Novel Inhibitors of the v-raf Murine Sarcoma Viral Oncogene Homologue B1 (BRAF) Based on a 2,6-Disubstituted Pyrazine Scaffold

Ion Niculescu-Duvaz,[†] Esteban Roman,[†] Steven R. Whittaker,[‡] Frank Friedlos,[†] Ruth Kirk,[‡] Ian J. Scanlon,[†] Lawrence C. Davies,[†] Dan Niculescu-Duvaz,[†] Richard Marais,[‡] and Caroline J. Springer*

The Institute of Cancer Research, Cancer Research UK Centre for Cancer Therapeutics, 15 Cotswold Road, Sutton, Surrey SM2 5NG, United Kingdom

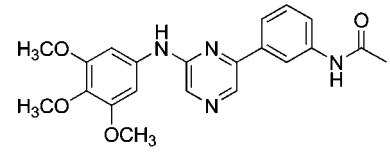
Received June 29, 2007

BRAF, a serine/threonine kinase, plays a key role in the development of certain types of cancer, particularly melanoma. 2-(3,4,5-Trimethoxyphenylamino)-6-(3-acetamidophenyl)-pyrazine, **1**, was identified as a low micromolar ($IC_{50} = 3.5\ \mu M$) BRAF inhibitor from a high-throughput screen of a library of 23000 compounds. This compound was chosen as the starting point of a program aimed at developing inhibitors of mutant ^{V600E}BRAF. We have already reported on the optimization of the trimethoxyphenylamino moiety of **1**. In this paper, we describe the synthesis of a series of compounds derived from **1** with the purpose of optimization of the pyrazine central core and the phenylacetamido moiety in order to increase the potency against ^{V600E}BRAF compared to CRAF. The biological activity of the new inhibitors was assessed against mutant ^{V600E}BRAF in vitro. Several compounds were identified with IC_{50}s of 300−500 nM for ^{V600E}BRAF, and all compounds that were assessed showed selectivity for ^{V600E}BRAF compared to CRAF by 5−>86-fold.

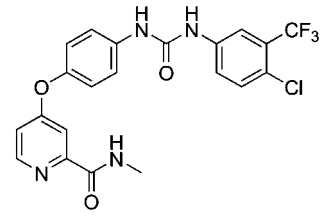
Introduction

The RAF−MEK−ERK signal transduction cascade is a conserved protein pathway that regulates cell growth, differentiation, and proliferation in response to external stimuli (growth factors, cytokines, or hormones). Phosphorylation of RAF stimulates its serine/threonine activity, triggering sequential phosphorylation of MEK and ERK. ERK further phosphorylates transcription factors such as ELK-1, regulating gene expression and controlling the response of the cell to external factors.[1] BRAF[a] is mutated in approximately 7% of human cancers, with particularly high frequency in melanoma (50−70%), ovarian (35%), thyroid (30%), and colorectal (10%) cancers.[2,3] The most common mutation (90%) is valine substitution by glutamic acid at position 600 (V600E). Mutated BRAF shows a 500-fold elevated kinase activity, providing cancer cells with both proliferation and survival signals.[4] Therefore, mutant BRAF is an important drug target for the treatment of human cancers.

The RAF family proteins (A, B, and C) are serine/threonine kinases.[5] A number of inhibitors, designed to target CRAF, are known. These include benzylidene oxindoles,[6] ZM 336,372,[7] and sorafenib, **2**.[8–10] Sorafenib inhibits ^{V600E}BRAF ($IC_{50} = 43$ nM) and, recently, isoquinolines[11,12] and triaryl imidazoles have been reported to have good activity against BRAF.[13,14] The most intensively studied RAF inhibitor, sorafenib (launched for renal cell carcinoma [RCC][15]) failed to show therapeutic activity in the treatment of malignant melanoma despite positive results in RCC. This failure can be attributed to its inability to reach a concentration in melanoma cells sufficient to inhibit ^{V600E}BRAF. Therefore, more potent ^{V600E}BRAF inhibitors are required for melanoma patients.



1



2

Figure 1

High-throughput screening, of a Biofocus library of 23000 compounds, provided us with a lead compound, **1**, that showed low micromolar potency against isolated ^{V600E}BRAF enzyme ($IC_{50} = 3.5\ \mu M$) and a tumor cell line driven by mutant BRAF (SRB, G $I_{50} = 3.6\ \mu M$). See Figure 1.

Three main structural domains were chosen for optimization of hit **1**: the trimethoxyphenyl moiety (ring A), the central pyrazine core (ring B), and the acetamidophenyl group (ring C). We have described previously the modifications of ring A.[16] Those efforts provided a few compounds that exhibited an improved biological profile with respect to the hit **1**. Herein we focus on the optimization of rings B and C with the aim of improving the inhibitory IC_{50} of the series for ^{V600E}BRAF and examining some key ^{V600E}BRAF inhibitors thus found for their selectivity compared to CRAF.

Rationale of the Design. The pyrazine hit **1** has a chemical structure significantly different from sorafenib and the other BRAF inhibitors. The design of new analogues was guided by medicinal chemistry considerations. The rationale for the synthesis of these compounds was to make inhibitors that are more selective for mutant BRAF compared to CRAF. The most

* To whom correspondence should be addressed. Phone: +44 20 8722 4214. Fax: +44 20 8722 4046. E-mail: caroline.springer@icr.ac.uk

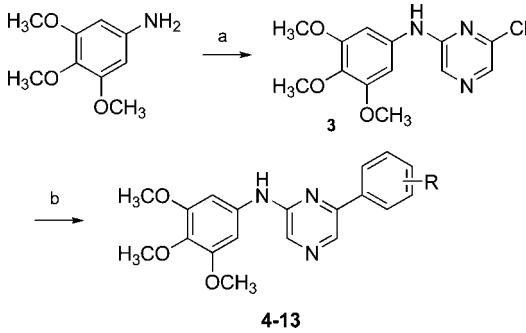
[†] Cancer Research UK Centre for Cancer Therapeutics at the Institute of Cancer Research.

[‡] Cancer Research UK Centre for Cell and Molecular Biology at the Institute of Cancer Research, 237 Fulham Road, London SW3 6JB, United Kingdom.

[a] Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homologue B1; CRAF, v-raf murine sarcoma viral oncogene homologue C1.

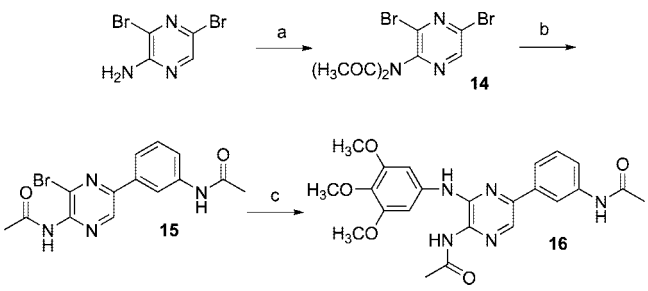
10.1021/jm070776b CCC: $40.75
Published on Web 05/13/2008

Scheme 1[a]



[a] Reagents and conditions: (a) $Pd(0)_2dba_3$, BINAP, NaOtBu, toluene, 90 °C; (b) $PdCl_2$·dppf:DCM 1:1, DME, Na_2CO_3 1M, 90 °C.

Scheme 2. Route for the Synthesis of Compound **16**[a]



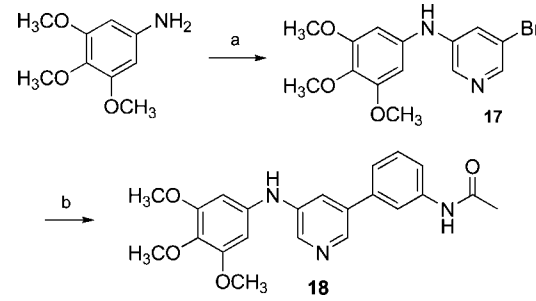
[a] Reagents and conditions: (a) Ac_2O, Na_2CO_3, reflux; (b) 3-acetamidophenyl boronic acid, $PdCl_2$·dppf:DCM 1:1, DME, Na_2CO_3 1M, 90 °C, microwave; (c) 3,4,5-trimethoxyaniline, $Pd_2(0)dba_3$, Xantphos, NaOtBu, toluene, 110 °C.

well-known RAF inhibitor, sorafenib, is often described as a BRAF inhibitor, but we find here that it has no selectivity for BRAF. Herein, we describe potent new inhibitors that are much more selective for mutant BRAF compared to CRAF.

Chemistry. Scheme 1 outlines the synthesis of **1** and related pyrazine analogues (compounds **4**−**13**). The amination of 2,6-dichloropyrazine with 3,4,5-trimethoxyaniline furnished the common intermediate **3**,[19,20] which was reacted with several boronic acids or esters, via Suzuki coupling,[21–23] to furnish the final targets. Several procedures were used for Suzuki couplings, with good results, including ligands such as 1,4-bis-(diphenylphosphino)-butane (dppb), 2,2′-bis-(diphenylphosphino)-1,1′-binaphtalene (BINAP), 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), dicyclohexylphosphino-2′-(*N*,*N*-dimethylaminobiphenyl) or imidazolium salts, and palladium catalyst such as tris-(dibenzylideneacetone)-dipalladium (0) ($Pd(0)_2dba_3$), [1,1′-bis-(diphenyl phosphino)-ferrocene]dichloropalladium (II) complex with DCM 1:1, ($PdCl_2$·dppf:DCM 1:1). The use of phase transfer agents such as tetrabutyl ammonium fluoride proved advantageous in some cases. Both conventional and microwave heating were employed.

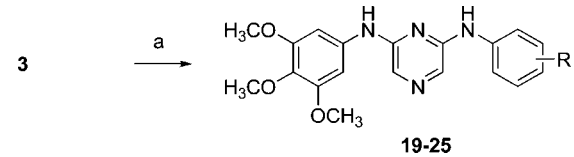
General Strategy for the Synthesis of 1 and Related Compounds. The synthesis of acetamidopyrazine **16** (see Scheme 2) involved an additional acetylation step. 3-Amino-2,6-dibromopyrazine was converted with acetic anhydride to the diamido pyrazine **14**, which was reacted with 3-acetamidophenylboronic acid via Suzuki coupling. During this process, one amido group was cleaved, giving intermediate **15**, which in turn was subjected to amination with 3,4,5-trimethoxyphenylamine to furnish acetamidopyrazine **16**. It was found that the Suzuki coupling yielded the 2-bromo-3-acetamido-6-(3-acetamidophenyl)-pyrazine isomer and not the 2-(3-acetamidophenyl)-3-acetamido-6-bromopyrazine isomer. This was ascertained by the analysis of

Scheme 3. Route for Central-Core Modified Derivatives[a]



[a] Reagents and conditions: (a) 3,5-dibromopyridine, $Pd(0)_2dba_3$, BINAP, NaOtBu, toluene, 90 °C; (b) $PdCl_2$·dppf:DCM 1:1,DME, Na_2CO_3 1M, 90 °C.

Scheme 4. Synthesis of the Diamino Analogues[a].



[a] Reagents and conditions: (a) aminoaryl compounds, $Pd(0)_2dba_3$, 1,3-bis-(2,6-di-i-propylphenyl)-4,5-dihydroimidazolium tetrafluoroborate, KOt-Bu, dioxane, 100 °C, microwave.

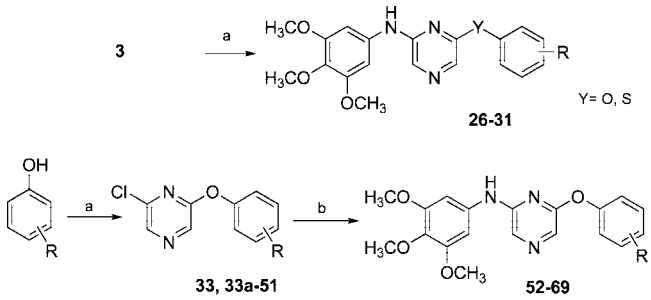
the NOESY spectrum of **15**, which shows a crossed peak between the singlet of the pyrazine central core and two of the peaks of the phenyl moiety, fully consistent with the expected isomer. Additionally, the 3-acetamido moiety behaved as an isolated system exhibiting no crossed peaks with the rest of the molecule. The other 6-(3-acetamido) group, on the other hand, interacted with the phenyl moiety, giving the expected crossed peaks. Following the NOESY crossed peaks, this last acetamido unit can also be linked to the pyrazine singlet. All these observations confirmed that the compound obtained was the expected isomer, the Suzuki coupling displacing the least hindered bromine.

Several modifications to the pyrazine central core were attempted by introduction of heterocycles other than pyrazine (see Scheme 3). Reaction of 3,4,5-trimethoxyaniline with 3,5-dibromopyridine yielded the corresponding intermediate **17**. For amination, we used Xantphos (for the dibromo heterocycles), BINAP, dicyclohexylphosphino-2′-(*N*,*N*-dimethylaminobiphenyl), or imidazolium ligands with Pd catalysts and conventional or microwave heating. The resulting intermediates were reacted with 3-acetamido-boronic acid under Suzuki conditions to obtain the desired compound **18**.

We attempted the introduction of a linker (O, N, or S) in between rings B and C to ascertain whether it would be beneficial in increasing the potency of these molecules. Therefore, the synthesis of the diamino analogues (see Scheme 4) was carried out from intermediate **3**, which was converted under harsher amination conditions with microwave or conventional heating to the desired compounds **19**−**25**. Higher loadings of ligands and catalysts were used to compensate for the loss of activity of the pyrazine system upon introduction of the first amino group.

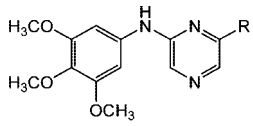
Synthesis of the Analogues with an Oxygen Linker. For the synthesis of the O-linker analogues, two strategies were followed. First, the common intermediate **3** (see Scheme 5) was reacted with the corresponding phenol under microwave heating conditions in the presence of potassium *tert*-butoxide. The same chemistry was used to synthesize compound **30** with a −S− linker. However, using this route, the overall yields are low

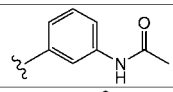
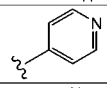
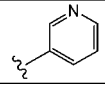
Scheme 5[a]



[a] Reagents and conditions: (a) KOtBu, DMF, 90 °C; (b) $Pd(0)_2dba_3$, dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino-biphenyl), NaOtBu, toluene, 90 °C.

Table 1. Replacement of the Ring C with Unsubstituted Aryl and Heteroaryl Systems



Compound number	R	^{V600E}BRAF IC_{50} (μM)
1		3.5
4		2.9
5		22

and the purification of the final compounds difficult. Therefore, we took the alternative approach, which involved the reaction of 2,6-dichloropyrazine with the corresponding potassium phenolate and the subsequent coupling of the resulting intermediates (**33**, **33a**−**51**) with 3,4,5-trimethoxyaniline to yield the desired products (**52**−**69**).

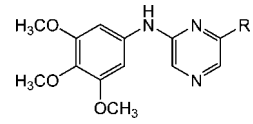
Several acetamidonaphthyl (4-, 5-, and 6-acetamido isomers) were synthesized in one step from the corresponding commercial amines by treatment with acetic anhydride. The resulting intermediates were reacted with 2,6-dichloropyrazine to produce the corresponding chloropyrazines (**50**, **51**), which were subsequently treated with a series of amines to give the desired final targets (**70**, **77**−**79**). The 2(3,4,5-trimethoxyphenylamino)-6-(4-acetamidonaphthyloxy)-pyrazine, **76**, was obtained by coupling of the intermediate **3** with the corresponding 4-acetamido-napthol. The oximes (**71**−**75**) were obtained by treating the corresponding ketones (**58**, **59**, **61**, **68**, **69**) with hydroxylamine in EtOH.

