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Telescoped synthesis of C3-functionalized (*E*)-arylamidines using Ugi–Mumm and regiospecific quinazolinone rearrangements†

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An efficient four-step, six-transformation protocol was developed to afford bioactive *N*-alkyl- or *N*-arylamide (*E*)-arylamidines featuring strategic amidine C3 modifications which were inaccessible or low yielding by previous methods. This synthetic approach, exemplified with 24 amidines and requiring only a single purification, highlights a multicomponent Ugi–Mumm rearrangement to afford highly diversified quinazolinones which undergo regiospecific rearrangement to afford new amidines. The method extensively broadens the structural scope of this new class of trisubstituted amidines and demonstrates the tolerance of regional C3 amidine steric bulk, visualized with X-ray crystallographic analysis.

Introduction

Trisubstituted amidines are known for a diverse therapeutic range that includes antiarrhythmic,[1a–c] anthelmintic,[2a–c] antiparasitic,[3a,b] antidepressant,[4a–e] and antipsychotic[5a–f] applications (Fig. 1). Derivatives of the antipsychotic tricyclic amidine, olanzapine, are also reported to be helpful in treating relapsing–remitting forms of multiple sclerosis.[6]

This *N*′,*N*,*N*-trisubstituted amidine motif was revealed to be critical in our discovery and development of novel (*E*)-amidobenzamidines as potent antiviral agents[7a,b] (**3**, Scheme 1). This unique scaffold originated from a regiospecific rearrangement of chloroalkylquinazolinone **1a** treated with 1,2-bis(methylamino)ethane to exclusively yield (*E*)-amidobenzamidine **3a** (Scheme 1). We subsequently reported a one-pot method[8] by which extended *N*-Boc-protected amino acids were converted to quinazolinones **1b** that could be efficiently transformed into more diverse amidines **3b**. Both methods relied on generation of quinazolinone intermediates **1a–b** from standard acylation of anthranilic acids, followed by amidation/cyclization.[7a,8,9]

In the context of our anti-infective programs and ongoing synthetic method development, we attempted substitution of the C3 position of benzamidine **3**; however, poor yields of C3-modified products were obtained. It was unclear if this was due to steric congestion of substitution at this site or fault of the method. It was also difficult to generate amidobenzamidines bearing *N*-alkyl substituents on the amide group. While a few *N*-alkyl substituted amides were made in low yield, it was desirable to construct an array to survey bioactivity. Given the importance of the scaffold to our program and the inadequate synthetic means to regionally diversify it, we sought a method that would comprehensively address these needs. In 2011, Mossetti reported[10] a Ugi–Mumm rearrangement,[11a–h]

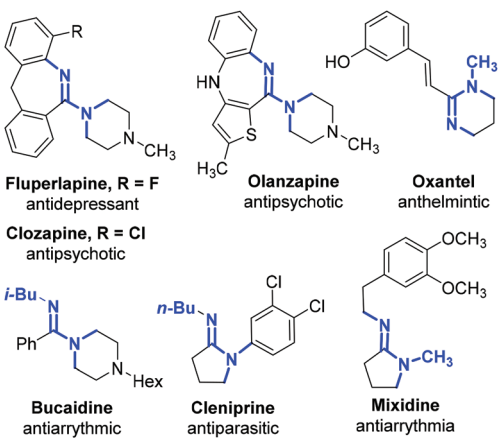

Fig. 1 Drugs of diverse application containing a trisubstituted amidine motif, highlighted in blue.

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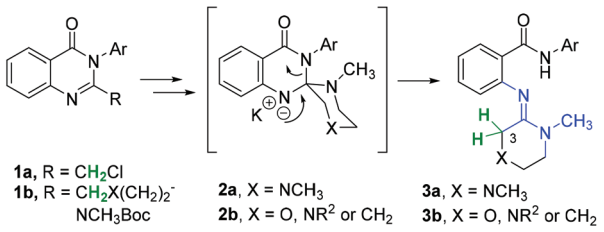
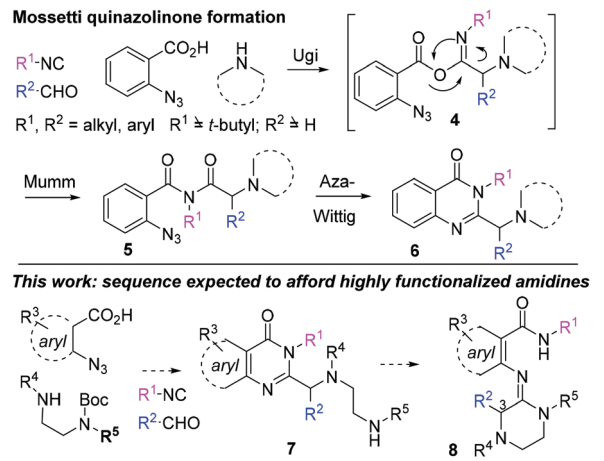


Scheme 1 Previous approaches to *N*-aryl benzamidines.[7a,8]

followed by Staudinger/aza-Wittig ring closure[12a,b] to generate quinazolinones **6** (Scheme 2). Importantly, these products bore R^1 and R^2 substituents that would be expected to afford the desired C3-substituted, *N*-alkyl amide derivatives **8** if a core containing a suitably tethered diamine, as shown in **7**, was subjected to our rearrangement conditions.

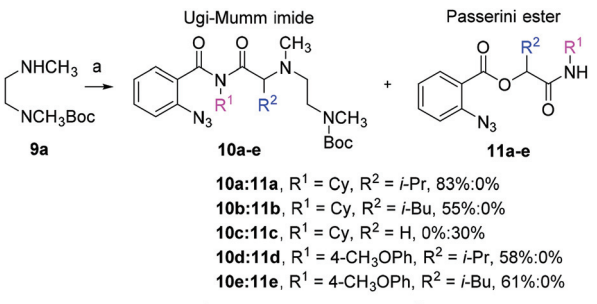
The approach potentially offered convenient access to R^1 and R^2 quinazolinone **7** substitutions and ultimately, potential corresponding substitutions in amidines **8** that were challenging to otherwise incorporate. Furthermore, the Ugi–Mumm-aza-Wittig protocol was furnished as a one-pot method.[10] Nonetheless, limitations of the method as published were also noted. The two-step overall yields for the 13 examples cited were evenly distributed between 40–81%, and use of aryl aldehydes required significantly longer reaction times (3 days). In some cases, Passerini product formation[10,13a–c] predominated over desired imide formation in the first step. Additionally, direct use of formaldehyde was not permitted in the Ugi–Mumm reaction, a feature that would limit access to C3-unsubstituted, *N*-alkyl amides that are important to ongoing projects in our lab. With these pros and cons in mind, we set out to see if this approach could advance our rearrangement strategies and medicinal chemistry goals. Specifically, we aimed to survey a broad range of Ugi substrates and explore the use of problematic Ugi–Mumm partners such as formaldehyde, aryl aldehydes, and heterocyclic azido acids. Importantly, the thrust of this effort was to determine if unique quinazolinones could be efficiently prepared and successfully transformed into novel, C3-substituted amidines to probe unexplored biological space.



Scheme 2 Known Ugi–Mumm quinazolinones and adaptation to *N*-alkyl amide/C3-substituted amidine construction.

Results and discussion

A brief feasibility study employing published reaction conditions[10] was done using 2-azidobenzoic acid, cyclohexyl- or 4-methoxyphenyl isocyanide, one of three aldehydes of variable steric demand and a requisite mono-*N*-Boc-protected 1,2-bis(methylamino)ethane **9a** used in our rearrangement chemistry (Scheme 3). Key intermediates were isolated to assess the efficiency of each reaction in the sequence. The desired imides **10a–b**, resulting from the Ugi–Mumm assembly with cyclohexyl isocyanide and bearing a C3-isopropyl or isobutyl group, were isolated in 83% and 55% yield, respectively (Scheme 3). While some starting material remained, by-products **11a–b** were not observed. Formaldehyde was not productive, only affording Passerini α-acyloxy carboximide **11c**. Use of 4-methoxyphenyl isocyanide with non-formaldehyde components also generated imides **10d–e** in 58–61% yield. Imides **10a–b** or **10d–e** were individually subjected to Staudinger/aza-Wittig conditions, and afforded corresponding quinazolinones in 60–88% yield. Subsequent TFA treatment to remove the *N*-Boc protecting group, followed by base-promoted rearrangement gave the amidines in 30–51% yield over two steps. The best outcome for this 4-step, 6-transformation sequence was observed for amidine **13a**, isolated in 32% overall yield, corre-



R^1	R^2	**12**, yield	**13**, yield	overall yield (**9a**→**13**)
Cy	*i*-Pr	**12a**, 76%	**13a**, 51%	**13a**, 32%
Cy	*i*-Bu	**12b**, 60%	**13b**, 45%	**13b**, 15%
4-CH_3OPh	*i*-Pr	**12d**, 81%	**13d**, 30%	**13d**, 14%
4-CH_3OPh	*i*-Bu	**12e**, 88%	**13e**, 30%	**13e**, 16%

