6-(4-Chlorophenyl)-3-substituted-thieno[3,2-*d*]pyrimidin-4(3*H*)-one-Based Melanin-Concentrating Hormone Receptor 1 Antagonist

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Genetic manipulation studies in mice at both the MCH receptor 1 (MCHR1) as well as the MCH peptide levels have implicated MCHR1 as a key player in energy homeostasis. The phenotype exhibited by these studies, that is, increased metabolic rate, resistance to high fat diet, and subsequent weight loss, has spurred considerable efforts to develop antagonists of MCHR1. In continuation of efforts directed toward this goal, the present work capitalizes on the putative binding mode of an MCH antagonist, resulting in the identification of several novel chemotypes that are potent and selective MCHR1 antagonists. In addition, the favorable pharmacokinetics of representative examples has allowed for the evaluation of an MCHR1 antagonist in a high fat diet-induced obese rodent model of obesity. The tolerability of the right-hand side of the template for diverse chemotypes accompanied by favorable effects on weight loss enhances the attractiveness of this template in the pursuit toward development of effective anti-obesity agents.

Introduction

Obesity is gradually becoming a leading cause of morbidity as a result of an increase in associated risk factors such as dyslipidemia, type 2 diabetes, stroke, cardiovascular disease, and cancer. There is an increasing amount of effort within the pharmaceutical industry to develop anti-obesity agents that offer significant efficacy as well as a cleaner safety profile than currently marketed anti-obesity agents such as Xenical. Most of the current efforts have focused on central targets. Some of the more promising approaches include 5HT2c agonists, CB1 antagonists, melanocortin receptor agonists, and melanin-concentrating hormone receptor 1 antagonists (MCHR1).

Melanin-concentrating hormone (MCH) is a cyclic 19-amino acid peptide produced by neurons in the lateral hypothalamus. This region plays an important role in controlling feeding behavior and is responsible for physiological effects on its cognate receptor MCHR1.[1,2] A closely related MCHR2 receptor has also been identified, but its functional resemblance is presently unknown largely due to the absence of MCHR2 expression in rodents.[3] In addition, because MCHR1 as well as MCHR2 are both expressed in humans, clinical studies in humans will determine if there is redundancy in the signaling pathways to compensate for the antagonism of the other. Genetic manipulation studies in mice involving the MCHR1 as well as the MCH peptide have been very useful in associating the MCHR as a key mediator of energy homeostasis. For example, acute ICV administration of MCH in rats stimulates food consumption and increases body weight.[4] Mice lacking MCH have reduced body weight and are lean due to hypophagia and increased metabolic rate,[5] whereas MCHR1(−/−) mice are hyperphagic and hypermetabolic with lower levels of insulin and leptin.[6] Overexpression of MCH in transgenic mice leads to obesity and insulin resistance.[7] In addition to central effects, the presence of MCHR1 in important metabolic organs such as the pancreas and tissues such as adipose may have beneficial functional consequences in energy homeostasis.[8]

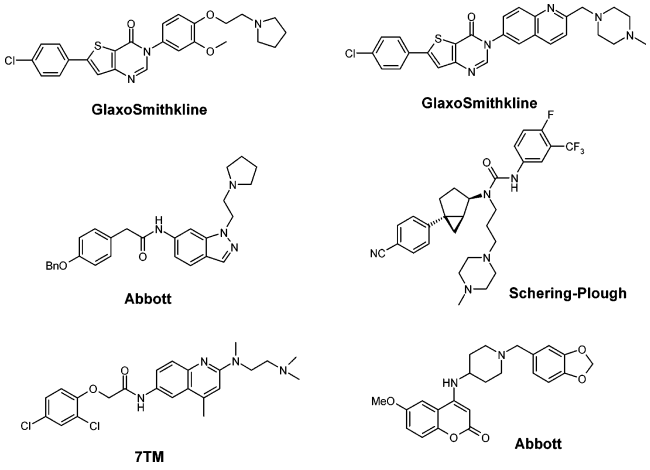

Figure 1.

There has been a recent flurry of papers disclosing the effects of an MCHR1 antagonist in diet-induced obese (DIO) animal models (Figure 1).[9] Early reports on the use of small molecule MCHR1 antagonists validating the genetic studies in rodents has recently spurred considerable efforts in the discovery of additional MCHR1 antagonists.[9a−d] Considering the contrasting effects of the MCH peptide versus MCHR1 knockouts, that is, hypophagic versus hyperphagic effects as described above, it is interesting to note the differences observed in the feeding effects of various small molecule antagonists of MCHR1 when administered to DIO animal models. For example, researchers from some laboratories observed an increase in energy expenditure without an effect on food intake,[9c,d,m−o,q,s] while others

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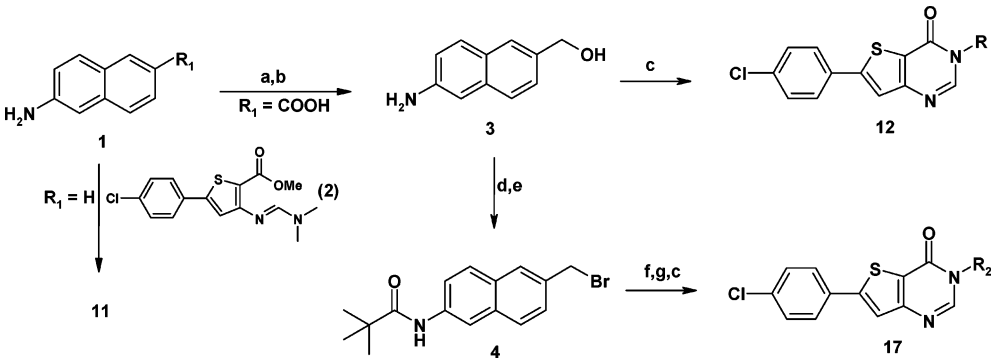
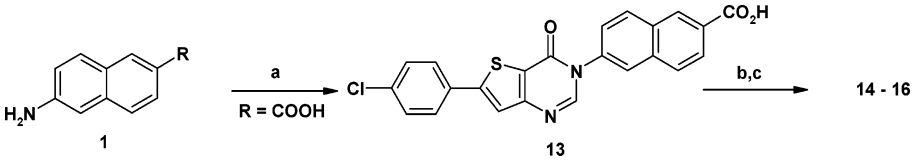
Scheme 1. Synthetic Route to Targets **12** and **17**[a]



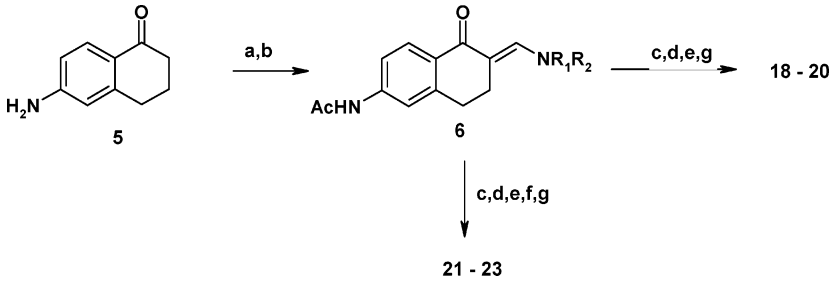
[a] Reagents and conditions: (a) MeOH, H_2SO_4, reflux; (b) $LiAlH_4$, THF; (c) **2**, PhOH, 100−135 °C; (d) $(CH_3)_3CCOCl$, Et_3N, $CHCl_3$; (e) PPh_3, CBr_4; (f) pyrrolidine, THF, reflux, 1.5 h; (g) 2 N HCl, EtOH, reflux.

Scheme 2. Synthetic Route to Targets **14**−**16**[a]



[a] Reagents and conditions: (a) $(CO)_2Cl_2$, CH_2Cl_2, DMF; (b) CH_2Cl_2, amine.

Scheme 3. Synthetic Route to Targets **18**−**23**[a]



[a] Reagents and conditions: (a) AcCl, CH_2Cl_2, Hunig's base; (b) DMF−DMA, 100 °C; (c) amine, EtOH, reflux; (d) $NaBH_4$, MeOH; (e) HCl, THF; (f) 10% Pd/C, H_2, 30 psi; (g) **2**, PhOH, 100−135 °C.

