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Design, Synthesis, and Biological Evaluation of New Diaminoquinazolines as β-Catenin/Tcf4 Pathway Inhibitors

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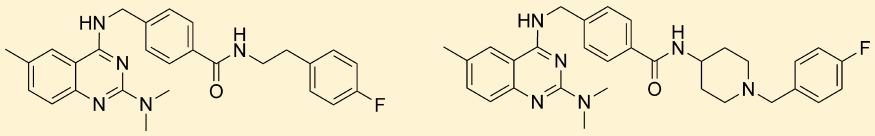

ABSTRACT: More than 50 new diaminoquinazoline derivatives have been synthesized and evaluated in a colon carcinoma cell growth inhibition assay using HCT116 and SW480 cells. Twenty compounds with good cell growth inhibitory activities (<4 μM) were tested as inhibitors of the β-catenin/T cell transcription factor 4 (Tcf4) signaling pathway using a HCT116 cell-based luciferase reporter assay. Results from the biological activities as well as the comparative molecular field analysis (CoMFA) of the properties of the molecules yielded a preliminary structure−activity relationship (SAR). Three potent compounds, **74**, **78**, and **86**, showed IC_{50} values <1 μM for growth inhibition of HCT116 cells and ∼1 μM for SW480 cells, as well as IC_{50} values of 1.5−2.5 μM for HCT116 cells with the luciferase reporter assay.

INTRODUCTION

The Wnt (wingless int-1) signaling pathway is involved in multiple developmental events during embryogenesis and is implicated in adult tissue homeostasis and tumorigenesis.[1,2] Mutations or deregulated expression of components of the Wnt pathway can induce diseases, most importantly cancers.[3] The Wnt signaling pathway is regulated by the Wnt ligands, the adenomatous polyposis coli (APC)-Axin complex, and the β-catenin.[4] When canonical Wnt signaling is activated, cytosolic β-catenin is stabilized and translocated into the nucleus, where it functions together with Tcf proteins, such as LEF1 (lymphoid enhancer-binding factor 1), Tcf1, Tcf3, and Tcf4, as a transcriptional activator for a large number of target genes (e.g., c-Myc and cyclin D1).[5] Transcriptional activation of β-catenin/Tcf target genes is a hallmark of colorectal cancer cells, and the constitutive activation of some of these genes is essential for creating and maintaining the malignant phenotype.[6]

Colorectal cancer is the second leading cause of cancer mortality in the United States. More than one million new cases are diagnosed worldwide each year with nearly 16% of these in the United States alone.[7] Besides surgical resection, which is rarely curative in advanced disease, current therapy for colon cancer relies on traditional cytotoxic agents that show only limited effects. Nearly 90% of all colorectal cancers have an activating mutation of the canonical Wnt signaling pathway.[8] Constant activation of Wnt/β-catenin signaling is thought to be an initiating event in colorectal carcinogenesis.[9] Most colorectal tumors, and certain other cancers, are characterized by an accumulation of β-catenin in the nucleus and is accompanied by dysregulation of the β-catenin/Tcf4 complex.[10] Consequently, the β-catenin/Tcf4 signaling pathway presents a novel target for therapeutic intervention in colorectal cancer.[11,12]

Over the past decade, several small-molecule inhibitors of the Wnt signaling pathway have been identified by high-throughput screening (HTS) and visual screening.[13−15] Most of these compounds are naturally occurring substances in biological materials, so that the structural modification is difficult. Recently, Dehnhardt et al.[16,17] reported the discovery of a novel class of small molecules built on a quinazoline core that can inhibit the β-catenin/Tcf4 pathway. Although a couple of compounds showed inhibitory activity on the growth of a β-catenin/RK3E tumor xenograft, many of this series of compounds had no desired pharmacokinetic (PK) properties.

In this study, we reported a series of 2,4-diaminoquinazoline analogues that were tested in a colon carcinoma cell growth inhibition assay on two cell lines, HCT116 and SW480. The compounds that showed good growth inhibitory activities were also tested in a cell-based luciferase reporter assay in HCT116 cells. Therefore, we provided the first characterization of the primary structure−activity relationship (SAR) based on the biological activity and the Comparative Molecular Field Analysis (CoMFA) results for these inhibitors of the β-catenin/Tcf4 signaling.

RESULTS AND DISCUSSION

Chemistry. The synthesis of the diaminoquinazoline analogues **17**−**34** is shown in Scheme 1. The side chains **3**−**9** were

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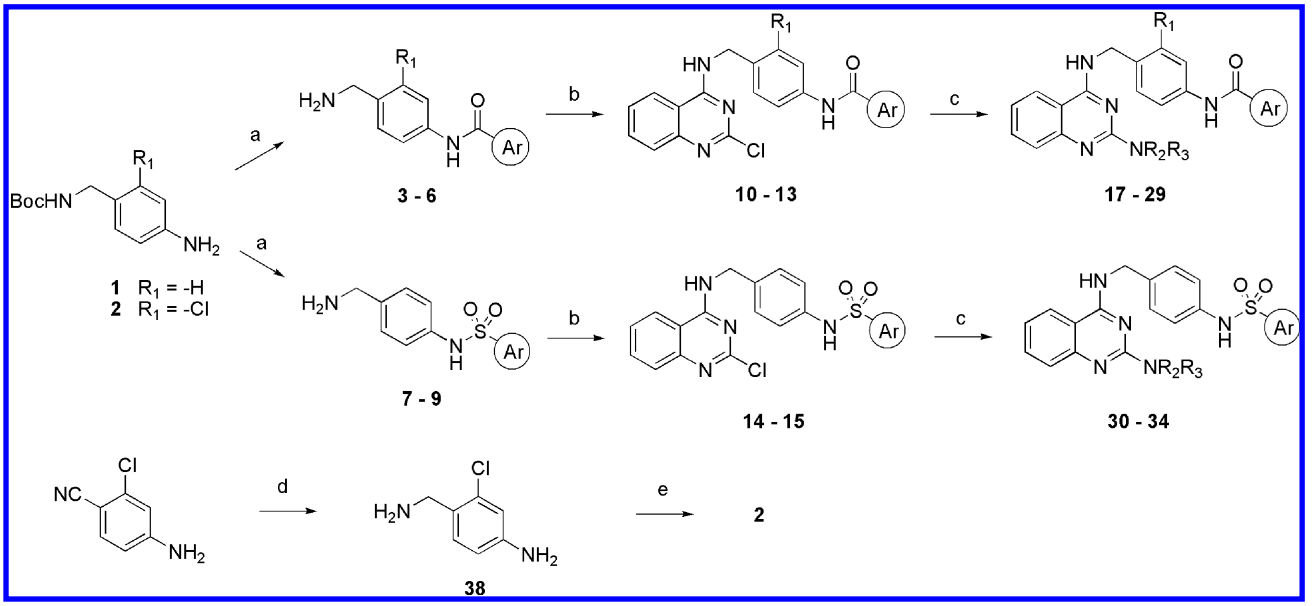
Scheme 1[a]



[a]Reagents and conditions: (a) (i) acyl chloride or sulfuryl chloride, TEA, CH_2Cl_2, rt, 2−8 h; (ii) TFA, rt, 3−12 h, 45−87%; (b) 2,4-dichloroquinazoline (**39**), TEA, THF−CH_2Cl_2, rt, 3−6 h, 70−98%; (c) amine, THF or dioxane, sealed tube or reflux, 100−120 °C, 8−16 h, 20−90%; (d) $LiAlH_4$, THF, 68%; (e) Boc_2O, TEA, CH_2Cl_2, 72%.

synthesized first through several steps from commercially available materials.[18,19] The quinazoline intermediates **10**−**15** were then obtained by the reaction of compounds **3**−**9** with 2,4-dichloroquinazoline (**39**). Subsequent amination at the 2-position of the quinazoline moiety was accomplished by heating with the appropriate amines in THF or dioxane at 100−120 °C, mostly carried out in sealed tubes, yield the final products **17**−**34**.[16,17]

Another series of diaminoquinazoline and 6-methyl-substituted analogues **62**−**91** were prepared from the benzoic acid **40**[20] as depicted in Scheme 2. The side chains **41**−**48** and the moiety **98**[21] were synthesized in a couple of steps from commercially available materials using the traditional amidation method.[22] The intermediates **49**−**60** were synthesized by the reaction of **41**−**48** with **39** or the 6-methylquinazoline **95**, which were prepared from *o*-aminobenzoic acid.[23,24] The final products **62**−**91** were obtained using the same methods used for the preparation of compounds **17**−**34**.

The 3-cyano-4-aminoquinoline intermediate **103** (Scheme 3) was prepared by reaction of the side chain **3** with the 3-cyanoquinoline moiety **102**, which was synthesized from phenyl isocyanate through a couple of steps.[25,26] The final compounds **104** and **105** were obtained using the established method for the preparation of **17**−**34**. The 2,4-diaminopyrimidine analogues **111**−**113** (Scheme 4) were prepared from the commercially available dichloropyrimidines (**107**, **108**) with the moiety **3**, using the similar methods to those described above.

Biology and SAR Study. The chemical structures and the bioactivities of the target compounds are depicted in Tables 1−8. The IC_{50} values for cell growth inhibition and reporter assay of compounds **17**−**29** are summarized in Table 1. The 4-fluorophenyl-substituted compounds (**17**−**22**) had better activities compared to the pyridine-4-yl analogues (**23**−**25**) and the *N*-methylpiperazine derivatives (**26**, **27**), which indicated that the 4-fluorophenyl group was an optimal moiety. The 2-amino substituents in the quinazoline core also had a relationship with the activity. Secondary or tertiary amines, such as the methylamino (**17**), dimethylamino (**18**), and *n*-propylamino (**21**) groups, were both suitable for maintaining the activity while the bulky dimethylaminopropylamino group (**20**) resulted in a decrease of activity. Introducing a chloro substituent into the molecule (**28**, **29**) had no evident influence on the bioactivity, which indicated that some modifications could be made to the phenyl ring. We then tested three promising compounds (**17**, **21**, and **22**) in a luciferase reporter assay in HCT116 cells. The IC_{50} values were ∼2-fold higher than in the related cell growth inhibition assay.

The structure and the bioactivity data of the benzsulfamide analogues **30**−**34** are depicted in Table 2. However, these analogues did not retain the bioactivity. The 2-*N*-methylpiperazine-substituted compound **32** in particular lost almost all activities. The other four derivatives had activities ∼4-fold lower than those of the related benzamide compounds.

Another series of the benzamide derivatives **62**−**69** were synthesized, and the bioactivities were evaluated to determine which modification was the most suitable, as shown in Table 3. Because these compounds can maintain the bioactivities, it indicates that more linking patterns of the benzene ring are available in the side chain. We investigated the effects of different amino substituents at the 2-position of the quinazoline core by introducing eight amines (e.g., cyclopropylamine, *n*-butylamine, allylamine, 3-methylpiperazine) onto the most potent 4-fluorophenylbenzamide quinazoline core. Most of these analogues showed similar cell growth inhibition IC_{50} values for HCT116 and SW480 cells. The *n*-propylamino (**65**)- and the *n*-butylamino (**66**)-substituted analogues were the most potent, with IC_{50} values of 1−1.6 μM (cell survival) and 381−684 nM (clonogenic growth). In contrast, the allylamino derivative **67** was less active, with an IC_{50} value greater than 10 μM (cell survival). We also tested the effects of five potent compounds on the luciferase reporter assay in HCT116 cells. Compounds **65** and **66** showed IC_{50} values of 1.5−3 μM for the luciferase reporter assay in HCT116 cells. However, the 3-methylpiperazine compound **69** had an IC_{50} value greater than 5 μM.

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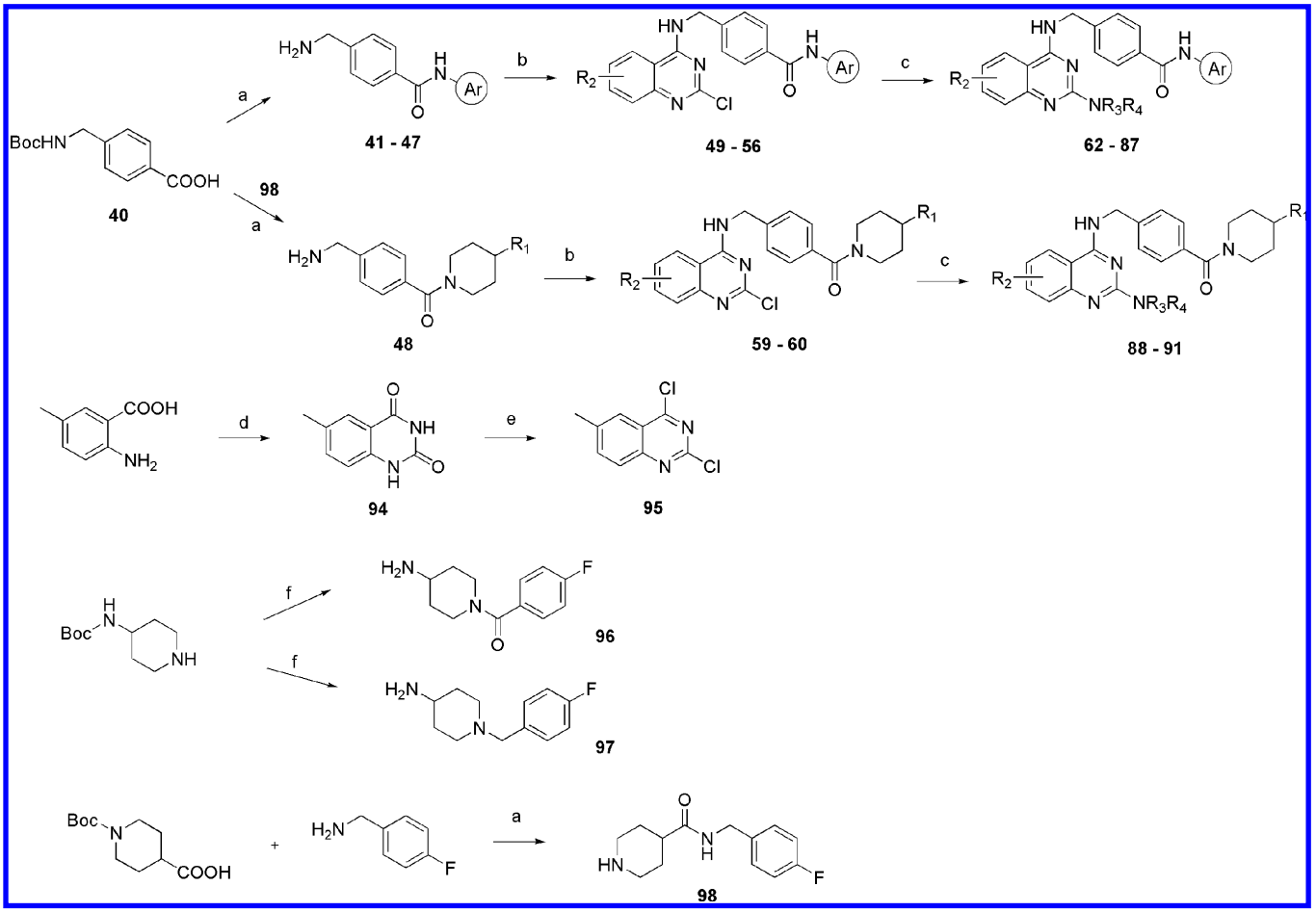
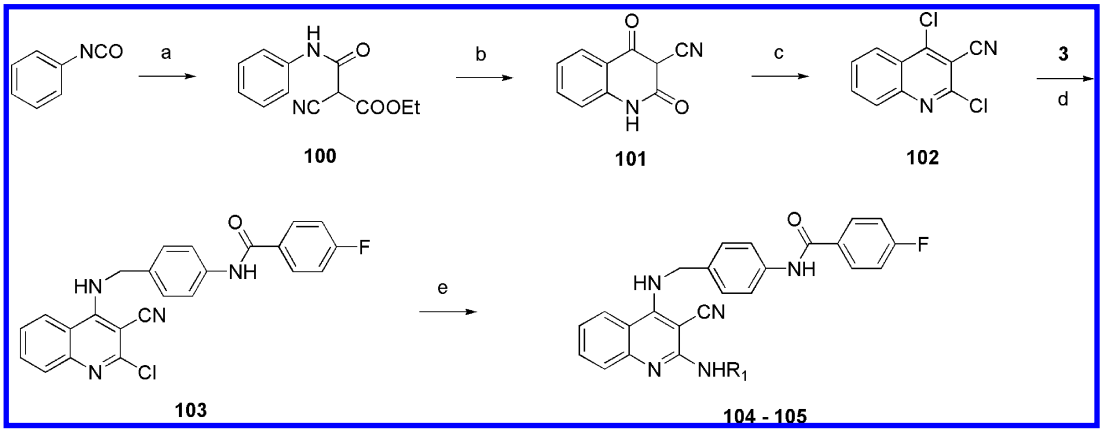
Scheme 2[a]