Structure−Activity Relationships. The biological activities of the compounds were determined using the determination of the potency against the ^{V600E}BRAF enzyme in vitro (IC_{50}, BRAF). The data are summarized in Tables 1−6.

We have shown previously[16] that replacement of the methoxy group from ring A with an imidazolyl moiety increased the potency against BRAF to $IC_{50} < 1\mu M$. In addition, not all 3-methoxy groups are required for activity; equipotent compounds with only two methoxy groups have been synthesized.

Modification of Ring C. There is a complete loss of activity when ring C is a phenyl or naphthyl system (data not shown),

Table 2. Substitution of the Phenyl Ring C



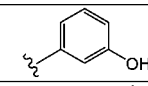
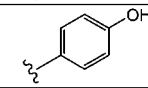
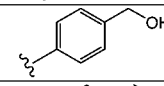
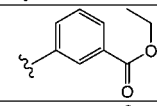
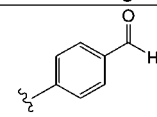
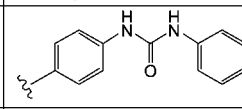
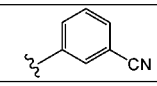
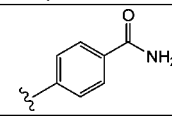
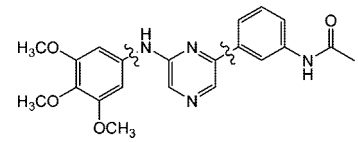
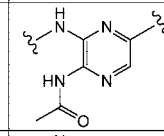
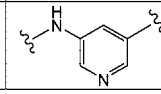
Compound number	R	^{V600E}BRAF IC_{50} (μM)
6		4.0
7		18
8		26
9		14
10		3
11		1.2
12		9.8
13		1.1

Table 3. Substitution of the Pyrazine Central Core with Other Heterocycles



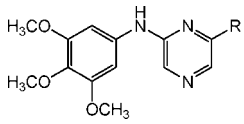
Compound number	Central core	BRAF IC_{50} (μM)
16		>100
18		26

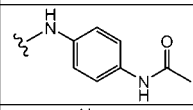
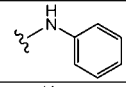
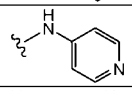
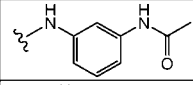
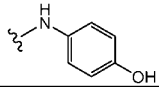
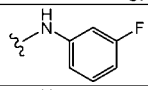
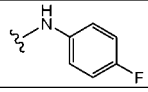
whereas replacement of ring C with a pyridine restores the activity (4-pyridyl-, **4**).

Replacement of the Acetamidophenyl Moiety (Ring C) by Simple Scaffolds. Introduction of other substituents in positions 3 and 4 of the phenyl ring C (see Table 2) resulted in some interesting observations.

Substitution in Position 3. Introduction of an extra methylene group on the 3-acetamido function results in a total loss of

Table 4. Introduction of Substituents an −N− Linker between Rings B and C



Compound number	R	^{V600E}BRAF IC_{50} (μM)
19		16
20		16
21		4.7
22		14
23		4.9
24		12
25		19

activity. None of the substituents replacing the 3-acetamido group is beneficial.

Substituents in Position 4. Attaching the acetamido moiety in position 4 results in a loss of activity. The only modification that is fully tolerated in this position is the carboxamide function (compound **13**), which results in a compound active on BRAF.

Modifications of Ring B. To assess the role of the pyrazine ring in binding, the pyrazine central core was replaced by pyridine (see Table 3). This modification was partially tolerated, resulting compound **18** being less active against the enzyme. Replacement of the pyrazine ring by other heterocycles such as pyrimidine or pyridazine renders the compounds inactive. Electronic effects might explain the decrease in activity shown by the pyridine compound **18**. Many kinase inhibitors have a hinge binding motif consisting of a hydrogen donor−hydrogen acceptor pair. The 3-acetamidopyrazine compound **16** proved to be inactive, possibly due to the steric hindrance of the hinge binding.

Linkers between Rings B and C. Three different linkers, −N−, −O−, and −S−, were explored between the central core (pyrazine ring B) and the phenyl ring C (see Tables 4 and 5). Introduction of an −NH− group as linker between rings B and C (compound **22**, see Table 4) offered no improvement over hit **1**, the equivalent with an −N− linker of the hit, was less active.

An oxygen atom as linker was also investigated (see Table 5) by using substituted phenyl rings, fused rings (1- and 2-naphthyl, quinolines, indanones, tetralones, etc.), and biphenyl systems as ring C. Regarding phenyl substitution, hydrophobic atoms such as F and Cl resulted in a decrease of potency with respect to the hit. Introduction of groups able to establish hydrogen bond interactions did not produce any improvement. The most promising systems turned out to be fused rings, especially the 1-naphthyloxy substituent (compound **26**), which is more potent on BRAF than hit **1**. By contrast, the 2-naphthyloxy derivative **26a** was devoid of activity. The most inhibitory BRAF compounds are the 4- and 5-acetamidonaphthyl-1-oxy derivatives **76** and **70** with IC_{50} of 410−560 nM (see Table 6).

A number of oximes were also synthesized (compounds **71**−**75**). They are more active than the precursor ketones, but none of them yield an inhibition of BRAF below 1 μM. Finally, we synthesized a number of compounds combining the most effective structural feature resulting from the foregoing SAR studies on rings A, B, and C (compounds **77**−**79**). The most effective compound (**79**) shows an IC_{50} of 310 nM.

Sorafenib was originally identified as an inhibitor of CRAF and subsequently found to inhibit mutant BRAF among other kinases.[17] Sorafenib is reportedly 6-fold more potent against CRAF than it is against ^{V600E}BRAF. Therefore, we sought to generate inhibitors that were capable of preferentially inhibiting ^{V600E}BRAF compared to CRAF in order specifically to target oncogenic BRAF. Compounds were tested for activity in a CRAF kinase assay and a selectivity index for inhibition of oncogenic BRAF over CRAF was calculated (see Table 7). In contrast to sorafenib, which in our hands displayed equal potency against both BRAF and CRAF, all pyrazine compounds tested proved to be 5−>86-fold more selective for BRAF compared to CRAF.

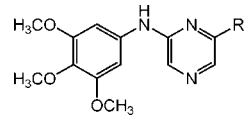
Conclusions

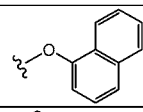
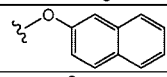
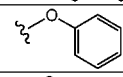
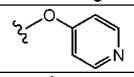
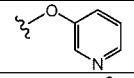
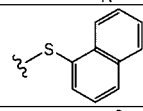
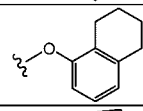
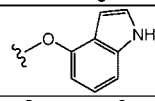
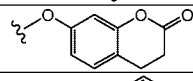
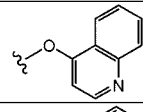
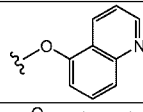
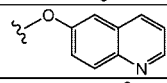
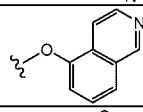
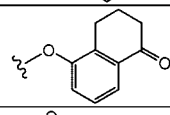
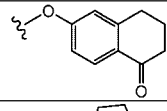
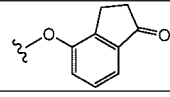
A 2,6-disubstituted pyrazine scaffold selected from a high-throughput screen led to a series of new inhibitors of ^{V600E}BRAF. Pyrazine inhibitors with potency <500 nM and 5−86-fold more selective for mutant BRAF compared to CRAF have now been obtained.

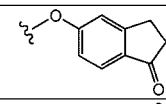
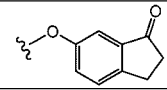
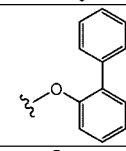
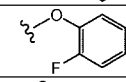
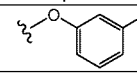
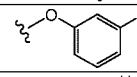
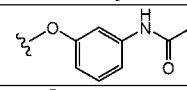
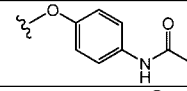
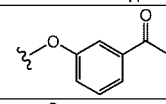
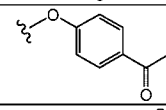
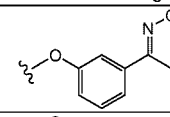
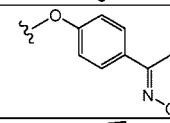
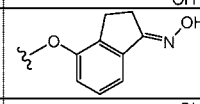
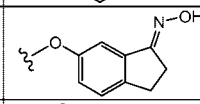
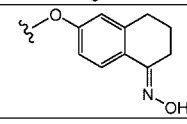
Experimental Section

All starting materials, reagents, and solvents for reactions were reagent grade and used as purchased. Chromatography solvents were HPLC grade and were used without further purification. Reactions were monitored by thin layer chromatography (TLC) analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was carried out on Merck silica gel 60 (0.015−0.040 mm) or in disposable Isolute Flash Si and Si II silica gel columns. Preparative TLC was performed on either Macherey−Nagel (809 023) precoated TLC plates SIL G-25 UV_{254} or Analtech (2015) precoated preparative TLC plates, 2000 μm with UV_{254}. LC-MS analyses were performed on a Micromass LCT/Waters Alliance 2795 HPLC system with a Discovery 5 μm, C18, 50 mm × 4.6 mm i.d. column from Supelco at a temperature of 22 °C using the following solvent system: solvent A, methanol; solvent B, 0.1% formic acid in water, at a flow rate of 1 mL/min. Gradient starting with 10% A/90% B from 0−0.5 min then 10% A/90% B to 90% A/10% B from 0.5 to 6.5 min and continuing at 90% A/10% B up to 10 min. From 10 to 10.5 min, the gradient reverted back to 10% A/ 90% B and was held until 12 min. UV detection was at 254 nm and ionization was positive or negative ion electrospray. The molecular weight scan range was 50−1000. Samples were supplied as 1 mg/mL in DMSO or methanol with 3 μL injected on a partial loop fill. NMR spectra were recorded in DMSO-d_6 on a Bruker DPX 250 operating at 250.13 MHz or on a Bruker Avance 500 operating at 500.26 MHz. The signal of the deuterated solvent was used as internal reference; the chemical shifts are expressed in ppm (δ). Preparative HPLC purifications were performed on an Axial Chromatospac Prep 10 (Jobin-Yvon) using Merck Kieselgel 60 (0.015−0.040). Microwave reactions were run on a CM discovery unit operating at 200 W with simultaneous stirring. The parallel

Table 5. Introduction of an −O− Linker between Rings B and C



Compound number	R	^{V600E}BRAF IC_{50} (μM)
26		1.2
26a		>100
27		31
28		16
29		45
30		9.8
31		18
32		7.4
52		44
53		1.5
54		10
55		29
56		3.8
57		29
58		76
59		18

Compound number	R	^{V600E}BRAF IC_{50} (μM)
60		70
61		22
62		10
63		45
64		56
65		36
66		13
67		5.5
68		19
69		34
71		11
72		26
73		1.4
74		86
75		92

synthesis in liquid phase were run on a Carousel (12 place reaction station) from Radley Discovery Technology.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-pyridyl)-pyrazine (4) (Method A). 2-(3,4,5-trimethoxyphenylamino)-6-chloropyrazine 3 (200 mg, 0.68 mmol), $PdCl_2$.dppf:DCM 1:1 (55 mg, 0.068 mmol) and 4-pyridyl boronic acid (100 mg, 0.82 mmol) were dissolved in DME (15 mL). To this solution, an aqueous solution of Na_2CO_3 (1.4 mL, 1M) was added under stirring and the reaction mixture was heated at 90 °C for 24 h. After cooling, Et_2O (25 mL) was added and the organic solution washed with brine (2 × 30 mL), dried ($MgSO_4$), and evaporated to dryness. The brown solid obtained was recrystallized from AcOEt, giving the title compound

Table 6. Combination of the Core with the Best Rings B and C

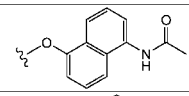
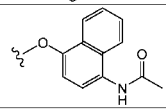
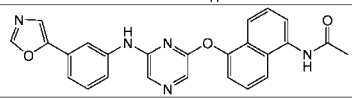
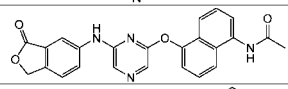
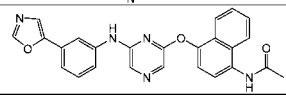
Compound number	R	^{V600E}BRAF IC_{50} (μM)
70		0.41
76		0.56
77		0.65
78		2.5
79		0.31

Table 7. Comparison of Compound Activity vs ^{V600E}BRAF and CRAF[a]

compound number	^{V600E}BRAF IC_{50} (μM)	CRAF IC_{50} (μM)	selectivity index
sorafenib	0.043	0.052	1
11	1.16	>100	>86
13	1.12	38.15	34
76	0.56	20.26	36
77	0.65	6.96	11
79	0.31	1.52	5

[a] A selectivity index was calculated (CRAF IC_{50}/^{V600E}BRAF IC_{50}) to indicate selectivity of compounds for oncogenic BRAF over CRAF.

