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Selective Modulation of Gq/Gs pathways by Naphtho Pyrano Pyrimidines As Antagonists of the Neuropeptide S Receptor

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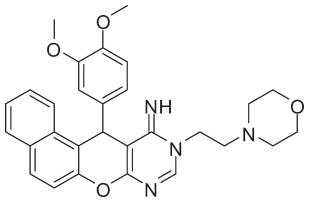
Abstract



Antagonists of the neuropeptide S receptor have been postulated as promising therapeutics in the treatment of respiratory, sleep, anxiety, and addictive disorders. Here, we present the SAR of a new series of orthosteric antagonists. Neuropeptide S receptor signaling is coupled to both Gq and Gs proteins, and we observe that different analogues in this structural series can selectively antagonize these two pathways. Many G-protein coupled receptors transduce signals through multiple pathways. Selective antagonism of these pathways may lead the way to the development of more targeted pharmacological profiles and therapies.

Keywords: Neuropeptide S receptor antagonist, sleep disorders, addiction disorders, naphtho pyrano pyrimidines, homogeneous time-resolved fluorescence, neuropeptide S radiolabel displacement assay

Neuropeptide S (NPS, SFRNGVGTGMKKTSFQRAK, human sequence) is a small peptide produced in the brain predominantly in a group of previously not well-described neurons located between the locus coeruleus (LC), the Barrington nucleus, and the parabrachial nuclei. NPS binds specifically with a G-protein coupled receptor expressed in several brain areas, neuropeptide S receptor (NPSR). Activation of NPSR induces transient increases in intracellular calcium and cAMP, suggesting coupling of this receptor to both Gs and Gq G-proteins. Animal functional studies have linked NPSR with susceptibility for asthma (*1*), the modulation of arousal, anxiety, and in the extinction of conditioned fear (*2*−*6*). Moreover, recently Padeña el al. (*7*) have shown that in a dose dependent manner, NPS reinstates cocaine-seeking behavior in a mouse model for addiction. Thus, NPSR may represent a novel drug target for the treatment of sleep, anxiety, and addiction disorders.

In addition to NPS peptidic analogues (*8*−*10*), two small molecule NPSR antagonist series have been reported (Figure 1). The first series, exemplified by *N*-(4-fluorobenzyl)-1-oxo-3,3-diphenyltetrahydro-1*H*-oxazolo[3,4-*a*]pyrazine-7(3*H*)-carboxamide (**1**), was able to partially reduce the NPS induced hyperlocomotion in mice (*11*, *12*). The second series, represented by *N*-(3-methyl-1-morpholinopentan-3-yl)-*N*-((1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)cyclohexanecarboxamide (**2**), also showed initial pharmacological results that point to its capacity to reduce the NPS induced hyperlocomotion (*13*).

In parallel with this recently reported work, we developed a new HTS assay for identifying NPSR antagonists (*14*). The assay was based on the use of HTRF (homogeneous time-resolved fluorescence) for the detection of cAMP (Figure 2). Antagonists of NPSR are able to decrease the signal induced by NPS in a dose dependent manner. Active compounds are also evaluated for their capacity to modulate Ca^{2+} signaling and for their capacity to compete with the NPS peptide in a radiolabel displacement assay.

Results and Discussion

Chemistry

In a high-throughput screen of 220,877 compounds, we identified 10-(2-morpholinoethyl)-12-(3,4 dimethoxyphenyl)-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-imine (Figure 1, **3a**) as a strong antagonist of NPSR signaling.

Compound **3a** inhibited cAMP and Ca^{2+} signaling with IC_{50} values of 4.87 and 1.38 μM, respectively. In radiolabeled peptide displacement studies, **3a** was able

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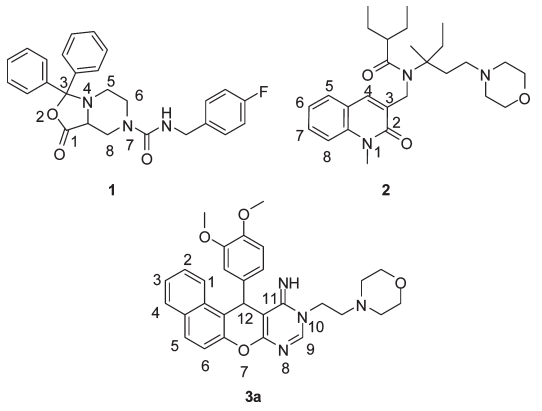


Figure 1. Previously described NPSR antagonists and the structure of our lead compound.

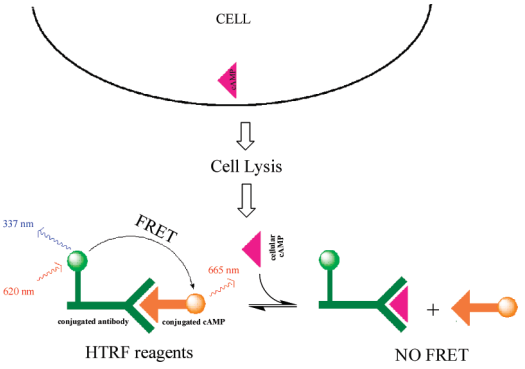
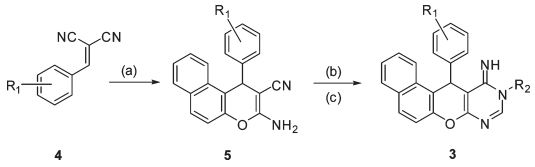


Figure 2. Schematic illustration of the assay principle of the HTRF cAMP assay.

to displace NPS with a K_i of 0.21 μM. On the basis of this activity, we decided to further explore this series' SAR. Schemes 1 through 5 show the main methodology involved in the synthesis of analogues. Scheme 1 describes analogues with substituents on the phenyl ring at position 12 and the nitrogen at position 10. Thus, amine **5** was synthesized by refluxing 2-naphthol and a suitable 2-arylidenemalononitrile **4** in ethanol with piperidine. Starting materials 2-arylidenemalononitrile (**4**) were either purchased or obtained by Knoevenagel condensation between the corresponding aldehyde and malononitrile using piperidine as a base. Compound **5** was then heated with triethylorthoformate to give the ethoxy-imino intermediate, which was subsequently reacted with the proper amine to obtain compound **3.**

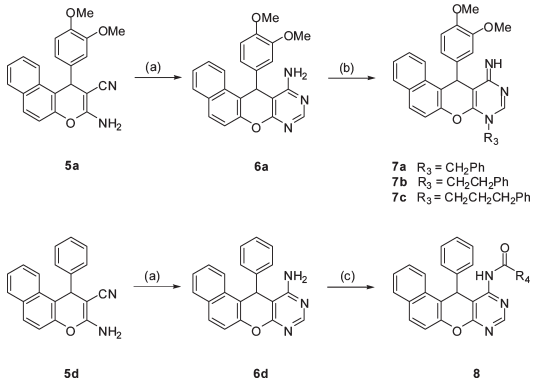
Scheme 2 shows the synthesis of analogues at positions 8 and 11. Thus, amine **5a** was dissolved into formamide and heated to give aminopyrimidine **6a.** This compound was then reacted with three different alkyl bromides to give compounds **7a**−**7c**. All three compounds were mixtures of the desired products and alkylation products at the other pyrimidine nitrogen (ratio: **7a**:**3n** = 8:1; **7b**:**3p** = 8:1, **7c**:**3r** = 3:1). Attempts to separate these mixtures by preparative HPLC were not successful. Alternatively, aminopyrimidine **6d** was

Scheme 1. Analogues at Positions 10 and 12[a]



[a] Reagents and conditions: (a) 2-naphthol, piperidine, EtOH, reflux; (b) $CH(OEt)_3$, 155 °C; (c) R_2NH_2, DBU, THF, 75 °C.

Scheme 2. Analogues at Positions 8 and 11[a]



[a] Reagents and conditions: (a) Formamide, 220 °C; (b) **7a**, benzyl bromide; MeCN, 100 °C; **7b** and **7c**, R_3Br; DMF, 150 °C; (c) R_4COCl, iPr$_2$NEt.

acylated using an acyl chloride in the presence of diisopropylethylamine to yield compounds with the general structure of **8**.

Additional compounds with pyrimidine ring substitution at position 9 were made by combining **5a** with several acyl chlorides and heating them in a microwave oven to obtain pyrimidinones **9a**−**9d**. Next, these pyrimidinones were exposed to phosphorus(V) oxychloride and heated to give chloropyrimidine intermediates, which were then reacted with ammonium hydroxide to give the final aminopyrimidines **10a**−**10c** (Scheme 3).

In order to investigate the effect of naphthyl regiosubstitution, compound **12** was synthesized in a fashion similar to that of the previously described compounds. Scheme 4 shows how 1-naphthol was substituted for 2-naphthol under the same conditions to get **12** in three steps.

Additional naphthyl ring modifications were explored with compounds **14a** and **14b**. Scheme 5 shows how they were synthesized using 3-methoxyphenol and 3-benzyloxyphenol, respectively, as starting materials.

Last, Scheme 6 discloses the synthesis of two compounds having an unsubstituted phenyl ring at the original naphthyl position. The methodology was developed starting with similar previously described procedures to obtain diamine **15**. The diamine was then converted to a dibromide intermediate with t-butylnitrite and copper(II) bromide. The dibromide intermediate

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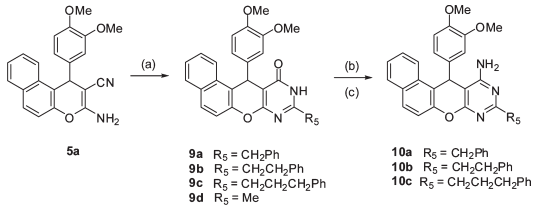
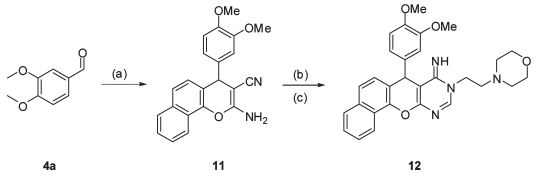
Scheme 3. Analogues at the 9 Position[a]



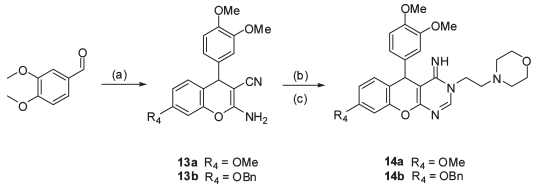
[a] Reagents and conditions: (a) R_5COCl, THF, Pyridine, MW, 120 °C; (b) $POCl_3$, 120 °C; (c) NH_4OH, THF, 130 °C.

Scheme 4. Modification of the Naphthyl Ring[a]



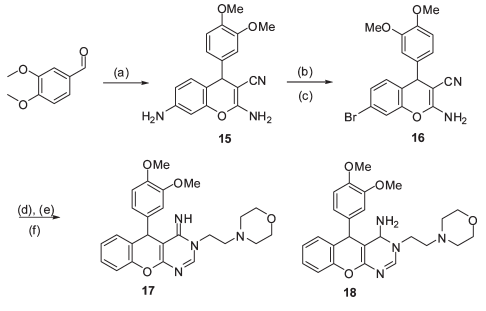
[a] Reagents and conditions: (a) 1-naphthol, malononitrile, piperidine, EtOH, reflux; (b) $CH(OEt)_3$, 155 °C; (c) 2-morpholinoethylamine, DBU, THF, 75 °C.

Scheme 5. Phenyl Analogues at the Naphthyl Region[a]



[a] Reagents and conditions: (a) 3-methoxyphenol (or 3-benzyloxyphenol), malononitrile, piperidine, EtOH, reflux; (b) $CH(OEt)_3$, 155 °C; (c) 2-morpholinoethylamine, DBU, THF, 75 °C.

Scheme 6. Additional Phenyl Analogues of the Naphthyl Ring[a]



[a] Reagents and conditions: (a) 3-aminophenol, malononitrile, piperidine, EtOH, reflux; (b) *t*-butyl nitrite, $CuBr_2$, MeCN, 0 °C; (c) NH_3, iPrOH, 150 °C; (d) $CH(OEt)_3$, 155 °C; (e) 2-morpholinoethylamine, DBU, THF, 75 °C; (f) $PdCl_2$, Et_3SiH, DCM.

was then selectively converted to the monoamine with ammonia in isopropanol to give **16**. Next, aminobromide **16** was cyclized by transforming it into the ethoxyimino intermediate, which, parallel to previous methods, was then reacted with morpholinoethylamine. Finally, reduction of the bromide with palladium(II) chloride and triethylsilane gave **17** as well as the over-reduced side-product **18**.

