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Synthesis and Structure-Activity Relationship Studies of HIV-1 Virion Infectivity Factor (Vif) Inhibitors that Block Viral Replication

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Abstract

The HIV-1 Vif protein, essential for in vivo viral replication, protects the virus from innate antiviral cellular factor APOBEC3G (A3G), and is an attractive target for developing antiviral therapeutics. Here we have evaluated the structure-activity relationships of RN18, a small molecule recently identified as an inhibitor of Vif function that blocks viral replication only in non-permissive cells expressing A3G, by inhibiting Vif-A3G interactions. Microwave-assisted cross-coupling reactions were developed to prepare a series of RN18 analogues with diverse linkages and substitutions on the phenyl rings. A dual cell-based assay system was used to assess antiviral activity against wild-type HIV-1 in both non-permissive (H9) and permissive (MT-4) cells that also allowed evaluation of specificity. In general, variations of phenyl substitutions were detrimental for antiviral potency and specificity, but isosteric replacements of amide and ether linkages were relatively well tolerated. These SAR data define structural requirements for Vif-specific activity, identify new compounds with improved antiviral potency and specificity, and provide leads for further exploration to develop new antiviral therapeutics.

Keywords

APOBEC3G; HIV-1 Vif; inhibitors; structure-activity relationships; drug discovery; antiviral agents

Introduction

Since the start of the AIDS epidemic in 1981, this disease has led to the death of nearly 30 million people globally. Although the overall growth of the epidemic appears to be slowing, nearly three million new infections and an estimated 1.8 million AIDS-related deaths are still very high.^[1] Over the past two decades, more than 25 anti-HIV drugs have been developed targeting several different stages of the virus life cycle.^[2] Among them inhibitors of HIV-1 reverse transcriptase and protease, when used in combinations in the highly active antiretroviral therapy (HAART),^[3] have proven to be highly effective in reducing AIDS-

related mortality throughout the world.^[1] However, the development of drug resistance and toxic side effects associated with HAART have created a need for more potent and less toxic therapies against other viral targets and host-virus interactions.^[4]

The HIV-1 virion infectivity factor (Vif) is one of only 6 regulatory proteins encoded by the virus, and is required for *in vivo* viral replication.^[5–7] Vif targets innate antiviral cellular factor APOBEC3G (A3G),^[8] a human DNA-editing enzyme, which, along with other APOBEC proteins, inhibits replication of retroviruses and retrotransposons.^[9–12] In the absence of Vif, A3G incorporates into virions and causes extensive mutations during reverse transcription by catalyzing Zn-dependent hydrolytic deamination of deoxycytidine (dC) to deoxyuridine (dU) in the newly synthesized minus strand of viral DNA, rendering the virus noninfectious.^[13] In addition to this deaminase-dependent mechanism, A3G can act in a deaminase-independent mechanism by directly inhibiting reverse transcription.^[14] Vif overcomes the innate antiviral activity of A3G in several different ways, including promoting its degradation in the E3-ubiquitin-proteasome pathway,^[15–17] modulating its expression by inhibiting translation,^[18] and directly interfering with packaging,^[19] thus protecting viral progeny from this innate antiviral defense mechanism.

Since HIV-1 Vif has no known cellular homologs, this protein represents an extremely attractive, yet unrealized, target for antiviral intervention. Although zinc-chelating agent *N,N,N,N*-tetrakis-(2-pyridylmethyl) ethylenediamine (PTEN) is reported to inhibit Vif activity and restore A3G function,^[20] this effect is due the requirement of zinc for Vif function and is unrelated to its interactions with A3G. Small molecules that specifically inhibit Vif function will restore cellular levels of A3G along with its antiviral activity, leading to the inhibition of viral replication.

We recently described the development of a fluorescence-based high throughput screening (HTS) assay to identify small molecules that specifically inhibit Vif-A3G interactions.^[21] Screening of a diverse 30K small molecule library identified two compounds, RN18 and RN19 (Figure 1), that specifically antagonize HIV-1 Vif function and inhibit viral replication only in the presence of A3G.^[21] RN18 and RN19 inhibit HIV-1 replication in a dose-dependent manner (IC_{50} = 6 μ M and 25 μ M, respectively) only in non-permissive cells (H9, CEM) expressing A3G, and not in permissive cells (MT-4), which do not express A3G. In addition, RN18 increases cellular levels of A3G in a Vif-dependent manner and increases A3G incorporation into the virions, leading to the production of less infectious viruses. These results strongly suggest that RN18 is a Vif-specific inhibitor of HIV-1 replication, and that targeting the Vif-A3G axis is a valid strategy for developing antiviral therapeutics for HIV-1 infection and for enhancing innate immunity against viruses.

Recently, Cen *et al.* reported the identification of two small molecules, IMB26 and IMB35, that inhibit HIV-1 replication by specifically stabilizing A3G.^[22] Unlike RN18, these molecules increase cellular A3G levels in a Vif-independent manner, suggesting a different mechanism of action unrelated to Vif. RN18 and RN19 remain the only Vif antagonists that inhibit HIV-1 replication by specifically targeting Vif-A3G interactions. To identify structural features required for the Vif-specific activity of RN18 and to improve antiviral potency and pharmacological properties, we prepared a series of closely related analogues with diverse ring linkages and substitutions. These analogues were tested for antiviral activity against wild-type HIV-1 in both non-permissive (H9) and permissive (MT-4) cells to determine their specificity. In addition, cytotoxicity was assessed to rule out non-specific antiviral activity. We report here the design, synthesis and structure-activity relationship studies of RN18 analogues, leading to the identification of several new compounds with improved antiviral potency, specificity and toxicity profiles.

Design and Synthesis

We envisioned preparing RN18 analogues with diverse ring linkages and substitutions using the two synthetic routes outlined in Figure 2. Both methods involve cross-coupling of substituted aryl halides with either thiols or phenols using Cu-based catalysts. The direct coupling of pre-assembled aryl iodides with substituted thiophenols can provide easy access to RN18 and A-ring analogues. This convergent method is particularly attractive as it allows access to analogues with diverse linkages between phenyl rings B and C, such as reverse amide, sulfonamide, and reverse sulfonamide. The second route involving initial coupling of aryl iodides and methyl 2-mercaptobenzoate is suitable for quickly assembling diverse C-ring analogues after ester hydrolysis followed by coupling with aryl or alkyl amines.

In recent years, a number of metal-catalyzed cross-coupling reactions have been developed for the coupling of aryl iodides and thiophenols.^[23–25] Among them, Ullmann-type Cu-catalyzed coupling methods are highly attractive because of their efficiency, mild reaction conditions, and broad substrate scope. Due to its simplicity of operation, we chose to use the cross-coupling method developed by Kwong and Buchwald using ethylene glycol as a ligand and potassium carbonate as a base in 2-propanol.^[26] Thus the coupling of 2-iodo-*N*-(2-methoxyphenyl)benzamide (**1a**) and thiophenol **2** under these conditions provided the aryl sulfide product **4a** in 60% yield after purification (Scheme 1). However, attempts to couple **1a** with 4-nitrothiophenol **3** under the same conditions were unsuccessful, presumably due to low reactivity of **3** in the cross-coupling reaction. Reaction conditions of Bates *et al.* involving neocuproine as a ligand and NaO*t*-Bu as a base also failed to provide the desired aryl sulfide **5a**.^[27] Microwave irradiation has been shown to enhance the efficiency of cross-coupling reactions, including copper(I) iodide-catalyzed coupling of aryl halides and thiophenols as observed by Wu *et al.*^[28] After initial optimization of microwave conditions, reaction of **1a** and **3** with copper(I) iodide, ethylene glycol, and potassium carbonate in 2-propanol followed by irradiating the resulting mixture in a microwave reactor (CEM Explorer) at 80 °C for 30 min twice provided the desired product **5a** (RN18) in 63% yield after purification by flash chromatography.

As illustrated in Scheme 1, the optimized cross-coupling conditions proved to be efficient, allowing the coupling of a variety of 2- and 3-substituted aryl iodide substrates **1a–g** with 4-nitrothiophenol **3**. The intermediate aryl iodides **1a–g**, were prepared by the reaction of appropriate anilines and acid chlorides or sulfonyl chlorides (see Supporting Information for details). Parallel reactions of aryl iodides **1a–g** and 4-nitrothiophenol under the optimized cross-coupling conditions provided the corresponding aryl sulfides **5a–g** in 25–62% isolated yield. The RN18 analogues **5a–g** contain a variety of linkages between rings B and C, including reverse amide (**5c**, **5f–g**), sulfonamide (**5d**), and reverse sulfonamides (**5e**). Reduction of the 4-nitro group in **5a–e** using SnCl₂·2H₂O in ethyl acetate provided the corresponding 4-amino analogues **6a–e**.

To prepare RN18 and series of C-ring analogues, we developed an alternate synthetic route as outlined in Scheme 2. This method involved initial cross-coupling of aryl iodides and methyl 2-mercaptobenzoate (**7**) to provide the corresponding esters **10–11**. In this case, re-optimization of microwave-assisted cross-coupling conditions was necessary due to the presence of a methyl ester in the thiophenol. Thus, reacting **7** and **8** with copper(I) iodide and potassium carbonate in 1,2-dimethoxyethane (DME) instead of 2-propanol and irradiating the resulting mixture in a microwave reactor at 80 °C for 30 min twice provided the ester **10** in 86% isolated yield; the reaction was scaled up to 30 mmol using open vessel microwave irradiation. The resulting esters **10–11** were hydrolyzed to obtain the corresponding acids **12–13** in excellent yield. Acid activation using oxalyl chloride followed by reaction of the resulting benzoyl chloride with a variety of aromatic and aliphatic amines

14a–h afforded C-ring analogues **15–16**. Similarly, activation of commercially available acid **17** with oxalyl chloride followed by reaction of the resulting benzoyl chloride with amines provided the ether-linked benzamide derivatives **18**. Reduction of the 4-nitro group in **18a** provided the corresponding 4-amino analogue **19a** (Scheme 2).