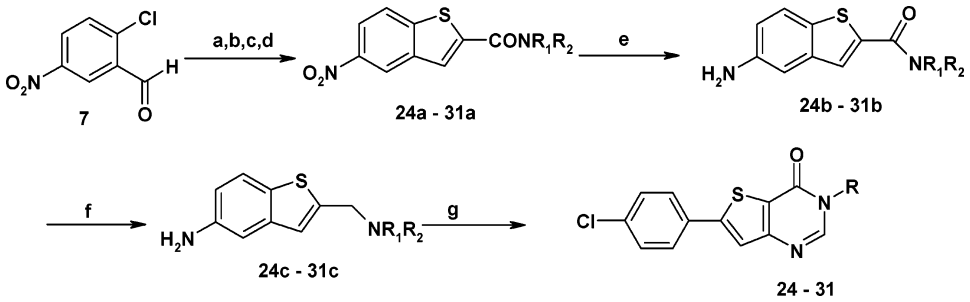
have reported a hypophagic effect as well as an increased metabolic rate,[9j,l,p,t] the latter phenotype being consistent with MCH peptide knockouts.

Reports from our laboratories have disclosed small molecule MCHR1 antagonists that have shown to reduce body weight in mice when fed on a high fat diet.[10] In the preceding work, a small molecule quinoline-based MCHR1 antagonist had been demonstrated to show weight loss in high-fat DIO mice. The present study was undertaken to explore replacements of the quinoline core to afford potent and selective MCHR1 antagonists. Identification of naphthalene as well as other heterocyclic right-hand side (RHS) analogues is described along with the efficacy of a representative example in a chronic setting in DIO mice.

Chemistry

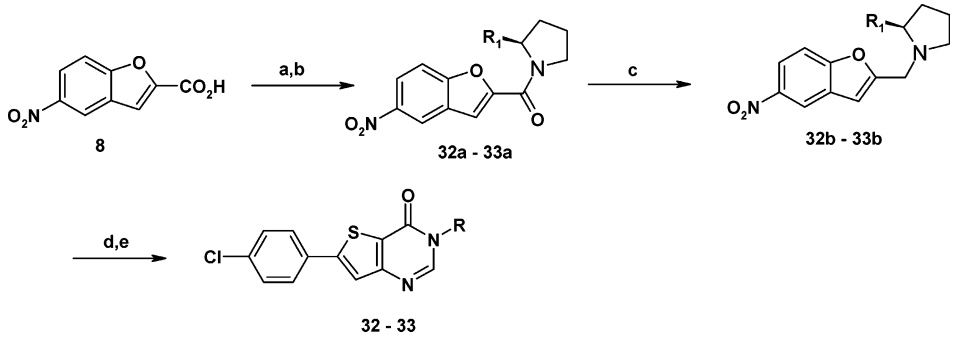
The synthesis of analogues containing the naphthyl group is as shown in Scheme 1. Treatment of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate **2** with commercially available 2-naphthalenamine **1** (R_1 = H) and phenol as a solvent afforded analogue **11**. Fisher esterification of **1** (R_1 = COOH) with sulfuric acid and methanol gave the intermediate ester, which was reduced with $LiAlH_4$ to afford the amino alcohol **3**. Coupling of the amino group in **3** with **2** afforded analogue **12**. Intermediate **3** was also used in the synthesis of compound **17**. This involved protection of the amino group in **3** with pivaloyl chloride, followed by the conversion of the alcohol using triphenylphosphine bromine complex to afford the bromide **4**. Sequential treatment of the bromide **4** with piperidine, followed by deprotection of the amine with 2 N HCl, provided the free amine, which was coupled to **2** to afford analogue **17**. The naphthyl analogues **13**−**16** were accessed using conditions shown in Scheme 2. Treatment of commercially available 6-amino-2-naphthalenecarboxylic acid **1** (R = COOH) with **2** afforded acid **13**. Intermediate **13** was treated with oxalyl chloride to afford the acid chloride, which was treated with various amines to provide the amides **14**−**16**. Analogues **18**−**23**, containing a di or tetrahydronaphthalene moiety, were synthesized as shown in Scheme 3. The amine precursors required in the synthesis of the final products **18**−**23** were synthesized according to literature procedures.[11] Protection of the amino group in **5** with acetyl chloride followed by treatment with *N*,*N*-dimethyl-1,1-bis(methyloxy)methanamine afforded the intermediate **6**. Displacement of the dimethylamino group in **6** with various amines followed by reduction with $NaBH_4$ and subsequent treatment with 4 N HCl, Pd/C/H_2, and **2** gave the dihydronaphthalene analogues **18**−**20**. The synthesis of tetrahydronaphthalene-containing compounds involved similar transformations on intermediate **6**, with an additional hydrogenation step prior to treatment with **2** to afford analogues **21**−**23**. The benzothiophene-containing targets were synthesized as shown in Scheme 4. Treatment of 2-chloro-5-nitrobenzaldehyde **7** with methyl

Scheme 4. Synthetic Route to Targets **24**−**31**[a]



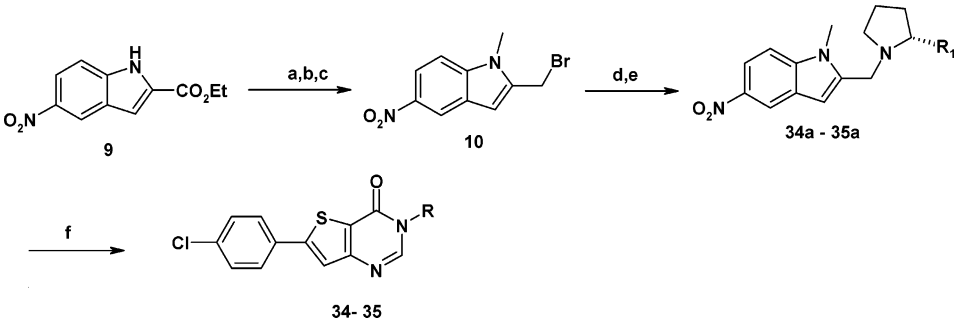
[a] Reagents and conditions: (a) methyl mercaptoacetate, THF; (b) DMF, KOH; (c) LiOH, THF, H_2O; (d) EDC, amine, Hunig's base; (e) 10% Pd/C, H_2, 30 psi; (f) $LiAlH_4$, THF, reflux; (g) **2**, PhOH, 100−135 °C.

Scheme 5. Synthetic Route to Targets **32** and **33**[a]



[a] Reagents and conditions: (a) SO_2Cl_2; (b) pyrrolidines, Et_3N, DMF; (c) $(CH_3)_3Al$, THF; (d) 10% Pd/C, H_2, 1 atm; (e) **3**, PhOH, 100−135 °C.

Scheme 6. Synthetic Route to Targets **34** and **35**[a]



[a] Reagents and conditions: (a) MeI, NaH, DMF; (b) $(CH_3)_3Al$, THF; (c) CBr_4, $(Ph)_3P$, CH_2Cl_2; (d) pyrrolidines, Et_3N, DMF; (e) 10% Pd/C, H_2, 50 psi; (f) **2**, PhOH, 100−135 °C.

mercaptoacetate in the presence of potassium hydroxide in DMF gave the intermediate methyl-5-nitro-1-benzothiophene-2-carboxylate. Hydrolysis of the ester with lithium hydroxide followed by coupling with various amines using EDC afforded the nitro amides **24a**−**31a**. Reduction of the nitro group with Pd/C under hydrogen to provide intermediates **24b**−**31b**, followed by subsequent reduction of the amide bond with $LiAlH_4$ in refluxing THF, afforded **24c**−**31c**. The amines **24c**−**31c** were then coupled with **2** to provide the desired analogues **24**−**31**. The synthesis of analogues containing the benzofuran moiety **32** and **33** is as shown in Scheme 5. Formation of the acid chloride by treatment with thionyl chloride was followed by addition of the appropriate amines to give the amides **32a**−**33a**. Reduction of the amide bond with allane in refluxing THF afforded intermediates **32b**−**33b**. The nitro group was reduced using Pd/C under hydrogen and then coupled with **2** to afford analogues **32** and **33**.

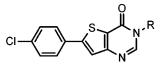
Analogues **34** and **35** were synthesized as shown in Scheme 6. The indole nitrogen of **9** was methylated using methyl iodide followed by subsequent reduction of the ester with allane to afford the intermediate alcohol, which on treatment with triphenylphosphine and carbon tetrabromide afforded the bromide **10**. The bromide of **10** was displaced with appropriate pyrrolidines to give the nitro compounds **34a**−**35a**. Reduction of the nitro group followed by coupling with **2** gave the desired analogues **34** and **35**.