SAR Investigation

Since its discovery by Sato and co-workers (*15*) and its deorphanization by Xu (*2*) in 2004, the neuropeptide S receptor (NPSR) has been implicated in important neurocircuits such as the control of sleep, stress, anxiety, and arousal. At the same time, important technologies have been developed to separately explore the signaling of GPCRs through different pathways, by the development of HTRF technologies to measure cAMP responses, and the development of kinetic fluorescence-based plate readers to measure transient calcium signaling (*16*). We used both to characterize the SAR of this series (PubChem AIDs: 434936, 434931 and 1464). The initial hit from the screen, compound **3a**, had antagonistic activity in the low micromolar range for both the cAMP and calcium pathways. Additional studies disclosed the capacity of the molecule to compete with the natural substrate, having a K_i of 210 nM. As we began characterizing the activity of analogues, we observed interesting variations in the relative modulation of cAMP and calcium signaling. Thus, the ability of a particular substituent to increase antagonistic activity with respect to cAMP did not always correspond with an equivalent effect on calcium signaling. There were compounds that had a greater impact on cAMP signaling, while others preferentially antagonized calcium signaling. It is not clear which one of these two pathways is more important in establishing a neurocircuit response; therefore, we have decided to measure and report on both pathways. Previous authors have focused their reports on calcium signaling (*8*−*12*). It is also not clear whether the assays used to measure the antagonism of cAMP and calcium signaling are equally sensitive. Regardless, we observe clear, reproducible differences in the relative antagonism of cAMP and calcium signaling for close analogues in the present series and believe that the relative antagonism of the two signaling pathways will critically affect *in vivo* activity and may explain why previous series have only shown a partial reversion of the NPS induced phenotype.

Initial exploration of the peripheral methoxy functional groups indicate that the elimination of these substituents diminishes the potency of the molecule 10-fold (Table 1, calcium IC_{50}). In addition, the meta-substituted methoxy substituent has the most impact on activity. Interestingly though, compound **3c** lacks the calcium selectivity of the other compounds.

During our SAR studies, we found that the introduction of an aromatic ring at the 10 position increased the potency of the molecule. Using this information, different methoxy and biomimetic functional groups were explored (Table 2). 2,3-Benzodioxine (**3k**) displayed the

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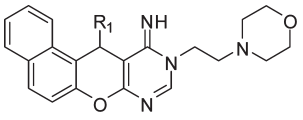
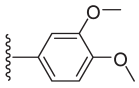
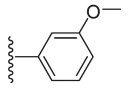
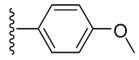
Table 1. Methoxy Scan at the 12 Position



Compound number	R1	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
3a		4.87	1.38
3b		12.24	1.74
3c		30.74	>30
3d		38.71	13.85

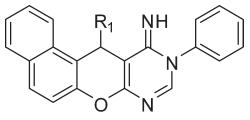
lowest calcium IC_{50} value followed by dihydrobenzofuran (**3i**) and the *meta*-methoxy analogue **3g**, showing the possibility of maintaining activity with more metabolically stable substituents. Compound **3e** had the lowest cAMP IC_{50} value, and the phenyl substituent at position 12 was kept constant for the carbonyl analogues at position 11 (Table 3).

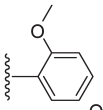
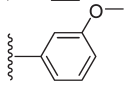
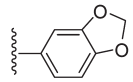
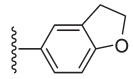
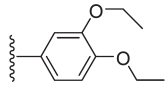
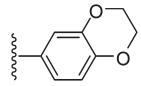
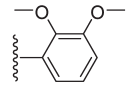
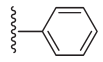
During the development of these series, a number of papers were published disclosing the activity of *N*-(4-fluorobenzyl)-1-oxo-3,3-diphenyltetrahydro-1*H*-oxazolo[3,4-*a*]pyrazine-7(3*H*)-carboxamide (**1**) and analogues as NPSR antagonists (*10*, *11*). Structural studies of that series have shown the importance of the diphenyl substituent at the 3 position for mantaining activity. In addition, NPS displacement assays demonstrate that both series bind in the same region of the receptor, at the NPS binding site.

With this in mind, we decided to compare the conformational ensembles of both series for similarity. Figure 3 shows one superposition of these structures maximizing the overlap of the aromatic regions. From this perspective, it can be seen that the main structural difference between these two molecules is on the *N*-(4-fluorobenzyl)-urea region. This region is crucial for the potency of the series, and its elimination yields almost inactive molecules. Thus, we rationalized that the introduction of functional groups within our series mimicking the effects of that benzyl urea region might increase the potency of our series.

We began by first synthesizing analogues with amine substitutions at position 11. Elimination of the ethylmorpholine substituent at position 10 (compound **6d**, Table 3) improved the calcium activity more than 30-fold. In general, amide derivatives of compound **6d**

Table 2. Analogues at the 12 Position Maintaining a Phenyl Ring at the 10 Position



Compound number	R1	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
3f		6.13	5.52
3g		2.44	0.55
3h		3.87	1.38
3i		3.07	0.55
3j		6.13	3.48
3k		3.07	0.35
3l		4.87	0.87
3e		1.94	0.69

reduced the activity of the molecule. However, dicarboxylic aliphatic chains (compounds **8f**, **8g**, and **8h**) are reasonably tolerated with only slightly higher calcium IC_{50} values, which increased along with chain length. Amide substituents having an appending phenyl ring also increase the IC_{50} value, abolishing activity completely when an aromatic ring is next to the carbonyl functionality (compounds **8b**, **8c**, and **8d**). The same depletion of activity can be observed with *t*-butyl carbamate (compound **8a**) as well as benzyl urea (compound **8e**).

While comparing the activity of compounds **3b** (Table 1) and **3g** (Table 2), one can see that the introduction of an aromatic ring at the 10 position increases the potency of the molecule. Thus, we decided to explore the impact of phenyl substituents with differing amounts of elongation from the pyrimidine ring. Table 4 shows that only the two carbon chain analogue (compound **3o**, calcium IC_{50}) was able to retain activity. Interestingly, introduction of *meta*- and *para*-methoxy substituents on the phenyl ring at position 12 shifts the tolerability of the elongated chain to the analogue with a single carbon linker, which was the only one able to

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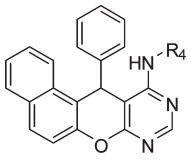
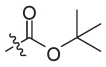
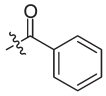
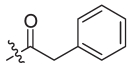
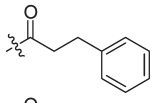
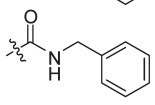
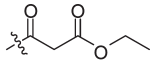
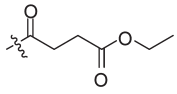
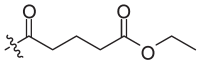
Table 3. Carbonyl Analogues at the 11 Position



Compound number	R4	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
6d	H	7.72	0.44
8a		12.24	>30
8b		97.23	>30
8c		7.72	1.74
8d		15.41	3.48
8e		77.23	>30
8f		3.87	0.55
8g		6.13	1.38
8h		3.87	2.76

maintain activity (compound **3n** versus **3p** and **3r**, calcium IC_{50}). Moreover, the impact of the aromatic ring chain length on the calcium signal does not correlate with that of cAMP. In Table 4, the cAMP IC_{50} column shows that the majority of analogues are well tolerated and do not diminish activity (**3e**, **3 m**, **3o**, and **3q**) to a large degree. Only the analogue with a butyl elongating chain, **3s**, deeply impacts the cAMP activity. Although compounds having *meta*- and *para*-methoxy substitutions on the phenyl ring at position 12 have a 5 to 10 times lower potency than the corresponding analogues without methoxy groups, they also show that elongation of the chain does not significantly impact cAMP activity. More importantly, these results showed a GPCR antagonist with selectivity toward either cAMP (**3m** and **3q**) or calcium (**3n**), thus making them important tools for further characterizing the relationship between different signaling pathways and neurocircuits modulated by NPS.

In further exploration of the impact of aromatic ring substitution at position 10, we synthesized additional analogues having functionalities on that part of the

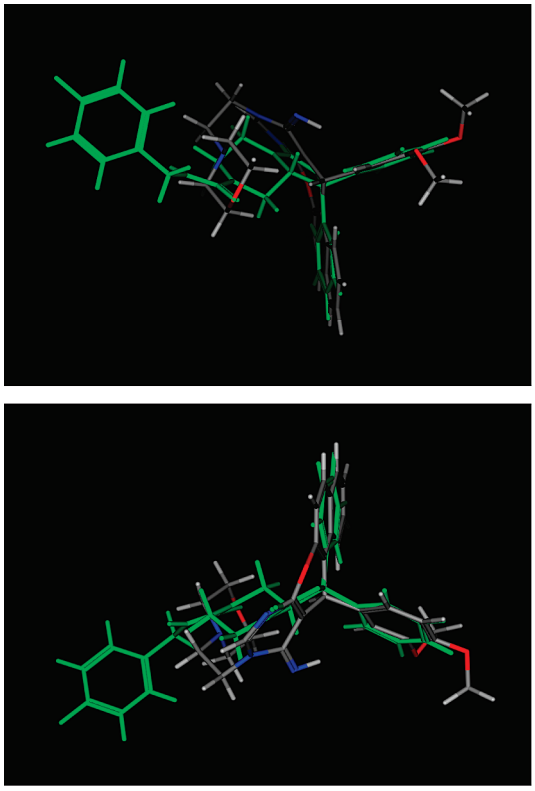


Figure 3. Molecular modeling overlap between **1** and **3** (green).

molecule. Table 5 shows that only the *meta*-fluoro halogenated analogue **3t** improved calcium signaling potency. Although none of the substituents increased antagonism of cAMP activity, it is worth mentioning that a number of analogues had a strong negative impact on it. The *ortho*-nitrile substituent **3aa** (Table 5) had no cAMP activity, giving us a compound completely selective toward the calcium pathway.

Tables 6 and 7 display the activity of compounds with substitutions at the 8 and 9 position, respectively. It can be seen that substituents on those regions of the molecule negatively impact both the calcium and the cAMP signals.

Last, Table 8 shows that the regioselectivity of the naphthyl ring (compounds **3a** and **12**) is important for maintaining activity in both assays. Replacement of the naphthyl aromatic ring by an unsubstituted phenyl ring (compound **17**) maintains the potency of the molecule, while substituents in the meta position are not well tolerated (**14a** and **14b**).

In conclusion, we disclose a new series of small molecule NPSR antagonists which explore the SAR affecting both calcium and cAMP signaling by the receptor. In general, aromatic substituents at the 10 and 12 positions can positively impact the potency of the molecule, while substitutions at positions 8 and 9 consistently reduce it. We found that elongating the distance between the aromatic ring and the pyrimidine core at

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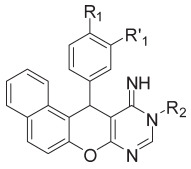
Table 4. Aromatic Scan at the 10 Position



Compound number	R2	R1 and R1'	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
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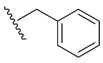
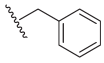
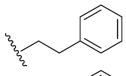
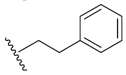
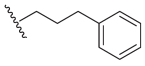
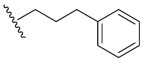
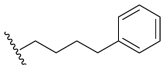
3m		H	3.07	>30
3n		-OMe	19.40	1.38
3o		H	4.87	3.48
3p		-OMe	24.42	>30
3q		H	3.87	>30
3r		-OMe	24.42	>30
3s		H	>100	>30

position 10 yielded cAMP selective compounds. In comparison, introducing an *ortho*-nitrile onto a directly attached aromatic ring at the same position produced a selective antagonist of calcium signaling. The development and use of these selective analogues can be relevant to the study of the involvement of different G coupling pathways in the neurobiology of the NPS receptor.

Methods

Biology

cAMP Assay. Intracellular cAMP level was measured using the LANCE cAMP detection kit (Perkin-Elmer, Waltham, MA). CHO-NPSR cells were seeded at 4 μL/well with 2000 cells in white, tissue culture treated 1536-well plates. After overnight incubation at 37 °C 5% CO_2, 23 nL of compounds were added to each well by a pintool station, followed by the addition of 1 μL of stimulation buffer (1× HBSS buffer, 0.1% BSA, 5 mM HEPES, 500 μM RO-201724, 1.5% Alexa-647 conjugated anti-cAMP antibody stock, and 100 nM NPS) by a BioRAPTR flying reagent dispenser (Beckman Coulter, Fullerton, CA). Cells were incubated at 37 °C for 1 h, and 1 μL of detection reagent (1× detection buffer provided by the manufacturer, 1% TritionX-100, biotin labeled cAMP 1:250 dilution, and Eu-W8044 1:750 dilution) was added. After 2 h of incubation at room temperature, plates were measured using the ViewLux ultraHTS microplate imager (Perkin-Elmer) under the LANCE setting. The results were expressed as a ratio of the acceptor fluorescence intensity (671/8 nm) divided by the donor fluorescence intensity (618/8 nm)

Intracellular Calcium Assay. Intracellular calcium was measured using the BD PBX NW calcium assay kit (BD Bioscience, Rockville, MD). Cells were seeded at 3 μL/well with 1500 cells in black, tissue culture treated, clear bottom 1536-well plates. After overnight incubation at 37 °C and 5% CO_2, cells were loaded with 3 μL of the calcium dye prepared according to the manufacturer's instructions and incubated for another 1 h. Twenty-three nanoliters of compounds prepared in DMSO were then added using a pintool station (Kalypsys, San Diego, CA). Fluorescence was monitored over time as cells were challenged with EC_{90} of agonists in a FDSS-7000 detector (Hamamatsu, Bridgewater, NJ).

