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A NOVEL ONE-POT SYNTHESIS OF *N*-SUBSTITUTED THIENO[3,2-*d*]PYRIMIDIN-4(3*H*)-ONES[#]

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[#] Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

Abstract – A novel synthetic route for the construction of thieno[3,2-*d*]pyrimidin-4(3*H*)-ones has been developed with the key step involving an $AlMe_3$-promoted ester-to-amide conversion. The yields within this initial set of analogs are comparable to those obtained via our previously reported routes and in at least one case far superior, thus serving to compliment other approaches to this useful chemical scaffold.

INTRODUCTION

Obesity has reached epidemic proportions in the United States and Europe and represents one of the most serious healthcare problems faced today.[1] In addition to detrimentally affecting quality of life, obesity is associated with numerous co-morbidities that negatively impact the overall health of the obese population and place tremendous economic burden on healthcare systems.[2] In response, research groups worldwide are searching for new treatment options to combat this burgeoning crisis. One promising pharmacological approach involves inhibition of the melanin-concentrating hormone receptor-1 (MCH R1), a hypothalamic G-protein coupled receptor which has been linked to the regulation of food intake and energy expenditure.[3] A research effort at GlaxoSmithKline identified a novel series of N-substituted-thienopyrimidinones (e.g. compound (**1**), Figure 1) which potently inhibit MCH R1 and significantly decrease body weight in rodent models of obesity.[4,5,6] Herein we wish to describe a new synthetic route to the thienopyrimidinone core that relies upon the conversion of a thiophene methyl ester to an N-substituted carboxamide using $AlMe_3$.

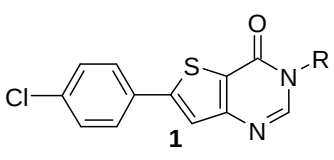

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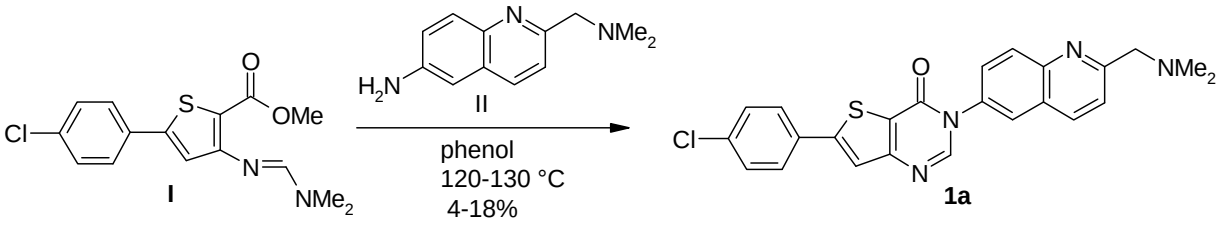
Figure 1. MCH R1 Antagonist (**1**).

RESULTS AND DISCUSSION

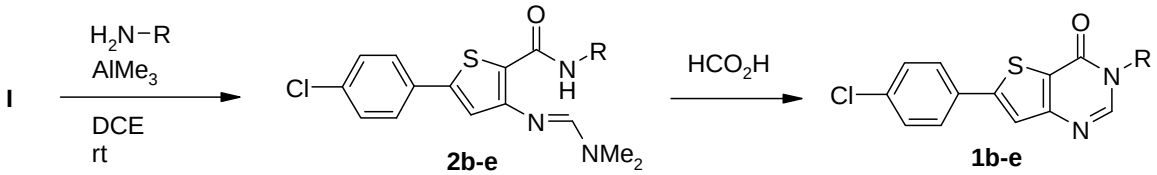
We recently described the syntheses of thienopyrimidinone analogs and the structure-activity relationships (SAR) with the MCH receptor.[4-7] A detailed analysis of the SAR suggested that a thienopyrimidinone N-substituted with a quinoline and a basic amine such as compound (**1a**) might yield a potent MCH antagonist. Our previous synthetic route (Scheme 1) involved heating a solution of intermediate **I** to 140 °C with substituted anilines in a minimal amount of phenol as solvent, thereby forming the desired products in modest yields (ranged from 46-65%).[4] Unfortunately, when 6-aminoquinoline **II**[6] was employed under the same reaction conditions, none of the desired product (**1a**) was observed.[8] The target compound was ultimately isolated, albeit in low yield, by lowering the reaction temperature to 120-130 °C. As predicted, compound (**1a**) was a potent inhibitor of MCH R1 (IC_{50} = 0.75 nM)[6] that also possessed a favorable pharmacokinetic profile and as a result, a more efficient synthesis was required to provide larger quantities of this compound for additional experiments.



