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Design, Synthesis and Biological Evaluation of Biphenylamide Derivatives as Hsp90 C-terminal Inhibitors

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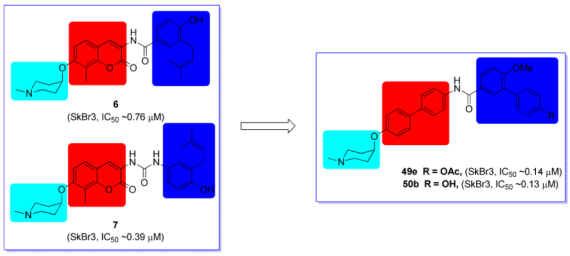
Abstract

Modulation of Hsp90 C-terminal function represents a promising therapeutic approach for the treatment of cancer and neurodegenerative diseases. Current drug discovery efforts toward Hsp90 C-terminal inhibition focus on novobiocin, an antibiotic that was transformed into an Hsp90 inhibitor. Based on structural information obtained during the development of novobiocin derivatives and molecular docking studies, scaffolds containing a biphenyl moiety in lieu of the coumarin ring present in novobiocin were identified as new Hsp90 C-terminal inhibitors. Structure-activity relationship studies produced new derivatives that inhibit the proliferation of breast cancer cell lines at nanomolar concentrations, which corresponded directly with Hsp90 inhibition.

Graphical abstract



Keywords

Heat shock protein 90; Hsp90 C-terminal inhibitors; Biphenyl; Structure-activity relationship; Breast cancer

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1. Introduction

The 90 kDa heat shock proteins (Hsp90) are highly conserved molecular chaperones responsible for the conformational stability of more than 200 client proteins, many of which are essential to cancer cell survival [1-3]. Abnormal expression of Hsp90 has been implicated in a variety of disease states: In cancer, over-expression of Hsp90 is critical for the maturation and biological activity of numerous oncogenic proteins (eg., Her2, Raf1, Akt, CDK4, Src, c-Met, etc.) that are distributed amongst all six hallmarks of cancer [4, 5]. In neurodegenerative diseases, Hsp90 serves as the master regulator of the prosurvival heat shock response, and provides buffering capabilities for damaged proteins that accumulate beyond normal concentrations and can result in neuronal death [6]. Research has demonstrated that small molecule Hsp90 N-terminal inhibitors manifest two cellular activities, the first of which is induced degradation of proteins that are dependent upon the Hsp90 protein folding machinery. The second is concomitant induction of the pro-survival heat shock response (HSR). The HSR expands the chaperone buffering capacity to counter misfolded proteins that accumulate upon exposure to cellular stress, and thus, aids cell survival. These contradictory effects can provide unique therapeutic opportunities for the treatment of cancer and neurodegenerative diseases, if segregated [7, 8]. 17 Small molecule Hsp90 N-terminal inhibitors have entered clinical trials for the treatment of various cancers, however, the heat shock response manifested by these compounds appears detrimental, as the concentration needed for client protein degradation also induces the pro-survival response [9]. Similarly, these two effects hinder their application as neuroprotective agents, as cytotoxic client protein degradation is observed at the same concentration that induces the prosurvival HSR.

Recent studies have identified small molecules that bind the Hsp90 C-terminus and allosterically modulate Hsp90 function [10, 11]. In contrast to N-terminal inhibitors, C-terminal inhibitors can segregate the heat shock response from client protein degradation, thus providing a therapeutic opportunity for the treatment of neurodegenerative diseases or elimination of the pro-survival, heat shock response for cancer [12, 13]. Although several scaffolds are now known to bind the C-terminus (Figure 1) [13-16], medicinal chemistry efforts have been most focused on analogs of novobiocin, which was the first Hsp90 C-terminal inhibitor identified [17]. The identification of new chemical scaffolds that target the Hsp90 C-terminal domain is needed to dissect the role played by Hsp90 C-terminal inhibitors during the Hsp90 protein folding cycle as well as to improve upon inhibitory activity.

2. Result and Discuss

Prior modifications to novobiocin have revealed some structure-activity relationships and identified analogues that exhibit improved inhibitory activity [14, 18-23]. As summarized in Figure 2, these studies identified the benzamide side chain as critical for anti-proliferative activity, and modifications to this region can further increase inhibitory activity. The noviose sugar contributes to solubility and efficacy, however, replacement with ionizable amines results in analogues that also exhibit improved inhibitory activity, but do not induce the HSR (**6**, Figure 2). The amide linker not only provides important hydrogen bonding

interactions, but it also serves to orient the aromatic side chain for interactions with the binding site. Recently, it was discovered that replacement of the amide with urea led to analogues that manifest greater anti-proliferative activity (**7**, Figure 2), presumably due to an extended hydrogen bonding network [24, 25]. In contrast to these modifications, studies on the coumarin ring system have produced only minor effects. Moreover, substitutions on the coumarin ring did not produce compounds with significantly altered activity, suggesting that the coumarin ring may serve to orient of the sugar and benzamide side chains within the binding pocket. Therefore, it was proposed that the coumarin ring could be replaced without compromising activity [19, 26].

Recently, it was observed that the optimum distance between the piperidine nitrogen and the hydrogen-bonding network of the amide/urea is critical for inhibitory activity [25, 27]. Based on this observation, it was hypothesized that replacement of the coumarin core with scaffolds that maintain this distance may provide compounds upon which new inhibitors could be developed. Attempts to replace the coumarin with fused ring systems did not produce improved inhibitory activities [19, 26], suggesting that a flexible ring system may be beneficial for projection of the amino and benzamide side chain. The biphenyl ring system is relatively flexible and could therefore adopt different conformations within the binding pocket, which may present additional interactions with the protein. As a privileged-structure, compounds derived from this scaffold are known to manifest diverse activities, including anti-tumor activity [28]. In addition, the substitution pattern on this moiety can be modified and the distance between the ionizable amine and amide tuned. Therefore, molecules enlisting biphenyl as a coumarin replacement were pursued. Since no co-crystal structure of a ligand bound to the Hsp90 C-terminus exists, three substitution patterns on the biphenyl core (*para-meta*, *meta-meta* and *para-para*) were pursued to identify structural requirements for this scaffold. As shown in Figure 2, a piperidine was used in lieu of the noviose sugar and a prenylated benzylamide side chain was chosen for attachment to the biphenyl core.

Based on existing models for Hsp90 C-terminal inhibition [29, 30], computational docking studies utilizing the C-terminal binding site were conducted and identified compounds **8d** [31] and **8e**, which contain the *para-meta* or *meta-meta* substitution pattern, to overlay well with the novobiocin lead compound, **6** (Figure 3A). In contrast, compound **8f**, which contains a *para-para* substitution, overlaid with the more active, urea-based analogue, **7** (Figure 3B). Interestingly, molecular studies suggested that compound **8f**, which contains *para-para* substitution, may project the N-methylpiperidine deeper into the binding pocket and increase interactions with the protein (Figure 3C).

Encouraged by these computational studies, compounds **8** and analogs thereof were pursued along with investigation of the aryl substitution pattern. As shown in Scheme 1, these analogs were envisioned for assembly via an amide coupling reaction between amine **9** and acid chloride **10**. The key intermediate, **9**, could then be obtained through a Suzuki coupling reaction between piperidine-containing iodide **11** and phenylboronic acid, **12**.

Preparation of the biphenylamides that serve as novobiocin mimics is described in Scheme 2. Mitsunobo etherification of 1-methyl-4-hydroxypiperidine (**13**) and iodophenols, **14a** or

14b, afforded iodides **11a**–**b**, which underwent subsequent Suzuki coupling with 3- or 4-aminophenylboronic acid to produce anilines **9a-c** (these compounds contain all three patterns of substitution; **9a**: *para-meta*; **9b**: *meta-meta*; **9c**: *para-para*). Amide coupling of anilines **9a**–**c** with prenylated acid chloride (**10a**) gave amides **8a–c,** while the same conditions gave compounds **8g-i** when treated with acid chloride **10b.** Solvolysis of the acetate present in **8a-c** in a solution of 10% triethylamine in methanol gave phenols **8d-f** in good yields.

Upon construction of this biphenyl-containing novobiocin library, the compounds were evaluated for anti-proliferative activity against SKBr3 (estrogen receptor negative, HER2 over-expressing breast cancer cells) and MCF-7 (estrogen receptor positive breast cancer cells) cell lines. Her2 and the ER are driving factors for these two cancers and are both Hsp90-dependent substrates. As shown in Table 1, the biphenyl-containing mimics exhibited low micromolar anti-proliferative activity, which is similar to that manifested by their coumarin counterparts. For analogues that contain a prenylated benzamide side chain (**8a-f**), the acetylated phenols (**8a-c**) exhibited comparable activity to the corresponding phenols (**8d-f**). Compounds containing the *meta-meta* (**8b**) and *para-para* (**8c**) biphenyl substitution patterns produced similar inhibitory activity and were more active than those containing the *para-meta* linkage (**8a**). Analogues containing the biaryl side chain (**8g-i**) showed improved anti-proliferative activity, and a *para-para* substituted biphenyl derivative **8i** exhibited submicromolar activity against both breast cancer cell lines, approximately 2~3-fold better than its *para-meta* and *meta-meta* counterparts.

To confirm the observed anti-proliferative activities manifested by these biphenyl analogues resulted from Hsp90 inhibition, Western blot analyses of cell lysates following incubation with these compounds were performed. Compounds **8e**, **8f**, **8h** and **8i** induced the degradation of Hsp90-dependent client proteins, including Her2, Raf and Akt, at concentrations near their anti-proliferative IC_{50} value. Since Hsp90-dependent client protein degradation occurs at concentrations that mirror those needed for cellular efficacy, it is clear that Hsp90 inhibition is directly linked to cell viability. In addition, Hsp90 levels remained constant at both low and high concentrations, which is a hallmark of C-terminal inhibition.

These biological assays suggest the biphenyl moiety can serve as a replacement for the coumarin ring and as a platform for the development of new Hsp90 C-terminal inhibitors. Considering the increased flexibility associated with this moiety in comparison to the coumarin ring, it was expected that the introduction of substituents onto the biphenyl system would provide additional interactions with the binding pocket. Since molecules containing a *para-para* substituted biphenyl moiety manifested superior Hsp90 inhibitory activity, modifications to this system were pursued. Prior SAR studies on the coumarin scaffold demonstrated that replacement of the lactone with quinoline resulted in slightly increased inhibitory activity [32]. Therefore, structural modifications were initiated by the inclusion of nitrogen at various positions throughout the biphenyl system. As illustrated in Scheme 2, the synthesis of derivatives containing nitrogen in the A ring commenced by Mitsunobo etherification of 1-methyl-4-hydroxypiperidine (**13**) and pyridinol **15a** to give bromide **16**, followed by a Suzuki coupling reaction to afford the nitro aromatic, **18a**. Alternatively, direct Suzuki coupling of **15b** gave phenol **17,** which then underwent Mitsunobu

etherification to give **18b**. Subsequent reduction of the nitro group (**18a-b**) and coupling with **10b** produced amides **19a** and **19b**. For construction of B-ring pyridines, the amide coupling reaction was performed first, between anilines **20a- b** and biaryl acid chloride **10b,** which enabled construction of bromides **21a-b**. These bromides were then converted to phenols **22a-b** via a Suzuki coupling reaction with 4-hydroxyphenylboronic acid. Finally, etherification of **22a-b** with 1-methyl-4-hydroxypiperidine (**13**) afforded compounds **19c-d** in good yields.

Upon construction of these nitrogen containing biphenyl derivatives, their anti-proliferative activity against SKBr3 and MCF-7 was investigated. As shown in Table 2, insertion of a nitrogen atom into the biphenyl ring system was detrimental, as all four derivatives manifested a 2-3 fold reduction in anti-proliferative activity. It appears that inclusion of a nitrogen atom into the B ring (**19c-d**) results in compounds that exhibit slightly better activity than inclusion of nitrogen into the A-ring, which correlates with the location of the lactone present in the coumarin ring system of novobiocin.

Although it was disappointing that nitrogen containing compounds did not manifest improved activity, the data suggested the binding site may be apolar. Therefore, to probe the surrounding binding pocket, additional functionalities were incorporated into the biphenyl ring system, which included a methyl, chloro, methoxy, nitro, amino or an acetamide, at all four positions. As outlined in Scheme 3, the synthesis of derivatives containing a methyl, chloride or methoxy substituent were pursued via a Suzuki coupling between bromides **23a-f** and 4-nitrophenylboronic acid, or 4-hydroxyphenylboronic acid and bromides **26a-f**, to afford phenols **24a-f** or **27a-f**, respectively. Mitsunobu etherification of the free phenols gave nitro derivatives, **25a-f** or **28a-f**, which underwent reduction and subsequent amide coupling with **10b** to afford biphenyl derivatives, **29a-i**.

The synthetic route used for the preparation of derivatives containing the nitro substituent was slightly altered. The Boc-protected 4-aminophenylboronic ester (**31**) was coupled with *ortho* or *meta* substituted nitro phenylbromides (**30a** or **30b**) to give phenols **32a-b**, which underwent Mitsunobu etherification to afford **33a-b**. Deprotection to afford the corresponding aniline in the presence of trifluoroacetic acid, followed by an amide coupling with acid chloride **10b,** produced the nitro-substituted derivatives, **34a-b**. The synthetic route used to produce analogs that contain a nitro substituent on the B-ring were pursued via nitro substituted 4-bromoanilines, **35a-b,** which were then reacted with acid chloride **10b** to afford amides **36a-b**, followed by Suzuki coupling with 4-hydroxyphenylboronic acid. Mitsunobo etherification of the resulting phenols with N-methyl piperidine gave nitro-derivatives, **34c-d**. Subsequent reduction gave anilines **38a- d,** and acylation afforded the acetamides **39a-d**, respectively.

Anti-proliferative activity manifested by the substituted biphenyl derivatives was determined against SKBr3 and MCF-7 breast cancer cells. As shown Table 3, such modifications to the biphenyl ring system did not significantly affect inhibitory activity for most derivatives. It appears that substitution *ortho* to the amide (**29d**, **29h**, **29l**, **34d**, **38d** and **39d**) is not tolerable, potentially due to disruption of the hydrogen bonding network and orientation of the amide side chain. Methyl and methoxy substituents at the C-2′ and C-3′ positions of the

A ring and at C-3 of the B ring generated compounds (**29a-c** and **29e-g**) that manifested similar anti-proliferative activities. For electron-withdrawing groups (Cl and NO_2), it appears that substitution at C-2′ is more tolerable than at C-3′ (**29j** vs **29i**, **34b** vs **34a**). Decreased activity manifested by **38** and **39,** when compared with **29a-h**, indicates that a hydrogen bond donor is less favorable.

Although structural modification to the biphenyl moiety did not produce improved activities against these breast cancer cell lines, it did reflect a similar trend observed for the coumarin core of novobiocin, suggesting the biphenyl moiety is playing a similar role for orientation of the sugar and benzamide side chains. Since SAR studies on novobiocin demonstrated modification to the benzamide side chain produced analogues that exhibit improved anti-proliferative activity, SAR studies on the amide side chain were sought [32]. Electron-donating, electron-withdrawing and sterically bulky substituents were installed onto the benzylamide side chain by a straightforward coupling reaction between aniline **9c** and substituted benzoyl chlorides (**40a**–**40s**), in the presence of pyridine to give **41a**–**41s** (Scheme 6).

To compensate for the entropic penalty paid by replacement of the rigid coumarin ring with a more flexible biaryl moiety, fused ring systems (such as naphthalene, quinolone, indole, and benzo[b]thiophenyl) were introduced into the side chain. Similar to those reported earlier, these compounds were synthesized through an amide coupling between aniline **9c** and the corresponding acid chlorides (**42a-b**, **43a-b** and **45a-b**), in the presence of pyridine to give **42a-b**, **44a-b** and **46a-b**.

Biphenyl derivatives containing the modified benzamide side chain were evaluated in anti-proliferative assays against both breast cancer cell lines. As shown in Table 4, a large number of the substituted derivatives were found to exhibit increased inhibitory activity compared to the unsubstituted compound **41a**, (except *p*-phenyl and *o*-phenyl substituted derivatives **41s** and **41q**). Compounds containing a *para*-halogen (**41b-d**, Cl, Br, I) or methoxy (**41f**) on the benzamide side chain manifested the most potent anti-proliferative activities, which were comparable to biaryl derivative **8i**. However, shifting the substitution from *para* to *meta* (**41b** vs **41h**, **41f** vs **41i**) resulted in decreased anti-proliferative activity. Consistent with this observation, installation of a *meta* substituent onto **41b** or **41e** manifested decreased inhibitory activity (**41b** *vs* **41j**, **41e** *vs* **41n** and **41p**). Interestingly, introduction of a *meta*-iodo substituent maintained activity (**41e** *vs* **41m**), suggesting that a bulky substituent at the *meta* position may provide beneficial interactions with the binding site. In fact, this phenomena was observed for the phenyl substituted derivatives as well, although *para*- and *ortho*- substitutions (**41q** and **41s**) did not produce compounds with enhanced anti-proliferative activity. However, *meta*-substitution (**41r**) produced inhibitors with comparable activity to lead compound **8i**. Introduction of a fused ring system onto the side chain resulted in interesting activity. Compounds containing a 1- or 2-naphthoxyl amide side chain (**43a** and **43b**) manifested good anti-proliferative activity. However, insertion of a nitrogen atom into the fused ring system (**45a** and **45b**) decreased activity. 2-Indonyl (**47a**), not 2-benzo[*b*]thiophenyl (**47b**), exhibited comparable activity to **43a** and **43b**, suggesting that inclusion of a hydrogen bond donor is favored over a hydrogen bond acceptor.

Confirmation that these molecules manifest their anti-proliferative activity through Hsp90 inhibition was determined by western blot analyses following incubation of these compounds with Mcf-7 cells for 24h. Analogs containing a halogen atom (**41b**, **41c**, **41d**) did not induce client protein degradation, while compounds **41f**, **41r**, **43a**, **43b** and **47a** induced the degradation of Hsp90-dependent client proteins Her2, Raf, and Akt. Hsp90 levels remained constant, indicating these compounds manifest their inhibitory activity through C-terminal inhibition.

Structure-activity relationships obtained from these biphenylamide inhibitors largely reflect the trends observed with novobiocin, suggesting that successful modifications to novobiocin may also be applied to this scaffold. Compounds **41q-s** suggest the biphenyl side chain is well accommodated, and comparison between compounds **41r** and **8i** indicate that additional substitutions may lead to even better inhibitory activity. To further verify the individual function of the two methoxy groups on compound **8i** and potential locations for further modification, **49a**, which lacks the 3′-methoxy on **8i**, and compound **49b**, which lacks the 4-methoxy substitution, additional compounds were synthesized. Biological evaluation of these compounds indicated the 4-methoxy is more beneficial (**49a** vs **49b**, vide infra). Additional modifications were sought to install substitutions onto the second phenyl ring, with the aim of exploiting interactions at this location (Scheme 8). These compounds were synthesized through an amide coupling reaction between aniline **9c** and acid chlorides **48c-h**, which were synthesized according to reported procedures [23, 25]. Ester hydrolysis of **49d** and **49e** gave phenols **50a** and **50b,** while nitro reduction converted **49h** to aniline **50c**. **50c** was then transformed to acetamide **50d** upon acylation.

As shown in Table 5, the anti-proliferative activities manifested by compounds containing a modified biaryl side chain suggest the 4-methoxy, not the 3′-methoxy is beneficial, since compound **49a** exhibited similar activity, while **49b** manifested decreased inhibitory activity compared to **8i**. Installation of a phenolic ester onto the second phenyl ring also appears beneficial (**49d** and **49e** vs **8i**). Although hydrolysis of the 4′-ester did not alter the anti-proliferative activity (**50b**), hydrolysis of the 3′-ester led to decreased activity (**50a**). The introduction of chlorine at the 3′-position resulted in increased activity, whereas installation of chlorine at the 4′-position did not (**49f** and **49g** vs **49a**). Replacement of the 3′-methoxy with a nitro group retained anti-proliferative activity against both breast cancer cell lines, however, the corresponding aniline and acetamide failed to exhibit improved potency.

Western blot analyses were performed to determine whether these compounds manifested their anti-proliferative activity through Hsp90 inhibition. Compounds, **49a**, **49e** and **49f** induced client protein degradation (Her2, Raf and Akt) at concentrations that mirrored their anti-proliferative IC_{50} values. Hsp90 levels remained constant or slightly decreased, suggesting these compounds modulate Hsp90 through C-terminal inhibition. Subsequent dose-dependent analysis of Hsp90-dependent client proteins in MCF-7 cells upon administration of compound **49e** (Figure 6B) demonstrated that Her2, Raf-1 and Akt underwent degradation in a concentration-dependent manner when exposed to **49e**, reflecting that anti-proliferative activity is directly linked to Hsp90 inhibition.

3. Conclusions

In conclusion, a small library of Hsp90 C-terminal inhibitors containing a biphenyl scaffold was designed and synthesized. These biphenyl derivatives were shown to serve as a suitable replacement for the coumarin ring system found in novobiocin. Western blot analyses demonstrated these compounds to manifest anti-proliferative activity through Hsp90 inhibition. Structural modifications to this scaffold led to structure-activity relationships and ultimately, small molecules that exhibit improved activities against these two breast cancer cell lines. Many of these molecules were shown to exhibit lead-like properties for the development of new Hsp90 C-terminal inhibitors. Identification of the biphenyl ring system provides rapid access to modifications that should enable succinct discovery of both structure-activity relationships and more potent Hsp90 C-terminal inhibitors.

4. Experimental section

4.1. Docking calculations

Initial receptor preparation before docking runs was performed using Schrödinger's 'Protein Preparation Wizard' program (see www.Schrodinger.com), starting from the most representative protein conformation of previous MD simulations of Hsp90 in complex with novobiocin in the ATP bound state [25]. Bond orders and atomic charges were assigned and hydrogen atoms were added. The assignments of protonation states for basic and acidic residues were based on the optimization of hydrogen bonding patterns. The final minimization of the protein was performed with the Preparation Wizard default.

The shape and properties of the resulting binding site were mapped onto a grid with dimensions of 36 Å (enclosing box) and 14 Å (ligand diameter midpoint box), centered on the centroid of novobiocin.

Rigid receptor and flexible ligand docking calculations were performed using the program Glide (version 5.8 Schrödinger, LLC, New York, NY, 2012) [33, 34]. Docking calculations were performed in Standard Precision mode (SP) with standard OPLS-AA (2001) force field [35], non-planar conformations of amide bonds were penalized, Van der Waals radii were scaled by 0.80 and the partial charge cut off was fixed to 0.15. No further modifications were applied to the default settings.

