Pharmacological Exploitation of the α1-Adrenoreceptor Antagonist Doxazosin to Develop a Novel Class of Antitumor Agents That Block Intracellular Protein Kinase B/Akt Activation

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The α1-adrenoreceptor antagonist doxazosin induces apoptosis in malignant cells with moderate potency via an α1-adrenoreceptor-independent mechanism. Here, we demonstrate that the ability of doxazosin to induce apoptosis in PC-3 prostate cancer cells was, in part, attributable to the inhibition of protein kinase B (PKB)/Akt activation. The separation of the effect of doxazosin on apoptosis from its original pharmacological activity provides molecular underpinnings to develop novel antitumor agents. Replacement of the (2,3-dihydro-benzo[1,4]dioxane)-carbonyl moiety of doxazosin with aryl-sulfonyl functions dramatically improves the potency in facilitating Akt deactivation and inducing apoptosis. The optimal compounds, **33** and **44**, were effective in apoptosis induction at low micromolar concentrations irrespective of androgen dependency and p53 functional status. Both agents were active in suppressing the growth of a panel of 60 cancer-cell lines with IC_{50} values of 2.2 and 1.5 μM, respectively. Together, these in vitro efficacy data suggest the translational potential of these agents in prostate cancer treatment.

Introduction

The α1-adrenoreceptor antagonist doxazosin (Cardura) has been safely used for the treatment of benign prostatic hyperplasia (BPH).[1] It relaxes prostate smooth muscle through the blockade of α1-adrenergic innervation to the prostate. In addition, this alpha-blocker also exhibits moderate potency in inducing apoptosis in prostate cancer cells[2−5] and shows synergistic antitumor effects in conjunction with radiation[6] or certain chemotherapeutics such as adriamycin and etoposide[7] against prostate cancer cells. In light of its potential use in the prevention/treatment of prostate cancer, the mechanism by which doxazosin mediates apoptosis has been the focus of many recent publications.[8] It is noteworthy that the in vitro antitumor activity of doxazosin is mediated via an α1-adrenoreceptor-independent pathway.[9] Putative mechanisms underlying doxazosin-mediated apoptosis include the upregulation of transforming growth factor β (TGF-β) signaling and increased gene expression of p21 and IκBα (inhibitor of NF-κB α).[10,11] From a drug discovery perspective, the separation of the effect of doxazosin on apoptosis in prostate cancer cells from its original pharmacological activity in normal cells provides a molecular basis to develop a novel class of apoptosis-inducing agents through lead optimization.

In this study, we obtained evidence that the ability of doxazosin to induce apoptotic death in PC-3 androgen-independent prostate cancer cells was, at least in part, attributable to the inhibition of intracellular protein kinase B (PKB)/Akt (designated as Akt from this point) activation. Our data indicate that the apoptosis-inducing potency of doxazosin was correlated with its efficacy in facilitating Akt dephosphorylation and that the overexpression of constitutively active Akt could partially protect cells from drug-induced apoptosis. Consequently, we carried out structural modifications of doxazosin to generate a novel class of apoptosis-inducing agents with improved efficacy in blocking intracellular Akt activation.

Chemistry

To optimize the apoptosis-inducing activity of doxazosin, we carried out the structural modifications in a systematic manner (Figure 1).

In strategy A, we replaced the 2,3-dihydrobenzo[1,4]-dioxane moiety with different aromatic acyl side chains to produce compounds **1**−**10** (Figure 2, Scheme 1; Table 1). In strategy B, we substituted the aryl carboxamide function with aryl sulfonamides to generate compounds **11**−**40** (Figure 2, Scheme 2; Tables 2 and 3). In strategy C, the piperazine moiety of the optimal compounds (**23** and **33)** was replaced by an ethylenediamine linker, generating compounds **41** and **42**, respectively (Figure 2, Scheme 3; Chart 1). In strategy D, we modified the methoxy side chains on the quinazoline ring of compound **33** to prepare compounds **43**−**46** (Figure 2, Scheme 4; Table 4).

All compounds were evaluated for their ability to induce apoptotic death in human androgen-independent PC-3 prostate cancer in RPMI 1640 medium containing 10% fetal bovine serum (FBS). For representative compounds tested in DU-145 and LNCaP prostate cancer cells, the IC_{50} values for inhibiting cell proliferation were similar in these three cell lines irrespective

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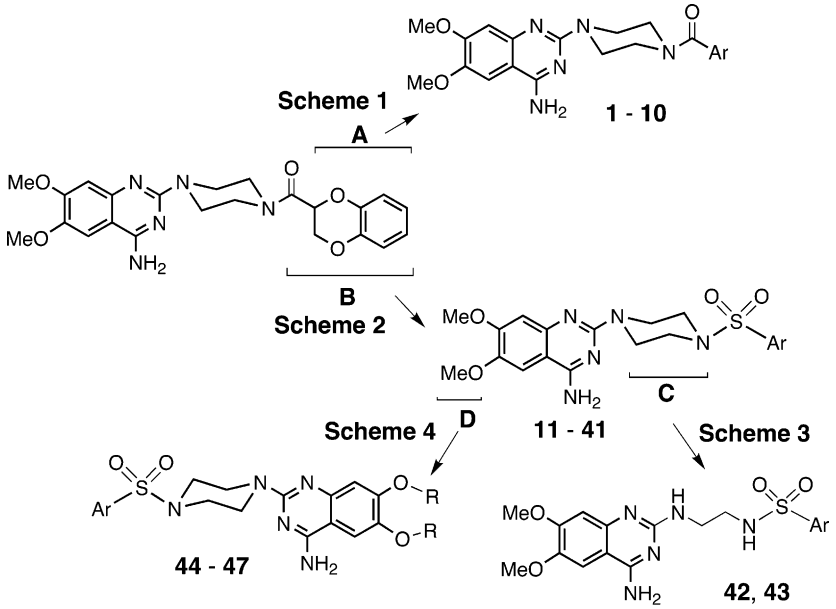
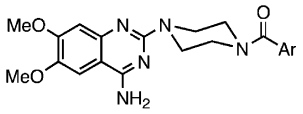


Figure 1. Overall strategy for the structural modification of doxazosin. A, B, C, and D denote four modification strategies that target the 2,3-dihydro-benzo[1,4]dioxane moiety, the terminal acyl function, the piperazine linker, and the methoxy side chain of the quinazoline base, respectively. The numbers indicate the designation of doxazosin derivatives.

Table 1. Structures and IC_{50} Values of Compounds **1**−**10**



entry	Ar	IC_{50}[a] (PC-3)	entry	Ar	IC_{50}[a] (PC-3)
doxazosin	2,3-dihydrobenzo[1,4]dioxane	45 ± 5	6	3,4-dimethoxyphenyl	71 ± 8
1	4-chlorophenyl	60 ± 8	7	1-naphthyl	59 ± 4
2	4-cyanophenyl	68 ± 6	8	4-aminophenyl	>100
3	benzyloxy	63 ± 6	9	4-*tert*-butylphenyl	47 ± 6
4	3-cyanophenyl	82 ± 5	10	4-(trifluoromethyl)phenyl	>100
5	4-nitrophenyl	75 ± 11			

[a] Values represent means + sd ($n = 6$).

of differences in androgen sensitivity, PTEN mutation, the functional status of p53 and Rb, and other biomarkers.

Results

Doxazosin-Induced Apoptosis, in Part, by Facilitating Akt Dephosphorylation. Exposure of PC-3 cells to doxazosin in 1% FBS-supplemented RPMI 1640 medium resulted in time- and dose-dependent apoptotic death, as evidenced by the disappearance of the native form of PARP (Figure 3A). The potency of doxazosin in inducing apoptosis, however, was moderate. Although PC-3 cells were susceptible to the drug-induced apoptosis at 25 μM and up, no appreciable apoptotic death was noted at 10 μM.

To shed light on the mechanism of doxazosin-mediated apoptosis, we investigated the effect of doxazosin on the phosphorylation state of Akt and ERKs, two signaling kinases that play a pivotal role in cell proliferation and survival[12,13] in PC-3 cells. The exposure of PC-3 cells to doxazosin caused Akt dephosphorylation in a dose- and time-dependent manner (Figure 3B, upper and lower panels, respectively). In contrast, doxazosin, even at 50 μM, did not affect the phosphorylation status of ERKs (Figure 3B), suggesting the specificity of the drug action on intracellular signaling pathways. It is also noteworthy that doxazosin exhibited no inhibitory effects on the kinase activity of immunoprecipitated Akt.

To examine the causal relationship between Akt deactivation and doxazosin-mediated apoptosis, we assessed the protective effect of the transient transfection of constitutively active Akt, $Akt^{T308D/S473D}$ (ref 14), on drug-induced PC-3 cell death. Western blot analysis using antibodies against Akt and the HA tag confirmed that transient transfection of $Akt^{T308D/S473D}$ led to a severalfold increase in Akt expression (Figure 4A). These transient transfectants were exposed to 25 μM doxazosin in a 1% FBS-supplemented medium to examine their susceptibility to drug-induced cell death vis-à-vis transfectants with an empty pcDNA vector (panel B). As shown, $Akt^{T308D/S473D}$ gave partial, yet significant, protection against doxazosin-induced apoptotic death.