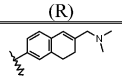
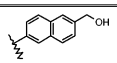
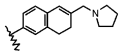
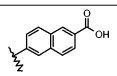
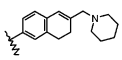
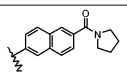
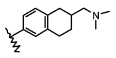
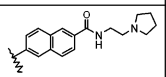
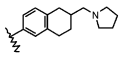
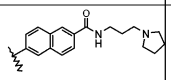
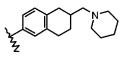
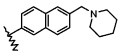
Results and Discussion

Having explored the structure/activity relationship in the quinoline series, the effect of including other RHS moieties was explored with the aim of affording potent, selective, and efficacious MCHR1 antagonists. Earlier efforts had identified unique structural features on the RHS of the template of the quinoline core that imparted a significant boost in activity. Specifically, the presence of an important interaction of an Asp123 residue in the protein with the MCHR1 antagonists was recognized.[10] In addition, there seemed to be a good correlation between the potencies and the basicity of the moiety under consideration. The present work explores alternate RHS chemotypes and the subsequent determination of SAR relationships.

As shown in Table 1, the naphthalene analogue **11** (IC_{50} > 10,000 nM) was inactive at MCHR1. Addition of a hydroxy-

Table 1. Inhibitory Potencies (IC_{50}) vs hMCHR1*



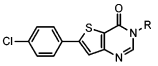
Cmpd	Structure (R)	IC_{50} (nM)	Cmpd	Structure (R)	IC_{50} (nM)
11		>10,000	**18**		2.7
12		31.6	**19**		0.87
13		>10,000	**20**		0.75
14		>10,000	**21**		1.1
15		5.0	**22**		1.3
16		1412	**23**		3.1
17		0.39			

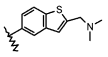
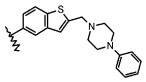
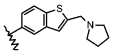
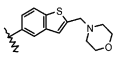
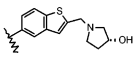
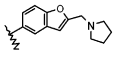
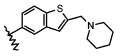
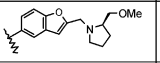
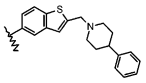
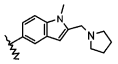
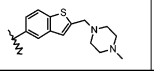
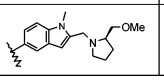
[a] Antagonism of human MCHR1 in CHO Gal4/Elk1-Luc$^+$ reporter assay. IC_{50} values represent averages of 2−3 experiments, with a standard deviation of 3-fold.

methylene group as in analogue **12** (IC_{50} = 31.6 nM) afforded a potent antagonist at the receptor. This resultant is consistent with our previous studies implying the presence of an interaction of Asp123 with the hydroxyl group.[10] Introduction of a carboxyl group as in **13** (IC_{50} > 10,000 nM) resulted in a loss in activity, indicating the presence of an unfavorable interaction of the negatively charged carboxyl group in **13** with Asp123. Replacement of a physiologically negatively charged carboxyl group in **13** with a neutral amide **14** (IC_{50} > 10,000 nM) also resulted in loss in activity. Interestingly, addition of a methylene spacer in the amide to incorporate a basic nitrogen resulted in analogue **15** (pK_a = 9.58, IC_{50} = 5.0 nM) that was equipotent to **12**. Incorporation of an additional methylene spacer in analogue **15** to afford compound **16** (IC_{50} = 1412 nM) resulted in a 282-fold loss in activity compared to **15**. This result suggests that optimal antagonism within the naphthlene series of compounds requires the presence of a hydroxyl group (analogue **12**) or a basic nitrogen, which is physiologically charged with an appropriate spatial orientation. Both options provide an opportunity for a hydrogen bond to the Asp123 residue of the receptor. Replacement of the hydroxyl in analogue **12** with an alternate hydrogen bond donor, such as a physiologically charged basic nitrogen to afford **17** (IC_{50} = 0.39 nM), resulted in an 81-fold boost in activity compared to that of **12**.

Modifications of the naphthyl core to afford di- and tetrahydronaphthylene analogues **18**−**23** gave MCHR1 antagonists that were equipotent in activity. Having explored the naphthalene analogues, efforts were directed to look at heterocyclic replacements that might offer physiochemical advantages in solubility over their lipophilic naphthalene counterparts. As shown in Table 2, efforts to replace the naphthylene moiety evolved from the use of the isosteric benzothiophene to other heteroatom-containing systems such as benzofuran and indoles, with the latter potentially offering beneficial physiochemical advantages over the more hydrophobic benzothiophene counterpart. The benzothiophene analogues **24**−**31** were potent MCHR1 antagonists. Analogues containing a single basic nitrogen, as in **24**−**28**, were of comparable potencies, whereas incorporation of an additional nitrogen, such as in piperazines **29** (IC_{50} = 5.7 nM, pK_a = 2.75 and 7.97 of the proximal and distal nitrogens, respectively) and **30** (IC_{50} = 29 nM, pK_a = 2.44 and 5.78 of the proximal and distal nitrogens, respectively), resulted in a 4.8-fold (vs **27**, pK_a = 8.29) and 5.0-fold (vs **28**, pK_a = 7.91) loss in activity. This modest loss in activity could be explained by the decrease in the basicity of the proximal nitrogens and a subsequent decrease in the percent ionized. Replacement of the sulfur with oxygen and nitrogen heteroatoms afforded analogues **32**−**35**. The benzofuran analogue **33** (IC_{50} = 9.5 nM) suffered an 8.6-fold loss in activity compared to **32** (IC_{50} = 1.1 nM), whereas there was no loss in activity when going from *N*-methylindole **34** (IC_{50} = 1.1 nM) to **35** (IC_{50} = 1.4 nM). In addition, there was no significant change in activity on making the S/O/N-methyl transitions (analogues **25**, **32**, and **34**).

Table 2. Inhibitory Potencies (IC_{50}) vs hMCHR1[a]



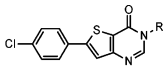
Cmpd	Structure (R)	IC_{50} (nM)	Cmpd	Structure (R)	IC_{50} (nM)
24		1.3	**30**		29
25		0.91	**31**		38
26		2.5	**32**		1.1
27		2.0	**33**		9.5
28		5.7	**34**		1.1
29		9.7	**35**		1.4

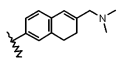
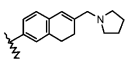
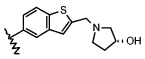
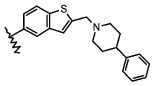
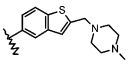
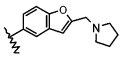
[a] Antagonism of human MCHR1 in CHO Gal4/Elk1-Luc$^+$ reporter assay. IC_{50} values represent averages of 2−3 experiments, with a standard deviation of 3-fold.

Pharmacokinetic Properties

Representative compounds from Tables 1 and 2 were evaluated for their pharmacokinetic properties in rats. As shown in Table 3, compound **18** had good oral bioavailability (67%) but suffered due to a very high total clearance (Cl = 80 mL/min/kg). To prevent potential metabolism due to *N*-demethylation, analogue **19** was synthesized. This resulted in a lower total clearance (Cl = 21.2 mL/min/kg), a better half-life ($t_{1/2}$ = 11 h), and a decent systemic exposure (F = 57%). The benzothiophene analogues **26**, **28**, and **29** were also profiled in rats, as shown in Table 3. The hydroxypyrrolidine **26** and phenylpiperidine analogue **28** had low percent oral bioavailibilities (36.1% and 27.9% respectively), with the latter having a very low clearance (Cl = 2.9 mL/min/kg). The piperazine analogue **29** on the other hand had good oral bioavailability (66%) and a longer half-life ($t_{1/2}$ = 9.1 h) with moderate clearance (39 mL/min/kg) and better solubility compared to that of analogues **26** and **28**. The benzofuran analogue **32** suffered from an extremely high clearance (Cl = 115 mL/min/kg) and a low half-

Table 3. Rat Pharmacokinetic Data for Representative Analogs[a]



Cmpd	R	Cl_{total} (mL/min/kg)	*V*ss (L/kg)	$t_{1/2}$[b](h)	F (%)
18		80	16	3	67
19		21.2	15.7	11	57
26		30.8	3.6	2.1	36.1
28		2.9	0.6	5.9	27.9
29		39	20.4	9.1	66
32		115	8.5	1.6	21

[a] Compounds were dosed in 20% DMSO/21% Solutol in 10 mM (final conc) MSA ($n = 2$); IV dosing done at 3 mg/kg, PO dosing done at 10 mg/kg. [b] Half-life for IV dosing; plasma drug levels were determined by LC-MS/MS.

life ($t_{1/2} = 1.6$ h). Due to its good systemic exposure and long half-life, analogue **29** was profiled in a DIO efficacy model.

Pharmacodynamics

The efficacy of compound **29** in inducing weight loss was evaluated in a high-fat (58% kcal of fat, Research Diets #D12331) DIO AKR/J mice. During a 21-day treatment, oral administration of compound **29** at 1, 3, and 10 mg/kg once daily caused a dose-dependent weight loss of −1.1, −3.2, and −11.8%, respectively, from pretreatment body weight values (48.6 ± 0.9 g, $n = 33$). There was a small reduction in body weight (−2.2%) in the vehicle-treated animals. In the same study, rimonabant, a CB1 receptor inverse agonist in Phase III clinical trials, caused −8.4% weight loss from pretreatment body weight value (Figure 2).