(40 mg). Yield: 17%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.64 (s, 3H), 3.83 (s, 6H), 7.22 (s, 2H), 8.07 (d, 2H, J = 4.73 Hz), 8.26 (s, 2H), 8.65 (d, 2H,), 8.72 (d, 1H, H_{Py}), 9.70 (s, 1H, NH). LC-MS: t_R = 6.20 min; *m/z*: 339.1 [M^+ + H, 100] calcd for $C_{18}H_{19}N_4O_3$.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-pyridyl)-pyrazine (5). Using method A (reaction time: 3 h) with 3-pyridylboronic acid (100 mg, 0.82 mmol), the title compound was obtained (120 mg). Yield: 52%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.67 (s, 3H), 3.85 (s, 6H), 7.26 (s, 2H, H), 7.58−7.62 (m, 1H), 8.25 (s, 1H), 8.49 (d, 1H, J = 7.9 Hz), 8.63 (s, 1H), 8.69 (d, 1H, J = 3.2 Hz), 9.51 (d, 1H, J = 2.2 Hz), 9.69 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 55.41, 60.20, 96.20, 123.79, 124.40, 129.80, 130.40, 132.50, 133.70, 134.59, 137.00, 145.49, 147.65, 150.20, 151.99, 152.90. LC-MS: t_R = 6.19 min; *m/z*: 339.1 [M^+ + H, 100] calcd for $C_{18}H_{19}N_4O_3$. HRMS: (M + H)$^+$ calcd for $C_{18}H_{19}N_4O_3$, 339.1457; found, 339.1445.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-hydroxyphenyl)-pyrazine (6) (Method B). In an oven-dried flask, the catalyst is prepared by adding under stirring and Ar atmosphere dppb (40 mg, 0.09 mmol) and $PdCl_2$(benzonitrile)$_2$ (30 mg, 0.077 mmol) to dry toluene (10 mL). After 30 min, **2** (112 mg, 0.38 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-phenol (100 mg, 0.45 mmol), EtOH (1.60 mL), and an aqueous solution of Na_2CO_3 (1.5 mL, 1M) in toluene (10 mL) were added and the reaction mixture was heated at 90 °C for 16 h. After cooling, AcOEt (50 mL) was added to the reaction, and the mixture was washed (2 × 100 mL), dried ($MgSO_4$), and evaporated to dryness. The solid obtained was purified by preparative HPLC (Kieselgel 60, 0.015−0.043; eluent: AcOEt) to furnish the title compound (74 mg). Yield: 55%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.63 (s, 3H), 3.82 (s, 6H), 6.87 (d, 1H, J = 9.8 Hz), 7.25 (s, 2H), 7.29 (t, 1H, J = 9.5 Hz), 7.52 (d, 1H, J = 6.5 Hz), 7.53 (s, 1H), 8.14 (s, 1H), 8.43 (s, 1H), 9.54 (s, 1H, OH), 9.59 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.61, 60.11, 95.70, 113.28, 116.46, 117.14, 129.80, 131.90, 133.44, 136.90, 138.04, 147.73, 151.38, 152.79, 157.87. LC-MS: t_R = 7.04 min; *m/z*: 354.5 [(M + H)$^+$, 100] calcd for ($C_{19}H_{20}N_3O_4$). HRMS: (M + H)$^+$ calcd for $C_{19}H_{20}N_3O_4$, 354.1454; found, 354.1425.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-hydroxyphenyl)-pyrazine (7). Using method B (reaction time: 48 h) with 4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)phenol (242 mg, 1.10 mmol), the title compound was obtained (83 mg). Yield: 60%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.63 (s, 3H), 3.82 (s, 6H), 6.88 (d, 2H, J = 8.5 Hz), 7.24 (s, 2H), 7.97 (d, 1H, J = 8.7), 8.05 (s, 1H), 8.40 (s, 1H), 9.46 (s, 1H, OH), 9.82 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.59, 60.11, 95.65, 96.22, 115.60, 127.37, 127.88, 129.02, 131.82, 132.06, 132.20, 133.27, 134.89, 136.72, 140.98, 147.89, 151.32, 152.37, 152.78, 158.90. LC-MS: t_R = 6.90 min; *m/z*: 354.4 [(M + H)$^+$, 100] calcd for $C_{19}H_{20}N_3O_4$. HRMS: (M + H)$^+$ calcd for $C_{19}H_{20}N_3O_4$, 354.1454; found, 354.1444.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-hydroxymethylphenyl)pyrazine (8). Using method B with 4-hydroxy-methylphenyl boronic acid (131 mg, 0.86 mmol), the title compound was obtained (22 mg). Yield: 8%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.69 (s, 3H), 3.90 (s, 6H), 4.57 (d, 2H, J = 5.7 Hz), 5.28 (t, 1H, J = 5.7 Hz), 7.26 (s, 2H), 7.45 (s, 2H, J = 8.2 Hz), 8.10 (d, 1H), 8.14 (s, 1H), 8.51 (s, 1H), 9.56 (s, 1H, NH). LC-MS: t_R = 6.84 min; *m/z*: 368.1 [(M + H)$^+$, 100] calcd for $C_{20}H_{21}N_3O_4$. HRMS: (M + H)$^+$ calcd for $C_{20}H_{21}N_3O_4$, 368.1610; found, 368.1606.

2-(3,4,5-Trimethoxyphenylamino)-6-(ethyl,3-benzoate)-pyrazine (9). Using method B (reaction time: 3 h) with ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-benzoate (450 mg, 1.63 mmol), the title compound was obtained (391 mg). Yield: 70%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.34 (t, 3H, CH_3CH_2, J = 7.1 Hz), 3.64 (s, 3H), 3.81 (s, 6H), 4.36 (q, 2H, CH_3CH_2), 7.22 (s, 2H), 7.67 (t, 1H, J = 7.8 Hz), 8.05 (d, 1H, J = 7.2 Hz), 8.20 (s, 1H), 8.36 (d, 1H, J = 7.8 Hz), 8.57 (s, 1H), 8.68 (s, 1H), 9.63 (s, 1H, NH). LC-MS: t_R = 8.65 min; *m/z*: 410.1 [(M + H)$^+$, 100] calcd for $C_{22}H_{24}N_3O_5$. HRMS: (M + H)$^+$ calcd for $C_{22}H_{23}N_3O_5$, 410, 1710; found, 410,1720.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-formylphenyl)-pyrazine (10). Using method A with 4-formylphenylboronic acid (123 mg, 0.82 mmol), the title compound was obtained (153 mg). Yield: 62%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.64 (s, 3H), 3.83 (s, 6H), 7.25 (s, 2H), 8.05 (d, 2H, J = 8.2 Hz), 8.23 (s, 1H), 8.35 (d, 2H), 8.64 (s, 1H), 9.68 (s, 1H, NH), 10.08 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.62, 60.12, 96.00, 126.97, 129.93, 130.68, 132.25, 132.87, 136.53, 136.64, 142.10, 146.30, 151.50, 152.84, 192.70. LC-MS: t_R = 7.34 min; *m/z*: 366.1 [(M + H)$^+$, 100] calcd for $C_{20}H_{20}N_3O_4$. HRMS: (M + H)$^+$ calcd for $C_{20}H_{20}N_3O_4$, 366.1454; found, 366.1458.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-phenylamino)-pyrazine (11a). Using method A (reaction time: 18 h) with 4-(4,4,5,5-tetramethyl-1,3,2-borolan-2-yl)-aniline (500 mg, 1.69 mmol), the title compound was obtained (350 mg). Yield: 59%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.63 (s, 3H), 3.82 (s, 6H), 5.53 (s, 2H, NH_2), 6.64 (d, 2H, J = 8.6 Hz), 7.24 (s, 2H), 7.84 (d, 2H), 7.95 (s, 1H), 8.34 (s, 1H), 9.38 (s, 1H, NH). LC-MS: t_R = 4.08 min; *m/z*: 352.9 [(M + H)$^+$, 100] calcd for $C_{19}H_{20}N_4O_3$.

1-{4-[6-(3,4,5-Trimethoxyphenylamino)-pyrazin-2-yl]phenyl}−3-phenyl urea (11). To 200 mg of 2-(3,4,5-trimethoxyphenylamino)-6-(4-phenylamino)-pyrazine (**11a**) dissolved in dry THF 68 mL (0.60 mmol) of phenyl isocyanate were added under stirring at 40 °C (block). After 20 h, the reaction mixture was evaporated under vacuum and the residue was recrystallized from AcOEt, when 130 mg of a yellow solid were obtained. Yield: 49%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.65 (s, 3H), 3.85 (s, 6H), 7.00 (t, 1H), 7.26 (s, 2H), 7.32 (s, 2H, J = 7.6 Hz), 7.48 (d, 2H), 7.60 (s, 2H, J = 8.7 Hz), 8.08 (d, 2H), 8.11 (s, 1H), 8.42 (s, 1H), 8.42 (s, 1H), 8.73 (s, 1H, NH_{urea}), 8.92 (s, 1H, NH_{urea}), 9.53 (s, 1H, NH). LC-MS: t_R = 7.05 min; *m/z*: 421.2 [(M + H)$^+$, 100] calcd for $C_{26}H_{25}N_5O_4$. HRMS: (M + H)$^+$ calcd for $C_{26}H_{25}N_5O_4$, 472.1979; found, 472.1978.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-cyanophenyl)-pyrazine (12). Using method A (reaction time: 18 h) with 3-(4,4,5,5-tetramethyl-1,3,2-borolan-2-yl)-benzonitrile (188 mg, 0.82 mmol), the title compound was obtained (44 mg). Yield: 18%. ^{1}H NMR (500 MHz,

DMSO-d_6) δ: 3.64 (s, 3H), 3.84 (s, 6H), 7.23 (s, 2H), 7.73 (t, 1H, J = 7.9 Hz), 7.93 (d, 1H, J = 7.7 Hz), 8.22 (s, 1H), 8.45 (d, 1H, J = 8.0 Hz), 8.57 (s, 1H), 8.64 (s, 1H), 9.68 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.62, 60.12, 96.00, 112.08, 118.46, 129.93, 130.10, 130.82, 132.25, 132.77, 134.84, 136.60, 137.79, 145.38, 151.43, 151.56, 152.82. LC-MS: t_R = 7.52 min; *m/z*: 363.1 [$(M + H)^+$, 100] calcd for $C_{20}H_{19}N_4O_3$. HRMS: $(M + H)^+$ calcd for $C_{20}H_{19}N_4O_3$, 363.1457; found, 363.1459.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-carboxamidophenyl)pyrazine (13). In a tube suitable for microwave and under Ar were placed **3** (150 mg, 0.51 mmol), 4-aminocarbonylphenylboronic acid (108 mg, 0.66 mmol), $Pd_2(0)dba_3$ (30 mg, 0.051 mmol), 1,3-bis(2,6-di-*i*-propylphenyl)-4,5-dihydro-imidazolium tetrafluoroborate (24 mg, 0.051 mmol), *tetra-n*-butylammonium bromide (16.8 mg, 0.051 mmol), and toluene (3 mL). The temperature was lowered to 0 °C and dropwise addition of a suspension of potassium methoxide (106.8 mg, 1.53 mmol) in MeOH (1.2 mL) followed. This mixture was stirred for 5 min at 0 °C, and then microwave irradiation for 30 min at 65 °C followed. The reaction mixture was dissolved in boiling AcOEt (75 mL) and filtered. The resulting organic layer was evaporated under vacuum to give a solid that gave, upon column chromatography (AcOEt), 124 mg of the title compound. Yield: 64%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.65 (s, 3H), 3.85 (s, 6H), 7.27 (s, 2H), 7.47 (bs, 1H, $CONH_2$), 8.02 (d, 2H, J = 8.4 Hz), 8.08 (bs, 1H, $CONH_2$), 8.21 (s, 1H), 8.23−8.34 (m, 3H), 8.61 (s, 1H), 9.64 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.61, 60.14, 95.93, 126.15, 127.99, 130.27, 132.14, 134.23, 134.89, 136.76, 139.12, 146.73, 151.47, 152.83, 167.31. LC-MS: t_R = 5.87 min; *m/z*: 381.1 $(M + H)^+$ calcd for $C_{20}H_{21}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{20}H_{21}N_4O_4$, 381.1563; found, 381.1570.

2-*N*,*N*-Diacetylamido-3,5-dibromo-pyrazine (14). 2-Amino-3,5-dibromo-pyrazine (1.01 g, 4.0 mmol) and sodium bicarbonate (1.02, 12mmol) were refluxed in acetyl chloride (20 mL) for 2 days. The solvent was evaporated, and the residue was partitioned between DCM and water. The organic layer was dried and evaporated to give 1.31 g of title compound as crystals. Yield: 97%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.26 (6H, s), 9.00 (1H, s). MS *m/z* (electrospray): 358/60/2 $(M + Na^+)$.

2-Bromo-3-acetamido-6-(3-acetamidophenyl)-pyrazine (15). In a microwave tube under stirring and an Ar atmosphere were placed **14** (200 mg, 0.59 mmol), 3-acetamidobenceneboronic acid (106 mg, 0.59 mmol), $PdCl_2$·dppf:DCM 1:1 complex (36 mg, 0.045 mmol), DME (3.0 mL), H_2O (0.6 mL), and Na_2CO_3 (126 mg, 1.19 mmol). The tube was heated by microwave irradiation at 90 °C for 30 min. Two batches were combined, filtered, and the precipitate washed with hot AcOEt (60 mL). The organic layer was evaporated under vacuum, and the resulting crude was chromatographed on silica (AcOEt) to give 26 mg of title compound. Yield: 7%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.07 (s, 3H), 2.12 (s, 3H), 7.46 (t, 1H, J = 7.9 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.82 (d, 1H, J = 7.7 Hz), 8.21 (bs, 1H), 9.05 (s, 1H), 10.17 (s, 1H), 10.46 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.04, 23.99, 117.03, 120.73, 121.29, 129.54, 134.45, 136.31, 138.55, 140.15, 145.67, 148.90, 168.55, 168.92. LC-MS: t_R = min; *m/z*: 349.1 $(M + H)^+$ calcd for $C_{14}H_{13}BrN_4O_2$.

2-(3,4,5-Trimethoxyphenylamino)-3-acetamido-6-(3-acetamidophenyl)-pyrazine (16). In a microwave tube under stirring and Ar atmosphere were placed **15** (32 mg, 0.091 mmol), 3,4,5-trimethoxyaniline (33.6 mg, 0.183 mmol), sodium *tert*-butoxide (18 mg, 0.1833 mmol), $Pd(0)_2dba_3$ (8.4 mg, 0.009 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (5.3 mg, 0.009 mmol), and dry toluene (1.5 mL). The tube was heated by microwave irradiation at 110 °C for 30 min. The reaction crude was filtered and the precipitate washed with boiling AcOEt (30 mL). The organic layers were evaporated under vacuum, and the resulting crude was chromatographed (AcOEt:EtOH 9:1) to produce the title compound (7 mg). Yield: 17%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.06 (s, 3H), 2.17 (s, 3H), 3.64 (s, 3H), 3.77 (s, 9H), 7.24 (s, 2H), 7.42 (t, 1H, J = 8.0 Hz), 7.64 (d, 1H, J = 7.7 Hz), 7.73 (d, 1H, J = 7.9 Hz), 8.22 (bs, 1H), 8.28 (s, 1H), 8.52 (s, 1H), 10.07 (s, 1H), 10.21 (s, 1H). LC-MS: t_R = 6.20 min; *m/z*: 452.2 $(M + H)^+$ calcd for $C_{23}H_{25}N_5O5$.

3-(3,4,5-Trimethoxyphenylamino)-5-bromopyridine (17) (Method C). To 1.00 g (4.2 mmol) 3,5-dibromopyridine dissolved in 40 mL of dry toluene in an oven-dried flask were added under stirring: $Pd(0)_2dba_3$ (82 mg, 0.09 mmol), BINAP (0.168 g, 0.27 mmol), 1.49 g (8.16 mmol) 3,4,5-trimethoxyaniline, and 0.914 g (9.52 mmol) sodium *tert*-butoxide. The reaction mixture was heated at 90 °C (bath temperature) for 18 h under N_2. After cooling, the toluene solution was filtered and evaporated in vacuo. The residue was retaken in 30 mL of AcOEt, washed (2 × 30 mL brine), dried, evaporated to a volume of 10 mL, and submitted to HPLC (Kieselgel 60, 0.015−0.043; eluent: AcOEt:cycloxane 2:1). A fraction of 167 mg of the title compound was collected. Yield: 11.7%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.64 (s, 3H), 3.78 (s, 6H), 6.43 (s, 2H), 7.52 (t, 1H, $H_{pyr\ 4}$, J = 2.1), 8.04 (d, 1H, J = 1.9 Hz, $H_{Pyr\ 2\ or\ 6}$), 8.14 (d, 1H, $H_{Pyr\ 6\ or\ 2}$ J = 2.3), 8.48 (s, 1H, NH). LC-MS: t_R = 6.28 min; ($C_{14}H_{15}BrN_2O_3$) *m/z*: 339.06 [M^+ + 1, 100].

