPR was tested with 1 μM 2-methylthio-ADP, $n \geq 2$. [b]PA was tested with 10 μM ADP, $n = 1$ unless shown with ± SD. See ref 9f and SI in ref 9f for detailed assay conditions. [c]Liver microsome stability: percentage of compound (0.5 μM) remaining after incubation for 10 min with 1 mg/mL human, rat, or mouse liver microsomes. [d]NT, not tested.

thiazole-4-carboxylic acid produced isocyanates in situ, which reacted with aniline **12b** to give the ureas **9k** and **9l**. Standard demethylation of ureas **9** provided compounds **10**. Alternatively, **12b** was demethylated first with BCl_3/Bu_4NI to give **13b**, which was converted to compounds **10** following the same urea formation procedures as used to convert from compounds **12** to compounds **9**.

The SAR of the C-3 modifications is shown in Table 1. Replacement of a methyl group with a CH_2CF_3 group resulted in **2c**, which showed a 5-fold loss in FLIPR potency and a 3-fold loss in potency in the PA assay while maintaining the same level of liver microsomal stability as that found for **2b**. Replacement of methyl group with ethyl ester improved FLIPR potency by 4-fold but was 3-fold weaker in PA assay (**2d** vs **2b**). However, when the C3 ethyl ester substitution was combined with 5-chlorothiazolo-[5,4-*b*]pyridine urea, the resulting compound **2e** showed over 2-fold improvement in both FLIPR and PA potency compared with **2a**. Converting the ethyl ester to more polar groups such as alcohol (**2f**), acid (**2g**), or amide (**2h**) all resulted in much reduced $P2Y_1$ activity. Though the C3 ethyl ester replacement showed improved potency, the liver microsomal stability decreased compared with the C3 *gem*-dimethyl analogues. As a result, we shifted our focus to installing bulkier aromatic substitutions at C4 position on the indoline to block the metabolism at C3 methyl groups.

The SAR of C4 aryl substitutions is shown in Table 2. Introducing the phenyl group at the C4 position resulted in a 4-fold improvement in potency compared with 4-chloro substitution as measured in the human PA inhibition assay

Table 2. Structure–Activity Relationship of 4-Aryl-Substituted 7-Hydroxylindolines



compd	Ar^1	FLIPR IC_{50}[a] (nM)	PA IC_{50}[b] (μM)	LM h, r, m[c] (% remaining)
10a	Ph	0.37 ± 0.04	0.18	76, 67, 48
10b	2-F-Ph	0.37 ± 0.20	0.08	62, 54, 48
10c	3-F-Ph	0.15 ± 0.07	0.24	67, 59, 56
10d	4-F-Ph	0.33 ± 0.14	0.16 ± 0.05	87, 89, 83
10e	4-Cl-Ph	0.13 ± 0.04	0.21 ± 0.07	84, 83, 78
10f	4-CF_3-Ph	1.51 ± 0.59	0.23	96, 94, 89
10g	2,4-diF-Ph	0.52 ± 0.28	0.16	81, 72, 79
10h	3,4-diF-Ph	1.8 ± 0.04	0.4	90, 81, 66
10i	3,5-diF-Ph	0.57 ± 0.20	0.18	63, 59, 64

[a]FLIPR was tested with 1 μM 2-methylthio-ADP, $n \geq 2$. [b]PA was tested with 10 μM ADP, $n = 1$ unless shown with ±SD. See ref 9f for detailed assay conditions. [c]Liver microsome stability: percentage of compound (0.5 μM) remaining after incubation for 10 min with 1 mg/mL human, rat, or mouse liver microsomes.

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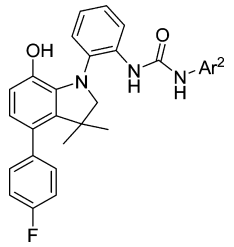
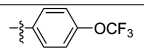
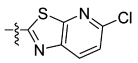
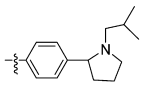
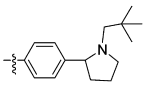
Table 3. Structure–Activity Relationship of Urea Substitutions[a]



compd #	Ar^2	FLIPR IC_{50} (nM)[a]	PA IC_{50} (μM)[b]	LM (h, r, m)[c] % remaining
10d		0.33±0.14	0.16±0.05	87, 89, 83
10j		0.13±0.08	0.23	75, 74, 65
10k		0.03±0.02	0.09±0.04	80, 0, 75
10l		0.08±0.00	0.43	95, 55, 52
10m		0.02±0.01	0.05	58, 39, 53
10n		0.04±0.01	0.09	45, 34, 52

[a]FLIPR was tested with 1 μM 2-methylthio-ADP, $n \geq 2$. [b]PA was tested with 10 μM ADP, $n = 1$ unless shown with ±SD. See ref 9f for detailed assay conditions. [c]Liver microsome stability: percentage of compound (0.5 μM) remaining after incubation for 10 min with 1 mg/mL human, rat, or mouse liver microsomes.

(**10a** vs **2b**). However, the metabolic stability of **10a** was only slightly improved in human and rat liver microsomes. A fluorine "walk" around the C4 phenyl ring was performed to improve the metabolic stability. Of the 2-, 3-, and 4-positions of the phenyl ring, fluoro substitution at the 2- and 4-positions (**10b** and **10d**) provided slightly more potent compounds than at the 3-position (**10c**) in PA assay. Between the 2- and 4-fluorophenyl analogues (**10b** and **10d**), the 4-fluorophenyl analogue **10d** was metabolically more stable than **10b**. While increasing the size of substitutions at the 4-position of phenyl from fluorine (**10d**) to chlorine (**10e**) resulted in analogues with essentially equivalent potency, the CF_3 substitution (**10f**) appeared to be slightly too large, as its potency decreased in both FLIPR and PA assays. The 2,4-, 3,4-, and 3,4-bis-substitutions (**10g–10i**) did not provide any additional boost in potency. As a result, 4-fluoro- and 4-chlorophenyl at the C4 position were chosen as templates to study the SAR of urea substitution.

Shown in Table 3 are some examples of aryl- and heteroaryl-substituted ureas with 4-fluorophenyl attached at the 4-position of the indoline. The 5-chlorothiazolo[5,4-*b*]pyridine urea analogue (**10j**) had comparable potency as the trifluoromethoxyphenyl urea **10d**. From a large number of heteroaryl ureas surveyed, the 2-chlorothiazole urea **10k** was identified with excellent potency (PA IC_{50} 90 pM). The 2-chloro substitution on the thiazole plays a crucial role in increasing potency, as the 2-methylthiazole analogue (**10l**) was found to be 5-fold less potent in the platelet aggregation assay. In an effort to improve the solubility of the neutral series, phenylureas substituted with basic groups such as pyrrolidines were prepared (**10m** and **10n**). Pyrrolidine-substituted phenylureas demonstrated superior potency in both the FLIPR and PA assays; however, their poor liver microsomal stability led to poor PK profiles. In a rat cassette PK study, at 0.5 mg/kg dose, **10m** exhibited high clearance (34 $mL \cdot min^{-1} \cdot kg^{-1}$) and a large volume of distribution (9.8 L/kg) with low oral bioavailability (4%).

Though the 7-hydroxy-4-arylindoline series of compounds demonstrated excellent potency, there was concern that they might be prone to oxidation due to the electron-rich nature of the ring system. To reduce the electron density of the 7-hydroxylindoline ring system, various electron-withdrawing groups were introduced at the 5- and 6- positions, with only fluorine being tolerated at either position (Table 4). The 5-fluoro analogue (**10o**) showed comparable potency and microsomal stability when compared to the unsubstituted compound **10d**. Between the 5-fluoro (**10o** and **10q**) and 6-fluoro analogues (**10p** and **10r**), the 5-fluoro analogues were slightly more potent (**10o** vs **10p** and **10q** vs **10r**) with comparable microsomal stability. As a result, subsequent SAR study focused on the 5-fluoro series.

In addition to phenyl and substituted phenyl groups at the C4 position, 5- and 6-membered heteroaryls were also explored (Table 5). A variety of heterocycles such as chlorothiophene (**10s**) as well as pyridines (**10t** and **10u**), pyrimidine (**10w**), and pyridazine (**10x**) afforded good potency. In general, small hydrophobic substituents such as halogens and the CF_3 group helped maintain the potency of these analogues.

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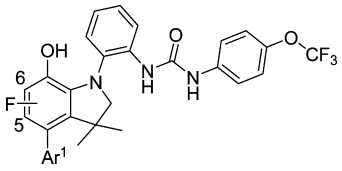
Table 4. 4-Aryl-5 (or 6)-F Analogues



compd		Ar^1	FLIPR IC_{50}[a] (nM)	PA IC_{50}[b] (μM)	LM h, r, m,[c] (% remaining)
10d		4-F-Ph	0.33 ± 0.14	0.16 ± 0.05	87, 88, 83
10o	5-F	4-F-Ph	0.23 ± 0.12	0.19 ± 0.07	73, 84, 77
10p	6-F	4-F-Ph	0.45(n = 1)	0.39	80, 71, 66
10q	5-F	4-Cl-Ph	1.06 ± 0.48	0.24 ± 0.09	83, 90, 79
10r	6-F	4-Cl-Ph	NT	0.30	88, 100, 80

[a]FLIPR was tested with 1 μM 2-methylthio-ADP, $n \geq 2$. [b]PA was tested with 10 μM ADP, n = 1 unless shown with ± SD. See ref 9f for detailed assay conditions. [c]Liver microsome stability: percentage of compound (0.5 μM) remaining after incubation for 10 min with 1 mg/mL human, rat, or mouse liver microsomes.

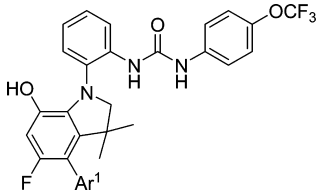
From the 4-aryl-7-hydroxylindoline neutral series, a large number of analogues were identified with desired in vitro profiles (excellent $P2Y_1$ potency and good liver microsomal stability). To differentiate these compounds, rat cassette PK studies[10] (4 in 1) were utilized, from which **10q** was found to have the best overall profile. As shown in Table 4, **10q** was found to be a potent $P2Y_1$ antagonist (FLIPR IC_{50} 1.1 nM; PA IC_{50} 0.24 μM) with good liver microsomal stability (greater than 80% remaining for all species). In a rat discrete PK study, upon dosing in solution (0.5 mg/kg iv and 15 mg/kg oral) with dimethylacetamide (DMAc)/cremophor/EtOH/water (10/10/10/70) as the vehicle, **10q** exhibited a desired profile of low clearance (1.3 $mL \cdot min^{-1} \cdot kg^{-1}$), small volume of distribution (0.4 L/kg), and good $t_{1/2}$ (12 h) with moderate oral bioavailability of 10%. As a result, **10q** was chosen to proceed to rabbit efficacy and bleeding models (in rabbit, **10q** showed PA IC_{50} = 0.087 μM).

