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Structure–activity relationships of 3,4-dihydro-1*H*-quinazolin-2-one derivatives as potential CDK5 inhibitors

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Abstract—Cyclin-dependent kinase 5 (CDK5) is a serine/threonine kinase that plays a critical role in the early development of the nervous system. Deregulation of CDK5 is believed to contribute to the abnormal phosphorylation of various cellular substrates associated with neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis, and ischemic stroke. Acyclic urea **3** was identified as a potent CDK5 inhibitor and co-crystallographic data of urea **3**/CDK2 enzyme were used to design a novel series of 3,4-dihydroquinazolin-2(1*H*)-ones as CDK5 inhibitors. In this investigation we present our synthetic studies toward this series of compounds and discuss their biological relevance as CDK5 inhibitors.

1. Introduction

Cyclin-dependent kinase 5 (CDK5) is a serine/threonine kinase that is expressed in most tissues, although its enzymatic activity is predominantly detected in the central nervous system.[1,2] Similar to other CDKs, monomeric CDK5 has negligible enzymatic activity and requires association with regulatory proteins for complete activation. The two non-cyclin proteins, p35 and p39, have been identified as CDK5 activators that are localized to the cell membrane. Unlike other cyclin-dependent kinases, CDK5 has no known involvement in cell-cycle progression but is critical for the early development of the central nervous system.[3] Among its many roles, CDK5 is involved in cellular processes such as neuronal differentiation,[4] cell adhesion,[5] and axonal guidance.[6] In addition to its involvement in the development of neurons, recent studies have suggested roles for CDK5 in associative learning[7,8] and regulation of dopamine signaling in drug addiction.[9–13]

Deregulation of CDK5 from extracellular insults has been implicated in the pathology of several neurodegenerative disorders.[14–18] Extracellular insults, such as amyloid-β peptides, oxidative stress, and excitotoxicity, result in the conversion of p35 to p25. As a consequence, CDK5 becomes delocalized to the cytoplasm where it hyperphosphorylates substrates such as tau, a constituent of neurofibrillary tangles commonly found in Alzheimer's diseased brains,[19,20] and neurofilaments that accumulate in neurons of patients with amyotrophic lateral sclerosis.[21] Recent animal studies have also implicated CDK5 in Niemann–Pick type C,[22] Parkinson's disease,[23] and ischemic stroke.[24–27] In the pursuit to treat CDK-related diseases, several compound classes have been identified as CDK5 inhibitors such as the paullones,[28] meridianins,[29] indirubins,[30,31] flavinols,[32] pyrazolo-quinoxalines,[33] purines,[34] and thiazoles.[35,36] In this report, we describe our investigation of 3,4-dihydro-1*H*-quinazolin-2-ones as potential CDK5 inhibitors for the treatment of neurodegenerative diseases.

Recently, X-ray crystal structure[37,38] and molecular modeling[39–41] of CDK5 complexes have provided scien-

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tists with useful tools in the design of selective CDK5 inhibitors. Prior to these most recent discoveries, we relied on the screening of our internal compound collection to provide us with leads for further optimization. Initial hits obtained from our screening collection were a series of acyclic ureas **1**–**3** (Fig. 1).[42] In our preliminary SAR investigations we found that phenyl-urea **1** was 10-fold less potent than the pyridyl-urea **2** (2990 vs 192 nM, respectively) in the in vitro human CDK5 enzyme assay. We hypothesized that an intramolecular hydrogen bond between N1 and the N3-hydrogen placed the 2-amino-pyridine ring and urea functionality of **2** in a planar geometry within the active site of CDK5. This intramolecular hydrogen bond hypothesis was supported by the X-ray crystal structure of a piperazine substituted analog urea **3** (CDK5 IC_{50} = 15 nM). Urea **3** was successfully co-crystallized with CDK2, a closely related homolog of CDK5,[43] and was also found to be a potent CDK5 inhibitor (Fig. 2).[44] In addition to reaffirming our hypothesis of the presence of an intramolecular hydrogen bond between N1 and N3-hydrogen, this X-ray crystal structure provided valuable information about other key interactions between the inhibitor and the enzyme. For example, it was observed that the N2–NH and the carbonyl oxygen of the urea were involved in a donor–acceptor hydrogen bond network to the Leu83 linker region of the CDK2 ATP binding site. Furthermore, the thiazolo-pyridine extends through a hydrophobic region (Ala31, Phe80, and Leu134) to form a hydrogen bond with the Lys33-Asp145 salt bridge of the ATP binding site.

Using the CDK2/compound **3** co-crystallographic data we developed a model of CDK5 that was used in the design of inhibitors reported in this investigation (Fig. 3). Figure 3 also illustrates the proposed binding mode of **1**, **2**, and **20a** (a cyclic urea derivative), to this CDK5 homology model. The most notable difference between the ATP binding pockets of CDK2 and CDK5 is the linker region where the Leu83-His84 residues of CDK2 are replaced with Cys83-Asp84 in

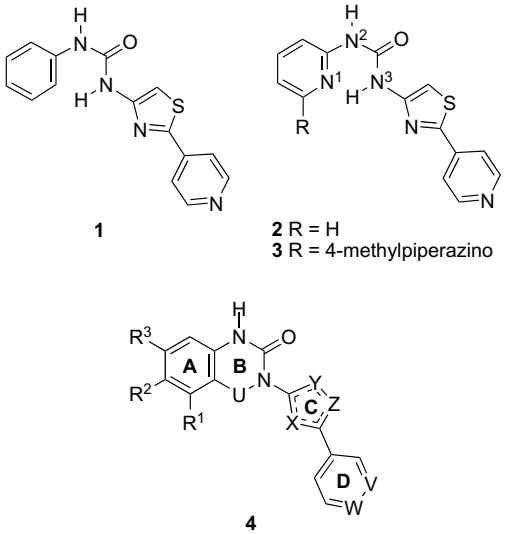


Figure 1.

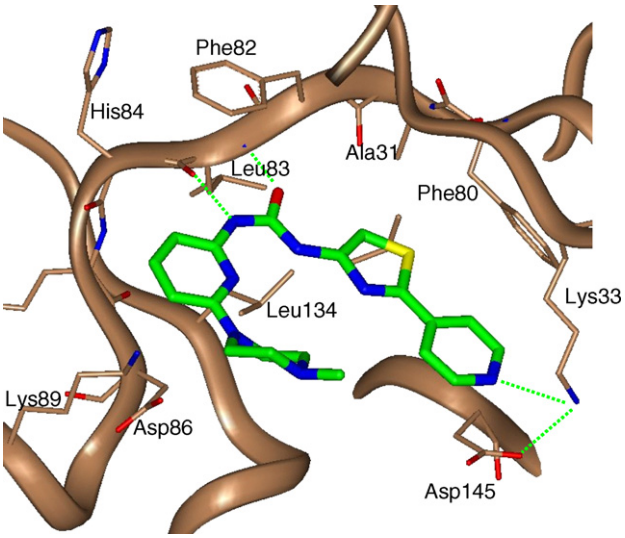


Figure 2. X-ray co-crystal of compound **3**/CDK2. Carbon atoms of compound **3** are shown in green, carbon atoms of active site residues in brown, nitrogen atoms are shown in blue, oxygen atoms are shown in red,and sulfur atoms are shown in yellow. Hydrogen bonding is shown in green and the backbone of the protein is traced with a solid brown ribbon.

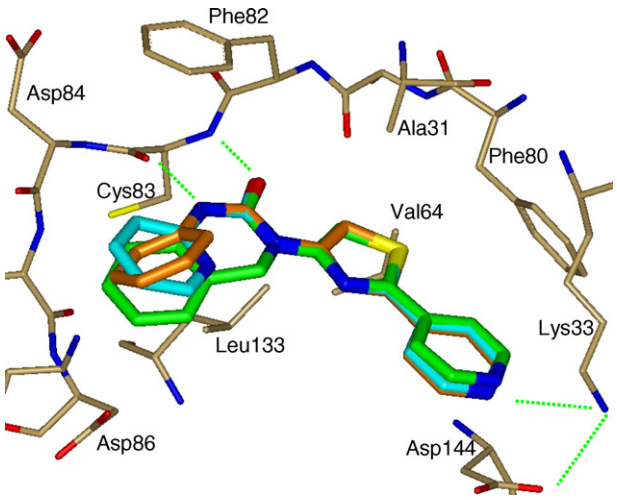


Figure 3. Docked models of compounds **1**, **2**, and **20a** in the active site of CDK5. Nitrogen atoms are shown in blue, oxygen atoms are shown in red, sulfur atoms are shown in yellow, and carbon atoms of active site residues in brown. Carbon atoms of compounds **1**, **2**, and **20a** are shown in orange, cyan, and green, respectively. Ligand–protein H-bonds are shown in green.

CDK5. Homologous to CDK2, the binding pocket of CDK5 conserves the key Phe80 residue of the hydrophobic pocket and maintains a Lys33-Asp144 salt bridge. With our preliminary biological evaluation of acyclic ureas **1** and **2**, and the crystallographic data of urea **3**, we proposed that constrained cyclic ureas with a general structure **4** would serve as effective inhibitors of CDK5, consistent with our modeling efforts. Herein, we describe the synthesis of 3,4-dihydro-1*H*-quinazolin-2-one analogs with general structure **4** along with the structure–activity relationships of this series of CDK5 inhibitors.

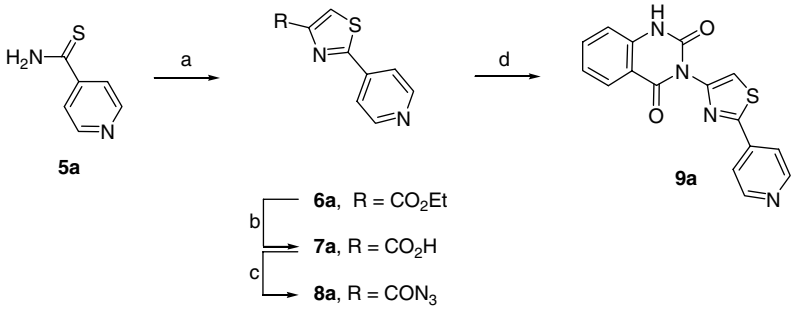
2. Chemistry

A variety of synthetic routes were employed to prepare the conformationally constrained compounds required for this investigation (Fig. 1, general structure **4**). For ease of discussion, these are divided into four main areas: conformational constraints to the B-ring (U), substituents on the aromatic A-ring (R^1–R^3), alternative aromatic C-rings (X, Y, and Z), and modifications to the pyridine D-ring (W and V).

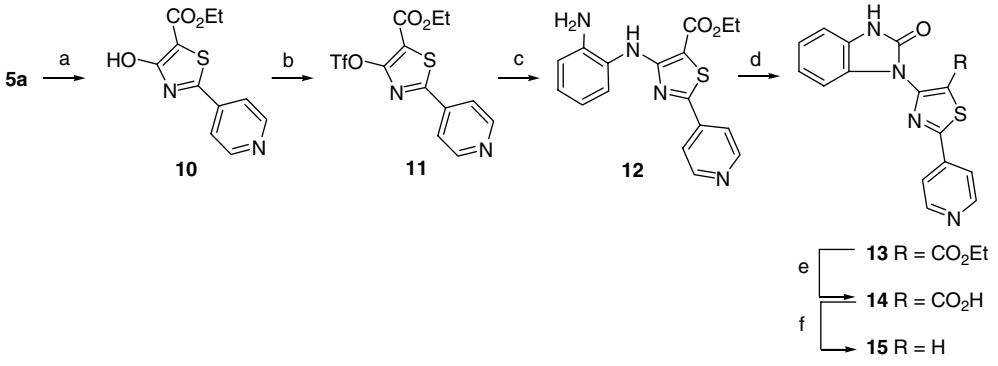
The initial focus of this study was the examination of conformationally restricting linking groups, and therefore, three different ring systems were prepared: a quinazoline-2,4-dione (U = carbonyl), a benzimidazolone (U = a single bond), and a dihydroquinazolinone (U = CH_2). Quinazolinedione **9a** was synthesized in three steps as shown in Scheme 1. Reaction of commercially available thioisonicotinamide **5a** with ethyl bromopyruvate followed by hydrolysis provided acid **7a**. Acid **7a** was converted to the acid chloride followed by treatment with sodium azide to give the corresponding acylazide **8a**. Quinazolinedione **9a** was obtained by a Curtius rearrangement of azide **8a** and trapping of the resulting isocyanate intermediate with methyl 2-aminobenzoate.

The 5-membered benzimidazolone derivative **15** (Fig. 1, U = a single bond) was prepared as outlined in Scheme 2. Treatment of thioisonicotinamide **5a** with diethyl bromomalonate provided hydroxy-thiazole **10**. Triflate **11** was obtained by the reaction of **10** with triflic anhydride. Displacement of the triflate with 1,2-phenylenediamine followed by cyclization with 1,1′-carbonyldiimidazole (CDI) provided benzimidazolone **13**.[45] Hydrolysis of ester **13** gave acid **14** and subsequent decarboxylation under acidic conditions provided the desired benzimidazolone **15**.

The majority of derivatives prepared in this study were 6-membered dihydroquinazolinones **20a**–**p** (Fig. 1, U = CH_2) and two general synthetic routes were employed to prepare these compounds. The first strategy involved a displacement of an activated benzyl intermediate to introduce the substituted benzene onto a thiazole-amine followed by cyclization to form the urea (Scheme 3). Alternatively, these derivatives were prepared by the addition of a benzylicamine to a thiazole triflate followed by subsequent urea formation (Scheme 4). Both methods proved to be useful in providing the appropriately substituted derivatives, and the synthetic route used was dictated mainly by the availability of the starting materials. The first method employed is outlined in Scheme 3. Acids **7a** and **7b** underwent Curtius rearrangements[46] using DPPA in refluxing toluene followed by treatment with allyl alcohol to afford carbamates **16a** and **16b**, respectively. Alkylation with the appropriate benzyl bromides **17b**–**k** vide supra under basic conditions provided carbamates **18b**–**k** and **18p**. Deprotection of



Scheme 1. Synthesis of quinazolinedione **9a**. Reagents and conditions: (a) ethyl bromopyruvate, EtOH, 80 °C, 68%; (b) NaOH, EtOH, 80 °C, 73%; (c) oxalyl chloride, NaN_3, THF; (d) methyl 2-aminobenzoate, toluene, 95 °C, 42%.

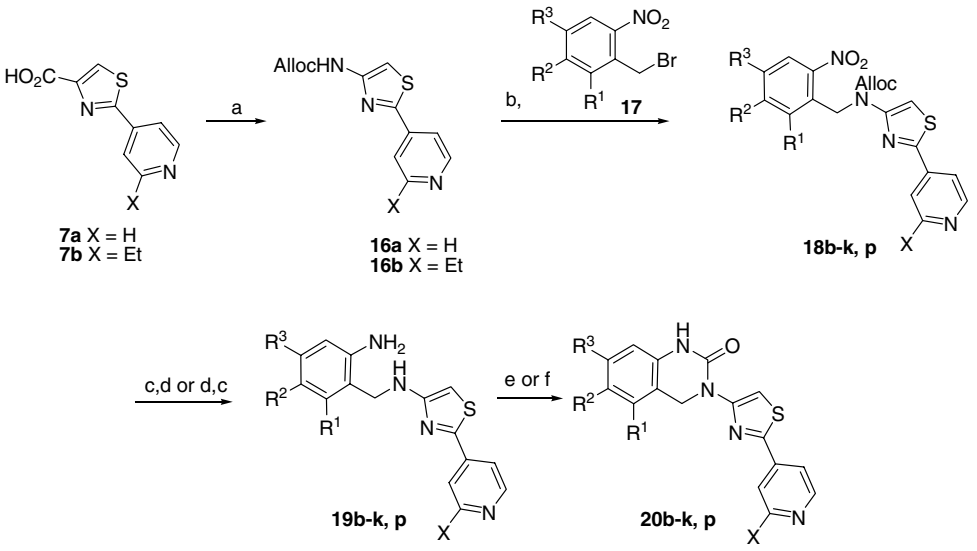


Scheme 2. Synthesis of 5-membered benzimidazolone **15**. Reagents and conditions: (a) diethyl bromomalonate, pyridine, EtOH, 80 °C, 44%; (b) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0 °C–rt, 55%; (c) 1,2-phenylenediamine, dioxane, reflux, 72%; (d) NaH, CDI, DMF, room temperature, 74%; (e) 1 N NaOH, MeOH, rt, 85%; (f) concd H_3PO_4, 120 °C, 96%.