[a]Reagents and conditions: (a) (i) amine, HOBt, DIC, DIEA, CH_2Cl_2, rt, 6−14 h; (ii) TFA, rt, 3−12 h; (b) **39** or **95**, TEA, THF−CH_2Cl_2, rt, 3−6 h, 70−98%; (c) amine, THF or dioxane, sealed tube or reflux, 100−120 °C, 8−16 h, 20−90%; (d) urea, 150−180 °C, 5 h; (e) $POCl_3$, reflux, 3 h, 56%, (f) (i) 4-fluorobenzoyl chloride or 4-fluorobenzyl chloride, TEA, CH_2Cl_2, rt, 2−8 h; (ii) TFA, rt, 12 h, 85−90%.

Scheme 3[a]



[a]Reagents and conditions: (a) ethyl cyanoacetate, TEA, DMF, rt, 1 h; (b) dichlorobenzene, reflux, 6 h; (c) $POCl_3$, PCl_5, reflux, 4 h, 35% for three steps; (d) TEA, THF−CH_2Cl_2, rt, 3 h; (e) amine, THF, sealed tube, 100−120 °C, 14 h, 58−79%.

Next, we endeavored to improve the potency and diversity of the chemical structures by preparing several 6-methylquinazoline derivatives, compounds **70**−**87**, which had varying "Ar" and 2-amino substituents. The structures and in vitro activities are tabulated in Table 4. The 6-chloropyridin-3-yl substituent analogues (**72**, **73**) had activities equal or even higher than that of the 4-fluorophenyl substituent (**70**), and the former had a better water solubility. The benzyl, phenethyl, and phenylcyclopropyl groups were introduced to the quinazoline core in order to extend the side chain. This modification resulted in an

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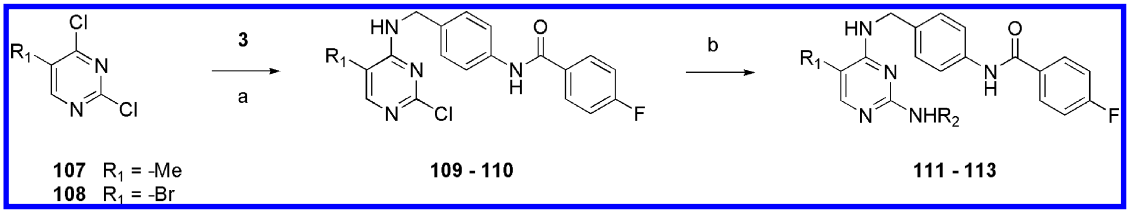
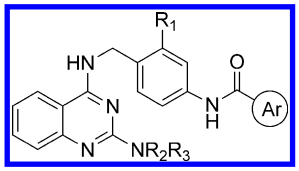
Scheme 4[a]



[a]Reagents and conditions: (a) TEA, THF−CH_2Cl_2, rt, 3 h, 58−75%; (b) amine, THF, sealed tube, 100−120 °C, 14 h, 32−45%.

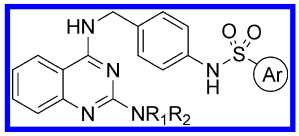
Table 1. Chemical Structure and Biological Activity of Compounds 17−29



				IC_{50} (μM)[a]		
					cell growth inhibition	
compd	R_1	Ar	NR_2R_3	reporter assay: HCT116	HCT116	SW480
17	H	4-fluorophenyl	methylamine	3.5	1.6	2.0
18	H	4-fluorophenyl	dimethylamine		1.3	2.2
19	H	4-fluorophenyl	4-methylpiperazine		1.8	2.5
20	H	4-fluorophenyl	dimethylaminopropylamine		10.0	14.0
21	H	4-fluorophenyl	*n*-propylamine	2.5	1.7	2.0
22	H	4-fluorophenyl	ethylamine	3.0	1.4	2.3
23	H	pyridin-4-yl	methylamine		>20	>20
24	H	pyridin-4-yl	dimethylamine		15.0	11.0
25	H	pyridin-4-yl	4-methylpiperazine		>20	>20
26	H	4-[(4-methylpiperazin-1-yl)methyl]phenyl	methylamine		10.0	11.0
27	H	4-[(4-methylpiperazin-1-yl)methyl]phenyl	dimethylaminopropylamine		>20	>20
28	Cl	4-fluorophenyl	methylamine		2.0	2.3
29	Cl	4-fluorophenyl	ethylamine		1.5	1.6

[a]The IC_{50} values are the average of three separate experiments. Standard deviations were below ±20%.

Table 2. Chemical Structure and Biological Activity of Compounds 30−34



			cell growth inhibition, IC_{50} (μM)[a]	
compd	Ar	NR_1R_2	HCT116	SW480
30	4-methylphenyl	methylamine	5.8	4.9
31	4-methylphenyl	dimethylamine	11.0	13.0
32	4-methylphenyl	4-methylpiperazine	>20	>20
33	4-fluorophenyl	methylamine	5.3	4.8
34	4-fluorophenyl	cyclopropylamine	4.9	4.1

[a]The IC_{50} values are the average of three separate experiments with standard deviation below ±20%.

improvement of the bioactivity. Most of these derivatives (**74**−**81**) showed IC_{50} values of 1−3 μM for HCT116 and SW480 cell growth inhibition, as well as for suppression of the luciferase reporter assay in HCT116 cells. The 2-dimethylamino-substituted compounds **74** and **78** had IC_{50} values of 0.9 μM and 0.6 μM, respectively, in the HCT116 cell line.

Extension the side chain of the 6-methyl quinazoline structures help to increase the bioactivity, another series of six compounds **82**−**87** were synthesized. The 4-fluorobenzoylpiperidine and 4-fluorobenzylpiperidine substituents were introduced into the molecule respectively. The benzoylpiperidine analogues **82** and **83** had bioactivity lower than that of the benzylpiperidine analogues **84**−**87**, which showed IC_{50} values of 2.5−3 μM for the luciferase reporter assay in HCT116 cells and 1−2 μM for cell growth inhibition of the two cell lines. The most potent 2-dimethylamino-substituted compound **86** had an IC_{50} value of 0.8 μM in the HCT116 cells.

We explored the structure−activity relationships further by preparing another four compounds **88**−**91**. The chemical structures and the biological data are depicted in Table 5. The (4-fluorobenzyl)piperidinecarboxamide moiety was introduced into the molecule to extend the side chain further. However, these analogues had an IC_{50} value ∼5 μM for the HCT116 and SW480 cell growth inhibition. One possible reason is that the piperidine core in the molecule is not a potential pharmacophore and the aromatic ring is more suitable.

Lastly, two other types of derivatives were synthesized and evaluated with the cell growth inhibition assay as shown in Table 6 and 7. The first type was the 3-cyano-2-aminoquinoline structure **104** and **105**. The purpose of this design was to find

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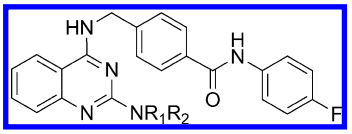
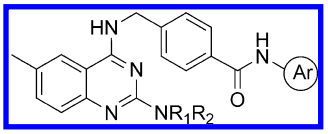
Table 3. Chemical Structure and Biological Activity of Compounds 62−69



			IC_{50} (μM)[a]	
			cell growth inhibition	
compd	NR_1R_2	reporter assay: HCT116	HCT116	SW480
62	methylamine		2.9	4.1
63	ethylamine	3.5	1.9	2.5
64	cyclopropylamine		2.7	2.6
65	*n*-propylamine	3.0	1.5	1.6
66	*n*-butylamine	1.5	1.4	1.0
67	allylamine		14.0	11.0
68	dimethylamine	3.0	1.9	2.6
69	(±)-3-methylpiperazine	>5.0	2.8	3.2

[a]The IC_{50} values are the average of three separate experiments with standard deviation below ±20%.

Table 4. Chemical Structure and Biological Activity of Compounds 70−87



				IC_{50} (μM)[a]	
				cell growth inhibition	
compd	Ar	NR_1R_2	reporter assay: HCT116	HCT116	SW480
70	4-fluorophenyl	*n*-propylamine		1.2	1.3
71	4-fluorophenyl	allylamine		13.0	10.0
72	6-chloropyridin-3-yl	dimethylamine	2.5	1.3	1.1
73	6-chloropyridin-3-yl	*n*-propylamine	2.5	1.5	2.1
74	4-fluorobenzyl	dimethylamine	2.0	0.9	1.1
75	4-fluorobenzyl	*n*-propylamine		4.4	2.2
76	4-fluorobenzyl	(±)-3-methylpiperazine		2.9	1.4
77	4-fluorophenethyl	methylamine	1.0	1.1	1.5
78	4-fluorophenethyl	dimethylamine	1.5	0.6	1.4
79	4-fluorophenethyl	*n*-propylamine	2.0	1.6	1.6
80	*trans*-2-phenylcyclopropyl	dimethylamine	3.0	1.3	2.4
81	*trans*-2-phenylcyclopropyl	ethylamine	3.5	1.7	1.8
82	1-(4-fluorobenzoyl)piperidine-4-yl	*n*-propylamine		6.8	5.5
83	1-(4-fluorobenzoyl)piperidine-4-yl	allylamine		6.9	5.2
84	1-(4-fluorobenzyl)piperidine-4-yl	methylamine	3.0	1.2	1.3
85	1-(4-fluorobenzyl)piperidine-4-yl	*n*-propylamine	3.0	1.6	1.1
86	1-(4-fluorobenzyl)piperidine-4-yl	dimethylamine	2.5	0.8	1.1
87	1-(4-fluorobenzyl)piperidine-4-yl	(±)-3-methylpiperazine	>5.0	2.0	1.0

[a]The IC_{50} values are the average of three separate experiments. Standard deviations were below ±20%.

out whether the 3-cyanoquinoline core could mimic the quinazoline structure. The second class was the 2,4-diaminopyrimidine structure **111−113**. This design was intended to confirm whether the benzene ring of the quinazoline core dominates the inhibitory action. Neither of these structures showed any cell growth inhibition when supplied to HCT116 and SW480 cells. These biological activity data tell us that the quinazoline core is the key pharmacophore of the inhibitors.

The top five compounds with the growth inhibition activities, **65**, **66**, **74**, **78**, and **86** were selected to test the clonogenic assays on HCT116 cell line, which are shown in Table 8. The five compounds have the IC_{50} values of 264−684 nM for the assays.

CoMFA Analysis. The SAR of the synthesized compounds was further studied using 19 analogues with diverse structures and bioactivities by applying CoMFA. The calculation method is described in the Experimental Section. These selected compounds include **18**, **20**, **23**, **24**, **30**, **65**, **67**, **70**, **71**, **74**, **77**, **78**, **86**, **90**, **104**, **105**, and **111−113**, which are shown in Tables 1−7.

Analysis of the 3D-QSAR Model. The CoMFA contour map of this series of compounds is shown in Figure 1. The CoMFA model gave a good cross-validated correlation with a q^2 value of 0.612 with five optimum components. The conventional correlation coefficient r^2 was 0.960, $F_{5,13}$ was 62.629, and the estimated standard error was 0.194. The calculated steric and

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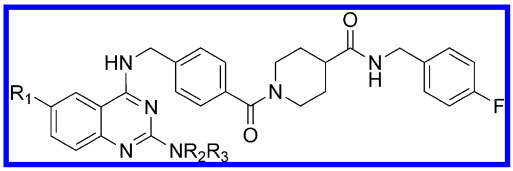
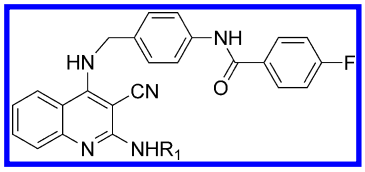
Table 5. Chemical Structure and Biological Activity of Compounds 88−91



compd	R_1	NR_2R_3	cell growth inhibition, IC_{50} (μM)[a] HCT116	SW480
88	H	dimethylamine	5.7	5.5
89	H	*n*-propylamine	5.5	5.7
90	Me	dimethylamine	5.6	5.6
91	Me	*n*-propylamine	4.6	5.2

[a]The IC_{50} values are the average of three separate experiments with standard deviation below ±20%.