Together, these data suggest that doxazosin-induced apoptosis in PC-3 cells was mediated, in part, through the inhibition of intracellular Akt activation. This premise was in line with the finding that the apoptosis-inducing potency of doxazosin was attenuated in 10 versus 1% FBS-supplemented medium, with the IC_{50} value increasing from 20 to 45 μM. This precipitous drop

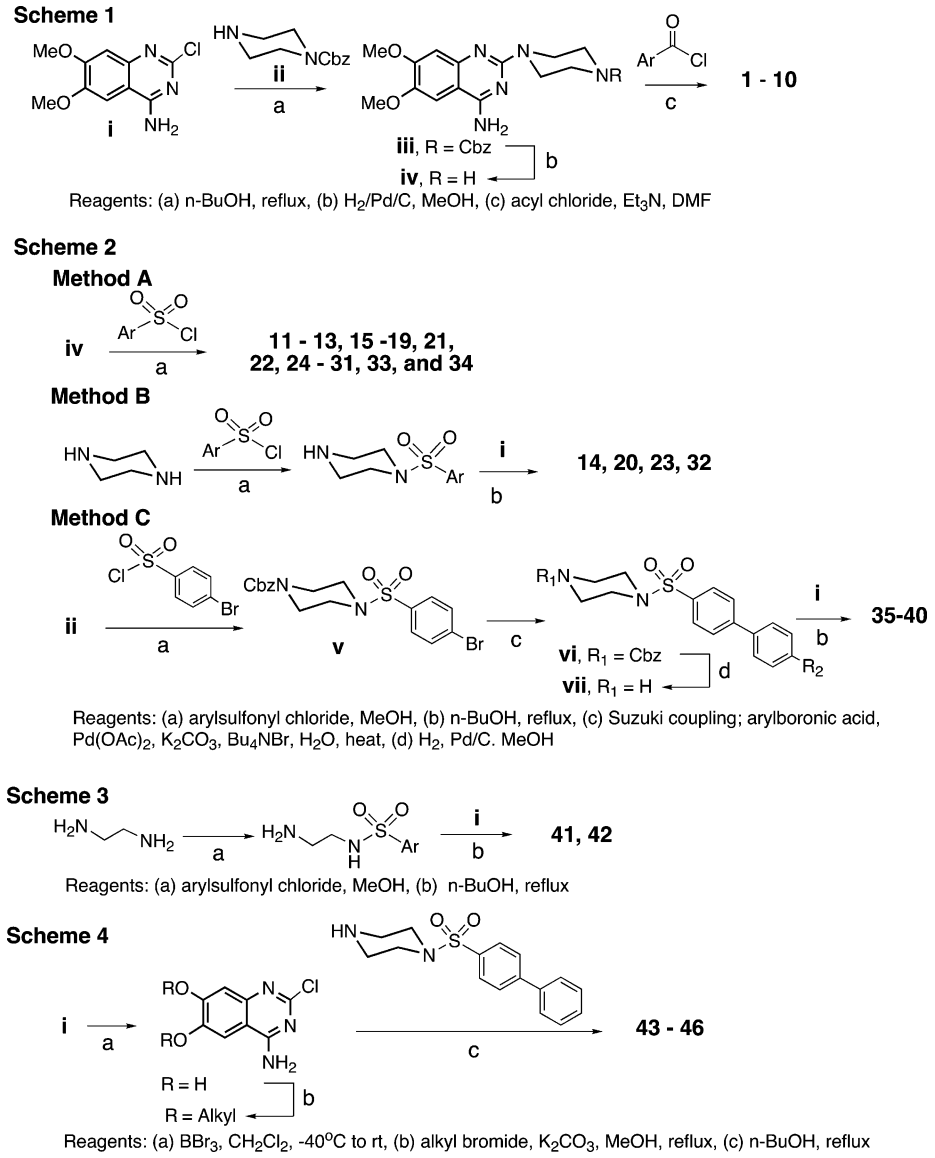
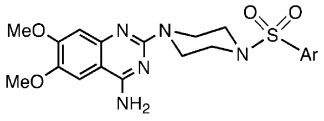


Figure 2. Synthetic schemes employed for the structural modifications of doxazosin.

Table 2. Structures and IC_{50} Values of Compounds **11**−**35**

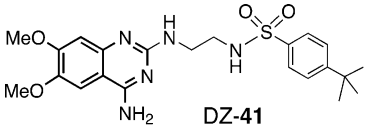


entry	Ar	IC_{50}[a] (PC-3)	entry	Ar	IC_{50}[a] (PC-3)
11	4-chlorophenyl	23 ± 3	24	3-carboxyphenyl	53 ± 4
12	4-bromophenyl	20 ± 2	25	4-carboxyphenyl	53 ± 5
13	4-iodophenyl	15 ± 2	26	2,5-dichlorophenyl	60 ± 7
14	5-chlorothienyl	25 ± 3	27	2,4-diaminophenyl	67 ± 5
15	2-nitrophenyl	35 ± 4	28	3-carboxy-4-chloro-5-fluorophenyl	56 ± 4
16	3-nitrophenyl	32 ± 5	29	3-carboxy-4,6-dichlorophenyl	52 ± 6
17	4-nitrophenyl	36 ± 3	30	1-naphthyl	14 ± 2
18	4-methylphenyl	30 ± 2	31	2-naphthyl	15 ± 2
19	4-(trifluoromethyl)phenyl	27 ± 3	32	1-(5-dimethylamino)naphthyl	29 ± 4
20	4-methoxyphenyl	39 ± 4	33	biphenyl-	4.2 ± 0.8
21	4-(trifluoromethoxy)phenyl	25 ± 2	34	2,4,6-tri-isopropylphenyl	24 ± 3
22	4-(methylsulfonyl)phenyl	17 ± 3	35	4-(phenanthren-9-yl)phenyl	5.2 ± 0.9
23	4-*tert*-butylphenyl	4.1 ± 0.7			

[a] Values represent means + sd (n = 6).

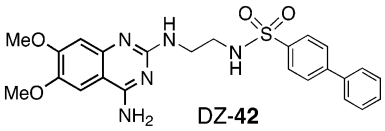
in potency was reminiscent for that noted for cyclooxygenase 2 inhibitor celecoxib,[15] which might be attributable to several factors. First, like celecoxib, doxazosin displays a high binding affinity with serum proteins,[16] resulting in lower intracellular drug concentrations. Second, continuous stimulation of phosphoinositide

Chart 1. Structures and IC_{50} Values of Compounds **41** and **42**



DZ-**41**

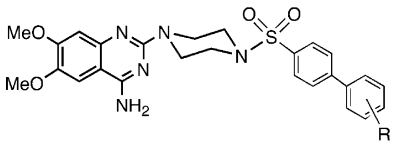
IC_{50}, 9.8 μM



DZ-**42**

IC_{50}, 7.5 μM

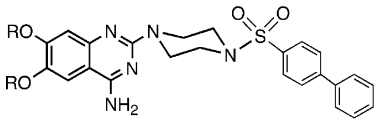
Table 3. Structures and IC_{50} Values of Compounds **36**−**40**



entry	R	IC_{50}[a] (PC-3)	entry	R	IC_{50}[a] (PC-3)
36	4-methyl	3.4 ± 0.4	39	4-*n*-butyl	3.4 ± 0.2
37	4-trifluoromethyl	3.3 ± 0.3	40	4-*tert*-butyl	10 ± 2
38	4-methylsulfonyl	7.2 ± 0.5			

[a] Values represent means + sd (n = 6).

Table 4. Structures and IC_{50} Values of Compounds **43**−**46**



entry	R	IC_{50}[a] (PC-3)	entry	R	IC_{50}[a] (PC-3)
43	allyl	3.3 ± 0.4	45	isopropyl	24 ± 5
44	*n*-propyl	2.5 ± 0.3	46	*n*-butyl	3.5 ± 0.4

[a] Values represent means + sd (n = 6).

3-kinase (PI3K)/Akt signaling through various growth factor receptors counters the inhibitory effect of doxazosin on Akt. Third, serum could upregulate Bcl-xL, which enhances the threshold to apoptotic signals emanating from PI3K/Akt inhibition.[17]

Role of the Aromatic Acyl Side Chains in Apoptosis Induction (Strategy A). Substitution of the 2,3-dihydro-benzo[1,4]dioxane moiety of doxazosin with different aromatic acyl side chains gave derivatives with varying potency in apoptosis induction (Table 1). In general, analogues with hydrophilic side chains exhibited lower apoptosis-inducing activity, whereas that of a hydrophobic aromatic system, for example, *tert*-butylphenyl, retained the in vitro efficacy. These findings, however, provided a proof of principle that doxazosin was amenable to structural optimization to develop a new class of apoptosis-inducing agents.