4.2. Chemistry

^{1}HNMR were recorded at 400 or 500 MHz (Bruker DRX-400 Bruker with a H/C/P/F QNP gradient probe) spectrometer and ^{13}C NMR spectra were recorded at 100 or 125 MHz (Bruker DRX 500 with broadband, inverse triple resonance, and high resolution magic angle spinning HR-MA probe spectrometer); chemical shifts are reported in δ (ppm) relative to the internal reference chloroform-*d* ($CDCl_3$, 7.27 ppm) or dimethyl sulfoxide-d_6 (DMSO-d_6, 2.50 ppm). High resolution mass spectra (FAB) were recorded with a LCT Premier (Waters Corp., Milford, MA) spectrometer. The purity of all compounds was determined to be >95% as determined by ^{1}HNMR and ^{13}CNMR spectra, unless otherwise noted. The most active 10 compounds were verified for >95% purity by HPLC analyses. TLC was performed on glassbacked silica gel plates (Uniplate) with spots visualized by UV light. All solvents were

reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure.

4.2.1. 4-(4-iodophenoxy)-1-methylpiperidine (11a): General procedure for the synthesis of compound 11a-b through Mitsunobu etherification— Diisopropylazodicarboxylate (1.89 g, 9.36 mmol) was added to an ice-cooled solution of iodophenol (0.92 g, 4.18 mmol), N-methyl-4-hydroxy-piperidine (480 mg, 4.18 mmol) and triphenylphosphine (2.46 g, 9.36 mmol) in anhydrous THF (10 mL). The reaction mixture was then allowed to stir at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated under reduced pressure and the residue was purified via column chromatography (SiO_2, CH_2Cl_2: methanol, 10:1) to afford a thick oil (1.02 g, 77 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 (d, *J* = 8.9 Hz, 2H), 6.69 (d, *J* = 2.0 Hz, 2H), 4.27 (m, 1H), 2.73 – 2.59 (m, 2H), 2.31 (s, 3H), 2.30 (m, 2H), 1.98 (m, 2H), 1.82 (m, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 157.34, 138.34, 118.50, 82.91, 72.18, 52.61, 46.28, 30.71. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{12}H_{17}INO$ 318.0355; found 318.0357.

4.2.2. 4-(3-iodophenoxy)-1-methylpiperidine (11b)—Compound **11b** was obtained as a yellow amorphous solid (611.1 mg, 46%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.26 (m, 2H), 6.98 (t, *J* = 9.3 Hz, 1H), 6.87 (dd, *J* = 7.8, 2.3 Hz, 1H), 4.39 – 4.20 (m, 1H), 2.75 – 2.58 (m, 2H), 2.35 – 2.30 (m, 2H), 2.32 (s, 3H), 1.99 (m, 2H), 1.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.22, 131.03, 130.11, 125.39, 115.72, 94.61, 72.37, 52.67, 46.36, 30.81. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{12}H_{17}INO$ 318.0355; found 318.0356.

4.2.1.1. 4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-amine (9a): General procedure for synthesis of 9a-c through Suzuki coupling: A mixture of iodide **11a** (250 mg, 0.79 mmol) aminophenylboronic acid (216 mg, 1.58 mmol), potassium carbonate solution (2M, 100 μL) and [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (57 mg, 0.08 mmol) was suspended in dry dioxane (15 mL) and purged with argon for 15 min. After 15 min, the mixture was heated in a sealed tube at 110 °C for 12 hours before concentrated to dryness. The residue so obtained was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford a brownish amorphous solid (149 mg, 67 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.99 – 6.92 (m, 3H), 6.88 (s, 1H), 6.66 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.45 – 4.34 (m, 1H), 3.74 (s, 2H), 2.79 (ddd, *J* = 11.8, 7.8, 3.8 Hz, 2H), 2.48 – 2.42 (m, 2H), 2.39 (s, 3H), 2.11 (ddt, *J* = 11.5, 7.3, 3.6 Hz, 2H), 1.94 (ddt, *J* = 14.0, 7.9, 3.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.77, 146.69, 141.94, 134.13, 129.65, 128.16, 117.28, 116.15, 113.60, 113.49, 71.45, 52.37, 45.96, 30.42. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{18}H_{23}N_2O$ 283.1810; found, 283.1808.

4.2.2.1. 3′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-amine (9b): Compound **9b** was obtained as a brownish amorphous (116 mg, 52%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (t, *J* = 7.9 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.03 (m, 2H, NH2), 6.98 – 6.96 (m, 1H), 6.86 – 6.83 (m, 1H), 6.80 (t, *J* = 2.0 Hz, 1H), 6.77 – 6.73 (m, 1H), 6.68 – 6.64 (m, 1H), 6.59 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.36 (m, 1H), 2.66 (m, 2H), 2.37 (m, 2H), 2.25 (s, 3H), 1.92 (s,

2H), 1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 157.29, 146.62, 143.06, 142.03, 129.70, 129.59, 119.98, 117.78, 115.03, 114.74, 114.64, 114.14, 72.15, 54.63, 45.46, 29.85. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{18}H_{23}N_2O$ 283.1810; found, 283.18108.

4.2.1.2. 4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-amine (9c): Compound **9c** was obtained as a yellowish amorphous solid (855.4 mg, 65%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 4.3 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 4.3 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.42 (m, 1H), 2.79 – 2.61 (m, 2H), 2.39 (m, 2H), 2.36 (s, 3H), 2.08 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.13, 152.41, 149.27, 129.99, 127.82, 124.74, 121.22, 116.52, 72.02, 52.41, 46.08, 30.53. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{18}H_{23}N_2O$ 283.1810; found, 283.1811.

4.2.3. 2-(3-methylbut-2-en-1-yl)-4-((4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-yl)carbamoyl)phenyl acetate (8a): General procedure for the synthesis of compounds 8a-c and 8g-i through amide coupling—A solution of acid chloride (75 mg, 0.27 mmol) in anhydrous dichloromethane (1 mL) was added to a solution of the aniline (50 mg, 0.18 mmol) and triethylamine (0.13 mL, 0.94 mmol) in anhydrous dichloromethane (1 mL). The resulting solution was allowed to stir at room temperature for 4 h. After 4 h, the solvent was removed and the residue was purified by column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford product as a white amorphous solid (48 mg, 59%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 2.9 Hz, 1H, NH), 7.94 (t, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 2.3 Hz, 1H), 7.72 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.59 – 7.57 (m, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.30 – 5.06 (m, 1H), 4.54 – 4.25 (m, 1H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.84 (ddd, *J* = 12.3, 8.9, 3.5 Hz, 2H), 2.62 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 3H), 2.13 (m, 2H), 1.94 (m, 2H), 1.71 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.29, 165.64, 156.77, 151.67, 141.58, 138.73, 134.50, 134.01, 133.76, 133.00, 129.75, 129.49, 128.47, 125.97, 122.89, 122.72, 120.97, 118.85, 118.79, 116.33, 70.11, 51.69, 45.36, 29.51, 29.02, 25.88, 21.04, 18.05. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{37}N_2O_4$ 513.2753; found, 513.2752.

4.2.4. 2-(3-methylbut-2-en-1-yl)-4-((3′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-yl)carbamoyl)phenyl acetate (8b)—Compound **8b** was obtained as a white amorphous solid (46 mg, 72%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.33 (s, 1H, NH), 7.85 (s, 1H), 7.71 (s, 1H), 7.66 – 7.61 (m, 1H), 7.61 – 7.56 (m, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.25 – 7.15 (m, 2H), 7.12 – 7.09 (m, 1H), 7.06 (d, *J* = 2.2 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.82 – 6.75 (m, 1H), 5.10 (m, 1H), 4.41 – 4.32 (m, 1H), 3.17 (d, *J* = 7.3 Hz, 2H), 2.74 (m, 2H), 2.46 (m, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 2.01 (m, 2H), 1.90 – 1.77 (m, 2H), 1.63 (s, 3H), 1.60 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.13, 165.52, 157.39, 151.55, 149.71, 142.36, 141.71, 138.60, 134.37, 133.87, 132.81, 129.89, 129.37, 125.82, 123.20, 122.59, 120.82, 120.05, 119.41, 119.08, 115.13, 114.78, 70.49, 51.85, 45.45, 29.71, 28.88, 25.85, 20.93, 17.94. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{37}N_2O_4$ 513.2753; found 513.2758.

4.2.5. 2-(3-methylbut-2-en-1-yl)-4-((4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)carbamoyl)phenyl acetate (8c)—Compound **8c** was obtained as a white amorphous solid (38 mg, 65%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.54 – 7.49 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 2H), 5.20 (m, 1H), 4.56 (m, 1H), 3.28 (d, *J* = 7.2 Hz, 2H), 3.03 (m, 2H), 2.95 – 2.84 (m, 2H), 2.60 (s, 3H), 2.32 (s, 3H), 2.19 (m, 2H), 2.09 – 2.00 (m, 2H), 1.72 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 169.75, 166.51, 155.99, 151.39, 137.20, 136.62, 134.11, 133.92, 133.68, 132.94, 129.75, 127.98, 126.91, 126.14, 122.38, 121.09, 120.89, 116.27, 68.57, 50.89, 44.31, 28.86, 28.40, 25.48, 20.64, 17.63. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{32}H_{37}N_2O_4$ 513.2753; found 513.2756.

4.2.3.1. 4-hydroxy-3-(3-methylbut-2-en-1-yl)-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-yl)benzamide (8d): General procedure for the synthesis of 8d-f through ester hydrolysis: Compound **8a** (24 mg, 0.047 mmol) was dissolved in a solution of 10% Et_3N in methanol (1 mL) and stirred at room temperature for 24 hours before concentrated to dryness. The light brown residue so obtained was purified by flash chromatography using dichloromethane and methanol (v/v, 10:1) as eluent to afford a light brown amorphous solid (19 mg, 86%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.89 – 7.82 (m, 2H), 7.70 (d, J = 2.4 Hz, 1H), 7.63 (dd, J = 8.3, 2.4 Hz, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.35 – 7.30 (m, 1H), 6.96 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.3 Hz, 1H), 5.37 – 5.28 (m, 1H), 4.40 (m, 1H), 3.41 (d, J = 7.3 Hz, 2H), 2.77 (m, 2H), 2.45 (m, 2H), 2.37 (s, 3H), 2.10 – 2.02 (m, 2H), 1.96 – 1.89 (m, 2H), 1.78 (s, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 165.93, 158.42, 157.18, 141.89, 138.74, 135.18, 133.63, 129.59, 129.52, 128.50, 128.15, 126.80, 126.73, 122.87, 121.46, 118.75, 118.68, 116.46, 115.78, 71.58, 52.43, 46.10, 30.47, 29.63, 26.07, 18.17. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{30}H_{35}N_2O_3$ 471.2648; found 471.2644.

4.2.4.1. 4-hydroxy-3-(3-methylbut-2-en-1-yl)-N-(3′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-yl)benzamide (8e): Compound **8e** was obtained as a light brown amorphous solid (26 mg, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.22 (td, *J* = 7.8, 1.5 Hz, 1H), 7.19 – 7.12 (m, 2H), 7.07 – 7.02 (m, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.72 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.68 (dd, *J* = 8.3, 1.5 Hz, 1H), 5.17 (m, 1H), 4.40 (m, 1H), 3.23 – 3.09 (m, 2H), 2.80 (td, *J* = 10.8, 9.4, 3.5 Hz, 2H), 2.63 (d, *J* = 11.5 Hz, 2H), 2.36 (s, 3H), 1.99 – 1.90 (m, 2H), 1.89 – 1.77 (m, 2H), 1.56 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 167.21, 158.50, 156.92, 142.61, 141.33, 138.86, 132.96, 129.92, 129.17, 129.14, 128.44, 126.57, 125.47, 122.84, 121.85, 120.32, 119.83, 119.50, 115.01, 114.73, 114.55, 68.65, 51.02, 46.34, 28.50, 28.28, 25.59, 17.59. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{30}H_{35}N_2O_3$ 471.2648; found 471.2648.

4.2.5.1. 4-hydroxy-3-(3-methylbut-2-en-1-yl)-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (8f): Compound **8f** was obtained as a white amorphous solid (16 mg, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (m, 3H), 7.68 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 – 7.47 (m, 4H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.37 (m, 1H), 4.63 (m, 1H), 3.38 – 3.34 (m, 2H), 3.26 – 3.13 (m, 2H), 3.11 (m, 2H), 2.73 (s, 3H), 2.25 (m,

2H), 2.12 (m, 2H), 1.75 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.21, 158.39, 155.60, 140.93, 137.36, 136.09, 134.00, 132.66, 129.13, 128.29, 127.84, 126.46, 125.37, 121.81, 121.05, 116.11, 114.35, 69.04, 50.58, 46.24, 28.14, 27.73, 25.39, 17.38. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{30}H_{35}N_2O_3$ 471.2648; found 471.2651.

4.2.6. 3′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-yl)-[1,1′-biphenyl]-3-carboxamide (8g)—Compound **8g** was obtained as a white amorphous solid (48 mg, 52%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.97 (s, 1H), 7.90 – 7.82 (m, 2H), 7.78 (s, 1H), 7.52 – 7.44 (m, 3H), 7.36 – 7.21 (m, 3H), 7.09 – 6.92 (m, 3H), 6.90 – 6.79 (m, 3H), 4.47 (s, 1H), 2.93 (ddd, *J* = 13.3, 10.4, 3.4 Hz, 2H), 2.84 – 2.73 (m, 2H), 2.26 (td, *J* = 10.5, 4.9 Hz, 2H), 2.04 – 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.26, 159.37, 159.32, 156.30, 141.41, 138.81, 138.61, 133.98, 130.67, 129.62, 129.43, 129.16, 128.47, 127.02, 122.66, 121.99, 118.63, 118.58, 116.15, 115.34, 112.93, 111.08, 68.68, 55.87, 55.35, 51.03, 44.81, 28.52. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{33}H_{35}N_2O_4$ 523.2597; found 523.2599.

4.2.7. 3′,6-dimethoxy-N-(3′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-3-yl)-[1,1′-biphenyl]-3-carboxamide (8h)—Compound **8h** was obtained as a white amorphous solid (114.7 mg, 62%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 (s, 1H, NH), 7.98 (s, 1H), 7.89 – 7.81 (m, 2H), 7.77 (s, 1H), 7.65 – 7.53 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.13 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.08 (d, *J* = 2.5 Hz, 1H), 7.08 – 6.92 (m, 3H), 6.83 (m, 2H), 4.41 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.77 (m, 2H), 2.57 – 2.47 (m, 2H), 2.37 (s, 3H), 2.08 (m, 2H), 1.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.47, 159.57, 159.51, 157.58, 150.01, 142.61, 142.01, 138.99, 130.87, 130.08, 129.79, 129.63, 129.36, 128.65, 127.21, 123.32, 122.16, 120.32, 119.43, 119.14, 115.52, 115.42, 114.94, 113.13, 111.27, 70.53, 56.05, 55.53, 51.96, 45.72, 29.91. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{33}H_{35}N_2O_4$ 523.2597; found 523.2593.

4.2.8. 3′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (8i)—Compound **8i** was obtained as a white amorphous solid (1.10 g, 78%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.09 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.89 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.57 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.05 (m, 2H), 2.99 (m, 2H), 2.63 (s, 3H), 2.20 (ddt, *J* = 14.3, 10.4, 3.4 Hz, 2H), 2.12 – 1.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.41, 159.27, 159.17, 155.86, 148.91, 138.93, 137.31, 136.39, 134.01, 130.38, 130.07, 129.04, 128.58, 128.00, 126.91, 122.01, 121.08, 116.23, 115.26, 112.75, 110.88, 68.10, 55.69, 55.21, 50.60, 44.10, 28.06. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{33}H_{35}N_2O_4$ 523.2597; found 523.2561.

4.2.9. 5-bromo-2-((1-methylpiperidin-4-yl)oxy)pyridine (16)—
Diisopropylazodicarboxylate (809 mg, 4.0 mmol) was added to a solution of 5-bromopyridin-2-ol (348 mg, 2.0 mmol), N-methyl-4-hydroxy-piperidine (230 mg, 2.0 mmol) and triphenylphosphine (1.08 g, 4.0 mmol) in anhydrous THF (40 mL), and the

resulting mixture was stirred at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness. The residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a thick oil (368 mg, 68%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.62 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.62 (dd, *J* = 8.8, 0.8 Hz, 1H), 5.01 (dt, *J* = 8.3, 4.2 Hz, 1H), 2.72 (m, 2H), 2.40 – 2.33 (m, 2H), 2.32 (s, 3H), 2.10 – 2.00 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.13, 147.58, 141.33, 113.49, 111.53, 70.64, 53.11, 46.28, 30.90. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{11}H_{16}BrN_2O$ 271.0446; found 271.0442.

4.2.10. 6-(4-nitrophenyl)pyridin-3-ol (17)—[1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) (42 mg, 0.05 mmol) and potassium carbonate solution (2M, 100 μL) were added to a solution of 6-bromopyridin-3-ol (174 mg, 1.0 mmol) and 4-nitrophenylboronic acid (334 mg, 2.0 mmol) in dioxane (15 mL) and purged with argon for 15 min. After 15 min, the mixture was heated at 110 °C for 12 hours before concentrated to dryness. The brown residue was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a brown amorphous solid (162 mg, 75 %).^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (m, 3H), 7.92 (dd, *J* = 9.1, 2.0 Hz, 2H), 7.59 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.22 – 7.14 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 154.26, 147.30, 146.13, 145.30, 138.20, 126.93, 124.01, 123.67, 122.60. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{11}H_{18}N_2O_3$ 226.1317; found 226.1319.

4.2.11. 2-((1-methylpiperidin-4-yl)oxy)-5-(4-nitrophenyl)pyridine (18a)—[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (43 mg, 0.05 mmol) and potassium carbonate solution (2M, 100 μL) were added to a solution of bromide **16** (250 mg, 0.92 mmol) and 4-nitrophenylboronic acid (462 mg, 2.76 mmol) in dioxane (15 mL) and purged with argon for 15 min. After 15 min, the mixture was heated at 110 °C for 12 hours before concentrated to dryness. The brown residue so obtained was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a brown amorphous solid (246 mg, 85%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 2.6 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.78 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 1H), 5.07 (m, 1H), 2.72 (m, 2H), 2.41 (m, 2H), 2.29 (s, 3H), 2.04 (m, 2H), 1.92 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 163.45, 147.00, 145.46, 144.39, 137.76, 127.77, 127.17, 124.37, 112.09, 69.69, 52.49, 45.60, 30.15. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{17}H_{20}N_3O_3$ 314.1505; found 314.1502.

4.2.12. 5-((1-methylpiperidin-4-yl)oxy)-2-(4-nitrophenyl)pyridine (18b)— Diisopropyl azodicarboxylate (279 mg, 1.38 mmol) was added to a solution of pridinol **17** (150 mg, 0.69 mmol), N-methyl-4-hydroxy-piperidine (80 mg, 0.69 mmol) and triphenylphosphine (362 mg, 1.38 mmol) in anhydrous THF (20 mL), and the resulting mixture was stirred at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated to the dryness and the remaining residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a light brown solid (126 mg, 58%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.46 – 8.38 (m, 1H), 8.28 (d, *J* = 8.9 Hz, 2H), 8.09 (d, *J* = 8.9 Hz, 2H), 7.74 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.30 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.45 (m, 1H), 2.72 (m, 2H), 2.40 – 2.35 (m, 1H), 2.33 (s, 3H), 2.11 – 2.00 (m, 2H),

1.92 – 1.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.01, 147.65, 147.22, 145.14, 139.63, 127.05, 124.20, 123.12, 121.88, 72.94, 52.50, 46.27, 30.70. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{17}H_{20}N_3O_3$ 314.1505; found 314.1506.

4.2.13. 3′,6-dimethoxy-N-(4-(6-((1-methylpiperidin-4-yl)oxy)pyridin-3-yl)phenyl)-[1,1′-biphenyl]-3-carboxamide (19a): General procedure for the synthesis of 19a-b through reduction/amide coupling—Palladium on carbon (10 mg) was added to a solution of nitro phenyl **18a** (82 mg, 0.27 mmol) in dry methanol (5 mL). The resulting mixture was stirred under hydrogen atmosphere for 2 hours. After 2 hours, the reaction mixture was filtered through celite. The filtrate was concentrated to dryness and used as such without further purification in the next step.

The amine (from the previous step) was dissolved in dry dichloromethane (0.5 ml) and added dropwise to an ice-cooled solution of acid chloride **10b** (150 mg, 0.54 mmol) and pyridine (42 mg, 0.54 mmol) in dry dichloromethane (1 ml). The resulting mixture was stirred at room temperature for additional 4 hours before concentrated to dryness. The remaining residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a light brown solid (68 mg, 48%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.85 (dd, *J* = 7.7, 3.1 Hz, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.72 – 7.70 (m, 1H), 7.68 – 7.63 (m, 2H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.23 (dd, *J* = 9.5, 6.4 Hz, 1H), 7.00 (m, 3H), 6.82 – 6.78 (m, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 5.13 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.98 (m, 2H), 2.90 – 2.71 (m, 2H), 2.52 (s, 3H), 2.16 (m, 2H), 2.02 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.42, 161.69, 159.35, 159.22, 144.52, 138.95, 137.98, 137.73, 133.34, 130.45, 130.07, 129.08, 128.65, 126.98, 126.96, 122.04, 121.22, 121.18, 115.32, 112.79, 111.38, 110.93, 66.64, 55.75, 55.26, 51.48, 44.36, 28.65. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{34}N_3O_4$ 524.2549; found 524.2551.

4.2.14. 3′,6-dimethoxy-N-(4-(5-((1-methylpiperidin-4-yl)oxy)pyridin-2-yl)phenyl)-[1,1′-biphenyl]-3-carboxamide (19b)—Compound **19b** was obtained as a light brown solid (19 mg, 45%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.33 (d, *J* = 2.9 Hz, 1H), 7.99 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.89 – 7.79 (m, 4H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.16 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.13 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.93 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.79 (m, 1H), 3.91, (s, 3H), 3.87 (s, 3H), 3.36 (m, 4H), 2.87 (s, 3H), 2.48 – 2.40 (sm 2H), 2.34 – 2.16 (m, 2H). 13C NMR (126 MHz, CDCl3) δ 166.57, 159.31, 159.15, 151.72, 150.82, 139.02, 138.89, 138.36, 134.22, 130.38, 130.13, 128.98, 128.58, 126.97, 126.86, 123.72, 121.96, 121.47, 120.79, 115.19, 112.72, 110.83, 66.83, 55.63, 55.13, 49.50, 43.31, 26.93. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{34}N_3O_4$ 524.2549; found 524.2546.

4.2.15. 5′-((6-bromopyridin-3-yl)carbamoyl)-2′-methoxy-[1,1′-biphenyl]-3-yl acetate (21a)—A solution of acid chloride **10b** (300 mg, 1.16 mmol) in dichloromethane (1 ml) was added to a solution of 6-bromopyridin-3-amine (200 mg, 1.16 mmol) and pyridine (162mg, 2.32 mmol) in dry dichloromethane (5 mL). The solution was then stirred at room temperature for 4 hours. After 4 hours, the reaction mixture was concentrated to dryness and the remaining residue was purified via column chromatography (SiO_2, 10:1,

CH_2Cl_2: methanol) to afford desired product as a light brown solid (416 mg, 87%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 2.8 Hz, 1H), 8.21 (s, 1H, NH), 8.17 (dd, *J* = 8.7, 2.9 Hz, 1H), 7.88 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.09 – 6.98 (m, 3H), 6.90 (dd, *J* = 8.2, 2.7 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.77, 159.94, 159.48, 141.64, 138.72, 136.00, 134.87, 130.96, 130.41, 129.84, 129.37, 128.84, 128.23, 126.05, 122.07, 115.57, 113.06, 111.32, 56.07, 55.52. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{21}H_{18}BrN_2O_4$ 441.0450; found 441.0453.