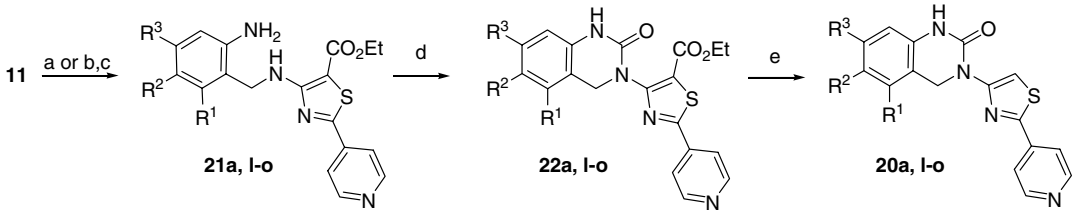
the Alloc group under palladium-mediated conditions and reduction of the nitro moiety with iron dust and ammonium chloride in refluxing aqueous ethanol provided the corresponding anilines **19b–k** and **19p**. Cyclization of anilines **19b–k** and **19p** with CDI or *p*-nitrophenyl chloroformate afforded urea derivatives **20b–k** and **20p**.

An alternate route that involved the displacement of a thiazolo-triflate with an appropriate benzylamine (Scheme 4) was utilized to prepare dihydroquinazolinone **20a** and analogs possessing a basic amine attached to the A-ring (**20l–o**). Treatment of triflate **11** with the appropriate benzylamines vide supra afforded thiazole esters **21a** and **21l–o**. The cyclic ureas **22a** and **22l–o** were obtained by reacting anilines **21a** and **21l–o** with sodium hydride and CDI in dimethylformamide. Basic ester hydrolysis followed by acidic decarboxylation provided the desired ureas **20a** and **20l–o**.

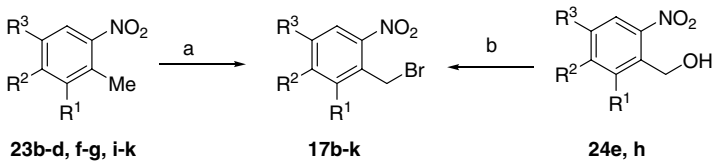
Several of the key intermediates needed for the synthesis of the compounds prepared in this study were substituted benzyl derivatives such as bromides **17b–k** (Scheme 5) and benzyl amines **27**, **30**, **32**, and **34** (Scheme 6). Intermediates **17b–k** were easily accessible from the corresponding 2-nitrotoluene compounds **23b–d**, **23f**, **23g**, **23i–k** or benzyl alcohols **24e**, **24h**. The bromides **17b–d**, **17f**, **17g**, and **17i–k** were prepared under radical conditions by reacting **23b–d**, **23f**, **23g**, and **23i–k** with AIBN and NBS in carbon tetrachloride. Alternatively, benzyl alcohols **24e** and **24h** were treated with phosphorus tribromide to provide bromides **17e** and **17h**. Amines **27** and **30** were readily obtained in two steps from the corresponding benzyl bromides **25**



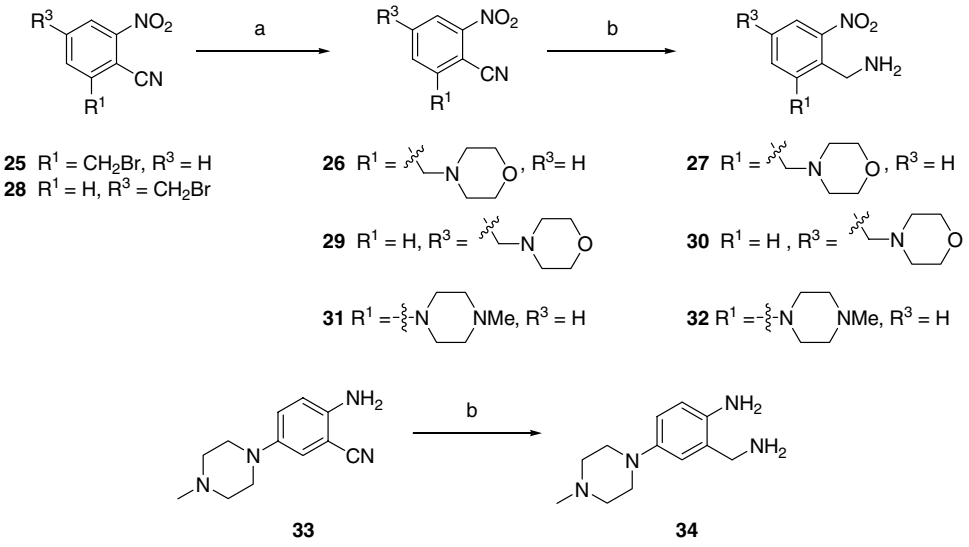
Scheme 3. Synthesis of dihydroquinazolinones—route A. Reagents and conditions: (a) DPPA, Et_3N, toluene then allyl alcohol, 80 °C, 21–23%; (b) NaH, DMF, 80 °C, 39–94%; (c) morpholine, $(Ph_3P)_4Pd$, CH_3CN, rt; (d) iron powder, NH_4Cl, 70% aq EtOH, 80 °C, 12–90% over two steps; (e) *p*-nitrophenyl chloroformate, Et_3N, toluene/THF, 80 °C, 3–23%; (f) CDI, NaH, DMF, rt, 16–93%.



Scheme 4. Synthesis of dihydroquinazolinones—route B. Reagents and conditions: (a) 2-aminobenzylamine or **34**, dioxane, reflux, 70–84%; (b) **27**, **30** or **32** (see Scheme 6), dioxane 80 °C; (c) iron dust, NH_4Cl, aq EtOH, 30–41% over two steps; (d) NaH, CDI, DMF, room temperature, 18–74%; (e) NaOH, MeOH, 50 °C then H_2SO_4, 120 °C, 10–48%.



Scheme 5. Synthesis of substituted benzyl bromides **17b–k**. Reagents: (a) AIBN, NBS, CCl_4, 22–100%; (b) PBr_3, CH_2Cl_2, 22–71%.



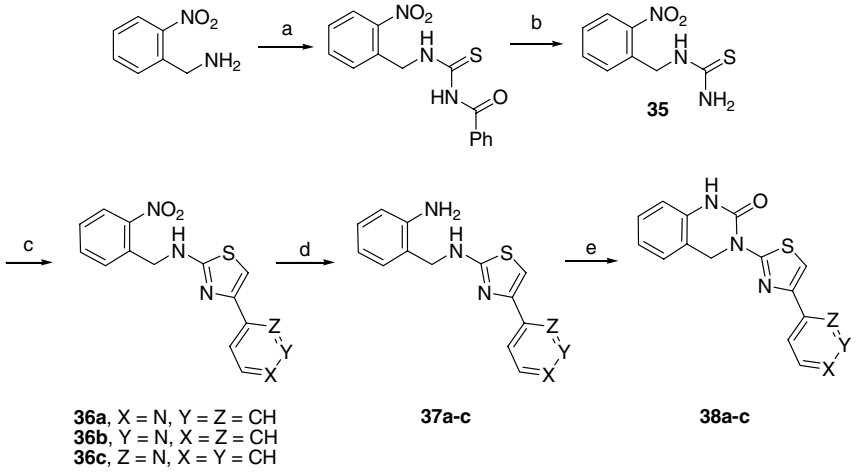
Scheme 6. Synthesis of substituted benzylamines. Reagents and conditions: (a) morpholine, DMF, rt, 71–75%; (b) BH_3·THF, 0 °C–rt, 58–89%.

and **28** (Scheme 6). Treatment of bromides **25** and **28** with morpholine followed by borane reduction provided amines **27** and **30**, respectively. Amines **32** and **34** were prepared by a borane reduction of the known nitriles **31**[47] and **33**[48], respectively.

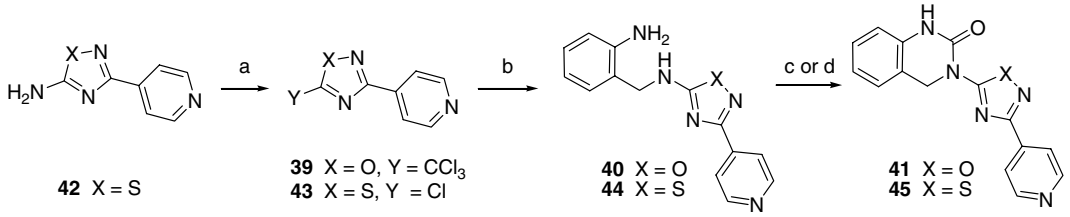
Several 5-membered aromatic heterocycles were prepared to evaluate the biological importance of the central thiazole C-ring such as the isomeric thiazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, and the 2,5-thiophene derivatives. To incorporate these modifications, linear reaction sequences were necessary. The synthetic route employed to prepare the isomeric thiazoles **38a–c** is shown in Scheme 7. Treatment of 2-nitrobenzylamine with benzoyl isothiocyanate followed by hydrolysis under basic conditions provided thiourea **35**. Thiazoles **36a–c** were obtained by heating **35** in the presence of the appropriate bromoacetylpyridinium hydrobromide[49] in aqueous methanol. Reduction of the nitro group with iron provided anilines **37a–c** and cyclization with *p*-nitrophenyl chloroformate afforded the desired isomeric thiazoles **38a–c**.

Oxadiazole **41** and thiadiazole **45** were prepared as summarized in Scheme 8. Addition of 2-aminobenzylamine to 5-trichlorooxadiazole **39**[50] afforded aniline **40**. The desired dihydroquinazoline **41** was obtained by cyclization with *p*-nitrophenyl chloroformate as previously described. Analogously, 5-amino-3-(4-pyridyl)thiadiazole **42** was converted to dihydroquinazoline **45** in three steps. The 5-amino-3-(4-pyridyl)thiadiazole **42**[51] was converted to the chloro derivative **43** using sodium nitrite and copper turnings in hydrochloric acid.[52] Displacement of the chloride with 2-aminobenzylamine afforded aniline **44** and treatment of amino-aniline **44** with CDI provided dihydroquinazoline **45**.

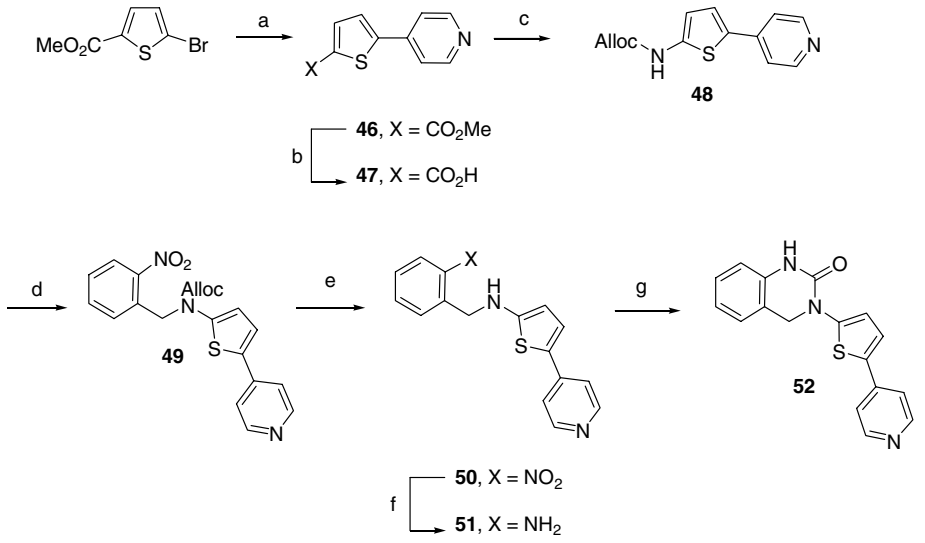
The final two C-ring analogs, thiophene **52** and phenyl derivative **57**, were prepared as shown in Schemes 9 and 10. A Suzuki coupling reaction between 4-pyridylboronic



Scheme 7. Synthesis of isomeric thiazole derivatives: Reagents and conditions: (a) benzoyl isothiocyanate, $CHCl_3$, 61 °C; (b) K_2CO_3, aq MeOH, reflux, 73% over two steps; (c) bromoacetylpyridinium hydrobromide, 50% aq MeOH, 45 °C; (d) iron dust, NH_4Cl, aq EtOH, 75 °C; (e) *p*-nitrophenyl chloroformate, Et_3N, THF, reflux, 1–6% over three steps.



Scheme 8. Synthesis of oxadiazole and thiadiazole derivatives. Reagents and conditions: (a) $NaNO_2$, AcOH, HCl, Cu turnings, H_2O, <15 °C, 56%; (b) 2-aminobenzylamine, THF, 60 °C, 11%; (c) *p*-nitrophenyl chloroformate, Et_3N, THF, room temperature, 42%; (d) CDI, NaH, DMF, rt, 5% over two steps.

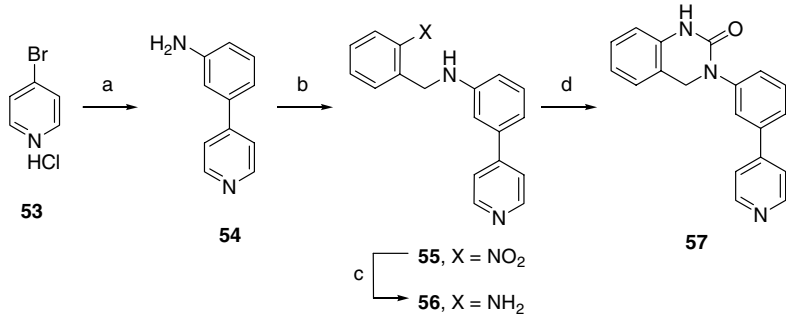


Scheme 9. Synthesis of thiophene derivative **52**. Reagents and conditions: (a) 4-Pyridineboronic acid, $(Ph_3)_4Pd$, Na_2CO_3, DME, reflux, 33%; (b) 1 N NaOH, EtOH, rt, 90%; (c) DPPA, Et_3N, allyl alcohol, toluene, 70 °C, 55%; (d) NaH, 2-nitrobenzyl bromide, DMF, rt, 76%; (e) morpholine, $(Ph_3P)_4Pd$, THF, rt, 88%; (f) iron dust, NH_4Cl, aq EtOH, 78 °C; (g) CDI, NaH, DMF, rt, 76% over two steps.

acid and methyl 5-bromothiophene-2-carboxylate[53] provided ester **46**. Hydrolysis of ester **46** was followed by Curtius rearrangement in the presence of allyl alcohol yielded carbamate **48**. Intermediate **49** was obtained by N-alkylation of carbamate **48** with 2-nitrobenzyl bromide. Deprotection of the alloc-protecting group under palladium-mediated conditions provided intermediate **50** and reduction of the nitro group afforded aniline **51**. Treatment of aniline **51** with CDI under basic conditions provided the desired quinazolinone **52**. The phenyl derivative **57** was prepared in four steps as shown in Scheme 10. A Suzuki reaction of 4-bromopyridine hydrochloride with 3-aminobenzeneboronic acid gave aniline **54**. Compound **56** was prepared by reacting aniline **54** with 2-nitrobenzyl bromide followed by hydrogenation of the resulting nitrobenzene **55**. Urea formation using *p*-nitrophenyl chloroformate provided the desired phenyl analog **57**.

3. Results and discussion

The derivatives prepared in this study were evaluated for their ability to inhibit purified human CDK5. Com-



Scheme 10. Synthesis of phenyl derivative **57**. Reagents and conditions: (a) $Pd(PPh_3)_4$, 3-aminobenzene boronic acid monohydrate, 2 M Na_2CO_3, toluene/ EtOH, 80 °C, 64%; (b) 2-nitrobenzyl bromide, K_2CO_3, CH_3CN, 55 °C, 15%; (c) Pd/C, H_2, EtOH, room temperature, 72%; (d) *p*-nitrophenyl chloroformate, Et_3N, toluene/THF, 70 °C, 23%.

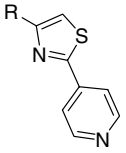
pounds were screened in an HTRF human CDK5/p25 assay that was run in the presence of 25 μM ATP and 1 μM histone-H1.[54] The IC_{50} values were determined from dose–response curves and are reported in Tables 1–5 as the average of at least two replications. The following structure–activity tables examine each of the various structural modifications studied in this investigation.

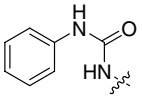
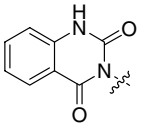
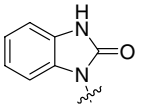
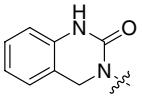
The first derivatives examined in this study were compounds with various B-ring compositions as shown in Table 1. The biological data for the acyclic urea **1** are included in Table 1 for comparison. Quinazolinedione **9a** (U = carbonyl) displayed an inhibition of CDK5 (IC_{50} = >10,000 nM) and was >3-fold less potent than compound **1**. The decrease in inhibition may result from a non-planar B–C ring system, a consequence of lone pair repulsion between the carbonyl oxygen and thiazole nitrogen. Constraining the B-ring to a 5-membered benzimidazolone (i.e., **15**) resulted in a slight improvement in activity (IC_{50} = 1,160 nM); however, significant improvement in activity was observed with dihydro-quinazolinone **20a** (U = CH_2). This increase in activity (**20a** vs **1**) is attributable to better van der Waals contacts of the A-ring (in **20a**) with Gln85, Lys89, Asp86, and Leu134. The puckering of the fused B ring also allows for better positioning of the phenyl ring of **20a** (relative to **1**) within the active site (Fig. 3).

