18 J. Med. Chem. 2010, 53, 18–36
DOI: 10.1021/jm9005912

Journal of Medicinal Chemistry Article

Structure−Activity Relationship Studies Leading to the Identification of (2*E*)-3-[l-[(2,4-Dichlorophenyl)methyl]-5-fluoro-3-methyl-l*H*-indol-7-yl]-*N*-[(4,5-dichloro-2-thienyl)sulfonyl]-2-propenamide (DG-041), a Potent and Selective Prostanoid EP3 Receptor Antagonist, as a Novel Antiplatelet Agent That Does Not Prolong Bleeding

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Received May 7, 2009

The EP_3 receptor on the platelet mediates prostaglandin E_2 potentiation of thrombogenic coagonists including collagen and adenosine diphosphate (ADP). A pharmacophore driven approach led to the identification of diverse peri-substituted heterocycles as potent and selective EP_3 receptor antagonists. A simultaneous chemical optimization and druglike assessment of prioritized molecules converged on a lead compound **50** (DG-041) that displayed favorable in vitro and functional activities as an inhibitor of human platelet aggregation. This agent is currently in human clinical trials for the treatment of atherothrombosis.

Introduction

The EP_3 receptor is one of eight G-protein-coupled receptors (GPCRs) that belong to the prostanoid receptor family.[1] Prostanoids are ubiquitous autocrine mediators involved in numerous physiological and pathological processes including inflammation. PGE_2, the natural ligand for the EP_3 receptor, is synthesized from arachidonic acid by sequential action of COX-1[a]/COX-2 and PGE synthase. PGE_2 is known to act through four GPCR receptors referred to as EP_{1-4}. Among these four, the EP_3 receptor is unique, as it signals through G_i (inhibitory G-protein). The other three EP receptors (EP_1, EP_2, and EP_4) are coupled via G_s (stimulatory G-protein).

In the blood compartment, EP_3 receptors are expressed on platelets. Their activation results in lowering intracellular cAMP levels. This step is associated with an increased sensitivity of platelets to a coagonist such as collagen or ADP, resulting in platelet activation and subsequent aggregation.[2,3] Studies of EP_3-null platelets, harvested from EP_3-gene knockout mice, suggest its role in the lesion-specific atherothrombosis over atherosclerotic plaque.[4] Plaque rupture exposes the collagen-rich subendothelial matrix to platelets in the context of PGE_2 produced by the inflamed plaque, thereby triggering thrombosis. Thrombosis is blocked, however, if the platelets lack EP_3.

Standard antiplatelet medications used to reduce risk of heart attack and stroke increase risk of severe or fatal bleeding.[5] This is because such medications have a global impact on platelet function. Irreversible COX-1 inhibitors (e.g., aspirin) or irreversible P_2Y_{12} ADP receptor antagonists (e.g., clopidogrel, prasugrel), reduce atherothrombosis but also negatively impact hemostasis by reducing platelet aggregation in response to vascular breech.[6] Since neither platelets nor the healthy arterial wall produces PGE_2, inhibition of the PGE_2-EP_3 signaling is not expected to affect bleeding.[2,4] Thus, EP_3 antagonists have the potential to lower risk of atherothrombosis without increasing bleeding risk. Recently, we reported the identification and pharmacology of **50**, a potent and selective EP_3 receptor antagonist, that is currently in phase II clinical trials as a novel antiplatelet agent.[7] In this report, we describe both discovery and the structure−activity relationship (SAR) studies of peri-substituted indole derivatives that yielded **50**.

Results and Discussion

Ligand-Based Design of EP_3 Receptor Antagonists. Considering structural information for both the endogenous ligand PGE_2 (**1**) and the reported EP_3 antagonist acylsulfonamides (**3**),[8] we developed a pharmacophore hypothesis and identified respective molecules to fit this putative model (Figure 1). Our initial medicinal chemistry effort focused on the synthesis of 1,3-disubstituted five-membered heterocycles, which appeared to fit this initial pharmacophore model. Unfortunately, in our hands these molecules featured weak EP_3 binding activity and no apparent structure−activity relationship (SAR) with the IC_{50} values in the low micromolar range. Representative examples (**4**−**9**) of this series are shown in Table 1.

Further comparison of PGE_2 (**1**) and sulprostone (**2**), an EP_3 selective synthetic agonist, suggested tolerance for structural variations in the acyclic portion of PGE_2 for binding to EP_3 . We reasoned that the proper spatial arrangement of peripheral pharmacophores should provide more

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[a] Abbreviations: ADP, adenosine diphosphate; CHO, Chinese hamster ovary; COX-1, cyclooxygenase 1; COX-2, cyclooxygenase 2; PAA, platelet aggregation; PGE, prostaglandin E; P_2Y_{12}, adenosine diphosphate G-protein-coupled receptor; clopidrogel, methyl (2*S*)-(2-chlorophenyl)(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetate; prasugrel, 5-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate.

 Published on Web 12/03/2009

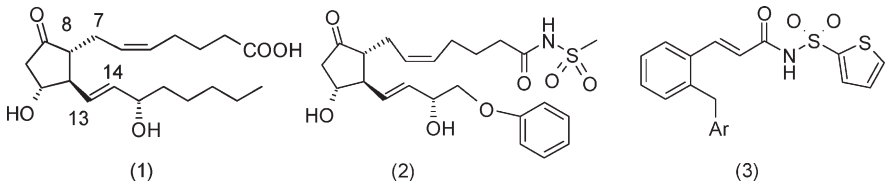
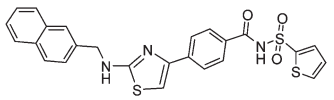
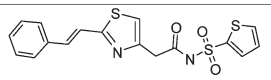
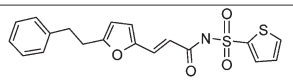
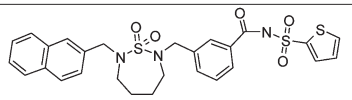
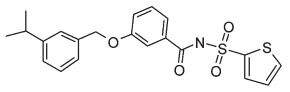
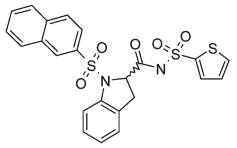


Figure 1. Known EP_3 agonists and antagonists.

Table 1. Representative Examples of 1,3-Disubstituted Heterocycles

Cmpd No.		hEP_3 IC_{50} (μM)
4		6.49
5		17.71
6		7.2
7		6.40
8		34.86
9		5.95

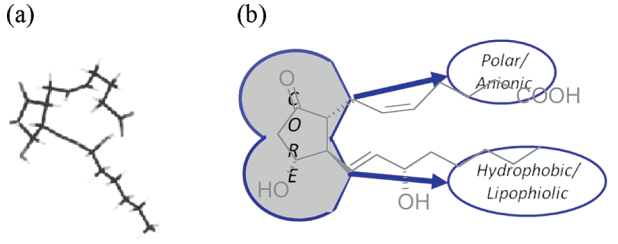
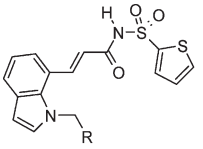


Figure 2. Knowledge of ligand conformation to aid design of small molecule antagonists: (a) energy minimized structure of PGE_2;[8] (b) representation of deCODE's hypothesis and its overlay on PGE_2.

potent EP_3 binders. Initial data for derivatives (**3**) also supported this notion. Energy minimization studies of PGE_2 (Figure 2a) and our structures were in agreement with the literature data.[9] Two main assumptions were applied to the design of new cores: (i) in order to ascertain optimal spatial orientation of the substituents, these were to project key binding elements, namely, polar and hydrophobic binding groups through nonvicinal arrangement, and (ii) the key anchor atoms of the core that would bear acidic and hydrophobic pharmacophoric features would most likely overlap with the C7/C13 or C8/C14 atoms of PGE_2 (Figure 2b).

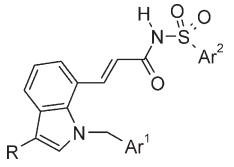


(**10**) R = 2-Napthyl
(**11**) R = Phenyl

Compound	(10)	(11)
hEP_3 (binding, IC_{50}, nM)	4.5	98
hEP_3 (CHO-cells, IC_{50} nM)	45	119

Figure 3. Initial hit from rational design.

Table 2. Indole-Core-Derived 1,7-Disubstituted Analogues[a]



compd	Ar^1	R	hEP_3 IC_{50} (nM)
11	phenyl	H	98
12	3,4-dichlorophenyl	CH_3	14.2
13	2,4-dichlorophenyl	H	2
14	2,6-dichlorophenyl	H	420
15	2,4-dichlorophenyl	CH_3	5
16	3,4-dimethylphenyl	H	71
17	3,5-dimethoxyphenyl	H	88
18	3,4-OCH_2O-phenyl	H	14
19	3-CF_3-phenyl	H	25
20	2-CF_3-phenyl	H	42
21	2-biphenyl	H	326
22	4-methoxy phenyl	H	34
23	3-pyridyl	H	4044
24	3-pyridyl	CH_3	2838
25	2-pyridyl	CH_3	10091

[a] Ar^2 = 2-thiophenyl.

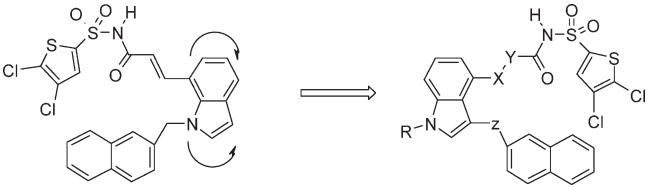


Figure 4. 1,7- vs 3,4-indole derivatives.

Table 3. 3,4-Disubstituted Indole Analogues (Z = CH_2)

compd	X−Y	R	hEP_3 IC_{50} nM
26	CH=CH	H	2.5
27	CH=CH	CH_3	2.7
28	CH_2−CH_2	H	2.4
29	CH_2−CH_2	CH_3	2.5
30	O−CH_2	H	3.0

In order to provide an element of preorganization for the final molecule, we selected peri-substituted bicyclic heterocycles as our initial templates. Gratifyingly, the

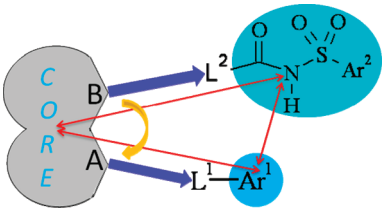
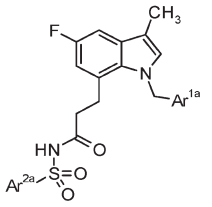
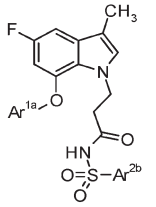
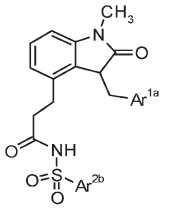
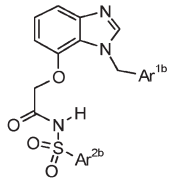
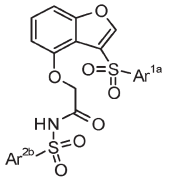
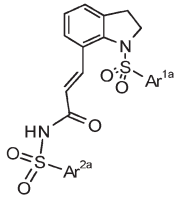
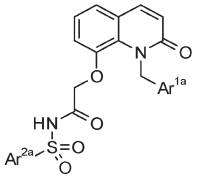
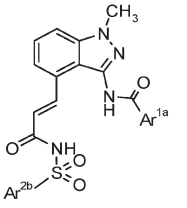
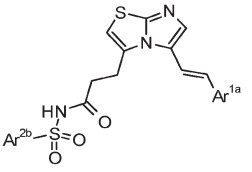
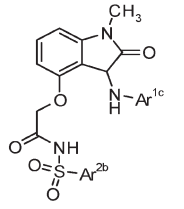
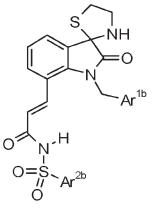
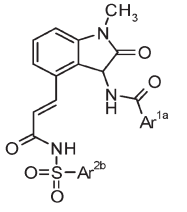


Figure 5. Generic pharmacophore highlighting vectors with solid blue arrows.

indole analogues (**10**) and (**11**) featured good activity in a human (h) EP_3 receptor-binding assay featuring nanomolar IC_{50} values (Figure 3). Pharmacologically, compounds **10** and **11** displayed full antagonist activity in a follow-up functional assay (45 and 119 nM, respectively, in CHO cells).

Following this initial success, we prepared a number of indole analogues to explore both electronic and steric requirements of this binding mode.[10] Compounds **11**–**25** (Table 2; hEP_3 binding IC_{50} values are shown) highlight

Table 4. Diverse Cores Provided Active Analogues with hEP_3 IC_{50} < 100 nM[a]

No	Ar_1-L_1-Core-L_2-Ar_2	hEP3 IC50 nM	No	Ar_1-L_1-Core-L_2-Ar_2	hEP3 IC50 nM
31		22	**32**		2.2
33		3	**34**		1.1
35		8.9	**36**		3.6
37		11	**38**		27.6
39		89.5	**40**		65.7
41		4.9	**42**		14.6

[a] Ar^{1a} = 2-naphthyl. Ar^{1b} = 2,4-dichlorophenyl. Ar^{1c} = 3,4-dichlorophenyl. Ar^{2a} = 2-thiophenyl. Ar^{2b} = 2,3-dichloro-5-thiophenyl.

representative SAR for the N-substituted derivatives of indole. Compared to the parent *N*-benzyl analogue **11**, more lipophilic meta and para substituents (examples **12**−**15** and **18**) provided good activity, 2,4-dichlorobenyl derivative **13** being the most active in these series. Incorporation of methyl group at C3 position of the indole core did not affect activity, as analogues **13** and **15** were essentially equally active. Piperonyl (**18**) and 4-methoxy (**22**) molecules featured better potency than the respective 3,5-dimethoxy ether **17**. Ortho substituents (see **20**, **21**, and **14**) afforded less potent compounds. More polar pyridyl derivatives **23**−**25** were considerably less active.

Considering the lipophilic nature of molecules **11**−**25**, we routinely determined hEP_3 IC_{50} values in the presence of varying concentrations of human serum albumin (HSA) and/or 10% human serum (HS). Notably, the 2,3-dichlorothiophene sulfonamide substituent consistently featured low fold shift ($< 10\times$) in the presence of plasma protein. Consequently, this sulfonamide moiety was favored in our SAR studies.

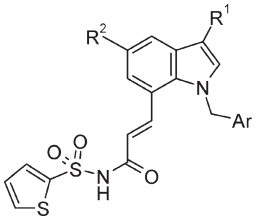
We further hypothesized that structural variations in the bicyclic core portion of the molecule should be tolerated as long as preorganization of the key binding elements, namely, "acidic proton and lipophilic tail", was maintained (Figure 4). For instance, 3,4- versus 1,7-substitution patterns provided similar trajectory for the key binding elements (Figure 4). Indeed, 3,4-disubstituted indole analogues showed similar or better potency compared to the respective 1,7-disubstituted molecules (**26**−**30**) in the binding assay (Table 3).

Utilizing the SAR gathered thus far, we further refined our pharmacophore hypothesis by studying torsional effects for the key vectors tethering the core to the putative binding elements via linkers L_1 and L_2 (Figure 5). A resulting pharmacophore model[11] yielded diverse [6.5], [6.6], and [5.5] bicyclic scaffolds as hits. The most active molecules in these series featuring $IC_{50} < 100$ nM in the hEP_3 binding assay are summarized in Table 4.

Lead Optimization. In order to further prioritize our lead candidates, we investigated their in vitro metabolic stability in multiple species including rat, dog, and human liver microsomes. Several peri-substituted 1,7-disubstituted indoles had low metabolic stability in the assay. This effect was irrespective of the *N*-indole substituents and was likely derived from the indole scaffold. As a confirmation, we incubated a representative molecule **11** with rat liver microsomes (RLM) followed by LC/MS/MS analysis of its metabolic profile. Studies revealed two major metabolites that matched mono- and bis-oxidative products most likely derived from the C3 and C5 positions of the parent indole core. The observed metabolic liability was successfully addressed by incorporating a methyl group at C3 carbon and a fluorine atom at C5 of the parent template. The resulting compounds **43** and **44** (Table 5) retained affinity against EP_3 and displayed adequate stability in the rat liver microsome assay.

Several 3,4-disubstituted indoles also displayed considerable metabolic instability, although the phenomenon was species-dependent. For example, compound **30** was stable upon incubation with mouse and rat liver microsomes (71% and 68% parent remaining after 30 min). However, it was rapidly metabolized (2% parent remaining after 30 min) in the presence of human liver microsomes (HLM) to yield an inactive molecule, a product of oxidation at the benzylic methylene carbon (Figure 4, Z = CO, X−Y = O−CH_2, **45**). The structure of **45** was confirmed by an independent synthesis.

Table 5. Metabolic Stability and hEP3 Receptor Binding Assay (IC_{50})



					% parent remaining[a]	
compd	Ar	R^1	R^2	hEP_3 IC_{50} (nM)	15 min	30 min
10	2-naphthyl	H	H	4.5	8	0
13	2,4-dichlorophenyl	H	H	1.9	22.2	4.2
43	2-naphthyl	CH_3	F	14	88	82
44	2,4-dichlorophenyl	CH_3	F	3	77	56

[a] Following incubation with rat liver microsomes.

