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Synthesis, Structure-Activity Relationships and Antiviral Activity of Allosteric Inhibitors of Flavivirus NS2B-NS3 Protease

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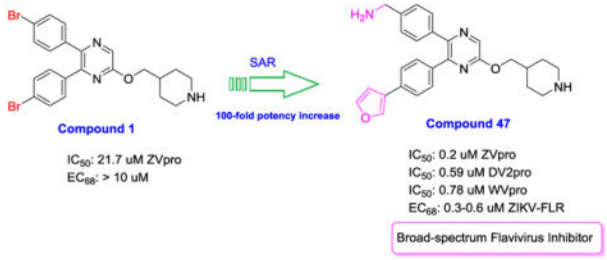
Abstract

Flaviviruses, including Zika, dengue and West Nile virus, are important human pathogens. The highly conserved NS2B-NS3 protease of Flavivirus is essential for viral replication and therefore a promising drug target. Through compound screen followed by medicinal chemistry studies, a novel series of 2,5,6-trisubstituted pyrazine compounds are found to be potent, allosteric inhibitors of Zika virus protease (ZVpro) with IC_{50} values as low as 130 nM. Their structure-activity relationships are discussed. The ZVpro inhibitors also inhibit homologous proteases of dengue and West Nile virus and their inhibitory activities are correlated. The most potent compounds **47** and **103** potently inhibited Zika virus replication in cells with EC_{68} values of 300–600 nM and in a mouse model of Zika infection. These compounds represent novel pharmacological leads for drug development against Flavivirus infections.

Graphical Abstract



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Supporting Information Available. Molecular Formula Strings for all compounds are available free of charge via the Internet at http://pubs.acs.org.

Keywords

Zika virus; NS2B-NS3 protease; allosteric inhibitor; structure-activity relationship

INTRODUCTION

Zika virus (ZIKV) is a species of the arthropod-borne Flavivirus in the *Flaviviridae* family of RNA viruses, which includes other important human pathogens such as yellow fever, dengue and West Nile virus. ZIKV was first discovered and isolated from a sentinel Rhesus monkey in the Zika Forest of Uganda in 1947[1]. The virus is transmitted among humans through Aedes mosquitoes. About 20% people infected with ZIKV show flu-like symptoms and can recover naturally. However, ZIKV infections has been found to cause a 20-fold increased incidence of severe neurological disorders, including birth defects of central nervous systems (mostly microcephaly)[2, 3] and Guillain-Barré syndrome[4, 5]. An outbreak of ZIKV in Brazil and the other 48 American countries in 2015–16 afflicted more than 2 million people[6] . During mid-2015 through Jan-2016, >4,000 cases of microcephaly with suspected ZIKV involvement were reported, as compared to <200 cases/year previously in Brazil[7, 8]. WHO announced that ZIKV is a “Public Health Emergency of International Concern”. Except for mosquito control, there have been no antiviral drugs or vaccines for the prevention and treatment of ZIKV infection[9, 10].

ZIKV contains a ~10.8 kb RNA genome encoding a polyprotein[11], which is cleaved by the viral NS2B-NS3 protease (ZVpro) as well as host proteases into three structural (C, prM/M, and E) proteins and seven non-structural proteins, including NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. NS3 contains a N-terminal serine protease domain (1–170), but complexation with NS2B is required for the catalytic activity[12]. In the active (or known as “closed”) conformation of ZVpro, NS2B is fully wrapped around NS3 and constitutes part of the active site of the enzyme[11, 13–16]. In the “open” conformation, NS2B is partially associated with NS3 and the enzyme is inactive. Due to its pivotal role in viral replication, ZVpro is a promising drug target for ZIKV infection[9, 12, 17].

Peptide-based covalent inhibitors of ZVpro and other Flavivirus proteases have been reported[12, 18–21], but they did not show significant antiviral activities in cell or animal models, presumably due to low cell permeability or metabolic stability. Non-peptidic inhibitors have also been disclosed, whose activities are relatively weak and interactions with the protease are less characterized[12–14, 22]. In a recent communication[15], we reported that several 2,5,6-trisubstituted pyrazine compounds are novel potent inhibitors of the NS2B-NS3 proteases of Zika and related dengue and West Nile viruses. These compounds inhibited *in vitro* and *in vivo* replication of ZIKV. X-ray crystallographic studies show these inhibitors bind to an allosteric pocket of dengue NS2B-NS3 protease. In this full article, we report the synthesis, comprehensive structure-activity relationships (SAR), and biological activities of 104 pyrazine and related compounds targeting ZVpro, which have led to the discovery of compound **47** with potent anti-ZIKV activity. Moreover, selected ZVpro inhibitors were found to also inhibit NS2B-NS3 proteases of dengue and West Nile virus, showing these compounds are broad-spectrum inhibitors of Flaviviruses.

RESULTS AND DISCUSSION

Chemical synthesis

Compounds **1–18** with the same R5 and R6 substituents were synthesized using general methods shown in Schemes 1. Synthesis of compounds **1–4** was started with a cyclization reaction of 4,4′-dibromo- or diiodo-benzil (**105**) with glycine amide (**106**) in the presence of sodium hydroxide to give 2-hydroxypyrazine **107**. The hydroxy group was alkylated with *tert*-butyloxycarbonyl (Boc)-protected 4-piperidinemethanol using a Mitsunobu reaction and the product was deprotected to give compound **1–4**.

For synthesis of compounds **5–18**, 6-chloro-2-aminopyrazine (**108**) was selectively iodized with N-iodosuccinimide to give 6-chloro-5-iodo-2-aminopyrazine (**109**), whose amino group was converted to a hydroxy by treatment with $NaNO_2$ in H_2SO_4. A Mitsunobu reaction between the hydroxy group and a Boc-protected piperidine- or piperazine-containing alcohol gave compound **110**. Palladium-catalyzed Suzuki reactions on the 5-iodo and 6-chloro groups followed by deprotection produced compounds **5–18**. Synthesis of compounds with different R5 and R6 substituents was also started from compound **108**. Two selective Suzuki reactions were performed to introduce the R5 and R6 substituents, followed by deprotection to produce compound **47** and its analogs. For compounds **33**, **35**, **36** and **37**, a nucleophilic aromatic substitution reaction was used to replace the 6-Cl of the pyrazine ring to generate the corresponding intermediates.

For synthesis of compounds with a 2-amino substituent (Scheme 2), mono-substitution of 1,6-dibromo-pyridine or -pyrazine (**111**) with (*N*-Boc-piperidin-4-yl)methylamine produced compound **112**, which was iodized to give 5-iodo product **113**. The target compounds can then be obtained following the reactions described above.

Scheme 2 also shows the synthesis of compounds **56**, **57**, **58** and **70**. Methyl 3-amino-6-iodopyrazine-2-carboxylate (**114**) was successively subjected to a Sandmeyer reaction to convert its 3-amino group to a -Cl, a nucleophilic substitution reaction on 6-I, and a Suzuki reaction on 3-Cl to give compound **117**. Upon hydrolysis of the methyl ester, the resulting acid was converted to an amide, followed by deprotection to give the target compounds.

The general methods for synthesis of compounds **20**-**24** and **34** are depicted in Scheme 3. The aldehyde group of 4,5-dibromothiophene-2-carbaldehyde (**127**) was reduced and converted to a -Cl to give **128**, which was reacted with (*N*-Boc-piperidin-4-yl)methylamine to produce compound **129**. Compound **130** was obtained using Suzuki coupling reactions, which was then deprotected to give tri-substituted thiophene **20**. Starting from 2-amino-6-chloropyrazine (**108**), compound **21** was synthesized through bromination, nucleophilic substitution, Suzuki coupling, and deprotection. The reaction between 3,5-dibromo-6-chloropyrazin-2-amine (**121**) and chloroacetaldehyde produced the imidazo[1,2-*a*]pyrazine core in compound **124**, from which compounds **22**-**24** were obtained using similar methods as described for compound **21**. The reaction between pyrazine compound **118** with a 6-Cl and potassium vinyltrifluoroborate gave compound **119** with a 6-vinyl group, which was subjected to an amination reaction to give, after removing the Boc groups, compound **34**.

Biochemical assay and initial inhibitor discovery

We applied a biochemical assay for recombinant ZVpro, containing NS2B (47–95) and NS3 (1–170) covalently connected with a flexible Gly_4-Ser-Gly_4 linker. This strategy has been commonly used for Flavivirus protease assay[12, 18, 19]. Benzoyl-norleucine-lysine-lysine-arginine-(7-amino-4-methylcoumarine) was used as the substrate. Upon ZVpro-mediated hydrolysis, there is a significant increase of fluorescence (Ex/Em: 360/460 nm). We screened our proprietary library of ~1,200 compounds synthesized targeting histone modifying enzymes such as lysine specific demethylase 1 (LSD1)[23]. 5,6-Di(4-bromophenyl)-2-(piperidin-4-ylmethoxy)pyrazine (Compound **1**, Table 1) was found to be an inhibitor of ZVpro with an IC_{50} value of 21.7 μM. Structure-activity relationship studies based on compound **1** were performed to find more potent inhibitors.

Structure-activity relationship studies

First, a series of pyrazine compounds with identical R^5 and R^6 substituents were synthesized and their inhibitory activities are shown in Table 1. Replacing the bromo groups at the *para*-position of the phenyl ring in compound **1** with *tert*-butyl groups in compound **7** (IC_{50}: 3.14 μM), thiophene-3-yl groups in **5** (IC_{50}: 1.42 μM), furan-3-yl groups in **6** (IC_{50}: 1.0 μM), and iodo groups in **2** (IC_{50}: 0.52 μM) increases the activity against ZVpro by ~7, 15, 20 and 40-fold, respectively. This suggests increased bulk and/or hydrophobicity are favorable. Interestingly, introduction of more polar hydroxymethyl groups at these positions as found in compound **8** (IC_{50}: 0.52 μM) also resulted in a 40-fold increase of the activity, while masking the hydroxy with an acetyl in compound **11** (IC_{50} >10 μM) or a pivaloyl group in **10** (IC_{50}: 9.8 μM) significantly reduced activity. Similarly, compound **12** (IC_{50}: 0.62 μM) with aminomethyl groups exhibits a comparable activity (to compounds **2** and **8**). An additional *ortho*-methyl group as found in compound **16** (IC_{50}: 2.14 μM) leads to a 3-fold activity reduction, suggesting the substitution is disfavored. While acetylation of the primary amine groups in **12** yielded inactive compound **15** (IC_{50} >10 μM), masking the amine with *N,N*-dimethyl groups as found in compound **18** (IC_{50}: 0.39 μM) increased the inhibitory activity.

Next, the length of R^2 sidechain was evaluated. Generally, a longer R^2 linker leads to significant reduction in activity. Compounds **3** (IC_{50}: 4.65 μM), **17** (IC_{50}: 1.62 μM), **4** (IC_{50} >10 μM), **9** (IC_{50}: 2.1 μM), **13** (IC_{50} >10 μM) and **14** (IC_{50} >10 μM) are less active than their analogs with a piperidin-4-ylmethoxy substituent.

Several analogs of compound **12** with different central aromatic rings were synthesized to evaluate their SARs (Table 2). Switching to a pyridine in compound **19**, thiophene in **20**, 3-aminopyrazine in **21**, and imidazo[1,2-a]pyrazine in compounds **22-24** resulted in considerable (3–30×) activity reduction.

Based on the SARs described above, the pyrazine core with a 2-piperidin-4-yl-methoxy group is favorable for ZVpro inhibition. We next synthesized compounds to optimize the R^5 substituent of compounds **12** and **18**. Compound **25** (IC_{50}: 8.1 μM, Table 3) containing a 4-hydroxyphenyl group at the R5 position exhibits more than 10-fold activity reduction, as compared to **12** (IC_{50}: 0.62 μM). Dimethyl analog **26** is also a weak inhibitor (IC_{50}: 20.5

μM). Acetylation of the 5-substituent (of **12**) is disfavored in **27** (IC_{50}: 30 μM). A pyrindin-4-yl group in compound **28** (IC_{50}: 0.32 μM) increases the inhibitory potency, while its analog **29** (IC_{50}: 1.7 μM) with a longer R2 side chain is less potent. Similar to compound **16**, adding an *ortho*-methoxy group to the 5-substituent of **28** resulted in a significant activity reduction in compound **30** (IC_{50}: 3.5 μM). Compound **31** with a pyrin-3-yl group at the R5 position is a weak inhibitor (IC_{50}: 9.9 μM).

We next wanted to optimize the R^6 substituent in potent compounds **8** and **12** and the results are summarized in Table 4. Surprisingly, adding a *meta*-F group to the phenyl ring for compound **32** (IC_{50} >50 μM) significantly reduced the activity, which might indicate a strict electronic and/or steric tolerance for the 6-phenyl ring. A series of smaller 6-substituents were introduced. Compounds **33** (IC_{50}: 7.3 μM) with a 2-aminoethylamino and **34** (IC_{50} >50 μM) with a 2-morpholinyl-ethyl group are weak inhibitors. Similarly, compounds **35** (IC_{50} >50 μM), **36** (IC_{50} >10 μM), **37** (IC_{50}: 6.6 μM), **38** (IC_{50} : 24.6 μM), **39** (IC_{50}: 5.8 μM), and **40** (IC_{50}: 11.1 μM) containing 5-membered heterocycles are significantly less active than **12**. Compounds **41**-**47** with a terminal aromatic group were evaluated. While compounds **41**-**45** show reduced activities, compound **46** (IC_{50}: 0.71μM) with a pyrazol-4-yl group retains the activity and compound **47** with a furan-3-yl group has a significantly enhanced activity with an IC_{50} value of 200 nM. More variety of the 4-substituent at the 6-phenyl ring were evaluated. As compared to **12**, an acetyl group in compound **48** (IC_{50}: 3.16 μM) and isopropyl in **49** (IC_{50}: 2.02 μM) reduce the inhibitory activity by 3- and 5-fold, while compound **50** with a hydroxy group (IC_{50}: 0.76 μM) shows a comparable activity. Compounds **51**-**55** with a fused bicyclic aromatic ring at the R^6 position were found to give reduced activities with IC_{50} values of 1.1–21 μM. Three aromatic amide 6-substituents in compounds **56**-**58** were found to be disfavored (IC_{50}: 12–17 μM).

With the discovery of compound **47** showing an IC_{50} of 200 nM against ZVpro (as well as potent cellular anti-ZIKV activity described below), it became the focus of the SAR studies. Switching the positions of the R5 and R6 substituents produced compound **59** (Table 5) with a reduced inhibitory activity (IC_{50}: 0.68 μM). Masking the primary amino group of **59** with one and two methyl groups for compounds **60** (IC_{50}: 3.3 μM) and **61** (IC_{50}: 1.8 μM) further reduces the potency. Similarly, mono- and di-methylation of **47** led to activity reduction for compounds **62** (IC_{50}: 0.53 μM) and **63** (IC_{50}: 6.1 μM). Compound **64** and **65** with a longer R2 sidechain are considerably less active than their corresponding analogs **59** and **47**. In addition, analogous compounds **66**-**71** with an -NH-containing R^2 substituent were synthesized. A simple change from -O- in **47** to -NH- in **66** (IC_{50}: 0.40 μM) resulted in a 2-fold activity decrease. Adding a F- to either the 6- (in **67**) or 5-subsituent (in **68**) led to a significant activity reduction. Changing the central pyrazine ring in **66** to a pyridine in **69** (IC_{50}: 0.79 μM) also reduced the potency. Insertion of an amide linker into the R^6 group for compound **70** is disfavored (IC_{50}: 1.1 μM). Compounds **71** and **72** with a thiophene-3-yl terminal group for the R6 were found to have modest activities, suggesting a thiophene is less favored than a furan-3-yl group.

Compounds **73**-**78** (Table 6) were synthesized to find how modifications of the R^2 substituent affects ZVpro inhibition. Changing the piperidine group to a cyclohexyl ring in

73 (IC_{50}: 3.2 μM) or a phenyl ring in **74** (IC_{50}: 3.2 μM) caused >15-fold activity loss. Shortening the R^2 length resulted in a 7-fold reduction of potency in **75** (IC_{50}: 1.6 μM). Changing to linear amines in **76** (IC_{50}: 1.3 μM) and **77** (IC_{50}: 2.1 μM) were also disfavored. Compound **78** (IC_{50}: 240 nM) bearing an additional (racemic) methyl group exhibits a comparable activity to that of compound **47**.

Compounds **79**-**83** (Table 7) were synthesized to fine-tune the terminal amino group of the R^5 substituent of compound **47**. Changing it to an amide group in **79** (IC_{50}: 1.1 μM) considerably reduced the activity by ~5×, while further activity reduction was observed upon addition of an *ortho*-F group for compound **80** (IC_{50}: 2.3 μM). A hydroxyamino group in **81** (IC_{50}: 1.2 μM) is less favored than a primary amine. Adding a methyl group to the R^5 phenyl ring in **82** (IC_{50}: 2.6 μM), or moving the aminomethyl group to the *meta*-position in compound **83** (IC_{50}: 2.9 μM) considerably reduced the activity.

Compounds **84**-**103** (Table 8) were synthesized to optimize the R^6 substituent of compound **47**. The substituent at the *ortho*-position for compounds **85**, **86**, **87**, and **88**, or at the *meta*-position for **89**, **90** and **91** of the phenyl ring dramatically decreased the inhibitory activity, showing a strict steric and/or electronic requirement for the pocket. Next, the furan-3-yl group is optimized. Changing it to an amide in compounds **91**-**93** (IC_{50}: 3.5–13 μM) was disfavored. Switching to saturated tetrahydrofuran-3-yl substituent for compound **94** (IC_{50}: 0.59 μM) resulted in 3-fold activity drop, while moving the tetrahydrofuran-3-yl group to the *meta*-position for **95** further reduced the potency. Moreover, a variety of analogous cyclic groups with different steric, electronic, or hydrogen bond forming properties were synthesized and evaluated, including a pyrrolin-1-yl group in compound **96** (IC_{50}: 2.5 μM), piperidin-1-yl group in **97** (IC_{50} >10 μM), cyclohexyl group in **98** (IC_{50}: 16.2 μM), piperdin-4-yl group in **99** (IC_{50}: 3.1 μM) and **100** (IC_{50}: 2.9 μM), peperazin-1-yl group in **101** (IC_{50}: 0.65 μM), and O-containing groups in compounds **102** (IC_{50}: 1.0 μM), **103** (IC_{50}: 130 nM) and **104** (IC_{50} >10 μM). It is of interest that compound **103** with a flexible tetrahydropyran-3-yl ring exhibited improved inhibitory activity as compared to **47**, while others are less active.

Activity against proteases of dengue and West Nile virus

Dengue and West Nile virus also belong to the Flavivirus family with a high homology to ZIKV, particularly for their NS2B-NS3 proteases. The proteases of the four serotypes of dengue viruses show 49–54% sequence identity and 71–73% similarity to ZVpro, while that of West Nile virus has 66% sequence identity and 78% similarity. 18 compounds with a wide range of inhibitory activities against ZVpro were tested for their activity against the protease of dengue serotype-2 and West Nile virus (DV2pro and WVpro). As shown in Table 9 and Figure 1, these ZVpro inhibitors also inhibit the activity of DV2pro and WVpro, and their activities are correlated with those against ZVpro, showing R^2 values of 0.76 and 0.77, respectively. These results suggest these three Flavivirus proteases exhibit similar susceptibility to this series of compounds. Moreover, compound **47** did not inhibit 5 selected human proteases at 10 μM[15], showing a high selectivity.

The crystal structures of compounds **46**, **47** and **66** in complex with DV2pro have been published in our previous communication[15] Given the high homology between DV2pro and ZVpro, particularly in the active site, the binding of these molecules to Zika protease is expected to be similar, which has been confirmed with our enzyme kinetics studies. Other analogs described above should adopt a similar binding pose in the protein. In addition, it could explain many of the SARs described above. For example, the crystal structures show there are strong hydrogen bond and electrostatic interactions between their -NH_2 group and Asp75, which explains, as compared to **47** (IC_{50} = 0.20 μM), compounds **62** (IC_{50} = 0.53 μM) and **63** (IC_{50} = 6.1 μM) with -NHMe and -$N(Me)_2$ exhibited significantly reduced activities. Moreover, the steric and hydrophobic nature of the R^6 binding pocket may explain many of the observed SARs for compounds in Table 8.

Anti-ZIKV activity

Antiviral activities of selected ZVpro inhibitors were evaluated in human U87 glioma cells and monkey Vero cells[15], in which ZIKV replicates rapidly. ZIKV does not cause cytopathic effects (CPE) in U87 cells[24], but it causes significant CPE and, eventually, cell death and lysis in ~5–7 days in Vero cells lacking interferon-mediated defense[25]. This feature can be conveniently used to detect ZIKV in Vero cells. The passage-3 stock of the FLR strain of ZIKV, which was isolated from the serum of a patient infected in Colombia in 2015[26], was used for the antiviral experiments. 0.01 multiplicity of infection (MOI, the number of infectious viral particles per cell) of ZIKV was added to a monolayer of cells to initiate viral infection. After 1h for virus attachment, cells were washed and incubated with fresh media containing increasing concentrations of a compound for 48h. The viral titer of the supernatant containing newly generated ZIKV was determined using an end-point dilution assay and the anti-ZIKV activity of the compound can be evaluated[15].

First, selected ZVpro inhibitors were tested for their cytotoxicity against U87 and Vero cells, using MTT assay. Compounds in Table 8 did not inhibit proliferation of these cells at 10 μM. These compounds were next evaluated for their anti-ZIKV activity using the method described above. As shown in Table 8, except for compounds **1** and **50**, other compounds inhibited ZIKV replication with EC_{68} (concentration at which the number of infectious ZIKV in the supernatant is reduced by 68% (half-log)) values of 0.3–5 μM. In addition, their anti-ZIKV activities are generally correlated with the inhibitory activities against ZVpro (Table 10), suggesting ZVpro is the cellular target. Compound **50**, a potent inhibitor of ZVpro, did not inhibit ZIKV replication at 10 μM. In addition to its 5-aminomethylphenyl substituent, compound **50** contains a polar 4-hydroxyphenyl (phenol) group at the 6-position, which might significantly reduce its cell permeability.

The most active compound **47** was found to potently inhibit replication of ZIKV strain HN16 and dengue virus (serotype-2, strain K0049) with comparable activities in our previous communication[15]. Compound **47** exhibited strong in vivo antiviral activity in a mouse model of ZIKV infection. Treatment with compound **47** (30 mg/kg) for 3 days inhibited ZIKV viral loads in plasma and brain by 96% and 98% (at 24h) and significantly prolonged survivals of the experimental mice[15].

CONCLUSION

Compound screening found 2,5,6-trisubstituted pyrazine compound **1** is a novel inhibitor of ZVpro. Iterative SAR and medicinal chemistry studies were performed find more potent inhibitors. The initial series of compounds with identical R5 and R6 groups led to the discovery of compound **12** with an IC_{50} of 620 nM. Subsequent scaffold hopping did not yield a better core, suggesting the importance of the central pyrazine ring. Next, optimization of the R6 group of compound **12** gave rise to a potent inhibitor **47** having a furanylphenyl substituent showing an IC_{50} of 200 nM. Further modification based on **47** produced compound **103** with an IC_{50} of 130 nM against ZVpro. Activity optimization for the R5 or R2 group did not yield more potent compounds. ZVpro inhibitors also inhibit activity of homologous proteases of dengue and West Nile virus and their inhibitory activities are well correlated with a R^2 of 0.77, showing these compounds are broad-spectrum inhibitors of Flavivirus proteases. Cell-based assays showed compounds **47** and **103** exhibited the most potent antiviral activity against ZIKV with EC_{68} values of 300–600 nM. Compound **47** also showed strong *in vivo* antiviral activity in a mouse model of ZIKV infection. Compound **47** and related compounds are potent, broadly active inhibitors of Flavivirus proteases and therefore, represent novel pharmacological leads for developing antiviral drugs against Zika, dengue or West Nile virus infections.

Experimental Section

All chemicals for synthesis were purchased from Alfa Aesar (Ward Hill, MA) or Aldrich (Milwaukee, WI). Unless otherwise stated, all solvents and reagents used as received. All reactions were performed using a Teflon-coated magnetic stir bar at the indicated temperature and were conducted under an inert atmosphere when stated. The identity of the synthesized compounds was characterized by ^{1}H and ^{13}C NMR on a Varian (Palo Alto, CA) 400-MR spectrometer and mass spectrometer (Shimadzu LCMS-2020). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). The identity of the potent inhibitors was confirmed with high resolution mass spectra (HRMS) using an Agilent 6550 iFunnel quadrupole-time-of-flight (Q-TOF) mass spectrometer with electrospray ionization (ESI). The purities of the final compounds were determined to be >95% with a Shimadzu Prominence HPLC using a Zorbax C18 (or C8) column (4.6 × 250 mm) monitored by UV at 254 nm.

General Synthetic Procedure for compounds 1–4: Sodium hydroxide solution (12.5 M, 3.2 mL, 40 mmol) was added over 30 min to a refluxing mixture of 4,4’-dibromobenzil (**105**, 7.36 g, 20 mmol), glycine amide hydrogen chloride (**106**, 2.21 g, 20 mmol), and 50 mL methanol. After refluxing for another 30 min, the mixture was treated with HCl (12 N, 2.5 mL), followed by $KHCO_3$ (2 g). The following yellow solid formed was filtered off, washed well with water and recrystallized from ^{t}BuOH. Yellow needles of 5,6-bis(4-bromophenyl)pyrazin-2-ol (**107**, 5.94 g) was obtained after filtration. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), and 7.15 (d, J = 8.4 Hz, 2H).

To a solution of 2-hydroxypyrazine **107** (1.12 g, 2.76 mmol) and *N*-Boc-4-piperidinemethanol (594 mg, 2.76 mmol) in anhydrous THF (27 mL) was added triphenylphosphine (1.16 g, 4.42 mmol) and DIAD (894 mg, 4.42 mmol). The reaction mixture was stirred at room temperture for 17 h. The solution was then concentrated and purified to give the product *tert*-butyl 4-(((5,6-bis(4-bromophenyl)pyrazin-2-yl)oxy)methyl)piperidine-1-carboxylate **1** precursor (1.5 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.47–7.41 (m, 4H), 7.30–7.24 (m, 4H), 4.26 (d, *J* = 6.8 Hz, 2H), 4.15 (br, 2H), 2.75 (t, *J* = 12.8 Hz, 2H), 2.03 (br, 1H), 1.81 (d, *J* = 13.2 Hz, 2H), 1.46 (s, 9H), and 1.35 – 1.25 (m, 2H).