3-(3,4,5-Trimethoxyphenylamino)-5-(3-acetamidophenyl)-pyridine (18). Using method A (reaction time: 4 h) with 3-(3,4,5-trimethoxyphenylamino)-5-bromo-pyridine, **25**, (160 mg, 0.97 mmol), the title compound was obtained (129 mg). Yield: 70%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.06 (s, 3H), 3.63 (s, 3H), 3.76 (s, 6H), 6.46 (s, 2H), 7.32 (d, 1H, J = 7.6 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.54 (d, 1H), 7.58 (m, 1H), 7.95 (s, 1H), 8.24 (s, 1H), 8.34 (s, 1H), 8.46 (s, 1H, NH), 10.11 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 24.03, 55.76, 60.12, 95.99, 117.19, 118.61, 119.24, 121.39, 129.47, 132.19, 135.86, 137.60, 137.88, 138.02, 138.17, 140.01, 140.70, 153.47, 168.45. LC-MS: t_R = 4.69 min; *m/z*: 394.1 [$(M + H)^+$, 100] calcd for $C_{22}H_{24}N_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{23}N_3O_4$, 394.1767; found, 394.1754.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-acetamidophenylamino)-pyrazine (19) (Method D). In a microwave tube, **3**, (150 mg, 0.51 mmol), 4-aminoacetanilide (114 mg, 0.76 mmol), $Pd_2(0)dba_3$ (23 mg, 0.025 mmol), 1,3-bis(2,6-di-*i*-propylphenyl)-4,5-dihydro-imidazolium tetrafluoroborate (24 mg, 0.051 mmol), potassium *tert*-butoxide (114 mg, 0.91 mmol), and dioxane (3.5 mL) were reacted under stirring and Ar at 100 °C for 30 min with microwave heating. The reaction mixture was filtered, and the insoluble solid was washed with boiling AcOEt (40 mL). The solution was evaporated under vacuum, and the resulting solid was chromatographed on silica gel using AcOEt as eluent to produce 86 mg of title compound. Yield: 29.8%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.01 (s, 3H), 3.62 (s, 3H), 3.63 (s, 6H), 6.85 (s, 2H), 7.40−7.52 (m, 6H), 9.01 (s, 1H), 9.04 (s, 1H), 9.80 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.82, 55.60, 60.13, 97.01, 119.17, 119.57, 121.33, 121.68, 132.23, 133.28, 136.07, 136.89, 150.22, 152.64, 167.70. LC-MS: t_R = 5.43 min; *m/z*: 410.2 $(M + H)^+$ calcd for $C_{21}H_{23}N_5O_4$.

2-(3,4,5-Trimethoxyphenylamino)-6-phenylamino-pyrazine (20). Using method D with aniline (71 mg, 0.76 mmol), the title compound was obtained (63 mg). Yield: 35%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.62 (s, 3H), 3.63 (s, 6H), 6.86 (s, 2H), 6.91 (t, 1H, J = 7.3 Hz), 7.22 (t, 2H, J = 9.4 Hz), 7.53 (s, 1H), 7.54 (s, 1H), 7.57 (d, 2H, J = 7.6 Hz), 9.05 (s, 1H), 9.14 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.60, 60.11, 97.01, 118.59, 121.00, 121.87, 121.92, 128.65, 132.26, 136.85, 140.86, 150.00, 150.17, 152.84. LC-MS: t_R = 6.42 min; *m/z*: 353.1 $(M + H)^+$ calcd for $C_{19}H_{21}N_4O_3$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{21}N_4O_3$, 353.1614; found, 353.1612.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-pyridinylamino)-pyrazine (21). Using method D with 4-aminopyridine (127 mg, 1.35 mmol), the title compound was obtained (25 mg). Yield: 10%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.64 (s, 3H), 3.68 (s, 6H), 6.83 (s, 2H), 7.55 (d, 2H, J = 6.3 Hz), 7.62 (s, 1H), 7.69 (s, 1H), 8.25 (d, 2H, J = 6.3 Hz), 9.23 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.66, 60.14, 97.52, 112.07, 122.57, 123.96, 132.67, 136.40, 147.39, 148.88, 149.83, 150.18, 152.93. LC-MS: t_R = 3.70 min; *m/z*: 354.2 $(M + H)^+$ calcd for $C_{18}H_{19}N_5O_3$.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-acetamidophenylamino)pyrazine (22). Using method D with 3-aminoacetanilide (114 mg, 0.76 mmol), the title compound was obtained (12 mg). Yield: 6%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.01 (s, 3H), 3.61 (s, 3H), 3.62 (s, 6H), 6.88 (s, 2H), 7.04 (d, 1H, J = 8.4 Hz), 7.11 (t, 1H, J = 7.9 Hz), 7.50 (d, 1H, J = 7.9 Hz), 7.53 (s, 1 H), 7.56 (s, 1 H), 7.67 (bs, 1 H), 9.05 (s, 1 H), 9.13 (s, 1 H), 9.81 (s, 1 H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.98, 55.58, 60.10, 96.74, 109.169, 112.22, 113.55, 121.87, 122.04, 128.74, 132.14, 136.92, 139.68, 141.08, 149.99, 150.18, 152.64, 168.15. LC-MS: t_R = 5.67 min; *m/z*: 410.1 $(M + H)^+$ calcd for $C_{21}H_{23}N_5O_4$.

2-(3,4,5-Trimethoxybenzylamino)-6-(4-oxyphenylamino)-pyrazine (23). 4-Hydroxyaniline (58.0 mg, 0.53 mmol), DMF (5 mL), potassium *tert*-butoxide (67 mg, 0.60 mmol), and K_2CO_3 (42 mg, 0.3 mmol) were stirred in Ar. After 5 min, 2-chloro-6-(3,4,5-trimethoxyphenylamino)-pyrazine (150 mg, 0.51 mmol) was added and the reaction mixture heated by microwaves (30 min, 110 °C). The reaction mixture was filtered, poured in water (20 mL), and extracted with AcOEt (2 × 20 mL) The organic layer was pooled, dried, and evaporated to a volume of 2−3 mL. After purification by flash chromatography (Isolute column, Flash SiII, 50 g, 150 mL; eluent: AcOEt), 48.9 mg of the title compound were obtained. Yield: 26%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.61 (s, 12H), 6.67 (d, 2H, J = 8.5 Hz), 6.86 (s, 2H), 7.31 (d, 2H), 7.42 (s, 2H), 8.75 (s, 1H, NH), 8.95 (s, 1H, NH), 9.07 (s, 1H, OH). LC-MS: t_R = 4.48 min; *m/z*: 353.1 [$(M + H)^+$, 100] calcd for $C_{19}H_{21}N_4O_3$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{21}N_4O_3$, 353.1614; found, 3353.1612.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-fluorophenylamino)-pyrazine (24). Using method D with 3-fluoroaniline (150 mg, 1.35 mmol), the title compound was obtained (60 mg). Yield: 23%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.62 (s, 3H), 3.65 (s, 6H), 6.65−6.72 (m, 1H), 6.81 (s, 2H), 7.24 (m, 2H), 7.56 (s, 1H), 7.58 (s, 1H), 7.67 (d, 1H, J = 13.0 Hz), 9.12 (s, 1H), 9.41 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.45, 60.07, 97.24, 106.71, 107.05, 114.04, 122.16, 122.49, 130.14, 132.43, 136.55, 142.71, 142.89, 149.52, 150.10, 152.89. LC-MS: t_R = 6.75 min; *m/z*: 371.1 [$(M + H)^+$, 100] calcd for $C_{19}H_{20}FN_4O_3$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{20}FN_4O_3$, 371.1519; found, 371.1528.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-fluorophenylamino)-pyrazine (25). Using method D with 4-fluoroaniline (150 mg, 1.35 mmol), the title compound was obtained (72 mg). Yield: 28%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.62 (s, 9H), 6.83 (s, 2H), 7.06 (t, 2H, J = 9.0 Hz), 7.51 (s, 1H), 7.57 (d, 2H, J = 9.1 Hz), 9.05 (s, 1H), 9.14 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.56, 60.12, 97.01, 114.94, 115.29, 120.38, 120.50, 121.62, 121.83, 132.29, 137.19, 137.22, 150.15, 152.84. LC-MS: t_R = 6.38 min; purity > 99%. HRMS: $(M + H)^+$ calcd for $C_{19}H_{20}FN_4O_3$, 371.1519; found, 371.1522.

2-(3,4,5-Trimethoxyphenylamino)-6-(naphthalen-1-yloxy)-pyrazine (26) (Method E). In a microwave tube were mixed under Ar and stirring, 1-naphthol (73 mg, 0.51 mmol), K_2CO_3 (35 mg, 0.25 mmol), potassium *tert*-butoxide (60 mg, 0.53 mmol), and DMF dry (3.5 mL). This mixture was stirred for 10 min, **2** (150 mg, 0.51 mmol) was added and the tube was heated for 30 min at 120 °C. The reaction crude was mixed with 40 mL of solution NaOH 1.5 M and extracted with DCM (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated under vacuum to give a solid that was chromatographed using DCM:AcOEt (7:3) as eluent to produce the title compound (66 mg). Yield: 32%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.19 (s, 6H), 3.47 (s, 3H), 6.58 (s, 2H), 7.32 (d, 1H, J = 8.5 Hz), 7.50−7.60 (m, 3H), 7.83 (d, 1H, J = 8.3 Hz), 7.91 (s, 1H), 7.96 (s, 1H), 7.98−8.03 (m, 2H), 9.49 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.17, 59.96, 95.53, 117.11, 120.88, 121.28, 124.80, 126.03, 126.54, 126.65, 126.72, 127.96, 128.32, 132.07, 134.45, 136.16, 149.40, 150.61, 152.58, 158.19. LC-MS: t_R = 8.50 min; *m/z*: $(M + H)^+$ calcd for $C_{23}H_{22}N_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{22}N_3O_4$, 404.1610; found. 404.1651.

2-(3,4,5-Trimethoxyphenylamino)-6-(naphthalen-2-yloxy)-pyrazine (26a). Using method E, with 2-naphthol (73 mg, 0.51 mmol), the title compound was obtained (78 mg). Yield: 38%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.06 (s, 9H), 3.45 (s, 3H), 6.69 (s, 2H), 7.37 (dd, 1H, J_1 = 2.3 Hz, J_2 = 8.9 Hz), 7.49−7.54 (m, 2H), 7.72 (d, 1H, J = 2.0 Hz), 7.84−7.89 (m, 2H), 7.92−7.99 (m, 3H), 9.55 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 54.81, 59.95, 95.64, 116.83, 121.05, 121.18, 125.53, 126.65, 127.15, 127.61, 128.51, 129.61, 130.45, 132.06, 133.78, 136.25, 150.57, 151.52, 152.57, 157.47. LC-MS: t_R = 8.62 min; *m/z*: 404.1 $(M + H)^+$ calcd for $C_{23}H_{22}N_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{22}N_3O_4$, 404.1610; found, 404.1590.

2-(3,4,5-Trimethoxyphenylamino)-6-(phenyloxy)-pyrazine (27). Following procedure E (no K_2CO_3 added) with phenol (48 mg, 0.51 mmol), the title compound was obtained (127 mg). Yield: 71%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.31 (s, 9H), 3.54 (s, 3H), 6.77 (s, 2H), 7.16−7.23 (m, 3H), 7.41 (t, 2H, J = 7.9 Hz), 7.75 (s, 1H), 7.95 (s, 1H), 9.53 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.33, 60.03, 95.77, 120.55, 121.17, 124.47, 128.42, 129.74, 132.15, 136.29, 150.52, 152.69, 153.86, 153.86, 157.23. LC-MS: t_R = 7.65 min; *m/z*: 354.1 $(M + H)^+$ calcd for $C_{19}H_{19}N_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{20}N_3O_4$, 354.1454; found, 354.1444.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-pyridinyloxy)-pyrazine (28). Using method E with 4-hydroxypyridine (48 mg, 0.51 mmol), the title compound was obtained (89 mg). Yield: 50%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.64 (s, 3H), 3.79 (s, 6H), 6.29 (d, 2H, J = 7.9 Hz), 7.07 (s, 2H), 8.19 (s, 1H), 8.32 (s, 1H), 8.43 (d, 2H, J = 8.0 Hz), 9.91 (bs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.61, 60.11, 96.50, 117.94, 121.98, 132.71, 132.79, 135.77, 136.52, 145.43, 150.31, 152.85, 178.22. LC-MS: t_R = 5.52 min; *m/z*: 355.1 $(M + H)^+$ calcd for $C_{18}H_{19}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{18}H_{19}N_4O_4$, 355.1406; found, 355.1418.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-pyridinyloxy)-pyrazine (29). Using method E with 3-hydroxypyridine (48 mg, 0.51 mmol), the title compound was obtained (46 mg). Yield: 26%. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.41 (s, 6H), 3.54 (s, 3H), 6.71 (s, 2H), 7.47 (m, 1H, J_1 = 0.6 Hz, J_2 = 4.7 Hz, J_3 = 8.4 Hz), 7.69 (m, 1H, J_1 = 1.4 Hz, J_2 = 2.8 Hz, J_3 = 8.4 Hz), 7.82 (s, 1H), 7.98 (s, 1H), 8.43 (dd, 1H, J_1 = 1.4 Hz, J_2 = 4.7 Hz), 8.54 (dd, 1H, J_1 = 0.5 Hz, J_2 = 2.8 Hz), 9.61 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.32, 60.04, 95.95, 120.94, 124.52, 128.42, 128.91, 132.34, 136.10, 142.68, 145.66, 150.31, 150.38, 152.71, 156.84. LC-MS: t_R = 6.27 min; *m/z*: 355.1 $(M + H)^+$ calcd for $C_{18}H_{19}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{18}H_{19}N_4O_4$, 355.1406; found, 355.1416.

2-(3,4,5-Trimethoxyphenylamino)-6-(naphthalen-1-ylthio)-pyrazine (30). Using method E with 1-thionaphthol (81 mg, 0.51 mmol), the title compound was obtained (68 mg). Yield: 32%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.60 (s, 3H), 3.61 (s, 6H), 6.94 (s, 2H), 7.25 (s, 1H), 7.57−7.63 (m, 3H), 7.91 (s, 1H), 7.95 (dd, 1H, J_1 = 1.2 Hz, J_2 = 7.1 Hz), 8.03−8.07 (m, 1H), 8.11 (d, 1H, J = 8.3 Hz), 8.26−8.30 (m, 1H), 9.54 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.55, 60.09, 96.41, 124.82, 126.23, 126.58, 126.74, 127.65, 128.90, 129.90, 130.63, 131.09, 132.52, 133.33, 133.97, 134.60, 136.13, 151.27, 152.55, 152.74. LC-MS: t_R = 8.54 min; *m/z*: 420.1 $(M + H)^+$ calcd for $C_{23}H_{22}N_3O_3S$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{22}N_3O_3S$, 420.1382; found, 420.1378.

2-(3,4,5-Trimethoxyphenylamino)-6-(5,6,7,8-tetrahydronaphthalen-1-yloxy)-pyrazine (31). Using method E with 5,6,7,8-tetrahydro-1-naphthol (75 mg, 0.51 mmol), the title compound was obtained (27 mg). Yield: 13%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.65−1.69 (m, 4H), 2.53−2.56 (m, 2H), 2.72−2.77 (m, 2H), 3.42 (s, 6H), 3.54 (s, 3H), 6.74 (s, 2H), 6.89 (d, 1H, J = 7.9 Hz), 6.95 (d, 1H, J = 6.6 Hz), 7.11 (t, 1H, J = 7.8 Hz), 7.71 (s, 1H), 7.91 (s, 1H), 9.55 (bs, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 22.01, 22.26, 23.12, 28.78, 55.36, 60.03, 95.72, 118.40, 120.56, 125.66, 126.09, 127.60, 129.06, 132.10, 136.39, 138.76, 150.59, 151.46, 152.70, 157.65. LC-MS: t_R = 8.62 min; *m/z*: 408.2 $(M + H)^+$ calcd for $C_{23}H_{26}N_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{26}N_3O_4$, 408.1923; found, 408.1916.