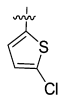
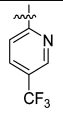
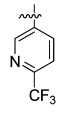
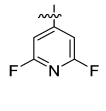
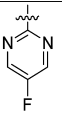
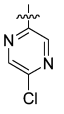
Antithrombotic activity was evaluated by thrombus weight reduction in a rabbit model of electrically induced carotid artery thrombosis (ECAT).[11] Bleeding time (BT) was measured for up to 20 min following cuticle incision. Compound **10q** was infused intravenously (iv), starting 30 min before electrical stimulation and maintained throughout the experiment. As shown in Figure 3, **10q** at doses of 0.003 + 0.01, 0.01 + 0.033, 0.03 + 0.1, 0.1 + 0.033, and 0.3 + 1 mg/kg + $mg \cdot kg^{-1} \cdot h^{-1}$ iv reduced thrombus formation by 22% ± 3%, 46% ± 3%, 50% ± 4%, 72% ± 3%, and 95% ± 3%, respectively, versus 3% ± 2% for the vehicle-treated group (n = 5–6 per group). It increased BT by (1.1 ± 0.1)-fold, (1.4 ± 0.1)-fold, (2.7 ± 0.2)-fold, (3.7 ± 0.2)-fold, and (4.7 ± 0.1)-fold versus (1 ± 0.05)-fold for the vehicle (n = 5–8 per group).

In rabbits, **10q** prevented arterial thrombosis as effectively as the $P2Y_{12}$ antagonists clopidogrel and prasugrel. However, at 90% antithrombotic dose, **10q** produced 4.7-fold increase in BT, which was less than the 6-fold BT increases produced by clopidogrel and prasugrel at 80% antithrombotic dose in the same model.

Despite the encouraging profile of **10q**, it could not proceed further into development due to its lower oral bioavailability and exposure when dosed as a suspension, a direct result of its poor aqueous solubility (less than 1 μg/mL, amorphous). However, the issue of lack of aqueous solubility of the neutral series could be solved in the basic series. We also postulated that since the bulky 4-aryl group could block the metabolism at C3, it might also be able to shield the basic nitrogen of the spiropiperidine from potential off-target side effects.

Table 5. 4-Heteroaryl Substitutions[a]



compd #	**10s**	**10t**	**10u**	**10v**	**10w**	**10x**
Ar^1						
FLIPR IC_{50} (nM)[a]	2.3±1.0	0.57±0.11	0.51±0.22	0.47±0.01	0.30	NT
PA IC_{50} (μM)[b]	0.13±0.03	0.11±0.04	0.15	0.16±0.06	0.95	0.26
LM (h, r, m)[c] % remaining	92, 79, 88	100, 97, 65	68, 69, 73	75, 80, 75	41, 61, 42	77, 83, 67

[a]FLIPR was tested with 1 μM 2-methylthio-ADP, $n \geq 2$. [b]PA was tested with 10 μM ADP, n = 1 unless shown with ± SD. See ref 9f for detailed assay conditions. [c]Liver microsome stability: percentage of compound (0.5 μM) remaining after incubation for 10 min with 1 mg/mL human, rat, or mouse liver microsomes.

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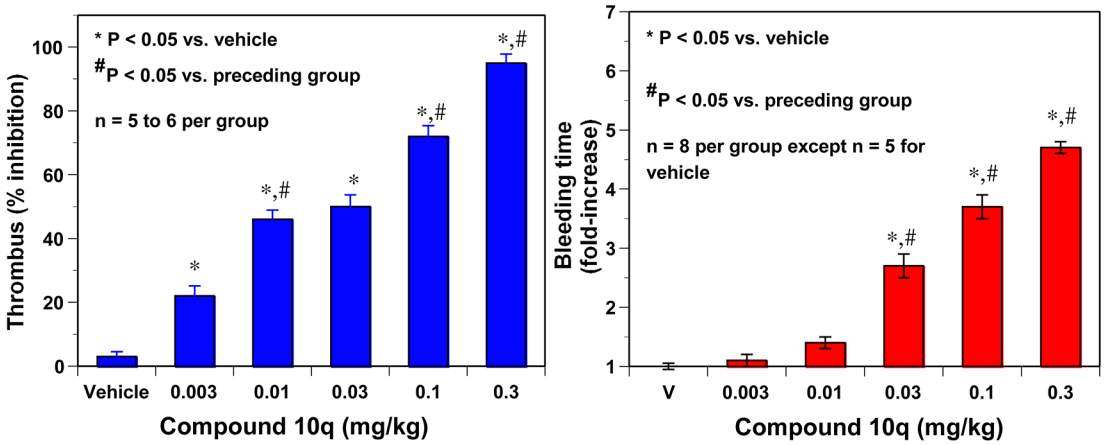
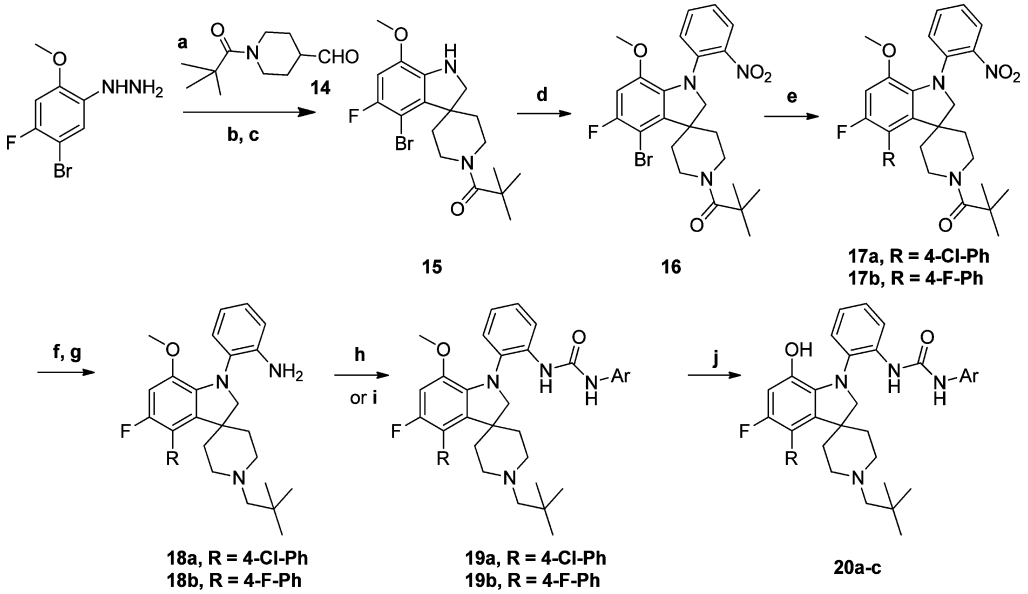


Figure 3. (A) Antithrombotic effects of **10q** in rabbit ECAT model. Vehicle: 10% DMAc/2.5% PVP-K12/1% Pluronic F-108/D5W. (B) Effects of **10q** on bleeding time in rabbit cuticle bleeding time model. For clarity, only the bolus doses are shown on the figures. Means ± SEM are shown; n = 5−6 per group.

Scheme 3. Synthesis of 4-Aryl-7-hydroxylspiroindoline Analogues[a]



[a]Reagents and conditions: (a) aldehyde **14**; (b) H_2SO_4, 40 °C; (c) $NaBH_4$, MeOH, 37−53%; (d) 1-bromo-2-nitrobenzene, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, 110 °C, 86−95%; (e) 4-F(or Cl)-phenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, dioxane, 100 °C, 49−100%; (f) Zn, NH_4Cl, 54−85%; (g) Red-Al, CH_2Cl_2, 61−88%; (h) $ClCO_2$-p-NO_2Ph, K_2CO_3, CH_2Cl_2, then NH_2Ar, DMAP, 75 °C, 80%; (i) OCN-p-OCF_3Ph, CH_2Cl_2, 54−85%; (j) BCl_3, Bu_4NI, CH_2Cl_2, −78 °C to rt, 18−42%.

Synthesis of the 4-aryl-7-hydroxylspiroindoline analogues proceeded in a similar fashion to the neutral analogues and is shown in Scheme 3. Fisher indoline synthesis, by reacting aldehyde **14** with (5-bromo-4-fluoro-2-methoxyphenyl)hydrazine followed by reduction with $NaBH_4$, afforded **15**. Buchwald N-arylation of **15** followed by Suzuki coupling of various boronic acids provided compounds **17**, which were sequentially reduced first with Zn/NH_4Cl and then with Red-Al to give compounds **18**. Ureas **19**, prepared in the same ways as described for the neutral series, were demethylated with BCl_3/Bu_4NI to generate the final compounds **20**.

The optimal aryl substitutions identified at the C4 position and on the urea in the neutral series were "mixed and matched" in the 5-fluoro-7-hydroxyspiroindoline basic series (Table 6). A number of potent and metabolically stable analogues were generated. Similar to the neutral series, rat cassette PK was used to differentiate these analogues. Of the analogues prepared, **20c** was identified to demonstrate the best overall potency/PK profile. It exhibited equivalent in vitro potency and liver microsomal stability compared with **1** but with a superior PK profile (lower clearance, smaller volume of distribution, comparable bioavailability, and higher exposure) in a rat PK study. In the in vitro hERG patch clamp assay, **20c** also showed improvement over **1** (57% vs 96% inhibition at 1 μM). Compound **20c** demonstrated good selectivity with IC_{50} values greater than 10 μM against $P2Y_{12}$ and $P2Y_2$ receptors and a panel of GPCRs. Compared with neutral compound **10q**, **20c** showed marginally improved solubility (amorphous, 3 μg/mL at pH = 3 vs less than 1 μg/mL for **10q** as amorphous solid). On the basis of its overall profile, **20c** was also advanced to the rabbit efficacy/bleeding models (**20c** rabbit PA IC_{50} = 0.59 μM) and demonstrated similar antithrombotic efficacy with less bleeding compared with known $P2Y_{12}$ antagonist prasugrel.[12]

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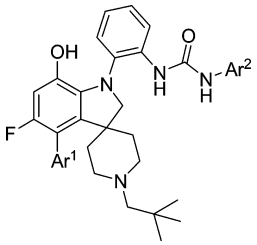
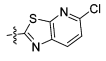
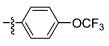
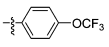
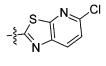
Table 6. Structure–Activity Relationship of 4-Aryl-5-Fluorospiroindoline Analogues



compd #	Ar^1	Ar^2	FLIPR IC_{50} (nM)	PA IC_{50} (uM)	LM (% remaining) (h, r, m)	Rat PK (F%, Cl: mL/min/kg Vdss: L/kg)
1	Cl		0.12±0.05	0.13	94, 93, 84	F: 36%; Cl: 10.4; Vdss: 5.4
20a	4-Cl-Ph		0.16±0.08	0.20	78, 72, 74	F: 15%; Cl: 3.7; Vdss: 1.3
20b	4-F-Ph		0.09±0.03	0.14±0.06	81, 80, 67	F: 17%; Cl: 4.2; Vdss: 1.0
20c (BMS-884775)	4-F-Ph		0.12±0.05	0.18±0.07	100, 93, 100	F: 30%; Cl: 4.0; Vdss: 2.1