Conclusion

With the optimized 6-(4-chlorophenyl)-3-substituted-thieno-[3,2-*d*]pyrimidin-4(3*H*)-one core developed from SAR work in the earlier report, efforts were directed toward exploring diverse RHS replacements at the 3-position that could capitalize on the putative interaction with the Asp123 residue of the MCHR1 receptor. Several new potent chemotypes were identified in the process with representative examples showing favorable pharmacokinetics. A representative analogue was shown to be efficacious when dosed orally in DIO mice. The tolerability of additional chemotypes at the 3-position enhances the utility of these MCHR1 antagonists for further development in the treatment of obesity.

Experimental Section

Chemistry. General Methods. Melting points were determined using a Thomas−Hoover melting point apparatus and are uncorrected. Unless stated otherwise, reagents were obtained from commercial sources and were used directly. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere. If not specified, reactions were carried out at ambient temperature. Silica gel (EM Science, 230−400 mesh) was used for

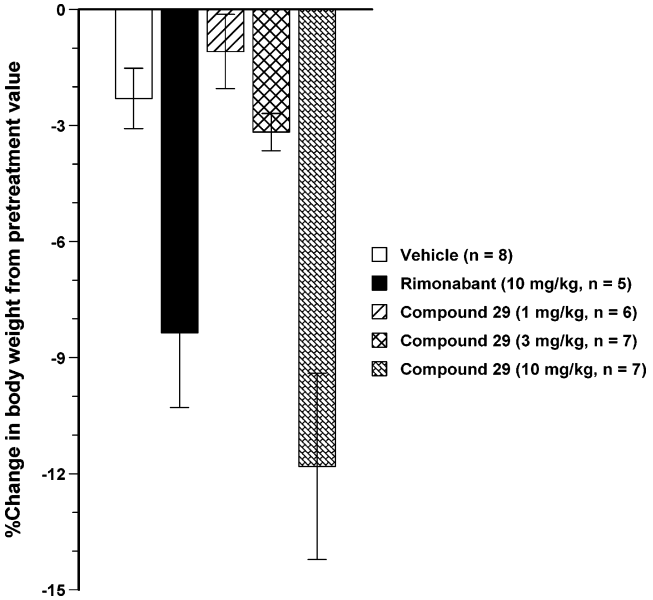


Figure 2. Effect of compound **29** at 1, 3, and 10 mg/kg (orally, qd) on body weight loss in high-fat DIO AKR/J mice. Weight loss is expressed as percentage weight change from pretreatment value for each treatment group. Rimonabant, a CB1 receptor inverse agonist, was used as internal control. Values are mean ± SEM, n = number of mice per group.

chromatographic purification unless otherwise indicated. Anhydrous solvents were obtained from Aldrich (Sure Seal). ^{1}H NMR spectra were recorded on a Varian spectrometer; chemical shifts are reported in parts per million (ppm) relative to TMS. The following abbreviations are used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High performance liquid chromatography (HPLC) was performed on a Beckman 126 with a Beckman 166 UV detector (monitoring at 215 nm) with a Rainin Dynamax-60A column using a gradient consisting of 20/80 A/B to 10/90 A/B over 20 min, where A = 1% aqueous trifluoroacetic acid (TFA) and B = 1% TFA in CH_3CN. Elemental analyses, performed by Atlantic Microlab, Inc., Norcross, GA, were within 0.4% of the theoretical values calculated for C, H, and N. For compounds that did not have elemental analysis, purity was determined by using two different methods. Method A, MeOH/H_2O from 0 to 100%; method B, CH_3CN/H_2O from 10 to 100%. Compounds were found to be >95% in purity by both method A and method B, unless otherwise as stated in the experimental.

General Procedure for the Synthesis of Final Products: 6-(4-Chlorophenyl)-3-(2-naphthalenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (11). To 2-naphthalenamine was added methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2** (0.145 g, 0.506 mmol) and 0.5 g of phenol as the solvent. The reaction mixture was heated from 100 to 135 °C over a period of 1.5 h. The crude mixture was loaded over a silica gel column using DCM/MeOH (95:5) to afford 6-(4-chlorophenyl)-3-[2-(morpholin-4-ylmethyl)quinolin-6-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one as a yellow solid (0.101 g, 44%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (s, 1H), 8.14 (s, 1H), 8.10−8.01 (m, 4H), 7.95 (d, J = 8.4 Hz, 2H), 7.67−7.62 (m, 3H), 7.59 (d, J = 8.4 Hz, 2H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-[6-(hydroxymethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (12): (a) Methyl 6-Amino-2-naphthalenecarboxylate. A mixture of 6-amino-2-naphthalenecarboxylic acid (5.00 g, 26.7 mmol), 10 mL of concentrated sulfuric acid, and 50 mL of methanol was heated at reflux for 1.5 h. The reaction mixture was cooled to room temperature and poured into ice, then extracted with dichloromethane. The organic phase was dried over sodium sulfate, and the solvent was removed under vacuum to give 5.11 g (95% yield) of methyl 6-amino-2-naphthalenecarboxylate as a gray solid. ^{1}H NMR (400 MHz, DMSO-d_6):

δ 8.36 (s, 1H), 7.79 (m, 2H), 7.57 (m, 1H), 7.05 (m, 1H), 6.86 (s, 1H), 5.88 (s, 2H), 3.88 (s, 3H).

(b) (6-Amino-2-naphthalenyl)methanol (3). Lithium aluminum hydride (41 mL of a 1.0 M solution in tetrathydrofuran) was added to a solution of methyl 6-amino-2-naphthalenecarboxylate (5.11 g, 25.4 mmol) in 100 mL of anhydrous tetrahydrofuran while cooling in an ice bath. The mixture was stirred at 5 °C for 2 h and quenched with 5 mL of water. The mixture was filtered, and the filter cake was washed with tetrahydrofuran (4 × 30 mL). The combined filtrates were evaporated to dryness to give 4.06 g of a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52 (m, 2H), 7.43 (m, 1H), 7.22(m, 1H), 6.88 (m, 1H), 6.77 (s, 1H), 5.28 (s, 2H), 5.08 (m, 1H), 4.51 (m, 2H).

6-(4-Chlorophenyl)-3-[6-(hydroxymethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (12). The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate **2** (1.86 g, 5.78 mmol) and (6-amino-2-naphthalenyl)methanol **3** (1.00 g, 5.78 mmol), with 0.5 g of phenol as the solvent. The reaction mixture was heated from 100 to 135 °C over a period of 1.5 h. The crude product was purified by trituration with methanol to give 1.20 g of a beige powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 1H), 8.12 (s, 1H), 8.07 (m, 1H), 8.03 (s, 1H), 7.96 (m, 4H), 7.59 (m, 4H), 5.43 (m, 1H), 4.73 (m, 2H). Elemental analysis was performed for C, H, and N.

6-[6-(4-Chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-naphthalenecarboxylic Acid (13). The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate **2** (1.09 g, 3.38 mmol) and 6-amino-2-naphthalenecarboxylic acid (0.63 g, 3.38 mmol), as described for analogue **11**. The crude product was triturated with methanol and dried under vacuum to give 0.345 g (25% yield) of an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (s, 1H), 8.60 (s, 1H), 8.28 (m, 1H), 8.23 (s, 1H), 8.09 (s, 2H), 8.03 (s, 1H), 7.96 (d, J = 8.6 Hz, 2H), 7.76 (m, 1H), 7.60 (d, J = 8.6 Hz, 2H). Elemental analysis was performed for C, H, and N.

General Procedure for the Synthesis of Compound 14−16. 6-(4-Chlorophenyl)-3-[6-(1-pyrrolidinylcarbonyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (14). Oxalyl chloride (0.015 mL, 0.17 mmol) and a catalytic amount of *N*,*N*-dimethylformamide were added to a suspension of 6-[6-(4-chlorophenyl)-4-oxothieno-[3,2-*d*]pyrimidin-3(4*H*)-yl]-2-naphthalenecarboxylic acid **13** (0.050 g, 0.12 mmol) in 2 mL of dichloromethane. The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum, and the residue was suspended in 2 mL of dichloromethane. Pyrrolidine (0.024 mL, 0.29 mmol) was added. The solvent was evaporated, and the residue was purified by chromatography on silica gel with a gradient of 0 to 10% methanol in dichloromethane to afford 0.020 g (36% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.21 (m, 2H), 8.17 (m, 1H), 8.05 (m, 1H), 8.01 (s, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.72 (m, 2H), 7.58 (d, J = 8.6 Hz, 2H), 3.52 (m, 2H), 3.46 (m, 2H), 1.90 (m, 2H), 1.83 (m, 2H). APCI-LCMS *m*/*z*: 486 (M + H). Purity was determined using method B.