Scheme 1. Original Synthetic Route to Analog (**1a**).

One alternative route envisioned the formation of N-substituted amides (**2**) which could then be cyclized to generate the corresponding thienopyrimidinones (**1**) (Scheme 2). From a mechanistic point-of-view, this approach would be complimentary to the synthesis in Scheme 1 which is believed to proceed via aniline displacement of dimethylamine from the amidine, followed by cyclization onto the ester.[9] The direct conversion of the methyl ester of **I** to N-substituted amides using $AlMe_3$ seemed feasible given the relatively mild reaction conditions and the reported generality of the method with respect to substrate compatibility.[10] The proposed route was attempted using aniline as the test substrate. Following the addition of aniline to a 2M solution of $AlMe_3$ in hexanes at room temperature (rt), methyl ester **I** was added and upon stirring for 16 h, the desired *N*-phenyl amide (**2b**) was isolated in 92% yield (Table 1, Entry 1). Heating the amidine-amide (**2b**) at reflux in formic acid produced the cyclized thienopyrimidinone (**1b**) in 81% yield.[11] Given the simplicity of the reaction sequence and the overall high yield, other amines were also examined to determine the scope of this method. Substituting aniline with β-napthylamine or 6-aminoquinoline gave the isolated amidine-amides (**2c** and **2d**) in good yields (Table 1, Entries 2 and 3, respectively). Both **2c** and **2d** were converted in very good yields to the corresponding thienopyrimidinones (**1c** and **1d**) upon refluxing in formic acid. The use of an aliphatic

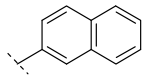
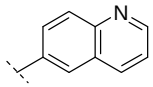
amine was examined next (Entry 4, Table 1). Using the same reaction conditions, benzylamine reacted with ester **I** to produce a mixture of the desired amide intermediate (**2e**) but also some of the cyclized thienopyrimidinone (**1e**). The two compounds were difficult to separate on silica gel so the crude mixture was refluxed with formic acid and the desired *N*-benzyl thienopyrimidinone (**1e**) was isolated in 56% yield.



R = phenyl (**b**); β-napthyl (**c**); 6-quinolyl (**d**); benzyl (**e**)

Scheme 2. Stepwise Synthesis of Amidine-Amide Intermediates (**2b-e**) and Thienopyrimidones (**1b-e**).

Table 1.

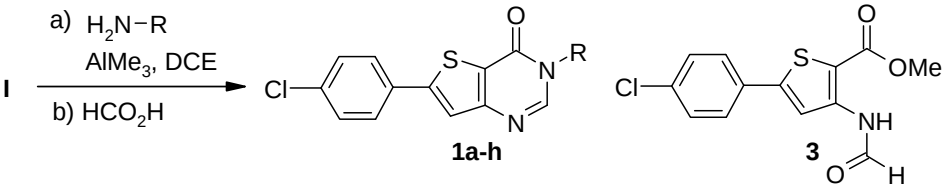
Entry	R	**I** → **2**[a] (Yield)[b]	**2** → **1**[a] (Yield)[c]
1	-Ph	**2b** (92%)	**1b** (81%)
2		**2c** (91%)	**1c** (92%)
3		**2d** (83%)	**1d** (77%)
4	-Bn	Mix of **2e** & **1e**	**1e** (56%)[d]

a) Purity >95% as determined by ^{1}H NMR, LCMS, and combustion analysis.
b) Yield for the conversion of ester **I** to product**s** (**2**).
c) Yield for the conversion of **2** to product**s** (**1**).
d) Yield for the conversion of ester **I** to product (**1e**).

The observation of the *N*-benzyl intermediate (**2e**) cyclizing to the thienopyrimidinone (**1e**) in the absence of formic acid suggested that it may not be necessary to isolate the amide intermediate and perhaps the entire process could be carried out in one-pot (Scheme 3). Aniline was again employed as a test substrate and after stirring with $AlMe_3$ and ester **I** for 16 h, formic acid was added slowly.[12] The biphasic mixture was heated at reflux for 8 h to provide the cyclized material (**1b**) in 84% yield (Table 2, Entry 1). Both β-napthylamine and 6-aminoquinoline (Table 2, Entries 3 and 4, respectively) were also re-examined using the one-pot approach and produced the desired thienopyrimidinones (**1c** and **1d**) in slightly better yields to that obtained by the two-step protocol.