Aryl Sulfonamide Derivatives Exhibited High Potency in Triggering Apoptosis (Strategy B). To explore the functional role of the acyl function in apoptosis induction further, we replaced the carboxamide moiety of compounds **1**, **5**, **7**, and **9** with sulfonamide, yielding compounds **11**, **17**, **30**, and **23**, respectively. As shown in Table 2, this substitution resulted in a substantial increase in apoptosis-inducing potency.

Among these four pairs of compounds, **23** exhibited 1 order of magnitude higher potency than its carboxamide counterpart **9**. To understand the structural basis for this improvement in potency, we compared the energy-minimized structures of compounds **9** and **23** (Figure 5).

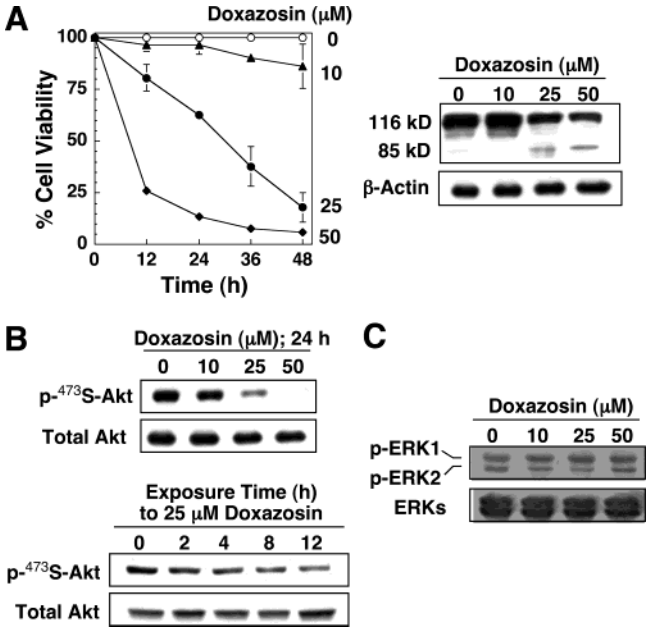


Figure 3. Induction of apoptosis in PC-3 cells by doxazosin. (A, left panel) Time- and dose-dependent effect of doxazosin on the cell viability of PC-3 cells in 1% FBS-supplemented RPMI 1640 medium. Values obtained from six replicates were plotted at each time point at the indicated concentrations of doxazosin. (A, right panel) Induction of poly(ADP-ribose) polymerase (PARP) cleavage by doxazosin at the indicated concentrations after 48 h of treatment. PARP proteolysis to the apoptosis-specific 85-kd fragment was monitored by Western blotting. Although there was no substantial accumulation of the 85-kd fragment, a significant decrease in the level of native protein was noted. (B) Dose- and time-dependent (upper and lower panels, respectively) effects of doxazosin on Akt phosphorylation. (C) dose-dependent effect of doxazosin on ERK phosphorylation. PC-3 cells were treated with doxazosin at the indicated concentrations for 24 h or at 25 μM for the indicated times and lysed, and proteins in the resulting supernatants were resolved on SDS-PAGE and subjected to Western blot analysis. The phosphorylation status of Akt and ERKs was determined by immunoblotting with the respective phosphospecific antibodies. Unphosphorylated Akt and ERKs, as immunostained by anti-Akt and anti-ERK antibodies, were used as internal standards for the comparison of phospho-Akt and phospho-ERK levels among samples of different preparations. The blots are representative of three independent experiments.

As shown, the core structural component, that is, the quinazoline base and the adjacent piperazine ring, conferred a high degree of structural rigidity to the molecule. The boat conformation of the piperazine ring oriented the N^1 appendage, that is, carbonyl or sulfonyl, perpendicular to the quinazoline planar structure. We rationalized that the discrepancy in potency was attributable to the transition from a trigonal-planar structure of a carboxamide moiety (upper panel) to a tetrahedronlike structure of sulfonamide (lower panel). As a result, the spatial arrangement of the aromatic

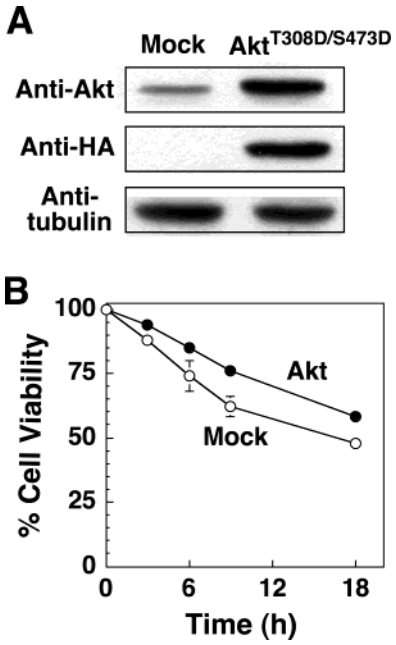


Figure 4. Protective effect of constitutive active Akt on doxazosin-induced apoptotic death in PC-3 cells. (A) Expression of Akt$^{T308D/S473D}$ in PC-3 transient transfection. Western blot analysis used antibodies against Akt and the HA tag. (**B**) Viability of PC-3 cells overexpressing Akt$^{T308D/S473D}$ vis-à-vis cells transfected with empty pcDNA vector (mock) in the presence of 25 μM doxazosin in 1% FBS-supplemented medium for 24 h. Values are means ± sd (n = 3).

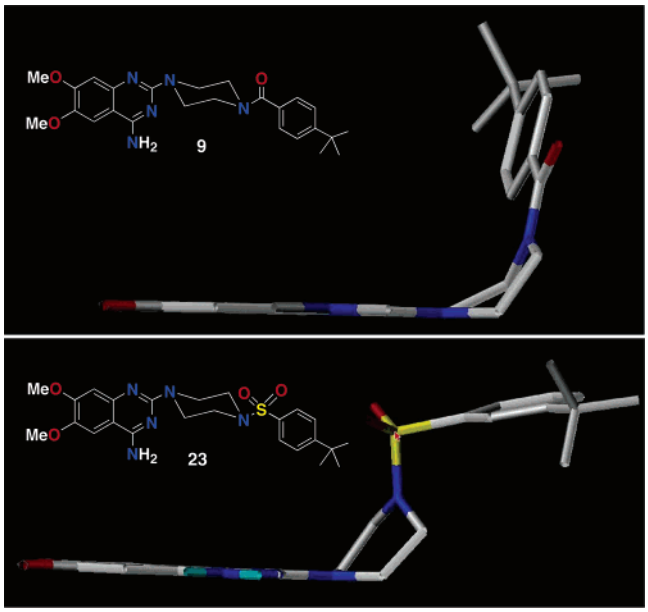


Figure 5. Comparison of chemical and 3D structures of compounds **9** and **23**. The 3D structures of small molecules were generated using the software SYBYL 6.9 (Tripos Associate; St. Louis, MO) on Silicon Graphics O2 (Silicon Graphics Inc.; Mountain View, CA). Energy minimization was carried out with default parameters (minimum rms gradient, 0.005 kcal/mol; maximum iterations, 1000; minimum energy change, 0.05 kcal/mol).

sidearm relative to the neighboring plane of the quinazoline system differed.

Further examinations of the impact of the aryl sulfonamide function on apoptosis-inducing potency confirmed the preference for bulky, hydrophobic aromatic systems (Table 2). Among the 25 derivatives examined,

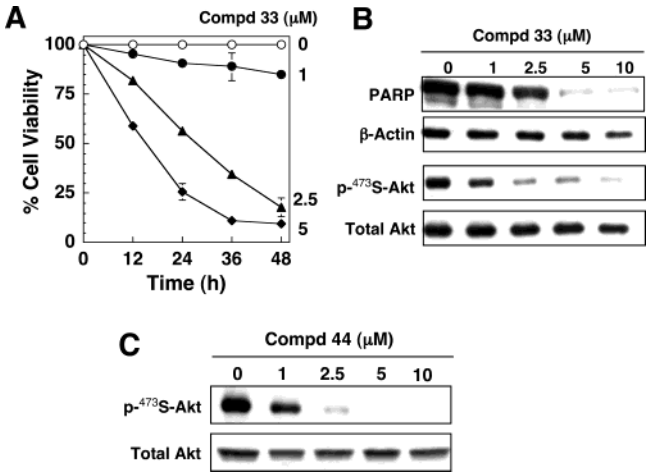


Figure 6. (A) Time- and dose-dependent effects of compound **33** on the cell viability of PC-3 cells in 1% FBS-supplemented RPMI 1640 medium. (B) Western blot analysis of RAPR proteolysis and Akt dephosphorylation in PC-3 cells treated with the indicated concentrations of **33** for 48 h. (C) Effects of compound **44** on Akt phosphorylation in PC-3 cells treated with the indicated concentrations for 48 h.

compounds **23**, **33**, and **35**, with the side chains of *tert*-butylphenyl, biphenyl, and phenanthren-9-yl-phenyl, respectively, represented the optimal compounds, with IC_{50} values in the range of 4−5 μM in 10% serum-containing medium at 48 h.