Radioligand Binding Assay. The radioligand binding assay was conducted as described before (*2*).Y^{10}-NPS labeled with ^{125}I was obtained from NEN Perkin-Elmer (Boston, MA). In the displacement binding assay, increasing concentrations of unlabeled human NPS or compounds were used to compete with 0.15 nM [^{125}I]Y^{10}-NPS. Nonspecific binding was determined in the presence of 1 μM unlabeled NPS. CHO-NPSR cells were first seeded into 24-well plates and cultured until reaching about 95% confluence. Cells were then washed once with 1 mL of PBS and incubated with radioligand with or without compounds in DMEM medium containing 0.1% bovine serine albumin at room temperature for 90 min. Cells were washed twice with ice-cold PBS and lysed with 0.5 mL of 1 N NaOH. Bound radioactivity was counted in a gamma counter. Data from duplicate experiments were analyzed using GraphPad Prism (GraphPad, San Diego, CA).

Chemical Synthesis

Synthesis of 3-Amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitrile (5)

General Procedure for the Knoevenagel Condensation: Synthesis of 2-Arylidenemalononitrile (***4***). The synthesis of several noncommercially available intermediates 2-arylidenemalononitriles (**4**) was carried using the same reaction conditions described for the following synthesis of 2-benzylidenemalononitrile and with final yields between 85 to 95%.

Piperidine (6.25 g, 73.4 mmol) was added to a stirred solution of benzaldehyde (7.4 g, 73.4 mmol) and malononitrile (4.85 g, 73.4 mmol) in ethanol (50 mL). After stirring overnight, the reaction mixture was concentrated in vacuum prior to the addition of dilute HCl (200 mL, 0.1 M) and the reaction products extracted into dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuum, subsequent recrystallization from dichloromethane/hexane afforded 2-benzylidenemalononitrile (93% yield), which was quickly taken on to the cyclization reaction.

Cyclization Reaction to Obtain 3-Amino-1-aryl-1H-benzo[f]chromene-2-carbonitrile (***5***). The synthesis of all intermediates 3-amino-1-aryl-1*H*-benzo[*f*]chromene-2-carbonitrile (**5**) was carried using the same reaction conditions described for the synthesis of 3-amino-1-phenyl-1*H*-benzo[f]chromene-2-carbonitrile and with final yields between 45 to 94%.

A solution of 2-benzylidenemalononitrile (5.35 g, 34.7 mmol) in ethanol (140 mL) was treated with naphthalen-2-ol (5 g, 34.7 mmol) and piperidine (17.13 mL, 173 mmol). The reaction mixture was refluxed for 45 min until complete precipitation.

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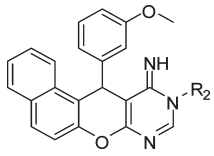
Table 5. Analogues with Aromatic Substitution at Position 10



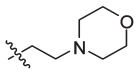
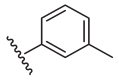
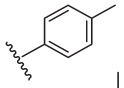
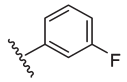
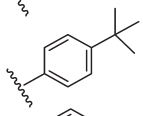
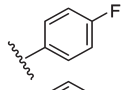
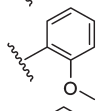
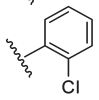
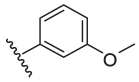
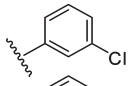
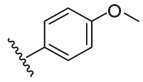
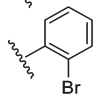
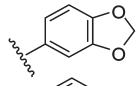
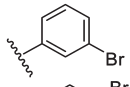
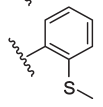
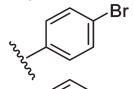
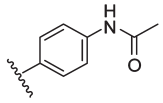
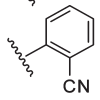
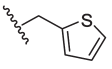
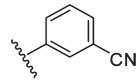
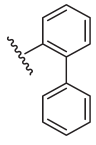
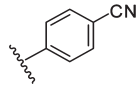
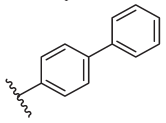
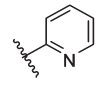
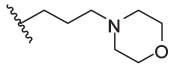
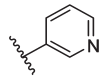
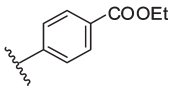
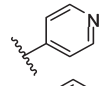
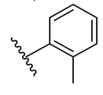
Compound number	R2	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)	Compound number	R2	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
3b		12.24	1.74	3ah		12.24	4.38
3g		2.44	0.55	3ai		12.24	3.48
3t		3.87	0.22	3aj		15.41	5.52
3u		15.41	3.48	3ak		6.13	1.10
3v		12.24	5.51	3al		9.72	5.52
3w		15.41	8.74	3am		9.72	4.38
3x		12.24	5.51	3an		6.13	0.55
3y		19.40	4.38	3ao		7.72	0.44
3z		15.41	2.76	3ap		19.40	5.52
3aa		>100	4.38	3aq		19.40	3.48
3ab		19.40	4.38	3ar		38.71	>30
3ac		5.52	15.41	3as		>100	>30
3ad		30.75	5.51	3at		6.13	1.74
3ae		12.24	2.76	3au		15.41	2.76
3af		19.40	4.38				
3ag		9.72	5.52				

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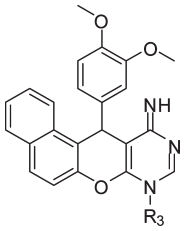
Table 6. Analogues with Modification at the 8 Position



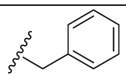
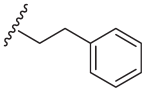
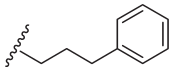
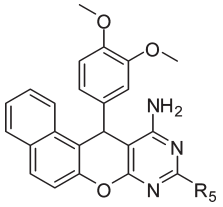
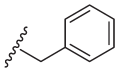
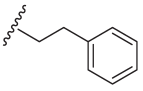
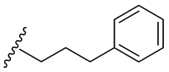
Compound number	R3	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
7a		48.73	>30
7b		>100	>30
7c		24.42	5.51

Table 7. Phenyl Scan at the 9 Position



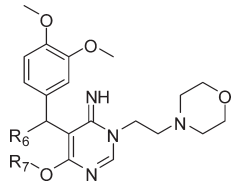
Compound number	R5	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
10a		77.23	>30
10b		48.73	>30
10c		77.23	>30

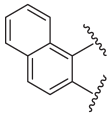
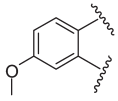
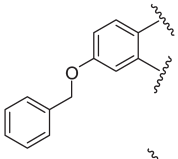
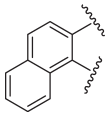
The solid product was collected by filtration and washed with cold ethanol to yield 3-amino-1-phenyl-1*H*-benzo[*f*]chromene-2-carbonitrile (82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.89−7.96 (m, 2 H), 7.81−7.87 (m, 1 H), 7.38−7.47 (m, 2 H), 7.34 (d, J = 9.00 Hz, 1 H), 7.26 (t, J = 7.43 Hz, 2 H), 7.11−7.21 (m, 3 H), 6.96 (s, 2 H), 5.29 (s, 1 H).

Synthesis of 10-Aryl-12-aryl-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-imine 3

Synthesis of (E)-Ethyl N-2-cyano-1-aryl-1H-benzo[f]chromen-3-ylformimidate. The synthesis of all intermediates (*E*)-ethyl *N*-2-cyano-1-aryl-1*H*-benzo[*f*]chromen-3-ylformimidate was carried using the same reaction conditions described for the synthesis of (*E*)-ethyl *N*-2-cyano-1-phenyl-1*H*-benzo[*f*]chromen-3-ylformimidate and with final yields between 73 to 89%.

Table 8. Modifications at the Naphthyl Ring



Compound number	R_6 and R_7	cAMP IC_{50} (uM)	Ca^{2+} IC_{50} (uM)
5a		4.87	1.38
17		6.13	0.69
14a		19.40	11.00
14b		>100	>30
12		48.73	8.74

A mixture of 3-amino-1-phenyl-1*H*-benzo[*f*]chromene-2-carbonitrile (**5d**) (3.5 g, 11.73 mmol), triethyl orthoformate (1.739 g, 11.73 mmol), and acetic anhydride (47 mL) was refluxed for 4 h. The solvent was removed under reduced pressure. The crude from the reaction was titrated with toluene, and the separated solid was filtered and recrystallized from toluene to yield (*E*)-ethyl *N*-2-cyano-1-phenyl-1*H*-benzo[*f*]chromen-3-ylformimidate, which was taken on crude to the ring closure reaction.

Ring Closure of 10-Aryl-12-aryl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3***). The synthesis of all final compounds of 10-aryl-12-aryl-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-imine (**3**) was carried using the same reaction conditions described for the synthesis of 10-(2-morpholinoethyl)-12-(3,4-dimethoxyphenyl)-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-imine (**3a**) and with final yields between 30 to 77%.

LDA (7.24 mL, 14.48 mmol, 2M) was added over a THF (48 mL) solution of (*E*)-ethyl *N*-2-cyano-1-(3,4-dimethoxyphenyl)-1*H*-benzo[*f*]chromen-3-ylformimidate (5 g, 12.06 mmol) and 2-morpholinoethanamine (1.57 g, 12.06 mmol) cooled down to −78 °C under nitrogen atmosphere. The reaction was stirred at room temperature for 16 h. The precipitate was filtered, washed with cold EtOH, and dried under vacuum to yield 0.531 g of clean desired 10-(2-morpholinoethyl)-12-(3,4-dimethoxyphenyl)-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-imine (**3a**) (8.83%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.30 (d, J = 8.61 Hz, 1 H),

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7.94−8.03 (m, 2 H), 7.83−7.93 (m, 3 H), 7.51 (t, J = 7.24 Hz, 1 H), 7.36−7.46 (m, 1 H), 7.23 (d, J = 1.96 Hz, 1 H), 6.85 (dd, J = 8.41, 2.15 Hz, 1 H), 6.72 (d, J = 8.61 Hz, 1 H), 5.81 (s, 1 H), 3.97−4.05 (m, 1 H), 3.84−3.93 (m, 1 H), 3.64 (s, 1 H), 3.57 (s, 1 H), 3.49−3.55 (m, 6 H), 3.45 (t, J = 4.50 Hz, 2 H), 3.11−3.20 (m, 4 H), 2.99−3.00 (m, 1 H), 2.45−2.49 (m, 1 H). HRMS (ESI): m/z calcd for $C_{29}H_{31}N_4O_4$ $[M + H]^+$ 499.2345; found, 499.2351.

10-(2-Morpholinoethyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3b**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.28 (d, J = 8.22 Hz, 1 H), 7.93−8.02 (m, 2 H), 7.83−7.94 (m, 2 H), 7.51 (t, J = 7.04 Hz, 1 H), 7.36−7.47 (m, 2 H), 7.03−7.17 (m, 2 H), 6.95 (d, J = 7.83 Hz, 1 H), 6.63 (dd, J = 7.83, 2.35 Hz, 1 H), 5.72 (s, 1 H), 3.94−4.06 (m, 1 H), 3.88 (dd, J = 13.30, 5.87 Hz, 1 H), 3.61 (s, 3 H), 3.49−3.57 (m, 2 H), 3.40−3.48 (m, 3 H), 3.17 (q, J = 6.52 Hz, 2 H), 2.51−2.60 (m, 1 H), 2.41−2.50 (m, 2 H). HRMS (ESI): m/z calcd for $C_{28}H_{29}N_4O_3$ $[M + H]^+$ 469.2239; found, 469.2240.

10-(2-Morpholinoethyl)-12-(4-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3c**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.25 (d, J = 8.61 Hz, 1 H), 7.95−8.04 (m, 2 H), 7.82−7.92 (m, 2 H), 7.32−7.54 (m, 5 H), 6.72 (d, J = 9.00 Hz, 2 H), 5.83 (s, 1 H), 3.95−4.08 (m, 1 H), 3.89 (dd, J = 13.30, 5.87 Hz, 1 H), 3.58 (s, 3 H), 3.49−3.56 (m, 2 H), 3.41−3.48 (m, 3 H), 3.09−3.22 (m, 2 H), 2.50−2.61 (m, 1 H), 2.41−2.50 (m, 2 H). HRMS (ESI): m/z calcd for $C_{28}H_{29}N_4O_3$ $[M + H]^+$ 469.2239; found, 469.2233.