Next, we prepared a series of analogues with aryl ether and benzyl ether linkages between rings A and B using synthetic methods outlined in Scheme 3. A set of ether-linked analogues with variations on the A-ring was prepared using a modified Ullmann cross-coupling method developed by Buck *et al.*, involving copper(I) chloride and 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as the catalyst system.^[29] Reactions of aryl bromides **1j–l**, prepared by the reaction of appropriate anilines with acid chloride or sulfonyl chloride (see Supporting Information for details), and substituted phenols **20–21** with copper(I) chloride, TMHD, and cesium carbonate in *N*-methylpyrrolidinone followed by irradiating the reaction mixture in a microwave reactor provided the desired ether-linked analogues **22–23**. Another set of ether-linked analogues was prepared using aryl boronic acids as donors in cross-coupling reactions with phenol (Scheme 3). Reaction of 2-substituted phenol **1k** and a variety of 4-substituted aryl boronic acids **24–28** using copper acetate as the catalyst and Et₃N as a base provided the corresponding ether-linked reverse amide derivatives **29–33**.

The benzyl ether-linked analogues **40–45** were prepared from 2-substituted phenols and a variety of substituted benzyl bromides (Scheme 3). The S_N2 displacement reactions, involving phenols **1j–k** and benzyl bromides **34–39**, were carried out in dimethylformamide (DMF) using K₂CO₃ as a base, followed by irradiating the reaction mixture in a microwave reactor at 90 °C for 30 min twice, providing the desired benzyl ether-linked derivatives **40–45** in good yield.

Results and Discussion

We determined the antiviral activities of RN18 analogues against wild-type HIV-1 in non-permissive H9 cells expressing A3G, as well as in permissive MT-4 cells, which do not express A3G, and examined cytotoxicity using MTT-based cell viability assays (Table 1). For antiviral assays, cells were infected with an X4-tropic HIV-1 variant (HIV-1_{LAI}) in the presence and absence of inhibitors and viral replication was assessed by measuring the reverse transcriptase (RT) activity. RN18 (**5a**), used as a control, inhibited RT activity and viral replication in a dose-dependent manner in non-permissive H9 cells with an IC₅₀ of 6 μM, but did not affect RT activity in permissive MT4 cells up to 100 μM.

The isosteric replacement of amide linkage between rings B and C did not significantly affect the antiviral potency, but had a major effect on specificity, as some analogues showed activity in both H9 and MT4 cells. The reverse amide analogue **5c** inhibited viral replication in H9 cells (H9 IC₅₀ = 5.5 μM) with similar potency as RN18, but also showed weak activity in MT4 cells (MT4 IC₅₀ = 52 μM). The sulfonamide analogue **5d**, which is also equipotent to RN18 in H9 cells (H9 IC₅₀ = 5.9 μM), did not show activity in MT4 cells up to 100 μM. Similar to the reverse amide analogue **5c**, the reverse sulfonamide compound **5e** also showed activity in both H9 (H9 IC₅₀ = 21.5 μM) and MT4 cells (MT4 IC₅₀ = 39 μM). The reverse amide derivative **5f** has an activity profile similar to **5c**, exhibiting potent activity in H9 cells (H9 IC₅₀ = 5.2 μM) and relatively weak activity in MT4 cells (MT4 IC₅₀ = 53.6 μM). These results suggest that amide or sulfonamide linkage between phenyl rings B and C is important for Vif-specific antiviral activity, as reversing the linkage may be detrimental for the specificity.

Compared to the A-ring 4-nitro compounds **5a–e**, the corresponding 4-amino analogues **6a–e** were generally less potent. Similar to the corresponding nitro compounds, the amide and

sulfonamide analogues **6a** and **6d** maintained specificity and inhibited viral replication only in H9 cells, but the reverse amide and reverse sulfonamide compounds **6c** and **6e** inhibited replication in both H9 and MT-4 cells. Only the sulfonamide analogue **6d** (H9 IC₅₀ = 9.3 μ M) exhibited antiviral potency and specificity profile similar to the parent nitro compound **5d**, suggesting that the phenyl ring A may be amenable to various substitutions.

The C-ring analogues **15b–f** with a variety of substitutions on the aromatic ring were all significantly less potent than RN18. Interestingly, the C-ring analogue **15h** with a non-aromatic group showed potent antiviral activity, but no specificity; it inhibited replication in both H9 (IC₅₀ = 3.9 μ M) and MT-4 cells (IC₅₀ = 3.7 μ M). However, unlike other non-specific analogues, **15h** was significantly less toxic, suggesting that its mechanism of action may be different from RN18. Similarly, analogues **16a** and **16d** with the 2-chloro-4-nitrophenyl A-ring exhibited potent antiviral activity, but lacked specificity, even though both contain amide linkage between rings B and C. In general, compounds with C-ring modifications showed reduced antiviral activity and specificity.

Next, we examined the role of thio-ether linkage between phenyl rings A and B by replacing it with either ether or benzyl ether. Compared to RN18, the corresponding ether analogue **18a** inhibited viral replication in both H9 (IC₅₀ = 4.7 μ M) and MT4 cells (IC₅₀ = 15.2 μ M), showing significant loss of specificity. Since **18a** also exhibited significant toxicity (CC₅₀ = 15 μ M), its antiviral effects are probably unrelated to Vif inhibition. The ether-linked analogues **19–33** with variations on the A ring provided interesting structure-activity relationships in this series. The A ring 1,3-benzodioxolane derivative **23h** selectively inhibited viral replication in H9 cells (IC₅₀ = 12.6 μ M) with no toxicity up to 100 μ M. The reverse amide derivative **30k** with the dimethylaminophenyl group potently inhibited replication in H9 cells (IC₅₀ = 2.5 μ M), weak activity in MT-4 cells (IC₅₀ = 68 μ M), and no toxicity up to 100 μ M, indicating significant specificity. The 4-methoxyphenyl derivative **31k** (H9 IC₅₀ = 9.7 μ M), though less potent than **30k**, also showed some specificity. These results suggest that, unlike the reverse amide thio-ether analogues, the ether-linked reverse amide analogues possess significant antiviral activity and their specificity can be influenced by variations at the phenyl ring A.

The benzyl ether-linked analogue **40j** potently inhibited HIV-1 replication in H9 cells (H9 IC₅₀ = 2.8 μ M), showed no activity in MT-4 cells (MT-4 IC₅₀ >100 μ M) and no toxicity up to 100 μ M, exhibiting a specificity profile similar to RN18. The reverse amide compound **40k** (H9 IC₅₀ = 34 μ M) has reduced antiviral potency but exhibited no specificity (MT-4 IC₅₀ = 26.6 μ M). Compared to **40j**, the 3-nitrophenyl analogue **41j** showed slightly reduced potency in H9 cells (IC₅₀ = 7.1 μ M) with a similar specificity profile (MT-4 IC₅₀ >100 μ M). In contrast, the 4-cyanophenyl analogue **42j** exhibited potent activity in H9 cells (IC₅₀ = 3.1 μ M), but has reduced specificity as it also inhibited replication in MT-4 cells (MT-4 IC₅₀ = 22.8 μ M). Surprisingly, the 4-methoxyphenyl (**43j**) and 4-methylbenzoate (**45k**) derivatives did not show any activity up to 100 μ M, further supporting the earlier observation that variations at the A ring significantly influence the activity and specificity profiles. Interestingly, the activity profiles of the benzyl ether-linked analogues are similar to the thio-ether compounds.

Overall, our structure-activity relationship studies indicate that variations of phenyl substitutions at rings A and C significantly affect the potency and specificity profiles of RN18 analogues, and that the isosteric replacement of ring linkages are fairly well tolerated. Although not entirely conclusive, rather stringent requirements for an amide or sulfonamide linkage between rings B and C, a thio or benzyl ether linkage between rings A and B, and a 2-methoxyphenyl group as the C-ring fragment, are evident for the Vif-specific antiviral activity and specificity. Nonetheless, we have identified several analogues with antiviral

potency, specificity, and toxicity profiles similar to or better than RN18. Specifically, the sulfonamide derivatives **5d** and **6d** and the benzyl ether-linked analogues **40j** and **41j** are interesting lead compounds warranting further SAR exploration.

One explanation for the observed SAR trends could be that we directly tested the compounds for cellular antiviral potency, which can be affected not only by in vivo specificity, but also by factors such as cell membrane permeability, solubility, protein binding, and stability under physiological conditions. Another reason could be the mechanism of action of RN18 and analogues, which likely involves inhibition of Vif-A3G protein-protein interactions. We have previously demonstrated that RN18 inhibits HIV-1 replication by specifically antagonizing Vif function, only in the presence of A3G, by inhibiting Vif-A3G interactions. It can be argued that RN18 analogues with similar activity and specificity profiles also exert their antiviral activity by specifically antagonizing Vif function, likely by inhibiting Vif-A3G interactions.