4.2.16. 5′-((5-bromopyridin-2-yl)carbamoyl)-2′-methoxy-[1,1′-biphenyl]-3-yl acetate (21b)—A solution of acid chloride **10b** (300 mg, 1.16 mmol) in dichloromethane (1 ml) was added to a solution of 5-bromopyridin-2-amine (200 mg, 1.16 mmol) and pyridine (162mg, 2.32 mmol) in dry dichloromethane (5 mL). The solution was then stirred at room temperature for 4 hours. After 4 hours, the reaction mixture was concentrated to dryness and the remaining residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a light brown solid (392 mg, 82%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.47 (t, *J* = 2.3 Hz, 1H), 8.19 (dt, *J* = 8.7, 3.0 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.06 (m, 1H), 7.05 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.90 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.93, 159.87, 159.43, 141.61, 138.79, 135.73, 135.03, 130.84, 130.44, 129.97, 129.33, 128.90, 128.18, 126.10, 122.09, 115.56, 112.99, 111.24, 56.03, 55.50. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{21}H_{18}BrN_2O_4$ 441.0450; found 441.0452.

4.2.17. N-(6-(4-hydroxyphenyl)pyridin-3-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (22a)—[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg, 0.05 mmol) and potassium carbonate solution (2M, 100 μL) were added to a solution of bromide **21a** (150 mg, 0.36 mmol) and 4-hydrophenylboronic acid (99 mg, 0.72 mmol) in dioxane (10 mL). The mixture was heated at 110 °C for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness. The brown residue so obtained was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a brown amorphous solid (117 mg, 76 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 2.6 Hz, 1H), 8.28 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.94 – 7.81 (m, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.04 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.01 (d, *J* = 2.6 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.83 – 6.77 (m, 3H), 3.78 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.82, 159.50, 159.21, 157.87, 153.08, 140.97, 138.90, 133.90, 130.48, 130.30, 130.28, 129.38, 129.06, 128.76, 128.10, 126.42, 122.04, 120.40, 115.64, 115.27, 112.82, 110.90, 55.73, 55.24. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{23}N_2O_4$ 427.1658; found 427.1655.

4.2.18. 5′-((5-(4-hydroxyphenyl)pyridin-2-yl)carbamoyl)-2′-methoxy-[1,1′-biphenyl]-3-yl acetate (22b)—[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (40 mg, 0.05 mmol) and patassium carbonate solution (2M, 100 μL) were added to a solution of bromide **21b** (116 mg, 0.28 mmol) and 4-hydrophenylboronic acid (78 mg, 0.56 mmol) in dioxane (10 mL). The mixture

was heated at 110 °C for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness. The brown residue so obtained was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a brown amorphous solid (110 mg, 92 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.46 – 8.38 (m, 2H), 7.98 – 7.93 (m, 2H), 7.91 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.10 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 8.9, 2.3 Hz, 3H), 3.89 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.44, 159.91, 159.44, 156.76, 150.25, 145.29, 138.87, 136.84, 133.07, 131.02, 130.26, 129.32, 129.21, 128.66, 128.15, 126.31, 122.20, 116.18, 115.38, 114.33, 113.28, 111.25, 56.03, 55.51. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{23}N_2O_4$ 427.1658; found 427.1660.

4.2.19. 3′,6-dimethoxy-N-(6-(4-((1-methylpiperidin-4-yl)oxy)phenyl)pyridin-3-yl)-[1,1′-biphenyl]-3-carboxamide (19c)—Diisopropylazodicarboxylate (36 mg, 0.18 mmol) was added to a solution of phenol **22a** (38 mg, 0.09 mmol), N-methyl-4-hydroxy-piperidine (21 mg, 0.18 mmol) and triphenylphosphine (47 mg, 0.18 mmol) in anhydrous THF (1 mL), and the resulting mixture was stirred at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness and the remaining residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a light brown solid (31 mg, 67%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.73 (d, *J* = 2.6 Hz, 1H), 8.56 (s, 1H), 8.32 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.93 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.88 – 7.82 (m, 3H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.89 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.48 – 4.31 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.76 (m, 2H), 2.47 (m, 2H), 2.37 (s, 3H), 2.08 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 165.91, 159.65, 159.43, 157.97, 152.85, 141.46, 138.87, 133.61, 131.94, 130.76, 130.03, 129.29, 128.80, 128.71, 128.11, 126.57, 122.12, 119.94, 116.25, 115.50, 113.04, 111.15, 71.14, 55.99, 55.47, 52.24, 45.89, 30.22. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{34}N_3O_4$ 524.2549; found 524.2549.

4.2.20. 3′,6-dimethoxy-N-(5-(4-((1-methylpiperidin-4-yl)oxy)phenyl)pyridin-2-yl)-[1,1′-biphenyl]-3-carboxamide (19d)—Diisopropylazodicarboxylate (40 mg, 0.2 mmol) was added to a solution of phenol **22b** (43 mg, 0.1 mmol), N-methyl-4-hydroxy-piperidine (24 mg, 0.2 mmol) and triphenylphosphine (52 mg, 0.2 mmol) in anhydrous THF (5 mL), and the resulting mixture was stirred at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness and the remaining residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford desired product as a light brown solid (34 mg, 65%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.35 (d, *J* = 2.5 Hz, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 7.90 – 7.81 (m, 3H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.04 – 6.98 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.82 – 6.78 (m, 1H), 4.58 (m, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 3.08 (m,, 4H), 2.65 (s, 3H), 2.25 (m, 2H), 2.06 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 165.73, 159.79, 159.20, 156.29, 150.46, 145.25, 138.69, 136.70, 132.33, 130.75, 130.71, 130.14, 129.08, 128.51, 128.13, 125.97, 121.96, 116.43, 115.17, 114.38, 112.96, 111.07, 66.72, 55.76, 55.21, 50.22, 43.80, 27.47. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{34}N_3O_4$ 524.2549; found 524.2548.

4.2.21. 3-methyl-4′-nitro-[1,1′-biphenyl]-4-ol (24a): General procedure for the synthesis of 24a-f through Suzuki coupling—[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg, 0.05 mmol) and patassium carbonate solution (2M, 100 μL) were added to a solution of bromide **23a** (187 mg, 1.00 mmol) and 4-nitrophenylboronic acid (249 mg, 1.50 mmol) in dioxane (5 mL). The mixture was refluxed at 110 °C for 12 hours before concentrated to dryness. The resulted brown residue was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a yellow amorphous solid (134 mg, 59%). Compound **24a** was prepared following the general procedure B to afford a yellow amorphous solid (134 mg, 59%). ^{1}H NMR (400 MHz, Chloroform-d + CD3OD) δ 8.28 (d, J = 8.9 Hz, 2H), 7.70 (d, J = 8.9 Hz, 2H), 7.44 (s, 1H), 7.42 – 7.36 (m, 1H), 6.91 (d, J = 8.3 Hz, 1H), 2.36 (s, 3H). 13C NMR (126 MHz, CDCl3) δ154.94, 146.75, 145.29, 129.30, 129.07, 125.97, 125.05, 123.15, 122.42, 114.36, 15.18. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{13}H_{12}NO_3$: 230.0817; found 230.0815.

4.2.22. 2-methyl-4′-nitro-[1,1′-biphenyl]-4-ol (24b)—Compound **24b** was obtained as a yellow amorphous solid (185 mg, 40%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.13 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.26 – 7.14 (m, 2H), 7.00 – 6.91 (m, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.57, 148.36, 146.85, 137.40, 132.38, 130.81, 130.34, 125.35, 121.08, 115.49, 20.90. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{13}H_{12}NO_3$: 230.0817; found 230.0822.

4.2.23. 3-chloro-4′-nitro-[1,1′-biphenyl]-4-ol (24c)—Compound **24c** was obtained as a yellow amorphous solid (180 mg, 74%). ^{1}H NMR (500 MHz, CDCl3) δ 8.34 – 8.23 (m, 2H), 7.71 – 7.64 (m, 2H), 7.62 (d, *J* = 2.3 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 5.74 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.10, 146.93, 145.83, 132.28, 127.88, 127.50, 127.24 (2C), 124.24 (2C), 120.75, 116.95. HRMS (ESI$^-$) m/z [M-H$^+$] calcd for $C_{12}H_8ClNO_3$ 248.0114, found 248.0117.

4.2.24. 2-chloro-4′-nitro-[1,1′-biphenyl]-4-ol (24d)—Compound **24d** was obtained as a yellow amorphous solid (180 mg, 74%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.25 – 8.14 (m, 2H), 7.58 – 7.43 (m, 2H), 7.11 (dt, *J* = 8.4, 1.8 Hz, 1H), 6.92 (t, *J* = 2.4 Hz, 1H), 6.80 – 6.71 (m, 1H). 13C NMR (126 MHz, CDCl3) δ 158.21, 146.82, 146.34, 132.64, 131.88, 130.64, 129.48, 123.32, 117.12, 114.74. HRMS (ESI$^-$) m/z [M+K]$^+$ calcd for $C_{12}H_8ClNO_3$ 288.0214, found 288.2896.

4.2.25. 3-methoxy-4′-nitro-[1,1′-biphenyl]-4-ol (24e)—Compound **24e** was obtained as a yellow amorphous solid (200 mg, 56%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.27 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.17 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.10 (d, *J* = 2.1 Hz, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 5.78 (s, 1H, OH), 3.99 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 147.70, 147.16, 146.86, 131.21, 127.37, 124.28, 120.99, 115.22, 109.76, 56.23. HRMS (ESI+) m/z: [M + H+] calcd for $C_{13}H_{12}NO_4$: 246.0766; found 246.0762.

4.2.26. 2-methoxy-4′-nitro-[1,1′-biphenyl]-4-ol (24f)—Compound **24f** was obtained as a yellow amorphous solid (160 mg, 44%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.23 (d,

J = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 1H), 6.62 – 6.45 (m, 2H), 4.96 (s, 1H, OH), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.18, 156.88, 145.60, 144.69, 130.92, 129.41, 122.65, 120.40, 107.07, 98.88, 55.01. HRMS (ESI+) m/z: [M + H+] calcd for $C_{13}H_{12}NO_4$: 246.0766; found 246.0769.

4.2.27. 2′-methyl-4′-nitro-[1,1′-biphenyl]-4-ol (27a): General procedure for the synthesis of 27a, 27c and 27e-f through Suzuki coupling—[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (82 mg, 0.10 mmol) and patassium carbonate solution (2M, 100 μL) were added to a solution of **26a** (621 mg, 2.36 mmol) and 4-hydroxyphenylboronic acid (326 mg, 2.36 mmol) in dioxane (40 mL). The mixture was refluxed at 110 °C for 12 hours before concentrated to dryness. The resulted brown residue was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a yellow amorphous solid (120 mg, 46%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.14 (s, 1H), 8.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.03 (s, 1H, OH), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.63, 148.42, 146.92, 137.46, 132.45, 130.88, 130.41, 125.42, 121.14, 115.56, 20.97. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{13}H_{12}NO_3$: 230.0817; found 230.0819.

4.2.28. 3′-methyl-4′-nitro-[1,1′-biphenyl]-4-ol (27b)—A mixture of boronic acid (300 mg, 2.175 mmol), 4-chloro-2-methyl-1-nitrobenzene (373 mg, 2.175 mmol), $Pd(OAc)_2$ (5 mg, 0.022 mmol), TBAB (723 mg, 2.175 mmol) and 2M Na_2CO_3 was irridated by microwave at 175° C for 10 min. The reaction mixture was then extracted by ethyl acetate. The organic layer was collected, dried (over Na_2SO_4) and concentrated under reduced pressure. The brown residue was purified by flash column chromatography (SiO_2, 10:1, EtOAc:Hexane) to afford desired product as a yellowish amorphous solid (80 mg, 17 %). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.40 (m, 4H), 7.03 – 6.85 (m, 2H), 4.89 (s, 1H), 2.69 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.97, 147.51, 145.34, 144.15, 134.24, 133.92, 131.29, 130.48, 128.50, 125.32, 124.59, 115.74, 20.87. HRMS (ESI^+) m/z [M+] calcd for $C_{13}H_{11}NO_3$ 229.0739, found 229.0742.

4.2.29. 2′-methoxy-4′-nitro-[1,1′-biphenyl]-4-ol (27c)—Compound **27c** was obtained as a yellow amorphous solid (152 mg, 27%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.82 (d, *J* = 2.2 Hz, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.45 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.87, 155.93, 147.77, 137.21, 131.11, 130.84, 129.03, 116.38, 115.45, 106.37, 56.29. HRMS (ESI+) m/z: [M + H+] calcd for $C_{13}H_{12}NO_4$: 246.0766; found 246.0763.

4.2.30. 3′-methoxy-4′-nitro-[1,1′-biphenyl]-4-ol (27d)—A mixture of boronic acid (300 mg, 2.18 mmol), 4-chloro-2-methoxy-1-nitrobenzene (408 mg, 2.18 mmol), $Pd(OAc)_2$ (5 mg, 0.022 mmol), TBAB (723 mg, 2.18 mmol) and 2M Na_2CO_3 (3.27 ml, 6.54 mmol) was irridated by microwave at 175° C for 10 min. The reaction mixture was then extracted by ethyl acetate. The organic layer was collected, dried (over Na_2SO_4) and concentrated under reduced pressure. The brown residue was purified by column chromatography (SiO_2, 10:1, EtOAc:Hexane) to afford desired product as a yellowish amorphous solid (95 mg, 18 %). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 (d, *J* = 8.5 Hz, 1H), 7.48 – 7.42 (m, 2H),

7.19 – 7.11 (m, 2H), 6.95 – 6.87 (m, 2H), 4.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.80, 152.76, 146.98, 136.59, 129.71, 127.71, 125.69, 117.48, 115.07, 110.41, 55.59. Exact Mass, Calculated for $C_{13}H_{11}NO_4$ (M-H): 244.0546; found (M-H): 244.0542.

4.2.31. 2′-chloro-4′-nitro-[1,1′-biphenyl]-4-ol (27e)—Compound **27e** obtained as a yellow amorphous solid (300 mg, 59%). ^{1}H NMR (500 MHz, CDCl3) δ 8.36 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.31 (m, 2H), 6.99 – 6.91 (m, 2H), 4.91 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.08, 147.01, 146.55, 133.51, 131.81, 130.77 (2C), 129.87, 125.33, 121.83, 115.35 (2C). HRMS (ESI^-) m/z [$M-H^+$] calcd for $C_{12}H_8ClNO_3$ 248.0114, found 248.0118.

4.2.32. 3′-chloro-4′-nitro-[1,1′-biphenyl]-4-ol (27f)—Compound **27f** was obtained as a yellow amorphous solid (259 mg, 42%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.52 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 – 7.41 (m, 2H), 6.95 – 6.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH_3OH) δ 154.32, 142.77, 141.49, 125.48, 124.80, 124.64, 123.86, 122.46, 121.13, 112.19. HRMS (ESI^-) m/z [$M-H^+$] calcd for $C_{12}H_8ClNO_3$ 248.0114, found 248.0108.

4.2.33. 1-methyl-4-((3-methyl-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)piperidine (25a): General procedure for the synthesis of 25a-f and 28a-f—
Diisopropylazodicarboxylate (0.94 mL, 6.20 mmol) was added to a solution of phenol (280 mg, 1.20 mmol), PPh_3 (1.28g, 6.20 mmol) and 4-hydroxy N-methyl piperidine(280 mg, 2.40 mmol) in THF (8 mL) at room temperature. The reaction mixture was stirred for 18 hours before the removal of solvent under reduced pressure. The remaining residue was purified by silica gel column chromatography (eluting with methylene chloride: methanol = 99:1 to 20:1) to yield **25a** as a light brown amorphous solid (180mg, 46%). Compound **25a** was prepared following the general procedure A to afford a yellow amorphous solid (180 mg, 46%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.35-8.18 (m, 2H), 7.75-7.62 (m, 2H), 7.49-7.36 (m, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 4.45 (s, 1H), 2.66 (s, 2H), 2.44-2.34 (m, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 2.11-1.86 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ156.59, 147.57, 146.54, 130.70, 130.04, 128.86, 127.15, 124.23, 113.06, 52.57, 46.47, 30.92, 29.85, 16.80. Exact Mass Calculated for $C_{19}H_{23}N_2O_3$ ($M+H^+$): 327.1709; found ($M+H^+$) 327.1724

4.2.35. 1-methyl-4-((2-methyl-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)piperidine (25b) —Compound **25b** was obtained as a yellow amorphous solid (300 mg, 61%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.26 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.47 – 7.37 (m, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.49 (s, 1H), 2.77 – 2.68 (m, 2H), 2.50 (s, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 2.15 – 2.08 (m, 2H), 2.02 – 1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.51, 147.61, 146.68, 130.96, 130.20, 127.28, 124.35, 113.11, 52.42, 46.27, 30.57, 16.90. IR 2954, 2923, 2852, 2358, 2341, 1593, 1514, 1485, 1340, 1307, 1274, 1247, 1135, 1108, 1039 cm^{-1}. Exact Mass: Calculated for $C_{19}H_{22}N2O_3$ (M+Na+) 349.1528; found 349.1528.

4.2.36. 4-((3-methoxy-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (25c)—Compound **25c** was obtained as a yellow amorphous solid (200 mg, 80%). ^{1}H NMR (500 MHz, Chloroform-d: Acetone d6 (10:1)) δ 8.25 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.18 – 7.08 (m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 4.44 (dp, *J* = 6.9, 3.4 Hz, 1H), 3.92 (s,

3H), 2.90 (ddd, *J* = 11.9, 8.6, 3.4 Hz, 2H), 2.70 −2.60 (m, 1H), 2.43 (s, 3H), 2.11 (ddd, *J* = 12.5, 8.5, 3.8 Hz, 2H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$: Acetone d6 (10:1)) δ 176.70, 151.31, 146.78, 132.86, 127.43, 124.20, 120.20, 117.41, 111.54, 56.26, 44.99, 22.83. Exact Mass: Calculated for $C_{19}H_{22}N_2O_4$ Na(M+Na) 365.1477; found 365.1473.

4.2.37. 4-((2-methoxy-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (25d)—Compound **25d** was obtained as a yellow amorphous solid (191 mg, 78%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 1H), 6.59 (m, 2H), 4.41 (m, 1H), 3.82 (s, 3H), 2.75 (m, 2H), 2.38 (m, 2H), 2.36 (s, 3H), 2.06 (m, 2H), 2.00 – 1.82 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.53, 157.90, 146.38, 145.52, 131.49, 130.18, 123.45, 121.25, 106.92, 101.09, 70.09, 55.80, 52.72, 46.31, 30.88. Exact Mass: Calculated for $C_{19}H_{22}N_2O_4$ (M+H) 343.1658; found 365.1658.

4.2.38. 4-((3-chloro-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (25e)—Compound **25e** was obtained as a yellow amorphous solid (200 mg, 83%). ^{1}H NMR (500 MHz, CDCl3) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.77 – 7.52 (m, 3H), 7.46 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 4.81 (m, 1H), 3.49 – 3.37 (m, 2H), 3.23 (m, 2H), 2.87 (s, 3H), 2.32 (m, 2H), 2.24 – 2.10 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH_3OH) δ 147.99, 142.90, 141.28, 129.32, 125.35, 123.24, 123.19, 122.97, 120.71, 120.08, 120.04, 111.82, 67.46, 54.11, 44.12, 26.76. HRMS (ESI^+) m/z [M+H^+] calcd for $C_{18}H_{19}ClN_2O_3$ 347.1163; found 347.1159.

4.2.39. 4-((2-chloro-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (25f)—Compound **25f** was obtained as a yellow amorphous solid (150 mg, 78%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 0.7 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.42 (m, 1H), 2.76 (m, 2H), 2.42 (m, 2H), 2.39 (s, 3H), 2.11 (m, 2H), 1.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 158.30, 147.19, 145.92, 133.15, 131.99, 130.72, 126.23, 123.55, 117.64, 115.13, 72.44, 52.65, 46.15, 30.40. HRMS (ESI^+) m/z [M+H^+] calcd for $C_{18}H_{19}ClN_2O_3$ 347.1163; found 347.1158.

4.2.40. 1-methyl-4-((2′-methyl-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)piperidine (28a)—Compound **28a** was obtained as a yellow amorphous solid (120 mg, 73%). ^{1}H NMR (500 MHz, Methanol-d4) δ 8.14 (d, *J* = 2.4 Hz, 1H), 8.09 – 8.02 (m, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 4.49 (q, *J* = 5.1, 4.6 Hz, 1H), 2.76 (s, 2H), 2.50 – 2.40 (m, 2H), 2.37 (s, 3H), 2.33 (s, 3H), 2.05 (ddd, *J* = 12.7, 6.5, 3.1 Hz, 2H), 1.91 – 1.81 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 158.59, 149.66, 148.08, 138.64, 133.53, 131.82, 131.22, 126.00, 124.48, 121.80, 116.90, 112.62, 79.50, 53.25, 46.10, 31.30, 20.88, 16.60. Exact Mass Calculated for $C_{19}H_{22}N_2O_4Na$ (M+Na): 365.1477; found 365.1481.

4.2.41. 1-methyl-4-((3′-methyl-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)piperidine (28b)—Compound **28b** was obtained as a yellow amorphous solid (80 mg, 75%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.52 – 7.46 (m,

2H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.46 (s, 1H), 2.83 – 2.79 (m, 2H), 2.69 (s, 3H), 2.56 – 2.48 (m, 2H), 2.42 (s, 3H), 2.18 – 2.14 (m, 2H), 1.98 – 1.94 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.10, 147.64, 145.77, 134.69, 131.60, 130.90, 128.79, 125.78, 125.02, 116.59, 71.39, 52.31, 45.99, 30.29, 21.34. Exact Mass Calculated for $C_{19}H_{22}N_2O_4$ (M+H): 327.1709; found: 327.1721.

4.2.42. 4-((2′-methoxy-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (28c)—Compound **28c** was obtained as a yellow amorphous solid (114 mg, 65%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.87 (m, 1H), 7.82 (d, *J* = 2.2 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.41 (m, 1H), 3.93 (s, 3H), 2.82 – 2.63 (m, 2H), 2.39 (m, 2H), 2.36 (s, 3H), 2.09 (m, 2H), 1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.69, 156.87, 147.77, 137.20, 130.97, 130.83, 128.90, 116.39, 115.79, 106.37, 70.23, 56.30, 52.29, 45.98, 30.45. Exact Mass Calculated for $C_{19}H_{22}N_2O_4Na$ ($M+Na^+$): 365.1477; found: 327.1483.

