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Identification of CKD-516: A Potent Tubulin Polymerization Inhibitor with Marked Antitumor Activity against Murine and Human Solid Tumors

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Tubulin polymerization inhibitors had emerged as one of promising anticancer therapeutics because of their dual mechanism of action, i.e. apoptosis by cell-cycle arrest and VDA, vascular disrupting agent. VDAs are believed to be more efficient, less toxic, and several of them are currently undergoing clinical trials. To identify novel tubulin inhibitors that possess potent cytotoxicity and strong inhibition of tubulin polymerization as well as potent in vivo antitumor efficacy, we have utilized benzophenone scaffold. Complete SAR analysis of newly synthesized analogues that were prepared by incorporation of small heterocycles (C2, C4, and C5 position) into B-ring along with the evaluation of their in vitro cytotoxicity, tubulin polymerization inhibition, and in vivo antitumor activity allowed us to identify **22** (S516). Compound **22** was found to have potent cytotoxicity against several cancer cells including P-gp overexpressing MDR positive cell line (HCT15). It also induced cell cycle arrest at G_2/M phase, which is associated with strong inhibition of tubulin polymerization. Its in vivo efficacy was improved by preparing its (L)-valine prodrug, **65** (CKD-516), which together with greatly improved aqueous solubility has shown marked antitumor efficacy against both murine tumors (CT26 and 3LL) and human xenogratfs (HCT116 and HCT15) in mice.

Introduction

Microtubules are long, filamentous, tube-shaped protein polymers that play a crucial role in the development and maintenance of cell shape such as transportation of vesicles and protein complexes, sustained shape, and regulation of motility and cell division. Microtubules consisting of tubulin heterodimers that polymerize parallel to a cylindrical axis with length of several micrometers are extremely important in the process of mitosis during which microtubules are at their highest dynamic instability during spindle formation and separation of chromosomes.[1]

Disruption of microtubules can induce cell cycle arrest in G_2-M phase and formation of abnormal mitotic spindles. Their importance in mitosis and cell division makes microtubules an attractive target for anticancer drug discovery. A number of naturally occurring compounds such as paclitaxel, epothilones, vinblastine, combretastatin A4 (CA-4), and colchicines exert their effect by changing dynamics of tubulin polymerization and depolymerization.

Microtubule targeted compounds can be classified into two main groups. One group is microtubule-stabilizing agents which stimulate microtubule polymerization and include paclitaxel, docetaxel, and epothilones.[2] The second group, known as the microtubule-destabilizing agents, inhibits microtubule polymerization and includes *Vinca* alkaloids, colchicines, and combretastatins and other synthetic analogues.[3]

In addition to their ability to inhibit microtubule dynamics by inhibiting tubulin polymerization, tubulin binders also target tumor endothelial cells, which results in a rapid occlusion of tumor vasculature, leading to vascular shutdown (known as vascular disrupting agents, VDA[a]).[4] VDAs act by destroying the endothelium of solid tumors resulting in the tumor death from the lack of oxygen and nutrients leading to tumor cell ischemia and necrosis. VDA differentiates from the conventional angiogenesis inhibitor as the latter inhibits the formation of new blood vessels while VDAs selectively target pre-existing tumor vasculature. VDAs such as DMXAA,[4a,b] CA-4P, and **66** (AC7700) are believed to be more efficient, less toxic, and several of them are currently undergoing clinical trials (Chart 1).

CA-4,[5] a naturally occurring stilbene derived from the South African tree *Combretum caffrum*, inhibits tubulin polymerization and shows a potent cytotoxicity against a broad spectrum of human cancer cell lines. Moreover, CA-4 has been demonstrated to elicit shutdown of blood flow to cancer cells and CA-4P, a water-soluble prodrug of CA-4 is in several phase 3 clinical trials.

Another potent tubulin polymerization inhibitor, **66** (AC7700 or AVE8062),[6] is the serine prodrug of **67** (AC7739), which was found to have more potent cytotoxicity

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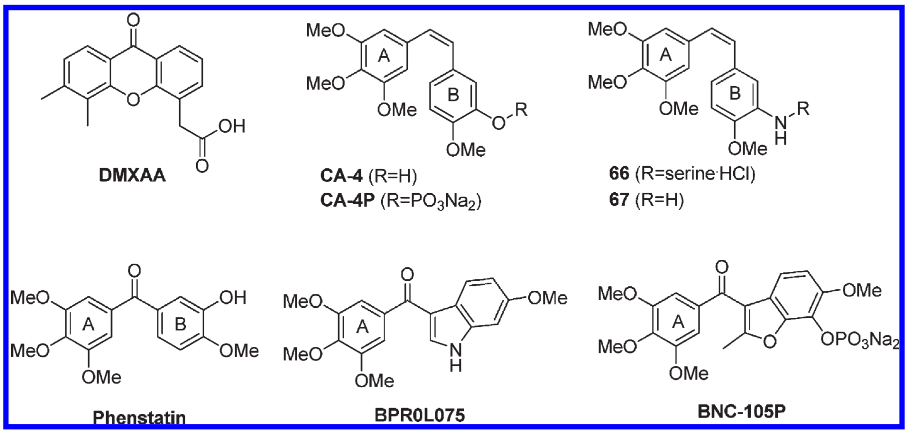
[a] Abbreviations: VDA, vascular disrupting agent; CA-4P, combretastatin A-4 monophosphate; PET, positron emission tomography; FDG, fluorodeoxyglucose; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; IR, inhibition ratio; P-gp, P-glycoprotein; MDR, multidrug resistance.

Chart 1. Known Tubulin Inhibitors and DMXAA



and antivascular activities compared with CA-4P and causes shape changes in proliferating endothelial cells, rapid shutdown of tumor blood flow, and extensive necrosis in experimental tumor models. Compound **66** is currently undergoing several phase 3 clinical trials for the treatment of solid tumors.

Benzophenone derivatives represented by phenstatin have been found to be potent cytotoxic agents comparable to CA-4.[7] Stilbene analogues such as CA-4P and **66** strictly require *cis* configuration, however, it was claimed that they are prone to isomerization during storage and administration[7a] and in the course of metabolism in liver microsomes. Benzophenone analogues have several advantages including no need of controlling the geometric selectivity as well as ease of synthesis for increased potency, stability and aqueous solubility. It was also suggested that the sp^2-hybridized carbonyl group in benzophenone constrains the two aryl rings in a quasi "*cis*" orientation. Recently, similar diarylketones analogues such as BPR0L075[8] and BNC-105P[9] were also reported as potent tubulin polymerization inhibitors (Chart 1).

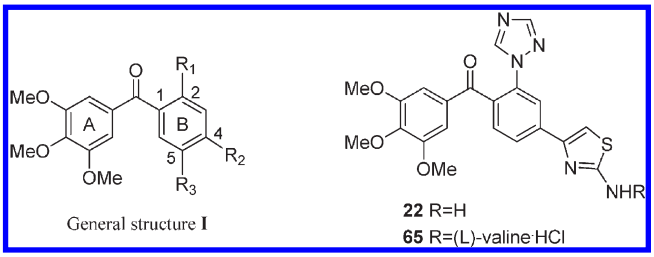
We have been developing anticancer drugs that target tubulin with benzophenone scaffold and this effort was culminated in a discovery of novel tubulin polymerization inhibitor, compound **65** (CKD-516), a valine prodrug of **22** (S516). Compound **22** was modified to **65** to increase water solubility and expected to be released from **65** in vivo by various peptidases. In vitro studies have shown that **22** was more cytotoxic than CA-4P and **66**, and this was further demonstrated in tubulin binding assay and cell cycle arrest. Moreover, **65** has shown marked antitumor efficacy in various human tumor xenograft models, which is superior to CA-4P and **66**. Interestingly, positron emission tomography (PET) imaging showed that **65** blocked the uptake of [^{18}F]-fluorodeoxyglucose (FDG) into tumor tissue in mouse and lasted 48 h after a single administration demonstrating VDA activity.

In this report, we describe complete SAR analysis of novel tubulin polymerization inhibitors, in vitro activity, and in vivo antitumor efficacy studies leading to the identification of **65** that is undergoing phase 1 clinical trial.

Results and Discussion

Design Strategy. Although combretastatin analogues such as CA-4P and **66** now progressed to phase 3 clinical trials for the treatment of various solid tumors, they have some limitations in terms of chemical structure as mentioned before. It needs tedious purification steps during the synthesis to separate *cis* isomer that is required for strong inhibition of cancer cell growth from *trans* isomer that has substantially low activity.[12]

Chart 2. Modification of B-Ring of Phenstatin

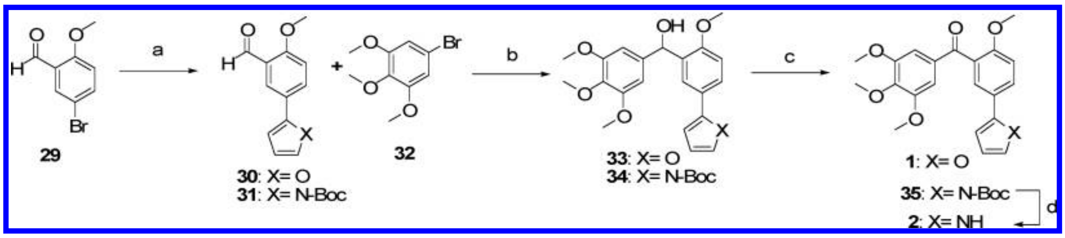


To overcome this, several groups have reported benzophenone derivatives as mimetics of combretastatin as sp^2-hybridized carbonyl group constrains the two aryl rings in a quasi *cis* orientation (structure I, Chart 2). Phenstatin, a representative benzophenone with same substituent patterns in B-ring as CA-4, was 2−10-fold less active in tumor cell growth inhibition. Liou et al reported that 2-amino or 3-aminobenzophenones with methoxy group at C4 or C5 position were more potent than phenstatin and CA-4P against several human cancer cell lines.[7a,b] In 2-aminobenzophenones,[7a] simple analogues where methoxy or dimethylamino group were substituted at C4, C5, or C6 positions were prepared, and it was found that there was only a slight difference in cytotoxic activity regardless of the position of methoxy group at C4 or C5, whereas C6 substitution abolished the cytotoxic activity. The inactivity of 4,5-dimethoxy analogue and 5,6-dimethoxy analogue led them to conclusion that bulky substituents on the B-ring are detrimental to activity. Similar trend was observed in 3-aminobenzophenone series,[7b] where C4 substitution was more preferable to C5 substitution and bulkier groups were not tolerated either.

In all cases, 2- or 3-amino group played an integral role for maximal cytotoxicity, however, no in vivo antitumor efficacy study has been reported for benzophenone series. We envisioned that a viable clinical candidate could be obtained within benzophenone series through systematic variation of B-ring by introducing more diverse functional groups, especially heteroaromatic groups, thereby improving cytotoxicity and other pharmacological properties such as metabolic stability, aqueous solubility, and permeability among others.

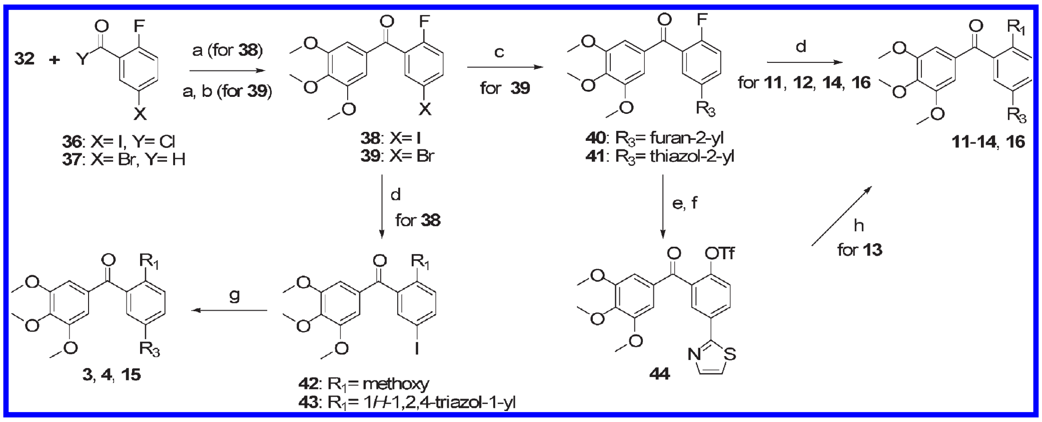
Although 2-or 3-amino benzophenone derivatives were highly cytotoxic, we realized that aminophenyl in B-ring is a potential toxicity liability because its quinone adduct formation is highly likely[13] thus hampering its use in clinical

Scheme 1. Synthesis of 2,5-Disubstituted Benzophenones (Method A)[a]



[a] Reagents and conditions: (a) R_3-$B(OH)_2$, Na_2CO_3, Pd(dppf)Cl_2, DME/H_2O v/v 3:1, reflux, 24 h, 26%, 39%; (b) *n*-BuLi, THF, −78 °C to rt or I_2 (cat.), Mg, THF, rt, 27%, 48%; (c) PCC or PDC, 4 Å molecular sieve, CH_2Cl_2, rt, 3 h, 25%, 61%; (d) TFA (excess), CH_2Cl_2, 4 h, 19%.

Scheme 2. Synthesis of 2,5-Disubstituted Benzophenones (Method B)[a]



[a] Reagents and conditions: (a) I_2 (cat.), Mg, THF, rt, 61%, 57%; (b) PDC, 4 Å molecular sieve, CH_2Cl_2, rt, 80%; (c) R_3-$B(OH)_2$, Na_2CO_3, Pd(dppf)Cl_2, DME/H_2O v/v 3:1, reflux, 24 h, 74% or R_3-ZnBr, Pd(PPh_3)$_4$, THF, 6 h, 47%; (d) CH_3ONa, CH_3OH, reflux, 3 h, 66% or R_1-azole, K_2CO_3, DMF, heating, 23−62%; (e) NaH, 2-(methylsulfonyl)ethanol, DMF, 0 °C to rt, 6 h, quant; (f) (TfO)$_2$O, pyridine, CH_2Cl_2, 0 °C to rt, 5 h, 73%; (g) R_3-$SnBu_3$, Pd(PPh_3)$_2Cl_2$, THF, reflux, 3 h, 67%, 17% or R_3-$B(OH)_2$, Na_2CO_3, Pd(dppf)Cl_2, DME/H_2O v/v 3:1, 130 °C, 15 min, microwave, 57%; (h) R_1-$B(OH)_2$, Na_2CO_3, Pd(dppf)Cl_2, DME/H_2O, v/v 3:1, sealed tube, 130 °C, 33%.

setting. In previous reports of benzophenones,[7a,b] B-ring modifications were limited to amino, hydroxy, chloro, and small alkoxy groups. Moreover, bulky groups in B-ring were not tolerated in most cases, as methoxy and ethoxy gave similar potency and further increase in the bulkiness of alkoxy resulted in sharp decrease in cytotoxicity, which is also observed in CA-4 analogues.[14] However, in our preliminary studies, several heteroaromatic groups were successfully introduced into B-ring without compromising cytotoxicity. Herein we describe our efforts to identify novel benzophenone analogues that possess potent cytotoxicity and strong inhibition of tubulin polymerization as well as desirable PK properties and in vivo antitumor activity.