Several aliphatic amines were studied as exemplified by Entries 4, 5 and 6 in Table 2. Interestingly, benzylamine (Entry 4) and n-butylamine (Entry 5) produced the desired cyclized products (**1e** and **1f**) in good yields but cyclohexylamine proved more troublesome. Analysis of the reaction mixture by LCMS indicated that the cyclohexylamide-amidine intermediate was formed but cyclization to the

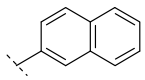
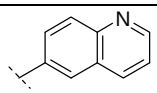
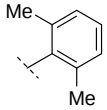
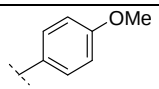
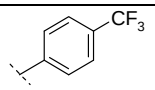
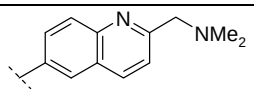
thienopyrimidinone (**1g**) was extremely slow. In fact, heating the solution at reflux in formic acid for 8 h showed little evidence of product and only amide-amidine intermediate remained (as determined by LCMS). The desired compound (**1g**) was eventually isolated in 48% yield after heating at reflux for 4 days. The slower rate of cyclization of the cyclohexyl-amide versus the benzyl- or butyl-amides is likely a result of the increased steric bulk near the reactive amide nitrogen atom. A related steric effect was also observed within the aniline series. While aniline worked well to give analog (**1b**) in 84% yield, the more sterically hindered 2,6-dimethylaniline gave none of the desired amide or cyclized thienopyrimidinone. In this case, only the formamide by-product (**3**) and unreacted ester **I** were isolated (Table 2, Entry 7).



R = 2-[(dimethylamino)methyl]-6-quinolyl (**a**); phenyl (**b**); β-napthyl (**c**); 6-quinolyl (**d**); benzyl (**e**); butyl (**f**); cyclohexyl (**g**); 4-MeO-phenyl (**h**)

Scheme 3. One-pot procedure for the synthesis of compounds (**1a-h**).

Table 2.

Entry	R	**I** → **1**[a] (Yield)[b]
1	-Ph	**1b** (84%)
2		**1c** (84%)
3		**1d** (83%)
4	-Bn	**1e** (63%)
5	-Bu	**1f** (78%)
6	-Cy	**1g** (48%)[c]
7		Mix of **I** & **3**
8		**1h** (67%)
9		Unreacted **I**
10		**1a** (30%) **1a** (63%)[d]

a) Purity >95% as determined by ^{1}H NMR, LCMS, and combustion analysis.

b) Yield for the one-pot conversion of ester **I** to product**s** (**1**).

c) Required heating at reflux in formic acid for 4 days.

d) The amine **II**, $AlMe_3$ and ester **I** were heated to 80 °C for 3 h.

Since the reaction appears sensitive to steric factors, several *para*-substituted aniline substrates were also included to study electronic effects. While the electron-rich 4-methoxyaniline gave the desired product (**1h**) in 67% yield (Table 2, Entry 8), the electron-deficient 4-trifluoromethylaniline failed to react (Table 2, Entry 9). As with 2,6-dimethylaniline, LCMS of the reaction mixture indicated that the amide intermediate was not forming under these conditions. More forcing conditions were also attempted but even upon heating the dimethylaluminum-trifluoromethylaniline complex with the ester **I**, no amide intermediate was observed. Fortunately, 6-aminoquinoline **II** was a compatible substrate and gave the desired product (**1a**) in 30% yield. The yield improved to 63% when the mixture of aniline **II**, ester **I** and $AlMe_3$ were heated to 80 °C in DCE for 3 h followed by refluxing in formic acid and represents a vast improvement over our initial synthetic approach. It is worth noting that both the ^1H and ^{13}C NMR spectra of compound (**1a**) were recorded in deuterated acetic acid due to the poor solubility of the compound in DMSO.[13] Interestingly, the benzylic protons of compound (**1a**) had completely exchanged with deuterium in this solvent after several days.

In summary, a novel synthetic route for the construction of thieno[3,2-*d*]pyrimidin-4(3*H*)-ones has been developed with the key step involving an $AlMe_3$-promoted ester-to-amide conversion. Although more studies are required to probe the generality of this approach, the initial results indicate that this is a useful method to prepare pyrimidinones. The yields within this limited set of analogs are comparable to those obtained via our previously reported routes and in at least one case far superior, thus serving to compliment other approaches to this useful chemical scaffold.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification unless noted. Aniline was filtered through a plug of silica gel or dried over $MgSO_4$ prior to use. Reactions involving air- or moisture-sensitive reagents were carried out under a nitrogen atmosphere and anhydrous solvents were obtained from Aldrich (Sure Seal). Silica gel column chromatography was performed with an automated ISCO chromatography system using pre-packed silica gel cartridges. IR spectra were recorded on a Bruker Vector 22 FTIR spectrometer. ^1H and ^{13}C NMR sprectra were recorded on a 400 MHz Varian spectrometer and chemical shifts are reported in parts per million (ppm) relative to TMS. Elemental analyses, performed by Atlantic Microlab, Inc. Norcross, GA, were within 0.4% of the theoretical values calculated for C, H, and N.

Methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (I): A suspension of methyl 3-amino-5-(4-chlorophenyl)-2-thiophenecarboxylate (5.00 g, 18.68 mmol) in DMF-DMA (75 mL, 564.58 mmol) was heated to 85 °C for 16 h then cooled to rt. The DMF-DMA was removed under vacuum to give **I** as a yellow solid in quantitative yield.

IR (solid): 1698; 1625; 1485; 1235; 1078; 807 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 7.82 (s, 1 H), 7.68 (d, *J*=8.79 Hz, 2 H), 7.45 (d, *J*=8.79 Hz, 2 H), 7.30 (s, 1 H), 3.67 (s, 3 H), 2.99 (s, 3 H), 2.92 (s, 3 H); ^{13}C (400 MHz, DMSO-d_6) δ ppm 162.9, 159.8, 157.1, 145.0, 134.0, 132.6, 129.8, 127.8, 123.0, 112.0, 51.8, 34.5; *Anal*. Calcd for $C_{15}H_{15}N_2O_2Cl_1S$: C, 55.81; H, 4.68; N, 8.68. Found: C, 55.59; H, 4.67; N, 8.75.

General procedure for the synthesis of products (2b-e) using $AlMe_3$ (Scheme 2):

A 2M solution of $AlMe_3$ in hexanes (0.81 mL, 1.61 mmol) was added to a solution of aniline (0.15 g, 1.61 mmol) in DCE (10 mL) at rt under N_2. After 15 min, methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (0.40 g, 1.24 mmol) was added as a solid and the solution was stirred at rt. The reactions times, workup procedures and purification techniques for the individual products are written below.

5-(4-Chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-*N*-phenyl-2-thiophene-carboxamide (2b): After 16 h, water (1 mL) was added slowly, followed by 1N NaOH (1 mL) resulting in a thick slurry. Ethyl acetate (100 mL) and water (100 mL) were added and the organic layer was separated, washed with saturated brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (increasing solvent gradient from 100% hexanes to 100% ethyl acetate over 30 min) to give 0.44 g (92%) of **2b** as a white solid. IR (solid): 1672, 1540, 1377, 810, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.68 (s, 1 H) 8.43 (s, 1 H) 7.81 (s, 1 H) 7.72 (d, *J*=8.43 Hz, 2 H) 7.63 (d, *J*=8.43 Hz, 2 H) 7.52 (d, *J*=8.43 Hz, 2 H) 7.33 (t, *J*=7.88 Hz, 2 H) 7.05 (t, *J*=7.33 Hz, 1 H) 3.15 (d, *J*=12.10 Hz, 6 H); ^{13}C (400 MHz, DMSO-d_6) δ ppm 161.2, 157.2, 151.9, 144.2, 139.5, 133.8, 133.0, 129.8, 129.8, 127.6, 123.8, 121.4, 119.6, 117.9, 35.4; *Anal*. Calcd for $C_{20}H_{18}N_3O_1Cl_1S$: C, 62.57; H, 4.73; N, 10.95. Found: C, 62.61; H, 4.81; N, 10.77.

5-(4-Chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-*N*-2-naphthalenyl-2-thiophene-carboxamide (2c): After 16 h, a white precipitate had formed. Water (1 mL) was added slowly, followed by 1N NaOH (1 mL) resulting in a thick slurry. Ethyl acetate (100 mL) and water (100 mL) were added and the organic layer which contained a white suspension of solid was separated and washed with saturated brine solution (100 mL). The solid was filtered and dried under vacuum to give 0.40 g (74%) of **2c** as a white powder. The organic filtrate was dried over $MgSO_4$, filtered and concentrated. The crude material was partially dissolved in hot ethyl acetate (ca. 50 mL), cooled to rt and the solid was filtered and dried to give another 0.092 g (17%) of the **2c** as a white powder.