4.2.43. 4-((3′-methoxy-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (28d)—Compound **28d** was obtained as a yellow amorphous solid (85 mg, 60%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.22 – 7.14 (m, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 1H), 4.03 (s, 3H), 2.89 – 2.69 (m, 2H), 2.52 – 2.42 (m, 2H), 2.37 (s, 3H), 2.15 (d, *J* = 16.9 Hz, 2H), 1.94 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.23, 153.75, 147.55, 137.94, 131.76, 128.73, 126.72, 118.62, 116.53, 111.59, 56.67, 52.30, 45.99, 30.34. Exact Mass Calculated for $C_{19}H_{22}N_2O_4$ (M+H): 343.1658; found 343.1658

4.2.44. 4-((2′-chloro-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (28e)—Compound **28e** was obtained as a yellow amorphous solid (225 mg, 81%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.35 (d, *J* = 2.3 Hz, 1H), 8.15 (dt, *J* = 8.4, 2.2 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.05 – 6.94 (m, 2H), 4.41 (dt, *J* = 7.2, 3.7 Hz, 1H), 2.83 – 2.65 (m, 2H), 2.34 (s, 3H), 2.07 (ddd, *J* = 13.9, 7.1, 3.5 Hz, 2H), 1.92 (ddd, *J* = 13.2, 7.9, 3.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.01, 146.90, 146.62, 133.42, 131.78, 130.57, 129.47, 125.32, 121.80, 115.58, 71.98, 52.60, 46.17, 30.74. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{18}H_{19}ClN_2O_3$ 347.1163, found 347.1136.

4.2.45. 4-((3′-chloro-4′-nitro-[1,1′-biphenyl]-4-yl)oxy)-1-methylpiperidine (28f)—Compound **25c** was obtained as a yellow amorphous solid (110 mg, 63%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.62 – 7.47 (m, 3H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.44 (m, 1H), 2.76 (m, 2H), 2.42 (m, 2H), 2.38 (s, 3H), 2.10 (m, 2H), 1.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.71, 146.52, 145.96, 130.06, 129.83, 128.80, 128.10, 126.65, 125.45, 116.72, 71.93, 52.54, 46.21, 30.62. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{18}H_{19}ClN_2O_3$ 347.1163, found 347.1159.

4.2.46. 3′,6-dimethoxy-N-(3′-methyl-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29a): General procedure for the synthesis of 29a-l—Palladium on carbon (10% w/w, 20 mg) was added to a solution of **25a** (164 mg, 0.5 mmol) in methanol. The reaction mixture was then stirred under hydrogen

atmosphere overnight before filtration. The filtrate was concentrated to dryness to get aniline. The aniline was dissolved in anhydrous dichloromethane and slowly added to an ice-cooled solution of 4-(chlorocarbonyl)-2-(3-methylbut-2-en-1-yl)phenyl acetate (276 mg, 1.0 mmol) and pyridine (0.2 mL) in anhydrous dichloromethane (2 mL). The reaction mixture was allowed to stir at room temperature for 4 hours. After 4 hours, the solvent was removed and the residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford **29a** as a white amorphous solid (210 mg, 78%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.98 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.42 – 7.40 (m, 1H), 7.37 – 7.32 (m, 2H), 7.17 – 7.14 (m, 1H), 7.12 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.93 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 4.58 (m, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.00 (m, 4H), 2.64 (s, 3H), 2.45 – 2.34 (m, 2H), 2.30 (s, 3H), 2.17 – 2.06 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.23, 159.32, 154.02, 149.81, 138.84, 137.10, 136.60, 133.49, 130.61, 129.75, 129.69, 129.15, 128.51, 127.79, 127.14, 127.08, 125.22, 122.01, 120.66, 115.33, 112.94, 112.83, 111.03, 67.89, 55.85, 55.35, 50.88, 44.64, 28.28, 16.63. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{34}H_{37}N_2O_4$ 537.2753; found 537.2754.

4.2.47. 3′,6-dimethoxy-N-(2′-methyl-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29b)—Compound **29b** was obtained as a white amorphous solid (45 mg, 81%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.87 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 2H), 7.34 – 7.33 (m, 1H), 7.31 – 7.26 (m, 2H), 7.06 (dt, *J* = 7.6, 1.3 Hz, 1H), 7.03 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 4.50 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.94 – 2.74 (m, 4H), 2.52 (s, 3H), 2.33 – 2.25 (m, 3H), 2.23 (m, 2H), 2.06 – 1.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.12, 159.34, 154.16, 138.83, 136.97, 136.71, 133.41, 130.69, 129.69, 129.60, 129.17, 128.45, 127.85, 127.61, 127.20, 127.10, 125.20, 121.99, 120.50, 115.33, 112.96, 112.87, 111.07, 68.06, 55.87, 55.35, 50.99, 44.88, 28.84, 16.64. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{34}H_{37}N_2O_4$ 537.2753; found 537.2756.

4.2.48. 3′,6-dimethoxy-N-(2-methyl-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29c)—Compound **29c** was obtained as a white amorphous solid (25 mg, 76%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (s, 1H), 7.87 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.50 (d, *J* = 2.3 Hz, 1H), 7.44 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.06 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.03 (dd, *J* = 2.7, 1.5 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.87 – 6.83 (m, 3H), 4.46 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 2.92 (m, 2H), 2.82 – 2.67 (m, 2H), 2.51 (s, 3H), 2.30 – 2.22 (m, 2H), 2.21 (s, 3H), 1.99 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.17, 159.33, 159.31, 155.62, 149.82, 138.85, 137.48, 137.01, 136.26, 134.56, 130.64, 130.56, 130.41, 129.62, 129.16, 128.44, 127.14, 122.00, 117.77, 115.46, 115.32, 112.95, 111.05, 69.02, 55.86, 55.35, 51.35, 44.89, 28.70, 20.75. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{34}H_{37}N_2O_4$ 537.2753; found 537.2762.

4.2.49. 3′,6-dimethoxy-N-(3-methyl-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29d)—Compound **29d** was obtained

as a white amorphous solid (13 mg, 58%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 (s, NH), 7.90 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.48 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.12 – 7.08 (m, 1H), 7.08 – 7.03 (m, 2H), 6.93 (dd, *J* = 8.5, 1.4 Hz, 2H), 6.91 – 6.87 (m, 1H), 4.52 – 4.38 (m, 1H), 3.86 (d, *J* = 1.2 Hz, 3H), 3.82 (d, *J* = 1.3 Hz, 3H), 2.92 – 2.54 (m, 4H), 2.44 (s, 3H), 2.34 (s, 3H), 2.11 (d, *J* = 10.8 Hz, 2H), 1.96 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.91, 159.56, 159.44, 156.55, 139.02, 138.03, 134.74, 133.89, 130.88, 130.78, 129.94, 129.33, 128.98, 128.58, 128.29 (2C), 127.10, 125.16, 124.33, 122.17, 116.44 (2C), 115.43, 113.08, 111.25, 69.95, 55.97, 55.37, 51.73, 45.43, 29.44, 18.24. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{34}H_{36}N_2O_4$ 537.2753, found 537.2757.

4.2.50. 3′,6-dimethoxy-N-(3′-methoxy-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29e)—Compound **29e** was obtained as a white amorphous solid (33 mg, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H, NH), 8.03 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.27 (s, 1H), 7.26 (d, *J* = 5.7 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 1H), 7.14 – 7.07 (m, 3H), 6.95 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.51 – 4.39 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.09 (m, 2H), 2.83 (m, 2H), 2.57 (s, 3H), 2.05 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.74, 158.92, 158.71, 150.62, 149.53, 145.14, 138.77, 138.30, 134.92, 134.04, 129.80, 129.20, 129.14, 129.10, 126.80, 126.44, 121.73, 120.62, 118.41, 115.14, 112.54, 111.40, 110.68, 71.29, 55.84, 55.67, 55.07, 51.02, 43.45, 28.64. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{34}H_{36}N_2O_5$ 553.2702; found 553.2700.

4.2.51. 3′,6-dimethoxy-N-(2′-methoxy-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29f)—Compound **29f** was obtained as a white amorphous solid (31 mg, 72%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (m, 2H), 7.77 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 7.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.03 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.49 – 6.44 (m, 1H), 4.41 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 2.90 – 2.67 (m, 2H), 2.64 (m, 2H), 2.44 (s, 3H), 2.23 – 2.10 (m, 2H), 2.01 – 1.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.09, 159.33, 159.30, 157.64, 138.85, 136.68, 134.22, 131.15, 130.67, 129.99, 129.61, 129.16, 128.40, 127.21, 123.46, 122.00, 119.79, 115.29, 112.99, 111.05, 106.57, 102.55, 100.79, 69.99, 55.86, 55.60, 55.35, 51.55, 45.22, 29.31. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{34}H_{36}N_2O_5$ 553.2702; found 553.2706.

4.2.52. 3′,6-dimethoxy-N-(2-methoxy-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29g)—Compound **29g** was obtained as a white amorphous solid (42 mg, 79%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (s, 1H), 7.98 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.17 – 7.13 (m, 2H), 7.12 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.96 – 6.91 (m, 3H), 4.55 (m, 1H), 3.91 (s, 3H), 3.87 (s, 6H), 3.01 (m, 2H), 2.90 (m, 2H), 2.61 (s, 3H), 2.41 – 2.27 (m, 2H), 2.10 – 2.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.22, 159.39, 159.33, 156.73, 155.57, 149.83, 138.81, 138.52, 130.73, 130.68, 130.58, 129.61, 129.17, 128.48, 127.00, 125.88, 122.00,

115.44, 115.36, 112.93, 112.07, 111.09, 103.77, 68.43, 55.87, 55.67, 55.36, 50.95, 44.75, 28.50. HRMS (ESI$^+$) m/z [M+H$^+$] calcd for $C_{34}H_{36}N_2O_5$ 553.2702; found 553.2699.

4.2.53. 3′,6-dimethoxy-N-(3-methoxy-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (29h)—Compound **29h** was obtained as a white amorphous solid (50 mg, 65%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.55 (d, *J* = 8.4 Hz, 1H), 8.51 (s, NH), 7.91 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.27 (s, 1H), 7.19 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.07 (dd, *J* = 5.3, 3.4 Hz, 2H), 6.99 – 6.95 (m, 2H), 6.93 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.59 (s, 1H), 3.97 (s, 3H), 3.87 (d, *J* = 15.2 Hz, 6H), 3.11 – 2.89 (m, 5H), 2.64 (s, 3H), 2.43 – 2.31 (m, 2H), 2.11 (dt, *J* = 14.3, 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.67, 159.22, 159.18, 155.89, 148.34, 138.81, 136.12, 134.27, 130.58, 129.61, 129.05, 128.10, 127.43, 126.81, 121.92, 119.95, 119.32, 116.15, 115.21, 112.87, 110.92, 108.31, 68.19, 55.82, 55.76, 55.23, 50.61, 44.45, 27.93. HRMS (ESI$^+$) m/z [M+H$^+$] calcd for $C_{34}H_{36}N_2O_5$ 553.2702; found 553.2713.

4.2.54. N-(3′-chloro-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (29i)—Compound **29i** was obtained as a white amorphous solid (20 mg, 47%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.08 (s, 1H), 7.94 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.85 (d, *J* = 2.4 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.41 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.13 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.10 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.92 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.55 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.05 – 2.87 (m, 2H), 2.78 (d, *J* = 16.2 Hz, 2H), 2.52 (s, 3H), 2.32 – 2.18 (m, 2H), 2.05 (dq, *J* = 14.6, 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.19, 159.35, 159.30, 151.60, 138.78, 137.59, 135.18, 134.98, 130.64, 129.63, 129.14, 128.77, 128.46, 127.18, 126.97, 125.98, 124.76, 121.96, 120.57, 116.34, 115.32, 112.91, 111.03, 55.84, 55.32, 51.08, 45.24, 29.69, 29.06. HRMS (ESI$^+$) m/z [M+H$^+$] calcd for $C_{33}H_{33}ClN_2O_4$ 557.2207; found 557.2215.

4.2.55. N-(2′-chloro-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (29j)—Compound **29j** was obtained as a white amorphous solid (90 mg, 87%). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.56 (s, 1H), 7.99 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.41 – 7.30 (m, 3H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 4.52 (s, 1H), 3.85 (d, *J* = 11.2 Hz, 6H), 3.01 (d, *J* = 8.7 Hz, 4H), 2.62 (s, 3H), 2.36 (d, *J* = 7.4 Hz, 2H), 2.12 – 1.98 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.20, 159.35, 159.31, 149.80, 138.79, 137.31, 135.06, 133.06, 132.06, 131.96, 130.69, 130.22, 130.15, 129.60, 129.15, 128.41, 127.04, 121.97, 119.69, 117.24, 115.29, 114.70, 112.97, 111.03, 67.62, 55.85, 55.33, 50.82, 45.61, 29.86. HRMS (ESI$^+$) m/z [M+] calcd for $C_{33}H_{33}ClN_2O_4$ 557.2207; found 557.2209.

4.2.56. N-(2-chloro-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (29k)—Compound **29k** was obtained as a white amorphous solid (35 mg, 39%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.77 (m, 3H),

7.32 – 7.20 (m, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.07 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.86 (s, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 2H), 6.62 (dd, *J* = 8.3, 2.7 Hz, 1H), 4.45 (m, 1H), 3.63 (s, 3H), 3.57 (s, 3H), 3.11 – 2.90 (m, 4H), 2.54 (s, 3H), 2.02 (m, 2H), 1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.39, 160.09, 159.95, 140.43, 139.92, 135.32, 132.62, 131.98, 131.70, 131.14, 130.57, 130.25, 129.89, 127.79, 127.40, 122.88, 122.30, 119.94, 117.34, 116.36, 116.31, 113.42, 111.78, 69.59, 56.68, 56.10, 50.37, 44.39, 27.88. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{33}H_{33}ClN_2O_4$ 557.2207; found 557.2211.

4.2.57. N-(3-chloro-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (29l)—Compound **29l** was obtained as a white amorphous solid (92 mg, 86%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.61 (d, *J* = 8.6 Hz, 1H), 8.43 (s, NH), 7.95 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.08 (m, 4H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.35 – 3.25 (m, 2H), 3.24 – 3.10 (m, 2H), 2.78 (s, 3H), 2.65 – 2.55 (m, 2H), 2.26 – 2.15 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 164.78, 159.68, 159.34, 138.69, 136.88, 133.72, 131.00, 129.84, 129.20, 128.26, 128.20, 127.27, 126.94, 126.79, 126.02, 123.38, 121.98, 121.69, 120.48, 116.24, 115.31, 113.06, 111.12, 71.59, 55.91, 55.34, 50.01, 43.62, 29.95. HRMS (ESI^+) m/z [M+] calcd for $C_{33}H_{33}ClN_2O_4$ 557.2207; found 557.2199.

4.2.48. tert-butyl (4′-hydroxy-3′-nitro-[1,1′-biphenyl]-4-yl)carbamate (32a): General procedure for the synthesis of 32a-b—Palladium tetraphenylphosphine (115 mg, 0.10 mmol) and potassium carbonate solution (2M, 100 μL) were added to a solution of 4-bromo-2-nitrophenol (150 mg, 0.69 mmol) and boronic ester (300 mg, 0.82 mmol) in dioxane (40 mL) and the mixture was refluxed at 110 °C for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness and the residue so obtained was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a yellow amorphous solid (136 mg, 60%). ^{1}H NMR (500 MHz, Chloroform-d) δ 10.58 (s, 1H), 8.29 (d, *J* = 2.3 Hz, 1H), 7.81 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.61 – 7.37 (m, 4H), 7.25 – 7.21 (m, 1H), 6.55 (s, 1H), 1.55 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.11, 151.21, 138.75, 138.34, 136.01, 135.15, 132.82, 127.25, 122.26, 120.39, 118.90, 81.15, 28.35. HRMS (ESI^-) m/z [$M-H^+$] calcd for $C_{17}H_{18}N_2O_5$ 329.1137, found 329.1133.

4.2.49. tert-butyl (4′-hydroxy-2′-nitro-[1,1′-biphenyl]-4-yl)carbamate (32b)—Compound **32b** was obtained as a yellow amorphous solid (210 mg, 72%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.40 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 2.6 Hz, 1H), 7.28 (d, *J* = 5.0 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.07 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.53 (s, 1H), 5.47 (s, 1H), 1.54 (s, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ 155.35, 153.00, 149.83, 138.39, 133.34, 132.05, 129.00, 128.64, 119.86, 118.99, 111.40, 81.16, 28.64. HRMS (ESI^-) m/z [$M-H^+$] calcd for $C_{17}H_{18}N_2O_5$ 329.1137, found 329.1132.

4.2.50. tert-butyl (4′-((1-methylpiperidin-4-yl)oxy)-3′-nitro-[1,1′-biphenyl]-4-yl)carbamate (33a): General procedure for the synthesis of 33a-b—Diisopropylazodicarboxylate (83 mg, 0.41 mmol) was added to an ice-cooled solution of

phenol **32a** (75 mg, 0.23 mmol), N-methyl-4-hydroxy-piperidine (31.5 mg, 0.27 mmol) and triphenylphosphine (150 mg, 0.54 mmol) in anhydrous THF (2 mL). The reaction mixture was then allowed to stir at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated under reduced pressure and the residue was purified via column chromatography (SiO_2, CH_2Cl_2: methanol, 10:1) to afford a yellow amorphous semi-solid (80 mg, 82%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.51 – 7.41 (m, 4H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.57 (s, 1NH), 4.70 (s, 1H), 2.85 (s, 2H), 2.70 (s, 2H), 2.48 (s, 3H), 2.24 (s, 2H), 2.06 (ddd, *J* = 15.0, 7.7, 3.9 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.49, 150.08, 141.99, 139.23, 134.69, 133.72, 132.74, 128.15, 124.54, 119.81, 117.21, 81.78, 51.83, 46.40, 30.62, 30.18, 29.24. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{23}H_{29}N_3O_5$ 428.2186; found 428.2177.

4.2.51. tert-butyl (4′-((1-methylpiperidin-4-yl)oxy)-2′-nitro-[1,1′-biphenyl]-4-yl)carbamate (33b)—Compound **32b** was obtained as a yellow amorphous solid (175 mg, 89%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.29 (d, *J* = 33.1 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.13 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.53 (s, NH), 4.42 (s, 1H), 2.73 (s, 2H), 2.36 (s, 3H), 2.15 – 2.01 (m, 2H), 1.91 (d, *J* = 11.4 Hz, 2H), 1.65 – 1.54 (m, 2H), 1.54 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.95, 152.90, 149.98, 138.48, 133.18, 131.97, 128.97, 128.51, 120.36, 118.84, 111.29, 81.09, 52.25, 46.19, 30.42, 30.03, 28.63. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{23}H_{29}N_3O_5$ 428.2186; found 428.2182.

4.2.52. N-(4-bromo-3-nitrophenyl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (36a): General procedure for the synthesis of 36a-b—A solution of acid chloride **10b** (200 mg, 0.72 mmol) in dry dimethylformamide (0.5 ml) was added slowly to a solution of aniline **35a** (150 mg, 0.69 mmol) and pyridine (160 mg, 2.30 mmol) in dimethylformamide (1 mL) and heated at 90 °C for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness; diluted with water and extracted with ethyl acetate (3 × 10 ml). The organic layers were combined, dried (over Na_2SO_4) and concentrated. The residue was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a light brown solid (283 mg, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 2.5 Hz, 1H), 7.97 (broad, 1H, NH), 7.90 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.76 (d, *J* = 2.5 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.13 – 7.05 (m, 3H), 6.94 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.35, 160.13, 159.57, 150.09, 138.71, 138.57, 135.53, 131.18, 129.76, 129.45, 128.81, 125.97, 124.32, 122.10, 116.92, 115.61, 113.18, 111.45, 108.40, 56.14, 55.56. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{21}H_{18}BrN_2O_5$ 457.0399, found 457.0402.

4.2.53. N-(4-bromo-2-nitrophenyl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (36b)—Compound **36b** was obtained as a yellow amorphous solid (80 mg, 43%). ^{1}H NMR (500 MHz, Chloroform-d) δ 11.30 (s, NH), 8.97 (d, *J* = 9.1 Hz, 1H), 8.43 (d, *J* = 2.4 Hz, 1H), 8.05 – 7.93 (m, 2H), 7.80 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.20 – 7.06 (m, 3H), 6.94 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.81, 160.78, 159.94, 139.61, 139.05, 137.11, 135.41, 131.81, 130.97, 129.82, 128.99, 126.57, 124.11, 122.53, 115.78, 115.65, 113.81, 111.79, 56.54, 55.92. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{21}H_{17}BrN_2O_5$ 457.0399, found 457.0402.

4.2.54. N-(4′-hydroxy-2-nitro-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (37a): General procedure for the synthesis of 37a-b—[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (42 mg, 0.05 mmol) and potassium carbonate solution (2M, 100 μL) were added to a solution of bromide **36a** (120 mg, 0.26 mmol) and 4-hydrophenylboronic acid (72 mg, 0.52 mmol) in dioxane (10 mL) and the mixture was refluxed at 110 °C for 12 hours. After 12 hours, the reaction mixture was concentrated to dryness and the residue so obtained was purified via column chromatography (SiO_2, 100:1, CH_2Cl_2: acetone) to afford desired product as a brown amorphous solid (52 mg, 43 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (s, 1H, NH), 8.16 (t, *J* = 1.8 Hz, 1H), 7.91 – 7.83 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.05 (m, 3H), 7.03 – 6.97 (m, 2H), 6.82 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.79 – 6.72 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.66, 159.52, 159.17, 156.95, 149.16, 138.84, 138.32, 131.98, 131.09, 130.42, 130.24, 129.07, 129.02, 128.78, 128.18, 127.52, 126.35, 123.76, 121.98, 115.52, 115.24, 112.74, 110.87, 55.67, 55.18. HRMS (ESI^+) m/z [M+Na^+] calcd for $C_{27}H_{22}N_2O_6Na$ 493.1376, found 493.1371.

4.2.55. N-(4′-hydroxy-3-nitro-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (37b)—Compound **37b** was obtained as a yellow amorphous solid (110 mg, 92%). ^{1}H NMR (500 MHz, Chloroform-d) δ 11.35 (s, OH), 9.05 (d, *J* = 8.8 Hz, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 8.09 – 7.95 (m, 2H), 7.90 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.21 – 7.05 (m, 3H), 6.98 – 6.89 (m, 3H), 3.93 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.90, 160.62, 159.94, 156.48, 139.16, 137.21, 136.56, 134.72, 134.65, 131.73, 131.41, 130.97, 129.81, 128.96, 128.75, 126.96, 123.77, 123.11, 122.58, 116.65, 115.77, 113.82, 111.76, 56.53, 55.93. HRMS (ESI^+) m/z [M+Na]$^+$ calcd for $C_{27}H_{22}N_2O_6$ 493.1376, found 493.3180.