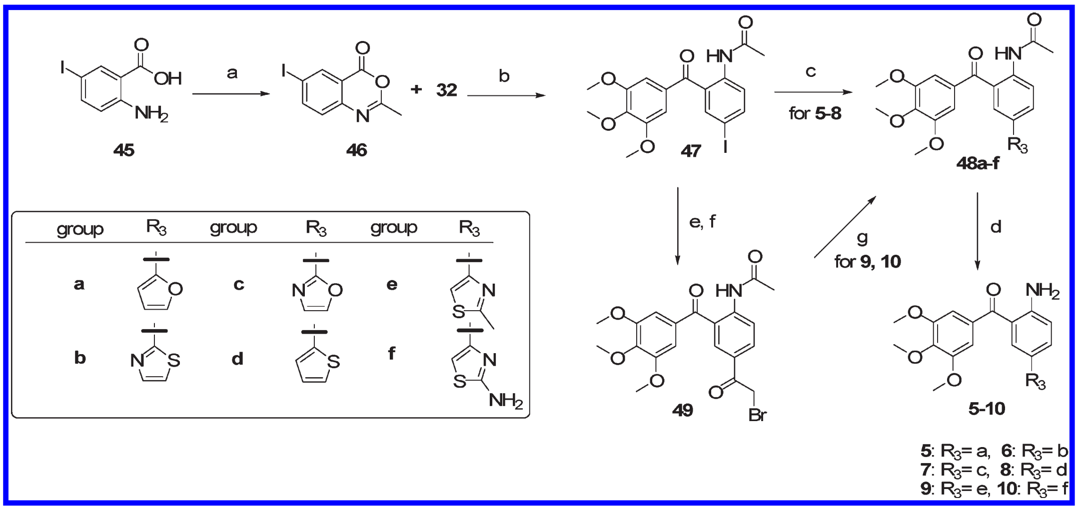
Chemistry. Several different approaches were employed depending on the substitution position in B-ring. The preparation of 2-methoxy substituted compounds (**1**, **2**) is shown in Scheme 1. Appropriate aldehydes (**30**, **31**), which were prepared by Suzuki coupling (Pd(dppf)Cl_2, DME/H_2O = 3/1, reflux) of **29** and suitable boronic acids, were subjected to condensation with lithiated **32** to give benzyl alcohols (**33**, **34**). Then, oxidation of benzhydrols with PCC or PDC provided the desired compounds with additional deprotection of Boc in the case of 2-pyrrole.

Other 2,4-disubstituted analogues were prepared according to Scheme 2. Grignard reaction of (3,4,5-trimethoxyphenyl)magnesium bromide (0 °C, overnight) with **37** followed by PDC oxidation (4 Å molecular sieve, CH_2Cl_2) yielded **39**, while compound **38** was directly synthesized from acid chloride (**36**). Next, two different reaction sequences were used depending both on R_1 and R_3. Starting from **39**, R_3 was first introduced by Suzuki (furyl-2-$B(OH)_2$) or Negishi coupling (thiazol-2-ZnBr, Pd(Ph_3P)$_4$/THF, THF, 6 h) under reflux condition to give **40** and **41**, which were reacted with suitable azoles in the presence of potassium carbonate in DMF to provide **11**, **12**, **14**, and **16**, respectively. In the case of **13**, Suzuki reaction of pyrimidinyl-5-boronic acid with **44** was employed, where **44** was prepared by two-step synthesis from **41**, i.e. fluoride was displaced to hydroxyl group with 2-(methylsulfonyl)ethanol/NaH[10] then triflate formation (Tf_2O/pyridine). Alternatively, starting from **38**, R_1 was first introduced by substitution reaction with either NaOMe (**42**) or 1,2,4-triazole (**43**), followed by Stille coupling (thiazole-2-$SnBu_3$ and oxazole-2-$SnBu_3$, Pd(PPh_3)Cl_2, THF, reflux) or Suzuki coupling (furyl-2-$B(OH)_2$) under microwave condition (130 °C, 15 min) to provide **3**, **4** and **15**, respectively.

The synthesis of 2-amino substituted analogues is depicted in Scheme 3. The known intermediate **46**[11] was reacted with Grignard reagent (3,4,5-trimethoxyphenyl)magnesium bromide to give **47**. Palladium catalyzed coupling of **47** with appropriate boronic acids or zinc bromide (thiazol-2-ZnBr) afforded **48a−d**, then final C2 amino substituted compounds (**5−8**) were obtained by deacetylation. Alternatively, **47** was converted to **49** by two steps (palladium coupling with tributyl(1-ethoxyvinyl)tin, followed by bromination with NBS), which was condensed with thiourea or thioacetamide in refluxing ethanol followed by removal of acetyl group to provide thiazole derivatives **9** and **10**, respectively.

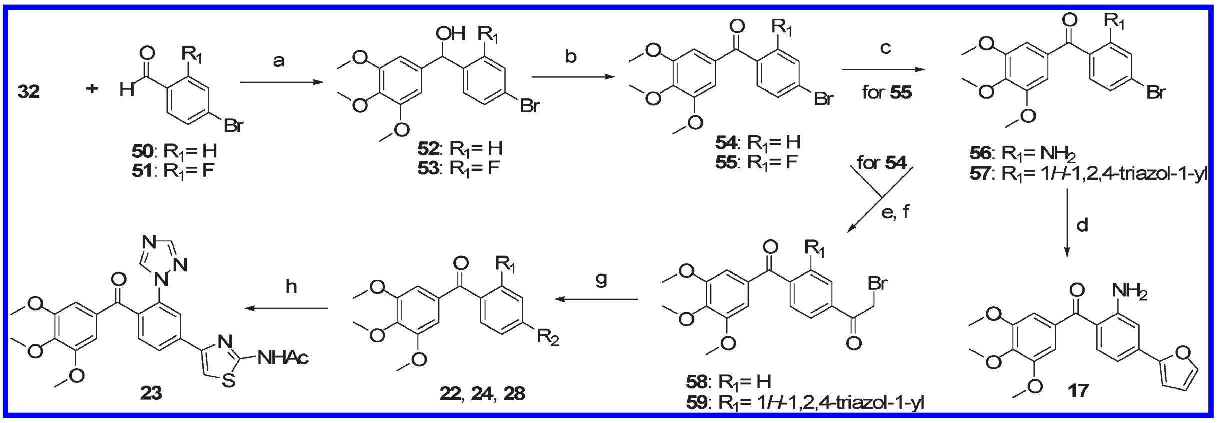
Similar synthetic methods were employed for the synthesis of C4-substituted analogues as depicted in Scheme 4. Key intermediates (**54**, **55**) were prepared according to the same

Scheme 3. Preparation of 2-Aminobenzophenones[a]



[a] Reagents and conditions: (a) Ac_2O, heating, 4 h; (b) I_2 (cat.), Mg, THF, rt, overnight, 16%; (c) R_3-$B(OH)_2$, Na_2CO_3, $Pd(dppf)Cl_2$, DME/H_2O, v/v 3:1, reflux, 24 h, 60% or R_3-ZnX, $Pd(PPh_3)_4$, THF, 24 h, X = Br, Cl, 46−67%; (d) CH_3ONa, CH_3OH, reflux, 35−88%; (e) tributyl (1-ethoxy vinyl)tin, $Pd(PPh_3)_2Cl_2$, THF, reflux, 6 h, 83%; (f) NBS, THF/H_2O v/v 1:1, 64%; (g) thiourea or thioacetamide, EtOH, reflux, 76%, 90%.

Scheme 4. Synthesis of 2,4-Disubstituted Benzophenones (Method A)[a]



[a] Reagents and conditions: (a) I_2 (cat.), Mg, THF, rt, 99%, 58%; (b) PDC, 4 Å molecular sieve, CH_2Cl_2, rt, 82%, 47%; (c) aq NH_4OH, IPA, 145 °C, sealed tube, 65% or 1, 2, 4-triazole, K_2CO_3, DMF, 130 °C, 12 h, 57%; (d) R_2-$B(OH)_2$, Na_2CO_3, $Pd(dppf)Cl_2$, DME/H_2O v/v 3:1, reflux, 24 h, 45%; (e) tributyl (1-ethoxy-vinyl)tin, $Pd(PPh_3)_2Cl_2$, THF, reflux, 6 h, 69%, 55%; (f) NBS, THF/H2O v/v 3:1, 31%, 75%; (g) thiourea or thioacetamide, EtOH, reflux, 48−96%; (h) AcCl, pyridine, CH_2Cl_2, rt, 12 h, 32%.

procedures as in Scheme 2 (Grignard reaction and PDC oxidation) starting from two aldehydes (**50**, **51**). Displacement of fluoride in **55** with amino group (aq NH_4OH, sealed tube, 145 °C) and following Suzuki coupling reaction (furyl-2-$B(OH)_2$) afforded **17**. Alternatively, reaction of **55** with 1,2,4-triazole (K_2CO_3, DMF, 130 °C) gave **57**, which was further manipulated with two-step sequences by the same procedure as in the synthesis of **50**, leading to the synthesis of **59**. Similarly, **58** was obtained starting from **54** that bears no substitution at C2. The resulting C4-bromoacetyl group of **59** was condensed with thioacetamide or thiourea (ethanol, reflux) to give **22** and **24**, respectively, and **23** was prepared by acetylation of **22**. Starting from **58**, the same sequence of reaction as in the synthesis of **22** (thioacetamide) afforded **28**.

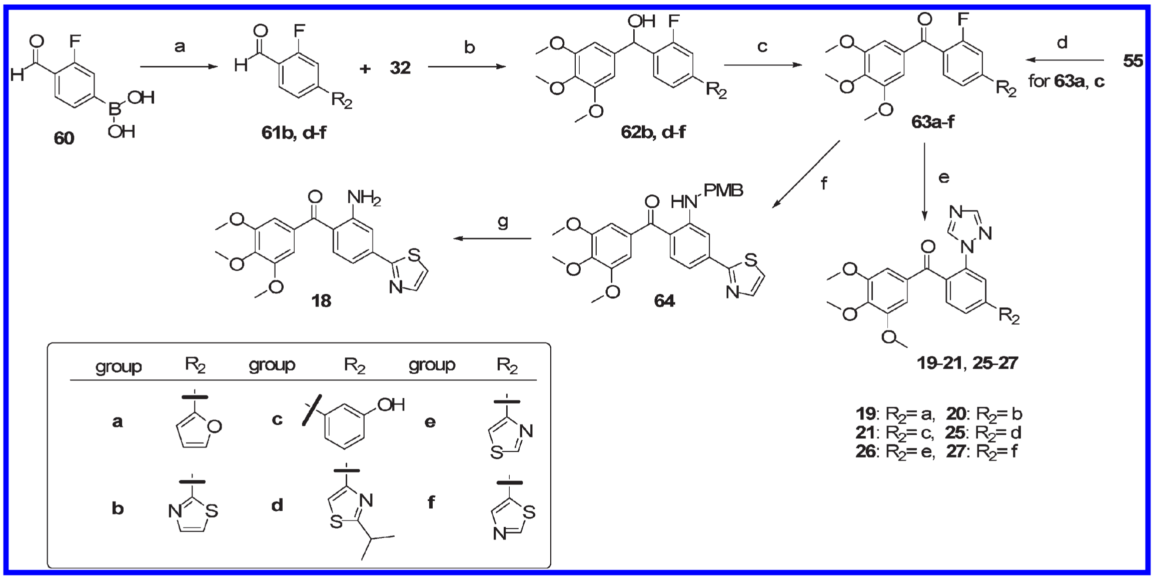
In Scheme 5, R_2 group was incorporated initially, that is, suitable aldehydes (**61b**,**d−f**) were prepared through Suzuki coupling reaction of boronic acid (**60**) with bromo containing heterocycles. Then, each aldehydes were subjected to two-step reaction sequences (Grignard reaction with **32** followed by PDC oxidation) to provide key intermediates **63b**, **63d−f**. Intermediate (**55**) synthesized in Scheme 4 was used as starting material to provide **63a**, and **63c** by Suzuki coupling reaction with suitable boronic acids. Introduction of 1,2,4-triazole group into **63** (except **63b**) led to the synthesis of final compounds (**19−21** and **25−27**).

Alternatively, reaction of **63b** with *p*-methoxybenzyl amine (K_2CO_3, DMF, 130 °C) gave **64**, which was deprotected under acidic condition (TFA, 0 °C) to afford **18**.

The synthesis of (L)-valine prodrug **65** was depicted in Scheme 6. Initial attempt of direct coupling of **22** with Fmoc-valine using various coupling reagents (e.g., DCC, EDC, HBTU) proved to be very inefficient and low yielding. Therefore, Fmoc-valine was first converted to corresponding acid chloride, then reacted with **22** under basic condition at low temperature (DIPEA, CH_2Cl_2, 0 °C, 60%). Finally, **65** was prepared by Fmoc deprotection (piperidine, CH_3CN, rt), followed by HCl (MeOH) treatment in quantitative yield.

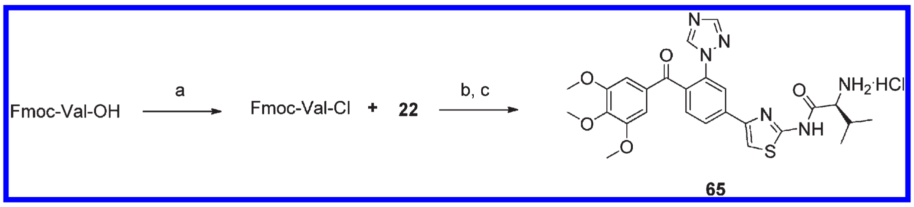
In Vitro Cell Growth Inhibition Assay. The synthesized compounds were initially screened for their cytotoxic activities against human leukemia cell lines (HL60) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The IC_{50} values represent the compound concentrations

Scheme 5. Synthesis of 2,4-Disubstituted Benzophenones (Method B)[a]



[a] Reagents and conditions: (a) R_2Br, Na_2CO_3, $Pd(dppf)Cl_2$, DME/H_2O v/v 3:1, reflux, 24 h, 56−93%; (b) I_2 (cat.), Mg, THF, rt, 32−22%; (c) PDC, 4 Å molecular sieve, CH_2Cl_2, rt, 89−56%; (d) R_2-$B(OH)_2$, Na_2CO_3, $Pd(dppf)Cl_2$, DME/H_2O v/v 3:1, reflux, 24 h, 62%, 71%; (e) sodium 1,2,4-triazole, DMF, 130 °C, 12 h, 38−30%; (f) $PMBNH_2$, K_2CO_3, DMF, 130 °C, 5 h, 75%; (g) TFA, 0 °C to rt, 6 h, 62%.

Scheme 6. Preparation of Compound **65**[a]



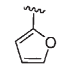
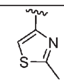
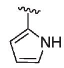
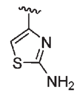
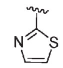
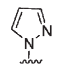
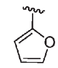
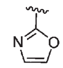
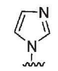
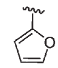
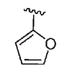
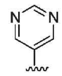
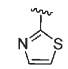
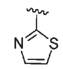
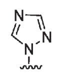
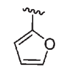
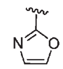
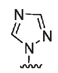
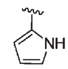
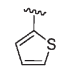
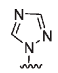
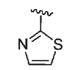
[a] Reagents and conditions: (a) DMF (cat.), $SOCl_2$, CH_2Cl_2, reflux; (b) DIPEA, pyridine, CH_2Cl_2, 0 °C to rt, overnight, 85%; (c) piperidine, CH_3CN, rt, 71%, then HCl (MeOH).

requiring in 50% decrease in cell proliferation after 3 days of incubation. On the basis of published reports[15] and our own preliminary study, we decided to probe the effect of substitutions at C4 or C5 in B-ring while R_1 group is maintained (i.e., disubstitution) with small group because C2,C4,C5-trisubstituted analogues pose no advantage in terms of cytotoxic activity and ease of synthesis. Since it is well-known that a trimethoxy group in the A-ring is essential for activity, most of compounds prepared in this study retain the trimethoxy group in A-ring. CA-4 and **67** were included for comparison. The effect of substitutions at both C2 (R_1) and C5 (R_3) was shown in Table 1.