CONCLUSIONS

To expand the SAR of a previously disclosed 7-hydroxyindoline $P2Y_1$ antagonist, **1**, two closely related series, neutral and basic, were pursued simultaneously. Removal of the basic nitrogen from **1** provided the neutral series with 7–10-fold loss of potency in human platelet aggregation assay and reduced liver microsomal stability. Introducing aryl groups to the 4-position of the 7-hydroxyindoline neutral series not only increased liver microsomal stability, by blocking the metabolism at C3 position, but also improved $P2Y_1$ potency. As a result, **10q** was identified with excellent potency and a desired PK profile (low clearance, small volume of distribution). Compound **10q** also demonstrated similar antithrombotic efficacy with less bleeding when compared to the known $P2Y_{12}$ antagonists clopidogrel and prasugrel in the rabbit model of electrically induced carotid artery thrombosis and cuticle bleeding. Applying the SAR from the neutral series to the basic series led to the discovery of **20c**, with an improved PK and liability profile over **1**. The results from in vivo studies of **10q** and **20c** support $P2Y_1$ receptor antagonism as a promising drug target for the development of a new and safer class of antiplatelet agents.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents, including anhydrous solvents, were obtained from commercial sources and used as received. All reactions were carried out under an atmosphere of argon and stirred continuously. ^1H and ^{13}C NMR spectra were taken on either Bruker (400 MHz) or JEOL (500 MHz) Fourier transform spectrometers. Chemical shifts were reported in parts per million (ppm) downfield from internal standard (tetramethylsilane, TMS). Purification of final compounds and intermediates was carried out via normal- or reverse-phase chromatography. Normal-phase chromatography was performed on an ISCO CombiFlash system with either an ISCO RediSep or a Biotage silica gel disposable column eluted with EtOAc/hexanes or methanol/CH_2Cl_2. Reverse-phase chromatography was performed on a Shimadzu preparative system on a Phenomenex Luna or Sunfire C18 preparative column with appropriate gradients of MeCN/H_2O/0.1% trifluoroacetic acid (TFA) or methanol/H_2O/0.1% TFA as eluent at a flow rate of 40 mL/min. Reactions were monitored either by analytical liquid chromatography–mass spectrometry (LCMS) or by thin-layer chromatography (TLC) on 0.25 mm E. Merck silica gel plates (60 F_{254}) and were visualized with UV light or by staining with various agents. LCMS data were obtained on a Shimadzu LC-10AT equipped with a SIL-10A injector, a SPD-10AV detector, running on Discovery VP software, and coupled with a Waters ZQ mass spectrometer running MassLynx version 3.5 software by the following methods.

Method A: Phenomenex Luna C18 column (4.6 × 50 mm) eluted at 4 mL/min with a 4 min linear gradient from 0% to 100% B and then 1 min at 100% B (where A = 10% methanol/90% H_2O/0.1% TFA and B = 90% methanol/10% H_2O/0.1% TFA).

Method B: Phenomenex Luna C18 column (2.0 × 30 mm) eluted with a 2 min linear gradient from 0% to 100% B and then 1 min at 100% B (where A = 10% methanol/90% H_2O/0.1% TFA and B = 90% methanol/10% H_2O/0.1% TFA).

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Method C: Phenomenex Luna C18 column (2.0 mm × 30 mm) eluted with a 2 min linear gradient from 0% to 100% B and then 1 min at 100% B (where A = 2% methanol/98% H_2O/0.1% formic acid and B = 100% methanol/0.1% formic acid).

Purity of final compounds was determined under the following HPLC conditions.

HPLC Method A (orthogonal): Sunfire C18 column (3.5 μm, 4.6 × 150 mm) eluted at 1.0 mL/min with gradient 10−100% B/A (where solvent A = 95% H_2O/5% MeCN/0.05% TFA and solvent B = : 5% H_2O/95% MeCN/0.05% TFA) over 10 min, and then 100% B over 5 min.

HPLC Method B (orthogonal): Xbridge Phenyl column (3.5 μm, 4.6 × 150 mm) eluted at 1.0 mL/min gradient 10−100% B/A (solvent A = 95% H_2O/5% MeCN/0.05% TFA; solvent B = 5% H_2O/95% MeCN/0.05% TFA) over 10 min and then 100% B over 5 min.

HPLC Method C (analytical): ZorbaxSB C18 column (4.6 × 75 mm) eluted at 2.5 mL/min with gradient 0−100% B/A (solvent A = 90% H_2O/10% MeCN/0.2% H_3PO_4; solvent B = 10% H_2O/90% MeOH/0.2% H_3PO_4) over 8 min and then 100% B over 3 min.

Ethyl 4-Chloro-7-methoxy-3-methyl-2,3-dihydro-1*H*-indole-3-carboxylate (5a). A solution of (5-chloro-2-methoxyphenyl)-hydrazine hydrochloride (1.70 g, 8.13 mmol) and ethyl 2-methyl-3-oxopropanoate hydrochloride (1.05 mg, 8.07 mmol) in dichloromethane (15 mL) was stirred at room temperature for 16 h before HCl (8.07 mL of 4 M in dioxane, 32.3 mmol) was added. After 2 h, the reaction mixture was concentrated and EtOH (15 mL) was added. At 0 °C, $NaBH_4$ (1.22 g, 32.3 mmol) was added portionwise. After 10 min, the reaction mixture was quenched with water, adjusted pH with 1 M HCl to pH ∼7, concentrated, and extracted with EtOAc (2×) The organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **5a** as a pale yellow oil (413 mg, 19% yield). LCMS (electrospray ionization, ESI) m/z 270.1 $(M + H)^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 6.68−6.60 (m, 2H), 4.28−4.13 (m, 2H), 3.98−3.85 (m, 2H), 3.81 (s, 3H), 3.46 (dd, J = 9.1, 1.3 Hz, 1H), 1.60 (s, 3H), 1.30−1.21 (m, 3H).

Ethyl 4-Chloro-7-methoxy-3-methyl-1-(2-nitrophenyl)-2,3-dihydro-1*H*-indole-3-carboxylate (6a). A mixture of **5a** (292 mg, 1.08 mmol), 1-bromo-2-nitrobenzene (262 mg, 1.30 mmol), *rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP; 47 mg, 0.076 mmol), tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$; 30 mg, 0.032 mmol], and Cs_2CO_3 (847 mg, 2.60 mmol) in toluene (10 mL) was purged with argon three times, sealed, and heated at 85 °C for 8 h. Another portion of 1-bromo-2-nitrobenzene (260 mg, 1.30 mmol), *rac*-BINAP (47 mg, 0.076 mmol), and $Pd_2(dba)_3$ (30 mg, 0.032 mmol) was added to the reaction mixture, which was purged with argon three times, sealed, and heated at 110 °C for 16 h. After cooling to room temperature, the reaction mixture was filtered, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **6a** (0.28 g, 65% yield) as an orange solid. LCMS (ESI) m/z 391.2 $(M + H)^+$. ^1H NMR (400 MHz, chloroform-*d*) δ 8.03 (dd, J = 8.3, 1.5 Hz, 1H), 7.52−7.41 (m, 1H), 7.20 (dd, J = 8.3, 1.0 Hz, 1H), 7.16−7.04 (m, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 4.50 (d, J = 9.3 Hz, 1H), 4.27−4.19 (m, 2H), 3.91 (d, J = 9.3 Hz, 1H), 3.51 (s, 3H), 1.69 (s, 3H), 1.26−1.21 (m, 3H).

Ethyl 1-(2-Aminophenyl)-4-chloro-7-methoxy-3-methyl-2,3-dihydro-1*H*-indole-3-carboxylate (7a). To a solution of **6a** (275 mg, 0.704 mmol) in MeOH (5 mL) and EtOAc (5 mL) were added zinc (920 mg, 14.1 mmol) and NH_4Cl (753 mg, 14.1 mmol). The reaction mixture was stirred at room temperature. After 1 h, the reaction mixture was filtered, concentrated, dissolved in dichloromethane, and filtered. The filtrate was concentrated and purified by flash chromatography, eluted with EtOAc/hexanes to give **7a** (210 mg, 83% yield) as an off-white solid. LCMS (ESI) m/z 361.1 $(M + H)^+$. ^1H NMR (400 MHz, acetonitrile-d_3) δ 7.05−6.93 (m, 1H), 6.89−6.72 (m, 4H), 6.65−6.54 (m, 1H), 4.40 (d, J = 10.6 Hz, 0.5H), 4.31 (br s, 1H), 4.24−4.13 (m, 3H), 3.89 (d, J = 9.6 Hz, 0.5H), 3.59 (d, J = 9.9 Hz, 0.5H), 3.55 (s, 1.5H), 3.49 (s, 1.5H), 3.31 (d, J = 10.6 Hz, 0.5H), 1.63 (s, 1.5H), 1.57 (s, 1.5H), 1.28−1.17 (m, 3H).

Ethyl 4-Chloro-7-methoxy-3-methyl-1-[2-({[4-(trifluoromethoxy)-phenyl]carbamoyl}amino)phenyl]-2,3-dihydro-1*H*-indole-3-carboxylate (8a−d). A solution of **7a** (52 mg, 0.14 mmol) and 1-isocyanato-4-(trifluoromethoxy)benzene (35 mg, 0.17 mmol) in dichloromethane (DCM; 2 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated and purified by flash chromatography, eluted with EtOAc/hexanes to give **8a−d** (78 mg, 96% yield) as a pale yellow solid. LCMS (ESI) m/z 564.1 $(M + H)^+$.

Ethyl 4-Chloro-7-hydroxy-3-methyl-1-[2-({[4-(trifluoromethoxy)phenyl]carbamoyl}amino)phenyl]-2,3-dihydro-1*H*-indole-3-carboxylate (2d). To a solution of **8a−d** (78 mg, 0.14 mmol) in DCM (3 mL) was added tetrabutylammonium iodide (257 mg, 0.696 mmol) at −78 °C under argon, and BCl_3 (1 M solution in DCM, 0.7 mL, 0.7 mmol) was added dropwise. The reaction mixture was gradually warmed up to room temperature and stirred for 16 h. The reaction mixture was concentrated and purified by flash chromatography, eluted with EtOAc/hexanes to give **2d** as a white solid (37 mg, 49% yield). LCMS (ESI) m/z 550.2 $(M + H)^+$; purity 100% (by HPLC method C). ^1H NMR (400 MHz, chloroform-*d*) (mixture of rotamers, major isomer reported) δ 8.30−8.22 (m, 2H), 7.49−7.40 (m, 3H), 7.35−7.29 (m, 1H), 7.22 (dd, J = 7.8, 1.3 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.06 (td, J = 7.6, 1.3 Hz, 1H), 6.69−6.59 (m, 2H), 4.34−4.25 (m, 2H), 4.16 (d, J = 9.9 Hz, 1H), 3.49 (d, J = 10.1 Hz, 1H), 1.85 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H).