Figure 6A indicates a dose-dependent effect of compound **33** on apoptosis in a 1% FBS-supplemented medium, as evidenced by PARP proteolysis (Figure 6B), with an IC_{50} value of approximately 2.5 μM at 48 h. Western blot analysis confirmed that this apoptotic effect was attributable, in part, to the inhibition of Akt activation (Figure 6B).

Further modifications of the biphenyl ring of compound **33** by adding alkyl chains such as CH_3, CF_3, or n-C_4H_9 at the 4′ position did not further improve the apoptosis-inducing potency (Table 3). However, a significant drop in potency was noted with the bulky *tert*-butyl substitution.

Importance of the Piperazine Ring to the Apoptosis-Inducing Potency (Strategy C). The 4-(4-amino-6,7-dimethoxy-quinaolin-2-yl)-piperazine moiety provided structural rigidity to the molecule, which might play a role in the ligand−protein interactions. To examine this premise, we replaced the piperazine ring of compounds **23** and **33** with an ethylenediamine linker, generating **41** and **42** (Chart 1).

This replacement resulted in a 2-fold decrease in apoptosis-inducing potency, suggesting the importance of this unique structural feature in maintaining the efficacy.

Role of the Alkoxy Substituent on the Quinazoline Ring in the Induction of Apoptosis (Strategy D). To optimize the activity of compound **33** in inducing apoptosis further, we replaced the methoxy side chains with alkoxy functions with different stereochemical properties (Table 4).

Among the four derivatives, compound **44** represented the optimal compound with a slight improvement in potency (IC_{50} = 2.5 μM in 10% FBS-supplemented medium), whereas its isopropyl counterpart **45** displayed a precipitous drop in potency (IC_{50} = 24 μM).

These data suggest a very subtle impact of the quinazoline side-chain structure on target binding. Again, the induction of apoptosis by compound **44** is characterized by the dephosphorylation of phospho-Akt in a dose-dependent manner, which was evident at concentrations as low as 1 μM (Figure 6C).

Discussion

The effect of doxazosin on apoptosis in benign and malignant prostate cancer cells suggests a plausible extension of its clinical use from BPH management to prostate cancer prevention.[8] Thus, elucidating the underlying mechanism will provide a molecular basis for developing more efficacious antitumor agents. In this paper, we obtained several lines of evidence that doxazosin mediated apoptosis, in part, through the down-regulation of Akt signaling in PC-3 cells. Because Akt plays a pivotal role in regulating cell growth and survival in cancer cells, this finding underpinned the pharmacological exploitation of doxazosin to develop a novel class of apoptosis-inducing agents that block intracellular Akt activation. However, the target whereby doxazosin and its derivatives mediate Akt downregulation is still under investigation, but kinase assay data indicate that these agents displayed no direct inhibition in vitro on protein kinase C isozymes or any of the upstream kinases of Akt, including phosphoinositide-dependent kinase-1 and phosphoinositide 3-kinase (data not shown). It is plausible that these quinazoline-based derivatives, through competing with ATP binding, interfere with a yet unidentified tyrosine kinase that uses Akt, but not ERKs, as a downstream effector. It is noteworthy that these doxazosin-derived agents are structurally distinct from existing quinazoline-based inhibitors of epidermal growth receptor tyrosine kinases[18] such as Iressa (ZD1839) and CP-358,744.

We found that the replacement of the (2,3-dihydrobenzo[1,4]dioxane)-carbonyl moiety of doxazosin with aryl sulfonyl substituents dramatically improved the potency in facilitating Akt dephosphorylation and inducing apoptosis. Structurally optimized agent **33** exhibited an order of magnitude higher potency than parent compound doxazosin in triggering apoptotic death in PC-3 cells. It is noteworthy that the structural rigidity incurred by the piperazine linker was integral in maintaining the high potency of these derivatives. Consequently, the use of a flexible linker such as ethylenediamine substantially reduced the apoptosis-inducing activity of **33**. Further structural optimization was accomplished by replacing the methoxy side chains on the quinazoline ring with propoxy functions. Both **33** and **44** were effective in suppressing the proliferation of different prostate cancer cell lines at low micromolar concentration levels. In addition, both agents were submitted to the Developmental Therapeutic Program (DTP) at the National Cancer Institute (NCI) for screening against 60 human tumor cells lines, representing leukemia, melanoma, and cancers of lung, colon, brain, ovary, breast, prostate, and kidney (http://dtp.nci.nih.gov/index.html). All of the tested cell lines showed high degree of sensitivity to the growth inhibitory effects of **33** and **44**. The mean GI_{50} values (concentration resulting in 50% growth inhibition) among these 60 cell lines were 2.2 and 1.5 μM, respectively. These data clearly demonstrate the in vitro efficacy of these agents and their potential application in cancer prevention and/or treatment. Testing of the in vivo efficacy of these agents in xenograft models constitutes the focus of the present investigation.

Conclusions

The present study demonstrates that doxazosin could be pharmacological exploited to develop a novel class of antitumor agents that mediate apoptosis in prostate cancer cells via the inhibition of intracellular Akt activation. In light of the importance of Akt signaling in prostate cancer carcinogenesis and progression, these novel agents may have translation potential in prostate cancer prevention and/or therapy.

Experimental Section

Chemical reagents and organic solvents were purchased from Aldrich unless otherwise mentioned. Nuclear magnetic resonance spectra (^{1}H NMR) were measured on a Bruker 250- or 400-MHz spectrometer. Chemical shifts (δ) are reported in ppm relative to the TMS peak. Electrospray ionization (ESI) mass spectrometry analyses were performed with a 3-T Finnigan FTMS-2000 Fourier transform mass spectrometer. Elemental analyses were within $\pm$0.4% of the calculated values. Flash column chromatography was performed with silica gel (230−400 mesh). Rabbit polyclonal antibodies against Akt, phospho-Ser473-Akt, ERKs, and phospho-ERKs were purchased from New England Biolabs (Beverly, MA). Rabbit antipoly(ADP-ribose) polymerase (PARP) antibodies were from BD PharMingen (San Diego, CA). Mouse antiactin monoclonal antibody was from ICN Pharmaceuticals (Costa Mesa, CA). Goat antirabbit immunoglobulin G (IgG)−horseradish peroxidase conjugates were from Jackson ImmunoResearch Laboratories.

General Procedures for the Synthesis of Amides 1−10 (Scheme 1). 4-(4-Amino-6,7-dimethoxy-quinazolin-2-yl)-piperazine-1-carboxylic Acid Benzyl Ester (iii). A mixture of 4-amino-2-chloro-6,7-dimethoxyquinazoline (2.51 g, 10 mmol) and benzyl 1-piperazine-carboxylate (2.24 g, 10 mmol) in 1-butanol (15 mL) was stirred under reflux overnight and cooled to 80 °C. The crude solid product was collected, washed with cold 1-butanol (2 × 10 mL), added to methanol (30 mL), and heated under reflux for 1 h. The white solid was filtered and washed with methanol (2 × 10 mL) to yield compound **iii**. ^{1}H NMR (DMSO-d_6) δ 3.59−3.61 (m, 4 H), 3.83−3.89 (m, 4 H), 3.85 (s, 3 H), 3.91 (s, 3 H), 5.14 (s, 2 H), 7.14 (s, 1 H), 7.34−7.88 (m, 5 H), 7.89 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{22}H_{26}N_5O_4$ 424.1979; found 424.1989. Anal. ($C_{22}H_{25}N_5O_4$·HCl) C, H, N.

[4-(4-Amino-6,7-dimethoxy-quinazolin-2-yl)-piperazin-1-yl]-(4-chlorophenyl)-methanone (1). Compound **iii** (2.12 g, 5.0 mmol) was dissolved in methanol (15 mL), and 10% palladium on charcoal (20 mg, 10% w/w) and triethylamine (0.2 mL) were added. The mixture was treated with hydrogen under atmospheric pressure for 6 h and filtered. The solvent was evaporated to obtain the intermediate 6,7-dimethoxy-2-piperazin-1-yl-quinazolin-4-ylamine (**iv**) without purification.^{1}H NMR (DMSO-d_6) δ 3.22 (br s, 4 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.98 (br s, 4 H), 7.54 (s, 1 H), 7.69 (s, 1 H). The intermediate amine (0.578 g, 2.0 mmol) was dissolved in dry DMF (10 mL), and triethylamine (0.202 g, 2.0 mmol) was added. The resulting mixture was treated dropwise with 4-chlorobenzoyl chloride (0.35 g, 2.0 mmol) over 15 min, stirred at room temperature for 4 h, and then concentrated. The crude solid product was washed with methanol, filtered, and recrystallized from ethanol to give compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.32−3.34 (m, 4 H), 3.38 (s, 3 H), 3.84 (s, 3 H), 3.77−3.88 (m, 4 H), 7.48−7.57 (m, 5 H), 7.73 (s, 1 H), 8.66 (br s, 1H), 8.88 (br s, 1 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{23}ClN_5O_3$ 428.1484; found 428.1492. Anal. ($C_{21}H_{22}ClN_5O_3$·HCl) C, H, N.