We first evaluated the effect of simple C2-methoxy and C2-aminobenzophenones with a variety of heteroaromatic groups introduced (**1**−**10**) at C5. In the case of 2-furyl group, slight cytotoxicity reduction was observed irrespective of C2 groups (**1** vs **5**) compared to reference compounds. A further decrease in cytotoxicity was observed with 2-pyrrole (**2**) and 4-thiazoles (**9** and **10**), showing 10-fold less activity than **67**. In contrast, introduction of 2-thiazole (**3** and **6**) and 2-oxazole (**4** and **7**) restore activity which is comparable to **67**. A number of other analogues where C2 amino group was modified (e.g., amide, sulfonamide, carbamate, and *N*-alkylation etc) were prepared, however, all of them exhibited substantial loss of activity (data not shown). Because suitable aqueous solubility is crucial in developing drugs for intravenous injection, we next explored the effect of C2 variations to improve overall property by introducing nitrogen containing heterocycles. With 2-furyl group at C5, both pyrazole (**11**), imidazole (**12**), and 1,2,4-triazole (**14**) substitution resulted in reduced activity compared to C2 methoxy and C2 amino analogues (**1** and **5**). Introduction of a 6-membered ring (5-pyrimidine at C2) with 2-thiazole at C5 (**13**) resulted in slightly lower activity (**3**) or similar activity (**6**). However, with 1,2,4-triazole at C2, there was a slight improvement in potency when 2-pyrrole (**15**) and 2-thiazole (**16**) were introduced. It is interesting to note that cytotoxicity of compound **16** with 1,2,4-triazole group at C2 was similar to C2 amino compound (**3**), indicating a tolerance of bulkier group at C2 position. By varying C5 with heteroaromatics, we were able to synthesize many potent compounds while keeping simple methoxy or amino at C2 (**1**−**10**). Moreover, it appeared that additional substitution at C2 with nitrogen containing heterocycles (**11**−**16**) looks promising for improved overall property, such as aqueous solubility by potential salt formation.

In an effort to obtain better potency, we next probed the effect of C4 substitutions (Table 2). Unexpectedly, compound **17**, in which 2-furyl group was attached at C4 with C2 amino group, resulted in 9-fold loss of cytotoxicity in comparison to C5 analogue (**5**). This trend was also observed in **18** where the activity was decreased more than one order of magnitude compared with compound **6**. This result indicates that a positional change can cause a dramatic effect on activity. Given that 1,2,4-triazole at C2 gave promising results in case of C5 variation, we decided to maintain this

Table 1. Inhibitory Effect of Benzophenones (I) on Proliferation of HL60 Cell Line with R_1 and R_3 variations[a]

compd	R_1	R_3	IC_{50} (nM)	compd	R_1	R_3	IC_{50} (nM)
1	MeO		38.2±3.7	**9**	NH_2		166±15.7
2	MeO		105±7.8	**10**	NH_2		108±51.1
3	MeO		12.0±1.7	**11**			204±35.8
4	MeO		16.2±2.5	**12**			110±16.9
5	NH_2		55.4±4.7	**13**			73.4±12.7
6	NH_2		20.8±10.5	**14**			105±47.0
7	NH_2		11.8±4.9	**15**			41.7±14.5
8	NH_2		48.5±12.6	**16**			32.0±1.6
CA-4			4.0±1.0	**67**			12.0±1.8

[a] R_2 = hydrogen. IC_{50} values are average of at least three determinations.

group while changing C4 substitutions with heterocycles. When 1,2,4-triazole was introduced instead of an amino group in **17** and **18**, cytotoxicity were slightly improved (**19** and **20**) although it is still inferior to **67** and CA-4. No beneficial effect was noted with C4 phenol group (**21**).

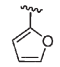
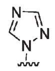
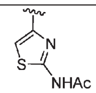
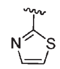
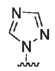
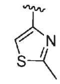
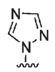
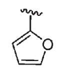
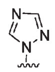
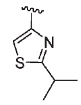
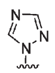
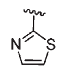
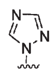
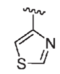
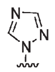
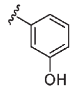
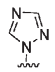
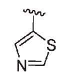
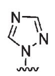
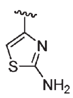
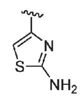
It is of special note that 2-amino-4-thiazole analogue (**22**) showed a remarkable improvement in cytotoxicity that was 3-fold more potent than **67** and was comparable to CA-4, presenting the most potent in our series. Acetylation resulted in substantial loss of activity (**23**), implying the steric limit at this position, which is also manifested with compounds **24** (2-methyl-4-thiazole) and **25** (2-isopropyl-4-thiazole), where complete loss of activity was noted in **25** (IC_{50} > 1 μM). Deletion of amino moiety of 4-thiazole in **22** (compound **26**) had a negative effect on activity, and this implies that amino moiety in thiazole group plays a crucial role in imparting cytotoxicity. There was no difference in activity between 4-thiazole and 5-thiazole (**26** vs **27**). When 1,2,4-triazole at C2 was removed (**28**), it suffered from substantial (> 20-fold) loss of activity. Taken together, an appropriate combination of C2 and C4 substitutions were necessary for potent cytotoxicity. In addition, compound **22** would present further advantage that amino moiety in 4-thiazole group may be able to form salts for improving aqueous solubility (vide infra).

In Vivo Antitumor Activity in Murine Model. Compounds that showed potent in vitro cytotoxicity were tested for in vivo antitumor activity in murine Lewis lung cancer, 3LL (Table 3). Preliminary results showed that ip administration of test compounds every 4 days (Q4D) gave the best results, thus this schedule was routinely used with few exceptions (e.g., **16**). CA-4P and **66** was included for comparison, however, CA-4P showed marginal activity even at highest dose with inhibition ratio (IR) = 40% at 100 mg/kg and on more frequent dose (Q2D) while **66** significantly inhibited tumor growth (IR = 55% at 80 mg/kg). Most compounds induced dose-dependent tumor growth inhibition, while compound **18** showed no activity, correlating well with its low in vitro cytotoxicity. Some analogues, although potent in vitro, failed to show any appreciable in vivo antitumor activity such as **7** (IR ~40%) and **4** (data not shown), indicating the importance of suitable physicochemical properties.

It is interesting to note that strong tumor growth inhibition was generally observed with thiazole substitution either at C4 or C5 (e.g., **3**, **6**, **9**, **20**, and **22**). For instance, compounds **6** (2-thiazole) and **7** (2-oxazole) exhibited quite different tumor growth inhibition (IR = 47% vs 19%, respectively, at 10 mg/kg), although their in vitro activities are very close. With 2-thiazole group, different in vivo profiles were noted depending on its substitution position (C4 vs. C5), as compound **20** showed slightly better in vivo activity than **16** despite its 3-times lower in vitro cytotoxicity. The body weights of these mice were not significantly affected showing the similar change with control groups at these doses. In the following study in human LX-1 lung cancer and CX-1 colon cancer mouse xenografts with selected compounds that showed potent efficacy in the murine model, compound **22** was found to have promising antitumor activity (IR > 65%) while other compounds showed marginal efficacy (IR < 30%), thus **22** was chosen for further evaluations.

In Vitro Characterization of Compound 22. Before further in vivo study, **22** was evaluated against several other cancer lines including HCT15, a P-glycoprotein (P-gp) overexpressing

Table 2. Inhibitory Effect of Benzophenones (I) on Proliferation of HL60 Cell Line with R_1 and R_2 Variations[a]

compd	R_1	R_2	IC_{50} (nM)	compd	R_1	R_2	IC_{50} (nM)
17	NH_2		477±56.0	**23**			130±32.1
18	NH_2		384±63.5	**24**			104±21.1
19			80.4±15.5	**25**			1,010±355
20			96.2±10.2	**26**			57.1±24.1
21			255±35.4	**27**			60.4±12.4
22			4.8±0.1	**28**	H		107±12.6
CA-4			4.0±1.0	**67**			12.0±1.8

[a] R_3 = hydrogen. IC_{50} values are average of at least three determinations.

Table 3. Antitumor Activities of Selected Compounds in Murine Tumor Model[a]

compd	doses (mg/kg)	IR (%)[b]	schedule
3	5	54**[d]	Q4D
	10	80**[d]	
6	5	25	Q4D
	10	47*[c]	
	20	67**[d]	
7	10	19	Q4D
	20	40	
9	20	30	Q4D
	40	60**[d]	
16	40	23	2 × /week
	80	50**[d]	
18	40	19	Q4D
	80	7	
20	50	39*[c]	Q4D
	100	58**[d]	
22	5	32*[c]	Q4D
	10	63**[d]	
CA-4P	50	20	Q2D
	100	40*[c]	
66	40	48**[d]	Q4D
	80	55**[d]	

[a] Mice bearing 3LL lung cancer were dosed ip with vehicle or test compounds on schedules specified. All data are expressed as mean values ($n = 7$ per group). [b] IR (%) = $(1 - T/C) \times 100$; T, tumor volume (treated); C, tumor volume (untreated). [c] *$p < 0.05$. [d] ** $p < 0.01$.

Table 4. Cancer Cell Growth Inhibition and Inhibition of Tubulin Polymerization by **22**[a]

	cytotoxicity, IC_{50} (nM)			antitubulin activity[b]
compd	HL-60	HCT116	HCT15[c]	IC_{50} (μM)
22	4.8 ± 0.1	42.8 ± 17.9	24.9 ± 2.7	4.29 ± 2.18
67	12.0 ± 1.8	269 ± 39.8	45.2 ± 14.6	6.50 ± 1.02
doxorubicin	81.0 ± 3.6	ND	> 1000	N/A

[a] ND: not determined. N/A: Not applicable. IC_{50} values are average of at least three determinations. [b] This was performed at 37 °C and turbidity were read at 340 nm for 1 h. [c] P-gp overexpressing cell line.

cell line following the same protocol described above together with **67** and doxorubicin as reference compounds (Table 4). The cytotoxicity of **22** were consistently better (3−6-fold) than **67** in all cell lines including HCT15, a P-gp overexpressing multidrug resistant (MDR) positive cell line, where it was highly resistant to doxorubicin (IC_{50} > 1000 nM).

To investigate whether the inhibition of cancer cell proliferation of **22** was associated with the microtubule system, its in vitro polymerization inhibitory activity was measured. The polymerization of purified tubulin at 37 °C in the presence of test compounds or DMSO control was monitored spectrophotometrically. Indeed, **22** inhibited tubulin polymerization in a concentration-dependent manner with an IC_{50} of 4.3 μM, which is slightly better than **67** (IC_{50} = 6.5 μM, Table 4). The IC_{50}s of tubulin polymerization are much higher than those required for cytotoxicity, and this phenomenon is well documented in the literature.[3d,5a] Several other compounds in Tables 1 and 2 were also found to inhibit tubulin polymerization, and these inhibition correlated well with their cell cytotoxicity (data not shown). The effect of **22** on the cell cycle was measured by flow cytometry against HL60 cells after 16 h. At 30 nM, **22** caused significant arrest of cells at the G_2/M phase relative to the untreated control (70% with **22** vs 12% with control), resulting in apoptosis with concomitant loss of G_0/G_1 phase.

Amino Acid Prodrugs of 22 to Improve Water Solubility. To be developed as a parenteral drug, a compound should have sufficient aqueous solubility,[16] as can be found in CA-4P[5] (sodium phosphate) and **66**[6] (serine·HCl). Because compound **22** had low solubility (< 100 μg/mL), we were looking at possible ways to improve aqueous solubility. Initially, salt formation approach of 2-amino moiety of thiazole group in **22** was tried but was not successful. Although several strong acids (HCl, H_2SO_4 etc) were able to form salts, they were dissociated quickly once dissolved in water due to low basicity of amino moiety. Next, an amino acid prodrug[17] was pursued as this approach was quite successful in the case of **66**, a serine prodrug of **67** (Chart 1). Thirteen amino acid prodrugs (as hydrochloride salts) were prepared according to Scheme 6, and their in vitro cytotoxicity (HL60) ranged between 50 and 100 nM, reflecting effective cleavage in vitro. The amide bonds in these prodrugs were expected to be cleaved to release **22** in vivo through the action of various peptidases present in plasma. However, in vivo cleavage characteristics of prodrugs could not be predicted precisely in vitro, all prodrugs were subjected to in vivo antitumor efficacy study (CX-1 or HCT116 xenograft). The L-valine prodrug (**65**, Chart 2) was singled out from this study with strong inhibition of tumor growth (IR = 64−88%), which is comparable to its parent compound **22**, whereas other analogues were found to have marginal activity indicating different pharmacokinetics with different amino acids.[18] Moreover, **65** (as hydrochloride salt) was found to have substantial aqueous solubility (930 mg/mL, deionized water) as expected.

Table 5. Inhibition of Human Tumor Xenografts Growth by **65**[a]

	HCT116			HCT15		
compd	dose (mg/kg)	BW change (%)	IR (%)	dose (mg/kg)	BW change (%)	IR (%)
control		−0.6			+3.4	
65	5	−2.0	36	5	+1.8	12
	10	+1.8	65**[b]	10	+6.6	69**[b]
66	100	−5.2	57**[b]	80	+5.5	66**[b]
paclitaxel		N/A		50		na

[a] Nude mice bearing HCT116 or HCT15 xenografts were dosed ip with vehicle or test compounds on a Q4d × 4 schedule. All data are expressed as mean values (n = 7 per group); N/A, not applicable; na, no activity. [b] **, $p < 0.01$.

In Vivo Antitumor Activity of 65 in Human Xenografts Model. With a substantial improvement of aqueous solubility, **65** was studied in more detail against murine and human xenografts models. The valine prodrug, **65** was expected to have better in vivo efficacy resulting from improved pharmacokinetics due to its increased solubility relative to its parent compound, **22**.[6c,15b] In the murine model, compound **65** induced significant tumor growth inhibition against both CT26 colon cancer (IR = 55% at 10 mg/kg) and 3LL lung cancer (IR = 68% at 10 mg/kg) on Q4D × 4 schedule, which is comparable to or slightly better than parent compound, **22**.

Once its antitumor efficacy was confirmed in murine model, **65** was further evaluated in various human tumor xenografts. Two human colon cancer lines were implanted in nude mice, i.e. HCT116 and HCT15, which is a MDR positive cell line overexpressing P-gp transporter. As shown in Table 5, the growth of HCT116 (IR = 36%, 65% at 5, and 10 mg/kg, respectively, vs 57% at 100 mg/kg of **66**) tumor was significantly inhibited in a dose-dependent manner, with the efficacy comparable to **66** at much lower doses. Drug resistance often develops through the expression of efflux pumps, such as P-gp and other MDR proteins.[19] Notably, **65** also showed potent antitumor activity against MDR positive cell line (HCT15), where paclitaxel was devoid of any efficacy (IR = 12%, 69% at 5, and 10 mg/kg, respectively, vs 66% at 80 mg/kg of **66**). In all cases, body weight changes were not so different from those of control groups, indicating a good tolerance of the compound at doses tested (Figure 1).