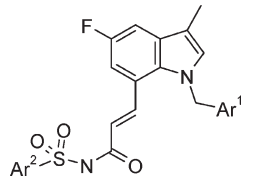
We subsequently conducted an extensive SAR study with the metabolically stable 1,7-disubstituted 3-methyl-5-fluoroindole core varying Ar^1 and Ar^2 substituents. The data (Table 6) indicated that more lipophilic meta and para monosubstituted, ortho/para disubstituted, and 2-naphthyl analogues as Ar^1 provided improved activity when compared to the unsubstituted *N*-benzyl analogue (**11**). Although several analogues exhibited good activity in the normal buffer, several of these showed relatively poor IC_{50} in the presence of 10% human serum (Table 7), indicating high plasma protein binding (PPB). As presented in Table 7, the analogues **30**, **50**, and **51**, containing 4,5-dichloro thiophene as Ar^2, provided low PPB potential.

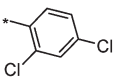
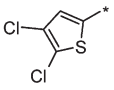
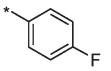
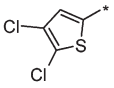
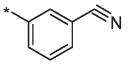
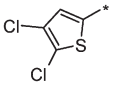
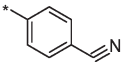
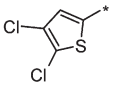
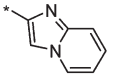
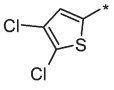
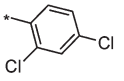
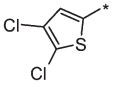
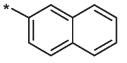
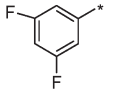
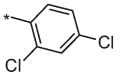
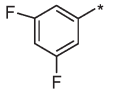
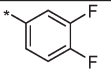
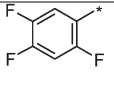
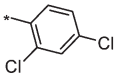
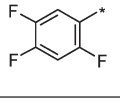
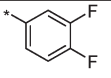
The analogues derived from diverse cores containing peri-substituents in general showed good to excellent selectivity when profiled against a panel of other EP receptors and the IP receptor. The selectivity data for a number of potent EP_3 antagonists from the 1,7-indole, 3,4-indole, and 1,7-benzimidazoles series are shown in Table 8. The 2,4-dichlorobenzyl derivatives (**13**, **30**, **34**, and **50**) from different structural series consistently yielded $>100-1000$ selectivity. The analogue **51** that contained 2-naphthyl substituent displayed lower selectivity for EP_1. Overall, molecule **50** afforded the best combination of in vitro activity and selectivity across receptor panels along with low potential for PPB (Tables 6, 7, and 8).

In the next optimization step, we varied the tether length for the acidic portion of the metabolically stable 1,7-disubstituted indole core. The molecule **44** (Table 5) featuring a two atom spacer C=C between the core and the acylsulfonamide group showed good EP_3 activity, metabolic stability, and low potential for PPB.[7]

Lead Candidate. Compound **50** was found to be a non-competitive antagonist of PGE_2 binding to EP_3. In addition, preincubation of EP_3 receptor with **50** followed by extensive washing completely abolished [^{3}H]PGE_2 binding (Figure 6A). This behavior was common for other potent EP_3 antagonists, including **30**. We speculated that the analogues bearing the indole core behave as quasi-irreversible EP_3 antagonists. In order to differentiate slow K_{off} rate from the covalent interaction of **50** with the receptor, we conducted a series of displacement binding experiments. Specifically, a solution of 1 mM dithiothreitol (DTT) as reducing agent did not affect the displacement curve

Table 6. SAR of 1,7-Disubstituted 3-Methyl-5-fluoroindole Series



Cmpd. No.	Ar^2	Ar^1	hEP_3 IC_{50} (nM)
44			3
46			180
47			3.7
48			6.6
49			1.3
50			4.6
51			7
52			2
53			314
54			13.8
55			267.4

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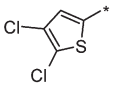
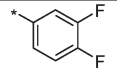
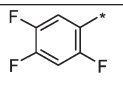
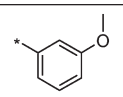
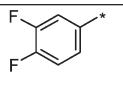
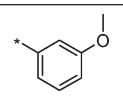
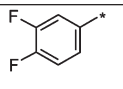
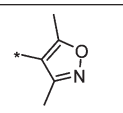
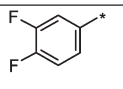
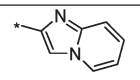
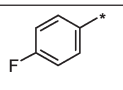
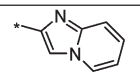
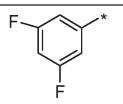
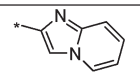
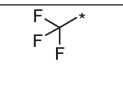
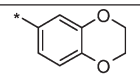
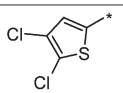
56			501
57			5.7
58			1.0
59			14.5
60			2.3
61			46.4
62			3.6
63			20% @ 1uM
64			68.7% @1uM
65			70% @1uM

(Figure 6C), ruling out the possibility that **50** acts as a Michael acceptor for the thiolate group of DTT or for an −SH group on EP_3.[12] Notably, molecule **30**, lacking an olefin moiety, also displayed quasi-irreversible antagonism against EP_3 presumably due to a slow K_{off}. The similar behavior of the analogues **66** and **67** (Figure 6B)[13] further supported this notion.

Studies with EP_3 gene knockout mice had shown that when animals were injected with arachidonic acid via the tail vein, thromboembolism in the lung and consequent mortality were greatly reduced.[4] We therefore explored the protection afforded by our lead compounds in this assay. Adult mice were gavaged with **30**, **50**, and **51** at 30 and 100 mg/kg single dose. All molecules were delivered as a soluble formulation in HPβCD. Compound **50** afforded roughly 70% protection in the assay (Figure 7). Although efficacious in the thromboembolism test, **30** was unstable upon incubation with human liver

microsomes (vide supra), so we prioritized **50** for further development.

Further efficacy assessement of compound **50** was carried out by measuring inhibition of collagen and sulprostone induced platelet aggregation (PAA) using whole human blood. Compound **50** furnished similar IC_{50} (218 nM) for PAA inhibition in blood derived from both male and female subjects (Figure 8).

Table 7. Fold-Shift in IC_{50} for Selected Analogues in the Presence of Plasma Proteins (Human Serum, HS)

compd	hEP_3 IC_{50} (nM)[a]	hEP_3 IC_{50} (nM) buffer + 10% HS[b]	fold-shift in IC_{50} in presence of 10% HS
10	4.5	378	84
11	98	6129	623
12	14.2	7155	504
13	2	357	178
16	71	4223	60
18	14	2208	158
19	25	4048	162
20	42	2710	65
22	34	5568	164
30	3	5	1.7
31	22	1146	52
32	2.2	2730	1241
33	3	635	212
34	1.1	79	72
35	8.9	2751	309
36	36	1552	43
37	27	7260	269
38	27.6	1683	61
41	4.9	880	180
42	14.6	2252	154
43	14	619	44
44	3	299	100
47	3.7	466	126
48	6.6	595	90
49	1.3	682	524
50	4.6	6	1.3
51	7	36	5.1
57	5.7	261	46
58	0.9	147	163
59	14.5	4790	330
60	2.3	393	170
61	46.4	6939	150
62	3.6	2045	568

[a] Normal assay buffer. [b] Assay buffer containing 10% human serum.

In ADME-PK studies, **50** showed similar metabolic profiles in mouse, rat, dog, monkey, and human liver microsome assays (Table 9). It featured weak to moderate inhibition of hCYP3A4, 2D6, and 2C19 isozymes but showed strong inhibition of hCYP2C9 (Table 10) with no potential to cause its metabolism-dependent inhibition. Although potentially of concern, drug−drug interaction studies conducted in healthy human volunteers showed that **50** does not inhibit CYP3A4 or CYP2C9, likely because of the relatively low free drug concentration in the presence of human plasma proteins (~0.7%).

Below is a summary of the ADME/PK study results for compound **50**. It exhibited high potential for GI permeability in Caco2 assay ($P_{app} = 11.2 \times 10^{-6}$ cm/s) with no significant efflux. The agent was marginally water-soluble (23 μg/mL, pH7) as measured by HPLC (shake flask method). We speculated that the limited solubility was rate-limiting for absorption through the intestinal wall. As a result, bioavailability (F, %) varied with formulation. Reduction in particle size (e.g., micronization) or utilization of solubility enhancing excipients increased F.[14] Following intravenous and oral dosing, compound **50** formulated with hydroxypropyl β-cyclodextran (HPβCD) showed favorable pharmacokinetic profiles in preclinical species (10 mg/kg oral dose; F of 27% and 54%, $t_{1/2}$ of 4.1 and 3.1 h, C_{max} of 2.7 and 18.1 μM for rat and dog, respectively).

Compound **50** was well tolerated in preclinical safety pharamacology and 3-month chronic toxicity studies in rat (up to 150 mg/kg) and dog (up to 20 mg/kg) following oral dosing. It was not genotoxic in AMES or in in vitro micronucleus assays. The compound **50** currently is in

Table 8. Prostanoid Receptor Selectivity[a] across Series in [^{3}H]Ligand Displacement Binding Assays

	IC_{50} (nM)					
compd	hEP_3	hEP_1	hEP_2	hEP_4	hIP	mEP_3
13	2	8104	> 10000	8178	ND	28
30	3	6354	12261	6498	ND	4
34	1.1	7959	4832	10172	5875	4
50	4.6	> 20000	4169	8039	14414	11
51	7	360	32921	3647	8823	5

[a] Experimental IC_{50} values (±SEM) from displacement binding analysis with a minimum of five experiments per value. Displacement binding was assessed with [^{3}H]PGE_2 for human EP_{1-4} receptors and the mouse EP_3 receptor, with [^{3}H]iloprost for the human IP receptor.

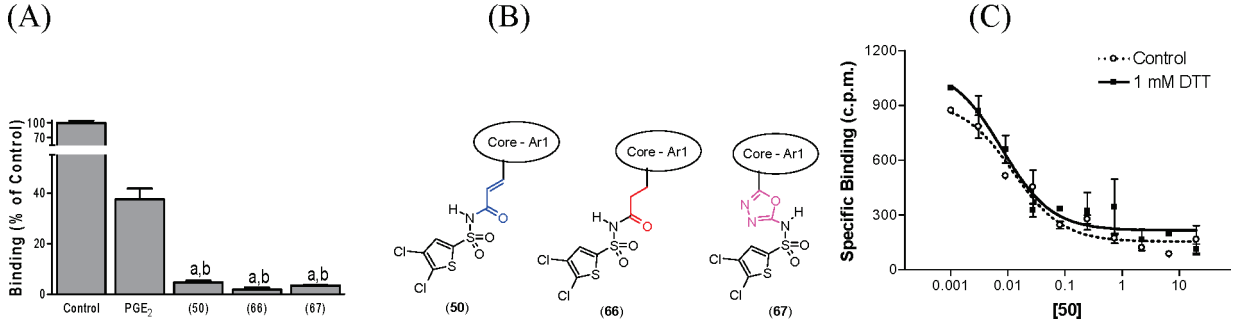


Figure 6. (A) Quasi-irreversibility of **50** and its structural analogues for binding to hEP_3 receptor. Membranes were washed three times for 1 h at room temperature and incubated with 2 nM [^{3}H]PGE_2 for an additional hour at 30 °C. Quantified binding is expressed as percentage of control (buffer only) membranes and shown as the mean ± SEM of three independent experiments. Statistical analysis was performed by impaired nonparametric Student t test using GraphPad Prism software: (a) $p < 0.01$ vs control; (b) $p < 0.01$ vs PGE_2-incubated membranes. (B) Structural features of probe analogues **50**, **66**, and **67**. All analogues have Ar_1 = 2,4-dichlorobenzyl and 3-methyl-5-fluoroindole as the core. (C) Effect of reducing agent dithiothreitol (DTT) on binding of **50** to hEP_3 DR.

human PhII clinical trials as a novel antiplatelet agent in cardiovascular disease.

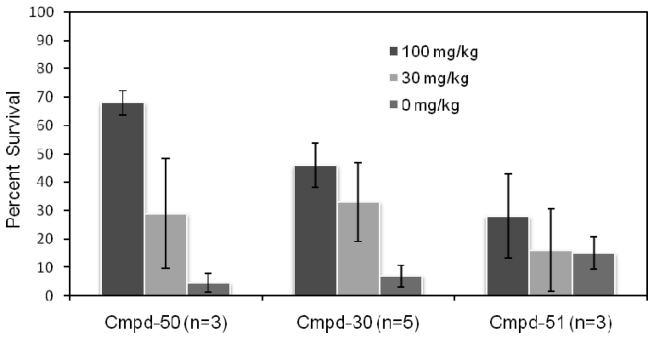


Figure 7. Protection from pulmonary thromboembolism by **30**, **50**, and **51**. Test compounds were given orally formulated in HPβCD. Thirty minutes after dosing, mice were challenged by injection of arachidonic acid (30 mg/kg) into the lateral tail vein.

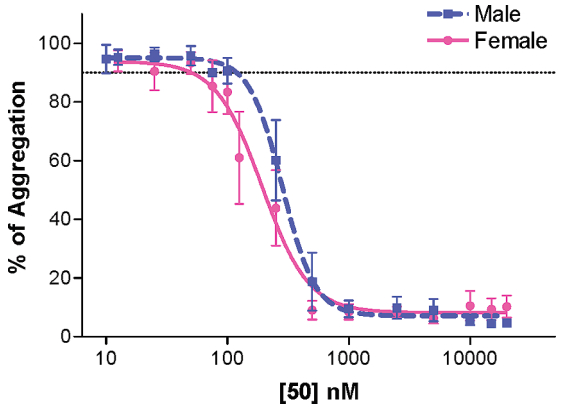


Figure 8. Inhibition of human platelet aggregation by compound **50**. Platelet aggregation was triggered by collagen combined with sulprostone,[1] a selective EP3 agonist.

Synthesis. Peri-substituted bicyclic analogues described here were synthesized as outlined in Schemes 1−6. Reaction of commercially available 7-formylindole (**68**) with triethyl phosphonoacetate followed by base hydrolysis of the ethyl ester **69** provided the acid **70**. Coupling of acid **70** with 2-thiophenesulfonamide using EDCI/HOBt provided the key intermediate **71**, which, following alkylation of the indole nitrogen, provided 1,7-disubstitued indole analogues **10**, **11**, **13**−**22**. As shown in Scheme 2, the C3 methylindole intermediate **73** was prepared by Heck coupling of the 3-methyl-7-bromoindole (**72**) with methyl acrylate. Base hydrolysis followed by formation of the acylsulfonamide **75** and indole nitrogen alkylation, as shown in Scheme 1, provided analogues **12**, **15**, **24**, and **25**.

The 3,4-disubstituted indole analogues were prepared starting from 4-bromoindole (**76**, Scheme 3). C3-Acylation of **76** was performed using $EtMgBr/ZnCl_2$ protocol, analogous to the procedure of Bergman and Venemalm.[15] Reduction of ketone **77** with borane followed by Heck coupling of the bromoaryl **78** provided the key 3,4-disubstituted intermediate **79**. Subsequent transformation of the ester via acid **80** provided the target compound **26**. N-Methylation of **79** afforded **81**, and subsequent derivatization of the corresponding acid **82** provided analogue **27**. Hydrogenation of **79**

Table 9. In Vitro Metabolic Stability of Compound **50**[a]

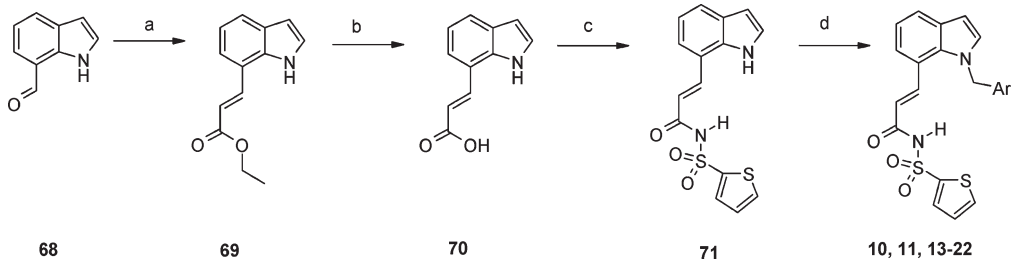
% parent remaining at 30 min				
mouse	rat	dog	monkey	human
72.0 ± 4.7	77.7 ± 0.4	88.6 ± 1.4	88.4 ± 3.6	80.9 ± 0.5

[a] 5 μM compound was incubated with mouse, rat, dog, monkey, and human liver microsomes, and % parent remaining was determined by LC/MS/MS.