4.2.56. 3′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-3′-nitro-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (34a): General procedure for the synthesis of 34a-b—A solution of trifluoroacetic acid (0.5 ml) in anhydrous dichloromethane (0.5 ml) was added to an ice-cooled solution of boc-protected aniline **33a** (65mg, 0.15 mmol) in anhydrous dichloromethane (0.5 ml) and allowed to stir at room temperature for 2 hours. After 2 hours, the reaction mixture was concentrated under high vacuum to afford a brownish amorphous semi-solid (48 mg, 98%), which was used as such without further purification in the next step.

Acid chloride (50 mg, 0.36 mmol) was added to a solution of aniline (50 mg, 0.18 mmol, obtained from previous step) and triethylamine (0.13 mL, 0.94 mmol) in anhydrous dichloromethane (5 mL) and stirred at room temperature for 4 hours. After 4 hours, the reaction mixture was concentrated and the residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford 3**4a** as a yellow amorphous solid (30 mg, 63%). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.28 (s, 1H), 8.05 (d, *J* = 2.4 Hz, 1H), 7.97 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.75 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.17 – 7.09 (m, 3H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.92 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 4.84 (s, 1H), 3.87 (d, *J* = 19.2 Hz, 6H), 3.30 – 2.89 (m, 4H), 2.67 (s, 3H), 2.54 – 2.37 (m, 2H), 2.16 – 2.09 (m, 2H). ^{13}C NMR (126

MHz, $CDCl_3$) δ 165.28, 159.41, 159.29, 148.60, 140.80, 138.72, 138.34, 134.09, 133.66, 132.21, 130.59, 129.71, 129.13, 128.58, 127.17, 126.81, 123.85, 121.95, 120.77, 116.04, 115.35, 112.86, 111.03, 69.03, 55.84, 55.32, 49.78, 44.39, 27.82. HRMS (ESI^+) m/z [M $+H^+$] calcd for $C_{33}H_{33}N_3O_6$ 568.2448, found 568.2445.

4.2.57. 3′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-2′-nitro-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (34b)—Compound **34b** was obtained as a yellow amorphous solid (125 mg, 63%). ^1H NMR (500 MHz, Chloroform-d) δ 7.95 (s, 1H), 7.87 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.32 – 7.26 (m, 3H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.06 (ddd, *J* = 9.0, 5.3, 1.9 Hz, 2H), 7.04 – 6.97 (m, 2H), 6.86 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 4.50 (s, 1H), 3.80 (d, *J* = 18.6 Hz, 6H), 2.86 (t, *J* = 10.5 Hz, 2H), 2.48 (s, 3H), 2.23 (s, 3H), 2.04 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.20, 159.43, 159.33, 156.29, 149.67, 138.77, 138.05, 133.07, 132.82, 130.74, 129.68, 129.17, 128.71, 128.56, 128.43, 126.92, 121.98, 120.33, 119.86, 115.29, 113.01, 111.24, 111.08, 70.27, 55.87, 55.35, 51.14, 44.96, 29.71. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{33}H_{33}N_3O_6$ 568.2448, found 568.2446.

4.2.58. 3′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-2-nitro-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (34c): General procedure for the synthesis of 34c-d—Diisopropylazodicarboxylate (93 mg, 0.46 mmol) was added to an ice-cooled solution of phenol **37a** (110 mg, 0.23 mmol), N-methyl-4-hydroxy-piperidine (27 mg, 0.23 mmol) and triphenylphosphine (128 mg, 0.46 mmol) in anhydrous THF (10 mL). The reaction mixture was then allowed to stir at room temperature for 12 hours. After 12 hours, the reaction mixture was concentrated under reduced pressure and the residue was purified via column chromatography (SiO_2, CH_2Cl_2: methanol, 10:1) to afford a yellow amorphous solid (85 mg, 65%). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.15 (s, 1H), 7.93 (dd, *J* = 8.5, 2.5 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.85 (s, 1H), 7.31 (dd, *J* = 8.4, 2.5 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.17 – 7.13 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.85 (m, 3H), 4.35 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.70 (m, 2H), 2.52 – 2.40 (m, 2H), 2.30 (s, 3H), 1.99 (m, 2H), 1.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.45, 159.66, 159.30, 157.16, 149.24, 138.93, 138.60, 132.22, 130.87, 130.58, 130.21, 129.71, 129.33, 129.18, 128.93, 126.43, 123.83, 122.11, 116.10, 115.66, 115.44, 112.86, 111.06, 70.57, 55.87, 55.39, 51.93, 45.64, 29.74. HRMS (ESI^+) m/z [M $+K^+$] calcd for $C_{33}H_{33}N_3O_6K$ 606.2006, found 606.2007.

4.2.59. 3′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-3-nitro-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (34d)—Compound **34d** was obtained as a yellow amorphous solid (25 mg, 39%) ^1H NMR (500 MHz, Chloroform-d) δ 11.34 (s, 1H), 9.05 (d, *J* = 8.8 Hz, 1H), 8.45 (d, *J* = 2.3 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 2H), 7.90 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.58 – 7.52 (m, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.18 – 7.10 (m, 3H), 7.04 – 6.99 (m, 2H), 6.96 – 6.92 (m, 1H), 4.43 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 2.83 – 2.72 (m, 2H), 2.51 – 2.41 (m, 2H), 2.39 (s, 3H), 2.11 (ddd, *J* = 11.3, 8.1, 3.7 Hz, 2H), 1.93 (tdd, *J* = 10.9, 7.2, 3.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.23, 159.99, 159.32, 157.55, 138.55, 136.58, 135.90, 134.07, 134.03, 131.09, 130.67, 130.34, 129.19, 128.33, 127.95,

126.34, 123.12, 122.47, 121.95, 116.52, 115.15, 113.19, 111.14, 71.62, 55.81, 55.36, 52.44, 45.84, 29.73. HRMS (ESI^+) m/z [M^+] calcd for $C_{33}H_{33}N_3O_6$ 567.2348, found 567.2339.

4.2.60. N-(3′-amino-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (38a): General procedure for the synthesis of 38a-d—Palladium on carbon (10%, 10 mg) was added to a solution of Nitro **34a** (60 mg, 0.1 mmol), followed by two drops of acetic acid. The resulted suspension was degased and stirred under hydrogen atmosphere for 12 hours before filtration. The filtrate was concentrated to dryness to afford aniline **38a** as a white amorphous solid (46 mg, 85%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 2.1 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 6.97 – 6.91 (m, 2H), 6.85 – 6.81 (m, 1H), 4.63 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.16 (m, 4H), 2.72 (s, 3H), 2.42 (m, 2H), 2.20 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.31, 159.57, 159.54, 143.58, 139.02, 137.56, 137.24, 137.04, 135.04, 130.92, 129.77, 129.38, 128.63, 127.48, 127.28, 122.19, 120.62, 117.47, 115.54, 114.63, 114.31, 113.16, 111.29, 69.10, 56.08, 55.56, 50.61, 44.37, 28.10. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{33}H_{36}N_3O_4$ 538.2706, found 538.2707.

4.2.61. N-(2′-amino-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (38b)—Compound **38b** was obtained as a white amorphous solid (28 mg, 39%). ^1H NMR (500 MHz, Chloroform-d) δ 8.03 (d, *J* = 2.9 Hz, 1H), 7.94 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.71 (dd, *J* = 8.5, 2.7 Hz, 2H), 7.42 (dd, *J* = 8.7, 2.6 Hz, 2H), 7.36 (td, *J* = 7.9, 2.8 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.05 (ddd, *J* = 18.4, 8.5, 2.7 Hz, 2H), 6.93 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.38 (dt, *J* = 8.5, 2.6 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 4.42 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (s, NH_2), 2.95 – 2.81 (m, 2H), 2.67 (s, 2H), 2.49 (s, 3H), 2.29 – 2.14 (m, 2H), 1.99 (d, *J* = 14.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.25, 159.34, 159.30, 157.35, 144.89, 138.79, 136.90, 135.13, 131.38, 130.65, 129.70, 129.63, 129.14, 128.45, 127.00, 121.96, 120.69, 120.60, 115.32, 112.91, 111.04, 106.02, 103.05, 69.81, 55.84, 55.32, 51.86, 45.30, 29.69. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{33}H_{35}N_3O_4$ 538.2706, found 538.2704.

4.2.62. N-(2-amino-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (38c)—Compound **38c** was obtained as a white amorphous solid (21 mg, 85%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.77 (s, 1H), 7.39 (d, *J* = 8.7 Hz, 3H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.07 (dd, *J* = 8.5, 2.2 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.94 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.58 (m, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.02 (m, 4H), 2.63 (s, 3H), 2.37 (m, 2H), 2.10 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.05, 159.33, 159.30, 155.73, 144.29, 138.82, 138.19, 132.21, 130.79, 130.69, 130.45, 129.51, 129.16, 128.34, 127.24, 123.26, 121.97, 116.17, 115.30, 112.96, 111.05, 110.21, 107.01, 69.03, 55.86, 55.34, 50.67, 44.57, 28.34. HRMS (ESI^+) m/z [$M+H^+$] calcd for $C_{33}H_{36}N_3O_4$ 538.2706, found 538.2709.

4.2.63. N-(3-amino-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (38d)—Compound **38d** was obtained as a white amorphous solid (25 mg, 90%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.87 (s, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.09 – 6.94 (m, 5H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.85 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.51 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.99 – 2.74 (m, 4H), 2.54 (s, 3H), 2.15 (m, 2H), 2.06 – 1.94 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.52, 159.32, 156.19, 141.22, 139.75, 138.96, 134.13, 130.65, 130.31, 129.19, 128.84, 128.42, 128.27, 126.33, 126.25, 123.71, 122.11, 118.33, 116.42, 116.23, 115.37, 112.96, 111.03, 68.80, 55.88, 55.39, 50.92, 44.54, 28.39. HRMS (ESI$^+$) m/z [M+K$^+$] calcd for $C_{33}H_{35}N_3O_4K$ 576.2265, found 576.2264.

4.2.64. N-(3′-acetamido-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (39a): General procedure for the synthesis of 39a-d—Aniline **38a** (23 mg, 0.04 mmol) was added to a solution of acetic anhydride in pyridine (1:3, v/v) and the resulting mixture was stirred at room temperature for 4 hours before being concentrated to dryness. The remaining residue was further dried under vacuum overnight to afford acetamide **39a** as a light brown amorphous solid (25 mg, 100%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.87 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.73 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.06 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.03 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.85 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 4.50 (m, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.15 (m, 2H), 2.94 – 2.82 (m, 2H), 2.61 (s, 3H), 2.35 – 2.26 (m, 2H), 2.18 (s, 3H), 2.17 – 2.07 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.51, 168.78, 165.41, 159.58, 159.53, 139.02, 137.46, 136.40, 134.43, 130.89, 129.89, 129.37, 128.65, 127.52, 127.20, 125.01, 123.84, 123.04, 122.20, 121.88, 120.81, 115.54, 113.15, 111.26, 69.90, 56.07, 55.55, 51.00, 44.13, 29.92, 28.34. HRMS (ESI$^+$) m/z [M+K$^+$] calcd for $C_{35}H_{37}N_3O_5K$ 618.2370, found 618.2373.

4.2.65. N-(2′-acetamido-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (39b)—Compound **39b** was obtained as a white amorphous solid (11 mg, 100%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.23 – 7.15 (m, 3H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.99 (dt, *J* = 7.7, 1.3 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.78 – 6.74 (m, 1H), 6.63 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.42 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 2.89 (m, 2H), 2.73 (m, 2H), 2.44 (s, 3H), 2.12 – 2.00 (m, 2H), 1.99 – 1.92 (m, 2H), 1.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 168.45, 165.21, 158.75, 158.51, 138.57, 138.17, 135.32, 132.82, 130.44, 129.80, 129.30, 128.91, 128.75, 128.52, 126.81, 126.77, 121.55, 120.50, 120.40, 114.95, 112.09, 110.31, 110.24, 70.60, 55.30, 54.76, 51.21, 44.76, 29.06, 23.74. HRMS (ESI$^+$) m/z [M+K$^+$] calcd for $C_{35}H_{37}N_3O_5K$ 618.2370, found 618.2372.

4.2.66. N-(2-acetamido-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′,6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (39c)—Compound **39c** was obtained as a white amorphous solid (15 mg, 100%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (dd, *J* =

8.5, 2.4 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 2.2 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.96 – 6.93 (m, 1H), 6.92 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.71 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.42 (m, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.91 (m, 2H), 2.80 (m, 2H), 2.47 (s, 3H), 2.02 (m, 2H), 1.92 – 1.87 (m, 2H), 1.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 170.20, 166.68, 159.26, 159.09, 156.03, 138.85, 137.89, 134.07, 131.30, 130.75, 130.48, 130.34, 130.26, 130.12, 128.87, 128.49, 126.70, 121.88, 118.69, 117.00, 115.93, 115.06, 112.68, 110.74, 69.73, 55.51, 50.71, 43.95, 29.51, 28.22. HRMS (ESI$^+$) m/z [M+K$^+$] calcd for $C_{35}H_{37}N_3O_5K$ 618.2370, found 618.2367.

4.2.67. N-(3-acetamido-4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′, 6-dimethoxy-[1,1′-biphenyl]-3-carboxamide (39d)—Compound **39b** was obtained as a white amorphous solid (10 mg, 100%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.00 – 6.98 (m, 1H), 6.98 – 6.94 (m, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.46 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 2.91 – 2.75 (m, 4H), 2.50 (s, 3H), 2.09 (m, 2H), 2.06 (s, 3H), 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 170.95, 166.15, 159.53, 159.19, 156.19, 138.82, 138.31, 133.28, 130.63, 130.56, 130.37, 129.94, 129.03, 128.35, 128.14, 126.19, 126.10, 124.58, 122.95, 121.96, 116.21, 115.17, 112.87, 110.98, 68.17, 55.71, 55.18, 50.64, 44.20, 28.12, 23.18. HRMS (ESI$^+$) m/z [M+K$^+$] calcd for $C_{35}H_{37}N_3O_5K$ 618.2370, found 618.2368.

4.2.68.1. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41a): General procedure for the synthesis of 41a-41s, 43a-b, 45a-b, 47a-b and 49a-h: Acid chloride **40a** (50 mg, 0.36 mmol) was added to a solution of aniline **9c** (50 mg, 0.18 mmol) and triethylamine (0.13 mL, 0.94 mmol) in anhydrous dichloromethane (5 mL). After 12 h, the solvent was removed and the residue was purified via column chromatography (SiO_2, 10:1, CH_2Cl_2: methanol) to afford **41a** as a white amorphous solid (51 mg, 74%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 6.9 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.61 – 7.53 (m, 5H), 7.53 – 7.49 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.71 (s, 1H), 3.27 (m, 4H), 2.82 (s, 3H), 2.43 – 2.29 (m, 2H), 2.25 – 2.11 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.69, 156.00, 137.67, 136.89, 135.17, 134.64, 132.09, 128.83, 128.43, 127.71, 127.27, 121.56, 116.58, 67.03, 50.55, 46.71, 27.76. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{25}H_{27}N_2O_2$ 387.2073; found 387.2071.

4.2.68.2. 4-chloro-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41b): Compound **41b** was obtained as a white amorphous solid (20 mg, 65%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.62 (m, 4H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.53 (s, 1H), 2.93 (m, 1H), 2.68 – 2.55 (m, 1H), 2.45 (s, 3H), 2.03 (m, 2H), 1.79 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.32, 156.16, 137.82, 136.36, 135.08, 133.56, 132.34, 129.61, 128.44, 127.44, 126.23, 120.67, 116.29, 69.80, 51.33, 44.20, 29.09. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{25}H_{26}ClN_2O_2$ 421.1683; found 421.1681.

4.2.68.3. 4-bromo-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41c): Compound **41c** was obtained as a white amorphous solid (25 mg, 70%).Compound **41c** was prepared from **19c** using general procedure C and acid chloride **7** to afford a white amorphous solid (28 mg, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.31 (m, 1H), 2.65 (d, *J* = 9.7 Hz, 2H), 2.40 (s, 2H), 2.25 (s, 3H), 1.93 (m, 2H), 1.79 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.49, 156.37, 137.82, 135.18, 133.98, 132.21, 131.43, 129.83, 127.46, 126.27, 125.36, 120.71, 116.27, 71.02, 52.10, 45.12, 29.96. HRMS (ESI^{+}) m/z: [M + H^{+}] calcd for $C_{25}H_{26}BrN_2O_2$ 465.1178; found 465.1181.

4.2.68.4. 4-iodo-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41d): Compound **41d** was obtained as a white amorphous solid (32 mg, 80%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.73 (m, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.94 – 6.76 (m, 2H), 4.39 (m, 1H), 2.74 (m, 2H), 2.48 (m, 2H), 2.34 (s, 3H), 2.13 – 1.97 (m, 2H), 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.30, 156.37, 137.69, 136.95, 136.87, 134.34, 133.60, 129.01, 127.90, 126.91, 121.11, 116.30, 98.61, 69.97, 51.89, 45.12, 29.41. HRMS (ESI^{+}) m/z: [M + H^{+}] calcd for $C_{25}H_{26}IN_2O_2$ 513.1039; found 513.1042.

4.2.68.5. 4-methyl-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41e): Compound **41e** was obtained as a white amorphous solid (35 mg, 69%).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.74 – 7.68 (m, 2H), 7.52 (ddd, *J* = 8.6, 4.5, 2.2 Hz, 4H), 7.36 – 7.18 (m, 2H), 7.06 – 6.76 (m, 2H), 4.60 (d, *J* = 10.7 Hz, 1H), 3.10 (m, 2H), 2.95 (m, 2H), 2.65 (s, 3H), 2.41 (s, 3H), 2.17 (m, 2H), 2.07 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.24, 155.74, 142.02, 137.08, 136.34, 133.76, 131.64, 128.78, 127.63, 127.13, 126.49, 121.01, 116.00, 69.53, 50.91, 43.73, 28.31, 20.66. HRMS (ESI^{+}) m/z: [M + H^{+}] calcd for $C_{26}H_{29}N_2O_2$ 401.2229; found 401.2231.

4.2.68.6. 4-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41f): Compound **41f** was obtained as a white amorphous solid (40 mg, 75%).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 6.6 Hz, 2H), 7.37 (d, *J* = 6.5 Hz, 2H), 6.89 – 6.75 (m, 4H), 4.43 (m, 1H), 3.72 (s, 3H), 2.94 – 2.83 (m, 2H), 2.77 (m, 2H), 2.46 (s, 3H), 2.15 – 2.01 (m, 2H), 1.94 – 1.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.65, 162.42, 155.92, 137.29, 136.42, 133.95, 129.23, 127.94, 126.85, 121.07, 116.22, 113.67, 68.59, 55.25, 50.89, 44.34, 28.40. HRMS (ESI^{+}) m/z: [M + H^{+}] calcd for $C_{26}H_{29}N_2O_3$ 417.2178; found 417.2176.

4.2.68.7. 4-(tert-butyl)-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41g): Compound **41g** was obtained as a white amorphous solid (38 mg, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H, NH), 7.90 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 4.2 Hz, 2H), 7.59 (d, *J* = 4.3 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.56 (m, 1H), 3.34 (s, 3H), 2.99 (m, 2H), 2.74 (m, 2H), 2.06 (m, 2H), 1.84 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 165.41, 156.04, 154.37, 138.15, 134.77, 132.48, 132.21, 129.14, 127.50, 126.19, 125.12, 120.51, 116.32, 69.87,

51.08, 43.71, 34.66, 30.84, 28.67. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{29}H_{35}N_2O_2$: 443.2699; found 443.2696.

4.2.68.8. 3-chloro-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41h): Compound **41h** was obtained as a white amorphous solid (30 mg, 73%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.64 – 7.58 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.36 – 7.28 (m, 2H), 6.85 (d, *J* = 7.5 Hz, 2H), 4.37 (m, 1H), 2.89 – 2.68 (m, 2H), 2.52 (m, 2H), 2.34 (s, 3H), 2.05 – 1.99 (m, 2H), 1.94 – 1.78 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.62, 156.37, 136.94, 136.90, 136.71, 134.53, 133.58, 131.61, 129.83, 127.91, 127.62, 126.92, 125.61, 121.14, 116.31, 70.25, 51.75, 45.20, 29.52. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{25}H_{26}ClN_2O_2$ 421.1683; found 421.1685.

4.2.68.9. 3-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41i): Compound **41i** was obtained as a white amorphous solid (38 mg, 74%).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.22 (m, 6H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.36 (m, 1H), 3.65 (s, 3H), 2.77 (m, 2H), 2.57 (m, 2H), 2.33 (s, 3H), 1.93 (m, 2H), 1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.97, 159.49, 155.97, 136.97, 136.54, 136.01, 133.59, 129.28, 127.68, 126.59, 121.08, 119.30, 117.47, 116.09, 112.44, 69.15, 54.93, 51.18, 44.33, 28.72. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{29}N_2O_3$ 417.2178; found 417.2175.

4.2.68.10. 4-chloro-3-methyl-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41j): Compound **41j** was obtained as a white amorphous solid (20 mg, 68%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H, NH), 7.97 (d, *J* = 2.2 Hz, 1H), 7.89 – 7.77 (m, 3H), 7.67 – 7.53 (m, 5H), 7.05 (d, *J* = 8.8 Hz, 2H), 4.51 (m, 1H), 2.88 (m, 2H), 2.63 – 2.52 (m, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 2.02 (m, 2H), 1.77 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.48, 156.20, 137.85, 136.51, 135.61, 135.04, 133.63, 132.29, 130.40, 128.86, 127.42, 126.88, 126.21, 120.63, 116.26, 70.60, 51.57, 44.44, 29.42, 19.62. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{28}ClN_2O_2$ 435.1839; found 435.1838.

4.2.68.11. 3-chloro-4-methyl-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41k): Compound **41k** was obtained as a white amorphous solid (40 mg, 80%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 1.9 Hz, 1H), 7.70 – 7.65 (m, 3H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.46 (m, 1H), 2.93 – 2.66 (m, 2H), 2.54 (m, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 2.16 – 2.07 (m, 2H), 1.98 – 1.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 165.03, 156.52, 140.36, 137.05, 136.88, 134.89, 134.17, 133.69, 131.29, 128.14, 128.05, 127.25, 125.60, 120.91, 116.45, 70.23, 51.78, 45.40, 29.35, 20.30. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{28}ClN_2O_2$ 435.1839; found 435.1841.

4.2.68.12. 3-bromo-4-methyl-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41l): Compound **41l** was obtained as a white amorphous solid (29 mg, 69%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 1.9 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.33 (d,, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.44 – 4.27 (m, 1H), 2.77 (m, 2H), 2.60 (m,

2H), 2.36 (s, 3H), 2.28 (s, 3H), 1.98 (m, 2H), 1.84 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 165.52, 156.08, 141.83, 136.97, 136.71, 134.04, 133.72, 131.30, 130.68, 127.86, 126.79, 126.25, 124.74, 121.13, 116.21, 69.55, 51.13, 44.60, 28.73, 22.65. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{28}BrN_2O_2$ 479.1334; found 479.1333.