To a solution of the above **1** precursor (1.5 g, 2.49 mmol) in CH_2Cl_2 (25 mL) was added dropwise hydrogen chloride (4 N in *p*-dioxane, 12.5 mL) at 0 °C. The solution was stirred overnight and precipitated solid was filtered off to give 1.1 g compound **1** as pale yellow powder. **2,3-bis(4-Bromophenyl)-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride (1)**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (br, 2H), 8.33 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.26 (d, *J* = 5.6 Hz, 2H), 3.26 (d, *J* = 12.0 Hz, 2H), 2.88 (t, *J* = 12.4 Hz, 2H), 2.11 (br, 1H), 1.90 (d, *J* = 12.8 Hz, 2H), 1.57–1.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 147.1, 143.4, 137.8, 137.4, 133.3, 132. 1, 131.9, 131.79, 131.70, 122.9, 122.0, 70.1, 43.1, 33.3, 25.5; MS (ESI) $[M+H]^+$ 504.2.

2,3-bis(4-Iodophenyl)-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride (2) was prepared from 4,4′-Iodobenzil, following the same procedure as compound **1**, as a hydrochloric acid salt (pale yellow powder). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.59 (s, 1H), 8.33 (s, 1H), 7.72–7.60 (m, 4H), 7.16–7.08 (m, 4H), 4.5 (s, 2H), 3.26 (s, 2H), 2.85 (brs, 2H), 2.10 (s, 1H), 1.87 (d, *J* = 10.4 Hz, 2H), 1.46 (s, 1H); MS (ESI) $[M+H]^+$ 598.0.

2,3-bis(4-iodophenyl)-5-(2-(piperidin-4-yl)ethoxy)pyrazine hydrochloride (3) was prepared from 4,4'-Iodobenzil, following the same procedure as compound **1**, as a hydrochloric acid salt (pale yellow powder). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.70 (s, 1H), 8.35 (s, 1H), 7.72 (dd, *J* = 15.6, 7.2 Hz, 4H), 7.16 (dd, *J* = 28.0, 7.2 Hz, 4H), 4.44 (s, 2H), 3.22 (d, *J* = 12.0 Hz, 2H), 2.82 (dd, *J* = 22.8, 11.6 Hz, 2H), 1.86 (d, *J* = 13.2 Hz, 2H), 1.75 (s, 3H), 1.40 (dd, *J* = 19.2, 10.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8, 146.8, 142.9, 137.8, 137.7, 137.4, 137.2, 137.1, 132.9, 131.6, 131.5, 130.8, 63.8, 43.0, 34.3, 30.2, 28.2; MS (ESI) $[M+H]^+$ 612.0

2,3-bis(4-Iodophenyl)-5-(3-(piperidin-4-yl)propoxy)pyrazine hydrochloride (4) was prepared from 4,4'-Iodobenzil, following the same procedure as compound 1, as a hydrochloric acid salt (pale yellow powder).1H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.67 (s, 1H), 8.36 (s, 1H), 7.72 (dd, J = 15.3, 8.2 Hz, 4H), 7.16 (dd, J = 26.0, 8.1 Hz, 4H), 4.38 (s, 2H), 3.21 (d, J = 10.8 Hz, 2H), 2.80 (d, J = 9.9 Hz, 2H), 1.79 (s, 4H), 1.56 (s, 1H), 1.41 – 1.27 (m, 4H); 13C NMR (100 MHz, DMSO-d_6) δ 157.9, 146.8, 142.9, 137.7, 137.4, 137.2, 137.1, 133.0, 131.6, 131.5, 95.8, 94.8, 66.4, 43.1, 32.6, 31.8, 28.3, 25.2; MS (ESI) [M +H]+ 626.0.

General Synthetic Procedure for compounds (5)-(18): To a solution of 2-amino-6-chloropyrazine (**108**, 8 g, 62 mmol) in DMSO (50 mL) was added N-iodosuccinimide (NIS, 15.3 g, 68 mmol) in portions. After stirring at room temperature for 72 h, the reaction was quenched with sodium thiosulfate aqueous solution (50 mL). The mixture was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 2:1) to afford 6-chloro-5-iodopyrazin-2-amine (**109**, 12.7 g, 80%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), and 4.73 (br, 2H).

To a suspension of **109** (3.78 g, 14.9 mmol) in sulfuric acid (18 mL) at 0 °C was added sodium nitrite (1.09 g, 15.8 mmol) in 3 portions. The resulting reaction mixture was stirred at 0 °C for 1 h. The mixture was then poured into a beaker with ice while stirring. The resulting precipitate was collected by filtration, washed with water and dried under vacuum to afford 6-chloro-5-iodopyrazin-2-ol (3.6 g) as a yellowish solid, which is used directly for the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H). Crude product 6-chloro-5-iodopyrazin-2-ol (3.6 g, 14 mmol), N-Boc-4-piperidinemethanol (3.1 g, 14.5 mmol), and triphenylphosphine (5.9 g, 22.5 mmol) were dissolved in THF (40 mL) and cooled to 0 °C. Diisopropyl azodicarboxylate (4.55 g, 22.5 mmol) was added dropwise under nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 12 h. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 10:1 to 5:1) to afford compound **110** (5.2 g, 77% for 2 steps) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 4.16 (d, J = 6.4 Hz, 4H), 2.73 (t, J = 12.0 Hz, 2H), 1.96 (s, 1H), 1.77 (d, J = 12.8 Hz, 2H), 1.46 (s, 9H), and 1.33 – 1.19 (m, 2H).

Compound **110** (1.94 mmol), arylboronic acid or aryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.51 mmol), tetrakis(triphenylphosphine)palladium (110 mg, 0.095 mmol), and sodium carbonate (610 mg, 5.75 mmol) in *p*-dioxane/H_2O (15/3 mL) were placed in a sealed tube. The mixture was degassed and heated to 110 °C for 24 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 1:2) to afford the R^5 and R^6 identically substituted product. To a solution of this intermediate (1.5 mmol) in DCM (5 mL) was added dropwise HCl (1.2 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give the final product hydrochloric salt.

For the synthesis precursors of **10** and **11** only: To a solution of the above R^5 and R^6 identically substituted product (R = 4-($OHCH_2$) -Ph, 0.2 mmol) and N-diisopropylethylamine (87 μL, 0.5 mmol) in anhydrous dichloromethane (3 mL) was added Acetyl chloride (18 μL, 0.25 mmol) or Pivaloyl chloride (31 μL, 0.25 mmol) at °C, respectively. The mixture was stirred for 2 h before it was quenched with saturated $NaHCO_3$. The mixture was extracted with ethyl acetate (3 × 80 mL) and the combined

organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 1.5:1 to 1:1) to afford precursors of **10** (112 mg, 95%) or **11** (124 mg, 92%) as colorless oil. For precursor of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.41 (dd, *J* = 25.6, 7.4 Hz, 4H), 7.29 – 7.18 (m, 4H), 5.09 (s, 4H), 4.27 (d, *J* = 6.0 Hz, 2H), 4.15 (s, 2H), 2.82 – 2.65 (m, 2H), 2.15 – 1.91 (m, 7H), 1.82 (d, *J* = 11.7 Hz, 2H), 1.51 – 1.34 (m, 9H), 1.29 (dd, *J* = 25.3, 13.6 Hz, 2H); For precursor of **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.44 (d, *J* = 6.9 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.26 (s, 4H), 5.10 (s, 4H), 4.29 (d, *J* = 6.0 Hz, 2H), 4.16 (s, 2H), 2.76 (t, *J* = 14.2 Hz, 2H), 2.01 (s, 1H), 1.83 (d, *J* = 13.0 Hz, 2H), 1.55 (s, 2H), 1.47 (s, 9H), 1.28–1.18 (m, 18H).

5-(Piperidin-4-ylmethoxy)-2,3-bis(4-(thiophen-3-yl)phenyl)pyrazine hydrochloride (5) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 1H), 8.79 (s, 1H), 8.34 (s, 1H), 7.94 – 7.85 (m, 2H), 7.68 (t, *J* = 7.7 Hz, 4H), 7.60 (dd, *J* = 5.5, 2.4 Hz, 2H), 7.55 (dd, *J* = 3.0, 1.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.29 (d, *J* = 6.3 Hz, 2H), 3.27 (d, *J* = 11.5 Hz, 2H), 2.88 (dd, *J* = 22.6, 11.5 Hz, 2H), 2.13 (s, 1H), 1.91 (d, *J* = 13.2 Hz, 2H), 1.54 (dd, *J* = 22.8, 11.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.6, 147.3, 143.8, 140.7, 140.6, 137.1, 136.7, 135.2, 134.5, 132.3, 130.2, 129.9, 127.3, 127.2, 126.1, 126.1, 125.8, 125.8, 121.7, 121.4, 69.5, 42.7, 33.0, 25.2; MS (ESI) $[M+H]^+$ 510.2.

2,3-bis(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride (6) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 8.19 (d, *J* = 6.0 Hz, 2H), 7.75 – 7.67 (m, 2H), 7.61 – 7.49 (m, 4H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.95 (s, 2H), 4.30 (d, *J* = 6.0 Hz, 2H), 3.30 (d, *J* = 11.6 Hz, 2H), 2.91 (t, *J* = 12.4 Hz, 2H), 2.14 (s, 1H), 1.94 (d, *J* = 13.6 Hz, 2H), 1.51 (dd, *J* = 24.4, 12.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 158.0, 147.7, 144.9, 144.8, 144.2, 140.3, 140.1, 137.3, 136.9, 132.6, 131.8, 130.5, 130.2, 125.7, 109.0; MS (ESI) $[M+H]^+$ 429.2.

2,3-bis(4-(tert-Butyl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride (7) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 – 8.27 (br, 4H), 8.30 (s, 1H), 7.38 – 7.26 (m, 8H), 4.27 (d, *J* = 6.2 Hz, 2H), 3.33 – 3.24 (m, 2H), 2.90 (t, *J* = 11.8 Hz, 2H), 2.13 (br, 1H), 1.93 (d, *J* = 13.0 Hz, 2H), 1.58 – 1.48 (m, 2H), 1.26 (s, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) 157.4, 151.2, 150.3, 147.4, 144.0, 135.7, 135.4, 131.9, 129.2, 129.0, 125.0, 124.9, 69.4, 42.7, 34.4, 34.3, 33.0, 31.1, 31.0, 25.2; HRMS (ESI^+) calcd for $C_{30}H_{40}N_3O$ $[M+H]^+$ 458.3166, found 458.3179.

((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))dimethanol hydrochloride (8) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.65 (s, 1H), 8.33 (s, 1H), 7.58 (d, *J* = 19.6 Hz, 2H), 7.36 (s, 2H), 7.26 (br, 6H), 4.49 (br, 4H), 3.56 (s, 2H), 3.28 (s, 2H), 2.89 (s, 2H), 2.14 (s, 1H), 1.92 (s, 2H), 1.52 (s, 2H); δ 158.0, 148.0, 144.6, 143.5, 142.6, 137.3, 137.0, 132.4, 132.0, 129.8, 129.5, 126.6, 69.8, 63.0, 62.9, 43.2, 33.4, 25.6; MS (ESI) $[M+H]^+$ 406.2

((5-(2-(Piperidin-4-yl)ethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))dimethanol hydrochloride (9) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.67 (s, 1H), 8.36 (s, 1H), 7.72 (dd, J = 15.3, 8.2 Hz, 4H), 7.16 (dd, J = 26.0, 8.1 Hz, 4H), 4.38 (s, 2H), 3.21 (d, J = 10.8 Hz, 2H), 2.80 (d, J = 9.9 Hz, 2H), 1.79 (s, 4H), 1.56 (s, 1H), 1.41 – 1.27 (m, 4H); 1H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.74 (s, 1H), 8.31 (s, 1H), 7.36 (d, J = 7.7 Hz, 2H), 7.31 – 7.21 (m, 6H), 4.49 (s, 4H), 4.45 (s, 2H), 3.21 (d, J = 11.4 Hz, 2H), 2.82 (dd, J = 22.4, 11.0 Hz, 2H), 1.87 (d, J = 13.8 Hz, 2H), 1.76 (s, 3H), 1.41 (dd, J = 22.8, 12.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.5, 147.6, 144.0, 143.0, 142.2, 137.1, 136.9, 136.6, 132.1, 129.3, 129.1, 126.1, 63.6, 62.5, 43.0, 34.4, 30.2, 28.2; MS (ESI) $[M+H]^+$ 420.2

((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))bis(methylene) bis(2,2-dimethylpropanoate) hydrochloride (10) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.69 (s, 1H), 8.36 (s, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.36 – 7.19 (m, 6H), 5.08 (s, 4H), 4.30 (d, J = 6.0 Hz, 2H), 3.27 (s, 2H), 2.90 (d, J = 11.2 Hz, 2H), 2.14 (s, 1H), 1.93 (d, J = 14.4 Hz, 2H), 1.61 – 1.45 (m, 2H), 1.16 (s, 18H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.6, 158.1, 147.8, 144.3, 138.3, 138.0, 137.4, 136.6, 132.9, 130.1, 129.9, 127.6, 127.6, 69.9, 65.4, 43.1, 38.7, 33.4, 27.3, 25.6; MS (ESI) $[M+H]^+$ 574.3.

N,N'-(((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))bis(methylene))diacetamide hydrochloride (11) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J = 8.4 Hz, 1H), 8.78 (d, J = 9.6 Hz, 1H), 8.36 (s, 1H), 7.42 (d, J = 7.6 Hz, 2H), 7.37 – 7.27 (m, 6H), 5.07 (d, J = 4.4 Hz, 4H), 4.30 (d, J = 6.0 Hz, 2H), 3.29 (d, J = 12.4 Hz, 2H), 2.90 (q, J = 11.6 Hz, 2H), 2.15 (s, 1H), 2.07 (s, 6H), 1.93 (d, J = 14.0 Hz, 2H), 1.54 (q, J = 11.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 157.6, 147.3, 143.8, 138.0, 137.7, 136.7, 135.8, 132.5, 129.6, 129.4, 127.7, 69.5, 65.02, 64.97, 42.6, 32.9, 25.1, 20.7; MS (ESI) $[M+H]^+$ 488.3.

((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (12) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.02 (s, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.11 (s, 6H), 4.10 (s, 2H), 3.89 (s, 4H), 3.22 (d, J = 10.0 Hz, 2H), 2.79 (t, J = 10.4 Hz, 2H), 1.99 (s, 1H), 1.84 (d, J = 11.6 Hz, 2H), 1.41 – 1.32 (m, 2H); MS (ESI) $[M+H]^+$ 404.2.

((5-(2-(Piperidin-4-yl)ethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (13) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.28 (s, 1H), 7.51 – 7.43 (m, 2H), 7.44 – 7.30 (m, 6H), 4.57 – 4.44 (m, 2H), 4.20 (s, 4H), 3.44 (d, J = 12.8 Hz, 2H), 3.00 (t, J = 12.6 Hz, 2H), 2.05 (d, J = 14.3 Hz, 2H), 1.93 – 1.78 (m, 3H), 1.50 (dd, J = 24.7, 13.4 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.8, 149.2, 143.4, 138.0, 137.8, 133.4, 132.8, 131.7, 130.4, 130.3, 128.7, 128.6, 64.9, 43.9, 42.6, 34.0, 30.2, 28.2; MS (ESI) $[M+H]^+$ 418.3.

((5-(2-(Piperazin-1-yl)ethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (14) was prepared following the same procedure as a hydrochloric acid salt.

^{1}H NMR (400 MHz, D_2O) δ 8.39 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.43 (dd, *J* = 7.8, 5.0 Hz, 6H), 4.90 (d, *J* = 4.7 Hz, 2H), 4.21 (s, 4H), 3.88 – 3.80 (m, 6H), 3.67 (d, *J* = 4.6 Hz, 4H); ^{13}C NMR (100 MHz, D_2O) δ 157.5, 148.8, 144.8, 138.2, 138.1, 133.4, 132.8, 132.5, 130.4, 130.3, 128.7, 128.7, 60.1, 56.0, 48.8, 42.6, 42.6, 40.6; MS (ESI) $[M+H]^+$ 419.3.

N,N'-(((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))bis(methylene))diacetamide hydrochloride (15) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (d, *J* = 10.1 Hz, 1H), 8.82 (d, *J* = 10.0 Hz, 1H), 8.45 (dt, *J* = 11.2, 5.7 Hz, 2H), 8.32 (d, *J* = 1.4 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 9.0 Hz, 4H), 4.28 (d, *J* = 6.3 Hz, 2H), 4.25 (d, *J* = 5.7 Hz, 4H), 3.28 (d, *J* = 12.1 Hz, 2H), 2.89 (q, *J* = 11.7 Hz, 2H), 2.14 (s, 1H), 1.92 (d, *J* = 12.7 Hz, 2H), 1.88 (s, 6H), 1.54 (dd, *J* = 23.1, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 169.3, 157.5, 147.4, 143.9, 140.2, 139.3, 137.0, 136.7, 132.2, 129.5, 129.3, 126.9, 126.9, 69.4, 54.9, 42.6, 41.7, 41.7, 33.0, 25.2, 22.6; MS (ESI) $[M+H]^+$ 488.3

((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(3-methyl-4,1-phenylene))dimethanamine hydrochloride (16) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.26 (s, 1H), 7.17 (d, *J* = 9.6 Hz, 2H), 7.02 (s, 4H), 4.20 (d, *J* = 5.6 Hz, 2H), 3.99 (s, 2H), 3.39 (d, *J* = 12.4 Hz, 2H), 2.96 (t, *J* = 11.2 Hz, 2H), 2.14 (br, 1H), 2.09 (br, 3H), 2.00 (br, 3H), 1.52 (dd, *J* = 23.6, 11.6 Hz, 2H); MS (ESI) $[M+H]^+$ 432.3.

N,N'-(((5-(2-(Piperidin-4-yl)ethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))bis(methylene))bis(Hydroxylamine) hydrochloride (17) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.16 (s, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 6H), 4.39 (s, 2H), 4.31 (s, 4H), 3.29 (d, *J* = 12.3 Hz, 2H), 2.85 (t, *J* = 12.2 Hz, 2H), 1.91 (d, *J* = 13.5 Hz, 2H), 1.82 – 1.71 (m, 3H), 1.41 – 1.31 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.8, 148.8, 143.8, 139.0, 138.9, 132.3, 130.52, 130.48, 130.3, 130.2, 129.2, 128.5, 64.8, 54.4, 43.9, 34.0, 30.2, 28.2; MS (ESI) $[M+H]^+$ 450.2.

1,1'-((5-(Piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))bis(N,N-dimethylmethanamine) hydrochloride (18) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.20 (s, 1H), 7.38 (d, *J* = 7.2 Hz, 2H), 7.30 (s, 6H), 4.26 (d, *J* = 4.0 Hz, 2H), 4.18 (s, 4H), 3.37 (d, *J* = 11.6 Hz, 2H), 2.94 (t, *J* = 12.4 Hz, 2H), 2.71 (s, 12H), 2.15 (s, 1H), 2.00 (d, *J* = 12.8 Hz, 2H), 1.51 (dd, *J* = 26.4, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 147.4, 143.7, 139.2, 138.8, 132.9, 131.0, 130.8, 130.8, 130.2, 129.9, 129.8, 69.6, 58.9, 58.8, 42.6, 41.5, 41.4, 32.9, 25.1; MS (ESI) $[M+H]^+$ 406.3.

General Synthetic Procedure for compounds 25–32, 38–55 and 72–104:

Compound **110** (1.2 g, 2.66 mmol), 4-[(tert-Butoxycarbonylamino)methyl]phenylboronic acid pinacol ester (2.66 mmol), tetrakis(triphenylphosphine)palladium (154 mg, 0.13 mmol), and sodium carbonate (564 mg, 5.32 mmol) in *p*-dioxane/H_2O (15/3 mL) were placed in a sealed tube. The mixture was

degassed and heated to 80 °C for 12 h. The reaction was cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 1:1) to afford the corresponding R^5 substituted product. For intermediate of **47**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.04 (s, 1H), 4.34 (d, *J* = 5.2 Hz, 2H), 4.21 (d, *J* = 6.4 Hz, 2H), 4.15 (s, 2H), 2.73 (t, *J* = 11.2 Hz, 2H), 1.99 – 1.92 (m, 1H), 1.79 (d, *J* = 12.4 Hz, 2H), 1.44 (s, 18H), and 1.30 – 1.20 (m, 2H).

The above R^5 substituted compound (1.94 mmol), arylboronic acid or aryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.51 mmol), tetrakis(triphenylphosphine)palladium (110 mg, 0.095 mmol), and sodium carbonate (610 mg, 5.75 mmol) in *p*-dioxane/H_2O (15/3 mL) were placed in a sealed tube. The mixture was degassed and heated to 110 °C for 24 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 1:2) to afford the corresponding R^6 substituted product. For precursor of **47**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.75 (s, 1H), 7.50 – 7.34 (m, 7H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.70 (s, 1H), 4.85 (s, 1H), 4.36 – 4.24 (m, 4H), 4.20 – 4.07 (m, 2H), 2.76 (t, *J* = 12.4 Hz, 2H), 2.03 – 1.97 (m, 1H), 1.84 (d, *J* = 12.4 Hz, 3H), 1.54 – 1.40 (m, 18H), and 1.37 – 1.27 (m, 2H).

To a solution of R^6 substituted compound (1.5 mmol) in DCM (5 mL) was added dropwise HCl (1.2 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give the final product hydrochloric salt.

4-(3-(4-(Aminomethyl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenol hydrochloride (25) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (bs, 1H), 8.76 (bs, 1H), 8.43 (bs, 3H), 8.28 (s, 1H), 7.42 (s, 4H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.8 Hz, 2H), 4.25 (d, *J* = 6 Hz, 2H), 3.99 (d, *J* = 6 Hz, 2H), 3.26 (d, *J* = 13.2 Hz, 2H), 2.87 (dd, *J* = 12.4 Hz, 24 Hz, 2H), 2.11 (bs, 1H), 1.89 (d, *J* = 12.4 Hz, 2H), 1.51 (dd, *J* = 12 Hz, 22.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d6) δ 162.8, 158.2, 147.7, 144.1, 139.3, 138.9, 133.0, 132.2, 130.2, 130.2, 130.10, 130.06, 70.0, 51.1, 43.0, 33.4, 25.6; MS (ESI) $[M+H]^+$ 391.1.

4-(3-(4-((Dimethylamino)methyl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenol hydrochloride (26) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.23 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.3 Hz, 2H), 4.31 (s, 4H), 3.51 (d, *J* = 12.6 Hz, 2H), 3.06 (t, *J* = 12.1 Hz, 2H), 2.23 (s, 1H), 2.10 (d, *J* = 13.8 Hz, 2H), 1.63 (dd, *J* = 23.6, 11.5 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.3, 155.9, 148.3, 144.3, 139.3, 131.5, 131.2, 130.6, 130.4, 129.7, 129.1, 115.0, 70.2, 60.5, 43.6, 42.0, 32.9, 25.0; MS (ESI) $[M+H]^+$ 419.2.

N-(4-(3-(4-(Aminomethyl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)benzyl)acetamide hydrochloride (27) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.15 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 4.23 (s, 4H), 4.06 (s, 2H), 3.38 (d, *J* = 12.8 Hz, 2H), 2.94 (t, *J* = 12.8 Hz, 2H), 2.13 (s, 1H), 1.99 (d, *J* = 13.6 Hz, 2H), 1.92 (s, 3H), 1.51 (dd, *J* = 24.0, 11.5 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 174.0, 158.6, 148.7, 144.4, 138.1, 136.4, 133.2, 131.9, 130.3, 129.8, 128.6, 126.9, 110.0, 70.2, 43.6, 42.65, 42.63, 32.9, 25.0, 21.8; MS (ESI) $[M+H]^+$ 446.2.

(4-(6-(Piperidin-4-ylmethoxy)-3-(pyridin-4-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (28) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.59 (d, *J* = 5.6 Hz, 2H), 8.40 (s, 1H), 7.81 (d, *J* = 6.0 Hz, 2H), 7.51 (dd, *J* = 21.2, 8.0 Hz, 4H), 4.42 (d, *J* = 6.0 Hz, 2H), 4.24 (s, 2H), 3.53 (d, *J* = 12.4 Hz, 2H), 3.09 (t, *J* = 12.4 Hz, 2H), 2.29 (s, 1H), 2.14 (d, *J* = 13.2 Hz, 2H), 1.66 (dd, *J* = 24.0, 11.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 158.3, 152.7, 149.3, 142.3, 138.7, 136.1, 135.1, 133.3, 131.7, 129.6, 128.8, 126.2, 69.6, 42.2, 41.4, 32.4, 24.6; MS (ESI) $[M+H]^+$ 476.2.

(4-(6-(2-(Piperidin-4-yl)ethoxy)-3-(pyridin-4-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (29) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.66 (s, 2H), 8.42 (s, 1H), 8.01 (s, 2H), 7.57 (br, 2H), 7.52 (br, 2H), 4.61 (s, 2H), 4.26 (s, 2H), 3.45 (d, *J* = 12.4 Hz, 2H), 3.01 (t, *J* = 12.4 Hz, 2H), 2.07 (d, *J* = 13.6 Hz, 2H), 1.92 (br, 3H), 1.51 (dd, *J* = 23.2, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 159.9, 155.7, 151.0, 140.9, 138.3, 136.8, 134.5, 134.2, 130.6, 129.2, 127.3, 65.2, 43.9, 42.6, 33.9, 30.2, 28.2 MS (ESI) $[M+H]^+$ 390.2.

(3-Methoxy-4-(6-(piperidin-4-ylmethoxy)-3-(pyridin-4-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (30) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.18 (bs, 1H), 8.88 (bs, 1H), 8.73 (bs, 2H), 8.65 (bs, 3H), 8.46 (s, 1H), 7.70 (bs, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.21 (s, 1H), 4.28 (d, *J* = 5.6 Hz, 2H), 4.04 (d, *J* = 4.4 Hz, 2H), 3.26 (s, 3H), 2.87 (d, *J* = 11.2 Hz, 2H), 2.12 (bs, 1H), 1.89 (d, *J* = 13.2 Hz, 2H), 1.52 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 159.7, 155.6, 147.5, 143.6, 141.6, 138.2, 133.8, 133.6, 126.1, 124.8, 122.2, 113.0, 70.4, 55.2, 43.0, 33.3, 25.5; MS (ESI) $[M+H]^+$ 406.2.