IR (solid): 3051; 1648; 1626; 1505; 1289; 812; 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 11.86 (s, 1 H) 8.45 (s, 1 H) 8.35 (s, 1 H) 7.89 (d, *J*=8.80 Hz, 1 H) 7.79 - 7.86 (m, 3 H) 7.73 (d, *J*=8.43 Hz, 2 H)

7.58 (d, *J*=8.80 Hz, 1 H) 7.52 (d, *J*=8.43 Hz, 2 H) 7.47 (t, *J*=7.88 Hz, 1 H) 7.39 (t, *J*=7.52 Hz, 1 H) 3.20 (s, 3 H) 3.19 (s, 3 H); ^{13}C (400 MHz, DMSO-d_6) δ ppm 161.4; 157.2; 152.1; 144.3; 137.0; 134.3; 133.8; 132.9; 130.4; 129.8; 129.5; 128.2; 127.9; 127.6; 127.2; 125.2; 121.3; 120.5; 118.0; 115.6; 35.4; *Anal*. Calcd for $C_{24}H_{20}N_3O_1Cl_1S \cdot ½\ H_2O$: C, 65.08; H, 4.78; N, 9.49. Found: C, 64.79; H, 4.56; 9.53.

5-(4-Chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-*N*-6-quinolinyl-2-thiophenecarboxamide (2d): After 48 h, water (1 mL) was added slowly, followed by 15% NH_4OH (50 mL) resulting in a thick slurry. Following the addition of ethyl acetate (100 mL), the organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow/green solid. The solid was washed with 2:1 ethyl acetate/Et_2O (10 mL) and dried under vacuum to give 0.45 g (83%) of **2d** as a yellow solid.

IR: 3403, 3000, 1618, 1540, 1378, 799 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.92 (s, 1 H) 8.73 (dd, *J*=4.21, 1.47 Hz, 1 H) 8.43 (s, 1 H) 8.39 (d, *J*=1.83 Hz, 1 H) 8.25 (d, *J*=8.06 Hz, 1 H) 7.95 (d, *J*=8.97 Hz, 1 H) 7.80 (s, 1 H) 7.68 - 7.76 (m, 3 H) 7.42 - 7.51 (m, 3 H) 3.17 (d, *J*=6.41 Hz, 6 H); ^{13}C (400 MHz, DMSO-d_6) δ ppm 161.5, 157.3, 152.4, 149.6, 145.3, 144.5, 137.3, 136.1, 133.8, 132.9, 130.6, 129.8, 129.2, 127.6, 123.8, 122.5, 121.0, 117.9, 115.4, 35.6; *Anal*. Calcd for $C_{23}H_{19}N_4O_1Cl_1S \cdot ½\ H_2O$: C, 62.23; H, 4.54; 12.62. Found: C, 62.43; H, 4.50; N, 12.51.

5-(4-Chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-*N*-(phenylmethyl)-2-thiophenecarboxamide (2e): After 48 h, water (1 mL) was added slowly, followed by 15% NH_4OH (50 mL) resulting in a thick slurry. Following the addition of ethyl acetate (100 mL), the organic layer was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to 0.45 g of yellow solid. ^{1}H NMR & LC/MS looks like a mixture of desired product (**2e**) and also cyclized material (**1e**). This was used directly in the next step.

General procedure for the synthesis of analogs (1b-e) (Scheme 2):

A solution of 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-*N*-substituted-2-thiophenecarboxamide (~0.25 mmol) in formic acid (10 mL) was heated to 100 °C. The reactions times, workup procedures and purification techniques for the individual products are written below.

6-(4-Chlorophenyl)-3-phenylthieno[3,2-*d*]pyrimidin-4(3*H*)-one (1b): After 6 h the solution was cooled to rt, concentrated to dryness and dried under vacuum to a white powder. The solid was recrystallized from hot DMSO to give 0.071 g (81%) of **1b** as a crystalline solid.

IR (solid): 1671.99, 1540.00, 1376.70, 810.12 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.39 (s, 1 H), 7.93 (s, 1 H), 7.88 (d, *J = 8.4 Hz*, 2 H), 7.55 – 7.48 (m, 7 H); ^{13}C (400 MHz, DMSO-d_6 + 1 drop TFA)

δ ppm 158.2; 156.7; 150.7; 149.9; 137.7; 135.1; 132.0; 130.0; 129.9; 129.6; 128.6; 128.2; 122.8; 122.5; *Anal*. Calcd for $C_{18}H_{11}N_2O_1Cl_1S \cdot ½\ H_2O$: C, 62.16; H, 3.48; N, 8.05. Found: C, 61.85; H, 3.21; N, 7.93.