With a satisfactory B-ring identified, we continued our SAR investigations on several aromatic C-ring analogs of compound **20a**. The enzymatic data for these derivatives are reported in Table 2. Compounds **38a**, **41**, **45**, **52**, and **57** were designed to investigate what effect altering the heteroatom positioning of the C-ring had on CDK5 inhibition. In our investigation we found the isomeric thiazole analog **38a** to be equipotent to the parent compound **20a**. Despite this favorable result, further aromatic modifications to the parent compound were not well tolerated. For example, the introduction of a third heteroatom into the heterocyclic C-ring (i.e., oxadiazole **41** and thiadiazole **45**) resulted in a significant decrease in potency as compared to **20a**; however, aromatic rings were devoid of nitrogens (i.e., **52** and **57**) and were also significantly less potent. From examination of the X-ray crystal structure of **3** and the homology models of **20a**, **52**, and **57** (Fig. 4) the dramatic differences in activity of C-ring modified compounds reported in this study could be rationalized. Compounds **20a**, **38a**, and **45** preserve the geometry necessary for maintaining favorable interactions between the linker region, the Lys33-Asp144 salt bridge and the ligand. To the contrary, compounds **52** and **57** do not preserve the optimal geometry necessary for maintaining a good interaction with the Lys33-Asp144 salt bridge, and hence, were significantly less potent.

A major focus of our SAR investigation was to examine the substitution pattern of A-ring analogs and the results for these derivatives are summarized in Table 3. We first

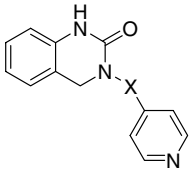
Table 1. SAR of modified B-ring compounds

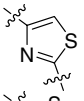
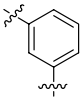


Compound	R	CDK5/p25 (IC_{50}, nM)[a]
1		2990 ± 7
9a		>10,000
15		1160 ± 206
20a		79 ± 40

[a] At least two independent experiments were performed for each compound to determine the IC_{50} values.

Table 2. SAR of C-ring modified compounds



Compound	X	CDK5/p25 (IC_{50}, nM)[a]
20a		79 ± 40
38a		77 ± 33
41		>10,000
45		616 ± 405
52		>10,000
57		>10,000

[a] At least two independent experiments were performed for each compound to determine the IC_{50} values.

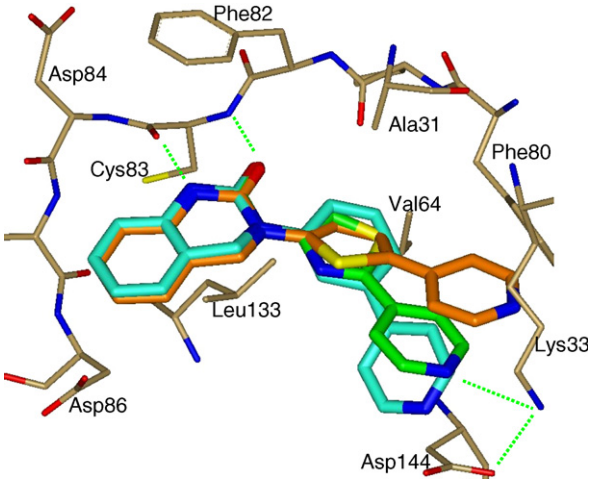


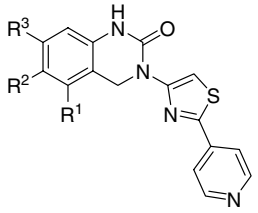
Figure 4. Docked models of compounds **20a**, **52**, and **57** in the active site of CDK5. Nitrogen atoms are shown in blue, oxygen atoms are shown in red, sulfur atoms are shown in yellow, and carbon atoms of active site residues are shown in brown. Carbon atoms of compounds **20a**, **52**, and **57** are shown in green, orange, and cyan, respectively. Ligand–protein H-bonds is shown in green.

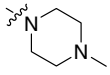
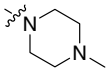
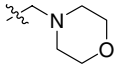
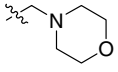
examined the effect of substitution at the R^1 position and, in general, we observed a loss in activity when this position was substituted. For example, the three equipotent halogenated analogs **20b–d** were 3-fold less active than the unsubstituted compound. A significant loss in activity was also observed with electron-donating substituents (**20e** and **20f**) vs. **20a**. In contrast to the results we obtained for R^1 modifications, substitutions at the R^2 and R^3 positions were well tolerated and the best activity was obtained for analog **20i** (R^3 = F). Close examination of modeling studies indicated the R^2 and R^3 positions are exposed to solvent and can accommodate a variety of substituents. Specifically, the R^3 region is surrounded by the residues Gln85, Asp86, and Lys89, which contribute to van der Waals contacts with R^3 substituents. This trend of increased potency ($R^3 > R^2 > R^1$) with respect to the position of substitution was observed in a number of analogs. For example, **20g** and **20i** were >3-fold more potent compared to **20b** (R^1 = F). Likewise, bromo analog **20j** (R^3 = Br) was 6-fold more potent than **20d** (R^1 = Br). Methyl substitution in the R^2 position was also preferred over the R^1 position (**20h** vs **20e**). Large aromatic substituents were also well tolerated in the R^3 position (i.e., **20k**).

In general, addition of a tertiary amine substituent directly onto the A-ring resulted in a decrease in activity (**20l** and **20m** vs **20a**). However, insertion of a methylene spacer between the phenyl ring and the amine did improve potency (**20o** vs **20a**). Molecular modeling studies suggest the additional carbon atom helps to direct the amine away from active site residues and toward the solvent exposed region of the pocket.

The results of D-ring modifications are reported in Table 4. Enzyme inhibition correlated directly with the

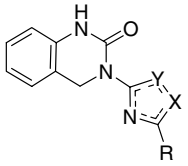
Table 3. SAR of substituted 3-(2-pyridin-4-yl-thiazol-4-yl)-3,4-dihydro-1*H*-quinazolin-2-ones

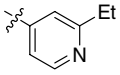


Compound	R^1	R^2	R^3	CDK5/p25 (IC_{50}, nM)[a]
20a	H	H	H	79 ± 40
20b	F	H	H	240 ± 57
20c	Cl	H	H	332 ± 147
20d	Br	H	H	228 ± 190
20e	Me	H	H	1260 ± 907
20f	OMe	H	H	362 ± 145
20g	H	F	H	72 ± 21
20h	H	Me	H	165 ± 13
20i	H	H	F	16 ± 11
20j	H	H	Br	38 ± 22
20k	H	H	Ph	113 ± 57
20l		H	H	829 ± 189
20m	H		H	1165 ± 251
20n		H	H	284 ± 85
20o	H	H		62 ± 28

[a] At least two independent experiments were performed for each compound to determine the IC_{50} values.

Table 4. In vitro inhibition of human CDK5 for 3-(2-aryl-thiazol-4-yl)-3,4-dihydro-1*H*-quinazolin-2-ones



Compound	X	Y	R	CDK5 inhibition IC_{50} (nM)[a]
20a	S	CH		79 ± 40
38a	CH	S		77 ± 33
38b	CH	S		399 ± 20
38c	CH	S		7,360 ± 976
20p	S	CH		746 ± 267

[a] At least two independent experiments were performed for each compound to determine the IC_{50} values.

Table 5. In vitro inhibition of human CDK5 and CDK2 for 3-(2-aryl-thiazol-4-yl)-3,4-dihydro-1*H*-quinazolin-2-ones[a]

Compound	CDK5 inhibition IC_{50} (nM)	CDK2 inhibition IC_{50} (nM)	p38α inhibition IC_{50} (nM)	JNK2 inhibition IC_{50} (nM)	Erk1 inhibition IC_{50} (nM)	PKA inhibition IC_{50} (nM)
20a	79 ± 40	142 ± 81	>10,000	>10,000	>10,000	>10,000
20i	16 ± 11	52 ± 17	>10,000	>10,000	>10,000	>10,000
20o	62 ± 28	529[b]	>10,000	>10,000	>10,000	>10,000

[a] At least two independent experiments were performed for each compound to determine the IC_{50} values.
[b] One experiment was performed to determine the IC_{50} value.

position of the nitrogen atom within the D-ring. The importance of H-bonding between the inhibitor D-ring and the Asp144 salt bridge is clearly demonstrated in the diminished activity of the 2- and 3-pyridyl analogs (**38b** and **38c** vs. **38a**). Introduction of alkyl substitution on the pyridine ring results in unfavorable repulsive interactions and interference with the salt bridge. This accounts for a 10-fold decrease in potency of **20p** relative to **20a**.

The compounds prepared for this study were evaluated for kinase selectivity by screening the most potent analogs against several serine/threonine kinases (Table 5). In general, most compounds were potent inhibitors for both CDK5 and CDK2 and significant CDK selectivity was not observed. However, good selectivity over several serine/threonine kinases was observed in a few representative examples.

4. Conclusions

Using crystallographic data from the acyclic urea **3**/CDK2 complex, we rationally designed and synthesized a series of 3,4-dihydro-1*H*-quinazolin-2-ones as potent CDK5 inhibitors. From our studies, we were able to generate structure activity relationships for the 3,4-dihydro-1*H*-quinazolin-2-one core. In comparison to the acyclic urea **1**, the constrained 6,6-bicyclic AB ring system showed a 10-fold improvement in activity. In general, substitution on the A-ring was well tolerated with a clear preference for substitution in the R^3 position. Although the isomeric thiazole **38a** was an acceptable replacement for the C-ring, other aromatic linking groups (i.e., benzene, thiadiazole, oxadiazole, or thiophene) were not well tolerated. The 4-pyridyl moiety proved to be the optimal D-ring moiety and illustrated the importance of H-bonding to the Asp145-Lys33 salt bridge to the inhibition of CDK5. Although compounds prepared in this study were potent inhibitors of both CDK5 and CDK2, only compounds **20i** and **20o** displayed moderate selectivity for CDK5. From this investigation we gained a better understanding of the structural requirements and limitations necessary for the preparation of selective CDK5 inhibitors. The compounds in this study may serve as molecular probes to better understand CDK5's role in the treatment of neurodegenerative disorders.

5. Experimental

5.1. General

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dichloromethane (CH_2Cl_2), dimethylformamide (DMF), dioxane, tetrahydrofuran (THF), ethylene glycol dimethyl ether (DME), and toluene were obtained from Aldrich Chemical Co. in Sure/Seal bottles. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen or argon atmosphere. Flash chromatography was performed using EM Science silica gel 60 (230–400 mesh ASTM) or prepacked silica gel cartridges (Biotage). Thin-layer chromatography (TLC) was performed with Analtech silica gel GF TLC plates (250 μm). Melting points were determined on a Thomas Hoover capillary melting point apparatus or a Buchi-545 melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Bruker DRX-400 NMR (400 MHz) spectrometer. Chemical shifts are expressed in ppm (δ) downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants. Low-resolution mass spectra were determined on a Perkin-Elmer-SCIEX API 165 mass spectrometer using ES ionization modes (positive or negative). High-resolution mass spectra were determined on an Agilent G1969A TOF spectrometer $[M+H]^+$ and are within ±5 ppm error. Combustion analyses were performed by Atlantic Microlab Inc. Norcross, GA.

5.2. Representative procedure for the synthesis of 2-(2-substituted-4-pyridyl)-1,3-thiazole-4-carboxylic acids 7a and 7b

5.2.1. 2-(4-Pyridyl)-1,3-thiazole-4-carboxylic acid (7a). A mixture of thioisonicotinamide **5a** (20.0 g, 144.7 mmol) and ethyl bromopyruvate (19.0 mL, 151.4 mmol) in 250 mL of EtOH was heated at 80 °C overnight. The reaction mixture was allowed to cool to room temperature and the solid was filtered. The filtrate was concentrated in vacuo and the solid was dried in vacuo to give 23.1 g (68%) of **6a** as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 1.35 (t, 3, J = 7.1 Hz), 4.39 (q, 2, J = 7.1 Hz), 8.36 (d, 2, J = 5.1 Hz), 8.87 (s, 1), 8.96 (d, 2, J = 5.1 Hz). MS (ESI, positive ion) m/z 235 (M+1).

A solution of NaOH (9.6 g, 240 mmol) in 75 mL H_2O was slowly added to a solution of ester **6a** (23.1 g, 98.5 mmol) in 250 mL of EtOH and the reaction mixture was heated at 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then concentrated in vacuo. The residue was dissolved in H_2O (50 mL) and acidified with 1 N HCl. The resulting precipitate was filtered and dried to give 14.8 g (73%) of **7a** as a gray-brown solid. ^{1}H NMR (DMSO-d_6): δ 7.94 (d, 2, J = 4.9 Hz), 8.66 (s, 1), 8.76 (d, 2, J = 4.5 Hz), 13.25 (br s, 1). MS (ESI, positive ion) m/z 207 (M+1).

5.2.2. 2-(2-Ethyl-4-pyridyl)-1,3-thiazole-4-carboxylic acid (7b). Yield 77% for two steps; ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 3, J = 7.5 Hz), 2.85 (q, 2, J = 7.5 Hz), 7.74 (dd, 2, J = 5.1, 1.5 Hz), 8.79 (s, 1), 8.63–8.65 (m, 2).

5.3. Azido(2-(pyridin-4-yl)thiazol-4-yl)methanone (8a)

To a suspension of acid **7a** (6.0 g, 29.1 mmol) in 150 mL of MeOH was added NaOH (1.28 g, 32.0 mmol) at room temperature. After 45 min the reaction mixture was concentrated in vacuo and dried under high vacuum for 60 h. The crude salt was suspended in 150 mL of CH_2Cl_2 and cooled in an ice bath. Oxalyl chloride (2.8 mL) was added slowly to the suspension followed by a catalytic amount of DMF (0.2 mL). The mixture was stirred for 2 h and warmed to room temperature. The reaction was cooled in an ice bath and a solution of NaN_3 (2.27 g) in 90 mL of water was added. After 3 h the reaction mixture was diluted with 90 mL of water and extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were filtered through Celite®, washed with brine (90 mL) and dried over $MgSO_4$. Concentration in vacuo afforded **8a** as a light brown solid. MS (ESI, positive ion) m/z 204 ($M+H-N_2$).

5.4. 3-(2-Pyridin-4-yl-thiazol-4-yl)-1*H*-quinazoline-2,4-dione (9a)

A mixture of azide **8a** (79 mg, 0.3 mmol) and methyl anthranilate (204 mg, 1.4 mmol) in 11 mL of toluene was heated at 95 °C. After 3 h the reaction mixture was allowed to cool to room temperature overnight. The precipitate was filtered, washed with toluene, and dried in vacuo. The crude material was added to a solution of KOH (107 mg, 1.9 mmol) in 15 mL of EtOH and the reaction mixture was heated to 75 °C. After 3 h the reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was diluted with H_2O and extracted with EtOAc. The organic solution was dried over $MgSO_4$ and concentrated to dryness to give 50 mg (42%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 7.25–7.30 (m, 2), 7.75 (t, 1, J = 7.0 Hz), 7.90 (t, 2, J = 4.5 Hz), 7.97 (d, 1, J = 8.2 Hz), 8.05 (s, 1), 8.73 (d, 2, J = 4.5 Hz), 11.76 (s, 1). MS (ESI, positive ion) m/z 323 (M+1). HRMS calcd for $C_{16}H_{10}N_4O_2S$ $[M+H]^+$ 323.0603, found 323.0599.

5.5. Ethyl 4-hydroxy-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (10)

To a solution of thioisonicotinamide **5a** (16.0 g, 115.9 mmol) in 300 mL of EtOH were added diethyl bromomalonate (19.8 mL, 116.1 mmol) and pyridine (37.5 mL, 463.7 mmol). The reaction mixture was heated at 80 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered. The filtrate was concentrated to approximately half its volume and filtered again. The combined solids were allowed to air-dry to give 12.8 g (44%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3, J = 7.2 Hz), 4.44 (q, 2, J = 7.1 Hz), 7.83 (dd, 2, J = 4.5, 1.6 Hz), 8.77 (dd, 2, J = 4.8, 1.3 Hz), 9.94 (br s, 1). MS (ESI, positive ion) m/z 251 (M+1).