N,N-Dimethyl-1-(4-(6-(piperidin-4-ylmethoxy)-3-(pyridin-3-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (31) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.70 (s, 1H), 8.61 (d, *J* = 5.4 Hz, 1H), 8.38 (d, *J* = 7.5 Hz, 1H), 8.31 (s, 1H), 7.85 (t, *J* = 6.8 Hz, 1H), 7.44 (dd, *J* = 19.5, 7.6 Hz, 4H), 4.31 (d, *J* = 6.0 Hz, 2H), 4.25 (s, 2H), 3.39 (d, *J* = 11.1 Hz, 2H), 2.96 (t, *J* = 12.8 Hz, 2H), 2.17 (s, 1H), 2.01 (d, *J* = 13.9 Hz, 2H), 1.53 (q, *J* = 12.7 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 159.7, 149.7, 147.1, 141.4, 140.2, 137.8, 137.7, 137.4, 134.2, 131.3, 130.8, 130.7, 126.9, 70.4, 60.5, 43.6, 42.2, 42.0, 32.8, 24.9; MS (ESI) $[M+H]^+$ 404.2.

(4-(3-(4-(Aminomethyl)-3-fluorophenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (32) was prepared following the same procedure as

a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.32 (s, 1H), 7.40 (d, *J* = 14.0 Hz, 5H), 7.28 (t, *J* = 8.4 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.25 (s, 2H), 4.19 (s, 2H), 3.51 (d, *J* = 12.4 Hz, 2H), 3.07 (t, *J* = 12.8 Hz, 2H), 2.27 (s, 1H), 2.12 (d, *J* = 14.0 Hz, 2H), 1.64 (dd, *J* = 23.6, 11.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 161.7, 159.2, 158.8, 147.6, 143.7, 140.9, 140.8, 137.7, 132.9, 132.6, 131.1, 131.0, 130.2, 128.8, 126.2, 126.2, 120.4, 120.2, 117.1, 116.8, 110.0, 70.3, 43.6, 42.6, 36.9, 36.8, 32.8, 25.0; MS (ESI) $[M+H]^+$ 422.2.

(4-(3-(1-Methyl-1H-pyrazol-4-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (38) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.28 (s, 1H), 9.06 (d, *J* = 9.6 Hz, 1H), 8.67 (s, 3H), 8.13 (s, 1H), 7.74 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.06 (s, 1H), 4.29 (d, *J* = 6.0 Hz, 2H), 4.09 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 3H), 3.27 (d, *J* = 11.6 Hz, 2H), 2.89 (dd, *J* = 22.4, 11.2 Hz, 2H), 2.13 (s, 1H), 1.92 (d, *J* = 13.2 Hz, 2H), 1.58 (dd, *J* = 23.6, 11.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 158.2, 142.9, 141.7, 139.4, 138.8, 134.7, 131.9, 130.8, 129.65, 129.60, 120.0, 69.7, 43.0, 42.3, 33.4, 25.6; MS (ESI) $[M+H]^+$ 379.2.

(4-(5-(Piperidin-4-ylmethoxy)-3-(1H-pyrazol-4-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (39) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.06 (s, 1H), 7.54 (d, *J* = 5.3 Hz, 4H), 7.43 (d, *J* = 7.6 Hz, 2H), 4.29 (d, *J* = 11.6 Hz, 4H), 3.51 (d, *J* = 12.4 Hz, 2H), 3.07 (t, *J* = 12.6 Hz, 2H), 2.21 (s, 1H), 2.10 (d, *J* = 14.0 Hz, 2H), 1.62 (q, *J* = 11.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.6, 142.3, 141.9, 137.6, 134.4, 133.6, 129.7, 129.7, 129.3, 119.2, 70.0, 43.6, 42.7, 32.8, 25.0; MS (ESI) $[M+H]^+$ 365.2.

(4-(3-(3,5-Dimethylisoxazol-4-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (**40)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.37 (s, 1H), 7.48 (s, 4H), 4.34 (d, *J* = 5.6 Hz, 2H), 4.21 (s, 2H), 3.52 (d, *J* = 12.4 Hz, 2H), 3.08 (t, *J* = 12.8 Hz, 2H), 2.27 (s, 1H), 2.13 (d, *J* = 14.0 Hz, 2H), 2.03 (s, 3H), 1.99 (s, 3H), 1.69 – 1.59 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 169.2, 160.4, 158.8, 145.1, 139.6, 137.5, 133.9, 132.9, 129.6, 129.0, 113.9, 70.3, 43.6, 42.6, 32.8, 24.9, 10.6, 9.5; MS (ESI) $[M+H]^+$ 394.2

(4-(3-(4-(3,5-Dimethylisoxazol-4-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (41) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.12 (s, 1H), 8.81 (s, 1H), 8.47 (s, 3H), 8.39 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.32 (m, 6H), 4.31 (d, *J* = 6.0 Hz, 2H), 4.02 (d, *J* = 5.2 Hz, 2H), 3.29 (d, *J* = 11.2 Hz, 2H), 2.91 (dd, *J* = 22.8, 12.4 Hz, 2H), 2.41 (s, 3H), 2.23 (s, 3H), 2.16 (s, 1H), 1.94 (d, *J* = 13.6 Hz, 2H), 1.56 (dd, *J* = 24.4, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 165.4, 158.0, 157.7, 147.3, 143.6, 138.4, 137.0, 133.8, 132.6, 130.3, 130.0, 129.5, 128.7, 128.6, 115.3, 69.6, 42.6, 41.8, 32.9, 25.2, 11.6, 10.6; MS (ESI) $[M+H]^+$ 470.2.

(4-(3-(4-(1H-1,2,3-Triazol-1-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (42) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.38 (s, 1H), 8.19 (s, 1H), 7.93 (s, 1H),

7.59 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 21.2, 8.0 Hz, 4H), 4.24 (d, *J* = 6.0 Hz, 2H), 4.16 (s, 2H), 3.50 (d, *J* = 12.4 Hz, 2H), 3.05 (t, *J* = 12.4 Hz, 2H), 2.16 (s, 1H), 2.06 (d, *J* = 13.6 Hz, 2H), 1.60 (dd, *J* = 24.2, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.5, 147.7, 143.5, 137.9, 136.3, 134.5, 132.8, 132.0, 131.2, 130.1, 128.8, 123.8, 120.3, 116.0, 70.1, 43.6, 42.6, 32.9, 25.0; MS (ESI) $[M+H]^+$ 442.2.

(1-(4-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)-1H-1,2,3-triazol-4-yl)methanol hydrochloride (43) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.18 (s, 1H), 8.87 (s, 1H), 8.73 (s, 1H), 8.49 (br, 3H), 8.42 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.43 (dd, *J* = 20.0, 8.0 Hz, 4H), 4.61 (s, 2H), 4.32 (d, *J* = 5.6 Hz, 2H), 4.04 (s, 2H), 3.29 (d, *J* = 10.4 Hz, 2H), 2.90 (dd, *J* = 22.4, 10.8 Hz, 2H), 1.94 (d, *J* = 13.2 Hz, 2H), 1.63 – 1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 157.8, 149.3, 146.7, 143.8, 138.2, 138.0, 136.6, 133.8, 132.9, 131.1, 129.6, 128.8, 120.9, 119.6, 69.7, 54.9, 42.6, 41.8, 32.9, 25.2; MS (ESI) $[M+H]^+$ 472.2.

(4-(3-(4-Phenoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (44) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.11 (s, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 7.13 (dd, *J* = 15.2, 7.6 Hz, 4H), 7.03 – 6.93 (m, 3H), 6.64 (d, *J* = 7.6 Hz, 2H), 6.46 (d, *J* = 7.6 Hz, 2H), 4.01 (s, 4H), 3.42 (d, *J* = 12.0 Hz, 2H), 2.93 (t, *J* = 12.6 Hz, 2H), 1.98 (s, 1H), 1.87 (d, *J* = 13.6 Hz, 2H), 1.49 (dd, *J* = 24.8, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.2, 157.3, 155.5, 148.1, 142.9, 138.3, 132.5, 131.9, 131.3, 129.9, 129.4, 128.9, 127.0, 124.1, 118.9, 117.4, 69.7, 43.4, 42.5, 32.8, 24.9; MS (ESI) $[M+H]^+$ 46.2.7

(4-(5-(Piperidin-4-ylmethoxy)-3-(4-(pyridin-4-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (45) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.77 (d, *J* = 6.0 Hz, 2H), 8.29 (d, *J* = 7.2 Hz, 3H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.41 (dd, *J* = 14.8, 7.6 Hz, 4H), 4.38 (d, *J* = 5.6 Hz, 2H), 4.18 (s, 2H), 3.51 (d, *J* = 12.0 Hz, 2H), 3.07 (t, *J* = 12.0 Hz, 2H), 2.27 (s, 1H), 2.13 (d, *J* = 13.2 Hz, 2H), 1.65 (dd, *J* = 23.2, 10.0 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.7, 157.1, 148.1, 144.0, 141.0, 140.7, 138.1, 134.6, 132.8, 132.5, 130.8, 130.2, 128.7, 127.8, 124.3, 70.2, 43.5, 42.6, 32.8, 24.9; MS (ESI) $[M+H]^+$ 452.2.

(4-(3-(4-(1H-Pyrazol-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methan-amine hydrochloride (46) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.18 (s, 2H), 8.15 (s, 1H), 7.41 (s, 2H), 7.34 – 7.27 (m, 6H), 4.20 (s, 2H), 4.14 (s, 2H), 3.49 (d, *J* = 12.9 Hz, 2H), 3.02 (t, *J* = 13.2 Hz, 2H), 2.12 (br, 1H), 2.03 (d, *J* = 15.3 Hz, 2H), 1.64 – 1.54 (m, 2H); ^{13}C NMR (100 MHz, D_2O) 158.5, 148.8, 143.2, 138.1, 135.9, 132.7, 131.11, 131.04, 131.02, 131.00, 130.95, 130.4, 130.1, 128.8, 125.1, 70.1, 43.5, 42.6, 32.9, 25.0; MS (ESI) $[M+H]^+$ 441.2.

(4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (47) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.24 (s, 1H), 7.94 (s, 1H), 7.61 (s, 1H), 7.51 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.41 (br, 6H), 6.85 (s, 1H), 4.35 (br, 2H), 4.17 (s, 2H), 3.50

(d, *J* = 13.3 Hz, 2H), 3.06 (t, *J* = 13.3 Hz, 2H), 2.12 (br, 1H), 2.11 (d, *J* = 14.6 Hz, 2H), 1.68 – 1.58 (m, 2H); ^{13}C NMR (100 MHz, D_2O) 158.4, 148.8, 144.5, 143.3, 139.4 (2), 138.3, 135.6, 132.6, 132.4, 131.1, 130.3, 130.0, 128.7, 125.0, 108.1, 70.0, 43.5, 42.6, 32.9, 24.9; HRMS (ESI$^+$) calcd for $C_{27}H_{29}N_4O_2$ $[M+H]^+$ 441.2291, found 441.2285.

1-(4-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)ethan-1-one hydrochloride (48) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.08 (br, 1H), 8.78 (br, 1H), 8.41 (br, 4H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.29 (d, *J* = 6 Hz, 2H), 3.99 (d, *J* = 5.2 Hz, 2H), 3.27 (d, *J* = 12.0 Hz, 2H), 2.88 (d, *J* = 10.4 Hz, 2H), 2.57 (s, 3H), 2.15 (br, 1H), 1.91 (d, *J* = 11.6 Hz, 2H), 1.53 (d, *J* = 12 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 198.0, 158.2, 147.2, 144.4, 143.0, 138.5, 136.9, 134.3, 133.6, 130.4, 130.0, 129.2, 128.6, 70.1, 55.4, 43.0, 42.2, 33.4, 25.6; MS (ESI) $[M+H]^+$ 417.2.

(4-(3-(4-Isopropylphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (**49)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.65 (s, 4H), 8.34 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.41 – 7.29 (m, 4H), 7.21 (d, *J* = 7.2 Hz, 2H), 4.29 (d, *J* = 6.0 Hz, 2H), 4.01 (s, 2H), 3.28 (d, *J* = 12.4 Hz, 2H), 2.90 (t, *J* = 10.8 Hz, 3H), 2.14 (s, 1H), 1.93 (d, *J* = 13.2 Hz, 2H), 1.55 (dd, *J* = 24.2, 11.8 Hz, 2H), 1.20 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 157.6, 149.0, 147.8, 143.4, 138.6, 135.6, 133.6, 132.1, 129.5, 129.4, 128.6, 126.2, 69.5, 42.6, 41.8, 33.1, 33.0, 25.2, 23.7; MS (ESI) $[M+H]^+$ 417.3.

4-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenol hydrochloride (50) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.79 (s, 1H), 8.25–9.82 (m, 5H), 7.34–7.40 (m, 4H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 4.27 (d, *J* = 6.4 Hz, 2H), 4.00 (d, *J* = 5.2 Hz, 2H), 3.27 (br, 2H), 2.89 (d, *J* = 11.2 Hz, 2H), 2.11 (br, 1H), 1.91 (d, *J* = 13.2 Hz, 2H), 1.48–1.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 158.5, 158.0, 148.4, 143.5, 139.5, 133.8, 131.8, 131.4, 129.8, 129.0, 128.8, 115.5, 69.8, 43.2, 42.3, 33.4, 25.6; MS (ESI) $[M+H]^+$ 391.2.

(4-(3-(1H-Benzo[d]imidazol-6-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (51) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d6): δ = 9.59 (s, 1H), 8.82 (s, 1H), 9.07 (s, 1H), 8.43 (bs, 4H), 7.95 (s, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.34–7.40 (m, 4H), 4.29 (d, *J* = 6.4 Hz, 2H), 3.98 (d, *J* = 6.4 Hz, 2H), 3.28 (d, *J* = 12 Hz, 2H), 2.90 (d, *J* = 11.6 Hz, 2H), 2.15 (bs, 1H), 1.92 (d, *J* = 12.8 Hz, 2H), 1.52–1.60 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d6): δ = 158.19, 147.32, 144.34, 141.85, 138.63, 136.45, 134.25, 131.12, 130.05, 129.21, 128.01, 116.12, 114.61, 65.35, 43.07, 42.20, 31.75, 15.61; MS (ESI) [M+H]+ 414.2.

(4-(3-(1H-Benzo[d]imidazol-4-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (52) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.43 (s, 1H), 9.06 (bs, 1H), 8.78

(bs, 1H), 8.50 (s, 1H), 8.39 (bs, 3H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.38–7.40 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 2H), 4.25 (d, *J* = 6.4 Hz, 2H), 3.93 (d, *J* = 4.8 Hz, 2H), 2.87 (d, *J* = 11.6 Hz, 4H), 2.11 (bs, 1H), 1.89 (d, *J* = 12.4 Hz, 2H), 1.51 (d, *J* = 11.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 170.8, 158.2, 144.9, 144.2, 142.0, 137.9, 134.6, 134.3, 129.8, 129.0, 127.0, 126.5, 125.8, 115.6, 114.9, 70.3, 65.4, 60.2, 34.6, 21.2; MS (ESI) $[M+H]^+$ 415.2.

(4-(3-(1H-Indol-2-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (53) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.51 (s, 1H), 9.11 (s, 1H), 8.88 (s, 1H), 8.53 (s, 3H), 8.24 (s, 1H), 7.64 – 7.47 (m, 5H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.19 – 7.05 (m, 1H), 7.00 – 6.89 (m, 1H), 4.51 (d, *J* = 4.6 Hz, 2H), 4.13 (d, *J* = 4.4 Hz, 2H), 3.31 (d, *J* = 8.9 Hz, 2H), 2.92 (dd, *J* = 21.7, 11.0 Hz, 2H), 2.17 (s, 1H), 1.99 (d, *J* = 11.7 Hz, 2H), 1.61 (dd, *J* = 22.3, 10.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 157.6, 143.7, 140.1, 139.2, 136.6, 134.3, 133.7, 131.2, 129.3, 129.1, 127.8, 122.9, 120.8, 119.6, 112.0, 104.2, 69.7, 42.6, 42.0, 33.1, 25.2; MS (ESI) $[M+H]^+$ 414.2.

(4-(3-(1H-Indol-4-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (54) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.27 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 9.2 Hz, 3H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 4.26 (d, *J* = 4.8 Hz, 2H), 4.09 (s, 2H), 3.49 (d, *J* = 12.4 Hz, 2H), 3.03 (t, *J* = 12.4 Hz, 2H), 2.18 (s, 1H), 2.05 (d, *J* = 14.0 Hz, 2H), 1.59 (dd, *J* = 25.6, 13.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.5, 149.8, 143.9, 138.4, 135.9, 132.3, 131.5, 129.6, 129.0, 128.4, 126.3, 126.1, 121.5, 121.2, 112.4, 70.2, 43.6, 42.6, 32.8, 24.9; MS (ESI) $[M+H]^+$ 414.2.

(4-(3-(1H-Indol-5-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (55) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.27 (s, 1H), 7.71 (s, 1H), 7.47 – 7.35 (m, 6H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 4.36 (s, 2H), 4.17 (s, 2H), 3.51 (d, *J* = 11.5 Hz, 2H), 3.06 (t, *J* = 13.1 Hz, 2H), 2.22 (s, 1H), 2.10 (d, *J* = 13.5 Hz, 2H), 1.65 (dd, *J* = 24.7, 12.0 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.6, 151.1, 143.4, 139.3, 136.1, 132.8, 130.6, 130.3, 129.1, 128.8, 127.6, 126.6, 123.6, 122.5, 111.6, 70.2, 43.7, 42.7, 33.2, 25.3; MS (ESI) $[M+H]^+$ 414.2.

(4-(3-(4-(Furan-3-yl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (59) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.01 (s, 1H), 7.69 (s, 1H), 7.41 (s, 1H), 7.21 (dd, *J* = 20.0, 7.6 Hz, 6H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.61 (s, 1H), 4.09 (d, *J* = 6.0 Hz, 2H), 3.98 (s, 2H), 3.34 (d, *J* = 12.4 Hz, 3H), 2.88 (t, *J* = 12.0 Hz, 2H), 2.00 (s, 1H), 1.91 (d, *J* = 14.0 Hz, 2H), 1.44 (dd, *J* = 23.6, 10.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.3, 148.5, 144.4, 143.8, 139.3, 138.2, 135.6, 133.3, 131.8, 131.6, 130.7, 130.2, 130.1, 128.7, 125.2, 108.2, 70.2, 43.5, 42.6, 32.9, 24.9; MS (ESI) $[M+H]^+$ 441.2

1-(4-(3-(4-(Furan-3-yl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)-N-methylmethanamine hydrochloride (60) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.17 (s, 1H), 7.85 (s, 1H), 7.57 (s, 1H),

7.48 – 7.24 (m, 6H), 7.18 (d, *J* = 7.4 Hz, 2H), 6.76 (s, 1H), 4.24 (d, *J* = 4.8 Hz, 2H), 4.16 (s, 2H), 3.49 (d, *J* = 10.4 Hz, 2H), 3.03 (t, *J* = 11.6 Hz, 2H), 2.68 (s, 3H), 2.17 (s, 1H), 2.06 (d, *J* = 12.4 Hz, 2H), 1.60 (dd, *J* = 24.4, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.3, 148.2, 144.4, 144.0, 139.3, 138.7, 135.8, 131.9, 131.8, 131.3, 130.3, 130.1, 129.6, 125.2, 125.1, 108.2, 70.2, 51.7, 43.6, 32.9, 32.0, 25.0; MS (ESI) $[M+H]^+$ 455.2.

1-(4-(3-(4-(Furan-3-yl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)-N,N-dimethylmethanamine hydrochloride (61) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.73 (s, 1H), 7.44 (s, 1H), 7.28 (t, *J* = 7.3 Hz, 4H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.64 (s, 1H), 4.16 – 4.11 (m, 4H), 3.36 (d, *J* = 12.6 Hz, 2H), 2.89 (d, *J* = 12.8 Hz, 2H), 2.67 (s, 6H), 2.05 (s, 1H), 1.94 (d, *J* = 13.4 Hz, 2H), 1.47 (dd, *J* = 24.5, 11.9 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.4, 148.2, 144.4, 144.1, 139.3, 135.8, 132.0, 131.8, 130.6, 130.4, 130.4, 130.1, 129.8, 125.2, 125.1, 108.2, 70.2, 60.5, 43.6, 42.0, 32.9, 24.9; MS (ESI) $[M+H]^+$ 469.2

1-(4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)-N-methylmethanamine hydrochloride (62) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.07 (s, 1H), 7.76 (s, 1H), 7.54 (s, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.24 – 7.16 (m, 4H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.67 (s, 1H), 4.1 – 4.00 (m, 4H), 3.43 (d, *J* = 6.1 Hz, 2H), 2.97 (t, *J* = 12.6 Hz, 2H), 2.64 (s, 3H), 2.06 (s, 2H), 1.95 (d, *J* = 13.2 Hz, 2H), 1.59 – 1.48 (m, 2H) ; ^{13}C NMR (100 MHz, D_2O) δ 158.5, 148.8, 144.7, 143.2, 139.5, 138.9, 135.6, 132.6, 131.3, 130.8, 130.4, 130.2, 129.9, 125.1, 116.0, 108.3, 70.1, 52.3, 43.7, 33.07, 32.11, 25.0; MS (ESI) $[M+H]^+$ 455.2.

1-(4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)-N,N-dimethylmethanamine hydrochloride (63) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.25 (s, 1H), 7.94 (s, 1H), 7.61 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.35 (m, 6H), 6.84 (s, 1H), 4.34 (d, *J* = 6.0 Hz, 2H), 4.29 (s, 2H), 3.50 (d, *J* = 11.6 Hz, 2H), 3.06 (t, *J* = 13.2 Hz, 2H), 2.24 (s, 1H), 2.11 (d, *J* = 14.4 Hz, 2H), 1.63 (dd, *J* = 24.0, 11.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.7, 149.1, 144.5, 143.6, 139.5, 135.8, 132.6, 131.6, 130.6, 130.4, 130.3, 129.2, 125.2, 125.1, 108.2, 70.1, 60.6, 43.5, 42.0, 32.9, 24.9; MS (ESI) $[M+H]^+$ 429.2.

(4-(3-(4-(Furan-3-yl)phenyl)-6-(2-(piperazin-1-yl)ethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (64) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.36 (s, 1H), 7.93 (s, 1H), 7.60 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 4H), 7.41 – 7.34 (m, 4H), 6.85 (s, 1H), 4.18 (s, 2H), 3.85 (s, 7H), 3.66 (s, 6H); ^{13}C NMR (100 MHz, D_2O) δ 157.3, 148.6, 145.1, 144.5, 139.4, 138.2, 135.8, 133.4, 132.3, 132.1, 130.3, 130.2, 128.7, 125.4, 125.2, 108.3, 60.0, 56.0, 48.8, 42.6, 40.5; MS (ESI) $[M+H]^+$ 456.2.

(4-(3-(4-(Furan-3-yl)phenyl)-5-(2-(piperidin-4-yl)ethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (65) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.00 (s, 1H), 7.71 (s, 1H), 7.44 (s, 1H), 7.28 – 7.04 (m, 6H), 6.61 (s, 1H), 4.19 (s, 1H), 3.99 (s, 2H), 3.25 (d, *J* = 11.2 Hz, 2H), 2.77 (t, *J* = 12.4 Hz, 1H), 1.80 (d, *J* = 13.6 Hz, 2H), 1.62 (s, 2H), 1.29 (dd, *J* = 21.2, 10.4 Hz, 1H);

^{13}C NMR (100 MHz, D_2O) δ 158.5, 149.0, 144.5, 143.2, 139.4, 138.3, 135.8, 132.6, 132.5, 131.2, 130.3, 130.1, 128.8, 125.1, 108.2, 64.7, 43.8, 42.6, 34.0, 30.2, 28.2; MS (ESI) $[M+H]^+$ 455.2.

2-Methoxy-4-(5-(piperidin-4-ylmethoxy)-3-(4-(thiophen-3-yl)phenyl)pyrazin-2-yl)benzamide hydrochloride (72) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (br, 1H), 8.57 (br, 1H), 8.39 (s, 1H), 7.96 (br, 1H), 7.74 (d, J = 7.9 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.65–7.59 (m, 2H), 7.55 (br, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.11 (s, 1H), 7.00 (d, J = 8.0 Hz, 1H), 4.33 (d, J = 6.2 Hz, 2H), 3.68 (s, 3H), 3.31 (d, J = 12.5 Hz, 2H), 2.96–2.88 (m, 2H), 2.16 (br, 1H), 1.94 (d, J = 13.6 Hz, 2H), 1.58–1.49 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 165.9, 157.9, 147.9, 143.2, 142.4, 140.6, 136.5, 135.4, 132.4, 132.1, 131.5, 130.7, 130.2, 128.8, 127.4, 126.2, 125.9, 121.9, 113.2, 69.6, 66.4, 42.8, 32.9, 26.3; MS (ESI) $[M+H]^+$ 501.2.

(4-(5-(Cyclohexylmethoxy)-3-(4-(furan-3-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (73) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (bs, 3H), 8.33 (s, 1H), 8.21 (s, 1H), 7.73 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.38–7.42 (m, 6H), 6.96 (s, 1H), 4.20 (d, J = 5.2 Hz, 2H), 3.99 (d, J = 4.8 Hz, 2H), 1.80 (d, J = 10.8 Hz, 2H), 1.70 (d, J = 11.2 Hz, 2H), 1.64 (d, J = 10.8 Hz, 1H), 1.21 (dd, J = 12.8 Hz, 25.6 Hz, 4H), 1.04–1.07 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 147.9, 144.9, 143.7, 140.4, 139.1, 137.0, 134.0, 132.8, 132.6, 130.5, 130.0, 129.1, 125.7, 125.6, 109.0, 71.6, 42.2, 37.3, 29.7, 26.4, 25.7. MS (ESI) $[M+H]^+$ 440.2.