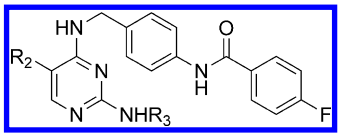
Table 6. Chemical Structure and Biological Activity of Compounds 104 and 105



compd	R_1	cell growth inhibition, IC_{50} (μM)[a] HCT116	SW480
104	Me	>20	>20
105	*n*-Pr	>20	>20

[a]The IC_{50} values are the average of three separate experiments. Standard deviations were below ±20%.

Table 7. Chemical Structure and Biological Activity of Compounds 111−113



compd	R_2	R_3	cell growth inhibition, IC_{50} (μM)[a] HCT116	SW480
111	Me	Me	>20	>20
112	Me	Et	>20	>20
113	Br	Me	>20	>20

[a]The IC_{50} values are the average of three separate experiments. Standard deviations were below ±20%.

Table 8. Clonogenic Assays of the Five Compounds on HCT116 Cells

compd	**65**	**66**	**74**	**78**	**86**
IC_{50} (*n*M)[a]	684	381	298	264	313

[a]The IC_{50} values are the average of three separate experiments. Standard deviations were below ±20%.

electrostatic fields contributed 48% and 52%, respectively, to the variations in the percent inhibition.

The CoMFA analysis and the biological activity data produced a preliminary SAR result, as shown in Figure 1 and Table 9. (1) The large green area showed that the activity could

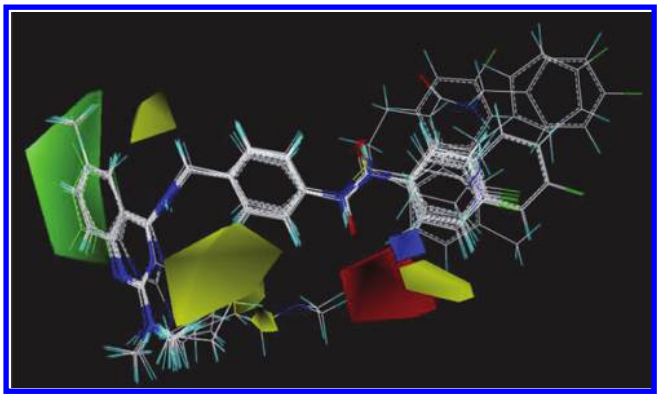


Figure 1. The CoMFA contour map of the selected 19 compounds.

be enhanced by increasing the steric bulk on the benzene ring of the quinazoline core. The bioactivities of the parent nucleus 6-methylquinazoline and quinazoline were much higher than those of the 3-cyano-2,4-diaminoquinoline and 2,4-diaminopyrimidine core. (2) The large yellow area indicated that the activity could be improved by decreasing the size of the 2-amino group of the quinazoline core. Generally, methylamine, dimethylamine, ethylamine, and *n*-propylamine groups had bioactivities better than those of the bulky substituents, such as 1-piperazine and 3-dimethylaminopropylamine. (3) The red area showed the difference between the two kinds of benzamides. As usual, better bioactivities were obtained for the *N*-phenyl-4-[(quinazolin-4-ylamino)methyl]benzamides (compounds **70−87**) than for their reversed amide bond analogues (compounds **17−29**). The benzamide linker also had activities higher than those of the benzsulfamide structure. (4) The substituents at the 4-position of quinazoline core also played an important role in the contribution of bioactivities, whereby properly extending the 4-substituents will enhance the activities. So far, the 4-fluorobenzyl, 4-fluorophenethyl, 4-fluorobenzylpiperidine, phenylcyclopropyl, and 6-chloropyridin-3-yl substituents have activities better than those of the other groups such as 4-pyridine and 4-methylphenyl.

CONCLUSIONS

More than 50 new diaminoquinazoline derivatives have been prepared and evaluated in HCT116 and SW480 cells using the colon carcinoma cell growth inhibition assay. Among these derivatives, 20 compounds with good growth inhibitory activities (<4 μM) were also tested as inhibitors of the β-catenin/Tcf4 signaling pathway in a cell-based luciferase reporter assay in the HCT116 cell line. The biological activity results, as well as the CoMFA analysis of the properties of the molecules, identified a preliminary SAR. (1) Compounds substituted with secondary or tertiary amines at the 2-position of the quinazoline core maintain the bioactivity, whereas substitution with bulky substituents reduce the activity. (2) The benzsulfamide analogues generally have activities ∼4-fold lower than those of the related benzamide compounds. (3) The 3-cyano-2-aminoquinoline and 2,4-diaminopyrimidine structures showed no cell growth inhibition activities, indicating that the quinazoline core is important for retaining bioactivity. (4) Generally the 4-[(quinazolin-4-ylamino)methyl]benzamides (**70−87**) had bioactivity better than that of their reversed amide bond analogues (**17− 29**). (5) Introducing suitably long side chains to the 4-position of the quinazoline core can boost the bioactivity. Three potent compounds, **74**, **78**, and **86**, had IC_{50} values of 264−313 nM for the clonogenic assay and 1.5−2.5 μM

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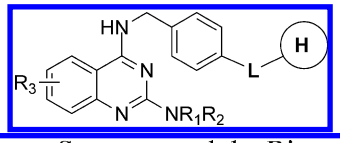
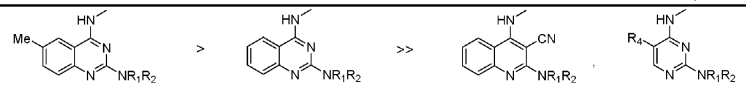
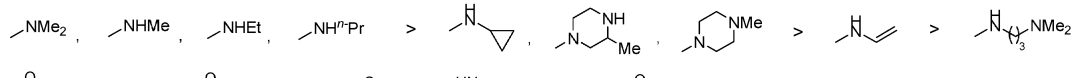
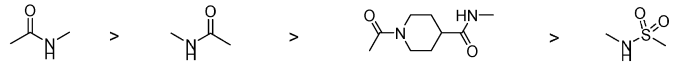
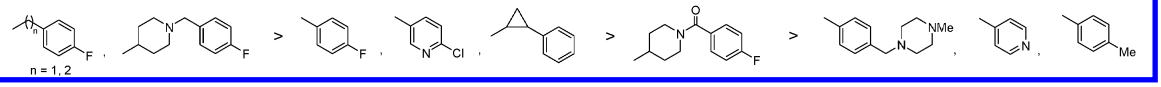
Table 9. Preliminary SAR Results of the Synthesized Compounds



Group	Structure and the Bioactivity Order
Skeleton	
-NR_1R_2	
L	
H	

for the luciferase reporter assay in HCT116 cells. Moreover, in the cell growth inhibition assays, their IC_{50} values were 0.6–0.9 μM in HCT 116 cells, as well as ~1 μM in SW480 cells. As such, they represent potential chemical probes for biological studies of β-catenin/Tcf4 signaling and promising candidates for developing new anticancer therapeutics that target renewable cancer stem cells.

EXPERIMENTAL SECTION

General Methods. All commercially available chemicals and solvents were purchased and used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker-BioSpin 300 MHz spectrometer using TMS as an internal standard. The mass spectra were obtained from a Thermo Q-Tof micro spectrometer. The HPLC results were generated using a Waters 2489 UV/visible detector and Waters 1525 binary HPLC pump.

The colon cancer cell lines HCT116 and SW480 were obtained from American Type Culture Collection (ATCC) and cultured in RPMI 1640 (Hyclone, Thermal Scientific) supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin. Cells were maintained in a humidified 5% CO_2 atmosphere at 37 °C.

General Procedures for the Synthesis of the Analogues. *Procedure A.* The *N*-Boc-4-aminobenzylamine **1** (2.2 g, 10 mmol) and triethylamine (2.8 mL, 20 mmol) were dissolved in CH_2Cl_2 (40 mL) and cooled in an ice–water bath under a N_2 atmosphere, and then 4-fluorobenzoyl chloride (1.2 mL, 10 mmol) was added. The reaction mixture was stirred at room temperature for 4 h to complete the reaction, trifluoroacetic acid (10 mL) was added to the suspension, and the resulting clear solution was stirred at room temperature overnight. The solvent was removed, and the residue was taken up in CH_2Cl_2 (100 mL) and ice (50 g) and the pH adjusted to >10 with 20% NaOH aqueous solution. The layers were allowed to separate, the aqueous layer was extracted once with CH_2Cl_2 (50 mL), and the combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4. Removal of Na_2SO_4 by filtration and evaporation of solvents produced *N*-[4-(aminomethyl)phenyl]-4-fluorobenzamide **3** (2.0 g, 82%), which was used directly in the next step. ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 2H), 7.35 (m, 4H), 7.67 (d, J = 9.0 Hz, 2H), 8.02 (m, 2H), 10.18 (s, 1H).

Procedure B. The 4-[Boc-amino(methyl)]benzoic acid **40** (2.5 g, 10 mmol), HOBt (1.4 g, 10 mmol), DIC (1.9 mL, 12 mmol), and DIEA (3.3 mL, 20 mmol) were dissolved in CH_2Cl_2 (50 mL) and stirred at room temperature for 1 h under a N_2 atmosphere, 4-fluoroaniline (0.96 mL, 10 mmol) was added, and the reaction mixture was stirred overnight to complete the reaction. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed once with brine. The organic layer was separated and dried over anhydrous Na_2SO_4. The product was separated by column chromatography with hexane/ethyl acetate and then suspended in CH_2Cl_2 (20 mL). TFA (10 mL) was added, and the reaction solution was stirred at room temperature for 6 h. The solvent was removed, and the residue was taken into CH_2Cl_2 (100 mL) and ice (50 g) and the pH adjusted to >10 with 20% NaOH aqueous solution. The layers were allowed to separate, and the aqueous layer was extracted once with CH_2Cl_2 (50 mL). The combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4. Removal of Na_2SO_4 by filtration and evaporation of solvents produced 4-aminomethyl-*N*-(4-fluorophenyl)benzamide **41** (1.83 g, 75%). ^{1}H NMR (DMSO-d_6) δ 3.78 (s, 2H), 7.17 (m, 2H), 7.46 (d, J = 9.0 Hz, 2H), 7.78 (m, 2H), 7.89 (d, J = 9.0 Hz, 2H), 10.21 (s, 1H).

Procedure C. A stirred suspension of the benzamide **41** (1.22 g, 5 mmol) obtained from procedure B and TEA (1.4 mL, 10 mmol) in THF (20 mL) at room temperature was combined with 2,4-dichloroquinazoline **39** (1.0 g, 5 mmol) dissolved in CH_2Cl_2 (10 mL), and the mixture was stirred for 3–6 h to complete the reaction. The reaction solution was diluted with CH_2Cl_2 (200 mL) and washed with water and brine in turn. The organic layer was then separated and dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 by filtration and evaporation of the solvents, the crude product was purified by column chromatography with hexane/CH_2Cl_2 to give 4-[[(2-chloroquinazolin-4-yl)amino]methyl]-*N*-(4-fluorophenyl)benzamide **49** (1.50 g, 71% yield). MS (ESI) m/z 407.2.

Procedure D. The 2-chloroquinazoline intermediate **49** (0.42 g, 1 mmol) obtained from procedure C was taken up in 2.0 M methylamine solution in THF (8 mL) in a sealed tube. (A sealed tube was used if the reactant amine was methylamine, dimethylamine, ethylamine, *n*-propylamine, cyclopropylamine, or allylamine; THF or dioxane was the solvent. For other amines, the reactions were carried out in dioxane in round-bottom flask.) The mixture was heated to 100–120 °C for 8–16 h to complete the reaction. The solution was diluted with CH_2Cl_2 (100 mL) and washed once with brine. The organic layer was separated and dried over anhydrous Na_2SO_4. After removal of Na_2SO_4 by filtration and evaporation of the solvents, the crude product was purified by column chromatography with CH_2Cl_2/MeOH/TEA to give the final products listed below in yield between 20% and 90%.

HPLC Conditions. Column: Waters XBridge BEH130 C18 4.6 mm × 250 mm × 5 μm; detection: 254 nm; flow rate: 1.0 mL/min; temperature: 25 °C; injection load: 5 μL; concentration: 0.5 mg/mL; run time: 25 min; mobile phase A: water (0.01% TFA); mobile phase B: 90% acetonitrile/water (0.01% TFA); gradient program: time (min): 0 18 20 25; % of mobile phase A: 100, 0, 100, 100; % of mobile phase B: 0, 100, 0, 0; Retention time range: 14–16 min.

4-Fluoro-*N*-[4-[[(2-(methylamino)quinazolin-4-yl)amino]-methyl]phenyl]benzamide (17). A preparation of *N*-[4-[[(2-chloroquinazolin-4-yl)amino]methyl]phenyl]-4-fluorobenzamide (**10**) was made starting from *N*-Boc-4-aminobenzylamine (**1**), 4-fluorobenzoyl chloride, and 2,4-dichloroquinazoline (**39**) following procedures

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A and C. The intermediate product **10** was aminated with methylamine following procedure D to yield the final product **17**. Starting from **39** (0.2 g, 1 mmol), 190 mg (51% yield) of the final product was isolated. HPLC purity 96.1%; ^{1}H NMR (DMSO-d_6) δ 2.80 (d, J = 3.0 Hz, 3H), 4.69 (d, J = 6.0 Hz, 2H), 6.45 (d, J = 3.0 Hz, 1H), 7.03 (t, J = 6.0 Hz, 1H), 7.28 (m, 1H), 7.36 (m, 4H), 7.46 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 6.0 Hz, 2H), 8.03 (m, 3H), 8.38 (br s, 1H), 10.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.3, 46.1, 115.5, 115.8, 120.3, 120.7, 123.1, 128.1, 130.7, 130.8, 131.8, 132.6, 135.7, 138.1, 152.5, 160.3, 162.8, 164.7, 166.1; MS (ESI) m/z 402.1.