Tumor vessels are typically devoid of associated vascular smooth-muscle cells and are more permeable than normal vessels.[20] To assess the ability of **65** as an antivascular agent in nude mice bearing HCT116, PET[4c] was used to monitor

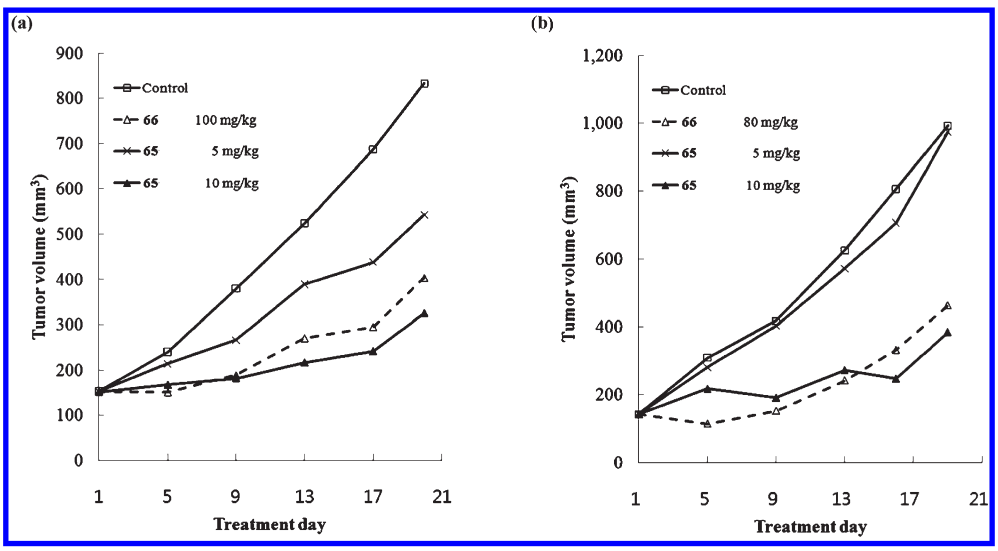


Figure 1. Antitumor activities of **65** in human xenografts. Nude mice bearing (a) human colon HCT116 and (b) human colon overexpressing P-gp transporter, HCT15 were treated when the tumor volumes reached ~150 mm^3 with vehicle control or test compounds (5 mg/kg and 10 mg/kg, ip, Q4D × 4). Compound **66** was used as a reference standard (100 mg/kg in HCT116 and 80 mg/kg in HCT15, respectively). Data are the means of tumor volume (mm^3) at each time point (n = 7 per group). Refer to Table 5 for statistical significances.

directly the vascular flow to tumor tissue. The influx of [^{18}F]-FDG was measured because the flux of this glucose analogue is related to glucose demand and metabolic activity in tissues. A complete reduction of [^{18}F]-FDG uptake into tumor tissue was observed in 4 h and lasted up to 48 h after a single ip administration of **65** (5 mg/kg). More detailed in vivo study, in vivo imaging analysis, and mechanistic aspects of **65** will be the subject of future publications.

Conclusion

To overcome the limitation of known tubulin inhibitors, we undertook the study starting from benzophenone class as this scaffold pose a couple of advantages, i.e. quasi "*cis*" conformation due to a carbonyl group, which is similar to stilbene as found in combretastatins as well as ease of synthesis. A number of analogues were prepared by systematic modification of simple benzophenones (phenstatin etc.) by introduction of small heterocycles at C2, C4, or C5 positions in B-ring with the intention of improving pharmacological properties along with cytotoxicity. In contrast to previous reports that bulky substituents were not tolerable both at C4 and C5 position, our study revealed that several heteroaromatic groups such as thiazole, 2-aminothiazole, triazole, oxazole, pyrrole, and furan were tolerable and in many cases gave far better activity than simply substituted benzophenones, and sometimes better than CA-4P and **66**, most advanced tubulin inhibitors being in phase 3 clinical trials.

Complete SAR analysis of newly synthesized analogues with the evaluation of in vitro cytotoxicity, tubulin polymerization inhibition, and in vivo antitumor activity led us to identify **22**. Compound **22** was found to have potent cytotoxicity against several cancer cell lines (HL60 and HCT116) including P-gp overexpressing MDR positive cell lines (HCT15) with concomitant inhibition of tubulin polymerization. Moreover, its inhibitory activity on tubulin polymerization caused significant arrest of HL60 cells at the G_2/M phase relative to the untreated control with loss of G_0/G_1 phase.

In vivo efficacy of **22** was further improved with amino acid prodrug where 2-amino moiety of C4 thiazole group was modified with L-valine (**65**) by altering its pharmacokinetics in vivo. Indeed, **65** induced significant growth inhibition against murine cancer (e.g., CT26 and 3LL) as well as against human xenografts (e.g., HCT116) in a dose-dependent manner. Often cancer cells acquire resistance through expression of P-gp transporter and it was also found that **65** showed marked antitumor activity against this cell line (HCT15). On the basis of these excellent profiles, **65** has been further evaluated in preclinical toxicology study and now progressed to phase 1 clinical trial.

Experimental Section

General. All chemicals were reagent grade and used as purchased. Moisture sensitive reactions were performed under an inert atmosphere of dry nitrogen with dried solvents. Reactions were monitored by TLC analysis using Merck silica gel 60 F-254 thin layer plates. Flash column chromatography was carried out on Merck silica gel 60 (230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (AVANCE II) at 400 and 100 MHz, respectively. The coupling constant (*J*) are reported in Hz. Identity of compounds were confirmed by recording their mass using LC/MS SL 1100 series (Agilent Technologies), where the MS was operated in positive electrospray ionization mode. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS600 or IT-TOF (Shimadzu) spectrometer (SNU analytical group, Seoul, Korea). Microwave mediated reactions were carried out in a Personal Chemistry (Biotage) microwave synthesizer. Tested compounds were >95% chemical purity as measured by HPLC. All compound tested in vivo were >95% purity. HPLC purity were measured with a reverse-phase HPLC (Kromasil C18, 4.6 mm × 250 mm, 5 μm, wavelength at 225 nm, 254, and 280 nm) with following conditions.

HPLC Conditions. Method 1 (Solvent A: 0.1% TFA−water. Solvent B: 100% acetonitrile. Flow rate of 1.0 mL/min at 25 °C.): From 50% of B to 80% of B in 15 min, then back to 50% of B in 15 min. Method 2 (Solvent A: 0.1% TFA−water. Solvent B: 100% acetonitrile. Flow rate of 1.0 mL/min at 25 °C.): From 30% of B to 70% B in 20 min, then back to 30% of B in 10 min. Method 3 (Solvent A: 50 mM KH_2PO_4 pH 3.0 solution. Solvent B: 100% acetonitrile. Flow rate of 1.0 mL/min at 25 °C.): From 25% of B to 45% of B in 30 min.

5-(Furan-2-yl)-2-methoxybenzaldehyde (30). Water (3 mL) was added to a solution of **29** (0.5 g, 2.32 mmol), furan-2-boronic acid (0.29 g, 2.56 mmol), sodium carbonate (0.37 g, 3.49 mmol), and Pd(dppf)Cl_2 (95 mg, 0.12 mmol) in DME (9 mL) at room temperature. The reaction mixture was heated at 110 °C for 24 h. After being cooled to rt, the suspension was diluted with CH_2Cl_2 (30 mL), washed with water (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1) afforded the desired product **30** (0.12 g, 26%) as a white solid. MS (ESI) *m*/*z* 203 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.10 (d, *J* = 2.4 Hz, 1H), 7.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.44 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.61 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.46 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.96 (s, 3H).

***tert*-Butyl 2-(3-formyl-4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (31).** This compound was made using the synthetic procedure described for **30**. Thus **29** (0.7 g, 3.26 mmol), *N*-Boc-pyrrole-2-boronic acid (0.75 g, 3.55 mmol), Pd(dppf)Cl_2 (0.13 g, 0.16 mmol), and sodium carbonate (1.03 g, 9.76 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 5:1) afforded the desired product **31** (0.38 g, 39%) as a brown solid. MS (ESI) *m*/*z* 302 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.21 (t, *J* = 3.3 Hz, 1H), 6.17 (m, 1H), 3.96 (s, 3H), 1.40 (s, 9H).

(5-(Furan-2-yl)-2-methoxyphenyl)(3,4,5-trimethoxyphenyl)-methanol (33). To a solution of **32** (0.15 g, 0.6 mmol) in dry THF (20 mL) was added dropwise *n*-BuLi (0.56 mL, 1.6 M in hexane, 0.9 mmol) at −78 °C. After 1 h, a solution of **30** (0.12 g, 0.6 mmol) in dry THF (4 mL) was added dropwise at −78 °C. After 1 h stirring at rt, water (10 mL) was added to the reaction mixture. It was extracted with EtOAc (60 mL × 2). The combined organic layers were washed with 1 N HCl and then brine water (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1) afforded the desired product **33** (59 mg, 27%) as a colorless oil. MS (ESI) *m*/*z* 353 $[M + H - H_2O]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.57 (m, 2H), 7.41 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.92 (dd, *J* = 6.9, 2.3 Hz, 1H), 6.66 (s, 2H), 6.49 (dd, *J* = 3.3, 0.7 Hz, 1H), 6.43 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.02 (brs, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 6H), 2.97 (brs, 1H).

***t*-Butyl-2-(3-(hydroxy(3,4,5-trimethoxyphenyl)methyl)-4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (34).** Grignard reagent was prepared in an oven-dried flask, with a magnetic stirrer. A solution of **32** (1.16 g, 4.7 mmol) in THF (6 mL) was added to a mixture of magnesium turnings (0.11 g, 4.7 mmol) in THF (4 mL) with a small piece of iodine. As soon as the solution became colorless (heating sometimes necessary), the resulting mixture was stirred at rt for 1 h. Then (3,4,5-trimethoxyphenyl)magnesium bromide (1.2 mL) was added slowly to a stirred solution of **31** (0.13 g, 0.43 mmol) in dry THF (6 mL) at 0 °C.

After complete addition, the reaction mixture was stirred at rt overnight. The reaction mixture was quenched with satd NH_4Cl solution (3 mL). The suspension was diluted with EtOAc (30 mL), washed with water (10 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1−4:1) afforded the desired product **34** (96 mg, 48%) as a yellow oil. MS (ESI) *m/z* 454 $[M + H - H_2O]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.25 (m, 2H), 7.21 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 1H), 6.18 (t, *J* = 3.2 Hz, 1H), 6.09 (m, 1H), 6.03 (s, 1H), 3.87 (s, 3H), 3.81 (s, 9H), 1.36 (s, 9H).

(5-(Furan-2-yl)-2-methoxyphenyl)(3,4,5-trimethoxyphenyl)-methanone (1). To a solution of **33** (59 mg, 0.16 mmol) in CH_2Cl_2 (5 mL) was added 4 Å molecular sieves (30 mg), pyridinium chlorochromate (52 mg, 0.24 mmol) at rt. The reaction mixture was stirred at rt for 3 h, the suspension was filtered over a Celite pad, and the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 5:1−2:1) to afford the desired product **1** (15 mg, 25%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.70 (s, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.02 (s, 2H), 6.90 (d, *J* = 3.2 Hz, 1H), 6.55 (m, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.75 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.40, 156.28, 153.19, 152.70, 142.99, 142.74, 132.43, 129.17, 127.25, 124.25, 123.74, 112.99, 112.52, 107.31, 105.49, 60.66, 56.41, 56.25. HRMS (EI) calcd for $C_{21}H_{20}O_6$ $[M]^+$ 368.1260, found 368.1263. HPLC (method 1) 98.8% (t_R = 11.07 min).

***tert*-Butyl 2-(4-Methoxy-3-(3,4,5-trimethoxybenzoyl)phenyl)-1*H*-pyrrole-1-carboxylate (35).** To a solution of **34** (96 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added 4 Å molecular sieves (200 mg) and pyridinium dichromate (115 mg, 0.31 mmol) at rt. The reaction mixture was stirred at rt for 5 h, then suspension was filtered over a Celite pad, and the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1−2:1) to afford the desired product **35** (57 mg, 61%) as a yellow solid. MS (ESI) *m/z* 468 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.31 (m, 2H), 7.15 (s, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.20 (t, *J* = 3.3 Hz, 1H), 6.17 (m, 1H), 3.92 (s, 3H), 3.85 (s, 6H), 3.80 (s, 3H), 1.43 (s, 9H).

(2-Methoxy-5-(1*H*-pyrrol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (2). To a solution of **35** (49 mg, 0.1 mmol) in CH_2Cl_2 (4 mL) was added TFA (excess) at rt. After 4 h stirring at rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) to afford the desired product **2** (7 mg, 19%) as a brown solid. MS (ESI) *m/z* 368 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.02 (s, 2H), 6.78 (m, 1H), 6.44 (m, 1H), 6.07 (m, 1H), 3.74 (s, 3H), 3.73 (s, 6H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.90, 155.02, 153.30, 142.77, 132.71, 130.76, 129.09, 127.20, 126.52, 123.94, 119.53, 113.04, 109.62, 107.45, 105.53, 60.79, 56.54, 56.30. HRMS (EI) calcd for $C_{21}H_{21}NO_5$ $[M]^+$ 367.1419, found 367.1417. HPLC (method 1) 97.8% (t_R = 9.75 min).

(2-Fluoro-5-iodophenyl)(3,4,5-trimethoxyphenyl)methanone (38). This compound was made using the same synthetic procedure as described for **34**. Then (3,4,5-trimethoxyphenyl)magnesium bromide (40 mL, 1.0 M in THF, prepared in advance with a small piece of iodine) was added slowly to a stirred solution of **36** (9.0 g, 31.6 mol) in dry THF (10 mL) at 0 °C. After complete addition, the reaction mixture was stirred at rt for 3 h and then quenched with satd NH_4Cl solution (10 mL). The suspension was diluted with EtOAc (300 mL), washed with water (100 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The solid product was stirred with hexane and filtered. The resultant solid was dried in vacuo to afford title compound **38** (8.0 g, 61%) as a white solid. MS (ESI) *m/z* 417 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (m, 1H), 7.86 (dd, *J* = 6.4, 2.2 Hz, 1H), 7.23 (dd, *J* = 18.6, 8.8 Hz, 1H), 7.03 (s, 2H), 3.78 (s, 6H), 3.77 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.41, 159.4 (d, J_{C-F} = 248 Hz), 153.29, 143.20, 142.27 (d, J_{C-F} = 8 Hz), 138.74, 131.82, 129.14 (d, J_{C-F} = 16 Hz), 119.33 (d, J_{C-F} = 23 Hz), 107.57, 89.13 (d, J_{C-F} = 3 Hz), 60.72, 56.55. HRMS (EI) calcd for $C_{16}H_{14}FIO_4$ $[M]^+$ 415.9921, found 415.9921.

(5-Bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanone (39). This compound was made using the same synthetic procedure as described for **34**, **35** using (3,4,5-trimethoxyphenyl)-magnesium bromide (40 mL, 1.5 M in THF, prepared in advance with a small piece of iodine). Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 9:1−3:1) afforded the desired product (5-bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanol (10.4 g, 57%) as a yellow oil. Next, a mixture of (5-bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanol (4.4 g, 0.12 mol), 4 Å molecular sieves (4.0 g), and pyridinium dichromate (6.7 g, 0.17 mol) in CH_2Cl_2 (20 mL) was stirred at rt for 4 h. The suspension was filtered over a Celite pad, and the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2, 5:1−1:1) to afford the desired product **39** (3.5 g, 80%) as a white solid. MS (ESI) *m/z* 369, 371 $[M + H]^+$, ^{79}Br and ^{81}Br. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 2H), 7.07 (s, 2H), 7.07 (t, *J* = 8.9 Hz, 1H), 3.93 (s, 3H), 3.85 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.43, 158.76 (d, J_{C-F} = 251 Hz), 153.10, 143.48, 135.55 (d, J_{C-F} = 8 Hz), 133.07 (d, J_{C-F} = 3 Hz), 131.64, 128.86 (d, J_{C-F} = 17 Hz), 118.11 (d, J_{C-F} = 23 Hz), 116.89 (d, J_{C-F} = 3 Hz), 107.53, 60.96, 56.34. HRMS (EI) calcd for $C_{16}H_{14}BrFO_4$ $[M]^+$ 368.0059, found 368.0061.