5.6. Ethyl 2-(4-pyridyl)-4-[(trifluoromethyl)sulfonyloxy]-1,3-thiazole-5-carboxylate (11)

Trifluoromethanesulfonic anhydride (20 g, 70.9 mmol) was added slowly to a cooled solution (0 °C) of compound **10** (12.7 g, 50.8 mmol) and pyridine (12.5 mL, 154.6 mmol) in 200 mL of anhydrous CH_2Cl_2. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated in vacuo and purified by flash chromatography on silica gel using hexane:EtOAc (2:1–6:4) as the eluant to give 10.7 g (55%) of a light-yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.43 (t, 3, J = 7.2 Hz), 4.47 (q, 2, J = 7.1 Hz), 7.80 (dd, 2, J = 4.5, 1.6 Hz), 8.82 (dd, 2, J = 4.6, 1.6 Hz), 9.94 (br s, 1). MS (ESI, positive ion) m/z 383 (M+1).

5.7. 4-(2-Amino-phenylamino)-2-pyridin-4-yl-thiazole-5-carboxylic acid ethyl ester (12)

A solution of 1,2-phenylenediamine (1.71 g, 15.8 mmol) and triflate **11** (2.01 g, 5.26 mmol) in 11 mL of dioxane was heated at reflux for 48 h. The solvent was removed in vacuo and the crude material was purified by flash chromatography on silica gel eluting with 2 M NH_3 in MeOH/CH_2Cl_2 (1:50) to give a brown solid. The material was recrystallized from MeOH to give 1.29 g (72%) of a yellow crystalline solid. ^{1}H NMR (DMSO-d_6): δ 1.53 (q, 3, J = 7.1 Hz), 4.54 (t, 2, J = 7.1 Hz), 5.04 (br s, 2), 6.88–6.92 (m, 1), 7.03–7.12 (m, 2), 7.38 (dd, 1, J = 7.9, 1.1 Hz), 8.08 (dd, 2, J = 4.5, 1.1 Hz), 8.79 (s, 1), 8.95 (dd, 2 , J = 4.5, 1.7 Hz). MS (ESI, positive ion) m/z 341 (M+1).

5.8. 4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-2-pyridin-4-yl-thiazole-5-carboxylic acid ethyl ester (13)

Aniline **12** (1.29 g, 3.79 mmol) and 1,1′-carbonyldiimidazole (1.84 g, 11.4 mmol) were dissolved in 38 mL of DMF and the solution was cooled to 0 °C. To the mixture was slowly added 95% NaH (335 mg, 13.3 mmol) and the mixture was allowed to warm to room temperature. After 3 days the reaction mixture was quenched with H_2O at 0 °C. The precipitate was filtered, washed with H_2O, and dried in vacuo to give 1.02 g (74%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 0.95 (q, 3, J = 7.1 Hz), 4.01 (t, 2, J = 7.1 Hz), 6.81–6.92 (m, 4), 7.79 (dd, 2, J = 4.5, 1.7 Hz), 8.59 (dd, 2, J = 4.5, 1.7 Hz), 11.06 (s, 1). MS (ESI, positive ion) m/z 367 (M+1).

5.9. 4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-2-pyridin-4-yl-thiazole-5-carboxylic acid (14)

To a suspension of ester **13** (822 mg, 2.24 mmol) in 5 mL of MeOH was added 1 N NaOH (5 mL, 5.0 mmol) at room temperature. After 1 h the reaction mixture was quenched with 10% HCl and the resulting precipitate was filtered to give 787 mg (85%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 7.07 (m, 4), 8.04 (m, 2), 8.82 (m, 2), 11.21 (br s, 1). MS (ESI, positive ion) m/z 339 (M+1); (ESI, negative ion) m/z 337 (M−1).

5.10. 1-(2-Pyridin-4-yl-thiazol-4-yl)-1,3-dihydro-benzoimidazol-2-one (15)

A mixture of acid **14** (157 mg, 0.4 mmol) and concentrated H_3PO_4 (2.5 mL) was heated to 120 °C. After 4 h the reaction mixture was cooled to 0 °C and quenched with ice H_2O. The solution was basified with concentrated NH_4OH to pH 10 and the resulting precipitate was filtered, washed with H_2O, and dried in vacuo to give 108 mg (96%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 7.11–7.17 (m, 4), 8.00 (m, 2), 8.16 (s, 2), 8.77 (dd, 2, J = 4.5, 1.6 Hz), 11.38 (br s, 1). MS (ESI, positive ion) m/z 295 (M+1). Anal. Calcd for $C_{15}H_{10}N_4OS$: C, 61.21; H, 3.42; N, 19.04. Found: C, 61.76; H, 3.74; N, 18.58.

5.11. Representative procedure for the synthesis of compounds 16a and 16b

5.11.1. *N*-[2-(4-pyridyl)(1,3-thiazol-4-yl)]prop-2-enyloxycarboxamide (16a). To a suspension of acid **7a** (14.8 g, 71.9 mmol) in 250 mL of toluene was added Et_3N (10.2 mL, 73.2 mmol) and the mixture was allowed to stir at room temperature for 1 h. Diphenylphosphoryl azide (23.5 mL, 108.9 mmol) was added and the reaction mixture was allowed to stir at room temperature for an additional 1 h. The reaction mixture was heated at 80 °C for 1 h and then the mixture was treated with allyl alcohol (49 mL, 721 mmol). After heating overnight the reaction mixture was allowed to cool to room temperature and was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and ether was added until a yellow solid precipitated from the solution. The precipitate was filtered and the filtrate was concentrated in vacuo. The filtrate residue was again dissolved in CH_2Cl_2 and ether was added until a yellow solid precipitated from the solution. The precipitate was filtered and the combined yellow solids were dried in vacuo to give 7.5 g (40%) of the title compound. The filtrate was concentrated in vacuo and purified by flash chromatography on silica gel using CH_2Cl_2:EtOAc (6:4) as the eluant to afford another 4.0 g (21%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 4.73 (s, 2), 5.31 (d, 1, J = 10.5 Hz), 5.41 (d, 1, J = 17.2 Hz), 5.97 (m, 1), 7.44 (br s, 1), 7.63 (br s, 1), 7.74 (d, 2, J = 4.5 Hz), 8.71 (d, 2, J = 4.5 Hz). MS (ESI, positive ion) m/z 262 (M+1).

5.11.2. *N*-[2-(2-Ethyl(4-pyridyl))(1,3-thiazol-4-yl)]prop-2-enyloxycarboxamide (16b). Yield: 23% of a yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3, J = 7.6 Hz), 2.89 (q, 2, J = 7.6 Hz), 4.72 (d, 2, J = 5.5 Hz), 5.29–5.40 (m, 2), 5.94–5.98 (m, 1), 7.41 (br s, 1), 7.53 (d, 1, J = 5.0 Hz), 7.61–7.64 (m, 2), 8.60 (d, 1, J = 5.2 Hz). MS (ESI, positive ion) m/z 290 (M+1).

5.12. Representative procedure for the synthesis of substituted benzyl bromides 17b–d, 17f, 17g, 17i–k, 25, and 28

5.12.1. 3-Bromo-2-(bromomethyl)-1-nitrobenzene (17d). To a heated (80 °C) solution of 2-bromo-6-nitrotoluene (3.33 g, 15.4 mmol) in 20 mL of CCl_4 were added N-bromosuccinimide (3.38 g, 19.0 mmol) and 2,2′-azobis(2-methylpropionitrile) (296 mg, 1.80 mmol). After stirring overnight the reaction mixture was allowed

to cool to room temperature and was filtered. The filtrate was concentrated in vacuo to give 4.55 g of a brown oil that was a mixture of starting material:desired product (1:2). This mixture was used without further purification. ^{1}H NMR ($CDCl_3$): δ 4.89 (s, 2), 7.36 (t, 1, J = 8.1 Hz), 7.89 (d, 1, J = 3.1 Hz), 7.90 (d, 1, J = 3.1 Hz).

5.12.2. 2-(Bromomethyl)-3-fluoro-1-nitrobenzene (17b). Yield: 22%; ^{1}H NMR ($CDCl_3$): δ 4.84 (s, 2), 7.40 (t, 1, J = 8.6 Hz), 7.46–7.50 (m, 1), 7.87 (d, 1, J = 8.2 Hz).

5.12.3. 2-(Bromomethyl)-3-chloro-1-nitrobenzene (17c). Yield: 55%; ^{1}H NMR ($CDCl_3$): δ 4.88 (s, 2), 7.44 (t, 1, J = 8.2 Hz), 7.70 (d, 1, J = 8.1 Hz), 7.88 (d, 1, J = 8.2 Hz).

5.12.4. 2-(Bromomethyl)-3-methoxy-1-nitrobenzene (17f). Yield: 100%; ^{1}H NMR ($CDCl_3$): δ 3.98 (s, 3), 5.15 (s, 2), 7.61 (t, 1, J = 7.9 Hz), 7.97 (d, 1, J = 7.9 Hz), 8.10 (d, 1, J = 7.9 Hz).

5.12.5. 2-(Bromomethyl)-4-fluoro-1-nitrobenzene (17g). Yield: 36%; ^{1}H NMR ($CDCl_3$): δ 4.83 (s, 2), 7.17 (td, 1, J = 6.6, 2.7 Hz), 7.33 (dd, 1, J = 8.7, 2.8 Hz), 8.16 (dd, 1, J = 9.1, 5.1 Hz).

5.12.6. 1-(Bromomethyl)-4-fluoro-2-nitrobenzene (17i). Yield: 41%; ^{1}H NMR ($CDCl_3$): δ 4.81 (s, 2), 7.35 (td, 1, J = 8.3, 2.6 Hz), 7.60 (dd, 1, J = 8.6, 5.4 Hz), 7.80 (dd, 1, J = 8.2, 2.6 Hz).

5.12.7. 4-Bromo-1-(bromomethyl)-2-nitrobenzene (17j). Yield: 51%; ^{1}H NMR ($CDCl_3$): δ 5.15 (s, 2), 7.61 (d, 1, J = 7.9 Hz), 7.97 (d, 1, J = 7.9 Hz), 8.10 (s, 1).

5.12.8. 1-(Bromomethyl)-2-nitro-4-phenylbenzene (17k). To a mixture of bromobenzene (3.3 mL, 29.6 mmol), 3-nitro-4-methylbenzene boronic acid (5.11 g, 28.3 mmol), and 2 M Na_2CO_3 (63 mL, 126.0 mmol) in 100 mL of toluene/15 mL of EtOH was added tetrakis(triphenylphosphine)palladium (0) (2.04 g, 1.8 mmol) and the mixture was stirred at 80 °C for 4 h. The reaction was cooled to room temperature and partitioned between EtOAc:H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexane:EtOAc (98:2) as eluant afforded 4.68 g (78%) of 1-methyl-2-nitro-4-phenylbenzene as a light orange solid. ^{1}H NMR ($CDCl_3$)δ 2.64 (s, 3), 7.38–7.42 (m, 2), 7.48 (t, 2, J = 7.8 Hz), 7.62 (d, 2, J = 7.7 Hz), 7.74 (dd, 1, J = 8.0, 1.8 Hz), 8.22 (s, 1).

Analogous to the procedure described for compound **17d**, 1-methyl-2-nitro-4-phenylbenzene (4.68 g, 22.0 mmol) provided the title compound as a white solid (1.40 g, 22%). ^{1}H NMR ($CDCl_3$) δ 4.88 (s, 2), 7.43–7.52 (m, 3), 7.60–7.65 (m, 3), 7.84 (dd, 1, J = 8.0, 1.9 Hz), 8.27 (d, 1, J = 1.8 Hz).

5.12.9. 6-(Bromomethyl)-2-nitrobenzenecarbonitrile (25). Yield: 66%; ^{1}H NMR ($CDCl_3$): δ 4.76 (s, 2), 7.81 (t, 1, J = 8.0 Hz), 7.95 (d, 1, J = 7.8 Hz), 8.28 (d, 1, J = 8.2 Hz).

5.12.10. 4-(Bromomethyl)-2-nitrobenzenecarbonitrile (28). Yield: 64%; ^{1}H NMR ($CDCl_3$): δ 4.55 (s, 2), 7.85 (d, 1, J = 7.9 Hz), 7.92 (d, 1, J = 7.9 Hz), 8.36 (s, 1,).

5.13. Representative procedure for the synthesis of substituted benzyl bromides 17e and 17h

5.13.1. 2-(Bromomethyl)-3-methyl-1-nitrobenzene (17h). Yield: 64%; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3), 4.47 (s, 2), 7.28 (d, 1, J = 6.4 Hz), 7.35–7.38 (m, 2).

5.13.2. 2-(Bromomethyl)-4-methyl-1-nitrobenzene (17e). 5-Methyl-2-nitrobenzyl alcohol (2.16 g, 12.9 mmol) was dissolved in 40 mL of dry CH_2Cl_2. Phosphorus tribromide (1.25 mL, 13.3 mmol) was added dropwise. The reaction mixture was stirred overnight. Saturated $NaHCO_3$ was cautiously added until pH 6. The reaction mixture was partitioned and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined CH_2Cl_2 layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to provide 2.11 g (71%) of the title compound as a yellow oil which crystallized upon standing. ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3), 4.82 (s, 2), 7.28 (d, 1, J = 6.1 Hz), 7.35 (s, 1), 7.99 (d, 1, J = 8.3 Hz).

5.14. Representative procedure for the synthesis of compounds 18b–k and 18p

5.14.1. *N*-[(6-Bromo-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18d). To a solution of carboxamide **16a** (1.02 g, 3.9 mmol) in 20 mL of dry DMF was added 60% NaH in portions. The reaction mixture was stirred for 45 min at room temperature and a solution of bromide **17d** (2.3 g, 5.14 mmol) in 5 mL of DMF was added dropwise. The reaction mixture was heated at 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature and partitioned between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH (97:3) as the eluant to afford 940 mg (50%) of a brown oil. ^{1}H NMR ($CDCl_3$): δ 4.68 (d, 2, J = 5.6 Hz), 5.20–5.30 (m, 2), 5.68 (s, 2), 5.83–5.94 (m, 1), 7.15–7.30 (m, 2), 7.58 (d, 1, J = 7.8 Hz), 7.67–7.76 (m, 3), 8.70 (d, 2, J = 5.5 Hz). MS (ESI, positive ion) m/z 476 (M+1).

5.14.2. *N*-[(6-Fluoro-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18b). Yield: 82%; ^{1}H NMR ($CDCl_3$): δ 4.70 (d, 2, J = 5.8 Hz), 5.22–5.31 (m, 2), 5.69 (s, 2), 5.86–5.95 (m, 1), 7.24 (t, 1, J = 9.4 Hz), 7.34–7.38 (m, 1), 7.60 (d, 1, J = 8.1 Hz), 7.69 (d, 2, J = 5.6 Hz), 8.69 (br s, 2).

5.14.3. *N*-[(6-Chloro-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18c). Yield: 72%; ^{1}H NMR ($CDCl_3$): δ 4.68 (d, 2, J = 5.8 Hz), 5.20–5.29 (m, 2), 5.69 (s, 2), 5.81–5.92 (m,

1), 7.29 (t, 1, J = 8.1 Hz), 7.56 (d, 2, J = 8.2 Hz), 7.71 (dd, 2, J = 4.6, 1.5 Hz), 8.70 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 431 (M+1).

5.14.4. *N*-[(6-Methyl-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18e). Yield: 75%; ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3), 4.73 (d, 2, J = 5.6), 5.21–5.27 (m, 2), 5.36 (s, 2), 5.85–5.90 (m, 1), 7.18 (d, 2, J = 7.6 Hz), 7.29 (t, 1, J = 7.6 Hz), 7.70 (dd, 1, J = 4.6, 1.6 Hz), 8.68 (dd, 2, J = 4.5, 1.7 Hz).

5.14.5. *N*-[(6-Methoxy-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18f). Yield: 83%; ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 3), 4.72 (d, 2, J = 4.8 Hz), 5.25 (dd, 2, J = 4.8, 10.5 Hz), 5.75 (s, 2), 5.95 (m, 1), 7.45 (d, 2, J = 7.8 Hz), 7.55 (t, 1, J = 7.8 Hz), 7.70 (d, 2, J = 4.8 Hz), 8.10 (d, 1, J = 7.8 Hz), 8.68 (d, 2, J = 4.8 Hz).

5.14.6. *N*-[(5-Fluoro-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18g). Yield: 58%; ^{1}H NMR ($CDCl_3$): δ 4.73 (d, 2, J = 5.2 Hz), 5.23–5.28 (m, 2), 5.71 (s, 2), 5.83–5.93 (m, 1), 7.00–7.15 (m, 2), 7.61 (d, 2, J = 4.7 Hz), 7.67 (s, 1), 8.16–8.20 (m, 1), 8.66 (d, 2, J = 5.9 Hz). MS (ESI, positive ion) m/z 415 (M+1).

5.14.7. *N*-[(5-Methyl-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18h). Yield: 88%; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3), 4.73 (d, 2, J = 5.6 Hz), 5.20–5.26 (m, 2), 5.70 (s, 2), 5.85–5.89 (m, 1), 7.16–7.19 (m, 2), 7.63 (d, 2, J = 4.8 Hz), 8.01 (d, 1, J = 8.3 Hz), 8.65 (d, 2, J = 5.0 Hz).