6-[6-(4-Chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-*N*-[2-(1-pyrrolidinyl)ethyl]-2-naphthalenecarboxamide (15). The acid chloride, obtained during the process of preparing analogue **14**, was treated with [2-(1-pyrrolidinyl)ethyl]amine instead of pyrrolidine to afford the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.56 (br s, 1H), 8.29 (s, 1H), 8.25 (m, 1H), 8.20 (m, 1H), 8.03 (m, 1H), 7.97 (m, 1H), 7.72 (d, J = 8 Hz, 2H), 7.66 (m, 1H), 7.61 (s, 1H), 7.50 (d, J = 8 Hz, 2H), 3.54 (m, 2H), 3.28 (m, 2H), 2.79 (m, 2H), 2.17 (m, 2H), 1.87 (m, 2H). APCI-LCMS *m*/*z*: 529 (M + H). Purity was determined using method A.

6-[6-(4-Chlorophenyl)-4-oxothieno[3,2-*d*]pyrimidin-3(4*H*)-yl]-*N*-[3-(1-pyrrolidinyl)propyl]-2-naphthalenecarboxamide (16). The acid chloride, obtained during the process of preparing analogue **14**, was treated with [3-(1-pyrrolidinyl)propyl]amine instead of pyrrolidine to afford the desired product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.49 (s, 1H), 8.25 (s, 1H), 8.11 (m, 1H), 8.04 (m, 1H), 7.96 (m, 1H), 7.93 (m, 1H), 7.69 (d, J = 8 Hz, 2H), 7.62 (m, 1H), 7.57 (s, 1H), 7.46 (d, J = 8 Hz, 2H), 3.70 (m, 2H), 2.80−2.95 (m, 6H), 1.98 (m, 6H). APCI-LCMS *m*/*z*: 543 (M + H). Purity was determined using method A.

6-(4-Chlorophenyl)-3-[6-(1-piperidinylmethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (17): (a) *N*-[6-(Hydroxymethyl)-2-naphthalenyl]-2,2-dimethylpropanamide. Triethylamine (1.2 mL, 8.67 mmol) was added to a suspension of (6-amino-2-naphthalenyl)methanol **3** (1.00 g, 5.78 mmol) in 60 mL of chloroform. The mixture was cooled in an ice bath and pivaloyl chloride (0.81 mL, 10.4 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h. After warming to room temperature, the mixture was diluted with chloroform and washed with 1 N aqueous hydrochloric acid and water, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by chromatography on silica gel with hexane/ethyl acetate to give 1.22 g (80% yield) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.78 (m, 3H), 7.47 (m, 3H), 4.83 (s, 2H), 1.66 (br s, 1H), 1.36 (s, 9H).

(b) *N*-[6-(Chloromethyl)-2-naphthalenyl]-2,2-dimethylpropanamide (4). A mixture of 6.63 g of polystyrene-triphenylphosphine resin (1.35 mmol/g, 8.95 mmol) and *N*-[6-(hydroxymethyl)-2-naphthalenyl]-2,2-dimethylpropanamide (1.15 g, 4.47 mmol) in 75 mL of carbon tetrachloride was heated at reflux for 30 min. The reaction mixture was cooled to room temperature and filtered. The resin on the filter was washed with 4 × 20 mL portions of dichloromethane, and the filtrates were combined and evaporated under vacuum to give 0.87 g (71% yield) of a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (m, 4H), 7.46 (m, 2H), 7.23 and 7.05 (m, 1H), 4.74 (s, 2H), 1.41 and 1.36 (s, 9H).

(c) 2,2-Dimethyl-*N*-[6-(1-piperidinylmethyl)-2-naphthalenyl]-propanamide. A mixture of *N*-[6-(chloromethyl)-2-naphthalenyl]-2,2-dimethylpropanamide **4** (0.200 g, 0.73 mmol), piperidine (0.18 mL, 1.81 mmol), and 2 mL of tetrahydrofuran was heated at reflux for 1.5 h. The solvent was evaporated under vacuum, and the residue was purified by chromatography on silica gel with dichloromethane/methanol to give 0.089 g (38% yield) of the product as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.80 (m, 2H), 7.75 (s, 1H), 7.52 (s, 1H), 7.48 (m, 2H), 3.65 (s, 2H), 2.47 (m, 4H), 1.65 (m, 4H), 1.48 (m, 2H), 1.40 (s, 9H).

(d) 6-(1-Piperidinylmethyl)-2-naphthalenamine. Aqueous hydrochloric acid (2 mL of a 2 N solution) was added to a suspension of 2,2-dimethyl-*N*-[6-(1-piperidinylmethyl)-2-naphthalenyl]propanamide from step c above (0.089 g, 0.27 mmol) in 1 mL of ethanol. The resulting solution was heated in a microwave at 110 °C for 40 min. The cooled reaction mixture was neutralized with solid sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over sodium sulfate, and the solvent was evaporated to give 0.041 g (63% yield) of 6-(1-piperidinylmethyl)-2-naphthalenamine. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (m, 2H), 7.53 (m, 1H), 7.38 (m, 1H), 6.95 (m, 2H), 4.0 (br s, 2H), 3.61 (s, 2H), 2.46 (m, 4H), 1.61 (m, 4H), 1.44 (m, 2H).

6-(4-Chlorophenyl)-3-[6-(1-piperidinylmethyl)-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (17). The title compound was prepared by reaction of methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate **2** (0.055 g, 0.17 mmol) and 6-(1-piperidinylmethyl)-2-naphthalenamine (step d above; 0.041 g, 0.17 mmol), as described in the synthesis of analogue **11**. The crude product was triturated with methanol to give 0.040 g (48% yield) of a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.56 (s, 1H), 8.11 (s, 1H), 8.03 (m, 2H), 7.95 (m, 4H), 7.61 (m, 4H), 3.63 (s, 2H), 2.38 (m, 4H), 1.52 (m, 4H), 1.42 (m, 4H). Treatment with trifluoroacetic acid, as described in example 31, step b, gave 0.035 g of the corresponding salt. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.58 (s, 1H), 8.18 (m, 4H), 8.05 (s, 1H), 7.97 (m, 1H), 7.79 (m, 2H), 7.60 (m, 2H), 4.52 (s, 2H), 3.41 (m, 2H), 2.95 (m, 2H), 1.82 (m, 2H), 1.70 (m, 2H), 1.40 (m, 1H), 1.07 (m, 1H). ES-LCMS *m*/*z*: 486 (M + H). Purity was determined using method A.

6-(4-Chlorophenyl)-3-{6-[(dimethylamino)methyl]-7,8-dihydro-2-naphthalenyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (18). The title compound was synthesized by treatment of 6-[(dimethylamino) methyl]-7,8-dihydro-2-naphthalenamine with methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2**, employing the general procedure described for analogue **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (s, 1H), 7.98 (s, 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.26 (m, 3H), 6.49 (s, 1H), 3.02 (s, 2H), 2.83 (t, J = 8.1 Hz, 2H), 2.32 (t, J = 8.1 Hz, 2H), 2.2 (s, 6H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (19). The title compound was synthesized by treatment of [6-(1-pyrrolidinylmethyl)-7,8-dihydro-2-naphthalenyl]amine with methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2**, employing the general procedure described for analogue **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (s, 1H), 7.98 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.26 (m, 3H), 6.50 (s, 1H), 3.18 (s, 2H), 2.83 (t, J = 8.0 Hz, 2H), 2.50 (br s, 4H), 2.32 (t, J = 8.0 Hz, 2H), 1.73 (br s, 4H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-[6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (20). The title compound was synthesized by treatment of [6-(1-piperidinylmethyl)-7,8-dihydro-2-naphthalenyl]amine with methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2**, employing the general procedure described for analogue **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.41 (s, 1H), 7.97 (s, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.25 (m, 3H), 6.47 (s, 1H), 3.02 (s, 2H), 2.82 (t, J = 8.0 Hz, 2H), 2.31 (m, 6H), 1.51 (m, 4H), 1.40 (br s, 2H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-{6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenyl}thieno[3,2-*d*]pyrimidin-4-(3*H*)-one (21). The title compound was synthesized by treatment of [(6-amino-1,2,3,4-tetrahydro-2-naphthalenyl)methyl]dimethylamine 6-[(dimethylamino)methyl]-5,6,7,8-tetrahydro-2-naphthalenamine with methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2**, employing the general procedure described for analogue **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.98 (s, 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.24 (m, 3H), 2.95 (m, 1H), 2.82 (m, 2H), 2.43 (m, 2H), 2.2 (br, 6H), 1.96 (m, 2H), 1.36 (m, 2H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-[6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4-(3*H*)-one (22). The title compound was synthesized by treatment of [6-(1-pyrrolidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]amine with methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2**, employing the general procedure described for analogue **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.98 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.26 (m, 3H), 2.99 (m, 1H), 2.83 (m, 2H), 2.46 (m, 7H), 1.98 (m, 2H), 1.72 (m, 4H), 1.39 (m, 1H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-[6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]thieno[3,2-*d*]pyrimidin-4-(3*H*)-one (23). The title compound was synthesized by treatment of [6-(1-piperidinylmethyl)-5,6,7,8-tetrahydro-2-naphthalenyl]amine with methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2**, employing the general procedure described for analogue **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (s, 1H), 7.98 (s, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.25 (m, 3H), 2.91 (m, 1H), 2.82 (m, 2H), 2.34 (m, 4H), 2.23 (d, J = 7.1 Hz, 2H), 1.97 (m, 2H), 1.53 (m, 4H), 1.40 (m, 4H). Elemental analysis was performed for C, H, and N.