(4-(5-(Benzyloxy)-3-(4-(furan-3-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (74) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.40–8.42 (m, 3H), 8.23 (s, 1H), 7.74 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.52–7.57 (m, 3H), 7.38–7.41 (m, 8H), 7.34–7.36 (m, 2H), 6.70 (s, 1H), 5.48 (s, 2H), 3.99 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 147.9, 145.0, 144.1, 140.4, 139.1, 137.0, 136.8, 134.0, 133.0, 132.7, 130.5, 130.0, 129.1, 128.9, 128.8, 128.6, 125.7, 125.6, 109.0, 68.1, 42.3; MS (ESI) $[M+H]^+$ 434.2.

(4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-yloxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (75) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 1H), 8.20 (s, 1H), 7.73 (s, 1H), 7.56 (d, J = 8 Hz, 2H), 7.38–7.40 (m, 4H), 7.29 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 6.96 (s, 1H), 5.27 (bs, 1H), 4.10 (d, J = 5.6 Hz, 2H), 3.65 (bs, 2H), 3.23 (bs, 2H), 2.00 (bs, 2H), 1.64–1.66 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.2, 156.3, 154.4, 147.6, 144.9, 144.3, 140.3, 137.4, 137.0, 133.1, 132.6, 130.4, 129.7, 127.0, 125.7, 109.0, 79.2, 78.3, 71.6, 43.5; MS (ESI) $[M+H]^+$ 427.2.

3-((5-(4-(Aminomethyl)phenyl)-6-(4-(furan-3-yl)phenyl)pyrazin-2-yl)oxy)propan-1-amine hydrochloride (76) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (bs, 3H), 8.36 (s, 1H), 8.22 (s, 1H), 8.09 (bs, 3H), 7.74 (s, 1H), 7.57 (d, J = 8 Hz, 2H), 7.37–7.42 (m, 6H), 6.97 (s, 1H), 4.48 (t, J = 6 Hz, 2H), 3.99 (d, J = 5.6 Hz, 2H), 2.96 (d, J = 6 Hz, 2H), 2.09–2.13 (m, 2H); ^{13}C NMR (100

MHz, DMSO-d_6) δ 158.0, 147.9, 145.0, 144.0, 140.4, 139.0, 136.8, 134.1, 132.9, 132.7, 130.5, 129.9, 129.1, 125.7, 125.6, 109.0, 64.0, 42.2, 36.6, 34.6; MS (ESI) $[M+H]^+$ 401.2.

2-((5-(4-(Aminomethyl)phenyl)-6-(4-(furan-3-yl)phenyl)pyrazin-2-yl)oxy)-N-methylethan-1-amine hydrochloride (77) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (bs, 1H), 8.20 (s, 1H), 7.73 (s, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.38–7.40 (m, 3H), 7.26–7.28 (m, 2H), 7.15 (d, J = 8 Hz, 2H), 6.96 (s, 1H), 4.53 (t, J = 5.2 Hz, 2H), 4.10 (d, J = 5.2 Hz, 2H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8, 156.3, 144.9, 144.4, 140.4, 140.3, 137.4, 137.0, 132.8, 132.6, 130.4, 129.7, 127.0, 125.7, 125.6, 109.0, 78.9, 78.3, 63.8, 43.5; MS (ESI) $[M+H]^+$ 401.2.

(4-(3-(4-(Furan-3-yl)phenyl)-5-(1-(piperidin-4-yl)ethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (**78)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (bs, 1H), 8.78 (bs, 1H), 8.45 (bs, 3H), 8.30 (s, 1H), 7.75 (s, 1H), 7.57 (d, J = 8 Hz, 2H), 7.39–7.41 (m, 6H), 7.26 (d, J = 8 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 5.14–5.16 (m, 1H), 3.99 (bs, 2H), 3.27 (d, J = 13.6 Hz, 2H), 2.83 (bs, 2H), 1.93 (bs, 2H), 1.81–1.84 (m, 1H), 1.52–1.56 (m, 2H), 1.32 (d, J = 6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, 154.8, 147.6, 143.9, 143.8, 138.8, 137.0, 132.9, 132.6, 130.2, 129.8, 127.3, 125.9, 125.5, 115.4, 108.6, 79.4, 75.1, 41.5, 28.4, 27.8, 16.9; MS (ESI) $[M+H]^+$ 455.2.

4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)benzamide hydrochloride (**79)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (br, 2H), 8.40 (s, 1H), 8.37 (s, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.81 (d, J = 7.7 Hz, 2H), 7.74 (s, 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.43–7.40 (m, 4H), 6.98 (s, 1H), 4.33 (d, J = 5.6 Hz, 2H), 3.09–3.05 (m, 2H), 2.92 (br, 2H), 2.16 (br, 1H), 1.94 (d, J = 14.6 Hz, 2H), 1.56–1.47 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 167.6, 158.0, 147.8, 144.6, 143.4, 141.4, 140.1, 136.3, 133.4, 132.5, 130.2, 129.4, 127.53, 127.46, 125.4, 125.3, 108.7, 69.7, 42.7, 33.0, 25.3; MS (ESI) $[M+H]^+$ 455.5.

2-Fluoro-4-(3-(4-(furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)benzamide hydrochloride (80) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (br, 1H), 8.48 (br, 1H), 8.39 (s, 1H), 7.77–7.75 (m, 1H), 7.74 (br, 1H), 7.66 (br, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.59 (t, J = 7.8 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.26–7.19 (m, 2H), 7.00 (s, 1H), 4.33 (d, J = 6.3 Hz, 2H), 3.33–3.30 (m, 2H), 2.96–2.87 (m, 2H), 2.16 (br, 1H), 1.94 (d, J = 14.6 Hz, 2H), 1.56–1.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 164.8, 159.0, 158.0, 147.9, 144.6, 142.9, 142.0, 140.1, 135.9, 132.6, 131.5, 130.2, 128.9, 128.7, 125.4, 125.3, 108.6, 70.0, 43.2, 35.3, 25.6; MS (ESI) $[M+H]^+$ 473.2.

N-(4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)benzyl)Hydroxylamine hydrochloride (81) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.20 (s, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 7.49 – 7.21 (m, 8H), 6.78 (s, 1H), 4.39 (d, J = 7.6 Hz, 2H), 4.26 (d, J = 6.4 Hz, 2H), 3.52 – 3.42 (m, 2H), 3.03 (s, 2H), 2.17 (s, 1H), 2.06 (d, J = 12.4 Hz, 2H), 1.59 (dd, J = 23.6,

10.4 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.6, 148.9, 144.4, 143.6, 139.4, 139.2, 135.7, 132.4, 131.5, 130.5, 130.3, 130.0, 128.4, 125.2, 115.8, 108.2, 70.1, 54.3, 43.5, 32.9, 24.9; MS (ESI) $[M+H]^+$ 457.2.

(4-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)-3-methylphenyl)methanamine hydrochloride (82) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.10 (s, 1H), 7.77 (s, 1H), 7.47 (s, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 3H), 6.67 (s, 1H), 4.18 (d, *J* = 6.0 Hz, 2H), 4.02 (s, 2H), 3.37 (d, *J* = 12.4 Hz, 2H), 2.92 (q, *J* = 11.2 Hz, 2H), 2.09 (br, 1H), 1.97 (d, *J* = 12.4 Hz, 2H), 1.8 (br, 3H), 1.49 (dd, *J* = 23.6, 11.6 Hz, 2H); MS (ESI) $[M+H]^+$ 455.2

(3-(3-(4-(Furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (83) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.14 (br, 1H), 8.84 (br, 1H), 8.48 (br, 3H), 8.37 (s, 1H), 8.24 (s, 1H), 7.76 (s, 1H), 7.72 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 4.33 (d, *J* = 6.2 Hz, 2H), 4.02 (q, *J* = 5.1 Hz, 2H), 3.29 (d, *J* = 12.3 Hz, 2H), 2.91 (q, *J* = 12.1 Hz, 2H), 2.16 (br, 1H), 1.94 (d, *J* = 14.6 Hz, 2H), 1.60 – 1.52 (m, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) 157.8, 147.4, 144.6, 143.6, 140.0, 138.9, 136.2, 134.4, 132.4, 132.3, 130.1, 129.9, 129.6, 128.5, 128.3, 125.3, 125.2, 108.6, 69.6, 42.7, 42.2, 33.0, 25.2; MS (ESI) $[M+H]^+$ 441.5.

(2-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)-5-(furan-3-yl)phenyl)methanol hydrochloride (84) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.34 (s, 1H), 7.97 (s, 1H), 7.70 (s, 1H), 7.64 (s, 1H), 7.43 – 7.29 (m, 5H), 7.10 (s, 1H), 6.88 (s, 1H), 4.54 (s, 2H), 4.27 (s, 2H), 4.14 (s, 2H), 3.51 (d, *J* = 12.0 Hz, 2H), 3.07 (t, *J* = 12.0 Hz, 2H), 2.22 (s, 1H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.63 (dd, *J* = 25.6, 13.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.3, 148.8, 144.5, 144.1, 139.5, 139.3, 137.8, 134.5, 132.9, 132.8, 132.5, 131.4, 129.9, 128.5, 125.2, 125.1, 124.5, 108.2, 70.2, 61.4, 43.6, 42.6, 32.8, 24.9; MS (ESI) $[M+H]^+$ 471.2.

(4-(3-(2-Fluoro-4-(furan-3-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (85) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.40 (d, *J* = 8.8 Hz, 1H), 9.04 (d, *J* = 8.8 Hz, 1H), 8.59 (br, 3H), 8.44 (s, 1H), 8.34 (s, 1H), 7.77 (s, 1H), 7.63 – 7.54 (m, 2H), 7.40 (dd, *J* = 23.6, 8.4 Hz, 5H), 7.05 (s, 1H), 4.26 (d, *J* = 6.0 Hz, 2H), 3.97 (d, *J* = 5.2 Hz, 2H), 3.26 (d, *J* = 11.6 Hz, 2H), 2.88 (dd, *J* = 22.0, 11.2 Hz, 2H), 2.14 (s, 1H), 1.91 (d, *J* = 12.6 Hz, 2H), 1.56 (dd, *J* = 23.2, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 160.3, 157.9, 157.8, 144.9, 144.7, 142.9, 140.8, 138.1, 135.2, 135.1, 133.8, 133.5, 132.4, 132.4, 128.6, 128.5, 124.6, 124.49, 124.47, 124.4, 121.8, 112.6, 112.4, 108.6, 69.8, 42.5, 41.7, 32.9, 25.1; MS (ESI) $[M+H]^+$ 459.2.

(4-(3-(4-(Furan-3-yl)-2-methoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (86) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.26 (s, 1H), 7.95 (s, 1H), 7.62 (s, 1H),

7.42 – 7.23 (m, 6H), 7.02 (s, 1H), 6.85 (s, 1H), 4.22 (s, 2H), 4.13 (s, 2H), 3.49 (d, *J* = 14.0 Hz, 2H), 3.31 (s, 3H), 3.03 (t, *J* = 13.2 Hz, 2H), 2.15 (s, 1H), 2.05 (d, *J* = 12.8 Hz, 2H), 1.59 (dd, *J* = 24.4, 13.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.8, 156.0, 146.8, 145.1, 144.5, 139.6, 138.6, 134.9, 132.4, 131.9, 131.8, 128.9, 128.4, 125.3, 125.2, 118.5, 108.8, 108.3, 70.2, 55.1, 43.6, 42.6, 32.9, 24.9; MS (ESI) $[M+H]^+$ 471.2.

(4-(3-(4-(Furan-3-yl)-2-methylphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (87) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.83 (s, 1H), 8.49 (s, 3H), 8.36 (s, 1H), 7.94 (s, 1H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.45 – 7.38 (m, 5H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 4.01 (d, *J* = 4.8 Hz, 2H), 3.29 (d, *J* = 12.0 Hz, 2H), 2.90 (d, *J* = 10.8 Hz, 2H), 2.34 (s, 3H), 2.14 (s, 1H), 1.93 (d, *J* = 13.2 Hz, 2H), 1.56 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 147.6, 143.6, 143.4, 140.9, 138.6, 136.6, 135.2, 133.6, 132.3, 132.1, 131.9, 129.5, 128.7, 128.4, 127.3, 124.4, 111.1, 69.6, 42.6, 41.8, 33.0, 25.2, 21.4; MS (ESI) $[M+H]^+$ 455.2

(4-(3-(4-(Furan-3-yl)-3-methylphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (88) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, *J* = 11.0 Hz, 1H), 8.99 (d, *J* = 8.8 Hz, 1H), 8.55 (s, 3H), 8.42 (s, 1H), 8.23 (s, 1H), 7.75 (s, 1H), 7.51 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.36 (dd, *J* = 23.4, 8.0 Hz, 4H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.98 (s, 1H), 4.22 (d, *J* = 6.0 Hz, 2H), 3.95 (d, *J* = 5.2 Hz, 2H), 3.26 (d, *J* = 11.6 Hz, 2H), 2.87 (q, *J* = 11.2 Hz, 2H), 2.11 (s, 1H), 2.06 (br, 3H), 1.91 (d, *J* = 13.2 Hz, 2H), 1.55 (dd, *J* = 22.8, 10.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.5, 148.4, 144.4, 144.0, 139.8, 138.1, 136.5, 136.1, 133.6, 133.0, 132.0, 130.6, 128.9, 128.5, 127.3, 125.3, 123.0, 108.6, 69.6, 42.5, 41.7, 33.0, 25.1, 19.5; MS (ESI) $[M+H]^+$ 455.2.

(4-(3-(4-(Furan-3-yl)-3-methoxyphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (89) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.85 (s, 1H), 8.48 (br, 3H), 8.37 (s, 1H), 8.16 (s, 1H), 7.73 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.50 – 7.36 (m, 4H), 7.04 (d, *J* = 21.6 Hz, 3H), 4.33 (d, *J* = 5.6 Hz, 2H), 4.01 (s, 2H), 3.67 (s, 3H), 3.29 (d, *J* = 10.0 Hz, 2H), 2.90 (dd, *J* = 21.6, 10.8 Hz, 2H), 2.16 (s, 1H), 1.94 (d, *J* = 12.4 Hz, 2H), 1.56 (dd, *J* = 22.4, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 155.5, 147.5, 143.8, 143.1, 141.9, 138.8, 137.1, 133.6, 132.4, 129.5, 128.7, 127.3, 121.9, 120.9, 120.8, 112.9, 109.3, 69.6, 55.3, 42.6, 41.8, 33.0, 25.2; MS (ESI) $[M+H]^+$ 471.2.

5-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)-2-(furan-3-yl)benzonitrile hydrochloride (90) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 8.92 (s, 1H), 8.54 (s, 3H), 8.41 (d, *J* = 2.1 Hz, 1H), 8.29 (s, 1H), 7.97 (s, 1H), 7.86 (s, 1H), 7.63 (dd, *J* = 27.6, 8.0 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.40 (d, *J* = 6.4 Hz, 2H), 7.02 (s, 1H), 4.30 (s, 2H), 4.00 (s, 2H), 3.26 (d, *J* = 11.2 Hz, 2H), 2.88 (dd, *J* = 19.6, 8.8 Hz, 2H), 2.13 (s, 1H), 1.91 (d, *J* = 13.2 Hz, 2H), 1.55 (dd, *J* = 22.0, 10.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8, 145.4, 144.6, 143.9, 141.9, 137.9, 137.5, 135.2, 134.9, 134.5, 134.0, 133.4, 129.6, 128.9, 128.6, 122.4, 118.6, 109.8, 108.7, 69.8, 42.6, 41.7, 32.9, 25.1; MS (ESI) $[M+H]^+$ 466.2

(4-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl) (pyrrolidin-1-yl)methanone hydrochloride (91) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (s, 1H), 8.92 (d, J = 9.2 Hz, 1H), 8.51 (br, 3H), 8.40 (s, 1H), 7.50 – 7.40 (m, 6H), 7.37 (d, J = 8.0 Hz, 2H), 4.30 (d, J = 6.0 Hz, 2H), 4.00 (s, 2H), 3.45 (t, J = 6.0 Hz, 2H), 3.36 (t, J = 6.0 Hz, 2H), 3.28 (d, J = 12.0 Hz, 2H), 2.90 (dd, J = 22.4, 10.4 Hz, 2H), 2.15 (s, 1H), 1.93 (d, J = 13.6 Hz, 2H), 1.83 (dt, J = 23.6, 11.6 Hz, 4H), 1.56 (dd, J = 23.6, 12.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 158.2, 147.6, 144.2, 139.6, 138.7, 137.6, 134.2, 133.3, 130.0, 129.9, 129.2, 127.4, 70.1, 49.3, 46.4, 43.0, 42.2, 33.4, 26.4, 25.6, 24.3; MS (ESI) $[M+H]^+$ 472.3.

(4-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl) (morpholino)methanone hydrochloride (92) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (d, J = 10.4 Hz, 1H), 8.98 (d, J = 9.6 Hz, 1H), 8.55 (s, 3H), 8.40 (s, 1H), 7.46 (dd, J = 9.6, 8.4 Hz, 4H), 7.41 – 7.32 (m, 4H), 4.29 (d, J = 6.0 Hz, 2H), 4.01 (d, J = 5.6 Hz, 2H), 3.60 (s, 11H), 3.28 (d, J = 11.6 Hz, 2H), 2.90 (dd, J = 22.4, 10.8 Hz, 2H), 2.15 (s, 1H), 1.93 (d, J = 12.8 Hz, 2H), 1.57 (q, J = 12.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 158.1, 147.5, 144.0, 139.5, 138.6, 135.8, 133.7, 133.2, 129.97, 129.95, 129.0, 127.3, 69.9, 66.6, 66.3, 42.9, 41.9, 33.1, 25.3; MS (ESI) $[M+H]^+$ 488.3

(4-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl) (piperidin-1-yl)methanone hydrochloride (93) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (s, 1H, NH), 8.86 (s, 1H, NH), 8.47 (s, 3H, NH), 8.37 (s, 1H), 7.46 – 7.20 (m, 8H), 4.26 (s, 2H), 3.97 (s, 2H), 3.53 (s, 2H), 3.24 (s, 4H), 2.86 (s, 2H), 2.11 (s, 1H), 1.90 (d, J = 13.2 Hz, 2H), 1.60 – 1.32 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.3, 157.7, 147.2, 143.7, 138.8, 138.3, 136.5, 133.8, 132.8, 129.6, 129.5, 128.7, 126.6, 69.6, 42.6, 41.8, 32.9, 25.1, 24.0; MS (ESI) $[M+H]^+$ 486.3.

(4-(5-(Piperidin-4-ylmethoxy)-3-(4-(tetraHydrofuran-3-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (94) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (bs, 1H), 8.86 (bs, 1H), 8.48 (bs, 3H), 8.31 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.32–7.40 (m, 4H), 7.21 (d, J = 8.4 Hz, 2H), 4.26 (d, J = 5.6 Hz, 2H), 3.99 (d, J = 7.6 Hz, 3H), 3.88–3.93 (m, 1H), 3.76 (dd, J = 8 Hz, 15.6 Hz, 1H), 3.35 (t, J = 8.4 Hz, 1H), 3.25 (d, J = 13.2 Hz, 2H), 2.87 (d, J = 11.2 Hz, 2H), 2.26–2.29 (m, 1H), 2.12 (bs, 1H), 1.88–1.92 (m, 3H), 1.52–1.56 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 148.0, 143.9, 143.8, 139.0, 136.5, 134.1, 132.7, 130.1, 129.9, 129.1, 127.6, 74.1, 69.9, 68.1, 55.4, 44.3, 43.0, 34.2, 33.4, 25.6; MS (ESI) $[M+H]^+$ 445.3.

(4-(5-(Piperidin-4-ylmethoxy)-3-(3-(tetraHydrofuran-3-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (95) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.14–7.33 (m, 8H), 4.23 (d, J = 5.6 Hz, 2H), 3.85 (t, J = 6.8 Hz, 1H), 3.65–3.67 (m, 4H), 3.21–3.27 (m, 4H), 3.08 (d, J = 12 Hz, 2H), 2.63–2.66 (m, 2H), 2.12 (bs, 1H), 1.98 (bs, 1H), 1.77 (d, J = 14 Hz, 2H), 1.60 (bs, 1H), 1.28–1.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 148.0,

144.6, 143.0, 138.6, 137.3, 132.7, 129.6, 128.9, 128.8, 128.2, 127.9, 127.6, 127.1, 74.0, 70.6, 67.9, 55.3, 44.6, 44.2, 34.7, 34.2, 27.8; MS (ESI) $[M+H]^+$ 444.6.

(4-(5-(Piperidin-4-ylmethoxy)-3-(4-(pyrrolidin-1-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (96) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.75 (s, 1H), 8.45 (s, 3H), 8.19 (s, 1H), 7.43 (q, J = 8.4 Hz, 4H), 7.26 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.8 Hz, 2H), 4.29 (d, J = 6.4 Hz, 2H), 4.02 (d, J = 6.0 Hz, 2H), 3.29 (d, J = 12.0 Hz, 2H), 3.23 (s, 4H), 2.90 (dd, J = 23.6, 12.4 Hz, 2H), 2.14 (s, 1H), 1.95 (s, 7H), 1.54 (dd, J = 24.2, 10.8 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.5, 148.2, 147.7, 142.6, 139.6, 133.3, 130.7, 130.3, 129.3, 128.6, 123.90, 111.1, 69.2, 47.2, 42.7, 41.8, 33.0, 25.2, 25.0; MS (ESI) $[M+H]^+$ 444.3.

(4-(3-(4-(Piperidin-1-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (97) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.32 (s, 1H), 7.59 (dd, J = 22.2, 7.9 Hz, 4H), 7.41 (br, 4H), 4.38 (s, 2H), 4.21 (s, 2H), 3.64 (br, 4H), 3.52 (d, J = 12.4 Hz, 2H), 3.09 (t, J = 12.0 Hz, 2H), 2.27 (s, 1H), 2.13 (d, J = 12.8 Hz, 2H), 2.03 (br, 4H), 1.77 (s, 2H), 1.66 (dd, J = 25.2, 12.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.8, 147.6, 143.8, 141.9, 139.3, 137.9, 132.8, 132.5, 131.8, 130.2, 128.8, 120.9, 70.2, 57.1, 43.6, 42.6, 32.9, 25.0, 23.3, 20.5; MS (ESI) $[M+H]^+$ 458.3.

(4-(3-(4-Cyclohexylphenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (**98)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (bs, 1H), 8.68 (bs, 1H), 8.37 (bs, 3H), 8.30 (s, 1H), 7.29–7.39 (m, 6H), 7.15 (d, J = 8 Hz, 2H), 4.27 (s, 2H), 3.99 (s, 2H), 3.27 (d, J = 11.6 Hz, 2H), 2.88 (d, J = 11.2 Hz, 2H), 2.11 (bs, 1H), 1.90 (d, J = 13.6 Hz, 3H), 1.65–1.76 (m, 5H), 1.51 (d, J = 12 Hz, 2H), 1.35 (bs, 4H), 1.12–1.20 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 148.7, 148.2, 143.8, 139.1, 136.0, 134.0, 132.6, 130.0, 129.9, 129.0, 127.0, 110.0, 69.9, 43.9, 43.1, 42.2, 34.2, 33.3, 26.7, 26.0, 25.6; MS (ESI) $[M+H]^+$ 457.3.

(4-(3-(4-(Piperidin-4-yl)phenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (99) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.24 (s, 1H), 7.38 (s, 6H), 7.25 (d, J = 7.6 Hz, 2H), 4.36 (d, J = 5.2 Hz, 2H), 4.18 (s, 2H), 3.51 (t, J = 12.0 Hz, 4H), 3.18 – 3.01 (m, 4H), 2.97 – 2.88 (m, 1H), 2.25 (s, 1H), 2.16 – 2.02 (m, 4H), 1.87 (dd, J = 26.4, 12.8 Hz, 2H), 1.63 (dd, J = 25.6, 12.0 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.7, 149.2, 145.21, 143.6, 138.4, 135.7, 132.5, 131.3, 130.1, 130.0, 128.7, 126.5, 70.1, 44.2, 43.5, 42.6, 38.8, 32.8, 29.1, 24.9; MS (ESI) $[M+H]^+$ 458.3.

(4-(5-(Piperidin-4-ylmethoxy)-3-(4-(1,2,3,6-tetraHydropyridin-4-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (100) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (s, 2H, NH), 9.15 (s, 1H, NH), 8.86 (s, 1H, NH), 8.49 (s, 4H), 8.34 (s, 1H), 7.44 – 7.32 (m, 8H), 6.24 (s, 6H), 4.26 (d, J = 5.2 Hz, 2H), 3.97 (d, J = 4.0 Hz, 2H), 3.69.18 (s, 2H), 3.60 – 3.24 (m, 4H), 2.90 – 2.85

(m, 2H), 2.65 (s, 2H), 2.11 (s, 1H), 1.88 (d, J = 12.0 Hz, 2H), 1.54 (dd, J = 25.6, 12.0 Hz, 2H); MS (ESI) $[M+H]^+$ 456.3.

(4-(3-(6-(Piperazin-1-yl)pyridin-3-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (101) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.20 (s, 1H), 7.97 (s, 1H), 7.79 (d, J = 12.0 Hz, 1H), 7.35 (s, 4H), 7.04 (d, J = 12.0 Hz, 1H), 4.27 (s, 2H), 4.09 (s, 1H), 3.83 (s, 4H), 3.35 (s, 6H), 2.94 (t, J = 12.0 Hz, 4H), 2.15 (s, 2H), 1.99 (d, J = 12.0 Hz, 2H), 1.50 (d, J = 12.0 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.9, 152.1, 144.6, 143.7, 143.3, 138.5, 137.4, 133.4, 133.2, 130.2, 129.2, 124.5, 111.8, 70.2, 43.6, 42.9, 42.6, 42.2, 32.8, 25.0; MS (ESI) $[M+H]^+$ 460.3.