5.14.8. *N*-[(4-Fluoro-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18i). Yield: 94%; ^{1}H NMR ($CDCl_3$): δ 4.71 (d, 2, J = 5.6 Hz), 5.22–5.24 (m, 2), 5.66 (s, 2), 5.83–5.95 (m, 1), 7.29 (dd, 1, J = 7.9, 2.6 Hz), 7.42 (br s, 1), 7.62 (dd, 2, J = 4.5, 1.5 Hz), 7.81 (dd, 1, J = 8.2, 2.6 Hz), 8.66 (dd, 2, J = 4.6, 1.4 Hz). MS (ESI, positive ion) m/z 415 (M+1).

5.14.9. *N*-[(4-Bromo-2-nitrophenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18j). Yield: 39%; ^{1}H NMR (DMSO-d_6): δ 4.55 (d, 2, J = 4.8 Hz), 5.15 (dd, 2, J = 10.5, 4.8 Hz), 5.65 (s, 2), 5.95 (m, 1), 7.45 (s, 1), 7.71 (t, 1, J = 7.9 Hz), 7.72 (d, 2, J = 4.8 Hz), 7.85 (d, 1, J = 7.9 Hz), 7.95 (d, 2, J = 7.9 Hz), 8.68 (d, 2, J = 4.8 Hz). MS (ESI, positive ion) m/z 477 (M+1).

5.14.10. *N*-[(2-Nitro-4-phenylphenyl)methyl]prop-2-enyloxy-*N*-(2-(4-pyridyl)(1,3-thiazol-4-yl))carboxamide (18k). Yield: 46%; ^{1}H NMR ($CDCl_3$; 400 MHz): δ 4.74 (d, 2, J = 5.5 Hz), 5.20–5.30 (m, 2), 5.74 (s, 2), 5.85–5.94 (m, 1), 7.40–7.49 (m, 4), 7.60 (d, 2, J = 7.7 Hz), 7.64 (dd, 2, J = 4.5, 1.5 Hz), 7.77 (dd, 1, J = 8.2, 1.8 Hz), 8.30 (d, 1, J = 1.8 Hz), 8.66 (dd, 2, J = 4.7, 1.5 Hz). MS (ESI, positive ion) m/z 473 (M+1).

5.14.11. *N*-[2-(2-Ethyl(4-pyridyl))(1,3-thiazol-4-yl)]-*N*-[(2-nitrophenyl)methyl]prop-2-enyloxycarboxamide (18p). Yield: 85%; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3, J = 7.7 Hz), 2.85 (q, 2, J = 7.6 Hz), 4.72 (d, 2, J = 5.5 Hz), 5.20–5.30 (m, 2), 5.70 (s, 2), 5.81–5.93 (m, 1), 7.30–7.41 (m, 4), 7.46 (s, 1), 7.53 (d, 1, J = 7.4 Hz), 8.06 (d, 1, J = 8.2 Hz), 8.55 (d, 1, J = 5.1 Hz). MS (ESI, positive ion) m/z 425 (M+1).

5.15. Representative procedure for the synthesis of compounds 19b–f, 19h, 19i, 19k, and 19p

5.15.1. [(2-Amino-6-bromophenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19d). To a solution of carboxamide **18d** (936 mg, 2.0 mmol) in 20 mL of acetonitrile were added morpholine (1.71 mL, 19.6 mmol) and tetrakis(triphenylphosphine)palladium (0) (205 mg, 0.2 mmol) at room temperature. After stirring overnight the reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc and washed with H_2O. The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude oil was purified by flash chromatography on silica gel using CH_2Cl_2:EtOAc (6:4) as the eluant to afford 400 mg (52%) of a brown oil. ^{1}H NMR ($CDCl_3$): δ 4.81 (d, 2, J = 4.0 Hz), 5.0 (br s, 1), 6.0 (s, 1), 7.33 (td, 1, J = 8.1, 2.8 Hz), 7.72 (dd, 2, J = 4.5, 1.6 Hz), 7.79 (d, 1, J = 7.2 Hz), 7.87 (d, 1, J = 7.1 Hz), 8.66 (dd, 2, J = 4.5, 1.6 Hz). MS (ESI, positive ion) m/z 392 (M+1).

The amine from the previous step (400 mg, 1.0 mmol) was dissolved in 35 mL of 70% aqueous EtOH. Iron powder (255 mg, 4.6 mmol) and NH_4Cl (28 mg, 0.5 mmol) were added and the reaction mixture was heated at 80 °C. After stirring for 3 h the reaction mixture was filtered while hot through a pad of Celite®, and the pad was rinsed liberally with EtOAc. The filtrate was concentrated in vacuo and the residue was partitioned between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 296 mg (80%) of a brown oil. ^{1}H NMR ($CDCl_3$): δ 4.60 (d, 2, J = 4.3 Hz), 6.08 (s, 1), 6.62 (d, 1, J = 6.8 Hz), 7.00 (m, 2), 7.73 (dd, 2, J = 4.6, 1.6 Hz), 8.68 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 362 (M+1).

5.15.2. [(2-Amino-6-fluorophenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19b). Yield: 23%; ^{1}H NMR ($CDCl_3$): δ 4.42 (br s, 5), 6.08 (s, 1), 6.47–6.51 (m, 2), 7.07 (q, 1, J = 6.5 Hz), 7.73 (dd, 2, J = 4.5, 1.5 Hz), 8.68 (dd, 2, J = 4.7, 1.4 Hz).

5.15.3. [(2-Amino-6-chlorophenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19c). Yield: 67%; ^{1}H NMR ($CDCl_3$): δ 4.46 (br s, 2), 4.53 (br s, 1), 4.58 (s, 2), 6.08 (s, 1), 6.61 (d, 1, J = 8.0 Hz), 6.83 (d, 1, J = 7.9 Hz), 7.03 (t, 1, J = 8.0 Hz), 7.73 (dd, 2, J = 4.6, 1.4 Hz), 8.68 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 317 (M+1).

5.15.4. [(2-Amino-6-methylphenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19e). Yield: 45%; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3), 4.12 (br s, 2), 4.33 (d, 2, J = 4.1 Hz), 4.52 (br s, 1), 6.00 (s, 1), 6.70 (t, 1, J = 7.5 Hz), 7.08 (d, 2,

J = 7.4 Hz), 7.74 (dd, 2, J = 4.6, 1.5 Hz), 8.68 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 297 (M+1).

5.15.5. [(2-Amino-6-methoxyphenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19f). Yield: 13%; ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 3), 4.21 (d, 2, J = 4.8 Hz), 5.12 (s, 2), 6.15 (s, 1), 6.52 (t, 1, J = 7.4 Hz), 6.62 (d, 1, J = 7.4 Hz), 6.72 (s, 1), 6.95 (t, 1, J = 7.4 Hz), 7.13 (d, 1, J = 7.4 Hz), 7.80 (d, 2, J = 4.8 Hz), 8.72 (d, 2, J = 4.8 Hz).

5.15.6. [(2-Amino-5-methylphenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19h). Yield: 12%; ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3), 4.28 (d, 2, J = 5.0 Hz), 5.99 (s, 1), 6.66 (d, 1, J = 8.0 Hz), 6.96–7.01 (m, 3), 7.74 (d, 2, J = 6.1 Hz), 8.67 (d, 2, J = 6.1 Hz). MS (ESI, positive ion) m/z 297 (M+1).

5.15.7. [(2-Amino-4-fluorophenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19i). Yield: 28%; ^{1}H NMR ($CDCl_3$): δ 4.28 (d, 2, J = 5.0 Hz), 4.32 (br s, 2), 4.48 (br s, 1), 6.00 (s, 1), 6.42 (m, 2), 7.12 (t, 1, J = 7.4 Hz), 7.73 (dd, 2, J = 4.6, 1.5 Hz), 8.68 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 301 (M+1).

5.15.8. [(2-Amino-4-phenylphenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19k). Yield: 13%; MS (ESI, positive ion) m/z 359 (M+1).

5.15.9. [(2-Aminophenyl)methyl][2-(2-ethyl(4-pyridyl))(1,3-thiazol-4-yl)]amine (19p). Yield: 48%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3, J = 7.6 Hz), 2.87 (q, 2, J = 7.6 Hz), 4.18 (br s, 2), 4.31 (s, 2), 4.53 (br s, 1), 5.98 (s, 1), 6.71–6.79 (m, 2), 7.13–7.20 (m, 2), 7.68 (d, 1, J = 5.2 Hz), 7.61 (s, 1), 8.57 (d, 1, J = 5.2 Hz). MS (ESI, positive ion) m/z 311 (M+1).

5.16. Representative procedure for the synthesis of compounds 19g and 19j

5.16.1. [(2-Amino-5-fluorophenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19g). A mixture of carboxamide **18 g** (949 mg, 2.3 mmol), iron powder (680 mg, 12.2 mmol), and NH_4Cl (79 mg, 1.5 mmol) was dissolved in 60 mL of acetonitrile and 30 mL of H_2O. The solution was stirred at 80 °C for 2 h and filtered while hot through a bed of Celite. The filtrate was concentrated in vacuo and the aqueous solution was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 875 mg (98%) of a tan solid. ^{1}H NMR ($CDCl_3$): δ 4.16 (br s, 2), 4.74 (d, 2, J = 4.6 Hz), 5.15 (s, 2), 5.24–5.33 (m, 2), 5.91–5.95 (m, 1), 6.57–6.60 (m,1), 6.75–6.85 (m, 2), 7.34 (br s, 1), 7.76 (dd, 2, J = 4.5, 1.5 Hz), 8.72 (dd, 2, J = 4.5, 1.5 Hz). MS (ESI, positive ion) m/z 385 (M+1).

The material (850 mg, 2.2 mmol) from the previous step, morpholine (4 mL, 45.7 mmol), and tetrakis(triphenylphosphine)palladium (0) (260 mg, 0.2 mmol) were dissolved in 30 mL of THF. The solution was stirred at room temperature for 4 h and then concentrated in vacuo. The residue was partitioned between EtOAc:H_2O and the aqueous layer was extracted with EtOAc (2×). The combined EtOAc layers were washed 1 N HCl (2×) and the combined acidic layers were neutralized with 5N NaOH and extracted with EtOAc (3×). The combined EtOAc layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 610 mg (92%) of a light-brown oil. ^{1}H NMR ($CDCl_3$): δ 4.01 (br s, 2), 4.29 (d, 2, J = 5.5), 4.58 (br s, 1), 5.98 (s, 1), 6.64–6.67 (m, 1), 6.87 (td, 1, J = 8.7, 2.6 Hz), 6.97 (dd, 1, J = 9.0, 2.7 Hz), 7.74 (d, 2, J = 6.0 Hz), 8.68 (d, 2, J = 6.1 Hz). MS (ESI, positive ion) m/z 301 (M+1).

5.16.2. [(2-Amino-4-bromophenyl)methyl](2-(4-pyridyl)(1,3-thiazol-4-yl))amine (19j). Yield: 67%; ^{1}H NMR (DMSO-d_6): δ 5.65 (s, 2), 7.45 (s, 1), 7.71 (t, 1, J = 7.9 Hz), 7.72 (d, 2, J = 4.8 Hz), 7.85 (d, 1, J = 7.9 Hz), 7.95 (d, 2, J = 7.9 Hz), 8.68 (d, 2, J = 4.8 Hz). MS (ESI, positive ion) m/z 363 (M+1).

5.17. Representative procedure for the synthesis of compounds 20d–f, 20h and 20i

5.17.1. 5-Bromo-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20d). Aniline **19d** (296 mg, 0.8 mmol), p-nitrophenyl chloroformate (175 mg, 0.9 mmol), and Et_3N (0.12 mL, 0.9 mmol) were dissolved in 10 mL of toluene/10 mL of THF and stirred at room temperature for 1 h. After heating the reaction at 80 °C overnight the mixture was allowed to cool to room temperature and was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O. The aqueous layer was extracted with CH_2Cl_2 (2×) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude solid was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH (99:1 to 97:3) as the eluant to afford 40 mg (12%) of an off-white solid. Mp 283-284 °C. ^{1}H NMR ($CDCl_3$): δ 5.38 (s, 2), 6.72 (d, 1, J = 7.6 Hz), 7.13 (t, 1, J = 7.8 Hz), 7.13–7.30 (m, 2), 7.83–7.86 (m, 3), 8.74 (d, 2, J = 5.7 Hz). MS (ESI, positive ion) m/z 388 (M+1). Anal. Calcd for $C_{16}H_{11}BrN_4OS$: C, 49.63; H, 2.86; N, 14.47. Found: C, 49.61; H, 2.99; N, 14.26.

5.17.2. 5-Methyl-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20e). Yield: 3%; ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3), 5.78 (s, 2), 6.70 (br s, 1), 6.96 (t, 1, J = 7.5 Hz), 7.09–7.12 (m, 2), 7.84 (dd, 2, J = 4.4, 1.7 Hz), 8.73 (dd, 2, J = 4.6, 1.4 Hz). MS (ESI, positive ion) m/z 323 (M+1). HRMS calcd for $C_{17}H15N_4OS$ $[M+H]^+$ 323.0967, found 323.09655.

5.17.3. 5-Methoxy-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20f). Yield: 23%; ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 3), 5.25 (s, 2), 6.95 (d, 1, J = 7.4 Hz), 7.05 (t, 1, J = 7.4 Hz), 7.23 (t, 1, J = 7.4 Hz), 7.35 (d, 1, J = 7.4 Hz), 8.05 (s, 1), 8.35 (d, 2, J = 4.8 Hz), 8.95 (d, 2, J = 4.8 Hz), 9.90 (s, 1). MS (ESI, positive ion) m/z 339 (M+1).

5.17.4. 6-Methyl-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20h). Yield: 20%; mp 259–261 °C. ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3), 5.31 (s, 2),

6.66 (d, 1, J = 8.0 Hz), 6.75 (s, 1), 7.03–7.07 (m, 2), 7.82 (d, 2, J = 5.7 Hz), 7.83 (s, 1), 8.73 (d, 2, J = 6.1 Hz). MS (ESI, positive ion) m/z 323 (M+1). Anal. Calcd for $C_{17}H_{14}N_4OS{\cdot}0.3H_2O$: C, 62.29; H, 4.53; N, 17.09. Found: C, 62.49; H, 4.53; N, 16.50.

5.17.5. 7-Fluoro-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20i). Yield: 22%; mp 285–286 °C. ^{1}H NMR ($CDCl_3$)δ 5.31 (s, 2), 6.53 (dd, 1, J = 9.1, 2.2 Hz), 6.75 (td, 1, J = 9.1, 2.2 Hz), 7.12 (br s, 1), 7.23 (t, 1, J = 6.0 Hz), 7.84 (m, 3), 8.74 (d, 2, J = 6.0 Hz). MS (ESI, positive ion) m/z 327 (M+1). Anal. Calcd for $C_{16}H_{11}FN_4OS$: C, 58.89; H, 3.40; N, 17.17. Found: C, 58.90; H, 3.47; N, 16.88.

5.18. Representative procedure for the synthesis of compounds 20b, 20c, 20g, 20j, 20k, and 20p

5.18.1. 6-Fluoro-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20g). To a mixture of amine **19g** (610 mg, 2.0 mmol) and 1,1′-carbonyldiimidazole (995 mg, 6.1 mmol) in 20 mL of anhydrous DMF was added 60% NaH (290 mg, 7.3 mmol) in portions at room temperature. After 4 h, the reaction mixture was diluted with H_2O and filtered. The precipitate was washed with H_2O (2× 10 mL) and stirred in a solution of H_2O:hexane (1:1) to remove any remaining mineral oil. The precipitate was filtered and dried in vacuo at 60 °C to afford 110 mg (17%) of a white solid. Mp 290–291 °C. ^{1}H NMR (DMSO-d_6): δ 5.24 (s, 2), 6.89–6.93 (m, 1), 7.08 (td, 1, J = 8.8, 2.8 Hz), 7.25 (dd, 1, J = 9.0, 2.6 Hz), 7.86 (s, 1), 7.93 (dd, 2, J = 4.5, 1.5 Hz), 8.74 (dd, 2, J = 4.5, 1.5 Hz), 9.84 (br s, 1) MS (ESI, positive ion) m/z 327 (M+1). Anal. Calcd for $C_{16}H_{11}FN_4OS{\cdot}0.1H_2O$: C, 58.56; H, 3.44; N, 17.07. Found: C, 58.31; H, 3.56; N, 16.82.