General Procedure for the Synthesis of Sulfonamides (Scheme 2). Method A. 2-[4-(4-Chlorobenzenesulfonyl)-piperazin-1-yl]-6,7-dimethoxy-quinazolin-4-yl-amine (11). To a solution of intermediate amine **iv** (0.578 g, 2.0 mmol) and triethylamine (0.276 g, 2.0 mmol) in methanol (10 mL) 4-chlorobenzenesulfonyl chloride (0.443 g, 2.1 mmol) was added to the solution. The mixture was stirred at room temperature for 1 h. The resulting solid was filtered and then washed with ethyl acetate (2 × 10 mL) to obtain the crude solid product. The crude product was stirred in methanol (10 mL) under reflux for 1 h, filtered and dried to obtain compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.27 (s, 4 H), 3.35 (s, 3 H), 3.85 (s, 3 H), 3.99 (s, 4 H), 7.55 (s, 1 H), 7.60−7.80 (m, 5 H), 8.63 (s, 1 H), 8.80 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{20}H_{23}ClN_5O_4S$ 464.1154, found 464.1158. Anal. ($C_{20}H_{22}ClN_5O_4S$·HCl) C, H, N.

Method B (14, 20, 23, 32). 2-[4-(5-Chlorothiophene-2-sulfonyl)-piperazin-1-yl]-6,7-dimethoxy-quinazolin-4-ylamine (14). A solution of piperazine (0.517 g, 6.0 mmol) and 5-chloro-thiophene-2-sulfonyl chloride (0.436 g, 2.0 mmol) in methanol (10 mL) was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was purified with silica gel chromatography to obtain 1-(5-chloro-thiophene-2-sulfonyl)-piperazine. The intermediate (0.266 g, 1.0 mmol) and 4-amino-2-chloro-6,7-dimethoxy-quinazoline (0.251 g, 1.0 mmol) in 1-butanol (5 mL) were stirred under reflux overnight and cooled to 80 °C. The collected solid product was washed with ethyl acetate (2 × 10 mL), stirred in methanol (30 mL) under reflux for 1 h, filtered, and washed with methanol (2 × 10 mL) to yield compound **14**. ^{1}H NMR (DMSO-d_6) δ 3.06−3.08 (m, 4 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.94 (s, 4 H),7.36 (s, 1 H), 7.37 (s, 1 H), 7.59 (s,1 H), 7.60 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{18}H_{21}ClN_5O_4S_2$ 470.0718; found 470.0740. Anal. ($C_{18}H_{20}ClN_5O_4S_2$·HCl) C, H, N.

Method C. 6,7-Dimethoxy-2-[4-(4-phenanthren-9-yl-benzenesulfonyl)-piperazin-1-yl]-quinazolin-4-ylamine (35). To a solution of cbz-protected *N*-piperazine (2.24 g, 10.0 mmol) and 4-bromobenzenesulfonyl chloride (2.55 g, 10.0 mmol) in methanol (20 mL) triethylamine (1.38 g, 10.0 mmol) was added to the solution. The mixture was stirred at room temperature for 2 h, concentrated, and purified by silica gel chromatography to afford 4-(4-bromo-benzenesulfonyl)-piperazine-1-carboxylic acid benzyl ester (**v**). Under argon, compound **v** (0.439 g, 1.0 mmol), K_2CO_3 (0.345 g, 2.5 mmol), Bu_4NBr (0.322 g, 1.0 mmol), and $Pd(OAc)_2$ (11 mg, 5 mol %) were added to a stirred solution of 4-phenanthrenylboronic acid (0.243 g, 1.1 mmol) in H_2O (5 mL). The reaction mixture was vigorously stirred at 70 °C for 1 h and cooled to room temperature, and ethyl acetate was added (10 mL). The organic layer was dried and concentrated to obtain compound **vi**. To a solution of compound **vi** (0.389 g, 0.5 mmol) in methanol (5 mL) 10% palladium on charcoal (5 mg, 10% w/w) was added. The mixture was treated with hydrogen under atmospheric pressure for 6 h and filtered. The solvent was evaporated to yield product **vii**. Following the procedure for the synthesis of compound **14**, compound **35** was synthesized.^{1}H NMR (DMSO-d_6) δ 3.20 (s, 4 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 3.99 (s, 4 H), 7.28 (s, 1 H), 7.60−7.78 (m, 7 H), 7.81 (d, J = 8.4 Hz, 2 H), 8.02 (d, J = 8.1 Hz), 8.4 (s, 1 H), 8.87 (d, J = 8.1 Hz, 1 H), 8.94 (d, J = 8.4 Hz, 1 H). HRMS (M + H)$^+$ calcd for $C_{34}H_{32}N_5O_4S$ 606.2169; found 606.2164. Anal. ($C_{34}H_{31}N_5O_4S$·HCl) C, H, N.

General Procedure for the Synthesis of Sulfonamides (Scheme 3). *N*-[2-(4-Amino-6,7-dimethoxyquinazolin-2-ylamino)-ethyl]-4-*tert*-butylbenzene Sulfonamide (41). A mixture of ethylenediamine (0.36 g, 6.0 mmol) and *tert*-butylbenzenesulfonyl chloride (0.464 g, 2.0 mmol) in methanol (15 mL) was stirred for 3 h, concentrated, and purified by silica gel chromatography to yield *N*-(2-amino-ethyl)-4-*tert*-butyl-benzenesulfonamide. Following the procedure for the synthesis of compound **14**, compound **42** was obtained. ^{1}H NMR (DMSO-d_6) δ 1.17 (s, 9 H), 3.11 (s, 2 H), 3.48 (s, 2 H), 3.86 (s, 3 H), 3.93 (s, 3 H), 6.90 (s, 1 H), 7.50 (d, J = 8.4 Hz, 2 H), 7.55 (s, 1 H), 7.70 (d, J = 8.4 Hz, 2 H). HRMS (M + H)$^+$ calcd for $C_{22}H_{30}N_5O_4S$ 460.2013; found 460.2010. Anal. ($C_{22}H_{29}N_5O_4S$·HCl) C, H, N.

General Procedure for the Synthesis of Sulfonamides (Scheme 4). 6,7-Bis-allyloxy-2-[4-(biphenyl-4-sulfonyl)-piperazin-1-yl]-quinazolin-4-ylamine (43). A solution of 4-amino-2-chloro-6,7-dimethoxyquinazoline (2.51 g, 10.0 mmol) in CH_2Cl_2 (30 mL) was cooled to −70 °C under argon, and boron tribromide (6.01 g, 12.0 mmol) was added. The mixture was allowed to warm to room temperature over a period of 4 h and was then cooled to −70 °C; methanol (30 mL) was added, and the solution was concentrated. The solid residue was washed with ethyl acetate to obtain 4-amino-2-chloro-6,7-dihydroxyquinazoline [^{1}H NMR (DMSO-d_6) δ 7.04 (s, 1 H), 7.51 (s, 1 H)]. A mixture of the first intermediate (0.21 g, 1.0 mmol), allyl bromide (0.432 g, 3.6 mmol), and K_2CO_3 (0.331 g, 2.4 mmol) in methanol (10 mL) was stirred under reflux for 12 h, concentrated, and purified by silica gel chromatography to afford 4-amino-2-chloro-6,7-diallyloxyquinazoline [^{1}H NMR (DMSO-d_6) δ 4.63 (d, J = 5.4 Hz, 2 H), 4.70 (d, J = 1.5 Hz, 2 H), 5.28 (d, J = 1.3 Hz, 2 H), 5.42 (d, J = 1.3 Hz, 1 H), 5.49 (d, J = 1.3 Hz, 1 H), 6.07−6.11 (m, 2 H), 7.06 (s, 1 H), 7.62 (s, 1 H)]. A solution of the second intermediate (0.291 g, 1.0 mmol) and 1-(biphenyl-4-sulfonyl)-piperazine (0.302 g, 1.0 mmol) in 1-butanol (5 mL) was stirred under reflux for 8 h and concentrated. The solid residue was stirred with methanol under reflux for 30 min, filtered, and washed with methanol to yield compound **44**. ^{1}H NMR (DMSO-d_6) δ 3.36 (br s, 4 H), 4.01 (br s, 4 H), 4.60−4.64 (m, 4 H), 5.26−5.35 (m, 4 H), 6.02−6.13 (m, 2 H), 7.30−7.52 (m, 4 H), 7.72−7.75 (m, 3 H), 7.83−7.86 (m, 4 H), 8.63 (s, 1 H), 8.83 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{30}H_{32}N_5O_4S$ 558.2169; found 558.2169. Anal. ($C_{30}H_{31}N_5O_4S$·HCl) C, H, N.

4-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-carbonyl]-benzonitrile (2). Compound **2** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.46−3.47 (m, 4 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 4.03−4.17 (m, 4 H), 7.51 (s, 1 H), 7.66 (d, J = 8.0 Hz, 2 H), 7.97 (d, J = 8.0 Hz, 2 H). HRMS (M + H)$^+$ calcd for $C_{22}H_{23}N_6O_3$ 419.1826; found 419.1812. Anal. ($C_{22}H_{22}N_6O_3$·HCl) C, H, N.