Conclusions

We have evaluated the structure-activity relationships of HIV-1 Vif inhibitor RN18, a small molecule recently discovered as a specific inhibitor of Vif function that blocks viral replication by targeting the Vif-A3G interactions. Two synthetic methods were developed, both involving microwave-assisted cross-coupling of aryl iodides and thiophenols, to provide excess to RN18 and series of analogues with diverse linkages and substitutions at the phenyl rings. Another series of analogues was prepared by replacing the thio-ether linkage with ether and benzyl ether. Compounds were tested for cytotoxicity and antiviral activity against wild-type HIV-1 in non-permissive H9 cells expressing A3G and permissive MT-4 cells, which do not express A3G.

Although not exhaustive, the SAR data indicate fairly stringent requirements for the Vif-A3G-specific antiviral activity of RN18 and analogues. An amide or sulfonamide linkage between rings B and C appears to be important for Vif-specific antiviral activity, as reversing the linkage may be detrimental for the specificity. A thio or benzyl ether linkage between rings A and B is generally preferred over the ether linkage, although some ether-linked reverse amide analogues show interesting activity and specificity profile that can be influenced by variations at the A ring. A limited exploration of the C-ring phenyl substitutions suggests a strong preference for a 2-methoxyphenyl group. However, variations at the phenyl ring A, involving both electron-withdrawing and donating groups, though influence the activity and specificity profile, appear to be relatively well tolerated. These SAR studies resulted in the identification of new analogues, such as **5d** and **40j**, which potently and selectively inhibit HIV-1 replication only in the presence of A3G, likely by inhibiting Vif-A3G interactions. These compounds are potential lead structures for further SAR exploration to enhance antiviral potency and pharmacological properties, and may serve as chemical probes of Vif function to understand HIV-1 biology and the APOBEC-mediated innate immune response.

This study provides further evidence that the Vif-A3G axis is a valid target for developing small molecule-based antiviral therapies for HIV-1 infection, and that more potent and selective inhibitors of Vif-A3G interactions may serve as effective anti-HIV-1 therapeutics.

Experimental Section

Chemistry

General— ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer. Chemical shifts are reported in ppm (δ scale) relative to the solvent signal and

coupling constant (J) values are reported in hertz (Hz). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hz, and integration. High-resolution mass spectra (HRMS) were recorded on Waters Q-TOF Premier mass spectrometer by direct infusion of solutions of each compound using electrospray ionization (ESI) in positive mode. Low-resolution mass spectra were obtained using Waters Alliance HT/Micromass ZQ system (ESI). Flash and column chromatography was performed using silica gel (230–400 mesh, Merck KGA). Analytical thin-layer chromatography (TLC) was performed using silica gel (60 F-254) coated aluminum plates (Merck KGA) and spots were visualized by exposure to ultraviolet light (UV) and/or exposure to an acidic solution of *p*-anisaldehyde followed by brief heating. Solvents and chemicals were purchased from Acros and Aldrich and were used as received.

Typical Procedure for the Synthesis of RN18 (5a) and Analogues

***N*-(2-Methoxyphenyl)-2-((4-nitrophenyl)thio)benzamide (5a) (RN-18):** Compound **1a** (0.355 g, 1.0 mmol), Cu(I)I (20 mg, 0.1 mmol), K₂CO₃ (0.277 g, 2.0 mmol), and 4-nitrothiophenol **3** (0.155 g, 1 mmol) were added to a 10 mL microwave reaction vessel with Teflon-lined septum. The tube was evacuated and backfilled with dry N₂ (3 cycles). Ethylene glycol (0.11 mL, 2.0 mmol) and 2-propanol (1.5 mL) were added by syringe at room temperature. The reaction vessel was irradiated in a microwave reactor (CEM, Explorer) at 80 °C and 150 Watt power for 30 min (2 ×). The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (10 mL), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc-hexanes (1:5) mixture to afford the product **5a** (RN18) as a pale yellow crystalline solid (0.24 g, 63%). A similar procedure was used to prepare multi-grams of RN18; details are provided in the Supporting Information. ¹H NMR (400 MHz, CDCl₃) δ 8.40 (d, J = 8.0 Hz, 1H), 8.38 (s, 1H, overlapping), 8.08–8.04 (m, 2H), 7.78 (dd, J = 7.6, 2.0 Hz, 1H), 7.57–7.48 (m, 3H), 7.30–7.26 (m, 2H), 7.06 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 6.97 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.85 (dd, J = 8.0, 1.2 Hz, 1H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.44, 148.22, 146.87, 146.15, 140.63, 135.76, 131.66, 130.09, 129.87, 129.49, 128.79 (2C), 127.54, 124.54, 124.35 (2C), 121.37, 120.05, 110.19, 55.88; HRMS (ESI) m/z : calcd for C₂₀H₁₇N₂O₄S [M + H]⁺ 381.0909; found 381.0916.

***N*-(2-Methoxyphenyl)-2-(phenylthio)benzamide (4a):** Reaction of **1a** and thiophenol gave the product **4a** as a white solid in 98% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H) 8.51 (d, J = 7.2 Hz, 1H), 7.72 (m, 1H), 7.42–7.38 (m, 2H), 7.34–7.28 (m, 5H), 7.21–7.19 (m, 1H), 7.07 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 7.0 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.89 (dd, J = 8.0, 1.6 Hz, 1H), 3.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.90, 148.37, 136.87, 136.12, 134.63, 132.81 (2C), 131.80, 131.17, 129.66 (2C), 128.97, 128.12, 127.95, 126.96, 124.21, 121.38, 120.20, 110.17, 55.56; HRMS (ESI) m/z : calcd for C₂₀H₁₇NO₂S [M + H]⁺ 335.0980; found 335.0984.

***N*-(2-Methoxyphenyl)-3-(4-nitrophenylthio)benzamide (5b):** Reaction of **1b** and 4-nitrothiophenol gave the product **5b** as a pale yellow solid in 62% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 8.48 (dd, J = 8.0, 1.6 Hz, 1H), 8.13–8.09 (m, 2H), 8.06 (t, J = 1.6 Hz, 1H), 7.93 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.69 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.28–7.25 (m, 2H, overlapping), 7.11 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.03 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H), 6.93 (dd, J = 8.0, 1.2 Hz, 1H), 3.92 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 164.16, 148.35, 147.18, 146.05, 137.46, 137.29, 133.05, 132.63, 130.58, 127.99, 127.89 (2C), 127.58, 124.55, 124.48, 121.49 (2C), 120.16, 110.20, 56.08; HRMS (ESI) m/z : calcd for C₂₀H₁₇N₂O₄S [M + H]⁺ 381.0909; found 381.0907.

***N*-(2-(4-Nitrophenylthio)phenyl)-2-methoxybenzamide (5c):** Reaction of **1c** and 4-nitrothiophenol gave the product **5c** as a pale yellow solid in 53% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 10.86 (s, 1H), 8.86 (dd, J = 8.4, 1.2 Hz, 1H), 8.24 (dd, J = 8.2, 1.8 Hz, 1H), 8.07–8.03 (m, 2H), 7.63 (dd, J = 7.6, 1.2 Hz, 1H), 7.60 (ddd, J = 8.0, 8.0, 1.6 Hz, 1H), 7.46 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 7.20 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.12–7.07 (m, 3H), 6.93 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.58, 157.29, 146.86, 145.49, 142.18, 137.45, 133.75, 132.64, 132.43, 125.46 (2C), 124.89, 124.37 (2C), 122.15, 121.56, 121.27, 117.05, 111.52, 55.98; HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 381.0909; found 381.0906.

***N*-(2-Methoxyphenyl)-2-((4-nitrophenyl)thio)benzenesulfonamide (5d):** Reaction of **1d** and 4-nitrothiophenol gave the product **5d** as an orange-brown crystalline solid in 47% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.21–8.18 (m, 1H), 8.05–8.02 (m, 2H), 7.81 (s, 1H), 7.51–7.45 (m, 4H), 7.15–7.11 (m, 2H), 6.99 (ddd, J = 8.0, 8.0, 2.0 Hz, 1H), 6.85 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 6.65 (dd, J = 8.4, 1.2 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.77, 146.25, 141.51, 136.95, 134.02, 131.98, 131.50, 129.43, 129.02 (2C), 125.86, 125.04, 124.27 (2C), 121.37, 119.40, 110.54, 105.0, 55.51; HRMS (ESI) m/z : calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M} + \text{H}]^+$ 417.0579; found 417.0587.

2-Methoxy-*N*-(2-(4-nitrophenylthio)phenyl)benzenesulfonamide (5e): Reaction of **1e** and 4-nitrothiophenol gave the product **5e** as a pale yellow crystalline solid in 25% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.10 (s, 1H), 7.99 (m, 2H), 7.91 (dd, J = 8.0, 1.2 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.47–7.39 (m, 3H), 7.09 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.01 (ddd, J = 8.0, 8.0, 0.8 Hz, 1H), 6.91 (m, 2H), 6.76 (d, J = 8.4 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.45, 146.68, 145.73, 140.66, 137.95, 135.53, 132.64, 131.03, 126.39, 125.84 (2C), 125.26, 124.40 (2C), 120.66, 119.46, 117.24, 112.18, 56.22; HRMS (ESI) m/z : calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M} + \text{H}]^+$ 417.0579; found 417.0596.