4-Fluoro-*N*-[4-[[(2-(dimethylamino)quinazolin-4-yl)amino]methyl]phenyl]benzamide (18). The intermediate **10** was aminated with dimethylamine following procedure D to yield the final product **18**. Starting from **39** (0.2 g, 1 mmol), 120 mg (29% yield) of the final product was isolated. HPLC purity 95.3%; ^{1}H NMR (DMSO-d_6) δ 3.13 (s, 6H), 4.47 (d, J = 6.0 Hz, 2H), 7.11 (t, J = 6.0 Hz, 1H), 7.32 (m, 5H), 7.54 (t, J = 6.0 Hz, 1H), 7.83 (d, J = 9.0 Hz, 2H), 7.98 (m, 2H), 8.28 (d, J = 9.0 Hz, 1H), 9.06 (t, J = 3.0 Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 37.2, 42.7, 110.5, 115.5, 115.8, 120.8, 121.9, 123.4, 125.6, 127.7, 130.4, 133.1, 134.5, 138.8, 152.9, 158.0, 159.3, 162.7, 165.5; MS (ESI) m/z 416.2.

4-Fluoro-*N*-[4-[[(2-(4-methylpiperazin-1-yl)quinazolin-4-yl)amino]methyl]phenyl]benzamide (19). The intermediate **10** was aminated with *N*-methylpiperazine following procedure D to yield the final product **19**. Starting from **39** (0.1 g, 0.5 mmol), 150 mg (64% yield) of the final product was isolated. HPLC purity 97.0%; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.43 (br s, 4H), 3.89 (br s, 4H), 4.70 (d, J = 6.0 Hz, 2H), 6.39 (br s, 1H), 7.04 (m, 3H), 7.28 (d, J = 6.0 Hz, 2H), 7.46 (m, 2H), 7.55 (d, J = 6.0 Hz, 2H), 7.60 (m, 1H), 7.87 (m, 2H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 43.9, 44.6, 46.1, 55.0, 110.4, 115.5, 115.8, 120.9, 121.3, 125.1, 128.4, 129.5, 129.6, 132.7, 135.1, 137.0, 158.2, 159.6, 163.1, 164.9, 166.5; MS (ESI) m/z 471.1.

***N*-[4-[[(2-(3-(Dimethylamino)propylamino)quinazolin-4-yl)amino]methyl]phenyl]-4-fluorobenzamide (20).** The intermediate **10** was aminated with *N,N*-dimethylpropane-1,3-diamine following procedure D to yield the final product **20**. Starting from **39** (0.1 g, 0.5 mmol), 130 mg (57% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 1.79 (br s, 2H), 2.43 (s, 6H), 2.69 (br s, 2H), 3.32 (m, 2H), 4.45 (d, J = 6.0 Hz, 2H), 6.87 (br s, 1H), 7.11 (t, J = 6.0 Hz, 1H), 7.30 (m, 5H), 7.54 (t, J = 6.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 8.01 (m, 2H), 8.33 (m, 1H), 9.19 (t, J = 3.0 Hz, 1H), 9.47 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 38.7, 42.7, 43.7, 45.8, 55.9, 115.5, 115.8, 120.9, 122.3, 123.6, 127.7, 130.3, 130.4, 131.2, 133.1, 134.7, 138.8, 158.5, 159.3, 162.6, 165.4, 165.9; MS (ESI) m/z 473.1.

4-Fluoro-*N*-[4-[[(2-(propylamino)quinazolin-4-yl)amino]methyl]phenyl]benzamide (21). The intermediate **10** was aminated with *n*-propylamine following procedure D to yield the final product **21**. Starting from **39** (0.1 g, 0.5 mmol), 56 mg (26% yield) of the final product was isolated. HPLC purity 96.3%; ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 6.0 Hz, 3H), 1.51 (m, 2H), 3.44 (m, 2H), 4.68 (d, J = 6.0 Hz, 2H), 6.48 (br s, 1H), 6.99 (m, 1H), 7.19 (m, 1H), 7.34 (d, J = 9.0 Hz, 2H), 7.46 (m, 2H), 7.68 (d, J = 9.0 Hz, 2H), 8.02 (m, 3H), 8.34 (br s, 1H), 10.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 22.3, 42.5, 42.9, 115.5, 115.8, 119.9, 120.7, 123.1, 128.0, 130.7, 130.8, 132.4, 132.6, 135.8, 138.0, 159.9, 160.2, 162.8, 164.7, 166.1; MS (ESI) m/z 430.0.

4-Fluoro-*N*-[4-[[(2-(ethylamino)quinazolin-4-yl)amino]methyl]phenyl]benzamide (22). The intermediate **10** was aminated with ethylamine following procedure D to yield the final product **22**. Starting from **39** (0.1 g, 0.5 mmol), 71 mg (34% yield) of the final product was isolated. HPLC purity 95.0%; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, J = 6.0 Hz, 3H), 3.31 (m, 2H), 4.67 (d, J = 6.0 Hz, 2H), 6.46 (br s, 1H), 6.99 (m, 1H), 7.19 (d, J = 6.0 Hz, 1H), 7.34 (m, 3H), 7.46 (m, 1H), 7.67 (d, J = 9.0 Hz, 2H), 8.00 (m, 3H), 8.38 (br s, 1H), 10.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.9, 35.7, 46.1, 115.6, 115.8, 120.2, 120.7, 123.1, 128.0, 130.7, 130.8, 132.4, 132.6, 135.7, 138.0, 159.5, 160.2, 163.1, 164.9, 166.1; MS (ESI) m/z 416.3.

***N*-[4-[[(2-(Methylamino)quinazolin-4-yl)amino]methyl]phenyl]isonicotinamide (23).** A preparation of *N*-[4-[[(2-chloroquinazolin-4-yl)amino]methyl]phenyl]isonicotinamide (**11**) was made starting from **1**, isonicotinoyl chloride, and **39** following procedures A and C. The intermediate product **11** was aminated with methylamine following procedure D to yield the final product **23**. Starting from **39** (0.1 g, 0.5 mmol), 98 mg (53% yield) of the final product was isolated. HPLC purity 95.7%; ^{1}H NMR (DMSO-d_6) δ 2.78 (d, J = 6.0 Hz, 3H), 4.68 (d, J = 6.0 Hz, 2H), 6.50 (br s, 1H), 7.02 (t, J = 6.0 Hz, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 9.0 Hz, 2H), 7.47 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 6.0 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 8.42 (br s, 1H), 8.75 (d, J = 6.0 Hz, 2H), 10.49 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.3, 45.9, 120.4, 120.8, 122.0, 123.2, 128.2, 132.7, 136.2, 137.6, 142.3, 150.6, 160.0, 164.2; MS (ESI) m/z 385.2.

***N*-[4-[[(2-(Dimethylamino)quinazolin-4-yl)amino]methyl]phenyl]isonicotinamide (24).** The intermediate **11** was aminated with dimethylamine following procedure D to yield the final product **24**. Starting from **39** (0.1 g, 0.5 mmol), 118 mg (61% yield) of the final product was isolated. HPLC purity 95.9%; ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 6H), 4.68 (d, J = 6.0 Hz, 2H), 7.03 (t, J = 6.0 Hz, 1H), 7.26 (d, J = 6.0 Hz, 1H), 7.37 (d, J = 9.0 Hz, 2H), 7.47 (t, J = 6.0 Hz, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 6.0 Hz, 2H), 8.02 (d, J = 6.0 Hz, 1H), 8.52 (t, J = 3.0 Hz, 1H), 8.76 (d, J = 6.0 Hz, 1H), 10.46 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.9, 43.8, 110.5, 120.4, 120.8, 121.9, 123.1, 125.3, 128.0, 132.7, 136.4, 137.5, 142.3, 150.7, 152.4, 159.6, 159.8, 164.2; MS (ESI) m/z 399.2.

***N*-[4-[[(2-(4-Methylpiperazin-1-yl)quinazolin-4-yl)amino]methyl]phenyl]isonicotinamide (25).** The intermediate **11** was aminated with *N*-methylpiperazine following procedure D to yield the final product **25**. Starting from **39** (0.1 g, 0.5 mmol), 105 mg (49% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.41 (br s, 4H), 3.86 (br s, 4H), 4.70 (d, J = 6.0 Hz, 2H), 6.34 (br s, 1H), 7.01 (br, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.44 (m, 2H), 7.58 (m, 3H), 7.67 (d, J = 6.0 Hz, 2H), 8.62 (d, J = 6.0 Hz, 2H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 43.8, 44.5, 45.8, 55.1, 110.5, 121.1, 121.2, 125.6, 128.4, 132.6, 135.8, 136.6, 141.9, 150.3, 152.1, 158.8, 159.7, 164.2; MS (ESI) m/z 454.1.

***N*-[4-[[(2-(Methylamino)quinazolin-4-yl)amino]methyl]phenyl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide (26).** A preparation of *N*-[4-[[(2-chloroquinazolin-4-yl)amino]methyl]phenyl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide (**12**) was made starting from **1**, 4-[(4-methylpiperazin-1-yl)methyl]benzoyl chloride,[27] and **39** following procedures A and C. The intermediate product **12** was aminated with methylamine following procedure D to yield the final product **26**. Starting from **39** (0.1 g, 0.5 mmol), 51 mg (21% yield) of the final product was isolated. HPLC purity 95.0%; ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 3H), 2.34 (br, 8H), 2.78 (d, J = 6.0 Hz, 3H), 3.50 (s, 2H), 4.66 (d, J = 6.0 Hz, 2H), 6.44 (d, J = 6.0 Hz, 1H), 7.01 (t, J = 6.0 Hz, 1H), 7.23 (m, 1H), 7.33 (d, J = 6.0 Hz, 2H), 7.41 (d, J = 9.0 Hz, 2H), 7.46 (t, J = 6.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 2H), 7.88 (d, J = 6.0 Hz, 2H), 8.02 (d, J = 6.0 Hz, 1H), 8.36 (br s, 1H), 10.16 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.3, 43.4, 46.1, 52.9, 55.1, 62.0, 120.3, 120.6, 123.1, 128.0, 128.1, 129.0, 131.9, 132.6, 134.0, 135.6, 138.2, 142.6, 152.4, 160.1, 160.2, 165.7; MS (ESI) m/z 496.2.

***N*-[4-[[(2-(3-(Dimethylamino)propylamino)quinazolin-4-yl)amino]methyl]phenyl]-4-[(4-methylpiperazin-1-yl)methyl]benzamide (27).** The intermediate **12** was aminated with *N,N*-dimethylpropane-1,3-diamine following procedure D to yield the final product **27**. Starting from **39** (0.1 g, 0.5 mmol), 60 mg (21% yield) of the final product was isolated. HPLC purity 95.4%; ^{1}H NMR (DMSO-d_6) δ 1.62 (br, 2H), 2.11 (s, 6H), 2.12 (s, 3H), 2.33 (br, 8H), 3.49 (s, 2H), 4.20 (br, 4H), 4.67 (d, J = 6.0 Hz, 2H), 7.00 (t, J = 6.0 Hz, 1H), 7.20 (m, 1H), 7.32 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 6.0 Hz, 2H), 9.45 (m, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 6.0 Hz, 2H), 7.99 (d, J = 6.0 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.8, 39.5, 45.5, 46.0, 46.1, 52.9, 55.1, 57.4, 62.0, 120.2, 120.6, 123.1, 128.0, 129.0, 132.6, 134.0, 135.5, 138.2, 142.6, 152.3, 159.7, 160.2, 165.7, 172.7; MS (ESI) m/z 567.3.

4-Fluoro-*N*-[3-chloro-4-[[(2-(methylamino)quinazolin-4-yl)amino]methyl]phenyl]benzamide (28). A mixture of 4-amino-2-chlorobenzonitrile (7.6 g, 0.05 mol) and $LiAlH_4$ (3.8 g, 0.1 mol) was suspended in anhydrous THF (50 mL) under a N_2 atmosphere and

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refluxed for 5 h to complete the reaction. The reaction mixture was poured carefully onto ice and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography with CH_2Cl_2/MeOH to give 4-(aminomethyl)-3-chloroaniline **38** (5.3 g, 68%) as a faint brown oil. Compound **38**, TEA (9.5 mL, 2 equiv), and Boc_2O (8.1 g, 1.1 equiv) were dissolved in CH_2Cl_2 (80 mL). The reaction mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2 (200 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography with hexane/CH_2Cl_2 to give *N*-Boc-4-amino-2-chlorobenzylamine **2** (6.2 g, 72%) as a faint yellow solid. MS (ESI) *m*/*z* 257.0.

A preparation of *N*-[3-chloro-4-[[(2-chloroquinazolin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (**13**) was made starting from **2**, 4-fluorobenzoyl chloride, and **39** following procedures A and C. The intermediate product **13** was aminated with methylamine following procedure D to yield the final product **28**. Starting from **39** (0.1 g, 0.5 mmol), 150 mg (71% yield) of the final product was isolated. HPLC purity 96.6%; ^{1}H NMR (DMSO-d_6) δ 2.76 (d, J = 3.0 Hz, 3H), 4.73 (d, J = 6.0 Hz, 2H), 6.44 (d, J = 3.0 Hz, 1H), 7.03 (t, J = 6.0 Hz, 1H), 7.32 (m, 1H), 7.38 (d, J = 6.0 Hz, 2H), 7.51 (m, 2H), 7.95 (d, J = 6.0 Hz, 2H), 8.02 (m, 2H), 8.36 (br s, 1H), 10.40 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.3, 41.5, 115.6, 115.9, 119.2, 120.4, 120.7, 120.9, 123.2, 129.2, 130.8, 130.9, 132.1, 132.4, 132.7, 139.3, 152.5, 160.2, 162.9, 164.9, 166.2; MS (ESI) *m*/*z* 435.9.

4-Fluoro-*N*-[3-chloro-4-[[(2-(ethylamino)quinazolin-4-yl)-amino]methyl]phenyl]benzamide (29). The intermediate product **13** was aminated with ethylamine following procedure D to yield the final product **29**. Starting from **39** (0.1 g, 0.5 mmol), 115 mg (52% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 1.03 (t, J = 6.0 Hz, 1H), 3.25 (q, J = 6.0 Hz, 2H), 4.74 (d, J = 6.0 Hz, 2H), 6.52 (br, 1H), 7.03 (t, J = 6.0 Hz, 1H), 7.24 (m, 1H), 7.32 (d, J = 9.0 Hz, 2H), 7.35 (m, 1H), 7.49 (m, 1H), 7.60 (m, 1H), 8.02 (m, 4H), 8.38 (br, 1H), 10.40 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 15.5, 35.7, 41.5, 115.6, 115.9, 119.2, 120.1, 120.3, 120.9, 123.1, 123.2, 129.0, 130.8, 130.9, 132.1, 132.7, 139.3, 159.5, 160.3, 162.9, 164.9, 166.2; MS (ESI) *m*/*z* 450.3.