***N*,*N*-Dialkyl-5-nitro-1-benzothiophene-2-carboxamides (24a−31a): (a) Methyl 5-Nitro-1-benzothiophene-2-carboxylate.** To a solution of 2-chloro-5-nitrobenzaldehyde (5.55 g, 30 mmol) and methyl mercaptoacetate (2.68 mL, 30 mmol) in DMF (60 mL) was added KOH (3.0 g) in 15 mL of water dropwise. After stirring for 1 h, the contents were poured into crushed ice, and the solid was filtered, washed with water, and dried. The crude product was taken directly to the next step. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.40 (s,1H), 8.36 (s, 1H), 8.34 (d, J = 7.8 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 3.90 (s, 3H). ES-LCMS *m*/*z*: 238 (M + H).

(b) 5-Nitro-1-benzothiophene-2-carboxylic Acid. To a solution of methyl 5-nitro-1-benzothiophene-2-carboxylate 14.0 g (60 mmol), obtained in step a, in THF (60 mL) was added 60 mL of 1 N LiOH, and the contents were stirred for 16 h. After acidification, ethyl acetate (100 mL) was added, and the organic layer was separated. The organic layer was dried with $MgSO_4$ and then concentrated to afford the acid in quantitative yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.40 (m,4H). ES-LCMS *m*/*z*: 223 (M + H).

General Procedure for the Preparation of Nitro-amides (24a−31a). To a solution of 5-nitro-1-benzothiophene-2-carboxylic acid, obtained in 54b (5.83 mmol), in DCM (30 mL) was added Hunig's base (6.99 mmol), EDC (6.41 mmol), HOBT (6.99 mmol), and piperidine (6.41 mmol), and the contents were stirred at room temperature for 16 h. After washing with satd sodium chloride solution, followed by satd $NaHCO_3$ solution, the organic layer was dried with $MgSO_4$ and concentrated to afford the desired product.

***N*,*N*-Dimethyl-5-nitro-1-benzothiophene-2-carboxamide (24a).** ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.35 (d, J = 8.9 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.10 (s, 1H), 3.29 (s, 3H), 3.10 (s, 3H).

1-[(5-Nitro-1-benzothien-2-yl)carbonyl]pyrrolidine (25a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.35 (d, J = 9.1 Hz, 1H), 8.11 (d, J = 9.1 Hz, 1H), 8.03 (s, 1H), 4.23 (m, 1H), 2.87 (m, 4H), 1.87 (m, 4H).

(3*R*)-1-[(5-Nitro-1-benzothien-2-yl)carbonyl]-3-pyrrolidinol (26a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 4.23 (m, 1H), 3.94 (br s, 1H), 2.81 (m, 4H), 1.89 (m, 2H).

1-[(5-Nitro-1-benzothien-2-yl)carbonyl]piperidine (27a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 7.97 (s, 1H), 3.68 (m, 4H), 1.69 (m, 6H).

1-[(5-Nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperidine (28a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.37 (d, J = 8.9 Hz, 1H), 8.29 (d, J = 8.8 Hz, 1H), 8.05 (s, 1H), 7.26 (m, 5H), 3.19 (m, 2H), 2.92 (m, 3H), 1.89 (m, 4H).

1-Methyl-4-[(5-nitro-1-benzothien-2-yl)carbonyl]piperazine (29a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 8.9 Hz, 1H), 8.01 (s, 1H), 3.72 (m, 4H), 2.47 (m, 4H), 2.25 (s, 3H).

1-[(5-Nitro-1-benzothien-2-yl)carbonyl]-4-phenylpiperazine (30a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.31 (d, J = 9.0 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.08 (s, 1H), 7.28 (m, 2H), 7.02 (m, 2H), 6.97 (m, 1H), 3.28 (m, 4H), 2.55 (m, 4H).

4-[(5-Nitro-1-benzothien-2-yl)carbonyl]morpholine (31a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.85 (s, 1H), 8.32 (d, J = 9.0 Hz, 1H), 8.25 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 3.67 (m, 8H).

General Procedure for the Synthesis of Compounds 24b−31b. To a solution of the nitro compound (5.80 mmol) in methanol (30 mL) was added 10% Pd/C (0.13 g), and the contents were kept under H_2 at 40 psi. After 4 h, the solution was filtered through Celite and then concentrated under vacuum to afford the amine.

5-Amino-*N*,*N*-dimethyl-1-benzothiophene-2-carboxamide (24b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63 (d, J = 8.7 Hz, 1H), 7.53 (s, 1H), 7.01 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.21 (br s, 2H), 3.21 (s, 6H).

[2-(1-Pyrrolidinylcarbonyl)-1-benzothien-5-yl]amine (25b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.53 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 7.04 (s, 1H), 6.86 (d, J = 8.5 Hz, 1H), 5.21 (br s, 2H), 4.22 (m, 1H), 2.87 (m, 4H), 1.88 (m, 4H).

(3*R*)-1-[(5-Amino-1-benzothien-2-yl)carbonyl]-3-pyrrolidinol (26b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.01 (s, 1H), 6.82 (d, J = 8.7 Hz, 1H), 5.23 (br s, 2H), 4.21 (m, 1H), 3.96 (br s, 1H), 2.84 (m, 4H), 1.90 (m, 2H).

[2-(1-Piperidinylcarbonyl)-1-benzothien-5-yl]amine (27b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63 (d, J = 8.7 Hz, 1H), 7.46 (s, 1H), 7.01 (s, 1H), 6.83 (d, J = 8.6 Hz, 1H), 5.20 (br s, 2H), 3.36 (m, 4H), 1.68 (m, 6H).

{2-[(4-Phenyl-1-piperidinyl)carbonyl]-1-benzothien-5-yl}-amine (28b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.64 (d, J = 8.6 Hz, 1H), 7.48 (s, 1H), 7.35 (m, 5H), 7.02 (s, 1H), 6.84 (d, J = 8.6 Hz, 1H), 5.21 (br s, 2H) 3.18 (m, 2H), 2.91 (m, 3H), 1.90 (m, 4H).

{2-[(4-Methyl-1-piperazinyl)carbonyl]-1-benzothien-5-yl}-amine (29b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.01 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.23 (br s, 2H), 3.69 (t, J = 4.7 Hz, 4H), 2.41 (t, J = 4.8 Hz, 4H), 2.12 (s, 3H).

{2-[(4-Phenyl-1-piperazinyl)carbonyl]-1-benzothien-5-yl}-amine (30b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65 (d, J = 8.7 Hz, 1H), 7.52 (s, 1H), 7.30 (m, 2H), 7.03 (m, 3H), 6.86 (m, 2H), 5.25 (br s, 2H), 3.24 (m, 4H), 2.56 (m, 4H).

[2-(4-Morpholinylcarbonyl)-1-benzothien-5-yl]amine (31b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.47 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 6.83 (s, 1H), 6.63 (d, J = 8.4 Hz, 1H), 5.23 (br s, 2H), 3.34 (m, 8H).

General Procedure for the Synthesis of Amines (24c−31c). To a solution of 2-(piperidin-1-ylcarbonyl)-1-benzothien-5-ylamine (1.0 g, 3.85 mmol) in THF (20 mL) was added a 1.0 M solution of LAH in THF (19.2 mL, 19.2 mmol), and the contents were refluxed for 20 h. After addition of 1 N sodium hydroxide, ethyl acetate was added and the organic layer was separated. Drying ($MgSO_4$) and concentration afforded the desired product that was directly carried to the next step.