4.2.68.13. 3-iodo-4-methyl-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41m): Compound **41m** was obtained as a white amorphous solid (36 mg, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H, NH), 8.42 (d, *J* = 1.8 Hz, 1H), 7.93 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.66 – 7.53 (m, 4H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 4.48 (m, 1H), 2.80 (m, 2H), 2.45 (s, 3H), 2.34 (m, 2H), 2.07 – 1.93 (m, 2H), 1.80 – 1.66 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 163.54, 156.27, 144.65, 137.79, 137.40, 135.07, 133.99, 132.21, 129.72, 127.70, 127.41, 126.19, 120.68, 116.23, 101.09, 71.05, 52.03, 45.16, 29.83, 27.51. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{26}H_{28}IN_2O_2$ 527.1195; found 527.1192.

4.2.68.14. 3,4-dichloro-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41n): Compound **41n** was obtained as a white amorphous solid (40 mg, 81%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 2.1 Hz, 1H), 7.50 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.29 – 7.16 (m, 4H), 7.13 (t, *J* = 4.1 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 4.26 (m, 1H), 2.72 (m, 2H), 2.60 (m, 2H), 2.29 (s, 3H), 1.88 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.64, 156.20, 136.95, 136.88, 135.92, 134.79, 133.72, 132.80, 130.51, 129.65, 127.98, 126.94, 126.82, 121.18, 116.29, 69.59, 51.17, 44.80, 28.69. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{25}H_{25}Cl_2N_2O_2$ 455.1293; found 455.1291.

4.2.68.15. 3,5-dichloro-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41o): Compound **41o** was obtained as a white amorphous solid (33 mg, 70%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (s, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.37 (m, 5H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.33 (m, 1H), 2.80 – 2.64 (m, 2H), 2.49 (m, 2H), 2.30 (s, 3H), 1.94 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 162.61, 156.44, 138.09, 137.46, 135.50, 134.33, 132.09, 130.95, 127.49, 126.53, 126.31, 120.78, 116.27, 71.35, 52.01, 45.26, 30.08. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{25}H_{25}Cl_2N_2O_2$ 455.1293; found 455.1296.

4.2.68.16. 2,4-dichloro-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzamide (41p): Compound **41p** was obtained as a white amorphous solid (22 mg, 63%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.47 – 7.33 (m, 4H), 7.27 – 7.18 (m, 2H), 7.09 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 4.49 (m, 1H), 3.07 – 2.90 (m, 4H), 2.58 (s, 3H), 2.13 (m, 2H), 2.00 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.97, 156.32, 137.13, 136.69, 136.57, 134.57, 133.67, 131.98, 130.25, 129.90, 128.03, 127.34, 127.10, 120.61, 116.34, 69.83, 51.49, 45.06, 29.19. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{25}H_{25}Cl_2N_2O_2$ 455.1293; found 455.1292.

4.2.68.17. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-2-carboxamide (41q): Compound **41q** was obtained as a white amorphous solid (18 mg, 66%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.24 (d, *J* = 4.5 Hz, 2H), 7.55 – 7.40 (m, 2H),

7.27 (t, *J* = 7.5 Hz, 1H), 7.19 (m, 6H), 7.06 (m, 4H), 6.69 (dd, *J* = 8.4, 3.0 Hz, 2H), 4.39 – 4.25 (m, 1H), 2.89 – 2.64 (m, 4H), 2.40 (s, 3H), 2.06 – 1.91 (m, 2H), 1.83 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 167.65, 155.87, 139.92, 139.09, 137.87, 136.96, 134.72, 132.51, 129.88, 129.67, 128.17, 128.13, 127.69, 127.35, 127.16, 127.11, 126.17, 119.79, 116.26, 69.25, 50.77, 43.29, 28.11. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{31}H_{31}N_2O_2$ 463.2386; found 463.2389.

4.2.68.18. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (41r): Compound **41r** was obtained as a white amorphous solid (30 mg, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.24 (s, 1H, NH), 8.03 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 4H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 2H), 4.63 (m, 1H), 3.15 (m, 2H), 2.96 (m, 2H), 2.64 (s, 3H), 2.11 (m, 2H), 1.96 – 1.78 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.73, 158.69, 155.89, 138.17, 137.46, 134.70, 132.63, 129.87, 129.37, 129.34, 129.08, 128.08, 127.44, 127.19, 126.88, 126.18, 120.69, 116.38, 111.38, 68.81, 50.55, 43.04, 28.02. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{31}H_{31}N_2O_2$ 463.2386; found 463.2387.

4.2.68.19. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-4-carboxamide (41s): Compound **41s** was obtained as a white amorphous solid (24 mg, 75%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.43 (dd, *J* = 13.4, 8.2 Hz, 4H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.29 (d, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.37 (m, 1H), 2.75 (m, 2H), 2.54 (m, 2H), 2.36 (s, 3H), 2.08 – 1.95 (m, 2H), 1.87 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 165.05, 156.23, 143.05, 139.05, 138.03, 134.95, 133.63, 132.28, 129.04, 128.35, 128.13, 127.41, 126.89, 126.55, 126.20, 120.62, 116.25, 70.83, 51.67, 44.67, 29.68. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{31}H_{31}N_2O_2$ 463.2386; found 463.2383.

4.2.68.20. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-2-naphthamide (43a): Compound **43a** was obtained as a white amorphous solid (36 mg, 60%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.35 (d, *J* = 1.8 Hz, 1H), 7.92 – 7.84 (m, 3H), 7.81 – 7.74 (m, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.35 (m, 6H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.40 (m, 1H), 2.78 (m, 2H), 2.59 (m, 2H), 2.38 (s, 3H), 2.04 (m, 2H), 1.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 167.04, 156.35, 137.18, 136.80, 134.88, 133.69, 132.61, 132.09, 128.98, 128.44, 127.97, 127.93, 127.84, 127.73, 127.01, 126.80, 123.86, 121.08, 116.35, 70.03, 51.61, 45.21, 29.65. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for C29H29N2O2 437.2229; found 437.2227.

4.2.68.21.N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-1-naphthamide (43b): Compound **43b** was obtained as a white amorphous solid (40 mg, 80%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.44 – 7.37 (m, 7H), 6.85 (d, *J* = 8.3 Hz, 2H), 4.41 (s, 1H), 2.85 (d, *J* = 12.0 Hz, 2H), 2.67 (s, 2H), 2.41 (s, 3H), 2.04 (t, *J* = 11.1 Hz, 2H), 1.90 (d, *J* = 14.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 168.82, 156.12, 137.24, 136.77, 134.38, 133.81, 133.61, 130.68, 130.02, 128.27, 127.96, 127.06,

127.00, 126.37, 125.19, 125.06, 124.65, 120.63, 116.28, 69.38, 51.34, 44.66, 28.95. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{29}H_{29}N_2O_2$ 437.2229; found 437.2231.

4.2.68.22. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)quinoline-3-carboxamide (45a): Compound **45a** was obtained as a white amorphous solid (35 mg, 78%). ^1H NMR (500 MHz, Chloroform-*d*) δ 9.29 (d, *J* = 2.3 Hz, 1H), 8.79 (d, *J* = 2.3 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.60 (t, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.51 – 4.40 (m, 1H), 2.93 – 2.79 (m, 2H), 2.69 (m, 2H), 2.45 (s, 3H), 2.11 – 2.07 (m, 2H), 2.00 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 164.54, 151.05, 148.52, 148.28, 138.45, 137.28, 137.08, 131.84, 131.14, 129.12, 128.46, 128.11, 127.97, 127.84, 127.25, 127.13, 121.24, 116.38, 68.04, 51.55, 45.14, 28.95. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{28}H_{28}N_3O_2$ 438.2182; found 438.2181.

4.2.68.23. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)quinoline-6-carboxamide (45b): Compound **45b** was obtained as a white amorphous solid (40 mg, 74%). ^1H NMR (500 MHz, DMSO-d_6) δ 10.61 (s, 1H, NH), 9.02 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.67 (d, *J* = 2.0 Hz, 1H), 8.55 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.28 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.68 – 7.63 (m, 3H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 4.50 (m, 1H), 3.33 (m, 2H), 2.84 (m, 2H), 2.38 – 2.34 (m, 3H), 2.02 (m, 2H), 1.77 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 165.12, 156.36, 152.34, 148.73, 138.08, 137.18, 135.11, 132.80, 132.36, 129.09, 128.55, 128.14, 127.56, 127.13, 126.38, 122.37, 120.77, 116.25, 70.88, 51.89, 44.82, 29.71. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{28}H_{28}N_3O_2$ 438.2182; found 438.2185.

4.2.68.24. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-1H-indole-2-carboxamide (47a): Compound **47a** was obtained as a white amorphous solid (38 mg, 80%). ^1H NMR (500 MHz, DMSO-d_6) δ 11.63 (d, *J* = 2.2 Hz, 1H, NH), 10.15 (s, 1H, NH), 7.71 (d, *J* = 8.7 Hz, 2H), 7.50 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.29 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.04 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.92 – 6.83 (m, 3H), 4.36 (m, 1H), 2.79 – 2.68 (m, 2H), 2.57 – 2.42 (m, 2H), 2.28 (s, 3H), 1.96 – 1.78 (m, 2H), 1.63 – 1.55 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 159.62, 156.10, 137.84, 136.78, 134.78, 132.42, 131.45, 127.42, 126.97, 126.30, 123.75, 121.70, 120.38, 119.88, 116.30, 112.34, 103.97, 69.99, 51.29, 44.04, 28.99. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{27}H_{28}N_3O_2$ 426.2182; found 426.2179.

4.2.68.25. N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)benzo[b]thiophene-2-carboxamide (47b): Compound **47b** was obtained as a white amorphous solid (50 mg, 81%). ^1H NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H, NH), 8.45 (s, 1H), 8.07 (dd, *J* = 7.4, 1.5 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.53 – 7.46 (m, 2H), 7.07 (d, *J* = 8.8 Hz, 2H), 4.68 – 4.46 (m, 1H), 3.06 – 2.96 (m, 2H), 2.85 – 2.74 (m, 2H), 2.54 (s, 3H), 2.17 – 2.03 (m, 2H), 1.91 – 1.78 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 160.23, 156.09, 140.44, 140.04, 139.12, 137.50, 135.17, 132.39, 127.47, 126.34, 125.89, 125.39, 125.04, 122.83, 122.71, 120.58, 116.33,

69.70, 50.70, 43.47, 28.36. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{27}H_{27}N_2O_2S$ 443.1793; found 443.1791.

4.2.68.26. 6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (49a): Compound **49a** was obtained as a white amorphous solid (33 mg, 78%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.25 (s, 1H, NH), 8.04 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.60 (dd, *J* = 8.6, 3.5 Hz, 4H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.58 (m, 1H), 3.86 (s, 3H), 3.11 – 2.93 (m, 2H), 2.78 (m, 2H), 2.52 (s, 3H), 2.08 (m, 2H), 1.85 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.68, 158.68, 156.01, 138.20, 137.49, 134.70, 132.52, 129.90, 129.36, 129.09, 128.06, 127.41, 127.17, 126.93, 126.16, 120.66, 116.33, 111.36, 69.61, 55.85, 50.89, 43.61, 28.55. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{32}H_{33}N_2O_3$ 493.2491; found 493.2495.

4.2.68.27. 3′-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (49b): Compound **49b** was obtained as a white amorphous solid (52 mg, 72%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.44 (s, 1H, NH), 8.24 (s, 1H), 7.96 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.93 – 7.84 (m, 3H), 7.68 – 7.57 (m, 4H), 7.44 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.35 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.33 (t, *J* = 2.1 Hz, 1H), 7.10 – 7.05 (m, 2H), 7.03 – 6.98 (m, 1H), 4.61 (m, 1H), 3.86 (s, 3H), 3.11 – 3.02 (m, 2H), 2.88 (s, 2H), 2.60 (s, 3H), 2.20 – 2.01 (m, 2H), 1.93 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 165.34, 159.78, 156.00, 140.99, 140.15, 138.02, 135.52, 134.95, 132.54, 130.08, 129.88, 129.06, 127.46, 126.97, 126.24, 125.86, 120.72, 119.23, 116.36, 113.34, 112.49, 69.66, 55.20, 50.77, 43.33, 28.33. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{32}H_{33}N_2O_3$ 493.2491; found 493.2494.

4.2.68.28. 4′,6-dimethoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (49c): Compound **49c** was obtained as a white amorphous solid (23 mg, 56%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.22 (s, 1H, NH), 7.99 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H), 7.64 – 7.60 (m, 3H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 1H), 4.65 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.25 – 2.96 (m, 4H), 2.68 (s, 3H), 2.11 (m, 2H), 1.91 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.78, 158.67, 158.50, 155.86, 138.25, 134.63, 132.70, 130.48, 129.63, 129.04, 128.52, 127.44, 126.91, 126.18, 120.63, 116.40, 113.56, 113.52, 111.29, 66.97, 55.82, 55.12, 51.23, 42.74, 28.33. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{33}H_{35}N_2O_4$ 523.2597; found 523.2602.

4.2.68.29. 2′-methoxy-5′-((4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)carbamoyl)-[1,1′-biphenyl]-3-yl acetate (49d): Compound **49d** was obtained as a white amorphous solid (32 mg, 76%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (s, 1H), 7.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.43 (m, 1H), 3.81 (s, 3H), 2.90 – 2.79 (m, 2H), 2.66 (m, 2H), 2.45 (s, 3H), 2.25 (s, 3H), 2.19 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.64, 165.09, 159.23, 156.27, 150.37, 138.92, 137.04, 136.58, 133.73, 129.62, 129.55, 129.12, 128.82, 128.05, 127.22, 127.18, 127.03, 122.77, 120.64, 120.51, 116.27, 111.11,

69.73, 55.86, 51.43, 45.19, 29.15, 21.21. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{34}H_{35}N_2O_5$ 551.2546; found 551.2543.

4.2.68.30. 2′-methoxy-5′-((4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)carbamoyl)-[1,1′-biphenyl]-4-yl acetate (49e): Compound **49e** was obtained as a white amorphous solid (55 mg, 66%). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.98 (s, 1H), 7.86 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.46 (m, 5H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.43 (m, 1H), 3.81 (s, 3H), 2.93 – 2.78 (m, 2H), 2.66 (s, 2H), 2.45 (s, 3H), 2.26 (s, 3H), 2.26 – 2.10 (m, 2H), 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.68, 165.08, 159.28, 156.27, 149.97, 137.10, 136.56, 135.14, 133.71, 130.58, 129.83, 129.63, 128.59, 128.04, 127.18, 127.15, 121.29, 120.51, 116.27, 111.06, 69.72, 55.81, 51.41, 45.17, 29.16, 21.21. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{34}H_{35}N_2O_5$ 551.2546; found 551.2545.

4.2.68.31. 3′-chloro-6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (49f): Compound **49f** was obtained as a white amorphous solid (32 mg, 80%). ^1H NMR (500 MHz, DMSO-d_6) δ 10.21 (s, 1H), 8.06 (dd, *J* = 8.6, 2.4 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.63 – 7.57 (m, 54H), 7.55 – 7.44 (m, 3H), 7.30 (d, *J* = 8.7 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.41 (m, 1H), 3.88 (s, 3H), 2.71 – 2.57 (m, 2H), 2.20 (m, 5H), 2.12 – 1.90 (m, 2H), 1.66 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.50, 158.58, 156.38, 139.55, 138.04, 134.86, 132.73, 132.09, 129.95, 129.81, 129.71, 128.97, 128.13, 127.70, 127.35, 127.12, 127.01, 126.13, 120.67, 116.17, 111.55, 71.85, 55.98, 52.32, 45.74, 30.51. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{32}ClN_2O_3$ 527.2101; found 527.2100.

4.2.68.32. 4′-chloro-6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (49g): Compound **49g** was obtained as a white amorphous solid (23 mg, 70%). ^1H NMR (500 MHz, DMSO-d_6) δ 10.23 (s, 1H, NH), 8.04 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.60 (m, 5H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 4.55 (m, 1H), 3.87 (s, 3H), 3.33 (s, 3H), 2.98 (m, 2H), 2.70 (m, 2H), 2.06 (m, 2H), 1.80 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.60, 158.61, 156.07, 138.16, 136.26, 134.76, 132.48, 132.02, 131.18, 129.78, 129.44, 128.10, 127.98, 127.43, 127.04, 126.19, 120.66, 116.33, 111.51, 69.88, 55.96, 51.10, 43.86, 28.74. HRMS (ESI^+) m/z: [M + H^+] calcd for $C_{32}H_{32}ClN_2O_3$ 527.2101; found 527.2105.

4.2.68.31. 6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-3′-nitro-[1,1′-biphenyl]-3-carboxamide (49h): Compound **49h** was obtained as a yellow amorphous solid (32 mg, 72%). ^1H NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H, NH), 8.42 (t, *J* = 2.0 Hz, 1H), 8.26 (dd, *J* = 8.2, 2.4 Hz, 1H), 8.11 (dd, *J* = 8.6, 2.3 Hz, 1H), 8.08 – 8.03 (m, 2H), 7.86 – 7.83 (m, 2H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.65 – 7.57 (m, 4H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 4.52 (m, 1H), 3.91 (s, 3H), 2.91 (m, 2H), 2.66 – 2.56 (m, 2H), 2.44 (s, 3H), 2.09 – 1.96 (m, 2H), 1.85 – 1.66 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 164.46, 158.58, 156.14, 147.68, 138.93, 138.06, 136.08, 134.82, 132.37, 130.15, 129.96, 129.71, 127.40, 127.21, 126.80, 126.18, 123.79, 122.14, 120.68, 116.27, 111.69, 69.71, 56.10,

51.67, 44.44, 29.14. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{32}H_{32}N_3O_5$ 538.2342; found 538.2346.

4.2.68.29.1. 3′-hydroxy-6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (50a): General procedure for the synthesis of 50a-b: Compounds **49d** (20 mg, 0.036 mmol) were dissolved in a solution of 10% Et_3N in methanol (1 mL) and stirred at room temperature for 24 hours before concentrated to dryness. The light brown residue so obtained was purified by flash chromatography using dichloromethane and methanol (v/v, 10:1) as eluent to give **50a** as a white amorphous solid (16 mg, 85%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.95 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.05 – 7.03 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.84 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.49 (m, 1H), 3.90 (s, 3H), 2.86 (m, 2H), 2.63 (m, 2H), 2.46 (s, 3H), 2.12 (m, 2H), 2.02 – 1.93 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.57, 159.32, 156.47, 156.29, 138.87, 137.19, 136.60, 133.67, 130.54, 130.01, 129.01, 128.41, 127.90, 126.91, 126.88, 121.04, 120.98, 116.35, 116.31, 114.33, 110.87, 69.62, 55.62, 51.63, 45.18, 29.42. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{32}H_{33}N_2O_4$ 509.2440, found 509.2442.

4.2.68.30.1. 4′-hydroxy-6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (50b): Compound **50b** was obtained as a white amorphous solid (16 mg, 90%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.90 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.56 – 7.50 (m, 4H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.55 (m, 1H), 3.89 (s, 3H), 3.00 (m, 2H), 2.84 (m, 2H), 2.57 (s, 3H), 2.20 (m, 2H), 2.06 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 166.53, 159.30, 156.25, 156.03, 137.23, 136.47, 133.88, 130.59, 130.56, 129.76, 128.81, 127.96, 127.80, 126.93, 126.91, 121.00, 116.26, 114.96, 110.79, 68.82, 55.63, 51.12, 44.67, 28.69. HRMS (ESI$^+$) m/z [M+H$^+$] calcd for $C_{32}H_{33}N_2O_4$ 509.2440, found 509.2441.

4.2.68.31.1. 3′-amino-6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (50c): Palladium on carbon (10%, 5 mg) was added to a solution of **49h** (25 mg, 0.047 mmol) in methanol (1 ml), followed by two drops of acetic acid. The resulted suspension was degased and stirred under hydrogen atmosphere for 12 hours before filtration. The filtrate was concentrated to dryness to afford aniline **50c** as a white amorphous solid (18 mg, 76%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.81 (m, 1H), 7.78 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.43 (m, 4H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.87 (m, 3H), 6.81 (s, 1H), 6.64 – 6.62 (m, 1H), 4.54 (m, 1H), 3.77 (s, 3H), 3.13 – 2.99 (m, 4H), 2.63 (s, 3H), 2.25 – 2.15 (m, 2H), 2.08 – 2.00 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 159.41, 156.00, 146.03, 138.68, 137.32, 136.51, 134.07, 130.83, 129.93, 128.98, 128.53, 128.09, 127.04, 126.93, 121.02, 120.98, 120.31, 116.69, 116.31, 114.71, 110.97, 68.71, 55.76, 50.83, 44.44, 28.31. HRMS (ESI$^+$) m/z: [M + H$^+$] calcd for $C_{32}H_{34}N_3O_3$ 508.2600; found 508.2598.

4.2.68.31.2. 3′-acetamido-6-methoxy-N-(4′-((1-methylpiperidin-4-yl)oxy)-[1,1′-biphenyl]-4-yl)-[1,1′-biphenyl]-3-carboxamide (50d): Aniline **50c** (10 mg, 0.02 mmol) was added to a solution of acetic anhydride in pyridine (1:3, v/v) and the resulting mixture was stirred at room temperature for 4 hours before being concentrated to dryness. The remaining residue was further dried under vacuum overnight to afford acetamide **50d** as a light brown amorphous solid (10 mg, 100%). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.76 (dd, J = 8.8, 2.7 Hz, 1H), 7.73 (s, 1H), 7.56 – 7.51 (m, 3H), 7.37 – 7.29 (m, 5H), 7.17 – 7.08 (m, 2H), 6.88 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 8.6 Hz, 2H), 4.34 (m, 1H), 3.67 (s, 3H), 2.81 (m, 2H), 2.62 (s, 1H), 2.36 (m, 2H), 1.96 (s, 3H), 1.94 (m, 2H), 1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$+CH3OH) δ 170.17, 166.64, 159.19, 155.91, 138.13, 137.98, 137.25, 136.38, 133.83, 130.00, 129.93, 128.69, 128.18, 127.79, 126.78, 126.67, 125.34, 121.11, 121.07, 118.95, 116.14, 110.77, 68.98, 55.39, 51.01, 44.30, 28.59, 23.26. HRMS (ESI$^+$) m/z [M +K$^+$] calcd for $C_{34}H_{35}N_3O_4K$ 588.2265, found 588.2270.

Anti-proliferation assays: Cells were maintained in a 1:1 mixture of Advanced DMEM/F12 (Gibco) supplemented with non-essential amino acids, L-glutamine (2 mM), streptomycin (500 g/mL), penicillin (100 units/mL), and 10% FBS. Cells were grown to confluence in a humidified atmosphere (37° C, 5% CO_2), seeded (2000/well, 100 μL) in 96-well plates, and allowed to attach overnight. Compound or GDA at varying concentrations in DMSO (1% DMSO final concentration) was added, and cells were returned to the incubator for 72 h. At 72 h, the number of viable cells was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Cells incubated in 1% DMSO were used at 100% proliferation, and values were adjusted accordingly. IC_{50} values were calculated from separate experiments performed in triplicate using GraphPad Prism.