10-(2-Morpholinoethyl)-12-phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3d**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.26 (d, J = 8.61 Hz, 1 H), 7.95−8.02 (m, 2 H), 7.82−7.93 (m, 2 H), 7.34−7.55 (m, 5 H), 7.16 (t, J = 7.63 Hz, 2 H), 7.04 (t, J = 7.43 Hz, 1 H), 5.89 (s, 1 H), 3.99 (dt, J = 13.60, 5.53 Hz, 1 H), 3.80−3.93 (m, 1 H), 3.48−3.56 (m, 3 H), 3.39−3.49 (m, 2 H), 3.10−3.22 (m, 2 H), 2.49−2.60 (m, 1 H), 2.40−2.49 (m, 2 H). HRMS (ESI): m/z calcd for $C_{27}H_{27}N_4O_2$ $[M + H]^+$ 439.2134; found, 439.2133.

10-Phenyl-12-phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3e**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 10.66 (br. s., 1 H), 8.29 (d, J = 8.61 Hz, 1 H), 8.16 (s, 1 H), 7.79−7.92 (m, 2 H), 7.59−7.76 (m, 5 H), 7.40−7.59 (m, 4 H), 7.34 (d, J = 7.83 Hz, 1 H), 7.23−7.30 (m, 2 H), 7.14−7.22 (m, 1 H), 6.46 (s, 1 H). HRMS (ESI): m/z calcd for $C_{27}H_{20}N_3O$ $[M + H]^+$ 402.1606; found, 402.1611.

10-Phenyl-12-(2-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3f**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 10.39 (br. s., 1 H), 8.07 (s, 1 H), 7.82 (d, J = 9.00 Hz, 1 H), 7.75−7.80 (m, 1 H), 7.66−7.73 (m, 1 H), 7.59 (br. s., 3 H), 7.35−7.46 (m, 3 H), 7.26 (br. s., 1 H), 7.19 (s, 1 H), 7.09−7.17 (m, 1 H), 6.89−6.97 (m, 2 H), 6.76 (t, J = 7.63 Hz, 1 H), 6.10 (s, 1 H), 4.06 (s, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{22}N_3O_2$ $[M + H]^+$ 432.1712; found, 432.1712.

10-Phenyl-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3g**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.26 (d, J = 8.22 Hz, 1 H), 8.04 (s, 1 H), 7.68−7.79 (m, 2 H), 7.56 (br. s., 3 H), 7.45 (t, J = 7.24 Hz, 1 H), 7.31−7.40 (m, 3 H), 7.27 (s, 2 H), 7.01−7.10 (m, 2 H), 6.58−6.65 (m, 1 H), 6.44 (s, 1 H), 3.64 (s, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{22}N_3O_2$ $[M + H]^+$ 432.1712; found, 432.1714.

10-Phenyl-12-(benzo[d][1,3]dioxole)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3h**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 11.16 (br.s, 1 H), 8.20 (d, J = 8.61 Hz, 1 H), 8.05 (s, 1 H), 7.74 (dd, J = 11.35, 8.61 Hz, 2 H), 7.59 (br. s., 3 H), 7.45 (t, J = 7.63 Hz, 1 H), 7.24−7.41 (m, 4 H), 7.13 (d, J = 7.83 Hz, 1 H), 6.98 (s, 1 H), 6.56 (d, J = 8.22 Hz, 1 H), 6.43 (s, 1 H), 5.73 (s, 1 H), 5.65 (s, 1 H). HRMS (ESI): m/z calcd for $C_{28}H_{20}N_3O_3$ $[M + H]^+$ 446.1504; found, 446.1504.

10-Phenyl-12-(2,3-dihydrobenzofuran-5-yl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3i**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.20 (d, J = 8.61 Hz, 1 H), 8.05 (s, 1 H), 7.64−7.79 (m, 3 H), 7.57 (br. s., 3 H), 7.22−7.46 (m, 7 H), 6.53 (d, J = 8.22 Hz, 1 H), 6.37 (s, 1 H), 4.25−4.43 (m, 2 H), 2.90−3.06 (m, 2 H). HRMS (ESI): m/z calcd for $C_{29}H_{22}N_3O_2$ $[M + H]^+$ 444.1712; found, 444.1711.

10-Phenyl-12-(3,4-diethoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3j**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 1 H), 8.21 (d, J = 8.61 Hz, 1 H), 7.95−8.09 (m, 2 H), 7.59−7.74 (m, 6 H), 7.45−7.57 (m, 2 H), 7.28 (d, J = 1.96 Hz, 1 H), 6.74−6.87 (m, 3 H), 6.29 (s, 1 H), 3.79−4.00 (m, 4 H), 1.15−1.30 (m, 6 H). HRMS (ESI): m/z calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$ 490.2125; found, 490.2130.

10-Phenyl-12-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3k**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (s, 1 H), 8.20 (d, J = 8.61 Hz, 2 H), 7.96−8.07 (m, 2 H), 7.61−7.74 (m, 6 H), 7.53 (td, J = 7.53, 0.98 Hz, 1 H), 6.98−7.05 (m, 1 H), 6.91 (dd, J = 8.41, 2.15 Hz, 1 H), 6.69−6.77 (m, 1 H), 6.29 (s, 1 H), 4.04−4.17 (m, 4 H). HRMS (ESI): m/z calcd for $C_{29}H_{22}N_3O_3$ $[M + H]^+$ 460.1656; found, 460.1664.

10-Phenyl-12-(2,3-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3l**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.33−8.97 (m, 1 H), 8.08 (s, 1 H), 7.94 (d, J = 8.22 Hz, 1 H), 7.77 (dd, J = 17.61, 8.61 Hz, 2 H), 7.55 (br. s., 3 H), 7.31−7.46 (m, 4 H), 7.22 (d, J = 3.91 Hz, 1 H), 6.99 (d, J = 7.43 Hz, 1 H), 6.83 (t, J = 8.02 Hz, 1 H), 6.68 (d, J = 7.04 Hz, 1 H), 6.13 (s, 1 H), 3.84 (s, 3 H), 3.69 (s, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_3$ $[M + H]^+$ 462.1817; found, 462.1818.

10-Benzyl-12-phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3m**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.04 (d, J = 8.22 Hz, 1 H), 7.75−7.83 (m, 3 H), 7.42−7.50 (m, 4 H), 7.28−7.41 (m, 5 H), 7.21−7.27 (m, 4 H), 7.13 (t, J = 7.24 Hz, 1 H), 5.53 (s, 1 H), 5.27−5.36 (m, 1 H), 4.87 (d, J = 14.87 Hz, 1 H). HRMS (ESI): m/z calcd for $C_{28}H_{22}N_3O$ $[M + H]^+$ 416.1763; found, 416.1754.

10-Benzyl-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3n**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.07 (br. s., 1 H), 8.88 (s, 1 H), 8.17 (d, J = 8.41 Hz, 1 H), 7.99 (dd, J = 14.87, 8.61 Hz, 2 H), 7.58−7.66 (m, 2 H), 7.45−7.55 (m, 1 H), 7.26−7.36 (m, 3 H), 7.16−7.25 (m, 3 H), 6.82−6.90 (m, 1 H), 6.76−6.82 (m, 1 H), 6.19 (s, 1 H), 5.45 (q, 2 H), 3.61 (d, 6 H). HRMS (ESI): m/z calcd for $C_{30}H_{26}N_3O_3$ $[M + H]^+$ 476.1974; found, 476.1978.

10-Phenethyl-12-phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3o**). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.08 (d, J = 8.61 Hz, 1 H), 7.77 (t, J = 8.02 Hz, 2 H), 7.34−7.54 (m, 6 H), 7.16−7.30 (m, 6 H), 7.13 (t, J = 7.43 Hz, 1 H), 6.94−7.01 (m, 2 H), 5.54 (s, 1 H), 4.16 (dt, J = 13.21,

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6.50 Hz, 1 H), 3.98 (dt, J = 13.40, 6.80 Hz, 1 H), 2.93−3.14 (m, 2 H). LCMS (4 min method): (electrospray + ve), m/z 430.1 $(MH)^+$. HPLC: t_R = 3.20 min; UV_{254} = 100%.

10-Phenethyl-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3p***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (s, 1 H), 8.32 (s, 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 7.99 (t, J = 9.19 Hz, 2 H), 7.65 (ddd, J = 8.41, 7.04, 1.37 Hz, 1 H), 7.57 (d, J = 9.00 Hz, 1 H), 7.48−7.54 (m, 1 H), 7.26 (d, J = 1.37 Hz, 1 H), 7.10−7.21 (m, 3 H), 6.90−6.97 (m, 2 H), 6.84−6.89 (m, 2 H), 6.24 (s, 1 H), 4.34−4.57 (m, 2 H), 3.68 (s, 3 H), 3.61 (s, 3 H), 2.97 (t, J = 6.94 Hz, 2 H). HRMS (ESI): m/z calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$ 490.2130; found, 490.2135.

10-Phenylpropyl-12-phenyl-12H-naphtho[1′,2′:5,6]pyrano-[2,3-d]pyrimidin-11-imine (***3q***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.06 (d, J = 8.22 Hz, 1 H), 7.77 (dd, J = 8.61, 5.09 Hz, 2 H), 7.63 (s, 1 H), 7.33−7.52 (m, 6 H), 7.06−7.32 (m, 7 H), 5.50 (s, 1 H), 5.28 (s, 1 H), 3.96−4.05 (m, 1 H), 3.64−3.79 (m, 1 H), 2.65 (t, J = 7.43 Hz, 2 H), 2.06−2.18 (m, 2 H). HRMS (ESI): m/z calcd for $C_{30}H_{26}N_3O$ $[M+H]^+$ 444.2076; found, 444.2076.

10-Phenylpropyl-12-(3,4-dimethoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3r***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (br. s., 1 H), 8.74 (s, 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 7.92−8.06 (m, 2 H), 7.56−7.69 (m, 2 H), 7.47−7.55 (m, 1 H), 7.26 (d, J = 2.15 Hz, 1 H), 7.15−7.23 (m, 2 H), 7.02−7.14 (m, 3 H), 6.81−6.87 (m, 1 H), 6.75−6.81 (m, 1 H), 6.19 (s, 1 H), 4.23 (t, J = 7.83 Hz, 2 H), 3.66 (s, 3 H), 3.59 (s, 3 H), 2.54−2.65 (m, 2 H), 1.91−2.04 (m, 2 H). HRMS (ESI): m/z calcd for $C_{32}H_{30}N_3O_3$ $[M + H]^+$ 504.2287; found, 504.2293.

10-Phenylbutyl-12-phenyl-12H-naphtho[1′,2′:5,6]pyrano-[2,3-d]pyrimidin-11-imine (***3s***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.06 (d, J = 8.61 Hz, 1 H), 7.78 (dd, J = 8.41, 6.46 Hz, 2 H), 7.68 (s, 1 H), 7.35−7.52 (m, 6 H), 7.07−7.30 (m, 7 H), 5.48−5.54 (m, 1 H), 5.07 (s, 1 H), 4.03 (ddd, J = 13.60, 7.92, 5.87 Hz, 1 H), 3.65−3.77 (m, 1 H), 2.57−2.67 (m, 2 H), 1.71−1.87 (m, 2 H), 1.64 (quin, J = 7.73 Hz, 2 H). HRMS (ESI): m/z calcd for $C_{31}H_{28}N_3O$ $[M + H]^+$ 458.2232; found, 458.2235.

10-(3-Fluorophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3t***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (s, 1 H), 8.70 (s, 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 7.95−8.08 (m, 2 H), 7.83 (br. s., 2 H), 7.60−7.70 (m, 2 H), 7.48−7.58 (m, 3 H), 7.12−7.23 (m, 2 H), 6.97 (dd, J = 7.34, 1.27 Hz, 1 H), 6.70−6.78 (m, 1 H), 6.35 (s, 1 H), 3.60−3.67 (m, 3 H). LCMS: (electrospray + ve), m/z 448.1 $(MH)^+$. HPLC: t_R = 4.69 min; UV_{254} = 100%.

10-(4-Fluorophenyl)-12-(3-methoxyphenyl)-12H- naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3u***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (br. s. One H), 8.73 (s, 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 8.02 (dd, J = 18.78, 8.61 Hz, 2 H), 7.69−7.81 (m, 2 H), 7.61−7.69 (m, 2 H), 7.46−7.59 (m, 3 H), 7.10−7.22 (m, 2 H), 6.94−7.00 (m, 1 H), 6.69−6.78 (m, 1 H), 6.34 (s, 1 H), 3.60−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{21}N_3O_2$ $[M + H]^+$ 450.1618; found, 450.1617.

10-(2-Chlorophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3v***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26−9.39 (m, 1 H), 8.81−8.91 (m, 2 H), 8.77 (br. s., 1 H), 8.52 (br. s., 1 H), 8.11−8.23 (m, 1 H), 7.91−8.09 (m, 2 H), 7.72 (br. s., 1 H), 7.61−7.69 (m, 2 H), 7.49−7.58 (m, 1 H), 7.10−7.23 (m, 2 H), 6.95−7.02 (m, 1 H), 6.75 (dd, J = 8.22, 2.15 Hz, 1 H), 6.35 (s, 1 H), 3.62−3.68 (m, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{21}N_3O_2Cl$ $[M + H]^+$ 466.1322; found, 466.1318.