(2-Fluoro-5-(furan-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (40). To a solution of **39** (0.25 g, 0.68 mmol), furan-2-boronic acid (0.11 g, 1.02 mmol), and Pd(dppf)Cl_2 (28 mg) in DME (3 mL) was added sodium carbonate (0.14 g, 1.35 mmol) in water (1 mL) at rt. The reaction mixture was heated in a microwave synthesizer at 120 °C for 500 s. After being cooled to rt, the mixture was diluted with EtOAc (20 mL) and then washed with water (10 mL) and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 5:1−3:1) afforded the desired product **40** (0.18 g, 74%) as a white solid. MS (ESI) *m/z* 357 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.20 (t, *J* = 9.3 Hz, 1H), 7.14 (s, 2H), 6.65 (d, *J* = 3.3 Hz, 1H), 6.48 (m, 1H), 3.96 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.85, 158.91 (d, J_{C-F} = 251 Hz), 153.07, 152.13, 143.25, 142.57, 132.14, 127.96 (d, J_{C-F} = 8 Hz), 127.59 (d, J_{C-F} = 4 Hz), 127.43 (d, J_{C-F} = 16 Hz), 125.74 (d, J_{C-F} = 3 Hz), 116.67 (d, J_{C-F} = 23 Hz), 111.85, 107.56, 105.64, 60.96, 56.33.

(2-Fluoro-5-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (41). To a solution of **39** (0.15 g, 0.4 mmol) and $Pd(PPh_3)_4$ (47 mg, 0.04 mmol) in THF (3 mL) was added 2-thiazolylzinc bromide (1.6 mL, 0.5 M in THF) at rt. The reaction mixture was heated in a microwave synthesizer at 110 °C for 400 s. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with satd NH_4Cl solution (10 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 5:1−1:3) afforded the desired product **41** (70 mg, 47%) as a white solid. MS (ESI) *m/z* 374 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (m, 1H), 8.12 (dd, *J* = 6.3, 2.3 Hz, 1H), 7.89 (d, *J* = 3.2 Hz, 1H), 7.39 (d, *J* = 3.2 Hz, 1H), 7.31−7.27 (m, 1H), 7.14 (d, *J* = 0.8 Hz, 2H), 3.97 (s, 3H), 3.88 (s, 6H).

(5-Iodo-2-methoxyphenyl)(3,4,5-trimethoxyphenyl)methanone (42). To a solution of **38** (0.37 g, 0.89 mmol) in MeOH (10 mL) was added NaOMe (10 mL, 25 wt % in methanol) at rt. The reaction mixture was heated at 80 °C overnight. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:2) afforded the desired product **42** (0.25 g, 66%) as a white solid. MS (ESI) m/z 429 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.7, 2.3 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.06 (s, 2H), 6.78 (d, J = 8.7 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 6H), 3.74 (s, 3H).

(5-Iodo-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanone (43). A mixture of **38** (1.02 g, 2.45 mmol), K_2CO_3 (1.02 g), and 1,2,4-triazole (0.22 g) in DMF (10 mL) was heated at 120 °C overnight. After being cooled to rt, the suspension was diluted with EtOAc (100 mL), washed with satd NH_4Cl solution (30 mL) and then brine (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:5) afforded the desired product **43** (0.65 g, 57%) as a white solid. MS (ESI) m/z 466 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.16 (dd, J = 8.4, 2.0 Hz, 1H), 7.94 (m, 3H), 7.62 (d, J = 8.4, 1H), 6.81 (s, 2H), 3.72 (s, 6H), 3.70 (s, 3H).

(2-Methoxy-5-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanone (3). To a solution of **42** (0.2 g, 0.47 mmol) and $Pd(PPh_3)_2Cl_2$ (17 mg, 0.02 mmol) in dry THF (20 mL) was added 2-tributylstannylthiazole (0.3 g, 0.8 mmol) at rt. The reaction mixture was refluxed for 6 h. After being cooled to rt, the suspension was diluted with EtOAc (70 mL), washed with satd NH_4Cl solution (30 mL) and then brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:2) afforded the desired product **3** (0.2 g, 67%) as a white solid. MS (ESI) m/z 386 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (dd, J = 8.7, 2.3 Hz, 1H), 7.86 (m, 2H), 7.72 (d, J = 3.2 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.02 (s, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.74 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 194.10, 166.72, 158.53, 153.33, 144.27, 142.91, 132.44, 130.41, 129.34, 127.07, 126.42, 120.59, 113.37, 107.47, 60.80, 56.57. HRMS (EI) calcd for $C_{20}H_{19}NO_5S$ $[M]^+$ 385.0984, found 385.0984. HPLC (method 1) 98.6% (t_R = 9.01 min).

(2-Methoxy-5-(oxazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanone (4). This compound was made using the same synthetic procedure as described for **3** using **42** (0.2 g, 0.47 mmol), 2-(tri*n*-butylstannyl)oxazole (0.28 g, 0.8 mmol), and $Pd(PPh_3)_2Cl_2$ (17 mg, 0.02 mmol). Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:2) afforded the desired product **4** (30 mg, 17%) as a white solid. MS (ESI) m/z 370 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.13 (dd, J = 8.7, 2.2 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.35 (m, 2H), 7.02 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.75 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.90, 160.63, 159.66, 153.27, 142.81, 140.33, 132.28, 130.12, 129.19, 128.88, 126.88, 120.09, 113.25, 107.33, 60.67, 56.45. HRMS (EI) calcd for $C_{20}H_{19}NO_6$ $[M]^+$ 369.1212, found 369.1217. HPLC (method 1) 95.7% (t_R = 7.57 min).

(5-(1*H*-Pyrrol-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (15). This compound was made using the synthetic procedure described for **30**. Thus **43** (0.3 g, 0.64 mmol), *N*-Boc-pyrrole-2-boronic acid (0.19 g), Pd(dppf)Cl_2 (52.3 mg), and sodium carbonate (0.14 g) were used. The reaction mixture was heated in a microwave synthesizer at 130 °C for 15 min. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 5:1) afforded the desired product **15** (0.15 g, 57%) as a brown solid. MS (ESI) m/z 405 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 8.99 (s, 1H), 7.99 (dd, J = 8.4, 2.1 Hz, 1H), 7.94 (s, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 6.94 (m, 1H), 6.89 (s, 2H), 6.74 (m, 1H), 6.17 (m, 1H), 3.72 (s, 6H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.33, 153.02, 152.49, 144.51, 142.61, 134.45, 133.84, 131.87, 131.79, 129.62, 126.18, 125.03, 123.89, 121.23, 110.11, 108.05, 107.00, 60.62, 56.44. HRMS (EI) calcd for $C_{22}H_{20}N_4O_4$ $[M]^+$ 404.1484, found 404.1487. HPLC (method A) 97.9% (t_R = 6.42 min).

4-(Thiazol-2-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl trifluoromethanesulfonate (44). To a solution of **41** (0.63 g, 1.7 mmol) and 2-(methylsulfonyl)ethanol (0.31 g) in DMF (5 mL) was added NaH (0.22 g) at 0 °C. The reaction mixture was stirred at rt for 6 h. The reaction was quenched with water. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL), and washed with satd NH_4Cl solution (30 mL) and then brine (20 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude corresponding (2-hydroxy-5-(thiazol-2-yl)phenyl)-(3,4,5-trimethoxyphenyl)methanone (0.27 g), which was used in the following step without further purification. To a solution of (2-hydroxy-5-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanone (0.39 g, 1.05 mmol) in CH_2Cl_2 (10 mL) was added pyridine (0.13 mL) and $(TfO)_2O$ (0.35 mL) at 0 °C. After 4 h stirring at rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with 1 N HCl solution (20 mL), H_2O (15 mL), dried over $MgSO_4$, filtered, concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:3) afforded the desired product **44** (0.38 g, 73%) as a colorless oil. MS (ESI) m/z 405 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 8.6, 2.3 Hz, 1H), 8.16 (d, J = 2.3 Hz, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 3.2 Hz, 1H), 7.09 (s, 2H), 3.96 (s, 3H), 3.85 (s, 6H).

(5-(Furan-2-yl)-2-(1*H*-pyrazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (11). A mixture of **40** (50 mg, 0.14 mmol), K_2CO_3 (58 mg), and pyrazole (19 mg, 0.28 mmol) in DMF (3 mL) was heated at 120 °C for 24 h. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with H_2O (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1−3:1) afforded the desired product **11** (35 mg, 62%) as a white solid. MS (ESI) m/z 405 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 7.9, 2.0 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 2.5, 0.4 Hz, 1H), 7.49 (m, 2H), 6.96 (s, 2H), 6.75 (dd, J = 3.4, 0.5 Hz, 1H), 6.51 (dd, J = 3.4, 1.8 Hz, 1H), 6.23 (dd, J = 2.3, 1.8 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.37, 152.75, 152.16, 142.92, 141.37, 131.50, 129.67, 126.17, 124.86, 123.83, 112.00, 107.79, 106.83, 106.52, 60.85, 56.21. HRMS (EI) calcd for $C_{23}H_{20}N_2O_5$ $[M]^+$ 404.1372, found 404.1373. HPLC (method 1) 97.2% (t_R = 11.09 min).

(5-(Furan-2-yl)-2-(1*H*-imidazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (12). A mixture of **40** (40 mg, 0.11 mmol), K_2CO_3 (78 mg), and imidazole (23 mg, 0.34 mmol) in DMF (3 mL) was heated at 120 °C for 24 h. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with H_2O (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:2) afforded the desired product **12** (27 mg, 61%) as a white solid. MS (ESI) m/z 405 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.4, 2.0 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 2.5, 0.4 Hz, 1H), 7.50 (dd, J = 1.7, 0.5 Hz, 1H), 7.48 (m, 1H), 6.75 (dd, J = 3.4, 0.5 Hz, 1H), 6.51 (dd, J = 3.4, 1.8 Hz, 1H), 6.23 (dd, J = 2.3, 1.8 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.91, 152.95, 151.74, 143.61, 143.22, 137.26, 135.49, 133.57, 130.89, 130.18, 126.28, 125.89, 124.44, 120.30, 112.09, 107.33, 107.02, 60.91, 56.33. HRMS (EI) calcd for $C_{23}H_{20}N_2O_5$ $[M]^+$ 404.1372, found 404.1367. HPLC (method 2) 98.4% (t_R = 11.68 min).

(5-(Furan-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (14). A solution of **40** (74 mg, 0.21 mmol) and sodium 1,2,4-triazole (38 mg, 0.41 mmol) in DMF (3 mL) was heated at 120 °C for 3 h. After being cooled to rt, the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 5:1−2:1) to afford the desired product **14** (20 mg, 23%) as a white solid. MS (ESI) *m*/*z* 405 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.94 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.89 (s, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 1.1 Hz, 1H), 6.98 (s, 2H), 6.79 (d, *J* = 3.3 Hz, 1H), 6.52 (dd, *J* = 3.3, 1.7 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.42, 152.94, 152.52, 151.63, 143.51, 143.35, 134.53, 133.32, 131.49, 130.85, 126.20, 125.00, 124.60, 112.13, 107.31, 107.25, 60.87, 56.24. HRMS (EI) calcd for $C_{22}H_{19}N_3O_5$ [M]$^+$ 405.1324, found 405.1321. HPLC (method 1) 97.5% (t_R = 7.83 min).

(5-(Thiazol-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (16). A solution of **41** (30 mg, 0.08 mmol) and sodium 1,2,4-triazole (22 mg, 0.24 mmol) in DMF (3 mL) was heated at 120 °C for 3 h. After being cooled to rt, the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:2) to afford the desired product **16** (16 mg, 47%) as a white solid. MS (ESI) *m*/*z* 423 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.28 (dd, *J* = 8.4, 2.1 Hz, 1H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.93 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 3.2 Hz, 1H), 6.98 (s, 2H), 3.90 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.10, 165.51, 153.00, 152.81, 144.33, 143.54, 143.35, 135.58, 134.61, 134.13, 130.67, 129.15, 127.65, 125.11, 120.34, 107.13, 61.00, 56.27. HRMS (EI) calcd for $C_{21}H_{18}N_4O_4S$ [M + H]$^+$ 422.1048, found 422.1049. HPLC (method 1) 95.9% (t_R = 5.82 min).

(2-(Pyrimidin-5-yl)-5-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (13). This compound was made using the synthetic procedure described for **30**. Thus **44** (0.34 g, 0.67 mmol), pyrimidine-5-boronic acid (0.12 g), Pd(dppf)Cl_2 (27.4 mg), and sodium carbonate (0.22 g) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:5−1:10) afforded the desired product **13** (96.5 mg, 33%) as a white solid. MS (ESI) *m*/*z* 434 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.78 (s, 2H), 8.30 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.16 (d, *J* = 1.7 Hz, 1H), 8.00 (d, *J* = 3.2 Hz, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 6.70 (s, 2H), 3.74 (s, 6H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.26, 165.88, 157.80, 156.35, 153.17, 144.72, 142.91, 139.55, 135.73, 133.51, 132.26, 131.91, 129.07, 127.01, 122.13, 108.02, 60.65, 56.56. HRMS (EI) calcd for $C_{23}H_{19}N_3O_4S$ [M]$^+$ 433.1096, found 433.1099. HPLC (method 1) 95.6% (t_R = 6.62 min).

6-Iodo-2-methyl-4*H*-benzo[d][1,3]oxazin-4-one (46). A solution of 2-amino-4-iodobenzoic acid (**45**, 7.2 g, 27.5 mmol) in acetic anhydride (26 mL) was heated at 120 °C for 4 h. After being cooled to rt, the mixture was triturated with hexane then filtered through Celite pad. It was used in the following step without purification. MS (ESI) *m*/*z* 288 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, *J* = 2.0 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 2.37 (s, 3H).

***N*-(4-Iodo-2-(3,4,5-trimethoxybenzoyl)phenyl)acetamide (47).** (3,4,5-Trimethoxyphenyl)magnesium bromide (10 mL, 0.7 N in THF solution, prepared in advance with a small piece of iodine) was the added slowly to a stirred solution of **46** (1.0 g, 3.48 mmol) in dry THF (5 mL) at rt. After complete addition, the reaction mixture was stirred at rt overnight. The reaction was quenched with satd NH_4Cl solution (30 mL). The aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were washed with water (20 mL) and then brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:2) afforded the desired product **47** (0.25 g, 16%) as a white solid. MS (ESI) *m*/*z* 455 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.96 (s, 1H), 7.89 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.68 (d, *J* = 2.1 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.94 (s, 2H), 3.76 (s, 9H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.78, 168.69, 152.83, 142.07, 140.39, 137.96, 136.10, 133.93, 132.11, 126.98, 107.48, 89.04, 60.65, 56.35, 23.45. HRMS (EI) calcd for $C_{18}H_{18}INO_5$ [M]$^+$ 455.0230, found 455.0227.