(4-(5-(Piperidin-4-ylmethoxy)-3-(6-(tetraHydro-2H-pyran-4-yl)pyridin-3-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (102) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (bs, 1H), 8.82–8.85 (m, 1H), 8.60 (s, 1H), 8.49 (bs, 3H), 8.43 (s, 1H), 8.01 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 4.28 (d, J = 6 Hz, 2H), 4.00 (d, J = 5.2 Hz, 2H), 3.93 (d, J = 10.8, 2H), 3.32–3.62 (m, 4H), 3.26 (d, J = 11.6 Hz, 2H), 3.14 (bs, 1H), 2.88 (d, J = 12 Hz, 2H), 2.14 (bs, 1H), 1.90 (d, J = 12.8 Hz, 2H), 1.59–1.74 (m, 4H), 1.51–1.59 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3, 146.2, 144.6, 144.0, 138.0, 134.6, 134.2, 133.6, 130.1, 129.4, 129.3, 129.2, 122.8, 70.3, 67.2, 65.4, 43.0, 42.2, 41.1, 34.6, 33.3, 31.8, 31.7, 25.5, 15.6; MS (ESI) $[M+H]^+$ 460.3.

(4-(5-(Piperidin-4-ylmethoxy)-3-(4-(tetraHydro-2H-pyran-4-yl)phenyl)pyrazin-2-yl)phenyl)methanamine hydrochloride (103) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (bs, 1H), 8.70–8.72 (m, 1H), 8.40 (bs, 3H), 8.32 (s, 1H), 7.32–7.41 (m, 6H), 7.20 (d, J = 8 Hz, 2H), 4.26 (d, J = 6 Hz, 2H), 3.99 (d, J = 5.2 Hz, 2H), 3.91 (d, J = 10.8 Hz, 2H), 2.88 (dd, J = 11.2 Hz, 22.8 Hz, 2H), 2.73–2.76 (m, 1H), 2.11 (bs, 1H), 1.90 (d, J = 13.2 Hz, 2H), 1.64 (bs, 4H), 1.51 (d, J = 12 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 148.1, 147.0, 143.8, 139.1, 136.3, 134.0, 132.6, 130.1, 129.9, 129.0, 127.0, 69.9, 67.7, 43.0, 42.2, 40.5, 33.8, 33.3, 25.6; MS (ESI) [M+H]+ 459.3.

(4-(3-(4-Morpholinophenyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (104) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 10.4 Hz, 1H), 8.91 (dd, J = 20.8, 10.8 Hz, 1H), 8.54 (s, 3H), 8.27 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 4.29 (d, J = 6.0 Hz, 2H), 4.01 (d, J = 5.2 Hz, 2H), 3.75 (br, 4H), 3.27 (d, J = 12.4 Hz, 2H), 3.18 (br, 4H), 2.89 (q, J = 11.6 Hz, 2H), 2.14 (s, 1H), 1.92 (d, J = 12.6 Hz, 2H), 1.55 (q, J = 11.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.6, 150.3, 147.6, 143.1, 139.0, 133.5, 131.3, 130.6, 129.4, 128.7, 114.6, 69.4, 65.8, 48.1, 42.6, 41.8, 40.2, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 33.0, 25.2; MS (ESI) $[M+H]^+$ 460.3.

General Synthetic Procedure for compounds 33, 35, 36, and 37.—To a solution of R^5 substituted compound (88 mg, 0.16 mmol) in DMSO (3 mL) was added pyrazole (17

mg, 0.25 mmol) and potassium carbonate (45 mg, 0.32 mmol). The resulting mixture was heated at 120 °C for 24 h before it was cooled to room temperature. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 2:1 to 1.5:1) to give corresponding R^6 substituted product (35 mg, 38%). For precursor of **35**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.21 (s, 4H), 4.86 (s, 1H), 4.29 (br, 1H), 4.25 (d, *J* = 6.8 Hz, 2H), 4.18 (br, 2H), 2.74 (t, *J* = 12.8 Hz, 2H), 2.03 (s, 1H), 1.81 (d, *J* = 12.8 Hz, 2H), 1.45 (br, 18H), 1.28–1.21 (m, 2)

To a solution of R^6 substituted compound (0.08 mmol) in DCM (5 mL) was added dropwise HCl (0.1 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give the final product hydrochloric salt.

N^1-(3-(4-(Aminomethyl)phenyl)-6-(piperidin-4-ylmethoxy)pyrazin-2-yl)ethane-1,2-diamine hydrochloride (33) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 7.62 – 7.43 (m, 4H), 7.41 (s, 1H), 4.24 (d, *J* = 6.0 Hz, 2H), 4.16 (s, 2H), 3.62 (d, *J* = 5.6 Hz, 2H), 3.38 (d, *J* = 11.2 Hz, 2H), 3.15 (s, 2H), 2.94 (t, *J* = 12.0 Hz, 2H), 2.10 (s, 1H), 1.98 (d, *J* = 13.6 Hz, 2H), 1.56 – 1.42 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 160.3, 152.8, 134.8, 131.4, 129.8, 129.4, 128.0, 112.4, 70.6, 43.6, 42.6, 38.5, 32.9, 25.0; MS (ESI) $[M+H]^+$ 357.2.

(4-(5-(Piperidin-4-ylmethoxy)-3-(1H-pyrazol-1-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (35). ^{1}H NMR (400 MHz, D_2O) δ 8.26 (s, 1H), 7.76 (s, 1H), 7.57 (s, 1H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 2H), 4.22 (d, *J* = 6.0 Hz, 2H), 4.07 (s, 2H), 3.37 (d, *J* = 12.4 Hz, 2H), 2.94 (t, *J* = 12.4 Hz, 2H), 2.13 (s, 1H), 1.98 (d, *J* = 13.2 Hz, 2H), 1.57 – 1.46 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.2, 142.2, 141.9, 138.6, 136.0, 134.2, 133.1, 132.1, 128.9, 128.8, 108.1, 70.5, 43.5, 42.6, 33.0, 25.0; 365.2; MS (ESI) $[M+H]^+$ 365.2

(4-(5-(Piperidin-4-ylmethoxy)-3-(1H-1,2,3-triazol-1-yl)pyrazin-2-yl)phenyl)methanamine hydrochloride (36) was prepared following the same procedure as a hydrochloric acid salt.. ^{1}H NMR (400 MHz, D_2O) δ 8.43 (s, 1H), 7.87 (s, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.6 Hz, 2H), 4.26 (d, *J* = 5.6 Hz, 2H), 4.07 (s, 2H), 3.38 (d, *J* = 12.4 Hz, 2H), 2.95 (t, *J* = 12.8 Hz, 2H), 2.16 (s, 1H), 1.99 (d, *J* = 13.6 Hz, 2H), 1.57 – 1.46 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 158.4, 141.1, 139.5, 137.1, 136.6, 135.4, 133.4, 129.0, 128.7, 70.7, 43.5, 42.6, 32.6, 24.8; MS (ESI) $[M+H]^+$ 366.2.

(4-(3-(1H-Imidazol-1-yl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (37) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 9.46 (s, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 2H), 7.59 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 4.36 (d, *J* = 6.0 Hz, 2H), 4.16 (s, 2H), 3.34 (d, *J* = 12.8 Hz, 2H), 2.90 (t, *J* = 12.8 Hz, 2H), 2.15 (s, 1H), 1.94 (d, *J* = 14.4 Hz, 2H), 1.46 (dd, *J* = 24.8, 11.6 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 156.6, 143.9, 139.6, 134.7, 134.4, 133.6, 129.8, 128.8, 125.1, 121.0, 119.0, 70.9, 43.5, 42.7, 32.6, 25.1; MS (ESI) $[M+H]^+$ 365.2.

General Synthetic Procedure for compounds 19, 66–69, and 71.—2,6-Dibromopyrazine (**111a**, X =N, 7.14 g, 30 mmol) or 2,6-dibromopyridine (**111b**, X = CH, 7.14 g, 30 mmol), *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (7.07 g, 33 mmol) and potassium carbonate (8.28 g, 60 mmol) in DMF (30 mL) were placed in a sealed tube. The mixture was stirred at 100 °C for 12 h. The reaction was cooled and quenched with saturated brine (50 mL). The mixture was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford **112a** or **112b** as a white solid, which was used in the next step without further purification. For compound **112a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H), 7.76 (s, 1H), 5.00 (s, 1H), 4.14 – 4.11 (m, 2H), 3.25 (t, *J* = 5.9 Hz, 2H), 2.68 (t, *J* = 11.8 Hz, 2H), 1.73 – 1.70 (m, 3H), 1.44 (s, 9H), and 1.21 – 1.09 (m, 2H). For compound **112b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.26 (d, *J* = 7.8 Hz, 1H), 4.76 (t, *J* = 5.4 Hz, 1H), 4.10 (br, 2H), 3.14 (t, *J* = 6.1 Hz, 2H), 2.67 (t, *J* = 12.8 Hz, 2H), 1.77 – 1.67 (m, 3H), 1.44 (s, 9H), and 1.19 – 1.09 (m, 2H).

To a solution of compound **112a** or **112b** (~30 mmol) in CH_3CN/DMSO (20/10 mL) was added N-Iodosuccinimide (8.1 g, 36 mmol). After stirring at room temperature for 24 h, the reaction was quenched with sodium thiosulfate aqueous solution (50 mL). The mixture was extracted with ethyl acetate (3 × 100 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 10:1 to 3:1) to give **113a** or **113b** as a white solid (8.95 g, 60% over two steps). For compound **113a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 4.86 (t, *J* = 5.6 Hz, 1H), 4.14 – 4.11 (m, 2H), 3.24 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 12.2 Hz, 2H), 1.73 – 1.69 (m, 3H), 1.45 (s, 9H), and 1.21 – 1.13 (m, 2H). For compound **113b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 1H), 6.10 (d, *J* = 8.5 Hz, 1H), 4.74 (t, *J* = 5.4 Hz, 1H), 4.14 – 4.09 (m, 2H), 3.14 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 12.2 Hz, 2H), 1.73 – 1.69 (m, 3H), 1.45 (s, 9H), and 1.20 – 1.11 (m, 2H).

Compound **113a** or **113b** (994 mg, 2 mmol), 4-((N-Boc-amino)methyl)phenylboronic acid (527 mg, 2.1 mmol), tetrakis(triphenylphosphine)palladium (69 mg, 3 mol%), and sodium carbonate (424 mg, 4 mmol) in *p*-dioxane/H_2O (15/3 mL) were placed in a sealed tube. The mixture was degassed and heated to 80 °C for 24 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 1:1) to give the corresponding R^5 substituted product **a** and **b** (842 mg, 73% yield for **a**). For compound **a** (Intermediate of **66**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 4.94 (t, *J* = 5.9 Hz, 1H), 4.88 (br, 1H), 4.37 (d, *J* = 5.9 Hz, 2H), 4.16 – 4.11 (m, 2H), 3.31 (t, *J* = 5.9 Hz, 2H), 2.71 (t, *J* = 12.2 Hz, 2H), 1.77 – 1.74 (m, 3H), 1.46 (s, 9H), 1.45 (s, 9H), and 1.25 – 1.15 (m, 2H). compound **b** (Intermediate of **69**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.88 (br, 2H), 4.36 (br, 2H), 4.16 – 4.11 (m, 2H), 3.18 (t, *J* = 5.9

Hz, 2H), 2.68 (t, *J* = 12.2 Hz, 2H), 2.10 (br, 1H), 1.77 – 1.74 (m, 2H), 1.46 (s, 9H), 1.45 (s, 9H), and 1.22 – 1.15 (m, 2H).

The above R^5 substituted compound **a** or **b** (1 mmol), 2-(4-(furan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 mmol), tetrakis(triphenylphosphine)palladium (57.7 mg, 5 mol%), and sodium carbonate (216 mg, 2 mmol) in *p*-dioxane/H_2O (8/2 mL) were placed in a sealed tube. The mixture was degassed and heated to 100 °C for 24 h. The reaction was then cooled and quenched with brine (10 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 1:2) to afford the corresponding R^6 substituted **a** or **b** (78% yield for **a**). For Compound **a** (precursor of **66**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.73 (s, 1H), 7.46 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.69 (s, 1H), 4.89 (t, *J* = 5.9 Hz, 1H), 4.85 (br, 1H), 4.28 (d, *J* = 5.9 Hz, 2H), 4.16 – 4.11 (m, 2H), 3.36 (t, *J* = 6.1 Hz, 2H), 2.71 (t, *J* = 11.8 Hz, 2H), 1.79 – 1.76 (m, 3H), 1.45 (s, 9H), 1.44 (s, 9H), and 1.26 – 1.16 (m, 2H). For Compound **b**(precursor of **69**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.45 (br, 1H), 7.34 (br, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.67 (s, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 4.83 (t, *J* = 5.5 Hz, 2H), 4.28 (d, *J* = 5.3 Hz, 2H), 4.14 – 4.09 (m, 2H), 3.25 (t, *J* = 5.8 Hz, 2H), 2.71 (t, *J* = 13.4 Hz, 2H), 1.81 – 1.78 (m, 3H), 1.46 (s, 9H), 1.45 (s, 9H), and 1.27 – 1.20 (m, 2H).

The above R^6 substituted (0.2 mmol) was dissolved in dichloromethane (2 mL). HCl (0.2 mL, 4 N in *p*-dioxane) was slowly added to the reaction mixture at 0 °C. After 0.5 h, the reaction was warmed to room temperature and stirred for 12 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give **66** and **69** hydrochloric salt as a white and pale-yellow powder, respectively.

5-(4-(Aminomethyl)phenyl)-6-(4-(furan-3-yl)phenyl)-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine hydrochloride (**66**). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (br, 2H), 8.67 (br, 2H), 8.38 (br, 4H), 8.21 (s, 1H), 8.02 (s, 1H), 7.75 (s, 1H), 7.54 (d, *J* = 7.3 Hz, 2H), 7.37–7.30 (m, 6H), 6.96 (s, 1H), 3.98 (br, 2H), 3.28–3.24 (m, 4H), 2.83 (q, *J* = 10.8 Hz, 2H), 1.89–1.85 (m, 3H), 1.46–1.38 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 153.0, 148.1, 144.5, 143.8, 139.8, 139.6, 137.9, 137.6, 132.5, 131.7, 130.0, 129.3, 128.5, 125.3, 125.1, 108.6, 55.0, 42.9, 41.9, 33.5, 26.4; MS (ESI) $[M+H]^+$ 440.5.

5-(4-(Aminomethyl)phenyl)-6-(4-(furan-3-yl)phenyl)-N-(piperidin-4-ylmethyl)pyridin-2-amine hydrochloride (69). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (br, 1H), 8.83 (br, 2H), 8.44 (br, 3H), 8.28 (s, 1H), 7.91 (br, 2H), 7.77 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.01 (s, 1H), 3.97 (d, *J* = 6.3 Hz, 2H), 3.38 (br, 2H), 3.28 (d, *J* = 13.5 Hz, 2H), 2.85 (q, *J* = 12.3 Hz, 2H), 1.95–1.91 (m, 3H), 1.48–1.40 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 153.9, 144.6, 140.4, 136.6, 133.2, 130.4, 129.5, 129.0, 125.3, 124.9, 123.1, 108.5, 46.3, 42.5, 41.6, 33.1, 25.9; MS (ESI) $[M+H]^+$ 439.6.

((6-((Piperidin-4-ylmethyl)amino)pyridine-2,3-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (**19)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.09 (d, *J* = 9.3 Hz, 2H), 7.44 (s, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 9.3 Hz, 2H), 4.21 (s, 2H), 4.15 (s, 2H), 3.52–3.46 (m, 4H), 3.05 (t, *J* = 13.2 Hz, 2H), 2.13–2.08 (m, 3H), 1.59–1.49 (m, 2H); ^{13}C NMR (100 MHz, D_2O) 152.8, 146.4, 144.5, 136.5, 134.8, 132.4, 132.2, 130.4, 130.2, 128.9, 128.8, 124.8, 110.3, 46.6, 43.6, 42.55, 42.48, 32.8, 25.9; MS (ESI) $[M+H]^+$ 402.3.

5-(4-(Aminomethyl)phenyl)-6-(2-fluoro-4-(furan-3-yl)phenyl)-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine hydrochloride (67) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O): δ 8.13 (s, 1H), 7.84 (br, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.33–7.26 (m, 3H), 6.72 (s, 1H), 4.21 (s, 2H), 3.72 (s, 2H), 3.44 (d, *J* = 13.1 Hz, 2H), 2.99–2.93 (m, 2H), 2.06–1.96 (m, 3H), 1.51–1.42 (m, 2H); ^{13}C NMR (100 MHz, D_2O): 159.4, 153.7, 152.2, 144.3, 140.1, 136.5, 136.1, 135.6, 132.9, 132.7, 130.4, 129.7, 129.3, 128.8, 128.6, 121.5, 112.5, 108.1, 45.3, 43.6, 42.6, 32.7, 26.0; MS (ESI) $[M+H]^+$ 458.2.

5-(4-(Aminomethyl)-3-fluorophenyl)-6-(4-(furan-3-yl)phenyl)-*N*-(piperidin-4-ylmethyl)pyrazin-2-amine hydrochloride (68) was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, D_2O) δ 8.11 (s, 1H), 7.81 (br, 1H), 7.47 (br, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.25 (br, 1H), 7.08–7.05 (m, 2H), 6.72 (s, 1H), 4.22 (d, *J* = 6.0 Hz, 2H), 4.10 (s, 2H), 3.36 (d, *J* = 13.6 Hz, 2H), 2.92 (t, *J* = 12.9 Hz, 2H), 2.11 (br, 1H), 1.98 (d, *J* = 14.8 Hz, 2H), 1.54–1.44 (m, 2H); ^{13}C NMR (100 MHz, D_2O): 160.5, 158.6, 148.8, 144.5, 141.2, 139.4, 138.5, 135.3, 132.6, 131.5, 131.1, 130.3, 125.9, 125.1, 125.0, 119.6, 116.6, 108.2, 70.6, 43.5, 36.7, 32.9, 25.0; MS (ESI) $[M+H]^+$ 458.6.

5-(4-(Aminomethyl)phenyl)-*N*-(piperidin-4-ylmethyl)-6-(4-(thiophen-3-yl)phenyl)pyridin-2-amine hydrochloride (**71)** was prepared following the same procedure as a hydrochloric acid salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (br, 2H), 8.61 (br, 2H), 8.31 (br, 4H), 7.95 (s, 1H), 7.71–7.58 (m, 3H), 7.38–7.35 (m, 4H), 7.18 (d, *J* = 8.1 Hz, 2H), 3.97 (q, *J* = 5.4 Hz, 2H), 3.35 (br, 2H), 3.28 (d, *J* = 13.5 Hz, 2H), 2.85 (q, *J* = 11.6 Hz, 2H), 1.95–1.91 (m, 3H), 1.46–1.36 (m, 2H); MS (ESI) $[M+H]^+$ 455.2.

General Synthetic Procedure for compounds 56, 57, 58, and 70.—To a solution of 3-amino-6-iodopyrazine-2-carboxylate (**114**, 1.8 g, 6.6 mmol) in 12N HCl-H_2O (v/v = 5/1, 54 mL) at - 10 °C was added sodium nitrite solution (0.7 M solution, 18 mL) in 3 portions. The resulting reaction mixture was stirred at - 10 °C for 1 h before Copper(I) chloride (0.78 g, 7.88 mmol) in 12 N HCl solution (1.8 mL) was added slowly and stirred for additional 2 h. The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude residue, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 20:1 to 10:1) to afford 3-Chrolo-6-iodopyrazine-2-carboxylate **115** (770 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 4.02 (s, 3H).

3-Chrolo-6-iodopyrazine-2-carboxylate (**115**, 298 mg, 1 mmol), *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (206 mg, 0.98 mmol) and potassium carbonate (300 mg, 2.2 mmol) in DMSO (6 mL) were placed in a sealed tube. The mixture was stirred at 50 °C for 12 h. The reaction was cooled and quenched with saturated brine (30 mL). The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a residue, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 2:1 to 1.5:1) to afford **116** (270 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.06 (t, *J* = 5.3 Hz, 1H), 4.07 (dd, *J* = 13.9, 6.9 Hz, 2H), 3.91 (s, 3H), 3.36 (t, *J* = 6.1 Hz, 2H), 2.65 (t, *J* = 11.5 Hz, 2H), 1.78 – 1.63 (m, 3H), 1.41 (s, 9H), 1.19 – 1.08 (m, 2H).

Compound **116** (270 mg, 0.70 mmol), 4-[(tert-Butoxycarbonylamino)methyl]phenylboronic acid pinacol ester (300 mg, 0.9 mmol), tetrakis(triphenylphosphine)palladium (40 mg, 0.035 mmol), and sodium carbonate (220 mg, 2.07 mmol) in *p*-dioxane/H_2O (10/2 mL) were placed in a sealed tube. The mixture was degassed and heated to 105 °C for 24 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 1.5:1 to 1:1) to afford the product **117** (244 mg, 63%), and a small portion of crude product (38 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.02 (t, *J* = 5.3 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H) 4.02 (dd, *J* = 13.9, 6.9 Hz, 2H), 3.88 (s, 3H), 3.36 (t, *J* = 6.1 Hz, 2H), 2.65 (t, *J* = 11.5 Hz, 2H), 1.78 – 1.63 (m, 3H), 1.41 (s, 9H), 1.19 – 1.08 (m, 2H).

To a solution of compounds **117** (244 mg, 0.44 mmol) in MeOH-H_2O (v/v = 4/1, 5 mL) was added Lithium hydroxide (105 mg, 4.4 mmol) at room temperature. It was allowed to stir for 24 h before removing the solvents to give a residue, which was acidified by 1N HCl and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude acid, which was used in the next step without further purification.

To a solution of the crude acid (70 mg) and 4-aminomethyl-1-Boc-piperidine (42 mg, 0.2 mmol) in DMF (3 mL) was added N, N-diisopropylethylamine (87 μL, 0.5 mmol) and HATU (114 mg, 0.3 mmol). The mixture was stirred for 12 h before it was quenched with H_2O. The mixture was extracted with ethyl acetate (3 × 80 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 1.5:1 to 1:1) to afford corresponding amides (62 mg) as colorless oil. For **56** precursor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.74 (br, 1H), 8.66 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.98 (br, 1H), 4.36 (d, *J* = 5.2 Hz, 2H), 4.16 (br, 1H), 3.47 (t, *J* = 5.6 Hz, 2H), 2.70 (br, 1H), 1.90–1.78 (m, 3H), 1.91 (s, 1H), 1.47 (s, 9H), 1.45 (s, 9H); For **57** precursor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.75 (t, *J* = 5.6 Hz, 1H), 8.68 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 4.93 (br, 1H), 4.38 (d, *J* = 5.2 Hz, 2H), 4.12 (br, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.71 (t, J = 13.3 Hz, 2H), 1.90–1.78 (m, 3H), 1.48 (s, 9H), 1.45 (s, 9H), 1.25 (s, 2H); For **58**

precursor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.75 (t, *J* = 5.4 Hz, 1H), 8.68 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 4.96 (s, 1H), 4.37 (d, *J* = 4.8 Hz, 2H), 4.22 – 4.06 (m, 2H), 3.48 (t, *J* = 6.0 Hz, 2H), 2.71 (t, *J* = 12.3 Hz, 2H), 1.49 – 1.42 (m, 3H), 1.49 – 1.42 (m, 18H), 1.25 – 1.20 (m, 2H).

To a solution of the above amides (1.5 mmol) in DCM (5 mL) was added dropwise HCl (1.2 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give the final product hydrochloric salt.

For the synthesis of **70** precursor: Compound **57** precursor (X = I, 65 mg, 0.088 mmol), furan-3-yl boronic acid (17 mg, 0.15 mmol), tetrakis(triphenylphosphine)palladium (10 mg, 0.009 mmol), and sodium carbonate (43 mg, 0.4 mmol) in *p*-dioxane/H_2O (4/1 mL) were placed in a sealed tube. The mixture was degassed and heated to 80 °C for 12 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 1.5:1 to 1:1) to afford the product **70** precursor (244 mg, 63%).

3-(4-(Aminomethyl)phenyl)-N-(4-chlorophenyl)-6-((piperidin-4-ylmethyl)amino)pyrazine-2-carboxamide hydrochloride (56). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 9.23 – 9.21 (m, 2H), 8.98 (s, 1H), 8.92 (d, *J* = 10.0 Hz, 2H), 8.74 (s, 1H), 8.65 (br, 3H), 8.25 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 4.04 (d, *J* = 5.6 Hz, 2H), 3.45 (s, 2H), 3.21 (d, *J* = 11.2 Hz, 2H), 2.79 (dd, *J* = 23.2, 11.2 Hz, 2H), 1.91 (s, 1H), 1.81 (d, *J* = 12.8 Hz, 2H), 1.43 (dd, *J* = 25.2, 13.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 153.4, 144.2, 136.9, 136.8, 135.7, 134.0, 129.4, 128.5, 128.1, 125.7, 124.5, 123.1, 44.8, 42.8, 41.9, 33.4, 26.3; MS (ESI) $[M+H]^+$ 451.2.

3-(4-(Aminomethyl)phenyl)-N-(4-iodophenyl)-6-((piperidin-4-ylmethyl)amino)pyrazine-2-carboxamide hydrochloride (57). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.03 – 8.87 (m, 2H), 8.69 (ddd, *J* = 31.6, 19.2, 8.4 Hz, 2H), 8.49 (br, 3H), 8.26 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.63 (dd, *J* = 29.2, 8.4 Hz, 4H), 4.06 (d, *J* = 5.2 Hz, 2H), 3.55 (s, 2H), 3.24 (d, *J* = 11.2 Hz, 2H), 2.81 (dd, *J* = 23.2, 11.2 Hz, 2H), 1.91 (s, 1H), 1.82 (d, *J* = 13.2 Hz, 2H), 1.42 (dd, *J* = 25.2, 13.2 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 165.3, 153.8, 144.6, 138.0, 137.7, 137.3, 136.1, 134.3, 129.8, 126.1, 124.9, 123.9, 88.8, 45.2, 43.2, 42.3, 33.8, 26.7; MS (ESI) $[M+H]^+$ 543.2.

3-(4-(Aminomethyl)phenyl)-N-(4-bromophenyl)-6-((piperidin-4-ylmethyl)amino)pyrazine-2-carboxamide hydrochloride (58). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.99 (s, 2H), 8.79 – 8.60 (m, 2H), 8.50 (s, 3H), 8.26 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.63 – 7.48 (m, 4H), 4.05 (dd, *J* = 11.2, 5.2 Hz, 2H), 3.45 (t, *J* = 6.0 Hz, 2H), 3.23 (d, *J* = 11.6 Hz, 2H), 2.86 – 2.72 (m, 2H), 1.91 (s, 1H), 1.81 (d, *J* = 13.2 Hz, 2H), 1.41 (dd, *J* = 23.6, 11.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9,

153.4, 144.2, 137.2, 136.9, 135.7, 133.9, 131.4, 129.3, 125.7, 124.5, 123.4, 116.2, 61.9, 44.8, 42.8, 41.9, 33.3, 31.5, 26.3; MS (ESI) $[M+H]^+$ 495.1.