Ethyl 4-Chloro-1-(2-{[(5-chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)carbamoyl]amino}phenyl)-7-methoxy-3-methyl-2,3-dihydro-1*H*-indole-3-carboxylate (8a−e). To a solution of **7a** (450 mg, 1.25 mmol) and 4-nitrophenyl chloroformate (277 mg, 1.37 mmol) in DCM (3 mL) was added K_2CO_3 (345 mg, 2.49 mmol). The reaction was stirred at room temperature (rt) overnight. The solid was filtered off, and 5-chlorothiazolo[5,4-*b*]pyridin-2-amine (232 mg, 1.25 mmol) and DMAP (5 mg, 0.033 mmol) were added. The reaction was sealed and microwaved at 100 °C for 15 min. The solid was filtered off, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **8a−e** as a white solid (164 mg, 23% yield). LCMS (ESI) m/z 572.2 $(M + H)^+$. ^1H NMR (400 MHz, methanol-d_4, 3:2 mixture of isomers) δ 8.18−8.06 (m, 1H), 7.79−7.64 (m, 1H), 7.36 (dd, J = 8.6, 2.8 Hz, 1H), 7.25−6.94 (m, 3H), 6.91−6.75 (m, 2H), 4.53 (d, J = 10.9 Hz, 1H), 4.26−4.09 (m, 2H), 3.91−3.74 (m, 1H), 3.53 (s, 1.3H), 3.43 (s, 1.7H), 1.68 (s, 1.7H), 1.63 (s, 1.3H), 1.25−1.13 (m, 3H).

Ethyl 4-Chloro-1-(2-{[(5-chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)carbamoyl]amino}phenyl)-7-hydroxy-3-methyl-2,3-dihydro-1*H*-indole-3-carboxylate (2e). Compound **2e** was prepared from **8a−e** according to the same procedure as described for **2d**. LCMS (ESI) m/z 558.1 $(M + H)^+$; purity >95%, retention time = 7.97 min (by HPLC method C). ^1H NMR (400 MHz, chloroform-*d*) δ 8.08 (d, J = 6.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.28 (m, 1H), 7.21−6.94 (m, 3H), 6.79−6.51 (m, 2H), 4.42 (d, J = 10.4 Hz, 1H), 4.31−4.11 (m, 2H), 3.42 (d, J = 9.9 Hz, 1H), 1.71 (s, 3H), 1.25 (t, J = 6.9 Hz, 3H).

1-{2-[4-Chloro-7-hydroxy-3-(hydroxymethyl)-3-methyl-2,3-dihydro-1*H*-indol-1-yl]phenyl}-3-(5-chloro-[1,3]thiazolo[5,4-*b*]-pyridin-2-yl)urea (2f). To a solution of **2e** (16 mg, 0.029 mmol) in tetrahydrofuran (THF; 1 mL) were added $LiBH_4$ (80 μL, 0.16 mmol, 2 M in THF) and toluene (1 mL). The reaction was heated at 100 °C for 6 h before cooling down to rt. The reaction mixture was quenched with 1 N HCl (1 mL), refluxed for 10 min, and then cooled down to rt. The pH was adjusted to 7 with concentrated $NaHCO_3$ (aq). The mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **2f** as a white solid (3.4 mg, 23% yield). LCMS (ESI) m/z 558.1 $(M + H)^+$; purity 97.9%, retention time = 7.42 min (by HPLC method C). ^1H NMR (400 MHz, chloroform-*d*) δ 8.74 (br s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 10.1 Hz, 1H), 7.16−7.01 (m, 3H), 6.45 (d, J = 7.8 Hz, 1H), 6.30 (br s, 1H), 4.32 (d, J = 11.4 Hz, 1H), 4.07 (d, J = 11.1 Hz, 1H), 3.59 (d, J = 10.6 Hz, 1H), 3.27 (d, J = 8.6 Hz, 1H), 1.46 (s, 3H).

Compounds 2a−c and 2h. Compounds **2a−c** and **2h** were prepared according to the procedure described for **2d**.

1-[2-(4-Chloro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)phenyl]-3-(5-chloro-[1,3]thiazolo[5,4-b]pyridin-2-yl)urea (2a). LCMS (ESI) m/z 500.3 $(M + H)^+$; orthogonal HPLC purity >95%,

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retention time = 11.69 min (by HPLC method A), >95%, retention time = 10.05 min (by HPLC method B). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.91 (br s, 1H), 7.51 (br s, 1H), 7.26 (m, *J* = 8.8 Hz, 2H), 7.13 (br s, 1H), 7.09−6.99 (m, 2H), 6.68 (d, *J* = 8.8 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 3.72 (d, *J* = 9.8 Hz, 1H), 3.12 (d, *J* = 9.8 Hz, 1H), 1.38 (s, 3H), 1.34 (s, 3H).

*3-[2-(4-Chloro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)phenyl]-1-[4-(trifluoromethoxy)phenyl]urea (**2b**).* LCMS (ESI) *m*/*z* 492.4 (M + H)$^+$; orthogonal HPLC purity 98.5%, retention time = 10.19 min (by HPLC method A), 98.1%, retention time = 11.70 min (by HPLC method B). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.55−7.48 (m, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.15−7.10 (m, 1H), 6.95 (d, *J* = 3.8 Hz, 2H), 6.82−6.72 (m, 2H), 3.82 (d, *J* = 9.9 Hz, 1H), 3.22 (d, *J* = 9.9 Hz, 1H), 1.52 (s, 3H), 1.50 (s, 3H).

*3-{2-[4-Chloro-7-hydroxy-3-methyl-3-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**2c**).* LCMS (ESI) *m*/*z* 560.2 (M + H)$^+$; purity 95.8%, retention time = 8.26 min (by HPLC method C). ^{1}H NMR (400 MHz, chloroform-*d*, 2:1 diastereomer mixture, major one reported) δ 7.87 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 4.8 Hz, 1H), 7.35−7.24 (m, 3H), 7.21−7.07 (m, 3H), 6.81−6.74 (m, 1H), 6.67−6.61 (m, 1H), 4.01 (d, *J* = 10.4 Hz, 1H), 3.26 (d, *J* = 10.6 Hz, 1H), 2.85−2.58 (m, 2H), 1.63 (s, 3H).

*4-Chloro-1-(2-{[(6-fluoro-1,3-benzothiazol-2-yl)carbamoyl]-amino}phenyl)-7-hydroxy-N,3-dimethyl-2,3-dihydro-1H-indole-3-carboxamide (**2h**).* LCMS (ESI) *m*/*z* 526.0 (M + H)$^+$; purity 98.3%, retention time = 7.05 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4,1:1 mixture of isomers, one reported) δ 8.11 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.62−7.53 (m, 1.5H), 7.31−7.01 (m, 4.5H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.64 (d, *J* = 6.8 Hz, 1H), 3.82 (d, *J* = 9.9 Hz, 1H), 3.66 (d, *J* = 10.1 Hz, 1H), 2.76 (s, 3H), 1.66 (s, 3H).

4-Chloro-1-(2-{[(5-chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)-carbamoyl]amino}phenyl)-7-methoxy-3-methyl-2,3-dihydro-1*H*-indole-3-carboxylic acid (8a−g). To a solution of **8a−e** (60 mg, 0.105 mmol) in THF (1 mL) and MeOH (1 mL) at rt was added NaOH (1 mL, 1 N solution). The reaction was stirred at rt for 6 days. The reaction mixture was partitioned between water and EtOAc. The EtOAc layer was washed with water 3 times. The aqueous layer was acidified with 1 N HCl and extracted with EtOAc until no more product was detected in the aqueous layer. The combined EtOAc layers were dried with Na_2SO_4 and concentrated to yield **8a−g** as an off-white solid (37 mg, 65%). LCMS (ESI) *m*/*z* 544.0 (M + H)$^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.14−8.02 (m, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.33−7.28 (m, 1H), 7.23−7.11 (m, 1H), 7.04−6.95 (m, 1H), 6.91−6.83 (m, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 4.44 (d, *J* = 10.4 Hz, 1H), 3.49−3.37 (m, 4H), 1.66 (s, 3H).

4-Chloro-1-(2-{[(5-chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)-carbamoyl]amino}phenyl)-7-hydroxy-3-methyl-2,3-dihydro-1*H*-indole-3-carboxylic acid (2g). To a solution of **8a−g** (18 mg, 0.033 mmol) in dichloroethane (DCE; 1 mL) was added BBr_3·Me_2S (50 μL, 0.05 mmol, 1 M in DCM). The reaction was heated at 85 °C for 12 h. The reaction was concentrated, redissolved in MeOH, and purified by reverse-phase preparative HPLC. After removal of solvents, **2g** was obtained as a gray solid (4.2 mg, 23% yield). *m*/*z* 529.9 (M + H)$^+$; purity 94.4%, retention time = 7.12 min (by HPLC method C). ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 8.80 (d, *J* = 18.7 Hz, 1H), 8.15−8.08 (m, 1H), 7.92−7.86 (m, 1H), 7.44−7.38 (m, 1H), 7.32−7.20 (m, 1H), 7.18−7.02 (m, 2H), 6.87−6.66 (m, 2H), 4.64−4.53 (d, *J* = 10.9 Hz, 1H), 3.32 (d, *J* = 10.9 Hz, 1H), 1.61 (s, 3H).

(5-Bromo-2-methoxyphenyl)hydrazine (4b). A suspension of 5-bromo-2-methoxyaniline (1.74 g, 8.62 mmol) in 6 M HCl (30 mL) was cooled to −10 °C, and a solution of sodium nitrite (0.714 g, 10.4 mmol) in water (3 mL) was added dropwise. After the addition, the reaction was stirred for an additional 30 min at −10 °C. A solution of tin(II) chloride (4.90 g, 25.9 mmol) in concentrated HCl (10 mL) was added slowly, resulting in precipitation. After 30 min, the precipitate was filtered, washed with 1 M HCl, suspended in 10% NaOH solution, and extracted with ether (3×). The combined organic layers were dried over $MgSO_4$ and evaporated to give **4b**, which was used directly in the next step without further purification. LCMS (ESI) *m*/*z* 200, 202 (M − NH_3 + H, M − NH_3 + 2 + H)$^+$.

4-Bromo-7-methoxy-3,3-dimethylindoline (5b). A solution of **4b** (1.60 g, 7.37 mmol) and isobutyraldehyde (0.673 mL, 7.37 mmol) in ethanol (30 mL) was stirred at room temperature. Sulfuric acid (1.97 mL, 36.9 mmol) was added to the reaction mixture at 0 °C for 0.5 h. The reaction was stirred at room temperature for 2 h and then diluted with EtOAc and washed with saturated $NaHCO_3$. The combined organics were dried over $MgSO_4$, filtered, and evaporated. The crude product was dissolved in MeOH and cooled to 0 °C. Sodium borohydride (0.558 g, 14.7 mmol) was added portionwise and the reaction was stirred for 15 min and then warmed to room temperature for 30 min. The reaction was quenched with water and extracted with EtOAc. The combined organics were dried over $MgSO_4$ and evaporated to give the crude product, which was purified by flash chromatography, eluted with EtOAc/hexanes to give **5b** (0.45 g, 24%). LCMS (ESI) *m*/*z* 256, 258 (M + H, M + 2 + H)$^+$. ^{1}H NMR (300 MHz, chloroform-*d*) δ 1.46 (s, 6H), 3.36 (s, 2H), 3.83 (s, 3H), 6.52 (d, *J* = 8.78 Hz, 1H), 6.74−6.89 (m, 1H).