6-(4-Chlorophenyl)-3-(2-naphthalenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1c): After 6 h the solution was cooled to rt, concentrated to dryness and dried under vacuum to a white powder. The crude product was recrystallized from hot DMSO (ca. 5 mL) to give 0.082 g (92%) of **1c**.
IR (solid): 3048, 1692, 1574, 1490, 1093, 810 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.53 (s, 1 H), 8.11 (s, 1 H), 8.06 - 7.98 (m, 4 H), 7.91 (d, *J*=8.06 Hz, 2 H), 7.64 - 7.54 (s, 5 H). *Anal.* Calcd for $C_{22}H_{13}N_2O_1Cl_1S \cdot 0.8\ H_2O$: C, 65.52; H, 3.65; N, 6.95. Found: C, 65.16; H, 3.28; N, 6.83.

6-(4-chlorophenyl)-3-(6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1d): After 6 h the solution was cooled to rt. Approximately half of the formic acid solvent was removed under reduced pressure then water (10 mL) was added. A white solid precipitated which was filtered, washed with water (10 mL), EtOH (10 mL), Et_2O (10 mL) and dried under vacuum to give 0.138 g (77%) of **1d** as a white solid.
IR (solid): 3322, 1685, 1489, 1214, 1095, 806 cm^{-1}; ^1H NMR (400 MHz, *d6-DMSO + 1 drop TFA*) δ ppm 9.19 (s, 1 H), 8.82 (s, 1 H), 8.57 (s, 1 H), 8.41 (s, 1 H), 8.26 (d, *J*=9.16 Hz, 1 H), 8.11 (d, *J*=8.42 Hz, 1 H), 7.98 (s, 1 H), 7.90 (m, 3 H), 7.55 (d, *J*=8.42 Hz, 2 H); *Anal*. Calcd. for $C_{21}H_{12}Cl_1N_3O_1S \cdot ½\ H_2O$: C, 63.24; H, 3.29; N, 10.54. Found: C, 63.48; H, 2.96; N, 10.54.

6-(4-Chlorophenyl)-3-(phenylmethyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1e): After 6 h the reation was cooled to rt and the formic acid was removed under reduced pressure. Ethyl acetate (100 mL) and saturated $NaHCO_3$ solution (100 mL) were added. The organic layer was washed with brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (increasing solvent gradient from 5% ethyl acetate/hexanes to 90% ethyl acetate/hexanes over 25 min) to give 0.123 g (56%) of **1e** as a white solid.
IR (solid): 3081, 1668, 1576, 1490, 1151, 826 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d_6*) δ ppm 8.63 (s, 1 H), 7.86 (s, 1 H), 7.84 (d, *J*=8.42 Hz, 2 H), 7.51 (d, *J*=8.42 Hz, 2 H), 7.32 - 7.25 (m, 5 H), 5.19 (s, 2 H); ^{13}C NMR (101 MHz, *DMSO-d_6*) δ ppm 158.41, 156.83, 150.53, 150.40, 137.35, 135.00, 131.95, 129.99, 129.33, 128.59, 128.43, 128.38, 122.56, 122.40, 49.40; *Anal*. Calcd for $C_{19}H_{13}N_2O_1Cl_1S$: C, 64.68; H, 3.52; N, 7.85. Found: C, 64.46; H, 3.52; N, 7.85.

General procedure for the one-pot synthesis of analogs (1a-h) (Scheme 3):

A 2M solution of $AlMe_3$ in hexanes (0.81 mL, 1.61 mmol) was added to a solution of amine (1.61 mmol) in DCE (10 mL) at rt under N_2. After 15 min, methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)-

methylidene]amino}-2-thiophenecarboxylate (0.40 g, 1.24 mmol) was added as a solid and the solution was stirred at rt. After 16 h, formic acid (10 mL) was added slowly and the mixture was heated to 100 °C. The reactions times, workup procedures and purification techniques for the individual products are written below.

6-(4-Chlorophenyl)-3-phenylthieno[3,2-*d*]pyrimidin-4(3*H*)-one (1b): Reaction performed according to the general procedure using methyl 5-(4-chlorophenyl)-3-{[(1*E*)-(dimethylamino)methylidene]amino}-2-thiophenecarboxylate (0.20 g, 0.62 mmol. After 8 h, the reaction was cooled to rt then water was added. The mixture was sonicated briefly then filtered to collect the white solid which was washed with MeOH and dried under vacuum. The crude product was partially dissolved in hot DMSO then cooled to rt. EtOH was added and the solid was collected, washed with EtOH and dried under vacuum to give 0.18 g (84%) of **1b** as a white powder.

6-(4-Chlorophenyl)-3-(2-naphthalenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1c): After 8 h, the reaction was cooled to rt then water was added. The mixture was sonicated briefly then filtered to collect the white solid which was washed with MeOH and dried under vacuum. The crude product was partially dissolved in hot DMSO then cooled to rt. EtOH was added and the solid was collected, washed with EtOH and dried under vacuum to give 0.40 g (84%) of **1c** as a white powder.