Table 10. hCYP Inhibition IC_{50} (μM) for Compound **50**

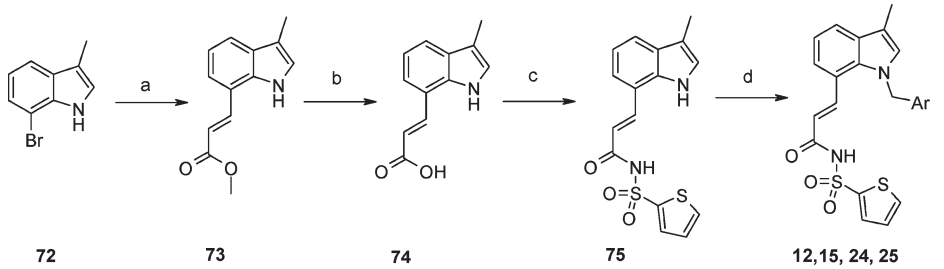
1A2	2C19	2C9	2D6	3A4 (DBF)	3A4 (BFC)
> 10	6.6	0.03	> 10	7.6	1.5

Scheme 1[a]



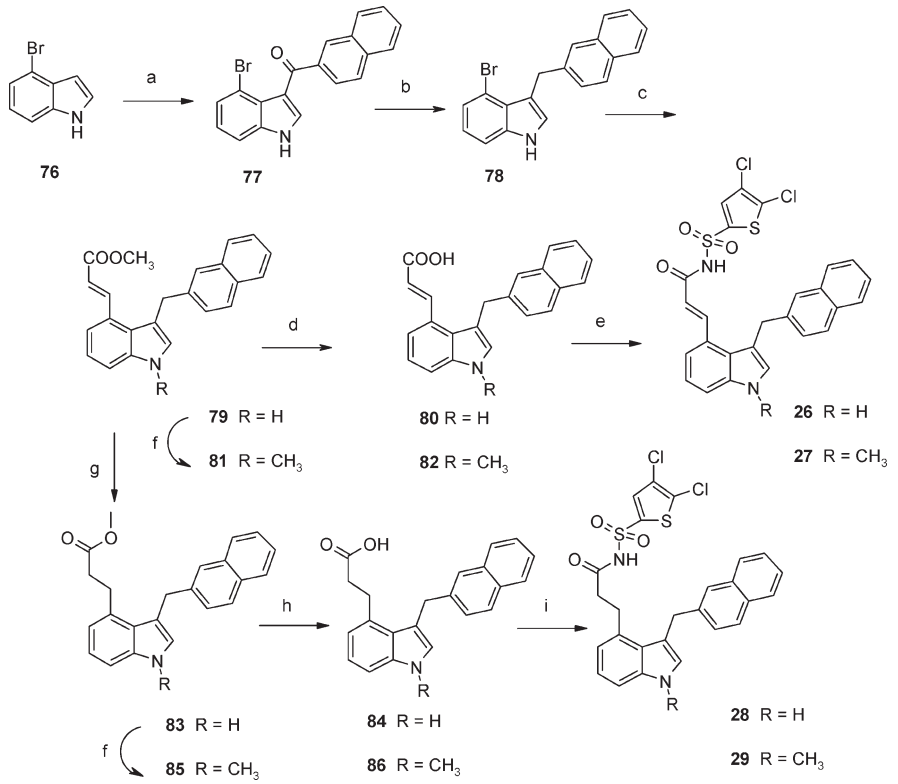
[a] (a) Triethylphosphonoacetate, NaH, THF, 78 °C, 14 h, 68%; (b) NaOH, EtOH, H_2O, 78 °C, 4 h, 86%; (c) 2-thiophenesulfonamide, DMAP, EDCI, CH_2Cl_2, room temp, 72 h, 56%; (d) NaH, DMF, Ar/(R)-CH_2Br(Cl).

Scheme 2[a]



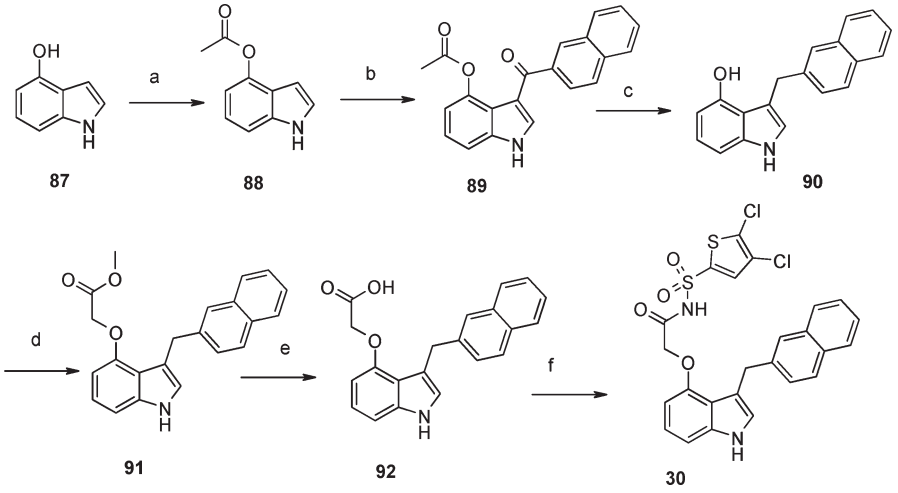
[a] (a) Methyl acrylate, Et_3N, $Pd(OAc)_2$, tri-*o*-tolylphosphine, 100 °C, 4 h, sealed tube, 82%; (b) aq NaOH, THF, CH_3OH, room temp, 16 h, 100%; (c) 2-thiophenesulfonamide, EDCI, DMAP, CH_2Cl_2, DMSO, room temp, 16 h, 58%; (d) NaH, DMF, Ar/R-CH_2Br(Cl).

Scheme 3[a]



[a] (a) CH_3MgBr, $ZnCl_2$, 2-naphthoyl chloride, CH_2Cl_2, rt, 16 h, 74%; (b) BH_3, THF, 0 °C to rt, 1.5 h; (c) methyl acrylate, $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, sealed tube, 100 °C, 2.5 h, 65%; (d) 1 N aqueous NaOH, THF, CH_3OH, 60 °C, 4 h, 100%; (e) 4,5-dichlorothiophene-2-sulfonamide, DMAP, EDCI, CH_2Cl_2, rt, 16 h, 42%; (f) NaH, THF, CH_3I, 0 °C to rt, 16 h; (g) H_2, 10% Pd/C, CH_3OH, 40 °C, 2 h, rt, 16 h, 86%; (h) 1 N aq NaOH, THF, CH_3OH, 60 °C, 4 h, 90%; (i) 4,5-dichlorothiophene-2-sulfonamide, DMAP, EDCI, CH_2Cl_2, rt, 16 h.

Scheme 4[a]



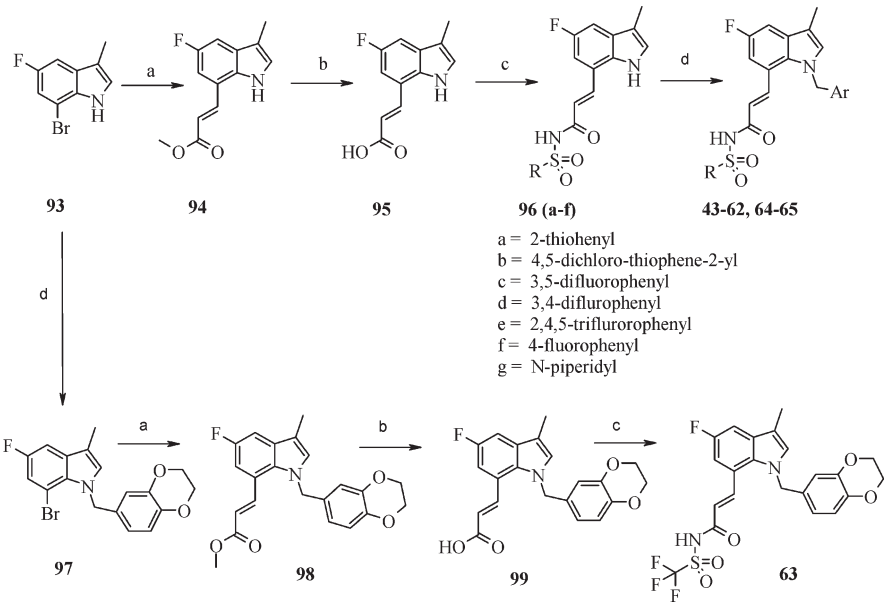
[a] (a) Ac_2O, pyridine, 25−32 °C, 15 min, 98%; (b) 2-naphthoyl chloride, CH_3MgBr, $ZnCl_2$, rt, 3 h, 65%; (c) BH_3, THF, 62%; (d) methyl 2-bromoacetate, K_2CO_3, DMF, rt, 17 h, 75%; (e) 2 N aq NaOH, THF, CH_3OH, rt, 1 h, 92%; (f) 4,5-dichlorothiophene-2-sulfonamide, DMAP, EDCI, CH_2Cl_2, rt, 16 h, 71%.

provided the saturated ester **83**, which was carried through a synthetic sequence analogous to synthesis of olefin analogues **26** and **27**, providing the R = NH and N-methyl saturated acylsulfonamide analogues **28** and **29**, respectively (Scheme 3).

The synthesis of compound **30** is outlined in Scheme 4. 4-Hydroxyindole (**87**) was protected as the acetate **88**, and subsequent Freidel−Crafts acylation with 2-naphthoyl chloride followed by reduction of ketone **89** with concomitant removal of the acetate protecting group provided 4-hydroxy-3-(2-naphthylmethyl)indole (**90**). O-Alkylation of **90** with methyl bromoacetate followed by base hydrolysis provided the acid **92**. EDCI-mediated coupling with 4,5-dichloro-2-thiophenesulfonamide provided the analogue **30**.

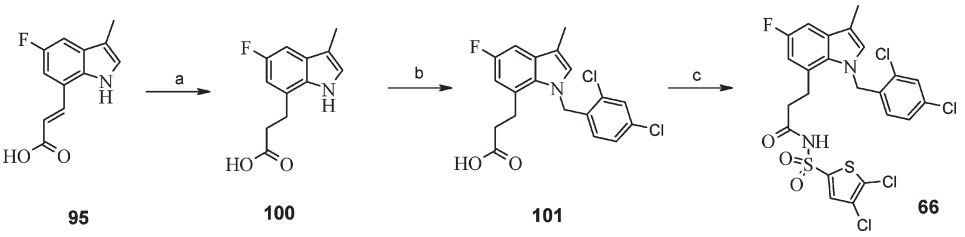
For 1,7-disubstituted analogues derived from the 5-fluoro-3-methylindole core, the 7-bromoindole intermediate **93** was prepared according to the method of Dobbs,[16] Bartoli et al.,[17]or Zegar et.al.[18] Following the synthetic

Scheme 5[a]



[a] (a) (*o*-Tol)$_3$P, methyl acrylate, Pd(OAc)$_2$; (b) aq MeOH, NaOH, 87%; (c) EDCI, DMAP, sulfonamide; (d) DMF, NaH, aryl bromide.

Scheme 6[a]



[a] (a) (*o*-Tol)$_3$P, methyl acrylate, Pd(OAc)$_2$, 98%; (b) aq MeOH, NaOH; (c) EDCI, DMAP, sulfonamide, 18%; (d) DMF, NaH, aryl bromide, 64%.

protocols described in Scheme 5, the target compounds **43** and those shown in Table 6 were obtained. For the synthesis of analogue **63**, the indole **93** was first N-alkylated to provide **97**. Heck coupling was carried out to provide, after base hydrolysis, the acid **99** which upon coupling with the trifluoromethanesulfonamide provided the analogue **63**. As shown in Scheme 6, the acrylic acid intermediate **95** was hydrogenated and the resulting saturated acid **100** was subsequently functionalized analogous to a two-step sequence used in Scheme 5 to provide analogue **66**. Preparation of compound **50** has been reported in ref 18.

Conclusion

In summary, on the basis of the structure of an endogenous ligand (PGE_2), we generated a pharmacophore hypothesis and devised multiple series of potent and selective EP_3 receptor antagonists. Subsequent refinement of this model following several rounds of SAR culminated in the identification of a lead compound **50** that currently is in phase II clinical trials. This agent featured high affinities for both hEP_3 ($IC_{50} = 4.6$ nM) and mEP_3 ($IC_{50} = 5.3$ nM) receptors in the absence of serum proteins. Compound **50** showed inhibitory activity against human platelet aggregation ($IC_{50} = 218$ nM). The compound displayed favorable preclinical PK and safety pharmacology profiles in rats and dogs. The in vivo profile of **50** is reported elsewhere.[7]

Experimental Section

Chemistry. General Methods. All reagents and anhydrous solvents were obtained from commercial sources and used without further purification unless otherwise noted. NMR spectra were recorded at 400 or 500 MHz (Varian Instruments) in the solvent indicated, and TMS was used as an internal reference. ACDLabs NMR software was used to process FIDs to generate spectral parameters (ppm/Hz). Coupling constants (*J*) are given in Hz. Mass spectra were obtained using either APCI or electrospray ionization (PE-SCIEX single-quad or Agilent mixed-mode units). Elemental analyses were carried out by Galbraith Laboratories, Inc. (Knoxville, TN) or Midwest Microlab, LLC (Indianapolis, IN). Column chromatography was carried out in the solvents indicated with silica gel (MP EcoChrom, 32-63D, 60 Å). Purity of all final products was determined by LC−MS and/or analytical HPLC to be ≥95%. HPLC purity of compounds was measured with a reverse phase HPLC (Phenomenex Prodigy C_{18} column, 4.6 mm × 150 mm, 5 μm, 254 nm) with two diverse solvent systems. In system 1, compounds were eluted using a gradient elution of 95/5 to 5/95 A/B over 20 min at a flow rate of 1.0 mL/min, where solvent A was aqueous 0.05% TFA and solvent B is acetonitrile (0.05% TFA). In system 2, compounds were eluted using a gradient of 95/5 to 5/95 A/C over 20 min at a flow rate of 1.0 mL/min, where solvent A was aqueous 0.05% TFA and solvent C is methanol. For HPLC data, peak area percent and retention time (t_R in minutes) are provided. The following compounds were purchased from commercial soureces and used as such, compounds

68, **76**, and **87**. Synthesis of compounds **50**, **93**, **94**, **95**, and **96b** have been reported previously.[18]

Preparation of Acylsulfonamides. General Procedure A. To a round-bottom flask (500 mL) that contained a solution of aryl(heteroaryl)sulfonamide (6 mmol), 4-dimethyaminopyridine (DMAP, 1.56 g, 13 mmol), and 1-[3-(dimethyamino)-propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 2.4 g, 13 mmol) in CH_2Cl_2 (150 mL) was added the carboxylic acid (6 mmol) at room temperature. The resulting mixture was allowed to stir at room temperature for 72 h, then was cooled to 5 °C and was acidified with addition of aqueous HCl (10%) until pH 1 was obtained, which was followed by extraction with CH_2Cl_2/MeOH (9/1, 3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was concentrated in vacuo to provide the crude product which was purified by flash chromatography (silica gel) to afford aryl-(heteroaryl)acylsulfonamide.

N-Alkylation of Indoles. General Procedure B. As an example, to a suspension of NaH (60% in mineral oil, 5 mg, 0.11 mmol) in DMF (5 mL) was added thiophene-2-sulfonic acid (3-1*H*-indol-7-ylacryloyl)amide, **71** (20 mg, 0.066 mmol), at 0 °C. [Except when the Ar/R-CH_2Br(Cl) was used in the form of a salt (e.g., HCl salt), an additional equiv of NaH was used.] The resulting mixture that resulted was allowed to warm to room temperature and was stirred for 2 h and then cooled to 0 °C. To this solution, $ArCH_2Br$ (or $ArCH_2Cl$) (0.072 mmol, 1.1 equiv) was added at 0 °C, and the resulting reaction mixture was allowed to warm to room temperature and was stirred for 16−48 h. The reaction mixture was cooled to 5 °C and was acidified with addition of aqueous HCl (10%) until pH 1 was obtained, which was followed by extraction with CH_2Cl_2/MeOH (9/1, 3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered, and the solvent was concentrated in vacuo to provide the crude product, which was purified by flash chromatography (silica gel, gradient elution, CH_2Cl_2 and then EtOAc/hexane, 1:8 to 1:2), recrystallization, or trituration from ethyl ether to afford the desired N-alkylated thiophene-2-sulfonic acid (3[CH_2R]-1*H*-indol-7-ylacryloyl)amides.

Thiophene-2-sulfonic Acid [(*E*)-3-(1-Naphthalen-2-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (10). Compound **10** was prepared from **71** using general procedure B. Yield: 61% (36% after recrystallization). ^{1}H NMR (500 MHz, CDCl3) δ 5.63 (s, 2H), 6.13 (d, J = 15.0 Hz, 1H), 6.64 (d, J = 3.5 Hz, 1H), 7.06−7.10 (m, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.23 (d, J = 3.5 Hz, 1H), 7.41−7.45 (m, 3H), 7.64−7.78 (m, 5H), 7.89 (dd, J = 4.0, 1.0 Hz, 1H), 8.29 (d, J = 15.0 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 53.5, 102.4, 118.3, 119.3, 120.0, 121.9, 124.0, 124.1, 125.3, 126.1, 126.4, 127.4, 127.7, 128.1, 129.1, 130.9, 131.5, 132.9, 133.4, 133.7, 133.9, 134.9, 135.0, 139.2, 144.0, 162.5. MS (ESI$^-$), mass calcd for $C_{26}H_{20}N_2O_3S_2$, 472.1; m/z found 471.5 (M − 1). LCMS 98%.