3-(4-(Aminomethyl)phenyl)-N-(4-(furan-3-yl)phenyl)-6-((piperidin-4-ylmethyl)amino)pyrazine-2-carboxamide hydrochloride (70) was prepared by cross coupling with **49** precursor followed by deprotection. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 9.01 (s, 1H), 8.90 (d, J = 8.0 Hz, 1H), 8.83 (t, J = 6.0 Hz, 1H), 8.66 – 8.56 (m, 1H), 8.46 (s, 3H), 8.29 (d, J = 8.0 Hz, 2H), 8.19 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 1.6 Hz, 1H), 7.63 (dd, J = 18.4, 8.4 Hz, 4H), 6.98 (s, 1H), 4.09 (q, J = 6.0 Hz, 2H), 3.44 (s, 2H), 3.26 (d, J = 12.0 Hz, 2H), 2.83 (dd, J = 24.4, 12.4 Hz, 2H), 1.95 (s, 1H), 1.85 (d, J = 12.8 Hz, 2H), 1.50 – 1.37 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 153.5, 144.3, 144.1, 139.1, 136.8, 136.5, 135.8, 133.9, 129.3, 128.1, 125.7, 125.4, 124.7, 121.7, 108.6, 44.8, 42.9, 41.9, 33.4, 26.3; MS (ESI) $[M+H]^+$ 483.2.

General Synthetic Procedure for compound 20—To a solution of 4,5-dibromothiophene-2-carboxaldehyde **127** (540 mg, 2 mmol) in MeOH (4 mL), $NaBH_4$ (79 mg, 2.1 mmol) was added slowly 0 °C. The reaction mixture was stirred at room temperature for 1 h and quenched with water (5 mL). The product was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4. Upon removal of the solvent carefully, the residual oil was dried and used in the next step without purification. It was dissolved in DMF (10 mL) and the solution was cooled to 0 °C. Cyanuric chloride (369 mg, 2 mmol) was added slowly at 0 °C and stirred at room temperature for 10 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL). The product was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4. Removal of the solvents *in vacuo* afforded compound **128** as a colorless oil, which is used without purification.

To a solution of 4-(aminomethyl)-1-BOC-piperidine (214 mg, 1 mmol) and potassium carbonate (166 mg, 1.2 mmol) in DMF (5 mL), then a solution of **128** (145 mg, 0.5 mmol) in DMF (3 mL) was added slowly at 0 °C and the mixture was stirred at room temperature for 10 h. Upon quenching with saturated $NaHCO_3$ (10 mL), the product was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4. A column chromatography (silica gel, hexanes: ethyl acetate from 40:1 to 2:1) for the residue oil gave compound **129** as a pale-yellow oil (69% yield for the three steps).

A mixture of **129** (186 mg, 0.4 mmol), 4-[(tert-Butoxycarbonylamino)methyl]phenylboronic acid pinacol ester (300 mg, 0.9 mmol), tetrakis(tri-phenylphosphine)palladium (46 mg, 0.04 mmol) and sodium carbonate (212 mg, 2 mmol) in 1,4-dioxane/H_2O (5/1 mL) were heated to 100 °C for 12 h. The reaction was then quenched with brine (10 mL). The product was extracted with diethyl ether (3 × 20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4. Upon removal of the solvent, the product was purified by column chromatography (silica gel, *n*-hexanes: ethyl acetate from 5:1 to 1:2) to give **130** as a white solid (260 mg, 90%).

To a solution of **130** (0.1 mmol) in dichloromethane (2 mL) at 0 °C, HCl (0.2 mL, 4 N in 1,4-dioxane) was added slowly and then stirred at room temperature for 12 h. Upon removal of the solvent carefully, the residual oil was treated with anhydrous diethyl ether and vacuum dried to give **20** (white powder) as a hydrochloric salt (92% yield).

((5-(((Piperidin-4-ylmethyl)amino)methyl)thiophene-2,3-diyl)bis(4,1-phenylene))dimethanamine Hydrochloride (20–1226). ^{1}H NMR (400 MHz, D_2O) δ 7.43 (s, 1H), 7.40 (br, 8H), 4.57 (s, 2H), 4.19 (s, 4H), 3.50 (d, *J* = 12.8 Hz, 2H), 3.15 (d, *J* = 6.8 Hz, 2H), 3.05 (t, *J* = 12.0 Hz, 2H), 2.18 (s, 1H), 2.08 (d, *J* = 14.0 Hz, 2H), 1.59–1.50 (m, 2H); ^{13}C NMR (100 MHz, D_2O) 140.6, 137.9, 136.1, 133.9, 133.8, 132.6, 131.8, 130.5, 129.9, 129.6, 129.1, 129.0, 50.8, 45.4, 43.1, 42.64, 42.57, 30.7, 25.8; MS (ESI) $[M+H]^+$ 421.6.

Synthesis of compound 21.: To a solution of 2-amino-6-chloropyrazine **108** (2.0 g, 15.5 mmol) in acetonitrile (20 mL) was added N-bromosuccinimide (6.9 g, 39 mmol) at 0 °C. The resulting mixture was allowed to warm to room temperature, and stirred for 18 h, and to this was added water. The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to afford a crude residue, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 2:1) to give **121** as a yellow solid (3.93 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 2H, NH).

To a solution of **121** (990 mg, 3.44 mmol) in 1,4-dioxane (10 mL) was added N-Boc-4-piperidinemethanol (832 mg, 3.85 mmol) and sodium hydroxide (320 mg, 8.0 mmol). The resulting mixture was heated at 75 for 4 h °C. After cooled to room temperature, it was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to afford a crude residue, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 2:1 to 1:1) to give **122** as a yellow solid (885 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (s, 1H), 4.84 (s, 1H), 4.22 (d, *J* = 6.4 Hz, 2H), 4.12 (s, 2H), 2.74 (t, *J* = 12.4 Hz, 2H), 1.98 (s, 1H), 1.76 (d, *J* = 13.0 Hz, 2H), 1.46 (s, 9H), 1.27 (d, *J* = 12.2 Hz, 2H).

Compound **122** (90 mg, 0.214 mmol), 4-[(*tert*-Boc-methyl]phenylboronic acid pinacol ester (166 mg, 0.5 mmol), Bis[di-tert-butyl(4-dimethylaminophenyl)phosphine] dichloropalladium(II) (15 mg, 0.021 mmol), and potassium phosphate (212 mg, 1 mmol) in *p*-doxane-H_2O (6/1.5 mL) were placed in a sealed tube. The mixture was degassed and heated to 110 °C for 16 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 2:1 to 1:2) to afford **123** (66 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.12 (s, 1H), 5.01 (s, 1H), 4.35 (s, 4H), 4.23 (s, 2H), 4.16 – 4.10 (m, 2H), 2.81 – 2.70 (m, 2H), 2.02 (s, 1H), 1.82 (d, *J* = 12.6 Hz, 2H), 1.49 (s, 27H), 1.28 (d, *J* = 6.8 Hz, 2H).

To a solution of compound **123** (66 mg, 0.092 mmol) in DCM (3 mL) was added dropwise HCl (0.3 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give **21** (44 mg, 91%) as a hydrochloric salt.

((5-Amino-6-(piperidin-4-ylmethoxy)pyrazine-2,3-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (21). ^{1}H NMR (400 MHz, D_2O) δ 7.85 (d, *J* = 6.4 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.61 (dd, *J* = 25.6, 7.2 Hz, 4H), 4.36 (d, *J* = 5.2 Hz, 2H), 4.29 (s, 2H), 4.27 (s, 2H), 3.48 (d, *J* = 12.8 Hz, 2H), 3.03 (t, *J* = 12.0 Hz, 2H), 2.23 (s, 1H), 2.05 (d, *J* = 13.6 Hz, 2H), 1.57 (dd, *J* = 24.0, 11.8 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 156.6, 151.7, 134.3, 133.9, 133.7, 133.0, 129.5, 129.42, 129.36, 128.8, 128.4, 127.6, 70.1, 43.5, 42.7, 32.7, 25.1; MS (ESI) $[M+H]^+$ 419.2.

General Synthetic Procedure for compounds 22–24.—To a solution of **121** (600 mg, 2.09 mmol) in isopropyl alcohol (10 mL) was added chloroacetaldehyde (50% wt in water, 1.7 mL, 14 mmol). The resulting mixture was refluxed at 105 °C for 18 h then cooled to room temperature and concentrated. The residue was dissolved in dichloromethane (30 mL) and washed sequentially with Sat. $NaHCO_3$ (10 mL), H_2O (10 mL), and Brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and removed in vacuo to give a residue, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 5:1 to 2:1) to afford **124** (260 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.90 (s, 1H).

A solution of **124** (122 mg, 0.39 mmol), alcohol nucleophiles (0.38 mmol), and sodium hydroxide (20 mg, 0.5 mmol) in 1,4-dioxane (3 mL), or A solution of amine nucleophiles (0.38 mmol), and N, N-diisopropylethylamine (87 μL, 0.5 mmol) in acetonitrile (3 mL) was heated at 75 for 4 h °C. After cooled to room temperature, it was concentrated, and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to afford a crude residue, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 2:1 to 1:2) to give **125** as a solid (885 mg, 58%). For intermediate of compound **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 1.1 Hz, 1H), 7.56 (s, 1H), 4.96 (s, 1H), 4.29 (s, 1H), 4.22 (s, 2H), 4.15 – 4.07 (m, 1H), 3.82 (s, 1H), 1.97 – 1.66 (m, 4H), 1.43 (s, 9H).

Compound **125** (0.16 mmol), 4-[(tert-Butoxycarbonylamino)methyl]phenylboronic acid pinacol ester (133 mg, 0.4 mmol), Bis[di-tert-butyl(4-dimethylaminophenyl)phosphine] dichloropalladium(II) (15 mg, 0.021 mmol), and potassium phosphate (127 mg, 0.6 mmol) in *p*-dioxane-H_2O (5/1 mL) were placed in a sealed tube. The mixture was degassed and heated to 110 °C for 16 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed in vacuo to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 2:1 to 1:2) to afford **126**. For precursor of compound **24**: ^{1}H NMR (400 MHz, $CDCl_3$)) δ 7.48 (s, 1H), 7.32 – 7.25 (m, 7H), 7.08 (d, *J* = 7.6 Hz, 2H), 5.60 (s, 1H), 4.97 (s, 1H), 4.79 (s, 1H), 4.42 – 4.35 (m, 4H), 4.24 (d, *J* = 3.6 Hz, 2H), 4.02 – 3.87 (m, 3H), 1.89 (br, 2H), 1.71 (br, 2H), 1.47 – 1.40 (m, 27H).

To a solution of compound **126** (0.08 mmol) in DCM (3 mL) was added dropwise HCl (0.1 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give final products as hydrochloric salts.

((8-(Piperidin-4-ylmethoxy)imidazo[1,2-a]pyrazine-5,6-diyl)bis(4,1-phenylene)) dimethanamine hydrochloride (22) was prepared following the general procedure. ^{1}H NMR (400 MHz, D_2O) δ 7.97 (s, 1H), 7.78 (s, 1H), 7.58 – 7.48 (m, 4H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.63 (d, *J* = 6.0 Hz, 2H), 4.23 (s, 2H), 4.13 (s, 2H), 3.50 (d, *J* = 12.4 Hz, 2H), 3.08 (t, *J* = 12.0 Hz, 2H), 2.37 (s, 1H), 2.16 (d, *J* = 13.6 Hz, 2H), 1.74 – 1.58 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 149.6, 138.7, 136.6, 134.9, 133.0, 131.4, 130.5, 130.0, 129.7, 128.5, 128.0, 124.9, 124.4, 116.2, 71.1, 43.5, 42.5, 32.7, 24.9; MS (ESI) $[M+H]^+$ 443.2

(S)-((8-(3-Aminopyrrolidin-1-yl)imidazo[1,2-a]pyrazine-5,6-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (23) was prepared following the general procedure. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (br, 3H), 8.52 (br, 3H), 8.36 (br, 3H), 7.65 – 7.59 (m, 3H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.33 (m, 4H), 7.21 (s, 1H), 5.16 (t, *J* = 13.2 Hz, 2H), 4.09 (s, 2H), 3.95 (s, 2H), 3.29 (s, 1H), 2.12 (s, 1H), 1.88 (s, 1H), 1.77 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.6, 137.7, 135.1, 134.6, 133.4, 132.9, 132.5, 132.3, 131.6, 130.4, 130.2, 128.8, 119.7, 115.2, 110.0, 52.8, 49.5, 47.3, 42.1, 42.0, 29.1; MS (ESI) $[M+H]^+$ 414.2.

(R)-((8-(3-Aminopiperidin-1-yl)imidazo[1,2-a]pyrazine-5,6-diyl)bis(4,1-phenylene))dimethanamine hydrochloride (24) was prepared following the general procedure. ^{1}H NMR (400 MHz, D_2O) δ 8.61 (br, 3H), 8.51 (br, 3H), 8.36 (br, 3H), 7.62 – 7.59 (m, 3H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.35 (dd, *J* = 13.6, 4.4 Hz, 2H), 7.19 (s, 1H), 5.14 (t, *J* = 9.8 Hz, 2H), 4.07 (d, *J* = 5.6 Hz, 2H), 3.93 (d, *J* = 5.6 Hz, 2H), 3.42 (s, 2H), 3.27 (s, 2H), 2.09 (s, 1H), 1.87 (d, *J* = 9.2 Hz, 2H), 1.71 – 1.56 (m, 2H); MS (ESI) $[M+H]^+$ 428.2.

Synthesis of compound 34.: Compound **118** (120 mg, 0.23 mmol), potassium vinyltrifluoroborate (39 mg, 0.29 mmol), tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol), and cesium carbonate (147 mg, 0.45 mmol) in THF-H_2O (5/1 mL) were placed in a sealed tube. The mixture was degassed and heated to 110 °C for 12 h. The reaction was then cooled and quenched with brine (20 mL). The product was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to give a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 4:1 to 2:1) to afford **119** (108 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.83 (dd, *J* = 16.9, 10.6 Hz, 1H), 6.43 (dd, *J* = 16.9, 2.1 Hz, 1H), 5.46 (dd, *J* = 10.6, 2.1 Hz, 1H), 5.06 (s, 1H), 4.34 (d, *J* = 5.0 Hz, 2H), 4.26 (d, *J* = 6.4 Hz, 2H), 4.18 – 4.06 (m, 2H), 2.73 (t, *J* = 10.8 Hz, 2H), 2.00 – 1.94 (m, 1H), 1.81 (d, *J* = 12.9 Hz, 2H), 1.45 (s, 18H), 1.35 – 1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 156.0, 154.9, 144.4, 143.6, 139.2, 136.8, 133.9, 132.9, 130.0, 127.4, 120.8, 79.5, 70.3, 44.4, 35.9, 28.5, 28.5, 22.0.

To a solution of compound **119** (80 mg, 0.15 mmol) in DBU (2 mL) was added morpholine (0.1 mL). The resulting mixture was heated at 120 °C for 24 h before it was cooled to room temperature. The mixture was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with water and brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* to afford a crude oil, which was purified by column chromatography (silica gel, hexanes: ethyl acetate from 1:1 to 1:2) to give **120** (52 mg, 57%).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 5.00 (s, 1H), 4.33 (d, *J* = 5.3 Hz, 2H), 4.18 (d, *J* = 6.4 Hz, 2H), 4.14 – 4.04 (m, 2H), 3.67 – 3.57 (m, 4H), 2.96 – 2.89 (m, 2H), 2.78 – 2.67 (m, 4H), 2.36 (s, 4H), 1.96 (s, 1H), 1.79 (d, *J* = 12.6 Hz, 2H), 1.44 (s, 18H), 1.31 – 1.24 (m, 2H).

To a solution of compound **120** (52 mg, 0.085 mmol) in DCM (3 mL) was added dropwise HCl (0.3 mL, 4 N in *p*-dioxane) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The volatiles were removed *in vacuo* to afford an oil, which was triturated in diether ether and solidified to give **34** (41 mg, 92%) as a hydrochloric salt.

(4-(3-(2-Morpholinoethyl)-5-(piperidin-4-ylmethoxy)pyrazin-2-yl)phenyl)methanamine hydrochloride (34). ^{1}H NMR (400 MHz, D_2O) δ 8.22 (s, 1H), 7.69 – 7.53 (m, 4H), 4.36 (d, *J* = 5.6 Hz, 2H), 4.28 (s, 2H), 4.08 (d, *J* = 13.2 Hz, 2H), 3.81 – 3.72 (m, 2H), 3.60 (t, *J* = 7.2 Hz, 2H), 3.56 – 3.41 (m, 4H), 3.30 (t, *J* = 7.2 Hz, 2H), 3.17 (t, *J* = 12.4 Hz, 2H), 3.08 (t, *J* = 12.8 Hz, 2H), 2.26 (s, 1H), 2.13 (d, *J* = 14.0 Hz, 2H), 1.65 (dd, *J* = 25.6, 13.2 Hz, 2H); ^{13}C NMR (100 MHz, D_2O) δ 159.0, 146.9, 144.2, 136.9, 133.4, 131.6, 129.7, 129.2, 70.2, 63.6, 55.2, 51.7, 43.6, 42.7, 32.8, 27.6, 25.0; MS (ESI) $[M+H]^+$ 412.3.

Activity and inhibition assays for Flavivirus proteases.: Expression and purification of Flavivirus proteases were performed as described previously[15]. Activity and inhibition assay for ZVpro was performed using the enzyme (1 nM) and benzoyl-norleucine-lysine-lysine-arginine 7-amino-4-methylcoumarine (Bz-Nle-Lys-Lys-Arg-AMC, 20 μM) as the substrate in a HEPES buffer (20mM, pH 7.3) containing 0.05% Triton X-100. To determine IC_{50}, triplicate samples of a compound with concentrations ranging from 1 nM to 10 μM were incubated with the enzyme for 10 min before adding the substrate to initiate the reaction in 96-well plate (100 μL final volume). The fluorescence signal (Ex: 360 nm, Em: 460 nm) of each well was monitored every 30s, using a Tecan microplate reader. The initial velocity data were imported into Prism (version 5.0), and IC_{50} values from 3 independent experiments with standard deviation were obtained by using a standard dose-response curve fitting. Enzyme inhibition assays for DV2pro and WVpro were performed similarly.

Cellular antiviral activity testing.: Anti-ZIKV activity was evaluated in human U87 glioma following our previous methods[15]. 2×10^4 U87 cells/well were seeded in 96-well plates and cultured in DMEM media with 2% FBS to form a monolayer of cells. 0.01 MOI (multiplicity of infection) of ZIKV was added. After incubation for 1h, the supernatant was removed and cells were washed with PBS. Fresh medium (150 μL/well) containing various concentrations of a compound in triplicate were added. Upon incubation at 37 °C for 48h, aliquots of the supernatant from each well were used to determine ZIKV titers. Half-log serial dilution of the viral supernatant (50 μL) was added to a monolayer of Vero cells in quadruplicate in 96-well plates and cultured for 7 days. CPE/cell lysis was determined with

microscope followed by MTT assay. $TCID_{50}$ was calculated based on the highest dilution in which ≥50% (i.e., ≥2 out of the 4 quadruplicate wells) of Vero cells were infected with ZIKV. Compared to controls, the ability for a compound to reduce $TCID_{50}$ can be determined. The results were from at least 2 independent experiments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVATIONS:

Ac-CoA	acetyl coenzyme A
AR	androgen receptor
SAR	structure-activity relationships
DMF	N,N-Dimethylformamide
LSD1	lysine specific demethylase 1
ZVpro	Zika virus protease
DV2pro	Dengue (serotype 2) virus protease
WVpro	West Nile virus protease
CPE	cytopathic effects
MOI	multiplicity of infection
NIS	N-iodosuccinimide

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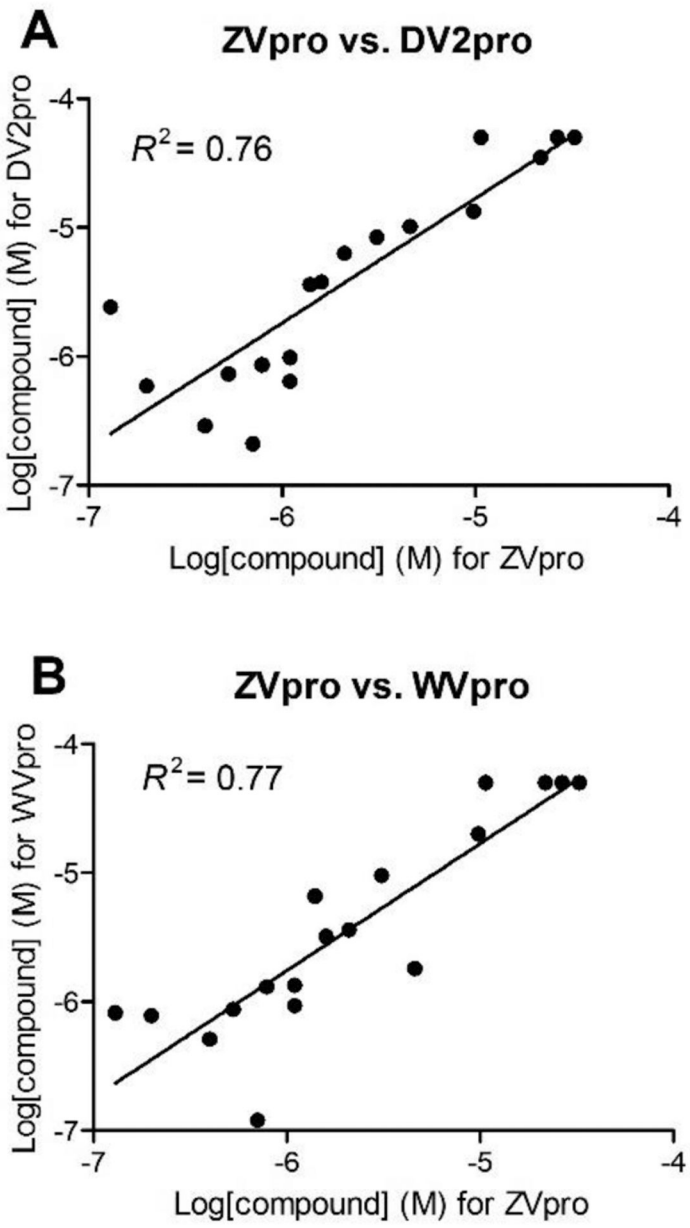
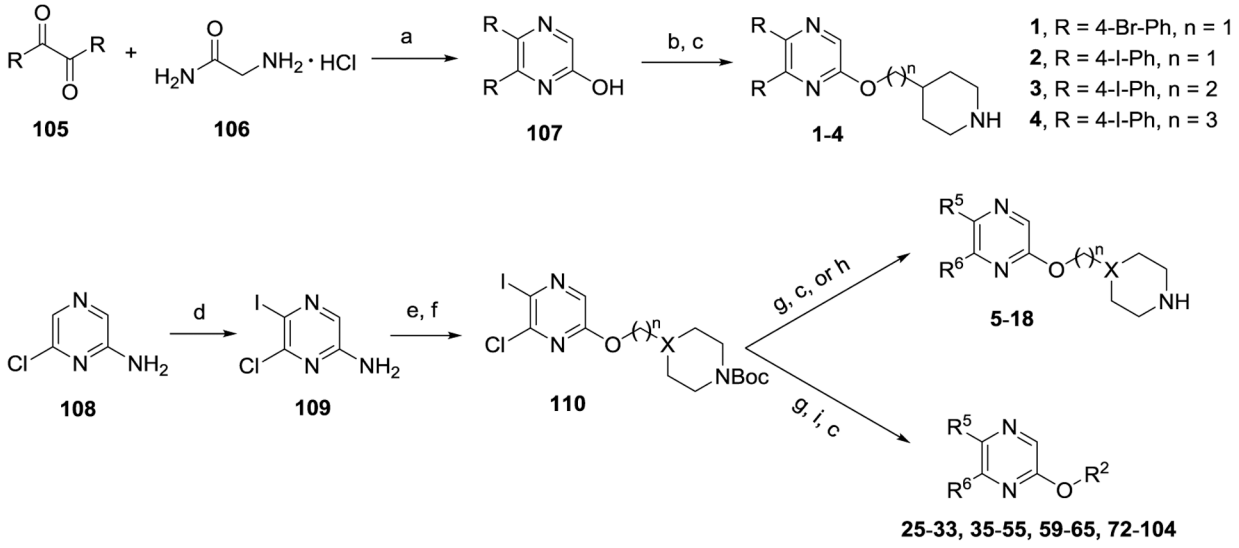


Figure 1.

Activities of ZVpro inhibitors are correlated with those of (**A**) DV2pro and (**B**) WVpro with R^2 values of 0.76 and 0.77, respectively.