6-(4-Chlorophenyl)-3-(6-quinolinyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1d): After 8 h, the reaction was cooled to rt then water (10 mL) was added followed by Et_2O (~50 mL). The mixture was sonicated briefly then filtered to collect a white solid which was washed with Et_2O and dried under vacuum. The crude product was heated in hot DMSO (10 mL) then cooled to rt. EtOH (5 mL) was added and the resultant solid was collected, washed with Et_2O and dried under vacuum to give 0.40 g (83%) of **1d** as a white powder.

6-(4-Chlorophenyl)-3-(phenylmethyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1e): After 8 h the reaction was cooled to rt then water (100 mL) was added followed by ethyl acetate (150 mL). The organic layer was washed with water (100 mL), brine solution (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified on silica gel (increasing solvent gradient from 5% ethyl acetate/hexanes to 100% ethyl acetate over 30 min) to give 0.27 g (63%) of **1e** as a white solid.

3-Butyl-6-(4-chlorophenyl)thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1f): After 8 h the reaction was cooled to rt then water (10 mL) was added followed by Et_2O (~50 mL). The mixture was sonicated briefly then filtered to collect a white solid which was washed with Et_2O and dried under vacuum to give 0.110 g (28%) of **1f** as a white solid. The filtrate was extracted with ethyl acetate (100 mL), washed with brine

(100 mL), dried over $MgSO_4$, filtered and concentrated. The material was purified on silica gel (increasing solvent gradient from 100% hexanes to 95% ethyl acetate/hexanes over 30 min) to give 0.20 g (51%) of **1f** as a white solid. The combined yield of **1f** was 78%.

IR (solid): 3058, 2951, 2862, 1661, 1454, 816 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.42 (s, 1 H), 7.83 (d, *J*=8.42 Hz, 2 H), 7.82 (s, 1 H), 7.51 (d, *J*=8.42 Hz, 2 H), 3.96 (t, *J*=7.33 Hz, 2 H), 1.59 - 1.68 (m, *J*=7.42, 7.42, 7.42, 7.42 Hz, 2 H), 1.22 - 1.32 (m, *J*=7.44, 7.44, 7.44, 7.44, 7.44 Hz, 2 H), 0.86 (t, *J*=7.33 Hz, 3 H); ^{13}C NMR (101 MHz, *DMSO-d*$_6$) δ ppm 158.34, 156.92, 150.49, 150.07, 134.94, 132.03, 130.00, 128.59, 122.47, 122.35, 46.28, 31.60, 19.90, 14.19; Anal. Calcd for $C_{16}H_{15}N_2O_1Cl_1S$: C, 60.28; H, 4.74; N, 8.79. Found: C, 60.31; H, 4.79; N, 8.75.

6-(4-Chlorophenyl)-3-cyclohexylthieno[3,2-*d*]pyrimidin-4(3*H*)-one (1g): After 4 days the reaction was cooled to rt and ethyl acetate (150 mL) and 15% NH_4OH solution (100 mL) were added. A grey powder was collected and dried to give 0.101 g (24%) of **1g**. The filtrate was washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The material was purified on silica gel (increasing solvent gradient from 100% hexanes to 100% ethyl acetate over 30 min) to give 0.104 g (24%) of **1g** as a white solid. The combined yield of **1g** was 48%. IR (solid): 2935, 1673, 1489, 1163, 826 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.50 (s, 1 H), 7.85 – 7.83 (m, 3 H), 7.52 (d, *J*=8.61 Hz, 2 H), 4.59 (m, 1 H), 1.85 - 1.75 (m, 6 H), 1.63 (m, 1 H), 1.40 – 1.32 (m, 2 H), 1.23 – 1.14 (m, 1 H); ^{13}C NMR (101 MHz, *DMSO-d*$_6$) δ ppm 157.61 (s), 156.57 (s), 150.17 (s), 147.98 (s), 134.93 (s), 132.04 (s), 130.00 (s), 128.57 (s), 122.34 (s), 122.24 (s), 54.01 (s), 32.19 (s), 26.24 (s), 25.30 (s); *Anal*. Calcd for $C_{18}H_{17}N_2O_1 Cl_1S \cdot ¼ H_2O$: C, 61.88; H, 5.05; N, 8.02. Found: C, 61.92; H, 4.92; N, 7.88.