***N*-[4-[[(2-(Methylamino)quinazolin-4-yl)amino]methyl]-phenyl]-4-methylbenzenesulfonamide (30).** A preparation of *N*-[4-[[(2-chloroquinazolin-4-yl)amino]methyl]phenyl]-4-methylbenzenesulfonamide (**14**) was made starting from **1**, tosyl chloride, and **39** following procedures A and C. The intermediate product **14** was aminated with methylamine following procedure D to yield the final product **30**. Starting from **39** (0.1 g, 0.5 mmol), 105 mg (51% yield) of the final product was isolated. HPLC purity 96.1%; ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H), 2.74 (d, J = 3.0 Hz, 3H), 4.57 (d, J = 6.0 Hz, 2H), 6.41 (d, J = 6.0 Hz, 1H), 6.96 (m, 1H), 7.01 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 7.24 (m, 1H), 7.29 (d, J = 9.0 Hz, 2H), 7.44 (t, J = 6.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.94 (d, J = 9.0 Hz, 1H), 8.28 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.3, 28.3, 43.1, 120.4, 123.1, 125.0, 127.1, 128.6, 130.0, 132.6, 136.0, 136.7, 137.2, 143.5, 152.4, 160.2; MS (ESI) *m*/*z* 434.2.

***N*-[4-[[(2-(Dimethylamino)quinazolin-4-yl)amino]methyl]-phenyl]-4-methylbenzenesulfonamide (31).** The intermediate product **14** was aminated with dimethylamine following procedure D to yield the final product **31**. Starting from **39** (0.1 g, 0.5 mmol), 125 mg (58% yield) of the final product was isolated. HPLC purity 95.2%; ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H), 3.01 (s, 6H), 4.57 (d, J = 6.0 Hz, 2H), 6.97 (m, 1H), 7.01 (d, J = 6.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 7.26 (m, 1H), 7.28 (d, J = 6.0 Hz, 2H), 7.44 (t, J = 6.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 6.0 Hz, 1H), 8.43 (t, J = 3.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.3, 36.9, 43.6, 110.5, 120.3, 120.4, 123.1, 125.3, 127.1, 128.5, 130.0, 132.6, 136.2, 136.7, 137.1, 143.5, 152.4, 159.5, 159.8; MS (ESI) *m*/*z* 448.1.

***N*-[4-[[(2-(4-Methylpiperazin-1-yl)quinazolin-4-yl)amino]-methyl]phenyl]-4-methylbenzenesulfonamide (32).** The intermediate product **14** was aminated with *N*-methylpiperazine following procedure D to yield the final product **32**. Starting from **39** (0.1 g, 0.5 mmol), 165 mg (68% yield) of the final product was isolated. HPLC purity 95.5%; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.44 (br s, 4H), 3.86 (br s, 4H), 4.64 (d, J = 3.0 Hz, 2H), 6.38 (br s, 1H), 6.98 (m, 1H), 7.02 (d, J = 9.0 Hz, 2H), 7.15 (m, 4H), 7.46 (m, 3H), 7.57 (d, J = 6.0 Hz, 1H), 7.64 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.5, 43.7, 44.4, 46.0, 54.9, 110.3, 121.2, 121.3, 121.7, 125.1, 127.1, 128.6, 129.5, 132.7, 135.5, 136.1, 136.4, 143.6, 158.2, 159.6; MS (ESI) *m*/*z* 503.1.

***N*-[4-[[(2-(Methylamino)quinazolin-4-yl)amino]methyl]-phenyl]-4-fluorobenzenesulfonamide (33).** A preparation of *N*-[4-[[(2-chloroquinazolin-4-yl)amino]methyl]phenyl]-4-fluorobenzenesulfonamide (**15**) was made starting from **1**, 4-fluorobenzenesulfonyl chloride, and **39** following procedures A and C. The intermediate product **15** was aminated with methylamine following procedure D to yield the final product **33**. Starting from **39** (0.1 g, 0.5 mmol), 57 mg (26% yield) of the final product was isolated. HPLC purity 96.5%; ^{1}H NMR (DMSO-d_6) δ 2.39 (s, 3H), 4.57 (d, J = 6.0 Hz, 2H), 6.56 (d, J = 3.0 Hz, 1H), 6.71 (br s, 1H), 6.95 (d, J = 9.0 Hz, 2H), 7.19 (t, J = 3.0 Hz, 1H), 7.27 (m, 1H), 7.35 (m, 4H), 7.81 (br s, 1H), 7.91 (br s, 1H), 8.48 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.3, 44.4, 112.8, 119.5, 119.7, 123.4, 123.9, 126.8, 127.0, 129.8, 132.2, 135.8, 136.2, 145.5, 156.5, 158.3, 169.9; MS (ESI) *m*/*z* 438.1.

***N*-[4-[[(2-(Cyclopropylamino)quinazolin-4-yl)amino]methyl]-phenyl]-4-fluorobenzenesulfonamide (34).** The intermediate product **15** was aminated with cyclopropylamine following procedure D to yield the final product **34**. Starting from **39** (0.1 g, 0.5 mmol), 80 mg (35% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 1.22 (m, 4H), 4.57 (d, J = 6.0 Hz, 2H), 6.39 (d, J = 3.0 Hz, 1H), 6.95 (m, 1H), 6.99 (d, J = 9.0 Hz, 2H), 7.21 (m, 3H), 7.34 (m, 2H), 7.76 (m, 2H), 7.93 (d, J = 6.0 Hz, 1H), 8.26 (d, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 7.7, 28.2, 46.2, 116.5, 116.9, 120.2, 120.8, 121.8, 123.1, 128.1, 129.0, 130.0, 132.5, 136.3, 136.6, 152.4, 160.1, 162.9, 166.3; MS (ESI) *m*/*z* 464.0.

***N*-(4-Fluorophenyl)-4-[[(2-(methylamino)quinazolin-4-yl)-amino]methyl]benzamide (62).** The intermediate product **49** (procedure C) was aminated with methylamine following procedure D to yield the final product **62**. Starting from **39** (0.1 g, 0.5 mmol), 140 mg (69% yield) of the final product was isolated. HPLC purity 97.0%; ^{1}H NMR (DMSO-d_6) δ 2.74 (d, J = 3.0 Hz, 3H), 4.60 (d, J = 6.0 Hz, 2H), 6.67 (d, J = 3.0 Hz, 1H), 6.99 (m, 1H), 7.03 (d, J = 6.0 Hz, 2H), 7.23 (d, J = 6.0 Hz, 2H), 7.26 (m, 1H), 7.35 (m, 2H), 7.46 (m, 1H), 7.79 (m, 2H), 7.96 (d, J = 9.0 Hz, 1H), 8.33 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.3, 43.1, 116.7, 117.0, 120.5, 120.8, 123.1, 123.4, 125.1, 128.7, 130.0, 130.2, 132.6, 136.4, 152.3, 160.1, 160.6, 163.0, 166.3; MS (ESI) *m*/*z* 402.3.

***N*-(4-Fluorophenyl)-4-[[(2-(ethylamino)quinazolin-4-yl)-amino]methyl]benzamide (63).** The intermediate product **49** was aminated with ethylamine following procedure D to yield the final product **62**. Starting from **39** (0.1 g, 0.5 mmol), 150 mg (72% yield) of the final product was isolated. HPLC purity 96.2%; ^{1}H NMR (DMSO-d_6) δ 1.06 (t, J = 6.0 Hz, 3H), 3.29 (d, J = 6.0 Hz, 2H), 4.78 (d, J = 6.0 Hz, 2H), 6.46 (br s, 1H), 7.02 (t, J = 6.0 Hz, 1H), 7.16 (d, J = 9.0 Hz, 2H), 7.23 (m, 1H), 7.42 (m, 1H), 7.50 (d, J = 6.0 Hz, 2H), 7.77 (m, 2H), 7.90 (d, J = 6.0 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 8.48 (br s, 1H), 10.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.9, 28.3, 43.6, 115.4, 115.7, 120.3, 122.5, 123.1, 125.1, 127.7, 128.0, 132.6, 133.6, 136.0, 144.3, 152.5, 157.0, 160.2, 160.4, 165.8; MS (ESI) *m*/*z* 416.3.

***N*-(4-Fluorophenyl)-4-[[(2-(cyclopropylamino)quinazolin-4-yl)amino]methyl]benzamide (64).** The intermediate product **49** was aminated with cyclopropylamine following procedure D to yield the final product **64**. Starting from **39** (0.1 g, 0.5 mmol), 130 mg (65% yield) of the final product was isolated. HPLC purity 95.8%; ^{1}H NMR (DMSO-d_6) δ 0.45 (m, 2H), 0.60 (m, 2H), 2.75 (m, 1H), 4.78 (d, J = 6.0 Hz, 2H), 6.88 (d, J = 3.0 Hz, 1H), 7.04 (t, J = 6.0 Hz, 1H), 7.16 (d, J = 9.0 Hz, 2H), 7.27 (d, J = 9.0 Hz, 1H), 7.50 (m, 3H), 7.77 (m, 2H), 7.89 (d, J = 9.0 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 8.50 (br s, 1H), 10.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 6.8, 24.3, 43.6, 115.4, 115.7, 120.5, 122.6, 123.1, 125.2, 127.7, 128.0, 132.6, 133.6, 136.0, 144.3, 152.5, 157.0, 160.2, 160.7, 165.7; MS (ESI) *m*/*z* 428.3.

***N*-(4-Fluorophenyl)-4-[[(2-(propylamino)quinazolin-4-yl)-amino]methyl]benzamide (65).** The intermediate product **49** was

aminated with *n*-propylamine following procedure D to yield the final product **65**. Starting from **39** (0.1 g, 0.5 mmol), 155 mg (72% yield) of the final product was isolated. HPLC purity 96.6%; ^{1}H NMR (DMSO-d_6) δ 0.85 (m, 3H), 1.55 (m, 2H), 3.22 (m, 2H), 4.78 (d, J = 6.0 Hz, 2H), 6.49 (br s, 1H), 7.02 (t, J = 6.0 Hz, 1H), 7.18 (d, J = 9.0 Hz, 2H), 7.22 (m, 1H), 7.43 (m, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.78 (m, 2H), 7.91 (d, J = 9.0 Hz, 2H), 8.02 (d, J = 6.0 Hz, 1H), 8.49 (br s, 1H), 10.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 22.4, 42.5, 42.9, 115.4, 115.7, 120.2, 122.5, 122.6, 123.1, 127.5, 128.0, 132.6, 133.5, 136.0, 144.4, 152.6, 157.1, 159.8, 160.2, 165.7; MS (ESI) m/z 430.3.

***N*-(4-Fluorophenyl)-4-[[(2-(butylamino)quinazolin-4-yl)-amino]methyl]benzamide (66).** The intermediate product **49** was aminated with *n*-butylamine following procedure D to yield the final product **66**. Starting from **39** (0.1 g, 0.5 mmol), 105 mg (49% yield) of the final product was isolated. HPLC purity 95.5%; ^{1}H NMR (DMSO-d_6) δ 0.85 (m, 3H), 1.30 (m, 2H), 1.45 (m, 3H), 3.24 (m, 2H), 4.78 (d, J = 6.0 Hz, 2H), 6.47 (br s, 1H), 7.02 (m, 1H), 7.18 (m, 3H), 7.40 (m, 1H), 7.49 (d, J = 9.0 Hz, 2H), 7.77 (m, 2H), 7.92 (d, J = 9.0 Hz, 2H), 8.01 (d, J = 9.0 Hz, 1H), 8.49 (br s, 1H), 10.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.2, 20.2, 31.3, 32.0, 46.1, 115.4, 115.7, 120.2, 122.5, 122.6, 123.1, 127.5, 128.0, 132.7, 133.5, 135.9, 144.4, 152.5, 157.1, 159.8, 160.2, 165.7; MS (ESI) m/z 444.2.

***N*-(4-Fluorophenyl)-4-[[(2-(allylamino)quinazolin-4-yl)-amino]methyl]benzamide (67).** The intermediate product **49** was aminated with allylamine following procedure D to yield the final product **67**. Starting from **39** (0.1 g, 0.5 mmol), 98 mg (47% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 3.93 (m, 2H), 4.13 (m, 1H), 4.78 (d, J = 6.0 Hz, 2H), 4.99 (m, 1H), 5.18 (m, 2H), 6.74 (br s, 1H), 7.03 (m, 1H), 7.18 (m, 2H), 7.25 (m, 1H), 7.45 (m, 1H), 7.51 (d, J = 6.0 Hz, 2H), 7.78 (m, 2H), 7.90 (d, J = 6.0 Hz, 1H), 8.05 (m, 1H), 8.61 (br s, 1H), 10.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 43.0, 43.5, 114.9, 115.4, 115.7, 122.5, 122.6, 123.2, 124.0, 127.7, 128.1, 132.8, 133.6, 136.0, 137.1, 144.2, 151.9, 157.1, 159.3, 160.3, 165.7; MS (ESI) m/z 428.2.

***N*-(4-Fluorophenyl)-4-[[(2-(dimethylamino)quinazolin-4-yl)-amino]methyl]benzamide (68).** The intermediate product **49** was aminated with dimethylamine following procedure D to yield the final product **68**. Starting from **39** (0.1 g, 0.5 mmol), 125 mg (62% yield) of the final product was isolated. HPLC purity 96.3%; ^{1}H NMR (DMSO-d_6) δ 3.04 (s, 6H), 4.75 (d, J = 6.0 Hz, 2H), 7.04 (m, 1H), 7.16 (m, 2H), 7.26 (m, 1H), 7.50 (d, J = 6.0 Hz, 2H), 7.76 (m, 2H), 7.88 (d, J = 6.0 Hz, 2H), 8.04 (d, J = 9.0 Hz, 1H), 8.64 (br s, 1H), 10.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.9, 44.0, 110.5, 115.4, 115.7, 120.5, 122.5, 123.1, 125.4, 127.5, 128.0, 132.7, 133.6, 136.0, 144.5, 152.5, 159.5, 159.8, 165.7; MS (ESI) m/z 416.1.