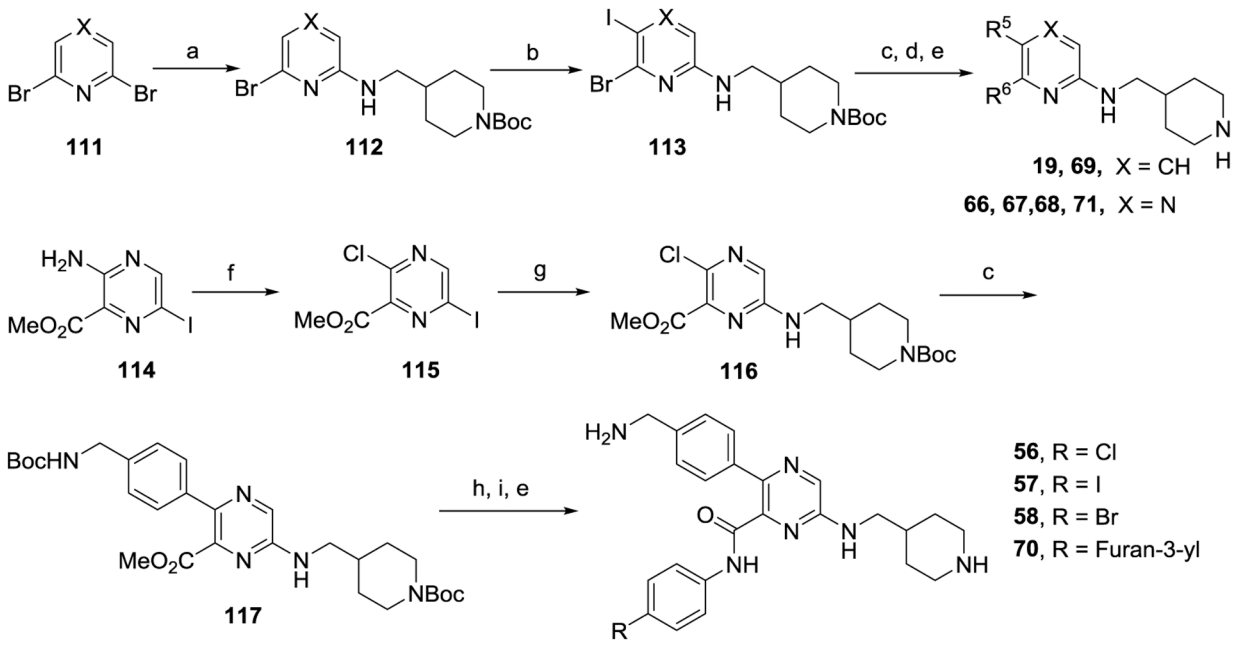
5, R^5, R^6 = 4-(thiophene-3-yl)-Ph; X = CH; n = 1
6, R^5, R^6 = 4-(furan-3-yl)-Ph; X = CH; n = 1
7, R^5, R^6 = 4-t-Bu-Ph; X = CH; n = 1
8, R^5, R^6 = 4-($OHCH_2$)-Ph; X = CH; n = 1
9, R^5, R^6 = 4-($OHCH_2$)-Ph; X = CH; n = 2
10, R^5, R^6 = 4-($PivOCH_2$)-Ph; X = CH; n = 1
11, R^5, R^6 = 4-($AcOCH_2$)-Ph; X = CH; n = 1
12, R^5, R^6 = 4-(NH_2CH_2)-Ph ; X = CH; n = 1
13, R^5, R^6 = 4-(NH_2CH_2)-Ph ; X = CH; n = 2
14, R^5, R^6 = 4-(NH_2CH_2)-Ph ; X = N; n = 2
15, R^5, R^6 = 4-($AcNHCH_2$)-Ph ; X = CH; n = 1
16, R^5, R^6 = 2-Me-4-(NH_2CH_2)-Ph ; X = CH; n = 1
17, R^5, R^6 = 4-($OHNHCH_2$)-Ph ; X = CH; n = 1
18, R^5, R^6 = 4-(Me_2NCH_2)-Ph ; X = CH; n = 1

25-28, 30-33, 35-55, 59-63, 72, and **79-104,** R^2 = Piperidin-4-yl-methyl
29, 65, R^2 = Piperidin-4-yl-ethyl
64, R^2 = Piperazin-1-yl-ethyl
73, R^2 = Cyclohexyl
74, R^2 = Benzyl
75, R^2 = Piperidin-4-yl
76, R^2 = $NH_2(CH_2)_3$
77, R^2 = $CH_3NH(CH_2)$
78, R^2 = 1-(Piperidin-4-yl)-ethoxy

Scheme 1.

Synthesis of pyrazine compounds **1**−**18**, **25**−**33**, **35**−**55**, **59**−**65**, **72**−**104**.[a]

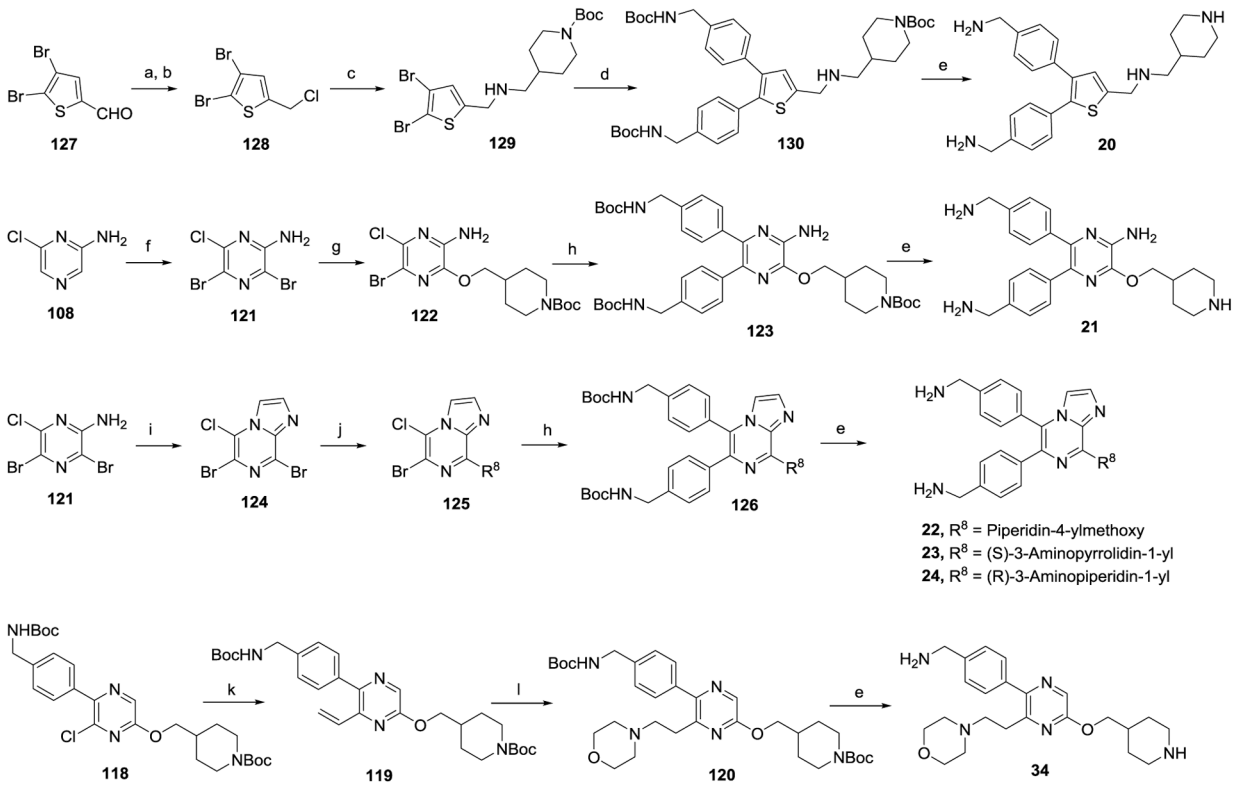
[a]*Reagents and conditions:* (a) NaOH, MeOH, reflux; (b) *N*-Boc-4-piperidinemethanol, PPh_3, diisopropyl azodicarboxylate, THF; (c) HCl (4 M in 1,4-dioxane), CH_2Cl_2, 0 °C; (d) *N*-iodosuccinimide, DMSO, 72 h; (e) $NaNO_2$, H_2SO_4 (conc.), 1 h; (f) Alcohols, PPh_3, diisopropyl azodicarboxylate, THF; (g) Aryl boronic acid or Aryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane-H_2O, 110 °C; (h) For synthesis of **10** and **11**, diisopropylethylamine, CH_2Cl_2, 0 °C, acetyl chloride and pivaloyl chloride; (i) For synthesis of **33**, **35**, **36** and **37**, K_2CO_3, DMSO, 110 °C, overnight; For other compounds: R^6-boronic acid or R^6-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane-H_2O, 110 °C.



Scheme 2.

Synthesis of compounds **19**, **56**−**58**, and **66**−**71**.[a]

[a]*Reagents and conditions:* (a) (*N*-Boc-piperidin-4-yl)methylamine, K_2CO_3, DMF, 100 °C, 12 h; (b) *N*-iodosuccinimide, CH_3CN-DMSO, 24 h; (c) Aryl boronic acid or aryl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane-H_2O, 80 °C; (d) 2-(4-(furan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, $Pd(PPh_3)_4$, Na_2CO_3, 1,4-dioxane-H_2O, 100 °C; (e) HCl (4 M in 1,4-dioxane), CH_2Cl_2, 0 °C; (f) $NaNO_2$, CuCl, HCl (12 M), −10 °C; (g) (*N*-Boc-piperidin-4-yl)methylamine, K_2CO_3, DMSO, 50 °C; (h) LiOH, H_2O-MeOH, rt; (i) An aniline, HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate), diisopropylethylamine, DMF.



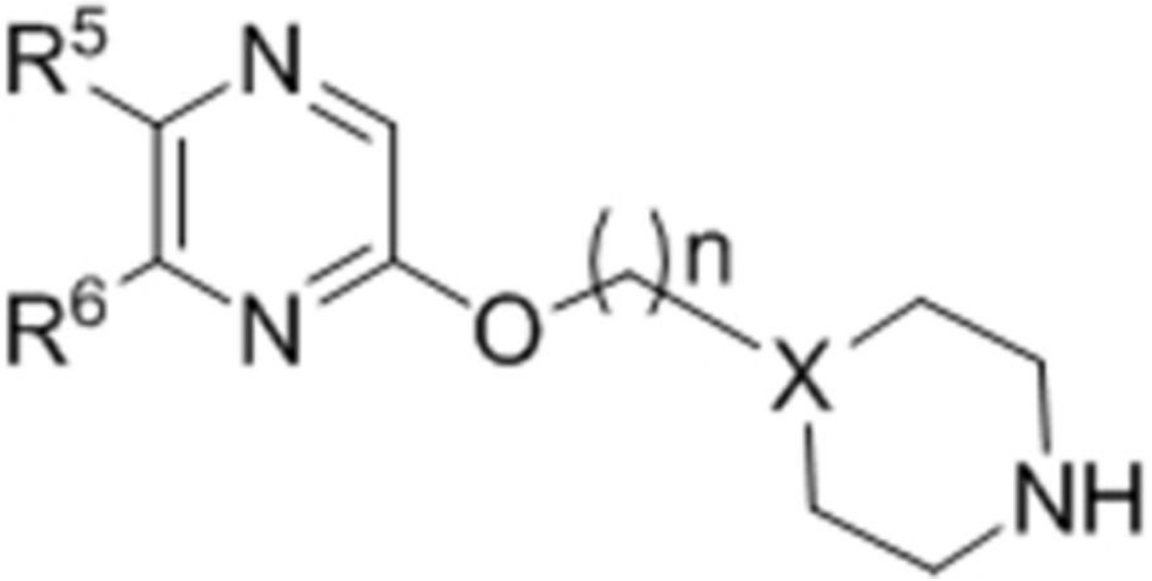
Scheme 3.

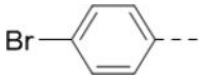
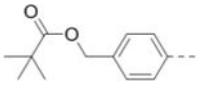
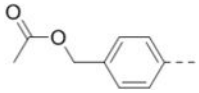
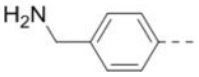
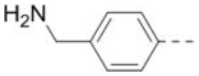
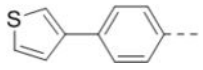
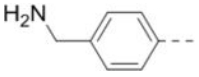
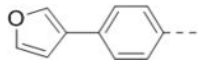
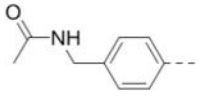
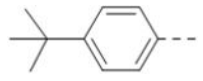
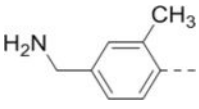
Synthesis of compounds **20**−**24** and **34**.[a]

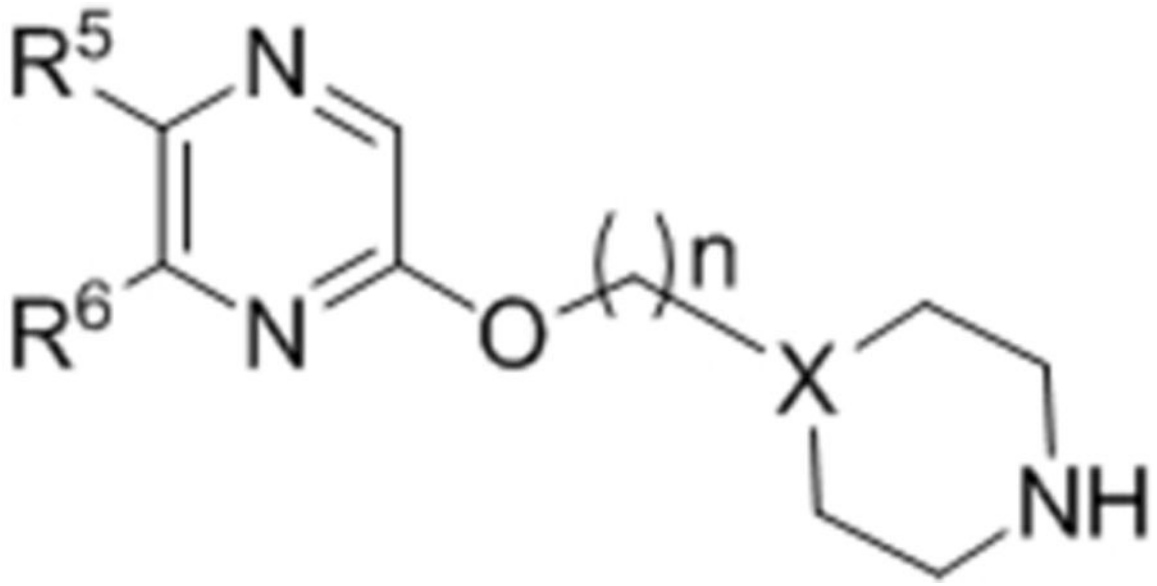
[a]*Reagents and conditions:* (a) $NaBH_4$, MeOH, 0 °C; (b) Cyanuric chloride, DMF; (c) 4-(aminomethyl)-1-Boc-piperidine, K_2CO_3, DMF; (d) Aryl-boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, 100 °C; (e) HCl (4 M in 1,4-dioxane); (f) *N*-bromosuccinimide, CH_3CN, 0 °C to rt, 18 h; (g) *N*-Boc-4-piperidinemethanol, NaOH, 1,4-dioxane, 75 °C, 4 h; (h) Aryl-boronic acid, $(A\text{-}^{ta}Phos)_2PdCl_2$, Na_2CO_3, 1,4-dioxane-H_2O, 100 °C, 16 h; (i) Chloroacetaldehyde, isopropyl alcohol, 105 °C, 18 h; (j) an alcohol, NaOH, 1,4-dioxane, 4 h, 75 °C; or an amine, diisopropylethylamine, CH_3CN, 4 h, 75 °C; (k) Potassium vinyltrifluoroborate, Cs_2CO_3, THF-H_2O, 100 °C; (l) Morpholine, DBU, 120 °C.

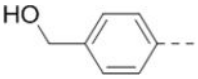
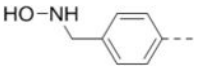
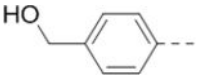
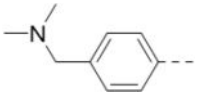
Table 1.

Structures and inhibitory activities of compounds **1–18**.[a]



Compd.	R^5=R^6	IC_{50} (μM)	Compd.	R^5=R^6	IC_{50} (μM)
1[b]		21.7	**10**		9.8
2		0.52	**11**		>10
3 (n = 2)		4.7	**12**		0.62
4 (n = 3)		>10	**13** (n = 2)		>10
5		1.4	**14** (X = N, n = 2)		>10
6		1.0	**15**		>10
7		3.1	**16**		2.1



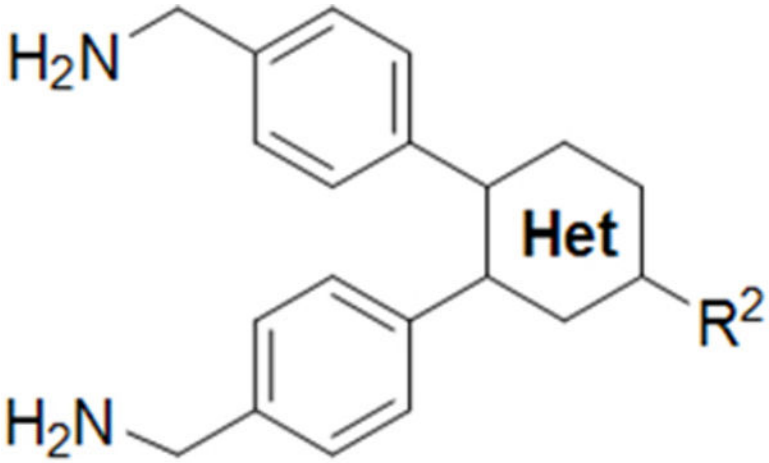
Compd.	R^5=R^6	IC_{50} (μM)	Compd.	R^5=R^6	IC_{50} (μM)
8		0.51	**17** (n = 2)		1.6
9 (n = 2)		2.1	**18**		0.39

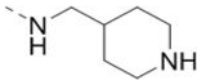
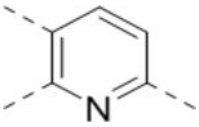
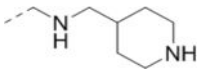
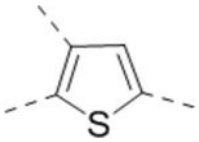
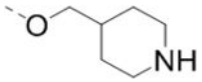
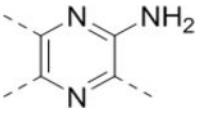
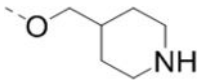
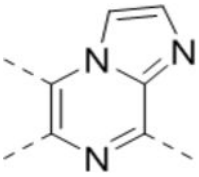
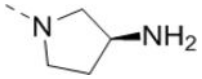
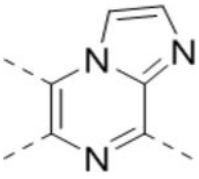
[a] Standard errors of all IC_{50} values are less than 30%.

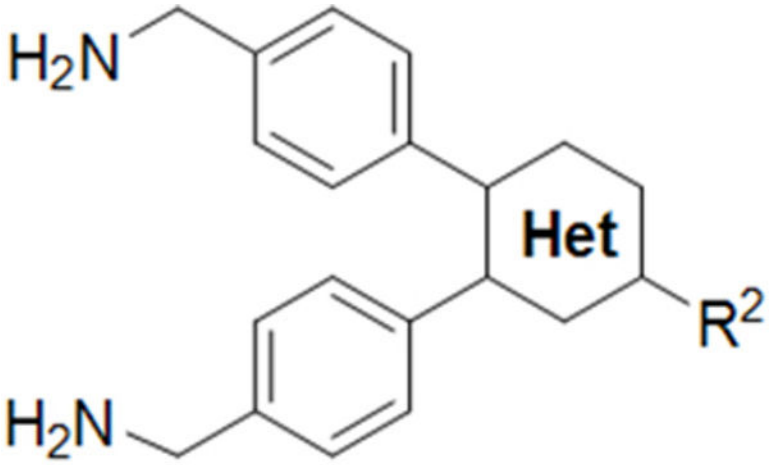
[b] Unless indicated, X = CH and n = 1.

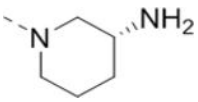
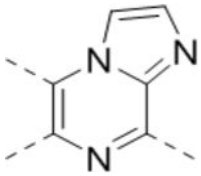
Table 2.

Structures and inhibitory activities of compounds **19–24**.[a]



Compd.	R^2	Heterocycle	IC_{50} (μM)
19			3.7
20			10.7
21			2.1
22			9.3
23			19.3

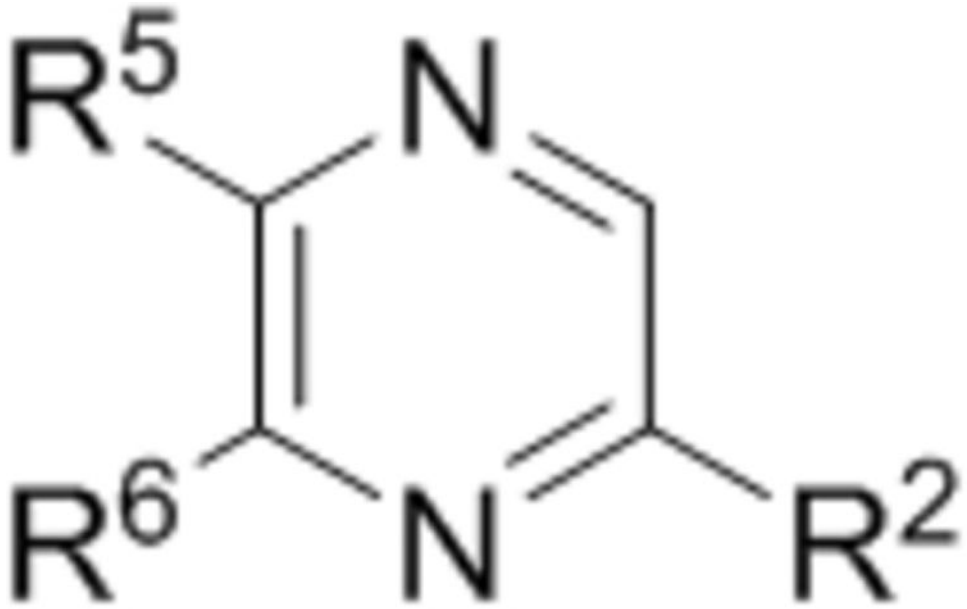


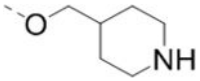
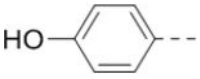
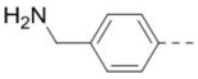
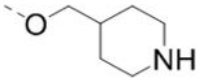
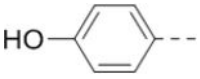
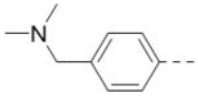
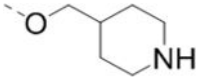
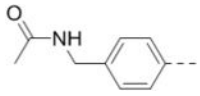
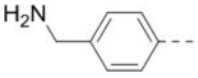
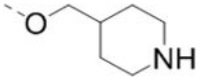
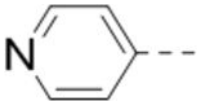
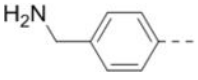
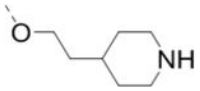
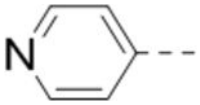
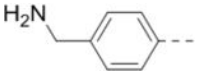
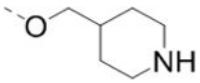
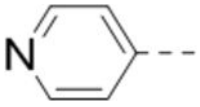
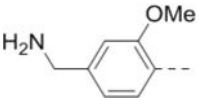
Compd.	R^2	Heterocycle	IC_{50} (μM)
24			3.5

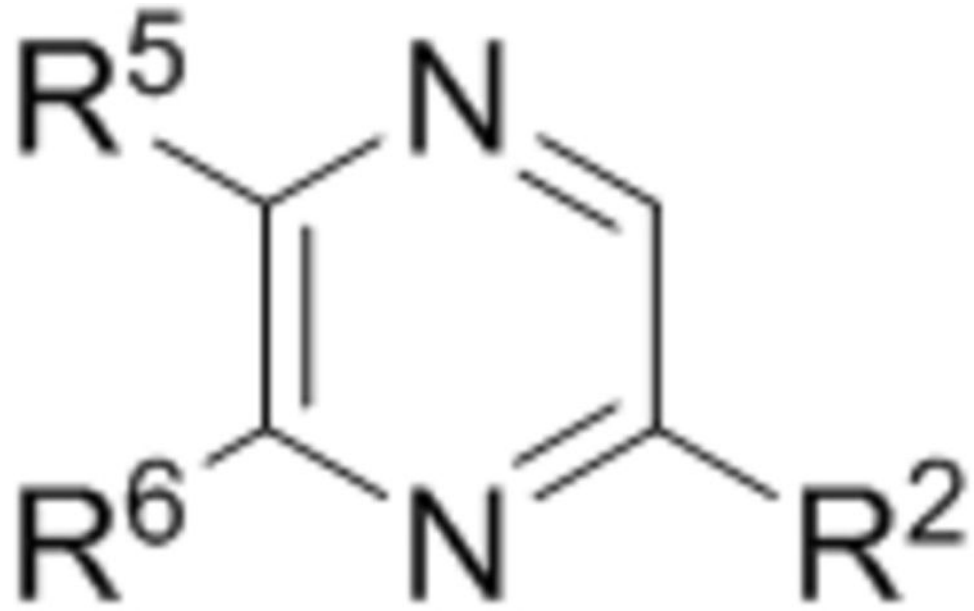
[a] Standard errors of all IC_{50} values are less than 30%.

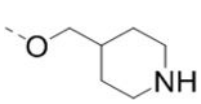
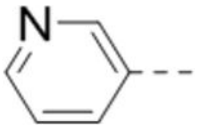
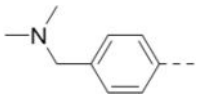
Table 3.