Thiophene-2-sulfonic Acid [(*E*)-3-(1-Benzyl-1*H*-indol-7-yl)acryloyl]amide (11). Compound **11** was prepared from **71** using general procedure B. Yield: 42%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (s, 2H), 6.14 (d, J = 15.0 Hz, 1H), 6.60 (d, J = 3.0 Hz, 1H), 7.00 (d, J = 7.5 Hz, 2H), 7.09 (t, J = 7.5 Hz, 1H), 7.13−7.16 (m, 2H), 7.20−7.28 (m, 5H), 7.69−7.71 (m, 2H), 7.93 (dd, J = 4.0, 1.0 Hz, 1H), 8.16 (d, J = 15.0 Hz, 1H). MS (ESI$^-$): mass calcd for $C_{22}H_{18}N_2O_3S_2$, 422.1; m/z found 421.3 (M − 1). LCMS 98%.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(3,4-Dichlorobenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}amide (12). Compound **12** was prepared from **75** using general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (d, J = 1.5 Hz, 3H), 5.34 (s, 2H), 6.26 (d, J = 15.0 Hz. 1H), 6.88, (s, 1H), 6.90 (dd, J = 8.0, 4.0 Hz, 1H), 7.05−7.10 (m, 2H), 7.11 (dd, J = 5.0, 4.0 Hz, 1H), 7.22−7.30 (m, 3H), 7.62 (d, J = 7.5 Hz, 1H), 7.67 (dd, J = 4.5, 1.5 Hz, 1H), 7.91 (dd, J = 4.0, 1.5 Hz, 1H), 8.17 (d, J = 15.0 Hz. 1H). MS (ESI$^-$): mass calcd for $C_{23}H_{18}Cl_2N_2O_3S_2$, 504.0; m/z found 503.3 (M − 1). LCMS 96%. HPLC system 2: 95%, t_R = 17.71 min.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(2,4-Dichlorobenzyl)-1*H*-indol-7-y l]acryloyl}amide (13). Compound **13** was prepared from **71** using general procedure B. Yield: 51% (36% after crystallization). ^{1}H NMR (500 MHz, acetone-d_6) δ 5.64 (s, 2H), 6.26 (d, J = 8.5 Hz, 1H), 6.40 (d, J = 15.5 Hz, 1H), 6.65 (d, J = 3.5 Hz, 1H), 7.09−7.44 (m, 6H), 7.72 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.96 (d, J = 15.5 Hz, 1H), 8.00 (d, J = 3.5 Hz, 1H). MS (ESI$^-$): mass calcd for $C_{22}H_{16}Cl_2N_2O_3S_2$, 490.0; m/z found 489.4 (M − 1). LCMS 97%.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(2,6-Dichlorobenzyl)-1*H*-indol-7-y l]acryloyl}amide (14). Compound **14** was prepared from **71** using general procedure B. Yield: 14%. ^{1}H NMR (500 MHz, acetone-d_6) δ 5.32 (s, 2H), 6.37−6.48 (m, 2H), 6.64 (d, J = 3.0 Hz, 1H), 6.88−7.22 (m, 3H), 7.30−7.55 (m, 3H), 7.64 (d, J = 6.0 Hz, 1H), 7.88−7.96 (m, 2H), 8.68 (d, J = 15.0 Hz, 1H). MS (ESI$^-$): mass calcd for $C_{22}H_{16}Cl_2N_2O_3S_2$, 490.0; m/z found 489.3 (M − 1). LCMS 97%.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(2,4-Dichlorobenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}amide (15). Compound **15** was prepared from **75** using general procedure B. Yield: 41%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.28 (d, J = 1.5 Hz, 3H), 5.52 (s, 2H), 6.14 (d, J = 8.5 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.20−7.30 (m, 4H), 7.52 (d, J = 1.5 Hz, 1H), 7.65 (dd, J = 7.5, 1.5 Hz, 1H), 7.76 (d, J = 15.0 Hz, 1H), 7.82 (m, 1H), 8.09 (m, 1H), 12.26 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{23}H_{18}Cl_2N_2O_3S_2$, 504.0; m/z found 503.3 (M − 1). LCMS 100%. HPLC system 1: 99%, t_R = 16.73 min. Anal. C, H, N.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(3,4-Dimethylbenzyl)-1*H*-indol-7-y l]acryloyl}amide (16). Compound **16** was prepared from **71** using general procedure B. Yield: 44%. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.28 (s, 6H), 5.51 (s, 2H), 6.45 (d, J = 15.0 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H), 6.92−6.96 (m, 1H), 7.03−7.09 (m, 3H), 7.22−7.29 (m, 2H), 7.33 (d, J = 3.0 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.87−7.89 (m, 1H), 7.98−8.02 (m, 1H), 8.02 (d, J = 15.0 Hz, 1H), 10.75 (br s, 1H). LCMS (ESI$^-$): mass calcd for $C_{24}H_{22}N_2O_3S_2$, 450.1; m/z found 449.4 (M − 1). LCMS 96%. HPLC system 1: 95.4%, t_R = 15.61 min.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(3,5-Dimethoxybenzyl)-1*H*-indol-7-yl]acryloyl}amide (17). Compound **17** was prepared from **71** using general procedure B. Yield: 10%. ^{1}H NMR (500 MHz, CD_3OD) δ 3.65 (s, 6H), 5.48 (s, 2H), 6.11 (d, J = 2.5 Hz, 2H), 6.28−6.32 (m, 2H), 6.57 (d, J = 3.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.14−7.18 (m, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 3.0 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.81−7.84 (m, 2H), 8.25 (d, J = 15.0 Hz, 1H). MS (API$^-$): mass calcd for $C_{24}H_{22}N_2O_5S_2$, 482.1; m/z found 480.8 (M − 1).

Thiophene-2-sulfonic Acid [(*E*)-3-(1-Benzo[1,3]dioxol-5-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (18). Compound **18** was prepared from **71** using general procedure B. Yield: 85%. ^{1}H NMR (500 MHz, acetone-d_6) δ 5.56 (s, 2H), 5.94 (s, 2H), 6.45 (s, 1H), 6.51(d, J = 15.0 Hz, 1H), 6.58−6.67 (m, 3H), 7.08 (t, J = 7.5 Hz, 1H), 7.27−7.31 (m, 2H), 7.47 (d, J = 3.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.95 (dd, J = 3.0, 1.5 Hz, 1H), 8.02 (dd, J = 4.5, 1.5 Hz, 1H), 8.35 (d, J = 15.0 Hz, 1H), 10.80 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{23}H_{18}N_2O_5S_2$, 466.1; m/z found 465.3 (M − 1). LCMS 97%.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(3-Trifluoromethylbenzyl)-1*H*-indol-7-yl]acryloyl}amide (19). Compound **19** was prepared from **71** using general procedure B. Yield: 85%. ^{1}H NMR (500 MHz, acetone-d_6) δ 5.75 (2H, s), 6.47 (d, J = 15.0 Hz, 1H), 6.65 (d, J = 3.0 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.24−7.34 (m, 4H), 7.45 (t, J = 8.0 Hz, 1H), 7.52−7.57 (m, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.92 (m, 1H), 8.00 (m, 1H), 8.23 (d, J = 15.0 Hz, 1H). MS (ESI$^-$): mass calcd for $C_{23}H_{17}F_3N_2O_3S_2$, 490.1; m/z found 489.4 (M − 1). LCMS 96%.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(2-Trifluoromethylbenzyl)-1*H*-indol-7-yl]acryloyl}amide (20). Compound **20** was prepared from **71** using general procedure B. Yield: 17%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.64 (2H, s), 6.18 (d, J = 15.0 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 3.0 Hz, 1H), 7.07 (d, J = 3.0 Hz,

1H), 7.11−7.14 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.31−7.38 (m, 2H), 7.69 (dd, J = 5.0, 1.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.82 (d, J = 15.0 Hz, 1H). MS (ESI^-): mass calcd for $C_{23}H_{17}F_3N_2O_3S_2$, 490.1; m/z found 489.4 (M − 1). LCMS 95%.

Thiophene-2-sulfonic Acid [(*E*)-3-(1-Biphenyl-2-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (21). Compound **21** was prepared from **71** using general procedure B. Yield: 17%. ^1H NMR (500 MHz, CD_3OD) δ 5.36 (2H, s), 6.18 (d, J = 15.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 7.11−7.37 (m, 13H), 7.82−7.91 (m, 2H), 7.92 (d, J = 15.0 Hz, 1H). MS (ESI^-): mass calcd for $C_{28}H_{22}N_2O_3S_2$, 498.1; m/z found 497.6 (M − 1). LCMS 96%.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(4-Methoxybenzyl)-1*H*-indol-7-yl]acryloyl}amide (22). Compound **22** was prepared from **71** using general procedure B. Yield: 77%. ^1H NMR (500 MHz, acetone-d_6); δ 3.74(s, 3H), 5.58 (s, 2H), 6.45 (d, J = 15.0 Hz, 1H), 6.61 (d, J = 3.0 Hz, 1H), 6.68 (dd, J = 6.5, 2.5 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.07 (t, J = 7.5 Hz, 1H), 7.25−7.30 (m, 2H), 7.47 (d, J = 3.0 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.95 (dd, J = 4.0, 1.5 Hz, 1H), 8.04 (dd, J = 5.0, 1.5 Hz, 1H), 8.37 (d, J = 15.0 Hz, 1H), 10.80 (br s, 1H). MS (ESI^-): mass calcd for $C_{23}H_{20}N_2O_4S_2$, 452.1; m/z found 451.3 (M − 1). LCMS 97%.

Thiophene-2-sulfonic Acid [(*E*)-3-(1-Pyridin-3-yl)-1*H*-indol-7-yl)acryloyl]amide (23). Compound **23** was prepared from **71** using general procedure B. Yield: 68%. ^1H NMR (400 MHz, DMSO-d_6), δ 5.63 (s, 2H), 6.28 (d, J = 15.2 Hz, 1H), 6.61 (d, J = 2.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.19 (m, 3H), 7.31 (m, 1H), 7.59 (d, J = 3.2 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.80 (m, 1H), 8.03 (m, 1H), 8.08 (d, J = 15.2 Hz, 1H), 8.12 (m, 1H), 8.40 (m, 1H), 12.38 (br s, 1H). MS ($APCI^+$): mass calcd for $C_{21}H_{17}N_3O_3S_2$, 423.1; m/z found 424.1 (M + 1). LCMS 97%. HPLC system 1: 95%, t_R = 9.57 min.

Thiophene-2-sulfonic Acid [(*E*)-3-(3-Methyl-1-pyridin-3-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (24). Compound **24** was prepared from **75** using general procedure B. ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.47 (s, 2H), 6.23 (d, J = 15.0 Hz, 1H), 6.92 (s, 1H), 7.12 (m, 2H), 7.24 (m, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 5.0 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.69 (m, 1H), 7.92 (d, J = 3.5 Hz, 1H), 8.23 (d, J = 15.0 Hz, 1H), 8.24 (s, 1H), 8.48 (d, J = 3.5 Hz, 1H). MS (ESI^-): mass calcd for $C_{22}H_{19}N_3O_3S_2$, 437.1; m/z found 436.4 (M − 1). LCMS 97%. HPLC system 1: 96%, t_R = 10.16 min.

Thiophene-2-sulfonic Acid [(*E*)-3-(3-Methyl-1-pyridin-2-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (25). Compound **25** was prepared from **75** using general procedure B. Yield: 58%. ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 5.55 (s, 2H), 6.26 (d, J = 15.2 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.15−7.21 (m, 2H), 7.24 (dd, J = 4.8, 4.4 Hz, 1H), 7.28 (s, 1H), 7.56−7.63 (m, 2H), 7.81 (dd, J = 4.0, 1.6 Hz, 1H), 8.07 (dd, J = 5.2, 1.6 Hz, 1H), 8.12 (d, J = 15.2 Hz, 1H), 8.39 (m, 1H), 12.25 (br s, 1H). MS (AP^+): mass calcd for $C_{22}H_{19}N_3O_3S_2$, 437.1; m/z found 438.1 (M + 1). LCMS 97.5%.

4,5-Dichlorothiophene-2-sulfonic Acid [(*E*)-3-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yl)acryloyl]amide (26). To a suspension of acid **80** (26.3 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was subsequently added 4,5-dichlorothiophene-2-sulfonamide (19 mg, 0.082 mmol), DMAP (20 mg, 0.16 mmol), and EDCI (31 mg, 0.16 mmol). The mixture was stirred at room temperature overnight. The solution was diluted with EtOAc (5 mL) and acidified with 10% aqueous HCl. The organic layer was washed with water, dried over ahydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by a column chromatography using 15−25% EtOAc/hexanes gradient elution to yield 18 mg (42%) of acylsulfonamide **26**. ^1H NMR (500 MHz, DMSO-d_6) δ 4.34 (s, 2H), 6.4 (d, J = 16.0, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.0 Hz, 1H), 7.36−7.42 (m, 4H), 7.46 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 7.0 Hz, 1H), 7.79 (s, 1H), 7.94 (s, 1H), 8.40 (d, J = 16.0 Hz, 1H), 11.20 (s, 1H), 12.5 (br s, 1H). MS (ESI^-): mass calcd for $C_{26}H_{18}Cl_2N_2O_3S_2$, 540.0; m/z found 539.6 (M − 1). LCMS 96%. HPLC system 2: 95%, t_R = 17.64 min.

4,5-Dichlorothiophene-2-sulfonic Acid [(*E*)-3-(1-Methyl-3-naphthalen-2-ylmethyl-1*H*-indol-4-yl)acryloyl]amide (27). To a suspension of the acid **82** (42 mg, 0.123 mmol) in CH_2Cl_2 (1 mL) was sequentially added 4,5-dichlorothiophene-2-sulfonamide (29 mg, 0.123 mmol), DMAP (30 mg, 0.246 mmol), and EDCI (47 mg, 0.246 mmol). The mixture was stirred at room temperature overnight. The solution was acidified with 10% aqueous HCl and extracted with EtOAc (2 × 5 mL). The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo to afford 50 mg of residue. Purification of this residue by column chromatography using CH_2Cl_2 gave 18 mg (26%) of the compound **27**. ^1H NMR (500 MHz, DMSO-d_6) δ 3.78 (s, 3H), 4.33 (s, 2H), 6.41 (d, J = 16.0 Hz, 1H), 7.15−7.18 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.348 (s, 1H), 7.37−7.43 (m, 4H), 7.51 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.8 (s, 1H), 8.38 (d, J = 16.0 Hz, 1H), 12.7 (br s, 1H). LCMS 98%. MS (ESI^-) m/z 553 (M − 1). HPLC system 2: 98.6%, t_R = 17.84 min.

4,5-Dichlorothiophene-2-sulfonic Acid [3-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yl)propionyl]amide (28). To a suspension of the propionic acid **84** (126 mg, 0.383 mmol) in CH_2Cl_2 (2 mL) was sequentially added 4,5-dichlorothiophene-2-sulfonamide (89 mg, 0.383 mmol), DMAP (93.5 mg, 0.765 mmol), and EDCI (147 mg, 0.765 mmol). The mixture was stirred at room temperature overnight. The solution was diluted with EtOAc (5 mL) and acidified with 10% aqueous HCl. The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by a column chromatography using CH_2Cl_2 as eluent to provide 65 mg (31%) of the acylsulfonamide **28**. ^1H NMR (500 MHz, DMSO-d_6) δ 2.49 (t, J = 8.0 Hz, 2H), 2.97 (t, J = 8.0 Hz, 2H), 4.29 (s, 2H), 6.56 (d, J = 7.0 Hz, 1H), 6.87 (t, J = 7.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.5, 1.5 Hz, 1H), 7.42−7.44 (m, 2H), 7.55 (s, 1H), 7.71 (m, 1H), 7.75 (d, J = 8.5 Hz. 1H), 7.83 (m, 1H), 7.85 (s, 1H), 10.96 (s, 1H), 12.56 (v br s, 1H). MS (ESI^-): mass calcd for $C_{26}H_{20}Cl_2N_2O_3S_2$, 542.0; m/z found 541.6 (M − 1). LCMS 98.5%. HPLC system 1: 99.8%, t_R = 12.16 min.

4,5-Dichlorothiophene-2-sulfonic Acid [3-(1-Methyl-3-naphthalen-2-ylmethyl-1*H*-indol-4-yl)propionyl]amide (29). To a suspension of the propionic acid **86** (120 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was sequentially added 4,5-dichlorothiophene-2-sulfonamide (78 mg, 0.34 mmol), DMAP (85 mg, 0.69 mmol), and EDCI (132 mg, 0.69 mmol). The mixture was stirred at room temperature overnight. The solution was acidified with 10% aqueous HCl and extracted with EtOAc (2 × 5 mL). The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 110 mg of a residue. This residue was triturated with MeOH to provide 80 mg (42%) of the compound **29**. ^1H NMR (500 MHz, DMSO-d_6) δ 2.52 (t, J = 8.0 Hz, 2H), 3.00 (t, J = 8.0 Hz, 2H), 3.71 (s, 3H), 4.28 (s, 2H), 6.62 (d, J = 7.0 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.01 (s, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.44 (m, 2H), 7.57 (s, 1H), 7.73 (m, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.85 (m, 2H), 12.6 (br s, 1H). MS (ESI^-): mass calcd for $C_{27}H_{22}Cl_2N_2O_3S_2$, 556.0; m/z found 554.9 (M − 1). LCMS 96.4%.