(±)-*N*-(4-Fluorophenyl)-4-[[(2-(3-methylpiperazin-1-yl)-quinazolin-4-yl)amino]methyl]benzamide (69). The intermediate product **49** was aminated with 2-methylpiperazine following procedure D to yield the final product **69**. Starting from **39** (0.1 g, 0.5 mmol), 165 mg (72% yield) of the final product was isolated. HPLC purity 95.8%; ^{1}H NMR (DMSO-d_6) δ 0.97 (d, J = 6.0 Hz, 3H), 2.56 (m, 4H), 2.77 (m, 2H), 4.73 (d, J = 6.0 Hz, 2H), 7.06 (t, J = 6.0 Hz, 1H), 7.16 (m, 2H), 7.26 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.77 (m, 2H), 7.89 (d, J = 9.0 Hz, 2H), 8.04 (d, J = 6.0 Hz, 1H), 8.64 (t, J = 6.0 Hz, 1H), 10.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 19.5, 44.0, 44.2, 45.5, 50.6, 51.0, 110.9, 115.4, 115.7, 120.8, 122.6, 123.1, 125.4, 127.5, 128.0, 132.8, 133.5, 144.4, 152.3, 157.3, 158.7, 160.0, 165.7; MS (ESI) m/z 471.2.

***N*-(4-Fluorophenyl)-4-[[6-methyl-(2-(propylamino)-quinazolin-4-yl)amino]methyl]benzamide (70).** A mixture of 2-amino-5-methylbenzoic acid (15.1 g, 0.1 mol) and urea (60 g, 1 mol) was heated to 150−180 °C for 5 h. The resulting solid was then allowed to cool to ∼100 °C, and water (100 mL) was added. The mixture was then ground and stirred for 20 min. The solid was filtered out and resuspended in water (200 mL), and NaOH (10 g, 0.25 mol) was added. The mixture was then heated to 100 °C to give a clear solution. The solution was acidified to pH ∼ 3 with 12 M HCl, and the resulting precipitate was collected and dried under reduced pressure to give 6-methylquinazoline-2,4-dione **94** (15.3 g, 87%) as a tan powder.

Compound **94** (10 g, 56 mmol) was suspended in $POCl_3$ (60 mL), and the mixture was stirred under reflux for 3−5 h to complete the reaction. The volatiles were removed under vacuum, and the residue was poured onto 200 g ice−water and stirred for 1 h. The resulting solid was collected and dried under reduced pressure. The crude product was purified by column chromatography with hexane/CH_2Cl_2 to give 2,4-dichloro-6-methylquinazoline **95** (6.6 g, 56%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.56 (s, 3H), 7.92 (d, J = 9.0 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 8.04 (s, 1H); MS (ESI) m/z 213.0.

A preparation of *N*-(4-fluorophenyl)-4-[[6-methyl-(2-chloroquinazolin-4-yl)amino]methyl]benzamide (**50**) was made starting from **41** (procedure B) and **95** following procedure C. The intermediate product **50** was aminated with *n*-propylamine following procedure D to yield the final product **70**. Starting from **95** (0.11 g, 0.5 mmol), 45 mg (20% yield) of the final product was isolated. HPLC purity 97.0%; ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 3H), 1.56 (m, 2H), 2.33 (s, 3H), 3.19 (m, 2H), 4.75 (d, J = 6.0 Hz, 2H), 6.38 (br s, 1H), 7.16 (m, 3H), 7.30 (m, 1H), 7.49 (d, J = 6.0 Hz, 2H), 7.76 (m, 2H), 7.83 (s, 1H), 7.89 (d, J = 2.0 Hz, 2H), 8.41 (br s, 1H), 10.23 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.1, 21.2, 23.1, 42.5, 43.0, 115.4, 115.7, 122.3, 122.5, 122.6, 127.6, 128.0, 129.2, 133.5, 134.3, 136.0, 144.4, 150.5, 157.1, 159.3, 159.9, 165.7; MS (ESI) m/z 444.1.

***N*-(4-Fluorophenyl)-4-[[6-methyl-(2-(allylamino)quinazolin-4-yl)amino]methyl]benzamide (71).** The intermediate product **50** was aminated with allylamine following procedure D to yield the final product **71**. Starting from **95** (0.11 g, 0.5 mmol), 95 mg (43% yield) of the final product was isolated. HPLC purity 96.4%; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.90 (br s, 2H), 4.11 (br s, 1H), 4.76 (d, J = 6.0 Hz, 2H), 5.01 (m, 1H), 5.17 (m, 2H), 6.55 (br s, 1H), 7.16 (m, 3H), 7.31 (m, 1H), 7.51 (d, J = 6.0 Hz, 2H), 7.78 (m, 2H), 7.85 (s, 1H), 7.90 (d, J = 2.0 Hz, 2H), 8.46 (br s, 1H), 10.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 42.9, 43.6, 114.8, 115.4, 115.7, 122.3, 122.6, 124.9, 127.7, 128.0, 129.4, 133.6, 134.3, 136.0, 137.4, 144.4, 150.5, 157.1, 159.1, 159.9, 165.7; MS (ESI) m/z 442.1.

***N*-(6-Chloropyridin-3-yl)-4-[[(2-(dimethylamino)-6-methyl-quinazolin-4-yl)amino]methyl]benzamide (72).** A preparation of *N*-(6-chloropyridin-3-yl)-4-[[(2-chloro-6-methylquinazolin-4-yl)-amino]methyl]benzamide (**51**) was made starting from **40**, 6-chloropyridin-3-amine, and **95** following procedures B and C. The intermediate product **51** was aminated with dimethylamine following procedure D to yield the final product **72**. Starting from **95** (0.1 g, 0.5 mmol), 120 mg (55% yield) of the final product was isolated. HPLC purity 95.7%; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.03 (s, 6H), 4.75 (d, J = 3.0 Hz, 2H), 7.18 (d, J = 9.0 Hz, 1H), 7.32 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 9.0 Hz, 2H), 7.85 (s, 1H), 7.92 (d, J = 9.0 Hz, 2H), 8.24 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 8.52 (t, J = 6.0 Hz, 1H), 8.78 (d, J = 3.0 Hz, 1H), 10.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 36.9, 44.1, 110.3, 122.3, 124.4, 125.3, 127.6, 128.2, 129.4, 131.2, 132.8, 134.3, 135.9, 141.9, 144.3, 145.1, 150.6, 159.2, 159.6, 166.2; MS (ESI) m/z 447.1.

***N*-(6-Chloropyridin-3-yl)-4-[[(2-(propylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (73).** The intermediate product **51** was aminated with *n*-propylamine following procedure D to yield the final product **73**. Starting from **95** (0.1 g, 0.5 mmol), 105 mg (48% yield) of the final product was isolated. HPLC purity 95.9%; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 6.0 Hz, 3H), 1.55 (m, 2H), 2.34 (s, 3H), 3.24 (m, 2H), 4.77 (d, J = 6.0 Hz, 2H), 7.19 (m, 2H), 7.35 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 9.0 Hz, 2H), 7.53 (s, 1H), 7.88 (d, J = 6.0 Hz, 2H), 7.95 (d, J = 9.0 Hz, 2H), 8.25 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 8.81 (d, J = 3.0 Hz, 1H), 10.57 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 21.2, 22.9, 42.9, 45.9, 122.5, 122.8, 124.4, 127.7, 128.2, 129.8, 131.3, 132.8, 134.6, 135.9, 141.9, 144.3, 144.7, 150.2, 159.6, 159.9, 166.2; MS (ESI) m/z 461.1.

***N*-(4-Fluorobenzyl)-4-[[(2-(dimethylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (74).** A preparation of *N*-(4-fluorobenzyl)-4-[[(2-chloro-6-methylquinazolin-4-yl)amino]methyl]-benzamide (**52**) was made starting from **40**, 4-fluorobenzylamine, and **95** following procedures B and C. The intermediate product **52** was aminated with dimethylamine following procedure D to yield the final product **74**. Starting from **95** (0.1 g, 0.5 mmol), 135 mg (63% yield) of

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the final product was isolated. HPLC purity 96.3%; ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H), 3.02 (s, 6H), 4.43 (d, J = 6.0 Hz, 2H), 4.71 (d, J = 6.0 Hz, 2H), 7.14 (m, 3H), 7.32 (m, 3H), 7.45 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 6.0 Hz, 2H), 7.86 (s, 1H), 8.56 (t, J = 6.0 Hz, 1H), 9.01 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 36.9, 42.3, 44.0, 110.2, 115.2, 115.5, 122.3, 125.1, 127.6, 129.6, 133.0, 134.4, 136.4, 144.1, 150.3, 159.1, 159.5, 162.0, 166.5; MS (ESI) m/z 444.0.

***N*-(4-Fluorobenzyl)-4-[[(2-(propylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (75).** The intermediate product **52** was aminated with *n*-propylamine following procedure D to yield the final product **75**. Starting from **95** (0.1 g, 0.5 mmol), 95 mg (39% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 3H), 1.46 (m, 2H), 2.32 (s, 3H), 3.17 (m, 2H), 4.43 (d, J = 6.0 Hz, 2H), 4.73 (d, J = 6.0 Hz, 2H), 6.47 (br s, 1H), 7.13 (m, 3H), 7.33 (m, 3H), 7.43 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 6.0 Hz, 2H), 7.86 (m, 1H), 8.49 (br s, 1H), 9.02 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 10.1, 21.2, 23.1, 42.3, 42.9, 43.7, 110.4, 115.2, 115.5, 122.4, 127.6, 129.5, 129.6, 133.0, 134.4, 136.4, 143.9, 149.9, 159.1, 159.9, 162.8, 166.4; MS (ESI) m/z 458.1.

(±)-*N*-(4-Fluorobenzyl)-4-[[(2-(3-methylpiperazin-1-yl)-6-methylquinazolin-4-yl)amino]methyl]benzamide (76). The intermediate product **52** was aminated with (±)-2-methylpiperazine following procedure D to yield the final product **76**. Starting from **95** (0.1 g, 0.5 mmol), 215 mg (87% yield) of the final product was isolated. HPLC purity 96.9%; ^{1}H NMR (DMSO-d_6) δ 1.01 (d, J = 6.0 Hz, 3H), 2.34 (s, 3H), 2.56 (m, 4H), 2.71 (m, 2H), 2.84 (m, 1H), 4.43 (d, J = 6.0 Hz, 2H), 4.69 (d, J = 6.0 Hz, 2H), 7.14 (m, 3H), 7.32 (m, 3H), 7.43 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 9.0 Hz, 2H), 7.86 (m, 1H), 8.49 (t, J = 6.0 Hz, 1H), 8.95 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 12.0, 19.6, 21.2, 42.3, 44.1, 45.6, 50.6, 51.2, 110.7, 115.2, 115.5, 122.2, 125.3, 127.6, 129.6, 133.0, 134.4, 136.4, 144.1, 150.5, 158.4, 159.7, 163.2, 166.4; MS (ESI) m/z 499.1.

***N*-(4-Fluorophenethyl)-4-[[(2-(methylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (77).** A preparation of *N*-(4-fluorophenethyl)-4-[[(2-chloro-6-methylquinazolin-4-yl)amino]methyl]-benzamide (**53**) was made starting from **40**, 2-(4-fluorophenyl)ethanamine, and **95** following procedures B and C. The intermediate product **53** was aminated with methylamine following procedure D to yield the final product **77**. Starting from **95** (0.1 g, 0.5 mmol), 185 mg (85% yield) of the final product was isolated. HPLC purity 96.0%; ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H), 2.76 (d, J = 3.0 Hz, 3H), 2.81 (t, J = 6.0 Hz, 2H), 3.44 (q, J = 6.0 Hz, 2H), 4.72 (d, J = 6.0 Hz, 2H), 7.07 (m, 2H), 7.23 (m, 3H), 7.32 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.82 (s, 1H), 8.32 (br s, 1H), 8.44 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 28.3, 34.6, 41.2, 43.6, 111.2, 115.2, 115.5, 122.3, 125.0, 127.5, 129.2, 130.9, 133.4, 134.2, 136.1, 143.7, 150.6, 159.8, 162.8, 166.5; MS (ESI) m/z 444.0.

***N*-(4-Fluorophenethyl)-4-[[(2-(dimethylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (78).** The intermediate product **53** was aminated with dimethylamine following procedure D to yield the final product **78**. Starting from **95** (0.1 g, 0.5 mmol), 140 mg (62% yield) of the final product was isolated. HPLC purity 95.5%; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3H), 2.81 (t, J = 6.0 Hz, 2H), 3.03 (s, 6H), 3.43 (q, J = 6.0 Hz, 2H), 4.71 (d, J = 6.0 Hz, 2H), 7.07 (m, 2H), 7.22 (m, 3H), 7.32 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.84 (s, 1H), 8.44 (t, J = 6.0 Hz, 1H), 8.48 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 34.6, 36.9, 41.2, 44.0, 110.2, 115.2, 115.5, 122.3, 125.2, 127.5, 129.4, 130.9, 133.4, 134.3, 136.1, 143.9, 150.5, 159.2, 159.6, 162.8, 166.5; MS (ESI) m/z 458.1.

***N*-(4-Fluorophenethyl)-4-[[(2-(propylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (79).** The intermediate product **53** was aminated with *n*-propylamine following procedure D to yield the final product **79**. Starting from **95** (0.1 g, 0.5 mmol), 90 mg (38% yield) of the final product was isolated. HPLC purity 96.2%; ^{1}H NMR (DMSO-d_6) δ 0.83 (t, J = 6.0 Hz, 3H), 1.45 (m, 2H), 2.33 (s, 3H), 2.83 (t, J = 6.0 Hz, 2H), 3.19 (m, 2H), 3.44 (q, J = 6.0 Hz, 2H), 4.72 (d, J = 6.0 Hz, 2H), 6.52 (br s, 1H), 7.07 (m, 2H), 7.23 (m, 3H), 7.32 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 2H), 7.75 (d, J = 6.0 Hz, 2H), 7.87 (s, 1H), 8.46(br s, 2H); ^{13}C NMR (DMSO-d_6) δ 11.9, 21.2, 23.0, 34.6, 41.2, 42.9, 43.7, 115.2, 115.5, 122.5, 127.5, 129.6, 130.8, 130.9, 133.4, 134.5, 136.1, 143.5, 158.8, 159.6, 159.9, 162.8, 166.4; MS (ESI) m/z 472.1.