2-(3,4,5-Trimethoxyphenylamino)-6-(1*H*-indol-4-yloxy)-pyrazine (32). Using method E with 4-hydroxyindole (67 mg, 0.51 mmol), the title compound was obtained (34 mg). Yield: 17%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.24 (s, 6H), 3.49 (s, 3H), 6.10−6.12 (m, 1H), 6.66 (s, 2H), 6.79 (d, 1H, J = 7.1 Hz), 7.07 (t,

1H, J = 7.8 Hz), 7.25−7.29 (m, 2H), 7.79 (s, 1H), 7.92 (s, 1H), 9.44 (s, 1H), 11.26 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.12, 59.96, 95.43, 98.04, 108.42, 109.87, 120.50, 120.91, 121.37, 125.36, 127.87, 131.91, 136.34, 138.13, 146.33, 150.59, 152.58, 157.84. LC-MS: t_R = 7.22 min; m/z: 393.1 $(M + H)^+$ calcd for $C_{21}H_{21}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{21}N_4O_4$, 393.1563; found, 393.1534.

2-Chloro-6-(quinolin-4-yloxy)-pyrazine (33) (Method F). In a carousel tube suitable for parallel synthesis were added 2,6-dichloropyrazine (250 mg, 1.69 mmol), 4-hydroxyquinoline (270 mg, 1.49 mmol), dry degassed DMF (10 mL), and potassium *tert*-butoxide (165 mg, 1.49 mmol). This mixture was stirred under Ar at 90 °C (block) for 5 h. The reaction mixture was diluted with AcOEt (20 mL), washed with brine (2 × 20 mL), dried, and evaporated under vacuum. Purification by column chromatography (AcOEt:cyclohexane, 1:1) afforded the title compound (60 mg). Yield: 14%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.45 (d, 1H, J = 4.9 Hz), 7.67 (t, 1H, J = 7.6 Hz), 7.86 (t, 1H, J = 7.8 Hz), 8.12 (d, 2H, J = 8.7 Hz), 8.67 (s, 1H), 8.82 (s, 1H), 8.94 (d, 1H, J = 4.9 Hz). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 111.15, 121.39, 121.52, 127.20, 129.11, 130.74, 134.54, 139.24, 144.48, 149.59. 151.42, 156.17, 157.21. LC-MS: t_R = 5.45 min; m/z: 258.0 $(M + H)^+$ calcd for $C_{13}H_9ClN_3O$. HRMS: $(M + H)^+$ calcd for $C_{13}H_9N_3OCl$, 258.0434; found, 258.0427.

2-Chloro-6-(quinoline-5-oxy)-pyrazine (33a). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.69 mmol) and 5-hydroxyquinoline (270 mg, 1.49 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) gave the title compound (264 mg). Yield: 61%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.54−7.58 (m, 2H), 7.84 (t, 1H, J = 8.1 Hz), 8.01 (d, 1H, J = 8.5 Hz), 8.37 (d, 1H, J = 8.0 Hz), 8.55 (s, 1H), 8.73 (s, 1H), 8.98 (dd, 1H, J = 1.4 Hz, J = 4.0 Hz). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 118.19, 121.82, 121.99, 126.94, 129.37, 129.99, 133.76, 137.84, 144.32, 147.74, 148.57. 151.27, 158.57. LC-MS: t_R = 5.71 min; m/z: 258.0 $(M + H)^+$ calcd for $C_{13}H_9ClN_3O$. HRMS: $(M + H)^+$ calcd for $C_{13}H_9N_3OCl$, 258.0434; found, 258.0433.

2-Chloro-6-(quinoline-6-oxy)-pyrazine (34). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.69 mmol) and 6-hydroxyquinoline (270 mg, 1.49 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) afforded the title compound (324 mg). Yield: 75%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.56−7.59 (m, 1H), 7.70 (dd, 1H, J_m = 2.6 Hz, J_o = 9.1 Hz), 7.87 (d, 1H, J = 2.4 Hz), 8.12 (d, 1H, J = 9.0 Hz), 8.37 (d, 1H, J = 8.1 Hz), 8.56 (s, 1H), 8.65 (s, 1H), 8.93 (dd, 1H, J = 1.0 Hz, J = 4.9 Hz). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 117.82, 122.01, 124.48, 128.50, 131.00, 133.86, 135.69, 137.88, 144.41, 145.64, 150.58. 150.38, 158.23. LC-MS: t_R = 6.07 min; m/z: 258.0 $(M + H)^+$ calcd for $C_{13}H_9ClN_3O$. HRMS: $(M + H)^+$ calcd for $C_{13}H_9N_3OCl$, 258.0434; found, 258.0433.

2-Chloro-6-(isoquinoline-5-oxy)-pyrazine (35). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.69 mmol) and 5-hydroxyisoquinoline (270 mg, 1.49 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) furnished the title compound (263 mg). Yield: 61%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.72−7.78 (m, 3H), 8.11 (d, 1H, J = 7.8 Hz), 8.53 (d, 1H, J = 5.9 Hz), 8.55 (s, 1H), 8.75 (s, 1H), 9.43 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 114.05, 122.20, 125.66, 127.72, 128.98, 129.26, 133.78, 137.86, 143.56, 144.26, 146.92. 152.51, 158.45. LC-MS: t_R = 4.94 min; m/z: 258.0 $(M + H)^+$ calcd for $C_{13}H_9ClN_3O$. HRMS: $(M + H)^+$ calcd for $C_{13}H_9N_3OCl$, 258.0434; found, 258.0448.

2-Chloro-6-(7-coumarinyloxy)-pyrazine (36). Using method F with 2,6-dichloropyrazine (200 mg, 1.35 mmol) and 17-hydroxy coumarine (242 mg, 1.49 mmol), 370 mg of the desired compound resulted after purification. Yield: 100%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 6.50 (d, 1H, J = 9.6 Hz), 7.29 (dd, 1H, J_o = 8.2 Hz, J_m = 2.2 Hz), 7.44 (d, 1H, J = 2.2 Hz), 7.84 (d, 1H, J = 8.4 Hz), 8.10 (d, 1H, J = 9.6 Hz), 8.60 (s, 1H), 8.65 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 109.02, 115.37, 115.89, 117.16, 129.86, 134.01, 138.39, 143.79, 144.37, 155.03. 155.35, 157.61, 159.66, 161.27. LC-MS: t_R = 6.30 min; m/z: 275.0 $(M + H)^+$ calcd for $C_{13}H_8ClN_2O_3$. HRMS: $(M + H)^+$ calcd for $C_{13}H_8ClN_2O_3$, 275.0223; found, 275.0231.

2-Chloro-6-(5-tetral-1-onyloxy)-pyrazine (37). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 5-hydroxy-tetralone (238 mg, 1.49 mmol). Purification by column chromathography (AcOEt:cyclohexane, 1:1) afforded the title compound (366 mg). Yield: 100%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.97−2.07 (m, 2H), 2.64 (t, 2H, J = 7.1 Hz), 2.77 (t, 2H, J = 6.8 Hz), 7.46−7.45 (m, 2H), 7.86 (dd, 1H, J_o = 7.4 Hz, J_m = 1.6 Hz), 8.54 (s, 1H), 8.63 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 21.69, 22.73, 38.05, 124.03, 126.82, 127.38, 133.36, 134.03, 136.79, 137.60, 144.40, 149.80, 157.96, 196.73. LC-MS: t_R = 6.94 min; m/z: 275.0 $(M + H)^+$ calcd for $C_{14}H_{12}ClN_2O_2$. HRMS: $(M + H)^+$ calcd for $C_{14}H_{12}ClN_2O_2$, 275.0587; found, 275.0595.

2-Chloro-6-(6-tetral-1-onyloxy)-pyrazine (38). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 6-hydroxy-tetralone (238 mg, 1.49 mmol). Crystallization from AcOEt furnished the title compound (365 mg). Yield: 100%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.02−2.12 (m, 2H), 2.63 (t, 2H, J = 5.9 Hz), 2.97 (t, 2H, J = 6.5 Hz), 7.20−7.26 (m, 2H), 7.96 (d, 1H, J = 8.3 Hz), 8.59 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 22.96, 29.92, 38.37, 119.23, 120.46, 128.70, 129.18, 134.08, 138.33, 144.44, 147.14, 156.34, 157.61, 196.35. LC-MS: t_R = 7.03 min; m/z: 275.0 $(M + H)^+$ calcd for $C_{14}H_{12}ClN_2O_2$. HRMS: $(M + H)^+$ calcd for $C_{14}H_{12}ClN_2O_2$, 275.0587; found, 275.0592.

2-Chloro-6-(indanone-4-oxy)-pyrazine (39). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 4-hydroxyindanone (219 mg, 1.49 mmol). Crystallization from AcOEt afforded the title compound (314 mg). Yield: 90%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.70 (t, 2H, J = 5.7 Hz), 2.94 (t, 2H, J = 5.7 Hz), 7.55−7.64 (m, 3H), 8.57 (s, 1H), 8.66 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 22.43, 35.68, 120.55, 127.24, 129.29, 133.55, 137.88, 139.26, 144.38, 146.50, 149.95, 157.62, 205.32. LC-MS: t_R = 6.48 min; m/z: 275.0 $(M + H)^+$ calcd for $C_{13}H_{10}ClN_2O_2$. HRMS: $(M + H)^+$ calcd for $C_{13}H_{10}ClN_2O_2$, 261.0431; found, 261.0432.

2-Chloro-6-(indanone-5-oxy)-pyrazine (40). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 5-hydroxyindanone (219 mg, 1.49 mmol). Crystallization from AcOEt produced the title compound (350 mg). Yield: 100%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.67 (t, 2H, J = 5.9 Hz), 3.13 (t, 2H, J = 5.5 Hz), 7.31 (dd, 1H, J_m = 1.9 Hz, J_o = 8.3 Hz), 7.47 (d, 1H, J = 1.3 Hz), 7.73 (d, 1H, J = 8.3 Hz), 8.59 (s, 1H), 8.64 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 25.45, 36.11, 120.56, 124.83, 134.07, 138.34, 144.42, 157.76, 204.61. LC-MS: t_R = 6.34 min; m/z: 261.0 $(M + H)^+$ calcd for $C_{13}H_{10}ClN_2O_2$.

2-Chloro-6-(indanone-6-oxy)-pyrazine (41). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 6-hydroxyindanone (219 mg, 1.49 mmol). Crystallization from AcOEt produced the title compound (330 mg). Yield: 94%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.74 (t, 2H, J = 5.8 Hz), 3.15 (t, 2H, J = 6.0 Hz), 7.50 (d, 1H, J = 2.2 Hz), 7.60 (dd, 1H, J_m = 2.3 Hz, J_o = 8.3 Hz), 7.70 (d, 1H, J = 8.3 Hz), 8.53 (s, 1H), 8.59 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 25.13, 36.59, 115.03, 128.01, 128.48, 133.84, 137.57, 138.21, 144.20, 152.51, 158.25, 205.56. LC-MS: t_R = 6.48 min; m/z: 261.0 $(M + H)^+$ calcd for $C_{13}H_{10}ClN_2O_2$. HRMS: $(M + H)^+$ calcd for $C_{13}H_{10}ClN_2O_2$, 261.0431; found, 261.0422.

2-Chloro-6-(2-phenyl−phenyl-oxy)-pyrazine (42). Method F was followed (reaction time: 20 h) with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 2-phenyl-phenol (268 mg, 1.49 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:2) produced the title compound (238 mg). Yield: 65%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.31−7.61 (m, 9H), 8.43 (s, 1H), 8.46 (s, 1H). LC: t_R = 8.40 min; m/z: 283.1 $(M + H)^+$ calcd for $C_{16}H_{11}ClN_2O$.

2-Chloro-6-(2-fluorophenyl-oxy)-pyrazine (43). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.69 mmol) and 2-fluorophenol (166 μL, 1.86 mmol). Purification by column chromathography (AcOEt:cyclohexane, 1:1) afforded the title compound (302 mg). Yield: 80%. ^{1}H NMR (500 MHz, DMSO-d_6)

δ: 7.31−7.45 (m, 4H), 8.56 (s, 1H), 8.67 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 116.94, 123.93, 125.47, 127.64, 133.10, 138.02, 144.33, 152.71, 154.68, 157.49. LC-MS: t_R = 7.19 min; *m/z*: 225.0 $(M + H)^+$ calcd for $C_{10}H_6ClFN_2O$. HRMS: $(M + H)^+$ calcd for $C_{10}H_6ClFN_2O$, 225.0231; found, 225.0222.

2-Chloro-6-(3-fluorophenyl-oxy)-pyrazine (44). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.69 mmol) and 3-fluorophenol (166 μL, 1.86 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) afforded the title compound (347 mg). Yield: 92%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.13−7.17 (m, 2H), 7.25 (d, 1H, J_F = 10.0 Hz), 7.52 (q, 1H, *J* = 8.1 Hz), 8.54 (s, 1H), 8.56 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 109.15, 112.56, 117.28, 131.17, 133.77, 137.95, 144.34, 153.74, 157.85, 161.35. LC-MS: t_R = 7.31 min; *m/z*: 224.0 $(M)^+$ calcd for $C_{10}H_6ClFN_2O$.

2-Chloro-6-(3-chlorophenyl-oxy)-pyrazine (45). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.69 mmol) and 3-chlorophenol (193 μL, 1.86 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1), afforded the title compound (346 mg). Yield: 85%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.32 (dd, 1H, J_o = 8.2 Hz, J_m = 1.9 Hz), 7.43 (d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, J_m = 1.9 Hz), 7.56 (t, 1H, *J* = 8.1 Hz), 8.59 (s, 1H), 8.62 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 118.73, 120.09, 121.50, 125.83, 131.84, 133.76, 137.92, 144.29, 153.14, 157.88. LC-MS: t_R = 7.89 min; *m/z*: 240.9 $(M + H)^+$ calcd for $C_{10}H_7Cl_2N_2O$. HRMS: $(M + H)^+$ calcd for $C_{10}H_7Cl_2N_2O$, 240.9935; found, 240.9933.

2-Chloro-6-(3-acetamidophenyl-oxy)-pyrazine (46). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 3-acetamidophenol (202 mg, 1.49 mmol). Crystallization from AcOEt e gave the title compound (350 mg). Yield: 99%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.06 (s, 3H), 6.90−6.95 (m, 1H), 7.76 (dd, 2H, J_m = 2.0 Hz, J_o = 7.6 Hz), 7.59 (s, 1H), 8.52 (s, 1H), 8.54 (s, 1H), 10.12 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 24.01, 111.39, 115.40, 116.02, 130.00, 133.66, 137.57, 140.82, 144.42, 152.57, 158.23, 168.55. LC-MS: t_R = 6.02 min; *m/z*: 264.0 $(M + H)^+$ calcd for $C_{12}H_{11}ClN_3O_2$. HRMS: $(M + H)^+$ calcd for $C_{12}H_{11}ClN_3O_2$, 264.0540; found, 264.0525.

2-Chloro-6-(4-acetamidophenyl-oxy)-pyrazine (47). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 4-acetamidophenol (202 mg, 1.49 mmol). Crystallization from AcOEt afforded the title compound (327 mg). Yield: 92%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.12 (s, 3H), 7.25 (d, 2H, *J* = 8.9 Hz), 7.71 (d, 2H, *J* = 8.9 Hz), 8.55 (s, 1H), 8.57 (s, 1H), 10.10 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.89, 120.29, 121.38, 133.46, 136.96, 137.22, 144.37, 158.58, 168.22. LC-MS: t_R = 5.90 min; *m/z*: 264.0 $(M + H)^+$ calcd for $C_{12}H_{11}ClN_3O_2$. HRMS: $(M + H)^+$ calcd for $C_{12}H_{11}ClN_3O_2$, 264.0540; found, 264.0545.