3-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-carbonyl]-benzonitrile (4). Compound **4** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.44−3.46 (m, 4 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.77−3.99 (m, 4 H), 6.97 (s, 1 H), 7.45 (s, 1 H), 7.60−7.64 (m, 1 H), 7.70−7.72 (m, 1 H), 7.82−7.93 (m, 2 H). HRMS (M + H)$^+$ calcd for $C_{22}H_{23}N_6O_3$ 419.1826; found 419.1823.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-(4-nitrophenyl)-methanone (5). Compound **5** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.21−3.35 (m, 4 H), 3.85(s, 3 H), 3.89 (s, 3 H), 3.93−3.96 (m, 4 H), 7.41 (s, 1 H), 7.73−7.76 (m, 3 H), 7.93−8.39 (m, 2 H), 8.83 (br s, 1 H), 8.90 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{21}H_{23}N_6O_5$ 439.1724; found 439.1718. Anal. ($C_{21}H_{22}N_6O_5$·HCl) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-(3,4-dimethoxyphenyl)-methanone (6). Compound **6** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 4 H), 3.79(s, 3 H), 3.81 (s, 3 H), 3.84(s, 3 H), 3.88 (s, 3 H), 4.26 (s, 4 H), 7.41 (s, 1 H), 7.00−7.05 (m, 3 H), 7.74 (s, 1 H), 8.54 (br s, 1 H), 8.90 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{23}H_{28}N_5O_5$ 454.2085; found 454.2071.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-naphthalen-1-yl-methanone (7). Compound **7** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.18−3.30 (m, 4 H), 3.67 (s, 3 H), 3.78 (s, 3 H), 3.97 (br s, 2 H), 4.08 (br s, 2 H), 7.48 (s, 1 H), 7.53−7.59 (m, 1 H), 7.60−7.61 (m, 3 H), 7.65 (s, 1 H), 7.96 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{25}H_{26}N_5O_3$ 444.2030; found 444.2030.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-(4-aminophenyl)-methanone (8). Compound **8** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.71(s, 4 H), 3.86(s, 3 H), 3.87 (s, 3 H), 3.92−3.97(m, 4 H), 6.65−6.68 (m, 2 H), 7.13 (d, J = 3.2 Hz, 1

H), 7.25 (d, $J = 3.4$ Hz, 1 H), 7.27 (d, $J = 3.3$ Hz, 1 H), 7.62 (d, $J = 3.2$ Hz, 1 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{25}N_6O_3$ 409.1983; found 409.1984.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-(4-*tert*-butylphenyl)-methanone (9). Compound **9** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 1.32 (s, 9 H), 3.66−3.74 (m, 4 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 3.93 (s, 4 H), 7.31−7.51 (m, 5 H), 7.73 (s, 1 H), 8.51 (s, 1 H), 8.97 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{25}H_{32}N_5O_3$ 450.2500; found 450.2485. Anal. ($C_{25}H_{31}N_5O_3$·HCl) C, H, N.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-(4-trifluoromethylphenyl)-methanone (10). Compound **10** was synthesized from the procedure described for compound **1**. ^{1}H NMR (DMSO-d_6) δ 3.50 (s, 4 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.0 (s, 4 H), 7.56 (s, 1 H), 7.70 (d, $J = 7.7$ Hz, 1 H), 7.87 (d, $J = 7.7$ Hz, 2 H), 8.59 (s, 1 H), 8.94 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{22}H_{23}F_3N_5O_3$ 462.1748; found 462.1708.

2-[4-(4-Bromobenzenesulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-yl-amine (12). Compound **12** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.13−3.14 (m, 4 H), 3.48−3.49 (m, 4 H), 3.83 (s, 3 H), 3.90 (s, 3 H), 6.99 (s, 1 H), 7.49 (s, 1 H), 7.74 (d, $J = 8.4$ Hz, 2 H), 7.83 (d, $J = 8.4$ Hz, 2 H). HRMS $(M + H)^+$ calcd for $C_{20}H_{23}BrN_5O_4S$ 508.0649; found 508.0646. Anal. ($C_{20}H_{22}BrN_5O_4S$·HCl) C, H, N.

2-[4-(4-Iodobenzenesulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-yl-amine (13). Compound **13** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 2.95 (s, 4 H), 3.77 (s, 3 H), 3.78−3.82 (m, 4 H), 3.82 (s, 3 H), 7.26−39 (m, 2 H), 7.38 (d, $J = 8.3$ Hz, 2 H), 8.01 (d, $J = 8.5$ Hz, 2 H). HRMS $(M + H)^+$ calcd for $C_{20}H_{23}IN_5O_4S$ 556.0510; found 556.0496. Anal. ($C_{20}H_{22}IN_5O_4S$·HCl) C, H, N.

2-[4-(5-Chlorothiophene-2-sulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine (14). Compound **14** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.06−3.08 (m, 4 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.94 (s, 4 H),7.36 (s, 1 H), 7.37 (s, 1 H), 7.59 (s,1 H), 7.60 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{18}H_{21}ClN_5O_4S_2$ 470.0718; found 470.0740.

6,7-Dimethoxy-2-[4-(2-nitrobenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (15). Compound **15** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.16 (s, 4 H), 3.34 (s, 3 H), 3.43 (s, 3 H), 3.74 (s, 4 H), 7.64 (s, 1 H), 7.95 (t, $J = 8.1$ Hz, 1 H), 8.21 (d, $J = 7.8$ Hz, 1 H), 8.41 (s, 1 H), 8.53 (s, 1 H), 8.56 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{20}H_{23}N_6O_6S$ 475.1394; found 475.1394.

6,7-Dimethoxy-2-[4-(3-nitrobenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (16). Compound **16** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.22 (s, 4 H), 3.68 (s, 3 H), 3.77 (s, 3 H), 3.82 (s, 4 H), 6.72 (s, 1 H), 7.19 (br s, 2 H), 7.42 (s, 1 H), 7.82−7.88 (m, 2 H), 7.98−8.07 (m, 2 H). HRMS $(M + H)^+$ calcd for $C_{20}H_{23}N_6O_6S$ 475.1394; found 475.1392. Anal. ($C_{20}H_{22}N_6O_6S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(4-nitrobenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (17). Compound **17** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.00 (s, 4 H), 3.66 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 4 H), 6.75 (s, 1 H), 7.16 (br s, 2 H), 7.38 (s, 1 H), 8.01 (d, $J = 8.6$ Hz, 2 H), 8.20 (d, $J = 8.5$, 2H). HRMS $(M + H)^+$ calcd for $C_{20}H_{23}N_6O_6S$ 475.1394; found 475.1379.

6,7-Dimethoxy-2-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-quinazolin-4-ylamine (18). Compound **18** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 29 (s, 3 H), 3.03−3.07 (m, 4 H), 3.82 (s, 3 H), 3.85(s, 3 H), 3.98−4.05 (m, 4 H), 7.45 (d, $J = 7.6$ Hz, 2 H), 7.52 (s, 1 H), 7.65 (d, $J = 7.3$ Hz, 2 H), 7.73 (s, 1 H), 8.55 (s, 1 H), 8.92 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{26}N_5O_4S$ 444.1700; found 444.1706. Anal. ($C_{21}H_{25}N_5O_4S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(4-trifluoromethylbenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (19). Compound **19** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 4 H), 3.79 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 4 H), 7.56 (s, 1 H), 7.80−8.03 (m, 5 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{23}F_3N_5O_3S$ 498.1417; found 498.1420. Anal. ($C_{21}H_{22}F_3N_5O_3S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(4-methoxybenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (20). Compound **20** was synthesized from the procedure described for compound **14**. ^{1}H NMR (DMSO-d_6) δ 2.95−2.97 (m, 4 H), 3.73 (s, 3 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 3.73−3.82 (m, 4 H), 6.98 (s, 1 H), 7.06 (d, $J = 21.1$ Hz, 2 H), 7.57 (d, $J = 19.1$ Hz, 2 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{26}N_5O_5S$ 460.1649; found 460.1652. Anal. ($C_{21}H_{25}N_5O_5S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(4-trifluoromethoxybenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (21). Compound **21** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.40 (s, 4 H), 3.66 (s, 3 H), 3.69 (s, 3 H), 3.71 (s, 4 H), 6.68 (s, 1 H), 7.00 (br s, 2 H), 7.23 (s, 1 H), 7.54−755 (m, 2 H), 7.86−7.88 (m, 2 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{23}F_3N_5O_5S$ 514.1367; found 514.1363. Anal. ($C_{21}H_{22}F_3N_5O_5S$·HCl) C, H, N.

2-[4-(4-Methanesulfonyl-benzenesulfonyl)-piperazin-1-yl]-6,7-dimethoxy-quinazolin-4-ylamine (22). Compound **22** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.00 (s, 4 H), 3.21 (s, 3 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.82 (s, 4 H), 6.69 (s, 1 H), 7.07 (br s, 2 H), 7.26 (s, 1 H), 8.01 (d, $J = 8.3$ Hz, 2 H), 8.16 (d, $J = 8.4$ Hz, 2 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{26}N_5O_6S_2$ 508.1319; found 508.1317. Anal. ($C_{21}H_{25}N_5O_6S_2$·HCl) C, H, N.