5.18.2. 5-Fluoro-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20b). Yield: 77%; mp 247–249 °C. ^{1}H NMR (DMSO-d_6): δ 5.27 (s, 2), 6.76 (d, 1, J = 8.0 Hz), 6.83 (t, 1, J = 8.7 Hz), 7.27 (q, 1, J = 6.5 Hz), 7.90–7.92 (m, 3), 8.74 (dd, 2, J = 4.5, 1.4 Hz), 10.05 (br s, 1). MS (ESI, positive ion) m/z 327 (M + 1). Anal. Calcd for $C_{16}H_{11}FN_4OS$: C, 58.89; H, 3.40; N, 17.17. Found: C, 59.35; H, 3.58; N, 16.90.

5.18.3. 5-Chloro-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20c). Yield: 16%; mp 292–293 °C. ^{1}H NMR (DMSO-d_6): δ 5.29 (s, 2), 6.89 (d, 1, J = 7.9 Hz), 7.09 (d, 1, J = 7.9 Hz), 7.25 (t, 1, J = 8.0 Hz), 7.90 (dd, 2, J = 4.6, 1.5 Hz), 7.92 (s, 1), 8.75 (dd, 2, J = 4.6, 1.4 Hz), 10.04 (s, 1). MS (ESI, positive ion) m/z 343 (M+1). Anal. Calcd for $C_{16}H_{11}ClN_4OS0.2H_2O$: C, 55.48; H, 3.32; N, 16.17. Found: C, 55.24; H, 3.47; N, 15.90.

5.18.4. 7-Bromo-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20j). Yield: 93%; ^{1}H NMR (DMSO-d_6): δ 5.25 (s, 2), 6.95 (d, 1, J = 7.4), 7.05 (d, 1, J = 7.4), 7.23 (d, 1, J = 7.4), 7.75 (s, 1), 7.87 (d, 2, J = 4.8), 8.75 (d, 2, J = 4.8), 9.93 (s, 1). HRMS calcd for $C_{16}H_{12}BrN_4OS$ $[M+H]^+$ 386.9915, found 386.9909.

5.18.5. 7-Phenyl-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20k). Yield: 17%; mp 248–250 °C. ^{1}H NMR (DMSO-d_6): δ 5.51 (s, 2), 7.38 (s, 1), 7.50 (d, 1, J = 7.8 Hz), 7.60–7.63 (m, 2), 7.70 (t, 2, J = 7.7 Hz), 7.83 (d, 2, J = 7.9 Hz), 8.11 (s, 1), 8.17 (dd, 2, J = 4.4, 1.4 Hz), 8.96 (dd, 2, J = 4.6, 1.4 Hz), 10.12 (s, 1). MS (ESI, positive ion) m/z 385 (M+1). Anal. Calcd for $C_{22}H_{16}N_4OS0{\cdot}4H_2O$: C, 67.47; H, 4.32; N, 14.31. Found: C, 67.86; H, 4.71; N, 13.77.

5.18.6. 3-[2-(2-Ethyl-4-pyridyl)-1,3-thiazol-4-yl]-1,3,4-trihydroquinazolin-2-one (20p). Yield: 57%; mp 239–240 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3, J = 7.6 Hz), 2.85 (q, 2, J = 7.6 Hz), 5.23 (s, 2), 6.92 (d, 1, J = 8.0 Hz), 6.98 (t, 1, J = 7.5 Hz), 7.22 (t, 1, J = 7.4 Hz), 7.32 (d, 1, J = 7.5 Hz), 7.74 (d, 1, J = 5.1 Hz), 7.78 (s, 1), 7.85 (s, 1), 8.62 (d, 1, J = 5.2 Hz). MS (ESI, positive ion) m/z 337 (M+1). Anal. Calcd for $C_{18}H_{16}N_4OS{\cdot}0.1H_2O$: C, 63.92; H, 4.83; N, 16.57. Found: C, 63.75; H, 4.81; N, 16.40.

5.19. 6-(Morpholin-4-ylmethyl)-2-nitrobenzenecarbonitrile (26)

A solution of bromide **25** (126 mg, 0.5 mmol) in 7 mL of DMF was treated with morpholine (0.21 mL, 2.4 mmol) resulting in an immediate color change from a light-yellow to an orange-tan. The reaction mixture was partitioned between EtOAc:H_2O and the aqueous layer was extracted with EtOAc (3×). The combined EtOAc layers were washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo to provide 97 mg (75%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.53–2.56 (m, 4), 3.72–3.75 (m, 4), 3.83 (s, 2), 7.77 (t, 1, J = 7.9 Hz), 7.99 (d, 1, J = 7.7 Hz), 8.22 (d, 1, J = 8.2 Hz). MS (ESI, positive ion) m/z 248 (M+1).

5.20. 4-(Morpholin-4-ylmethyl)-2-nitrobenzenecarbonitrile (29)

To a solution of bromide **28** (1.92 g, 7.9 mmol) in 40 mL of CH_3CN was added morpholine (1.0 mL, 11.4 mmol) and the reaction mixture changed immediately from a light-yellow to a orange-tan color. The reaction mixture was concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using CH_2Cl_2:MeOH (1:0–96:4) as the eluant provided the title compound as 1.4 g (71%) of a light-brown oil. ^{1}H NMR ($CDCl_3$): δ 2.47–2.49 (m, 4), 3.65 (s, 2), 3.73–3.75 (m, 4), 7.82 (d, 1, J = 7.9 Hz), 7.88 (d, 1, J = 7.9 Hz), 8.35 (s, 1). MS (ESI, positive ion) m/z 248 (M+1).

5.21. Representative procedure for the synthesis of substituted benzylamines 27, 30, and 32

5.21.1. [6-(Morpholin-4-ylmethyl)-2-nitrophenyl]methylamine (27). Nitrile **26** (1.59 g, 6.4 mmol) was added as a solid to 35 mL of 1 M BH_3THF (35 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated to half its volume, carefully poured into 40 mL of 10% aq

HCl, and stirred at reflux for 3 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to remove any remaining THF. The resulting aqueous solution was washed with benzene (2×) and neutralized with 1 N NaOH. The aqueous solution was then extracted with CH_2Cl_2 (2×) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to provide 975 mg (60%) of the title compound as a light-brown oil. ^{1}H NMR ($CDCl_3$): δ 2.48–2.51 (m, 4), 3.61 (s, 2), 3.67–3.70 (m, 4), 3.88 (s, 2), 7.34 (t, 1, J = 7.7 Hz), 7.49 (d, 1, J = 7.5 Hz), 7.77 (d, 1, J = 8.1 Hz). MS (ESI, positive ion) m/z 252 (M+1).

5.21.2. [4-(Morpholin-4-ylmethyl)-2-nitrophenyl]methylamine (30). Yield: 60%; ^{1}H NMR ($CDCl_3$): δ 2.44–2.49 (m, 4), 3.55 (s, 2), 3.71–3.73 (m, 4), 4.09 (s, 2), 7.55 (d, 1, J = 7.9 Hz), 7.60 (d, 1, J = 7.9 Hz), 7.98 (s, 1). MS (ESI, positive ion) m/z 252 (M+1).

5.21.3. (2-(4-Methylpiperazin-1-yl)-6-nitrophenyl)methanamine (32). Yield: 89%; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3), 2.52–2.60 (m, 4), 3.00–3.10 (m, 4), 4.04 (s, 2), 7.30–7.40 (m, 2), 7.56 (dd, 1, J = 2.4, 7.2 Hz). MS (ESI, positive ion) m/z 251 (M+1).

5.22. 2-(Aminomethyl)-4-(4-methylpiperazinyl)phenylamine (34)

To a stirred solution of nitrile **33** (1.7 g, 7.86 mmol) in dry THF (15 mL) was added a solution of 1 M BH_3THF (27.5 mL, 27.5 mmol) dropwise. After stirring for 2 h at room temperature the mixture was allowed to cool to 0 °C and quenched slowly with 10% aqueous HCl. The resulting mixture was heated at reflux for 2 h then cooled to room temperature. The mixture was washed with ether and the aqueous layer was neutralized with 5 N NaOH. The aqueous solution was extracted with CH_2Cl_2 (3×) and the combined organic layers were dried over $MgSO_4$ to provide the title compound as a light-yellow oil (1.0 g, 58%). NMR ($CDCl_3$): δ 2.35 (s, 3), 2.55 (m, 4), 3.10 (m, 4), 3.58 (s, 2), 3.87 (s, 2), 6.70 (d, 1, J = 8.7 Hz), 6.81 (m, 3).

5.23. Representative procedure for the synthesis of compounds 21a and 21m

5.23.1. Ethyl-4-{[(2-aminophenyl)methyl]amino}-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (21a). A mixture of triflate **11** (2.17 g, 5.68 mmol) and 2-aminobenzylamine (2.08 g, 17.03 mmol) in 12 mL of dioxane was heated at reflux for 16 h. The reaction mixture was cooled to room temperature and the resulting precipitate was collected by filtration to give 1.69 g (84%) of a bright-yellow solid. ^{1}H NMR (DMSO-d_6): δ 1.32 (t, 3, J = 7.1 Hz), 4.12 (d, 2, J = 6.3 Hz), 4.27 (q, 2, J = 7.1 Hz), 4.76 (d, 2, J = 6.3 Hz), 6.68–6.77 (m, 2), 6.96 (br s, 1), 7.09–7.20 (m, 2), 7.79 (m, 2), 8.73 (m, 2). MS (ESI, positive ion) m/z 355 (M+1).

5.23.2. Ethyl-4-({[2-amino-5-(4-methylpiperazinyl)phenyl]methyl}amino)-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (21m). Yield: 70%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3, J = 7.1), 2.35 (s, 3), 2.55 (m, 4), 3.10 (m, 4), 4.15 (s, 2), 4.35 (q, 2, J = 7.1), 4.78 (d, 2, J = 6.0), 6.70 (m, 2), 6.95 (t, 1, J = 6.0), 7.05 (d, 1, J = 8.7), 7.82 (d, 2, J = 5.3), 8.75 (d, 2, J = 5.3). MS (ESI, positive ion) m/z 453 (M+1).

5.24. Representative procedure for the synthesis of compounds 21l, 21n and 21o

5.24.1. Ethyl-4-({[2-amino-6-(morpholin-4-ylmethyl)phenyl]methyl}amino)-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (21n). A mixture of triflate **11** (1.49 g, 3.9 mmol) and amine **27** (975 mg, 3.9 mmol) in 25 mL of dioxane was heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature and the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica gel using CH_2Cl_2:EtOAc (7:3 to 1:1) as the eluant to afford 660 mg of an orange-yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3, J = 7.1 Hz), 2.46–2.49 (m, 4), 3.71–3.76 (m, 6), 4.30 (q, 2, J = 7.1 Hz), 5.16 (d, 2, J = 6.3 Hz), 7.38 (t, 1, J = 7.8 Hz), 7.48 (br s, 1), 7.55 (d, 1, J = 7.7 Hz), 7.75–7.79 (m, 3), 8.75 (dd, 2, J = 6.0, 1.5 Hz). MS (ESI, positive ion) m/z 484 (M+1).

The material from the previous step was dissolved in 30 mL of acetonitrile/15 mL of H_2O. Iron powder (460 mg, 8.2 mmol) and NH_4Cl (90 mg, 1.7 mmol) were added and the solution was heated at 80 °C for 2 h. The reaction mixture was filtered while hot and concentrated to an aqueous solution. The aqueous solution was extracted with EtOAc (3×) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to provide 530 mg (30%) of the title compound as a light-brown oil. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3, J = 7.1 Hz), 2.46–2.50 (m, 4), 3.53 (s, 2), 3.87–3.90 (m, 4), 4.29 (q, 2, J = 7.1 Hz), 4.63 (br s, 2), 4.86 (d, 2, J = 6.6 Hz), 6.63–6.66 (m, 2), 7.56 (br s, 1), 7.80 (d, 2, J = 6.0 Hz), 8.76 (d, 2, J = 4.7 Hz). MS (ESI, positive ion) m/z 454 (M+1).

5.24.2. Ethyl-4-(2-amino-6-(4-methylpiperazin-1-yl)benzylamino)-2-(pyridin-4-yl)thiazole-5-carboxylate (21l). Yield: 41%; ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3, J = 7.2 Hz), 2.39 (s, 3), 2.66 (br s, 4), 2.94–2.99 (m, 4), 4.27 (q, 2, J = 7.2 Hz), 4.36 (br s, 2), 4.88 (d, 2, J = 6.4 Hz), 6.50 (d, 1, J = 8.0 Hz), 6.68 (d, 1, J = 7.2 Hz), 7.07 (t, 1, J = 8.0 Hz), 7.16 (br s, 1), 7.79 (dd, 2, J = 4.8, 1.6 Hz), 8.75 (dd, 2, J = 4.8, 1.6 Hz). MS (ESI, positive ion) m/z 453 (M+1).

5.24.3. Ethyl-4-({[2-amino-4-(morpholin-4-ylmethyl)phenyl]methyl}amino)-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (21o). Yield: 38%; ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3, J = 7.1 Hz), 2.46–2.51 (m, 4), 3.45 (br s, 2), 3.67–3.72 (m, 4), 4.15 (br s, 2), 4.30 (q, 2, J = 7.1 Hz), 4.76 (d, 2, J = 6.1 Hz), 6.68–6.6.74 (m, 2), 6.95 (br s, 1), 7.14 (d, 1, J = 7.6 Hz), 7.81 (dd, 2, J = 4.5, 1.5 Hz), 8.75 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 454 (M+1).

5.25. Representative procedure for the synthesis of Ethyl-4-(substituted-2-oxo(1,3,4-trihydroquinazolin-3-yl))-2-(4-pyridyl)-1,3-thiazole-5-carboxylates 22a and 22l–o

5.25.1. Ethyl-4-(2-oxo(1,3,4-trihydroquinazolin-3-yl))-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (22a). To a mixture of amine **21a** (1.69 g, 4.76 mmol) and 1,1′-carbonyldiimidazole (2.30 g, 14.28 mmol) in 50 mL of DMF was added 95% NaH (361 mg, 14.28 mmol) slowly at room temperature. After 18 h the reaction mixture was quenched with water and the resulting precipitate was filtered, washed with water, and dried in vacuo to give 1.12 g (61%) of the title compound as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 1.21 (t, 3, J = 7.1 Hz), 4.22 (q, 2, J = 7.1 Hz), 4.97 (s, 2), 6.96 (m, 2), 7.23 (m, 2), 7.96 (dd, 2, J = 4.6, 1.3 Hz), 8.79 (dd, 2, J = 4.6, 1.3 Hz), 9.93 (s, 1). MS (ESI, positive ion) m/z 381 (M+1).

5.25.2. Ethyl-4-(5-(4-methylpiperazin-1-yl)-2-oxo-1,2-dihydroquinazolin-3(4H)-yl)-2-(pyridin-4-yl)thiazole-5-carboxylate (22l). Yield: 50%; ^{1}H NMR (DMSO-d_6): δ 1.19 (t, 3, J = 7.2 Hz), 2.19 (s, 3), 2.35–2.55 (m, 4), 2.80–2.85 (m, 4), 4.20 (q, 2, J = 7.2 Hz), 4.86 (s, 2), 6.68 (d, 1, J = 8.0 Hz), 6.76 (d, 1, J = 8.0 Hz), 7.20 (t, 1, J = 8.0 Hz), 7.97 (dd, 2, J = 4.4 1.6 Hz), 8.80 (dd, 2, J = 4.4, 1.6 Hz), 9.94 (s, 1). MS (ESI, positive ion) m/z 479 (M+1).

5.25.3. Ethyl-4-[6-(4-methylpiperazinyl)-2-oxo(1,3,4-trihydroquinazolin-3-yl)]-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (22m). Yield: 18%; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3, J = 7.1 Hz), 2.35 (s, 3), 3.50 (m, 4), 3.72 (m, 4), 4.25 (q, 2, J = 7.1 Hz), 5.05 (s, 2), 6.71 (d, 1, J = 8.6 Hz), 6.82 (d, 1, J = 8.6 Hz), 6.87 (s, 1), 7.85 (s, 1), 8.13 (d, 2, J = 5.3 Hz), 8.75 (d, 2, J = 5.3 Hz), 10.75 (s, 1). MS (ESI, positive ion) m/z 479 (M+1).

5.25.4. Ethyl-4-[5-(morpholin-4-ylmethyl)-2-oxo(1,3,4-trihydroquinazolin-3-yl)]-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (22n). Yield: 59%; mp 115–117 °C. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3, J = 7.1 Hz), 2.38-2.41 (m, 4), 3.45 (s, 2), 3.63-3.67 (m, 4), 4.34 (q, 2, J = 7.1 Hz), 5.12 (s, 2), 6.70 (d, 1, J = 7.8 Hz), 6.94 (d, 1, J = 7.5 Hz), 7.16 (t, 1, J = 7.8 Hz), 7.22 (s, 1), 7.84 (dd, 2, J = 4.6, 1.6 Hz), 8.79 (dd, 2, J = 4.5, 1.6 Hz). MS (ESI, positive ion) m/z 480 (M+1).