[(5-Amino-1-benzothien-2-yl)methyl]dimethylamine (24c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.53 (d, J = 8.6 Hz, 1H), 7.48 (s, 1H), 7.02 (s, 1H), 6.89 (d, J = 8.6 Hz, 1H), 5.03 (br s, 2H), 3.63 (s, 2H), 2.21 (s, 6H).

[2-(1-Pyrrolidinylmethyl)-1-benzothien-5-yl]amine (25c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52 (d, J = 8.6 Hz, 1H), 6.95 (s, 1H), 6.84 (s, 1H), 6.63 (d, J = 8.6 Hz, 1H), 5.20 (br s, 2H), 3.78 (s, 2H), 2.80 (m, 4H), 1.87 (m, 4H).

(3*R*)-1-[(5-Amino-1-benzothien-2-yl)methyl]-3-pyrrolidinol (26c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.43 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.82 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.01 (br s, 2H), 4.61 (br s, 1H), 4.23 (m, 1H), 3.77 (s, 2H), 2.65 (m, 2H), 2.31 (m, 2H), 1.98 (m, 1H), 1.45 (m, 1H).

[2-(1-Piperidinylmethyl)-1-benzothien-5-yl]amine (27c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50 (d, J = 8.6 Hz, 1H), 7.46 (s, 1H), 7.0 (s, 1H), 6.88 (d, J = 8.6 Hz, 1H), 5.02 (br s, 2H), 3.66 (s, 2H), 2.54 (m, 4H), 1.54 (m, 6H).

{2-[(4-Phenyl-1-piperidinyl)methyl]-1-benzothien-5-yl}-amine (28c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.51 (d, J = 8.5 Hz, 1H), 7.34 (m, 5H), 7.05 (s, 1H), 6.90 (s, 1H), 6.69 (d, J = 8.6 Hz, 1H), 5.03 (br s, 2H), 3.75 (s, 2H), 3.18 (m, 5H), 1.90 (m, 4H).

{2-[(4-Methyl-1-piperazinyl)methyl]-1-benzothien-5-yl}-amine (29c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.01 (s, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.23 (br s, 2H), 3.69 (t, J = 4.7 Hz, 4H), 2.41 (t, J = 4.8 Hz, 4H), 2.12 (s, 3H).

{2-[(4-Phenyl-1-piperazinyl)methyl]-1-benzothien-5-yl}-amine (30c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.53 (d, J = 8.6 Hz, 1H), 7.20 (m, 2H), 7.02 (s, 1H), 7.0−6.65 (m, 5H), 5.04 (br s, 2H), 3.78 (s, 2H), 3.24 (m, 4H), 2.54 (m, 4H).

[2-(4-Morpholinylmethyl)-1-benzothien-5-yl]amine (31c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 6.81 (s, 1H), 6.64 (d, J = 8.4 Hz, 1H), 5.0 (br s, 2H), 3.57 (t, J = 4.6 Hz, 4H), 2.49 (m, 4H).

General Procedure for the Synthesis of Target Compounds 24−31. To the amines (0.506 mmol) was added methyl-3-{[(1*E*)-(dimethylamino)methylidene]amino}-5-phenyl-2-thiophenecarboxylate **2** (0.145 g, 0.506 mmol) and 0.5 g of phenol as the solvent. The reaction mixture was heated from 100 to 135 °C over a period of 1.5 h. The crude mixture was loaded over a silica gel column using DCM/MeOH (95:5) to afford the desired compounds in 30−40% yield.

6-(4-Chlorophenyl)-3-{2-[(dimethylamino)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (24). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.28 (d, J = 8.6 Hz, 1H), 8.19 (s, 1H), 8.05 (m, 2H), 7.99 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 7.65 (d, J = 8.4 Hz, 2H) 3.57 (s, 2H), 2.82 (s, 6H). Elemental analysis was performed for C, H, and N.

FP55- -6-(4-chlorophenyl)-3-[2-(1-pyrrolidinylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (25). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.53 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.99 (m, 3H), 7.64 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 3.96 (s, 2H), 2.54 (m, 4H), 1.80 (m, 4H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-(2-{[(3*R*)-3-hydroxypyrrolidin-1-yl]-methyl}-1-benzothien-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (26). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.99 (s, 1H), 7.93 (m, 3H), 7.58 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.6 Hz, 1H), 7.35 (s, 1H), 4.73 (br s, 1H), 4.21 (m, 1H), 3.90 (s, 2H), 2.81−2.48 (m, 3H), 2.41 (m, 1H), 1.98 (m, 1H), 1.48 (m, 1H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-[2-(piperidin-1-ylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (27). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.28 (m, 2H), 8.05 (m, 3H), 8.00 (d, J = 8.6 Hz, 1H), 7.82 (s, 1H), 7.64 (m, 2H), 3.81 (s, 2H), 2.48 (m, 4H), 1.65 (m, 6H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-{2-[(4-phenylpiperidin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (28). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.53 (s, 1H), 8.14 (d, J = 8.6 Hz, 1H), 8.04 (s, 1H), 7.99 (m, 3H), 7.64 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.35 (m, 6H), 3.90 (s, 2H), 3.09 (m, 5H), 1.91 (m, 4H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-{2-[(4-methylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (29). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.98 (s, 1H), 7.93 (m, 3H), 7.58 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6, Hz, 1H), 7.36 (s, 1H), 3.79 (s, 2H), 2.41−2.22 (m, 8H), 2.14 (s, 3H). Elemental analysis was performed for C, H, and N.

6-(4-Chlorophenyl)-3-{2-[(4-phenylpiperazin-1-yl)methyl]-1-benzothien-5-yl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (30). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.15 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 7.99 (m, 6H), 7.64 (d, J = 8.5 Hz, 1H), 7.51 (m, 1H), 7.39 (s, 1H), 7.27 (m, 1H), 6.98−6.81 (m, 2H), 3.93 (s, 2H), 3.24 (m, 4H), 2.54 (m, 4H). ES-LCMS *m*/*z*: 569 (M + H). Purity was determined using method A.

6-(4-Chlorophenyl)-3-[2-(morpholin-4-ylmethyl)-1-benzothien-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (31). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.48 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.98 (m, 3H), 7.58 (d, J = 8.6 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.38 (s, 1H), 7.16 (m, 1H), 3.81 (s, 2H), 3.60 (m, 4H) 2.49 (m, 4H). ES-LCMS *m*/*z*: 494 (M + H). Purity was determined using method A.

6-(4-Methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt (32): (a) 1-[(5-Nitro-1-benzofuran-2-yl)carbonyl]pyrrolidine (32a). 5-Nitro-1-benzofuran-2-carboxylic acid (0.50 g, 2.41 mmol) was suspended in thionyl chloride (5 mL) and heated to reflux. The reaction was stirred for 16 h and concentrated to dryness. The residue was taken up in DMF (5 mL) and pyrrolidine (0.343 g, 4.82 mmol) and triethylamine (0.488 g, 4.82 mmol) were added, and the mixture was heated to 80 °C, stirred for 2 h, cooled to rt, and water (50 mL) was added. Solid was collected and taken up in EtOAc (50 mL). Organics were washed with water (3 × 150 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.454 g (1.75 mmol, 72%) of the product as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.61 (dd, J = 2.2 Hz, 1H), 8.32 (dd, J = 2.2 Hz, 9.0 Hz, 1H), 7.63 (d, J = 9.0 Hz, 1H), 7.51 (s, 1H), 3.94 (t, J = 6.8 Hz, 2H), 3.71 (t, J = 7.0 Hz, 2H), 2.06 (p, J = 6.7 Hz, 2H), 1.97 (p, J = 7.0 Hz, 2H).

(b) 1-[(5-Nitro-1-benzofuran-2-yl)methyl]pyrrolidine (32b). 1-[(5-Nitro-1-benzofuran-2-yl)carbonyl]pyrrolidine (0.363 g, 1.40

mmol) was suspended in dry THF (5 mL). Allane (4 mL of a 1 M soln) was added, and the mixture was heated to 70 °C, stirred for 2 h, cooled to rt, quenched with methanol (10 mL), diluted with water (50 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.210 g (0.854 mmol, 61%) of the product as a dark golden oil. ^{1}H NMR ($CDCl_3$): δ 8.45 (d, J = 2.2 Hz, 1H), 8.19 (dd, J = 2.2 Hz, 8.8 Hz, 1H), 7.53 (d, J = 9 Hz, 1H), 6.74 (s, 1H), 3.85 (s, 2H), 2.65 (br s, 4H), 1.85 (br s, 4H).