***N*-(*trans*-2-Phenylcyclopropyl)-4-[[(2-(dimethylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (80).** A preparation of *N*-(*trans*-2-phenylcyclopropyl)-4-[[(2-chloro-6-methylquinazolin-4-yl)amino]methyl]benzamide (**54**) was made starting from **40**, *trans*-2-phenylcyclopropylamine hydrochloride, and **95** following procedures B and C. The intermediate product **54** was aminated with dimethylamine following procedure D to yield the final product **80**. Starting from **95** (0.1 g, 0.5 mmol), 140 mg (62% yield) of the final product was isolated. HPLC purity 96.1%; ^{1}H NMR (DMSO-d_6) δ 1.19 (m, 1H), 1.33 (m, 1H), 2.05 (m, 1H), 2.34 (s, 3H), 3.03 (s, 6H), 4.71 (d, J = 6.0 Hz, 2H), 7.14 (m, 2H), 7.25 (m, 3H), 7.34 (d, J = 9.0 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.85 (s, 1H), 8.32 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 15.7, 21.3, 24.4, 33.6, 37.0, 44.1, 110.2, 122.3, 124.8, 126.0, 126.3, 127.6, 128.6, 129.6, 133.1, 134.4, 141.9, 143.9, 149.9, 158.9, 159.5, 167.6; MS (ESI) m/z 452.1.

***N*-(*trans*-2-Phenylcyclopropyl)-4-[[(2-(ethylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (81).** The intermediate product **54** was aminated with ethylamine following procedure D to yield the final product **81**. Starting from **95** (0.1 g, 0.5 mmol), 120 mg (53% yield) of the final product was isolated. HPLC purity 95.5%; ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 6.0 Hz, 3H), 1.20 (m, 1H), 1.34 (m, 1H), 2.06 (m, 1H), 2.33 (s, 3H), 3.01 (m, 1H), 3.27 (p, J = 6.0 Hz, 2H), 4.73 (d, J = 6.0 Hz, 2H), 6.29 (br s, 1H), 7.15 (m, 4H), 7.26 (m, 2H), 7.43 (d, J = 6.0 Hz, 2H), 7.77 (d, J = 6.0 Hz, 2H), 7.84 (m, 1H), 8.36 (br s, 1H), 8.61 (d, J = 3.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 15.6, 15.7, 21.2, 24.4, 33.6, 35.7, 43.6, 111.1, 122.3, 126.0, 126.3, 127.7, 128.0, 128.6, 129.2, 133.1, 134.2, 141.9, 143.9, 150.6, 159.2, 159.9, 167.6; MS (ESI) m/z 452.1.

***N*-[1-(4-Fluorobenzoyl)piperidin-4-yl]-4-[[(2-(propylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (82).** A preparation of (4-aminopiperidin-1-yl)(4-fluorophenyl)methanone (**96**) was made starting from 4-Boc-aminopiperidine and 4-fluorobenzoyl chloride following procedure A. ^{1}H NMR (DMSO-d_6) δ 1.67 (br, 4H), 2.92 (m, 4H), 7.24 (m, 2H), 7.41 (m, 2H).

A preparation of *N*-[1-(4-fluorobenzoyl)piperidin-4-yl]-4-[[(2-chloro-6-methylquinazolin-4-yl)amino]methyl]benzamide (**55**) was made starting from **40**, **96**, and **95** following procedures B and C. The intermediate product **55** was aminated with *n*-propylamine following procedure D to yield the final product **82**. Starting from **95** (0.1 g, 0.5 mmol), 175 mg (64% yield) of the final product was isolated. HPLC purity 95.8%; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 6.0 Hz, 3H), 1.46 (m, 4H), 1.82 (m, 2H), 2.32 (s, 3H), 3.17 (m, 2H), 3.47 (m, 4H), 4.72 (d, J = 3.0 Hz, 2H), 6.33 (br s, 1H), 7.13 (d, J = 6.0 Hz, 1H), 7.26 (m, 3H), 7.42 (d, J = 6.0 Hz, 2H), 7.45 (m, 1H), 7.77 (d, J = 6.0 Hz, 2H), 7.80 (m, 1H), 8.23 (d, J = 6.0 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 12.0, 21.2, 23.1, 42.9, 43.6, 46.1, 46.8, 115.7, 116.0, 122.3, 125.0, 127.4, 127.6, 129.0, 129.6, 129.7, 133.0, 133.3, 134.2, 143.9, 150.7, 159.9, 161.3, 164.5, 165.9, 168.6; MS (ESI) m/z 555.2.

***N*-[1-(4-Fluorobenzoyl)piperidin-4-yl]-4-[[(2-(allylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (83).** The intermediate product **55** was aminated with allylamine following procedure D to yield the final product **83**. Starting from **95** (0.1 g, 0.5 mmol), 130 mg (47% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 1.49 (br s, 2H), 1.82 (br s, 2H), 2.33 (s, 3H), 3.10 (m, 4H), 3.54 (m, 4H), 4.73 (d, J = 3.0 Hz, 2H), 5.03 (m, 2H), 5.87 (m, 1H), 6.63 (br s, 1H), 7.26 (m, 4H), 7.42 (m, 3H), 7.78 (d, J = 6.0 Hz, 2H), 7.84 (m, 1H), 8.25 (d, J = 6.0 Hz, 1H), 8.50 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 31.5, 43.6, 46.8, 114.9, 115.7, 116.0, 122.4, 127.6, 129.7, 133.0, 134.4, 137.2, 143.7, 158.8, 160.0, 161.3, 164.5, 165.9, 168.6; MS (ESI) m/z 553.1.

***N*-[1-(4-Fluorobenzyl)piperidin-4-yl]-4-[[(2-(methylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (84).** A preparation of 1-(4-fluorobenzyl)piperidin-4-amine (**97**) was made starting from 4-Boc-aminopiperidine and 4-fluorobenzyl chloride following procedure A. ^{1}H NMR (DMSO-d_6) δ 1.67 (m, 2H), 1.91 (m, 2H), 2.66 (m, 2H), 2.94 (m, 2H), 3.38 (s, 2H), 7.08 (m, 2H), 7.32 (m, 2H).

A preparation of *N*-[1-(4-fluorobenzyl)piperidin-4-yl]-4-[[(2-chloro-6-methylquinazolin-4-yl)amino]methyl]benzamide (**56**) was made starting from **40**, **97**, and **95** following procedures B and C. The intermediate product **56** was aminated with methylamine following procedure D to yield the final product **84**. Starting from **95** (0.1 g, 0.5 mmol), 210 mg (82% yield) of the final product was isolated. HPLC purity 95.6%; ^{1}H NMR (DMSO-d_6) δ 1.56 (m, 2H), 1.75 (m, 2H), 2.31 (s, 3H), 2.75 (m, 4H), 2.90 (d, J = 3.0 Hz, 3H), 3.41 (s, 2H), 3.73 (m, 1H), 4.71 (d, J = 3.0 Hz, 2H), 6.29 (br s, 1H), 7.14 (m, 4H), 7.28 (d, J = 6.0 Hz, 2H), 7.32 (m, 1H), 7.41 (d, J = 6.0 Hz, 2H), 7.69 (br s, 2H), 7.80 (m, 2H), 8.14 (d, J = 6.0 Hz, 1H), 8.33 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 27.9, 28.3, 31.9, 47.3, 52.6, 61.6, 115.1, 115.4, 122.2, 125.0, 127.5, 129.0, 130.9, 133.6, 133.9, 134.2, 135.2, 143.6, 150.2, 160.0, 160.4, 165.9; MS (ESI) m/z 513.2.

***N*-[1-(4-Fluorobenzyl)piperidin-4-yl]-4-[[(2-(propylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (85).** The intermediate product **56** was aminated with *n*-propylamine following procedure D to yield the final product **85**. Starting from **95** (0.1 g, 0.5 mmol), 210 mg (78% yield) of the final product was isolated. HPLC purity 96.0%; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 6.0 Hz, 3H), 1.53 (m, 4H), 1.74 (m, 2H), 2.32 (s, 3H), 2.76 (m, 2H), 3.19 (m, 4H), 3.40 (s, 2H), 3.75 (m, 1H), 4.71 (d, J = 6.0 Hz, 2H), 6.34 (br s, 1H), 7.11 (m, 3H), 7.28 (m, 3H), 7.40 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.0 Hz, 2H), 7.80 (m, 2H), 8.14 (d, J = 6.0 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 12.1, 21.2, 22.4, 23.1, 32.0, 43.0, 47.3, 52.6, 61.7, 115.1, 115.4, 122.4, 125.1, 127.6, 128.9, 131.0, 133.6, 134.0, 134.2, 135.2, 143.7, 151.0, 160.1, 161.4, 166.1; MS (ESI) m/z 541.3.

***N*-[1-(4-Fluorobenzyl)piperidin-4-yl]-4-[[(2-(dimethylamino)-6-methylquinazolin-4-yl)amino]methyl]benzamide (86).** The intermediate product **56** was aminated with dimethylamine following procedure D to yield the final product **86**. Starting from **95** (0.1 g, 0.5 mmol), 150 mg (56% yield) of the final product was isolated. HPLC purity 95.3%; ^{1}H NMR (DMSO-d_6) δ 1.55 (m, 2H), 1.74 (m, 2H), 2.33 (s, 3H), 2.72 (m, 4H), 3.02 (s, 6H), 3.41 (s, 2H), 3.74 (m, 1H), 4.70 (d, J = 6.0 Hz, 2H), 7.10 (m, 2H), 7.18 (m, 1H), 7.30 (m, 3H), 7.42 (d, J = 6.0 Hz, 2H), 7.76 (d, J = 6.0 Hz, 2H), 7.84 (s, 1H), 8.12 (d, J = 6.0 Hz, 1H), 8.48 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 31.9, 36.9, 44.0, 47.3, 52.5, 61.6, 110.3, 115.1, 115.4, 122.3, 125.2, 127.4, 127.6, 129.4, 130.9, 133.6, 134.3, 135.2, 143.8, 150.6, 159.2, 159.5, 163.2, 166.0; MS (ESI) m/z 527.3.

(±)-*N*-[1-(4-Fluorobenzyl)piperidin-4-yl]-4-[[(2-(3-methylpiperazin-1-yl)-6-methylquinazolin-4-yl)amino]methyl]-benzamide (87). The intermediate product **56** was aminated with (±)-2-methylpiperazine following procedure D to yield the final product **87**. Starting from **95** (0.1 g, 0.5 mmol), 140 mg (48% yield) of the final product was isolated. HPLC purity 95.1%; ^{1}H NMR (DMSO-d_6) δ 0.95 (d, J = 6.0 Hz, 3H), 1.56 (m, 2H), 1.74 (m, 2H), 2.34 (s, 3H), 2.56 (m, 4H), 2.78 (m, 6H), 3.41 (s, 2H), 3.74 (m, 1H), 4.68 (d, J = 3.0 Hz, 2H), 7.10 (m, 2H), 7.17 (m, 1H), 7.30 (m, 3H), 7.42 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.83 (s, 1H), 8.10 (d, J = 6.0 Hz, 1H), 8.48 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 19.6, 21.2, 31.9, 44.1, 45.6, 47.3, 50.6, 51.1, 51.6, 52.6, 61.6, 110.7, 115.1, 115.4, 122.2, 125.4, 127.4, 127.6, 129.7, 130.9, 133.6, 134.4, 135.2, 143.7, 150.5, 158.4, 160.0, 163.2, 165.9; MS (ESI) m/z 582.3.

1-[4-[[(2-(Dimethylamino)quinazolin-4-yl)amino]methyl]-benzoyl]-*N*-(4-fluorobenzyl)piperidine-4-carboxamide (88). A prepration of *N*-(4-fluorobenzyl)piperidine-4-carboxamide (**98**) was made starting from 1-Boc-piperidine-4-carboxylic acid and 4-fluorobenzylamine following procedure B.

A preparation of 1-[4-[[(2-chloroquinazolin-4-yl)amino]methyl]-benzoyl]-*N*-(4-fluorobenzyl)piperidine-4-carboxamide (**59**) was made starting from **40**, **98**, and **39** following procedure B and C. The intermediate product **59** was aminated with dimethylamine following procedure D to yield the final product **88**. Starting from **39** (0.1 g, 0.5 mmol), 135 mg (49% yield) of the final product was isolated. HPLC purity 95.9%; ^{1}H NMR (DMSO-d_6) δ 1.53 (m, 2H), 1.72 (br, 2H), 2.90 (br, 2H), 3.06 (s, 6H), 3.35 (br, 2H), 4.23 (d, J = 6.0 Hz, 3H), 4.73 (d, J = 3.0 Hz, 3H), 7.10 (m, 3H), 7.24 (m, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H), 7.48 (m, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.34 (t, J = 6.0 Hz, 1H), 8.59 (t, J = 6.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 28.9, 36.9, 41.6, 42.2, 44.0, 110.5, 115.2, 115.5, 120.6, 123.1, 125.1, 127.2, 127.7, 129.4, 132.8, 135.0, 136.2, 141.9, 152.0, 159.4, 159.9, 163.1, 169.4, 174.2; MS (ESI) m/z 541.1.

1-[4-[[(2-(Propylamino)quinazolin-4-yl)amino]methyl]-benzoyl]-*N*-(4-fluorobenzyl)piperidine-4-carboxamide (89). The intermediate product **59** was aminated with *n*-propylamine following procedure D to yield the final product **89**. Starting from **39** (0.1 g, 0.5 mmol), 160 mg (57% yield) of the final product was isolated. HPLC purity 96.0%; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, J = 6.0 Hz, 3H), 1.54 (m, 4H), 1.72 (br, 2H), 2.90 (br, 2H), 3.23 (m, 2H), 3.66 (br, 2H), 4.24 (d, J = 6.0 Hz, 2H), 4.75 (s, 2H), 6.45 (br s, 1H), 7.01 (m, 1H), 7.10 (m, 2H), 7.24 (m, 3H), 7.32 (d, J = 6.0 Hz, 2H), 7.42 (d, J = 6.0 Hz, 2H), 7.49 (m, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.35 (t, J = 6.0 Hz, 1H), 8.44 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 22.4, 23.1, 28.8, 41.6, 42.2, 42.9, 111.4, 115.2, 115.5, 119.9, 123.1, 125.0, 127.1, 127.6, 129.4, 132.6, 135.1, 136.2, 141.9, 152.7, 159.9, 160.3, 163.1, 169.5, 174.2; MS (ESI) m/z 555.2.