2-(2-Methoxyphenyl)-*N*-(2-((4-nitrophenyl)thio)phenyl)acetamide (5f): Reaction of **1f** and 4-nitrothiophenol gave the product **5f** in 45% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.59 (dd, J = 8.0, 1.2 Hz, 1H), 8.46 (s, 1H), 7.98–7.94 (m, 2H), 7.54–7.49 (m, 2H), 7.18–7.11 (m, 2H), 7.07 (dd, J = 7.6, 1.6 Hz, 1H), 6.83–6.79 (m, 3H), 6.66 (d, J = 8.4 Hz, 1H), 3.67 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.91, 157.10, 146.10, 145.63, 141.23, 137.35, 132.64, 131.42, 129.43, 125.55 (2C), 124.96, 124.26 (2C), 122.50, 121.31, 121.29, 116.54, 110.74, 55.59, 40.30; HRMS (ESI) m/z : calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 395.1066; found 395.1058.

2-(2-Fluorophenyl)-*N*-(2-((4-nitrophenyl)thio)phenyl)acetamide (5g): Reaction of **1g** and 4-nitrothiophenol gave the product **5g** in 37% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.57 (dd, J = 8.0, 1.2 Hz, 1H), 8.19 (s, 1H), 8.02–7.98 (m, 2H), 7.57–7.52 (m, 2H), 7.22–7.11 (m, 3H), 7.0 (ddd, J = 8.0, 8.0, 1.2 Hz, 1H), 6.87–6.84 (m, 3H), 3.67 (d, J = 1.2 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.26, 160.92 (d, J = 245.4 Hz), 145.80, 145.74, 140.62, 137.43, 132.76, 131.76 (d, J = 3.7 Hz), 129.96 (d, J = 8.1 Hz), 125.52 (2C), 125.32, 124.94 (d, J = 3.7 Hz), 124.36 (2C), 121.21, 121.07, 116.68, 115.88 (d, J = 22.0 Hz), 38.56 (J = 2.9 Hz); HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{16}\text{FN}_2\text{O}_3\text{S}$ $[\text{M} + \text{H}]^+$ 383.0866; found 383.0862.

Typical Procedure for the Synthesis of Analogues 6a–e

2-((4-Aminophenyl)thio)-*N*-(2-methoxyphenyl)benzamide (6a): A solution of the nitro compound **5a** (0.5 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.56 g, 2.5 mmol) in EtOAc (10 mL) was heated at 80 °C for 3 hours. The reaction mixture was allowed to reach room temperature and treated with saturated aqueous NaHCO_3 solution till basic. The aqueous layer was extracted

with ethyl acetate (3 × 25 mL); the combined organic portion was washed with saturated aqueous NaCl solution (25 mL), dried (Na₂SO₄), filtered, and evaporated. The residue was purified by flash chromatography on silica gel eluting with EtOAc-hexanes (2:3) mixture to afford the product **6a** as an off-white solid in 90% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 3.2 Hz, 1H), 8.56 (s, 1H), 7.62 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.33–7.29 (m, 2H), 7.24 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.17 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.08 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.02 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H), 6.98 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.69–6.65 (m, 2H), 3.89 (s, 3H), 3.84 (br s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 166.15, 148.38, 146.77, 139.92, 136.82 (2C), 134.64, 130.98, 128.85, 128.82, 128.39, 128.04, 125.36, 124.16, 121.43, 120.83, 120.23, 116.60 (2C), 110.22, 56.03; HRMS (ESI) *m/z*: calcd for C₂₀H₁₉N₂O₂S [M + H]⁺ 351.1167; found 351.1169.

3-(4-Aminophenylthio)-N-(2-methoxyphenyl)benzamide (6b): Reduction of the nitro group in **5b** gave the product **6b** as an off-white solid in 65% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.44 (s, 1H), 7.59 (m, 2H), 7.37–7.30 (m, 3H), 7.25 (m, 1H), 7.07 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 7.00 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.72–6.69 (m, 2H), 3.90 (s, 3H), 3.87 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 165.09, 148.34, 147.80, 141.68, 136.86 (2C), 136.19, 130.00, 129.34, 127.90, 125.29, 124.16, 123.95, 121.40, 120.02, 119.15, 116.23 (2C), 110.14, 56.02; HRMS (ESI) *m/z*: calcd for C₂₀H₁₉N₂O₂S [M + H]⁺ 351.1167; found 351.1170.

N-(2-(4-Aminophenylthio)phenyl)-2-methoxybenzamide (6c): Reduction of the nitro group in **5c** gave the product **6c** in 78% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 10.96 (s, 1H), 8.67 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.29 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H), 7.38 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.13–7.09 (m, 3H), 7.02 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H, overlapping), 6.59–6.54 (m, 2H), 3.99 (s, 3H), 3.71 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 163.73, 157.66, 146.34, 139.70, 134.11, 133.53, 132.80, 132.41 (2C), 129.30, 125.06, 124.46, 122.71, 122.10, 121.67, 121.54, 116.19 (2C), 111.63, 56.27; HRMS (ESI) *m/z*: calcd for C₂₀H₁₉N₂O₂S [M + H]⁺ 351.1167; found 351.1173.

2-((4-Aminophenyl)thio)-N-(2-methoxyphenyl)benzenesulfonamide (6d): Reduction of the nitro group in **5d** gave the product **6d** as an off-white solid in 83% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 1H), 7.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.54 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.24–7.18 (m, 3H), 7.08 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.99 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 6.91 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.85 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.69–6.65 (m, 2H), 3.89 (br s, 2H), 3.71 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.10, 148.06, 140.76, 137.09 (2C), 135.40, 132.87, 130.63, 129.29, 126.52, 124.75, 124.63, 121.31, 119.56, 118.93, 116.19 (2C), 110.74, 55.92; HRMS (ESI) *m/z*: calcd for C₁₉H₁₉N₂O₃S₂ [M + H]⁺ 387.0837; found 387.0843.

N-(2-(4-aminophenylthio)phenyl)-2-methoxybenzenesulfonamide (6e): Reduction of the nitro group in **5e** gave the product **6e** in 75% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 7.91 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.61 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.48 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.2 Hz, 1H, overlapping), 7.15 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.0–6.87 (m, 5H), 6.56–6.52 (m, 2H), 3.85 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.71, 146.44, 138.16, 135.26, 134.85, 132.33 (2C), 131.18, 129.51 (2C), 126.60, 125.15, 124.66, 122.47, 120.37, 119.21, 116.13, 112.12, 56.32; HRMS (ESI) *m/z*: calcd for C₁₉H₁₉N₂O₃S₂ [M + H]⁺ 387.0837; found 387.0842.

Typical Procedure for the Synthesis of Intermediate Esters 10–11

Methyl 2-(4-nitrophenylthio)benzoate (10): 4-Iodonitrobenzene **8** (0.5 g, 2.0 mmol), Cu(I)I (50 mg, 0.26 mmol), and K₂CO₃ (0.552 g, 4.0 mmol) were added to a 10 mL microwave reaction vessel with Teflon-lined septum. The tube was evacuated and backfilled with dry N₂ (3 cycles). 1,2-Dimethoxyethane (2 mL) was added by syringe at room temperature followed by methyl thiosalicylate **7** (0.34 g, 2 mmol). The reaction vessel was irradiated in a microwave reactor (CEM, Explorer) at 80 °C and 150 Watt power for 30 min (2 ×). The reaction mixture was allowed to reach room temperature, diluted with EtOAc (10 mL) and filtered; solids were repeatedly washed with EtOAc. The combined filtrate was concentrated to provide an orange solid. The crude product was purified by flash column chromatography on silica gel eluting with EtOAc-hexanes (1:6) mixture to afford the product **10** as a pale yellow crystalline solid (0.5 g, 86%). ¹H NMR (400 MHz, CDCl₃) δ 8.15 (m, 2H), 7.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.47 (m, 2H), 7.39 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.32 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.89 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.82, 146.93, 144.95, 136.71, 132.71, 131.88 (2 C), 131.72, 131.25, 131.07, 127.30, 124.42 (2 C), 52.56; MS (ESI): *m/z* 312.50 (M + Na)⁺.

Methyl 2-(2-chloro-4-nitrophenylthio)benzoate (11): Reaction of methyl thiosalicylate **7** and 2-chloro-1-iodo-4-nitrobenzene **9** gave the product **11** as a yellow crystalline solid in 70% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.26 (d, *J* = 2.4 Hz, 1H), 7.99–7.95 (m, 2H), 7.50–7.43 (m, 2H), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.81, 146.72, 145.46, 134.60, 133.83, 133.36, 133.17, 133.02, 131.59, 131.40, 128.80, 125.04, 121.22, 52.76; MS (ESI): *m/z* 346.50 (M + Na)⁺.

Typical Procedure for Synthesis of Analogues 15–16

2-(4-Nitrophenylthio)-N-(2-methoxyphenyl)benzamide (15a) (RN-18): A solution of ester **10** (0.72 g, 2.5 mmol) in MeOH (25 mL) was treated with Ba(OH)₂·8H₂O (1.18 g, 3.75 mmol) and the resulting mixture was heated at 80 °C for 3 hours. Reaction mixture was cooled to room temperature and solvents were removed under reduced pressure. The residue was treated with 1M HCl solution in Et₂O (25 mL) and filtered; the solids were washed with Et₂O (40 mL) and filtered. The combined filtrate was dried (MgSO₄), filtered, and concentrated to provide the acid **12** as a light brown solid (0.66 g, 96%), which was used as such in the next reaction.