5.25.5. Ethyl-4-[7-(morpholin-4-ylmethyl)-2-oxo(1,3,4-trihydroquinazolin-3-yl)]-2-(4-pyridyl)-1,3-thiazole-5-carboxylate (22o). Yield: 74%; ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 3, J = 7.1 Hz), 2.44–2.49 (m, 4), 3.46 (s, 2), 3.67-3.72 (m, 4), 4.34 (q, 2, J = 7.1 Hz), 5.00 (s, 2), 6.79 (s, 1), 6.98 (d, 1, J = 7.7 Hz), 7.03-7.09 (m, 1), 7.34 (s, 1), 7.84 (dd, 2, J = 4.5, 1.3 Hz), 8.78 (dd, 2, J = 4.5, 1.4 Hz). MS (ESI, positive ion) m/z 480 (M+1).

5.26. Representative procedure for the synthesis of compounds 20a and 20l–o

5.26.1. 3-(2-(Pyridin-4-yl)thiazol-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one (20a). To a solution of ester **22a** (1.10 g, 2.89 mmol) in 6.0 mL of MeOH at room temperature was added 6 mL of 1 N NaOH. The reaction mixture was heated at 50 °C for 30 min and cooled to room temperature. The reaction mixture was acidified to pH 2 with 10% aqueous HCl solution and the precipitate was collected by filtration to give 1.02 g (99%) of the corresponding acid as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 4.93 (s, 2), 6.90 (d, 1, J = 8.4 Hz), 6.96 (t, 1, J = 7.5 Hz), 7.22 (t, 2, J = 7.0 Hz), 7.96 (dd, 2, J = 4.6, 1.5 Hz), 8.77 (dd, 2, J = 4.6, 1.5 Hz), 9.83 (s, 1). MS (ESI, positive ion) m/z 353 (M+1). The acid (89 mg, 0.25 mmol) was dissolved in 2 mL of H_2SO_4 and heated at 120 °C. After 4 h the reaction mixture was cooled to 0 °C and quenched with ice water. The mixture was basified to pH 10 and the resultant precipitate was purified by flash chromatography using 2 M NH_3 in MeOH:CH_2Cl_2 (1:60) as eluant to afford 34 mg (44%) of the title compound as a white solid. ^{1}H NMR (DMSO-d_6): δ 5.24 (s, 2), 6.91 (d, 1, J = 7.7 Hz), 6.98 (t, 1, J = 7.5 Hz), 7.22 (t, 1, J = 7.5 Hz), 7.31 (d, 1, J = 7.7 Hz), 7.87 (s, 1), 7.93 (dd, 2, J = 4.6, 1.3 Hz), 8.73 (dd, 2, J = 4.6, 1.3 Hz), 9.81 (s, 1). MS (ESI, positive ion) m/z 309 (M+1). Anal. Calcd for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17. Found: C, 62.44; H, 4.15; N, 17.90.

5.26.2. 5-(4-Methylpiperazin-1-yl)-3-(2-(pyridin-4-yl)thiazol-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one (20l). Yield: 40%; ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3), 2.50–2.65 (m, 4), 2.85–2.93 (m, 4), 5.22 (s, 2), 6.66 (d, 1, J = 7.6 Hz), 6.73 (d, 1, J = 7.6 Hz), 7.18 (t, 1, J = 8.0 Hz), 7.86 (s, 1), 7.89 (dd, 2, J = 4.6, 1.6 Hz), 8.74 (dd, 2, J = 4.6, 1.6 Hz), 9.80 (s, 1). MS (ESI, positive ion) m/z 407 (M+1). HRMS calcd for $C_{21}H_{23}N_6OS$ $[M+H]^+$ 407.1654, found 407.1648.

5.26.3. 6-(4-Methylpiperazinyl)-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydro-quinazolin-2-one (20m). Yield: 25%; ^{1}H NMR (DMSO-d_6): δ 2.35 (s, 3), 3.50 (m, 4), 3.72 (m, 4), 5.05 (s, 2), 6.71 (d, 1, J = 8.6 Hz), 6.82 (d, 1, J = 8.6 Hz), 6.87 (s, 1), 7.85 (s, 1), 8.13 (d, 2, J = 5.3 Hz), 8.75 (d, 2, J = 5.3 Hz), 9.45 (s, 1). MS (ESI, positive ion) m/z 407 (M+1). HRMS calcd for $C_{21}H_{23}N_6OS$ $[M+H]^+$ 407.1654, found 407.1657.

5.26.4. 5-(Morpholin-4-ylmethyl)-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one Hydrochloride Dihydrate (20n). The free base was dissolved in CH_2Cl_2 (15 mL) and of MeOH (6 mL), and 1 N ethereal HCl (0.36 mL, 0.4 mmol) was added. After stirring for 2 h, the reaction mixture was concentrated in vacuo. The resulting residue was stirred in ether and the resulting precipitate was filtered and washed with ether to give 140 mg (48%) of an orange solid. Mp 261–263 °C. ^{1}H NMR ($CDCl_3$): δ 3.26–3.31 (m, 4), 3.63–3.71 (m, 2), 3.84–3.88 (m, 2), 4.37 (s, 2), 5.29 (s, 2), 6.96 (d, 1, J = 7.7 Hz), 7.23 (d, 1, J = 7.7 Hz), 7.27 (t, 1, J = 7.7 Hz), 7.85 (s, 1), 8.02 (d, 2, J = 4.5 Hz), 8.72 (d, 2, J = 4.5 Hz), 9.97 (s, 1), 10.36 (br s, 1). MS (ESI, positive ion) m/z 408 (M+1). Anal. Calcd for $C_{21}H_{21}N_5O_2S1.0HCl2H_2O$: C, 52.55; H, 5.46; N, 14.59. Found: C, 52.52; H 5.30; N, 14.42.

5.26.5. 7-(Morpholin-4-ylmethyl)-3-(2-(4-pyridyl)(1,3-thiazol-4-yl))-1,3,4-trihydroquinazolin-2-one (20o). Yield: 10%; mp 249–250 °C. ^{1}H NMR ($CDCl_3$): δ 2.43–2.49 (m, 4), 3.47 (s, 2), 3.70–3.76 (m, 4), 5.33 (s, 2), 6.79 (s, 2), 7.01 (d, 1, J = 7.7 Hz), 7.21 (d, 1, J = 7.7 Hz), 7.84 (m, 3), 8.73 (dd, 2, J = 4.6, 1.5 Hz). MS (ESI, positive ion) m/z 408 (M+1). Anal. Calcd for $C_{21}H_{21}N_5O_2S0.4H_2O$: C, 60.82; H, 5.30; N, 16.89. Found C, 60.81; H, 5.24; N, 16.67.

5.27. Amino{[(2-nitrophenyl)methyl]amino}methane-1-thione (35)

To a solution of 2-nitrobenzylamine hydrochloride (4.93 g, 26.1 mmol) and Et_3N (10 mL, 71.8 mmol) in 300 mL of $CHCl_3$ was added benzoyl isothiocyanate (3.4 mL, 25.3 mmol) and the resulting yellow solution was heated at 61 °C. After 1.5 h the solvent was removed in vacuo and the residue was dissolved in 70% aqueous MeOH. To the solution was added K_2CO_3 (4.06 g, 29.4 mmol) and the reaction mixture was heated at reflux for 30 min. The yellow-orange mixture was cooled to room temperature and the crude material was purified by flash chromatography on silica gel with hexanes:EtOAc (4:1–1:3) as eluant to afford 4.05 g (73%) of the title compound as a purple solid. ^{1}H NMR (CD_3OD): δ 5.03 (br s, 2), 5.89 (br s, 2), 6.98 (br s, 1), 7.42–7.57 (m, 1), 7.60–7.73 (m, 1), 7.87 (br s, 1), 8.08 (d, 1, J = 8.0 Hz). MS (ESI, positive ion) m/z : 212 (M+1).

5.28. [(2-Nitrophenyl)methyl](4-(4-pyridyl)(1,3-thiazol-2-yl))amine (36a)

To a heated (45 °C) slurry of thiourea **35** (841 mg, 4.0 mmol) in 50 mL of 50% aqueous MeOH was added 4-(bromoacetyl)pyridine hydrobromide (1.16 g, 4.1 mmol) and the reaction mixture was stirred at 45 °C for 1.5 h. The reaction mixture was cooled to room temperature and the solids were filtered and washed with water. Drying in vacuo over P_2O_5 overnight gave 1.08 g (86%) of a pale yellow powder. ^{1}H NMR (DMSO-d_6): δ 4.84 (d, 2, J = 5.7 Hz), 7.47 (s, 1), 7.50–7.58 (m, 1), 7.65–7.77 (m, 2), 7.69 (d, 2, J = 5.6 Hz), 8.04 (d, 1, J = 8.1 Hz), 8.41 (t, 1, J = 5.7 Hz), 8.53 (d, 1, J = 5.6 Hz). MS (ESI, positive ion) m/z 313 (M+1), (ESI, negative ion) 311 (M−1).

5.29. 3-(4-(4-Pyridyl)-1,3-thiazol-2-yl)-1,3,4-trihydroquinazolin-2-one (38a)

A slurry of compound **36a** (924 mg, 3.0 mmol), iron dust (872 mg, 15.6 mmol), and NH_4Cl (119 mg, 2.2 mmol) in 30 mL of 50% aqueous EtOH was heated at 75 °C. After 1.5 h the reaction mixture was cooled to room temperature and the EtOH removed in vacuo. The aqueous solution was extracted sequentially with EtOAc and CH_2Cl_2, and the combined organics were washed with brine and dried over Na_2SO_4. Concentration in vacuo gave 264 mg (32%) of aniline **37a** as a solid. Crude **37a** was dissolved in 10 mL of THF and to this solution were added p-nitrophenyl chloroformate (398 mg, 2.0 mmol) and Et_3N (0.4 mL, 2.9 mmol). The reaction mixture was heated at reflux for 9 h and was allowed to cool to room temperature. Purification by flash chromatography on silica gel using hexanes:EtOAc (4:1) followed by CH_2Cl_2:MeOH (9:1) as eluant gave 34 mg (12%) of a white solid. Mp >267 °C. ^{1}H NMR (DMSO-d_6): δ 5.38 (s, 1), 6.94 (d, 1, J = 7.5 Hz), 7.02 (t, 1, J = 7.5 Hz), 7.23 (t, 1, J = 7.5 Hz), 7.35 (d, 1, J = 7.5 Hz), 7.92 (d, 2, J = 6.1 Hz), 7.96 (s, 1), 8.61 (d, 2, J = 6.1 Hz). MS (ESI, positive ion) m/z 309 (M+1), (ESI negative ion) 307 (M−1). Anal. Calcd for $C_{16}H_{12}N_4OS0.06$ MeOH: C, 62.16; H, 3.98; N, 18.06. Found: C, 62.21; H, 4.05; N, 18.04. HRMS calcd for $C_{16}H_{13}N_4OS$ $[M+H]^+$ 309.0810, found 309.0816.

5.30. 3-(4-(3-Pyridyl)-1,3-thiazol-2-yl)-1,3,4-trihydroquinazolin-2-one (38b)

To a heated (45 °C) slurry of thiourea **35** (1.03 g, 4.87 mmol) in 50 mL of 50% aqueous MeOH was added 3-(bromoacetyl)pyridine hydrobromide (1.37 g, 4.87 mmol). After 2 h the mixture was allowed to cool to room temperature and the solvent was removed in vacuo to give **36 b** as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 1.72 (s, 6), 3.83 (s, 4), 6.69 (br s, 1), 7.25 (t, 1, J = 3.9 Hz), 7.69 (br s, 1), 7.75 (br s, 1), 8.30 (s, 1), 11.34 (s, 1). MS (ESI, positive ion) m/z 313 (M+1).

A mixture of crude **36b**, iron dust (1.39 g, 24.9 mmol), and NH_4Cl (198 mg, 3.7 mmol) in 50 mL of 50% EtOH was heated at reflux. After 1 h the reaction mixture was cooled to room temperature and the solvent was removed in vacuo to give compound **37b**. MS (ESI, positive ion) m/z 283 (M+1).

The crude **37b** was dissolved in 20 mL of THF and to this solution were added p-nitrophenyl chloroformate (860 mg, 4.2 mmol) and Et_3N (0.85 mL, 6.1 mmol). The reaction mixture was heated at reflux for 1 h and cooled to room temperature overnight. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel with hexanes:EtOAc (1:1) followed by $CHCl_3$:MeOH (19:1) as eluant to give 84 mg (6%, three steps) of the title compound as an off-white solid. Mp 269–272 °C. ^{1}H NMR (DMSO-d_6): δ 5.39 (s, 2), 6.94 (d, 1, J = 7.9 Hz), 7.03 (t, 1, J = 7.6 Hz), 7.24 (t, 1, J = 7.6 Hz), 7.39 (d, 1, J = 7.6 Hz), 7.48 (dd, 1, J = 7.9, 4.7 Hz), 7.86 (s, 1), 8.33 (d, 2, J = 9.0 Hz), 8.53 (d, 1, J = 4.7 Hz) 9.22 (s, 1), 10.26 (s, 1). MS (ESI, positive ion) m/z 309 (M+1). HRMS calcd for $C_{16}H_{13}N_4OS$ $[M+H]^+$ 309.0810, found 309.0817.

5.31. 3-(4-(2-Pyridyl)-1,3-thiazol-2-yl)-1,3,4-trihydroquinazolin-2-one (38c)

To a heated (45 °C) slurry of thiourea **35** (1.04 g, 4.9 mmol) in 10 mL of 50% aqueous MeOH was added an aqueous solution of 2-(bromoacetyl)pyridine hydrobromide (1.34 g, 4.9 mmol). After 2 h the reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo to give compound **36 c**. MS (ESI, positive ion) m/z 313 (M+1).

A mixture of crude **36c**, iron dust (1.41 g, 25.2 mmol), and NH_4Cl (190 mg, 3.5 mmol) in 50 mL of 50% EtOH was heated at reflux. After 1 h the reaction mixture was cooled to room temperature and the solvent was removed in vacuo to give compound **37 c**. MS (ESI, positive ion) *m/z* 283 (M+1).

The residue from the previous step was dissolved in 20 mL of THF and to this solution were added *p*-nitrophenyl chloroformate (1.17 g, 5.8 mmol) and Et_3N (1 mL, 7.2 mmol). The reaction mixture was heated at reflux for 3 h and was allowed to cool to room temperature. The solvent was removed in vacuo and the crude material was purified by flash chromatography on silica gel with hexanes:EtOAc (4:1–0:1) as eluant to give 13 mg (1%, three steps) of a tan solid. Mp >275 °C. ^1H NMR (DMSO-d_6): δ 5.39 (s, 2), 6.94 (d, 1, $J = 7.9$ Hz), 7.03 (t, 1, $J = 7.6$ Hz), 7.24 (t, 1, $J = 7.6$ Hz), 7.31–7.36 (m, 1), 7.38 (d, 1, $J = 7.6$ Hz), 7.86 (s, 1), 7.92 (t, 1, $J = 7.6$ Hz), 8.13 (d, 1, $J = 7.9$ Hz), 8.61 (d, 1, $J = 4.3$ Hz), 10.25 (s, 1). MS (ESI, positive ion) *m/z* 309 (M+1); (ESI negative ion) *m/z* 307 (M−1). Anal. Calcd for $C_{16}H_{12}N_4OS0.5H_2O$: C, 60.55; H, 4.13; N, 17.65. Found: C, 60.20; H, 4.17; N, 16.92.

5.32. [(2-Aminophenyl)methyl](3-(4-pyridyl)(1,2,4-oxadiazol-5-yl))amine (40)

A flask charged with oxadiazole **39** (528 mg, 2.0 mmol) and 2-aminobenzylamine (224 mg, 1.8 mmol) was heated at 60 °C. After 9 h the reaction mixture was allowed to cool to room temperature and the solids were washed with MeOH, filtered, and dried in vacuo to give 51 mg (11%) of a beige powder. ^1H NMR (DMSO-d_6): δ 4.37 (d, 2, $J = 5.6$ Hz), 5.08 (s, 2), 6.54 (t, 1, $J = 7.5$ Hz), 6.66 (d, 1, $J = 7.5$ Hz), 6.99 (t, 1, $J = 7.5$ Hz), 7.07 (d, 1, $J = 7.5$ Hz), 7.81 (d, 2, $J = 5.3$ Hz), 8.74 (d, 2, $J = 5.3$ Hz), 8.97 (br t, 1, $J = 5.6$ Hz). MS (ESI, positive ion) *m/z* 268 (M+1), (ESI, negative ion) *m/z* 266 (M−1).