1-[4-[[(2-(Dimethylamino)-6-methylquinazolin-4-yl)amino]-methyl]benzoyl]-*N*-(4-fluorobenzyl)piperidine-4-carboxamide (90). A preparation of 1-[4-[[(2-chloro-6-methylquinazolin-4-yl)-amino]methyl]benzoyl]-*N*-(4-fluorobenzyl)piperidine-4-carboxamide (**60**) was made starting from **40**, **98**, and **95** following procedures B and C. The intermediate product **60** was aminated with dimethylamine following procedure D to yield the final product **90**. Starting from **95** (0.1 g, 0.5 mmol), 120 mg (43% yield) of the final product was isolated. HPLC purity 95.4%; ^{1}H NMR (DMSO-d_6) δ 1.53 (m, 2H), 1.72 (br, 2H), 2.35 (s, 3H), 2.90 (br, 2H), 3.08 (s, 6H), 3.31 (br s, 2H), 4.22 (d, J = 6.0 Hz, 3H), 4.73 (d, J = 3.0 Hz, 3H), 7.10 (m, 2H), 7.24 (m, 2H), 7.31 (m, 3H), 7.37 (m, 1H), 7.43 (d, J = 9.0 Hz, 2H), 7.91 (s, 1H), 8.35 (t, J = 6.0 Hz, 1H), 8.79 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.2, 28.9, 37.2, 41.6, 42.2, 44.1, 110.1, 115.2, 115.5, 122.6, 123.6, 127.2, 127.8, 129.4, 130.4, 134.8, 135.1, 136.3, 141.6, 159.4, 159.9, 163.1, 169.4, 174.2; MS (ESI) m/z 555.2.

1-[4-[[(2-(Propylamino)-6-methylquinazolin-4-yl)amino]-methyl]benzoyl]-*N*-(4-fluorobenzyl)piperidine-4-carboxamide (91). The intermediate product **60** was aminated with *n*-propylamine following procedure D to yield the final product **91**. Starting from **95** (0.1 g, 0.5 mmol), 65 mg (22% yield) of the final product was isolated. HPLC purity 96.0%; ^{1}H NMR (DMSO-d_6) δ 0.84 (t, J = 6.0 Hz, 3H), 1.52 (m, 4H), 1.71 (br, 2H), 2.37 (s, 3H), 2.90 (br, 2H), 3.26 (m, 2H), 3.55 (br, 2H), 4.22 (d, J = 6.0 Hz, 2H), 4.78 (d, J = 3.0 Hz, 2H), 7.10 (m, 2H), 7.24 (m, 2H), 7.33 (d, J = 9.0 Hz, 2H), 7.43 (d, J = 9.0 Hz, 2H), 7.53 (m, 1H), 7.71 (br, 1H), 8.11 (br s, 1H), 8.37 (t, J = 6.0 Hz, 1H), 8.44 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.6, 21.1, 22.6, 28.8, 41.6, 42.1, 42.9, 111.3, 115.2, 115.5, 119.8, 123.0, 125.1, 127.2, 127.8, 129.4, 132.6, 135.4, 136.3, 141.9, 152.7, 160.0, 160.3, 163.1, 169.3, 174.2; MS (ESI) m/z 569.2.

***N*-[4-[[(3-Cyano-2-(methylamino)quinolin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (104).** Phenyl isocyanate (11 mL, 0.1 mol) was added to a solution of ethyl cyanoacetate (10.6 mL, 0.1 mol) and TEA (28 mL, 0.4 mol) in DMF (100 mL). The reaction mixture was stirred at room temperature for 1 h, and then the solution was added to ice–water (500 g) and acidified to pH ~ 4 with 12 M HCl. The resulting solid was collected by suction filtration and dried under reduced pressure to give ethyl 2-cyano-3-oxo-3-(phenylamino)propanoate **100** (19 g, 82%), which was suspended in dichlorobenzene (100 mL), refluxed for 6 h, and then cooled to room temperature. The resulting solid was collected by suction filtration, washed once with ethanol, and dried under reduced pressure to give 3-cyano-2,4-dioxo-tetrahydroquinoline **101** (9.2 g, 61%). MS (ESI) m/z 187.0.

Compound **101** (4.0 g, 21 mmol) and PCl_5 (3.0 g, 14 mmol) were added to $POCl_3$ (50 mL), and the reaction suspension was refluxed for 4 h. The solvent was removed, and the residue was added into ice–water (100 g) and stirred for 1 h. The resulting solid was collected by suction filtration. The crude product was purified by column chromatography with hexane/CH_2Cl_2 to give 3-cyano-2,4-dichloroquinoline **102** (3.3 g, 70%). ^{1}H NMR (DMSO-d_6) δ 7.92 (m, 1H), 8.09 (br s, 2H), 8.28 (d, J = 9.0 Hz, 1H); MS (ESI) m/z 223.0.

A preparation of *N*-[4-[[(3-cyano-2-chloroquinolin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (**103**) was made from **3** and **102** following procedure C. The intermediate product **103** was aminated with methylamine following procedure D to yield the final product **104**. Starting from **102** (0.11 g, 0.5 mmol), 120 mg (56% yield) of the final product was isolated. HPLC purity 95.2%; ^{1}H NMR (DMSO-d_6) δ 2.84 (d, J = 6.0 Hz, 3H), 4.98 (d, J = 6.0 Hz, 2H), 6.35 (d, J = 3.0 Hz, 1H), 7.15 (m, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.34 (s, 1H), 7.39 (m, 1H), 7.51 (m, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.99 (m, 2H), 8.17 (d, J = 9.0 Hz, 1H), 8.23 (t, J = 6.0 Hz, 1H), 10.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.7, 46.4, 72.1, 114.9, 115.6, 115.9, 118.9, 120.9, 121.5, 122.1, 127.1, 127.4, 130.8, 132.0, 134.6, 138.3, 148.9, 154.4, 156.9, 162.9, 164.8, 166.1; MS (ESI) m/z 426.1.

***N*-[4-[[(3-Cyano-2-(propylamino)quinolin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (105).** The intermediate product **103** was aminated with *n*-propylamine following procedure D to yield the final product **105**. Starting from **102** (0.11 g, 0.5 mmol), 75 mg (33% yield) of the final product was isolated. HPLC purity 95.7%; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, J = 6.0 Hz, 3H), 1.52 (m, 2H), 3.03 (m, 2H), 4.98 (d, J = 6.0 Hz, 2H), 6.16 (br s, 1H), 7.15 (m, 1H), 7.32 (d, J = 9.0 Hz, 2H), 7.36 (m, 1H),7.70 (d, J = 9.0 Hz, 2H), 8.01 (m, 2H), 8.21 (m, 2H), 10.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 22.6, 42.9, 46.4, 72.0, 114.9, 115.6, 115.9, 119.0, 121.0, 122.1, 127.4, 127.5, 129.0, 130.8, 132.0, 134.6, 138.4, 146.6, 128.9, 154.4, 156.3, 164.8, 166.1; MS (ESI) m/z 454.1.

***N*-[4-[[(2-(Methylamino)-5-methylpyrimidin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (111).** A preparation of *N*-[4-[[(2-chloro-5-methylpyrimidin-4-yl)amino]methyl]phenyl]-4-fluorobenzamide (**109**) was made from **3** and 2,4-dichloro-5-methylpyrimidine (**107**) following procedure C. The intermediate product **109** was aminated with methylamine following procedure D to yield the final product **111**. Starting from **107** (0.16 g, 1 mmol), 76 mg (21% yield) of the final product was isolated. HPLC purity 96.6%; ^{1}H NMR (DMSO-d_6) δ 1.88 (s, 3H), 2.80 (d, J = 3.0 Hz, 3H), 4.52 (d, J = 6.0 Hz, 2H), 6.18 (m, 1H), 7.30 (d, J = 9.0 Hz, 4H), 7.46 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 9.0 Hz, 2H), 8.03 (d, J = 9.0 Hz, 2H), 10.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.4, 28.3, 43.3, 115.4, 115.7, 120.8, 127.8, 129.7, 130.9, 136.4, 137.9, 152.9, 161.4, 162.1, 164.6, 166.1; MS (ESI) m/z 366.0.

***N*-[4-[[(2-(Ethylamino)-5-methylpyrimidin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (112).** The intermediate product **109** was aminated with ethylamine following procedure D to yield the final product **112**. Starting from **107** (0.16 g, 1 mmol), 95 mg (25% yield) of the final product was isolated. HPLC purity 96.0%; ^{1}H NMR (DMSO-d_6) δ 1.03 (t, J = 6.0 Hz, 3H), 1.87 (s, 3H), 3.33 (p, J = 6.0 Hz, 2H), 4.51 (d, J = 6.0 Hz, 2H), 6.15 (br s, 1H), 6.99 (br s, 1H), 7.28 (d, J = 9.0 Hz, 2H), 7.35 (m, 2H), 7.46 (m, 2H), 7.67 (d, J = 9.0 Hz, 2H), 8.03 (m, 2H), 10.24 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.4, 15.5, 35.8, 45.9, 115.5, 115.8, 120.7, 127.9, 130.8, 131.7, 136.6, 137.8, 153.2, 153.9, 161.4, 164.7, 166.1; MS (ESI) m/z 380.3.

***N*-[4-[[(5-Bromo-2-(methylamino)pyrimidin-4-yl)amino]-methyl]phenyl]-4-fluorobenzamide (113).** A preparation of *N*-[4-[[(5-bromo-2-chloropyrimidin-4-yl)amino]methyl]phenyl]-4-fluorobenzamide (**110**) was made from **3** and 5-bromo-2,4-dichloropyrimidine (**108**) following procedure C. The intermediate product **110** was aminated with methylamine following procedure D to yield the final product **113**. Starting from **108** (0.23 g, 1 mmol), 110 mg (26% yield) of the final product was isolated. HPLC purity 95.8%; ^{1}H NMR (DMSO-d_6) δ 2.70 (d, J = 3.0 Hz, 3H), 4.51 (d, J = 6.0 Hz, 2H), 6.63 (br s, 1H), 7.33 (m, 4H), 7.68 (d, J = 6.0 Hz, 2H), 7.83 (br s, 1H), 8.01 (m, 2H), 10.22 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.4, 43.5, 115.5, 115.8, 120.7, 128.1, 130.8, 131.8, 135.9, 138.1, 156.3, 158.2, 161.7, 164.7, 166.1; MS (ESI) m/z 431.9.

Luciferase Reporter Gene Assay. The HCT116 colorectal cancer cell line has a deletion mutation in β-catenin (WT/Δ45S) and thus contains a constitutively activated β-catenin/Tcf4 signaling pathway. This can be monitored by a luciferase reporter with Tcf4 binding sites in its promoter. Briefly, 1×10^4 HCT116 cells/well (in 96-well plates) were cotransfected with 50 ng rof eporter vector TOP-FLASH (containing Tcf4 binding sites) and 50 ng of pTK-β-gal (served as an internal control). At 4 h post-transfection, fresh medium containing various concentrations of candidate compounds was added to the cells. Luciferase activities were determined 24 h after compound addition using a "Firefly Luciferase Assay Kit" (Biotium, Inc. Hayward, CA). The luciferase activities were normalized to the activities of β-galactosidase and were expressed as a percentage of the control luciferase activity.

Colon Carcinoma Cell Growth Inhibition Assay. The colon cell growth inhibition assay is an in vitro assay that helps to determine if the lead compounds inhibit the β-catenin/Tcf4 signaling pathway. Inhibition is inferred by observation of an inhibition of growth of colon cell lines at concentrations similar to the IC_{50} in the reporter assay. A compound of interest was considered inhibitory when growth inhibition occurred at the concentrations similar to the IC_{50} in the reporter assay. The assay readout was based on Promega's Cell Titer-blue cell viability assay, which is designed to provide a homogeneous fluorometric method for estimating the number of viable cells present in multiwell plates. This homogeneous method is based on the ability of living cells to convert a redox dye (resazurin) into a fluorescent end product (resorufin). Viable cells retain the ability to reduce resazurin into resorufin. Nonviable cells rapidly lose metabolic capacity, do not reduce the indicator dye, and thus do not generate a fluorescent signal. Both HCT116 and SW480 cell lines were grown in RPMI 1640 + 10% FBS + penicillin/streptomycin. Cells were trypsinized and plated at 2×10^3 cells/well in opaque 96-well plates. Compounds were added 24 h later so that concentration curves could be generated starting at 10 μg/mL with nine subsequent 2-fold dilutions. The plates were incubated with compounds for 3 days, at which time the cells were lysed with Promega's Cell Titer-blue reagent. The resulting luminescence was read on a Synergy 2 reader.

Clonogenic Assays. HCT116 cells were mixed in RPMI 1640 + 10% FBS + penicillin/streptomycin and plated at 300 cells/well onto six-well plates, 8 h prior to treatments with or without inhibitors (1.5 μM highest final concentration). Cells were incubated for 9 days, and colonies were counted after being fixed with 10% acetic acid in methanol and stained with 0.05% Crystal violet solution.

CoMFA Calculation. CoMFA study was performed using SYBYL-X suite software (Tripos, Inc.). The conformation of compound **78** with the lowest free energy from confirmation searching was used as the template, and the other 18 selected compounds were superposed with the 4-benzylamine-pyrimidine core. The molecules were placed into a three-dimension cubic lattice with 0.2 nm spacing. The minimum-σ (column filtering) was set to 8.36 kJ/mol to improve the signal-to-noise ratio by omitting those lattice points, whose energy variation was below this threshold. The method of partial least-squares (PLS) implemented in the Quantitative Structure–Activity Relationship (QSAR) module of SYBYL was used to construct and validate the models. The CoMFA descriptors were used as independent variables, and pIC_{50} values were used as dependent variables. Each CoMFA descriptor column of a QSAR Molecular Spreadsheet contains the magnitudes of the steric (van der Waals) and the electrostatic (Coulombic) fields exerted by the atoms in the tabulated molecules on an sp^3 carbon with a +1.0 net charge as the probe. Steric and electrostatic energy cutoffs were set at 125.4 kJ/mol. Cross-validation was performed with the leave-one-out procedure. The optimum number of the components, N, retained for final PLS analyses was defined as the one that yielded the highest crossvalidated q^2. The robustness of the models was internally evaluated by calculating the r^2, s, and F test values from the training set.

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■ ABBREVIATIONS USED

Tcf4, T-cell transcription factor 4; Wnt, wingless int-1; APC, adenomatous polyposis coli; Tcf, T-cell factor; LEF1, lymphoid enhancer-binding factor 1; PK, pharmacokinetic; CoMFA, comparative molecular field analysis; SAR, structure−activity relationship; HTS, high-throughput screening; PLS, partial least-squares; QSAR, quantitative structure−activity relationship; HPLC, high-performance liquid chromatography; NMR, nuclear magnetic resonance; ESI-MS, electrospray ionization mass spectrometry; THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; DIC, *N,N′*-diisopropylcarbodiimide; HOBt, *N*-hydroxybenzotrizole; TFA, trifluoroacetic acid; TEA, triethylamine; DIEA, *N,N*-diisopropylethylamine

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