Western blot analyses: MCF-7 cells were cultured as described above and treated with various concentrations of drug, GDA in DMSO (1% DMSO final concentration), or vehicle (DMSO) for 24 h. Cells were harvested in cold PBS and lysed in RIPA lysis buffer containing 1 mM PMSF, 2 mM sodium orthovanadate, and protease inhibitors on ice for 1 h. Lysates were clarified at 14000g for 10 min at 4° C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (20 g) were electrophoresed under reducing conditions, transferred to a nitrocellulose membrane, and immunoblotted with the corresponding specific antibodies. Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate, and visualized.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A small library of biphenylamide derivatives was designed and analogues synthesized.
- Compounds were evaluated for anti-proliferative activity against cancer cell lines.
- Hsp90 inhibition was confirmed by Western blot analysis.
- Several analogues showed low nanomolar inhibitory activity.

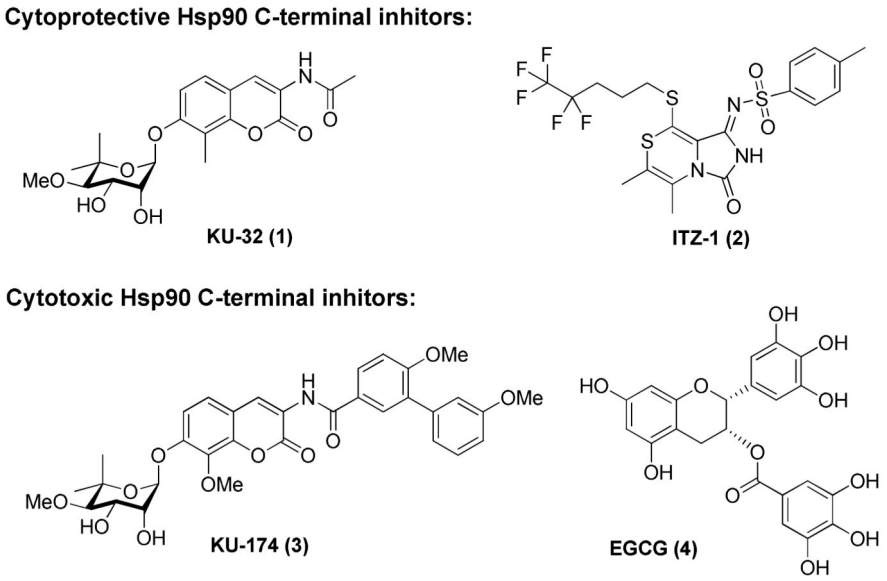


Figure 1.
Small molecules that target the Hsp90 C-terminus.

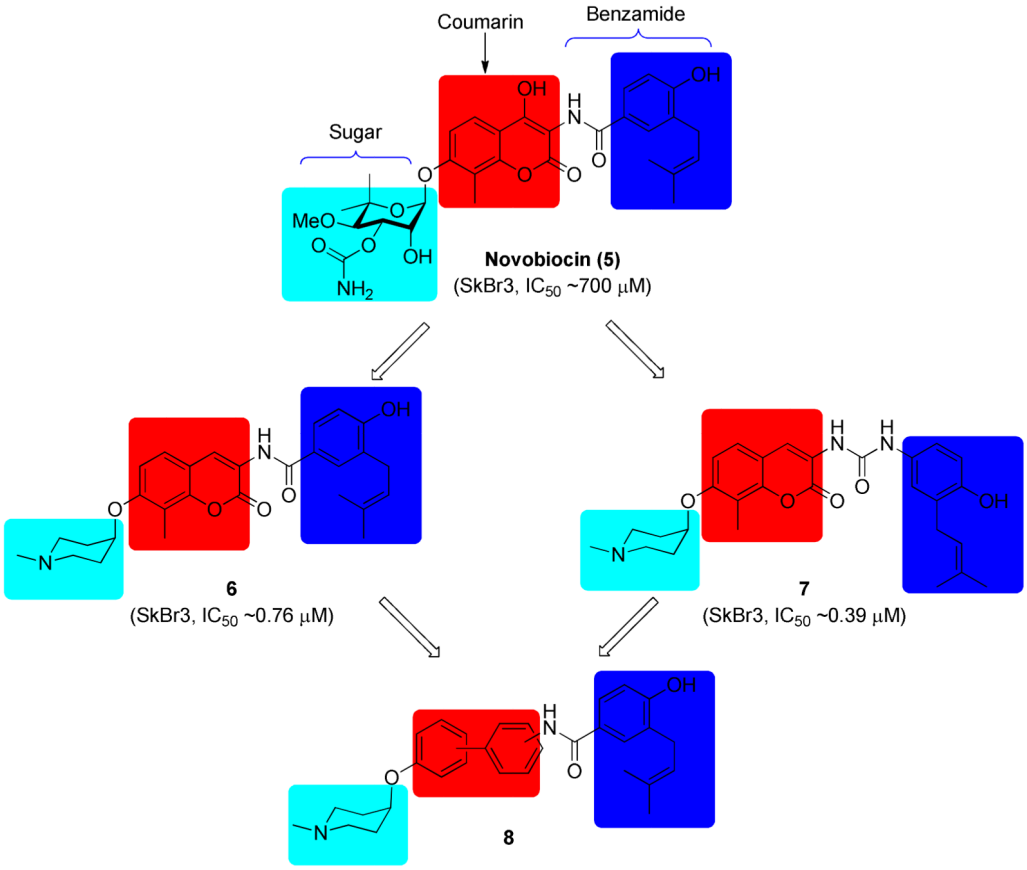


Figure 2.
Rationale for proposed coumarin replacements.

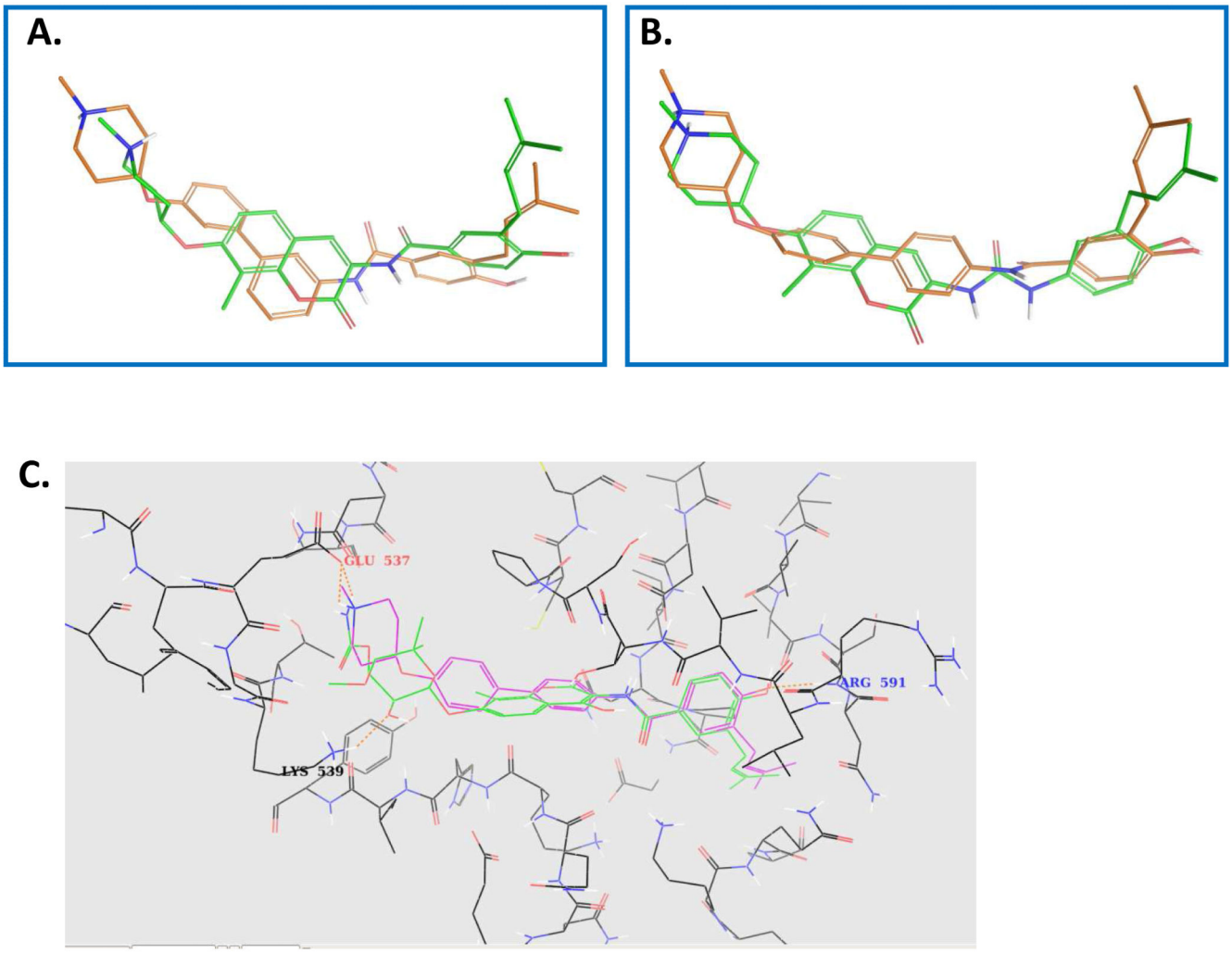


Figure 3.

Molecular docking in the putative Hsp90 C-terminal binding site: **A.** overlay of compounds **6** (red) and **8e** (green); **B.** overlay of compounds **7** (red) and **8f** (green); **C.** molecular overlay of novobiocin (green) and **8f** (magenta) docked into the Hsp90 C-terminal binding site (line representation).

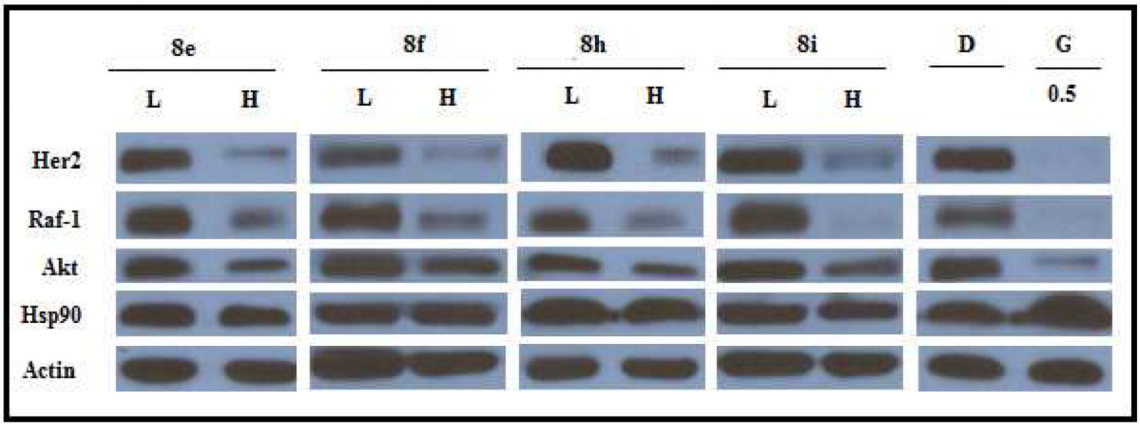


Figure 4.

Western blot analyses of Hsp90-dependent client proteins from MCF-7 breast cancer cell lysate upon treatment with biphenyl derivatives. Concentrations (in μM) were indicated above each lane. H represents a concentration equal to 5-fold of the anti-proliferative activity. L represents a concentration equal to 0.5-fold of the anti-proliferative activity. Geldanamycin (G, 0.5 μM) and dimethylsulfoxide (D, 100%) were employed as positive and negative controls.

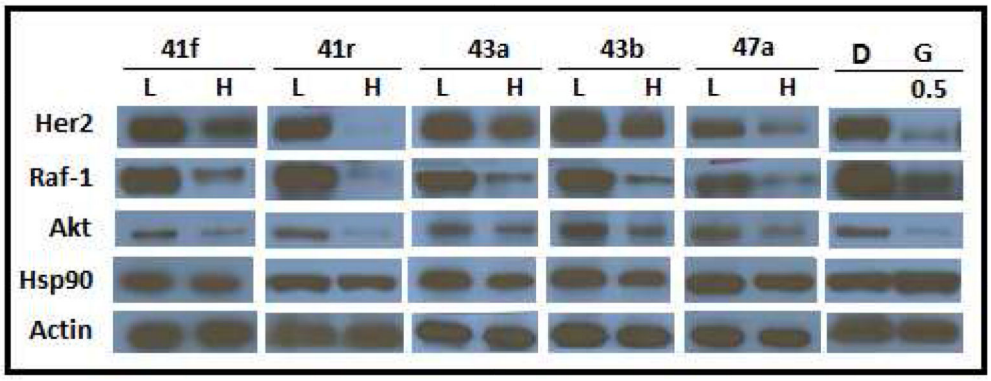


Figure 5.

Western blot analyses of Hsp90-dependent client proteins from MCF-7 breast cancer cell lysate upon treatment with biphenyl derivatives. Concentrations (in μM) were indicated above each lane. H represents a concentration equal to 5-fold of the anti-proliferative activity. L represents a concentration equal to 0.5-fold of the anti-proliferative activity. Geldanamycin (G, 0.5 μM) and dimethylsulfoxide (D, 100%) were employed as positive and negative controls.

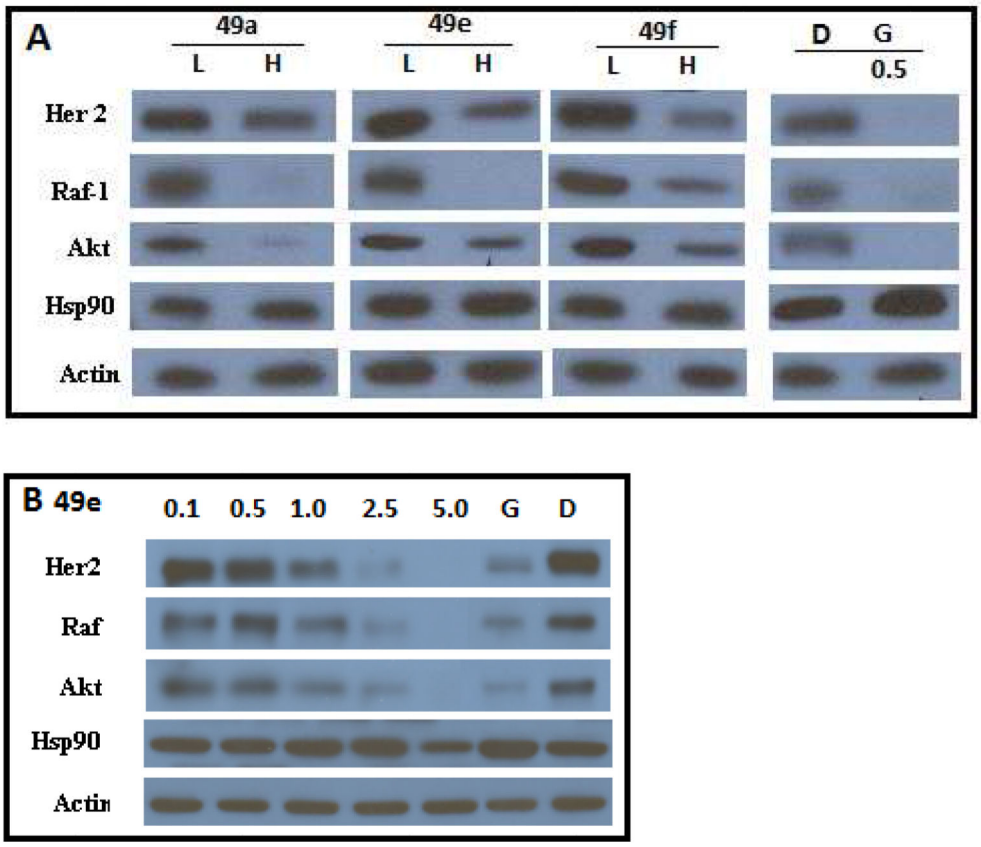
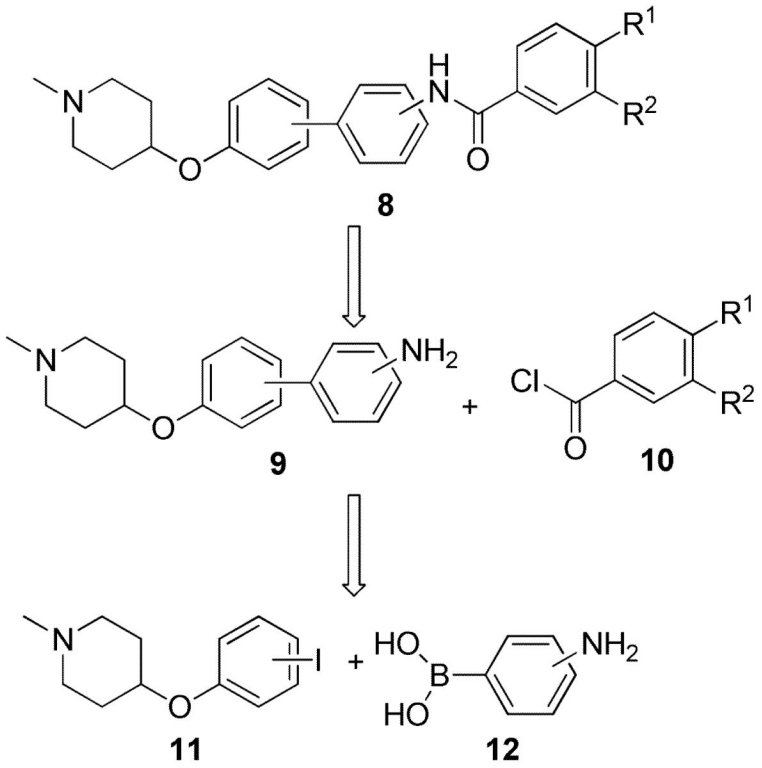
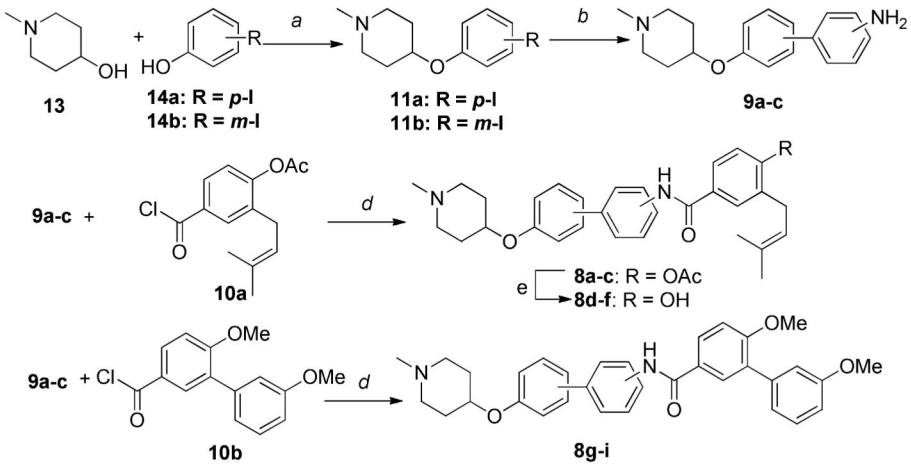


Figure 6.

Western blot analyses of Hsp90-dependent client proteins from MCF-7 breast cancer cell lysate upon treatment with biphenyl derivatives. Concentrations (in μM) were indicated above each lane. H represents a concentration equal to 5-fold of the anti-proliferative activity. L represents a concentration equal to 0.5-fold of the anti-proliferative activity. Geldanamycin (G, 0.5 μM) and dimethylsulfoxide (D, 100%) were employed as positive and negative controls.



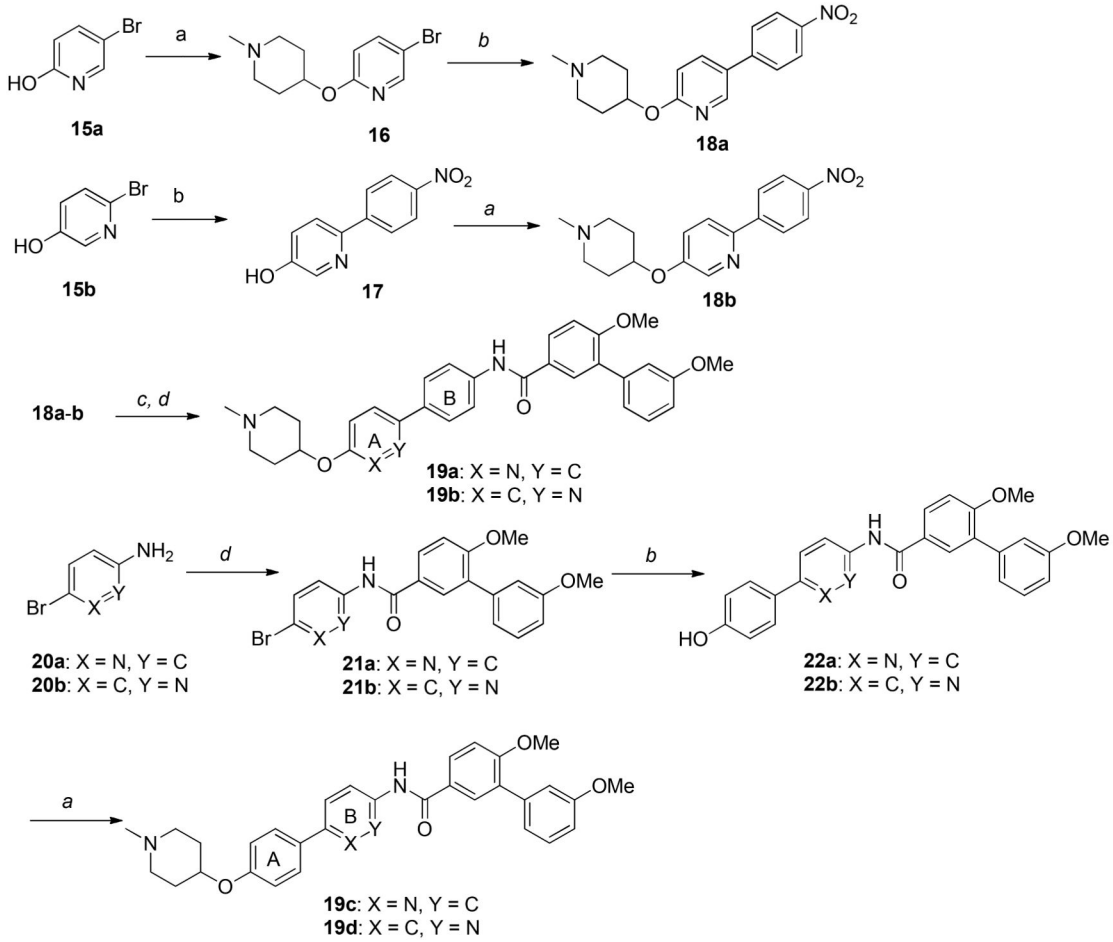
Scheme 1.
Retrosynthesis of biphenyl inhibitors.