***N*-(4-(Furan-2-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl)acetamide (48a).** This compound was made using the synthetic procedure described for **30**. Thus **47** (1.89 g, 4.15 mmol), furan-2-boronic acid (0.56 g, 4.98 mmol), Pd(dppf)Cl_2 (0.17 g, 0.21 mmol), and sodium carbonate (0.88 g, 8.3 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product **48a** (1.02 g, 60%) as a white solid. MS (ESI) *m*/*z* 396 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.60 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.83 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.42 (m, 1H), 7.03 (s, 2H), 6.57 (m, 1H), 6.45 (m, 1H), 3.97 (s, 3H), 3.87 (s, 6H), 2.22 (s, 3H).

***N*-(4-(Thiazol-2-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl)acetamide (48b).** To a solution of **47** (96.7 mg, 0.21 mmol) and $Pd(PPh_3)_4$ (24.3 mg, 10 mol %) was added 2-thiazolylzinc bromide (0.56 mL, 0.5 M in THF) at rt. The reaction mixture was heated at 100 °C overnight. After being cooled to rt, the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:2) to afford the desired product **48b** (40 mg, 46%) as a white solid. MS (ESI) *m*/*z* 413 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.12 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.96 (d, *J* = 2.2 Hz, 1H), 7.91 (d, *J* = 3.2 Hz, 1H), 7.79 (d, *J* = 3.2 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.02 (s, 2H), 3.76 (s, 9H), 1.84 (s, 3H).

***N*-(4-(Oxazol-2-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl)acetamide (48c).** To a solution of oxazole (1.07 g, 15.5 mmol) in THF (20 mL) was added *n*-BuLi (5 mL, 1.6 M in THF) at −78 °C. After stirring 20 min, $ZnCl_2$ (15.5 mL) was added dropwise at −78 °C. The cooling bath was removed and the contents were warmed to rt. **47** (1.3 g, 2.86 mmol) and $Pd(PPh_3)_4$ (0.33 g) was added at rt. The reaction mixture was heated at 100 °C overnight. After being cooled to rt, the solution was evaporated to dryness. The residue was dissolved in EtOAc (100 mL), washed with satd NH_4Cl solution (30 mL) and then brine, dried over $MgSO_4$, filtered, concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:5) afforded the desired product **48c** (0.65 g, 57%) as a white solid. MS (ESI) *m*/*z* 397 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.73 (d, *J* = 8.8 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 8.22 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.69 (d, *J* = 0.8 Hz, 1H), 7.20 (d, *J* = 0.8 Hz, 1H), 7.02 (s, 2H), 3.98 (s, 3H), 3.87 (s, 6H), 2.25 (s, 3H).

***N*-(4-(Thiophen-2-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl)acetamide (48d).** This compound was made using the synthetic procedure described for **48b**. Thus **47** (0.1 g, 0.23 mmol), 2-thienylzinc bromide (0.7 mL), and $Pd(PPh_3)_4$ (26.6 mg) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1) afforded the desired product **48d** (63.4 mg, 67%) as a white solid. MS (ESI) *m*/*z* 412 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97(s, 1H), 7.86 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.63 (d, *J* = 2.2 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.52 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.6 Hz, 1H), 7.01 (s, 2H), 3.77 (s, 9H), 1.79 (s, 3H).

***N*-(4-(2-Bromoacetyl)-2-(3,4,5-trimethoxybenzoyl)phenyl)acetamide (49).** To a solution of **47** (0.73 g, 1.83 mmol) in dry THF (5 mL) was added $Pd(PPh_3)_2Cl_2$ (77 mg, 0.11 mmol) and tributyl (1-ethoxy vinyl)tin (1.19 g, 3.29 mmol) at rt. The reaction mixture was refluxed for 6 h. After being cooled to rt, the resulting mixture was diluted with EtOAc (50 mL), washed with satd KF solution (15 mL) and brine (15 mL), then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 10:1−2:1) afforded the desired product

N-(4-(1-ethoxyvinyl)-2-(3,4,5-trimethoxy-benzoyl)phenyl)acetamide (0.73 g, 83%) as a yellow oil. Next, to a solution of the above product (0.18 g, 0.45 mmol) in THF/water (10 mL, v/v 1:1) was added NBS (0.08 g, 0.45 mmol) at rt. After stirring 1 h, water (10 mL) was added to the reaction mixture. The resulting mixture was diluted with EtOAc (50 mL), washed with brine (2 × 15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 10:1−3:1) afforded the desired product **49** (0.13 g, 64%) as a white solid. MS (ESI) *m*/*z* 450, 452 $[M + H]^+$, ^{79}Br and ^{81}Br. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.17 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.00 (s, 2H), 4.90 (s, 2H), 3.77 (s, 6H), 3.76 (s, 3H), 1.89 (s, 3H).

***N*-(4-(2-Methylthiazol-4-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl)-acetamide (48e).** A mixture of **49** (0.45 g, 1.0 mmol) and thioacetamide (0.11 g, 1.5 mmol) in EtOH (5 mL) was refluxed for 2 h. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with satd $NaHCO_3$ solution (30 mL) and then brine, dried over $MgSO_4$, filtered, concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1−1:5) to afford the desired product **48e** (0.32 g, 76%) as a yellow solid. MS (ESI) *m*/*z* 427 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.10 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.97 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.01 (s, 2H), 3.76 (s, 3H), 3.75 (s, 6H), 2.69 (s, 3H), 1.80 (s, 3H).

***N*-(4-(2-Aminothiazol-4-yl)-2-(3,4,5-trimethoxybenzoyl)phenyl)-acetamide (48f).** This compound was made using the synthetic procedure described for **48e**. Thus **49** (0.29 g, 0.63 mmol) and thiourea (63 mg, 0.83 mmol) were used. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1−5:1) afforded the desired product **48f** (0.24 g, 90%) as a yellow solid. MS (ESI) *m*/*z* 428 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.96 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.14 (brs, 2H), 7.06 (s, 1H), 7.00 (s, 2H), 3.75 (s, 9H).

(2-Amino-5-(furan-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (5). To a solution of **48a** (1.02 g, 2.58 mmol) in MeOH (20 mL) was added NaOMe (1.39 g, 25.8 mmol) at rt. The reaction mixture was refluxed for 8 h. After being cooled to rt, the solution was evaporated to dryness. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) to give **5** (0.5 g, 55%) as a yellow solid. MS (ESI) *m*/*z* 354 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, *J* = 2.1 Hz, 1H), 7.65 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.58 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.19 (s, 2H), 6.94−6.91 (m, 3H), 6.59 (dd, *J* = 3.4, 0.7 Hz, 1H), 6.48 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.79 (s, 6H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.33, 153.06, 152.45, 151.06, 141.47, 140.20, 134.59, 129.86, 128.03, 117.47, 117.06, 116.08, 111.71, 106.66, 102.67, 60.15, 56.05. HRMS (EI) calcd for $C_{20}H_{19}NO_5$ $[M]^+$ 353.1263, found 353.1263. HPLC (method 1) 97.7% (t_R = 10.70 min).

(2-Amino-5-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (6). This compound was made using the synthetic procedure described for **5**. Thus **48b** (0.5 g, 1.21 mmol) and NaOMe (0.33 g) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:3) afforded the desired product **6** (0.24 g, 54%) as a yellow solid. MS (ESI) *m*/*z* 371 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 2.2 Hz, 1H), 7.86 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.75 (d, *J* = 3.2 Hz, 1H), 7.56 (d, *J* = 3.2 Hz, 1H), 7.46 (s, 2H), 6.98−6.96 (m, 3H), 3.80 (s, 6H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.60, 167.64, 153.49, 152.99, 143.72, 140.79, 134.84, 132.21, 132.18, 120.03, 118.56, 117.98, 116.37, 107.24, 60.67, 56.56. HRMS (EI) calcd for $C_{19}H_{18}N_2O_4S$ $[M]^+$ 370.0987, found 370.0986. HPLC (method 1) 97.1% (t_R = 7.34 min).

(2-Amino-5-(oxazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (7). This compound was made using the synthetic procedure described for **5**. Thus **48c** (0.59 g, 1.5 mmol) and NaOMe (0.81 g) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:5) afforded the desired product **7** (0.45 g, 85%) as a yellow solid. MS (ESI) *m*/*z* 355 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.0 Hz, 1H), 7.97 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.59 (d, *J* = 0.8 Hz, 1H), 7.12 (d, *J* = 0.8 Hz, 1H), 6.96 (s, 2H), 6.81 (d, *J* = 8.6 Hz, 1H), 6.29 (brs, 2H), 3.95 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.37, 161.68, 152.93, 152.15, 141.33, 137.74, 134.38, 132.52, 131.86, 128.07, 117.64, 117.35, 115.38, 107.14, 60.96, 56.32. HRMS (EI) calcd for $C_{19}H_{18}N_2O_5$ $[M]^+$ 354.1215, found 354.1213. HPLC (method 1) 96.5% (t_R = 6.48 min).

(2-Amino-5-(thiophen-2-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanone (8). This compound was made using the synthetic procedure described for **5**. Thus **48d** (59 mg, 0.14 mmol) and NaOMe (77.5 mg) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:3) afforded the desired product **8** (22 mg, 41%) as a yellow solid. MS (ESI) *m*/*z* 354 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67−7.64 (m, 2H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.22−7.20 (m, 3H), 7.03 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.94−6.92 (m, 3H), 3.81 (s, 6H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.62, 152.95, 151.70, 143.98, 140.72, 134.96, 131.89, 130.65, 128.78, 123.96, 121.81, 120.56, 118.13, 116.62, 107.19, 60.67, 56.54. HRMS (EI) calcd for $C_{20}H_{19}NO_4S$ $[M]^+$ 369.1035, found 369.1036. HPLC (method 1) 99.6% (t_R = 11.99 min).

(2-Amino-5-(2-methylthiazol-4-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (9). This compound was made using the synthetic procedure described for **5**. Thus **48e** (0.13 g, 0.3 mmol) and NaOMe (0.17 g) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:2) afforded the desired product **9** (0.1 g, 88%) as a yellow solid. MS (ESI) *m*/*z* 385 $[M + H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.55 (s, 1H), 7.17 (brs, 2H), 6.96 (s, 2H), 6.92 (d, *J* = 8.7 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.73, 165.60, 154.13, 152.95, 151.88, 140.81, 135.04, 132.24, 131.59, 121.36, 117.74, 116.52, 110.46, 107.49, 60.66, 56.57, 19.31. HRMS (EI) calcd for $C_{20}H_{20}N_2O_4S$ $[M]^+$ 384.1144, found 384.1142. HPLC (method 1) 98.2% (t_R = 8.72 min).

(2-Amino-5-(2-aminothiazol-4-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (10). This compound was made using the synthetic procedure described for **5**. Thus **48f** (0.24 g, 0.56 mmol) and NaOMe (0.3 g) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product **10** (75 mg, 35%) as a yellow solid. MS (ESI) *m*/*z* 386 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.1 Hz, 1H), 7.72 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.97 (s, 2H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.44 (s, 1H), 6.04 (s, 2H), 4.94 (s, 2H), 3.94 (s, 3H), 3.88 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.93, 167.06, 152.92, 150.77, 150.39, 134.99, 131.99, 131.87, 123.09, 118.02, 117.37, 107.18, 107.14, 100.29, 61.15, 56.45. HPLC (method 1) 95.4% (t_R = 2.79 min).

(4-Bromophenyl)(3,4,5-trimethoxyphenyl)methanol (52). This compound was made using the synthetic procedure described for **34**. Thus (3,4,5-trimethoxyphenyl)magnesium bromide (8.0 mL, 1.0 M in THF, prepared in advance) and 4-bromo-benzaldehyde (1.0 g, 5.4 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1) afforded the desired product **52** (2.0 g, 99%) as a colorless oil. MS (ESI) *m*/*z* 335, 337 $[M + H - H_2O]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.26 (m, 2H), 6.56 (s, 2H), 5.71 (d, *J* = 3.2 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 6H), 2.54 (d, *J* = 3.4 Hz, 1H).

(4-Bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanol (53). This compound was made using the synthetic procedure described for **34**. Thus (3,4,5-trimethoxyphenyl)magnesium bromide (18.0 mL, 1.0 M in THF, prepared in advance) and 4-bromo-2-fluorobenzaldehyde (3.0 g, 14.8 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1−3:1) afforded the desired product **53** (3.2 g, 58%) as a colorless oil. MS (ESI) m/z 353, 355 [M + H − H_2O]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 1H), 7.29 (dd, J = 8.4, 1.8 Hz, 1H), 7.20 (dd, J = 9.7, 1.8 Hz, 1H), 6.58 (s, 2H), 5.99 (d, J = 3.4 Hz, 1H), 3.81 (s, 6H), 3.80 (s, 3H), 2.59 (d, J = 3.7 Hz, 1H).

(4-Bromophenyl)(3,4,5-trimethoxyphenyl)methanone (54). This compound was made using the synthetic procedure described for **35**. Thus **52** (2.0 g, 5.7 mmol), 4 Å molecular sieves (2.0 g), and pyridinium dichromate (3.2 g, 8.5 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/CH_2Cl_2, 1:40) afforded the desired product **54** (1.6 g, 82%) as a white solid. MS (ESI) m/z 351, 353 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (m, 2H), 7.71 (m, 2H), 7.02 (s, 2H), 3.81 (s, 6H), 3.77 (s, 3H).

(4-Bromo-2-fluorophenyl)(3,4,5-trimethoxyphenyl)methanone (55). This compound was made using the synthetic procedure described for **35**. Thus **53** (3.2 g, 8.6 mmol), 4 Å molecular sieves (2.7 g), and pyridinium dichromate (4.8 g, 12.9 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/CH_2Cl_2, 2:1) afforded the desired product **55** (1.5 g, 47%) as a white solid. MS (ESI) m/z 369, 371 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (dd, J = 9.7, 1.6 Hz, 1H), 7.59 (m, 2H), 7.05 (s, 2H), 3.79 (s, 6H), 3.78 (s, 3H).

(2-Amino-4-bromophenyl)(3,4,5-trimethoxyphenyl)methanone (56). To a solution of **55** (0.32 g, 0.87 mmol) in 2-propanol (3 mL) was added aq NH_4OH (3 mL) at rt. The reaction mixture was heated in a sealed tube at 145 °C overnight. After being cooled to rt, the solution was evaporated to dryness. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1−1:2) to give **56** (0.21 g, 65%) as a yellow solid. MS (ESI) m/z 367 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 1H), 6.93 (d, J = 1.8 Hz), 6.86 (s, 2H), 6.75 (m, 1H), 3.92 (s, 3H), 3.87 (s, 6H).

(4-Bromo-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (57). A mixture of **55** (1.7 g, 4.6 mmol), K_2CO_3 (3.14 g) and 1,2,4-triazole (0.94 g) in DMF (10 mL) was heated at 120 °C overnight. After being cooled to rt, the suspension was diluted with EtOAc (150 mL), washed with satd NH_4Cl solution (40 mL) and then brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:3) afforded the desired product **57** (1.1 g, 58%) as a white solid. MS (ESI) m/z 418, 420 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.15 (d, J = 1.8 Hz, 1H), 7.96 (s, 1H), 7.86 (dd, J = 8.2, 1.9 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 6.85 (s, 2H), 3.73 (s, 6H), 3.71 (s, 3H).