Structures and inhibitory activities of compounds **25–31**.[a]



Compd.	R^2	R^5	R^6	IC_{50} (μM)
25				8.1
26				20.5
27				30.0
28				0.32
29				1.7
30				3.5

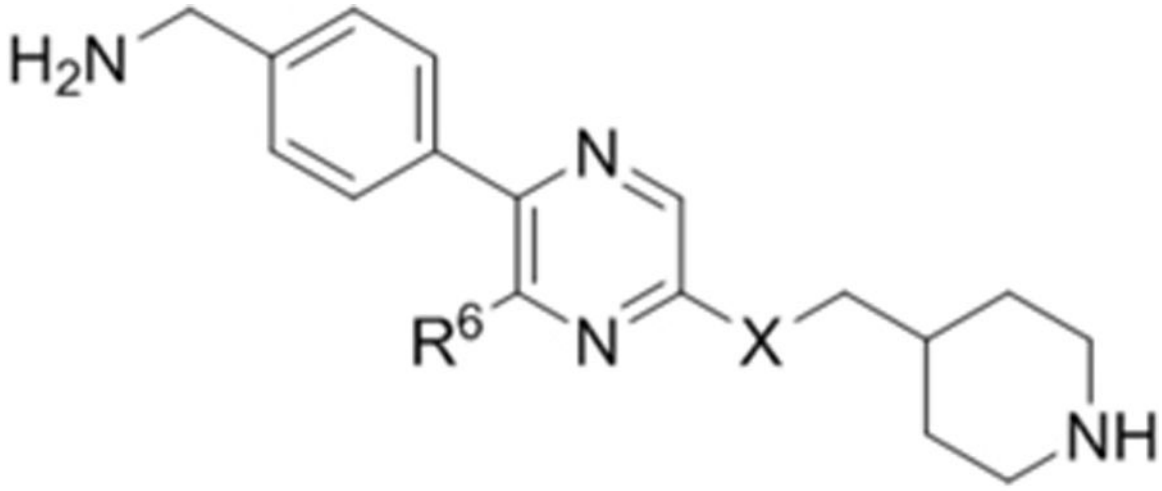


Compd.	R^2	R^5	R^6	IC_{50} (μM)
31				9.9

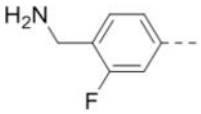
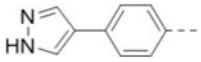
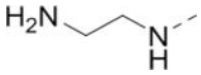
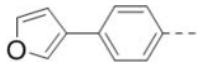
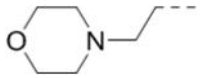
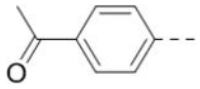
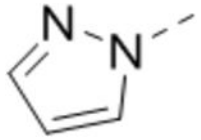
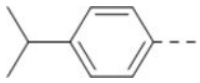
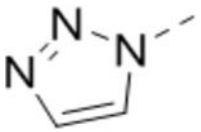
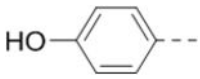
[a]Standard errors of all IC_{50} values are less than 30%.

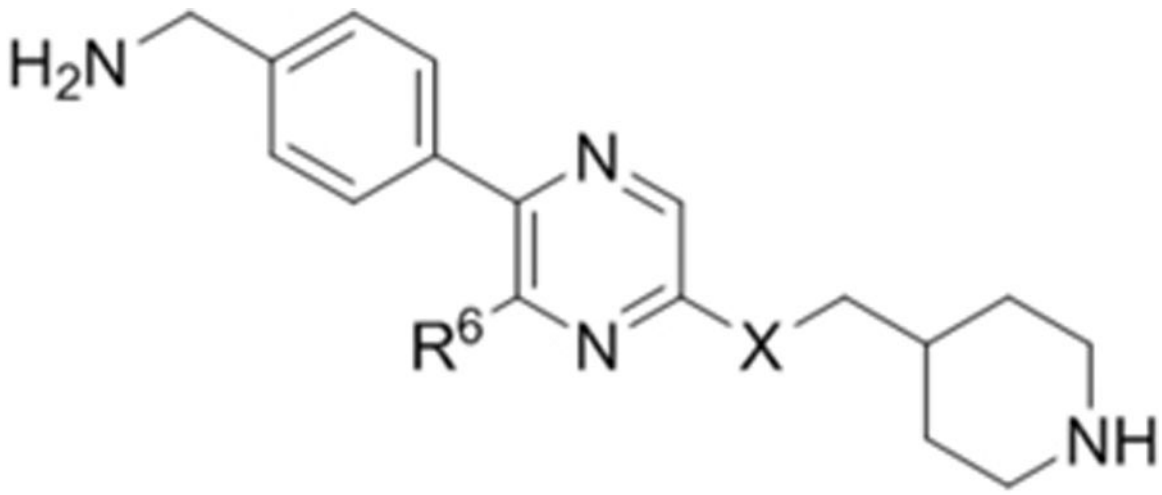
Table 4.

Structures and inhibitory activities of compounds **32–58**.[a]

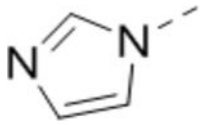
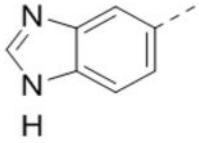
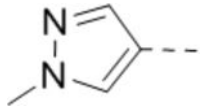
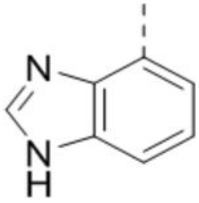
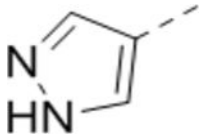
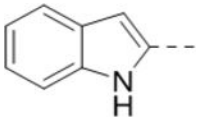
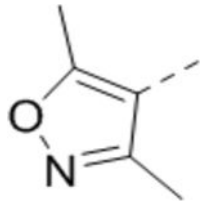
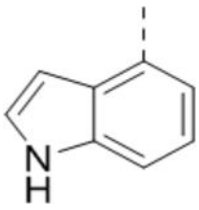


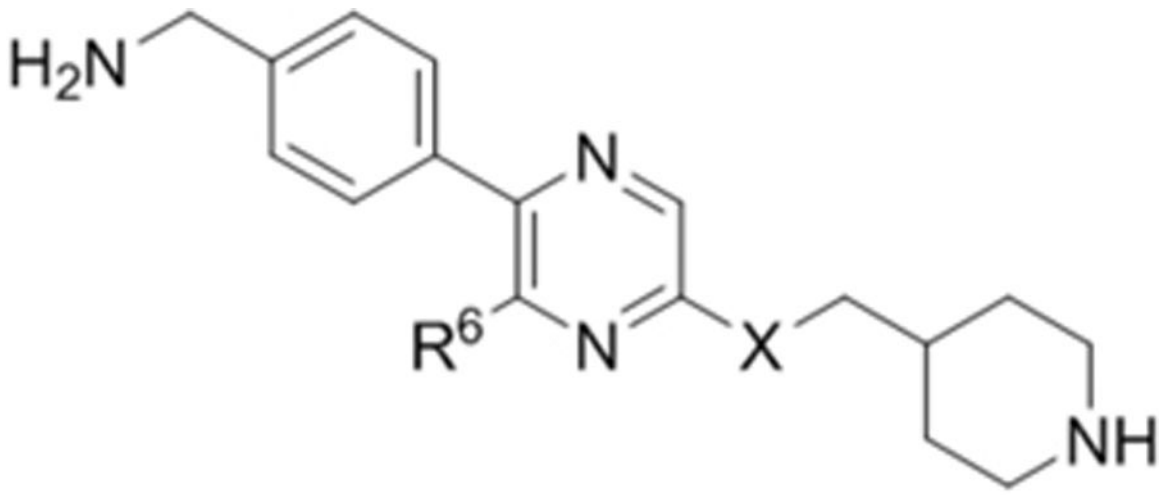
For **56**, **57**, and **58**, X =NH
For others, X = O

Compd.	R6	IC50 (μM)	Compd.	R6	IC50 (μM)
32		>50	**46**		0.71
33		7.3	**47**		0.20
34		>50	**48**		3.2
35		>50	**49**		2.0
36		>10	**50**		0.76

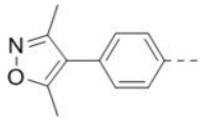
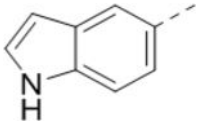
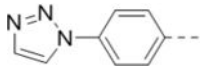
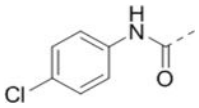
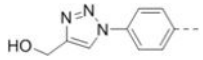
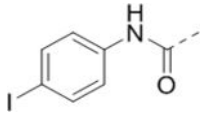
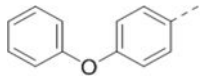
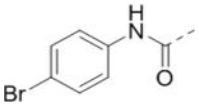
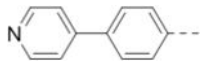


For **56**, **57**, and **58**, X =NH
For others, X = O

Compd.	R6	IC50 (μM)	Compd.	R6	IC50 (μM)
37		6.6	**51**		2.22
38		24.6	**52**		1.6
39		5.8	**53**		21.1
40		11.1	**54**		7.1



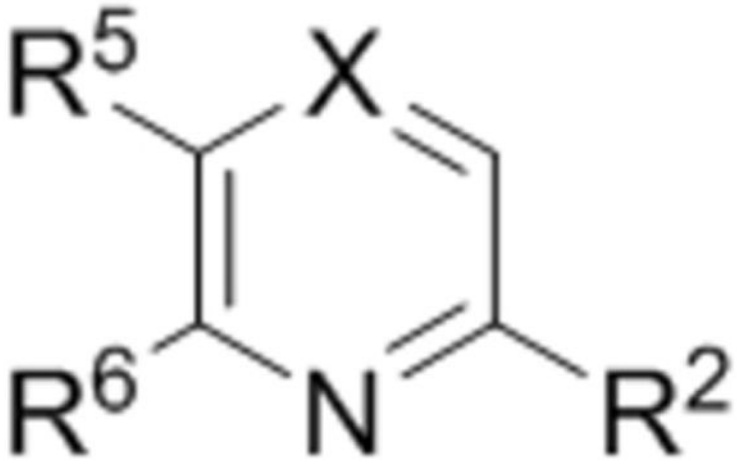
For **56**, **57**, and **58**, X =NH
For others, X = O

Compd.	R6	IC50 (μM)	Compd.	R6	IC50 (μM)
41		>10	**55**		1.1
42		>10	**56**		17
43		>10	**57**		12.6
44		32.6	**58**		12.6
45		26.5			

[a]Standard errors of all IC50 values are less than 30%.

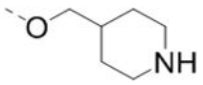
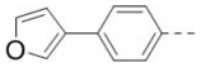
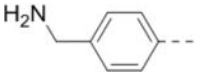
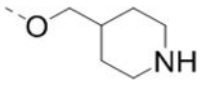
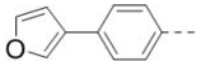
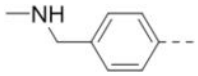
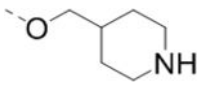
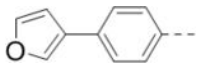
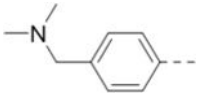
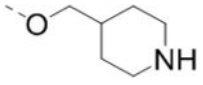
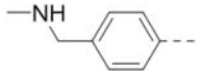
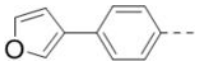
Table 5.

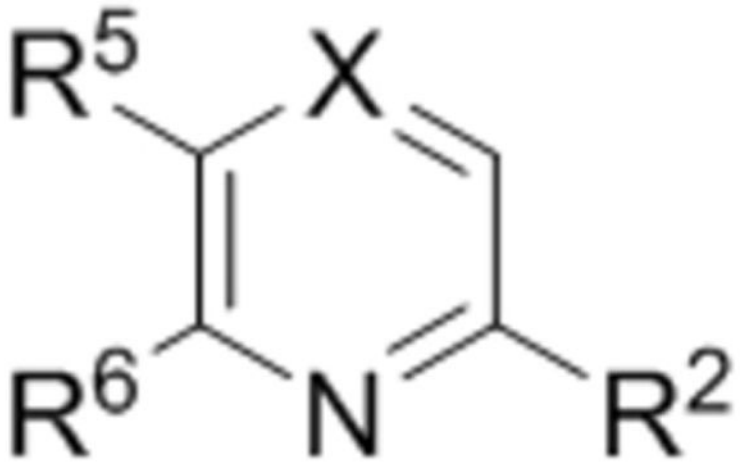
Structures and inhibitory activities of compounds **59–72**.[a]



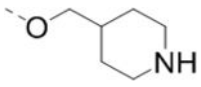
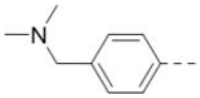
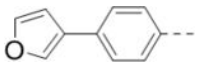
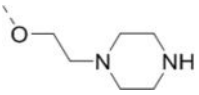
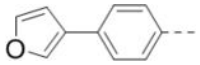
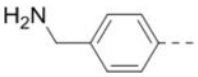
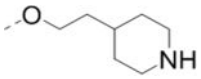
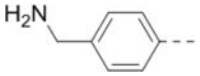
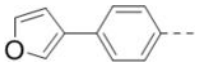
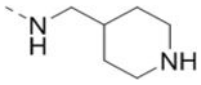
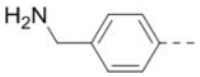
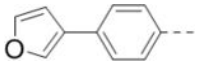
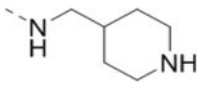
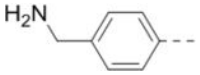
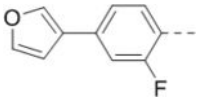
For **69**, X = CH

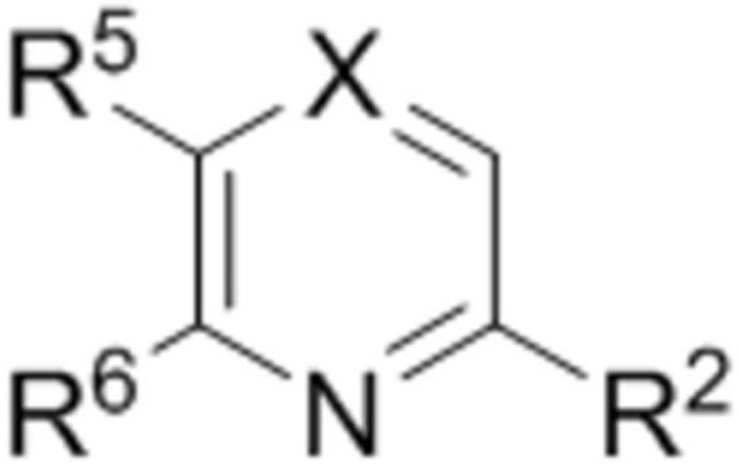
For others, X = N

Compd.	R^2	R^5	R^6	IC_{50} (μM)
59				0.68
60				3.3
61				1.8
62				0.53

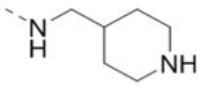
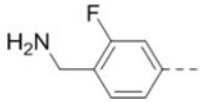
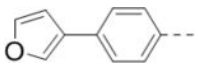
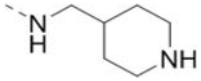
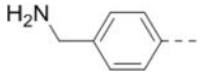
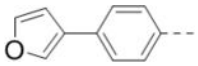
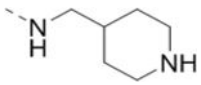
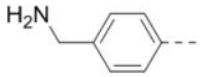
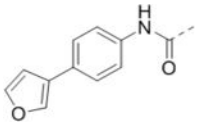
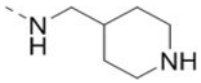
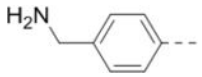
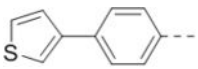


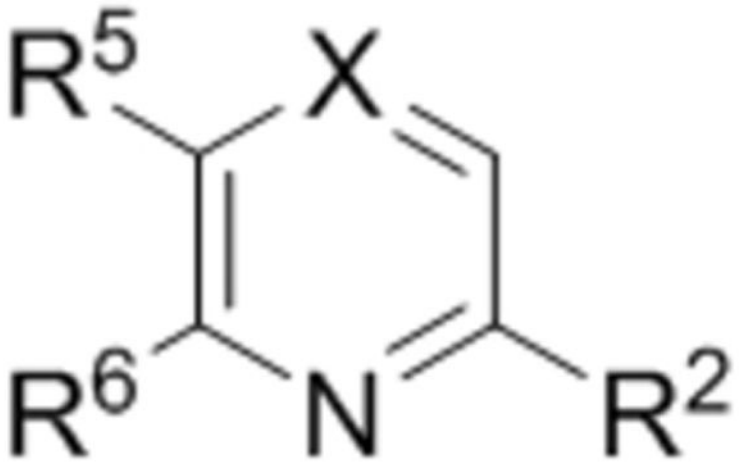
For **69**, X = CH
For others, X = N

Compd.	R^2	R^5	R^6	IC_{50} (μM)
63				6.1
64				1.8
65				1.3
66				0.40
67				2.3



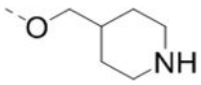
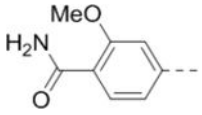
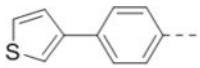
For **69**, X = CH
For others, X = N

Compd.	R^2	R^5	R^6	IC_{50} (μM)
68				5.3
69				0.79
70				1.1
71				18.5



For **69**, X = CH

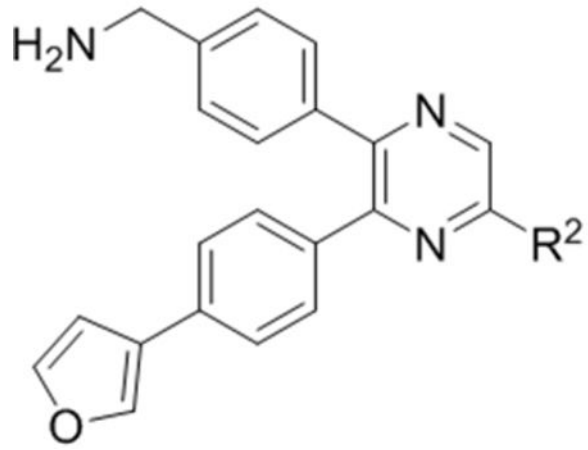
For others, X = N

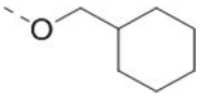
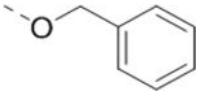
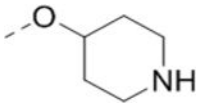
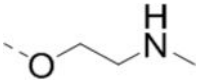
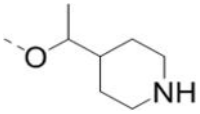
Compd.	R^2	R^5	R^6	IC_{50} (μM)
72				4.7

[a]Standard errors of all IC_{50} values are less than 30%.

Table 6.

Structures and inhibitory activities of compounds **73–78**.[a]

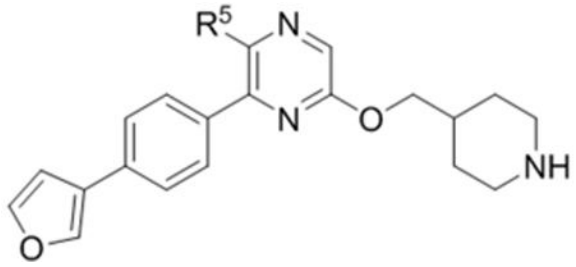


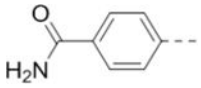
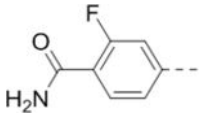
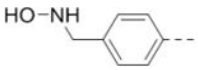
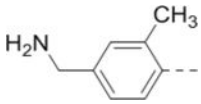
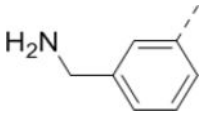
Compd.	R^8	IC_{50} (μM)
73		3.2
74		3.2
75		1.6
76		1.3
77		2.1
78		0.24

[a]Standard errors of all IC_{50} values are less than 30%.

Table 7.

Structures and inhibitory activities of compounds **79–83**.[a]

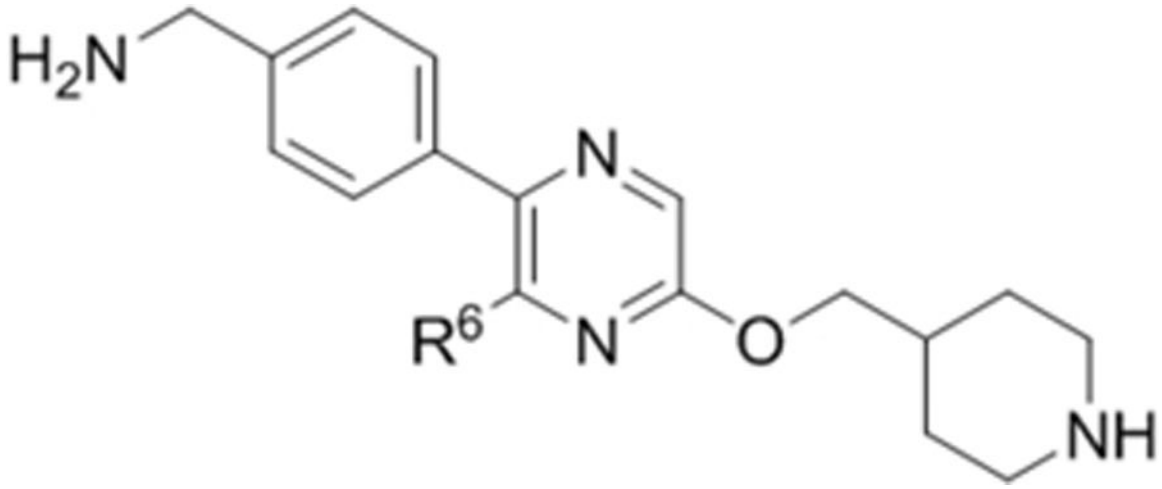


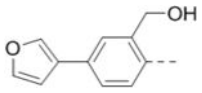
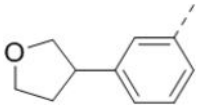
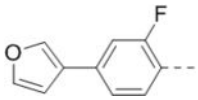
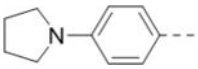
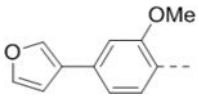
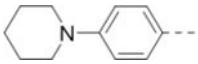
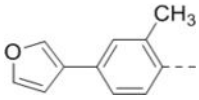
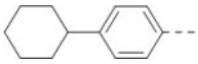
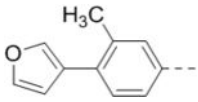
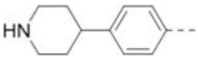
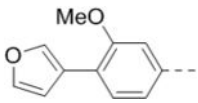
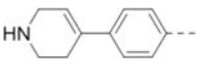
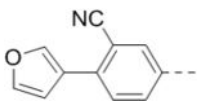
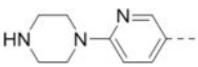
Compd.	R^5	IC_{50} (μM)
79		1.1
80		2.3
81		1.2
82		2.6
83		2.9

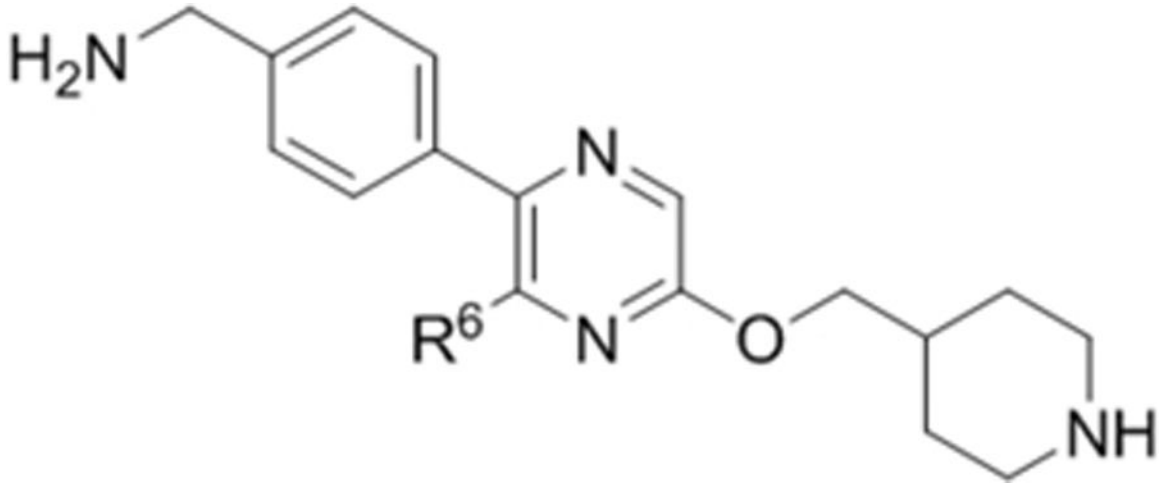
[a]Standard errors of all IC_{50} values are less than 30%.

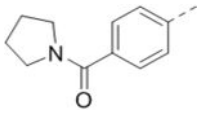
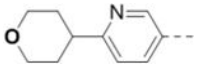
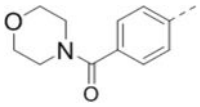
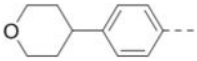
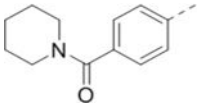
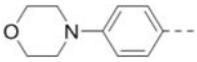
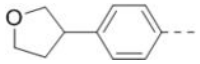
Table 8.

Structures and inhibitory activities of compounds **84–104**.[a]



Compd.	R6	IC50 (μM)	Compd.	R6	IC50 (μM)
84		>10	**95**		>10
85		8.4	**96**		2.5
86		1.9	**97**		>10
87		17.1	**98**		16.2
88		10.6	**99**		3.1
89		8.0	**100**		2.9
90		1.8	**101**		0.65



Compd.	R6	IC50 (μM)	Compd.	R6	IC50 (μM)
91		13.0	**102**		1.0
92		>10	**103**		0.13
93		3.5	**104**		>10
94		0.59			

[a]Standard errors of all IC50 values are less than 30%.

Table 9.

Inhibitory activity IC_{50} (μM) against Flavivirus proteases ZVpro, DV2pro and WVpro.[a]

	ZVpro	DV2pro	WVpro
44	32.6	>50	>50
45	26.5	>50	>50
1	21.7	35	>50
20	10.7	>50	>50
10	9.8	13.4	20.0
3	4.6	10.2	1.8
7	3.1	8.4	9.5
16	2.1	6.3	3.6
17	1.6	3.8	3.2
5	1.4	3.6	6.6
55	1.1	0.64	0.93
79	1.1	0.98	1.34
69	0.79	0.86	1.3
46	0.71	0.21	0.12
62	0.53	0.73	0.87
66	0.40	0.29	0.51
47	0.20	0.59	0.78
103	0.13	2.4	0.82

[a]Standard errors of all IC_{50} values are less than 30%.

Table 10.

Antiviral EC_{68} (μM) against ZIKV-FLR in U87 cells.

	ZVpro IC_{50} (μM)	ZIKV-FLR EC_{68} (μM)
1	21.7	>10
50	0.76	>10
7	3.1	5.0
102	1.0	3
79	1.1	2.5
55	1.1	2.5
46	0.71	2.5
69	0.79	1.2
59	0.68	1.2
62	0.53	1.2
66	0.40	1.2
78	0.24	1.2
103	0.13	0.6
47	0.20	0.3–0.6