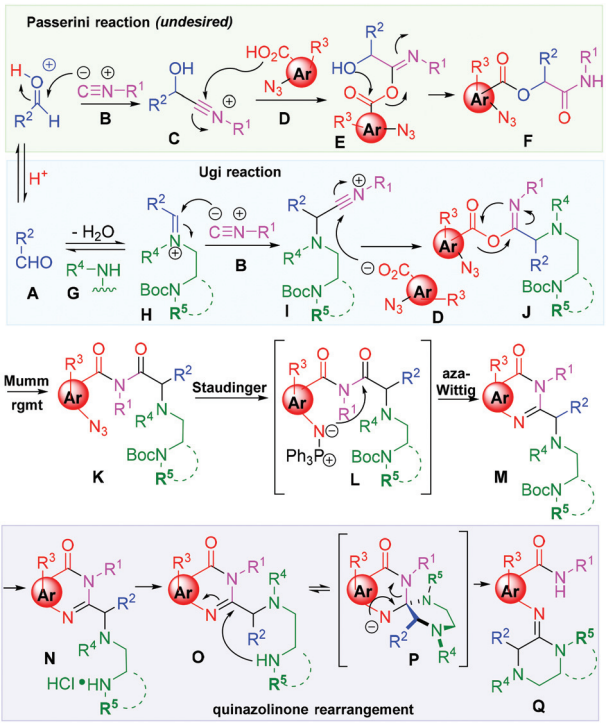
Scheme 3 Pilot chemistry to *N*-alkyl/C3 modified amidines. Reaction conditions: (a) 2-Azidobenzoic acid, R^1NC, R^2CHO (1 eq. each), 4 Å MS, CH_2Cl_2, rt, 12 h; (b) PPh_3, toluene, reflux, 12 h; (c) TFA, CH_2Cl_2, 0 °C–rt, 12 h; (d) aq. K_2CO_3, CH_3CN, μW, 150 °C, 1 h. Yields are based on isolated and purified products.

sponded to a 75% average yield per step, and confirmed that a C3-isopropyl group was well tolerated in the quinazolinone rearrangement. We then set out to (a) maximize imide formation, (b) minimize Passerini side reactions, (c) improve quinazolinone and amidine yields, (d) streamline the overall process, and (e) generate diversely functionalized *N*-alkyl/C3-modified amidines.

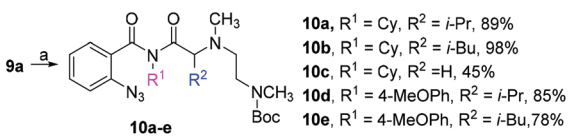
To start, the mechanism of each step was considered (Scheme 4). Fortunately, the historic Ugi, Mumm, Staudinger and aza-Wittig reactions have been substantially reviewed, and mechanisms for each are well documented.[11a–g,12c] For our own quinazolinone rearrangement, control experiments were previously executed and published[7a,8] that support the following discussion. Contrary to our previous work in which chloroalkylquinazolinones were prepared by a standard three-step process, this effort required an alternate assembly of the requisite *N*-alkylamide/C3-substituted amidines (Scheme 4). Specifically, the formation of an iminium ion **H** between aldehyde **A** and amine **G** was a critical part of this effort. Any unreacted aldehyde could participate in a competing three-component Passerini reaction. In that circumstance, isocyanide **B** adds to the activated aldehyde, forming nitrilium ion **C** that is intercepted by acid **D**, forming an *O*-acylimidate **E**. Pericyclic acyl transfer then affords undesired α-acyloxy carboxamide **F**.

In the desired pathway, favoring complete formation of iminium ion **H** was a priority, as subsequent addition of isocyanide **B** would irreversibly afford nitrilium ion **I** and push the process towards the desired outcome. Interception of **I** with acid **D** would afford a different *O*-acylimidate intermediate **J**; however, in this case, *O*-to-*N*-acyl transfer *via* Mumm rearrangement would provide imide **K**. Staudinger/aza-Wittig ring closure would form quinazolinone **M** featuring an *N*-alkyl amide (R^1), R^2 substitution from the incorporated aldehyde, and an appended Boc-protected amine of suitable length that, once liberated and rendered basic (**O**), will undergo rearrangement to amidine **Q**. Previous work has shown that tethered amines capable of forming a 5- or 6-membered spirocyclic intermediate such as **P** (latter case shown only), productively affords an amidine. Amine tethers of longer length require formation of unfavored ring sizes and do not rearrange.[7a,8] Attention was first directed to promoting complete imide formation and preventing side reactions (see ESI†). Imide **10d** formation was used initially to scout reaction parameters. According to the published protocol, equimolar quantities of Ugi–Mumm components were combined concomitantly with molecular sieves in CH_2Cl_2 at ambient temperature.[10,14] We observed that 2-azidobenzoic acid was poorly soluble in CH_2Cl_2, likely contributing to suboptimal conversion. Adding the acid as a 1.0 M solution in 3 : 1 CH_2Cl_2/CH_3OH resulted in a 10% increase in the isolated imide **10d** (68%). This change, in combination with stoichiometric increase of the other reagents to 1.5 equiv. relative to the 2-azidobenzoic acid, improved imide **10d** yield (85%), though Passerini product **11d** formation was also noted. By implementing these changes and premixing the aldehyde and amine for 6–12 min prior to the addition of acid and isocyanide, Passerini product **11d** formation was avoided, and **10d** was obtained in 92% yield. Further optimization of stoichiometry revealed that a 2 : 4 : 1 : 4 ratio of diamine : aldehyde : carboxylic acid : isocyanide was ideal, resulting in significantly improved yields across all pilot examples **10a–e**, which notably included the first successful direct implementation of formaldehyde (**10c**, 45%, Scheme 5).

The intramolecular Staudinger/aza-Wittig pilot reactions afforded quinazolinones in reasonable yields (Scheme 3). As such, focus shifted to optimization of the quinazolinone rearrangement. Historically, quinazolinone *N*-Boc deprotection was effected with TFA (12 h), followed by neutralization with aqueous Na_2CO_3 to promote amidine formation.[7a,8] While productive for substrates not bearing C3 amidine substitution and/or *N*-alkyl amides, in the present cases, impurities formed in addition to the desired amidines. Resultantly, purification



Scheme 4 Mechanistic considerations for a Ugi–Mumm–Staudinger-aza-Wittig- and rearrangement of functionalized quinazolinones leading to *N*-alkylamide/C3 functionalized arylamidines and avoiding Passerini by-products.



Scheme 5 Optimized Ugi–Mumm imide formation. Conditions: (a) **9a**, R^2CHO, 6–12 min, then 2-azidobenzoic acid in 3 : 1 CH_2Cl_2/CH_3OH, R^1NC, (2 : 4 : 1 : 4), 4 Å MS, CH_2Cl_2, rt, 12 h. Yields are based on isolated and purified products.

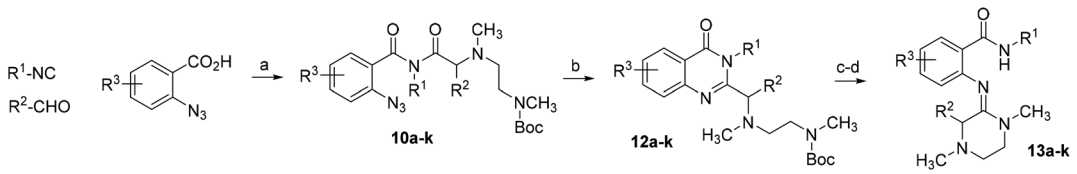
was more complicated and yields were diminished. To address this, we explored other deprotection/base catalyzed conditions. Ultimately, treating **12a** with 4 M HCl in dioxane for 12 h, followed by microwave irradiation in Et_3N/CH_3OH yielded amidine **13a** in 66% yield (45% overall), as compared to 53% (32% overall). With optimized conditions in hand, we sampled a variety of Ugi–Mumm coupling partners to assess efficiency of the stepwise protocol (Table 1). Five aldehydes, ranging in size from formaldehyde to benzaldehyde, were successfully transformed into C3-modified amidines in acceptable yield. This effort revealed that (a) benzaldehyde could be efficiently incorporated in 12 h instead of 3 days, (b) direct use of formaldehyde was feasible and (c) that C3-amidine carbon substitution was reasonably accommodated despite the increased steric demand introduced at this position.

We anticipated that yields may be enhanced if the six-transformation sequence could be executed without purification of intermediates.[15] In our estimation, this approach had a good chance of success given that the Mossetti team had demonstrated that their version of the Ugi–Mumm–Staudinger/aza-Wittig sequence could be done without isolation of the imide resulting from the Ugi–Mumm rearrangement.[10] Further, we had reported previously a differentiated telescoped method by which simplified quinazolinones were converted to benzamidines.[8] Nonetheless, it was uncertain if the new process was amenable to being streamlined in this way, as excess reagents in the Ugi reaction and the new process as a whole introduced by-products that would be carried throughout and may interfere with the efficiency of progressive reactions.