4-Bromo-7-methoxy-3,3-dimethyl-1-(2-nitrophenyl)-2,3-dihydro-1*H*-indole (6b). A solution of **5b** (1.61 g, 6.29 mmol) in toluene (20 mL) was purged with nitrogen for 3 min and added to a sealable flask containing 1-bromo-2-nitrobenzene (1.52 g, 7.54 mmol), $Pd_2(dba)_3$ (0.288 g, 0.314 mmol), *rac*-BINAP (0.391 g, 0.629 mmol), and Cs_2CO_3 (6.14 g, 18.86 mmol). The reaction was sealed and heated to 110 °C for 16 h. The reaction was cooled, filtered through Celite, and concentrated. The crude mixture was purified by flash chromatography, eluted with EtOAc/hexanes to give **6b** as a brown solid (2.18 g, 92%). LCMS (ESI) *m*/*z* 377.0 (M + H)$^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.48−7.40 (m, 1H), 7.14 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.09−7.03 (m, 1H), 7.01−6.97 (m, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 3.87−3.72 (m, 2H), 3.53 (s, 3H), 1.50 (s, 6H).

2-(4-Bromo-7-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)aniline (7b). To a solution of **6b** (1.62 g, 4.41 mmol) in ethanol (40 mL) were added zinc (2.95 g, 45.1 mmol) and ammonium chloride (2.41 g, 45.1 mmol), and the reaction was stirred at room temperature, filtered through Celite, and concentrated. The crude product was purified by flash chromatography, eluted with EtOAc/hexanes to give **7b** as a white solid (1.195 g, 76%). LCMS (ESI) *m*/*z* 347, 349 (M + H, M + 2 + H)$^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.07−6.84 (m, 1H), 6.79−6.70 (m, 1H), 6.69−6.63 (m, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 3.92 (br s, 3H), 3.76 (d, *J* = 9.9 Hz, 1H), 3.48 (s, 3H), 3.23 (d, *J* = 9.9 Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H).

3-[2-(4-Bromo-7-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl)phenyl]-1-[4-(trifluoromethoxy)phenyl]urea (8b). Compound **8b** was prepared according to the procedure described for **8a−d.** LCMS (ESI) *m*/*z* 552.0 (M + 2 + H)$^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.91 (d, *J* = 8.2 Hz, 1H), 7.42−7.39 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.04−6.97 (m, 1H), 6.88−6.81 (m, 3H), 6.57−6.53 (m, 1H), 3.71 (d, *J* = 9.9 Hz, 1H), 3.34 (s, 3H), 3.10 (d, *J* = 9.9 Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H).

3-[2-(7-Methoxy-3,3-dimethyl-4-phenyl-2,3-dihydro-1*H*-indol-1-yl)phenyl]-1-[4-(trifluoromethoxy)phenyl]urea (9a). Compound **8b** (52 mg, 0.094 mmol), phenylboronic acid (14 mg, 0.115 mmol), $Pd(PPh_3)_4$ (11 mg, 9.5 μmol), and Na_2CO_3 (0.12 mL, 2 M, 0.24 mmol) in dimethyl ether (DME; 2 mL) was bubbled with Ar for 3 min. The reaction was sealed and refluxed at 100 °C for 50 h. The reaction mixture was cooled down to rt and the solid was filtered off, rinsed with EtOAc, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **9a** as an off-white solid (51 mg, 99% yield). LCMS (ESI) *m*/*z* 548.1 (M + H)$^+$. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.39−7.29 (m, 7H), 7.17−7.02 (m, 5H), 6.76−6.73 (m, 2H), 3.66 (d, *J* = 10.1 Hz, 1H), 3.57 (s, 3H), 3.25 (d, *J* = 10.1 Hz, 1H), 1.06 (s, 3H), 0.96 (s, 3H).

3-[2-(7-Hydroxy-3,3-dimethyl-4-phenyl-2,3-dihydro-1*H*-indol-1-yl)phenyl]-1-[4-(trifluoromethoxy)phenyl]urea (10a). To a solution of **9a** (51 mg, 0.093 mmol) in DCE (2 mL) was added $(CH_3)_2S$·BBr_3 (0.4 mL, 0.4 mmol, 1 M in DCM). The reaction was heated at 85 °C for 16 h before cooling down to rt. HCl (1 N, 1 mL) was added, and the mixture was heated at 65 °C for 1 h before cooling down to rt. The reaction mixture was partitioned between water and EtOAc. The combined EtOAc layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give

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48 mg of off-white solid, which was further purified by reverse-phase preparative HPLC to yield **10a** as a white solid (7 mg, 14% yield). LCMS (ESI) m/z 534.0 $(M + H)^+$; purity 99%, retention time = 8.39 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.90−7.84 (m, 1H), 7.54−7.50 (m, 2H), 7.38−7.26 (m, 5H), 7.17 (d, J = 8.3 Hz, 2H), 7.11−6.94 (m, 3H), 6.62 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 3.73 (d, J = 9.9 Hz, 1H), 3.11 (d, J = 9.9 Hz, 1H), 1.07 (s, 3H), 1.06 (s, 3H).

Compounds 10b−i, 10p, and 10r. Compounds **10b−i**, **10p**, and **10r** were prepared according to the procedure described for **10a**.

*3-{2-[4-(2-Fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10b**).* LCMS (ESI) m/z 552.3 $(M + H)^+$; purity 95.6%, retention time = 8.32 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.89 (d, J = 8.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.43−6.92 (m, 9H), 6.65 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 7.1 Hz, 1H), 3.87−3.65 (m, 1H), 3.11 (d, J = 9.9 Hz, 1H), 1.14−0.99 (m, 6H).

*3-{2-[4-(3-Fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10c**).* LCMS (ESI) m/z 552.0 $(M + H)^+$; purity >95%, retention time = 8.42 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.95−7.83 (m, 1H), 7.54−7.49 (m, 2H), 7.37 (td, J = 7.9, 6.2 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.13−6.95 (m, 6H), 6.63 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 3.74 (d, J = 9.9 Hz, 1H), 3.12 (d, J = 9.9 Hz, 1H), 1.09 (s, 6H).

*3-{2-[4-(4-Fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10d**).* LCMS (ESI) m/z 552.0 $(M + H)^+$; purity 99.8%, retention time = 8.34 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.93−7.82 (m, 1H), 7.55−7.47 (m, 2H), 7.32−7.25 (m, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.13−7.05 (m, 3H), 7.04−6.95 (m, 2H), 6.62 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 3.74 (d, J = 9.9 Hz, 1H), 3.11 (d, J = 9.9 Hz, 1H), 1.07 (s, 6H).

*3-{2-[4-(4-Chlorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10e**).* LCMS (ESI) m/z 568.0 $(M + H)^+$; purity 99.7%, retention time = 8.62 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.91−7.84 (m, 1H), 7.56−7.49 (m, 2H), 7.40−7.34 (m, 2H), 7.31−7.24 (m, 2H), 7.21−7.14 (m, 2H), 7.12−7.05 (m, 1H), 7.03−6.93 (m, 2H), 6.63 (d, J = 8.1 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 3.74 (d, J = 9.9 Hz, 1H), 3.11 (d, J = 9.9 Hz, 1H), 1.08 (s, 6H).

*3-{2-{7-Hydroxy-3,3-dimethyl-4-[4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-indol-1-yl}phenyl)-1-[4-(trifluoromethoxy)phenyl]urea (**10f**).* LCMS (ESI) m/z 602.1 $(M + H)^+$; purity 95.8%, retention time = 8.54 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88 (dd, J = 8.2, 1.1 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.55−7.46 (m, 4H), 7.17 (d, J = 8.2 Hz, 2H), 7.13−7.06 (m, 1H), 7.04−6.96 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.56−6.51 (m, 1H), 3.75 (d, J = 9.9 Hz, 1H), 3.12 (d, J = 9.9 Hz, 1H), 1.08 (s, 6H).

*3-{2-[4-(2,4-Difluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10g**).* LCMS (ESI) m/z 570.0 $(M + H)^+$; purity 99.2%, retention time = 8.32 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.89 (d, J = 7.8 Hz, 1H), 7.55−7.49 (m, 2H), 7.30 (d, J = 16.4 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.13−6.95 (m, 5H), 6.65 (d, J = 7.8 Hz, 1H), 6.51 (br s, 1H), 3.85−3.66 (m, 1H), 3.12 (d, J = 9.6 Hz, 1H), 1.14−0.98 (m, 6H).

*3-{2-[4-(3,4-Difluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10h**).* LCMS (ESI) m/z 570.0 $(M + H)^+$; purity 100%, retention time = 8.44 min (HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.90−7.84 (m, 1H), 7.55−7.48 (m, 2H), 7.31−7.14 (m, 4H), 7.09 (ddd, J = 8.3, 6.0, 2.4 Hz, 2H), 7.03−6.94 (m, 2H), 6.63 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 3.74 (d, J = 10.1 Hz, 1H), 3.12 (d, J = 9.9 Hz, 1H), 1.10 (d, J = 2.8 Hz, 6H).

*3-{2-[4-(3,5-Difluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-1-[4-(trifluoromethoxy)phenyl]urea (**10i**).* LCMS (ESI) m/z 570.0 $(M + H)^+$; purity 100%, retention time = 8.46 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.92−7.84 (m, 1H), 7.55−7.49 (m, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.10 (ddd, J = 8.3, 6.3, 2.4 Hz, 1H), 7.03−6.86 (m, 5H), 6.64 (d, J = 8.3 Hz, 1H), 6.56−6.51 (m, 1H), 3.74 (d, J = 9.9 Hz, 1H), 3.14 (d, J = 9.9 Hz, 1H), 1.12 (d, J = 4.8 Hz, 6H).

*1-{2-[6-Fluoro-4-(4-fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]urea (**10p**).* LCMS (ESI) m/z 570.3 $(M + H)^+$; orthogonal HPLC purity >94.8%, retention time = 10.53 min (by HPLC method A), >98%, retention time = 11.93 min (by HPLC method B). ^{1}H NMR (400 MHz, chloroform-d) δ 7.80 (d, J = 7.8 Hz, 1H), 7.45−7.29 (m, 3H), 7.25−7.01 (m, 10H), 6.44 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 9.6 Hz, 1H), 3.23 (d, J = 9.6 Hz, 1H), 1.00 (s, 3H), 0.95 (s, 3H).

*1-{2-[4-(4-Chlorophenyl)-6-fluoro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]urea (**10r**).* LCMS (ESI) m/z 586.0 $(M + H)^+$; orthogonal HPLC purity 97.8%, retention time = 10.87 min (by HPLC method A), 97.9%, retention time = 12.59 min (by HPLC method B). ^{1}H NMR (400 MHz, chloroform-d) δ 8.01 (br s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.64 (s, 1H), 7.39−7.28 (m, 4H), 7.25−7.16 (m, 5H), 7.09 (d, J = 8.3 Hz, 2H), 6.46 (d, J = 10.9 Hz, 1H), 3.54 (d, J = 9.6 Hz, 1H), 3.29 (d, J = 9.6 Hz, 1H), 1.01 (s, 3H), 0.90 (s, 3H).