4,5-Dichlorothiophene-2-sulfonic Acid [2-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yloxy)acetyl]amide (30). To the solution of the acid **92** (2.87 g, 8.65 mmol, 1 equiv) in CH_2Cl_2 (80 mL) was added DMAP (2.11 g, 17.3 mmol, 2 equiv), 4,5-dichloro-2-thiophenesulfonamide (2.11 g, 9.1 mmol, 1.05 equiv), and EDCI (3.22 g, 17.3 mmol, 2 equiv). The mixture was stirred at room temperature for 16 h and then quenched with 10% aqueous HCl (5 mL) followed by dilution with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (100 mL), brine (2 × 100 mL), and then dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford a residue

(3.31 g, 63%). This residue was triturated with MeOH (12 mL), heated to reflux, then cooled to 0 °C and filtered to provide 2.97 g (71%) of the sulfonamide **30**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.33 (s, 2H), 4.68 (s, 2H), 6.18 (d, J = 7.5 Hz, 1H), 6.87 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 7.41 (m, 2H), 7.46 (dd, J = 8.5, 1.5 Hz, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.79−7.81 (m, 2H), 7.89 (s, 1H), 10.92 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{25}H_{18}Cl_2N_2O_4S_2$, 544.0; m/z found 543.3 (M − 1). HPLC system 1: 97.2%, t_R = 16.65 min. Anal. C, H, N, S.

Thiophene-2-sulfonic Acid [(*E*)-3-(5-Fluoro-3-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (43). Compound **43** was prepared from intermediate compound **96a** using general procedure B. To a solution of compound **96a** (45 mg, 0.012 mmol) in DMF (3 mL), NaH (60% in oil, 15 mg, 0.370 mmol) was added at 0 °C and stirred at room temperature for 1 h followed by addition of 2-(bromomethyl)naphthalene (53 mg, 0.24 mmol). The reaction mixture was stirred at room temperature overnight and diluted with CH_2Cl_2 (12 mL). The reaction mixture was washed with dilute aqueous HCl (2 × 8 mL), water (4 × 8 mL), brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was concentrated in vacuo, and the residue was washed with Et_2O/hexane to give 55 mg (90%) of the compound **43**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.28 (s, 3H), 5.65 (s, 2H), 6.28 (d, J = 15.5 Hz, 1H), 6.99 (dd, J = 10.0, 2.5 Hz, 1H), 7.09 (dd, J = 8.5, 1.5 Hz, 1H), 7.26 (dd, J = 5.0, 4.0 Hz, 1H), 7.40−7.48 (m, 4H), 7.51 (s, 1H), 7.60 (dd, J = 9.0, 1.5 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.86 (dd, J = 3.5, 1.5 Hz, 1H), 8.10 (dd, J = 5.0, 1.0 Hz, 1H), 8.19 (d, J = 15.5 Hz, 1H), 12.30 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{27}H_{21}FN_2O_3S_2$, 504.1; m/z found 503.4 (M − 1). LCMS 96%. HPLC system 2: 96.7%, t_R = 17.67 min.

Thiophene-2-sulfonic Acid {(*E*)-3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}amide (44). Compound **44** was prepared from **96a** by a procedure similar to that described for the synthesis of compound **43**. Yield 87% ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.25 (s, 3H), 5.52 (s, 2H), 6.15 (d, J = 8.0 Hz, 1H), 6.25 (d, J = 15.0 Hz, 1H), 7.02 (dd, J = 10.5, 2.0 Hz, 1H), 7.22 (m, 2H), 7.33 (s, 1H), 7.43 (dd, J = 10.0, 2.0 Hz, 1H), 7.51 (m, 1H), 7.66 (d, J = 15.0 Hz, 1H), 7.76 (m, 1H), 8.01 (d, J = 4.5 Hz, 1H), 12.4 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{23}H_{17}Cl_2N_2O_3S_2$, 522.0; m/z found 521.6 (M − 1). HPLC system 2: 99.4%, t_R = 17.76 min.

4,5-Dichlorothiophene-2-sulfonic Acid {2-[3-(Naphthalene-2-carbonyl)-1*H*-indol-4-yloxy]acetyl}amide (45). To an 8 mL vial equipped with a magnetic stir bar and a screw cap was added compound **30** (58.5 mg, 0.107 mmol) followed by anhydrous THF (1 mL) and water (0.050 mL). To this stirring light-yellow solution was added DDQ (73 mg, 0.322 mmol) in one portion, immediately turning the solution black. The mixture was allowed to stir at room temperature overnight. The solution was concentrated to dryness and purified via preparative TLC utilizing 7:3 hexanes/EtOAc as eluent to give 9 mg (15%) of an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.61 (s, 2H), 6.66 (d, J = 7.2 Hz, 1H), 7.12−7.20 (m, 2H), 7.56−7.70 (m, 3H), 7.90 (d, J = 1.2 Hz, 1H), 7.94 (dd, J = 8.8, 1.2 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 8.41 (s, 1H), 12.17 (br s, 1H). MS (AP$^+$) mass calcd for $C_{25}H_{16}Cl_2N_2O_5S_2$, 558.0; m/z found 559.0 (M + 1). LCMS 98.0%.

4,5-Dichlorothiophene-2-sulfonic Acid {(*E*)-3-[5-Fluoro-1-(4-fluorobenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}amide (46). The target compound was prepared from **96b** using general procedure A. Yield 57%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.25 (d, J = 0.8 Hz, 3H), 5.51 (s, 2H), 6.28 (d, J = 15.0 Hz, 1H), 7.00−6.91 (m, 5H), 7.03 (dd, J = 10.0, 2.5 Hz, 1H), 7.41 (m, 2H), 7.90 (s, 1H), 8.03 (d, J = 15.0 Hz, 1H). MS (ESI$^-$) mass calcd for $C_{23}H_{16}Cl_2F_2N_2O_3S_2$, 540.0; m/z found 539.4 (M − 1). LCMS 97%. HPLC system 1: 98.3%, t_R = 17.79 min. HPLC system 2: 98.9%, t_R = 17.81 min.

4,5-Dichlorothiophene-2-sulfonic Acid {(*E*)-3-[1-(3-Cyanobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}amide (47). Compound **96b** (250 mg, 0.58 mmol) was alkylated using NaH (60%) (69.2 mg, 1.73 mmol) and 3-(bromomethyl)benzonitrile (192 mg, 0.98 mmol) in anhydrous THF (2.8 mL) in a manner analogous to the preparation of compound **43**. After filtration, 186 mg (59%) of compound **47** was isolated as a lime-green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26 (s, 3H), 5.59 (s, 2H), 6.32 (d, J = 15.6 Hz, 1H), 7.05 (dd, J = 10.0, 2.4 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.37 (br s, 1H), 7.40−7.47 (m, 3H), 7.69 (d, J = 7.6 Hz, 1H), 7.90 (s, 1H), 7.94 (d, J = 15.6 Hz, 1H). MS (ESI$^-$): mass calcd for $C_{24}H_{16}Cl_2FN_3O_3S_2$, 547.0; m/z found 546.2 (M − 1). HPLC system 2: 99.4%, t_R = 17.81 min.

4,5-Dichlorothiophene-2-sulfonic Acid {(*E*)-3-[1-(4-Cyanobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}amide (48). Compound **96b** (250 mg, 0.58 mmol) was alkylated using NaH (60%) (69.2 mg, 1.73 mmol) and 4-(bromomethyl)benzonitrile (192 mg, 0.98 mmol) in anhydrous THF (2.8 mL) in a manner analogous to the preparation of compound **43**. After filtration, 90.8 mg (29%) of compound **49** was isolated as a lime-green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.26 (s, 3H), 5.64 (s, 2H), 6.22 (d, J = 15.2 Hz, 1H), 7.03 (m, 3H), 7.43 (m, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.91−7.95 (m, 2H). MS (ESI$^-$): mass calcd for $C_{24}H_{16}Cl_2FN_2O_3S_2$, 547.0; m/z found 546.2 (M − 1). HPLC system 1: 98.3%, t_R = 16.85 min. HPLC system 2: 99.3%, t_R = 17.73 min.

4,5-Dichlorothiophene-2-sulfonic Acid [(*E*)-3-(5-Fluoro-1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-methyl-1*H*-indol-7-yl)acryloyl]amide (49). Compound **49** was prepared through the alkylation of indole derivative **96b** with 2-chloromethylimidazo[1,2-*a*]pyridine according to general procedure B. Yield: 72%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H), 5.49 (s, 2H), 6.24 (d, J = 15.6 Hz, 1H), 6.87 (ddd, J = 6.8, 6.8, 1.2 Hz, 1H), 7.04 (dd, J = 10.4, 2.4 Hz, 1H), 7.18−7.27 (m, 2H), 7.36 (s, 1H), 7.45−7.50 (m, 2H), 8.22 (d, J = 15.6 Hz, 1H), 8.27 (s, 1H), 8.42 (m, 1H). MS (ESI$^-$): mass calcd for $C_{24}H_{17}Cl_2FN_4O_3S_2$, 562.0; m/z found 561.1 (M − 1). HPLC system 1: 95.1%, t_R = 22.32 min

4,5-Dichlorothiophene-2-sulfonic Acid [(*E*)-3-(5-Fluoro-3-methyl-1-naphthalen-2-ylmethyl-1*H*-indol-7-yl)acryloyl]amide (51). Compound **96b** (52 mg, 0.12 mmol) was alkylated using NaH (60% in oil, 15 mg, 037 mmol) and 2-(bromomethyl)-naphthalene (53 mg, 0.24 mmol) in anhydrous DMF (3 mL), in a manner analogous to the preparation of compound **43**. The crude product was purified by column chromatography on silica gel with 1−5% MeOH/CH_2Cl_2 as eluent to give 44 mg (64%) of compound **51**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.29 (s, 3H), 5.68 (s, 2H), 6.28 (d, J = 15.2 Hz, 1H), 7.02 (dd, J = 10.0, 2.0 Hz, 1H), 7.10 (m, 1H), 7.40−7.50 (m, 3H), 7.54 (m, 2H), 7.64 (d, J = 7.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.94 (s, 1H), 8.21 (d, J = 15.2 Hz, 1H), 12.50 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{27}H_{19}Cl_2FN_2O_3S_2$, 572.0; m/z found 571.3 (M − 1). LCMS 98%. HPLC system 2: 99.6%, t_R = 17.81 min.

***N*-{(*E*)-3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}-3,5-difluorobenzenesulfonamide (52).** Compound **52** was synthesized from **96c** following general procedure B. Yield: 55%. ^{1}H NMR (500 MHz, acetone-d_6) δ 2.30 (s, 3H), 5.54 (s, 2H), 6.28 (d, J = 8.0 Hz, 1H), 6.41 (d, J = 15.5 Hz, 1H), 6.86 (br s, 1H), 7.03 (dd, J = 10.5, 2.5 Hz, 1H), 7.17 (dd, J = 8.0, 2.0 Hz, 1H), 7.28 (s, 1H), 7.23−7.39 (m, 2H), 7.49−7.53 (m, 2H), 7.68−7.70 (m, 1H), 7.84 (d, J = 15.5 Hz, 1H). MS (ESI$^-$): mass calcd for $C_{25}H_{17}Cl_2FN_2O_3S$, 552.0; m/z found 551.3 (M − 1). HPLC system 1: 96.1%, t_R = 17.68 min. HPLC system 2: 97.2%, t_R = 17.8 min.

***N*-{(*E*)-3-[1-(3,4-Difluorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}-3,5-difluorobenzenesulfonamide (53).** Compound **53** was synthesized from **96c** following general procedure B. Yield: 73%, as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (d, J = 1.2 Hz, 3H), 5.34 (s, 2H), 6.11 (d, J = 15.2 Hz, 1H),

6.69 (ddd, J = 9.6, 7.2, 2.0 Hz, 1H), 6.80 (m, 1H), 6.95 (s, 1H), 6.97 (dd, J = 9.6, 2.4 Hz, 1H), 7.03 (ddd, J = 10.0, 8.0, 8.0 Hz, 1H), 7.12 (dddd, J = 10.8, 8.4, 2.4, 2.4 Hz, 1H), 7.29 (dd, J = 8.4, 2.4 Hz, 1H), 7.64−7.70 (m, 2H), 8.09 (dd, J = 15.2 Hz, J = 1.2 Hz, 1H), 8.23 (br s, 1H). MS (ESI^-): mass calcd for $C_{25}H_{17}F_5N_2O_3S$, 520.1; m/z found 519.7. LCMS 98%. HPLC system 2: 99%, t_R = 17.72 min.

***N*-{(*E*)-3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}-2,4,5-trifluorobenzenesulfonamide (54).** In an 8 mL vial equipped with a stir bar was placed (2*E*)-3-[1-(2,4-dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]prop-2-enoic acid (41 mg, 0.11 mmol), 2,4,5-trifluorobenzenesulfonamide (23.2 mg, 0.11 mmol), DMAP (31.6 mg, 0.26 mmol), anhydrous CH_2Cl_2 (2 mL), and EDCI (51.8 mg, 0.27 mmol) at room temperature. The vial was sealed with a cap and allowed to react for 22 h at room temperature. The contents of the vial were washed with 1 M aqueous HCl (5 mL), water (3 × 5 mL) and then brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to a light-greenish solid. This crude material was dissolved in boiling Et_2O (1 mL) followed by the addition of hexanes (1 mL). The resulting solid was collected by suction filtration to provide 23.9 mg (39%) of compound **55** as a lime-green solid. ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 5.37 (s, 2H), 6.18 (d, J = 15.2 Hz, 1H), 6.31 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.82 (dd, J = 10.0, 2.8 Hz, 1H), 7.04 (dd, J = 2.0, 8.4 Hz, 1H), 7.07−7.13 (m, 1H), 7.31 (dd, J = 8.8, 2.8 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.82 (d, J = 14.8 Hz, 1H), 7.98−8.04 (m, 1H). MS (ESI^-): mass calcd for $C_{25}H_{16}Cl_2F_4N_2O_3S$, 570.0; m/z found 569.4 (M − 1). LCMS 97%. HPLC system 1: 97.9%, t_R = 17.64 min. HPLC system 2: 99.6%, t_R = 17.77 min.

***N*-{(*E*)-3-[1-(3,4-Difluorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}-3,4-difluorobenzenesulfonamide (55).** Compound **55** was prepared via the alkylation of indole derivative **96d** with 3,4-difluorobenzyl bromide according to general procedure B. Yield: 73%. ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 5.33 (s, 2H), 6.09 (d, J = 15.0 Hz, 1H) 6.71 (m, 1H), 6.77 (m, 1H), 6.94−6.97 (m, 2H), 7.03 (dd, J = 10.0, 8.5 Hz, 1H), 7.29 (dd, J = 8.0, 2.5 Hz, 1H), 7.36 (dd, J = 16.5, 9.0 Hz, 1H), 7.92 (m, 1H), 7.99 (m, 1H), 8.07 (d, J = 15.0 Hz, 1H), 8.40 (br s, 1H). MS (ESI^-): mass calcd for $C_{25}H_{17}F_5N_2O_3S$, 520.1; m/z found 519.8 (M − 1). HPLC system 1: 97.9%, t_R = 17.80 min. HPLC system 2: 97.8%, t_R = 17.84 min.

Synthesis of 4,5-Dichlorothiophene-2-sulfonic Acid {(*E*)-3-[1-(3,4-Difluorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}amide (56). Compound **96b** (70 mg, 0.16 mmol) was alkylated using NaH (60%) (8.5 mg, 0.36 mmol) and 3,4-difluorobenzyl bromide (50 mg, 0.24 mmol) in anhydrous DMF (2.8 mL) in a manner analogous to the preparation of compound **43**. After filtration and column chromatography, 50 mg (55%) of compound **56** was isolated as a yellow solid . ^1H NMR (400 MHz, DMSO-d_6) δ 2.25 (d, J = 0.8 Hz, 3H), 5.51 (s, 2H), 6.28 (d, J = 15.6 Hz, 1H), 6.66 (m, 1H), 6.99 (ddd, J = 10.0, 7.6, 2.0 Hz, 1H), 7.04 (dd, J = 10.0, 2.4 Hz, 1H), 7.23 (ddd, J = 10.8, 8.2, 8.2 Hz, 1H), 7.41 (s, 1H), 7.43 (dd, J = 8.8, 2.4 Hz, 1H), 7.87 (s, 1H), 7.98 (d, J = 15.6 Hz, 1H). MS (ESI^-): mass calcd for $C_{23}H_{15}Cl_2F_3N_2O_3S$, 558.0; m/z found 557.2 (M − 1). LCMS 96.2%.

2,4,5-Trifluoro-*N*-{(*E*)-3-[5-fluoro-1-(3-methoxybenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}benzenesulfonamide (57). Compound **57** was prepared via the alkylation of indole derivative **96d** with 3-methoxybenzyl bromide according to general procedure B. Yield: 30%. ^1H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 3.64 (s, 3H), 5.42 (s, 2H), 6.34 (s, 1H), 6.38 (d, J = 15.2 Hz, 1H), 6.49 (t, J = 2.0 Hz, 1H), 6.73 (dd, J = 8.4, 2.8 Hz, 1H), 7.02−7.09 (m, 2H), 7.40 (s, 1H), 7.43 (dd, J = 8.8, 2.4 Hz, 1H), 7.92−8.07 (m, 3H). MS (ESI^-): mass calcd for $C_{26}H_{20}F_4N_2O_4S$, 532.1; m/z found 531.5 (M − 1). HPLC system 2: 98.8%, t_R = 17.63 min.