10-(3-Chlorophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3w***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.27 (br. s., 1 H), 8.76 (d, J = 6.85 Hz, 1 H), 8.38 (br. s., 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 8.02 (dd, J = 18.49, 8.51 Hz, 2 H), 7.76−7.81 (m, 1 H), 7.59−7.75 (m, 4 H), 7.48−7.56 (m, 1 H), 7.10−7.22 (m, 2 H), 6.93−7.02 (m, 1 H), 6.75 (dd, J = 8.02, 2.15 Hz, 1 H), 6.35 (d, J = 6.06 Hz, 1 H), 3.60−3.66 (m, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{21}N_3O_2Cl$ $[M + H]^+$ 466.1322; found, 466.1318.

10-(2-Bromophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3x***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.45 (br. s., 1 H), 8.83 (br. s., 1 H), 8.16 (d, J = 19.37 Hz, 1 H), 7.99 (br. s., 3 H), 7.83 (br. s., 1 H), 7.65 (br. s., 3 H), 7.52 (br. s., 1 H), 7.16 (br. s., 2 H), 7.00 (br. s., 1 H), 6.88 (br. s., 1 H), 6.76 (br. s., 1 H), 6.39 (br. s., 1 H), 3.60−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{21}N_3O_2Br$ $[M + H]^+$ 510.0817; found, 510.0810.

10-(3-Bromophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3y***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.27 (br. s., 1 H), 8.76 (d, J = 6.85 Hz, 1 H), 8.20 (d, J = 8.61 Hz, 1 H), 7.94−8.08 (m, 3 H), 7.87−7.93 (m, 1 H), 7.59−7.70 (m, 4 H), 7.48−7.57 (m, 1 H), 7.10−7.22 (m, 2 H), 6.97 (d, J = 6.65 Hz, 1 H), 6.75 (dd, J = 8.02, 2.15 Hz, 1 H), 6.34 (d, J = 5.09 Hz, 1 H), 3.61−3.68 (m, 3 H). HRMS (ESI): m/z calcd for $C_{28}H_{21}N_3O_2Br$ $[M + H]^+$ 510.0817; found, 510.0819.

10-(4-Bromophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3z***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.29 (br. s., 1 H), 8.71−8.82 (m, 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 8.02 (dd, J = 19.27, 8.51 Hz, 2 H), 7.71 (br. s., 2 H), 7.46−7.69 (m, 5 H), 7.09−7.22 (m, 2 H), 6.94−7.02 (m, 1 H), 6.75 (dd, J = 7.92, 2.25 Hz, 1 H), 6.35 (br. s., 1 H), 3.60−3.67 (m, 3 H). LCMS: (electrospray + ve), m/z 511.9 $(MH)^+$. HPLC: t_R = 3.23 min; UV_{254} = 90%.

10-(2-Cyanophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3aa***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.15 (s, 1 H), 9.98−10.08 (m, 1 H), 8.82 (d, J = 8.61 Hz, 1 H), 8.55 (dd, J = 8.31, 1.27 Hz, 1 H), 8.18 (ddd, J = 8.75, 7.29, 1.37 Hz, 1 H), 8.09 (d, J = 9.00 Hz, 1 H), 7.92−8.05 (m, 3 H), 7.71 (d, J = 9.00 Hz, 1 H), 7.63 (ddd, J = 8.36, 6.99, 1.27 Hz, 1 H), 7.52 (ddd, J = 8.12, 6.94, 0.98 Hz, 1 H), 7.17−7.24 (m, 1 H), 7.10 (t, J = 8.02 Hz, 1 H), 6.97 (d, J = 8.41 Hz, 1 H), 6.63−6.70 (m, 1 H), 6.37 (s, 1 H), 3.62−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{21}N_4O_2$ $[M + H]^+$ 457.1664; found, 457.1665.

10-(3-Cya[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3ab***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.32 (br. s., 1 H), 8.71−8.80 (m, 1 H), 8.17−8.23 (m, 2 H), 7.96−8.08 (m, 3 H), 7.93 (br. s., 1 H), 7.61−7.70 (m, 2 H), 7.48−7.57 (m, 2 H), 7.10−7.25 (m, 2 H), 6.91−7.03 (m, 1 H), 6.75 (d, J = 8.41 Hz, 1 H), 6.34 (br. s., 1 H), 3.61−3.69 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{21}N_4O_2$ $[M + H]^+$ 457.1664; found, 457.1664.

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10-(4-Cyanophenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3ac**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (br. s., 1 H), 8.74−8.80 (m, 1 H), 8.19 (m, 3 H), 7.84−8.08 (m, 4 H), 7.61−7.70 (m, 2 H), 7.47−7.58 (m, 1 H), 7.09−7.24 (m, 2 H), 6.92−7.01 (m, 1 H), 6.72−6.79 (m, 1 H), 6.34 (s, 1 H), 3.59−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{21}N_4O_2$ $[M + H]^+$ 457.1664; found, 457.1661.

10-(2-Pyridyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (**3ad**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.43 (s, 1 H), 8.35−8.41 (m, 2 H), 8.13 (d, J = 8.41 Hz, 1 H), 7.94 (t, J = 9.00 Hz, 2 H), 7.74−7.82 (m, 1 H), 7.51−7.61 (m, 2 H), 7.41−7.48 (m, 1 H), 7.16−7.21 (m, 1 H), 7.04−7.13 (m, 2 H), 6.89−6.95 (m, 1 H), 6.71 (s, 1 H), 6.59−6.66 (m, 1 H), 3.59 (s, 3 H). LCMS: (electrospray + ve), m/z 433.1 $(MH)^+$. HPLC: t_R = 5.01 min; UV_{254} = 90%.

10-(3-Pyridyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (**3ae**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.31 (br. s., 1 H), 8.83−8.91 (m, 1 H), 8.77 (br. s., 1 H), 8.52 (br. s., 1 H), 8.12−8.23 (m, 2 H), 7.91−8.08 (m, 2 H), 7.72 (br. s., 1 H), 7.60−7.69 (m, 2 H), 7.48−7.58 (m, 1 H), 7.12−7.22 (m, 2 H), 6.94−7.03 (m, 1 H), 6.75 (dd, J = 8.22, 2.15 Hz, 1 H), 6.35 (s, 1 H), 3.61−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{27}H_{21}N_4O_2$ $[M + H]^+$ 433.1664; found, 433.1666.

10-(4-Pyridyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (**3af**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.40 (br. s., 1 H), 8.63 (s, 1 H), 8.58 (d, J = 7.04 Hz, 1 H), 8.11−8.23 (m, 2 H), 7.93−8.04 (m, 2 H), 7.55−7.67 (m, 3 H), 7.44−7.53 (m, 1 H), 7.02−7.11 (m, 2 H), 6.85−6.93 (m, 1 H), 6.72−6.79 (m, 1 H), 6.57−6.65 (m, 2 H), 3.53−3.59 (m, 3 H). HRMS (ESI): m/z calcd for $C_{27}H_{21}N_4O_2$ $[M + H]^+$ 433.1664; found, 433.1665.

10-(2-Tolyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (**3ag**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.39 (br. s., 1 H), 8.71 (d, J = 7.63 Hz, 1 H), 8.20 (d, J = 8.61 Hz, 2 H), 7.94−8.10 (m, 2 H), 7.43−7.70 (m, 5 H), 7.14−7.23 (m, 2 H), 6.88−7.03 (m, 2 H), 6.70−6.78 (m, 1 H), 6.40 (d, J = 18.98 Hz, 1 H), 3.61−3.68 (m, 3 H), 2.10 (s, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_2$ $[M + H]^+$ 446.1868; found, 446.1863.

10-(3-Tolyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (**3ah**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (br. s., 1 H), 8.72 (s, 1 H), 8.21 (d, J = 8.41 Hz, 1 H), 8.02 (dd, J = 17.51, 8.31 Hz, 2 H), 7.60−7.68 (m, 2 H), 7.38−7.60 (m, 5 H), 7.11−7.21 (m, 2 H), 6.98 (d, J = 7.43 Hz, 1 H), 6.74 (dd, J = 8.02, 2.15 Hz, 1 H), 6.36 (s, 1 H), 3.59−3.68 (m, 3 H), 2.33−2.42 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_2$ $[M + H]^+$ 446.1868; found, 446.1867.

10-(4-Tolyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (**3ai**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.23 (br. s., 1 H), 8.69 (s, 1 H), 8.20 (d, J = 8.22 Hz, 2 H), 7.95−8.07 (m, 2 H), 7.59−7.69 (m, 2 H), 7.43−7.56 (m, 4 H), 7.11−7.21 (m, 2 H), 6.95−7.01 (m, 1 H), 6.70−6.78 (m, 1 H), 6.36 (s, 1 H), 3.60−3.67 (m, 3 H), 2.41 (s, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_2$ $[M + H]^+$ 446.1868; found, 446.1865.

10-(4-tert-Butylphenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3aj**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.46 (br. s., 1 H), 8.90 (s, 1 H), 8.14−8.22 (m, 1 H), 7.95−8.09 (m, 2 H), 7.74−7.85 (m, 1 H), 7.59−7.70 (m, 3 H), 7.43−7.58 (m, 3 H), 7.11−7.21 (m, 3 H), 6.68−6.78 (m, 1 H), 6.36−6.43 (m, 1 H), 3.60−3.68 (m, 3 H), 1.13−1.21 (m, 3 H), 0.81−0.88 (m, 6 H). HRMS (ESI): m/z calcd for $C_{32}H_{30}N_3O_2$ $[M + H]^+$ 488.2338; found, 488.2337.

10-2-Methoxyphenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3ak**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (br. s., 1 H), 8.68−8.74 (m, 1 H), 8.16−8.24 (m, 1 H), 7.96−8.08 (m, 2 H), 7.58−7.72 (m, 3 H), 7.47−7.56 (m, 1 H), 7.36 (ddd, J = 13.60, 8.51, 0.98 Hz, 1 H), 7.09−7.27 (m, 3 H), 6.94−7.02 (m, 1 H), 6.84−6.91 (m, 1 H), 6.71−6.80 (m, 1 H), 6.35−6.43 (m, 1 H), 3.59−3.68 (m, 6 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_3$ $[M + H]^+$ 462.1817; found, 462.1815.

10-3-Methoxyphenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3al**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (br. s., 1 H), 8.74 (d, J = 1.96 Hz, 1 H), 8.28 (br. s., 1 H), 8.21 (d, J = 8.41 Hz, 1 H), 7.46−7.69 (m, 4 H), 7.37 (m, 1 H), 7.09−7.31 (m, 5 H), 6.98 (br. s., 1 H), 6.74 (dd, J = 8.02, 2.15 Hz, 1 H), 6.32−6.40 (m, 1 H), 3.78 (s, 3 H), 3.61−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_3$ $[M + H]^+$ 462.1817; found, 462.1812.

10-4-Methoxyphenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3am**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (br. s., 1 H), 8.69 (s, 1 H), 8.20 (d, J = 8.22 Hz, 2 H), 7.96−8.07 (m, 2 H), 7.60−7.68 (m, 3 H), 7.46−7.60 (m, 2 H), 7.11−7.25 (m, 3 H), 6.93−7.00 (m, 1 H), 6.71−6.78 (m, 1 H), 6.35 (s, 1 H), 3.81−3.86 (m, 3 H), 3.60−3.66 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_3$ $[M + H]^+$ 462.1817; found, 462.1814.

10-(Benzo[d][1,3]dioxole)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3an**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.25 (br. s., 1 H), 8.71 (d, J=3.33 Hz, 1 H), 8.24−8.36 (m, 1 H), 8.19 (d, J = 8.61 Hz, 1 H), 7.96−8.07 (m, 2 H), 7.59−7.69 (m, 2 H), 7.48−7.56 (m, 1 H), 7.30 (d, J = 1.96 Hz, 1 H), 7.06−7.24 (m, 3 H), 6.97 (d, J = 8.41 Hz, 1 H), 6.74 (d, J = 8.61 Hz, 1 H), 6.34 (d, J = 7.43 Hz, 1 H), 6.12−6.23 (m, 2 H), 3.59−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{22}N_3O_4$ $[M+H]^+$ 476.1610; found, 476.1614.

10-(2-(Methylthio)phenyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3ao**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.40 (br. s., 1 H), 8.74 (s, 1 H), 8.42 (br. s., 1 H), 8.20 (t, J = 9.29 Hz, 1 H), 7.96−8.09 (m, 2 H), 7.59−7.74 (m, 5 H), 7.41−7.58 (m, 3 H), 7.11−7.22 (m, 2 H), 6.99 (dd, J = 7.83, 0.78 Hz, 1 H), 6.87 (dd, J = 7.34, 1.27 Hz, 1 H), 6.75 (dd, J = 7.92, 2.25 Hz, 1 H), 6.40 (d, J = 2.74 Hz, 1 H), 3.58−3.68 (m, 3 H), 2.29−2.36 (m, 3 H). HRMS (ESI): m/z calcd for $C_{29}H_{24}N_3O_2S$ $[M + H]^+$ 478.1589; found, 478.1589.