6-(4-Chlorophenyl)-3-[4-(methyloxy)phenyl]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1h): After 8 h the reaction was cooled to rt then water (10 mL) was added followed by Et_2O (~50 mL). The mixture was sonicated briefly then filtered to collect a white solid which was washed with Et_2O and dried under vacuum to give 0.306 g (67%) of **1h** as a white solid.

IR (solid): 3063, 2833, 1697, 1513, 1254, 812 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.38 (s, 1 H), 7.96 (s, 1 H), 7.91 (d, *J*=8.43 Hz, 2 H), 7.56 (d, *J*=8.43 Hz, 2 H), 7.45 (d, *J*=8.80 Hz, 2 H), 7.08 (d, *J*=9.16 Hz, 2 H), 3.81 (s, 3 H); ^{13}C NMR (101 MHz, *DMSO-d*$_6$) δ ppm 160.11, 158.23, 156.90, 150.55, 150.20, 135.03, 131.98, 130.33, 130.04, 129.41, 128.62, 122.74, 122.51, 115.01, 56.18; *Anal*. Calcd for $C_{19}H_{13}N_2O_2Cl_1S$: C, 61.87; H, 3.55; N, 7.60. Found: C, 61.59; H, 3.60; N, 7.50.

6-(4-Chlorophenyl)-3-{2-[(dimethylamino)methyl]-6-quinolinyl}thieno[3,2-*d*]pyrimidin-4(3*H*)-one (1a): The reaction was carried out according to the general procedure except that the solution of 2-[(dimethylamino)methyl]-6-quinolinamine (0.34 g, 1.69 mmol), $AlMe_3$ (2M hexanes, 0.96 mL) and

ester **I** (0.50 g, 1.54 mmol) in DCE (10 mL) were heated to 80 °C under N_2 for 3 h followed by the addition of formic acid. After 4 h, the reaction was cooled to rt then water (300 mL), 1N NaOH (50 mL) and CH_2Cl_2 (400 mL) were added. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The resulting solid was partially dissolved in hot $CHCl_3$, filtered to remove the insoluble material and concentrated to give 0.33 g (49%) of **1a**. The filtered solid was dissolved in CH_2Cl_2, washed with 1N NaOH, dried over $MgSO_4$, filtered and concentrated to give 0.10 g (14%) of the **1a**. A total combined yield of **1a** was 63%.

IR (solid): 3068, 2772, 1662, 1521, 1093, 845 cm^{-1}; ^1H NMR (400 MHz, *d3-AcOD*) δ ppm 8.58 (s, 1 H), 8.54 (d, *J*=8.61 Hz, 1 H), 8.30 (d, *J*=8.97 Hz, 1 H), 8.21 (d, *J*=2.01 Hz, 1 H), 8.01 (dd, *J*=9.06, 2.29 Hz, 1 H), 7.78 - 7.84 (m, 4 H), 7.51 (d, *J*=8.42 Hz, 2 H), 4.84 (s, 2 H), 3.10 (s, 6 H); ^{13}C NMR (101 MHz, *d3-AcOD*) δ ppm 157.2, 156.8, 153.1, 152.9, 149.3, 146.8, 139.1, 136.0, 131.4, 129.9, 129.8, 129.6, 128.1, 127.9, 126.8, 122.9, 122.6, 120.4, 94.6, 61.2, 43.5; Anal. Calcd for $C_{24}H_{19}N_4O_1Cl_1S$: C, 64.49; H, 4.28; N, 12.54. Found: C, 64.26; H, 4.17; N, 12.17.

Methyl 5-(4-chlorophenyl)-3-(formylamino)-2-thiophenecarboxylate (3): IR (solid): 3333, 1662, 1580, 1443, 1266, 1089, 832 cm^{-1}; ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 10.39 (s, 1 H), 8.40 (s, 1 H), 8.30 (s, 1 H), 7.70 (d, *J*=8.42 Hz, 2 H), 7.49 (d, *J*=8.42 Hz, 2 H), 3.82 (s, 3 H); ^{13}C NMR (101 MHz, *DMSO-d*$_6$) δ ppm 163.19, 160.93, 147.51, 143.20, 134.76, 131.70, 130.03, 128.19, 119.56, 110.92, 52.83; *Anal.* Calcd for $C_{13}H_{10}N_1O_3Cl_1S$: C, 52.80; H, 3.41; N, 4.74. Found: C, 52.77; H, 3.32; N, 4.74.

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8. Anaylsis of the reaction by ^{1}H NMR and LCMS yielded little information. It appears decomposition of the starting materials and/or product occurred.
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12. The formic acid should be added with caution since vigorous gas evolution occurs.
13. Almost all of the compounds in this study have poor solubility in typical NMR solvents, including DMSO.