5.33. 3-(3-(4-Pyridyl)-1,2,4-oxadiazol-5-yl)-1,3,4-trihydroquinazolin-2-one (41)

To a solution of aniline **40** (51 mg, 0.2 mmol) in 2 mL of THF were added *p*-nitrophenyl chloroformate (82 mg, 0.4 mmol) and Et_3N (0.050 mL, 0.4 mmol) at room temperature. After 3 h the solvent was removed in vacuo and the residue was partitioned between H_2O/CH_2Cl_2. The aqueous layer was extracted consecutively with $CHCl_3$ and EtOAc, and the combined organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the residue was washed with EtOAc, filtered, and dried in vacuo to give 25 mg (42%) of an off-white powder. Mp 264–267 °C. ^1H NMR (DMSO-d_6): δ 5.23 (s, 2), 6.95 (d, 1, $J = 7.8$ Hz), 7.04 (t, 1, $J = 7.5$ Hz), 7.27 (t, 1, $J = 7.8$ Hz), 7.35 (d, 1, $J = 7.5$ Hz), 7.93 (d, 1, $J = 6.1$ Hz), 8.82 (d, 1, $J = 6.1$ Hz), 10.47 (s, 1). MS (ESI, positive ion) *m/z* 294 (M+1); (ESI negative ion) 292 (M−1). Anal. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.20; H, 3.77; N, 23.75.

5.34. 5-Chloro-3-(4-pyridyl)-1,2,4-thiadiazole (43)

To a cooled (<15 °C) suspension of thiadiazole **42** (765 mg, 4.3 mmol) in 13 mL of glacial acetic acid and 3 mL of concentrated HCl were added copper turnings (81 mg, 1.3 mmol). To this suspension was added a solution of $NaNO_2$ (312 mg, 4.5 mmol) in 1 mL of H_2O dropwise over a period of 30 min. After 4 h, a second portion of $NaNO_2$ (312 mg, 4.5 mmol) in 1 mL of H_2O was added while maintaining an internal temperature at <15 °C. After 1 h, the reaction mixture was poured into 40 mL of H_2O and extracted with $CHCl_3$. The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give 477 mg (56%) of a white powder. ^1H NMR ($CDCl_3$): δ 8.79 (d, 2, $J = 6.0$ Hz), 8.11 (d, 2, $J = 6.0$ Hz). MS (ESI, positive ion) *m/z* 198 (M+1).

5.35. 3-(3-(4-Pyridyl)-1,2,4-thiadiazol-5-yl)-1,3,4-trihydroquinazolin-2-one (45)

To a solution of thiadiazole **43** (202 mg, 1.0 mmol) in 10 mL of THF was added 2-aminobenzylamine (122 mg, 1.0 mmol) at room temperature. After 2 h, the reaction mixture was heated at 60 °C. After 15 h, the reaction mixture was allowed to cool to room temperature and the solvent was removed in vacuo to give aniline **44**.

The crude residue from the previous step was dissolved in 10 mL of DMF and 1,1′-carbonyldiimidazole (352 mg, 2.2 mmol) was added followed by 95% NaH (58 mg, 2.4 mmol) at room temperature. After 18 h, 20 mL of H_2O was added and the white precipitate was washed sequentially with H_2O, MeOH, and CH_2Cl_2. The crude material was purified by flash chromatography with CH_2Cl_2:MeOH (39:1–19:1) as eluant to give 18 mg (5%) as a white amorphous solid. Mp >290. ^1H NMR (DMSO-d_6): δ 5.43 (s, 2) 6.97 (d, 1, $J = 7.8$ Hz), 7.07 (t, 1, $J = 7.4$ Hz), 7.27 (t, 1, $J = 7.4$ Hz), 7.39 (d, 1, $J = 7.2$ Hz), 8.12 (d, 2, $J = 6.0$ Hz), 8.77 (d, 2, $J = 6.0$ Hz), 10.75 (br s, 1,). MS (ESI, positive ion) *m/z* 310 (M+1), (ESI negative ion) 308 (M−1). HRMS calcd for $C_{15}H_{11}N_5OS$ $[M+H]^+$ 310.0763. Found: 310.0764.

5.36. Methyl-5-(4-pyridyl)thiophene-2-carboxylate (46)

To a solution of 5-bromothiophene-2-carboxylate (4.02 g, 18 mmol) and 4-pyridine boronic acid (2.0 g, 16 mmol) in 150 mL of DME was added $PdCl_2dppfCH_2Cl_2$ (1.27 g, 1.7 mmol) followed by 12 mL of 2 M Na_2CO_3 solution. The reaction mixture was heated to reflux for 16 h and cooled to room temperature. The solvent was removed in vacuo, partitioned between EtOAc/H_2O, and filtered. The organic layer was extracted with 1 N HCl (3× 50 mL) and the combined acidic layers were neutralized with 1 N NaOH. The resulting precipitate was extracted with EtOAc (3× 50 mL) and the combined organic extracts were concentrated in vacuo to give 1.18 g (33%) of a pale-green powder. ^1H NMR ($CDCl_3$): δ 3.93 (s, 3), 7.47 (d, 1, $J = 3.9$ Hz), 7.51 (d, 2, $J = 6.1$ Hz), 7.80 (d, 1,

J = 3.9 Hz), 8.66 (d, 2, J = 6.1 Hz). MS (ESI, positive ion) m/z 220 (M+1).

5.37. 5-(4-Pyridyl)thiophene-2-carboxylic acid (47)

To a solution of ester **46** (2.44 g, 11.1 mmol) in 130 mL EtOH was added 30 mL of 1 N NaOH at room temperature. After 2 h the solvent was removed in vacuo. The residue was dissolved in 100 mL of H_2O, and acidified with 1 N HCl to pH 5. The resulting white precipitate was filtered, washed with H_2O and dried in vacuo to give 2.06 g (90%) of an off-white powder. ^{1}H NMR (DMSO-d_6/CF_3CO_2D): δ 8.94 (d, 2, J = 6.4 Hz), 8.40 (d, 2, J = 6.4 Hz), 8.22 (d, 1, J = 3.6 Hz), 7.88 (d, 1, J = 3.6 Hz). MS (ESI, positive ion) m/z 206 (M+1); (ESI negative ion) 204 (M−1).

5.38. Prop-2-enyloxy-*N*-(5-(4-pyridyl)(2-thienyl))carboxamide (48)

To a suspension of acid **47** (1.21 g, 6.0 mmol) in 50 mL of toluene was added Et_3N (1.0 mL, 7.2 mmol) at room temperature. After 1 h diphenylphosphoryl azide (2.1 mL, 9.7 mmol) was added and after an additional hour the reaction mixture was heated to 80 °C. After 1 h, allyl alcohol (4.0 mL, 62 mmol) was added and the reaction mixture was allowed to cool to 70 °C. After 15 h, the reaction mixture was cooled to room temperature, concentrated in vacuo and purified by flash chromatography with hexanes:EtOAc: CH_2Cl_2:MeOH (3:1:0:0–0:0:99:1) as eluant to give 860 mg (55%) as a pale-yellow amorphous solid. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, 2, J = 6.2 Hz), 7.41 (d, 2, J = 6.2 Hz), 6.59 (d, 1, J = 4.0 Hz), 5.90–6.01 (m, 1), 5.39 (d, 1, J = 17.2 Hz), 5.30 (d, 1, J = 10.5 Hz), 4.73 (d, 2, J = 5.8 Hz), 3.50 (d, 1, J = 4.0 Hz). MS (ESI, positive ion) m/z 261 (M+1); (ESI, negative ion) m/z 259 (M−1).

5.39. *N*-[(2-Nitrophenyl)methyl]prop-2-enyloxy-*N*-(5-(4-pyridyl)(2-thienyl))carboxamide (49)

To a room temperature slurry of 95% NaH (101 mg, 4.2 mmol) in 20 mL of DMF was added a solution of carboxamide **48** (882 mg, 3.4 mmol) in 15 mL of DMF. After 1 h a solution of 2-nitrobenzyl bromide (814 mg, 3.8 mmol) in 10 mL of DMF was added. After 17 h the reaction mixture was concentrated in vacuo and purified by flash chromatography with hexanes:EtOAc (3:1) followed by CH_2Cl_2:MeOH (19:1) as eluant to give 1.01 g (76%) as a pale-yellow amorphous solid. ^{1}H NMR ($CDCl_3$): δ 8.54 (d, 2, J = 6.0 Hz), 8.19 (m, 1), 7.62 (t, 1, J = 7.6 Hz), 7.49 (t, 1, J = 7.6 Hz), 7.30–7.43 (m, 3), 7.19 (d, 1, J = 4.0 Hz), 6.38 (br s, 1), 5.87 (br s, 1), 5.50 (br s, 2), 5.24 (d, 2, J = 10.4 Hz), 4.75 (d, 2, J = 5.6 Hz). MS (ESI, positive ion) m/z 396 (M+1); (ESI, negative ion) m/z 394 (M−1).

5.40. [(2-Nitrophenyl)methyl](5-(4-pyridyl)(2-thienyl))-amine (50)

To a solution of carboxamide **49** (776 mg, 2.0 mmol) and morpholine (1.8 mL, 21 mmol) in 20 mL of THF was added tetrakis(triphenylphosphine)palladium (0) (128 mg, 0.1 mmol) at room temperature. After 16.5 h the reaction mixture was concentrated in vacuo and purified by flash chromatography with hexanes:EtOAc (3:1–1:4) as eluant to give 535 mg (88%) as a red foam. ^{1}H NMR ($CDCl_3$): δ 8.45 (d, 2, J = 6.1 Hz), 8.10 (d, 1, J = 8.1 Hz), 7.68 (d, 1, J = 7.8 Hz), 7.63 (t, 1, J = 7.4 Hz), 7.48 (t, 1, J = 7.7 Hz), 7.25 (d, 2, J = 6.1 Hz), 7.17 (d, 1, J = 4.0 Hz), 6.00 (d, 1, J = 4.0 Hz), 4.95 (br t, 1, J = 6.0 Hz), 4.73 (d, 2, J = 6.0 Hz). MS (ESI, positive ion) m/z 312 (M+1); (ESI, negative ion) m/z 310 (M−1).

5.41. 3-(5-(4-Pyridyl)-2-thienyl)-1,3,4-trihydroquinazolin-2-one (52)

To a solution of amine **50** (535 mg, 1.7 mmol) and NH_4Cl (95 mg, 1.8 mmol) in 20 mL of 70% aqueous EtOH was added iron dust (482 mg, 8.6 mmol) and the reaction mixture was heated at 78 °C. After 1 h the reaction mixture was filtered through a pad of Celite® and the pad was washed with hot EtOH. The filtrate was concentrated in vacuo and the residue was azeotroped twice with benzene. The crude **51** was dissolved in 20 mL of DMF and to this solution were added 1,1′-carbonyldiimidazole (754 mg, 4.6 mmol) and 95% NaH (132 mg, 5.5 mmol) at room temperature, resulting in gas evolution. After 16 h, 40 mL of H_2O was carefully added and the precipitate was filtered, washed sequentially with H_2O and MeOH, and dried in vacuo to give 400 mg (76%) of an off-white amorphous solid. Mp 301–305 °C. ^{1}H NMR (DMSO-d_6): δ 5.07 (s, 2), 6.83 (d, 1, J = 4.1 Hz), 6.90 (d, 1, J = 7.5 Hz), 7.00 (t, 1, J = 7.5 Hz), 7.22 (t, 1, J = 7.5 Hz), 7.26 (d, 1, J = 7.5 Hz), 7.57 (d, 2, J = 5.5 Hz), 7.66 (d, 1, J = 4.1 Hz), 8.49 (d, 2, J = 5.5 Hz), 10.06 (s, 1). MS (ESI, positive ion) m/z 308 (M+1); (ESI, negative ion) m/z 306 (M−1). Anal. Calcd for $C_{17}H_{13}N_3OS\cdot 0.1H_2O$: C, 66.04; H, 4.30; N, 13.59. Found: C, 66.21; H, 4.50; N, 13.55.

5.42. 3-(Pyridin-4-yl)benzenamine (54)

To a mixture of 4-bromopyridine hydrochloride (4.50 g, 23.2 mmol) and 3-aminobenzene boronic acid monohydrate (4.00 g, 25.9 mmol) in 55 mL of 8:3 toluene/EtOH were added 2 M Na_2CO_3 (50 mL, 100 mmol) and tetrakis(triphenylphosphine)palladium (0) (1.017 g, 0.88 mmol) and the mixture was heated at 80 °C overnight. The reaction mixture was allowed to cool to room temperature and partitioned between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were washed with 2% aqueous HCl (2× 25 mL). The acidic aqueous layers were combined, neutralized with 1 N NaOH, and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 2.52 g (64%) of an orange solid. ^{1}H NMR ($CDCl_3$): δ 3.81 (br s, 2), 6.77 (d, 1, J = 7.9 Hz), 6.94 (br s, 1), 7.04 (d, 1, J = 7.6 Hz), 7.27 (t, 1, J = 7.8 Hz), 7.48 (d, 2, J = 4.6 Hz), 8.64 (d, 2, J = 4.6 Hz). MS (ESI, positive ion) m/z 171 (M+1).

5.43. *N*-(2-Nitrobenzyl)-3-(pyridin-4-yl)benzenamine (55)

A mixture of compound **54** (1.02 g, 6.00 mmol), 2-nitrobenzyl bromide (1.32 g, 6.09 mmol), and K_2CO_3 (1.04 g, 7.51 mmol) in 20 mL of CH_3CN was heated at 55 °C. After 4 days the reaction mixture was cooled to 25 °C and partitioned between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (2×) and the combined organics were washed with brine and dried over $MgSO_4$. The crude residue was purified by flash chromatography on silica gel using CH_2Cl_2:EtOAc (8:2) as the eluant to afford 280 mg (15%) of a light-orange solid. ^{1}H NMR (DMSO-d_6): δ 4.65 (d, 2, J = 6.1 Hz), 6.53 (t, 1, J = 3.9 Hz), 6.66 (d, 1, J = 5.9 Hz), 6.96 (m, 2), 7.20 (t, 1, J = 7.8 Hz), 7.56 (d, 2, J = 4.5 Hz), 7.65–7.72 (m, 2), 8.08 (d, 1, J = 8.2 Hz), 8.59 (d, 2, J = 4.5 Hz). MS (ESI, positive ion) m/z 306 (M+1).

5.44. *N*-(2-Aminobenzyl)-3-(pyridin-4-yl)benzenamine (56)

A mixture of compound **55** (280 mg, 0.92 mmol) and 10% palladium on carbon (84 mg) in 20 mL of EtOH was stirred under 1 atm of H_2 at room temperature overnight. The reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated to dryness to provide 182 mg (72%) of a light-brown solid. ^{1}H NMR (DMSO-d_6): δ 4.22 (d, 2, J = 4.8 Hz), 5.04 (br s, 2), 6.24 (br s, 1), 6.59 (t, 1, J = 7.4 Hz), 6.71–6.77 (m, 2), 6.97–7.03 (m, 3), 7.19 (d, 1, J = 7.4 Hz), 7.25 (t, 1, J = 7.8 Hz), 7.63 (d, 2, J = 4.5 Hz), 8.65 (d, 2, J = 4.5 Hz).

5.45. 3-(3-(Pyridin-4-yl)phenyl)-3,4-dihydroquinazolin-2(1*H*)-one (57)

To a solution of compound **56** (182 mg, 0.66 mmol) in 5 mL of toluene/5 mL of THF were added *p*-nitrophenyl chloroformate (135 mg, 0.67 mmol) and Et_3N (0.09 mL, 0.65 mmol). After 1 h at room temperature the reaction mixture was heated at 70 °C overnight. Additional *p*-nitrophenyl chloroformate was added until the reaction was complete. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2, and washed with H_2O and brine, and dried over $MgSO_4$. Purification by flash chromatography on silica gel with MeOH:CH_2Cl_2 (2:98) as eluant gave 45 mg (23%) of the title compound as a white solid. Mp 208–210 °C. ^{1}H NMR ($CDCl_3$): δ 8.70 (d, 2, J = 6.0 Hz), 7.67 (s, 1,), 7.39–7.58 (m, 5), 7.12 (d, 1, J = 8.0 Hz), 7.03 (t, 1, J = 7.3 Hz), 6.83 (s, 1), 6.77 (d, 1, J = 8.0 Hz), 4.91 (s, 2). MS (ESI, positive ion) m/z 302 (M+1). Anal. Calcd for $C_{19}H_{16}N_3OH_2O$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.23; H, 5.31; N, 13.06.

5.46. Biological methods: CDK5 and CDK2 assays

These assays were preformed according to the protocols previously described.[54]

5.47. Molecular modeling

Representative molecules were generated using Insight II (2000) software[55] with in-house X-ray structure of 1 as the starting point. Ab initio (Gaussian 98) calculations (energy minimizations) using Density Functional Theory as implemented in Gaussian 98[56] software, utilizing the B3LYP hybrid density functional and the 6-31G$_*$ basis set at B3LYP/6-31G$_*$ level were carried out on these molecules. These were aligned using Insight II, Transform/Superimpose options. Solvation free energies were calculated[57] using the Polarizable Continuum Model (PCM) implemented in Gaussian 98 software.

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