2-[4-(4-*tert*-Butylbenzenesulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine (23). Compound **23** was synthesized from the procedure described for compound **14**. ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 9 H), 2.90 (s, 4 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 3.90−3.98 (m, 4 H), 6.70 (s, 3 H), 7.17 (br s, 1 H), 7.26 (s, 1 H), 7.45−7.68 (m, 3 H). HRMS $(M + H)^+$ calcd for $C_{24}H_{32}N_5O_4S$ 486.2170; found 486.2173. Anal. ($C_{24}H_{31}N_5O_4S$·HCl) C, H, N.

3-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-sulfonyl]-benzoic acid (24). Compound **24** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 2.99 (s, 4 H), 3.77 (s, 3 H), 3.82 (s, 7 H), 6.78 (s, 1 H), 7.38 (br s, 1 H), 7.44 (s, 1 H), 7.78 (t, $J = 7.6$ Hz, 1 H), 8.00 (d, $J = 7.4$ Hz, 1 H), 8.21−8.23 (m, 2 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{24}N_5O_6S$ 474.1442; found 474.1426.

[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazin-1-yl]-(4-trifluoromethylphenyl)-methanone (25). Compound **25** was synthesized from the procedure described for compound **11**.^{1}H NMR (DMSO-d_6) δ 3.34 (br s, 4 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.95 (s, 4 H), 6.83 (s, 1 H), 7.41−7.51 (br s, 2 H), 7.66−7.71(m, 2 H), 7.85−7.94 (m, 2 H), 10.20 (br s, 1 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{24}N_5O_6S$ 474.1442; found 474.1479.

2-[4-(2,5-Dichlorobenzenesulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine (26). Compound **26** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.33 (br s, 4 H), 3.64 (s, 3 H), 3.78−3.82 (m, 4 H), 3.82 (s, 3 H), 6.74 (s, 1 H), 7.21 (br s, 2 H), 7.43-(s, 1 H), 7.69−7.96 (m, 2 H), 7.97 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{20}H_{22}Cl_2N_5O_4S$ 498.0764; found 498.0768.

4-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-sulfonyl]-benzene-1,3-diamine (27). Compound **27** was synthesized from the procedure described for compound **11** followed by hydrogenation to get the diamine product. ^{1}H NMR (DMSO-d_6) δ 3.09 (s, 4 H), 3.34 (s, 3 H), 3.67 (s, 3 H), 3.86−3.89 (m, 4 H), 6.28 (d, $J = 8.5$ Hz, 1 H), 6.74 (s, 1 H), 7.31 (d, $J = 9.0$ Hz, 1 H), 7.66 (s, 1 H), 8.23 (s, 1 H), 8.64 (s, 1 H), 8.85 (s, 1 H), 8.99 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{20}H_{26}N_7O_6S$ 460.1761; found 460.1758. Anal. ($C_{20}H_{25}N_7O_6S$·HCl) C, H, N.

5-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-sulfonyl]-2-chloro-4-fluorobenzoic Acid (28). Compound **28** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.15 (s, 4 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 3.80 (s, 4 H), 6.76 (s, 1 H), 7.37 (br s, 1 H), 7.42 (s, 1 H), 7.82 (s, 1 H), 8.12 (s, 1 H). HRMS $(M + H)^+$ calcd for $C_{21}H_{22}ClFN_5O_6S$ 526.0958; found 526.0943.

5-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-piperazine-1-sulfonyl]-2,4-dichlorobenzoic Acid (29). Compound **29** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.37 (br s, 4 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.95 (s, 4 H), 7.47 (s, 1 H), 7.71 (s, 2 H), 7.43(s, 1 H), 8.03 (s, 1 H), 8.33 (s, 1 H), 8.62 (br s, 1 H), 8.86 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{21}H_{22}Cl_2N_5O_6S$ 542.0662; found 542.0657.

6,7-Dimethoxy-2-[4-(naphthalene-1-sulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (30). Compound **30** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.08 (s, 4 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 3.95 (s, 4 H), 7.66 (s, 1 H), 7.68−7.78 (m, 4 H), 8.11 (d, J = 8.0 Hz, 1 H), 8.18 (d, J = 7.4 Hz, 1 H), 8.31 (d, J = 8.2 Hz, 1 H), 8.71 (d, J = 8.6 Hz, 1 H), 10.29 (br s, 2 H). HRMS (M + H)$^+$ calcd for $C_{24}H_{26}N_5O_4S$ 480.1700; found 480.1696. Anal. ($C_{24}H_{25}N_5O_4S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(naphthalene-2-sulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (31). Compound **31** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.00−3.08 (m, 4 H), 3.39 (s, 3 H), 3.43 (s, 3 H), 3.74−3.81 (m, 4 H), 6.67 (s, 1 H), 7.12 (br s, 2 H), 7.36 (s, 1 H), 7.66−7.73 (m, 2 H), 7.77 (d, J = 8.7 Hz, 1 H), 8.05 (d, J = 7.7 Hz, 1 H), 8.14 (d, J = 8.7 Hz, 1 H), 8.20 (d, J = 7.7 Hz, 1 H), 8.45 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{24}H_{26}N_5O_4S$ 480.1700; found 480.1708. Anal. ($C_{24}H_{25}N_5O_4S$·HCl) C, H, N.

2-[4-(5-Dimethylaminonaphthalene-1-sulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine (32). Compound **32** was synthesized from the procedure described for compound **14**. ^{1}H NMR (DMSO-d_6) δ 2.82 (s, 6 H), 3.27−3.29 (m, 4 H), 3.44 (s, 3 H), 3.81 (s, 3 H), 3.85−3.91 (m, 4 H), 7.27 (d, J = 7.6 Hz, 1 H), 7.61 (s, 1 H), 7.61−7.70 (m, 3 H), 8.17 (d, J = 7.4 Hz, 1 H), 8.35 (d, J = 8.64 Hz, 1 H), 8.53 (d, J = 8.5 Hz, 1 H), 8.63 (br s, 1 H), 8.85 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{26}H_{31}N_6O_4S$ 523.2122; found 523.2153.

2-[4-(Biphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-ylamine (33). Compound **33** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 3.02−3.03 (m, 4 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 3.98−3.46 (m, 4 H), 7.38−7.52 (m, 4 H), 7.68−7.74 (m, 3 H), 7.85 (d, J = 8.2 Hz, 2 H), 7.94 (d, J = 8.2 Hz, 2 H). HRMS (M + H)$^+$ calcd for $C_{26}H_{28}N_5O_4S$ 506.1857; found 506.1840. Anal. ($C_{26}H_{27}N_5O_4S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(2,4,6-triisopropylbenzenesulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (34). Compound **34** was synthesized from the procedure described for compound **11**. ^{1}H NMR (DMSO-d_6) δ 1.22 (s, 9 H), 1.24 (s, 9 H), 2.92−2.98 (m, 1 H), 3.23 (s, 4 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 3.94 (s, 4 H), 4.01−4.15 (m, 2 H), 7.32 (s, 2 H), 7.44 (s, 1 H), 7.76 (s, 1 H), 8.69 (br s, 1 H), 8.96 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{29}H_{42}N_5O_4S$ 556.2952; found 556.2944.

6,7-Dimethoxy-2-[4-(4′-methylbiphenyl-4-sulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (36). Compound **36** was synthesized from the procedure described for compound **35**. ^{1}H NMR (CD_3OD-d_4) δ 2.28 (s, 3 H), 3.12 (s, 4 H), 3.78 (s, 3 H), 3.84 (s, 3 H), 3.86 (s, 4 H), 6.88−6.90 (m, 3 H), 7.18 (d, J = 8.1 Hz, 1 H), 7.36 (s, 1 H), 7.38−7.40 (m, 2 H), 7.44 (d, J = 8.1 Hz, 1 H), 7.46−7.78 (m, 2 H). HRMS (M + H)$^+$ calcd for $C_{27}H_{30}N_5O_4S$ 520.2013; found 520.2040. Anal. ($C_{27}H_{29}N_5O_4S$·HCl) C, H, N.

6,7-Dimethoxy-2-[4-(4′-trifluoromethylbiphenyl-4-sulfonyl)-piperazin-1-yl]-quinazolin-4-yl-amine (37). Compound **37** was synthesized from the procedure described for compound **35**. ^{1}H NMR (DMSO-d_6) δ 3.05 (s, 4 H), 3.78 (s, 3 H), 3.82 (s, 2 H), 3.91 (s, 3 H),7.53 (s, 1 H), 7.71−7.89 (m, 4 H), 7.94−8.07 (m, 4 H), 10.16 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{27}H_{26}$ $F_3N_5O_4S$ 574.1730; found 574.1728. Anal. ($C_{27}H_{25}$ $F_3N_5O_4S$·HCl) C, H, N.