2-Chloro-6-(acetophenone-3-oxy)-pyrazine (48). Method F was followed with 2,6-dichloropyrazine (220 mg, 1.49 mmol) and 3-hydroxyacetophenone (200 mg, 1.47 mmol). Crystallization from AcOEt gave the title compound (370 mg). Yield: 96%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.61 (s, 3H), 7.57 (dd, 1H, J_m = 1.2 Hz, J_o = 9.0 Hz), 7.65 (t, 1H, *J* = 7.8 Hz), 7.82 (d, 1H, J_m = 2.0 Hz), 7.88 (dd, 1H, J_m = 1.3 Hz, J_o = 7.5 Hz), 8.55 (s, 1H), 8.61 (s, 1H). LC-MS: t_R = 6.52 min; *m/z*: 249.0 $(M + H)^+$ calcd for $C_{12}H_9ClN_2O_2$ 248.0.

2-Chloro-6-(acetophenone-4-oxy)-pyrazine (49). Method F was followed with 2,6-dichloropyrazine (220 mg, 1.49 mmol) and 4-hydroxyacetophenone (200 mg, 1.47 mmol). Crystallization from AcOEt furnished the title compound (365 mg). Yield: 99%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.61 (s, 3H), 7.42 (d, 2H, *J* = 8.7 Hz), 8.08 (d, 2H, *J* = 8.7 Hz), 8.59 (s, 1H), 8.63 (s, 1H). LC-MS: t_R = 6.52 min; *m/z*: 249.0 $(M + H)^+$ calcd for $C_{12}H_9ClN_2O_2$.

2-Chloro-6-(6-acetamido-naphthyl-1-oxy)-pyrazine (50). Method F was followed with 2,6-dichloropyrazine (250 mg, 1.68 mmol) and 6-acetamido-1-naphthol (350 mg, 1.72 mmol). Crystallization from AcOEt produced the title compound (526 mg). Yield: 100%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.12 (s, 3H), 7.29 (d, 1H, *J* = 7.4 Hz), 7.53 (t, 1H, *J* = 7.9 Hz), 7.57−7.62 (m, 1H), 7.80 (d, 1H, *J* = 8.2 Hz), 7.85 (d, 1H, *J* = 9.1 Hz), 8.42 (d, 1H, *J* = 1.3 Hz), 8.53 (s, 1H), 8.67 (s, 1H), 10.23 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.89, 120.29, 121.38, 133.46, 136.96, 137.22, 144.37, 158.58, 168.22. LC-MS: t_R = 5.90 min; *m/z*: 264.0 $(M + H)^+$ calcd for $C_{12}H_{11}ClN_3O_2$. HRMS: $(M + H)^+$ calcd for $C_{12}H_{11}ClN_3O_2$, 264.0540; found, 264.0545.

2-Chloro-6-(5-acetamido-naphthyl-1-oxy)-pyrazine (51). Method F was followed with 2,6-dichloropyrazine (200 mg, 1.34 mmol) and 5-acetamido-1-naphthol (270 mg, 1.49 mmol). Crystallization from AcOEt gave the title compound (379 mg). Yield: 90%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.27 (s, 3H), 7.54 (t, 1H, *J* = 8.0 Hz), 7.59 (d, 1H, *J* = 7.5 Hz), 7.68 (t, 1H, *J* = 8.0 Hz), 7.80 (d, 1H, *J* = 7.2 Hz), 7.83 (d, 1H, *J* = 6.4 Hz), 8.13 (d, 1H, *J* = 8.4 Hz), 8.59 (s, 1H), 8.78 (s, 1H), 10.10 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.47, 117.94, 118.14, 120.98, 122.31, 125.65, 126.51, 127.12, 129.19, 133.58, 134.22, 137.59, 144.42, 148.21, 158.81, 168.99. LC-MS: t_R = 6.30 min; *m/z*: 313.1 $(M)^+$ calcd for $C_{16}H_{12}ClN_3O_2$.

2-(3,4,5-Trimethoxyphenylamino)-6-(7-coumarinyloxy)-pyrazine (52) (Method G). In a tube suitable for parallel synthesis, 2-chloro-6-(coumarin-1-yl-6-oxy)-pyrazine (200 mg, 0.72 mmol) was reacted with 3,4,5-trimethoxyaniline (158 mg, 0.86 mmol) in dry, degassed toluene (10 mL) in the presence of $Pd(0)_2 \cdot dba_3$ (20 mg, 0.022 mmol, 3 mol %), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl (16 mg, 0.044 mmol, 6% mol) and sodium *tert*-butoxide (138 mg, 1.44 mmol). This mixture was stirred at 90 °C for 20 h under a N_2 atmosphere. The reaction content was evaporated to dryness in vacuum, and the solid residue was retaken in hot AcOEt (2 × 10 mL). The solutions were filtered, pooled, washed with 0.1N HCl (10 mL) and water, dried ($MgSO_4$), and evaporated again. The solid residue was purified by column chromatography (AcOEt:EtOH, 1:1) to give the title compound (102 mg). Yield: 34%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.31 (s, 6H), 3.39 (s, 3H), 6.47 (d, 1H, *J* = 9.6 Hz), 6.77 (s, 2H), 7.22 (dd, 1H, J_o = 8.5 Hz, J_m = 2.3 Hz), 7.34 (d, 1H, *J* = 2.2 Hz), 7.72 (d, 1H, *J* = 8.5 Hz), 7.84 (s, 1H), 8.03 (s, 1H), 8.10 (d, 1H, *J* = 9.62 Hz), 9.63 (s, 1H, NH). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.16, 60.04, 96.23, 108.23, 114.70, 115.49, 117.27, 121.24, 129.45, 129.66, 132.09, 143.89, 150.52, 152.67, 154.59, 156.51, 156.75, 159.74. LC-MS: t_R = 6.93 min; *m/z*: 422.1 $(M + H)^+$ calcd for $C_{22}H_{20}N_3O_6$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{20}N_3O_6$, 422.1352; found, 422.1341.

2-(3,4,5-Trimethoxyphenylamino)-6-(quinoline-4-oxy)-pyrazine (53). Using method G with 2-chloro-6-(quinolyl-4-oxy)-pyrazine (150 mg, 0.58 mmol) and 3,4,5-trimethoxyaniline (128 mg, 0.70 mmol), the title compound (48 mg) was obtained after crystallization from AcOEt. Yield: 20%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.22 (s, 6H), 3.49 (s, 3H), 6.67 (s, 2H), 7.16 (d, 1H, *J* = 5.0 Hz), 7.66 (t, 1H, *J* = 7.7 Hz), 7.84 (t, 1H), 8.02 (s, 1H), 8.08 (d, 1H, *J* = 8.1 Hz), 8.09 (s, 1H), 8.16 (d, 1H, *J* = 8.1 Hz), 8.80 (d, 1H, *J* = 5.0 Hz), 9.71 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.01, 59.98, 95.78, 110.29, 121.47, 121.63, 121.81, 126.91, 128.99, 130.28, 132.21, 135.94, 149.51, 150.67, 151.32, 152.58, 156.37, 157.59. LC-MS: t_R = 6.80 min; *m/z*: 406.7 $(M + H)^+$ calcd for $C_{22}H_{22}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{21}N_4O_4$, 405.1563; found, 405.1564.

2-(3,4,5-Trimethoxyphenylamino)-6-(quinoline-5-oxy)-pyrazine (54). Method G was followed with 2-chloro-6-(quinolyl-5-oxy)-pyrazine (150 mg, 0.58 mmol) and 3,4,5-trimethoxyaniline (128 mg, 0.70 mmol). Crystallization (AcOEt) afforded the title compound (77 mg). Yield: 33%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.18 (s, 6H), 3.47 (s, 3H), 6.57 (s, 2H), 7.43 (d, 1H, *J* = 7.5 Hz), 7.53−7.57 (m, 1H), 7.78 (t, 1H, *J* = 8.5 Hz), 7.93 (d, 1H, *J* = 8.3 Hz), 8.37 (d, 1H, *J* = 8.0 Hz), 7.94 (s, 1H), 7.99 (s, 1H), 8.40 (d, 1H, *J* = 8.3 Hz), 8.96 (dd, 1H, J_a = 1.5 Hz, J_b = 3.7 Hz), 9.56 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.12, 59.97, 95.56, 117.40, 120.93, 121.78, 122.04, 125.78, 128.72, 129.39, 130.08, 132.11, 136.08, 148.60, 149.19, 150.56, 151.17, 152.56, 157.89. LC-MS: t_R = 7.00 min; *m/z*: 405.1 $(M + H)^+$ calcd for $C_{22}H_{22}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{21}N_4O_4$, 405.1563; found, 405.1561.

2-(3,4,5-Trimethoxyphenylamino)-6-(quinoline-6-oxy)-pyrazine (55). Method G was followed with 2-chloro-6-(quinolyl-6-oxy)-pyrazine (150 mg, 0.58 mmol) and 3,4,5-trimethoxyaniline (128 mg, 0.70 mmol). Crystallization (AcOEt) gave the title compound (149 mg). Yield: 64%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.06 (s, 6H), 3.45 (s, 3H), 6.68 (s, 2H), 7.50−7.55 (m, 1H), 7.63 (d, 1H, J = 9.1 Hz), 7.80 (s, 1H), 7.87 (s, 1H), 8.00 (s, 1H), 8.08 (d, 1H, J = 9.1 Hz), 8.33 (d, 1H, J = 8.2 Hz), 8.89 (d, 1H, J = 2.5 Hz), 9.60 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 54.84, 59.97, 95.87, 116.89, 121.19, 121.88, 124.52, 128.62, 128.83, 130.72, 132.23, 135.36, 136.17, 145.26, 149.89, 150.57, 151.60, 152.58, 157.24. LC-MS: t_R = 6.88 min; m/z: 405.1 $(M + H)^+$ calcd for $C_{22}H_{21}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{21}N_4O_4$, 405.1563; found, 405.1571.

2-(3,4,5-Trimethoxyphenylamino)-6-(isoquinoline-5-oxy)-pyrazine (56). Method G was followed with 2-chloro-6-(isoquinolyl-5-oxy)-pyrazine (150 mg, 0.58 mmol) and 3,4,5-trimethoxyaniline (128 mg, 0.70 mmol). Crystallization (AcOEt) and purification by column chromatography (AcOEt) afforded the title compound (67 mg). Yield: 29%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.20 (s, 6H), 3.48 (s, 3H), 6.55 (s, 2H), 7.62 (d, 1H, J = 7.5 Hz), 7.71 (t, 1H, J = 7.9 Hz), 7.80 (d, 1H, J = 5.8 Hz), 7.95 (s, 1H), 7.99 (s, 1H), 8.03 (d, 1H, J = 8.1 Hz), 8.52 (d, 1H, J = 5.8 Hz), 9.41 (s, 1H), 9.55 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.27, 59.99, 95.91, 114.19, 120.90, 121.33, 124.41, 127.71, 128.77, 129.24, 129.31, 132.35, 136.03, 143.38, 148.42, 150.55, 152.42, 152.60, 157.78. LC-MS: t_R = 6.42 min; m/z: 405.1 $(M + H)^+$ calcd for $C_{22}H_{22}N_4O_4$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{21}N_4O_4$, 405.1563; found, 405.1579.

2-(3,4,5-Trimethoxyphenylamino)-6-(5-tetral-1-one-oxy)-pyrazine (57). Method G was followed with 2-chloro-6-(tetralon-1-yl-5-oxy)-pyrazine (200 mg, 0.73 mmol) and 3,4,5-trimethoxyaniline (160 mg, 0.87 mmol). Purification by column chromatography (AcOEt) afforded the title compound (193 mg). Yield: 63%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.99−2.02 (m, 2H), 2.60 (t, 2H, J = 5.9 Hz), 2.77 (t, 2H, J = 5.9 Hz), 3.41 (s, 6H), 3.55 (s, 3H), 6.69 (s, 2H), 7.40−7.44 (m, 2H), 7.88 (d, 1H, J = 6.8 Hz), 7.81 (s, 1H), 7.95 (s, 1H), 9.52 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 21.95, 22.97, 55.52, 60.06, 96.28, 120.55, 123.11, 127.20, 128.06, 136.67, 152.72, 197.00. LC-MS: t_R = 7.49 min; m/z: 422.1 $(M + H)^+$ calcd for $C_{23}H_{24}N_3O_5$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{24}N_3O_5$, 422.1716; found, 422.1717.

2-(3,4,5-Trimethoxyphenylamino)-6-(6-tetral-1-one-oxy)-pyrazine (58). Method G was followed with 2-chloro-6-(tetralon-1-yl-6-oxy)-pyrazine (200 mg, 0.73 mmol) and 3,4,5-trimethoxyaniline (160 mg, 0.87 mmol). Purification by column chromatography (AcOEt) gave the title compound (182 mg). Yield: 59%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.02−2.09 (m, 2H), 2.62 (t, 2H, J = 6.8 Hz), 2.92 (t, 2H, J = 5.8 Hz), 3.40 (s, 6H), 3.55 (s, 3H), 6.79 (s, 2H), 7.13 (dd, 1H, J_o = 8.5 Hz, J_m = 2.4 Hz), 7.18 (d, 1H, J = 2.2 Hz), 7.82 (s, 1H), 7.92 (d, 1H, J = 8.5 Hz), 8.02 (s, 1H), 9.63 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 22.72, 28.90, 55.15, 59.71, 60.04, 96.06, 118.66, 119.71, 121.39, 128.62, 129.42, 132.32, 136.12, 147.04, 150.57, 152.66, 156.43, 158.01, 196.28. LC: t_R = 7.49 min; m/z: 422.2 $(M + H)^+$ calcd for $C_{23}H_{24}N_3O_5$.

2-(3,4,5-Trimethoxyphenylamino)-6-(indanone-4-oxy)-pyrazine (59). Method G was followed with 2-chloro-6-(indanone-4-oxy)-pyrazine (200 mg, 0.77 mmol) and 3,4,5-trimethoxyaniline (169 mg, 0.92 mmol). Purification by column chromatography (AcOEt) produced the title compound (71 mg). Yield: 23%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.69 (t, 2H, J = 3.7 Hz), 2.98 (t, 2H, J = 5.2 Hz), 3.43 (s, 6H), 3.59 (s, 3H), 6.75 (s, 2H), 7.56−7.62 (m, 3H), 7.90 (s, 1H), 8.04 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 22.68, 35.68, 55.45, 60.04, 96.06, 119.46, 120.72, 126.71, 128.54, 129.16, 132.51, 136.11, 139.04, 146.34, 150.51, 151.32, 152.70, 156.89, 205.47. LC: t_R = 7.10 min; m/z: 408.1 $(M + H)^+$ calcd for $C_{22}H_{22}N_3O_5$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{22}N_3O_5$, 408.1559; found, 408.1552.