4-(4-Fluorophenyl)-7-methoxy-3,3-dimethyl-1-(2-nitrophenyl)-2,3-dihydro-1*H*-indole (11b). To a mixture of **6b** (407 mg, 1.08 mmol), 4-fluorophenylboronic acid (181 mg, 1.30 mmol), and $Pd(PPh_3)_4$ (125 mg, 0.11 mmol) in DME (8 mL) was added Na_2CO_3 (2.7 mL, 2.70 mmol, 1 M aq). The reaction was bubbled through Ar for 3 min, sealed, and heated at 100 °C for 50 h before gradually cooling down to rt. The solid was filtered off, rinsed with EtOAc, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **11b** as a red-orange solid (415 mg, 98% yield). LCMS (ESI) m/z 393.0 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-d) δ 8.05 (dd, J = 8.3, 1.5 Hz, 1H), 7.44 (ddd, J = 8.4, 7.0, 1.8 Hz, 1H), 7.31−7.27 (m, 2H), 7.15 (dd, J = 8.3, 1.3 Hz, 1H), 7.09−6.97 (m, 3H), 6.76−6.66 (m, 2H), 3.77 (d, J = 9.3 Hz, 1H), 3.64 (d, J = 9.6 Hz, 1H), 3.60 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H).

2-[4-(4-Fluorophenyl)-7-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl]aniline (12b). To a solution of **11b** (415 mg, 1.06 mmol) in MeOH (5 mL) and EtOAc (5 mL) were added Zn (1.3 g, 19.88 mmol) and NH_4Cl (1.1 g, 20.56 mmol). The reaction was stirred at rt for 1 h. The solid was filtered off, rinsed with MeOH, and concentrated to yield a crude product, to which were added EtOAc and Na_2CO_3 (1 N aq) to adjust pH > 7. The EtOAc layer was dried over $MgSO_4$ and concentrated to yield **12b** as a white solid (369 mg, 96% yield). LCMS (ESI) m/z 363.1 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-d) δ 7.32−7.26 (m, 2H), 7.11−6.91 (m, 4H), 6.81−6.65 (m, 3H), 6.59 (d, J = 8.1 Hz, 1H), 3.96 (br s, 2H), 3.64 (d, J = 9.6 Hz, 1H), 3.55 (s, 3H), 3.17 (d, J = 9.6 Hz, 1H), 1.15 (s, 3H), 1.03 (s, 3H).

1-(2-Aminophenyl)-4-(4-fluorophenyl)-3,3-dimethyl-2,3-dihydro-1*H*-indol-7-ol (13b). To a solution of **12b** (1.3536 g, 3.73 mmol) in DCM (18.67 mL) was added tetrabutylammonium iodide (TBAI; 7.90 g, 21.40 mmol). The reaction was cooled to −78 °C, and BCl_3 in heptanes (9.64 mL, 9.64 mmol) was gradually added. The reaction was allowed to warm to rt over 3 h before it was recooled to 0 °C. Ice was added and MeOH was gradually added. After being stirred for 30 min, the reaction was partitioned between DCM and water with a small amount of saturated $NaHCO_3$. Aqueous was extracted 2× with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography, eluted with EtOAc/hexanes, gave **13b** as a dark green oil (1.17 g, 90% yield). LCMS (ESI) m/z 349.0 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-d) δ 7.29 (br s, 2H), 7.18−7.01 (m, 4H), 6.89−6.76 (m, 2H), 6.70 (d, J = 8.1 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 4.70 (s, 1H), 3.58 (d, J = 9.1 Hz, 1H), 3.24 (d, J = 8.6 Hz, 1H), 1.19 (br s, 3H), 1.04 (br s, 3H).

3-(5-Chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)-1-{2-[4-(4-fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl]-phenyl}urea (10j). To a solution of **13b** (36 mg, 0.10 mmol) in DCM (10 mL) were added 4-nitrophenyl chloroformate (24.6 mg, 0.12 mmol) and Na_2CO_3 (20 mg, 0.61 mmol). The reaction was stirred at rt for 3 h. The solid was filtered off and used in the next step without further purification. LCMS (ESI) m/z 514.3 $(M + H)^+$. The crude product from the above reaction was dissolved in DCM (3 mL), and 5-chlorothiazolo-[5,4-*b*]pyridin-2-amine (37.1 mg, 0.2 mmol) and DMAP (6 mg, 0.05 mmol) were added. The reaction was sealed and microwaved at

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100 °C for 15 min. The solid was filtered off, concentrated, dissolved in MeOH, and purified by reverse-phase preparative HPLC to give **10j** as a gray solid (8.5 mg, 15% for two steps). LCMS (ESI) m/z 560.0 $(M + H)^+$; HPLC purity 99.2%, retention time = 8.59 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.11−7.98 (m, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.33−7.26 (m, 2H), 7.18−7.01 (m, 5H), 6.61 (d, J = 7.4 Hz, 1H), 6.52 (d, J = 7.4 Hz, 1H), 3.72 (d, J = 9.6 Hz, 1H), 3.14 (d, J = 9.6 Hz, 1H), 1.10 (s, 3H), 1.07 (s, 3H).

3-(2-Chloro-1,3-thiazol-4-yl)-1-{2-[4-(4-fluorophenyl)-7-methoxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl]phenyl}urea (9k). A solution of 2-chloro-1,3-thiazole-4-carboxylic acid (25 mg, 0.15 mmol), diphenylphosphoryl azide (DPPA; 44 mg, 0.16 mmol), and NEt_3 (77 μL, 0.55 mmol) in toluene (2 mL) was heated to 100 °C, and **12b** (50 mg, 0.14 mmol) in toluene (2 mL) was added. The reaction was heated at 100 °C for 1 h before cooling down to rt. The reaction mixture was concentrated and purified by flash chromatography, eluted with EtOAc/hexanes to give **9k** as a white solid (20 mg, 28% yield). LCMS (ESI) m/z 523.0 $(M + H)^+$.

3-(2-Chloro-1,3-thiazol-4-yl)-1-{2-[4-(4-fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl]phenyl}urea (10k). To a solution of **9k** (20 mg, 0.04 mmol) in DCM (2 mL) was added $AlCl_3$ (51 mg, 0.04 mmol). The reaction was sealed and microwaved at 100 °C for 10 min. The reaction mixture was quenched with MeOH and purified by reverse-phase preparative HPLC to give **10k** as an off-white solid (10.4 mg, 53% yield). LCMS (ESI) m/z 509.0 $(M + H)^+$; purity 100%, retention time = 8.23 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.91 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 8.6, 5.6 Hz, 2H), 7.18 (s, 1H), 7.13−7.05 (m, 3H), 7.02−6.97 (m, 2H), 6.61 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 3.75 (d, J = 9.9 Hz, 1H), 3.07 (d, J = 9.9 Hz, 1H), 1.07 (d, J = 3.8 Hz, 6H).

1-{2-[4-(4-Fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1*H*-indol-1-yl]phenyl}-3-(2-methyl-1,3-thiazol-4-yl)urea (10l). Compound **10l** was prepared according to the same procedure described for **10k**. LCMS (ESI) m/z 489.0 $(M + H)^+$; purity 100%, retention time = 7.98 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.95−7.88 (m, 1H), 7.32−7.25 (m, 2H), 7.13−7.05 (m, 3H), 7.03−6.94 (m, 2H), 6.90 (br s, 1H), 6.61 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 8.1 Hz, 1H), 3.73 (d, J = 9.9 Hz, 1H), 3.08 (d, J = 9.9 Hz, 1H), 2.51 (s, 3H), 1.06 (d, J = 8.8 Hz, 6H).

Compounds 10m−o, 10q, and 10s−x. *1-{2-[4-(4-Fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-{4-[1-(2-methylpropyl)pyrrolidin-2-yl]phenyl}urea (**10m**).* LCMS (ESI) m/z 593.2 $(M + H)^+$; purity 99.7%, retention time = 6.82 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88−7.84 (m, 1H), 7.63−7.58 (m, 2H), 7.48−7.43 (m, 2H), 7.32−7.25 (m, 2H), 7.14−7.06 (m, 3H), 7.03−6.98 (m, 2H), 6.63 (d, J = 8.1 Hz, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.40−4.32 (m, 1H), 3.98 (s, 2H), 3.88 (dt, J = 12.3, 6.3 Hz, 1H), 3.75 (d, J = 9.9 Hz, 1H), 3.11 (d, J = 9.9 Hz, 1H), 2.97 (dd, J = 12.9, 5.6 Hz, 1H), 2.84 (dd, J = 12.9, 8.6 Hz, 1H), 2.55−2.45 (m, 1H), 2.37−2.22 (m, 3H), 2.03−1.90 (m, 1H), 1.07 (d, J = 2.8 Hz, 6H), 0.95−0.86 (m, 6H).

*3-{4-[1-(2,2-Dimethylpropyl)pyrrolidin-2-yl]phenyl}-1-{2-[4-(4-fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]-phenyl}urea (**10n**).* LCMS (ESI) m/z 607.2 $(M + H)^+$; purity 97.6%, retention time = 7.08 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.86 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.6 Hz, 2H), 7.29 (dd, J = 8.7, 5.4 Hz, 2H), 7.13−7.06 (m, 3H), 7.03−6.99 (m, 2H), 6.62 (d, J = 8.1 Hz, 1H), 6.55−6.50 (m, 1H), 4.36 (d, J = 10.9 Hz, 1H), 4.10−4.00 (m, 1H), 3.75 (d, J = 9.9 Hz, 1H), 3.46−3.38 (m, 1H), 3.15−3.01 (m, 3H), 2.52−2.39 (m, 1H), 2.37−2.23 (m, 3H), 1.07 (d, J = 3.0 Hz, 6H), 0.89 (s, 9H).

*1-{2-[5-Fluoro-4-(4-fluorophenyl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]urea (**10o**).* LCMS (ESI) m/z 570.0 $(M + H)^+$; purity 98.8%, retention time = 8.42 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.88 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.30 (br s, 2H), 7.21−7.04 (m, 5H), 6.99 (br s, 2H), 6.45 (d, J = 10.6 Hz, 1H), 3.77 (d, J = 10.1 Hz, 1H), 3.10 (d, J = 9.9 Hz, 1H), 1.04 (d, J = 9.3 Hz, 6H).