Scheme 2.

Synthesis of novobiocin mimics that contain a biphenyl moiety.

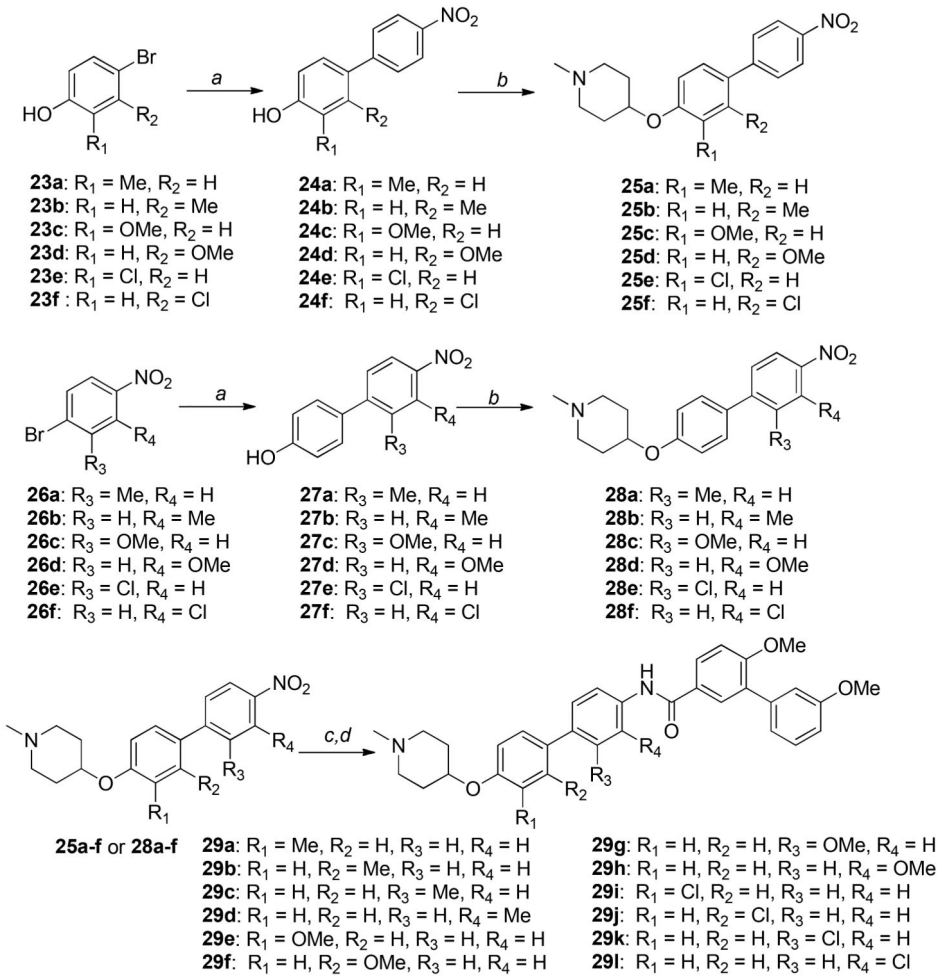
Reagents and conditions: *a* Ph_3P, DIAD, THF, r. t., 12 h, 46%~77%; *b* $Pd(dppf)_2Cl_2$, 3- or 4-amino phenylboronic acid, 2M K_2C0_3, Dioxane, 110 °C, 12 h, 52%~67%; *c* Pd/C, MeOH, r. t., 2 h, 100%; *d* pyridine, DCM, r. t., 4h, 52%~78%; *e* 10% Et_3N/MeOH, r. t., 24 h, 72~86%.



Scheme 3.

Synthesis of pyridine biphenyl derivatives.

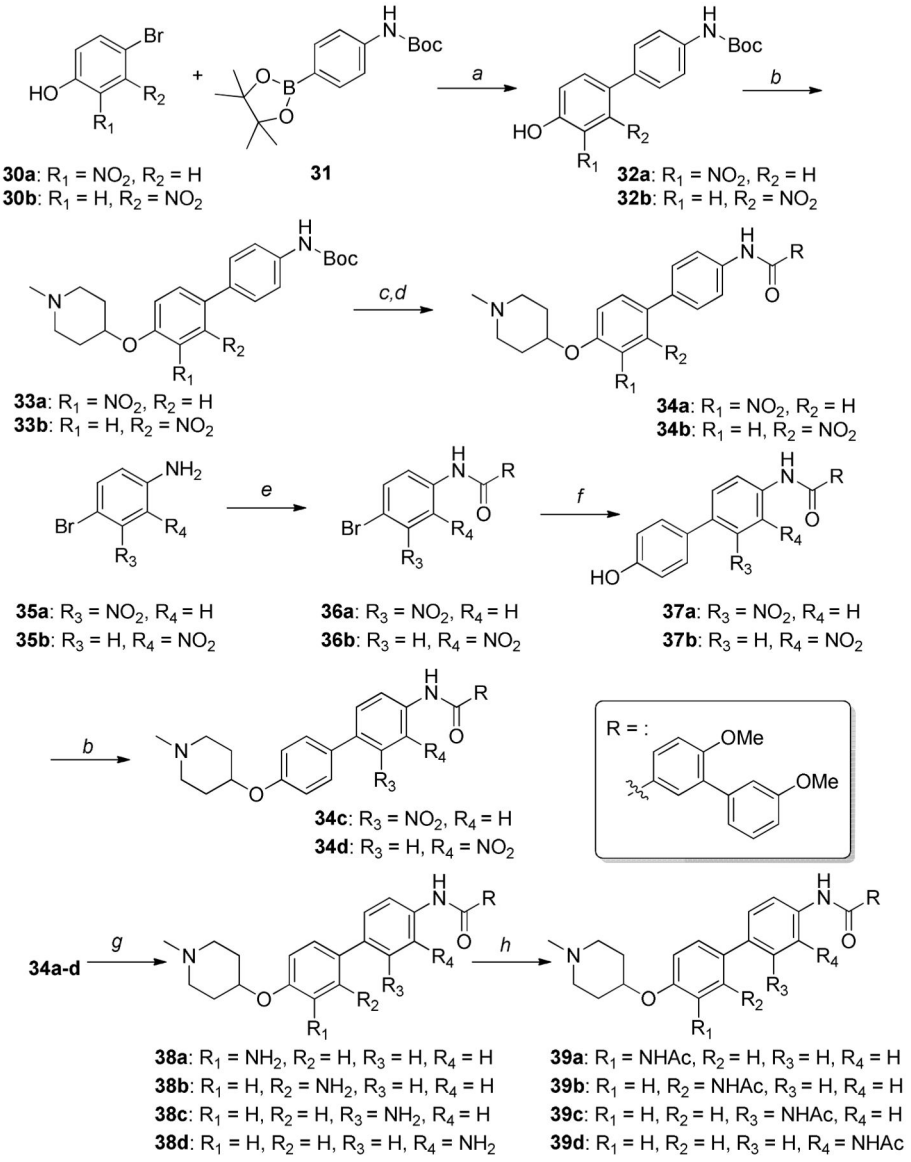
Reagents and conditions: *a* Ph_3P, DIAD, THF, r. t., 12 h, 58%~68%; *b* $Pd(dppf)_2Cl_2$, 2M K_2CO_3, Dioxane, 110 °C, 12 h, 75%%~92%; *c* Pd/C, MeOH, r. t., 2 h, 100%; *d* pyridine, DCM, r. t., 4 h, 45%~87%.



Scheme 4.

Synthesis of novobiocin mimics that contain a substituted biphenyl moiety.

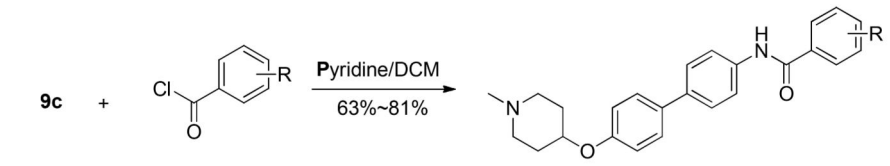
Reagents and conditions: *a* $Pd(dppf)_2Cl_2$, 2M K_2CO_3, Dioxane, 110 °C, 12 h, 17%%~74%; *b* Ph_3P, DIAD, THF, r. t., 12 h, 46%~80%; *c* Pd/C, MeOH, r. t., 2 h, 100%; *d* pyridine, DCM, r. t., 4 h, 39%~87%.



Scheme 5.

Synthesis of novobiocin mimics that contain nitro substitution.

Reagents and conditions: *a* $Pd(PPh_3)_4$, 2M K_2CO_3, Dioxane, 110 °C, 12 h, 60%~72%; *b* Ph_3P, DIAD, THF, r. t., 12 h, 39%~89%; *c* 10% TFA/DCM, r. t., 2 h, 98%; *d* pyridine, DCM, r. t., 4 h, 63%; *d* pyridine, DMF, 90 °C, 12 h, 43%~90%; *f* $Pd(dppf)_2Cl_2$, 2M K_2CO_3, Dioxane, 120 °C, 12 h, 41%~65%; *g* pd/C MeOH, AcOH(cat.), r. t., 12 h, 100%; *h* Ac_2O, pyridine, r. t., 12 h, 85~90%.

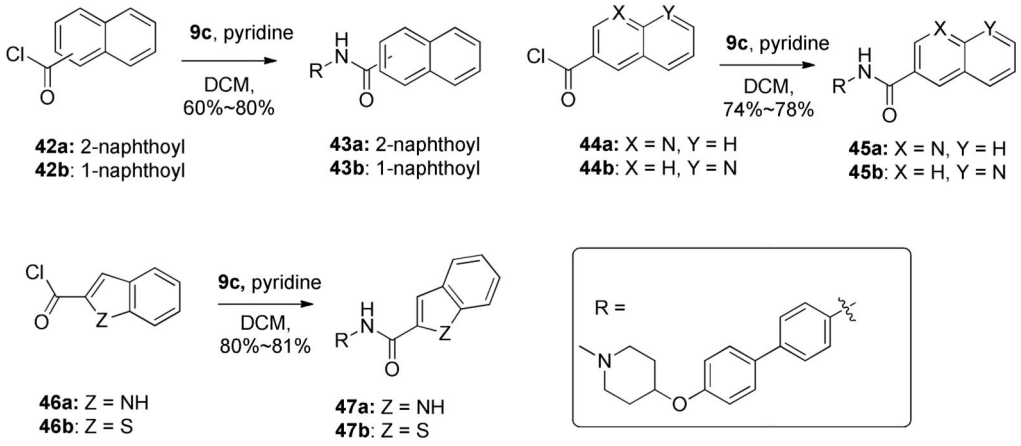


40a: R = H
40b: R = *p*-Cl
40c: R = *p*-Br
40d: R = *p*-I
40e: R = *p*-methyl
40f: R = *p*-methoxy
40g: R = *p*-t-butyl
40h: R = *m*-Cl
40i: R = *m*-methoxy
40j: R = 3-methyl-4-chloro
40k: R = 3-chloro-4-methyl
40l: R = 3-bromo-4-methyl
40m: R = 3-iodo-4-methyl
40n: R = 3,4-dichloro
40o: R = 3,5-dichloro
40p: R = 2,4-dichloro
40q: R = 2-phenyl
40r: R = 3-phenyl
40s: R = 4-phenyl

41a: R = H
41b: R = *p*-Cl
41c: R = *p*-Br
41d: R = *p*-I
41e: R = *p*-methyl
41f: R = *p*-methoxy
41g: R = *p*-t-butyl
41h: R = *m*-Cl
41i: R = *m*-methoxy
41j: R = 3-methyl-4-chloro
41k: R = 3-chloro-4-methyl
41l: R = 3-bromo-4-methyl
41m: R = 3-iodo-4-methyl
41n: R = 3,4-dichloro
41o: R = 3,5-dichloro
41p: R = 2,4-dichloro
41q: R = 2-phenyl
41r: R = 3-phenyl
41s: R = 4-phenyl

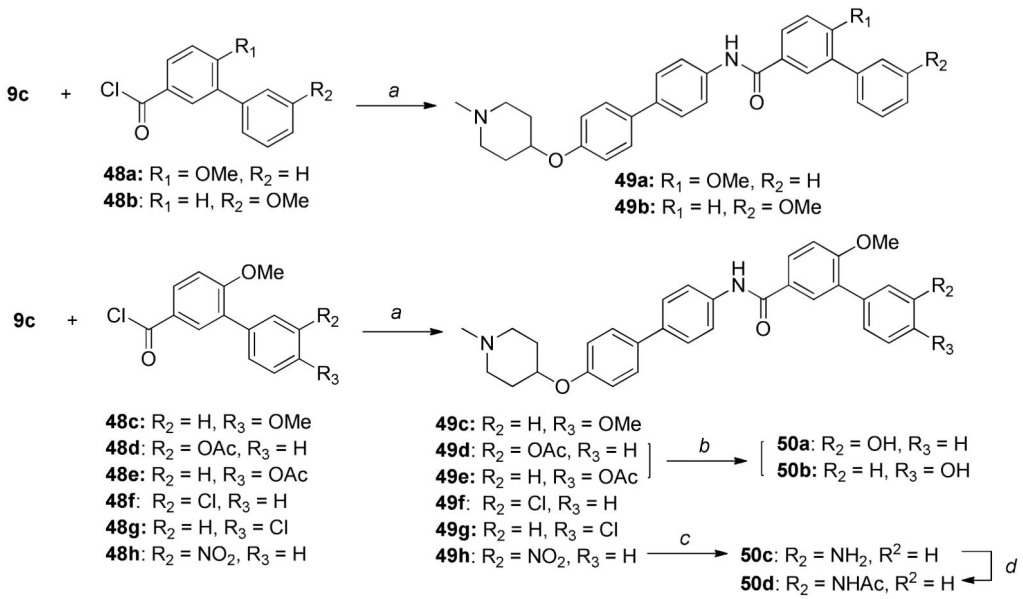
Scheme 6.

Synthesis of biphenyl derivatives containing a modified benzylamide side chain.



Scheme 7.

Synthesis of biphenyl derivatives containing a fused-aromatic side chain.



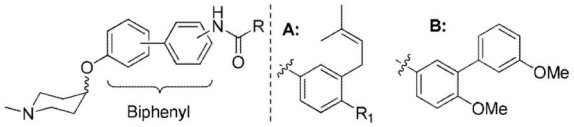
Scheme 8.

Synthesis of biphenyl derivatives containing a substituted biaryl side chain.

Reagents and conditions: *a* pyridine, DCM, r. t., 4 h, 56%~81%; *b* Et_3N, MeOH, r. t., 24 h, 85%~90%; *c* Pd/C, MeOH, r. t., 12 h, 76%, *d* Ac_2O, pyridine, r. t., 12 h, 76%.

Table 1

Anti-proliferative activity of novobiocin mimics.

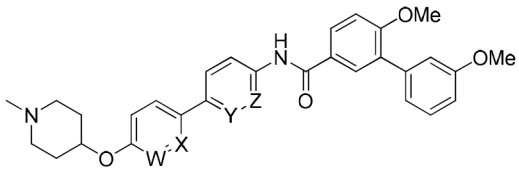


Entry	Biphenyl	R	SKBr3 (IC_{50}, μM)	MCF-7 (IC_{50}, μM)
5	--	--	~700	--
6	--	--	0.76±0.14 [a]	1.09±0.08
7	--	--	0.39±0.06	0.37±0.05
8a	*para-meta*	A (R_1 = OAc)	3.47±0.47[a]	2.71±0.40
8b	*meta-meta*	A (R_1 = OAc)	1.76±0.16	1.70±0.21
8c	*para-para*	A (R_1 = OAc)	1.82±0.21	1.37±0.18
8d	*para-meta*	A (R_1 = OH)	2.94±0.11	2.21±0.06
8e	*meta-meta*	A (R_1 = OH)	2.79±0.40	1.17±0.05
8f	*para-para*	A (R_1 = OH)	2.27±0.08	1.85±0.32
8g	*para-meta*	B	3.65±0.14	1.25±0.02
8h	*meta-meta*	B	1.62±0.07	2.00±0.07
8i	*para-para*	B	0.47±0.06	0.71±0.02

[a]Values represent mean ± standard deviation for at least two separate experiments performed in triplicate.

Table 2

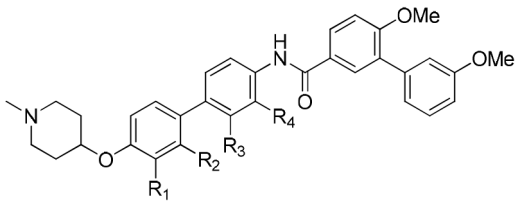
Anti-proliferative activity manifested by pyridine biphenyl derivatives.



Entry	W	X	Y	Z	SKBr3 (IC_{50}, μM)	MCF-7 (IC_{50}, μM)
8i	C	C	C	C	0.47±0.06	0.71±0.02
19a	N	C	C	C	1.67±0.09	1.56±0.19
19b	C	N	C	C	1.91±0.21	1.30±0.15
19c	C	C	N	C	1.21±0.13	1.02±0.01
19d	C	C	C	N	1.07±0.01	1.15±0.16

Table 3

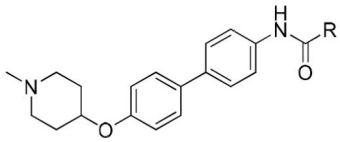
Anti-proliferative activity manifested by substituted biphenyl derivatives.



Entry	R_1	R_2	R_3	R_4	SKBr3 (IC_{50}, μM)	MCF-7 (IC_{50}, μM)
8i	H	H	H	H	0.47±0.06	0.71±0.02
29a	Me	H	H	H	0.83±0.03	1.69±0.08
29b	H	Me	H	H	1.18±0.11	1.21±0.03
29c	H	H	Me	H	0.97±0.01	1.57±0.56
29d	H	H	H	Me	2.47±0.39	1.43±0.35
29e	OMe	H	H	H	0.68±0.13	1.32±0.08
29f	H	OMe	H	H	1.41±0.35	1.35±0.16
29g	H	H	OMe	H	0.90±0.08	1.50±0.08
29h	H	H	H	OMe	3.92±0.21	1.22±0.04
29i	Cl	H	H	H	1.84±0.57	1.48±0.12
29j	H	Cl	H	H	1.28±0.14	1.48±0.33
29k	H	H	Cl	H	2.21±0.18	3.44±0.21
29l	H	H	H	Cl	4.29±0.65	1.80±0.19
34a	NO2	H	H	H	2.07±0.17	1.23±0.25
34b	H	NO2	H	H	1.18±0.15	1.30±0.12
34c	H	H	NO2	H	2.48±0.77	3.32±0.25
34d	H	H	H	NO2	3.40±0.14	1.15±0.01
38a	NH2	H	H	H	2.23±0.49	5.95±1.22
38b	H	NH2	H	H	2.13±0.06	1.76±0.37
38c	H	H	NH2	H	3.90±0.18	2.07±0.23
38d	H	H	H	NH2	3.21±0.45	2.25±0.49
39a	NHAc	H	H	H	2.66±0.76	1.84±0.43
39b	H	NHAc	H	H	3.39±0.66	1.36±0.23
39c	H	H	NHAc	H	2.52±0.26	4.66±0.49
39d	H	H	H	NHAc	3.51±0.56	1.66±0.59

Table 4

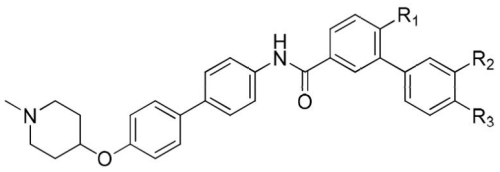
Anti-proliferative activity manifested by biphenyl derivatives that contain a modified benzylamide side chain.



Entry	R	SKBr3 (IC_{50}, μM)	MCF-7 (IC_{50}, μM)
41a	phenyl	4.13±0.22	3.95±0.13
41b	4-chlorophenyl	0.57±0.01	0.52±0.03
41c	4-bromophenyl	0.52±0.21	0.52±0.15
41d	4-iodophenyl	0.31±0.09	0.58±0.01
41e	4-methylphenyl	0.98±0.19	1.27±0.13
41f	4-methoxyphenyl	0.49±0.01	0.65±0.04
41g	4-t-butylphenyl	1.26±0.37	1.08±0.08
41h	3-chlorophenyl	1.94±0.37	2.83±0.69
41i	3 -methoxyphenyl	2.87±0.51	5.31±0.70
41j	3 -methyl -4 -chl orophenyl	1.11±0.42	1.03±0.16
41k	3-chloro-4-methylphenyl	1.96±0.24	2.28±0.49
41l	3 -bromo-4-methylphenyl	2.80±0.18	3.35±0.36
41m	3-iodo-4-methylphenyl	0.93±0.20	1.17±0.20
41n	3,4-dichl orophenyl	1.20±0.08	1.60±0.16
41o	3,5-dichl orophenyl	0.81±0.28	1.68±0.13
41p	2,4-dichlorophenyl	0.80±0.22	1.37±0.33
41q	2-biphenyl	6.26±1.54	6.67±0.83
41r	3-biphenyl	0.73±0.07	1.15±0.18
41s	4-biphenyl	4.59±0.06	4.44±0.60
43a	1-naphthoyl	0.22±0.13	0.58±0.02
43b	2-naphthoyl	0.35±0.02	0.49±0.11
45a	2-quinolinyl	2.42±0.62	2.76±0.76
45b	6-quinolinyl	1.31±0.18	2.07±0.16
47a	2-indolyl	0.64±0.08	0.58±0.02
47b	2-benzo[b]thiophenyl	1.32±0.23	2.01±0.58
8i	--	0.47±0.06	0.71±0.02

Table 5

Anti-proliferative activity of biphenyl derivatives with a modified biaryl side chain.



Entry	R1	R2	R3	SKBr3	MCF-7
41r	H	H	H	0.73±0.07	1.15±0.18
8i	OMe	OMe	H	0.47±0.06	0.71±0.02
49a	OMe	H	H	0.51±0.11	0.84±0.01
49b	H	OMe	H	0.81±0.14	1.02±0.08
49c	OMe	H	OMe	0.63±0.04	0.79±0.13
49d	OMe	OAc	H	0.27±0.05	0.62±0.07
50a	OMe	OH	H	1.56±0.35	1.08±0.34
49e	OMe	H	OAc	0.14±0.01	0.64±0.08
50b	OMe	H	OH	0.13±0.02	0.50±0.01
49f	OMe	Cl	H	0.33±0.03	0.32±0.09
49g	OMe	H	Cl	1.06±0.05	0.82±0.13
49h	OMe	NO_2	H	0.40±0.07	1.09±0.28
50c	OMe	NH_2	H	1.52±0.55	1.67±0.68
50d	OMe	NHAc	H	3.37±0.74	1.43±0.28