3,4-Difluoro-*N*-{(*E*)-3-[5-fluoro-1-(3-methoxybenzyl)-3-methyl-1*H*-indol-7-yl]acryloyl}benzenesulfonamide (58). Compound **58** was prepared via the alkylation of indole derivative **96d** with 3-methoxybenzyl bromide according to general procedure B. Yield: 19%. ^1H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3H), 3.66 (s, 3H), 5.43 (s, 2H), 6.37 (dd, J = 11.2, 4.0 Hz, 2H), 6.51 (dd, J = 2.0, 1.6 Hz, 1H), 6.74 (dd, J = 8.4, 2.0 Hz, 1H), 7.03 (dd, J = 10.4, 2.4 Hz, 1H), 7.07 (dd, J = 8.0, 7.6 Hz, 1H), 7.40 (s, 1H), 7.43 (dd, J = 8.8, 2.4 Hz, 1H), 7.76 (m, 1H), 7.86 (m, 1H), 7.97−8.03 (m, 2H), 12.50 (br s, 1H). LCMS 97%. MS (ESI^-): mass calcd for $C_{26}H_{21}F_3N_2O_4S$, 514.1; m/z found 513.7 (M − 1). HPLC system 1: 98.8%, t_R = 16.37 min.

***N*-{(*E*)-3-[1-(3,5-Dimethylisoxazol-4-ylmethyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}-3,4-difluorobenzenesulfonamide (59).** Compound **59** was prepared through the alkylation of indole derivative **96e** with 4-bromomethyl-3,5-dimethylisoxazole according to general procedure B, except KO^{t}Bu was used as the base. Yield: 31%. ^1H NMR (400 MHz, DMSO-d_6) δ 1.71 (s, 3H), 1.77 (s, 3H), 2.21 (s, 3H), 5.29 (s, 2H), 6.38 (d, J = 15.2 Hz, 1H), 7.08 (dd, J = 10.4, 2.4 Hz, 1H), 7.21 (s, 1H), 7.43 (dd, J = 8.8, 2.8 Hz, 1H), 7.77 (m, 1H), 7.88 (m, 1H), 8.00 (d, J = 2.8 Hz, 1H), 8.03 (m, 1H), 12.22 (s, 1H). MS (ESI^-): mass calcd for $C_{24}H_{20}F_3N_3O_4S$, 503.1; m/z found 502.4 (M − 1). HPLC system 1: 98.2%, t_R = 15.19 min.

3,4-Difluoro-*N*-[(*E*)-3-(5-fluoro-1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-methyl-1*H*-indol-7-yl)acryloyl]benzenesulfonamide (60). Compound **60** was prepared through the alkylation of indole derivative **96d** and 2-chloromethylimidazo[1,2-*a*]pyridine according to general procedure B. Yield: 12%. ^1H NMR (400 MHz, DMSO-d_6) δ 2.25 (s, 3 H), 5.79 (s, 2 H), 6.34 (d, J = 16 Hz, 1 H), 7.08 (dd, J = 10.0, 2.0 Hz, 1 H), 7.38 (s, 1 H), 7.43 (t, J = 2 Hz, 1 H), 7.49 (dd, J = 9.0, 2.0 Hz, 1 H), 7.72−8.02 (m, 7 H), 8.69 (d, J = 7.0 Hz, 1 H). MS (ESI^-): mass calcd for $C_{26}H_{19}F_3N_4O_3S$, 524.1; m/z found 523.6 (M − 1). LCMS 97%. HPLC system 1: 97.6%, t_R = 14.96 min.

4-Fluoro-*N*-[(*E*)-3-(5-fluoro-1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-methyl-1*H*-indol-7-yl)acryloyl]benzenesulfonamide (61). Compound **61** was prepared through the alkylation of indole derivative **96f** with 2-chloromethylimidazo[1,2-*a*]pyridine according to general procedure B. Yield: 67%. ^1H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3 H), 5.74 (s, 2 H), 6.39 (d, J = 16.0 Hz, 1 H), 7.07 (dd, J = 10.0, 2.0 Hz, 1 H), 7.32−7.36 (m, 1 H), 7.38 (s, 1 H), 7.45−7.52 (m, 3 H), 7.79 (d, J = 3.0 Hz, 2 H), 7.81 (s, 1 H), 8.00−8.07 (m, 3 H), 8.63 (d, J = 7.0 Hz, 1 H). MS (ESI^-): mass calcd for $C_{26}H_{20}F_2N_4O_3S$, 506.1; m/z found 506.0. (M − 1). LCMS 96%.

3,5-Difluoro-*N*-[(*E*)-3-(5-fluoro-1-imidazo[1,2-*a*]pyridin-2-ylmethyl-3-methyl-1*H*-indol-7-yl)acryloyl]benzenesulfonamide (62). Compound **62** was prepared through the alkylation of indole derivative **96c** and 2-chloromethylimidazo[1,2-*a*]pyridine according to general procedure B. Yield: 68%. 1H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3 H), 5.77 (s, 2 H), 6.44 (d, J = 15 Hz, 1 H), 7.09 (dd, J = 10.0, 2.0 Hz, 1 H), 7.34−7.37 (m, 1 H), 7.40 (s, 1 H), 7.47 (dd, J = 9.0, 2.0 Hz, 1 H), 7.62−7.65 (m, 2 H), 7.72−7.80 (m, 3 H), 7.86 (s, 1 H), 8.07 (d, J = 15 Hz, 1 H), 8.66 (d, J = 7 Hz, 1 H). MS (ESI^-): mass calcd for $C_{26}H_{19}F_3N_4O_3S$, 524.1; m/z found 523.6 (M − 1). HPLC system 1: 98.1%, t_R = 10.96 min.

***N*-{(*E*)-3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-ylmethyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}-*C*,*C*,*C*-trifluoromethanesulfonamide (63).** A mixture of the acid **99** (0.100 g, 0.27 mmol), EDCI (0.104 g, 0.54 mmol), DMAP (0.066 g, 0.54 mmol), and $CF_3SO_2NH_2$ (0.049 g, 0.33 mmol) in anhydrous CH_2Cl_2 (10 mL) was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL). The solution was successively washed with 1 N HCl (2 × 5 mL), brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed by flash silica gel (4 g) and eluted with 1% MeOH in CH_2Cl_2 to yield 0.050 g (37%) of compound **63**. ^1H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H), 4.16 (m, 4H), 4.70 (br s, 1H, w /water peak), 5.34 (s, 2H), 6.28 (d, J = 15.6 Hz, 1H), 6.38 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 8.4, 2.0 Hz, 1H), 6.74 (d,

J = 8.4 Hz, 1H), 7.08 (dd, J = 10.4, 2.4 Hz, 1H), 7.26−7.34 (m, 2H), 7.94 (d, J = 15.6 Hz, 1H). MS (APCI$^-$): mass calcd for $C_{22}H_{18}F_4N_2O_5S$, 498.1; m/z found 497.0 (M − 1). LCMS 98.6%. HPLC system 1: 98.7%, t_R = 15.57 min.

4,5-Dichlorothiophene-2-sulfonic Acid {(*E*)-3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-ylmethyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}amide (64). Compound **64** was prepared through the alkylation of indole derivative **96b** with 6-bromomethyl-2,3-dihydrobenzo[1,4]dioxine according to general procedure B. Yield: 45%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H), 4.14 (m, 4H), 5.36 (s, 2H), 6.32 (d, J = 0.8 Hz, 1H), 6.34 (d, J = 15.6 Hz, 1H), 6.45 (dd, J = 8.4, 2.0 Hz, 1H), 6.65 (d, J = 9.2 Hz, 1H), 7.0 (dd, J = 10.0, 2.4 Hz, 1H), 7.36 (s, 1H), 7.41 (dd, J = 8.8, 2.4 Hz, 1H), 7.90 (s, 1H), 8.08 (d, J = 15.6 Hz, 1H). MS (APCI$^-$): mass calcd for $C_{25}H_{19}Cl_2FN_2O_5S_2$, 580.0; m/z found 578.9 (M − 1). LCMS 96.9%. HPLC system 1: 97.7%, t_R = 17.35 min. HPLC system 2: 99.3%, t_R = 17.81 min.

Piperidine-1-sulfonic Acid {(E)-3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acryloyl}amide (65). Compound **65** was prepared analogous to synthesis of **54**, piperidine-1-sulfonamide was used according to general procedure A. Yield: 49%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53 (m, 6H), 2.26 (s, 3 H), 3.17 (m, 4H), 5.57 (s, 2H), 6.15 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 15.6 Hz, 1H), 7.03 (dd, J = 10.4, 2.4 Hz, 1 H), 7.27 (dd, J = 8.4, 2.0 Hz, 1H), 7.37 (s, 1H), 7.46 (dd, J = 9.2, 2.4 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 15.6 Hz, 1H), 11.43 (s, 1H). MS (ESI$^-$): mass calcd for $C_{24}H_{24}Cl_2FN_3O_3S$, 523.1; m/z found 522.0 (M − 1). LCMS 99.1%. HPLC system 1: 99.3%, t_R = 17.88 min. HPLC system 2: 98.9%, t_R = 17.47 min.

4,5-Dichlorothiophene-2-sulfonic Acid {3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]propionyl}amide (66). To a solution of acid **101** (0.16 mmol, 1.0 equiv), 4,5-dichloro-2-thiophenesulfonamide (0.16 mmol, 1.0 equiv), and DMAP (0.38 mmol, 2.4 equiv) in CH_2Cl_2 was added EDCI (0.39 mmol, 2.5 equiv). The reaction mixture was stirred at room temperature for 16 h and acidified to pH 1−2 with 1 N HCl. The organic layer was washed with successive portions of water and brine and dried over anhudrous $MgSO_4$. The filtrate was concentrated in vacuo and the residue purified by flash chromatography on silica gel, using MeOH in CH_2Cl_2 as eluent, to afford the title compound **66** in 64% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3H), 2.49 (m, 2H), 2.76 (m, 2H), 5.49 (s, 2H), 6.46 (d, J = 7.6 Hz, 1H), 6.66 (dd, J = 10.8, 2.4 Hz, 1H), 7.14 (dd, J = 9.2, 2.8 Hz, 1H), 7.25 (s, 1H), 7.27 (dd, J = 8.4, 2.0 Hz, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.80 (s, 1H), 7.96 (s, 1H). MS (ESI$^-$): mass calcd for $C_{23}H_{17}Cl_4FN_2O_3S_2$, 594.3; m/z found 593.2 (M − 1). LC/MS 95.7%.

3-(1*H*-Indol-7-yl)acrylic Acid Ethyl Ester (69). To a round-bottom flask (100 mL) that contained a suspension of NaH (60% in mineral oil, 320 mg, 8 mmol) in THF (20 mL) was added triethyl phosphonoacetate (1.5 g, 6.6 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature, stirred for 2 h, and then cooled to 0 °C. To this solution, indole-7-carboxaldehyde, **68** (450 mg, 3 mmol), was added at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 2 h, then heated and stirred at 78 °C for 14 h. The reaction mixture was cooled to 5 °C, quenched with the addition of saturated aqueous NH_4Cl solution (15 mL) followed by extraction with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography with gradient elution (silica gel, EtOAc/hexanes, 1:20 to 1:8) to afford 450 mg (68%) of compound **69** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3H), 4.30 (q, J = 7.5 Hz, 2H), 6.55 (d, J = 16.0 Hz, 1H), 6.58 (dd, J = 3.5, 2.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 3.0 Hz, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 8.10 (d, J = 16.0 Hz, 1H), 8.97 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 60.5, 103.1, 117.9, 118.3, 120.0, 122.0, 123.3, 124.9, 128.9, 134.3, 141.2, 167.5. MS (ESI$^+$): mass calcd for $C_{13}H_{13}NO_2$, 215.1; m/z found 216.3 (M + 1). LCMS 97%. HPLC system 1: 98%, t_R = 14.32 min.

3-(1*H*-Indol-7-yl)acrylic Acid (70). To a round-bottom flask (500 mL) that contained a solution of NaOH (1.2 g, 30 mmol) in EtOH (100 mL) and H_2O (30 mL) was added the ester **69** (3.2 g, 15 mmol) at 5 °C. The resulting mixture was allowed to warm to room temperature and stir for 10 min, then heated to 78 °C and stirred for 4 h. The reaction mixture was cooled to 5 °C and was acidified with addition of aqueous HCl (10%) until pH 1, which was followed by extraction with CH_2Cl_2/MeOH (95/5, 3 × 150 mL). The combined organic layers were washed with brine (2 × 20 mL), dried over anhudrous Na_2SO_4, filtered, and the solvent was removed in vacuo to provide a residue which was purified by recrystallization from acetone/EtOAc/hexane to yield 2.4 g (86%) of the acrylic acid **70** as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.58 (dd, J = 3.5, 1.5 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 3.0 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 8.12 (d, J = 16.5 Hz, 1H), 11.56 (s, 1H), 12.38 (s, 1H). ^{13}C NMR (125 MHz, acetone-d_6) δ 103.3, 118.6, 119.3, 120.5, 122.1, 123.9, 126.6, 130.4, 135.7, 142.1, 168.4. MS (APCI$^-$): mass calcd for $C_{11}H_9NO_2$, 187.1; m/z found 186.2 (M − 1). LCMS 99%. HPLC system 1: 99%, t_R = 11.35 min.

Synthesis of Thiophene-2-sulfonic Acid ((*E*)-3-1*H*-Indol-7-yl-acryloyl)amide (71). To a round-bottom flask (500 mL) that contained a solution of 2-thiophene sulfonamide (1.05 g, 6 mmol), DMAP (1.56 g, 13 mmol) and EDCI (2.4 g, 13 mmol) in CH_2Cl_2 (150 mL) was added the acrylic acid **70** (1.2 g, 6 mmol) at room temperature. The resulting mixture was allowed to stir at room temperature for 72 h, then was cooled to 5 °C and was acidified with aqueous HCl (10%) until pH 1, which was followed by extraction of CH_2Cl_2/MeOH (9/1, 3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to provide the crude product which was purified by flash chromatography (silica gel, CH_2Cl_2/EtOAc/hexane = 1:10, 20:20:10) to afford 1.2 g, (56%) of the acylsulfonamide **71** as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.47 (m, 1H), 6.67 (d, J = 16.0 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 3.5 Hz, 1H), 7.37−7.39 (m, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 3.5 Hz, 1H), 7.98 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 15.5 Hz, 1H), 11.54 (s, 1H). MS (ESI$^-$): mass calcd for $C_{15}H_{12}N_2O_3S_2$, 332.0; m/z found 331.1 (M − 1). LCMS 99%. HPLC system 1: 99%, t_R = 12.95 min.

7-Bromo-3-methyl-1*H*-indole (72). 2-Bromonitrobenzene was reacted with allylmagnesium bromide according to the literature procedure[16] to provide compound **72** in 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (d, J = 1.2 Hz, 3H), 7.00 (t, J = 7.6 Hz, 1H), 7.03 (m, 1H), 7.34 (ddd, J = 7.2, 0.4, 0.4 Hz, 1H), 7.52 (ddd, J = 7.2, 0.8, 0.8 Hz, 1H), 8.07 (br s, 1H). MS (ESI$^+$): mass calcd for C_9H_8BrN, 209.0; m/z found 130.1 (M − Br). LCMS 99.2%.

(*E*)-3-(3-Methyl-1*H*-indol-7-yl)acrylic Acid Methyl Ester (73). To a mixture of compound **72** (300 mg, 1.42 mmol) and methyl acrylate (183 mg, 2.13 mmol) in Et_3N (1 mL), palladium(II) acetate (31 mg, 0.14 mmol) and tri-*o*-tolylphosphine (129 mg, 0.42 mmol) were added under argon at room temperature. The reaction mixture was stirred at 100 °C for 4 h in a sealed pressure tube and then cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water (3 × 30 mL), brine, and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel with EtOAc/hexane as an eluent to give 250 mg (82%) of compound **73** as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.84 (s, 3H), 6.49 (d, J = 16.0 Hz, 1H), 7.03 (s, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 8.01 (d, J = 16.0 Hz, 1H), 8.40 (br s, 1H). MS (AP$^-$): mass calcd for $C_{13}H_{13}NO_2$, 215.1; m/z found 214.1 (M − 1). LCMS 99.6%.

(*E*)-3-(3-Methyl-1*H*-indol-7-yl)acrylic Acid (74). To a solution of compound **73** (180 mg, 0.84 mmol) in THF (5 mL) and

MeOH (4 mL), 2 N aqueous NaOH (4 mL) was added at room temperature. The reaction mixture was stirred at room temperature overnight, and then the pH was adjusted to acidic by adding 2 N aqueous HCl. The reaction mixture was extracted with EtOAc (2 × 30 mL). The combined organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. After removal of solvent, 170 mg (100%) of compound **74** was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.26 (s, 3H), 6.59 (d, J = 16 Hz, 1H), 7.05 (m, 1H), 7.15 (s, 1H), 7.50 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 8.08 (d, J = 16 Hz, 1H), 11.2 (s, 1H), 12.3 (br s, 1H). MS (AP^-): mass calcd for $C_{12}H_{11}NO_2$, 201.1; m/z found 200.1 (M − 1). LCMS 95.3%.