2-[4-(4′-Methanesulfonyl-biphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-dimethoxy-quinazolin-4-ylamine (38). Compound **38** was synthesized from the procedure described for compound **35**. ^{1}H NMR (DMSO-d_6) δ 2.91 (s, 4 H), 3.26 (s, 3 H), 3.78 (s, 2 H), 3.83 (s, 3 H), 3.91 (s, 4 H), 6.97 (s, 1 H), 7.55 (s, 1 H), 7.88 (d, J = 8.2 Hz, 2 H), 8.08 (m, 6 H). HRMS (M + H)$^+$ calcd for $C_{27}H_{30}N_5O_6S_2$ 584.1632; found 584.1658. Anal. ($C_{27}H_{29}N_5O_6S_2$·HCl) C, H, N.

2-[4-(4′-Butylbiphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-yl-amine (39). Compound **39** was synthesized from the procedure described for compound **35**. ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.29−1.34 (m, 2 H), 1.55−1.59 (m, 2 H), 2.60−2.64 (m, 2 H), 3.13 (s, 4 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 3.97 (s, 4 H), 7.31−7.33 (m, 3 H), 7.63−7.69 (m, 3 H), 7.82 (d, J = 8.3 Hz, 2 H), 7.91 (d, J = 8.4 Hz, 2 H), 8.66 (br s, 1 H), 8.79 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{30}H_{36}N_5O_4S$ 562.2483; found 562.2458. Anal. ($C_{30}H_{35}N_5O_4S$·HCl) C, H, N.

2-[4-(4′-*tert*-Butylbiphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-dimethoxyquinazolin-4-yl-amine (40). Compound **40** was synthesized from the procedure described for compound **35**. ^{1}H NMR (DMSO-d_6) δ 1.31 (s, 9 H), 3.14 (s, 4 H), 3.81 (s, 3 H), 3.86 (s, 3 H), 3.95 (s, 4 H), 7.19 (s, 1 H), 7.45−7.53 (m, 2 H), 7.60−7.66 (m, 3 H), 7.82−7.84 (m, 2 H), 7.92 (d, J = 8.3 Hz, 2 H), 8.66 (br s, 1 H), 8.81 (br s, 1 H). HRMS (M + H)$^+$ calcd for $C_{30}H_{36}N_5O_4S$ 562.2483; found 562.2471. Anal. ($C_{30}H_{35}N_5O_4S$·HCl) C, H, N.

***N*-[2-(4-Amino-6,7-dimethoxyquinazolin-2-ylamino)-ethyl]-4-biphenylsulfonamide (42).** Compound **42** was synthesized from the procedure described for compound **41**. ^{1}H NMR (DMSO-d_6) δ 3.05 (s, 2 H), 3.46 (s, 2 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 6.91(br s, NH), 7.40−7.47 (m, 3 H), 7.60−7.64 (m, 3 H), 7.78−7.83 (m, 2 H), 7.86−7.88 (m, 2 H), 8.01 (s, 1 H). HRMS (M + H)$^+$ calcd for $C_{24}H_{26}N_5O_4S$ 480.1700; found 480.1687. Anal. ($C_{24}H_{25}N_5O_4S$·HCl) C, H, N.

2-[4-(Biphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-dipropoxyquinazolin-4-yl-amine (44). Compound **44** was synthesized from the procedure described for compound **43**. ^{1}H NMR (DMSO-d_6) δ 0.99 (t, J = 7.3 Hz, 6 H), 1.71−1.83 (m, 4 H), 3.12 (br s, 4 H), 3.93−4.14 (m, 8 H), 7.33 (s, 1 H), 7.44−7.54 (m, 3 H), 7.65 (s, 1 H), 7.75−7.79 (m, 2 H), 7.86 (d, J = 8.3 Hz, 2 H), 7.94 (d, J = 8.3 Hz, 2 H). HRMS (M + H)$^+$ calcd for $C_{30}H_{36}N_5O_4S$ 562.2483; found 562.2466. Anal. ($C_{30}H_{35}N_5O_4S$·HCl) C, H, N.

2-[4-(Biphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-diisopropoxyquinazolin-4-yl-amine (45). Compound **45** was synthesized from the procedure described for compound **43**. ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 3 H), 1.27 (s, 3 H), 1.33 (s, 3 H), 1.35 (s, 3 H), 3.12 (br s, 4 H), 3.96 (br s, 4 H), 4.41−4.66 (m, 2 H), 7.36 (s, 1 H), 7.41−7.53 (m, 3 H), 7.68−7.84 (m, 3 H), 7.83−7.86 (m, 4 H), 8.59 (br s, NH), 8.76 (br s, NH). HRMS (M + H)$^+$ calcd for $C_{30}H_{36}N_5O_4S$ 562.2483; found 562.2478. Anal. ($C_{30}H_{35}N_5O_4S$·HCl) C, H, N.

2-[4-(Biphenyl-4-sulfonyl)-piperazin-1-yl]-6,7-dibutoxyquinazolin-4-ylamine (46). Compound **46** was synthesized from the procedure described for compound **43**. ^{1}H NMR (DMSO-d_6) δ 0.934 (t, J = 7.5 Hz, 6 H), 1.44 (q, J = 7.5 Hz, 4 H), 1.66−1.812 (m, 4 H), 3.13 (br s, 4 H), 3.91 (br s, 4 H), 3.91−4.08 (m, 4 H), 7.21 (s, 1 H), 7.41−7.53 (m, 3 H), 7.64 (s, 1 H), 7.73 (d, J = 8.0 Hz, 1 H), 7.74 (s, 1 H), 7.829−7.864 (m, 3 H), 7.94 (d, J = 8.0 Hz, 2 H). HRMS (M + H)$^+$ calcd for $C_{32}H_{40}N_5O_4S$ 590.2795; found 590.2770. Anal. ($C_{32}H_{39}N_5O_4S$·HCl) C, H, N.

Cell Culture. PC-3 (p53$^{-/-}$) human androgen-nonresponsive prostate cancer cells were purchased from the American Type Tissue Collection (Manassas, VA). Cells were cultured in an RPMI 1640 medium (Gibco, Grand Island, NY) supplemented with 10% fetal bovine serum (FBS; Gibco) at 37 °C in a humidified incubator containing 5% CO_2.

Cell Viability Assay. Effects of the test agent on cell viability were assessed by the MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide]) assay in 96-well, flat-bottomed plates in which 8000 PC-3 or DU-145 cells/well were seeded. Cells were exposed to the test agent at the indicated concentrations, in six replicates, in 10% FBS-supplemented RPMI-1640 medium at 37 °C in 5% CO_2 for 48 h. The medium was removed and was replaced by 150 μL of 0.5 mg/mL MTT in RPMI 1640 medium, and the cells were incubated in the CO_2 incubator at 37 °C for 2 h. Supernatants were removed from the wells, and the reduced MTT dye was

solubilized with 200 μL/well DMSO. The absorbance was determined on a plate reader at 570 nm.

Western Blot Analysis. PC-3 cells (1.5×10^6) treated with the test agent at the indicated concentrations in the RPMI 1640 medium for 24 h were collected and sonicated. Protein concentrations of the lysates were determined by using a Bradford protein assay kit (Bio-Rad, Hercules, CA); equivalent amounts of proteins from each lysate were resolved in 10% SDS-polyacrylamide gel and then transferred onto Immobilon-nitrocellulose membranes (Millipore, Bellerica, MA) in a semidry transfer cell. The transblotted membrane was washed twice with tris-buffered saline (TBS) containing 0.1% Tween 20 (TBST). After blocking with TBST containing 5% nonfat milk for 40 min, the membrane was incubated with the primary antibody (1:1000 dilution) in TBST-1% nonfat milk at 4 °C overnight. After treatment with the primary antibody, the membrane was washed three times with TBST for a total of 15 min, followed by goat antirabbit or antimouse IgG−horseradish peroxidase conjugates (diluted 1:3000) for 1 h at room temperature and was washed three times with TBST for a total of 1 h. The immunoblots were visualized by enhanced chemiluminescence.

Transient Transfection. The constitutively active Akt construct HA-PKB-T308D/S473D was kindly provided by Dr. Brain Hemmings (Friedrich Miescher Institute, Basel, Switzerland). PC-3 cells were seeded into T-75 flasks (1.5×10^6/flask). Aliquots containing 3 μg of each plasmid or a control pcDNA3.1(+) vector in 750 μL of Opti-MEM medium (Invitrogen-Life Technologies, Inc.,) were incubated with 9 μL of FuGene 6 reagent (Roche Diagnostics Corp., Indianapolis, IN) for 15 min. Each flask was washed with Opti-MEM medium and then received the plasmid−FuGene 6 mixture and 4 mL of Opti-MEM medium. The flask was placed in a CO_2 incubator for 4 h, and the transfection medium was replaced with 10% FBS-supplemented RPMI 1640. After 24 h, Mock- and Akt-transfected PC-3 cells were seeded into 96-well plates at 5000 cells/well in 10% FBS-supplemented RPMI 1640. On the next day, cells were treated in four replicates with the indicated concentrations of OSU-03012 in 1% FBS-containing medium for 24 h. An MTT assay was used to determine the cell viability.

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Supporting Information Available: Elemental analysis data for compounds **1**−**46**. This material is available free of charge via the Internet at http://pubs.acs.org.

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