2-(3,4,5-Trimethoxyphenylamino)-6-(indanone-5-oxy)-pyrazine (60). Method G was followed with 2-chloro-6-(indanone-5-oxy)-pyrazine (200 mg, 0.77 mmol) and 3,4,5-trimethoxyaniline (169 mg, 0.92 mmol). Purification by column chromatography (AcOEt) afforded the title compound (61 mg). Yield: 20%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.68 (t, 2H, J = 5.6 Hz), 3.08 (t, 2H, J = 5.0 Hz), 3.39 (s, 6H), 3.55 (s, 3H), 6.77 (s, 2H), 7.21 (dd, 1H, J_m = 1.9 Hz, J_o = 8.3 Hz), 7.40 (s, 1H), 7.68 (d, 1H, J = 8.3 Hz), 7.84 (s, 1H), 8.02 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 25.36, 36.04, 55.15, 60.05, 96.21, 118.03, 120.08, 121.40, 124.56, 129.45, 132.44, 132.96, 136.09, 150.61, 152.68, 156.57, 157.62, 159.52, 204.62. LC-MS: t_R = 7.11 min; m/z: 408.1 $[(M + H)^+$ calcd for $C_{22}H_{22}N_3O_5$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{22}N_3O_5$, 408.1559; found, 408.1561.

2-(3,4,5-Trimethoxyphenylamino)-6-(indanone-6-oxy)-pyrazine (61). Method G was followed with 2-chloro-6-(indanone-6-oxy)-pyrazine (200 mg, 0.77 mmol) and 3,4,5-trimethoxyaniline (169 mg, 0.92 mmol). Purification by column chromatography (AcOEt) furnished the title compound (30 mg). Yield: 10%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.73 (t, 2H, J = 5.4 Hz), 3.13 (t, 2H, J = 5.8 Hz), 3.37 (s, 6H), 3.54 (s, 3H), 6.72 (s, 2H), 7.37 (d, 1H, J = 2.2 Hz), 7.52 (dd, 1H, J_m = 2.3 Hz, J_o = 7.2 Hz), 7.64 (d, 1H, J = 8.3 Hz), 7.81 (s, 1H), 7.98 (s, 1H), 9.57 (s, 1H). LC: t_R = 6.94 min; m/z: 408.1 $(M + H)^+$ calcd for $C_{22}H_{22}N_3O_5$.

2-(3,4,5-Trimethoxyphenylamino)-6-[(2-phenyl)-phenyl-oxy]-pyrazine (62). Method G was followed with 2-chloro-6-[(2-phenyl)-phenyl-oxy]-pyrazine (110 mg, 0.39 mmol) and 3,4,5-trimethoxyaniline (84 mg, 0.46 mmol). Purification by column chromatography (AcOEt) afforded the title compound (101 mg). Yield: 60%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.41 (s, 6H), 3.55 (s, 3H), 6.79 (s, 2H), 7.22−7.49 (m, 9H), 7.66 (s, 1H), 7.88 (s, 1H), 9.51 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.33, 60.03, 95.51, 121.09, 122.25, 125.32, 127.35, 127.99, 128.29, 128.57, 128.91, 130.83, 132.05, 133.73, 136.40, 137.20, 150.59, 152.71, 157.61. LC-MS: t_R = 8.25 min; m/z: 430.1 $(M + H)^+$ calcd for $C_{25}H_{24}N_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{25}H_{24}N_3O_4$, 430.1767; found, 430.1758.

2-(3,4,5-Trimethoxyphenylamino)-6-(2-fluorophenyl-oxy)-pyrazine (63). Method G was followed with 2-chloro-6-(2-fluorophenyloxy)-pyrazine (200 mg, 0.89 mmol) and 3,4,5-trimethoxyaniline (196 mg, 1.07 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) afforded the title compound (234 mg). Yield: 71%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.42 (s, 6H), 3.54 (s, 3H), 6.69 (s, 2H), 7.24−7.41 (m, 4H), 7.83 (s, 1H), 7.96 (s, 1H), 9.57 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.73, 60.04, 95.77, 116.92, 120.15, 123.79, 125.26, 126.52, 128.47, 132.28, 136.13, 140.27, 150.39, 152.71, 154.80, 156.98, 170.32. LC-MS: t_R = 7.50 min; m/z: 372.1 $(M + H)^+$ calcd for $C_{19}H_{19}FN_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{19}FN_3O_4$, 372.1360; found, 372.1363.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-fluorophenyl-oxy)-pyrazine (64). Method G was followed with 2-chloro-6-(3-fluorophenyloxy)-pyrazine (200 mg, 0.89 mmol) and 3,4,5-trimethoxyaniline (196 mg, 1.07 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) gave the title compound (200 mg). Yield: 61%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.44 (s, 6H), 3.55 (s, 3H), 6.77 (s, 2H), 7.02−7.09 (m, 2H), 7.16 (d, 1H, J_F = 8.8 Hz), 7.43 (q, 1H, J = 8.5 Hz), 7.78 (s, 1H), 7.98 (s, 1H), 9.61 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.23, 60.04, 95.80, 108.46, 111.40, 116.74, 121.14, 128.99, 130.94, 132.18, 136.21, 150.49, 152.68, 154.98, 156.73, 161.60, 163.55, 170.32. LC-MS: t_R = 7.82 min; m/z: 372.1 $(M + H)^+$ calcd for $C_{19}H_{19}FN_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{19}FN_3O_4$, 372.1360; found, 372.1357.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-chlorophenyl-oxy)-pyrazine (65). Method G was followed with 2-chloro-6-(3-chlorophenyloxy)-pyrazine (200 mg, 0.83 mmol) and 3,4,5-trimethoxyaniline (183 mg, 1.00 mmol). Purification by column chromatography (AcOEt:cyclohexane, 1:1) produced the title compound (165 mg). Yield: 43%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.43 (s, 6H), 3.54 (s, 3H), 6.76 (s, 2H), 7.18 (d, 1H, J = 6.5 Hz), 7.28 (d, 1H, J = 6.7 Hz), 7.36 (s, 1H), 7.43 (t, 1H, J = 8.1 Hz), 7.79 (s, 1H), 7.98 (s, 1H), 9.62 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 55.32, 60.04, 95.75, 119.55, 120.80, 121.27, 124.58, 128.98, 131.14, 132.17, 133.71, 136.20, 138.57, 150.47, 152.68, 153.24, 154.69, 156.67, 170.32. LC-MS: t_R = 8.19 min; m/z: 388.1 $(M + H)^+$ calcd

for $C_{19}H_{18}ClN_3O_4$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{18}ClN_3O_4$, 388.1064; found, 388.1051.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-acetamidophenyl-oxy)-pyrazine (66). Method G was followed with 2-chloro-6-(3-acetamidophenyl-oxy)-pyrazine (150 mg, 0.57 mmol) and 3,4,5-trimethoxyaniline (125 mg, 0.68 mmol). Crystallization (AcOEt) gave the title compound (81 mg). Yield: 35%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.03 (s, 3H), 3.44 (s, 6H), 3.56 (s, 3H), 6.80 (s, 2H), 6.82−6.87 (m, 1H), 7.31−7.49 (m, 2H), 7.50 (s, 1H), 7.76 (s, 1H), 7.97 (s, 1H), 9.55 (s, 1H), 10.04 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.98, 55.30, 60.03, 95.75, 110.84, 114.83, 121.21, 128.57, 129.75, 132.14, 136.27, 140.69, 150.60, 152.69, 154.20, 157.21, 168.47. LC-MS: t_R = 6.86 min; *m/z*: 411.2 $(M + H)^+$ calcd for $C_{21}H_{23}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{23}N_4O_5$, 411.1668; found, 411.1677.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-acetamidophenyl-oxy)-pyrazine (67). Method G was followed with 2-chloro-6-(4-acetamidophenyl-oxy)-pyrazine (150 mg, 0.57 mmol) and 3,4,5-trimethoxyaniline (125 mg, 0.68 mmol). Crystallization (AcOEt) furnished the title compound (87 mg). Yield: 37%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.07 (s, 3H), 3.43 (s, 6H), 3.55 (s, 3H), 6.77 (s, 2H), 7.13 (d, 2H, J = 8.9 Hz), 7.60 (d, 2H, J = 8.9 Hz), 7.73 (s, 1H), 7.93 (s, 1H), 9.51 (s, 1H), 9.98 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.87, 55.29, 60.04, 95.71, 120.14, 120.92, 128.01, 132.13, 136.35, 148.77, 150.49, 152.70, 157.62, 168.11. LC-MS: t_R = 6.69 min; *m/z*: 411.2 $(M + H)^+$ calcd for $C_{21}H_{23}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{23}N_4O_5$, 411.1668; found, 411.1654.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-methcarbonylphenyl-oxy)-pyrazine (68). Method G was followed with 2-chloro-6-(acetophenone-3-oxy)-pyrazine (200 mg, 0.80 mmol) and 3,4,5-trimethoxyaniline (176 mg, 0.96 mmol). Purification by column chromatography (AcOEt:cyclohexane, 9:1) gave the title compound (85 mg). Yield: 27%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.61 (s, 3H), 3.39 (s, 6H), 3.54 (s, 3H), 6.74 (s, 2H), 7.49 (dd, 1H, J_m = 2.3 Hz, J_o = 9.3 Hz), 7.59 (t, 1H, J = 8.0 Hz), 7.73 (d, 1H, J_m = 2.0 Hz), 7.81 (s, 1H), 7.82 (d, 1H, J = 6.8 Hz), 7.99 (s, 1H), 9.57 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 26.77, 55.32, 60.03, 96.13, 119.90, 121.13, 124.40, 128.74, 130.20, 132.38, 136.13, 138.50, 145.11, 150.48, 152.68, 153.27, 154.02, 156.99, 197.24. LC-MS: t_R = 7.14 min; *m/z*: 396.2 $(M + H)^+$ calcd for $C_{21}H_{22}N_3O_5$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{22}N_3O_5$, 396.1559; found, 396.1554.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-methcarbonylphenyl-oxy)-pyrazine (69). Method G was followed with 2-chloro-6-(acetophenone-4-oxy)-pyrazine (150 mg, 0.60 mmol) and 3,4,5-trimethoxyaniline (148 mg, 0.72 mmol). Purification by column chromatography (AcOEt:cyclohexane, 9:1) afforded the title compound (85 mg). Yield: 34%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.56 (s, 3H), 3.43 (s, 6H), 3.59 (s, 3H), 6.82 (s, 2H), 7.37 (d, 2H, J = 8.7 Hz), 7.89 (s, 1H), 8.07 (d, 2H, J = 6.7 Hz), 8.08 (s, 1H), 9.68 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 26.57, 55.33, 60.02, 95.58, 120.24, 121.36, 129.41, 130.24, 132.30, 133.08, 136.12, 150.55, 152.67, 156.50, 157.95, 196.62. LC-MS: t_R = 7.21 min; *m/z*: 396.2 $(M + H)^+$ calcd for $C_{21}H_{22}N_3O_5$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{22}N_3O_5$, 396.1559; found, 396.1567.

2-(3,4,5-Trimethoxyphenylamino)-6-(5-methcarbonylaminonaphthyl-oxy)-pyrazine (70). Method G was followed with 2-chloro-6-(5-acetamidonaphthyl-oxy)-pyrazine (200 mg, 0.64 mmol) and 3,4,5-trimethoxyaniline (140 mg, 0.76 mmol). Purification by column chromatography (AcOEt) produced the title compound (72 mg). Yield: 24%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.23 (s, 3H), 3.32 (s, 6H), 3.49 (s, 3H), 6.60 (s, 2H), 7.35 (d, 1H, J = 7.4 Hz), 7.52 (t, 1H, J = 7.9 Hz), 7.56 (t, 1H, J = 7.9 Hz), 7.75 (d, 1H, J = 7.3 Hz), 7.84 (d, 1H, J = 8.4 Hz), 7.93 (s, 1H), 7.97 (s, 1H), 7.99 (d, 1H, J = 7.7 Hz), 9.50 (s, 1H), 9.97 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.45, 55.11, 59.96, 95.56, 117.23, 118.39, 119.74, 120.35, 120.93, 122.37, 125.70, 126.16, 127.61, 128.38, 129.24, 132.03, 134.05, 136.17, 145.13, 149.70, 150.64, 152.59, 153.26, 158.19, 168.99. LC-MS: t_R = 7.01 min; *m/z*: 461.2 $(M + H)^+$ calcd for $C_{25}H_{25}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{25}H_{25}N_4O_5$, 461.1825; found, 461.1839.

2-(3,4,5-Trimethoxyphenylamino)-6-(3-hydroxyiminoeth-2-yl-phenoxy)-pyrazine (71) (Method H). 2-(3,4,5-Trimethoxyphenylamino)-6-(acetophenone-3-oxy)-pyrazine (90 mg, 0.22 mmol) and hydrazine hydrate solution 50% (40 μL, 0.96 mmol) were refluxed for 1.5 h in EtOH (5 mL). The reaction mixture was evaporated to dryness. Purification by column chromatography (AcOEt:EtOH, 9:1) furnished the title compound (37 mg). Yield: 41%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.61 (s, 3H), 3.39 (s, 6H), 3.54 (s, 3H), 7.18−7.21 (m, 1H), 7.43−7.50 (m, 3H), 7.79 (s, 1H), 7.97 (s, 1H), 9.55 (s, 1H), 11.29 (s, 1H). LC-MS: t_R = 7.29 min; *m/z*: 410.1$(M)^+$ calcd for $C_{21}H_{22}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{23}N_4O_5$, 411.1668; found, 411.1678.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-hydroxyiminoeth-2-yl-phenoxy)-pyrazine (72). Method H was followed with 2-(3,4,5-trimethoxyphenylamino)-6-(acetophenone-4-oxy)-pyrazine (90 mg, 0.22 mmol) and hydrazine hydrate solution 50% (40 μL, 0.96 mmol). Purification by column chromatography (AcOEt:EtOH, 9:1) afforded the title compound (30 mg). Yield: 33%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.56 (s, 3H), 3.44 (s, 6H), 3.60 (s, 3H), 6.83 (s, 2H), 7.26 (d, 2H, J = 8.7 Hz), 7.74 (d, 2H, J = 8.7 Hz), 7.84 (s, 1H), 8.02 (s, 1H), 9.63 (s, 1H), 11.25 (s, 1H). LC-MS: t_R = 7.35 min; *m/z*: 410.1$(M)^+$ calcd for $C_{21}H_{22}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{21}H_{23}N_4O_5$, 411.1668; found, 411.1636.

2-(3,4,5-Trimethoxyphenylamino)-6-(indanone-oxime-4-oxy)-pyrazine (73). Method H was followed (reaction time: 5 h) with 2-(3,4,5-trimethoxyphenylamino)-6-(indanone-4-oxy)-pyrazine (70 mg, 0.17 mmol) and hydrazine hydrate solution (32 μL, 0.51 mmol). The title compound was obtained (30 mg) by crystallization (AcOEt). Yield: 42%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.78 (m, 2H), 3.36 (m, 2H), 3.38 (s, 6H), 3.53 (s, 3H), 6.72 (s, 2H), 7.18 (d, 1H, J = 7.6 Hz), 7.33 (t, 1H, J = 7.7 Hz), 7.44 (d, 1H, J = 7.3 Hz), 7.80 (s, 1H), 7.96 (s, 1H), 9.57 (s, 1H), 11.02 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 24.55, 25.42, 55.43, 60.03, 95.87, 117.18, 119.46, 120.75, 121.77, 126.71, 128.22, 128.35, 128.78, 129.15, 132.31, 136.10, 138.94, 139.31, 150.59, 152.71, 157.08, 160.49. LC-MS: t_R = 7.24 min; *m/z*: 423.2 $(M + H)^+$ calcd for $C_{22}H_{23}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{22}H_{23}N_4O_5$, 423.1668; found, 423.1654.