As we assessed this option, it was determined that the presence of triphenylphosphine oxide by-product complicated purification and yields of the reactions following the aza-Wittig reaction. As such, polymer-bound triphenylphosphine was used in the Staudinger/aza-Wittig reaction to simplify end-stage, triphenylphosphine oxide removal.[16] With this change, the undesired by-product was filtered off after the reaction, greatly facilitating work-up and clean isolation of quinazolinone. As such, a telescoped version of the sequence using 2-azidobenzoic acid, isobutyraldehyde, cyclohexylisocyanide and **9a** was attempted, affording amidine **13a** *in an improved 61% overall yield* (*versus* 45% stepwise) and in 64% yield when executed at 1.0 mmol scale. Amidines **13a–k**, first prepared by our stepwise approach at the start of this project, were then generated by the streamlined protocol, revealing an 11–40% improvement in yield (Scheme 6). Encouraged by these results, a more extensive survey of the telescoped protocol was examined. With the exception of 2-azido-6-fluorobenzoic acid and 2-azido-6-methylbenzoic acid, substituted azido benzoic acids[17] were generally well-tolerated throughout the sequence (Scheme 6, **13l–n**). Use of these 6-substituted benzoic acids exclusively led to Passerini α-acyloxy carboxamide formation. Presumably, 6-substitution may present significant steric repulsion in the Mumm-rearrangement, thus favoring Passerini by-product formation. Compared to most substituted acids, 2-azido 4-fluorobenzoic acid led to lower yield of amidine **13l** (21%, or 68% average yield over 4 steps); however, this starting material was limited by poor solubility.

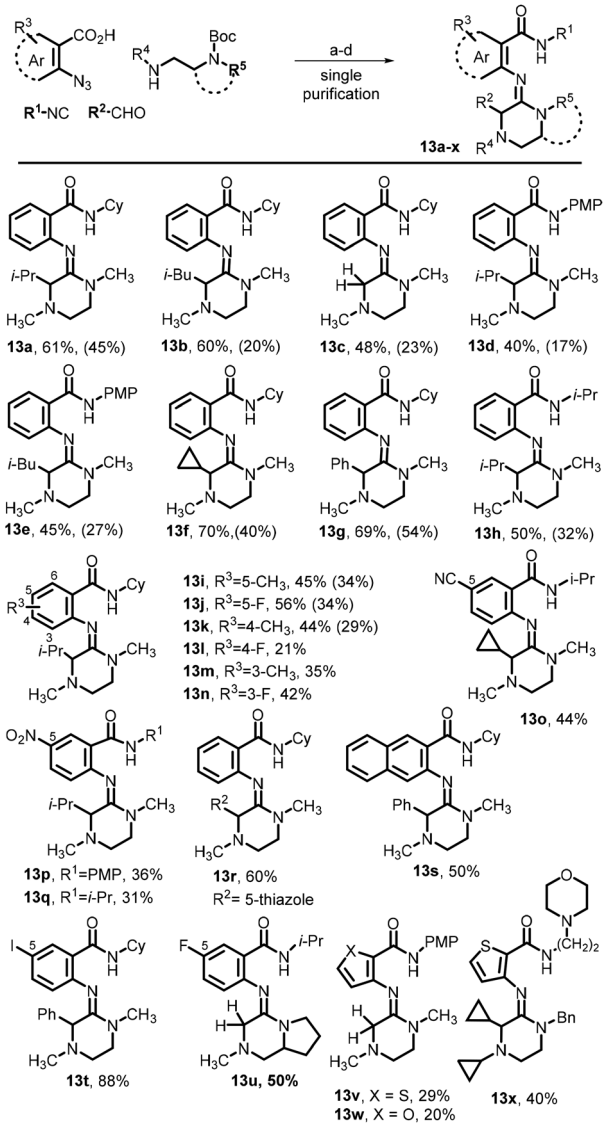
Introduction of C3 amidine substituents was motivated in part to evaluate the tolerance of regional steric bulk. The absence of (*Z*)-amidines was attributed to the planar *N*-amidine substituent that would otherwise clash with the phenyl ring core if a (*Z*)-configuration was adopted.[7a,8]

Table 1 Feasibility assessment and yields for optimized stepwise sequence leading to novel quinazolinones and benzamidines[a,b]



Entry	Isocyanide R^1	Aldehyde R^2	Acid R^3	Imide **10a–k** Cmpd	Imide **10a–k** Yield (%)	Quinazolinone **12a–k** Cmpd	Quinazolinone **12a–k** Yield (%)	Benzamidine **13a–k** Cmpd	Benzamidine **13a–k** Yield (%)	Overall yield **13a–k** (%)
1	Cyclohexyl	Isopropyl	H	**10a**	89	**12a**	76	**13a**	66	45
2	Cyclohexyl	Isobutyl	H	**10b**	98	**12b**	60	**13b**	34	20
3	Cyclohexyl	H	H	**10c**	45	**12c**	89	**13c**	58	23
4	4-CH_3O-phenyl	Isopropyl	H	**10d**	85	**12d**	88	**13d**	23[c]	17
5	4-CH_3O-phenyl	Isobutyl	H	**10e**	78	**12e**	88	**13e**	39[c]	27
6	Cyclohexyl	Cyclopropyl	H	**10f**	89	**12f**	70	**13f**	65	40
7	Cyclohexyl	Phenyl	H	**10g**	97	**12g**	82	**13g**	68	54
8	Isopropyl	Isopropyl	H	**10h**	88	**12h**	71	**13h**	52	32
9	Cyclohexyl	Isopropyl	5-CH_3	**10i**	78	**12i**	69	**13i**	64	34
10	Cyclohexyl	Isopropyl	5-F	**10j**	ND	**12j**	84	**13j**	40	34
11	Cyclohexyl	Isopropyl	4-CH_3	**10k**	67	**12k**	70	**13k**	61	29

[a] Conditions: (a) **9a**, R^2CHO, 6–12 min, then 2-azidobenzoic acid in 3 : 1 CH_2Cl_2/CH_3OH, R^1NC, (2 : 4 : 1 : 4), 4 Å MS, CH_2Cl_2, rt, 12 h; (b) PPh_3, toluene, rt, 30 min, then 110 °C, 12 h; (c) 4 N HCl, dioxane, 0 °C–rt, 12 h; (d) Et_3N, CH_3OH, MWI 100 °C, 30 min. [b] Isolated yields: avg of $n \geq 2$ expts. [c] 1 h reaction time; ND = not determined, crude material advanced.



Scheme 6 Amidines resulting from a telescoped Ugi–Mumm–Staudinger/aza-Wittig-quinazolinone rearrangement sequence. Conditions: (a) Amine, R^2CHO, 6–12 min, then 2-azidobenzoic acid in 3 : 1 CH_2Cl_2/CH_3OH, R^1NC, (2 : 4 : 1 : 4), 4 Å MS, CH_2Cl_2, rt, 12 h; (b) PS-PPh_3, tol, rt, 30 min, then 110 °C, 12 h; (c) 4 N HCl, dioxane, 0 °C–rt, 12 h; (d) Et_3N, CH_3OH, MWI 100 °C, 30 min. Yields: avg of $n \geq 2$ expts. Parenthetical yields: stepwise protocol. PMP = *p*-methoxyphenyl, Cy = cyclohexyl.

Introduction of C3 substituents would force the amidine ring to potentially adopt a more extreme puckered and/or twist to accommodate the increased steric bulk. To further test the tolerance of substitution in this region, two analogs were also prepared that featured a methyl group (**13m**) or a fluorine atom (**13n**) positioned off of the core phenyl ring which would be oriented towards the amidine C3-substituted isopropyl group. Surprisingly, 3-substituted azido acids, which were expected to yield poorly due to increased regional congestion with C3-substituted isopropyl group, still generated amidines **13m** and **13n** in 35% and 42% yield, respectively. To understand how C3 substitutions were accommodated, we pursued crystallization of multiple compounds in the set. Fortunately, an X-ray crystal structure of amidine **13t**, featuring a C3-positioned phenyl ring, revealed a puckered and twisted amidine ring (Fig. 2). As a result, the amidine N–C double bond is out of the plane of the core phenyl ring, thus allowing the α-amidine substituent to adopt an energetically favorable arrangement relative to the core. Nonetheless, limitations were found. Benzofuran- and benzothiophene-derived azido acids, in combination with cyclopropanecarboxaldehyde, led to isolation of the free-based aminoalkylquinazolinones that would not rearrange to the corresponding amidines even under forcing conditions, likely due to increased steric intolerance. Despite this, smaller heterocyclic azido acids (ref. 18) competently rearranged to amidines, **13v–x**. Amidines **13u** and **13x** were generated with unsymmetrical diamines, thereby demonstrating the potential for extensive library generation and incorporation of chiral components.

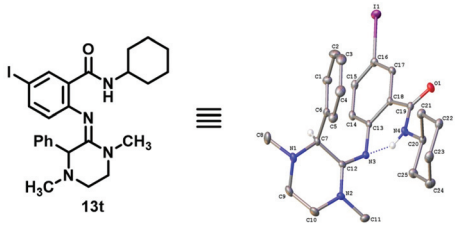


Fig. 2 Molecular drawing of **13t** shown with 50% probability ellipsoids. The conformation of the amidine ring is a distorted envelope the puckering amplitude Q = 0.5488(11) Ang.