(2-Fluoro-4-(furan-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (17). This compound was made using the synthetic procedure described for **30**. Thus **56** (78.6 mg, 0.22 mmol), furan-2-boronic acid (31.2 mg), Pd(dppf)Cl_2 (8.8 mg), and sodium carbonate (45.6 mg) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:2) afforded the desired product **17** (34.9 mg, 45%) as a yellow solid. MS (ESI) m/z 354 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2H), 7.06 (s, 1H), 6.93 (s, 1H), 6.91 (s, 2H), 6.76 (d, J = 2.9 Hz, 1H), 6.50 (m, 1H), 3.92 (s, 3H), 3.87 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.37, 152.90, 152.81, 151.26, 143.14, 140.78, 135.63, 135.28, 134. 86, 124.82, 117.05, 111.97, 111.35, 111.26, 107.64, 106.78, 60.93, 56.27. HRMS (EI) calcd for $C_{20}H_{19}NO_5$ [M]$^+$ 353.1263, found 353.1266. HPLC (method 2) 96.4% (t_R = 19.57 min).

2-Bromo-1-(4-(3,4,5-trimethoxybenzoyl)phenyl)ethanone (58). This compound was made using the synthetic procedure described for **49**. Thus **54** (0.3 g, 0.85 mmol), tributyl (1-ethoxy vinyl)tin (0.52 g, 1.45 mmo), and Pd$(PPh_3)_2Cl_2$ (30 mg, 0.04 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1) afforded the desired product (4-(1-ethoxyvinyl)phenyl)(3,4,5-trimethoxyphenyl)methanone (0.2 g, 69%) as a waxy solid. Next, to a solution of (4-(1-ethoxyvinyl)phenyl)(3,4,5-trimethoxyphenyl)methanone (0.2 g, 0.58 mmol) in THF/water (10 mL, v/v 1:1) was added NBS (0.14 g, 0.76 mmol) at rt. After stirring 2 h, water (10 mL) was added to the reaction mixture. The resulting mixture was diluted with EtOAc (40 mL), washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude corresponding desired product **58** (71 mg, 31%) as a waxy solid. It was used in the following step without further purification.

1-(3-(1*H*-1,2,4-Triazol-1-yl)-4-(3,4,5-trimethoxybenzoyl)phenyl)-2-bromoethanone (59). This compound was made using the synthetic procedure described for **49**. Thus **57** (1.1 g, 2.65 mmol), tributyl (1-ethoxy vinyl)tin (1.53 mL), and Pd$(PPh_3)_2Cl_2$ (93.1 mg) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 20:1−1:2) afforded the desired product (4-(1-ethoxyvinyl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (0.61 g, 54.6%) as a waxy solid. Next, to a solution of (4-(1-ethoxyvinyl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (0.61 g, 1.45 mmol) was added NBS (0.33 g) at rt. After stirring 2 h, water (10 mL) was added to the reaction mixture. The resulting mixture was diluted with EtOAc (50 mL), washed with brine (2 × 15 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude corresponding desired product **59** (0.5 g, 75%) as a waxy solid. It was used in the following step without further purification.

(4-(2-Aminothiazol-4-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)-(3,4,5-trimethoxyphenyl)methanone (22). A solution of **59** (64.6 mg, 0.14 mmol), thiourea (16 mg) in ethanol (3 mL) was refluxed for 2 h. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with satd $NaHCO_3$ solution (20 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 30:1−10:1) to afford the desired product **22** (29.3 mg, 48%) as a white solid. MS (ESI) m/z 438 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.06 (dd, J = 8.0, 1.6 Hz, 1H), 7.97 (s, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.24 (brs, 2H), 6.86 (s, 2H), 3.73 (s, 6H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.07, 168.97, 152.94, 152.66, 148.22, 144.80, 142.33, 138.48, 135.65, 132.06, 131.94, 130.95, 125.94, 121.54, 106.72, 105.51, 60.60, 56.36. HRMS (EI) calcd for $C_{21}H_{19}N_5O_4S$ [M]$^+$ 437.1157, found 437.1155. HPLC (method 3) 97.6% (t_R = 19.02 min).

(4-(2-Methylthiazol-4-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)-(3,4,5-trimethoxyphenyl)methanone (24). A solution of **59** (53.3 mg, 0.12 mmol) and thioacetamide (13 mg) in ethanol (3 mL) was refluxed for 2 h. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with satd $NaHCO_3$ solution (20 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:2−1:5) to afford the desired product **24** (12.3 mg, 24%) as a white solid. MS (ESI) m/z 437 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 8.0, 1.6 Hz, 1H), 7.91 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 6.96 (s, 2H), 3.88 (s, 3H), 3.79 (s, 6H), 2.79 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.47, 166.86, 152.90, 152.57, 152.46, 143.66, 143.01, 137.89, 135.64, 132.99, 131.13, 130.54, 126.21, 122.44, 115.17, 107.01, 60.97, 56.22, 19.38. HRMS (EI) calcd for $C_{22}H_{20}N_4O_4S$ [M]$^+$ 436.1205, found 436.1205. HPLC (method 1) 100% (t_R = 7.08 min).

(4-(2-Aminothiazol-4-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (28). This compound was made using the synthetic procedure described for **22**. Thus **58** (71 mg, 0.18 mmol) and thiourea (18 mg, 0.23 mmol) were used. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 1:2−1:5) to afford the desired product **28** (64 mg, 96%) as a white solid.

MS (ESI) *m/z* 371 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.26 (brs, 2H), 7.03 (s, 2H), 3.81 (s, 6H), 3.77 (s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6) δ 194.17, 168.54, 152.64, 148.35, 141.22, 138.30, 135.48, 132.42, 130.34, 125.47, 107.19, 104.53, 60.21, 56.02. HRMS (EI) calcd for $C_{19}H_{18}N_2O_4S$ [M]$^+$ 370.0987, found 370.0988. HPLC (method 1) 99.4% (t_R = 3.26 min).

***N*-(4-(3-(1*H*-1,2,4-Triazol-1-yl)-4-(3,4,5-trimethoxybenzoyl)-phenyl)thiazol-2-yl)-acetamide (23).** To a solution of **22** (36.9 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was added pyridine (8.2 μL) and acetyl chloride (9.4 μL) at rt. After 2 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 20:1−10:1) to give **23** (13.1 mg, 32%) as a white solid. MS (ESI) *m/z* 479 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 9.02 (s, 1H), 8.25 (d, *J* = 14.0 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.96 (d, *J* = 3.2 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 1H), 6.85 (s, 2H), 3.71 (s, 6H), 3.69 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.01, 169.32, 158.88, 152.99, 152.71, 147.09, 144.80, 137.93, 135.79, 132.66, 131.87, 131.16, 126.05, 121.79, 111.50, 106.94, 60.61, 56.43, 22.93. HRMS (EI) calcd for $C_{23}H_{21}N_5O_5S$ [M]$^+$ 479.1263, found 479.1263. HPLC (method 1) 97.3% (t_R = 4.84 min).

2-Fluoro-4-(thiazol-2-yl)benzaldehyde (61b). To a solution of 3-fluoro-4-formylphenylboronic acid (0.61 g, 3.66 mmol), 2-bromothiazole (0.5 g, 3.05 mmol), and Pd(dppf)Cl_2 (0.12 g) in DME (10 mL) was added sodium carbonate (0.65 g, 6.1 mmol) in water (3 mL) at rt. The reaction mixture was heated in a sealed tube at 150 °C for 2 h. After being cooled to rt, the mixture was diluted with EtOAc (20 mL), washed with water (10 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 9:1−5:1) to afford the desired product **61b** (0.35 g, 56%) as a white solid. MS (ESI) *m/z* 208 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H), 8.05 (d, *J* = 3.2 Hz, 1H), 7.98 (d, *J* = 3.2 Hz, 1H), 7.96−7.92 (m, 3H).

2-Fluoro-4-(2-isopropylthiazol-4-yl)benzaldehyde (61d). This compound was made using the synthetic procedure described for **61b**. Thus 3-fluoro-4-formylphenylboronic acid (0.2 g, 0.16 mmol), 4-bromo-2-isopropylthiazole (0.2 mg, 0.97 mmol), Pd-(dppf)Cl_2 (40 mg, 0.05 mmol), and sodium carbonate (0.2 g, 1.9 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1−5:1) afforded the desired product **61d** (77 mg, 32%) as a white solid. MS (ESI) *m/z* 250 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.89 (t, *J* = 7.8 Hz, 1H), 7.78 (m, 1H), 7.53 (s, 1H), 3.37 (m, 1H), 1.45 (d, *J* = 6.8 Hz, 6H).

2-Fluoro-4-(thiazol-4-yl)benzaldehyde (61e). This compound was made using the synthetic procedure described for **61b**. Thus 3-fluoro-4-formylphenylboronic acid (0.37 g, 2.19 mmol), 4-bromothiazole (0.3 g, 1.83 mmol), Pd(dppf)Cl_2 (75 mg, 0.09 mmol), and sodium carbonate (0.39 g, 3.7 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1−5:1) afforded the desired product **61e** (0.23 g, 59%) as a white solid. MS (ESI) *m/z* 208 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (d, *J* = 0.4 Hz, 1H), 8.91 (d, *J* = 1.9 Hz, 1H), 7.94 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.83−7.79 (m, 2H), 7.74 (d, *J* = 1.9 Hz, 1H).

2-Fluoro-4-(thiazol-5-yl)benzaldehyde (61f). This compound was made using the synthetic procedure described for **61b**. Thus 3-fluoro-4-formylphenylboronic acid (0.25 g, 1.46 mmol), 5-bromothiazole (0.2 g, 1.22 mmol), Pd(dppf)Cl_2 (50 mg, 0.06 mmol), and sodium carbonate (0.19 g, 1.83 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1) afforded the desired product **61f** (0.24 g, 93%) as a white solid. MS (ESI) *m/z* 208 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 9.23 (d, *J* = 0.7 Hz, 1H), 8.59 (d, *J* = 0.7 Hz, 1H), 7.89 (t, *J* = 7.9 Hz, 1H), 7.85 (dd, *J* = 11.9, 1.6 Hz, 1H), 7.70 (dt, *J* = 8.0, 1.3 Hz, 1H).

(2-Fluoro-4-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanol (62b). To a solution of **61b** (0.35 g, 1.69 mmol) in dry THF (5 mL) was added dropwise (3,4,5-trimethoxyphenyl)-magnesium bromide (2.0 mL, 1.0 M in THF, prepared in advance with a small piece of iodine) at 0 °C. After complete addition, the reaction mixture was stirred at rt overnight. The reaction was quenched with satd NH_4Cl solution (1 mL). The suspension was diluted with EtOAc (50 mL), washed with water (20 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 7:1−3:1) afforded the desired product (0.2 g, 32%) as a yellow solid. MS (ESI) *m/z* 376 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 3.3 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.61 (m, 2H), 7.34 (d, *J* = 3.2 Hz, 1H), 6.62 (s, 2H), 6.05 (s, 1H), 3.80 (s, 9H).

(2-Fluoro-4-(2-isopropylthiazol-4-yl)phenyl)(3,4,5-trimethoxy-phenyl)methanol (62d). This compound was made using the synthetic procedure described for **62b**. Thus **61d** (77 mg, 0.31 mmol) and (3,4,5-trimethoxyphenyl)magnesium bromide (0.5 mL, 1.0 M in THF, prepared in advance) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product (83 mg, 64%) as a colorless oil. MS (ESI) *m/z* 418 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.52 (m, 1H), 7.33 (s, 1H), 6.64 (s, 2H), 6.09 (s, 1H), 3.82 (s, 9H), 3.35 (m, 1H), 2.37 (s, 1H), 1.43 (d, *J* = 6.8 Hz, 6H).

(2-Fluoro-4-(thiazol-4-yl)phenyl)(3,4,5-trimethoxyphenyl)methanol (62e). This compound was made using the synthetic procedure described for **62b**. Thus **61e** (0.23 g, 1.03 mmol) and (3,4,5-trimethoxyphenyl)magnesium bromide (2.0 mL, 1.0 M in THF, prepared in advance) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product (0.37 g, 90%) as a colorless oil. MS (ESI) *m/z* 376, 358 [M + H − H_2O]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.0 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.58 (dd, *J* = 11.5, 1.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 6.64 (s, 2H), 6.09 (d, *J* = 3.8 Hz, 1H), 3.82 (s, 6H), 3.81 (s, 3H), 2.78 (d, *J* = 3.9 Hz, 1H).

(2-Fluoro-4-(thiazol-5-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanol (62f). This compound was made using the synthetic procedure described for **62b**. Thus **61e** (0.13 g, 0.63 mmol) and (3,4,5-trimethoxyphenyl)magnesium bromide (1.0 mL, 1.0 M in THF, prepared in advance) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product (53 mg, 22%) as a yellow oil. MS (ESI) *m/z* 376 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 0.6 Hz, 1H), 8.01 (d, *J* = 0.6 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.35 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.23 (dd, *J* = 11.0, 1.8 Hz, 1H), 6.65 (s, 2H), 6.08 (d, *J* = 3.6 Hz, 1H), 3.83 (s, 6H), 3.81 (s, 3H), 2.96 (d, *J* = 3.8 Hz, 1H).

(2-Fluoro-4-(furan-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (63a). To a solution of **55** (0.8 g, 2.17 mmol), furan-2-boronic acid (0.36 g, 3.25 mmol), and Pd(dppf)Cl_2 (88 mg, 0.11 mmol) in DME (10 mL) was added sodium carbonate (0.46 g, 4.33 mmol) in water (3 mL) at rt. The reaction mixture was heated in a sealed tube at 150 °C for 2 h. After being cooled to rt, the mixture was diluted with EtOAc (20 mL), washed with water (10 mL) and brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/CH_2Cl_2, 2:1) afforded the desired product **63a** (0.48 g, 62%) as a white solid. MS (ESI) *m/z* 357 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 3H), 7.45 (d, *J* = 10.9 Hz, 1H), 7.10 (s, 2H), 6.81 (d, *J* = 3.4 Hz, 1H), 6.53 (m, 1H), 3.94 (s, 3H), 3.86 (s, 6H).

(2-Fluoro-4-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (63b). To a solution of **62b** (0.2 g, 0.52 mmol) in CH_2Cl_2 (20 mL) was added 4 Å molecular sieves (0.2 g) and pyridinium dichromate (0.3 g, 0.78 mmol) at rt. The reaction mixture was stirred at rt for 5 h, the suspension was filtered over a Celite pad, and the solution was evaporated to dryness. The residue was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2, 2:1) to afford the desired product **63b** (0.17 g, 89%) as a white solid. MS (ESI) m/z 374 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (d, J = 3.2 Hz, 1H), 7.96−7.92 (m, 3H), 7.71 (t, J = 7.4 Hz, 1H), 7.09 (s, 2H), 3.80 (s, 6H), 3.79 (s, 3H).

(3-Fluoro-5′-hydroxybiphenyl-4-yl)(3,4,5-trimethoxyphenyl)-methanone (63c). This compound was made using the synthetic procedure described for **63a**. Thus **55** (80 mg, 0.22 mmol), 3-hydroxyphenylboronic acid (45 mg, 0.33 mmol), Pd(dppf)Cl_2 (9 mg, 0.01 mmol), and sodium carbonate (46 mg, 0.43 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−2:1) afforded the desired product **63c** (60 mg, 71%) as a white solid. MS (ESI) m/z 383 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (t, J = 7.5 Hz, 1H), 7.46 (dd, J = 8.0, 1.6 Hz, 1H), 7.34 (m, 2H), 7.20 (d, J = 6.8 Hz, 1H), 7.14 (s, 2H), 7.11 (s, 1H), 6.90 (m, 1H), 5.31 (brs, 1H), 3.95 (s, 3H), 3.87 (s, 6H).