Thiophene-2-sulfonic Acid [(*E*)-3-(3-Methyl-1*H*-indol-7-yl)acryloyl]amide (75). A mixture of the acid **74** (170 mg, 0.84 mmol), 2-thiophenesulfonamide (163 mg, 1 mmol), DMAP (207 mg, 1.7 mmol) and EDCI (325 mg, 1.7 mmol) in CH_2Cl_2 (20 mL), and DMSO (0.5 mL) was stirred at room temperature overnight. The solution was diluted with CH_2Cl_2, washed with diluted aqueous HCl, water, brine, and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel with MeOH/CH_2Cl_2 as an eluent to give 170 mg (58%) of compound **75**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.32 (s, 3H), 6.60 (d, J = 15.5 Hz, 1H), 7.02 (s, 1H), 7.08−7.14 (m, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.65 (m, 2H), 7.92 (m, 1H), 8.11 (d, J = 15.5 Hz, 1H), 8.54 (br s, 1H). MS (ESI^-): mass calcd for $C_{16}H_{14}N_2O_3S_2$, 346.0; m/z found 345.1 (M − 1). LCMS 97.6%.

(4-Bromo-1*H*-indol-3-yl)naphthalen-2-ylmethanone (77). To a solution of 4-bromoindole (Aldrich Chemical Co.) (**76**, 5.0 g, 25.5 mmol) in 100 mL of anhydrous CH_2Cl_2 was added 3 M MeMgBr in Et_2O (8.95 mL, 26.7 mmol) dropwise at 20 °C. A slightly exothermic reaction was observed, and the temperature of the mixture rose to 28 °C. The resulting orange solution was stirred for 10 min at room temperature. Then 1 M $ZnCl_2$ solution in Et_2O (76.5 mL, 765 mmol) was added via an addition funnel. The reaction mixture was stirred for 0.5 h. Then a solution of 2-naphthoyl chloride (5.1 g, 26.7 mmol) in 25 mL of CH_2Cl_2 was added. During the addition, the color changed from light-orange to dark-red. The resulting mixture was stirred at room temperature overnight. TLC (30% EtOAc/hexanes) showed the reaction was complete, and then the mixture was quenched with saturated solution of NH_4Cl (100 mL). The suspension was stirred for 15 min. The solid was filtered off and washed several times with CH_2Cl_2. The filtrate was washed with saturated NH_4Cl, water, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford 7 g of a residue. The solid was taken into 10% aqueous HCl and was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give about 500 mg of additional residue. The combined residues (7.5 g) were washed with 15 mL of MTBE. Then the solvent was decanted and then washed with 10 mL MTBE/hexane (1:1), and the suspension was filtered to afford 4.61 g of **77**. The filtrate was concentrated and the residue was purified by column chromatography using EtOAc/hexane (20−50% gradient) to give 2 g of pure **77**. A total of 6.61 g (74%) of product **77** was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.17−7.203 (t, J = 8.5 Hz, 1H), 7.38 (dd, J = 8, 0.5 Hz, 1H), 7.58 (dd, J = 8.0, 0.5 Hz, 1H), 7.57−7.68 (m, 2H), 7.94 (s, 1H), 7.96 (dd, J = 8.5, 1.5 Hz, 1H), 8.00−8.09 (m, 3H), 8.04 (s, 1H), 12.2 (s, 1H).

4-Bromo-3-naphthalen-2-ylmethyl-1*H*-indole (78). To a 100 mL round-bottomed flask containing 2.1 g (6 mmol) of **77** and 50 mL of anhydrous THF, under N_2 at 0 °C, was added dropwise 18 mL (18 mmol, 3 equiv) of $BH_3 \cdot$THF (1 M in THF). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, and 10 mL of MeOH was added dropwise (with gas evolution). After 0.5 h at room temperature, the mixture was concentrated in vacuo to obtain 2 g of **78** as a light-yellow oil that was used without purification for next step. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.48 (s, 2H), 6.98 (t, J = 8 Hz, 1H), 7.14 (dd, J = 7.5, 0.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.40−7.45 (m, 4H), 7.63 (s, 1H), 7.76−7.86 (m, 4H), 11.29 (s, 1H).

(*E*)-3-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yl)acrylic Acid Methyl Ester (79). To a pressure resistant tube containing 1.5 g of **78** (4.46 mmol) in 2 mL of Et_3N were added $Pd(OAc)_2$ (50 mg, 0.22 mmol), tri-*o*-tolylphosphine (270 mg, 0.88 mmol), and methyl acrylate (500 mg, 5.8 mmol). Mixture was heated to 100 °C for 2.5 h. A bulky precipitate formed. TLC (20% EA/hexane) indicated the reaction completion. The reaction mixture was cooled to room temperature, the suspension was diluted with water and extracted with CH_2Cl_2, the combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, concentrated in vacuo to give 1.6 g of a residue, which was purified by column chromatography using 10−25% EtOAc/hexane gradient elution to provide 1 g (65%) of compound **79**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.68 (s, 3H), 4.37 (s, 2H), 6.35 (d, J = 16 Hz, 1H), 7.08−7.11 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7 Hz, 1H), 7.39−7.48 (m, 6H), 7.73 (s, 1H), 7.74−7.84 (m, 3H), 8.29 (d, J = 16 Hz, 1H), 11.22 (s, 1H).

(*E*)-3-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yl)acrylic Acid (80). To a solution of the methyl ester **79** (1 g, 2.9 mmol) in a mixture of THF/MeOH (3:2, 50 mL) was added 20 mL of 1 N aqueous NaOH,. The mixture was stirred at 60 °C for 4 h. TLC (EtOAc/hexane, 1:1) indicated the reaction completion. The reaction mixture was concentrated in vacuo, and to this residue a solution of 10% aqueous HCl was added to bring the mixture to pH 2. A gummy dark-brown solid formed. The mixture was stirred at room temperature for 0.5 h when solid started crashing out. The suspension was filtered off to afford, after washing with water and drying, 0.95 g (100%) of the compound **80**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.36 (s, 2H), 6.28 (d, J = 16 Hz, 1H), 7.09−7.105 (t, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.34 (d, J = 7 Hz, 1H), 7.40−7.45 (m, 4H), 7.73 (s, 1H), 7.75−7.84 (m, 4H), 8.33 (d, J = 16 Hz, 1H), 11.18 (s, 1H), 12.22 (s, 1H).

(*E*)-3-(1-Methyl-3-naphthalen-2-ylmethyl-1*H*-indol-4-yl)acrylic Acid Methyl Ester (81). To a suspension of NaH (60% dispersion in mineral oil, 47 mg, 1.17 mmol) in 3 mL of anhydrous THF at 0 °C was added the methyl ester **79** (200 mg, 0.58 mmol). The mixture was stirred at room temperature for 1 h, then cooled to 0 °C, and CH_3I (0.180 mL, 2.9 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with 10% aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to afford 200 mg of compound **81**. This material was used for next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.35 (s, 2H), 6.32 (d, J = 16 Hz, 1H), 7. 16 (t, J = 7.5 Hz, 1H), 7.27 (s, 1H), 7.37−7.45 (m, 4H), 7.50 (d, J = 8 Hz, 1H), 7.76−7.85 (m, 4H), 8.33 (d, J = 16 Hz, 1H).

(*E*)-3-(1-Methyl-3-naphthalen-2-ylmethyl-1*H*-indol-4-yl)acrylic Acid (82). To a solution of the methyl ester **81**, (200 mg, 0.448 mmol) in a mixture of THF/MeOH (3:2) was added 2 mL of 1 N aqueous NaOH. The mixture was stirred at 60 °C for 4 h. TLC (EtOAc/hexanes, 1:4) indicated the reaction completion. The reaction mixture was concentrated in vacuo, and to this residue a solution of 10% aqueous HCl was added to give a mixture of pH 2. The oily mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to provide 180 mg (90%, for two steps from **80**) of the acid **82**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.78 (s, 3H), 4.35 (s, 2H), 6.31 (d, J = 16 Hz, 1H), 7.15−7.18 (t, J = 8 Hz, 1H), 7.27 (s, 1H), 7.37−7.44 (m, 4H), 7.50 (d, J = 8 Hz, 1H), 7.76−7.85 (m, 4H), 8.33 (d, J = 16 Hz, 1H), 12.22 (s, 1H).

3-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yl)propionic Acid Methyl Ester (83). To a solution of the acrylate **79**, (500 mg, 1.46 mg) in 30 mL of MeOH under N_2 was added 200 mg of 10% Pd/C. The mixture was stirred at 40 °C under H_2 for 2 h, then at room temperature overnight. The reaction mixture was filtered

through a Celite plug using MeOH and CH_2Cl_2. The solvent was removed and residue was purified by column chromatography using 10−20% EtOAc/hexanes to afford 435 mg (86%) of the compound **83**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.37 (t, J = 8.5 Hz, 2H), 3.03 (t, J = 8.5, 2H), 3.51 (s, 3H), 4.35 (s, 2H), 6.69 (d, J = 7.0 Hz, 1H), 6.95−6.98 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.22 (d, J = 7 Hz, 1H), 7.36 (dd, J = 8.0, 1.5 Hz, 1H), 7.42−7.44 (m, 2H), 7.61 (s, 1H), 7.75 (m, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.86 (m, 1H), 10.9 (s, 1H).

3-(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yl)propionic Acid (84). To a solution of the methyl ester **83** (130 mg, 0.380 mmol) in a mixture of THF/MeOH (3:2) was added 2 mL of 1 N aqueous NaOH. The mixture was stirred at 60 °C for 4 h. TLC (EtOAc/hexanes, 1:1) indicated the reaction completion. The reaction mixture was concentrated in vacuo, and to this residue a solution of 10% aqueous HCl was added bringing the solution to pH 2. The oily mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 126 mg (quantitative) of compound **84**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.41 (t, J = 8.0 Hz, 2H), 3.14 (t, J = 8.0 Hz, 2H), 4.35 (s, 2H), 6.71 (d, J = 7.0 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.36 (dd, J = 8.0, 1.5 Hz, 1H), 7.42−7.44 (m, 2H), 7.62 (s, 1H), 7.74−7.76 (m, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.86 (m, 1H), 10.9 (s, 1H), 12.05 (br s, 1H).

3-(1-Methyl-3-naphthalen-2-ylmethyl-1*H*-indol-4-yl)propionic Acid Methyl Ester (85). To a suspension of NaH (60% dispersion in mineral oil, 35 mg, 0.87 mmol) in 3 mL of anhydrous THF at 0 °C was added the methyl ester **83** (200 mg, 0.58 mmol). The mixture was stirred at room temperature for 1 h, then cooled to 0 °C, and CH_3I (0.180 mL, 2.9 mmol) was added. The reaction mixture was stirred at room temperature overnight. The mixture was quenched with 10% aqueous HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford 160 mg (77%) of the compound **85**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.52 (t, J = 8.0 Hz, 2H), 3.24 (t, J = 8.0 Hz, 2H), 3.58 (s, 3H), 3.71 (s, 3H), 4.41 (s, 2H), 6.66 (s, 1H), 6.85 (d, J = 7.0 Hz, 1H), 7.12−7.19 (m, 2H), 7.38−7.43 (m, 3H), 7.64 (s, 1H), 7.73 (m, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.80 (m, 1H).

3-(1-Methyl-3-naphthalen-2-ylmethyl-1*H*-indol-4-yl)propionic Acid (86). To a solution of the methyl ester **85** (160 mg, 0.448 mmol) in a mixture of THF/MeOH (3:2) was added 2 mL of 1 N aqueous NaOH. The mixture was stirred at 60 °C for 4 h. TLC (EtOAc/hexanes, 1:4) indicated the reaction completion. The reaction mixture was concentrated in vacuo, and to this residue a solution of 10% aqueous HCl was added to obtain pH 2. The oily mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo to give 120 mg (78%) of compound **86**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.4 (t, J = 8.0 Hz, 2H), 3.06 (t, J = 8.0 Hz, 2H), 3.71 (s, 3H), 4.34 (s, 2H), 6.78 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 7.04 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.38- 7.45 (m, 3H), 7.64 (s, 1H), 7.76 (m, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.85 (m, 1H), 12.07 (br s, 1H).

Acetic Acid 1*H*-Indol-4-yl Ester (88). Ac_2O (16.75 mL, 170 mmol, 1.5 equiv) was added slowly (over 7 min) to a solution of 4-hydroxyindole (**87**), 15 g, 110 mmol, 1 equiv) in pyridine (113 mL) at room temperature. Temperature rose from 25 to 32 °C. After beirng stirred for an additional 5 min, the reaction mixture was cooled in an ice bath, and 10% aqueous HCl (340 mL) followed by EtOAc (565 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were washed with 10% aqueous HCl (2 × 50 mL), water (2 × 300 mL), brine (300 mL) and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent in vacuo afforded 19.3 g (98%) of the compound **88** as a light-brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.43 (br s, 1H), 6.86 (d, J = 16.0 Hz, 1H), 7.14 (m, 2H), 7.24 (m, 1H), 8.20 (br s, 1H). MS (AP^-): mass calcd for $C_{10}H_9NO_2$, 175.1; m/z found 174.2 (M − 1).

Acetic Acid 3-(Naphthalene-2-carbonyl)-1*H*-indol-4-yl Ester (89). MeMgBr (26 mL, 78 mmol, 1.05 equiv, 3.0 M solution in Et_2O) was added slowly (over 10 min) via syringe to a solution of the acetate **88** (13 g, 74 mmol, 1 equiv) in anhydrous CH_2Cl_2 (260 mL) at room temperature. After the mixture was stirred for 5 min at room temperature, $ZnCl_2$ (223 mL, 3.0 equiv, 1.0 M solution in Et_2O) was added via syringe over 5 min at room temperature. After the mixture was stirred for 10 min at room temperature, a solution of 2-naphthoyl chloride (14.85 g, 1.05 equiv) in anhydrous CH_2Cl_2 (87 mL) was added over 3 min. The reaction mixture was stirred for 3 h at room temperature and then was poured into saturated aqueous NH_4Cl (866 mL), and the mixture was diluted with CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with water (2 × 500 mL), brine (500 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 24.4 g (100%) of brown solid. MTBE (100 mL) was added to the solid, heated to reflux, cooled to 30−40 °C, and filtered. The residue was washed on filter with MTBE (50 mL, 25 mL, 2 × 5 mL), then with Et_2O (2 × 5 mL) to afford 16.0 g (65%) of **89** as a light-brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 6.89 (d, 1H), 7.03 (d, J = 16.5 Hz, 1H), 7.09 (m, 2H), 7.52 (t, J = 15.0 Hz, 1H), 7.56 (t, J = 15.0 Hz, 1H), 7.79 (m, 3H), 7.88 (d, J = 16.0 Hz, 1H), 8.12 (br s, 1H), 9.35 (br s, 1H). MS (ESI^-): mass calcd for $C_{21}H_{15}NO_3$, 329.3; m/z found 328.1 (M − 1).

3-Naphthalen-2-ylmethyl-1*H*-indol-4-ol (90). $BH_3\cdot$THF (1 M in THF, 120 mL, 120 mmol, 3.3 equiv) was added slowly to a solution of **89** (12.0 g, 36.4 mmol, 1 equiv) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stir overnight. The reaction mixture was quenched by slow addition of MeOH (120 mL), evaporated, and coevaporated with MeOH (3 × 120 mL). The residue was purified by silica gel chromatography (150 g) using CH_2Cl_2 as eluent to afford 6.2 g (62%) of the compound **90**. ^{1}H NMR (DMSO-d_6) δ 4.35 (s, 2H), 6.30 (d, J = 7.0 Hz, 1H), 6.79 (m, 2H), 6.87 (d, J = 1.5 Hz, 1H), 7.43 (m, 2H), 7.49 (dd, J = 8.5, 1.5 Hz, 1H), 7.73 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 7.0 Hz, 1H), 9.2 (s, 1H), 10.67 (s, 1H). MS (ESI^-): mass calcd for $C_{19}H_{15}NO$, 273.1; m/z found 271 (M − 2).

(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yloxy)acetic Acid Methyl Ester (91). A solution of methyl bromoacetate (3.10 g, 1.9 mL, 20.3 mmol, 1.05 equiv) in DMF (20 mL) was added slowly to the mixture of **90** (5.29 g, 19.4 mmol, 1 equiv) and K_2CO_3 (3.21 g, 23.2 mmol, 1.2 equiv) in DMF (51 mL). Reaction mixture was stirred at room temperature overnight (17 h). Water−brine (5:1, 180 mL) was added, and the resulting solution was extracted with EtOAc (180 mL, 140 mL, 70 mL). The organic layer was washed with brine (2 × 210 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 7.8 g of a solid. This residue was washed with Et_2O (20 mL) and filtered to afford 5.0 g (75%) of the compound **91** as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 3H), 4.38 (s, 2H), 4.80 (s, 2H), 6.34 (d, J = 7.5, 1H), 6.90−6.97 (m, 2H), 6.99 (d, J = 1.5 Hz, 1H), 7.42 (m, 2H), 7.50 (dd, J = 8.5, 1.5 Hz, 1H), 7.76−7.83 (m, 4H), 10.88 (s, 1H). MS (ESI^+): mass calcd for $C_{22}H_{19}NO_3$, 345.4; m/z found 346.5 (M + 1).