Conclusions

The *N′*,*N*,*N*-trisubstituted amidine framework features prominently in a variety of approved drugs with diverse pharmacological value. Having discovered a series of structurally unique, antiviral (*E*)-amidobenzamidines bearing this motif, we explored a new strategy by which the scaffold could be bi-directionally functionalized. Ultimately, a multicomponent, dual rearrangement strategy was developed that efficiently afforded a diverse assortment of C3-functionalized (*E*)-arylamidines bearing either *N*-alkyl or *N*-aryl amides. As part of this effort, a stepwise approach was first scouted and optimized before refining this process such that only a single, final purification was necessary. By implementing the Ugi–Mumm rearrangement, a broad array of aldehydes, including formaldehyde, was used to deliver novel quinazolinones that transformed into both α-substituted and unsubstituted (*E*)-arylamidines in moderate to excellent yield over the 4-step, 6-transformation sequence. Further, we demonstrated that the α-amidine position was quite permissive of bulky substituents, a feature visualized with the aid of an X-ray structure of a C3-phenyl derivative. Moreover, heterocycles were successfully incorporated into the amidine scaffold, enriching our understanding of bio-

logical targets with which these compounds interact. The compounds are currently being screened across a spectrum of biological assays to evaluate known and orthogonal activity. Results from those studies will detailed separately.

Experimental

General information

Compounds not described in ESI† were purchased from commercial vendors. All synthesized compounds were characterized with the following instrumentation: Varian Unity-Inova 400 MHz NMR spectrometer (operating at 400 and 101 MHz, respectively) or a Varian Unity-Inova 500 MHz NMR spectrometer (operating at 500 and 126 MHz, respectively) in $CDCl_3$ ($CDCl_3$: ^1H = δ 7.26 ppm, ^{13}C = δ 77.16 ppm). Microwave irradiated (MWI) reactions were carried out using an Anton Paar Monowave 300 Microwave Synthesis Reactor. Flash chromatography separations were carried out using a Teledyne Isco CombiFlash Rf 200 purification system with silica gel columns (normal-phase). High resolution mass spectra (HRMS) were performed by Analytical Instrument Center at the School of Pharmacy on an Electron Spray Injection (ESI) mass spectrometer. Melting points were measured on OptiMelt MPA100 Automated Melting Point System.

General procedure for the telescoped synthesis of C3-functionalized (*E*)-arylamidines

(*E*)-*N*-Cyclohexyl-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene) amino)benzamide 13a. An oven-dried, 10 mL round bottom flask under nitrogen was charged with activated, powdered, 4 Å molecular sieves (50 mg). The flask was placed under vacuum and flame-dried, then backfilled with nitrogen. *N*,*N*′-Dimethylethylenediamine (115 mg, 0.61 mmol, 2.0 equiv.) was dissolved in dry CH_2Cl_2 (0.5 mL, 1.3 M) and added to the reaction vessel. Isobutyraldehyde (112 μL, 1.2 mmol, 4.0 equiv.) was dissolved in dry CH_2Cl_2 (0.46 mL, 2.6 M) in a 1-dram glass vial and added dropwise over 1 min *via* syringe to the reaction vessel while stirring at rt. Upon completion of the addition, 2-azidobenzoic acid (50 mg, 0.31 mmol, 1.0 equiv.) was dissolved in a 3 : 1 mixture of dry CH_2Cl_2/MeOH (0.4 mL, 0.8 M), taken up into a syringe and the needle was placed into the septum of the reaction vessel. Cyclohexyl isocyanide (153 μL, 1.2 mmol, 4.0 equiv.) was dissolved in dry CH_2Cl_2 (0.3 mL, 3.6 M) in a 1-dram glass vial, taken up into a syringe and the needle was placed into the septum of the reaction vessel. 2-Azidobenzoic acid was added dropwise to the reaction vessel while stirring over 1 min followed immediately by cyclohexyl isocyanide. The reaction mixture was stirred at rt for 12 h after which the reaction was complete as judged by complete consumption of carboxylic acid **1** on TLC (10% MeOH/CH_2Cl_2). The crude reaction mixture was filtered through a 0.45 μM syringe filter and the filtrate was concentrated *in vacuo*. To a flame-dried, 10 mL round bottom flask under nitrogen was added triphenylphosphine on resin (438 mg, 0.61 mmol, 1.4 meq g^{-1}, 2.0 equiv.) followed by dry toluene (1.0 mL). A solution of the crude reaction mixture in dry toluene (2.0 mL) was added dropwise and the reaction mixture was stirred at rt for 1 h. After 1 h at rt, the reaction mixture was heated to 110 °C and stirred for 12 h at reflux after which the reaction was complete as judged by complete consumption of the intermediate by TLC (30% EtOAc/hexanes). The crude reaction mixture was filtered through a pad of Celite, rinsed with CH_2Cl_2 (10 mL × 5), and the filtrate was concentrated *in vacuo*. To a flame-dried, 10 mL round bottom flask under nitrogen was dissolved the crude reaction mixture in dry CH_2Cl_2 (3.0 mL, 0.1 M) and the solution cooled to 0 °C in an ice-bath while stirring for 20 min. HCl in dioxane (4.0 M, 0.8 mL, 10.0 equiv.) was added dropwise. The reaction mixture was allowed to slowly warm to rt. The reaction mixture was stirred at rt for 12 h after which the reaction was complete as judged by complete consumption of intermediate on TLC (30% EtOAc/hexanes). The reaction mixture was dried *in vacuo*. Triethylamine (0.4 mL, 3.1 mmol, 10.0 equiv.) was added to a solution of the crude reaction mixture in MeOH (3.1 mL, 0.1 M) in a 10 mL microwave vial and the reaction mixture was heated in a microwave reactor at 100 °C for 1 h. The reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (10 mL) and washed with water (10 mL), then saturated brine solution (10 mL), the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by normal-phase chromatography (0–60% EtOAc/Hex) to yield the benzamidine, **13a** (69 mg, 61%) as a pale-yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 8.0 Hz, 1H), 8.17 (dd, J = 7.9, 1.7 Hz, 1H), 7.28–7.24 (m, 1H), 7.05–7.01 (m, 1H), 6.59 (dd, J = 7.8, 1.2 Hz, 1H), 3.95 (tdt, J = 11.5, 7.9, 3.9 Hz, 1H), 3.47–3.39 (m, 2H), 3.36 (ddd, J = 12.3, 7.1, 4.6 Hz, 1H), 3.23 (ddd, J = 11.9, 7.0, 4.4 Hz, 1H), 3.11 (s, 3H), 2.63 (ddd, J = 12.0, 6.6, 4.7 Hz, 1H), 2.49 (s, 3H), 2.07–1.97 (m, 2H), 1.76–1.69 (m, 3H), 1.68–1.61 (m, 1H), 1.38 (ddt, J = 17.9, 12.8, 6.4 Hz, 2H), 1.21–1.10 (m, 3H), 0.79 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 160.5, 148.5, 131.2, 131.1, 125.8, 122.4, 122.0, 63.9, 48.7, 48.4, 47.8, 45.0, 37.4, 33.8, 33.7, 32.4, 25.9, 25.3, 20.1, 19.2; HRMS (ESI): Calculated for $C_{22}H_{34}N_4O$ (M^+ + H): 371.28054; Found: 371.28091.

(*E*)-*N*-Cyclohexyl-2-((3-isobutyl-1,4-dimethylpiperazin-2-ylidene) amino)benzamide 13b. Obtained using isovaleraldehyde following general procedure. Purified by normal-phase chromatography (0–10% MeOH/CH_2Cl_2) to yield the benzamidine, **13b** (71 mg, 60%) as a pale-yellow gum. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.1 Hz, 1H), 8.18 (dd, J = 7.9, 1.6 Hz, 1H), 7.30–7.25 (m, 2H), 7.05 (td, J = 7.6, 1.1 Hz, 1H), 6.61 (dd, J = 7.8, 1.1 Hz, 1H), 3.97 (dddd, J = 14.6, 10.6, 7.9, 3.9 Hz, 1H), 3.61 (td, J = 11.8, 5.3 Hz, 1H), 3.49 (dd, J = 10.6, 3.7 Hz, 1H), 3.41 (ddd, J = 14.0, 11.7, 5.2 Hz, 1H), 3.12 (ddd, J = 12.1, 5.3, 1.7 Hz, 1H), 3.08 (s, 3H), 2.73–2.66 (m, 1H), 2.50 (s, 3H), 2.02–1.94 (m, 2H), 1.71 (dq, J = 11.7, 4.0 Hz, 2H), 1.63 (dt, J = 12.6, 3.8 Hz, 1H), 1.54 (ddd, J = 14.1, 10.6, 3.9 Hz, 1H), 1.49–1.34 (m, 3H), 1.16 (dddd, J = 26.0, 15.5, 12.6, 5.6 Hz, 3H), 0.91 (ddd, J = 13.6, 9.7, 3.6 Hz, 1H), 0.66 (d, J = 6.6 Hz, 3H), 0.27 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7,

161.8, 148.6, 131.4, 131.3, 125.6, 122.9, 122.4, 56.8, 48.2, 44.9, 43.8, 42.2, 40.1, 37.3, 33.8, 33.6, 25.9, 25.1, 25.1, 24.4, 23.4, 20.3. HRMS (ESI): Calculated for $C_{23}H_{36}N_4O$ (M^+ + H): 385.29619; Found: 385.29719.