To a solution of the above acid **12** (0.66 g, 2.4 mmol) in dry CH₂Cl₂ (8 mL) was added oxalyl chloride (1 mL) followed by a drop of dimethylformamide (DMF). The mixture was stirred at room temperature for 4 hours. Solvents were removed under reduced pressure and the residue was dried using high vacuum to give the corresponding acid chloride as a yellow solid. A solution of 2-methoxyaniline (0.3 g, 2.4 mmol) in dry CH₂Cl₂ (10 mL) under nitrogen atmosphere was cooled to 0 °C and Et₃N (0.75 mL, 5.4 mmol) was added followed by the slow addition of the above acid chloride solution in dry CH₂Cl₂ (10 mL). The resulting mixture was warmed to room temperature and stirred overnight. Reaction mixture was diluted with CH₂Cl₂ (20 mL) and water (10 mL) and layers were separated; the organic portion was washed with saturated aqueous NaCl solution, dried (Na₂SO₄), filtered, and evaporated to afford a yellow solid. The product was purified by flash chromatography on silica gel eluting with EtOAc-hexanes (1:5) mixture to give the product **15a** (RN18) as a yellow crystalline solid (0.83 g, 90%). Analytical data is identical to the product **5a** prepared by direct cross-coupling method.

N-(2-Hydroxyphenyl)-2-((4-nitrophenyl)thio)benzamide 15b: Reaction of acid **12** and 2-hydroxyaniline **14b** gave the product **15b** in 66% isolated yield. ¹H NMR (400 MHz,

CDCl_3) δ 8.41 (br s, 1H), 8.11–8.08 (m, 2H), 8.04 (s, 1H), 7.92 (m, 1H), 7.63–7.56 (m, 3H), 7.30–7.26 (m, 2H, overlapping), 7.14 (ddd, $J = 8.0, 8.0, 1.6$ Hz, 1H), 7.09 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.0 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.88 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.77, 149.67, 148.20, 147.28, 142.24, 136.97, 132.54, 130.91, 130.67, 130.15, 129.48 (2C), 126.99, 126.79, 125.09 (2C), 123.50, 120.54, 116.80; HRMS (ESI) m/z : calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 367.0753; found 367.0758.

***N*-(2-Fluorophenyl)-2-((4-nitrophenyl)thio)benzamide 15c**: Reaction of acid **12** and 2-fluoroaniline **14c** gave the product **15c** in 79% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.34 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.25 (s, 1H), 8.07 (m, 2H), 7.86 (dd, $J = 7.6, 2.0$ Hz, 1H), 7.60–7.53 (m, 3H), 7.28 (m, 2H), 7.13 (m, 1H), 7.08 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.37, 152.78 ($J = 241.8$ Hz), 146.33, 146.19, 139.49, 136.06, 132.17, 130.13, 130.06, 129.78, 128.61 (2C), 126.21 ($J = 10.3$ Hz), 125.14 ($J = 8.1$ Hz), 124.94 ($J = 3.7$ Hz), 124.50 (2C), 121.90, 115.09 ($J = 19.0$ Hz); HRMS (ESI) m/z : calcd for $\text{C}_{19}\text{H}_{14}\text{FN}_2\text{O}_3\text{S}$ $[\text{M} + \text{H}]^+$ 369.0709; found 369.0711.

***N*-(Benzo[d][1,3]dioxol-5-yl)-2-((4-nitrophenyl)thio)benzamide 15d**: Reaction of acid **12** and benzo[d][1,3]dioxol-5-amine **14d** gave the product **15d** in 87% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.09–8.06 (m, 2H), 7.81 (m, 2H), 7.58–7.50 (m, 3H), 7.28–7.25 (m, 2H, overlapping), 7.20 (s, 1H), 6.74 (d, $J = 1.2$ Hz, 2H), 5.95 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.50, 148.10, 146.24, 144.90, 140.03, 135.94, 131.91, 131.80, 130.14, 129.93, 128.50 (2C), 124.52 (2C), 113.40, 108.36, 105.0, 102.98, 101.64; HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$ 395.0702; found 395.0692.

***N*-(2-(Hydroxymethyl)phenyl)-2-((4-nitrophenyl)thio)benzamide 15e**: Reaction of acid **12** and (2-aminophenyl)methanol **14e** gave the product **15e** in 84% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 9.13 (s, 1H), 8.12–8.06 (m, 3H), 7.76 (m, 1H), 7.54–7.48 (m, 3H), 7.36–7.30 (m, 3H), 7.19 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.11 (ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 4.69 (s, 2H), 2.06 (br s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.17, 146.77, 146.25, 140.27, 137.40, 135.34, 131.74, 130.66, 129.82, 129.69, 129.53, 129.08, 129.05, 129.03 (2C), 125.04, 124.43 (2C), 122.74, 64.75; HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 381.0909; found 389.0909.

***N*-(3-(Hydroxymethyl)phenyl)-2-((4-nitrophenyl)thio)benzamide 15f**: Reaction of acid **12** and (3-aminophenyl)methanol **14f** gave the product **15f** in 90% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.07–8.03 (m, 2H), 7.96 (br s, 1H), 7.78 (m, 1H), 7.58–7.49 (m, 4H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.31–7.25 (m, 3H, overlapping), 7.12 (d, $J = 7.6$ Hz, 1H), 4.65 (s, 2H), 1.93 (br s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.53, 146.08, 145.96, 142.06, 139.78, 137.56, 135.51, 131.57, 129.71, 129.47, 129.38, 129.19, 128.39 (2C), 124.18 (2C), 123.24, 119.07, 118.35, 67.73; HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 381.0909; found 389.0911.

Morpholino(2-((4-nitrophenyl)thio)phenyl)methanone 15g: Reaction of acid **12** and morpholine **14g** gave the product **15g** in 99% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.10–8.06 (m, 2H), 7.57–7.44 (m, 3H), 7.39 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.26–7.21 (m, 2H), 3.75 (br s, 4H), 3.55 (t, $J = 4.8$ Hz, 2H), 3.21 (t, $J = 5.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.61, 146.60, 145.69, 141.27, 136.17, 130.41, 130.29, 127.56, 127.48 (2C), 124.03 (2C), 66.63, 66.58, 47.28, 41.94; HRMS (ESI) m/z : calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 345.0909; found 345.0900.

***tert*-Butyl 4-(2-((4-nitrophenyl)thio)benzoyl)piperazine-1-carboxylate 15h**: Reaction of acid **12** and 1-Boc-piperazine **14h** gave the product **15h** in 99% isolated yield. ^1H NMR

(400 MHz, CDCl₃) δ 8.10–8.06 (m, 2H), 7.57–7.44 (m, 3H), 7.38 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.25–7.21 (m, 2H), 3.71 (br s, 2H), 3.49 (t, *J* = 5.2 Hz, 2H), 3.35 (t, *J* = 4.8 Hz, 2H), 3.18 (t, *J* = 5.6 Hz, 2H), 1.45 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 168.01, 154.67, 146.77, 146.03, 141.62, 136.39, 130.73, 130.57, 127.86, 127.84 (2C), 127.77, 124.36 (2C), 80.72, 47.03 (2C), 41.76 (2C), 28.57 (3C); HRMS (ESI) *m/z* calcd for C₂₂H₂₅N₃O₅Na [M + Na]⁺ 466.1413; found 466.1401.

2-(2-Chloro-4-nitrophenylthio)-N-(2-methoxyphenyl)benzamide 16a: Reaction of acid **13** and 2-methoxyaniline **14a** gave the product **16a** as an orange solid in 92% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (br s, 1H), 8.36 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.15 (d, *J* = 2.4 Hz, 1H), 7.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.62–7.52 (m, 3H), 7.05 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 6.94 (m, 2H), 6.85 (dd, *J* = 8.0, 0.8 Hz, 1H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.04, 148.21, 146.62, 145.85, 141.54, 136.70, 132.02, 131.88, 130.69, 129.79, 128.50, 127.87, 127.37, 124.65, 124.51, 122.14, 121.20, 120.03, 110.12, 55.80; MS (ESI): *m/z* 437.61 (M + Na)⁺; HRMS (ESI) *m/z* calcd for C₂₀H₁₆ClN₂O₄S [M + H]⁺ 415.0519; found 415.0511.

N-(Benzo[d][1,3]dioxol-5-yl)-2-((2-chloro-4-nitrophenyl)thio)benzamide 16d: Reaction of acid **13** and benzo[d][1,3]dioxol-5-amine **14d** gave the product **16d** as an orange solid in 79% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 2.4 Hz, 1H), 7.92 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.91–7.86 (m, 2H), 7.65–7.56 (m, 3H), 7.19 (d, *J* = 1.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.78–6.72 (m, 2H), 5.95 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 165.10, 148.14, 146.12, 145.07, 140.96, 136.94, 132.20, 131.62, 131.06, 130.51, 130.39, 128.34, 127.40, 124.88, 122.41, 113.61, 108.37, 103.11, 101.64; HRMS (ESI) *m/z* calcd for C₂₀H₁₄ClN₂O₅S [M + H]⁺ 429.0312; found 429.0310.