(2-Fluoro-4-(2-isopropylthiazol-4-yl)phenyl)(3,4,5-trimethoxy-phenyl)methanone (63d). This compound was made using the synthetic procedure described for **63b**. Thus **62d** (83 mg, 0.2 mmol), 4 Å molecular sieves (0.1 g), and pyridinium dichromate (0.11 g, 0.3 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1) afforded the desired product **63d** (70 mg, 84%) as a white solid. MS (ESI) m/z 416 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.48 (s, 1H), 7.11 (s. 2H), 3.93 (s, 3H), 3.85 (s, 6H).

(2-Fluoro-4-(thiazol-4-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (63e). This compound was made using the synthetic procedure described for **63b**. Thus **62e** (0.37 g, 0.98 mmol), 4 Å molecular sieves (0.4 g), and pyridinium dichromate (0.56 g, 1.48 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product **63e** (0.18 g, 48%) as a white solid. MS (ESI) m/z 374 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 7.9, 1.6 Hz, 1H), 7.79 (dd, J = 10.9, 1.4 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 1.1 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 6H).

(2-Fluoro-4-(thiazol-5-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (63f). This compound was made using the synthetic procedure described for **63b**. Thus **62f** (0.87 g, 2.31 mmol), 4 Å molecular sieves (0.9 g), and pyridinium dichromate (1.13 g, 3.0 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product **63f** (0.48 g, 56%) as a white solid. MS (ESI) m/z 374 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 0.5 Hz, 1H), 8.19 (d, J = 0.6 Hz, 1H), 7.59 (dd, J = 7.9, 7.2 Hz, 1H), 7.48 (dd, J = 8.0, 1.7 Hz, 1H), 7.39 (dd, J = 10.4, 1.6 Hz, 1H), 7.11 (d, J = 1.1 Hz, 2H), 3.94 (s, 3H), 3.86 (s, 6H).

(4-(Furan-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (19). A solution of **63a** (0.48 g, 1.35 mmol) and sodium 1,2,4-triazole (0.37 g, 4.04 mmol) in DMF (8 mL) was heated at 120 °C for 4 h. After being cooled to rt, the suspension was diluted with EtOAc (50 mL), washed with satd NH_4Cl solution (20 mL) and then brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:1) afforded the desired product **19** (0.21 g, 38%) as a white solid. MS (ESI) m/z 406 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.29 (s, 1H), 7.92 (s, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.83 (dd, J = 8.0, 1.6 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.56 (dd, J = 1.7, 0.5 Hz, 1H), 6.95 (s, 2H), 6.87 (dd, J = 3.4, 0.5 Hz, 1H), 6.55 (dd, J = 3.4, 1.8 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.26, 152.92, 152.53, 151.50, 143.75, 143.67, 143.22, 135.75, 134.13, 132.22, 131.10, 130.60, 123.59, 119.73, 112.26, 108.07, 107.18, 60.90, 56.24. HRMS (EI) calcd for $C_{22}H_{19}N_3O_5$ [M]$^+$ 405.1324, found 405.1321. HPLC (method 1) 97.8% (t_R = 8.19 min).

(4-(Thiazol-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (20). This compound was made using the synthetic procedure described for **19**. Thus **63b** (50 mg, 0.13 mmol) and sodium 1,2,4-triazole (37 mg, 0.4 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:2) afforded the desired product **20** (29 mg, 53%) as a white solid. MS (ESI) m/z 423 [M + H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.33 (d, J = 1.7 Hz, 1H), 8.21 (dd, J = 8.0, 1.7 Hz, 1H), 8.06 (d, J = 3.2 Hz, 1H), 7.99 (s, 1H), 7.97 (d, J = 3.2 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 6.89 (s, 2H), 3.74 (s, 6H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.68, 165.26, 153.05, 152.80, 144.98, 144.81, 142.69, 136.32, 135.85, 134.73, 131.62, 131.42, 126.74, 122.81, 121.92, 106.94, 60.64, 56.48. HRMS (EI) calcd for $C_{21}H_{18}N_4O_4S$ [M]$^+$ 422.1048, found 422.1043. HPLC (method 1) 100% (t_R = 6.02 min).

(5′-Hydroxy-3-(1*H*-1,2,4-triazol-1-yl)biphenyl-4-yl)(3,4,5-trimethoxyphenyl)methanone (21). This compound was made using the synthetic procedure described for **19**. Thus **63c** (57 mg, 0.15 mmol) and sodium 1,2,4-triazole (41 mg, 0.45 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:2) afforded the desired product **21** (5 mg, 8%) as a white solid. MS (ESI) m/z 432 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.3 (s, 1H), 7.94 (s, 1H), 7.80 (m, 1H), 7.76 (dd, J = 8.0, 1.7 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.23 (m, 1H), 7.14 (m, 1H), 6.99 (s, 2H), 6.92 (m, 1H), 3.90 (s, 3H), 3.81 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) 193.07, 158.47, 158.32, 153.00, 152.65, 144.82, 143.93, 142.41, 139.75, 135.68, 132.41, 131.91, 131.00, 130.65, 127.06, 122.51, 118.39, 118.36, 116.15, 116.05, 114.36, 114.27, 106.77, 60.62, 56.40. HRMS (EI) calcd for $C_{24}H_{21}N_3O_5$ [M]$^+$ 431.1481, found 431.1478. HPLC (method 1) 98.5% (t_R = 5.87 min).

(4-(2-Isopropylthiazol-4-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)-(3,4,5trimethoxy-phenyl)methanone (25). This compound was made using the synthetic procedure described for **19**. Thus **63d** (63 mg, 0.15 mmol) and sodium 1,2,4-triazole (21 mg, 0.23 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 5:1) afforded the desired product **25** (9 mg, 13%) as a white solid. MS (ESI) m/z 465 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.08 (dd, J = 8.04, 1.6 Hz, 1H), 7.92 (s, 1H), 7.64 (d, J = 9.4 Hz, 1H), 7.56 (s, 1H), 6.97 (s, 2H), 3.89 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.47, 178.84, 152.93, 152.55, 152.20, 143.19, 138.19, 135.63, 133.03, 131.18, 130.43, 126.27, 122.55, 114.27, 107.18, 60.91, 56.25, 33.49, 23.14. HRMS (EI) calcd for $C_{24}H_{24}N_4O_4S$ [M]$^+$ 464.1518, found 464.1513. HPLC (method 1) 97.2% (t_R = 11.74 min).

(4-(Thiazol-4-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (26). This compound was made using the synthetic procedure described for **19**. Thus **63e** (0.1 g, 0.27 mmol) and sodium 1,2,4-triazole (75 mg, 0.82 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:3) afforded the desired product **26** (40 mg, 35%) as a white solid. MS (ESI) m/z 423 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 1.9 Hz, 1H), 8.35 (s, 1H), 8.22 (d, J = 1.5 Hz, 1H), 8.11 (dd, J = 8.0, 1.6 Hz, 1H), 7.91 (s, 1H), 7.77 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 6.97 (s, 2H), 3.88 (s, 3H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.41, 153.80, 153.70, 152.92, 152.60, 143.65, 143.07, 137.54, 135.68, 133.30, 131.07, 130.60, 126.39, 122.57, 115.41, 107.04, 60.97, 56.23. HRMS (EI) calcd for $C_{21}H_{18}N_4O_4S$ [M]$^+$ 422.1048, found 422.1045. HPLC (method 1) 95.4% (t_R = 5.79 min).

(4-(Thiazol-5-yl)-2-(1*H*-1,2,4-triazol-1-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (27). This compound was made using the synthetic procedure described for **19**. Thus **63f** (60 g, 0.16 mmol) and sodium 1,2,4-triazole (44 mg, 0.48 mmol) were used. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 3:1−1:2) afforded the desired product **27** (20 mg, 30%) as a white solid. MS (ESI) m/z 423 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 0.4 Hz, 1H), 8.29 (s, 1H), 8.26 (d, J = 0.5 Hz, 1H), 7.95 (s, 1H), 7.84

(d, J = 1.7 Hz, 1H), 7.79 (dd, J = 8.0, 1.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 6.96 (s, 2H), 3.89 (s, 3H), 3.82 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.00, 153.72, 152.99, 152.80, 143.87, 143.40, 140.82, 136.83, 135.84, 134.81, 133.50, 130.84, 130.70, 126.96, 123.03, 107.14, 60.98, 56.30. HRMS (EI) calcd for $C_{21}H_{18}N_4O_4S$ $[M]^+$ 422.1048, found 422.1051. HPLC (method 1) 98.1% (t_R = 4.75 min).

(2-(4-Methoxybenzylamino)-4-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)methanone (64). To a solution of **63b** (0.41 g, 1.09 mmol) and K_2CO_3 (0.45 g) in DMF (5 mL) was added 4-methoxybenzylamine (0.21 mL) at rt. The reaction mixture was heated at 130 °C for 5 h. After being cooled to rt, the suspension was diluted with EtOAc (50 mL), washed with satd NH_4Cl solution (20 mL) and then brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:2) afforded the desired product **64** (0.40 g, 75%) as a yellow solid. MS (ESI) m/z 491 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (m, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.43 (m, 1H), 7.36 (m, 3H), 7.16 (dd, J = 8.3, 1.6 Hz, 1H), 6.90 (s, 3H), 6.88 (s, 1H), 4.50 (d, J = 5.2 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 6H), 3.79 (s, 3H).

(2-Amino-4-(thiazol-2-yl)phenyl)(3,4,5-trimethoxyphenyl)-methanone (18). A solution of **64** (0.4 g, 0.82 mmol) in TFA (3 mL) was stirred for 1 h at rt. The reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (50 mL) and washed with satd $NaHCO_3$ solution (20 mL) and then brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 2:1−1:2) afforded the desired product **18** (0.19 g, 62%) as a white solid. MS (ESI) m/z 371 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 3.2 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.38 (m, 2H), 7.18 (dd, J = 8.3, 1.6 Hz, 1H), 6.92 (s, 2H), 3.92 (s, 3H), 3.86 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.38, 167.14, 152.85, 151.01, 144.04, 141.10, 138.03, 134.90, 134.82, 119.95, 119.04, 114.44, 113.74, 106.93, 60.94, 56.28. HRMS (EI) calcd for $C_{19}H_{18}N_2O_4S$ $[M]^+$ 370.0987, found 370.0988. HPLC (method 1) 94.0% (t_R = 8.91 min).

(*S*)-*N*-(4-(3-(1*H*-1,2,4-Triazol-1-yl)-4-(3,4,5-trimethoxybenzoyl)phenyl)thiazol-2-yl)-2-amino-3-methylbutanamide hydrochloride (65, CKD-516). To a solution of Fmoc-Val-OH (2.04 g, 6.01 mmol) in CH_2Cl_2 (7 mL) was added DMF (2 drops) and $SOCl_2$ (0.66 mL) at rt. The reaction was refluxed for 3 h. After being cooled to rt, the reaction mixture was concentrated to dryness under reduced pressure. The solid product was stirred with hexane and filtered through in vacuo. It was used in the following step without purification. Thus, to a solution of **22** (0.21 g, 0.4 mmol) and Fomc-Val-Cl (0.43 g) in CH_2Cl_2 (10 mL) was added DIPEA (0.1 mL) and pyridine (0.1 mL) at rt. After stirring 2 h, the suspension was diluted with EtOAc (100 mL), washed with satd NH_4Cl solution (30 mL) and then brine (25 mL) and then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexane/EtOAc, 1:1−1:5) afforded the desired product (*S*)-(9*H*-fluoren-9-yl)methyl 1-(4-(3-(1*H*-1,2,4-triazol-1-yl)-4-(3,4,5-trimethoxybenzoyl)phenyl)thiazol-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (0.26 g, 85%) as a white solid. Next, to a solution of the above product (0.26 g, 0.34 mmol) in CH_3CN (3 mL) was added piperidine (0.04 mL) at rt. After stirring for 12 h, the reaction mixture was concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with satd NH_4Cl solution (30 mL) and then brine and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 30:1−10:1) to afford the coupling product (0.13 g, 71%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.30 (d, J = 1.5 Hz, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.99 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 6.87 (s, 2H), 5.44 (brs, 2H), 3.73 (s, 6H), 3.71 (s, 3H), 3.29 (d, J = 5.9 Hz, 1H), 1.93 (m, 1H), 0.89 (dd, J = 15.2, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.61, 174.69, 158.64, 152.56, 152.33, 146.76, 144.41, 141.97, 137.52, 135.36, 132.16, 131.45, 130.77, 125.64, 121.31, 111.22, 106.33, 60.22, 60.20, 55.96, 31.85, 19.49, 17.57. HPLC (method 3) 98.7% (t_R = 13.04 min).

To a solution of the above product (0.13 g, 0.24 mmol) in MeOH (3 mL) was added HCl (4.0 M in dioxane) at rt. After stirring 20 min, the mixture was treated with Et_2O then filtered and dried in vacuo at rt to afford the desired product CKD-516 (0.11 g, 76%) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.10 (s, 1H), 8.62 (brs, 3H), 8.32 (d, J = 1.6 Hz, 1H), 8.18 (dd, J = 8.0, 1.6 Hz, 1H), 8.13 (s, 1H), 7.99 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 6.87 (s, 2H), 3.97 (m, 1H), 3.73 (s, 6H), 3.70 (s, 3H), 2.25 (m, 1H), 0.99 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.57, 167.61, 157.34, 152.57, 152.36, 147.12, 144.42, 142.01, 137.13, 135.37, 132.38, 131.40, 130.84, 125.72, 121.36, 112.14, 106.35, 60.21, 57.43, 55.98, 29.95, 18.37, 17.91. HRMS (ESI) calcd for $C_{26}H_{29}ClN_6O_5S$ $[M + H]^+$ 537.1915, found 537.1915. HPLC (method 3) 98.3% (t_R = 12.77 min). Anal. Calcd for $C_{26}H_{29}ClN_6O_5S$: C, 52.83; H, 5.29; N, 14.22; O, 16.24; S, 5.42. Found: C, 51.28; H, 5.13; N, 13.67; O, 16.43; S, 5.27.

Cancer Cell Lines. HL60 (leukemia), HCT-116, and HCT-15 (colorectal cancer) cell lines were obtained from the ATCC (USA). HCT-116 was grown in McCoy's 5A medium containing 10% heat-inactivated fetal bovine serum, and the others were grown in RPMI-1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) at 37 °C under a humidified 5% CO_2 atmosphere.

MTT Assay. HL60 cells were seeded into 96-well plates and the compound diluents were added. After 72 h incubation at 37 °C in a humidified 5% CO_2 atmosphere, cell viability was determined by addition of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, final concentration of 0.25 mg/mL).

Animals. Male BALB/C nu/nu mice were obtained from the Central Animal Lab. Inc. (Seoul, Korea). Procedures involving animals and their care were conducted in conformity with institutional guidelines, which are in compliance with Korean Animal Welfare Act. Mice were used with 5−6 weeks of age.

Antitumor Activity in Mouse Xenografts. HCT-116, HCT-15 cells were implanted sc in the flanks of nude mice. After 20−25 days, tumors from several animals were excised. The viable portion of the tumor was fragmented and implanted sc in the flanks of nude mice. Therapy was started after tumor volumes reached to 100−200 mm^3. Tested compounds were administered ip dissolved in a vehicle mixture of Cermophore:EtOH:saline = 1:1:8. Compounds were administered on days 2, 6, 10, and 14. The mice were observed daily for mortality and signs of toxicity. Tumors and body weights were measured 2−3 times per week. Tumor volume was monitored using external measurements with a caliper and tumor volumes were calculated using the formula (width^2 × length)/2.

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