(*E*)-2-((3-Isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)-*N*-(4-methoxyphenyl)benzamide 13d. Obtained using 4-methoxyphenyl isocyanide following general procedure. Purified by normal-phase chromatography (0–10% MeOH/CH_2Cl_2) to yield the benzamidine, **13d** (120 mg, 40%) as a pale-yellow waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.97 (s, 1H), 8.24 (dd, J = 8.0, 1.7 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.36–7.29 (m, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 7.9 Hz, 1H), 3.79 (d, J = 1.3 Hz, 3H), 3.46–3.35 (m, 3H), 3.27–3.21 (m, 1H), 3.19 (s, 3H), 2.63 (dt, J = 11.9, 5.7 Hz, 1H), 2.52 (s, 3H), 1.75 (h, J = 6.8 Hz, 1H), 0.77 (d, J = 6.7 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 161.0, 156.1, 148.6, 132.0, 131.7, 131.3, 125.9, 122.6, 122.3, 122.0, 114.3, 64.0, 55.6, 48.3, 47.7, 44.9, 37.6, 32.5, 20.0, 19.3. HRMS (ESI): Calculated for $C_{23}H_{30}N_4O_2$ (M^+ + H): 395.24415; Found: 395.24443.

(*E*)-2-((3-Isobutyl-1,4-dimethylpiperazin-2-ylidene)amino)-*N*-(4-methoxyphenyl)benzamide 13e. Obtained using isovaleraldehyde and 4-methoxyphenyl isocyanide following general procedure. Purified by normal-phase chromatography (0–20% EtOAc/CH_2Cl_2) to yield the benzamidine, **13e** (56 mg, 45%) as a light-brown solid. M.p.: 109–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.25 (dd, J = 8.0, 1.7 Hz, 1H), 7.62–7.50 (m, 2H), 7.34 (td, J = 7.6, 1.7 Hz, 1H), 7.19–7.06 (m, 1H), 6.94–6.85 (m, 2H), 6.76–6.64 (m, 1H), 3.80 (s, 3H), 3.61 (ddd, J = 12.4, 8.8, 4.4 Hz, 2H), 3.38 (ddd, J = 14.0, 11.6, 5.3 Hz, 1H), 3.18 (s, 3H), 3.11 (ddd, J = 12.1, 5.4, 1.7 Hz, 1H), 2.69 (dd, J = 14.3, 5.1 Hz, 1H), 2.50 (s, 3H), 1.56 (ddd, J = 14.0, 10.6, 3.7 Hz, 1H), 1.47 (dqd, J = 10.4, 6.6, 3.9 Hz, 0H), 0.92 (ddd, J = 13.5, 9.7, 3.5 Hz, 1H), 0.65 (d, J = 6.7 Hz, 3H), 0.28 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 162.2, 155.9, 148.5, 132.1, 131.7, 131.3, 125.6, 123.0, 122.5, 121.6, 114.2, 77.4, 77.0, 76.7, 56.8, 55.5, 44.7, 43.4, 42.1, 39.9, 37.3, 24.4, 23.3, 20.2. HRMS (ESI): Calculated for $C_{24}H_{32}N_4O_2$ (M^+ + H): 409.25980; Found: 409.25931.

(*E*)-*N*-Cyclohexyl-2-((3-cyclopropyl-1,4-dimethylpiperazin-2-ylidene)amino)benzamide 13f. Obtained using cyclopropanecarboxaldehyde following general procedure. Purified by normal-phase chromatography (0–5% MeOH/CH_2Cl_2) to yield amidine **13f** (80 mg, 70%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 8.1 Hz, 1H), 8.18 (dt, J = 7.9, 1.5 Hz, 1H), 7.28–7.21 (m, 1H), 7.09–7.01 (m, 1H), 6.56 (d, J = 7.8 Hz, 1H), 3.96 (dtt, J = 11.2, 7.8, 4.1 Hz, 1H), 3.58–3.44 (m, 2H), 3.30 (dd, J = 10.3, 4.2 Hz, 1H), 3.09 (s, 3H), 2.92 (d, J = 8.6 Hz, 1H), 2.76 (dd, J = 11.8, 4.6 Hz, 1H), 2.46 (s, 3H), 1.98 (d, J = 12.9 Hz, 2H), 1.78–1.62 (m, 4H), 1.41 (qd, J = 12.5, 6.0 Hz, 3H), 1.23–1.06 (m, 3H), 0.90 (ddt, J = 13.8, 8.8, 4.3 Hz, 1H), 0.40 (td, J = 8.7, 4.5 Hz, 1H), 0.28 (tt, J = 8.6, 5.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 160.4, 148.9, 131.3, 131.1, 126.4, 122.6, 122.3, 62.1, 48.3, 47.4, 45.5, 42.3, 37.3, 33.8, 33.7, 25.9, 25.2, 25.2, 11.6, 4.1, 3.7, 1.2. HRMS (ESI): Calculated for $C_{22}H_{32}N_4O$ (M^+ + H): 369.26489; Found: 369.26570.

(*E*)-*N*-Cyclohexyl-2-((1,4-dimethyl-3-phenylpiperazin-2-ylidene)amino)benzamide 13g. Obtained using benzaldehyde following general procedure. Purified by normal-phase chromatography (0–10% MeOH/CH_2Cl_2) to yield benzamidine, **13g** (85 mg, 68%) as a pale-yellow gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 7.7 Hz, 1H), 7.88 (dd, J = 7.9, 1.5 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.5 Hz, 2H), 7.08–7.03 (m, 1H), 6.93–6.89 (m, 1H), 6.85 (d, J = 7.2 Hz, 2H), 6.37 (d, J = 7.7 Hz, 1H), 4.41 (s, 1H), 3.86–3.83 (m, 1H), 3.57–3.51 (m, 2H), 3.24 (s, 3H), 3.03–2.95 (m, 1H), 2.62–2.58 (m, 1H), 2.16 (s, 3H), 2.05–1.94 (m, 2H), 1.80–1.69 (m, 2H), 1.68–1.584 (m, 1H), 1.46–1.34 (m, 2H), 1.23–1.11 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 165.2, 157.6, 148.1, 135.7, 130.8, 130.6, 129.3, 128.0, 127.9, 125.5, 123.2, 122.1, 65.3, 49.1, 48.3, 46.6, 42.1, 37.4, 33.7, 33.7, 25.9, 25.2, 25.2. HRMS (ESI): Calculated for $C_{25}H_{32}N_4O$ (M^+ + H): 405.26489; Found: 405.26680.

(*E*)-*N*-Isopropyl-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)benzamide 13h. Obtained using isopropyl isocyanide following general procedure. Purified by normal-phase chromatography (0–5% MeOH/CH_2Cl_2) to yield the benzamidine, **13h** (51 mg, 50%) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, J = 7.6 Hz, 1H), 8.18 (dd, J = 7.9, 1.6 Hz, 1H), 7.28 (dd, J = 7.5, 1.7 Hz, 1H), 7.06–7.02 (m, 1H), 6.60 (dd, J = 7.9, 1.2 Hz, 1H), 4.31–4.22 (m, 1H), 3.48–3.41 (m, 2H), 3.36 (ddd, J = 12.2, 7.0, 4.6 Hz, 1H), 3.24 (ddd, J = 11.8, 7.0, 4.4 Hz, 1H), 3.13 (s, 3H), 2.64 (ddd, J = 12.0, 6.7, 4.7 Hz, 1H), 2.50 (s, 3H), 1.72 (h, J = 6.7 Hz, 1H), 1.22 (d, J = 6.5 Hz, 6H), 0.80 (d, J = 6.7 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 160.5, 148.6, 131.3, 131.2, 125.8, 122.4, 122.1, 64.0, 48.8, 47.9, 45.1, 41.3, 37.3, 32.5, 23.3, 23.2, 20.2, 19.3. HRMS (ESI): Calculated for $C_{19}H_{30}N_4O$ (M^+ + H): 331.24924; Found: 331.24986.