6-(4-Methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one Maleate Salt (32). 1-[(5-Nitro-1-benzofuran-2-yl)methyl]pyrrolidine (0.210 g, 0.85 mmol) was taken up in EtOAc (20 mL) and hydrogenated over 10% Pd/C using H_2 (1 atm). The reaction was filtered through Celite and concentrated. The residue was taken up in a minimal amount of CH_2Cl_2, and phenol (0.5 g) and methyl 5-(4-chlorophenyl)-3-{[(dimethylamino)methylene]amino}thiophene-2-carboxylate (0.275 g, 0.85 mmol) were added. The mixture was heated to 130 °C, stirred for 1 h, cooled to rt, and purified on a chromatatron (100% CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH). The isolated product was taken up in CH_2Cl_2 (5 mL), and 1 equiv of maelic acid was added. This was stirred overnight, and the precipitate was collected to give 0.089 g (0.154 mmol, 18%) of the desired product as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.3 (br s, 1H), 8.5 (s, 1H), 7.99 (s, 1H), 7.92 (m, 3H), 7.80 (d, J = 8.8 Hz, 1H), 7.55 (m, 3H), 7.2 (s, 1H), 6.0 (s, 2H), 4.8 (br s, 2H), 3.4 (br s 4H), 1.9 (br s, 4H). Elemental analysis was performed for C, H, and N.

3-(2-{[(2*R*)-2-(Methoxymethyl)pyrrolidin-1-yl]methyl}-1-benzofuran-5-yl)-6-(4-methylphenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one Maleate Salt (33). The title compound was synthesized using the same procedure as that for 6-(4-Methylphenyl)-3-[2-(pyrrolidin-1-ylmethyl)-1-benzofuran-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one maleate salt, using (2*R*)-2-(methoxymethyl)pyrrolidine instead of pyrrolidine. ^{1}H NMR ($CDCl_3$): δ 8.3 (s, 1H), 7.80−7.75 (m, 3H), 7.6 (s, 1H), 7.5−7.4 (m, 3H), 7.10 (s, 1H) 6.4 (br s, 3H), 4.85−4.6 (m, 2H), 4.0−3.8 (br s, 2H), 3.8−3.7 (br s, 2H), 3.4 (s, 3H), 3.25 (br s, 1H), 2.2 (br s, 2H), 1.9 (br s, 2H). APCI-LCMS *m*/*z*: 507 (M + H). Purity was determined using method A.

6-(4-Chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1*H*-indol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride (34): (a) Ethyl 1-Methyl-5-nitro-1*H*-indole-2-carboxylate. Ethyl 5-nitro-1*H*-indole-2-carboxylate (1.75 g, 7.46 mmol) was dissolved in DMF (30 mL), and sodium hydride (0.6 g of a 60% dispersion) was added. The reaction was stirred at rt for 30 min, and methyl iodide (1.324 g, 9.33 mmol) was added. The reaction was stirred overnight at rt. The reaction was diluted with water (100 mL), and the precipitate was collected by suction filtration. The precipitate was taken up in EtOAc (100 mL) and washed with water (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to afford 1.175 g (4.74 mmol, 63%) of the product as a red brown solid. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, J = 2 Hz, 1H), 8.25 (dd, J = 2.2 Hz, 11.3 Hz, 1H), 7.45 (s, 1H), 7.43 (d, J = 11.3 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 4.13 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H).

(b) (1-Methyl-5-nitro-1*H*-indol-2-yl)methanol. Ethyl 1-methyl-5-nitro-1*H*-indole-2-carboxylate (1.175 g, 4.74 mmol) was dissolved in THF (50 mL). Allane (11 mL of a 1 M soln) was added. The reaction was heated to 70 °C, stirred for 6 h, cooled to rt, quenched with methanol (50 mL), diluted with water (100 mL), and extracted with EtOAc (2 × 100 mL). The combined organic extracts were washed with water (3 × 150 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.664 g (3.22 mmol, 90%) of the product as a red brown solid. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, J = 2 Hz, 1H), 8.14 (dd, J = 2.2 Hz, 9.1 Hz, 1H), 7.35 (d, J = 9.2 Hz, 1H), 6.62 (s, 1H), 4.82 (s, 2H), 3.90 (s, 3H).

(c) 2-(Bromomethyl)-1-methyl-5-nitro-1*H*-indole (10). (1-Methyl-5-nitro-1*H*-indol-2-yl)methanol (0.664 g, 3.223 mmol) was dissolved in CH_2Cl_2 (50 mL). Carbon tetrabromide (1.336 g, 4.03 mmol) was added, and the mixture was cooled to 0 °C and then triphenylphosphine (1.268 g, 4.83 mmol) was added in small portions over 1 h. The reaction was stirred overnight and washed with water (1 × 100 mL), and the organic layers were dried over $MgSO_4$, filtered, concentrated, and then filtered on chromatatron plate to remove baseline impurities. The solid was taken up in a minimal amount of CH_2Cl_2 and tritrated with hexane to give 0.238 g (0.853 mmol, 26%) of the desired product as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 8.55 (d, J = 2.2 Hz, 1H), 8.16 (dd, J = 2.2 Hz, 9.1 Hz, 1H), 7.35 (d, J = 9.1 Hz, 1H), 6.76 (s, 1H), 4.65 (s, 2H), 3.92 (s, 3H).

(d) 1-Methyl-5-nitro-2-(pyrrolidin-1-ylmethyl)-1*H*-indole (34a). 2-(Bromomethyl)-1-methyl-5-nitro-1*H*-indole (0.134 g, 0.50 mmol) was taken up in DMF (5 mL). Pyrrolidine (0.060 mL, 0.75 mmol) was added along with triethylamine (0.134 mL, 1 mmol), The reaction was heated to 80 °C, stirred for 2 h, cooled to rt, and partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was removed, and the organic layers were washed with water (3 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.112 g (0.432 mmol, 87%) of the product as a yellow semisolid. ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 2.2 Hz, 1H), 8.09 (dd, J = 2.2 Hz, 9.1 Hz, 1H), 7.30 (d, J = 9.1 Hz, 1H), 6.53 (s, 1H), 3.85 (s, 3H), 3.78 (s, 2H), 2.5 (br s, 4H), 1.8 (br s, 4H).

6-(4-Chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1*H*-indol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one Hydrochloride (34). 1-Methyl-5-nitro-2-(pyrrolidin-1-ylmethyl)-1*H*-indole (0.112 g, 0.43 mmol) was taken up in EtOAc (10 mL) and hydrogenated over 10% Pd/C on a Parr hydrogenator under 50 psi of H_2. After 2 h, the reaction mixture was filtered through Celite, concentrated, taken up in a minimal amount of CH_2Cl_2, and methyl 5-(4-chlorophenyl)-3-{[(dimethylamino)methylene]amino}thiophene-2-carboxylate (0.115 g, 0.43 mmol) and phenol (0.5 g) were added. The mixture was heated to 130 °C, stirred for 30 min, cooled to rt, and purified on a chromatatron (100% CH_2Cl_2 to 80:20 CH_2Cl_2/MeOH). The product was treated with 1 N HCl in Et_2O, stirred for 2 h, and concentrated to give 0.071 g (0.139 mmol, 33%) of the product as a cream colored solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.2 (br s, 1H), 8.5 (s, 1H), 8.05 (s, 1H), 7.92 (d, J = 7.5 Hz, 2H), 7.77 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.34 (dd, J = 2.1 Hz, 8.1 Hz, 1H), 6.85 (s, 1H), 4.68 (d, J = 5.5 Hz, 2H), 3.2 (br s, 2H, 2.05 (br s, 2H), 1.95 (br s, 2H). LRMS (M + H) 475.

6-(4-Chlorophenyl)-3-(2-{[(2*R*)-2-(methoxymethyl)pyrrolidin-1-yl]methyl}-1-methyl-1*H*-indol-5-yl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one Hydrochloride (35). The title compound was synthesized using the same procedures as that for 6-(4-chlorophenyl)-3-[1-methyl-2-(pyrrolidin-1-ylmethyl)-1*H*-indol-5-yl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hydrochloride, using (2*R*)-2-(methoxymethyl)pyrrolidine instead of pyrrolidine. ^{1}H NMR ($CDCl_3$): δ 12.9 (br s, 1H), 8.6 (s, 1H), 7.80 (s, 1H, 7.68 (d, J = 8.5 Hz, 2H), 7.65 (s, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.9 Hz, 1H), 6.80 (s, 1H), 4.94 (d, J = 14,3 Hz, 1H), 4.46 (m, 2H), 4.03 (s, 3H), 3.74−3.60 (m, 2H), 3.55 (s, 3H), 3.00 (br s, 2H), 2.28 (br s, 1H), 2.17 (br s, 1H), 1.96 (br s, 2H). Elemental analysis was performed for C, H, and N.

Supporting Information Available: Elemental analysis and HPLC traces for compounds in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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