*1-{2-[4-(4-Chlorophenyl)-5-fluoro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]urea (**10q**).* LCMS (ESI) m/z 585.9 $(M + H)^+$; orthogonal HPLC purity >99.9%, retention time = 12.35 min (by HPLC method A), 100%, retention time = 10.59 min (by HPLC method B). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (br s, 1H), 9.56 (s, 1H), 8.29 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.61−7.55 (m, 2H), 7.54−7.49 (m, 2H), 7.36 (br s, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.05 (ddd, J = 8.4, 5.9, 2.9 Hz, 1H), 6.94−6.89 (m, 2H), 6.54 (d, J = 10.9 Hz, 1H), 3.82 (d, J = 10.1 Hz, 1H), 2.97 (d, J = 10.1 Hz, 1H), 1.00 (d, J = 16.7 Hz, 6H). ^{19}F NMR (376 MHz, DMSO-d_6) δ −57.57, −123.72. ^{13}C NMR (151 MHz, DMSO-d_6) δ 152.40, 144.85, 144.77, 142.43, 140.72, 140.70, 139.23, 138.61, 133.77, 132.54, 132.45, 131.75, 127.92, 124.04, 122.72, 121.03, 119.40, 119.34, 117.65, 115.90, 115.77, 101.89, 101,71, 70.86, 29.19, 26.54. Anal. Calcd for $C_{30}H_{24}N_3O_3ClF_4$: C, 61.51; H, 4.14; F, 12.96; N, 7.17; Cl, 6.05. Found: C, 61.68; H, 4.16; N, 7.14.

*1-{2-[4-(5-Chlorothiophen-2-yl)-5-fluoro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]-urea (**10s**).* LCMS (ESI) m/z 592.0 $(M + H)^+$; orthogonal HPLC purity 93.3%, retention time = 10.32 min (by HPLC method A), 98.0%, retention time = 12.49 min (by HPLC method B). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.89 (br s, 1H), 9.55 (s, 1H), 8.28 (s, 1H), 8.03 (dd, J = 8.4, 0.8 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 3.9 Hz, 1 H), 7.00−7.09 (m, 1H), 6.95 (d, J = 3.9 Hz, 1H), 6.86−6.90 (m, 2H), 6.54 (d, J = 11.0 Hz, 1H), 3.82 (d, J = 10.2 Hz, 1H), 2.99 (d, J = 10.2 Hz, 1H), 1.13 (s, 6 H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.89 (d, J = 238.1 Hz), 152.40, 146.20 (d, J = 11.6 Hz), 142.46, 139.21, 138.37, 133.81, 132.29, 132.10, 129.35, 128.26, 126.79, 124.16, 121.80, 121.74, 120.19 (q, J = 255.5 Hz), 119.50, 118.98, 107.46 (d, J = 18.5 Hz), 101.92 (d, J = 27.7 Hz), 70.80, 44.06 (d, J = 2.3 Hz), 28.92, 26.23. ^{19}F NMR (376 MHz, DMSO-d_6) δ −57.17 (s, 3F), −120.93 (s, 1F).

*1-(2-{5-Fluoro-7-hydroxy-3,3-dimethyl-4-[5-(trifluoromethyl)-pyridin-2-yl]-2,3-dihydro-1H-indol-1-yl}phenyl)-3-[4-(trifluoromethoxy)phenyl]urea (**10t**).* LCMS (ESI) m/z 620.9 $(M + H)^+$; orthogonal HPLC purity 96.0%, retention time = 10.37 min (by HPLC method A), 98.3%, retention time = 12.59 min (by HPLC method B). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.90 (br s, 1H), 9.57 (s, 1H), 9.09 (dd, J = 1.5, 0.7 Hz, 1H), 8.30 (s, 1H), 8.28 (dd, J = 8.0, 2.2 Hz, 1H), 8.05 (dd, J = 8.3, 1.1 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 9.1 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 7.06 (ddd, J = 8.3, 6.4, 2.3 Hz, 1H), 6.87−6.96 (m, 2H), 6.61 (d, J = 11.3 Hz, 1H), 3.83 (d, J = 10.2 Hz, 1H), 3.00 (d, J = 10.2 Hz, 1H), 1.10 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 157.52, 154.98 (d, J = 237.0 Hz), 152.42, 145.87 (d, J = 11.6 Hz), 145.61 (q, J = 4.6 Hz), 142.46, 141.28 (d, J = 3.5 Hz), 139.22, 138.61, 133.62, 133.58 (q, J = 2.3 Hz), 132.12, 126.45, 124.02 (q, J = 32.4 Hz), 124.00, 123.75 (q, J = 272.8 Hz), 121.82, 121.71, 121.62, 120.19 (q, J = 254.3 Hz),119.62, 118.97, 115.49 (d, J = 18.5 Hz), 101.90 (d, J = 26.6 Hz), 71.01, 43.84 (d, J = 2.3 Hz), 28.70, 25.88. ^{19}F NMR (376 MHz, DMSO-d_6) δ −57.23 (s, 3F), −60.88 (s, 3F), −125.00 (s, 1F).

*1-(2-{5-Fluoro-7-hydroxy-3,3-dimethyl-4-[6-(trifluoromethyl)-pyridin-3-yl]-2,3-dihydro-1H-indol-1-yl}phenyl)-3-[4-(trifluoromethoxy)phenyl]urea (**10u**).* LCMS (ESI) m/z 621.3 $(M + H)^+$; orthogonal HPLC purity 98.4%, retention time = 10.10 min (by HPLC method A), >95%, retention time = 11.39 min (by HPLC method B). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.69 (br s, 1H), 8.05 (br s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.58−7.52 (m, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.16−7.10 (m, 1H), 7.05−7.00 (m, 2H), 6.54 (d, J = 10.9 Hz, 1H), 3.82 (d, J = 9.9 Hz, 1H), 3.17 (d, J = 10.1 Hz, 1H), 1.09 (d, J = 1.0 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.89 (d, J = 236.5 Hz), 152.38, 151.26, 145.72 (q, J = 34.3 Hz), 145.66 (d, J = 11.4 Hz), 142.43 (q, J = 1.9 Hz), 140.95, 140.39, 139.19, 138.37, 133.81, 133.39, 132.19, 124.19, 121.80, 121.75, 121.66 (q, J = 273.7 Hz), 120.19, 120.17 (q, J = 255.6 Hz), 119.48, 118.96, 111.98 (d, J = 19.1 Hz), 101.95 (d, J = 26.7 Hz), 70.71, 43.78, 29.26, 26.78.

*1-{2-[4-(2,6-Difluoropyridin-4-yl)-5-fluoro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)-phenyl]urea (**10v**).* LCMS (ESI) m/z 589.0 $(M + H)^+$; orthogonal HPLC purity 99.6%, retention time = 9.98 min (by HPLC method A), >99%, retention time = 11.67 min (by HPLC method B). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.80 (d, J = 7.8 Hz, 1H), 7.46−7.40 (m, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.04−6.97 (m, 1H), 6.93−6.86 (m, 4H), 6.40 (d, J = 10.9 Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H), 3.06 (d, J = 10.1 Hz, 1H), 1.03 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 160.04 (dd, J = 244.1,

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15.3 Hz), 153.90 (d, J = 237.2 Hz), 153.12 (d, J = 16.6 Hz), 152.38, 145.83 (d, J = 11.1 Hz), 142.44, 139.99, 139.18, 138.36, 133.76, 132.23, 124.17, 121.78, 121.74, 121.69, 120.17 (q, J = 255.2 Hz), 119.56, 118.97, 112.42 (d, J = 19.4 Hz), 108.98 (dd, J = 33.3, 4.2 Hz), 102.05 (d, J = 26.4 Hz), 70.76, 43.78, 29.05, 26.52.

*1-{2-[5-Fluoro-4-(5-fluoropyrimidin-2-yl)-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]-urea (**10w**).* LCMS (ESI) m/z 571.9 $(M + H)^+$; orthogonal HPLC purity 99.0%, retention time = 10.83 min (by HPLC method A), 92.3%, retention time = 9.34 min (by HPLC method B). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.84−8.75 (s, 2H), 7.89−7.76 (m, 1H), 7.50−7.37 (m, 2H), 7.17−7.07 (m, 2H), 7.04−6.97 (m, 1H), 6.93−6.84 (m, 2H), 6.40 (d, J = 11.0 Hz, 1H), 3.70 (d, J = 10.4 Hz, 1H), 3.06−3.01 (m, 1H), 1.02 (s, 3H), 0.98−0.92 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.70 (d, J = 5.5 Hz), 155.44 (d, J = 238.6 Hz), 154.03 (d, J = 482.7 Hz), 152.40, 145.78 (d, J = 11.1 Hz), 145.12 (d, J = 19.4 Hz), 142.43, 141.30 (d, J = 4.2 Hz), 139.20, 138.63, 133.50, 131.63, 123.94, 121.82, 121.74, 121.68, 120.17 (q, J = 255.2 Hz), 119.50, 118.95, 115.01 (d, J = 18.0 Hz), 101.85 (d, J = 26.4 Hz), 70.90, 43.68, 28.29, 25.50.

*1-{2-[4-(5-Chloropyrazin-2-yl)-5-fluoro-7-hydroxy-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl]phenyl}-3-[4-(trifluoromethoxy)phenyl]-urea (**10x**).* LCMS (ESI) m/z 588.2 $(M + H)^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.79 (d, J = 1.8 Hz, 1H), 8.52 (t, J = 1.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.56−7.48 (m, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.10 (ddd, J = 8.3, 5.7, 3.1 Hz, 1H), 7.01−6.96 (m, 2H), 6.52 (d, J = 11.0 Hz, 1H), 3.78 (d, J = 9.7 Hz, 1H), 3.14 (d, J = 10.1 Hz, 1H), 1.14 (s, 3H), 1.10 (s, 3H).

1-(4-Bromo-5-fluoro-7-methoxy-1,2-dihydrospiro[indole-3,4′-piperidine]-1′-yl)-2,2-dimethylpropan-1-one (15). A solution of (5-bromo-4-fluoro-2-methoxyphenyl)hydrazine (964 mg, 4.1 mmol) and aldehyde **14** (874 mg, 4.43 mmol) in DCM (15 mL) was stirred at rt for 2 h before it was cooled down to 0 °C. HCl (4 mL, 4 M in 1,6-dioxane) was added and the reaction was gradually warmed up to rt and stirred at rt overnight. The reaction mixture was concentrated to yield a solid mixture, which was dissolved in MeOH (20 mL) and cooled down to rt, and $NaBH_4$ (621 mg, 16.4 mmol) was added portionwise. After 10 min, the reaction mixture was quenched with 1 N HCl, adjusted with concentrated $NaHCO_3$ (aq) to neutral pH, extracted with EtOAc (50 mL × 2), dried over Na_2SO_4, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **15** as a beige solid (610 mg, 37% yield). LCMS (ESI) m/z 401.2 $(M + H)^+$. ^{1}H NMR (400 MHz, methanol-d_4) δ 6.72 (dd, J = 10.5, 1.1 Hz, 1H), 4.46 (d, J = 13.1 Hz, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 2.98 (t, J = 12.5 Hz, 2H), 2.59 (td, J = 13.3, 4.2 Hz, 2H), 1.65 (d, J = 13.1 Hz, 2H), 1.31 (s, 9H).