(*E*)-*N*-Cyclohexyl-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)-5-methylbenzamide 13i. Obtained using 2-azido-5-methylbenzoic acid following general procedure. Purified by normal-phase chromatography (0–5% MeOH/CH_2Cl_2) to yield the benzamidine, **13i** (53 mg, 45%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.0, 2.2 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.93 (tdt, J = 11.4, 7.8, 3.9 Hz, 1H), 3.48–3.36 (m, 2H), 3.34 (ddd, J = 12.0, 7.0, 4.6 Hz, 1H), 3.22 (ddd, J = 11.8, 7.0, 4.5 Hz, 1H), 3.09 (s, 3H), 2.62 (ddd, J = 11.9, 6.6, 4.7 Hz, 1H), 2.48 (s, 3H), 2.30 (s, 3H), 2.07–1.94 (m, 3H), 1.73 (ddt, J = 11.9, 8.0, 4.5 Hz, 2H), 1.71–1.58 (m, 1H), 1.38 (tdt, J = 16.5, 12.1, 3.8 Hz, 2H), 1.13 (qdt, J = 10.6, 6.7, 3.2 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H), 0.63 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 160.6, 146.0, 131.9, 131.5, 125.5, 122.3, 64.0, 48.7, 48.5, 47.9, 45.0, 37.4, 33.8, 33.8, 32.5, 25.9, 25.3, 20.8, 20.1, 19.3. HRMS (ESI): Calculated for $C_{23}H_{36}N_4O$ (M^+ + H): 385.29619; Found: 385.29605.

(*E*)-*N*-Cyclohexyl-5-fluoro-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)benzamide 13j. Obtained using 2-azido-5-fluorobenzoic acid following general procedure. Purified by normal-phase chromatography (0–5% MeOH/CH_2Cl_2) to yield the benzamidine, **13j** (67 mg, 56%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 7.4 Hz, 1H), 7.90 (dd,

J = 10.1, 2.9 Hz, 1H), 6.99 (td, J = 8.4, 3.1 Hz, 1H), 6.56 (dd, J = 8.6, 4.9 Hz, 1H), 4.03–3.87 (m, 1H), 3.48–3.46 (m, 1H), 3.41–3.31 (m, 2H), 3.28–3.22 (m, 1H), 3.13 (s, 3H), 2.70–2.60 (m, 1H), 2.50 (s, 3H), 2.10–1.95 (m, 2H), 1.80–1.59 (m, 4H), 1.51–1.35 (m, 2H), 1.24–1.18 (m, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.09. ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 164.6, 160.9, 159.6, 157.2, 149.9, 127.1, 127.1, 123.5, 123.4, 118.1, 117.8, 117.3, 117.1, 63.9, 48.7, 48.6, 47.8, 45.1, 37.3, 33.7, 33.6, 32.5, 25.8, 25.2, 20.0, 19.1. HRMS (ESI): Calculated for $C_{22}H_{33}FN_4O$ (M^+ + H): 389.27112; Found: 389.27059.

(*E*)-*N*-Cyclohexyl-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)-4-methylbenzamide 13k. Obtained using 2-azido-4-methylbenzoic acid following general procedure. Purified by normal-phase chromatography (0–5% MeOH/CH_2Cl_2) to yield the benzamidine, **13k** (53 mg, 45%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.39 (s, 1H), 3.94 (dtd, J = 11.3, 7.6, 4.1 Hz, 1H), 3.49–3.30 (m, 3H), 3.23 (ddd, J = 11.8, 6.9, 4.5 Hz, 1H), 3.10 (s, 3H), 2.63 (ddd, J = 12.0, 6.7, 4.7 Hz, 1H), 2.50 (s, 3H), 2.29 (s, 3H), 2.01 (tt, J = 8.4, 3.8 Hz, 2H), 1.78–1.59 (m, 4H), 1.46–1.31 (m, 2H), 1.21–1.06 (m, 3H), 0.80 (d, J = 6.7 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 160.5, 148.4, 141.3, 131.3, 123.3, 123.1, 123.0, 64.1, 48.8, 48.4, 47.9, 45.01, 37.4, 33.9, 33.8, 32.6, 25.9, 25.3, 21.4, 20.1, 19.4. HRMS (ESI): Calculated for $C_{23}H_{36}N_4O$ (M^+ + H): 385.29619; Found: 385.29585.

(*E*)-*N*-Cyclohexyl-4-fluoro-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)benzamide 13l. Obtained using 2-azido-4-fluorobenzoic acid following general procedure. Purified by normal-phase chromatography (0–40% EtOAc/hexane) to yield the benzamidine, **13l** (25 mg, 21%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 8.0 Hz, 1H), 8.19 (dd, J = 8.8, 7.1 Hz, 1H), 6.73 (td, J = 8.4, 2.5 Hz, 1H), 6.30 (dd, J = 10.3, 2.5 Hz, 1H), 3.94 (tdt, J = 11.5, 7.9, 3.9 Hz, 1H), 3.52–3.42 (m, 2H), 3.37 (ddd, J = 12.3, 6.8, 4.7 Hz, 1H), 3.24 (ddd, J = 11.7, 6.8, 4.5 Hz, 1H), 3.13 (s, 3H), 2.65 (ddd, J = 12.0, 6.8, 4.7 Hz, 1H), 2.52 (s, 3H), 2.02 (dt, J = 11.8, 4.1 Hz, 2H), 1.70 (ddt, J = 29.4, 14.9, 5.2 Hz, 5H), 1.40 (qd, J = 12.5, 3.3 Hz, 2H), 1.22–1.06 (m, 3H), 0.82 (d, J = 6.7 Hz, 3H), 0.68 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.97. ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 165.0, 162.7, 160.8, 150.5, 150.4, 133.5, 133.4, 122.2, 122.2, 108.9, 108.7, 108.6, 108.4, 63.8, 48.6, 48.4, 47.7, 45.1, 37.3, 33.8, 33.7, 32.5, 29.7, 25.8, 25.2, 20.1, 19.1. HRMS (ESI): Calculated for $C_{22}H_{33}FN_4O$ (M^+ + H): 389.27116; Found: 389.27155.

(*E*)-*N*-Cyclohexyl-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)-3-methylbenzamide 13m. Obtained using 2-azido-3-methylbenzoic acid following general procedure. Purified by normal phase chromatography (0–30% EtOAc/CH_2Cl_2) to yield the benzamidine, **13m** (41 mg, 35%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 7.9 Hz, 1H), 8.04 (dd, J = 7.9, 1.6 Hz, 1H), 7.23 (dd, J = 7.4, 1.5 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 3.92 (dtt, J = 11.6, 8.0, 4.0 Hz, 1H), 3.60 (ddd, J = 12.6, 9.6, 3.2 Hz, 1H), 3.20 (s, 4H), 3.13 (s, 1H), 3.05 (ddd, J = 15.4, 8.6, 3.7 Hz, 1H), 2.94 (d, J = 3.0 Hz, 1H), 2.62 (ddd, J = 11.4, 9.6, 3.6 Hz, 1H), 2.38 (s, 3H), 2.11 (d, J = 3.8 Hz, 4H), 2.07–1.94 (m, 1H), 1.72 (tdd, J = 12.8, 8.1, 5.1 Hz, 1H), 1.63 (qd, J = 7.0, 3.0 Hz, 1H), 1.49–1.30 (m, 2H), 1.14 (tddd, J = 11.6, 8.7, 6.3, 3.8 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 0.67 (d, J = 6.9 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 160.5, 147.5, 133.2, 129.1, 127.8, 126.0, 121.6, 65.8, 51.5, 49.0, 48.4, 47.4, 37.2, 33.8, 33.7, 32.8, 25.8, 25.3, 25.2, 21.2, 19.2, 17.6. HRMS (ESI): Calculated for $C_{22}H_{33}FN_4O$ (M^+ + H): 389.27112; Found: 389.27196.

(*E*)-*N*-Cyclohexyl-3-fluoro-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)benzamide 13n. Obtained using 2-azido-3-fluorobenzoic acid following general procedure. Purified by normal-phase chromatography (0–15% EtOAc/CH_2Cl_2) to yield the benzamidine, **13n** (65 mg, 42%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.10 (ddd, J = 10.1, 8.0, 1.6 Hz, 1H), 6.94 (td, J = 8.0, 5.1 Hz, 1H), 3.94 (tdt, J = 11.4, 7.8, 3.8 Hz, 1H), 3.51 (ddd, J = 12.1, 8.0, 3.8 Hz, 1H), 3.33 (ddd, J = 12.6, 5.9, 4.1 Hz, 1H), 3.19 (s, 3H), 3.12 (t, J = 3.2 Hz, 2H), 2.66 (ddd, J = 12.1, 8.0, 4.1 Hz, 1H), 2.45 (s, 3H), 2.07–1.97 (m, 2H), 1.77–1.61 (m, 4H), 1.46–1.34 (m, 2H), 1.16 (dddd, J = 12.4, 8.6, 6.8, 2.7 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −127.01. ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 162.9, 153.8, 151.4, 137.2, 137.1, 127.9, 126.7, 121.4, 121.4, 118.0, 117.8, 66.0, 49.9, 48.6, 48.3, 46.0, 37.5, 33.8, 33.7, 33.6, 29.8, 25.9, 25.3, 20.6, 18.7. HRMS (ESI): Calculated for $C_{22}H_{33}FN_4O$ (M^+ + H): 389.27112; Found: 389.27196.