Typical Procedure for Synthesis of Analogues 18a,e,g

N-(2-Methoxyphenyl)-2-(4-nitrophenoxy)benzamide 18a: To a solution of acid **17** (0.5 g, 1.93 mmol) in dry CH₂Cl₂ (8 mL) was added oxalyl chloride (1 mL) followed by a drop of dimethylformamide (DMF). The reaction mixture was stirred at room temperature for 4 hours. Solvents were removed under reduced pressure and the residue was dried under high vacuum to give the corresponding acid chloride as a pale yellow solid. A solution of 2-methoxyaniline (0.26 g, 2.11 mmol) in dry CH₂Cl₂ (10 mL) under nitrogen atmosphere was cooled to 0 °C and Et₃N (0.47 mL, 3.37 mmol) was added followed by the slow addition of the above acid chloride solution in dry CH₂Cl₂ (10 mL). The resulting mixture was warmed to room temperature and stirred overnight. Reaction mixture was diluted with CH₂Cl₂ (20 mL) and water (10 mL) and layers were separated; the organic portion was washed with saturated aqueous NaCl solution, dried (Na₂SO₄), filtered, and evaporated to afford a yellow solid. The product was purified by flash chromatography on silica gel eluting with EtOAc-hexanes (1:4) mixture to give the product **18a** as a pale yellow crystalline solid (0.63 g, 90%). ¹H NMR (400 MHz, CDCl₃) δ 9.77 (s, 1H), 8.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.32 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.29–8.25 (m, 2H), 7.54 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.41 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H), 7.18–7.14 (m, 2H), 7.07–7.03 (m, 2H), 6.98 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H), 6.86 (dd, *J* = 7.6, 1.2 Hz, 1H), 3.75 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.04, 161.86, 152.84, 148.30, 143.91, 133.51, 132.91, 128.01, 126.73, 126.33 (2C), 126.12, 124.25, 121.50, 120.66, 120.39, 118.42 (2C), 110.16, 55.88; HRMS (ESI) *m/z* calcd for C₂₀H₁₇N₂O₅ [M + H]⁺ 365.1137; found 365.1129.

N-(2-(hydroxymethyl)phenyl)-2-(4-nitrophenoxy)benzamide 18e: Reaction of acid **17** and 2-aminobenzylalcohol **14e** gave the product **18e** as a light orange crystalline solid in 86% isolated yield. ¹H NMR (400 MHz, CDCl₃) δ 9.82 (s, 1H), 8.26–8.21 (m, 3H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.53 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1H), 7.40–7.33 (m, 2H), 7.22–7.16 (m, 3H),

7.10 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.01 (dd, $J = 8.0, 0.8$ Hz, 1H), 4.61 (d, $J = 5.2$ Hz, 2H), 2.01 (t, $J = 6.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.07, 161.52, 152.86, 143.58, 137.04, 133.22, 132.32, 130.44, 129.02, 128.99, 126.46, 125.96 (2C), 125.53, 124.71, 123.09, 119.99, 118.53 (2C), 63.88; HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 365.1137; found 365.1145.

Morpholino(2-(4-nitrophenoxy)phenyl)methanone 18g: Reaction of acid **17** and morpholine gave the product **18g** as a colorless crystalline solid in 93% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.23–8.18 (m, 2H), 7.50–7.43 (m, 2H), 7.34 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.06 (dd, $J = 8.0, 0.8$ Hz, 1H), 7.03–6.99 (m, 2H), 3.70–3.62 (m, 6H), 3.39–3.32 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.46, 162.77, 150.60, 143.32, 131.58, 129.48, 129.35, 126.44, 126.26 (2C), 121.24, 117.33 (2C), 67.12, 67.01, 47.70, 42.41; HRMS (ESI) m/z : calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 329.1137; found 329.1132.

2-(4-Aminophenoxy)-N-(2-methoxyphenyl)benzamide 19a: Reduction of the nitro group in **18a** gave the product **19a** in 78% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 10.70 (s, 1H), 8.63 (dd, $J = 7.6, 2.0$ Hz, 1H), 8.33 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.36 (ddd, $J = 7.6, 7.6, 2.0$ Hz, 1H), 7.17 (ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 7.05–6.96 (m, 4H), 6.86–6.83 (m, 2H), 6.76–6.72 (m, 2H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.58, 156.85, 148.36, 146.76, 143.69, 132.72, 132.15, 128.53, 123.41, 123.23, 122.62, 121.39 (2C), 121.08, 120.05, 116.49, 116.18 (2C), 109.94, 55.61; HRMS (ESI) m/z : calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 335.1396; found 335.1393.

Typical Procedure for the Synthesis of Analogues 22–23

2-(4-Methoxyphenoxy)-N-(2-methoxyphenyl)benzamide 22h: 2-Bromo-*N*-(2-methoxyphenyl)benzamide **1h** (0.20 g, 0.65 mmol), 4-methoxyphenol **20** (0.19 g, 1.25 mmol), Cu(I) chloride (32.0 mg, 0.33 mmol), and Cs_2CO_3 (0.43 g, 1.31 mmol) were added to a 10 mL microwave reaction vessel with Teflon-lined septum. The tube was evacuated and backfilled with dry N_2 (3 cycles). 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) (0.014 mL, 0.065 mmol) and *N*-methylpyrrolidone (2 mL) were added by syringe at room temperature and the reaction vessel was irradiated in a microwave reactor (CEM, Explorer) at 120 °C and 150 Watt power for 30 min (2 $\times$). The reaction mixture was cooled to reach room temperature, diluted with ethyl acetate (10 mL) and filtered; the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc-hexanes (1:8) mixture to give the compound **22h** (0.08 g, 36%). ^1H NMR (400 MHz, CDCl_3) δ 10.63 (s, 1H), 8.63 (dd, $J = 7.2, 2.0$ Hz, 1H), 8.35 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.38 (ddd, $J = 7.6, 7.6, 2.0$ Hz, 1H), 7.20 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.13–7.09 (m, 2H), 7.06–6.98 (m, 2H), 6.97–6.93 (m, 2H), 6.84 (m, 2H), 3.84 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.74, 156.96, 156.73, 148.72, 148.59, 133.06, 132.56, 128.74, 123.87, 123.76, 123.29, 121.54 (2C), 121.43, 120.37, 117.13, 115.32 (2C), 110.18, 55.92, 55.89; HRMS (ESI) m/z : calcd for $\text{C}_{21}\text{H}_{20}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 350.1392; found 350.1381.

2-(4-Methoxyphenoxy)-N-(2-methoxyphenyl)benzenesulfonamide 22i: Reaction of 2-bromo-*N*-(2-methoxyphenyl)benzenesulfonamide **1i** and 4-methoxyphenol **20** gave compound **22i** in 32% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 8.00 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.70 (s, 1H), 7.52 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.34 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.05 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 6.97 (ddd, $J = 7.6, 7.6, 1.6$ Hz, 1H), 6.92–6.86 (m, 4H), 6.83 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 6.76 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.70 (dd, $J = 8.0, 0.8$ Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.10, 156.30, 148.52, 148.42, 134.72, 131.43, 128.00, 126.74, 124.26, 121.98 (2C), 121.93, 121.29, 118.52,

116.77, 115.16 (2C), 110.55, 55.92, 55.66; HRMS (ESI) m/z : calcd for $C_{20}H_{20}NO_5S$ $[M + H]^+$ 386.1062; found 386.1058.

2-(Benzo[d][1,3]dioxol-5-yloxy)-N-(2-methoxyphenyl)benzamide 23h: Reaction of 2-bromo-*N*-(2-methoxyphenyl)benzamide **1h** and benzo[d][1,3]dioxol-5-ol **21** gave the product **23h** in 30% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.63 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.34 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.40 (ddd, $J = 7.6, 7.6, 2.0$ Hz, 1H), 7.21 (ddd, $J = 8.0, 8.0, 0.8$ Hz, 1H), 7.06–6.98 (m, 2H), 6.90–6.82 (m, 3H), 6.69 (d, $J = 2.4$ Hz, 1H), 6.63 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.02 (s, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.64, 156.36, 149.90, 148.88, 148.57, 144.96, 133.11, 132.58, 128.67, 124.06, 123.81, 123.59, 121.43, 120.38, 117.47, 112.80, 110.20, 108.71, 102.68, 102.07, 55.94; HRMS (ESI) m/z : calcd for $C_{21}H_{18}NO_5$ $[M + H]^+$ 364.1185; found 364.1184.

Typical Procedure for the Synthesis of Analogues 29–33

2-Methoxy-N-(2-(4-nitrophenoxy)phenyl)benzamide 29k: Et_3N (0.57 mL, 4.10 mmol) was added to a mixture of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** (0.20 g, 0.82 mmol), 4-nitrophenylboronic acid **24** (0.15 g, 0.82 mmol), $Cu(OAc)_2$ (0.15 g, 0.82 mmol) and powdered 4A molecular sieves in CH_2Cl_2 . The resulting heterogeneous mixture was stirred at room temperature overnight. The resulting slurry was filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography eluting with $EtOAc$ -hexanes (1:4) mixture to provide the product **29k** (0.04 g, 12.7%). 1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.76 (dd, $J = 8.0, 1.2$ Hz, 1H), 8.27 (dd, $J = 7.6, 2.0$ Hz, 1H), 8.24 (m, 2H), 7.47 (ddd, $J = 7.6, 7.6, 2.0$ Hz, 1H), 7.32 (ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 7.15–7.08 (m, 4H), 7.03 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.51, 162.99, 157.40, 143.70, 143.32, 133.78, 132.77, 131.97, 126.77, 126.42 (2C), 124.56, 122.41, 121.92, 121.59, 120.30, 117.07 (2C), 111.75, 56.14; HRMS (ESI) m/z : calcd for $C_{20}H_{17}N_2O_5$ $[M + H]^+$ 365.1137; found 365.1140.