10-(4-N-Acetylphenyl)-12-(3-methoxyphenyl)-12H-naphtho-[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3ap**). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.69 (s, 1 H), 8.21 (d, J = 8.41 Hz, 1 H), 8.02 (dd, J = 18.19, 8.61 Hz, 2 H), 7.61−7.73 (m, 4 H), 7.47−7.59 (m, 3 H), 7.12−7.22 (m, 2 H), 6.93−7.01 (m, 1 H), 6.69−6.79 (m, 1 H), 6.38 (s, 1 H), 4.06 (d, J=5.28 Hz, 1 H), 3.64 (s, 3 H), 3.13 (d, J= 5.09 Hz, 3 H). LCMS: (electrospray +ve), m/z 488.2 $(MH)^+$. HPLC: t_R = 5.40 min, UV_{254} = 100%.

10-(Thiophen-2-ylmethyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (**3aq**). ^{1}H NMR

(400 MHz, DMSO-d_6) δ ppm 9.29 (br. s., 1 H), 8.93 (s, 1 H), 8.16 (d, J = 8.61 Hz, 1 H), 7.94−8.05 (m, 2 H), 7.55−7.68 (m, 3 H), 7.50 (t, J = 7.34 Hz, 1 H), 7.23 (d, J = 2.74 Hz, 1 H), 7.09−7.18 (m, 2 H), 7.00 (dd, J = 5.09, 3.52 Hz, 1 H), 6.92 (d, J = 8.41 Hz, 1 H), 6.71 (dd, J = 8.12, 2.05 Hz, 1 H), 6.26 (s, 1 H), 5.62 (s, 2 H), 3.58−3.67 (m, 3 H). HRMS (ESI): m/z calcd for $C_{27}H_{22}N_3O_2S$ $[M + H]^+$ 452.1432; found, 452.1432.

10-(Biphenyl-2-yl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3ar***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (br. s., 1 H), 8.77 (s, 1 H), 8.49 (br. s., 1 H), 8.08−8.15 (m, 1 H), 7.94−8.05 (m, 2 H), 7.72−7.84 (m, 2 H), 7.55−7.68 (m, 3 H), 7.44−7.54 (m, 1 H), 7.28−7.35 (m, 1 H), 7.19−7.27 (m, 1 H), 7.15 (t, J = 8.02 Hz, 1 H), 7.00−7.10 (m, 1 H), 6.85−6.98 (m, 3 H), 6.79 (dd, J = 8.22, 2.35 Hz, 1 H), 6.66−6.75 (m, 1 H), 6.25 (s, 1 H), 3.64−3.69 (m, 3 H). HRMS (ESI): m/z calcd for $C_{34}H_{26}N_3O_2$ $[M + H]^+$ 508.2025; found, 508.2018.

10-(Biphenyl-4-yl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3as***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.30 (br. s., 1 H), 8.75−8.81 (m, 1 H), 8.31−8.43 (m, 1 H), 8.22 (d, J = 8.41 Hz, 1 H), 7.94−8.08 (m, 4 H), 7.71−7.80 (m, 4 H), 7.60−7.69 (m, 2 H), 7.47−7.56 (m, 2 H), 7.39−7.46 (m, 1 H), 7.13−7.22 (m, 2 H), 6.99 (dd, J = 7.73, 0.88 Hz, 1 H), 6.70−6.79 (m, 1 H), 6.39 (s, 1 H), 3.61−3.68 (m, 3 H). HRMS (ESI): m/z calcd for $C_{34}H_{26}N_3O_2$ $[M + H]^+$ 508.2025; found, 508.2021.

10-(2-Morpholinopropyl)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3at***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (s, 1 H), 8.20 (d, J = 8.41 Hz, 1 H), 8.01 (dd, J = 16.82, 8.61 Hz, 2 H), 7.59−7.69 (m, 2 H), 7.52 (t, J = 7.53 Hz, 1 H), 7.12−7.20 (m, 2 H), 6.91−6.98 (m, 1 H), 6.73 (dd, J = 8.02, 2.15 Hz, 1 H), 6.29 (s, 1 H), 4.23 (t, J = 7.04 Hz, 2 H), 3.93 (br. s., 2 H), 3.65 (s, 3 H), 3.58 (br. s., 2 H), 2.83−3.23 (m, 8 H). HRMS (ESI): m/z calcd for $C_{29}H_{31}N_4O_3$ $[M + H]^+$ 483.2391; found, 483.2396.

10-(4-Ethylbenzoate)-12-(3-methoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***3au***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.28 (br. s., 1 H), 8.76 (s, 1 H), 8.20 (d, J = 8.61 Hz, 3 H), 7.97−8.08 (m, 2 H), 7.81 (t, J = 8.12 Hz, 2 H), 7.60−7.69 (m, 2 H), 7.48−7.57 (m, 1 H), 7.11−7.22 (m, 2 H), 6.94−7.01 (m, 1 H), 6.68−6.80 (m, 1 H), 6.35 (s, 1 H), 4.31−4.43 (m, 2 H), 3.60−3.66 (m, 3 H), 1.27−1.37 (m, 3 H). HRMS (ESI): m/z calcd for $C_{31}H_{26}N_3O_4$ $[M + H]^+$ 504.1923; found, 504.1924.

Synthesis of 12-(3,4-Dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-amine (***6a***). Compound **5a** (200 mg, 0.558 mmol, 1.0 equiv) was taken up in formamide (8 mL) and heated to 220 °C for 20 min. Upon completion, we concentrated the mixture and taken up in ethyl acetate and water. The layers were separated, and the water layer was extracted with ethyl acetate. The combined organic extracts were then washed with water and brine, then dried over Na_2SO_4, and concentrated to give a brown solid, which was chromatographed with 0−7% MeOH/DCM gradient elution to give 12-(3,4-dimethoxyphenyl)-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-amine (**6a**) (124 mg, 57.7% yield) as a tan solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.31 (s, 1 H), 8.06 (d, J = 8.41 Hz, 1 H), 7.79 (dd, J = 8.31, 4.01 Hz, 2 H), 7.43−7.53 (m, 2 H), 7.39 (t, J = 7.53 Hz, 1 H), 7.09 (dd, J = 8.02, 1.96 Hz, 1 H), 6.76 (d, J = 8.02 Hz, 1 H), 6.71 (d, J = 1.96 Hz, 1 H), 5.46 (s, 1 H), 5.11 (s, 2 H), 3.78 (s, 3 H), 3.68 (s, 3 H).

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-amine (***6d***). A mixture of 3-amino-1-phenyl-1*H*-benzo[*f*]chromene-2-carbonitrile (**5d**) (3.5 g, 11.73 mmol) and formamide was refluxed for 3 h. The solvent was removed under vacuum, and the solid was recrystallized from toluene to yield 3.2 g of pure product (84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.21 (d, J = 8.22 Hz, 1 H), 8.11 (s, 1 H), 7.90−7.98 (m, 2 H), 7.55−7.62 (m, 1 H), 7.40−7.54 (m, 4 H), 7.15−7.25 (m, 4 H), 7.04−7.13 (m, 1 H), 6.05 (s, 1 H). HRMS (ESI): m/z calcd for $C_{21}H_{16}N_3O$ $[M + H]^+$ 326.1293; found, 326.1293.

Synthesis of 8-Aryl-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-imine (***7a***−***7c***). To compound **6.1** (20 mg, 0.052 mmol) in acetonitrile (1 mL) was added the bromide (0.078 mmol, 1.5 equiv). The mixture was heated to 90 °C in a sealed tube for 4 h. The mixture was dried down and taken up in methanol and purified via HPLC to give products **7a** (8:1 ratio **7a**:**3n**), **7b** (8:1 ratio **7b**:**3p**), and **7c** (3:1 ratio **7c**:**3r**) with yields from 20 to 50%.

8-Benzyl-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (***7a***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.36 (s, 1 H), 9.03 (s, 1 H), 8.78 (s, 1 H), 8.14 (d, J = 8.41 Hz, 1 H), 7.99 (dd, J = 18.00, 8.22 Hz, 2 H), 7.56−7.67 (m, 3 H), 7.48−7.55 (m, 1 H), 7.39−7.46 (m, 2 H), 7.31−7.38 (m, 1 H), 7.00 (dd, J = 8.31, 2.05 Hz, 1 H), 6.87 (d, J = 2.15 Hz, 1 H), 6.77 (d, J = 8.41 Hz, 1 H), 6.03 (s, 1 H), 5.56 (d, J = 1.96 Hz, 2 H), 3.59 (s, 3 H), 3.44 (s, 3 H). HRMS (ESI): m/z calcd for $C_{30}H_{26}N_3O_3$ $[M + H]^+$ 476.1974; found, 476.1974.

8-Phenethyl-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (***7b***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (s, 1 H), 8.68 (br. s., 1 H), 8.59 (s, 1 H), 8.14 (d, J = 8.22 Hz, 1 H), 8.02 (dd, J = 18.88, 8.31 Hz, 2 H), 7.66 (d, J = 8.80 Hz, 2 H), 7.48−7.57 (m, 1 H), 7.29 (d, J = 7.43 Hz, 5 H), 6.74−6.82 (m, 1 H), 6.71 (d, J = 9.98 Hz, 1 H), 6.00 (s, 1 H), 4.60 (m, 2H), 3.68 (s, 3 H), 3.62 (s, 3 H), 3.14−3.29 (m, 2 H). HRMS (ESI): m/z calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$ 490.2130; found, 490.2129.

8-(3-Phenylpropyl)-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidin-11-imine (***7c***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.22 (s, 1 H), 8.72 (s, 1 H), 8.65 (s, 1 H), 8.15 (d, J = 8.61 Hz, 1 H), 7.94−8.08 (m, 2 H), 7.65 (ddd, J = 8.41, 7.04, 1.17 Hz, 1 H), 7.48−7.57 (m, 2 H), 7.19−7.27 (m, 3 H), 7.13−7.18 (m, 2 H), 6.93 (dd, J = 8.31, 2.25 Hz, 1 H), 6.78 (d, J = 8.61 Hz, 1 H), 6.00 (s, 1 H), 4.25−4.46 (m, 2 H), 3.56−3.64 (m, 6 H), 2.69−2.79 (m, 2 H), 2.16−2.27 (m, 2 H). HRMS (ESI): m/z calcd for $C_{32}H_{30}N_3O_3$ $[M + H]^+$ 504.2287; found, 504.2293.

General Method for the Synthesis of Amide (***8***). LDA (0.37 mL, 2M, 0.74 mmol) was added to a cooled down (−78 °C) THF solution (3 mL) of 12-phenyl-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidin-11-amine (**6d**) (200 mg, 0.61 mmol) and the corresponding acid chloride (0.74 mmol). The reaction was allowed to reach room temperature and stirred for 24 h. Then, the mixture was poured in ice water and extracted with dichloromethane. The organic layer was then collected and dried over Na_2SO_4, filtered, and concentrated

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under vacuum. The crude material was chromatographed over silica gel to yield the corresponding acylated amide with yields between 20 to 40%.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl tert butyl carbamate (***8a***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.77 (s, 1 H), 7.94 (d, *J* = 8.61 Hz, 1 H), 7.77−7.87 (m, 2 H), 7.43−7.53 (m, 2 H), 7.39 (t, *J* = 6.85 Hz, 1 H), 7.31 (d, *J* = 7.04 Hz, 2 H), 7.19 (t, *J* = 7.63 Hz, 2 H), 7.06−7.13 (m, 1 H), 5.69 (s, 1 H), 1.20 (br. s., 9 H). HRMS (ESI): *m*/*z* calcd for $C_{26}H_{24}N_3O_3$ $[M + H]^+$ 426.1817; found, 426.1797.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl phenyl amide (***8b***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.96 (br. s., 1 H), 8.48 (s, 1 H), 7.87−8.01 (m, 3 H), 7.80 (t, *J* = 9.59 Hz, 2 H), 7.64 (t, *J* = 7.43 Hz, 1 H), 7.45−7.59 (m, 3 H), 7.38 (dt, *J* = 13.99, 6.90 Hz, 2 H), 7.06−7.24 (m, 4 H), 6.29 (s, 1 H), 5.28 (s, 1 H). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{20}N_3O_2$ $[M + H]^+$ 430.1550; found, 430.1543.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl benzyl amide (***8c***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.54 (s, 1 H), 8.12 (s, 1 H), 7.77−7.90 (m, 3 H), 7.37−7.54 (m, 8 H), 7.03−7.14 (m, 3 H), 6.88−6.98 (m, 2 H), 5.87 (s, 1 H), 3.89−4.09 (m, 2 H). HRMS (ESI): *m*/*z* calcd for $C_{29}H_{22}N_3O_2$ $[M + H]^+$ 444.1712; found, 444.1713.