(3-Naphthalen-2-ylmethyl-1*H*-indol-4-yloxy)acetic Acid (92). A solution 2 N aqueous NaOH (9.5 mL, 19 mmol, 2 equiv) was added to a solution of **91** (3.3 g, 9.55 mmol, 1 equiv) in THF−MeOH, 2:1 (132 mL). The reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated to ~20 mL, and 10% aqueous HCl (10 mL) was added followed by water (50 mL). The mixture was extracted with EtOAc (250 mL), and the organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 2.95 g (92%) of the acid **92** as an off-white solid. ^{1}H NMR (500 MHz,

DMSO-d_6) δ 4.38 (s, 2H), 4.70 (s, 2H), 6.34 (d, J = 6.5 Hz, 1H), 6.89−6.95 (m, 2H), 6.97 (d, J = 2.0 Hz, 1H), 7.42 (m, 2H), 7.52 (dd, J = 8.5, 1.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.85 (s, 1H), 10.85 (d, J = 1.0 Hz, 1H), 12.75 (br s, 1H).

Thiophene-2-sulfonic Acid [(*E*)-3-(5-Fluoro-3-methyl-1*H*-indol-7-yl)acryloyl]amide (96a). A mixture of the acid **95** (100 mg, 0.46 mmol), 2-thiophenesulfonamide (90 mg, 0.55 mmol), DMAP (112 mg, 0.92 mmol), and EDCI (176 mg, 0.92 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature overnight. The solution was diluted with CH_2Cl_2 and washed with diluted aqueous HCl and water. The resulting solid was filtered washed with water and CH_2Cl_2 to give 55 mg of compound **96a**. The remaining CH_2Cl_2 mother liquid was purified by column chromatography on silica gel with CH_2Cl_2/MeOH as an eluent to give 45 mg of acylsulfonamide **96a**. A total of 100 mg (60%) of compound **96a** was obtained. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.22 (s, 3H), 6.69 (d, J = 15.0 Hz, 1H), 7.19 (dd, J = 10.0, 2.0 Hz, 1H), 7.22−7.25 (m, 2H), 7.37 (dd, J = 9.0, 2.0 Hz, 1H), 7.86 (m, 1H), 8.06 (m, 1H), 8.10 (d, J = 15.0 Hz, 1H), 11.35 (s, 1H), 12.42 (br s, 1H).).

3,5-Difluoro-*N*-[(*E*)-3-(5-fluoro-3-methyl-1*H*-indol-7-yl)acryloyl]benzenesulfonamide (96c). Compound **96c** was prepared through the coupling of acid **95** with the 3,5-difluorobenzenesulfonamide according to general procedure A. Yield: 51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3 H), 6.70 (d, J = 16.0 Hz, 1 H), 7.21 (dd, J = 10.0, 2.0 Hz, 1 H), 7.25 (s, 1 H), 7.38 (dd, J = 10.0, 2.0 Hz, 1 H), 7.57−7.77 (m, 3 H), 8.10 (d, J = 16.0 Hz, 1 H), 11.33 (s, 1 H), 12.56 (bs, 1 H). MS (ESI$^-$): mass calcd for $C_{18}H_{13}F_3N_2O_3S$, 394.4; m/z found 393.5 (M − 1). LCMS 98%.

3,4-Difluoro-*N*-[(*E*)-3-(5-fluoro-3-methyl-1*H*-indol-7-yl)acryloyl]benzenesulfonamide (96d). Compound **96d** was prepared through the coupling of **95** with 3,4-difluorobenzenesulfonamide according to general procedure A. Yield: 41%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3 H), 6.69 (d, J = 16.0 Hz, 1 H), 7.20 (dd, J = 10.0, 2.0 Hz, 1 H), 7.25 (s, 1 H), 7.37 (dd, J = 10.0, 2.0 Hz, 1 H), 7.75 (m, 1 H), 7.88 (m, 1 H), 8.04 (m, 1 H), 8.10 (s, 1 H), 11.32 (s, 1 H), 12.47 (br s, 1 H). MS (ESI$^-$): mass calcd for $C_{18}H_{13}F_3N_2O_3S$, 394.4; m/z found 393.5 (M − 1). LCMS 99%.

2,4,5-Trifluoro-*N*-[(*E*)-3-(5-fluoro-3-methyl-1*H*-indol-7-yl)acryloyl]benzenesulfonamide (96e). Compound **96e** was prepared through the coupling of **95** with 2,4,5-trifluorobenzenesulfonamide according to general procedure A, and the material was used as such for the next step. Yield: 49%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.22 (s, 3H), 6.72 (d, J = 15.5 Hz, 1H), 7.20 (dd, J = 10.0, 2.0 Hz, 1H), 7.25 (s, 1H), 7.38 (dd, J = 9.5, 2.0 Hz, 1H), 7.92 (m, 1H), 8.07 (m, 1H), 8.09 (d, J = 15.5 Hz, 1H), 11.31 (s, 1H), 12.85 (br s, 1H). MS (ESI$^-$): mass calcd for $C_{18}H_{12}F_4N_2O_3S$, 412.1; m/z found 411.4 (M − 1). LCMS 96%.

4-Fluoro-*N*-[(*E*)-3-(5-fluoro-3-methyl-1*H*-indol-7-yl)acryloyl]-benzenesulfonamide (96f). Compound **96f** was prepared through the coupling of **95** with 4-fluorobenzenesulfonamide according to general procedure A. Yield: 53%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (s, 3 H), 6.69 (d, J = 16 Hz, 1 H), 7.18 (dd, J = 10.0, 2.0 Hz, 1 H), 7.24 (s, 1 H), 7.37 (dd, J = 10.0, 2.0 Hz, 1 H), 7.48−7.52 (m, 2 H), 8.03 (s, 1 H), 8.04−8.09 (m, 2 H), 11.31 (s, 1 H), 12.35 (br s, 1 H). MS (ESI$^-$): mass calcd for $C_{18}H_{14}F_2N_2O_3S$, 376.4; m/z found 375.5 (M − 1). LCMS 96%.

7-Bromo-1-(2,3-dihydrobenzo[1,4]dioxin-6-ylmethyl)-5-fluoro-3-methyl-1*H*-indole (97). A solution of bromoindole **93** (5.00 g, 21.90 mmol) in anhydrous DMF (100 mL) was cooled to 5 °C. NaH (60% in mineral oil, 1.314 g, 32.85 mmol) was added portionwise over a period of 15 min. The cooling bath was removed, and the mixture was allowed to warm to room temperature and stirred for 1.5 h. The mixture was recooled to 5 °C, and 6-(bromomethyl)-2,3-dihydro-1,4-benzodioxine (6.024 g, 26.30 mmol) was added dropwise. The cooling bath was removed, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (300 mL) followed by addition of saturated aqueous NH_4Cl (100 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was chromatographed on flash silica (145 g), eluting with 5% EtOAc in hexanes to yield 6.56 g (80%) of compound **97**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (d, J = 0.8 Hz, 3H), 4.21 (s, 4 H), 5.59 (s, 2H), 6.50−6.54 (m, 2H), 6.77 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 7.14 (m, (overlapping dd), 2H).

(*E*)-3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-ylmethyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acrylic Acid Methyl Ester (98). Compound **97** (2.163 g, 5.75 mmol), methyl acrylate (1.56 mL, 17.24 mmol), tri-*o*-tolylphosphine (0.525 g, 1.73 mmol), $Pd(OAc)_2$ (0.130 g, 0.58 mmol), and Et_3N (4.00 mL, 29.00 mmol) were heated in a sealed tube under nitrogen atmosphere for 4 h at 100 °C. The mixture was cooled to room temperature, and the solids were filtered off and washed on with EtOAc. The combined filtrates were diluted with EtOAc (200 mL), washed successively with 1 N aqueous HCl (2 × 30 mL) and brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (8 mL), and the solution was diluted with hexanes (200 mL). The precipitate was filtered off and dried to yield 1.49 g (68%) of compound **98**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.79 (s, 3H), 4.21 (s, 4 H), 5.30 (s, 2H), 6.22 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1 H), 6.56 (dd, J = 8.4, 2.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 7.01 (dd, J = 10.0, 2.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.4 Hz, 1H), 8.12 (d, J = 15.6 Hz, 1H). MS (APCI$^+$): mass calcd for $C_{22}H_{20}FNO_4$, 381.4; m/z found 382.0 (M + 1).

(*E*)-3-[1-(2,3-Dihydrobenzo[1,4]dioxin-6-ylmethyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]acrylic Acid (99). To a solution of methyl acrylate **98** (1.43 g, 3.75 mmol) in a mixture of MeOH (30 mL) and THF (30 mL) was added 2 N aqueous solution of NaOH (30 mL). The mixture was stirred overnight at room temperature. Most volatiles were removed under reduced pressure. The residue was diluted with water (20 mL), and the pH was adjusted to 2 with concentrated HCl. The precipitate was filtered off, washed on funnel with water, and dried in air to yield 1.20 g (87%) of the acid **99**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.24 (s, 3H), 4.16 (t, J = 4.8 Hz, 4 H), 5.37 (s, 2H), 6.31 (d, J = 15.6 Hz, 1H), 6.42 (d, J = 2.0 Hz, 1 H), 6.47 (dd, J = 8.4, 2.0 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.20 (dd, J = 10.4, 2.4 Hz, 1H), 7.35 (s, 1H), 7.38 (dd, J = 8.8, 2.4 Hz, 1H), 8.05 (d, J = 15.6 Hz, 1H), 12.40 (br s, 1H). LCMS 100%. MS (APCI$^-$) m/z 366.1 (M − H). MS (APCI$^-$): mass calcd for $C_{21}H_{18}FNO_4$, 367.4; m/z found 366.1 (M − 1). LCMS 100%.

3-(5-Fluoro-3-methyl-1*H*-indol-7-yl)propionic Acid (100). To a solution of the acid **95** in EtOH was added 10% by weight of 10% Pd/C. The reaction vessel was degassed, the atmosphere replaced with hydrogen, and the process repeated 3 times. The suspension was stirred under 1 atm of hydrogen for 16 h at room temperature. An additional 10% by weight of 10% Pd/C was added, and the reaction was allowed to proceed an additional 16 h at room temperature. The reaction was filtered through a pad of Celite and the cake washed with EtOH. The filtrate was concentrated in vacuo to afford compound **100** in 98% yield. ^{1}H NMR (400 MHz, DMSO-d_6): 2.20 (s, 3H), 2.62 (dd, J = 7.6 Hz, 2H), 3.04 (dd, J = 7.6 Hz, 2H), 6.76 (dd, J = 10.4, 2.4 Hz, 1H), 7.05 (dd, J = 9.6, 2.4 Hz, 1H), 7.15 (s, 1H), 10.86 (s, 1H), 12.15 (s, 1H).

3-[1-(2,4-Dichlorobenzyl)-5-fluoro-3-methyl-1*H*-indol-7-yl]-propionic Acid (101). To a solution of **100** (2.03 mmol, 1.0 equiv) in anhydrous THF at 0−5 °C was added 60% NaH (6.1 mmol, 3.0 equiv) over 3 min. The resultant mixture was allowed to warm to room temperature and stir for 30 min. The reaction mixture was then cooled to 0−5 °C, and 2,4-dichlorobenzyl chloride (4.1 mmol, 2.0 equiv) was added. The reaction mixture was allowed to warm naturally to room temperature and stirred for 16 h, then cooled to 0−5 °C. Additional 60% NaH (2.2 mmol, 1.1 equiv) was added, and the mixture was warmed to room temperature and stirred for 30 min before cooling again to 0−5 °C. Additional 2,4-dichlorobenzyl chloride (4.0 mmol,

2.0 equiv) was added, and the mixture again was allowed to warm to room temperature and stir for 16 h. The mixture was diluted with EtOAc and acidified to pH 1−2 with 1 N HCl. The organic portion was washed with successive portions of water, and brine and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuo and the residue purified by flash chromatography on silica gel using acetone in CH_2Cl_2 as eluent to afford compound **101** in 18% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.23 (s, 3H), 2.45 (dd, J = 8.4, 7.2 Hz, 2H), 2.84 (dd, J = 8.0, 7.6 Hz, 2H), 5.56 (s, 2H), 6.53 (d, J = 8.4 Hz, 1H), 6.77 (dd, J = 10.4, 2.4 Hz, 1H), 7.16 (dd, J = 9.2, 2.4 Hz, 1H), 7.26 (s, 1H), 7.28 (dd, J = 8.4, 2.4 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 12.19 (s, 1H) .

Biological Assays. Displacement Binding Assays. The primary binding assays were established using membranes prepared from cell lines expressing the hEP_3 and other various prostanoid receptors. An amount of 10 μg of membrane protein expressing hEP_3 receptor was incubated for 60 min at 30 °C with binding buffer in the presence of various concentrations of the test compound (dose response of 20×10^{-6} to 10^{-9} M, dilution factor 3×) and 2 nM [^{3}H]PGE_2 radioligand. For hIP and hFP displacement binding experiments, [^{3}H]iloprost (one tritium-labeled analogue of PGI_2, 10−20 Ci/mmol, Amersham Biosciences) and [5,6,8,9,11,12,14,15(n)-^{3}H]$PGF_{2\alpha}$ (160−240 Ci/mmol, Amersham Biosciences) were used as radioligand, respectively. Nonspecific binding was determined by adding, in specific wells, 10 μM unlabeled PGE_2 (Cayman Chemicals, Inc.) in the incubation mixture. Unlabeled PGI_2 or $PGF_{2\alpha}$ (Cayman Chemicals, Inc.) was used for binding experiment using hIP or hFP receptors, respectively. The specific binding was calculated by subtracting the nonspecific binding (membranes incubated with cold and labeled ligand) from the total binding (membranes incubated only with tritiated radioligand). In all binding studies, reactions were terminated by filtering the mixture through a glass fiber filter (Packard Biosciences, PerkinElmer, MA). Filters were then washed three times with binding buffer, and the radioactivity associated with filters was quantified in 7 mL of scintillation liquid (Ultima Gold, PerkinElmer, Boston, MA) using a liquid scintillation counter (TRI-CARB 2100TR, Packard Biosciences, PerkinElmer, MA). IC_{50} values were calculated using GraphPad Prism for Windows (GraphPad Software, San Diego, CA).

Functional Assay. Stably transfected CHO-K1 cells expressing the hEP_3 receptor were plated into 96-well plates at a cell density of 10^5 cells/well and cultured overnight at 37 °C and 5% CO_2 in culture media supplemented with 10% FIBS, 2% PS (penicillin−streptomycin, GIBCO), and 1 mg/mL geneticin (GIBCO). Cells were washed once with phosphate-buffered saline (PBS) and preincubated in fresh serum- and antibiotic-free medium containing 1 mM IBMX (3-isobutyl-1-methylxanthine, Sigma) for 30 min at 37 °C. After preincubation, fresh medium was added without aspiration, containing PGE_2 at the appropriate concentration (dose response from 10^{-4} to 10^{-13} M) in the presence of 5 μM forskolin (Sigma). Similarly, cells were challenged with the test compound at the appropriate concentrations (dose response of 10^{-4}−10^{-13} M) in the presence of 5 μM forskolin (Sigma) and 5 nM PGE_2. Cells were then incubated for an additional 10 min at 37 °C. Reactions were terminated by aspiration of medium and addition of 200 μL of lysis buffer 1B (cAMP EIA system kit, Amersham). cAMP levels were determined using a commercially available cAMP EIA system kit (Amersham). Raw OD values, measured using a Spectra MAX190 plate reader (Molecular Devices), were transformed into an amount of cAMP (fmol/well) using GraphPad Prism for Windows (GraphPad Software, San Diego, CA). For IC_{50} calculations in a dose−response experiment, sigmoidal nonlineal regressions were performed.

Mouse Thromboembolism Studies. Arachidonic acid (30 mg/kg) was used to induce pulmonary thromboembolism in C57BL/6 mice via injection of the tail vein.[2] The thromboembolism challenge was done 30 min following a single oral dose of the test compounds. The test compounds were formulated in 40% hydroxylpropyl-β-cyclodextrin (HPβCD) in 50 mM phosphate buffer, pH 7.4, containing PVP (0.25% w/v) and lysine hydrochloride (50 mM) solution at 5 mg/mL. The data are presented as percent survival.

Platelet Aggregation Assays. These assays were perfomed with human platelet rich plasma (PRP). Blood was taken by venipuncture from nonsmoking volunteers of both sexes after overnight fasting into 3.2% sodium citrate tubes. Individual experiments were performed with blood from a single subject. Platelet-rich plasma (PRP) was obtained by centrifugation of whole blood at 100g for 15 min at 25 °C. Platelet aggregation was measured by light absorbance using a platelet aggregometer (model 490, Chronolog Corp., Havertown, PA) according to the manufacturer's instructions using collagen (0.25 μg/mL) and sulprostone (100 nM) to stimulate platelet aggregation.

Acknowledgment. The authors acknowledge technical contributions of Jenny Lin for providing guidance and overall analytical support, Denise Anderson for running mass spectral analyses, Dr. Nelson Zhao for acquiring NMR spectra, Miriam Goldsmith for preparing compounds **30** and **45**, Hua Cao for preparing compounds **63** and **64**, Matthew O' Connell for preparing compounds **57**−**59**, James Burgeson for preparing compounds **49** and **60**−**62**, and Drs. Livia Enecha, Lei Zhao, and Kris Pupek for preparing compounds **40**, **46**, and **65**, respectively. The authors also thank Dr. Kari Stefansson for helpful discussions and encouragement during the course of this work.

Supporting Information Available: Synthetic schemes and experimental and supporting data for compounds **31**−**33**, **35**−**37**, and **39**−**42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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