2-(3,4,5-Trimethoxyphenylamino)-6-(tetralonyl-1-oxime-5-oxy)-pyrazine (74). Method H was followed (reaction time: 4.5 h) with 2-(3,4,5-trimethoxy phenylamino)-6-(tetralon-1-yl-5-oxy)-pyrazine (100 mg, 0.24 mmol) and hydrazine hydrate solution (44 μL, 0.70 mmol). The title compound was obtained (55 mg) by crystallization (AcOEt). Yield: 53%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.69 (t, 2H, J = 5.9 Hz), 2.64−2.65 (m, 4H), 3.40 (s, 6H), 3.53 (s, 3H), 6.71 (s, 2H), 7.13 (d, 1H, J = 7.9 Hz), 7.25 (t, 2H, J = 7.9 Hz), 7.76 (d, 1H, J = 5.2 Hz), 7.77 (s, 1H), 7.93 (s, 1H), 9.53 (s, 1H), 11.27 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 20.29, 22.82, 55.54, 60.04, 95.92, 120.21, 120.53, 121.36, 126.70, 127.76, 132.33, 150.55, 151.00, 152.08, 152.72, 157.64, 196.90. LC-MS: t_R = 7.60 min; *m/z*: 437.2 $(M + H)^+$ calcd for $C_{23}H_{25}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{25}N_4O_5$, 437.1825; found, 437.1812.

2-(3,4,5-Trimethoxyphenylamino)-6-(tetralonyl-1-oxime-6-oxy)-pyrazine (75). Method H was followed (reaction time: 4.5 h) with 2-(3,4,5-trimethoxy phenylamino)-6-(tetralon-1-yl-6-oxy)-pyrazine (100 mg, 0.24 mmol) and hydrazine hydrate solution (44 μL, 0.70 mmol). Crystallization (AcOEt) afforded the title compound (32 mg). Yield: 30%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.75 (t, 2H, J = 5.2 Hz), 2.61−2.68 (m, 4H), 3.40 (s, 6H), 3.54 (s, 3H), 6.79 (s, 2H), 7.03−7.18 (m, 2H), 7.78 (s, 1H), 7.87 (d, 1H, J = 8.4 Hz), 7.96 (s, 1H), 9.60 (s, 1H), 11.10 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 20.93, 22.78, 28.91, 55.22, 60.04, 95.92, 118.72, 120.02, 121.17, 124.89, 127.66, 128.57, 132.37, 136.27, 150.58, 151.89, 152.69, 157.10, 196.27. LC-MS: t_R = 7.72 min; *m/z*: 437.2 $(M + H)^+$ calcd for $C_{23}H_{25}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{23}H_{25}N_4O_5$, 437.1825; found, 437.1822.

2-(3,4,5-Trimethoxyphenylamino)-6-(4-methaminocarbonyl-naphthyloxy)-pyrazine (76). Using method E with *N*-(4-hydroxynaphthalen-1-yl)acetamide (200 mg, 0.99 mmol), the title compound

was obtained (31 mg). Yield: 6.7%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.21 (s, 3H), 3.20 (s, 9H), 3.48 (s, 3H), 6.61 (s, 2H), 7.31 (d, 1H, J = 8.2 Hz), 7.59 (t, 2H, J = 7.6 Hz), 7.70 (d, 1H, J = 8.3 Hz), 7.91 (s, 1H), 7.96−7.99 (m, 2H), 8.13 (d, 1H, J = 7.8 Hz), 9.49 (s, 1H), 9.93 (s, 1H). ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 23.44, 55.10, 59.95, 95.38, 116.77, 120.89, 121.48, 121.61, 123.18, 126.38, 126.53, 127.11, 128.23, 128.71, 130.90, 131.98, 136.18, 146.44, 150.64, 152.59, 158.26, 168.93. LC-MS: t_R = 7.29 min; m/z: 461.1 $(M + H)^+$ calcd for $C_{25}H_{25}N_4O_5$. HRMS: $(M + H)^+$ calcd for $C_{25}H_{25}N_4O_5$, 461.1825; found, 461.1811.

2[(3-Oxazol-5-yl)phenylamino]-6-(5-methaminocarbonylnaphthyl-oxy)pyrazine (77). Using method D (conventional heating, reaction time: 20 h) with 2-chloro-6-(5-acetamidonapht-1-yloxy)-pyrazine (150 mg, 0.48 mmol) and 3-(1,3-oxazol-5-yl-aniline) (96 mg, 0.60 mmol), the title compound was obtained (71 mg). Yield: 34%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.22 (s, 3H), 6.95 (t, 1H, J = 7.9 Hz), 7.06 (d, 1H, J = 8.5 Hz), 7.15 (d, 1H, J = 7.6 Hz), 7.44−7.46 (m, 2H), 7.49−7.52 (m, 2H), 7.57 (d, 1H, J = 7.6 Hz), 7.74 (d, 1H, J = 6.6 Hz), 7.77 (d, 1H, J = 8.2 Hz), 7.94 (s, 1H), 7.96 (s, 1H), 8.02 (d, 1H, J = 8.4 Hz), 8.36 (s, 1H), 9.68 (bs, 1H), 9.99 (bs, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 23.44, 113.35, 117.19, 117.82, 117.99, 118.40, 120.07, 120.86, 121.74, 122.02, 125.49, 126.10, 127.53, 127.61, 127.69, 129.22, 134.08, 140.57, 149.18, 149.98, 150.28, 151.61, 154.70, 158.28, 168.90. LC: t_R = 7.20 min; m/z: 438.1 $(M + H)^+$ calcd for $C_{25}H_{20}N_5O_3$. HRMS: $(M + H)^+$ calcd for $C_{25}H_{20}N_5O_3$, 438.1560; found, 438.1564.

2-(3-oxo-1,3-Dihydroisobenzofuran-5-ylamino)-6-(5-methaminocarbonylnaphthyl-oxy) pyrazine (78). Using method D with 2-chloro-6-(5-acetamidonaphthyl-oxy)-pyrazine (150 mg, 0.48 mmol) and 6-amino-1,3-dihydroisobenzofuran-1-one (89 mg, 0.60 mmol), the title compound was obtained (8 mg). Yield: 4%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.21 (s, 3H), 5.24 (s, 2H), 7.17 (d, 1H, J = 8.5 Hz), 7.45−7.51 (m, 3H), 7.63 (d, 1H, J = 8.2 Hz), 7.68−7.75 (m, 3H), 7.92 (s, 1H), 7.98 (s, 1H), 8.05 (d, 1H, J = 8.7 Hz), 9.92 (bs, 1H), 10.00 (bs, 1H). LC-MS: t_R = 6.72 min; m/z 427.1 $(M + H)^+$ calcd for $C_{24}H_{18}N_4O_4$.

2[(3-Oxazol-5-yl)phenylamino]-6-(4-methaminocarbonylnaphthyl-oxy)pyrazine (79). Using method D with 2-chloro-6-(4-acetamidonaphthalen-1-yloxy)pyrazine (150 mg, 0.48 mmol) and 3-(1,3-oxazol-5-yl-aniline) (115 mg, 0.71 mmol), the title compound was obtained (97 mg). Yield: 46%. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.22 (s, 3H), 6.95 (t, 1H, J = 7.9 Hz), 7.10 (d, 1H, J = 8.2 Hz), 7.14 (d, 1H, J = 7.7 Hz), 7.41 (d, 1H, J = 8.2 Hz), 7.44 (bs, 2H), 7.54 (t, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.4 Hz), 7.70 (d, 1H, J = 8.1 Hz), 7.91 (d, 1H, J = 8.5 Hz), 7.95 (bs, 2H), 8.16 (d, 1H, J = 8.4 Hz), 8.37 (s, 1H), 9.70 (bs, 1H), 9.99 (bs, 1H). ^{13}C NMR (125.8 MHz, DMSO-d_6) δ: 23.43, 113.25, 117.10, 117.70, 117.81, 120.71, 121.66, 121.77, 123.32, 126.27, 126.53, 127.31, 127.45, 127.53, 128.92, 129.39, 131.23, 140.63, 146.10, 149.99, 150.27. LC-MS: t_R = 7.29 min; m/z: 438.1 $(M + H)^+$ calcd for $C_{19}H_{20}N_5O_3$. HRMS: $(M + H)^+$ calcd for $C_{19}H_{20}N_5O_3$, 438.1566; found, 438.1565.

^{V600E}BRAF Kinase Assay. Full-length rabbit MEK1 protein was expressed with a GST tag at the N-terminus and a C-terminal histidine tag in *Escherichia coli* JM109 bacteria and purified by nickel-agarose affinity chromatography. ^{V600E}BRAF was generated by infection of SF9 insect cells cultured in SF-900 II medium (Invitrogen, Paisley, Scotland) with a baculovirus containing full-length human BRAF with an N-terminal histidine tag. Assay buffer was 20 mM MOPS, pH 7.2 containing 5 mM EGTA, 10 mM $MgCl_2$, 0.1% β-ME and 25 mM β-glycerophosphate. All incubations were at room temperature with shaking. One μg GST-MEK1, 0.07 μL of insect cell ^{V600E}BRAF lysate, and 0.5μL of inhibitor at the required concentrations (0.001 to 100 μM final concentration) were added to the wells of a glutathione-coated plate and the plate preincubated for 10 min. ATP in assay buffer (10 μL), to give a final concentration of 100 μM, was added to each well and the plates incubated for 45 min. The plates were then washed 3× with 200 μL of 0.1% Tween 20/water. Primary antibody (rabbit antiphospho MEK1/2 diluted 1/2000, Cell Signaling Technologies, Hitchin, UK) and Eu-labeled antirabbit secondary antibody (diluted 1/1000, Perkin-Elmer, Turku, Finland) were preincubated for 30 min and 50 μL added to the washed plates, which were incubated for a further hour. The plates were washed as before, and 100 μL DELFIA enhancement solution (Perkin-Elmer, Turku, Finland) added. The plates were sealed and incubated for 30 min and europium counts measured on a Victor 2 reader (Perkin-Elmer, Turku, Finland).

Acknowledgment. This work is supported by Cancer Research UK (refs: C309/A2187 and C107/A3096), the Wellcome Trust, and The Institute of Cancer Research. We thank Professor Paul Workman for helpful discussions and support and John Harris, Biofocus, for useful discussions. We also thank Meirion Richards for his help in evaluating the purity of the compounds and the accurate mass.

Supporting Information Available: Tables of purity and HPLC traces for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Wellbrock, C.; Karasarides, M.; Marais, R. The RAF proteins take center stage. *Nat. Rev. Mol. Cell Biol.* **2004**, *5*, 875–885.
(2) Davies, H.; Bignell, G. R.; Cox, C.; Stephen, P.; et al. Mutation of the BRAF gene in human cancers. *Nature* **2002**, *417*, 949–954.
(3) Tuveson, D. A.; Weber, B. L.; Herlyn, M. BRAF as a potential therapeutic target in melanoma and other malignancies. *Cancer Cell* **2003**, *4*, 95–98.
(4) Garnett, M. J.; Marais, R. Guilty as charged: B-RAF is a human oncogene. *Cancer Cell* **2004**, *4*, 313–319.
(5) Chiloeches, A.; Marais, R. Mitogen-activated protein kinase cascades as therapeutic targets in cancer. *Targets for Cancer Chemotherapy: Transcription Factors and Other Nuclear Proteins*; Humana Press Inc.: Totowa, NJ, 2002; pp 179−206.
(6) Wood, E.; Crosby, R. M.; Dickerson, S.; Frye, S. V.; Griffin, R.; et al. A prodrug approach to the design of cRaf1 kinase inhibitors with improved cellular activity. *Anti-Cancer Drug Des.* **2001**, *16*, 1–6.
(7) Hall-Jackson, C. A.; Eyers, P. A.; Cohen, P.; Boyle, F. T.; Hewitt, N.; et al. Paradoxical activation of Raf by a novel Raf inhibitor. *Chem. Biol.* **1999**, *6*, 559–568.
(8) Wilhelm, S. M.; Carter, C.; Tang, L. Y.; Wilkie, D.; McNabola, A.; et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* **2004**, *64*, 7099–7109.
(9) Bollag, G.; Freeman, S.; Lyons, G. F.; Post, L. E. Raf pathway inhibition in oncology. *Curr. Opin. Investig. Drugs* **2004**, *4*, 1436–1441.
(10) Smith, R. A.; Dumas, J.; Adnane, L.; Wilhelm, S. M. Recent advances in the research and development of RAF kinase inhibitors. *Curr. Top. Med. Chem.* **2006**, *6*, 1071–1089.
(11) Batt, D. B.; Bold, G.; Kim, S.; Ramsey, T. M.; Sabio, M. L. *Use of Isoquinoline Derivatives for Treating Cancer and MAP Kinase Related Diseases*; Novartis AG: Basel, Switzerland, 2004; p 85.
(12) Fink, C. A.; Perez, L. B.; Ramsey, T. M.; Yusuf, N.; Versace, R. W. *1,4-Disubstituted Isoquinoline Derivatives as RAF-Kinase Inhibitors Useful for the Treatment of Proliferative Diseases*; Novartis AG: Basel, Switzerland, 2005; p 144.
(13) Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; et al. The identification of potent and selective imidazole-based inhibitors of B-RAF kinase. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 378–381.
(14) King, A. J.; Patrick, D. R.; Batorsky, R. S.; Ho, M. L.; Do, H. T.; et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. *Cancer Res.* **2006**, *66*, 11100–11105.
(15) Ahmad, T.; Eisen, T. Kinase inhibition with BAY 43-9006 in renal cell carcinoma. *Clin. Cancer Res.* **2004**, *10*, 6388S–6392S.
(16) Niculescu-Duvaz, I.; Roman, E.; Wittaker, S. R.; Friedlos, F.; Kirk, R.; et al. Novel inhibitors of B-RAF based on a disubstituted pyrazine scaffold. Generation of a nanomolar lead. *J. Med. Chem.* **2006**, *49*, 407–416.
(17) Wan, P. T. C.; Garnett, M. J.; Roe, M. S.; Lee, S.; Niculescu-Duvaz, D.; et al. Mechanism of activation of of the RAF/ERK signaling pathway by oncogenic mutations of B-RAF. *Cell* **2004**, *116*, 855–867.
(18) Liao, J. J.-L. Molecular recognition of protein kinase binding pockets for design of potent and selective kinase inhibitors. *J. Med. Chem.* **2007**, *50*, 409–424.

(19) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. Simple, efficient catalyst system for the palladium-catalyzed amination of aryl chlorides, bromides and triflates. *J. Org. Chem.* **2000**, *65*, 1158–1174.

(20) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. Amination reaction of aryl halides with nitrogen-containing reagents mediated by palladium/imidazolium salts. *J. Org. Chem.* **2001**, *66*, 7729–7737.

(21) Kotha, S.; Lahiri, K.; khashinath, D. Recent applications of the Suzuki−Miyaura cross coupling reactions in organic synthesis. *Tetrahedron* **2002**, *58*, 9633–9695.

(22) Littke, A.; Fu, G. C. Palladium catalysed coupling reaction of aryl chlorides. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

(23) Tokarski, J. S.; Newitt, J. A.; Chang, C. Y. J.; Cheng, J. D.; Witteking, M.; et al. The structure of Dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against Imatinib-resistant ABL mutants. *Cancer Res.* **2006**, *66*, 5790–5797.

JM070776B