N-(2-(4-(Dimethylamino)phenoxy)phenyl)-2-methoxybenzamide 30k: Reaction of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** and (4-(dimethylamino)phenyl)boronic acid **25** gave the product **30k** in 24% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.84 (s, 1H), 8.72 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.32 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.47 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.14–7.07 (m, 2H), 7.02–6.94 (m, 4H), 6.80 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.77–6.73 (m, 2H), 3.84 (s, 3H), 2.94 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.36, 157.65, 147.94, 147.69, 133.33, 132.63, 130.44, 123.67, 123.35, 122.25, 121.64, 120.90, 120.36 (2C), 116.33, 114.17 (2C), 111.70, 56.16, 41.41 (2C); HRMS (ESI) m/z : calcd for $C_{22}H_{23}N_2O_3$ $[M + H]^+$ 363.1709; found 363.1704.

2-Methoxy-N-(2-(4-methoxyphenoxy)phenyl)benzamide 31k: Reaction of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** and 4-methoxyphenylboronic acid **26** gave the product **31k** in 18% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.72 (dd, $J = 7.6, 1.6$ Hz, 1H), 8.31 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.47 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.15–7.10 (m, 2H), 7.04–6.95 (m, 4H), 6.92–6.88 (m, 2H), 6.82 (dd, $J = 8.4, 1.6$ Hz, 1H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.39, 157.61, 156.18, 150.56, 147.02, 133.40, 132.66, 130.81, 123.98, 123.81, 122.15, 121.70, 121.14, 120.10 (2C), 117.07, 115.22 (2C), 111.70, 56.10, 55.91; HRMS (ESI) m/z : calcd for $C_{21}H_{20}NO_4$ $[M + H]^+$ 350.1392; found 350.1372.

4-(2-(2-Methoxybenzamido)phenoxy)phenyl acetate 32k: Reaction of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** and (4-acetoxyphenyl)boronic acid **27** gave the product **32k** in 12% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.75 (dd, $J = 8.4, 1.6$ Hz, 1H), 8.29 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.47 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.19

(ddd, $J = 8.0, 8.0, 1.6$ Hz, 1H), 7.11 (ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 7.08–7.02 (m, 5H), 6.96–6.92 (m, 2H), 3.75 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.87, 163.51, 157.58, 154.96, 146.47, 145.70, 133.52, 132.66, 131.43, 124.99, 124.06, 123.23 (2C), 121.98, 121.70, 121.50, 118.91 (2C), 118.64, 111.71, 56.11, 21.32; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 378.1341; found 378.1339.

Methyl 4-(2-(2-methoxybenzamido)phenoxy)benzoate 33k: Reaction of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** and (4-(methoxycarbonyl)phenyl)boronic acid **28** gave the product **33k** in 22% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 10.45 (s, 1H), 8.76 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.28 (dd, $J = 7.6, 2.0$ Hz, 1H), 8.06–8.02 (m, 2H), 7.46 (ddd, $J = 7.6, 7.6, 2.0$ Hz, 1H), 7.27 (ddd, $J = 8.0, 8.0, 1.6$ Hz, 1H, overlapping), 7.13–7.04 (m, 4H), 7.0 (dd, $J = 8.4, 1.6$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.66, 163.50, 161.69, 157.49, 144.28, 133.60, 132.72, 132.15 (2C), 131.98, 126.01, 125.21, 124.28, 121.90, 121.81, 121.77, 119.98, 116.93 (2C), 111.68, 56.03, 52.35; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 378.1341; found 378.1336.

Typical Procedure for the Synthesis of Analogues 40–45

***N*-(2-Methoxyphenyl)-2-((4-nitrobenzyl)oxy)benzamide 40j:** 2-Hydroxy-*N*-(2-methoxyphenyl)benzamide **1j** (0.245 g, 1.0 mmol), 1-(bromomethyl)-4-nitrobenzene **34** (0.22 g, 1.0 mmol), and K_2CO_3 (0.29 g, 2.1 mmol) were added to a 10 mL microwave reaction vessel with Teflon-lined septum. The tube was evacuated and backfilled with dry N_2 (3 cycles). Dry DMF (4 mL) was added by syringe at room temperature and the reaction mixture was irradiated in a microwave reactor (CEM, Explorer) at 90 °C and 150 Watt power for 30 min (2 $\times$). The reaction mixture was allowed to reach room temperature, diluted with EtOAc (10 mL) and filtered through a Celite pad; the filter cake was repeatedly washed with EtOAc. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with EtOAc-hexanes (1:4) mixture to provide the product **40j** as a yellow crystalline solid (0.2 g, 53%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.38 (s, 1H), 8.40 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.25 (d, $J = 8.8$ Hz, 2H), 8.05 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.78 (d, $J = 8.8$ Hz, 2H), 7.52 (m, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 7.09–6.99 (m, 2H), 6.94 (ddd, $J = 8.0, 8.0, 1.2$ Hz, 1H), 5.61 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 162.96, 156.26, 148.91, 147.98, 144.59, 134.09, 132.27, 129.37 (2C), 128.30, 124.62, 124.44 (2C), 122.79, 122.39, 121.23, 120.46, 114.54, 111.34, 69.91, 56.26; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 379.1294; found 379.1284.

***N*-(2-(4-Nitrobenzyloxy)phenyl)-2-methoxybenzamide 40k:** Reaction of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** and 1-(bromomethyl)-4-nitrobenzene **34** gave the product **40k** in 51% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 10.47 (s, 1H), 8.68 (m, 1H), 8.32–8.26 (m, 3H), 7.67 (d, $J = 8.8$ Hz, 2H), 7.48 (ddd, $J = 7.6, 7.6, 1.8$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H), 7.09–7.02 (m, 2H), 6.94 (m, 2H), 5.26 (s, 2H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.33, 157.46, 148.09, 147.35, 144.11, 133.48, 132.77, 128.96, 128.65 (2C), 124.19, 123.84, 122.46, 122.17, 121.86, 121.37, 111.78, 111.56, 69.84, 55.94; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 379.1294; found 379.1289.

***N*-(2-Methoxyphenyl)-2-((3-nitrobenzyl)oxy)benzamide 41j:** Reaction of 2-hydroxy-*N*-(2-methoxyphenyl)benzamide **1j** and 1-(bromomethyl)-3-nitrobenzene **35** gave the product **41j** as a yellow solid in 86% isolated yield. ^1H NMR (400 MHz, CDCl_3) δ 10.20 (s, 1H), 8.62 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.35 (t, $J = 2.0$ Hz, 1H), 8.27 (dd, $J = 7.6, 2.0$ Hz, 1H), 8.20 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.84 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.47–7.43 (m, 1H), 7.17 (ddd, $J = 7.6, 7.6, 0.8$ Hz, 1H), 7.07–6.98 (m, 3H), 6.82 (dd, $J = 8.0, 1.6$ Hz, 1H), 5.42 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.13, 155.94, 148.68, 148.37,

138.32, 133.54, 133.22, 132.91, 130.19, 128.35, 123.96, 123.75, 123.62, 122.72, 122.46, 121.47, 120.66, 113.51, 110.09, 70.49, 55.63; HRMS (ESI) m/z : calcd for $C_{21}H_{19}N_2O_5$ $[M + H]^+$ 379.1294; found 379.1291.

2-(4-nitrilebenzyloxy)-N-(2-methoxyphenyl)benzamide 42j: Reaction of 2-hydroxy-*N*-(2-methoxyphenyl)benzamide **1j** and 4-(bromomethyl)benzonitrile **36** gave the product **42j** in 40% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.63 (dd, $J = 7.6, 2.0$ Hz, 1H), 8.28 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.68 (m, 2H), 7.59 (d, $J = 8.0$ Hz, 2H), 7.44 (ddd, $J = 8.0, 8.0, 2.0$ Hz, 1H), 7.16 (ddd, $J = 8.0, 8.0, 0.8$ Hz, 1H), 7.08–6.99 (m, 2H), 6.97 (d, $J = 8.0$ Hz, 1H), 6.84 (dd, $J = 8.0, 1.6$ Hz, 1H), 5.39 (s, 2H), 3.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.13, 155.95, 148.31, 141.51, 133.22, 132.91, 132.80 (2C), 128.38, 127.97 (2C), 123.98, 123.52, 122.58, 121.48, 120.63, 118.63, 113.25, 112.48, 110.03, 70.47, 55.54; HRMS (ESI) m/z : calcd for $C_{22}H_{19}N_2O_3$ $[M + H]^+$ 359.1396; found 359.1387.

2-(4-methoxybenzyloxy)-N-(2-methoxyphenyl)benzamide 43j: Reaction of 2-hydroxy-*N*-(2-methoxyphenyl)benzamide **1j** and 1-(bromomethyl)-4-methoxybenzene **37** gave the product **43j** in 50% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.64 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.31 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.45–7.38 (m, 3H), 7.11 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.08–6.97 (m, 3H), 6.91–6.88 (m, 2H), 6.82 (dd, $J = 7.6, 1.6$ Hz, 1H), 5.26 (s, 2H), 3.80 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.40, 159.96, 156.74, 148.66, 133.15, 132.77, 129.51 (2C), 128.61, 128.10, 123.74, 123.04, 121.88, 121.21, 120.80, 114.34 (2C), 113.54, 109.91, 71.35, 55.57, 55.52; HRMS (ESI) m/z : calcd for $C_{22}H_{22}NO_4$ $[M + H]^+$ 364.1549; found 364.1547.