(*E*)-5-Cyano-2-((3-cyclopropyl-1,4-dimethylpiperazin-2-ylidene)amino)-*N*-isopropylbenzamide 13o. Obtained using cyclopropanecarboxaldehyde, 2-azido-5-cyanobenzoic acid and isopropyl isocyanide following general procedure. Purified by normal-phase chromatography (0–15% MeOH/EtOAc) to yield the benzamidine, **13o** (48 mg, 44%) as a light-brown solid. M.p.: 147–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.7 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H), 7.50 (dd, J = 8.2, 2.1 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 4.32–4.18 (m, 1H), 3.58 (td, J = 11.0, 5.5 Hz, 1H), 3.45 (ddd, J = 12.8, 10.4, 5.1 Hz, 1H), 3.35 (ddd, J = 11.7, 5.1, 2.4 Hz, 1H), 3.13 (s, 3H), 2.93 (d, J = 8.4 Hz, 1H), 2.79 (ddd, J = 13.2, 5.7, 2.3 Hz, 1H), 2.46 (s, 3H), 1.23 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.5 Hz, 3H), 0.89 (dtd, J = 13.3, 8.3, 5.0 Hz, 1H), 0.51–0.40 (m, 1H), 0.36–0.25 (m, 1H), 0.14 (dq, J = 10.5, 5.2 Hz, 1H), −0.48 (dq, J = 10.3, 5.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 160.6, 153.0, 135.7, 134.2, 126.8, 123.3, 119.2, 105.0, 61.9, 47.2, 45.3, 42.3, 41.4, 37.2, 23.1, 23.0, 11.5, 3.9, 3.6. HRMS (ESI): Calculated for $C_{20}H_{27}N_5O$ (M^+ + H): 354.22884; Found: 354.22999.

(*E*)-2-((3-Isopropyl-1,4-dimethylpiperazin-2-ylidene)amino)-*N*-(4-methoxyphenyl)-5-nitrobenzamide 13p. Obtained using 2-azido-5-nitrobenzoic acid 4-methoxyphenyl isocyanide following general procedure. Purified by normal-phase chromatography (0–3% EtOAc/CH_2Cl_2) to yield the benzamidine, **13p** (49 mg, 36%) as yellow solid. M.p.: 167–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 9.17 (d, J = 2.8 Hz, 1H), 8.16 (dd, J = 8.8, 2.9 Hz, 1H), 7.59–7.46 (m, 2H), 6.97–6.84 (m, 2H), 6.71 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.57–3.46 (m, 2H), 3.45 (d, J = 6.4 Hz, 1H), 3.27 (s, 4H), 2.76–2.65 (m, 1H), 2.55 (s, 3H),

1.76 (h, J = 6.7 Hz, 1H), 0.80 (d, J = 6.7 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 162.0, 156.3, 154.3, 142.3, 131.3, 127.8, 126.4, 125.7, 122.6, 121.8, 114.3, 64.3, 55.5, 48.0, 47.5, 44.9, 37.8, 32.8, 20.0, 19.1. Calculated for HRMS (ESI): $C_{23}H_{29}N_5O_4$ (M^+ + H): 440.22923; Found: 440.22903.

(*E*)-*N*-Isopropyl-2-((3-isopropyl-1,4-dimethylpiperazin-2-ylidene) amino)-5-nitrobenzamide 13q. Obtained using 2-azido-5-nitrobenzoic acid and isopropyl isocyanide following general procedure. Purified by normal-phase chromatography (0–7% EtOAc/CH_2Cl_2) to yield the benzamidine, **13q** (36 mg, 31%) as a yellow-orange solid. M.p.: 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 2.8 Hz, 1H), 8.93 (d, J = 7.6 Hz, 1H), 8.12 (dd, J = 8.8, 2.9 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 4.27 (dq, J = 13.2, 6.5 Hz, 1H), 3.53 (ddd, J = 11.9, 6.9, 4.5 Hz, 1H), 3.46 (dd, J = 6.7, 4.9 Hz, 1H), 3.42 (d, J = 6.0 Hz, 1H), 3.25 (ddd, J = 12.6, 6.6, 4.5 Hz, 1H), 3.19 (s, 3H), 2.71 (ddd, J = 12.1, 6.9, 4.8 Hz, 1H), 2.53 (s, 3H), 1.71 (h, J = 6.7 Hz, 1H), 1.23 (dd, J = 6.6, 1.4 Hz, 6H), 0.83 (d, J = 6.7 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 161.3, 154.4, 142.0, 127.68, 126.0, 125.6, 122.5, 77.4, 77.0, 76.7, 64.2, 48.5, 47.7, 45.1, 41.6, 37.4, 32.9, 23.02, 23.0, 20.1, 19.0. Calculated for HRMS (ESI): $C_{19}H_{29}N_5O_3$ (M^+ + H): 376.23432; Found: 376.23487.

(*E*)-*N*-Cyclohexyl-2-((1,4-dimethyl-3-(thiazol-5-yl)piperazin-2-ylidene)amino)benzamide 13r. Obtained using 5-thiazolecarboxaldehyde following general procedure. Purified by normal-phase chromatography (0.5–3.5% MeOH/CH_2Cl_2) to yield the benzamidine, **13r** (76 mg, 60%) as an amber gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.99 (dd, J = 7.9, 1.7 Hz, 1H), 7.30 (s, 1H), 7.15 (td, J = 7.6, 1.7 Hz, 1H), 7.06–6.99 (m, 1H), 6.38 (d, J = 7.8 Hz, 1H), 4.86 (s, 1H), 3.87 (dtd, J = 10.9, 7.4, 4.0 Hz, 1H), 3.55 (td, J = 11.0, 5.1 Hz, 1H), 3.38 (ddd, J = 11.5, 4.6, 2.7 Hz, 1H), 3.18 (s, 3H), 2.97 (ddd, J = 12.6, 10.6, 4.6 Hz, 1H), 2.64 (ddd, J = 12.9, 5.3, 2.4 Hz, 1H), 2.17 (s, 3H), 2.03–1.94 (m, 2H), 1.79–1.61 (m, 5H), 1.46–1.32 (m, 1H), 1.16 (dq, J = 14.3, 11.5, 11.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 156.3, 153.5, 147.3, 143.9, 131.1, 131.0, 130.9, 125.8, 122.8, 122.6, 56.5, 49.2, 48.4, 45.8, 41.6, 37.3, 33.6, 25.8, 25.1. HRMS (ESI): Calculated for $C_{22}H_{29}N_5OS$ (M^+ + H): 412.21656; Found: 412.21798.

(*E*)-*N*-Cyclohexyl-3-((1,4-dimethyl-3-phenylpiperazin-2-ylidene) amino)-2-naphthamide 13s. Obtained using benzaldehyde and 3-azido-2-naphthanoic acid following general procedure. Purified by normal-phase chromatography (0–20% EtOAc/CH_2Cl_2) to yield the naphthamidine, **13s** (69 mg, 50%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.0 Hz, 1H), 8.47 (s, 1H), 7.79 (dd, J = 8.3, 1.2 Hz, 1H), 7.36 (d, J = 3.8 Hz, 2H), 7.29 (dd, J = 8.2, 3.9 Hz, 1H), 7.23–7.17 (m, 1H), 7.09 (t, J = 7.6 Hz, 2H), 6.81 (dd, J = 7.9, 1.4 Hz, 2H), 6.66 (s, 1H), 4.51 (s, 1H), 3.90 (tdt, J = 11.3, 7.8, 3.9 Hz, 1H), 3.63–3.51 (m, 2H), 3.29 (s, 3H), 3.02 (ddd, J = 12.5, 8.7, 5.0 Hz, 1H), 2.62 (dt, J = 12.5, 4.7 Hz, 1H), 2.14 (s, 3H), 2.10–1.98 (m, 2H), 1.84–1.57 (m, 2H), 1.53–1.35 (m, 2H), 1.28–1.13 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 157.8, 145.04, 135.7, 134.7, 131.7, 129.3, 129.3, 128.9, 127.9, 127.8, 127.0, 126.1, 126.0, 124.0, 119.1, 64.9, 49.2, 48.4, 46.3, 42.0, 37.4, 33.6, 25.8, 25.2, 25.1. Calculated for HRMS (ESI): $C_{29}H_{34}N4O$ (M^+ + H): 455.28054; Found: 455.28019.

(*E*)-*N*-Cyclohexyl-2-((1,4-dimethyl-3-phenylpiperazin-2-ylidene) amino)-5-iodobenzamide 13t. Obtained using benzaldehyde and 2-azido-5-iodobenzoic acid following general procedure. Purified by normal-phase chromatography (0–15% EtOAc/CH_2Cl_2) to yield benzamidine **13t** (144 mg, 88%) as pale yellow oil. Recrystallized from acetonitrile to form clear colorless crystal (see ESI† for crystallographic Experimental section). M.p.: 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 7.9 Hz, 1H), 8.15 (d, J = 2.2 Hz, 1H), 7.32 (dd, J = 8.3, 2.3 Hz, 1H), 7.24–7.18 (m, 1H), 7.14 (d, J = 7.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 0H), 6.85 (d, J = 6.9 Hz, 1H), 6.12 (d, J = 8.3 Hz, 1H), 4.33 (s, 1H), 3.80 (dtd, J = 10.9, 7.3, 3.9 Hz, 1H), 3.64–3.42 (m, 2H), 3.22 (s, 3H), 2.98 (ddd, J = 12.7, 7.6, 5.2 Hz, 1H), 2.59 (dt, J = 12.5, 5.0 Hz, 1H), 2.15 (s, 3H), 2.04–1.88 (m, 2H), 1.80–1.61 (m, 2H), 1.48–1.32 (m, 2H), 1.15 (dtdd, J = 23.1, 11.8, 7.9, 3.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 157.7, 147.9, 139.3, 139.0, 135.4, 129.2, 128.0, 128.0, 127.4, 125.2, 84.9, 65.5, 49.2, 48.3, 46.8, 42.1, 37.3, 33.5, 33.5, 25.8, 25.1, 25.1. Calculated for HRMS (ESI): $C_{21}H_{35}IN4O$ (M^+ + H): 531.16154; Found: 531.16069.