Synthesis of 12-Phenyl-12 h-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl phenethyl amide (***8d***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 9.13 (br. s., 1 H), 8.52 (s, 1 H), 7.93 (d, *J* = 8.61 Hz, 1 H), 7.75−7.86 (m, 2 H), 7.18−7.54 (m, 9 H), 6.97−7.15 (m, 4 H), 6.06 (s, 1 H), 2.90−3.21 (m, 3 H), 2.71 (t, *J* = 7.83 Hz, 1 H). HRMS (ESI): *m*/*z* calcd for $C_{30}H_{24}N_3O_2$ $[M + H]^+$ 458.1868; found, 458.1867.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl (3-benzyl) urea (***8e***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 9.89 (t, *J* = 5.67 Hz, 1 H), 8.44 (s, 1 H), 8.11−8.22 (m, 2 H), 7.78−7.86 (m, 2 H), 7.55 (d, *J* = 7.43 Hz, 2 H), 7.36−7.51 (m, 3 H), 7.31 (t, *J* = 7.63 Hz, 2 H), 7.14−7.25 (m, 5 H), 5.96 (s, 1 H), 4.46−4.63 (m, 2 H). HRMS (ESI): *m*/*z* calcd for $C_{29}H_{23}N_4O_2$ $[M + H]^+$ 459.1821; found, 459.1817.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl (ethyl propanoate)amide (***8f***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.59 (s, 1 H), 8.08 (d, *J* = 8.22 Hz, 1 H), 7.80 (dd, *J* = 8.41, 4.11 Hz, 2 H), 7.31−7.54 (m, 6 H), 7.07−7.25 (m, 3 H), 6.14 (s, 1 H), 3.70−3.90 (m, 2 H), 3.41−3.51 (s, 1 H), 1.20−1.36 (m, 3 H). HRMS (ESI): *m*/*z* calcd for $C_{26}H_{22}N_3O_4$ $[M + H]^+$ 440.1610; found, 440.1612.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl (ethyl butanoate)amide (***8g***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.92 (s, 1 H), 8.56 (s, 1 H), 8.06 (d, *J* = 8.22 Hz, 1 H), 7.75−7.84 (m, 2 H), 7.34−7.51 (m, 4 H), 7.18−7.30 (m, 2 H), 7.08−7.17 (m, 1 H), 6.08 (s, 1 H), 5.28 (s, 1 H), 4.21 (q, *J* = 7.04 Hz, 2 H), 2.89−3.11 (m, 2 H), 2.64−2.89 (m, 2 H), 1.21−1.32 (m, 3 H). HRMS (ESI): *m*/*z* calcd for $C_{27}H_{24}N_3O_4$ $[M + H]^+$ 454.1767; found, 454.1762.

Synthesis of 12-Phenyl-12H-naphtho[1′,2′:5,6]pyrano[2,3-d]pyrimidin-11-yl (ethyl pentanoate)amide (***8h***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.70 (s, 1 H), 8.58 (s, 1 H), 8.05 (d, *J* = 8.22 Hz, 1 H), 7.76−7.83 (m, 2 H), 7.43−7.50 (m, 2 H), 7.39 (t, *J* = 6.85 Hz, 1 H), 7.33 (d, *J* = 7.04 Hz, 2 H), 7.22 (t, *J* = 7.63 Hz, 2 H), 7.12 (t, *J* = 7.43 Hz, 1 H), 6.12 (s, 1 H), 4.11−4.20 (m, 2 H), 2.80 (t, *J* = 7.24 Hz, 2 H), 2.44 (t, *J* = 7.24 Hz, 2 H), 2.02−2.14 (m, 2 H), 1.22−1.29 (m, 3 H). HRMS (ESI): *m*/*z* calcd for $C_{28}H_{26}N_3O_4$ $[M + H]^+$ 468.1923; found, 468.1927.

Synthesis of 11-oxo-9 Aryl-12-phenyl-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidine ***9a−9d***. Compound **4a** (100 mg, 0.279 mmol, 1.0 equiv) and the acetyl chloride (0.419 mmol, 1.5 equiv) were taken up in THF (2 mL) with pyridine (0.558 mmol, 2.0 equiv). The mixture was stirred at 120 °C for 30 min. Upon consumption of the starting material, we concentrated the reaction mixture *in vacuo*, and the residue was taken up in acetonitrile and submitted for HPLC purification to give products **9a**−**9d** with yields from 10 to 40%.

11-Oxo-9-benzyl-12-phenyl-12H-naphtho[1′,2′:5,6]-pyrano-[2,3-d]pyrimidine (***9a***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.90 (d, *J* = 7.83 Hz, 1 H), 7.77−7.84 (m, 2 H), 7.26−7.48 (m, 8 H), 6.98 (d, *J* = 2.15 Hz, 1 H), 6.83 (dd, *J* = 8.31, 2.05 Hz, 1 H), 6.64 (d, *J* = 8.41 Hz, 1 H), 5.81 (s, 1 H), 4.02 (d, *J* = 1.57 Hz, 2 H), 3.69−3.75 (m, 6 H). HRMS (ESI): *m*/*z* calcd for $C_{30}H_{25}N_2O_4$ $[M + H]^+$ 477.1814; found, 477.1811.

11-Oxo-9-phenethyl-12-phenyl-12H-naphtho[1′,2′:5,6-]pyrano[2,3-d]pyrimidine (***9b***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 11.64 (br. s., 1 H), 7.93 (d, *J* = 8.41 Hz, 1 H), 7.76−7.87 (m, 2 H), 7.36−7.52 (m, 4 H), 7.27−7.36 (m, 4 H), 6.92 (d, *J* = 2.15 Hz, 1 H), 6.84 (dd, *J* = 8.31, 2.05 Hz, 1 H), 6.55 (d, *J* = 8.41 Hz, 1 H), 5.83 (s, 1 H), 3.60−3.73 (m, 6 H), 3.12−3.23 (m, 2 H), 2.99 (dd, *J* = 10.37, 6.06 Hz, 2 H). HRMS (ESI): *m*/*z* calcd for $C_{31}H_{27}N_2O_4$ $[M + H]^+$ 491.1971; found, 491.1962.

11-Oxo-9-((3-phenyl)-propanyl)-12-phenyl-12H-naphtho-[1′,2′:5,6-]pyrano[2,3-d]pyrimidin (***9c***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 12.85 (br. s., 1 H), 7.94 (d, *J* = 8.22 Hz, 1 H), 7.82 (d, *J* = 8.61 Hz, 2 H), 7.35−7.52 (m, 4 H), 7.25 (m, 3 H) 7.10−7.20 (m, 1 H), 6.78−6.96 (m, 2 H), 6.60 (d, *J* = 8.22 Hz, 1 H), 5.79 (s, 1 H), 3.59−3.73 (m, 6 H), 2.69−2.89 (m, 4 H), 2.16−2.34 (m, 2 H). HRMS (ESI): *m*/*z* calcd for $C_{32}H_{29}N_2O_4$ $[M + H]^+$ 505.2127; found, 505.2113.

11-Oxo-9-methyl-12-phenyl-12H-naphtho[1′,2′:5,6-]pyrano-[2,3-d]pyrimidin (***9d***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 12.51 (br. s., 1 H), 7.94 (d, *J* = 8.41 Hz, 1 H), 7.80 (d, *J* = 8.80 Hz, 2 H), 7.35−7.48 (m, 3 H), 6.95 (d, *J* = 1.76 Hz, 1 H), 6.87 (dd, *J* = 8.31, 2.05 Hz, 1 H), 6.65 (d, *J* = 8.22 Hz, 1 H), 5.81 (s, 1 H), 3.73 (d, *J* = 1.57 Hz, 6 H), 2.51 (s, 3 H). HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}N_2O_4$ $[M + H]^+$ 401.1501; found, 401.1502.

Synthesis of 11-(Amino)-9-aryl-12-phenyl-12H-naphtho-[1′,2′:5,6]-pyrano[2,3-d]pyrimidine (***10a−10c***). Compound **9.1**, **9.2**, or **9.3** (0.059 mmol, 1.0 equiv) was taken up in phosphorus(V) oxychloride (1.0 mL) and heated to 120 °C for 20 min. Upon completion, we poured the mixture over crushed ice. It was then taken up in ethyl acetate, and to it was added saturated sodium bicarbonate. The layers were separated, and the organic layer was washed with sodium bicarbonate. The combined aqueous layers were extracted with ethyl acetate. The combined organic extracts were then washed with water and brine, dried over $MgSO_4$, and concentrated

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to give a yellow oil which was taken up in THF (1.0 mL). Ammonium hydroxide (6.92 μL, 0.178 mmol, 3.0 equiv) was added to the mixture, and it was heated to 130 °C for 30 min in a microwave oven. Upon completion, we concentrated the mixture *in vacuo* and submitted it for purification to give products **10a**−**10c** with yields from 10 to 50%.

Synthesis of 11-(Amino)-9 benzyl-12-phenyl-12H-naphtho-[1′,2′:5,6]-pyrano[2,3-d]pyrimidine (***10a***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 (d, J = 8.41 Hz, 1 H), 7.89 (d, J = 8.80 Hz, 2 H), 7.54 (td, J = 7.68, 1.27 Hz, 1 H), 7.38−7.48 (m, 2 H), 7.25 (d, J = 3.13 Hz, 3 H), 7.22−7.23 (m, 1 H), 7.21 (d, J = 2.15 Hz, 2 H), 7.13−7.19 (m, 2 H), 6.79 (dd, J = 8.41, 2.15 Hz, 1 H), 6.68−6.75 (m, 1 H), 5.88 (s, 1 H), 3.83 (s, 2 H), 3.62 (s, 3 H), 3.56 (s, 3 H). HRMS (ESI): m/z calcd for $C_{30}H_{26}N_3O_3$ $[M + H]^+$ 476.1974; found, 476.1979.

Synthesis of 11-(Amino)-9 phenethyl-12-phenyl-12H-naphtho[1′,2′:5,6-]pyrano[2,3-d]pyrimidine (***10b***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.18 (d, J = 8.61 Hz, 1 H), 7.90 (d, J = 9.00 Hz, 2 H), 7.51−7.59 (m, 1 H), 7.38−7.50 (m, 2 H), 7.09−7.26 (m, 8 H), 6.83 (dd, J = 8.31, 2.05 Hz, 1 H), 6.74 (d, J = 8.41 Hz, 1 H), 5.90 (s, 1 H), 3.55−3.67 (m, 6 H), 2.92−3.03 (m, 2 H), 2.81 (t, J = 7.92 Hz, 2 H). HRMS (ESI): m/z calcd for $C_{31}H_{28}N_3O_3$ $[M + H]^+$ 490.2130; found, 490.2133.

Synthesis of 11-(Amino)-9-((3-phenyl)-propanyl)-12-phenyl-12H-naphtho[1′,2′:5,6]-pyrano[2,3-d]pyrimidine (***10c***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.17 (d, J = 8.22 Hz, 1 H), 7.90 (d, J = 8.80 Hz, 2 H), 7.55 (ddd, J = 8.41, 6.94, 1.08 Hz, 1 H,) 7.37−7.49 (m, 2 H), 7.09−7.29 (m, 8 H), 6.82 (dd, J = 8.41, 2.15 Hz, 1 H), 6.73 (d, J = 8.41 Hz, 1 H), 5.90 (s, 1 H), 3.62 (s, 3 H), 3.57 (s, 3 H), 2.49−2.64 (m, 4 H), 1.90−2.01 (m, 2 H). HRMS (ESI): m/z calcd for $C_{32}H_{30}N_3O_3$ $[M + H]^+$ 504.2287; found, 504.2287.