1-{4-Bromo-5-fluoro-7-methoxy-1-(2-nitrophenyl)-1,2-dihydrospiro[indole-3,4′-piperidine]-1′-yl}-2,2-dimethylpropan-1-one (16). A mixture of **15** (610 mg, 1.53 mmol), 1-bromo-2-nitrobenzene (370 mg, 1.83 mmol), Cs_2CO_3(1.5 g, 4.58 mmol), BINAP (95 mg, 0.15 mmol), and $Pd_2(dba)_3$ (70 mg, 0.08 mmol) in toluene (20 mL) was degassed with Ar, sealed, and heated at 110 °C for 16 h before cooling down to rt. The solid was filtered off, rinsed with EtOAc, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **16** as a brown solid (685 mg, 86% yield). LCMS (ESI) m/z 522.3 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-d) δ 7.92 (dd, J = 8.3, 1.5 Hz, 1H), 7.44−7.38 (m, 1H), 7.13−7.02 (m, 2H), 6.51 (d, J = 10.1 Hz, 1H), 4.53−4.33 (m, 2H), 4.11 (d, J = 9.9 Hz, 1H), 3.89 (d, J = 9.9 Hz, 1H), 3.46 (s, 3H), 2.89−2.75 (m, 2H), 2.72−2.61 (m, 1H), 2.54 (td, J = 13.1, 4.5 Hz, 1H), 1.75 (d, J = 11.6 Hz, 1H), 1.54 (br s, 1H), 1.24 (s, 9H).

1-{5-Fluoro-4-(4-fluorophenyl)-7-methoxy-1-(2-nitrophenyl)-1,2-dihydrospiro[indole-3,4′-piperidine]-1′-yl}-2,2-dimethylpropan-1-one (17b). A mixture of **16** (101 mg, 0.194 mmol), 4-fluorophenylboronic acid (33 mg, 0.233 mmol), $Pd(PPh_3)_4$ (24 mg, 0.019 mmol), and Na_2CO_3 (0.5 mL, 1 M aq) in DME (4 mL) was degassed with Ar, sealed, and heated at 100 °C for 48 h before cooling down to rt. The reaction mixture was partitioned between water and ether, washed with brine, dried over $MgSO_4$, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **17b** as an orange solid (88 mg, 85% yield). LCMS (ESI) m/z 536.4 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-d) δ 8.05 (dd, J = 8.1, 1.5 Hz, 1H), 7.47 (ddd, J = 8.3, 7.1, 1.5 Hz, 1H), 7.24 (d, J = 5.6 Hz, 2H), 7.20−7.15 (m, 1H), 7.13−7.04 (m, 3H), 6.57 (d, J = 10.6 Hz, 1H), 4.22 (br s, 2H), 3.84 (d, J = 9.9 Hz, 1H), 3.59 (s, 3H), 2.72 (t, J = 12.9 Hz, 1H), 2.56 (t, J = 12.8 Hz, 1H), 1.81 (d, J = 13.4 Hz, 1H), 1.61 (td, J = 13.4, 4.3 Hz, 3H), 1.47 (dd, J = 13.6, 2.0 Hz, 1H), 1.18−1.03 (m, 9H).

2-{1′-(2,2-Dimethylpropyl)-5-fluoro-4-(4-fluorophenyl)-7-methoxy-1,2-dihydrospiro[indole-3,4′-piperidine]-1-yl}aniline (18b). To a solution of **17b** (2.29 g, 4.28 mmol) in EtOAc (21.38 mL) and MeOH (21.38 mL) were added ammonium chloride (4.57 g, 86 mmol) and zinc (5.59 g, 86 mmol). The reaction was stirred at rt for 1 h. The solid was filtered off, rinsed with EtOAc, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give aniline as a white solid (1.44 g, 67% yield). LCMS (ESI) m/z 506.3 $(M + H)^+$. To a solution of the above aniline (1.44 g, 2.85 mmol) in DCM (28.5 mL) was added RED-Al (4.34 mL, 14.24 mmol) dropwise for 20 min. The reaction turned cloudy and was stirred at rt overnight. The reaction was quenched by adding drops of aqueous $NaHCO_3$ into the reaction mixture. It was then diluted with DCM and washed with aqueous $NaHCO_3$. The aqueous layer was extracted again with DCM. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **18b** as a white foam (858 mg, 61% yield). LCMS (ESI) m/z 492.4 $(M + H)^+$.

3-(5-Chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)-1-(2-{1′-(2,2-dimethylpropyl)-5-fluoro-4-(4-fluorophenyl)-7-methoxy-1,2-dihydrospiro[indole-3,4′-piperidine]-1-yl}phenyl)urea (19c). To a solution of **18b** (858 mg, 1.745 mmol) and K_2CO_3 (482 mg, 3.49 mmol) in DCE (15 mL) was added 4-nitrophenyl chloroformate (387 mg, 1.920 mmol) portionwise, and the solution was stirred for 1 h at rt. 5-Chlorothiazolo[5,4-*b*]pyridin-2-amine (486 mg, 2.62 mmol) and DMAP (213 mg, 1.745 mmol) were added, and the mixture was stirred at 75 °C for 4.5 h. The reaction was diluted with DCM and washed with 1 N NaOH (30 mL × 2) and brine consecutively. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography, eluted with EtOAc/hexanes to give **19c** as a pale yellow solid (981 mg, 80% yield). LCMS (ESI) m/z 703.5 $(M + H)^+$. ^{1}H NMR (400 MHz, chloroform-d) δ 8.04 (br s, 1H), 7.44 (br s, 1H), 7.35−7.27 (m, 1H), 7.22 (d, J = 8.6 Hz, 2H), 7.16−7.03 (m, 5H), 6.58 (d, J = 10.9 Hz, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.56 (s, 3H), 3.26 (d, J = 10.1 Hz, 1H), 2.36 (t, J = 13.0 Hz, 2H), 2.10−1.93 (m, 2H), 1.82−1.70 (m, 2H), 1.65−1.58 (m, 1H), 1.39−1.11 (m, 3H), 0.63 (s, 9H).

3-(5-Chloro-[1,3]thiazolo[5,4-*b*]pyridin-2-yl)-1-(2-{1′-(2,2-dimethylpropyl)-5-fluoro-4-(4-fluorophenyl)-7-hydroxy-1,2-dihydrospiro[indole-3,4′-piperidine]-1-yl}phenyl)urea (20c). To a solution of **19c** (1.27 g, 1.806 mmol) in DCM (36.1 mL) was added tetrabutylammonium iodide (4.00 g, 10.84 mmol). The reaction was cooled down to −78 °C and degassed several times with vacuum/argon. Trichloroborane (9.03 mL, 9.03 mmol) was added dropwise. The reaction was slowly warmed to rt overnight. MeOH and H_2O were added, and the mixture was stirred for 30 min. The reaction was concentrated and diluted with DCM; washed with saturated $NaHCO_3$, NH_4Cl, and brine; dried over $MgSO_4$; filtered; and concentrated. The crude mixture was purified by flash chromatography, eluted with EtOAc/hexanes to give **19c** as a brownish solid, which was further purified by reverse-phase preparative HPLC to give **20c** as a brownish solid (430 mg, 30% yield). Compound **20c** could be converted to the methanesulfonate salt by dissolving in EtOAc/EtOH, followed by addition of methanesulfonic acid (MSA; 1.1 equiv). The salt precipitate was filtered and washed with EtOH. LCMS (ESI) m/z 689.3 $(M + H)^+$; orthogonal HPLC purity 100%, retention time = 7.71 min (by HPLC method A), 100%, retention time = 9.29 min (by HPLC method B). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 11.81 (s, 1H), 9.66 (s, 1H), 9.13 (br s, 1H), 8.75 (br s, 1H), 8.15 (dd, J = 8.20, 1.26 Hz, 1H), 8.04 (d, J = 8.51 Hz, 1H), 7.50 (J = 8.51 Hz, 1H), 7.50−7.24 (m, 4H), 7.20 (J = 8.20 Hz, 1H), 7.17 (dd, J = 7.88, 1.58 Hz, 1H), 7.06 (m, 1H), 6.56 (J = 10.7, 1H), 4.06 (d, J = 10.09 Hz, 1H), 3.27 (d, J = 10.40 Hz, 1H), 2.93−3.22 (m, 4H), 2.39 (dd, J = 13.24, 3.78 Hz, 1H), 2.21 (dd, J = 13.08, 3.63 Hz, 1H), 1.61−2.11 (m, 4H), 0.90 (s, 9H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 162.75, 160.80, 159.16, 155.54, 154.63, 153.68, 151.32, 144.32, 144.12, 141.91, 138.03, 136.18, 134.40, 133.87, 133.30, 132.83, 129.58, 129.34, 125.65, 124.22, 123.19, 121.89, 119.04, 116.07, 115.48, 102.74, 65.70, 56.03, 49.80,

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44.24, 30.97, 26.48. Anal. Calcd for $C_{36}H_{35}ClF_2N_6O_2S{\cdot}0.93CH_4SO_3$: C, 55.37; H, 5.49; N, 10.09. Found: C, 55.28; H, 5.23; N, 9.98.

Compounds 20a and 20b. Compounds **20a** and **20b** were prepared according to the procedure described for **20c**.

*1-(2-{4-(4-Chlorophenyl)-1′-(2,2-dimethylpropyl)-5-fluoro-7-hydroxy-1,2-dihydrospiro[indole-3,4′-piperidine]-1-yl}phenyl)-3-[4-(trifluoromethoxy)phenyl]urea (**20a**).* LCMS (ESI) *m/z* 697.5 $(M + H)^+$; purity 94.3%, retention time = 6.87 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4, mixture of two rotamers) δ 7.96–7.84 (m, 1H), 7.57–7.44 (m, 5H), 7.38–7.31 (m, 1H), 7.27–7.10 (m, 3H), 7.06–6.97 (m, 2H), 6.58–6.48 (m, 1H), 4.11–4.01 (m, 1H), 3.55–3.46 (m, 1H), 3.18–3.01 (m, 3H), 2.50–2.33 (m, 2H), 2.28–1.94 (m, 3H), 1.90–1.71 (m, 2H), 1.03–0.96 (s, 9H).

*1-(2-{1′-(2,2-Dimethylpropyl)-5-fluoro-4-(4-fluorophenyl)-7-hydroxy-1,2-dihydrospiro[indole-3,4′-piperidine]-1-yl}phenyl)-3-[4-(trifluoromethoxy)phenyl]urea (**20b**).* LCMS (ESI) *m/z* 681.2 $(M + H)^+$; purity 95.9%, retention time = 6.66 min (by HPLC method C). ^{1}H NMR (400 MHz, methanol-d_4, mixture of two rotamers) δ 7.97–7.86 (m, 1H), 7.58–7.51 (m, 2H), 7.51–7.32 (m, 2H), 7.31–7.22 (m, 2H), 7.19 (d, J = 8.8 Hz, 2H), 7.13 (ddd, J = 8.2, 6.1, 2.7 Hz, 1H), 7.06–7.00 (m, 2H), 6.57–6.48 (m, 1H), 4.11–4.03 (m, 1H), 3.53–3.46 (m, 1H), 3.20–2.91 (m, 4H), 2.50–2.33 (m, 2H), 2.28–1.69 (m, 4H), 1.05–0.92 (s, 9H).

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Notes

The authors declare no competing financial interest.

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