(*E*)-3-((1-Benzyl-3,4-dicyclopropylpiperazin-2-ylidene)amino)-*N*-(2-morpholinoethyl) thiophene-2-carboxamide 13x. Obtained using *tert*-butyl benzyl((2-cyclopropylamino)ethyl) carbamate, cyclopropanecarboxaldehyde, 3-azidothiophene-2-carboxylic acid, and 2-morphalinoethyl isocyanide following general procedure. Purified by normal-phase chromatography (0–3% MeOH/CH_2Cl_2) to yield the thiophene carboxamidine, **13x** (54 mg, 40%) as a pale-yellow gum. (54 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, J = 5.9 Hz, 1H), 7.43–7.24 (m, 7H), 6.49 (d, J = 5.2 Hz, 1H), 5.29 (d, J = 15.3 Hz, 1H), 4.40 (d, J = 15.3 Hz, 1H), 3.64–3.47 (m, 6H), 3.32 (ddd, J = 24.2, 11.5, 7.1 Hz, 3H), 3.19 (dq, J = 13.0, 6.4 Hz, 1H), 2.97 (q, J = 6.2, 5.1 Hz, 1H), 2.39–2.16 (m, 7H), 1.11 (dp, J = 12.5, 4.3, 3.7 Hz, 1H), 0.62–0.26 (m, 5H), 0.16 (dq, J = 10.0, 5.1 Hz, 1H), −0.30 (dq, J = 10.2, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 162.3, 149.1, 137.5, 129.0, 127.8, 127.5, 127.1, 124.0, 122.9, 66.9, 62.2, 58.0, 53.5, 51.6, 45.2, 43.6, 36.1, 34.2, 12.3, 7.9, 6.7, 3.9, 3.8. HRMS (ESI): Calculated for $C_{28}H_{37}N_5O_2$ (M^+ + H): 508.274073; Found: 508.27490.

Modified procedure for the telescoped synthesis of C3-unsubstituted (*E*)-arylamidines

An oven-dried, 10 mL round bottom flask under nitrogen was charged with activated, powdered 4 Å molecular sieves (150 mg). The flask was placed under vacuum and flame-dried, then backfilled with nitrogen, *N*,*N*′-Dimethylethylenediamine (115 mg, 0.61 mmol, 2.0 equiv.) was dissolved in dry CH_2Cl_2 (0.9 mL, 0.7 M) and added to the reaction vessel. Formalin, 37 wt% in H_2O (0.1 mL, 1.2 mmol, 4.0 equiv.) was measured with syringe added dropwise over a minute to the reaction vessel while stirring at rt. Remainder of the procedure follows general procedure.

(*E*)-*N*-Cyclohexyl-2-((1,4-dimethylpiperazin-2-ylidene)amino) benzamide 13c. Obtained using 2-azidobenzoic acid and cyclo-

hexyl isocyanide following modified procedure. Purified by normal-phase chromatography (0–10% MeOH/CH_2Cl_2) to yield the benzamidine, **13c** (48 mg, 48%) as an amber gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 8.12 (dd, J = 7.9, 1.7 Hz, 1H), 7.29–7.25 (m, 1H), 7.09–7.04 (m, 1H), 6.65 (d, J = 7.8 Hz, 1H), 3.94 (tdt, J = 11.0, 7.8, 3.8 Hz, 1H), 3.37 (t, J = 5.5 Hz, 2H), 3.12 (s, 3H), 2.95 (s, 2H), 2.61 (t, J = 5.6 Hz, 2H), 2.19 (s, 3H), 1.99 (dq, J = 12.4, 4.0 Hz, 2H), 1.71 (dp, J = 11.9, 3.9 Hz, 2H), 1.63 (dt, J = 12.2, 3.9 Hz, 1H), 1.40 (tdd, J = 15.5, 12.0, 3.6 Hz, 2H), 1.15 (td, J = 12.4, 9.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 155.5, 148.3, 131.3, 131.2, 126.0, 123.2, 122.7, 55.1, 52.4, 49.7, 48.4, 45.5, 36.5, 33.6, 25.9, 25.1. HRMS (ESI): Calculated for $C_{19}H_{28}N_4O$ (M^+ + H): 329.23359; Found: 329.23434.

(*E*)-5-Fluoro-*N*-isopropyl-2-((2-methylhexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-ylidene)amino) benzamide 13u. Obtained using *tert*-butyl 2-((methylamino)methyl)pyrrolidine-1-carboxylate, 2-azido-5-fluorobenzoic acid, and isopropyl isocyanide following modified procedure. Purified by normal-phase chromatography (0–3% EtOAc/CH_2Cl_2) to yield the benzamidine, **13u** (51 mg, 50%) as a pale-yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 7.7 Hz, 1H), 7.85 (dd, J = 10.0, 3.1 Hz, 1H), 7.07–6.94 (m, 1H), 6.69 (dd, J = 8.7, 5.0 Hz, 1H), 4.31–4.15 (m, 1H), 3.78–3.51 (m, 3H), 3.30 (d, J = 16.3 Hz, 1H), 3.08 (dd, J = 10.8, 3.8 Hz, 1H), 2.56 (d, J = 16.2 Hz, 1H), 2.24 (s, 3H), 2.09 (dq, J = 11.8, 6.2, 5.7 Hz, 2H), 1.95 (dd, J = 12.7, 8.7 Hz, 2H), 1.48 (qd, J = 11.7, 7.9 Hz, 1H), 1.19 (dd, J = 6.5, 1.6 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.28. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 164.7, 164.7, 159.9, 157.5, 154.5, 144.7, 144.7, 144.6, 127.2, 127.1, 124.7, 124.6, 118.3, 118.1, 117.2, 116.9, 57.9, 57.8, 54.2, 45.8, 45.2, 41.3, 30.4, 23.1, 23.0, 22.5. HRMS (ESI): Calculated for $C_{18}H_{25}FN_4O$ (M^+ + H): 333.20852; Found: 333.20814.

(*E*)-3-((1,4-Dimethylpiperazin-2-ylidene)amino)-*N*-(4-methoxyphenyl)thiophene-2-carboxamide 13v. Obtained using 3-azidothiophene-2-carboxylic acid and 4-methoxyphenyl isocyanide following modified procedure. Purified by normal-phase chromatography (0–3% MeOH/EtOAc) to yield the thiophene carboxamidine, **13v** (32 mg, 29%) as a light-brown solid. M.p.: 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.55–7.46 (m, 2H), 7.35 (d, J = 5.2 Hz, 1H), 6.89–6.83 (m, 2H), 6.60 (d, J = 5.2 Hz, 1H), 3.80 (s, 3H), 3.43 (t, J = 5.6 Hz, 2H), 3.22 (s, 4H), 2.67 (t, J = 5.6 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 157.1, 155.7, 147.9, 132.1, 128.1, 124.5, 123.8, 121.2, 114.2, 55.5, 55.4, 52.0, 49.7, 45.5, 36.7. HRMS (ESI): Calculated for $C_{18}H_{22}N_4O_2S$ (M^+ + H): 359.15362; Found: 359.15459.

(*E*)-3-((1,4-Dimethylpiperazin-2-ylidene)amino)-*N*-(4-methoxyphenyl)furan-2-carboxamide 13w. Obtained using 3-azidofuran-2-carboxylic acid and 4-methoxyphenyl isocyanide following modified procedure. Purified by normal-phase chromatography (5–30% EtOAc/CH_2Cl_2) to yield furan carboxamidine, **13w** (21 mg, 20%) as a light-brown solid. M.p.: 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 1.9 Hz, 1H), 6.87 (d, J = 9.1 Hz, 2H), 6.17 (d, J = 1.9 Hz, 1H), 3.79 (s, 3H), 3.43 (t, J = 5.6 Hz, 2H), 3.31 (s, 2H), 3.20 (s, 3H), 2.69 (t, J = 5.6 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 157.5, 155.7, 143.8, 137.5, 136.7, 132.0, 121.2, 114.2, 108.9, 55.5, 55.4, 51.9, 49.7, 45.5, 36.9. HRMS (ESI): Calculated for $C_{18}H_{22}N_4O_3$ (M^+ + H): 343.17647; Found: 343.17700.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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