Synthesis of 2-Amino-4-(3,4-dimethoxyphenyl)-4H-benzo-[h]chromene-3-carbonitrile (***11***). To 3,4-dimethoxybenzaldehyde (100 mg, 0.602 mmol, 1.0 equiv) and malononitrile (0.038 mL, 0.602 mmol, 1.0 equiv) in ethanol (4 mL) was added 1-naphthol (87 mg, 0.602 mmol, 1.0 equiv) and piperidine (0.298 mL, 3.01 mmol, 5.0 equiv). The mixture was heated to 90 °C in a sealed vial for 18 h, Upon completion, we concentrated the mixture *in vacuo* and chromatographed with 0−40% ethyl acetate/hexanes gradient elution to give 2-amino-4-(3,4-dimethoxyphenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile (**11**) (84 mg, 38.9% yield) as a tan solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 8.16 (dd, J = 8.22, 0.78 Hz, 1 H), 7.73−7.82 (m, 1 H), 7.46−7.62 (m, 3 H), 7.02 (d, J = 8.41 Hz, 1 H), 6.74−6.83 (m, 2 H), 6.71 (d, J = 1.96 Hz, 1 H), 4.82 (s, 1 H), 4.70 (s, 2 H), 3.76−3.86 (m, 6 H);

10-2-Morpholinoethyl)-12-(3,4-dimethoxyphenyl)-12H-naphtho[1′,2′:3,4]pyrano[2,3-d]pyrimidin-11-imine (***12***). Compound **11** (84 mg, 0.234 mmol, 1.0 equiv) was taken up in triethyl orthoformate (1.5 mL) and heated to 155 °C for 48 h in a sealed tube. Upon completion, we concentrated the mixture *in vacuo* to give a yellow oil, which was was taken up in THF (1.5 mL). To it was added 2-morpholinoethylamine (0.037 mL, 0.281 mmol, 1.2 equiv) followed by DBU (0.042 mL, 0.281 mmol, 1.2 equiv). The mixture was heated to 75 °C in a sealed tube for 24 h. Upon completion, we concentrated the mixture *in vacuo* and submitted it for HPLC purification to give compound **12** as a tan solid (12 mg, 15%). 1H NMR (400 MHz, DMSO-d_6) δ ppm 9.73 (br. s., 1 H), 8.34 (s, 1 H), 8.26 (d, J = 7.83 Hz, 1 H), 7.89 (d, J = 7.83 Hz, 1 H), 7.60−7.69 (m, 2 H), 7.53−7.60 (m, 1 H), 7.37 (d, J = 8.61 Hz, 1 H), 7.08 (d, J = 2.15 Hz, 1 H), 6.79 (d, J = 8.41 Hz, 1 H), 6.65 (dd, J = 8.31, 2.05 Hz, 1 H), 5.27 (s, 1 H), 3.73−3.84 (m, 4 H), 3.71 (s, 3 H), 3.59−3.65 (m, 3 H), 3.24 (br. s., 4 H), 3.00 (br. s., 2 H) 2.87 (br. s., 2 H). HRMS (ESI): m/z calcd for $C_{29}H_{31}N_4O_4$ $[M + H]^+$ 499.2345; found, 499.2346.

Synthesis of 2-Amino-4-(3,4-dimethoxyphenyl)-7-Alkyl-4H-chromene-3-carbonitrile (***13a−13b***). To 3,4-dimethoxybenzaldehyde (200 mg, 1.204 mmol, 1.0 equiv) and malononitrile (0.076 mL, 1.204 mmol, 1.0 equiv) in ethanol (8 mL) was added 3-methoxyphenol or 3-(benzyloxy)phenol (1.204 mmol, 1.0 equiv) and piperidine (0.596 mL, 6.02 mmol, 5.0 equiv). The mixture was heated in a sealed vial to 90 °C for 18 h. Upon completion, we concentrated the mixture *in vacuo* and chromatographed it with 10% ethyl acetate/dichloromethane gradient elution to give compounds **13a** and **13b** as yellow solids with 16% and 20% yields, respectively.

2-Amino-4-(3,4-dimethoxyphenyl)-7-methoxy-4H-chromene-3-carbonitrile (***13a***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 6.86 (d, J = 8.61 Hz, 1 H), 6.76−6.82 (m, 1 H), 6.69−6.74 (m, 1 H), 6.66 (d, J = 1.96 Hz, 1 H), 6.60 (dd, J = 8.61, 2.54 Hz, 1 H), 6.52 (d, J = 2.54 Hz, 1 H), 4.62 (s, 1 H), 4.53 (s, 2 H), 3.82 (d, J = 8.41 Hz, 6 H), 3.77 (s, 3 H);

2-Amino-7-(benzyloxy)-4-(3,4-dimethoxyphenyl)-4H-chromene-3-carbonitrile (***13b***). ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.30−7.42 (m, 5 H), 6.84−6.89 (m, 1 H), 6.77−6.81 (m, 1 H), 6.64−6.75 (m, 3 H), 6.59 (d, J = 2.54 Hz, 1 H), 5.02 (s, 2 H), 4.62 (s, 1 H), 4.52 (s, 2 H), 3.80−3.86 (m, 6 H);

Synthesis of 5-(3,4-dimethoxyphenyl)-8-alkyl-3-(2-morpholinoethyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-imine (***14a−14b***). Compound **13a** or **13b** (0.201 mmol, 1.0 equiv) was taken up in triethyl orthoformate (2 mL) and heated to 150 °C in a sealed tube overnight. Upon completion, we concentrated the mixture *in vacuo* to give a yellow oil, which was taken up in THF (2 mL). To it was added 2-morpholinoethylamine (0.032 mL, 0.243 mmol, 1.2 equiv) followed by DBU (0.037 mL, 0.243 mmol, 1.2 equiv). The mixture was heated to 75 °C in a sealed tube for 24 h. Upon completion, we concentrated the mixture *in vacuo* and submitted it for HPLC purification to give compounds **14a** and **14b** as tan solids with yields of 15% and 20%, respectively.

5-(3,4-Dimethoxyphenyl)-8-methoxy-3-(2-morpholinoethyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-imine (***14a***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.54 (br. s., 1 H), 8.26 (s, 1 H), 7.17 (d, J = 8.61 Hz, 1 H), 6.94 (d, J = 2.15 Hz, 1 H), 6.74−6.81 (m, 2 H), 6.67 (dd, J = 8.61, 2.54 Hz, 1 H), 6.57 (dd, J = 8.41, 1.96 Hz, 1 H), 5.05 (s, 1 H), 3.70 (d, J = 12.52 Hz, 6 H), 3.62 (s, 3 H), 3.20 (br. s., 8 H), 2.96 (br. s., 4 H). HRMS (ESI): m/z calcd for $C_{26}H_{32}N_4O_5$ $[M + H]^+$ 480.2372; found, 480.2375.

8-(Benzyloxy)-5-(3,4-dimethoxyphenyl)-3-(2-morpholinoethyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-imine (***14b***). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (s, 1 H), 7.26−7.44 (m, 6 H), 7.23 (d, J = 8.61 Hz, 1 H), 6.99 (dd, J = 9.39, 2.15 Hz, 2 H), 6.85 (dd, J = 8.51, 2.45 Hz, 1 H), 6.79 (d, J = 8.22 Hz, 1 H), 6.62 (dd, J = 8.31, 2.05 Hz, 1 H), 5.31 (s, 1 H), 5.10 (s, 2 H), 3.69 (s, 3 H), 3.63 (s, 3 H), 3.47 (br. s., 8 H), 2.95 (br. s., 4 H). HRMS (ESI): m/z calcd for $C_{32}H_{35}N_4O_5$ $[M + H]^+$ 555.2607; found, 555.2611.

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Synthesis of 2,7-Diamino-4-(3,4-dimethoxyphenyl)-4H-chromene-3-carbonitrile (***15***). To 3,4-dimethoxybenzaldehyde (2 g, 12.04 mmol, 1.0 equiv) and malononitrile (0.758 mL, 12.04 mmol, 1.0 equiv) in ethanol (80 mL) was added 3-aminophenol (1.313 g, 12.04 mmol, 1.0 equiv) and piperidine (5.96 mL, 60.2 mmol, 5.0 equiv). The mixture was heated to reflux for 6 h. Upon completion, we concentrated the mixture *in vacuo*, and it was taken up in methanol, after which a precipitate formed and was filtered and washed with cold methanol to compound **15** (1.967 g, 6.08 mmol, 50.5% yield) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.83 (dd, J = 8.41, 2.74 Hz, 1 H), 6.65−6.74 (m, 3 H), 6.57−6.65 (m, 2 H), 6.23 (dt, J = 8.41, 2.54 Hz, 1 H), 6.15 (t, J = 2.45 Hz, 1 H), 5.17 (s, 2 H), 4.43 (d, J = 2.15 Hz, 1 H), 3.67 (dd, J = 4.60, 2.84 Hz, 6 H);

Synthesis of 2,7-Dibromo-4-(3,4-dimethoxyphenyl)-4H-chromene-3-carbonitrile. To compound **15** (417 mg, 1.290 mmol, 1.0 equiv) in acetonitrile (20 mL) at 0 °C was added *tert*-butyl nitrite (0.375 mL, 2.84 mmol, 2.2 equiv) followed by copper(II) bromide (634 mg, 2.84 mmol, 2.2 equiv). The mixture was stirred at 0 °C for 1 h. Upon completion, we took up the mixture in saturated ammonium chloride and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were then washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a black oil, which was chromatographed with 0−20% ethylacetate/hexane gradient elution to give 2,7-dibromo-4-(3,4-dimethoxyphenyl)-4*H*-chromene-3-carbonitrile (164 mg, 0.364 mmol, 28.2% yield) as a yellow solid. ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 7.27 (d, J = 1.96 Hz, 1 H), 7.23 (d, J = 1.96 Hz, 1 H), 7.21 (d, J = 1.96 Hz, 1 H), 6.83 (dd, J = 8.31, 6.36 Hz, 2 H), 6.68−6.73 (m, 1 H), 6.64 (d, J = 2.15 Hz, 1 H), 4.72 (s, 1 H), 3.79−3.88 (m, 6 H).

Synthesis of 2-Amino-7-bromo-4-(3,4-dimethoxyphenyl)-4H-chromene-3-carbonitrile (***16***). 2,7-Dibromo-4-(3,4-dimethoxyphenyl)-4*H*-chromene-3-carbonitrile (164 mg, 0.364 mmol, 1.0 equiv) was taken up in ammonia in isopropanol (5 mL). The mixture was heated in a microwave at 150 °C for 1 h. Upon completion, we concentrated the mixture *in vacuo* and chromatographed it with 2−7% methanol/dichloromethane gradient elution to give compound **16** (39 mg, 0.101 mmol, 27.7% yield) as a yellow oil, which was taken on quickly to the next reaction.

Synthesis of 5-(3,4-Dimethoxyphenyl)-3-(2-morpholinoethyl)-3H-chromeno[2,3-d]pyrimidin-4(5H)-imine (***17***). Compound **16** (155 mg, 0.400 mmol, 1.0 equiv) was taken up in triethyl orthoformate (4 mL) and heated to 155 °C in a microwave for 2 h. Upon completion, we concentrated the mixture *in vacuo* to give a yellow oil, which was taken up in THF (5 mL). To it was added 2-morpholinoethylamine (0.062 mL, 0.479 mmol, 1.2 equiv) followed by DBU (0.072 mL, 0.479 mmol, 1.2 equiv). The mixture was heated to 75 °C in a microwave for 1 h. Upon completion, we concentrated the mixture *in vacuo* and chromatographed it with 2−7% methanol/dichloromethane gradient elution to give 8-bromo-5-(3,4-dimethoxyphenyl)-3-(2-morpholinoethyl)-3*H*-chromeno[2,3-*d*]pyrimidin-4(5*H*)-imine (11 mg, 0.021 mmol, 5.22% yield) as a tan solid, which was taken up in dichloromethane (1 mL). To it was added palladium(II) chloride (0.740 mg, 4.17 μmol, 0.2 equiv) and triethylsilane (4.00 μL, 0.025 mmol, 1.2 equiv). The mixture stirred at rt for 24 h. Upon completion, we concentrated the mixture *in vacuo* and submitted it for HPLC purification to give compound **17**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.65 (br. s., 1 H), 8.27 (s, 1 H), 7.14−7.32 (m, 3 H), 7.01−7.13 (m, 2 H), 6.98 (d, J = 2.15 Hz, 1 H), 6.78 (d, J = 8.41 Hz, 1 H), 6.58 (dd, J = 8.31, 2.05 Hz, 1 H), 5.15 (s, 1 H), 3.81 (br. s., 2 H), 3.66−3.72 (m, 3 H), 3.62 (s, 3 H), 3.58 (br. s., 2 H), 3.22 (br. s., 4 H), 2.96 (br. s., 4 H). HRMS (ESI): m/z calcd for $C_{25}H_{30}N_4O_4$ $[M + H]^+$ 450.2267; found, 450.2272.

Synthesis of 5-(3,4-Dimethoxyphenyl)-3-(2-morpholinoethyl)-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-4-amine (***18***). Synthesis of compound **18** was the same as that for compound **17**, except 2.2 equivalents of triethylsilane was used. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.98 (br. s., 1 H), 8.23 (br. s., 2 H), 7.18−7.31 (m, 2 H), 7.11−7.18 (m, 2 H), 6.92 (s, 1 H), 6.74−6.88 (m, 2 H), 5.24 (s, 1 H), 4.87 (d, J = 11.15 Hz, 1 H), 4.53 (dd, J = 11.15, 2.74 Hz, 1 H), 3.80 (d, J = 11.54 Hz, 2 H), 3.61−3.72 (m, 6 H), 3.51−3.61 (m, 2 H), 3.13 (d, J = 0.78 Hz, 3 H), 2.75−3.08 (m, 4 H). HRMS (ESI): m/z calcd for $C_{25}H_{31}N_4O_4$ $[M + H]^+$ 451.2345; found, 451.2345.

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Abbreviations

NPSR, neuropeptide S receptor; cAMP, cyclic adenosine monophosphate; HTS, high-throughput screen; HTRF, homogeneous time-resolved fluorescence.

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