2-((benzo[d][1,3]dioxol-6-yl)methoxy)-N-(2-methoxyphenyl)benzamide 44j: Reaction of 2-hydroxy-*N*-(2-methoxyphenyl)benzamide **1j** and 5-(bromomethyl)benzo[d][1,3]dioxole **38** gave the product **44j** in 47% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.63 (dd, $J = 8.0, 2.0$ Hz, 1H), 8.30 (dd, $J = 7.6, 2.0$ Hz, 1H), 7.42 (ddd, $J = 8.4, 7.6, 2.0$ Hz, 1H), 7.12 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.07–6.97 (m, 4H), 6.94 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.85 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 5.95 (s, 2H), 5.23 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.35, 156.54, 148.66, 148.32, 147.98, 133.13, 132.79, 129.86, 128.56, 123.80, 123.13, 121.97, 121.59, 121.27, 120.84, 113.51, 109.97, 108.58, 108.49, 101.46, 71.47, 55.62; HRMS (ESI) m/z : calcd for $C_{22}H_{20}NO_5$ $[M + H]^+$ 378.1341; found 378.1340.

Methyl 4-((2-(2-methoxybenzamido)phenoxy)methyl)benzoate 45k: Reaction of *N*-(2-hydroxyphenyl)-2-methoxybenzamide **1k** and methyl 4-(bromomethyl)benzoate **39** gave the product **45k** in 76% isolated yield. 1H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 8.71 (m, 1H), 8.30 (dd, $J = 7.6, 1.6$ Hz, 1H), 8.09 (m, 2H), 7.58 (m, 2H), 7.45 (ddd, $J = 7.6, 7.6, 1.6$ Hz, 1H), 7.11 (ddd, $J = 7.6, 7.6, 1.2$ Hz, 1H), 7.06 (m, 2H), 6.98 (m, 1H), 6.90 (dd, $J = 8.4, 0.8$ Hz, 1H), 5.18 (s, 2H), 3.94 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.90, 163.33, 157.54, 147.68, 141.77, 133.33, 132.73, 130.46, 130.25 (2C), 128.96, 128.40 (2C), 123.70, 122.16, 122.07, 121.63, 121.04, 111.62, 111.33, 70.50, 55.67, 52.53; HRMS (ESI) m/z : calcd for $C_{23}H_{22}NO_5$ $[M + H]^+$ 392.1498; found 392.1484.

Biology

Antiviral assays—Antiviral assays were carried out as previously described.^[21] Briefly, H9 or MT4 cells were maintained in RPMI Medium 1640 (Invitrogen) containing 25 mM HEPES and L-glutamine with 10% FBS, 100 units/ml penicillin, and 100 mg/ml streptomycin (Invitrogen) at 37 °C in a humidified incubator (5% CO_2). Cells were seeded at 2×10^5 per well in a 24-well plate, treated overnight with various concentrations of RN18 or analogues (all at 0.1% DMSO) and infected with HIV-1 (X4-tropic HIV-1 variant

[HIV-1_{LAI}]) at 2×10^5 c.p.m. reverse transcriptase per well. All cells were maintained in the presence of DMSO, RN18 or analogues for 14 days, and viral replication was monitored every 2 days by measuring reverse transcriptase activity in culture supernatants. The average % relative infectivity at day 7 was determined from 3 separate reverse transcriptase assays. Grafit software was used to fit curves and to determine IC₅₀ values. **CAUTION!** Use extreme caution when handling the X4-tropic HIV-1 variant strain, limiting all laboratory procedures to the safety of a BL2+ laboratory facility.

Cell viability assays—The cytotoxicity of RN18 analogues was assessed in HeLa cells using an MTT-based cell viability assay.^[30] Briefly, HeLa cells were harvested in the log phase of growth and seeded at 1×10^3 cells per well (180 μ L) in a 96-well plate by using DMEM (Invitrogen) supplemented with fetal bovine serum (10%; Invitrogen). Cells were incubated under a humidified atmosphere at 37 °C with CO₂ (5%) for the duration of the assay. At 24 h post-seeding, $10 \times$ stock solutions (20 μ L; RN18 or analogues in DMEM) were added to the appropriate wells. Each test plate included two negative controls: DMEM (20 μ L), and 2) media (20 μ L) with DMSO (10 %; the final concentration of DMSO was 1%, the highest added to the cells). At 72 h post drug addition, the MTT solution (50 μ L of 2 mg mL⁻¹ solution) prepared in PBS (Invitrogen) was carefully dispensed into each well. After 4 h incubation at 37 °C, CO₂ (5 %), the medium was aspirated from all wells and DMSO (100 μ L) was added and mixed by using a multichannel pipette. Absorbance was read at 550 nm by using a Safire plate reader (TECAN) and the percentage viability was calculated for each specific concentration. The results were expressed as RA (drug concentrations inhibiting relative MTT absorbance, RA, by 50%), by using the equation: RA (%) = ($A_{\text{treatedgroup}}/A_{\text{controlgroup}}$) $\times$ 100%. The CC₅₀ for each compound was calculated by using Grafit software.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Chemical Structures of HIV-1 Vif Inhibitors RN18 and RN19.

Figure 2.

a) A convergent route for the synthesis of RN18 and analogues; b) alternate route for the synthesis of RN18 and C-ring analogues.

Scheme 1.

Reagents and conditions: a) Cu(I)I, K₂CO₃, *i*PrOH, HOCH₂CH₂OH, MW (150 WT), 80 °C, 30 min (2 ×); b) SnCl₂·2H₂O, EtOAc, 80 °C, 3 h.

Scheme 2.

Reagents and conditions: a) Cu(I)I, K₂CO₃, 1,2-DME, MW (150 WT), 80 °C, 30 min (2 ×); (b) Ba(OH)₂·8H₂O, MeOH, 80 °C, 2 h; (c) (i) (COCl)₂, CH₂Cl₂, DMF, RT, 8 h, (ii) R' R''NH (**14a-h**), Et₃N, CH₂Cl₂, 0 °C to RT, overnight; d) SnCl₂·2H₂O, EtOAc, 80 °C, 3 h.

Scheme 5.

Reagents and conditions: (a) Cu(I)Cl, Cs₂CO₃, CH₂(*Co*-t-Bu)₂, NMP, MW (150 WT), 120 °C, 30 min (2 ×); (b) Cu(OAc)₂, CH₂Cl₂, PhOH, Et₃N, 4A MS, RT, overnight; (c) K₂CO₃, DMF, MW (150 WT), 90 °C, 30 min (2 ×).

Table 1

Antiviral potency in permissive and non-permissive cells and cytotoxicity of HIV-1 Vif inhibitors.

Compd.	R ²	X	Y	R ¹	Antiviral Activity		Toxicity CC ₅₀ (μM)
					H9 cells	MT4 cells	
5a (RN18)	4-NO ₂	S			6	>100	>100
4a	H	S			>100	>100	>100
5b	4-NO ₂	S (1,3)			NT	NT	NT
5c	4-NO ₂	S			5.5	52.0	>100
5d	4-NO ₂	S			5.9	>100	>100
5e	4-NO ₂	S			21.5	39	>100
5f	4-NO ₂	S			5.2	53.6	>100
5g	4-NO ₂	S			29.7	>100	>100

Compd.	R ²	X	Y	R ¹	Antiviral Activity		Toxicity CC ₅₀ (μM)
					IC ₅₀ (μM)		
					H9 cells	MT4 cells	
6a	4-NH ₂	S			20	>100	>100
6b	4-NH ₂	S (1,3)			NT	NT	NT
6c	4-NH ₂	S			37.8	39.8	60
6d	4-NH ₂	S			9.3	>100	>100
6e	4-NH ₂	S			20.8	21.0	65
15b	4-NO ₂	S			25	50	NT
15c	4-NO ₂	S			>100	>100	NT
15d	4-NO ₂	S			50	>100	NT
15e	4-NO ₂	S			112	93	>100

Compd.	R ²	X	Y	R ¹	Antiviral Activity		Toxicity CC ₅₀ (μM)
					IC ₅₀ (μM)	MT4 cells	
15f	4-NO ₂	S			50	52	>100
15h	4-NO ₂	S			3.9	3.7	70
16a	2-Cl-4-NO ₂	S			5	5	50
16d	2-Cl-4-NO ₂	S			25	10	>100
18a	4-NO ₂	O			4.7	15.2	15
18e	4-NO ₂	O			9.2	15.6	25
19a	4-NH ₂	O			43.2	72.2	>100
23h	3,4-OCH ₂ O-	O			12.6	102.5	>100
29k	4-NO ₂	O			4.9	26.3	>100

Compd.	R ²	X	Y	R ¹	Antiviral Activity		Toxicity CC ₅₀ (μM)
					H9 cells	MT4 cells	
30k	4-NMe ₂	O			2.5	68	>100
31k	4-OCH ₃	O			9.7	50.3	>100
32k	4-OCOCH ₃	O			43.2	>100	>100
33k	4-CO ₂ CH ₃	O			10.7	40.6	>100
40j	4-NO ₂	CH ₂ O			2.8	>100	>100
40k	4-NO ₂	CH ₂ O			34.0	26.6	>100
41j	3-NO ₂	CH ₂ O			7.1	>100	>100
42j	4-CN	CH ₂ O			3.1	22.8	NT
43j	4-OCH ₃	CH ₂ O			>100	>100	>100

Compd.	R ²	X	Y	R ¹	Antiviral Activity		Toxicity CC ₅₀ (μM)
					IC ₅₀ (μM)	MT4 cells	
44j	3,4-OCH ₂ O-	CH ₂ O			12.9	45.2	NT
45k	4-CO ₂ Me	CH ₂ O			>100	>100	>100

NT: not tested.